Safety of quadrivalent recombinant influenza vaccine in pregnant women and their infants

Nicky Klein, MD, PhD
Director, Kaiser Permanente Vaccine Study Center
Kaiser Permanente Northern California

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Disclosures

- Sanofi provide related research support for 'Flublok v. Standard Dose Vaccine Effectiveness Among Kaiser Permanente Northern California Adults 18-64 Years' (NCT03694392).

- Sanofi provided all the recombinant influenza vaccine for this study (1.2 million doses).

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Background

- Since 2004, the US Advisory Committee on Immunization Practices (ACIP) has recommended that all pregnant women receive an inactivated influenza vaccine during any trimester of pregnancy.
  - includes recombinant influenza vaccine (RIV), which has been available since 2013

- There has been limited data regarding the safety of RIV during pregnancy.

- We conducted a post-licensure observational study to assess the safety of RIV4 during pregnancy.

Study Setting: Kaiser Permanente Northern California (KPNC)

- Integrated Healthcare Delivery System
- Annual membership of >4 million (~65% aged 18–64 years).
- Members receive nearly all their care at KPNC facilities (259 medical clinics, 21 hospitals).
- KPNC has an electronic medical record (EMR) that captures all healthcare encounters, diagnoses, lab tests, vaccines, and medications.

- Within KPNC, routine influenza PCR testing begins in early fall. Flu PCR tests are ordered at physician's discretion.

Study Objective

- **Primary objective:** Evaluate the safety of quadrivalent recombinant influenza vaccine compared with quadrivalent inactivated influenza vaccines in pregnant women and their offspring

Study Design

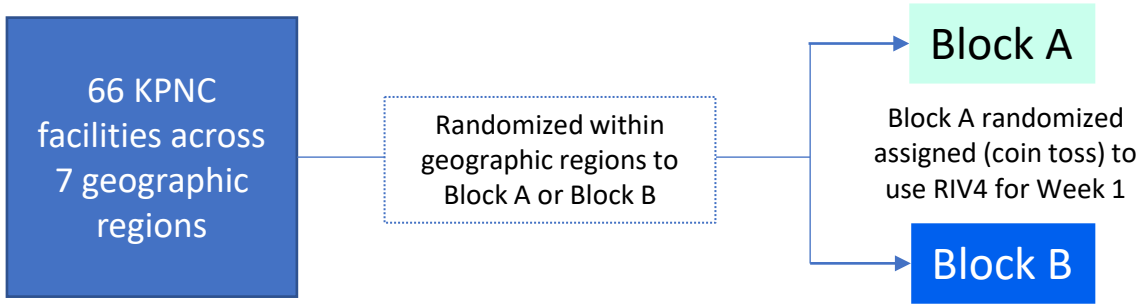
- Study included all routinely influenza-vaccinated pregnant women and their live born infants at Kaiser Permanente Northern California (KPNC) during the 2018-2019 and 2019-2020 influenza seasons.

- All vaccinated pregnant women were a subset of a separate, cluster randomized effectiveness trial which compared the relative vaccine effectiveness (rVE) of RIV4 vs. SD-IIV4 against influenza and influenza-related outcome.

Larger Relative Vaccine Effectiveness Study Context

- Cluster randomized observational study of all KPNC adults vaccinated with either RIV4 or SD-IIV4 during 2018-2021 influenza seasons.
- KPNC aimed to administer 400,000 RIV4 doses and 400,000 SD-IIV4 doses to adults 18–64 years during each of the 3 seasons.
- To minimize geographic and socioeconomic imbalances between facilities and achieve balance in covariates, we cluster-randomized facilities within each of 7 service areas to receive RIV4 or SD-IIV4 on an alternating weekly basis.
  - Randomization accounted for facility size, facilities within each service areas
  - Goal was to achieve balance in covariate distribution between those who received RIV4 vs. SD-IIV4 (e.g., similar proportion of RIV4 vs. SD-IIV4 who were female)

