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

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BACKGROUND: The Advisory Committee on Immunization Practices (ACIP) and the American College of Obstetricians and Gynecologists (ACOG) recommend that all pregnant persons receive any licensed, recommended, and age-appropriate inactivated influenza vaccine (SD-IIV) or recombinant influenza vaccine (RIV) to protect against influenza and influenza-related complications. RIV was safe and efficacious in pre- and postlicensure studies, however there is limited RIV safety data in pregnant persons.

OBJECTIVE: To evaluate the safety of quadrivalent recombinant influenza vaccine (RIV4) versus a quadrivalent standard-dose, inactivated influenza (SD-IIV4) in a large cohort of pregnant persons and their infants.

STUDY DESIGN: This postlicensure observational safety study conducted at Kaiser Permanente Northern California evaluated the subset of pregnant persons vaccinated in routine care as part of a larger cluster-randomized vaccine effectiveness study comparing RIV4 vs. SD-IIV4 (ClinicalTrials.gov NCT03694392). We identified pregnancy (spontaneous abortion, preterm labor, stillbirth/fetal death, congenital/fetal anomalies detected during pregnancy, eclampsia/pre-eclampsia, placental abruption), birth (preterm birth, low birth weight, small for gestational age), and neonatal/infant outcomes (infant death, failure to thrive, congenital anomalies detected after delivery) using diagnostic codes among pregnant persons ≥18 years immunized with RIV4 or SD-IIV4 during the 2018/19 and 2019/20 influenza seasons and their infants. We used conditional logistic regression adjusted for age group, race, ethnicity, trimester of influenza vaccination, comorbidities, and BMI, stratified by gestational age to estimate the odds ratio (OR) of pregnancy outcomes following vaccination with RIV4 vs. SD-IIV4. Using logistic regression, we separately estimated the adjusted OR of birth and neonatal/infant outcomes in the first year of life (eg, death) in infants of RIV4 vs. SD-IIV4 vaccinated pregnant persons.

RESULTS: The study population included 48,781 pregnant persons (RIV4 = 14,981; SD-IIV4 = 33,800) and 47,394 live births (RIV4 = 14,538; SD-IIV4 = 32,856). There was no statistical difference in any pregnancy outcome or in birth and neonatal/infant outcome between RIV4 vs. SD-IIV4 vaccinated pregnant persons and their infants.

CONCLUSION: Compared with receipt of a SD-IIV4 during pregnancy, this large study did not identify any pregnancy, birth, or neonatal/infant safety concerns following receipt of a RIV4 during pregnancy and demonstrates that the safety of RIV4 in pregnancy was similar to SD-IIV4. This study provides additional evidence regarding the safety of influenza vaccination in pregnant persons and further supports ACIP and ACOG recommendations that all pregnant persons receive an inactivated or recombinant influenza vaccine.

Key words: Flublok, infant outcomes, influenza vaccine, maternal vaccination, neonatal outcomes, pregnancy outcomes, pregnancy safety, real-world evidence, recombinant

Introduction

Influenza is an acute respiratory disease caused by infection with influenza viruses, which results in an estimated 3% to 11% of the US population having influenza-related disease each year.[1] Compared with nonpregnant adults, pregnant persons are at increased risk of morbidity and mortality due to influenza.[2] Some studies also suggest that severe influenza infection during pregnancy may increase the risk of adverse outcomes such as preterm birth and low birth weight (LBW) in newborns.[3]

Vaccination is the most effective way to prevent influenza infection and its associated complications in both pregnant persons and their newborns. Since 2004, the Advisory Committee on

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N.P.K. has received research support from Sanofi, GlaxoSmithKline, Merck, Pfizer, and Seqirus. R. I., S.GB., A.S., O.T., H.K., and A.I. are/were employees of Sanofi and may/may not hold stock. No other disclosures were reported. This study was sponsored by Sanofi.

This study was funded by Sanofi. The funder provided financial support for the conduct of the research. The funder had a role in the study design, analysis plan, interpretation of the data, and the decision to submit the article for publication. The funder did not have a role in the collection and conduct of analysis.

Tweetable statement: Large cohort study of pregnant persons and their infants shows use of recombinant influenza vaccines is safe during pregnancy.

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2666-5778/$36.00

http://dx.doi.org/10.1016/j.xagr.2024.100395

AJOG Global Reports at a Glance

Why was this study conducted?

Recombinant influenza vaccines were safe and efficacious in pre- and postlicensure studies, however there is limited safety data on their use in pregnant persons.

What are the key findings?

Compared with receipt of a quadrivalent standard-dose inactivated influenza vaccine during pregnancy, this large study did not identify any pregnancy, birth, or neonatal/infant safety concerns following receipt of a quadrivalent recombinant influenza vaccine (RIV4) during pregnancy and supports the safety of RIV4 in pregnancy.

What does this add to what is known?

This study provides additional evidence regarding the safety of influenza vaccination in pregnant persons and further supports ACIP recommendations that all pregnant persons receive an inactivated or recombinant influenza vaccine.

Immunization Practices (ACIP), which provides guidance to the Centers for Disease Control and Prevention (CDC), and the American College of Obstetricians and Gynecologists (ACOG) have recommended that persons who are pregnant (in any trimester) or who might be pregnant during the influenza season receive any licensed, recommended, age-appropriate inactivated influenza vaccine or recombinant influenza vaccine.

Substantial evidence exists that inactivated influenza vaccines in pregnancy are safe. Similarly, pre- and postlicensure studies also support the safety of the recombinant influenza vaccine in pregnancy.[4,5] However less is known about the safety of the more recently licensed recombinant influenza vaccine in pregnancy when compared with inactivated influenza vaccines.[6]

We conducted a large cluster-randomized study that assessed the effectiveness of quadrivalent recombinant influenza vaccine (RIV4) compared with quadrivalent standard-dose inactivated-influenza vaccine (SD-IIV4) administered as part of routine care to all adults 18 to 64 years, including pregnant persons, at Kaiser Permanente Northern California (KPNC).[7] This current study evaluated the safety of RIV4 compared with SD-IIV4 in the subset of vaccinated pregnant persons and their infants from the larger study during the 2018−2019 and 2019−2020 influenza seasons.

