

From the Vaccine Safety Datalink (VSD) Maternal Tdap vaccination and structural birth defects in offspring

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Background

- **Tetanus, diphtheria, and acellular pertussis (Tdap) vaccine has been routinely recommended for unvaccinated pregnant women**
 - 2010 California
 - 2011 United States
- **Fall 2012 ACIP – Tdap to be administered during every pregnancy, with preference between 27–36 weeks gestation**
- **Many countries have implemented maternal Tdap immunization programs**

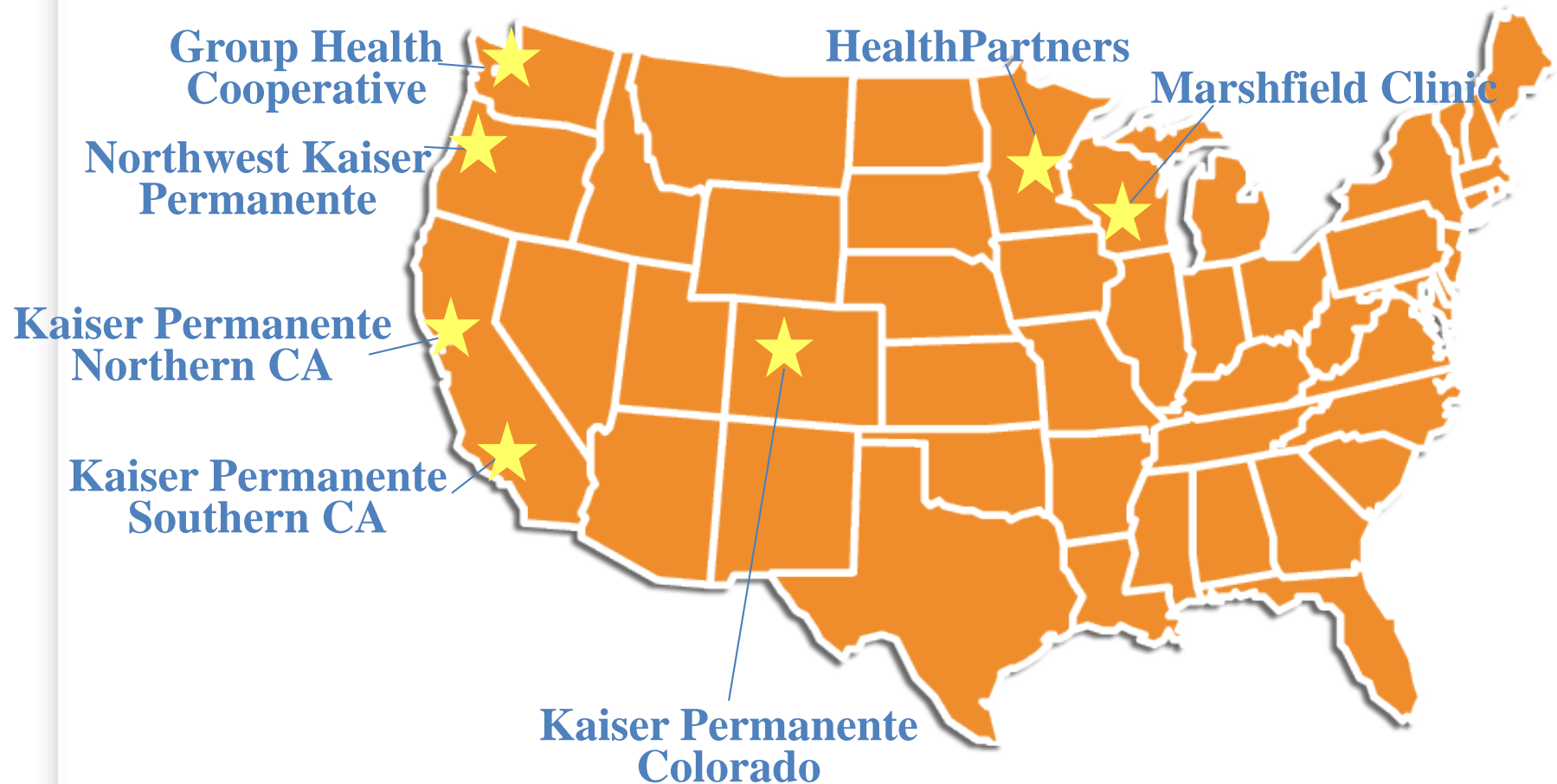


Objectives

- **To evaluate risks for structural birth defects following maternal Tdap vaccination within the Vaccine Safety Datalink (VSD)**
 - **Any birth defect**
 - **Major structural defects**
 - **Microcephaly**

