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Number needed to vaccinate to prevent hospitalizations of pregnant women due to inter-pandemic influenza in Sweden, 2003–2009

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ABSTRACT

Background: The evidence of increased risk of severe disease for healthy pregnant women due to inter-pandemic influenza consists mainly of observational studies of health service utilization in USA and Canada. However, these results can be context dependent and estimates in a European setting are sparse. For policy purposes we therefore decided to elucidate the potential value of vaccination in Sweden.
Materials and methods: We conducted a retrospective, register-based study of hospitalizations due to inter-pandemic influenza or respiratory infection attributable to influenza in pregnant women in Sweden. With aggregated data from 2003 to 2009 we assessed the number needed to vaccinate (NNV) to prevent one such hospitalization.
Results: We included on average 96,000 pregnant women/year and identified 9–48 hospitalizations/season fulfilling the case definition. Assuming 80% vaccine effectiveness the NNV was >1,900 pregnant women. The estimate is higher than those found in the USA, Canada, and UK. The difference may be explained by differing methods to estimate NNV, but also differences in propensity to hospitalize and the basic health status of the pregnant women.
Conclusions: Because of the increased risk associated with influenza A(H1N1)pdm09, vaccination is presently offered to all pregnant women in Sweden, but vaccination against other inter-pandemic influenza types seems disputable. The study illustrates the context dependence of preventive health measures and points to the need for national NNV estimates and international harmonization of study methods for comparisons between countries.

1. Introduction

Before the influenza pandemic in 2009 most European countries; including Sweden; recommended vaccination only of pregnant women with clinical risk-conditions; e.g. chronic heart diseases [1]. During the pandemic; all pregnant women were considered a priority group for vaccination; based on evidence of an increased risk of severe disease and death associated with the pandemic strain [2]. In the post-pandemic phase; Sweden has decided to recommend pregnant women vaccination against influenza A(H1N1)pdm09 with the trivalent vaccine; as long as influenza A(H1N1)pdm09 continues to circulate and exhibit a higher propensity to cause viral pneumonia than seasonal influenza. However; many European countries continued to recommend vaccination to all pregnant women; not just against A(H1N1)pdm09 but also against other strains included in the seasonal vaccine [3].

There are plausible mechanisms related to mechanical and immunological changes that may render women more vulnerable to respiratory infections during pregnancy [4,5]. The European Centre for Disease Prevention and Control (ECDC) has concluded that vaccination of pregnant women could reduce the number of influenza-related hospitalizations and deaths in this group and potentially the burden of influenza in children younger than six months [6]. The WHO SAGE committee has referred to "compelling evidence of substantial risk of severe disease in this group. . ." [7], and WHO has subsequently recommended pregnant women as the

Abbreviations: NNV, number needed to vaccinate; ECDC, European Centre for Disease Prevention and Control; RIRI, respiratory infection that can possibly be related to influenza; NBHW, National Board of Health and Welfare; GAM, generalized additive regression model; VE, vaccine effectiveness.

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highest priority group for vaccination against seasonal influenza. However, a recent systematic review [8] concluded that pregnancy as a risk factor for seasonal influenza, as opposed to pandemic influenza including A(H1N1)pdm09, is not sufficiently studied. Furthermore, ECDC has concluded that European studies of the disease burden of seasonal influenza in pregnant women are needed [6]. Whereas an increased risk of influenza-associated deaths for pregnant women has been documented during pandemics [9–13], deaths in pregnant women due to *inter-pandemic* influenza have only been described in occasional case reports [14–16], suggesting that this outcome is unusual. Moreover, the evidence of an increased risk of severe disease for healthy pregnant women due to seasonal, inter-pandemic influenza mainly consists of observational studies of health service utilization in USA and Canada [17,18]. Albeit healthcare utilization often being applied as an indicator of disease severity, it should be interpreted with caution since healthcare utilization may be context dependent. For example, despite similar symptoms and severity, there may be differences in healthcare seeking behaviour, access to healthcare or medical recommendations. Furthermore, the relative risk does not inform on burden of hospitalization, and a sufficient absolute risk is needed to motivate vaccination. Hospitalization rates of 15 and 25 per 10,000 pregnant women or third trimester women have been found in Canada and USA, respectively [17,18], and in a study set in the UK the rate was estimated to 13 per 10,000 pregnant women [19]. Since these rates may be context dependent and estimates in a European setting are sparse, it was deemed that a national estimate for Sweden was necessary for policy purposes. Therefore we conducted a study of hospitalizations due to seasonal, inter-pandemic influenza or respiratory infection attributable to inter-pandemic influenza among pregnant women in Sweden and assessed the number needed to vaccinate (NNV) to prevent one such hospitalization.

