Case-Control Study of Inactivated Influenza Vaccine and Spontaneous Abortion in the Vaccine Safety Datalink, 2012-13, 2013-14, and 2014-15

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Background

- Matched case-control study in 2005-06 and 2006-07 in VSD found no association between spontaneous abortion (SAB) and inactivated influenza vaccine (IIV) receipt in a 28 day risk window (Irving, Obst Gyn 2013)
- After the 2009 pandemic, CDC funded another matched case-control study in VSD to examine the association between SAB and influenza vaccination during the 2010-11 and 2011-12 seasons.
  - Individual matching by VSD site, maternal age group, date of LMP
  - Case status and dates confirmed by medical record review
  - Vaccine association with SAB was assessed in 3 risk windows before SAB: 1-28 days (primary), 29-56 days, and >56 days.

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Association of spontaneous abortion with receipt of inactivated influenza vaccine containing H1N1pdm09 in 2010–11 and 2011–12

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- SAB was associated with IIV receipt in the 28 day risk window (odds ratio=2.0, 95% CI 1.1-3.6). No association in other risk windows.
- IIV-SAB association was statistically significant in 2010-11 but not 2011-12
- In both seasons, statistically significant association only in women who had received influenza vaccine in the prior influenza season (i.e., effect modification)
- These findings could not be clearly attributed to bias or confounding