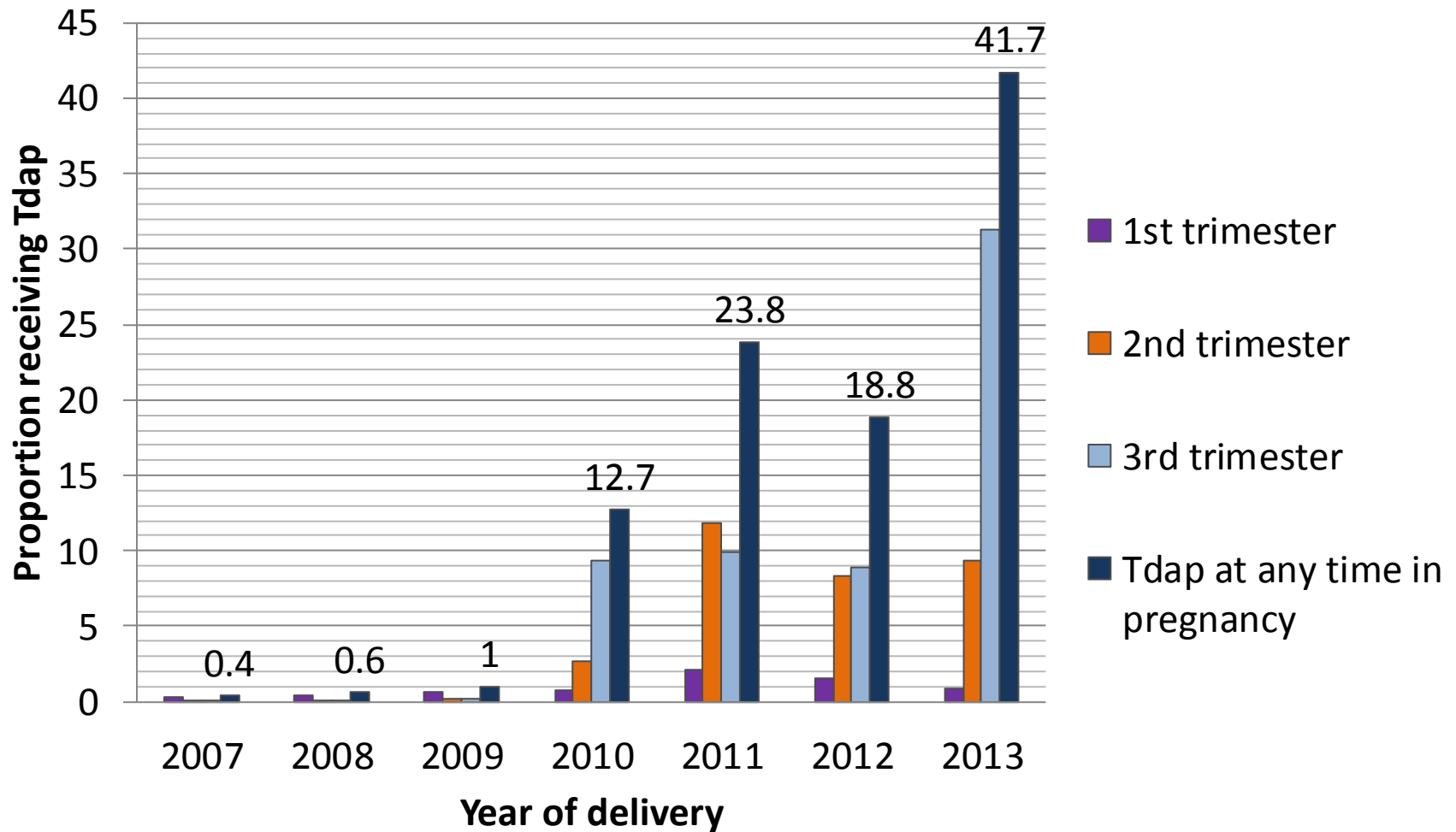


VSD sites with data on Tdap in pregnancy





Receipt of Tdap during pregnancy by trimester, live births between 2007 and 2013, within VSD





Methods

- **Observational cohort study of pregnant women and their infants, from 7 VSD sites**
- **Pregnancies ending in a live birth 1/1/07–9/1/13**
- **Identified through a validated automated algorithm, based on administrative, electronic health record (EHR) and birth certificate data¹**



Inclusions

- **Pregnant women**
 - Continuous insurance enrollment from 6 months prior to last menstrual period (LMP) through 6 weeks postpartum
 - At least 1 outpatient visit during pregnancy
- **Infants**
 - Birth weight and gestational age available
 - If surviving to 12 months of age
 - Insurance enrollment for 4 months
 - At least 1 outpatient visit by 1 year of age
 - For infant deaths during first year, insurance and utilization criteria not applied



Exclusions

- Identified from ICD-9-CM¹ codes and pharmacy files
 - Multiple gestation births
 - Exposures or conditions potentially increasing risk for birth defect
 - Live virus vaccine
 - Pre-existing diabetes
 - Teratogenic medication
 - Maternal or infant TORCH² infection
 - Chromosomal abnormalities

1. *International Classification of Diseases, Ninth Revision, Clinical Modification*

2. Toxoplasma, Other, Rubella, Cytomegalovirus, Herpes



Maternal Tdap

- **Tdap administrations identified using claims/EHR data (standardized VSD files)**
