

Pregnancy Outcomes with ccIV4 (Flucelvax); Post Marketing Study

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ACIP Meeting

October 25, 2023

Study Overview

Purpose	Post-marketing commitment
Main Objective	Evaluate specific pregnancy and fetus/infant outcomes
Study Design	Prospective, observational safety study
Study Population	Patients immunized with cclIV4 as part of routine obstetrical care
Scientific Oversight Committee	Teratologist, blinded to exposure timing, reviewed and classified reported malformations using the MACDP criteria Independent experts in maternal-fetal medicine, pediatrics, clinical research, infectious disease, epidemiology, and teratology reviewed safety data and aligned on malformation classification(s)

Outcomes

Pregnancy Outcomes

- **Live birth**
- **Stillbirth:**
 - Fetal death occurring ≥ 20 weeks' gestation, or if gestational age was unknown, a fetus that weighed 500 gm or more
- **Spontaneous abortion:**
 - Fetal death < 20 weeks' gestation, including missed abortion, incomplete abortion, and inevitable abortion
- **Elective termination**
 - Voluntary interruption of pregnancy, including pregnancy termination that occurred electively, to preserve maternal health, or due to fetal abnormalities

Events of Interest

- **Preterm birth:**
 - A live-born infant born at gestational age < 37 weeks
- **Low birth weight:**
 - A live-born infant whose birth weight is < 2500 gm
- **Major Congenital Malformation:**
 - Any major structural or chromosomal defect or combination of three or more conditional defects in live- or stillborn infants, or fetal losses of any gestational age, including outcomes prior to 20 weeks' gestation or weighing < 500 gm

Eligibility/Ineligibility Criteria

Eligible Cases:

- Pregnant patients were enrolled prospectively
- Sufficient information to confirm that vaccination with cclIV4 occurred during routine obstetrical care
- HCP's contact information to allow for follow-up
- Subjects may have self-enrolled or may have been enrolled by a participating OB/GYN clinic after providing informed consent

Ineligible Cases:

- Retrospective cases
- Persons who had prior knowledge of an adverse pregnancy outcome

Study Enrollment Over Three US Influenza Seasons

	Persons Enrolled
2017/2018	10
2018/2019	268
2019/2020	415
Total Enrolled	693
Lost to Follow-up	(27)
Ineligible	(1)
Primary Analysis Population	665

Demographics

Primary analysis population (PAP)	
Maternal age at conception (years)	N=665
Mean (SD)	28.0 (5.3)
Median	28.0
Min, max	17, 45
Paternal age at enrollment (years)	N=612
Mean (SD)	30.4 (6.2)
Median	30.0
Min, max	17, 59
Ethnicity n (%)	N=665
Hispanic or Latino	44 (6.6%)
Not Hispanic or Latino	437 (65.7%)
Missing*	184 (27.7%)
Race n (%)	N=665
White	399 (60.0%)
Black or African American	194 (29.2%)
Asian	29 (4.4%)
American Indian or Alaskan Native	1 (0.2%)
Native Hawaiian or Other Pacific Islander	2 (0.3%)
Other	28 (4.2%)
Unknown	12 (1.8%)