Design of RIV4 and SD-IIV4 Relative Vaccine Effectiveness Study



	Week 1	Week 2	Week 3	Week 4
Facility 1	RIV4	SD-IIV4	RIV4	SD-IIV4
Facility 2	SD-IIV4	RIV4	SD-IIV4	RIV4
Facility 3	SD-IIV4	RIV4	SD-IIV4	RIV4
Facility 4	RIV4	SD-IIV4	RIV4	SD-IIV4
Facility 5	SD-IIV4	RIV4	SD-IIV4	RIV4
Facility 6	RIV4	SD-IIV4	RIV4	SD-IIV4

- Overall RIV4 vs SD-IIV4 rVE study included ~1.6 million influenza-vaccinated adults 18-64 yrs
  - Study ultimately only included 2 seasons (2018-2020) due to the COVID-19 pandemic
- Current study focused on the subset of vaccinated pregnant women and their offspring from this overall rVE study

Preliminary data

Study Outcomes

Pregnancy	• Spontaneous abortion • Preterm labor • Stillbirth/fetal death • Congenital/fetal anomalies detected during pregnancy • Eclampsia • Placental abruption
Birth	• Preterm birth • Low birthweight • Small for gestational age
Neonatal/Infant (through 365 days)	• Infant death • Congenital anomalies • Failure to thrive

Preliminary data

Statistical Analysis

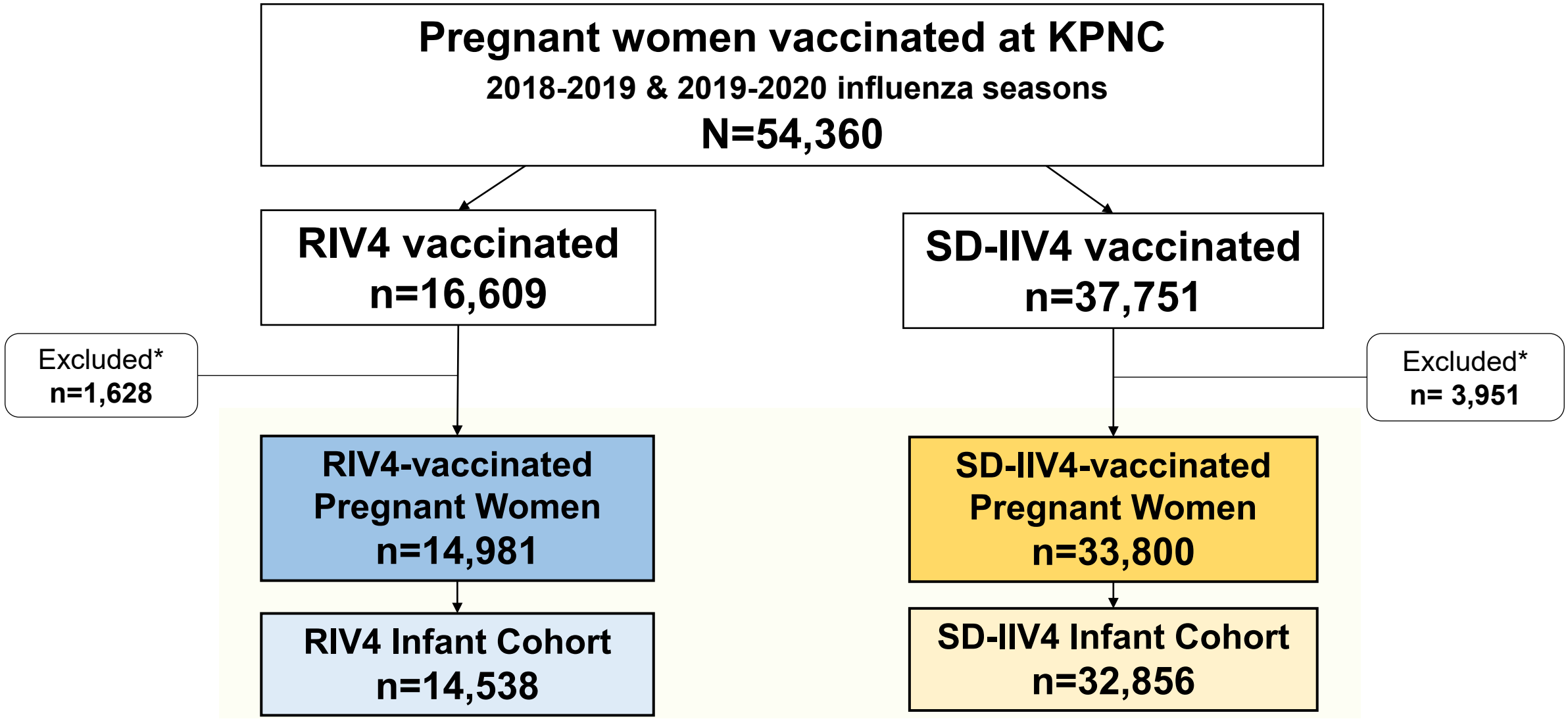
Pregnancy outcomes:

