Evaluating the Risk of Spontaneous Abortion Following Administration of Influenza Vaccines Containing H1N1pdm09 and H3N2 Viral Antigens

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Trivalent Inactivated Influenza Vaccine and Spontaneous Abortion

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- 2005-06 and 2006-07
- Matched case-control study
- 243 matched pairs (82% ultrasound confirmed)
- **SAB not associated with influenza vaccination in 28-day exposure window (OR 1.2; CI 0.5-2.9, P=.63)**
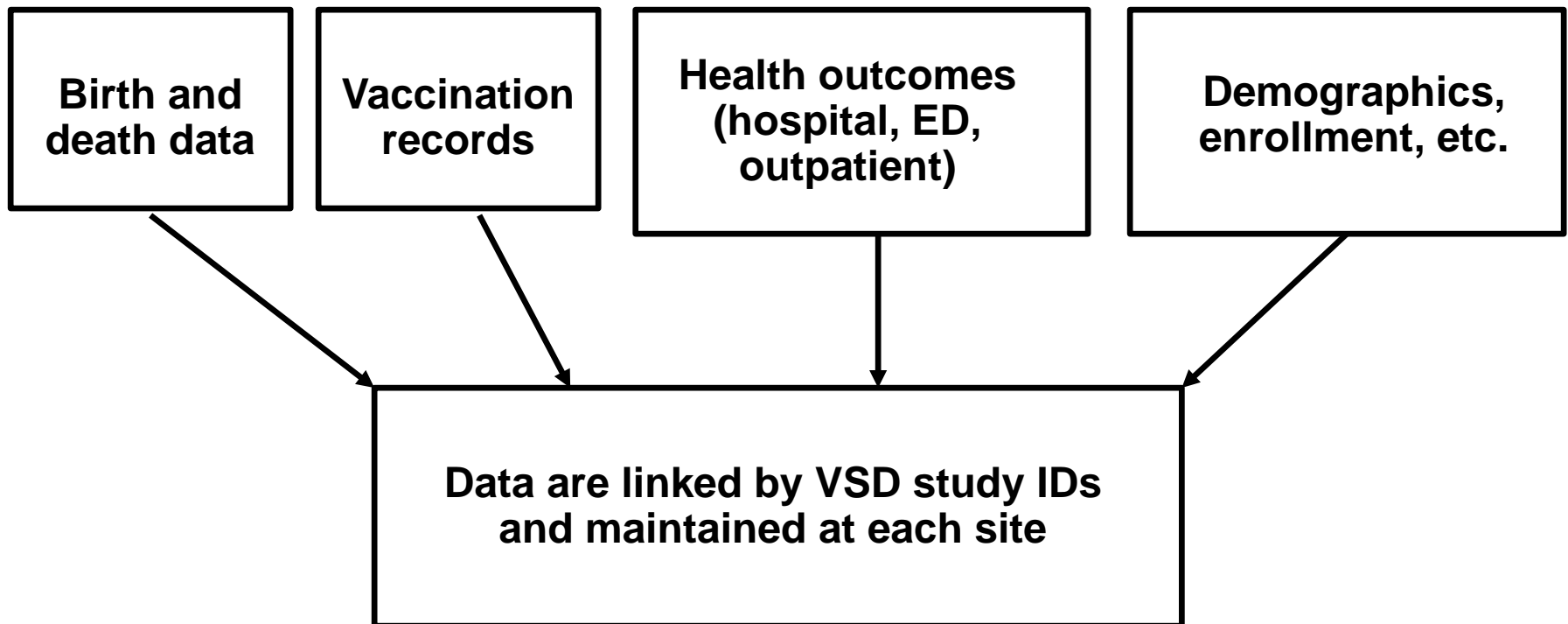
Association of spontaneous abortion with receipt of inactivated influenza vaccine containing H1N1pdm09 in 2010–11 and 2011–12

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Vaccine Safety Datalink (VSD)

➤ Established in 1990 to improve vaccine safety using active surveillance and epidemiological studies

➤ Collaboration between CDC and 8 integrated healthcare plans

➤ Standardized data files on 9-10 million persons per year (~3% of US population)