Materials and methods

Setting

KPNC is an integrated healthcare delivery system with 4.6 million members, over 1 million of whom are persons ≥18 to <50 years of age. Members receive nearly all their care at KPNC-owned facilities, which includes 209 medical clinics and 21 hospitals. KPNC's electronic medical record (EMR) captures all medical services, including vaccinations, and inpatient, outpatient, and emergency department diagnoses. KPNC members comprise approximately a third of Northern California's population and are broadly representative of adults in the state with regard to racial, ethnic, and socioeconomic demographics, although the very lowest incomes are underrepresented.[8]

The KPNC Institutional Review Board approved this study and determined that informed consent could be waived under 45 CFR 46.116(f), as the required criteria were met.

Study population

This was a retrospective observational safety study that included all pregnant persons ≥18 years who sought influenza vaccination and were routinely vaccinated as part of standard of care in the KPNC outpatient setting with either RIV4 or SD-IIV4 during the 2018−2019 (September 16, 2018-May 16, 2019) and 2019−2020 (September 3, 2019-May 15, 2020) influenza seasons during pregnancy or within 28 days preceding conception.[7]

Vaccinated pregnant persons were a subset of a larger real-world cluster-randomized influenza vaccine effectiveness study in KPNC adults aged ≥18 years to <65 years.[7] Briefly, in the larger study, all KPNC clinics were randomized to administer either RIV4 or SD-IIV4 the first week influenza vaccines were administered, which was then followed by alternating formulations weekly until the end of the influenza vaccination season. This design was intended to achieve balance and limit confounding between adults vaccinated with RIV4 and SD-IIV4 who would be similarly distributed with respect to observed and unobserved risk factors in the study population during the weeks when influenza was circulating.

KPNC's pregnancy database, which includes nearly all pregnancies at KPNC, was used to identify pregnancy cases.[9] The pregnancy population included all pregnant persons documented as receiving RIV4 or SD-IIV4 at KPNC in the 28 days preceding the estimated date of conception, up through the end of pregnancy. The date of conception was defined as 14 days following the last menstrual period (LMP), which was based on ultrasound dating if available or self-reported LMP. We excluded pregnant persons if they received any other influenza vaccine during pregnancy (including influenza vaccines administered in 2 different influenza seasons during the same pregnancy), were immunized in the inpatient setting, or did not have any prenatal visits. We identified pregnancies starting at the first prenatal visit and calculated maternal age as of the LMP.

The infant study population included all live-born infants born to eligible influenza-vaccinated pregnant persons described above. There were no exclusions for the infant cohort.

Outcomes

We included pregnancy, birth, and neonatal/infant outcomes based on prior influenza vaccine safety studies in pregnant persons.[10] We identified incident outcomes in the EMR using 10th

International Classification of Diseases (ICD-10) codes and/or other relevant data that were collected in the course of routine clinical care (eg, calculated gestational age, infant birthweight), as appropriate (Supplemental Table 1).

Pregnancy outcomes were spontaneous abortion, preterm labor, stillbirth/fetal death, congenital/fetal anomalies detected during pregnancy, pre-eclampsia/eclampsia, and placental abruption diagnosed during pregnancy, delivery, or the puerperium. Outcomes that occurred on the day of vaccination were excluded.

Birth outcomes were preterm birth (<37 weeks gestation), low birth weight (LBW; <2500 grams), and small for gestational age (SGA) diagnosed at birth.

Neonatal/infant outcomes were infant death, failure to thrive, and any congenital anomalies detected after delivery (using CDC guidelines[11]) diagnosed between the day of birth and 365 days postbirth.

For the infant outcome congenital anomalies detected after delivery, we included cases regardless of whether there had been any congenital/fetal anomalies identified during pregnancy since the infant's anomaly may not have been related to the broadly-defined congenital/fetal anomalies category detected during pregnancy.

Covariates

Demographic covariates for pregnant persons included race (Asian, Black, multiracial, Native American, Pacific Islander, White, unknown), ethnicity (Hispanic, non-Hispanic), maternal age group at start of pregnancy (17−24 years, 24−34 years, 35−44 years, ≥45 years), trimester of maternal vaccination (preconception 28 days prior to conception; first, second or third trimester), comorbidities (asthma, coronary heart disease [CHD], chronic obstructive pulmonary disease [COPD], diabetes), and body mass index closest to the estimated date of conception (BMI; <18.5 kg/m^2, 18.5 to <25 kg/m^2, 25 to <30 kg/m^2, 30 to <35 kg/m^2, 35 to <40 kg/m^2, ≥40 kg/m^2, unknown).

Demographic covariates for infants included infant sex, race, ethnicity, and trimester of maternal influenza vaccination.

Statistical methods

We calculated incidence proportions and 95% confidence intervals (CIs) of all outcomes for each vaccine cohort separately. CIs were computed using Wilson's Score method. Pregnancy, birth, and neonatal/infant outcome rates were calculated by dividing the number of cases of each outcome by the total number of pregnant persons or the total number of live births, expressed as a percentage.

For pregnancy outcomes, we estimated the adjusted odds ratio (OR_{Adj}) of RIV4 versus SD-IIV4 vaccinated pregnant persons for each outcome using conditional logistic regression, stratified by gestational age. Models were adjusted for race, ethnicity, maternal age group at conception, trimester of maternal vaccination, chronic conditions, and BMI. Outcomes that occurred on the day of vaccination were not counted.

For birth and neonatal/infant outcomes, we estimated the OR_{Adj} of maternal RIV4 versus SD-IIV4 vaccination during pregnancy for each outcome using logistic regression. All models (except for the infant mortality outcome) were adjusted for infant sex, infant race, infant ethnicity, maternal age group, and trimester of maternal influenza vaccination. Given the small number of infant mortality cases, race and ethnicity were combined into a single covariate in the analysis. "Hispanic" ethnicity took precedence when included in the combined race/ethnicity category (eg, an infant whose ethnicity was identified as "Hispanic" regardless of any race category was coded as "Hispanic" in the combined race/ethnicity covariate).