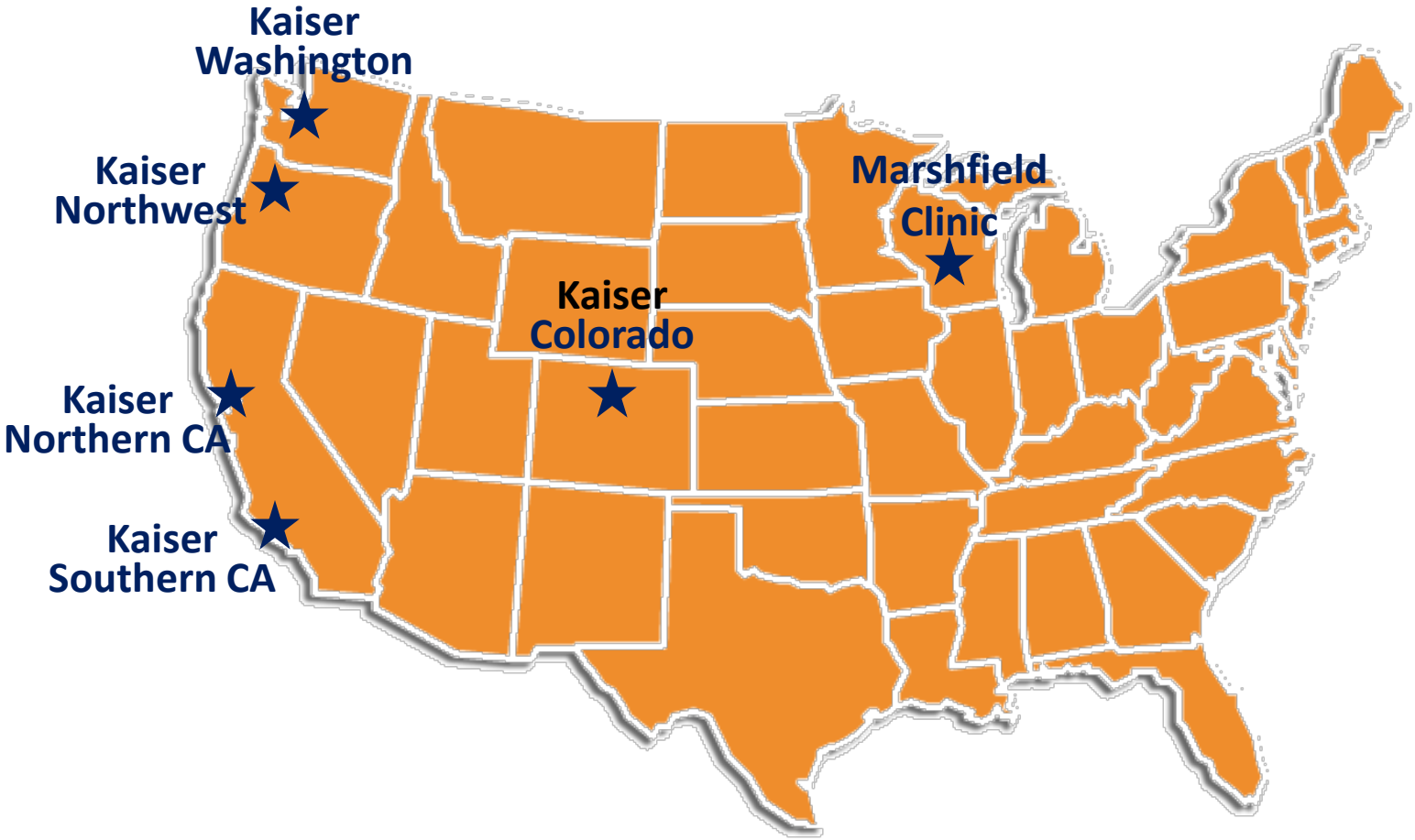
Study Objectives

- Evaluate the IIV-SAB association in the 28 days before SAB among women who received influenza vaccine during the prior season
- Evaluate the IIV-SAB association in the 28 days before the SAB among women who did not receive the vaccine during the prior season
- Secondary objectives
  - Evaluate the IIV-SAB association for vaccine receipt relative to conception
  - Evaluate the association in each of the three seasons

Input from Scientific Advisory Groups

- VSD/CDC meeting in late 2015 primarily to advise on study design
- ACIP Maternal Influenza Vaccination Safety Sub-Work Group
  - Sub-work group of the Influenza Work Group
  - Mission: provide advice on the analytic plan and recommendations to enhance the interpretability of the results

Participating VSD Sites



Study Design

- Matched case-control
  - Matched on age group (18-24, 25-34, 35-44), site, last menstrual period (LMP), influenza vaccination status in previous season
  - 1:1 matching ratio
  - 50% in each season vaccinated in previous influenza season
- Eligibility criteria
  - 18 to 44 years old (as of LMP)
  - Enrolled in VSD site ≥ 20 months prior to LMP
  - LMP documented in record
  - Confirmed SAB (cases) or live birth (controls)

Case/control Identification

- Potential cases identified using ICD-9 codes assigned during influenza season
  - Medical record review & adjudication of potential cases
  - SAB: 6 to <20 weeks gestational age
  - Date of SAB was the *reference date* for each case-control pair
- Controls identified using a VSD pregnancy database or ICD-9/ICD-10 codes for live births

Vaccine Exposures

- Receipt of IIV documented in medical record
- Primary risk window: 28 days before reference date
  - Other risk windows: 29-56 and >56 days
- Secondary windows relative to conception
  - >42 days before, 0-42 days before, 1-28 days after (and before the reference date), and >28 days after (and before the reference date)
- All other vaccinations during pregnancy

Determination of Date of SAB and Gestational Age

- All cases were adjudicated to confirm SAB and estimate gestational age and date of SAB
  - Blinded to vaccination status
- Adjudication process
  - Under direction of obstetrician co-investigator
  - Followed established adjudication algorithm
  - Estimate incorporates information from medical record: U/S data, clinical events (e.g., hemorrhaging), LMP, ICD coding, etc.

Analytic Methods

- Conditional logistic regression
- Referent group: women not vaccinated as of the reference date
- Separate models for women with and without prior season vaccination, and all women combined. Confounding assessed separately for each model.

