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# Identifying birth defects in automated data sources in the Vaccine Safety Datalink

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## Abstract

**Purpose—**The Vaccine Safety Datalink (VSD), a collaboration between the Centers for Disease Control and Prevention and several large healthcare organizations, aims to monitor safety of vaccines administered in the USA. We present definitions and prevalence estimates for major structural birth defects to be used in studies of maternal vaccine safety.

**Methods—**In this observational study, we created and refined algorithms for identifying major structural birth defects from electronic healthcare data, conducted formal chart reviews for severe cardiac defects, and conducted limited chart validation for other defects. We estimated prevalence

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

ETHICS STATEMENT

For this study, we analyzed data from seven participating Vaccine Safety Datalink (VSD) sites. The study was approved by the institutional review board at each participating VSD site and the Centers for Disease Control and Prevention.

SUPPORTING INFORMATION

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for selected defects by VSD site and birth year and compared these estimates to those in a US and European surveillance system.

**Results—**We developed algorithms to enumerate >50 major structural birth defects from standardized administrative and healthcare data based on utilization patterns and expert opinion, applying criteria for number, timing, and setting of diagnoses. Our birth cohort included 497 894 infants across seven sites. The period prevalence for all selected major birth defects in the VSD from 2004 to 2013 was 1.7 per 100 live births. Cardiac defects were most common (65.4 per 10 000 live births), with one-fourth classified as severe, requiring emergent intervention. For most major structural birth defects, prevalence estimates were stable over time and across sites and similar to those reported in other population-based surveillance systems.

**Conclusions—**Our algorithms can efficiently identify many major structural birth defects in large healthcare datasets and can be used in studies evaluating the safety of vaccines administered to pregnant women.

### Keywords

congenital anomalies; electronic health data; prevalence; validity; pharmacoepidemiology; pharmacoepidemiology

## INTRODUCTION

Vaccine and medication exposures during the first trimester of pregnancy are common.[1–4] Currently, few medications and no vaccines are classified as definite human teratogens.[5] Nevertheless, concerns persist regarding first trimester exposures to medications and vaccines where teratogenic risks are unknown.[6]

Only the inactivated influenza vaccine (IIV) is currently recommended for routine administration throughout pregnancy, including the first trimester.[7] The tetanus, reduced diphtheria, and acellular pertussis (Tdap) vaccines are preferentially administered in the third trimester.[8,9] Additional vaccines are recommended for reproductive age women; thus, unintentional exposures during pregnancy can occur.[10,11]

Large, linked databases, capturing both administrative and electronic healthcare data, provide a potentially robust system for examining associations between vaccine exposures during pregnancy and birth defect risk in offspring. The Vaccine Safety Datalink (VSD), a collaboration between the Centers for Disease Control and Prevention's Immunization Safety Office and several large integrated healthcare systems in the USA, is one such system.[12] The VSD includes data on approximately 2.5 million reproductive age women and over 100 000 live births annually.

To date, the VSD has been used to describe receipt of Tdap and IIV in pregnant women[3,9,13] and to estimate rates of inadvertent vaccination during pregnancy.[14] The VSD has also reported on maternal vaccine safety, focusing on obstetric and birth out-comes.[9,15–19] Birth defect risk following maternal vaccination has not been extensively studied within the VSD. Prior work by others highlighted difficulties in accurately enumerating birth defects from hospital discharge or birth certificate data.[20–25] As an alternative, many systems evaluating

birth defects rely on expert adjudication of healthcare records[26]; however, this process can be time-intensive and cost-intensive. Strategies are needed to study maternal exposures and birth defect risk that take advantage of clinical data warehouses, including inpatient and outpatient diagnoses over time, and do not require manual chart abstraction. We aim to describe and validate an approach for efficiently identifying birth defects among live births within the VSD from automated data sources, for use in studies of maternal vaccine safety.