Results

There were 48,781 vaccinated pregnant persons (RIV4 = 14,981; SD-IIV4 = 33,800) in the final pregnancy cohort (Figure 1). The demographic and baseline characteristics of the pregnancy cohort were similar (Tables 1 and 2). Most pregnant persons were 25−34 years of age (63.3%) or 35−44 years of age (25.6%) (Table 1) and were White (35.2%) or Asian (29.8%). Overall, approximately 1.9% of pregnant persons did not report a race or ethnicity (Supplemental Table 2 for combined race/ethnicity). The proportion of Asian, White, and non-Hispanic pregnant persons was slightly higher in the RIV4 than in the SD-IIV4 cohort. In both seasons, delays in RIV4 shipments to KPNC occasionally left some clinics temporarily without enough RIV4 to comply with the weekly schedule. SD-IIV4 was used to prevent interruptions to patient care.[7]

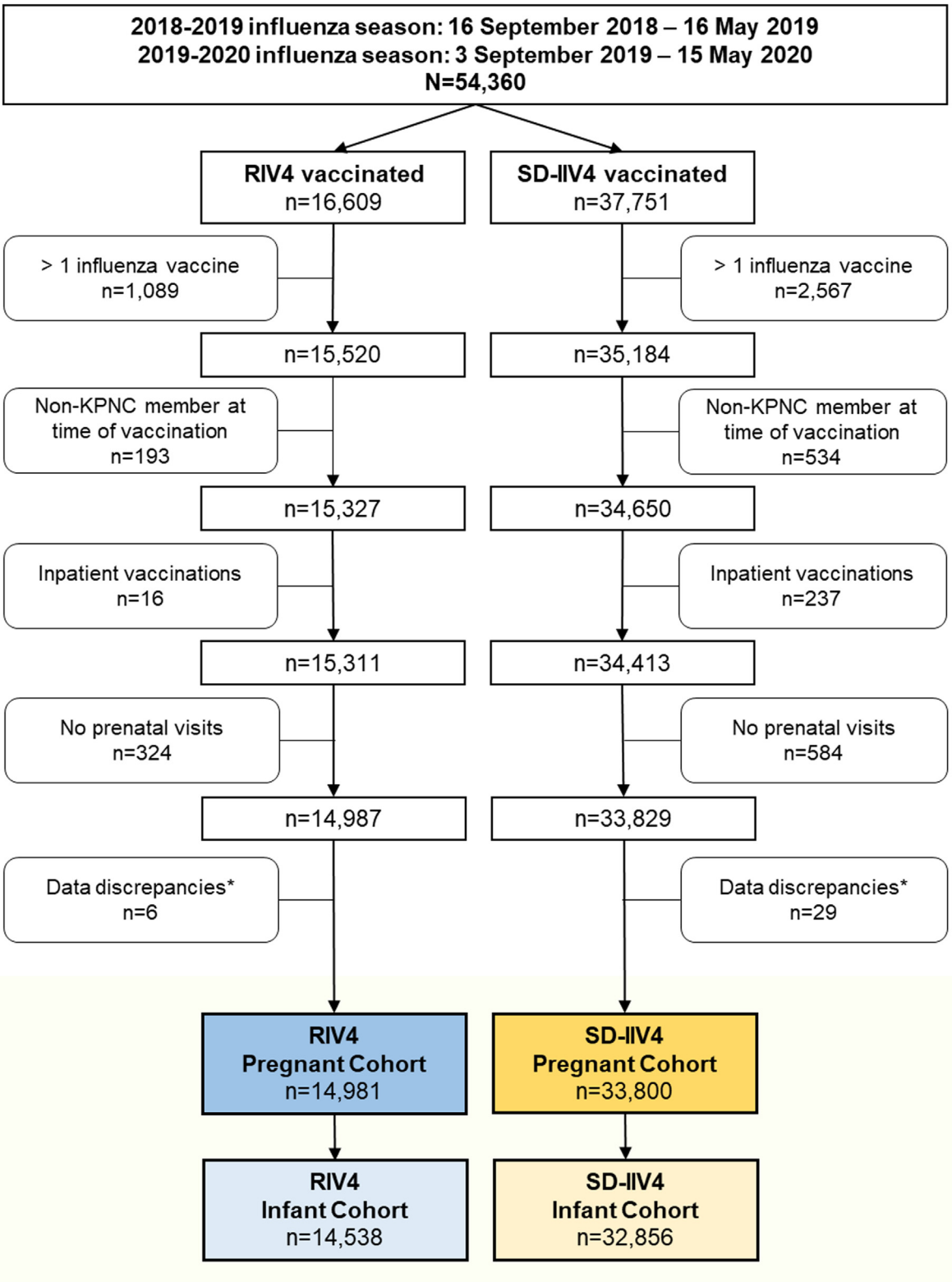
Approximately 14.0% of pregnant persons had at least 1 predefined comorbidity, with asthma (12.5%) being the most common. Among pregnant persons who received RIV4 compared with SD-IIV4, a slightly higher proportion were vaccinated in the 28 days prior to conception (5.0% RIV4 vs. 4.0% SD-IIV4) and in the first trimester (34.0% RIV4 vs. 31.9% SD-IIV4) than later in the pregnancy. The proportion of pregnant persons who received a tetanus, diphtheria, and acellular pertussis vaccine on the same day as the influenza vaccine were similar (13.9% RIV4; 14.1% SD-IIV4; Supplemental Table 3). Most pregnancies (98.4%) were singleton pregnancies.

There were 47,394 infants born to vaccinated pregnant persons (RIV4 = 14,538; SD-IIV4 = 32,856) in the final infant cohort (Figure 1). Among the infant cohort, 51.4% were male (Table 2). The highest proportions of infants were White (30.7%) or Asian (25.7%), with approximately 13.3% not having a race or ethnicity reported (see Supplemental Table 2 for combined infant race/ethnicity). Similar to the pregnancy cohort, the proportions of infants of Asian, White, and Hispanic ethnicity were higher in the RIV4 cohort than in the SD-IIV4 cohort (Table 2, Supplemental Table 2).

Pregnancy outcomes

The most common pregnancy adverse outcome was eclampsia/pre-eclampsia (8.4%; Table 3), followed by preterm labor (3.5%), spontaneous abortion (3.0%), and congenital/fetal anomalies detected during pregnancy (2.4%). The proportion with placental abruption (0.7%) and/or that resulted in stillbirths/fetal death (0.4%) was low. The proportion of pregnant persons

FIGURE 1
KPNC study population of influenza vaccinated pregnant persons and their infants.



RIV4, quadrivalent recombinant influenza vaccine; *SD-IIV4*, quadrivalent standard-dose inactivated influenza vaccine.

*Includes discrepancies such as missing sex, males identified as pregnant, date of death occurring before date of birth, etc.