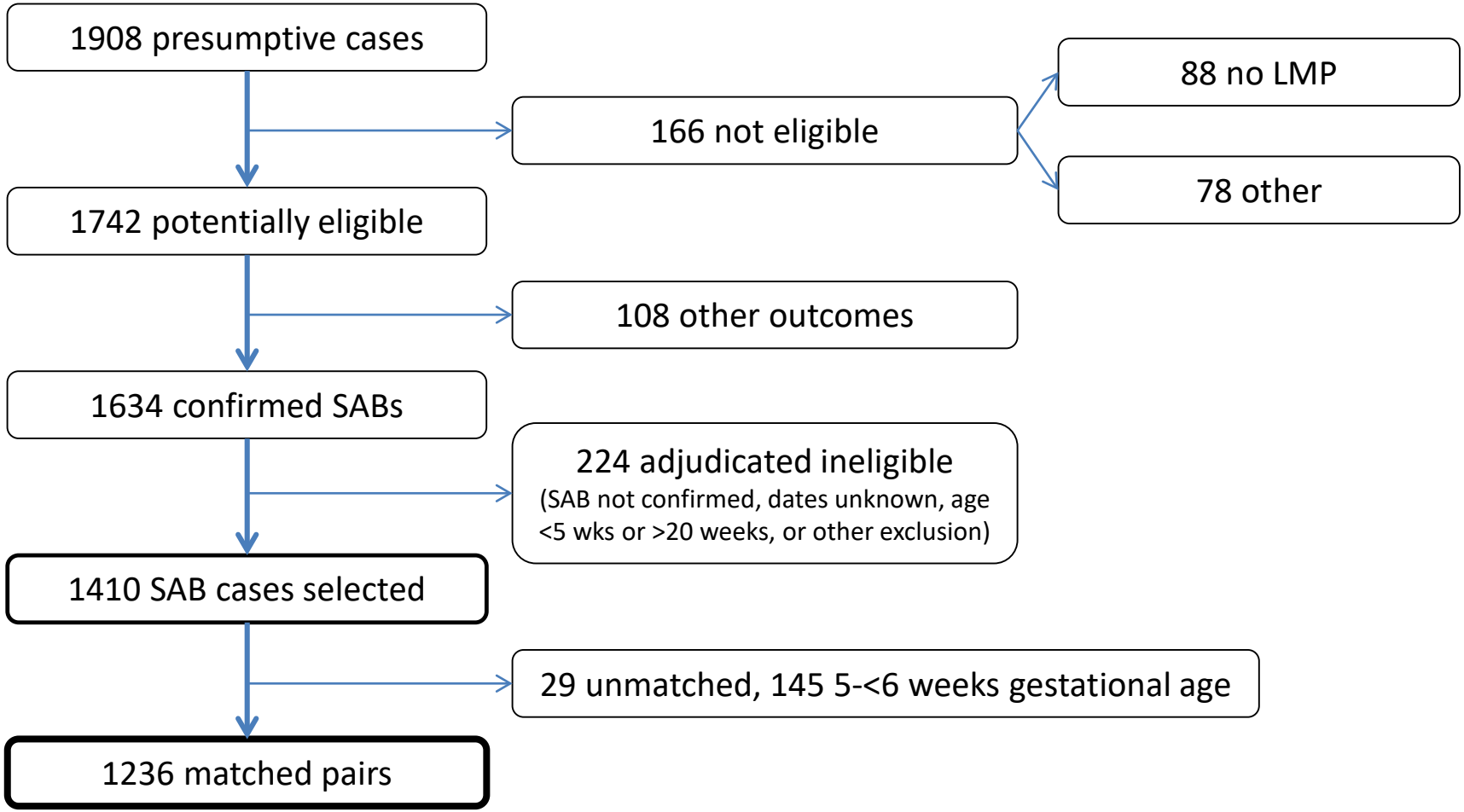
Prior season vaccination=Yes	Prior season vaccination=No	Overall
Maternal age*	**Maternal age***	**Maternal age***
BMI*	**BMI***	**BMI***
Health care utilization*	**Health care utilization***	**Health care utilization***
Race	Race	Race
Ethnicity	Ethnicity	Ethnicity
Diabetes		Diabetes
Asthma		Asthma
Febrile illness (14 days)		Febrile illness (14 days)
	Parity	Parity
		Hypertension

**a priori* covariates included as natural cubic spline.

Power

- Power to detect OR in the 28 days before the reference date, stratum- and season-specific estimate
  - ~250 matched pairs → 82% power for an OR of 3.5
- Power for data pooled by strata
  - ~500 matched pairs in each season → 82% power for an OR of 2.3
- Power for data pooled by strata and season
  - ~1500 matched pairs → 83% power for an OR of 1.6