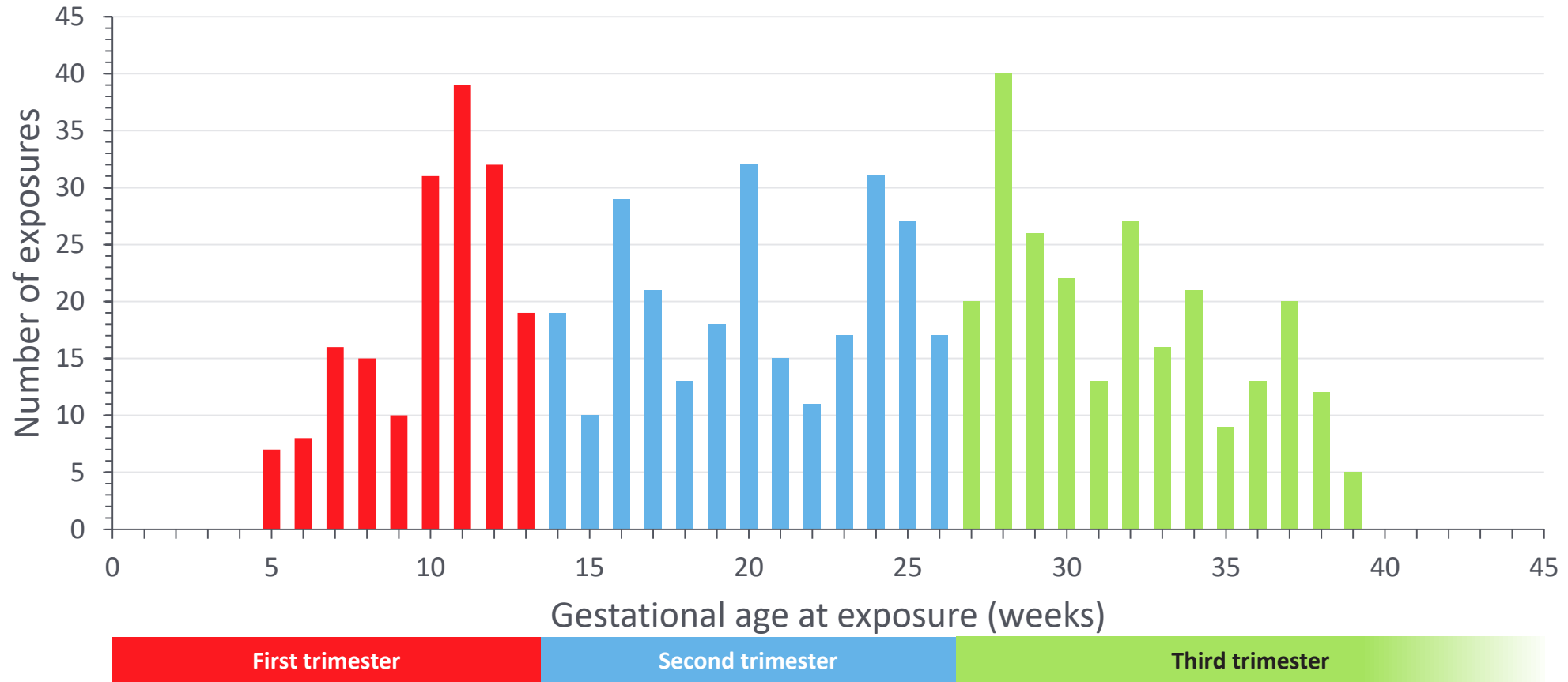
Baseline Characteristics

Primary analysis population (PAP)

Pre-Pregnancy BMI (kg/m²)	N=661
Mean (SD)	29.6 (8.2)
Median	28.1
Min, max	15.0, 64.8
Number of previous pregnancies, n (%)	N=665
0	195 (29.3%)
1	186 (28.0%)
2	135 (20.3%)
≥3	149 (22.4%)
Family history of congenital malformations, n (%)	N=665
Offspring	8 (1.2%)
Maternal history	40 (6.0%)
Paternal history	40 (6.0%)
Any family history	78 (11.7%)
Any concurrent condition, n (%)	527 (79.2%)
Any concomitant medications, n (%)	651 (97.9%)
Substance use, n (%)	
Any tobacco use	84 (12.6%)
Any alcohol use	1 (0.2%)
Any illicit drug use	N/A

Exposure by Gestational Age

Number of patients by gestational age at exposure to cclIV4 (in weeks)
Among all subjects identified (N=693)