- **Exposure windows:**
 1. **<14 weeks gestation**
 2. **27–36 weeks gestation¹**
 3. **Any week during pregnancy**

1. Analyses of vaccinations occurring from 27-36 weeks gestation were restricted to years when Tdap was routinely recommended in California (2010-2013) and the U.S. (2012-2013)



Outcomes

- 1. Any structural birth defect
(ICD-9-CM codes: 740.0–759.9)**
- 2. Selected *major* structural birth defects**
 - Affecting life expectancy, health status, or physical or social functioning**
 - Monitored in U.S. and European birth defect surveillance systems**
 - Outcome specific algorithms applied**
- 3. Microcephaly**



Algorithms for CNS defects

Central Nervous System	Encephalocele, Cranial Meningocele, Encephalomyelocele (742.0); Spina bifida (741.0x, 741.9x); Microcephaly (742.1)	1 inpatient diagnosis or 2 outpatient diagnoses or 1 outpatient diagnosis and death in first year
	Holoprosencephaly (742.2)	2 outpatient diagnoses or 1 outpatient diagnosis and death in first year



Statistical analyses

- Compared baseline characteristics between vaccinated and unvaccinated women
- Logistic regression to estimate propensity scores
 - **Maternal demographics** (Age, race/ethnicity, poverty, VSD site, and delivery year)
 - **Healthcare utilization** (Kotelchuck Index, hospitalization before 20 weeks gestation)
 - **Maternal comorbidity** (Hypertension, smoking, and heart, pulmonary, or renal disease)