Identification and Confirmation of Spontaneous Abortions



Descriptive Characteristics: Age and BMI

	Vaccinated in previous season			Not vaccinated in previous season		
	Cases	Controls	P	Cases	Controls	P
N	627	627		609	609	
Age in years at LMP			<0.001			<0.001
18-19	23 (4)	10 (2)		9 (1)	12 (2)	
20-23	30 (5)	32 (5)		43 (7)	44 (7)	
24-27	58 (9)	64 (10)		64 (11)	70 (11)	
28-31	88 (14)	104 (17)		139 (23)	120 (20)	
32-35	162 (26)	187 (30)		105 (17)	151 (25)	
36-39	156 (25)	191 (30)		147 (24)	175 (29)	
40-44	110 (18)	39 (6)		102 (17)	37 (6)	
Median (IQR)	35.0 (31, 39)	34.9 (30, 37)	<0.001	34.4 (29, 39)	34.2 (29, 37)	0.001
BMI			0.01			0.16
<18.5	10 (2)	19 (3)		10 (2)	14 (2)	
18.5-<25	286 (46)	309 (49)		232 (39)	278 (46)	
25-<30	141 (23)	169 (27)		169 (28)	164 (27)	
≥30	189 (30)	129 (21)		189 (32)	152 (25)	
Median (IQR)	25.4 (22, 32)	24.8 (22, 29)	0.01	26.3 (23, 32)	25.4 (22, 30)	0.002

Other Descriptive Characteristics

	Vaccinated in previous season			Not vaccinated in prev. season		
	Cases	Controls	P	Cases	Controls	P
White	346 (55)	381 (61)	0.04	353 (58)	380 (62)	0.11
Black/African-American	41 (7)	27 (4)	0.10	68 (11)	42 (7)	0.01
Asian	124 (20)	158 (25)	0.02	65 (11)	108 (18)	0.001
Hispanic	199 (32)	151 (24)	0.002	182 (30)	169 (28)	0.41
Parity (≥1)	445 (71)	452 (72)	0.75	324 (54)	355 (58)	0.07
Diabetes	21 (3)	8 (1)	0.02	9 (1)	11 (2)	0.82
Asthma	83 (13)	60 (10)	0.06	72 (12)	63 (10)	0.46
Febrile illness in the 1-14 days before reference/event date	8 (1)	2 (0)	0.11	7 (1)	3 (0)	0.34
No. of days with outpt. dx, vax, or hosp. in 365 days before LMP, median (IQR)	6 (3, 11)	6 (3, 10)	0.35	4 (2, 8)	4 (2, 8)	0.35
Previous SAB						
≥1	217 (35)	207 (33)	0.58	175 (29)	175 (29)	1.00
≥2	74 (12)	63 (10)	0.37	57 (9)	58 (10)	1.00

Case and Control Vaccine Exposures by Season and Risk Window

	2012-13				2013-14				2014-15			
	Vaccinated in previous season?				Vaccinated in previous season?				Vaccinated in previous season?			
	Yes		No		Yes		No		Yes		No	
Days from vax to ref date	Case N (%)	Contrl N (%)	Case N (%)	Contrl N (%)	Case N (%)	Contrl N (%)	Case N (%)	Contrl N (%)	Case N (%)	Contrl N (%)	Case N (%)	Contrl N (%)
1-28	21 (9)	27 (11)	12 (5)	18 (8)	30 (13)	25 (11)	10 (4)	20 (9)	19 (8)	12 (5)	13 (6)	17 (7)
29-56	23 (10)	27 (11)	2 (1)	5 (2)	16 (7)	27 (12)	1 (0)	9 (4)	18 (8)	18 (8)	3 (1)	4 (2)
>56	85 (35)	97 (40)	16 (7)	20 (9)	88 (39)	80 (36)	23 (10)	22 (10)	78 (34)	89 (39)	25 (11)	31 (14)
Not vaccinated	109 (45)	85 (35)	201 (87)	188 (81)	91 (40)	90 (40)	187 (84)	172 (77)	115 (50)	108 (47)	187 (82)	177 (77)

Odds Ratios for SAB and Vaccination Stratified by Season and Prior Season Vaccination