2. Methods

We conducted a retrospective, register-based study of inter-pandemic seasons, using ICD-10 codes that indicate influenza hospitalizations. Data for the study was collected from calendar week 1, 2000 to calendar week 53, 2009. For reasons explained later our modelling and NNV estimation subsequently required restriction to calendar week 46, 2003–calendar week 20, 2009.

Since an influenza diagnosis may not have been established for all admitted with influenza, we combined hospitalizations with a main ICD-10 diagnosis of influenza and hospitalizations with a main diagnosis of a respiratory infection that can possibly be related to influenza (RIRI) (Table 1). Regardless of the number of times the diagnosed individuals were admitted and discharged during a calendar week, a maximum of one hospitalization episode per week and person was included.

There is no register on all pregnancies in Sweden, but there is a Medical Birth Register. Therefore only pregnant women who had given birth in Sweden were eligible for our study. The register includes women who delivered a living child, or a deceased child after 27 weeks (before June 2008) or after 21 weeks (thereafter).

The national registration numbers of the women who had given birth during the study period were collected from the Swedish Medical Birth Register and linked to the National Patient Register. Both registers are kept by the National Board of Health and Welfare (NBHW). Identified cases with a main diagnosis belonging to either influenza or RIRI were categorized as such. Nearly all pregnant women in Sweden regularly attend prenatal care [20]. Nonetheless 3–8% of the women lacked a registered date of their last period, or an ultrasound estimated date of beginning of their pregnancy, and were excluded from the study. Based on the date of the beginning of the pregnancy trimesters were approximated (1st: ≤84 days, 2nd: 85–182 days, 3rd: ≥183 days). Finally, the number of pregnant women was aggregated by calendar week, year and trimester. The data was extracted and aggregated by the NBHW and thereafter delivered to the investigators. Since the study was carried out with aggregated data it did not require a review by an Ethics Review Board.

To estimate the number of hospitalizations with RIRI that could be attributed to influenza but for which the main diagnosis was not influenza, we fitted a generalized additive (GAM) quasi-Poisson regression model with identity link [21] to the RIRI hospitalizations. The model included: *calendar week*, which modelled the baseline with a cyclic penalized cubic regression spline function; and *the weekly number of laboratory influenza reports* with one parameter for each season, which modelled hospitalizations above the baseline that could be attributed to influenza. By using identity link we could assume that these hospitalizations were proportional to the laboratory influenza cases. We also calculated Wald confidence intervals for the proportions. During the included time period, 94–95% of all pregnant women were 20–39 years old [22]. Therefore the included laboratory data on the weekly national number of confirmed laboratory results of influenza during the surveillance seasons, i.e. calendar weeks 40–20, for seasons 2003/04–2008/09, were collected for the 20–39 years age group. This laboratory surveillance data was collected from the Swedish Institute for Communicable Disease Control and linked to the weekly patient data. Data by age group was only available from calendar week 46, 2003 and onwards, and data beyond calendar week 20, 2009 were excluded to avoid the inclusion of the pandemic influenza A(H1N1)pdm09.

The estimated proportions were multiplied with the weekly number of laboratory influenza cases, resulting in the weekly number of RIRI hospitalizations attributed to influenza among pregnant women. The weekly numbers were then aggregated per season.

For each season, 2003/04–2008/09 we also extracted the total number of main diagnoses of influenza in the register data during the extended season, defined as the time between calendar week 27 one year to calendar week 26 the following year. In 2009 the last included week was week 20. There were no influenza diagnoses outside the surveillance season.

We then added the influenza diagnoses in each extended season to the estimated RIRI hospitalizations attributed to influenza, calculated from the model, and thereby obtained an estimate of the total number of influenza hospitalizations of pregnant women per season.

As part of our main analysis we also calculated the NNV per season [23]

$$\mathrm{NNV}_i = \frac{1}{\mathrm{VE}_i\left(\frac{cases_i}{n_k}\right)}, \quad (1)$$

where VE = vaccine effectiveness against influenza, cases = total number of influenza hospitalizations per season, n = number of unvaccinated pregnant women, i = season and k = year the season turned into. We assumed that all pregnant women were unvaccinated, and thus n was the number of pregnant women between 2003 and 2009. The VE was allowed to vary in order to carry out a sensitivity analysis: 40–80%. This wide range of VE was chosen since estimations of the VE and its confidence intervals have varied widely between studies [24,25] and the match to the circulating subtype of influenza may vary. We also calculated the mean NNV using the average n and the average *cases*.

To create the possible worst and best case scenarios of NNV, we first calculated the 95% confidence intervals of number of hospitalizations attributable to influenza for each season. For the worst possible scenario, the most severe season, we substituted the *cases*