DEVELOPING THE INFRASTRUCTURE TO ASSESS PREGNANCY OUTCOMES FOLLOWING VACCINATION: INFLUENZA VACCINES AND SPONTANEOUS ABORTION AS A USE CASE
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BACKGROUND
- Sentinel is an active surveillance system that uses pre-existing electronic healthcare data from multiple sources to monitor the safety of FDA-regulated medical products. Strengths include its large population and availability of medical records for review.
- Pre-market clinical trials typically exclude pregnant women. Limited data exist on the safety of vaccine use during early pregnancy with respect to pregnancy outcomes. We investigated capabilities of Sentinel to assess pregnancy outcomes following maternal immunization.
- A “use case” example, influenza vaccines and spontaneous abortion (SAB), was utilized to develop and assess these capabilities.
- The use case was selected because influenza vaccines are recommended by CDC for routine use during pregnancy. Further, SAB is one of the most commonly reported pregnancy outcomes in passive surveillance. The use case was not selected on the basis of any concerns of a possible association.

OBJECTIVES
- To validate algorithms to identify SAB and pregnancy start among live births.
- To develop a case-time control approach to study influenza vaccines and SAB

METHODS
Study Population
- Women ages 18–34 with pregnancies ending in a live birth or SAB who:
  - Were continuously enrolled in a health plan associated with 2 Sentinel Data Partners for at least 90 days before pregnancy start through end of pregnancy.
  - Received any influenza vaccine licensed for use in the U.S. from 4–weeks gestation through end of pregnancy in the 2008–09 or 2010–11 seasons

Algorithms
- SAB algorithm:
  - Diagnosis codes for SAB, missed abortion, or treatment of incomplete or missed abortion in any medical care setting
  - Livebirth algorithm:
    - Maternal diagnosis and procedure codes for delivery (excluding stillbirth) in inpatient setting
  - Pregnancy start algorithm (live births only)
    - Gestational age (GA) was assigned based on presence/absence of maternal and infant codes for post-term or pre-term birth.
    - If there were no codes for post-term/pre-term birth, GA of 273 days was assigned.
  - Validation of algorithms
    - Full text medical records were retrieved by the Data Partners.
    - Redacted charts were reviewed by clinicians to confirm SAB, livebirth, and GA.
    - Presumptive SAB cases were confirmed if there was documentation of intrauterine pregnancy and unintentional pregnancy loss.

Case-time control design
- The case-time control design is a variant of the case-control study that includes controls to adjust for seasonal and gestational age.
- For controls, we set an index date equivalent to each SAB case’s gestational age at SAB.
- Risk windows:
  - 1–28 days prior to SAB or index date
  - Vaccination during the following gestational periods: 4 through 4 weeks, 2 through 5 weeks, and 6 through 11 weeks
- Control window: Time within 4 weeks gestation through the date of SAB or index date, excluding the risk interval

RESULTS

Table 1. Positive predictive value of SAB algorithm by age, code, and medical care setting

<table>
<thead>
<tr>
<th>Code type</th>
<th>Procedure code</th>
<th>Diagnosis and procedure code</th>
<th>Odds ratio and 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal age</td>
<td>1</td>
<td>9</td>
<td>66.7% (29.9 to 92.5%)</td>
</tr>
<tr>
<td>18 to &lt;25 years</td>
<td>14</td>
<td>44</td>
<td>43.2% (28.4 to 59.0%)</td>
</tr>
<tr>
<td>25 to &lt;30 years</td>
<td>15</td>
<td>58</td>
<td>58.8% (44.2 to 72.4%)</td>
</tr>
<tr>
<td>30 to &lt;35 years</td>
<td>11</td>
<td>66</td>
<td>57.5% (46.4 to 68.0%)</td>
</tr>
</tbody>
</table>

Figure 3. Validation of pregnancy start algorithm in livebirths (N=133)
- Confidence intervals were wide, but there was no evidence to suggest that the PPV of the SAB algorithm differed by age, code type, diagnosis code, or setting of medical care.

Figure 4. Odds ratios estimates from case-time control design, by risk interval
- Of the 185 livebirth controls identified in the claims data, we obtained pregnancy related medical charts for 147 (79%). A total of 133 eligible livebirth controls had dating information (last menstrual period, ultrasound, or GA at delivery) in the medical chart.
- A total of 124 (95%) of the live births had an algorithm-derived pregnancy start that was within 14 days before or after their “gold standard” (chart-derived) estimate.

CONCLUSIONS
- The PPV of algorithm to identify pregnancy start in pregnancies ending in a livebirth was relatively high. The low PPV of the SAB algorithm suggests that rigorous validation is needed to study pregnancy outcomes with Sentinel.
- Using a case-time control approach, we successfully implemented a use case (influenza vaccines and SAB). Findings support that it may be feasible to assess pregnancy outcomes following vaccination with Sentinel.

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