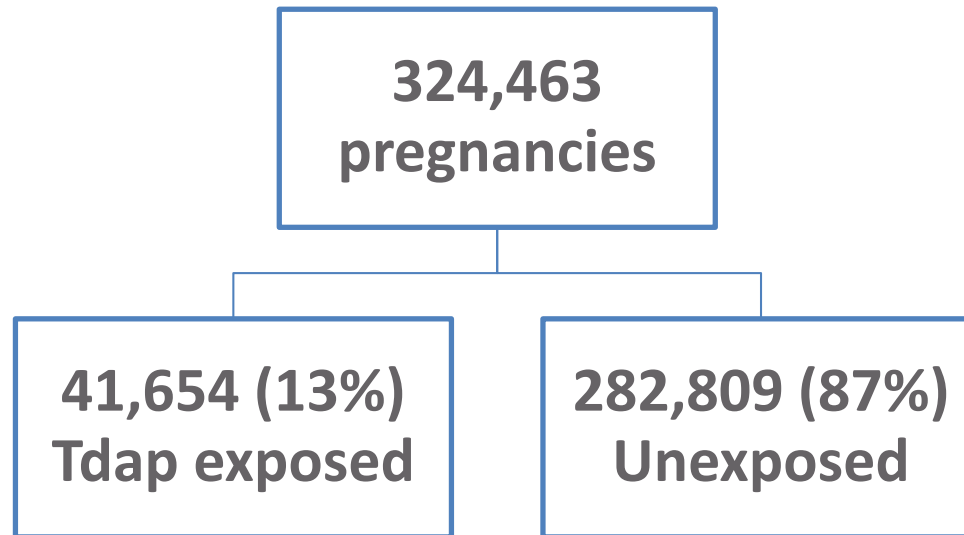


Statistical analyses

- Prevalence differences estimated using Poisson distribution with identity link and robust variance
- Prevalence ratios estimated using generalized linear models w/ Poisson distribution



Results



- **3,321 women vaccinated before 14 weeks gestation**
- **20,568 women vaccinated between 27–36 weeks gestation**



Baseline characteristics

	Tdap during pregnancy	Unexposed
	N=41,654	N=282,809
Maternal Age		
<18 years	0.7%	1.3%
18-24	11.9%	12.9%
25-34	63.5%	61.9%
≥35 years	24.0%	23.9%
Race/ethnicity		
Black	6.3%	7.2%
Asian	17.4%	16.1%
Hispanic	32.4%	29.1%
White	35.1%	39.0%
Other	8.7%	8.6%



Baseline characteristics, continued

	Tdap during pregnancy	Unexposed
	N=41,654	N=282,809
Prenatal care index		
Adequate/Plus	80.0%	72.3%
Intermediate	17.7%	22.7%
Inadequate	2.3%	5.0%
Care in 1st trimester	96.3%	93.8%
Received another vaccine during pregnancy	64.1%	40.9%
Smoking	8.9%	9.3%
Hypertension	1.8%	2.1%



Any structural birth defect following maternal Tdap

	Tdap N (%)	Unexposed N (%)	Prevalence Difference¹ (95% CI)	Prevalence Ratio² (95% CI)
Tdap before 14 weeks gestation	208 (6.3)	17,422 (6.2)	-0.51 (-1.32, 0.30)	0.94 (0.82, 1.07)
Tdap between 27-36 weeks gestation	1,435 (7.0)	8,367 (7.0)	0.14 (-0.25, 0.53)	1.02 (0.96, 1.08)
Tdap any time in pregnancy	2,816 (6.8)	17,422 (6.2)	-0.13 (-0.41, 0.15)	0.98 (0.94, 1.03)



Major structural birth defects following maternal Tdap

	Tdap N (%)	Unexposed N (%)	Prevalence Difference¹ (95% CI)	Prevalence Ratio² (95% CI)
Tdap before 14 weeks gestation	59 (1.8)	4,521 (1.6)	0.17 (-0.29, 0.62)	1.10 (0.85, 1.42)
Tdap between 27-36 weeks gestation	356 (1.7)	1,920 (1.6)	0.15 (-0.04, 0.35)	1.09 (0.97, 1.23)
Tdap any time in pregnancy	717 (1.7)	4,449 (1.6)	0.10 (-0.04, 0.25)	1.06 (0.98, 1.16)

