Clinical Trial to compare safety of Recombinant Influenza Vaccine (RIV4) versus Quadrivalent Inactivated Influenza Vaccine (IIV4) in Pregnancy

(ClinicalTrials.gov NCT03969641)

Geeta Swamy, MD

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Disclaimer

- The findings and conclusions in this presentation are those of the presenter and do not necessarily represent the official position of the Centers for Disease Control and Prevention
- Mention of a product or company name is for identification purposes only and does not constitute endorsement by CDC
- This study was supported by the CDC Clinical Immunization Safety Assessment (CISA) Project

Study Rationale

- ACIP currently recommends that persons who are or will be pregnant during the influenza season receive an age-appropriate quadrivalent inactivated influenza vaccine (IIV4) or RIV4 (Flublok® Quadrivalent)*
- Prelicensure studies for RIV excluded pregnant people
- While there is no specific reason to expect RIV to be unsafe during pregnancy, data on the safety of RIV in pregnancy are limited
- This rigorous randomized controlled trial of RIV4 vs. IIV4 in pregnant people was implemented to provide information on the safety of RIV4 during pregnancy, including infant health outcomes

* Prevention and Control of Seasonal Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices — United States, 2022–23 Influenza Season | MMWR (cdc.gov)

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Study Aims and Objectives: Primary Objective (PO)

- **PO1**: To compare the proportions of adverse birth outcomes in pregnant women vaccinated with RIV4 versus IIV4

Research hypothesis: The proportion of pregnant women with adverse birth outcomes will be non-inferior (not higher) after receipt of RIV4 compared to IIV4

Study Aims and Objectives: Secondary Objectives (SO)

- **SO1**: To compare proportions of preterm birth after RIV4 versus IIV4 vaccination
- **SO2**: To compare proportions of combined fetal and neonatal death after RIV4 versus IIV4 vaccination
- **SO3**: To compare proportions of spontaneous abortion after RIV4 versus IIV4 vaccination
- **SO4:** To compare proportions of moderate/severe solicited reactogenicity events in pregnant women vaccinated with RIV4 versus IIV4

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Design / Population / Recruitment

- Prospective, double-blinded, randomized (1:1)
  -- RIV4 group (Flublok® Quadrivalent)
  -- IIV4 group (FluLaval)
- Population – 382 pregnant women (≥18 years) at ≤34 weeks gestation who planned on receiving RIV or IIV during their current pregnancy (goal 430)
  – Year 1 (2019-20) goal : 226 participants (233 actual)
  – Year 2 (2020-21) goal: 204 participants (149 actual)
- Participants were recruited and enrolled at Duke University Medical Center, Cincinnati Children's Hospital Medical Center, and Boston Medical Center (CISA sites)

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Study Procedures Summary

- After randomization pregnant participants received study influenza vaccine; study staff and participants blinded to RIV4 or IIV4
- Solicited local and system reactions collected during Day 1 (vaccination day) through Day 8 using memory aid (REDCap electronic or paper)
- Serious adverse events and other health outcomes assessed throughout pregnancy and 90 days after delivery for mothers and infants
- Blood collected in pregnant participants before vaccination on Day 1, post-vaccination on Day 29 and at delivery (and infant cord blood at Duke) for influenza immunogenicity

Primary Outcome Measure

POM1: Proportions of adverse birth outcomes in pregnant women vaccinated with RIV4 versus IIV4 (assessed in modified intention to treat (mITT) population)

Adverse birth outcome is a composite of occurrence of at least one of the following: preterm birth, spontaneous abortion, fetal death, or neonatal death

- *Preterm birth: born alive less than 37 weeks 0 days*
- *Spontaneous abortion: pregnancy loss prior to 20 weeks 0 days*
- *Fetal death: intrauterine death of fetus at or after 20 weeks 0 days*
- *Neonatal death: infant death within first 28 days of life*

Secondary Outcome Measures

- **SOM1**: Proportions of preterm birth after RIV4 versus IIV4 vaccination
- **SOM2**: Proportions of combined fetal and neonatal death after RIV4 versus IIV4 vaccination
- **SOM3**: Proportions of spontaneous abortion after RIV4 versus IIV4 vaccination
- **SOM4**: Proportions of pregnant women with moderate/severe solicited reactogenicity events (local and systemic) within 8 days after vaccination with RIV4 versus IIV4