## METHODS

In this observational study, we developed a list of selected major structural birth defects, created and refined algorithms for identifying these defects from standardized electronic healthcare data, conducted limited chart validation, and compared prevalence estimates within the VSD with those in population-based surveillance systems. Members of our research team, with clinical and research expertise in pediatrics (EOK, JDN), maternal fetal medicine (HSL), epidemiology (GVB, AN), birth defect surveillance and epidemiology (PAR), pediatric cardiology (SS), and pharmacoepidemiology (TC), reviewed specific birth defect diagnoses, groupings of defects, and criteria for diagnostic certainty as applied for case classification in the National Birth Defects Prevention Study[27] and in the European Surveillance of Congenital Anomalies (European Registration of Congenital Anomalies and Twins (EUROCAT)).[28] We focused on isolated birth defects that would likely require urgent or emergent medical attention and would significantly impact health or long-term function.[29] We did not consider minor defects[30] or defects primarily attributed to prematurity. In addition, we excluded anencephaly as many cases are detected prenatally and electively terminated[31]; these cases would be difficult to detect in our current data sources. Defects selected were grouped by organ system: central nervous system, opthamologic, otologic, cardiac, orofacial/respiratory, gastrointestinal, genitourinary/renal, and musculoskel-etal. Cardiac defects were also classified as severe (requiring emergent intervention) versus other cardiac defects.

### Algorithms for non-cardiac birth defects

Starting with our list of major structural birth defects (Table 1), we applied an iterative process, guided by data and expert opinion, to develop algorithms for each defect. We created a cohort of all pregnant women aged 14–49 years with live births at any of the seven VSD sites from January 2004 to September 2013. Women were required to have continuous insurance enrollment from 6 months prior to conception to 6 weeks after delivery. Infants surviving to age 1 year were required to have continuous insurance enrollment for at least 4 months, including 1 month in the first 3 months of life, and to have at least one outpatient visit.

We selected infants with at least one *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) code for a birth defect from Table 1; created data tables for each defect with number, timing, and setting of diagnoses (inpatient/emergency versus outpatient) stratified by VSD site; and identified deaths occurring before age 1 year from standardized mortality files. The VSD generates these files from state death records and administrative and electronic health data. We reviewed these tables to identify

patterns in healthcare utilization, considering typical clinical presentations and expected age at diagnosis; limited chart reviews were conducted (by EOK) for all birth defects at one VSD site. Next, algorithms for each defect were evaluated across the VSD live birth cohort. Variability by VSD site and birth year, along with comparisons to expected prevalence estimates, was evaluated. Lastly, algorithms were refined, and several defects were excluded, as described in the succeeding texts.

### Algorithms for severe cardiac defects

As the most prevalent group of birth defects, we developed and validated algorithms for severe cardiac defects, by using formal chart reviews within a subset of the VSD birth cohort. We selected live births from January 2007 to December 2011 from two VSD sites, having at least one ICD-9-CM code for a severe cardiac defect (Table 1) and minimum insurance enrollment of 3 months prior to age 1 year. Minimum enrollment criteria were not applied in cases of infant mortality. For chart validation of severe cardiac defects, infants with chromosomal syndromes or congenital rubella syndrome were excluded. To focus on cases where final diagnosis could be confirmed, we selected cases with at least one cardiac procedure (cardiac surgery, cardiac catheterization, or echocar-diogram) and with the medical record available for review. Trained chart abstractors reviewed records for clinical encounters occurring up to age 1 year. For each potential case, abstractors recorded impressions from each echocardiogram, cardiac catheterization, or cardiac surgery into REDCap.[32] Final classification of case status was made by a pediatrician (EOK) in consultation with a pediatric cardiologist (SS), with intraoperative diagnoses considered as the definitive diagnoses. Results of cardiac catheterization or echo-cardiogram were used if intraoperative diagnoses were not available. Data from one VSD site were used for algorithm development, and data from the second VSD site were used for validation. Algorithms aimed to maximize the positive predictive value (PPV) and minimize false negatives. PPV and false negative rates are reported, with associated 95% confidence intervals (CIs) for development and validation samples.

### Prevalence estimates

We applied algorithms developed for each birth defect to estimate prevalence by VSD site and birth year. Between-site variability in prevalence was estimated by using the coefficient of variation. We compared defect prevalence estimates within the VSD cohort to those reported in US state-based Iowa Registry for Congenital and Inherited Disorders and the EUROCAT. These surveillance systems were selected for comparison, as they have validated methodologies and publicly available data for most defects. Iowa conducts active surveillance with cases validated through chart review and expert adjudication. EUROCAT is a network of 43 population-based congenital anomaly registries and includes data from 23 European countries with 1.7 million births per year. Registries reporting to EUROCAT agree to apply standardized case definitions and conduct routine data quality monitoring.

# RESULTS

## Non-cardiac birth defects

Our VSD birth cohort included 497 894 infants across seven VSD sites, including 40 704 (8.2%) with at least two birth defect diagnoses in different encounters (ICD-9-CM codes 740.0–759.9) and 21 702 (4.4%) with at least one ICD-9-CM code retained from the initial list of >50 major structural birth defects (Table 1). Characteristics of this population are in Table 2.