1. Prevalence difference per 100 live births; Adjusted by propensity score
2. Prevalence ratio adjusted by propensity score



Microcephaly following maternal Tdap

	Tdap N (per 10,000 live births)	Unexposed N (per 10,000 live births)	Prevalence Difference¹ (95% CI)	Prevalence Ratio² (95% CI)
Tdap before 14 weeks gestation	4 (12)	348 (12)	-1 (-12, 9)	0.96 (0.36, 2.58)
Tdap between 27-36 weeks gestation	21 (10)	146 (12)	-1, (-5, 4)	1.01 (0.63, 1.61)
Tdap any time in pregnancy	38 (9)	346 (12)	-1 (-4, 2)	0.86 (0.60, 1.24)

1. Prevalence difference per 10,000 live births; Adjusted by propensity score
2. Prevalence ratio adjusted by propensity score



Limitations

- **Birth defects identified through diagnostic codes using outcome specific algorithms rather than clinical exam or direct review of charts**
- **Potential for missing diagnoses due to lapses in insurance coverage**
- **Limited to live births – unable to study stillbirths, elective terminations, spontaneous abortions**



Summary

- **Maternal Tdap vaccination during pregnancy was NOT associated with increased risk for birth defects, including microcephaly, among live birth offspring**
- **Results support safety of maternal Tdap vaccination, for the infant outcomes evaluated**



Acknowledgements

HealthPartners VSD team

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Additional slides



Structural birth defect algorithm development

- **Specific defects based on National Birth Defects Prevention Study (NBDPS) and European Surveillance of Congenital Anomalies (EUROCAT) registries and expert consultation**
- **Iterative process to optimize algorithms**
 - **Compared prevalence rates within VSD to those in other surveillance systems**
 - **Evaluated prevalence rates by year and by site**
 - **Limited chart reviews of potential cases from one VSD site to refine algorithms**

Table 3. Final algorithms for selected major structural defects for use in Vaccine Safety Datalink studies of maternal vaccine safety

