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

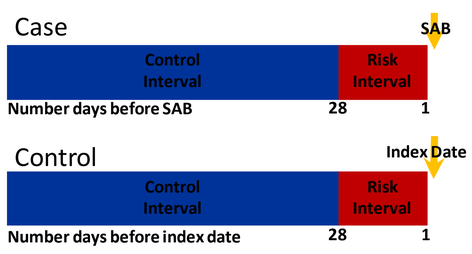
Algorithms

- 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 stillbirths) 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

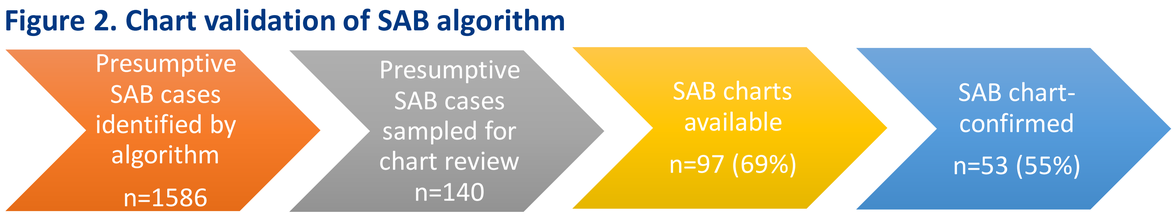
- The case-time control design is a variant of the case-cross-over study that includes controls to adjust for temporal trends in exposure.
- Vaccinated SAB cases were matched up to 6 vaccinated controls each, on Data Partner and age at pregnancy start, which inherently adjusts for seasonality and gestational 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

Figure 1. Case-time control design, 1-28 day risk interval



RESULTS

Figure 2. Chart validation of SAB algorithm



Reasons why SAB was not confirmed (when charts available, N=44)

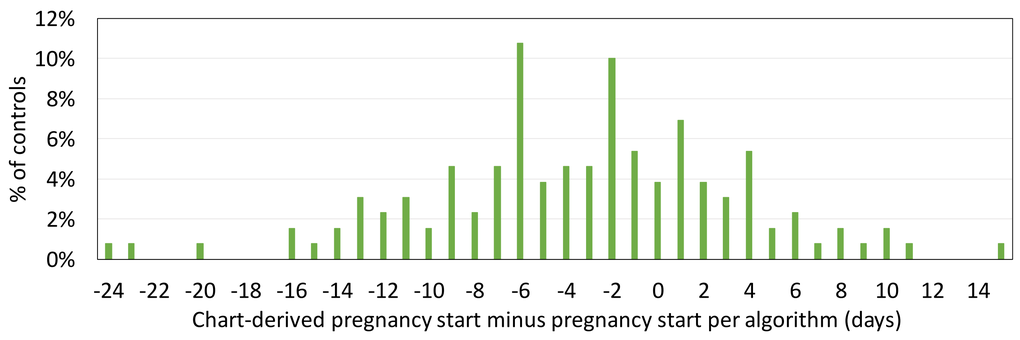
- Pregnancy not confirmed N=4
- Pregnancy outcome unknown N=26
  - Location of pregnancy not documented in obtained records N=24
  - Intrauterine pregnancy with unknown outcome N=2
- Other pregnancy outcome confirmed N=14
  - Ectopic pregnancy N=5 ; stillbirth N=1; induced abortion N=5; livebirth N=3

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

	Cases with medical charts	Chart-confirmed cases	Positive predictive value (95% CI)
Overall	97	53	54.6% (44.2 to 64.8%)
Maternal age			
18 to <25 years	17	10	58.8% (32.9 to 81.6%)
25 to <30 years	29	13	44.8% (26.5 to 64.3%)
30 to <35 years	51	30	58.8% (44.2 to 72.4%)
Code type			
Procedure code	1	0	0 -----
Diagnosis code	87	50	57.5% (46.4 to 68.0%)
Diagnosis and procedure code	9	3	33.3% (7.5 to 70.0%)
Diagnosis code			
632 (missed abortion) and 634*(spontaneous abortion)	9	6	66.7% (29.9 to 92.5%)
632 without 634*	43	28	65.1% (49.1 to 79.0%)
634* without 632	44	19	43.2% (28.4 to 59.0%)
No diagnosis codes	1	0	0 -----
Setting			
Ambulatory visit and emergency department	2	2	100% (15.8 to 100%)
Ambulatory visit only	80	44	55.0% (43.5 to 66.2%)
Emergency department only	11	5	45.5% (16.8 to 76.6%)
Inpatient	4		50.0% (6.8 to 93.2%)

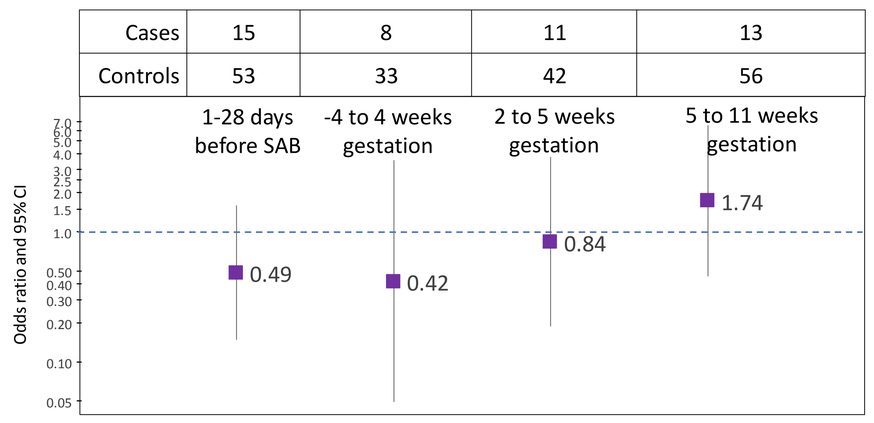
- Confidence intervals were wide, but there was no evidence to suggest that the PPV of the SAB algorithm differed by age, code type, diagnosis code, or setting of medical care.

Figure 3. Validation of pregnancy start algorithm in livebirths (N=133)



- 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.

Figure 4. Odds ratios estimates from case-time control design, by risk interval



- Due to small numbers, confidence intervals for odds ratio estimates were wide. However, there was no evidence for an increased risk of SAB after influenza vaccine.

LIMITATIONS

- The case-time control design was underpowered due to case exclusions after chart review. Further, charts were not obtained for 31% of SAB cases.
- We only sought out one chart per case to confirm the SAB. Confirmation of an intrauterine pregnancy and pregnancy loss can occur over several healthcare visits.

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.

ACKNOWLEDGEMENTS/DISCLOSURES

This work was supported by the FDA through the Department of Health and Human Services Contract No. HHSF223201400030I. The views presented are of the authors and not the FDA. The authors have no conflicts of interest to disclose. Many thanks to HealthCore (Anthem) and staff at Aetna: Annemarie Klein, Smita Bhatia, and Kevin Walsh.