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## Commentary

## Commentary on: “Association of spontaneous abortion with receipt of inactivated influenza vaccine containing H1N1pdm09 in 2010–11 and 2011–12” ☆

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In this issue, Donahue et al. [1] using U.S. data from the Vaccine Safety Datalink (VSD) present unexpected findings of an association between spontaneous abortion (SAb) and influenza vaccination during the 2010–11 and 2011–12 seasons. Using a case-control design, they identified 485 cases of SAb and 485 individually-matched controls from 6 geographically-diverse health plans across the U.S. The authors replicated the design and analysis of an earlier VSD study in which they found no vaccine-associated risk for SAb in the 2005–6 and 2006–7 seasons [2]. In contrast, in the 2010–11 and 2011–12 seasons, the authors reported a doubling of risk for SAb when maternal vaccination was received within 28 days prior to the SAb event. There was no association noted with an exposure window longer than 28 days since receipt of vaccination.

Of interest, larger effect sizes were seen among women who were vaccinated within the 28-day window in the 2010–11 season and, of particular interest, specifically among those women who had also received an influenza vaccine in the previous season. Indeed for women in the 28-day window in both seasons combined, among those who also received a pH1N1-containing vaccine in the previous influenza season, the adjusted odds ratio (aOR) and 95% confidence interval (CI) was 7.7 (95% CI 2.2–27.3); in contrast for women who had not been vaccinated in the previous season, the aOR approximated the null. In their examination of effect modification by previous vaccination season-by-season, the aOR for vaccination in the 2010–11 season within the 28-day risk window among women who were also vaccinated with the monovalent pH1N1 vaccine in 2009–10 was 32.5 (95% CI 2.9–359.0). In the 2011–12 season, that same comparison yielded an aOR of 6.4 (95% CI 1.0–41.2). Odds were also increased among older women who had also received the previous year vaccination.

SAb is one of the most challenging birth outcomes to study in observational research. Among other factors, the high proportion of abortions that take place in clinically-unrecognized pregnancies and the lack of consistency in accurate capture of these events in medical records when SAb do occur, make such research difficult to carry out [3]. As the authors describe extensively in their

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discussion, there are numerous factors to take into consideration in interpreting their results. Misclassification of exposure is thought to be common with influenza vaccine, particularly since the 2009–10 season, when increasing numbers of influenza vaccines were obtained in non-clinical settings [4]. However, as Donahue et al. point out, there is no reason to think exposure misclassification was differential in this study. Their findings, as in any observational study, could also be attributed to unmeasured confounding. For example, there could be differential repeated maternal vaccination rates among women with sub- or infertility who are attempting pregnancy and at increased risk of SAB [5]. Similarly, there could be differential vaccine-seeking behavior in women with psychiatric disorders and their treatments who may be at higher risk of SAB [6].

Another important consideration is consistency of these findings, or lack thereof, with the existing literature. Although sparse, previous studies have not found an association between receipt of influenza vaccine and SAB. The Vaccines and Medications in Pregnancy Surveillance System (VAMPSS) cohort arm reported a Hazard Ratio (HR) of 1.09 (95% CI 0.49–2.40) for SAB among 380 vaccine-exposed and 267 unexposed pregnancies in the combined 4 seasons from 2010 to 2014 [7]. The numbers of SAB events were too small to provide stable estimates for specific seasons; however, among the four seasons, SAB rates (accounting for gestational timing of enrollment) were highest in the 2010–11 season. Three additional studies that included an evaluation of risk of SAB following receipt of an influenza vaccine formulations available in 2009 also found no evidence of an increased risk (reviewed in McMillan et al. [8]).

Another consideration is biologic plausibility. Donahue et al.'s *a priori* hypothesis was that the 28-day window would be relevant to SAB since this is the average time to peak immune response following vaccination. However, how does one interpret a current pregnancy risk that requires previous season vaccination? The authors speculated that this could represent a “two-hit” phenomenon, where the adverse response to the antigen is increased with the second or “booster” dose of the same strain of vaccine. Interestingly, for another vaccine, human papilloma virus (HPV)-16/18 AS04-adjuvanted vaccine, Baril et al. [9] reported an aHR of 2.55 (95% CI 1.09–5.93) for SAB following receipt of 2 doses of vaccine within the 6-week window from 36 days before and 45 days after the first day of the last menstrual period. No associations were found with single doses of the HPV vaccine or other gestational windows of exposure.

Donahue et al. also postulate that the repeat vaccination finding may be consistent with a potential increase in the Th1 proinflammatory response associated with the pH1N1-containing vaccines. This strain specificity may be consistent with the previous null finding in the VSD study of SAB in the 2005–6 and 2006–7 seasons [2], years when no pH1N1 strain was included in the vaccine formulations. Their finding should prompt future analyses to examine modification by previous year vaccination in years with and without pH1N1 strains, and to compare repeat vaccination in consecutive seasons where the strains in the formulation were similar or the same.

One important take-away message from this study is that seasonal vaccine formulations are not all the same. As with other

studies of drug safety in pregnancy, specific drugs require targeted post-marketing surveillance studies to monitor for safety [10], and the challenges are even greater for influenza vaccines, whose antigens and other components typically change each year (and even by manufacturer).

The current findings cannot be considered causal, and could be due to chance. Nevertheless, it is important to consider these in the context of previous work, which taken as a whole does not support any change in the Advisory Committee on Immunization Practices recommendations to vaccinate against influenza during pregnancy. In the meantime, it is important to search for opportunities to ask the same research question in other datasets.

### Conflict of interest

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