Review of the number, timing, and setting of birth defect diagnoses (Supplementary data table), along with our limited chart reviews at one VSD site, allowed for optimization of algorithms (Table 3). For example, we identified seven potential cases of pyloric stenosis at one VSD site by using ICD-9-CM code 750.5. Of these, three confirmed cases all had an inpatient pyloric stenosis diagnosis, and the four "false positive" cases had only outpatient diagnoses; thus, our algorithm for pyloric stenosis required an inpatient diagnosis. Similarly, of the four potential cases of choanal atresia/stenosis, two confirmed cases had many (≥5) outpatient diagnoses, whereas the two false positive cases each had one outpatient diagnosis; thus, our algorithm for choanal atresia/stenosis required ≥2 outpatient diagnoses.

We excluded four birth defects due to lack of specificity in their corresponding ICD-9-CM codes. Specifically, chart reviews for seven infants with ICD-9-CM code 762.8x: "Other specified abnormalities of the chorion and amnion," identified one infant with amniotic band syndrome. The expected prevalence of cloacal exstrophy is approximately 1 per 200 000 live births,[33] yet by using ICD-9-CM code 751.5: "Other anomalies of the intestine" at one VSD site with 15 598 births, seven potential cases were identified. On chart review, none of the seven cases had cloacal exstrophy. For craniosynostosis, estimates across the VSD cohort were 10-fold higher than the expected prevalence of 4 per 10 000 live births[34]; chart review confirmed only 2 of 13 potential cases with ICD-9-CM code 756.0: "Anomalies of skull and face bones." Even with a specific ICD-9-CM code, 742.3, for congenital hydrocephalus, chart review identified that 7 of 11 potential cases were acquired hydrocephalus.

Using automated codes, some birth defects could not be distinguished from other similar defects. For example, until October 2009, gastroschisis and omphalocele shared a single ICD-9-CM code (756.79) and were reported as a single outcome. Although there are separate ICD-9-CM codes for cleft palate (749.0), cleft lip (749.1), and cleft palate with cleft lip (749.2), cases often had two or three of these codes. Because we could not distinguish between the cleft types without chart review, we grouped these as "cleft lip and/or cleft palate." The final list of major structural birth defects is in Table 3.

## Cardiac defects

Based on ICD-9-CM codes alone from one VSD site, we identified 163 potential cases with 1 of 15 prespecified severe cardiac defects (Table 1). Of these, 89 had an echocardiogram, cardiac catheterization, or cardiac surgical procedure, and 49 received care within the health system. Charts were unavailable for 5 of the 49; thus, chart abstraction was completed for 44 potential cases.

We found that one ICD-9-CM code (747.3: “Anomalies of pulmonary artery”) occurred in 11 of 44 potential cases and was a source for error. After reviewing echocardiogram reports, along with consultation notes from pediatric cardiologists, these 11 cases all had peripheral pulmonary stenosis, a benign condition; therefore, our final sample for algorithm development comprised 33 cases, excluding pulmonary stenosis (ICD-9-CM code 747.3).

Using these 33 cases, we tested two algorithms: (1) one inpatient or two outpatient diagnoses (or one inpatient or outpatient diagnosis in cases of infant mortality) with 30 cases identified and (2) two inpatient or one inpatient and one outpatient diagnosis (or one diagnosis in cases of infant mortality), with 26 cases identified. The PPV was 77% (n = 23/30), 95% CI: 58–90% for algorithm 1 and 88% (n = 23/26), 95% CI: 70–97% for algorithm 2. Our validation sample from the second VSD site comprised 64 potential severe cardiac defect cases based on ICD-9-CM codes. Of these, 34 had an echocardiogram, cardiac catheterization, or cardiac surgery. Two of the 34 had an ICD-9-CM code of 747.3 and were excluded, leaving 32 potential cases in the validation sample. The PPV in our validation sample was 100% (95% CI: 89–100%) for both algorithm 1 and algorithm 2. There was one false negative in the validation sample, resulting in a 3% (95% CI: 0–16%) false negative rate.