* All outcome measures were assessed in the mITT population

Statistical Methods

- mITT Population was the primary analysis population
  - The mITT Population includes any participant that was enrolled, randomized into the study, and received study product
- Per Protocol Population is a subset of mITT and excludes participants with serious protocol violations
- Statistical Testing
  - Noninferiority: the upper bound of a stratified (by study site) Newcombe binomial confidence interval with Cochran-Mantel-Haenszel (CMH) weighting of the difference
  - Other Objectives: comparisons between the RIV4 group and the IIV4 group using an exact Mantel-Haenszel statistic (calculated in Proc Logistic in SAS) in a stratified analysis by site

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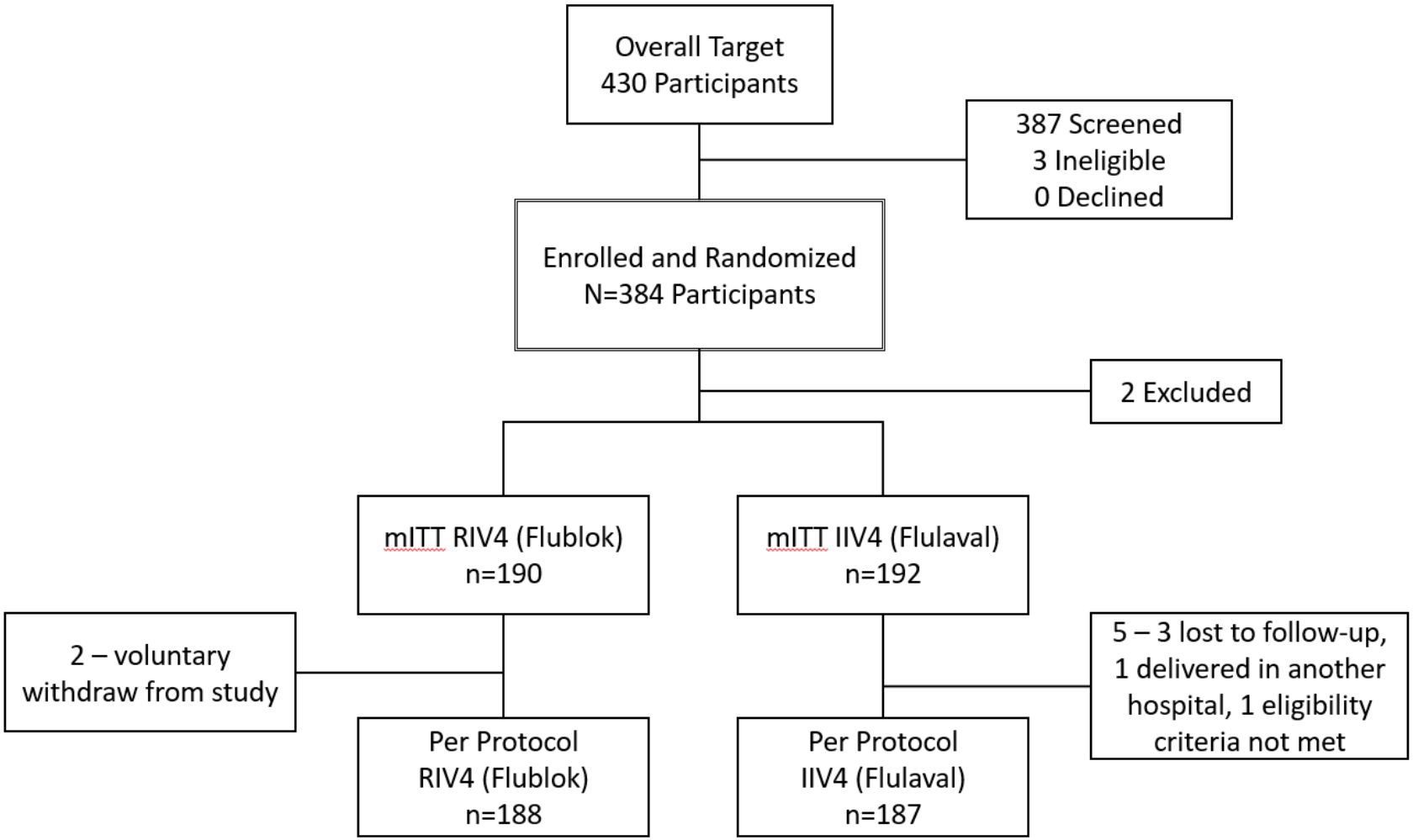
Study Consort Diagram