Birth and death data	**Vaccination records**	**Health outcomes (hospital, ED, outpatient)**	**Demographics, enrollment, etc.**

Data are linked by VSD study IDs and maintained at each site

Vaccine Safety Datalink

Kaiser Permanente Washington

Northwest Kaiser Permanente

No. CA Kaiser Permanente

So. CA Kaiser Permanente

Health Partners

Marshfield Clinic

Harvard Pilgrim

Kaiser Permanente Colorado

CDC

Case Identification

- Potential cases identified using ICD-9 codes

- Medical record review of all potential cases

- SAB from 5 to <20 weeks gestational age

- Adjudication to confirm SAB and estimate SAB date
  - Ultrasound (primary, 89% of cases had ≥1 ultrasound)
  - Date of clinical diagnosis if ultrasound not available

- Date of SAB was the *reference date* for each case-control pair

Control Selection

- Initially identified using ICD-9 codes for live births and stillbirths

- Controls that had an LMP within 7 days of a case were selected and sorted by proximity to the case LMP. Controls were reviewed from this list until a match was found.

Vaccine Exposures

- Receipt of seasonal IIV documented in medical record

- Primary exposure window: 28 days before reference date

  - Also examined 29-56 and >56 days

- All other vaccinations during pregnancy were abstracted

Analysis – Main Effects Model

- Matched on age (<, ≥ 30 years), LMP, site

- Conditional logistic regression

- Model covariates
  - Maternal age (quadratic spline)
  - Smoking during pregnancy
  - Diabetes mellitus (history of type 1 or 2—not gestational)
  - Concomitant Tdap vaccination
  - Pre-pregnancy body mass index (quadratic spline)
  - Previous health care utilization (quadratic spline)
    - # days with health care encounter during 12 months before LMP

Selected characteristics of SAB cases and controls

	Cases (n=485)	Controls (n-=485)	P
Maternal age (median, years)	31.8	31.6	0.02
Smoked during pregnancy, N (%)	52 (11)	34 (7)	0.05
BMI (median)	25.7	24.9	0.08
Same season influenza vaccination before reference date among vaccinated in previous season, N (%)*	56 (56.0)	53 (41.7)	
1-28 days before reference date	17 (17.0)	4 (3.1)	
29-56 days before reference date	5 (5.0)	5 (3.9)	
>56 days before reference date	34 (34.0)	44 (34.6)	
Same season influenza vaccination before reference date among not vaccinated in previous season, N (%)*	71 (18.6)	70 (19.7)	
1-28 days before reference date	21 (5.5)	20 (5.6)	
29-56 days before reference date	12 (3.1)	11 (3.1)	
>56 days before reference date	38 (10.0)	39 (11.0)	

*Statistical tests in prior season flu vac strata are not presented; the tests restrict the analyses to matched pairs concordant on prior season vac status and exclude substantial data. % computed using stratum-specific denominators.

Odds of influenza vaccination in SAB cases compared to controls by timing of vaccination

	Discordant pairs	Crude odds ratio	Adjusted odds ratio, (95% CI)[a]	P
Exposure before reference date[b]				
1-28 days	48	1.6	2.0, (1.1-3.6)	0.03
29-56 days	20	1.1	0.9, (0.4-2.1)	0.89
>56 days	97	0.9	0.9, (0.6-1.4)	0.65

[a]Adjusted for maternal age (spline), BMI (spline), smoking during pregnancy, maternal diabetes, concomitant Tdap and IIV vaccination, and health care utilization (spline). CI=Confidence Interval
[b]Women in the exposure windows were compared to women who were unvaccinated as of the reference date

Odds of influenza vaccination in SAB cases compared to controls by timing of vaccination in each influenza season

	2010-2011		2011-2012	
	Discordant pairs	Adjusted odds ratio, (95% CI)[a]	Discordant pairs	Adjusted odds ratio, (95% CI)[a]
Time from vaccination to reference date[b]				
1-28 days	25	3.7, (1.4-9.4)	23	1.4, (0.6-3.3)
29-56 days	14	1.8, (0.6-5.1)	6	0.1, (0.0-0.9)
>56 days	51	1.0, (0.5-1.9)	46	0.9, (0.4-1.7)

[a]Adjusted for maternal age (spline), BMI (spline), smoking during pregnancy, maternal diabetes, concomitant Tdap and IIV vaccination, and health care utilization (spline). CI=Confidence Interval
[b]Women in these exposure windows were compared to women who were unvaccinated as of the reference date.