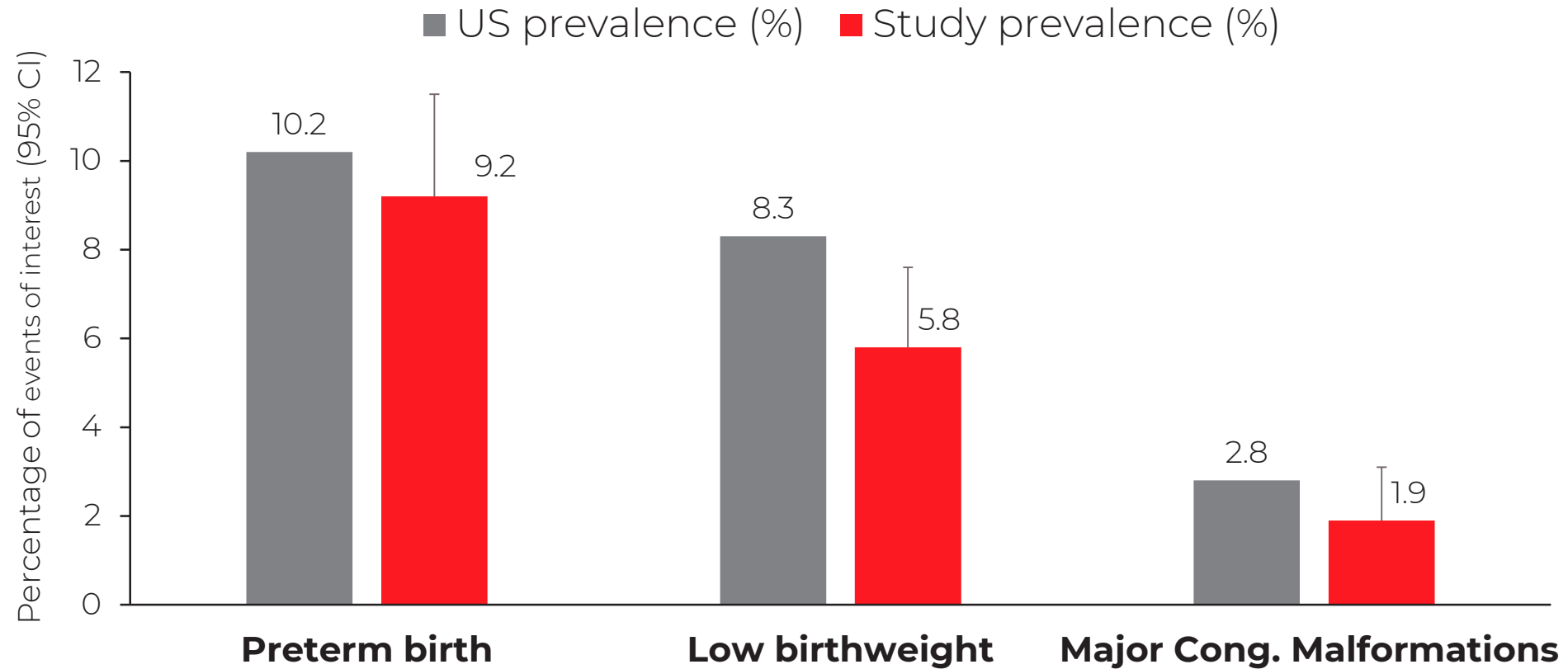


Results: Pregnancy Outcomes

Outcome	Vaccine Exposure			Overall
	First Trimester	Second Trimester	Third Trimester	
Primary Analysis Population	n=178	n= 277	n= 210	n=665
Live Birth, n % (95% CI)	172 96.6% (92.8-98.8)	277 100% (98.7-100)	210 100% (98.3-100)	659 99.1% (98.0-99.7)
Stillbirth	0 0 (0.0-2.1)	0 0 (0.0-1.3)	0 0 (0.0-1.7)	0 0 (0.0-0.6)
Enrollment <20 weeks gestation	n=147	n= 64	N/A	n=211
Spontaneous Abortion*	4 2.7% (0.7-6.8)	0 0 (0.0-5.6)	N/A	4 1.9% (0.5-4.8)
Elective Termination*	1 0.7% (0.0-3.7)	0 0 (0.0-5.6)	N/A	1 0.5% (0.0-2.6)

⁹ *Calculated using the population enrolled at <20 weeks of gestation (n = 211) as the denominator.

Results: Events of Interest



CDC, Centers for Disease Control and Prevention; CI, confidence interval; MACDP, Metropolitan Atlanta Congenital Defects Program; MCM, major congenital malformation; NCHS, National Center for Health Statistics; NVSS, National Vital Statistics System. 1. Martin JA, et al. *NCHS Data Brief*. 2020;387:1–8; 2. Martin JA, et al. *Natl Vital Stat Rep*. 2019;68:1–47; 3. Correa A, et al. *Birth Defects Res A Clin Mol Teratol*. 2007;79:65–93.

Results: Major Congenital Malformations

		Timing of Vaccine/ Weeks GA	Preferred MACDP term
Trimester of Vaccine	First	5.4	Sex chromosome – XYY
		10.7	Talipes equinovarus
	Second	16.1	Renal agenesis, right
		16.1	Polycystic kidneys *
		16.4	Clubfoot, cardiomegaly, aorta malformation (unknown), hypoplasia of upper or lower limb
		18.1	Situs inversus abdominus
		19.9	Hirschsprung's Disease
		23.0	Fluid around kidneys
		24.9	Micropenis, microphthalmos
		Third	30.3
	32.1		Trisomy 21, atrial septal defect, patent ductus arteriosus
	33.0		Absent foreskin
	33.3		Hypospadias
	33.4		Absent forearm

Key:

- Defect with known cause
- No temporal association
- Unable to assess temporality

¹¹ GA – Gestational Age, MACDP - Metropolitan Atlanta Congenital Defects Program
 *One infant who died 24h after birth had polycystic kidneys and fetal anhydramnios reported during pregnancy.

Strengths and Limitations

Strengths

- >660 Subject enrolled across multiple influenza seasons
- Diverse population which included racial and ethnic groups as well as a broad range of maternal ages
- Enrollment occurred at five study sites in four states

Limitations

- Effect of potential confounders (previous pregnancy outcomes, pregnancy complications, etc.)
- Potential for missing data or limited level of detail collected as part of routine care
- MACDP counts MCMs detected up to the age of 6 years

Conclusion

- The findings are consistent with published data from various databases and surveillance systems that monitor the safety of influenza vaccines¹⁻⁵
- The independent expert committee found no evidence of a safety concern
- These data support the use of cclIV4 for immunization against influenza in this population

1. Chambers CD, et al. *Vaccine*. 2016;34(37):4443–4449; 2. Zerbo O, et al. *Vaccine*. 2017;35(24):3186–3190; 3. Donahue JG, et al. *Vaccine*. 2019;37(44):6673–6681; 4. Moro P, et al. *Drug Saf*. 2017;40(2):145–152; 5. Louik C, et al. *Vaccine*. 2016;34(37):4450–4459.