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Demographics

	RIV4 N= 190	IIV4 N= 192
	N (%) or Median (Range)	N (%) or Median (Range)
Black Race	63 (33.2%)	63 (32.8%)
White Race	98 (51.6%)	114 (59.38%)
American Indian/Alaskan Native	1 (0.5%)	0 (0%)
Asian	6 (3.2%)	1 (0.5%)
Native Hawaiian or other Pacific Islander	1 (0.5%)	1 (0.5%)
Other Race	12 (6.3%)	10 (5.2%)
Unknown Race	8 (4.2%)	3 (1.6%)
Refused Race	1 (0.5%)	0 (0%)
Hispanic or Latino Ethnicity	24 (12.6%)	25 (13.0%)
Gestational Age Group at enrollment		
<20 weeks	65 (34.2%)	78 (40.6%)
20 – 34 weeks	125 (65.8%)	114 (59.4%)
Gestational Age at Enrollment (weeks)	23.3 (7.6 – 34.0)	22.0 (6.3 – 34.0)

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Primary Outcome Results

Proportions of adverse birth outcomes in pregnant women vaccinated with RIV4 versus IIV4

	Adverse Birth Outcomes					
	Yes		Non-inferiority Test 10% Margin			
Group	N	%	Diff	Lower CI	Upper CI	p-value
RIV4 (Flublok)	17	9.09	.	.	.	.
IIV4 (Flulaval)	21	11.17	-0.0214	-8.2%	3.92%	<.0001

Ho: RIV4 – IIV4 ≥ 0.10 (10%)

Conclusion: The rate of adverse birth outcomes in RIV4 is considered not worse/not higher than the rate in IIV4 and the noninferiority criteria was met. The upper limit of the 95% CI of the difference for RIV4 minus IIV4 was 3.9% and the non-inferiority margin was 10%; therefore, the null hypothesis of inferiority was rejected.

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Secondary Outcome 1 Results

Proportions of preterm birth after RIV4 versus IIV4 vaccination

	Preterm Births			
	Yes		Odds Ratio (95% CI)	Exact p-value
Group	N	%	Odds	p-value
RIV4 (Flublok)	14	7.57	.	.
IIV4 (Flulaval)	19	10.22	0.72 (0.35, 1.48)	0.4645

Secondary Outcome 2 & 3 Results

Proportions of combined fetal and neonatal death* after RIV4 versus IIV4 vaccination

	Fetal Deaths			
	Yes		Odds Ratio (95% CI)	Exact p-value
Group	N	%	Odds	p-value
RIV4 (Flublok)	2	1.07		.
IIV4 (Flulaval)	0	0.00	Not estimable	

Proportions of spontaneous abortion after RIV4 versus IIV4 vaccination in pregnant women enrolled at <20 weeks gestational age

	Spontaneous Abortions			
	Yes		Odds Ratio (95% CI)	Exact p-value
Group	N	%	Odds	p-value
RIV4 (Flublok)	1	1.54		.
IIV4 (Flulaval)	2	2.56	0.50 (0.04, 5.47)	0.6235