- Compared the odds of a pregnancy outcome among RIV4 vaccinated pregnant women with SD-IIV4 vaccinated pregnant women.
  - Conditional logistic regression (conditioned on gestational age)
  - Adjusted for maternal race, ethnicity, age group, BMI, presence of any chronic condition (asthma, CHD, COPD, diabetes), and trimester of influenza vaccination

Birth and neonatal/infant outcomes:

- Compared the odds of birth and neonatal outcomes among RIV4 vaccinated pregnant women with SD-IIV4 vaccinated pregnant women.
  - Logistic regression
  - Adjusted for infant sex, race, ethnicity, maternal age group, and maternal trimester of influenza vaccination

Final Population: Flu Vaccinated Pregnant Women and their Infants



RIV4: Quadrivalent recombinant influenza vaccine (Flublok Quadrivalent)
SD-IIV4: Quadrivalent standard-dose inactivated influenza vaccine (Fluarix Quadrivalent or Flulaval Quadrivalent)
*Excludes individuals who received ≥1 influenza vaccination in the same day and in the same season; data discrepancies such as missing sex, males identified as pregnant, date of death occurring before date of birth, etc.; not a KPNC member at time of vaccination; vaccinated in inpatient setting; or did not have a prenatal visit during pregnancy

Preliminary data

Demographics: Pregnant Women

		RIV4 N=14,981 (%)	SD-IIV4 N=33,800 (%)
Maternal age*	17-24 years	1,544 (10.3)	3711 (11.0)
	24-35 years	9,586 (64.0)	21,297 (63.0)
	35-44 years	3,812 (25.4)	8680 (25.7)
	≥45 years	39 (0.3)	112 (0.3)
Trimester of vaccination	28 days prior to conception	750 (5.0)	1,367 (4.0)
	1st trimester	5,092 (34.0)	10,787 (31.9)
	2nd trimester	4,851 (32.4)	11,470 (33.9)
	3rd trimester	4,288 (28.6)	10,176 (30.1)
Race	Asian	4,620 (30.8)	9,916 (29.3)
	Black	620 (4.1)	1,589 (4.7)
	Multiracial	744 (5.0)	1,678 (5.0)
	Native American	46 (0.3)	102 (0.3)
	Pacific Islander	153 (1.0)	287 (0.3)
	White	5,506 (36.8)	11,666 (34.5)
	Unknown	3,292 (22.0)	8,562 (25.3)
Hispanic	Hispanic	3,450 (23.0)	8,898 (26.3)
	Non-Hispanic	11,531 (77.0)	24,902 (73.7)
Comorbidity†	Asthma, CHD, COPD, or diabetes	2,036 (13.6)	4,779 (14.1)

*All subjects were 18 years of age at the time of immunization; †Asthma, CHD, COPD, or diabetes assessed during the 3 years prior to vaccination

Preliminary data

Results: Pregnancy Outcomes

Outcome	RIV4 N=14,981 n (%)	SD-IIV4 N=33,800 n (%)	Adjusted OR (95% CI)*	P-value
Spontaneous abortion	470 (3.1)	1,013 (3.0)	0.95 (0.85, 1.05)	0.31
Preterm labor	546 (3.6)	1,170 (3.5)	1.06 (0.99, 1.14)	0.09
Stillbirth/fetal death	63 (0.4)	153 (0.5)	0.84 (0.68, 1.04)	0.12
Congenital/fetal anomalies detected during pregnancy	356 (2.4)	798 (2.4)	1.00 (0.91, 1.09)	0.96
Eclampsia/pre-eclampsia	1,235 (8.4)	2,793 (8.4)	1.01 (0.96, 1.06)	0.64
Placental abruption	115 (0.8)	237 (0.7)	1.12 (0.96, 1.31)	0.15