## Prevalence estimates for selected major structural birth defects in the Vaccine Safety Datalink population

To provide further face validity for our final list of major structural birth defects and algorithms (Table 3 ), we estimated prevalence for each defect or group of defects and compared estimates to those published for Iowa's state-based birth defects surveillance program and for the European birth defects surveillance system (EUROCAT). For many defects, prevalence estimates in the VSD were close to those reported in other surveillance systems. As examples, anotia/microtia occurred in 2.5 per 10 000 VSD live births from 2004 to 2013 compared with 2.4 in Iowa per 10 000 live births for the period 2007–2011. Respective estimates for biliary atresia were 1.2 in the VSD and 0.5 in Iowa per 10 000 live births. For other defects, prevalence estimates in the VSD were similar to those reported in EUROCAT. For example, from 2004 to 2013, spina bifida occurred in 1.9 per 10 000 VSD live births compared with 1.7–2.0 per 10 000 EUROCAT live births from 2004 to 2012. Also, estimates for congenital diaphragmatic hernia were 1.7 in the VSD and 1.8–2.1 in EUROCAT per 10 000 live births. For some defects, such as micro-cephaly and congenital hydronephrosis, estimates in the VSD, based on diagnostic code algorithms, remained higher than those from the selected population-based surveillance systems (Table 4).

For the period 2004–2013, the period prevalence estimate for all selected major structural defects was 1.7 per 100 live births, with a 2.6% ($p < 0.001$) relative increase per year (Figure 1). The lower prevalence of birth defects in 2013 is due to truncation of the follow-up period. We also evaluated prevalence by organ system. Cardiac defects were the most common group of defects, followed by genitourinary and gastrointestinal defects (Figure 2). Based on the diagnosis code algorithm, severe cardiac defects occurred in 16.9 per 10 000 live births. If also requiring a diagnostic imaging or surgical procedure, this rate would

decrease to 13.0 per 10 000 live births. Coefficients of variation (by VSD site) ranged from 3.1% for facial and respiratory defects to 11.8% for central nervous system defects.

## DISCUSSION

This report describes an innovative approach for identifying infants with major structural birth defects by using healthcare data from a large VSD birth cohort. Through review of healthcare utilization patterns and expert opinion, our multidisciplinary team developed and optimized algorithms for selected major structural birth defects, applying minimum criteria for number, timing, and setting of diagnoses. Requiring a single ICD-9-CM code in the first year of life, we estimated a 4.4 per 100 live births period prevalence for these defects in the VSD cohort. Applying our algorithms, the period prevalence for the same defects in the VSD cohort was 1.7 per 100 live births. These estimates are similar to the frequently cited background rate of major birth defects in the USA of 3 per 100 live births.[35] For most specific defects, with application of our algorithms, prevalence estimates were similar to those reported in the Iowa or European surveillance systems.

Along with automated review of data, we applied validation procedures for severe cardiac defects, due to their increased prevalence and prior research demonstrating the inconsistent validity of cardiac defect ICD-9-CM codes. A study of hospital discharge data for 66 infants born in 2001 at one Minnesota hospital reported a PPV of 36% for all cardiac defect discharge diagnoses. The low PPV in this cohort was attributed, in part, to including patients with minor cardiac defects, related to prematurity.[21] A comparison of birth records and claims data at hospital discharge for Medicaid patients born in Tennessee from 1985 to 2000 produced a PPV of 67% for detecting cardiac defects through inpatient claims or birth certificate data.[22] More recently, a study of live births delivered from 2001 to 2007 at 11 integrated health systems that compared administrative, claims, and birth certificate data to those available through chart review reported that use of ICD-9-CM codes alone produced PPV of 71% for detecting a cardiac defect; however, for specific cardiac defects, PPVs were higher (e.g., ventricular septal defects 95%).[36] We were reassured that in our validation sample, when requiring a cardiac imaging procedure or intervention, along with two inpatient or one inpatient and one outpatient diagnoses, we achieved a PPV of 100% (89–100%) for identifying a severe cardiac defect. To be parsimonious with algorithms for other defects, our final algorithms for any cardiac defect and severe cardiac defects were based on diagnoses alone. We did not require imaging or other procedures and did not exclude infants with chromosomal syndromes or congenital infections.

