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A population-based analysis of predictors of influenza vaccination uptake in pregnant women: The effect of gestational and calendar time

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ABSTRACT

Pregnant women are vaccinated against influenza less frequently than other high-risk groups. To design effective vaccination strategies, we must understand how decisions regarding vaccination may vary by trimester and over vaccination campaigns. We used a Cox model indexed by calendar time to estimate the effect of gestational trimester and other factors on vaccination uptake in a large cohort of pregnant women in Catalonia (Spain) during 2008–09 to 2012–13 influenza vaccination campaigns. We analyzed 247,316 pregnancies. Vaccination coverage was 3.7%, 5.2%, 4.8%, 5.6% and 4.6% from 2008–09 to 2012–13 seasonal vaccination campaigns and 8.3% for the 2009 pandemic vaccination campaign. Pregnant women previously vaccinated had higher uptake than women not previously vaccinated and the hazard ratios (HRs) comparing these 2 groups decreased from 10, the first day of seasonal campaigns, to 1.3 the last day. During the pandemic campaign, HRs decreased over the course of the campaign from 8.6 to 1.9. Women in second and third trimester had higher uptake than women in first trimester, with HR = 2.8 and 2.3, respectively, at the start of seasonal campaigns. Influenza vaccination coverage among this cohort of pregnant women was alarmingly low. Our analysis reveals that gestational and calendar time have distinct and interacting effects on vaccination uptake; women in their second trimester and third trimester and previously vaccinated were more prone to be vaccinated, but this effect wanes as the influenza season progresses.

1. Background

Since the 1918–1919 influenza pandemic, several studies have reported that pregnant women are at significant risk for influenza-related mortality and morbidity not only during pandemics but also during interpandemic periods (Harris, 1919; Callaghan et al., 2010). Also, the rates of influenza-related hospitalizations are higher during second and third trimester of pregnancy compared to first trimester, and even higher for women suffering comorbidities (Callaghan et al., 2010; Dodds et al., 2007; Neuzil et al., 1998; Hewagama et al., 2010). Influenza vaccination is the best strategy to protect both mothers and their infants during their first 6 months of life, as newborns cannot be immunized during this time (Zaman et al., 2008). Moreover, available data have indicated that influenza vaccination during pregnancy is safe for both mother and fetus (Tamma et al., 2009; Kharbanda et al., 2012). Despite compelling evidence supporting influenza vaccination, health care providers (HCPs) fail to recommend it and uptake is suboptimal worldwide (Yuen and Tarrant, 2014). Since 1998, the Advisory Committee on Immunization Practices and the American College of Obstetrics and Gynecology have recommended influenza vaccination for pregnant women (Swamy and Phillips, 2015). However, in Europe, only 10 out of 27 EU member States, including Spain, recommended vaccination for pregnant women during the 2008–09 influenza season (Mereckiene et al., 2010) and according to Vaccine European New Integrated Collaboration Efforts survey, this number increased from 16 in 2009–10 to 22 in 2010–11 (Mereckiene et al., 2014). Even though there was a significant shift in vaccination policies in recent years, European reports have shown that vaccination uptake in pregnant women still lags well behind other high-risk groups, like elderly people or people with comorbidities (Mereckiene et al., 2014). To improve vaccination coverage among pregnant women, it is important to understand the dynamics of vaccination in this high-risk group. Unlike in other sub-populations, the analysis of predictors of vaccination is complicated by the temporary nature of pregnancy and the interaction between calendar and gestational time, that is, the timing of vaccine administration with respect to gestational age. Most studies estimate vaccine coverage using surveys administered after delivery or in the last trimester of pregnancy, and coverage is calculated as the proportion of women vaccinated. This approach can miss vaccinations delivered in earlier

Abbreviations: HCP, health care provider; HR, hazard ratio; CI, confidence interval; MCP, maternal care provider; Information System for the Development of Research in Primary Care, SIDIAP.

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trimesters and it does not account for the longitudinal and time-varying nature of gestational age and potential interactions with the timing of vaccination. Both phenomena of interest must be examined together to identify specific periods during pregnancy or vaccination campaigns with lower uptake. In this study, we sought to estimate influenza vaccination uptake using different measures of disease frequency, and to analyze the time-varying effects of gestational age and other predictors on vaccination uptake, using a large database of electronic health records of pregnant women in Catalonia, Spain.

2. Methods

2.1. Study population and data sources

Pregnancy status and vaccination details were collected for each woman included in this study from the primary care electronic health record system of the Catalan Institute of Health. The Catalan Institute of Health manages 274 (80%) of all Catalan primary care practices; consequently, pregnant women attending these practices represent the largest cohort of pregnant women of this region. A pregnant woman with a "pregnancy confirmed" code in the electronic health record system, with at least one antenatal visit and with a minimum of one month of pregnancy was eligible for the study population. The Information System for the Development of Research in Primary Care (Catalan acronym SIDIAP) provided the anonymized database for this study (Bolíbar et al., 2012). The Ethics Committee of Vall d'Hebron Hospital approved the study protocol, and since patient data were anonymized, no informed consent was required.