*SD-IIV4 was the reference group for all analyses. Conditional logistic regressions adjusted for maternal race, ethnicity, maternal age group, trimester of influenza vaccine receive, chronic conditions, and BMI

Preliminary data

Infant Demographics

		RIV4 N=14,538 (%)	SD-IIV4 N=32,856 (%)
Sex	Male	7,437 (51.2)	16,940 (51.6)
	Female	7,101 (48.8)	15,916 (48.4)
Race	Asian	3,863 (26.6)	8,300 (25.3)
	Black	496 (3.4)	1,257 (3.8)
	Multiracial	949 (6.5)	1,949 (5.9)
	Native American	20 (0.1)	66 (0.2)
	Pacific Islander	128 (0.9)	298 (0.9)
	White	4,690 (32.3)	9,880 (30.1)
	Unknown	4,392 (30.2)	11,106 (33.8)
Hispanic	Hispanic	3,059 (21.0)	7,857 (23.5)
	Non-Hispanic	11,479 (79.0)	24,999 (76.1)
Gestational Age	Preterm (<37 weeks)	1,061 (7.3)	2,450 (7.5)

Preliminary data

Results: Birth/Infant Outcomes

Outcome	RIV4 N=14,538 n (%)	SD-IIV4 N=32,856 n (%)	Adjusted OR (95% CI)*	P-value
Birth				
Preterm birth	1,061 (7.3)	2,450 (7.5)	0.98 (0.91, 1.05)	0.54
Low birth weight	852 (5.9)	1,918 (5.8)	1.00 (0.92, 1.09)	0.92
Small for gestational age	1,277 (8.8)	2,846 (8.7)	1.01 (0.94, 1.09)	0.72
Infant (up to 365 days)				
Infant death	27 (0.2)	59 (0.2)	1.05 (0.66, 1.65)	0.85
Congenital anomalies	6,259 (43.1)	14,018 (42.7)	1.01 (0.97, 1.05)	0.53
Major congenital anomalies	*1,113 (7.7)*	*2,531 (7.7)*	*N/A*	*N/A*
Minor congenital anomalies	*5,698 (39.2)*	*12,762 (38.8)*	*N/A*	*N/A*
Failure to thrive	150 (1.0)	372 (1.1)	0.90 (0.75, 1.09)	0.29

*SD-IIV4 was the reference group for all analyses. Logistic regressions adjusted for infant sex, infant race, infant ethnicity, maternal age group, and maternal trimester of influenza vaccine receipt

Study Strengths

- All pregnant women in this study were a subset of a large modified cluster-randomized rVE study of RIV4 vs. SD-IIV4 (~1.6 million adults).
  - RIV4 recipients were very similar to SD-IIV4 recipients with respect to risk factors for adverse outcomes.
  - Fewer sources of bias than in most observational studies.

Preliminary data

Study Limitations

- There were slight imbalances in the timing of vaccination that may have been related to provider preferences.
  - The proportion of pregnant women who received RIV4 during preconception or first trimester was relatively higher than in the SD-IIV4 group.
  - Historically, the KPNC OB/GYN clinics have been accustomed to using SD-IIV4 in pregnant woman.
  - It is possible that providers preferred to administer SD-IIV4 once they knew an individual was pregnant.

- However, since demographic and covariate factors were similar between the two groups, such slight imbalances were unlikely to have affected the analyses.

Summary

- Within a large population of influenza-vaccinated pregnant women, comparing RIV4 with SD-IIV4 there were no differences in pregnancy, birth and neonatal/infant outcomes.

- No safety concerns were identified after RIV4 use in pregnancy.

- The proportion of pregnancies or live births with outcomes was lower than published US rates from most other studies.

- This study provides reassuring safety evidence regarding the continued use of influenza vaccines in pregnant women.

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*BioNTech - Cambridge, Massachusetts (United States)
‡Moderna - Cambridge, Massachusetts (United States)