Organ System	Specific Diagnoses (ICD-9-CM Codes)	Algorithm
Central Nervous System	Encephalocele, Cranial Meningocele, Encephalomyelocele (742.0); Spina Bifida (741.0x, 741.9x); Microcephalus (742.1)	1 inpatient diagnosis or 2 outpatient diagnoses or 1 outpatient diagnosis and death in first year
	Holoprosencephaly (742.2)	2 outpatient diagnoses or 1 outpatient diagnosis and death in first year
Eye	Anophthalmia, Microphthalmia (743.00, 743.10-743.12); Cataracts and Other Lens Defects. (743.30-743.36 743.2x)	2 outpatient diagnosis or 1 outpatient diagnosis and death in first year
Ear	Anotia, Microtia (744.01, 744.23)	2 outpatient diagnoses or 1 diagnosis and death in first year
Cardiac	Severe Cardiac Defects: Single Ventricle, Tricuspid Atresia, Ebstein's Anomaly, Hypoplastic Left Heart, Hypoplastic Right Heart, Common Truncus, Transposition, Atrioventricular Septal Defects, Tetralogy of Fallot, Aortic Valve Atresia/Stenosis, Coarctation, Total Anomalous Pulmonary Venous Return, Anomalous Coronary Artery (745.0, 745.1x, 745.2-745.3, 745.6x, 745.7, 746.00, 746.01, 746.1-746.3, 746.7, 746.85, 747.1x, 747.22, 747.41)	2 inpatient diagnoses or 1 inpatient and 1 outpatient diagnosis or 1 diagnosis and death in first year
	Other Cardiac Defects: Septal Defects, Heterotaxy, PAPVR (745.4, 745.8, 745.9, 747.42, 759.3)	2 diagnoses (inpatient or outpatient) or 1 diagnosis and death in first year
Orofacial /Respiratory	Choanal Atresia (748.0)	2 outpatient diagnoses or 1 outpatient diagnosis and death in first year
	Cleft Lip / Cleft Palate (749.1, 749.10-749.14, 749.2, 749.20-749.25, 749.0, 749.00-749.04)	1 inpatient diagnosis or 2 outpatient diagnoses or 1 outpatient diagnoses and death in first year
Gastrointestinal	Biliary Atresia (751.61); Intestinal Atresia/Stenosis (751.1, 751.2)	1 inpatient diagnosis or 2 outpatient diagnoses or 1 outpatient diagnosis and death in first year
	Esophageal Atresia +/- Tracheoesophageal Fistula (750.3)	2 outpatient diagnoses or 1 inpatient and 1 outpatient diagnosis or 1 inpatient or outpatient diagnosis and death in first year
	Pyloric Stenosis (750.5)	1 inpatient diagnosis or 1 outpatient diagnosis and death in first year
	Exstrophy, Bladder (753.5)	1 inpatient diagnosis by 3 months of age and 1 outpatient diagnosis by one year or 1 inpatient diagnosis and death in the first year
Genitourinary/Renal	Hypospadias- 2nd or 3rd Degree (752.61); Renal Dysplasia (753.15)	2 outpatient diagnoses or 1 outpatient diagnosis and death in first year; hypospadias limited to males
	Renal Agenesis/Hypoplasia (753.0)	1 inpatient diagnosis and 1 outpatient diagnosis or 1 diagnosis and death in first year
	Congenital Hydronephrosis (753.2x); Posterior Urethral Valve and/or Prune Belly (753.60, 756.72)	2 outpatient diagnoses or 1 diagnosis and death in first year; posterior urethral valves limited to boys
Musculoskeletal	Gastroschisis or Omphalocele (756.72, 756.73, 756.79); Diaphragmatic Hernia (756.6)	1 inpatient diagnosis by 3 months of age or 1 diagnosis and death in first year
	Limb Deficiency (755.2-755.9)	1 inpatient or 2 outpatient diagnoses) and 1 diagnosis within 3 months or 1 inpatient or outpatient diagnosis and death in first year
	Sacral Agenesis (756.13)	1 inpatient diagnosis or 2 outpatient diagnoses or 1 diagnosis and death in first year

Table 4. Prevalence estimates for selected major structural defects in the Vaccine Safety Datalink and other surveillance systems.