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TABLE 1
Demographics and baseline characteristics of pregnant persons vaccinated with RIV4 or SD-IIV4 during the 2018/19 and 2019/20 influenza seasons at Kaiser Permanente Northern California

		RIV4 N = 14,981		SD-IIV4 N = 33,800		Total N = 48,781	
		n	% (95% CI)	n	% (95% CI)	n	% (95% CI)
Maternal age group at conception[a]	17 – 24 years	1544	10.3 (9.8, 10.8)	3711	11.0 (10.6, 11.3)	5255	10.8 (10.5, 11.1)
	25 – 34 years	9586	64.0 (63.2, 64.8)	21,297	63.0 (62.5, 63.5)	30,883	63.3 (62.9, 63.7)
	35 – 44 years	3812	25.4 (24.7, 26.2)	8680	25.7 (25.2, 26.1)	12,492	25.6 (25.2, 26.0)
	≥ 45 years	39	0.3 (0.2, 0.4)	112	0.3 (0.3, 0.4)	151	0.3 (0.3, 0.4)
Race	Asian	4620	30.8 (30.1, 31.6)	9916	29.3 (28.9, 29.8)	14,536	29.8 (29.4, 30.2)
	Black	620	4.1 (3.8, 4.5)	1589	4.7 (4.5, 4.9)	2209	4.5 (4.3, 4.7)
	Multiracial	744	5.0 (4.6, 5.3)	1678	5.0 (4.7, 5.2)	2422	5.0 (4.8, 5.2)
	Native American	46	0.3 (0.2, 0.4)	102	0.3 (0.2, 0.4)	148	0.3 (0.3, 0.4)
	Pacific Islander	153	1.0 (0.9, 1.2)	287	0.8 (0.8, 1.0)	440	0.9 (0.8, 1.0)
	White	5506	36.8 (36.0, 37.5)	11,666	34.5 (34.0, 35.0)	17,172	35.2 (34.8, 35.6)
	Unknown[b]	3292	22.0 (21.3, 22.6)	8562	25.3 (24.9, 25.8)	11,854	24.3 (23.9, 24.7)
Ethnicity	Hispanic	3450	23.0 (22.4, 23.7)	8898	26.3 (25.9, 26.8)	12,348	25.3 (24.9, 25.7)
	non-Hispanic	11,531	77.0 (76.3, 77.6)	24,902	73.7 (73.2, 74.1)	36,433	74.7 (74.3, 75.1)
Body mass index[c]	< 18.5 kg/m^2	313	2.1 (1.9, 2.3)	611	1.8 (1.7, 2.0)	924	1.9 (1.8, 2.0)
	18.5 - <25 kg/m^2	5883	39.3 (38.5, 40.1)	12,894	38.1 (37.6, 38.7)	18,777	38.5 (38.1, 38.9)
	25 - < 30 kg/m^2	3806	25.4 (24.7, 26.1)	8475	25.1 (24.6, 25.5)	12,281	25.2 (24.8, 25.6)
	30 - < 35 kg/m^2	1951	13.0 (12.5, 13.6)	4514	13.4 (13.0, 13.7)	6465	13.3 (13.0, 13.6)
	35 - < 40 kg/m^2	883	5.9 (5.5, 6.3)	2163	6.4 (6.1, 6.7)	3046	6.2 (6.0, 6.5)
	≥ 40 kg/m^2	596	4.0 (3.7, 4.3)	1431	4.2 (4.0, 4.5)	2027	4.2 (4.0, 4.3)
	Unknown	1549	10.3 (9.8, 10.7)	3712	11.0 (10.7, 11.3)	5261	10.7 (10.5, 11.1)
Comorbidities (3 years prior to vaccination)[d]	Asthma	1817	12.1 (11.6, 12.7)	4275	12.6 (12.3, 13.0)	6092	12.5 (12.2, 12.8)
	CHD	10	0.1 (0.03, 0.1)	19	0.1 (0.03, 0.1)	29	0.1 (0.04, 0.1)
	COPD	6	0.04 (0.01, 0.1)	7	0.02 (0.01, 0.04)	13	0.03 (0.01, 0.05)
	Diabetes	252	1.7 (1.5, 1.9)	609	1.8 (1.7, 1.9)	861	1.8 (1.7, 1.9)
	Any of the above comorbidities	2036	13.6 (13.0, 14.1)	4779	14.1 (13.8, 14.5)	6815	14.0 (13.7, 14.3)
Timing of vaccine receipt	28 days prior to conception	750	5.0 (4.7, 5.4)	1367	4.0 (3.8, 4.3)	2117	4.3 (4.2, 4.5)
	First trimester	5092	34.0 (33.2, 34.8)	10,787	31.9 (31.4, 32.4)	15,879	32.6 (32.1, 33.0)
	Second trimester	4851	32.4 (31.6, 33.1)	11,470	33.9 (33.4, 34.4)	16,321	33.5 (33.0, 33.9)
	Third trimester	4288	28.6 (27.9, 29.4)	10,176	30.1 (29.6, 30.6)	14,464	29.7 (29.2, 30.1)
Pregnancy plurality[e]	Singleton pregnancy	14,743	98.4 (98.2, 98.6)	33,259	98.4 (98.3, 98.5)	48,002	98.4 (98.3, 98.5)
	Twin pregnancy	235	1.6 (1.4, 1.8)	531	1.6 (1.4, 1.7)	766	1.6 (1.5, 1.7)
	Triplet pregnancy	3	0.02 (0.004, 0.1)	10	0.03 (0.01, 0.1)	13	0.03 (0.01, 0.05)

RIV4, quadrivalent recombinant influenza vaccine; *SD-IIV4*, quadrivalent standard-dose inactivated influenza vaccine.

[a] All pregnant women included in study cohort were at least 18 years of age at the time of influenza vaccination. Maternal age during pregnancy is calculated based on the estimated pregnancy start date (ie, there were 72 persons who were 17 years of age at pregnancy start, and all 72 were 18 years of age at the time of influenza vaccination); [b] Approximately 92% of "Unknown" race pregnant persons in each vaccine group were Hispanic (RIV4: 3015; SD-IIV4: 7934); 1.9% of pregnant persons did not report a race or ethnicity; [c] Assessed 3 years prior to start of pregnancy up through the end of the 1st trimester. The BMI recorded closest to the estimated date of conception was used; [d] "Any comorbidity" includes individuals with asthma, CHD, COPD, and/or diabetes diagnosed in the 3 years prior to influenza vaccination; individual rows for those with asthma, CHD, COPD, or diabetes may not be mutually exclusive; [e] Each count represented in "Pregnancy plurality" refers to a single pregnancy that is a singleton, twin, or triplet pregnancy. Counts do not refer to the total number of live or nonlive births.