Association between SAB and IIV in 28 day exposure window is restricted to women who received pH1N1-containing vaccine in previous season[a]

pH1N1-containing vax in the previous season[c]	Time from vaccination to reference date in current season[b]					
	1-28 days		29-56 days		>56 days	
	No. of cases/ controls	OR (95% CI)	No. of cases/ controls	OR (95% CI)	No. of cases/ controls	OR (95% CI)
Yes	14/4	7.7 (2.2-27.3)	3/4	1.2 (0.2-6.5)	34/40	1.4 (0.7-3.0)
No	21/19	1.3 (0.7-2.7)	12/11	1.0 (0.4-2.5)	37/38	0.9 (0.5-1.6)

P=0.02

[a]Adjusted for maternal age (spline), BMI (spline), smoking during pregnancy, maternal diabetes, concomitant Tdap and IIV vaccination, and health care utilization (spline).
[b]Women in these exposure windows were compared to women who were unvaccinated as of the reference date.
[c]Recipients of the monovalent pH1N1 vaccine in 2009-10 may or may not have also received the seasonal vaccine.

<u>2010-11 Season</u>: SAB association after vaccination in 28 day exposure window is modified by prior receipt of pH1N1-containing vaccine[a]

	Time from vaccination to reference date[b]					
	1-28 days		29-56 days		>56 days	
	No. of cases/ controls	OR (95% CI)	No. of cases/ controls	OR (95% CI)	No. of cases/ controls	OR (95% CI)
Prior vaccine receipt (2009-10)						
pH1N1 +/- seasonal vaccine	6/2	32.5, (2.9-359)	2/1	4.1, (0.3-63)	16/18	3.2, (1.0-10.5)
Both vaccines	5/2	31.5, (2.3-425)	1/1	2.4, (0.1-58)	11/12	3.0, (0.6-14.0)
Seasonal only	3/3	3.3, (0.5-20.1)	4/3	1.5, (0.2-12)	10/9	2.8, (0.8-10.2)
Unvaccinated	10/5	3.4, (0.8-14.2)	7/4	2.5, (0.6-11)	12/13	0.6, (0.2-1.6)

[a]Adjusted for maternal age (spline), BMI (spline), smoking during pregnancy, maternal diabetes, concomitant Tdap and IIV vaccination, and health care utilization (spline).
[b]Women in these exposure windows were compared against women who were unvaccinated as of the reference date.

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2011-12 Season: SAB association after vaccination in 28 day exposure window is modified by prior receipt of pH1N1-containing vaccine[a]

	Time from vaccination to reference date[b]					
	1-28 days		29-56 days		>56 days	
Prior vaccine receipt (2010-11)	No. of cases/ controls	OR (95% CI)	No. of cases/ controls	OR (95% CI)	No. of cases/ controls	OR (95% CI)
Vaccinated	8/2	6.4, (1.0-41.2)	1/3	0.3, (0.0-4.0)	18/22	0.9, (0.3-2.5)
Unvaccinated	8/11	0.7, (0.3-2.2)	1/4	0.04, (0.0-0.8)	15/16	1.0, (0.4-2.7)

[a]Adjusted for maternal age (spline), BMI (spline), smoking during pregnancy, maternal diabetes, concomitant Tdap and IIV vaccination, and health care utilization (spline).
[b]Women in these exposure windows were compared against women who were unvaccinated as of the reference date.

Additional analyses

An obvious question is whether women with early pregnancy loss were different than controls. More specifically, were cases more likely than controls to be vaccinated because they presented with early signs/symptoms of SAB?