2.2. Measures

We defined the start of pregnancy as the reported date of the last menstrual period, and since delivery date was not always captured for women who gave birth in private clinics, we defined 40 weeks after pregnancy start as the "maximum" pregnancy end date. Individual women were counted more than once if they were pregnant in multiple influenza vaccination campaigns, because influenza vaccine should be administered during each influenza season. Thus, the unit of analysis was the pregnancy and for the final study population we selected all pregnancies that overlapped with any seasonal influenza vaccination campaign from 2008–09 to 2012–13 or with the 2009 pandemic influenza vaccination campaign.

We separately analyzed the pandemic and seasonal influenza vaccination campaigns: the seasonal campaigns began on October 1st, 2008 to 2012 and ended on January 31st, 2009 to 2013, while the pandemic campaign began on November 16th, 2009 (when the pandemic vaccine was available in Catalonia) and ended on January 31st, 2010.

We collected the dates of vaccinations during seasonal and pandemic influenza vaccination campaigns from the electronic health records. If a woman had more than one record per campaign, the first one was considered the true vaccination date. We separated the data into pandemic and seasonal cohorts. We report vaccination uptake for both cohorts in three ways:

a) *Vaccination coverage*: The proportion of women vaccinated among those who were ever pregnant within a vaccination campaign. A woman, who was only pregnant for a single day, would be included in the denominator with equal weight as one who was pregnant for the entire campaign. A woman vaccinated before pregnancy (but during the campaign) would be included in the numerator.
b) *Vaccination incidence rate* (*or incidence density*): The number of vaccinations during a given influenza vaccination campaign divided by the total person-time contributed by each pregnant women followed through the vaccination campaign.
c) *Cohort coverage*: This measure estimates the proportion of women vaccinated during their pregnancy among those who were unvaccinated at the start of their pregnancy according to each predictor of vaccination. In our survival analysis the event (vaccination) must occur after the start of follow-up (first day of a vaccination campaign). Follow-up time continued until the woman was vaccinated, was no longer pregnant, or the influenza vaccination campaign ended, whichever came earliest. This estimate excluded women vaccinated before pregnancy or after they gave birth.

The following variables were considered potential predictors of influenza vaccination uptake: maternal age (<25, 25–34 and ≥35 years), country of origin (Spanish or immigrant), parity (primiparous/multiparous), number of pre-natal visits (≤5, 6–10, ≥11), high-risk status (yes/no), record of previous seasonal influenza vaccination (yes/no), smoking status (non-smoker, former smoker, smoker), pre-pregnancy body mass index (<30, ≥30 kg/m^2) and socioeconomic status (residential urbanness: urban least deprived, urban most deprived, and rural). Using the International Classification of Diseases codes, 10th revision, a pregnant woman was categorized as high-risk status if she had an underlying medical condition that would have made her eligible for the influenza vaccine irrespective or her pregnancy status (Supplemental Table 1). Women from urban areas were classified into 2 levels according the MEDEA index. This index has only been validated for urban populations and is based on socioeconomic indicators in the Spanish census. It has 4 quartiles, being quartile 1 the least deprived and quartile 4 the most deprived (Domínguez-Berjón et al., 2008). Finally, we included gestational trimester (first, 0 to 13 weeks; second, 14 to 27 weeks and third, 28 to 40 weeks) as a time-dependent variable in the analysis, using two indicator variables representing second and third trimester compared to first. For the seasonal campaigns, the year of the campaign was also included as an indicator variable, and if potential predictors had missing data we created an "unknown" category (additional information is provided in Supplemental Appendix 1).

2.3. Statistical analysis

To determine the most relevant predictors of vaccination uptake, we fitted a Cox regression model to our data. Survival time began on the first day of the vaccination campaign; pregnancies beginning before the start of the campaign had a "delayed" (left-truncated) entry into the cohort. If a woman had more than one pregnancy in a single vaccination campaign, we included only the first pregnancy for the analysis, but if a single pregnancy overlapped two consecutive campaigns, this woman could contribute survival time to both campaigns. We developed two models: one that pooled together all five seasonal campaigns, and another for the pandemic campaign. Variables that were statistically significant in the univariate analysis or were thought to be important predictors were considered for inclusion in the multivariate model. We examined the proportionality assumption using the Schoenfeld test and log-minus-log plots. When non-proportionality was identified, we introduced interaction terms between the predictor of interest and calendar time, transforming calendar time with the log function and separately with B-splines (degree 2, 3 and 4) to determine whether more flexible interactions with time could improve the model fit. As we added parameters, we used the minimum Akaike Information Criterion to select the final model. All statistical analyses were conducted using R version 3.2.3 (R Core Team, 2015).

3. Results

From the 2008–09 to 2012–13 seasonal influenza vaccination campaigns, there were 51,708; 51,077; 50,953; 48,620 and 44,958 eligible pregnancies, respectively. For the pandemic vaccination campaign 45,259 pregnancies were included. The demographic and clinical characteristics of women in both cohorts are shown in Table 1. During seasonal campaigns, vaccination coverage was 3.7%, 5.2%, 4.8%, 5.6% and