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TABLE 2
Demographics and baseline characteristics of infants born to pregnant persons vaccinated with RIV4 or SD-IIV4 during the 2018/19 and 2019/20 influenza seasons at Kaiser Permanente Northern California

		RIV4 N = 14,538		SD-IIV4 N = 32,856		Total N = 47,394	
		n	% (95% CI)	n	% (95% CI)	n	% (95% CI)
Infant sex	Male	7437	51.2 (50.3, 52.0)	16,940	51.6 (51.0, 52.1)	24,377	51.4 (51.0, 51.9)
	Female	7101	48.8 (48.0, 49.7)	15,916	48.4 (47.9, 49.0)	23,017	48.6 (48.1, 49.0)
Infant race	Asian	3863	26.6 (25.9, 27.3)	8300	25.3 (24.8, 25.7)	12,163	25.7 (25.3, 26.1)
	Black	496	3.4 (3.1, 3.7)	1257	3.8 (3.6, 4.0)	1753	3.7 (3.5, 3.9)
	Multiracial	949	6.5 (6.1, 6.9)	1949	5.9 (5.7, 6.2)	2898	6.1 (5.9, 6.3)
	Native American	20	0.1 (0.1, 0.2)	66	0.2 (0.2, 0.3)	86	0.2 (0.1, 0.2)
	Pacific Islander	128	0.9 (0.7, 1.0)	298	0.9 (0.8, 1.0)	426	0.9 (0.8, 1.0)
	White	4690	32.3 (31.5, 33.0)	9880	30.1 (29.6, 30.6)	14,570	30.7 (30.3, 31.2)
	Unknown[a]	4392	30.2 (29.5, 31.0)	11,106	33.8 (33.3, 34.3)	15,498	32.7 (32.3, 33.1)
Infant ethnicity	Hispanic	3059	21.0 (20.4, 21.7)	7857	23.9 (23.5, 24.4)	10,916	23.0 (22.7, 23.4)
	non-Hispanic	11,479	79.0 (78.3, 79.6)	24,999	76.1 (75.6, 76.5)	36,478	77.0 (76.6, 77.3)
Timing of vaccine receipt	28 days prior to conception	615	4.2 (3.9, 4.6)	1077	3.3 (3.1, 3.5)	1692	3.6 (3.4, 3.7)
	First trimester	4690	32.3 (31.5, 33.0)	9888	30.1 (29.6, 30.6)	14,578	30.8 (30.3, 31.2)
	Second trimester	4896	33.7 (32.9, 34.5)	11,602	35.3 (34.8, 35.8)	16,498	34.8 (34.4, 35.2)
	Third trimester	4337	29.8 (29.1, 30.6)	10,289	31.3 (30.8, 31.8)	14,626	30.9 (30.4, 31.3)

RIV4, quadrivalent recombinant influenza vaccine; *SD-IIV4*, quadrivalent standard-dose inactivated influenza vaccine.

[a] Approximately 59% of "Unknown" race infants in each vaccine group were Hispanic (RIV4: 2492; SD-IIV4: 6720); 13.3% of infant did not have a race or ethnicity reported.

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experiencing a pregnancy outcome between the RIV4 and SD-IIV4 vaccinated groups were similar.

In adjusted analyses comparing vaccination with RIV4 versus SD-IIV4 during pregnancy, there were no associations with any of the predefined pregnancy outcomes (Table 3).

Birth and neonatal/infant outcomes

The most common adverse birth outcome was SGA (8.7%), followed by preterm birth (7.4%), and LBW (5.8%) (Table 4). The most common adverse neonatal/infant outcome was congenital anomalies detected after delivery (42.8%). Major congenital anomalies were reported in 7.7% of infants, and minor congenital anomalies were reported in 39.0% of infants. The proportion of infants with a failure to thrive diagnosis (1.1%) and/or infant death (0.2%) was low. The proportion of live-born infants experiencing a birth or neonatal/infant outcome between the RIV4 and SD-IIV4 vaccinated groups were similar.

There was a total of 86 infant deaths, all of which were reviewed by study investigators. None were considered related to vaccination. There was no difference in the proportion of infant deaths among persons vaccinated during pregnancy with RIV4 versus SD-IIV4 (RIV4: n = 27 [0.19%]; SD-IIV4: n = 59 [0.18%]).

In adjusted analyses comparing vaccination with RIV4 versus SD-IIV4 during pregnancy, there were no associations with any of the predefined birth or neonatal/infant outcomes (Table 4).

Comment

Principal findings

In this large, real-world, retrospective cohort study of pregnant persons and their infants, we found that the proportion of pregnancy, birth, or neonatal/infant outcomes were the same following maternal vaccination with RIV4 as those following maternal vaccination with SD-IIV4. This safety study was conducted using a subset of pregnant persons from a larger cluster-randomized study, which was subject to less bias than most observational studies given the randomized study design and produced comparable demographic and baseline characteristics between the 2 vaccine groups. The findings in this study add to the body of evidence regarding the safety of influenza vaccination during pregnancy, and further support current ACIP recommendations for pregnant persons to receive an inactivated or recombinant influenza vaccine.[12-21]

Results in the context of what is known

In general, the proportions of most adverse outcomes in this study were lower than or similar to national rates. The proportion of pregnant persons with placental abruption (0.7%) was similar to national rates (0.3−1.0%),[22] while the proportion with spontaneous abortion (3.0% versus 10−20%[23]), still birth/fetal death (0.4% versus 0.57%[24]), preterm labor (3.5% vs. 6%[25]), and

TABLE 3
Adjusted odds ratios (OR) for pregnancy outcomes among pregnant persons vaccinated with RIV4 or SD-IIV4 during the 2018/19 and 2019/20 influenza seasons, Kaiser Permanente Northern California