Using an iterative process, we identified major structural birth defects that could be consistently identified within large linked databases across multiple health systems, and our algorithms took advantage of longitudinal data over the first year of life. Infants with these defects generally have multiple medical visits after hospital discharge. Strengths of our approach include our access to a large, geographically diverse sample of births over a 10-year period and the ability to perform chart validation for a subset of births. In the end, we strived for a balance between sensitivity and specificity. For example, we excluded defects, such as craniosynostosis and cloacal exstrophy, which lack a specific ICD-9-CM code. Conversely, we retained mi-crocephaly, where prevalence in the VSD was higher than that

observed in EUROCAT, but close to other reported background rates (2 to 12 per 10 000, from the National Birth Defects Prevention Network).[37] Microcephaly can be challenging to confirm or rule out, even with expert adjudication,[38] but remains an important outcome for public health monitoring.[39]

Several limitations with our work should be noted. First, we were not able to conduct chart validation of birth defects at each VSD site and thus cannot report positive and negative predictive values for each defect examined. Instead, we relied on alternative strategies for validation, exploring variability of prevalence estimates for defects by site and birth year, and comparing estimates in the VSD to other surveillance programs. Our definitions are for use in ongoing studies of maternal vaccine safety and not intended to replace existing population-based birth defect surveillance programs. Second, although it would be important to enumerate defects occurring in cases of fetal demise and planned terminations, this was not possible within our automated data structure; thus, prevalence estimates reported should only be compared with other live birth populations. Third, our algorithms are specific to ICD-9-CM codes. Additional work would be needed for use with ICD-10-CM diagnoses. Similarly, although we explored the addition of diagnostic imaging or procedure codes for refining algorithms for non-cardiac defects, we ultimately selected algorithms based on the number and timing of diagnostic codes alone. Finally, our population is not representative of the US population. It was limited to women with continuous insurance enrollment and at least one medical visit during pregnancy. Our population may not include women at highest risk for having an infant with a birth defect.

To date, studies on maternal vaccination during pregnancy and risks for birth defects in offspring have been largely reassuring. For influenza vaccines, data on more than 25 000 women vaccinated during pregnancy have not detected increased risks for birth defects.[40] Results from passive and active surveillance have not revealed increased risks for other vaccines that may be administered during pregnancy; however, prior studies have been limited by varied definitions for birth defects, use of non-biologically feasible exposure windows (beyond first trimester), and insufficient power. Although inadvertent or unintentional vaccination affects <1% of pregnancies, IIV is now administered in approximately one-half of pregnancies with 30% of these vaccinations in the first trimester[3,14]; thus, there is a need for continued monitoring of potential risks. The algorithms we describe can be used in ongoing investigations of maternal vaccine safety.[41]

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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**KEY POINTS**

- Large, linked databases, capturing both administrative and electronic healthcare data, provide a potentially robust system for examining associations between vaccine exposures during pregnancy and risks for birth defects in offspring.
- Algorithms can be developed for efficiently and accurately enumerating many major structural birth defects in large linked healthcare datasets.
- Some defects, enumerated in other birth defect surveillance systems, could not be identified due to lack of specificity in their ICD-9-CM codes.
- For many structural birth defects, prevalence rates in the Vaccine Safety Datalink were stable across sites and similar to those reported in population-based surveillance systems.