Specific Diagnoses (ICD-9 codes)	Rates in the VSD per 10,000 Live Births (2004-2013)	Rates in Selected U.S. State-Based Surveillance Programs* per 10,000 Live Births (2007-2011)		Rates in EUROCAT per 10,000 Live Births** (2004-2012)
<u>Encephalocele</u> , <u>Cranial Meningocele</u> , <u>Encephalomyelocele</u> (742.0)	0.64	1.0 (Colorado)	1.0 (Iowa)	0.23-0.44
<u>Spina Bifida</u> (741.0x, 741.9x);	1.89	3.8 (Colorado)	4.3 (Iowa)	1.68-2.0
<u>Microcephalus</u> (742.1)	12.9	NA		2.12-2.96
<u>Holoprosencephaly</u> (742.2)	3.29	1.1 (Colorado)	1.7 (Iowa)	0.23-0.40
<u>Anophthalmia</u> , <u>Microphthalmia</u> (743.00, 743.10-743.12);	0.82	1.8 (Colorado)	2.2 (Iowa)	0.61-0.96
<u>Cataracts and Other Lens Defects</u> (743.30-743.36 743.2x)	3.76	1.9 (Colorado)	2.7 (Iowa)	1.3-1.7
<u>Anotia</u> , <u>Microtia</u> (744.01, 744.23)	2.5	2.9 (Colorado)	2.4 (Iowa)	0.20-0.45
Severe Cardiac Defects: Single Ventricle, Tricuspid Atresia, <u>Ebstein's Anomaly</u> , <u>Hypoplastic Left Heart</u> , <u>Hypoplastic Right Heart</u> , Common Truncus, Transposition, Atrioventricular Septal Defects, Tetralogy of <u>Fallot</u> , Aortic Valve Atresia/Stenosis, <u>Coarctation</u> , Total Anomalous Pulmonary Venous Return, Anomalous Coronary Artery (745.0, 745.1x, 745.2-745.3, 745.6x, 745.7, 746.00, 746.01, 746.1-746.3, 746.7, 746.85, 747.1x, 747.22, 747.41)	16.9	33.3*** (Colorado)	34.9*** (Iowa)	16.6-20.0
<u>Choanal Atresia</u> (748.0)	0.52	2.3 (Colorado)	1.6 (Iowa)	0.6-1.0
<u>Cleft Lip and/or Cleft Palate</u> (749.1, 749.10-749.14, 749.2, 749.20-749.25, 749.0, 749.00-749.04)	14.5	21.0 (Colorado)	16.9 (Iowa)	12.1-14.7
<u>Biliary Atresia</u> (751.61)	1.16	1.1 (Colorado)	0.5 (Iowa)	NA
<u>Intestinal Atresia/Stenosis</u> (751.1, 751.2)	7.75	11.2 (Colorado)	8.4 (Iowa)	4.1-4.9
<u>Esophageal Atresia +/- Tracheoesophageal Fistula</u> (750.3)	1.39	3.9 (Colorado)	2.6 (Iowa)	1.9-2.6
<u>Exstrophy, Bladder</u> (753.5)	0.26	0.4 (Colorado)	0.2 (Iowa)	0.3-0.8
<u>Hypospadias- 2nd or 3rd Degree</u> (752.61)	59.2****	114.9**** (Colorado)	56.0**** (Iowa)	16.2-19.9
<u>Renal Dysplasia</u> (753.15)	0.74	NA		2.2-2.8
<u>Renal Agenesis/Hypoplasia</u> (753.0)	1.63	5.5 (Colorado)	6.1 (Iowa)	0.2-0.4
<u>Congenital Hydronephrosis</u> (753.2x)	39.7	NA		9.0-10.9
<u>Posterior Urethral Valve and/or Prune Belly</u> (753.60, 756.72)	0.51	2.7 (Colorado)	1.2 (Iowa)	0.4-1.0
<u>Gastroschisis</u> or <u>Omphalocele</u> (756.72, 756.73, 756.79)	5.12	6.6 (Colorado)	8.6 (Iowa)	3.5-3.9
<u>Diaphragmatic Hernia</u> (756.6)	1.67	3.1 (Colorado)	2.8 (Iowa)	1.8-2.1
<u>Limb Deficiency</u> (755.2-755.9)	1.53	4.1 (Colorado)	6.2 (Iowa)	3.2-4.3
<u>Sacral Agenesis</u> (756.13)	0.22	NA		NA

*U.S.-based surveillance programs is from the Iowa Registry for Congenital and Inherited Disorders and Colorado Responds to Children with Special Health Care Needs, 2007-2011. Birth Defects Research (Part A) 100: S1-S170 (2014);

EUROCAT prevalence rates are ranges for 2004-2012; *Data not available for anomalous coronary artery ****Hypospadias prevalence is per 10,000 male live births



Exposure groups, by timing of maternal Tdap

Exposed	Years	VSD sites
Tdap before 14 weeks gestation	2007-2013	All sites
Tdap at 27-36 weeks gestation¹	2010-2013	California sites
	2012-2013	Other sites
Tdap at any time in pregnancy	2007-2013	All sites

Comparison: Tdap unexposed pregnant women

1. Given differences in vaccine recommendations by year across sites, analysis of 27-36 weeks gestation were limited to 2010-2013 for California VSD sites and 2012-2012 other participating VSD sites