		RIV4 N = 14,981		SD-IIV4 N = 33,800		Total N = 48,781		Reference: SD-IIV4	
		n	% (95% CI)	n	% (95% CI)	n	% (95% CI)	$OR_{Adjusted}$[b] (95% CI)	*P*-value
Pregnancy outcomes	Spontaneous abortion	470	3.1 (2.9, 3.4)	1013	3.0 (2.8, 3.2)	1483	3.0 (2.9, 3.2)	0.95 (0.85, 1.05)	.31
	Preterm labor	546	3.6 (3.4, 4.0)	1170	3.5 (3.3, 3.7)	1716	3.5 (3.4, 3.7)	1.06 (0.99, 1.14)	.09
	Stillbirth/fetal death	63	0.4 (0.3, 0.5)	153	0.5 (0.4, 0.5)	216	0.4 (0.4, 0.5)	0.84 (0.68, 1.04)	.12
	Congenital/fetal anomalies detected during pregnancy	356	2.4 (2.1, 2.6)	798	2.4 (2.2, 2.5)	1154	2.4 (2.2, 2.5)	1.00 (0.91, 1.09)	.96
	Eclampsia/pre-eclampsia[a]	1235	8.4 (7.9, 8.8)	2793	8.4 (8.1, 8.7)	4028	8.4 (8.1, 8.6)	1.01 (0.96, 1.06)	.64
	Placental abruption	115	0.8 (0.6, 0.9)	237	0.7 (0.6, 0.8)	352	0.7 (0.6, 0.8)	1.12 (0.96, 1.31)	.15

RIV4, quadrivalent recombinant influenza vaccine; *SD-IIV4*, quadrivalent standard-dose inactivated influenza vaccine.

[a] Eclampsia was assessed in pregnant persons following vaccination during pregnancy up through 42 days after delivery. 619 persons were excluded for this outcome because they received a second influenza vaccine in the postpartum period between Day 0 (delivery) and Day 42.; [b] All pregnancy outcome models used conditional logistic regression and were adjusted for maternal age group, race, ethnicity, BMI, comorbidities (yes/no), and trimester of influenza vaccination.

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eclampsia/pre-eclampsia (8.4% versus 10%[26]) was lower than national rates. Similarly, the proportion of infants with preterm birth (7.4% vs. 12%[25]), LBW (5.8% vs. 8.24%[27]), SGA (8.7% vs. 11.1%[28]), and infant death (0.2% vs. 0.54%[29]) was lower than national rates.

In contrast, the proportions of major (7.7%) and minor (39.0%) congenital anomalies detected after delivery in our study were higher than previously reported national rates,[30,31] though this is likely because we included all "Q**" ICD-10 codes ("Congenital malformations, deformations and chromosomal abnormalities"). Minor anomalies were identified using the subset of Q** codes recommended by the CDC's Birth Defects Surveillance Toolkit, while all other Q** codes were considered major anomalies. This list is more exhaustive than the limited set of codes used in other published studies. To our knowledge, no studies have been published that use the CDC's Birth Defects Surveillance Toolkit guidance, making it difficult to directly compare to our findings. Importantly however, the proportion of infants with congenital anomalies in each vaccine group was similar and not statistically different in our study. Additionally, our cohort had lower proportions of specific major congenital anomalies (eg, encephalocele, spina bifida, and cleft palate) than what has been reported by the National Birth Defects Prevention Network.[30]

The results in this study are consistent with a prior randomized clinical trial that included infants born to 382 pregnant persons vaccinated with RIV4 or SD-IIV4 during the 2019−2020 or 2020−2021 influenza seasons, which found that there was no increased rate of adverse outcomes (preterm birth, spontaneous abortion, still birth/fetal death, neonatal death) among infants whose mothers received RIV4 compared with SD-IIV4.[32] Our results for several outcomes (preterm labor, still birth/fetal death, preterm live birth, neonatal death, congenital anomalies detected after delivery, LBW, and SGA) are also consistent with those found in another KPNC cohort study of influenza-vaccinated and unvaccinated pregnant persons and their infants using data from 2007−2018.[33] As our prior cohort study only included lower-risk singleton pregnancies that reached at least 24 weeks gestation, the proportion of some outcomes such as congenital anomalies, LBW, SGA, and preterm live birth in the current study were captured at slightly higher proportions than in our prior study.

Strengths and limitations

This study had several strengths. A major strength was that this study was a subset of a large, cluster-randomized vaccine effectiveness study. By alternating the administration of RIV4 and SD-IIV4 weekly at every KPNC facility, including in OB/GYN clinics, imbalances in covariates between pregnant persons in either vaccine group were minimized. KPNC's capture of EMR data among pregnant persons and their infants is especially comprehensive, which gives us a high degree of confidence that our outcomes of interest are well documented and well balanced, minimizing confounding which is often associated with observational real-world studies. Additionally, the study included nearly all pregnant persons ≥18 years of age who received an influenza vaccine at KPNC. Finally, the findings may be generalizable to other pregnant persons, as the influenza vaccination rate among KPNC pregnant persons for the 2 study years (~54% and ~58%) was similar to what has been reported nationally by the CDC in the same years (~54% and 61%).[34]

This study had limitations. While the study population was a subset of the larger cluster-randomized study, imbalances in the quantity of RIV4 versus SD-IIV4 administered to pregnant persons may have been attributed to provider preference, availability of either vaccine

TABLE 4
Adjusted odds ratios (OR) for birth and neonatal/infant outcomes among live infants born to pregnant persons vaccinated with RIV4 or SD-IIV4 during the 2018/19 and 2019/20 influenza seasons, Kaiser Permanente Northern California

		RIV4 N = 14,538		SD-IIV4 N = 32,856		Total N = 47,394		Reference: SD-IIV4	
		n	% (95% CI)	n	% (95% CI)	n	% (95% CI)	$OR_{Adjusted}$[a] (95% CI)	*P*-value
Birth outcomes	Preterm infant	1061	7.3 (6.9, 7.7)	2450	7.5 (7.2, 7.7)	3511	7.4 (7.2, 7.6)	0.98 (0.91, 1.05)	.54
	Low birth weight	852	5.9 (5.5, 6.3)	1918	5.8 (5.6, 6.1)	2770	5.8 (5.6, 6.1)	1.00 (0.92, 1.09)	.92
	Small for gestational age	1277	8.8 (8.3, 9.3)	2846	8.7 (8.4, 9.0)	4123	8.7 (8.4, 9.0)	1.01 (0.94, 1.09)	.72
Neonatal/infant outcomes	Infant death	27	0.2 (0.1, 0.3)	59	0.2 (0.1, 0.2)	86	0.2 (0.1, 0.2)	1.05 (0.66, 1.65)	.85
	Congenital anomalies	6259	43.1 (42.2, 43.9)	14,018	42.7 (42.1, 43.2)	20,277	42.8 (42.3, 43.2)	1.01 (0.97, 1.05)	.53
	Major	1113	7.7 (7.2, 8.1)	2531	7.7 (7.4, 8.0)	3644	7.7 (7.5, 7.9)	N/A	
	Minor	5698	39.2 (38.4, 40.0)	12,762	38.8 (38.3, 39.4)	18,460	39.0 (38.5, 39.4)	N/A	
	Failure to thrive	150	1.0 (0.9, 1.2)	372	1.1 (1.0, 1.3)	522	1.1 (1.0, 1.2)	0.90 (0.75, 1.09)	.29

N.A., not analyzed; *RIV4*, quadrivalent recombinant influenza vaccine; *SD-IIV4*, quadrivalent standard-dose inactivated influenza vaccine.