		2012-13			2013-14			2014-15		
	Days vax to ref. date	Disc. pairs[a]	Crude OR[b]	aOR (95% CI)	Disc. pairs[a]	Crude OR[b]	aOR (95% CI)	Disc. pairs[a]	Crude OR[b]	aOR (95% CI)
Vaccinated in previous season	1-28	6/15	0.5	0.5 (0.2, 1.1)	11/14	1.0	1.1 (0.6, 2.3)	8/6	1.4	1.7 (0.7, 4.0)
	29-56	4/11	0.6	0.6 (0.3, 1.3)	4/9	0.5	0.8 (0.3, 1.8)	6/6	0.9	1.0 (0.4, 2.5)
	>56	22/32	0.5	0.5 (0.3, 0.9)	25/21	1.0	0.9 (0.5, 1.7)	19/31	0.6	0.5 (0.3, 1.0)
Not vaccinated in previous season	1-28	9/13	0.5	0.7 (0.3, 1.6)	8/18	0.4	0.6 (0.2, 1.4)	11/13	0.8	0.7 (0.3, 1.8)
	29-56	2/2	0.7	1.8 (0.2, 14.9)	0/6	0.1	0.1 (0.0, 1.2)	2/1	0.6	0.5 (0.1, 3.0)
	>56	12/19	0.7	0.8 (0.4, 1.8)	15/14	0.9	1.3 (0.6, 2.8)	14/18	0.9	0.8 (0.4, 1.7)

[a]Discordant pairs: the first number is the number of matched pairs where the case was vaccinated in the relevant exposure window and the control was unvaccinated as of the reference date; the second number is the number of matched pairs where the control was vaccinated in the window and the case was unvaccinated as of the reference date.

[b]Crude odds ratios are adjusted for matching variables: VSD site, LMP, vaccination in previous season, age group (18-24, 25-34, 35-44).

Odds Ratios for SAB and Vaccination Stratified by Season and Prior Season Vaccination

		2012-13			2013-14			2014-15		
	Days vax to ref. date	Disc. pairs[a]	Crude OR[b]	aOR (95% CI)	Disc. pairs[a]	Crude OR[b]	aOR (95% CI)	Disc. pairs[a]	Crude OR[b]	aOR (95% CI)
Vaccinated in previous season	1-28	6/15	0.5	0.5 (0.2, 1.1)	11/14	1.0	1.1 (0.6, 2.3)	8/6	1.4	1.7 (0.7, 4.0)
	29-56	4/11	0.6	0.6 (0.3, 1.3)	4/9	0.5	0.8 (0.3, 1.8)	6/6	0.9	1.0 (0.4, 2.5)
	>56	22/32	0.5	0.5 (0.3, 0.9)	25/21	1.0	0.9 (0.5, 1.7)	19/31	0.6	0.5 (0.3, 1.0)
Not vaccinated in previous season	1-28	9/13	0.5	0.7 (0.3, 1.6)	8/18	0.4	0.6 (0.2, 1.4)	11/13	0.8	0.7 (0.3, 1.8)
	29-56	2/2	0.7	1.8 (0.2, 14.9)	0/6	0.1	0.1 (0.0, 1.2)	2/1	0.6	0.5 (0.1, 3.0)
	>56	12/19	0.7	0.8 (0.4, 1.8)	15/14	0.9	1.3 (0.6, 2.8)	14/18	0.9	0.8 (0.4, 1.7)

[a]Discordant pairs: the first number is the number of matched pairs where the case was vaccinated in the relevant exposure window and the control was unvaccinated as of the reference date; the second number is the number of matched pairs where the control was vaccinated in the window and the case was unvaccinated as of the reference date.

[b]Crude odds ratios are adjusted for matching variables: VSD site, LMP, vaccination in previous season, age group (18-24, 25-34, 35-44).

Odds Ratios for SAB and Vaccination by Vaccination Status in Previous Season, Across All Seasons

		All seasons combined		
	Days from vaccination to reference date	Disc. pairs[a]	Crude OR[b]	aOR (95% CI)
Vaccinated in previous season	1-28	25/35	0.9	0.9 (0.6, 1.5)
	29-56	14/26	0.6	0.7 (0.5, 1.2)
	>56	66/84	0.7	0.6 (0.5, 0.9)
Not vaccinated in previous season	1-28	28/44	0.6	0.7 (0.4, 1.1)
	29-56	4/9	0.4	0.4 (0.1, 1.3)
	>56	41/51	0.8	0.9 (0.6, 1.4)

[a]Discordant pairs: the first number is the number of matched pairs where the case was vaccinated in the relevant exposure window and the control was unvaccinated as of the reference date; the second number is the number of matched pairs where the control was vaccinated in the window and the case was unvaccinated as of the reference date.