Outpatient diagnoses assigned on date of influenza vaccination

- ≥1 diagnoses in vaccinated cases vs. controls: 58% vs. 52%, P=0.39
  - Mean number of diagnoses: 1.7 vs. 1.6, P=0.64
- Most diagnoses were V codes (e.g., routine pregnancy visit)
- 3 cases, 0 controls had diagnoses of specific SAB symptoms in 1-28 day exposure window
  - Complications related to pregnancy, pain, bleeding, disorders of menstruation, other symptoms asso. w/ female genital organs
- Exclude 3 pairs – OR in 1-28 day exposure window among those vaccinated in the previous season was 7.0 (95% CI 1.9-25.2)

Summary of additional post-hoc analyses

Association between SAB and IIV receipt in the 1-28 days before the reference date by receipt of pH1N1-containing vaccine in the previous season (2010-11 and 2011-12 seasons combined)

Study population	Matched pairs	Vaccinated in previous season?	
		Yes	No
Complete (original analysis)	451	7.7 (2.2-27.3)	1.3 (0.7-2.7)
Exclude pairs for 3 cases with early SAB signs/symptoms at time of vaccination	448	7.0 (1.9-25.2)	1.3 (0.6-2.6)
Exclude those with history of ≥2 SABs	387	6.5 (1.7-24.3)	1.1 (0.5-2.4)
Exclude unknown vax manufacturer	419	5.9 (1.6-21.5)	1.2 (0.6-2.5)
Women with ≥1 pregnancy ultrasound	398	6.9 (1.7-28.0)	1.3 (0.6-2.9)
Adjusted for current year influenza diagnosis code before reference date	451	7.9 (2.2-28.0)	1.3 (0.7-2.7)

OR adjusted for age, BMI, smoking, diabetes, concomitant Tdap-TIV vaccination, and health care utilization.
Referent exposure group for OR calculations: women unvaccinated as of the reference date.

Summary of Key Findings

- SAB was significantly associated with IIV receipt in the 28 day exposure window

    - This finding differs from the results of a similar study conducted before 2009 pandemic

- Association between IIV and SAB was significant in 2010-11 but not 2011-12

- In both seasons, the association was elevated only in the 28-day window and only in women who had received pH1N1-containing vaccine in the prior influenza season

Study Criticisms

- Lack of biologic plausibility
  - True, but multiple examples of vaccine- and drug-related adverse events identified without known biologic plausibility
- Early SABs likely due to chromosomal abnormalities
  - True, but misclassification should be nondifferential (bias towards the null)
- Small sample size in some analyses
- Crude matching/inadequate adjustment for age
  - Age adjusted in all analyses
- No adjustment for history of SAB
  - Possibility of introducing bias
  - Similar OR when excluding those with ≥2 SABs

Follow-up IIV-SAB Study in VSD

Evaluating the Risk of Spontaneous Abortion Following Seasonal inactivated Influenza Vaccines Administered during the 2012-13, 2013-14, and 2014-15 Influenza Seasons

Task Order VSD-2015-01
Marshfield Clinic Research Institute

Similarities between previous study and follow-up study

- Design: matched case-control
- Age: 18-44 years
- Other eligibility: LMP in medical record, outcomes confirmed
- Exclusions: ectopic, elective abortion, SAB <5 weeks gestational age
- Case/control ascertainment
- Exposure ascertainment
- Medical record review
  - Adjudication: gestational age and date of SAB

Differences between previous study and follow-up study

Feature	Previous study	Follow-up study
Objectives	Estimate overall IIV-SAB association	Estimate assn. in women vaccinated in prev. season
Study period	2010-11, 2011-12	2012-13, 2013-14, 2014-15
Study size	485 matched pairs	1500 matched pairs
Power	80% for OR=2.2, overall	80% for OR=2.2, each season
Matching	Age (2 groups-<≥30 yr), LMP, site	**Age** (3 groups-18-24, 25-34, ≥35 yr), **vax in prev. season**, LMP, site
Controls	Women with stillbirths/live births	Women with live births

Timeline

- Follow-up case-control study is underway
- Preliminary results by late 2018 or early 2019

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