[a] All birth and neonatal/infant outcome models used logistic regression and were adjusted for infant sex, infant race, infant ethnicity, maternal age group, and trimester of maternal influenza vaccination. For the infant mortality outcome, infant race/ethnicity was combined given the small number of cases of death, whereby Hispanic ethnicity was treated as a race category. Infants who identified as Hispanic ethnicity and a specified race were coded as that race.

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due to logistical constraints, or other factors affecting real-world practice. Historically for example, the KPNC OB/GYN clinics have been accustomed to using SD-IIV4 in pregnant persons. This could explain why, among pregnant persons who received RIV4, there was a higher proportion who were vaccinated in the preconception period and first trimester versus later in the pregnancy, when compared with SD-IIV4 vaccinees. Additionally, beyond age and some of the comorbidities, our analysis did not adjust for other factors potentially associated with high-risk pregnancies, such as nonsingleton pregnancies. Given that the demographic and baseline characteristics between the 2 groups were well balanced however, it is unlikely that the proportion of high-risk pregnancies would have been differential between the 2 groups.

Conclusions

In conclusion, this large study did not identify any safety concerns regarding pregnancy, birth, or neonatal/infant outcomes in persons who received RIV4 compared with SD-IIV4 during pregnancy and among their infants. These findings support the safety profile of RIV4 and provide further evidence regarding the safety of influenza vaccinations administered during pregnancy. ■

CRediT authorship contribution statement

Amber Hsiao: Writing – original draft, Writing – review & editing, Project administration. **Arnold Yee:** Writing – review & editing, Formal analysis, Data curation. **Ruvim Izikson:** Writing – review & editing, Conceptualization. **Bruce Fireman:** Writing – review & editing, Methodology. **John Hansen:** Writing – review & editing, Project administration. **Ned Lewis:** Writing – review & editing, Formal analysis. **Sonja Gandhi-Banga:** Writing – review & editing. **Alexandre Selmani:** Writing – review & editing. **Oxana Talanova:** Writing – review & editing. **Heidi Kabler:** Writing – review & editing. **Ajinkya Inamdar:** Writing – review & editing. **Nicola P. Klein:** Writing – review & editing, Supervision, Investigation, Funding acquisition. ■

Appendix

SUPPLEMENTAL TABLE 1
Definitions for pregnancy, birth, and neonatal/infant outcomes

Outcome category	Outcome	Source or ICD-10 Code[a]
Pregnancy outcomes[b]	Spontaneous abortion	KPNC EMR
	Preterm labor	O60.* Preterm labor, in addition to gestational age <37 weeks
	Stillbirth/fetal death	KPNC Pregnancy Table
	Eclampsia/pre-eclampsia	O14.* Pre-eclampsia
		O15.* Eclampsia
	Placental abruption	O45.* Premature separation of placenta
	Congenital/fetal anomalies detected during pregnancy	O35.* Maternal care for known or suspected fetal abnormality and damage
Birth outcomes[c]	Preterm birth	<37 weeks gestational age
	Low birth weight	Infant birthweight <2500 grams
	Small for gestational age	Infant birthweight percentile relative to gestational age and sex as recorded in the EMR
Neonatal/infant outcomes[c]	Infant death	KPNC EMR
	Failure to thrive	P92.6 Failure to thrive in newborn
		R62.51 Failure to thrive (child)
	Congenital anomalies	Q* Congenital malformations, deformations and chromosomal abnormalities
	Major congenital anomalies	Q* excluding the minor congenital anomalies listed below
	Minor congenital anomalies (per CDC[d])	These include sub-categories of each specified code if they exist:
		Q10.1 Congenital ectropion
		Q10.2 Congenital entropion
		Q10.3 Other congenital malformations of eyelid
		Q10.5 Congenital stenosis and stricture of lacrimal duct
		Q13.0 Coloboma of iris
		Q13.2 Other congenital malformations of iris
		Q13.5 Blue sclera
		Q15.8 Other specified congenital malformations of eye
		Q17.0 Accessory auricle
		Q17.1 Macrotia
		Q17.3 Other misshapen ear
		Q17.4 Misplaced ear
		Q17.5 Prominent ear
		Q17.8 Other specified congenital malformations of ear
		Q18.0 Sinus, fistula and cyst of branchial cleft
		Q18.1 Preauricular sinus and cyst
		Q18.3 Webbing of neck
		Q18.4 Macrostomia
		Q18.5 Microstomia

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SUPPLEMENTAL TABLE 1
Definitions for pregnancy, birth, and neonatal/infant outcomes *(continued)*

Outcome category	Outcome	Source or ICD-10 Code[a]
		Q18.6 Macrocheilia
		Q18.8 Other specified congenital malformations of face and neck
		Q27.0 Congenital absence and hypoplasia of umbilical artery
		Q30.2 Fissured, notched and cleft nose
		Q30.8 Other congenital malformations of nose
		Q35.7 Cleft uvula
		Q38.1 Ankyloglossia
		Q38.2 Macroglossia
		Q38.3 Other congenital malformations of tongue
		Q38.4 Congenital malformations of salivary glands and ducts
		Q38.5 Congenital malformations of palate, not elsewhere classified
		Q38.6 Other congenital malformations of mouth
		Q43.5 Ectopic anus
		Q52.3 Imperforate hymen
		Q52.4 Other congenital malformations of vagina
		Q52.5 Fusion of labia
		Q52.6 Congenital malformation of clitoris
		Q52.8 Other specified congenital malformations of female genitalia
		Q53.1 Undescended testicle, unilateral
		Q53.2 Undescended testicle, bilateral
		Q53.9 Undescended testicle, unspecified
		Q54.4 Congenital chordee
		Q55.1 Hypoplasia of testis and scrotum
		Q55.20 Unspecified congenital malformations of testis and scrotum
		Q55.22 Retractile testis
		Q55.61 Curvature of penis (lateral)
		Q55.64 Hidden penis
		Q55.69 Other congenital malformation of penis
		Q55.9 Congenital malformation of male genital organ, unspecified
		Q66.2 Congenital metatarsus (primus) varus
		Q66.3 Other congenital varus deformities of feet
		Q66.5 Congenital pes planus
		Q66.6 Other congenital valgus deformities of feet
		Q66.7 Congenital pes cavus
		Q66.8 Other congenital deformities of feet
		Q67.0 Congenital facial asymmetry
		Q67.1 Congenital compression facies
		Q67.2 Dolichocephaly
		Q67.3 Plagiocephaly
		Q67.4 Other congenital deformities of skull, face and jaw