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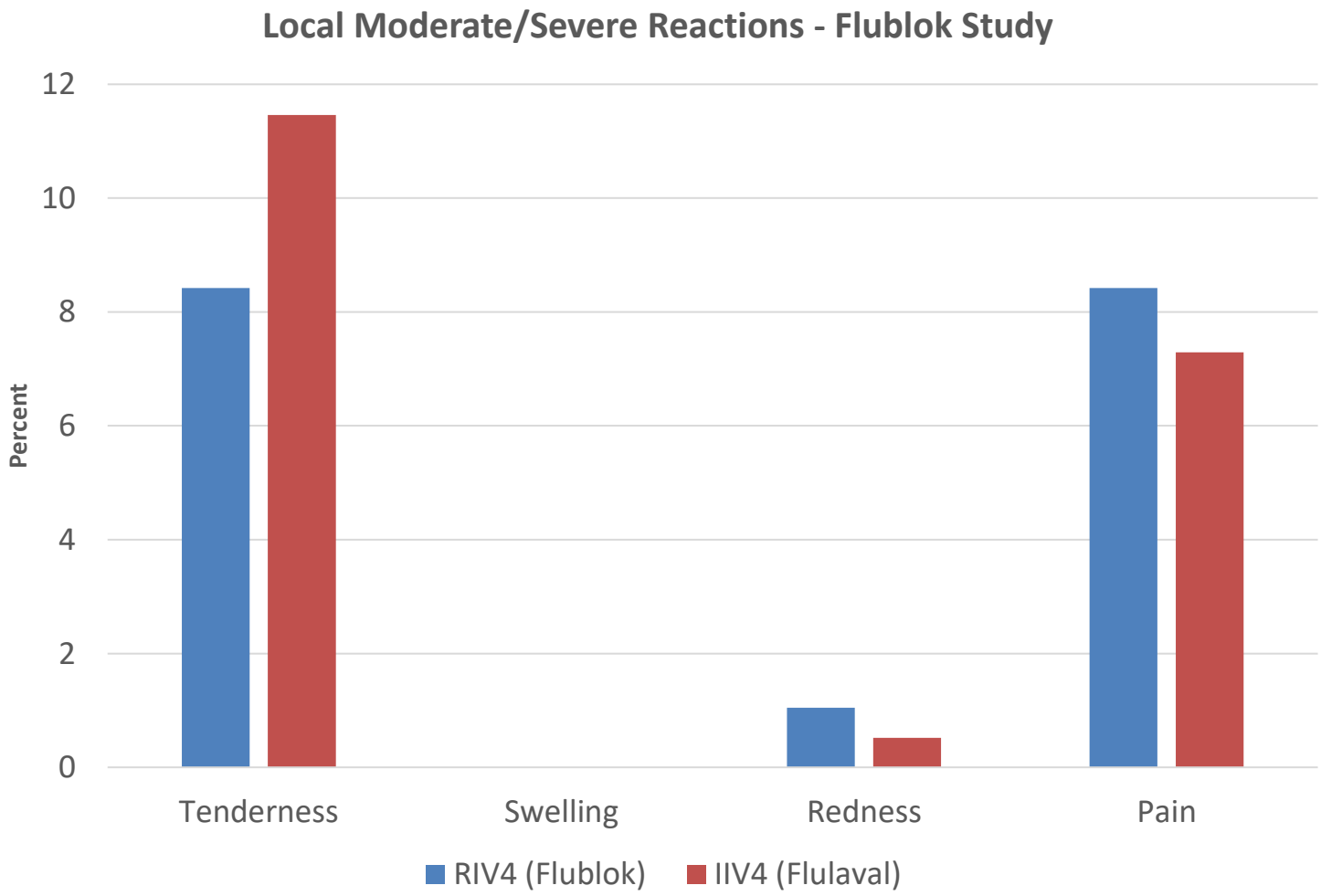
*No neonatal deaths occurred in study



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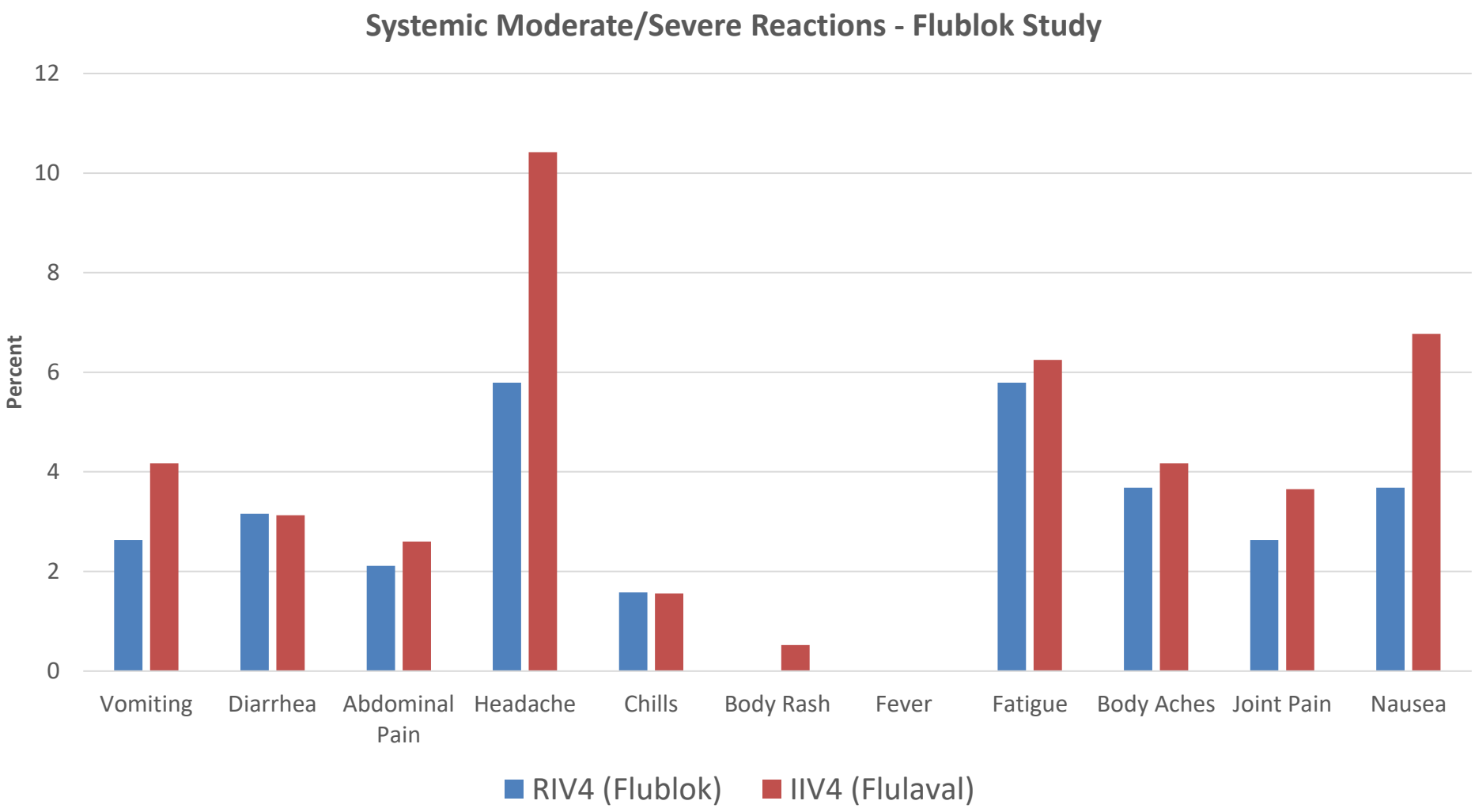
*No statistically significant difference