[b]Crude odds ratios are adjusted for matching variables: VSD site, LMP, vaccination in previous season, age group (18-24, 25-34, 35-44).

Odds Ratios for SAB and Vaccination Among All Women, Stratified by Season

	2012-13			2013-14			2014-15		
Days vax to ref. date	Disc. pairs[a]	Crude OR[b]	aOR (95% CI)	Disc. pairs[a]	Crude OR[b]	aOR (95% CI)	Disc. pairs[a]	Crude OR[b]	aOR (95% CI)
1-28	15/28	0.5	0.6 (0.3, 1.0)	19/32	0.7	0.8 (0.5, 1.4)	19/19	1.1	1.1 (0.6, 2.0)
29-56	6/13	0.6	0.7 (0.3, 1.5)	4/15	0.3	0.5 (0.2, 1.0)	8/7	0.8	0.8 (0.4, 1.7)
>56	34/51	0.6	0.6 (0.4, 1.0)	40/35	0.9	1.0 (0.6, 1.6)	33/48	0.7	0.6 (0.4, 1.0)

[a]Discordant pairs: the first number is the number of matched pairs where the case was vaccinated in the relevant exposure window and the control was unvaccinated as of the reference date; the second number is the number of matched pairs where the control was vaccinated in the window and the case was unvaccinated as of the reference date.

[b]Crude odds ratios are adjusted for matching variables: VSD site, LMP, vaccination in previous season, age group (18-24, 25-34, 35-44).

Odds Ratios for SAB and Vaccination Among All Women, All Seasons Combined

	All seasons combined		
Time from vaccination to reference date	Disc. pairs[a]	Crude OR[b]	aOR (95% CI)
1-28 days	53/79	0.7	0.8 (0.6, 1.1)
29-56 days	18/35	0.6	0.6 (0.4, 1.0)
>56 days	107/134	0.7	0.7 (0.6, 0.9)

[a]Discordant pairs: the first number is the number of matched pairs where the case was vaccinated in the relevant exposure window and the control was unvaccinated as of the reference date; the second number is the number of matched pairs where the control was vaccinated in the window and the case was unvaccinated as of the reference date.

[b]Crude odds ratios are adjusted for matching variables: VSD site, LMP, vaccination in previous season, age group (18-24, 25-34, 35-44).

Odds Ratios for SAB and Vaccination Relative to Conception, Stratified by Season and Prior Season Vaccination

		2012-13			2013-14			2014-15		
	Days between vax and conception	Disc. pairs[a]	Crude OR[b]	aOR (95%CI)	Disc. pairs[a]	Crude OR[b]	aOR (95%CI)	Disc. pairs[a]	Crude OR[b]	aOR (95%CI)
Vaccinated in previous season	>42 before	18/25	0.6	0.6 (0.3, 1.0)	17/14	1.0	0.8 (0.4, 1.7)	12/20	0.6	0.5 (0.2, 1.0)
	0-42 before	8/9	0.7	0.8 (0.4, 1.7)	9/11	1.0	1.1 (0.5, 2.3)	8/16	0.7	0.6 (0.3, 1.2)
	1-28 after	3/14	0.3	0.3 (0.1, 0.7)	9/7	0.9	1.3 (0.6, 3.0)	7/4	1.6	2.1 (0.8, 5.2)
	>28 after	3/10	0.5	0.5 (0.2, 1.3)	5/12	0.7	0.8 (0.3, 1.8)	6/3	1.2	1.6 (0.5, 4.6)
Not vaccinated in previous season	>42 before	8/11	0.9	1.0 (0.4, 2.7)	10/10	0.8	0.9 (0.4, 2.3)	9/13	0.7	0.6 (0.3, 1.4)
	0-42 before	3/8	0.3	0.4 (0.1, 1.6)	4/6	1.0	1.6 (0.5, 5.2)	6/5	1.7	1.6 (0.5, 5.0)
	1-28 after	7/3	1.8	3.2 (0.9, 11.9)	3/4	0.4	1.0 (0.2, 4.5)	6/6	0.8	0.4 (0.1, 1.4)
	>28 after	5/12	0.3	0.4 (0.1, 1.2)	6/18	0.4	0.4 (0.2, 1.0)	6/8	0.8	0.9 (0.3, 3.0)