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SUPPLEMENTAL TABLE 1
Definitions for pregnancy, birth, and neonatal/infant outcomes *(continued)*

Outcome category	Outcome	Source or ICD-10 Code[a]
		Q67.6 Pectus excavatum
		Q67.7 Pectus carinatum
		Q67.8 Other congenital deformities of chest
		Q68.0 Congenital deformity of sternocleidomastoid muscle
		Q68.1 Congenital deformity of finger(s) and hand
		Q68.2 Congenital deformity of knee
		Q68.8 Other specified congenital musculoskeletal deformities
		Q69.0 Accessory finger(s)
		Q69.2 Accessory toe(s)
		Q70.3 Webbed toes
		Q74.1 Congenital malformation of knee
		Q75.0 Craniosynostosis
		Q75.2 Hypertelorism
		Q75.3 Macrocephaly
		Q75.8 Other specified congenital malformations of skull and face bones
		Q76.0 Spina bifida occulta
		Q76.42 Congenital lordosis
		Q79.59 Other congenital malformations of abdominal wall
		Q82.5 Congenital non-neoplastic nevus
		Q82.6 Congenital sacral dimple
		Q82.8 Other specified congenital malformations of skin
		Q83.2 Absent nipple
		Q83.3 Accessory nipple
		Q83.8 Other congenital malformations of breast
		Q84.1 Congenital morphological disturbances of hair, not elsewhere classified
		Q84.2 Other congenital malformations of hair
		Q84.3 Anonychia
		Q84.5 Enlarged and hypertrophic nails
		Q84.6 Other congenital malformations of nails
		Q84.8 Other specified congenital malformations of integument

[a] Asterisk within ICD10 cards indicates that all sub-categories are included. For example, Q* would capture any ICD10 code beginning with Q.O35.* captures any ICD10 code beginning with "O35.", so would include O35.0 and its sub-categories O35.0, O35.1, O35.2, O35.3, O35.4, O35.5, O35.6, O35.7, O35.8, O35.9, etc; [b] Pregnancy outcomes were assessed during pregnancy, except for eclampsia/pre-eclampsia, which was assessed during pregnancy up through 42 days after delivery; [c] Birth outcomes were assessed at birth, and neonatal/infant outcomes were assessed on the day of birth through 365 days of life; [d] Centers for Disease Control and Prevention, Birth Defects Surveillance Toolkit, Appendices. Available at: https://www.cdc.gov/ncbddd/birthdefects/surveillancemanual/appendices/appendices.html; minor congenital anomalies: https://www.cdc.gov/ncbddd/birthdefects/surveillancemanual/appendices/appendix-b.html

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SUPPLEMENTAL TABLE 2

Combined race/ethnicity of pregnant women and infants born to pregnant women vaccinated with RIV4 or SD-IIV4 during the 2018/19 and 2019/20 influenza seasons at Kaiser Permanente Northern California

Pregnant cohort race/ethnicity	RIV4 N = 14,981 n (%)	SD-IIV4 N = 33,800 n (%)	Total N = 48,781 n (%)
Asian	4617 (30.8)	9897 (29.3)	14,514 (29.8)
Black	616 (4.1)	1579 (4.7)	2195 (4.5)
Hispanic	3450 (23.0)	8898 (26.3)	12,348 (25.3)
Multiracial	375 (2.5)	894 (2.6)	1269 (2.6)
Native American	45 (0.3)	100 (0.3)	145 (0.3)
Pacific Islander	148 (1.0)	284 (0.8)	432 (0.9)
White	5453 (36.4)	11,520 (34.1)	16,973 (34.8)
Unknown	277 (1.8)	628 (1.9)	905 (1.9)

Infant cohort race/ethnicity	RIV4 N = 14,538 n (%)	SD-IIV4 N = 32,856 n (%)	Total N = 47,394 n (%)
Asian	3863 (26.6)	8300 (25.3)	12,163 (25.7)
Black	496 (3.4)	1256 (3.8)	1752 (3.7)
Hispanic	3059 (21.0)	7857 (23.9)	10,916 (23.0)
Multiracial	385 (2.6)	820 (2.5)	1205 (2.5)
Native American	20 (0.1)	66 (0.2)	86 (0.2)
Pacific Islander	128 (0.9)	298 (0.9)	426 (0.9)
White	4687 (32.2)	9873 (30.0)	14,560 (30.7)
Unknown	1900 (13.1)	4386 (13.3)	6286 (13.3)

RIV4, quadrivalent recombinant influenza vaccine; *SD-IIV4*, quadrivalent standard-dose inactivated influenza vaccine.

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SUPPLEMENTAL TABLE 3

Number and percentage with concomitant vaccinations for pregnant women vaccinated with RIV4 or SD-IIV4 during the 2018-2019 and 2019-2020 influenza seasons at Kaiser Permanente Northern California

	RIV4 N = 14,981 n (%)	SD-IIV4 N = 33,800 n (%)	Total N = 48,781 n (%)
Tdap	2080 (13.9)	4776 (14.1)	6856 (14.1)
Other vaccines[a]	48 (0.3)	131 (0.38)	179 (0.36)

RIV4, quadrivalent recombinant influenza vaccine; *SD-IIV4*, quadrivalent standard-dose inactivated influenza vaccine.

[a] Other vaccines include hepatitis A/B, HPV, meningococcal ACWY/B, MMR, pneumococcal conjugate vaccine, pneumococcal polysaccharide vaccine, polio, tetanus-diphtheria, typhoid, and/or varicella

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