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*No statistically significant difference

Exploratory Outcomes
Maternal Serious Adverse Events

Participants with 1+ Maternal SAEs					
		Yes		95% CI- Diff in Proportions	
Outcome	Group	N	%	95% CI	Difference 95% CI
All Maternal SAEs	RIV4 (Flublok)	14	7.37	(4.09, 12.05)	.
	IIV4 (Flulaval)	12	6.25	(3.27, 10.66)	1.12 (-3.93, 6.17)

- All SAEs were **NOT RELATED** to vaccination, as judged by study investigators
  - antenatal hospitalizations - preeclampsia, preterm labor, preterm premature rupture of membranes, hyperemesis, substance use, end-stage renal disease, vaginal bleeding
  - postpartum hospitalizations – preeclampsia, postoperative infection

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Exploratory Outcomes

Small-for-Gestational Age				
	Yes		95% CI- Diff in Proportions	
Group	N	%	Odds Ratio (95% CI)	Exact p-value
RIV4 (Flublok)	8	4.37		.
IIV4 (Flulaval)	14	7.61	0.55 (0.23, 1.35)	0.1970

Clinical Chorioamnionitis				
	Yes		95% CI- Diff in Proportions	
Group	N	%	Odds Ratio (95% CI)	Exact p-value
RIV4 (Flublok)	7	3.68		.
IIV4 (Flulaval)	4	2.08	1.80 (0.52, 6.28)	0.3770

Preeclampsia or Eclampsia				
	Yes		95% CI- Diff in Proportions	
Group	N	%	Odds Ratio (95% CI)	Exact p-value
RIV4 (Flublok)	15	7.89		.
IIV4 (Flulaval)	13	6.77	1.18 (0.55, 2.54)	0.6999

Exploratory Outcomes
Infant Serious Adverse Events

Infants with +1 SAEs					
		Yes		95% CI - Diff in Proportions	
Outcome	Group	N	%	95% CI	Difference 95% CI
All Infant SAEs	RIV4 (Flublok)	11	5.79	(2.93, 10.12)	
	IIV4 (Flulaval)	18	9.38	(5.65, 14.41)	-3.59 (-8.88, 1.71)

- All SAEs were **NOT RELATED** to vaccination as judged by study investigators
  - congenital malformations
    - IIV4: renal anomaly x 2, trisomy 21, VSD/renal/absent thyroid, craniosynostosis, short femur, atrial septal defect, anomalous S1 hemivertebra, sagittal synostosis, ectopic kidney
    - RIV4: cardiac/DiGeorge, extra digit, bilateral pyelectasis, pyloric stenosis

Summary

- First randomized clinical trial to compare safety of RIV4 and IIV4 in pregnant women; enrolled 382 participants (89% of goal enrollment)
- RIV4 non-inferior to IIV4 for adverse birth outcomes, consistent with study hypothesis
- Safety profile of RIV4 and IIV4 similar for moderate/severe reactogenicity events and maternal and infant health outcomes assessed
- From the standpoint of safety, the study supports the ACIP recommendation to include RIV4 as option for pregnant persons
- Influenza immunogenicity analyses is in progress

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