[a]Discordant pairs: the first number is the number of matched pairs where the case was vaccinated in the relevant exposure window and the control was unvaccinated as of the reference date, the second number is the number of matched pairs where the control was vaccinated in the window and the case was unvaccinated as of the reference date.

[b]Crude odds ratios are adjusted for matching variables: VSD site, LMP, vaccination in previous season, age group (18-24, 25-34, 35-44).

Odds Ratios for SAB and Vaccination Relative to Conception, All Seasons Combined

		All seasons combined		
	Days between vaccination and conception	Disc. Pairs[a]	Crude OR[b]	aOR (95% CI)
Vaccinated in previous season	>42 days before	47/59	0.7	0.6 (0.4, 0.9)
	0-42 day before	25/36	0.8	0.8 (0.5, 1.2)
	1-28 days after	19/25	0.7	0.9 (0.5, 1.4)
	>28 days after	14/25	0.7	0.8 (0.5, 1.4)
Not vaccinated in previous season	>42 days before	27/34	0.8	0.8 (0.5, 1.3)
	0-42 day before	13/19	0.9	1.1 (0.6, 2.2)
	1-28 days after	16/13	0.9	1.1 (0.5, 2.2)
	>28 days after	17/38	0.4	0.5 (0.3, 0.9)

[a]Discordant pairs: the first number is the number of matched pairs where the case was vaccinated in the relevant exposure window and the control was unvaccinated as of the reference date, the second number is the number of matched pairs where the control was vaccinated in the window and the case was unvaccinated as of the reference date.

[b]Crude odds ratios are adjusted for matching variables: VSD site, LMP, vaccination in previous season, age group (18-24, 25-34, 35-44).

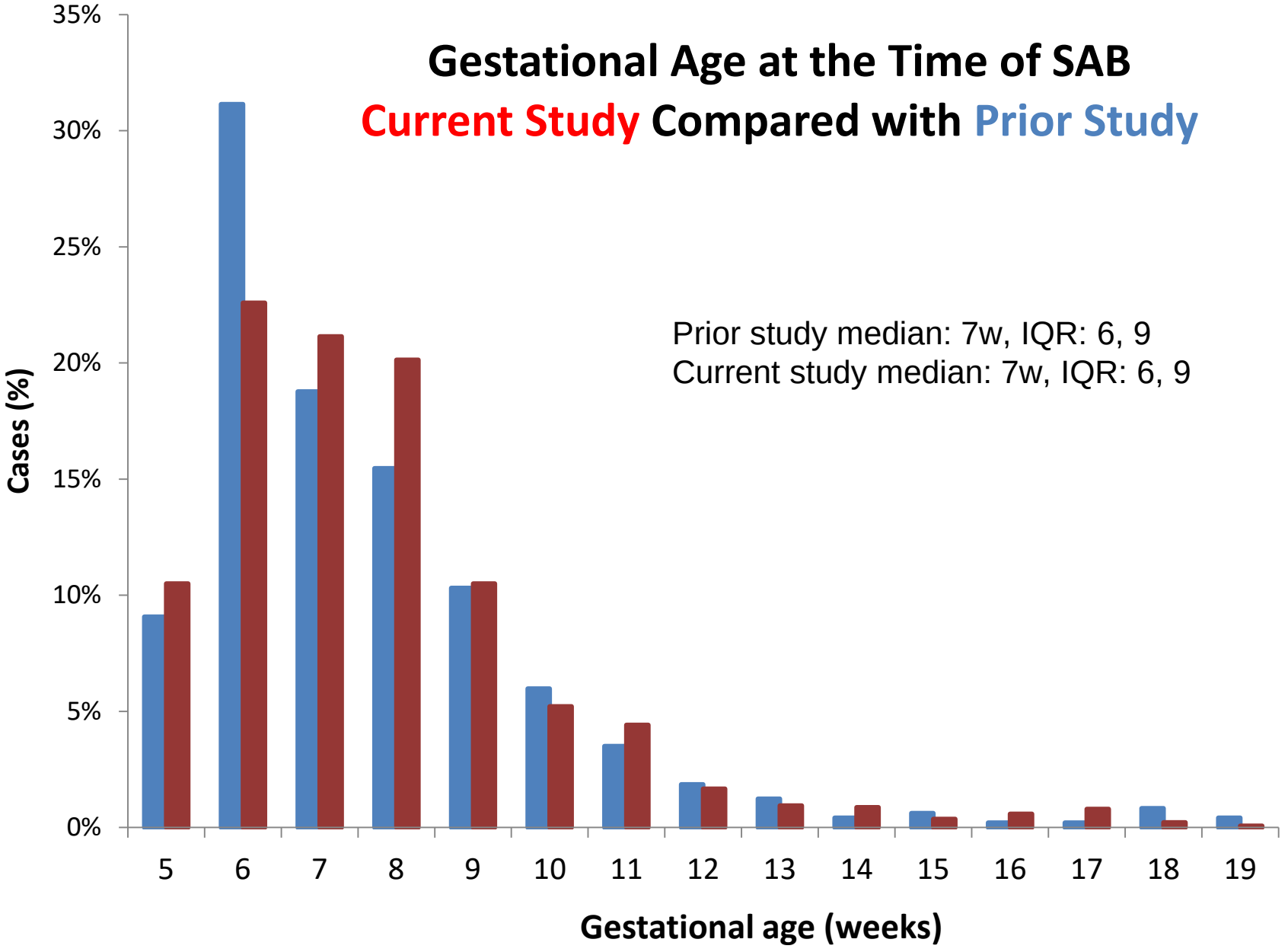
Secondary Analyses

- Similar findings when gestational age range expanded to include 5 to <20 weeks
- Similar findings after exclusion of women with history of ≥2 SABs

Comparison of Current IIV-SAB Study with Previous IIV-SAB Studies

	IIV-SAB-1 (2005-07)		IIV-SAB-2 (2010-12)		IIV-SAB-3 (2012-15)	
	Cases	Controls	Cases	Controls	Cases	Controls
Mean age (years)	31.7	29.3	31.8	31.2	33.8	33.1
Parity (1+)	64%	64%	57%	56%	63%	65%
Previous SAB	33%	27%	29%	26%	31%	31%
Febrile illness in 1st trimester	2%	2%	1%	0	2%	1%
Smoker	10%	10%	11%	7%	5%	5%
Diabetes	4%	0	1%	2%	2%	1%
Asthma	10%	11%	11%	12%	12%	10%
Hypertension	4%	4%	2%	3%	4%	3%
1 or more ultrasounds[a]	82%	NA	89%	NA	93%	NA
Median gestational age (weeks) at time of SAB	7.1	NA	7.0	NA	7.0	NA
Mean difference in LMP between case, matched control (median)	-0.41 (0)		-0.55 (0)		0 (0)	

[a]Cases only
NA=Not applicable


Gestational Age at the Time of SAB
Current Study Compared with Prior Study
Prior study median: 7w, IQR: 6, 9
Current study median: 7w, IQR: 6, 9
Cases (%)
35%
30%
25%
20%
15%
10%
5%
0%
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
Gestational age (weeks)

Methodologic Differences Between Current and Prior VSD Study

- Different seasons (2012-13, 2013-14, and 2014-2015)
- Current study matched on previous season influenza vaccination status
- Current study matched on 3 age groups (18-24, 25-34, and 35-44 years) rather than 2 age groups
- Study population was ~3 times larger compared to prior study (2762 vs. 970)

Major Findings

- No significant association between influenza vaccine receipt and SAB, regardless of prior season vaccination status
- Odds ratios were less than or close to 1.0 in all risk windows
- No significant associations in season-specific analyses
- Findings support safety of influenza vaccine in early pregnancy

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