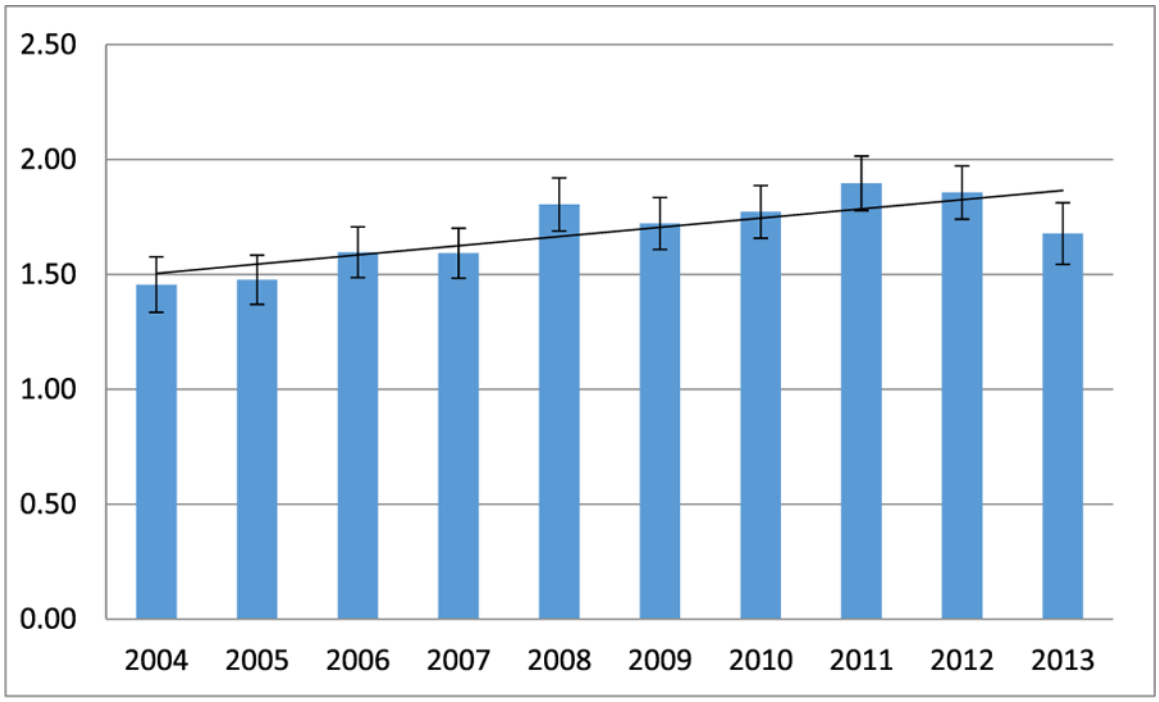


**Figure 1.**

Prevalence estimates of selected major structural birth per 100 live births defects across seven Vaccine Safety Datalink sites, by year 2004–2013. Period prevalence rate is 1.7 per 100 live births with a 2.6% change increase per year. The lower prevalence of birth defects in 2013 is due to truncation of the follow-up period

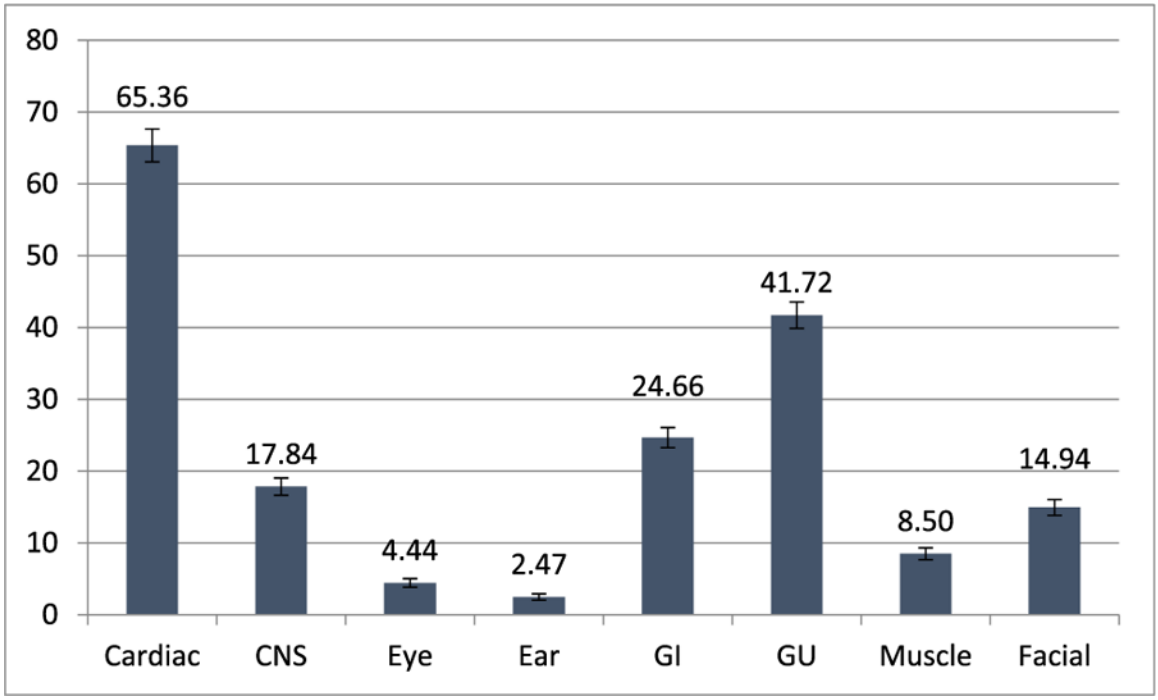


**Figure 2.**

Prevalence estimates and 95% confidence intervals of selected major birth defects per 10 000 live births, by system, 2004–2013. CNS, central nervous system; GI, gastrointestinal; GU, genitourinary/renal; Muscle, Musculoskeletal; Facial, orofacial

**Table 1.**

Initial list of major structural birth defects for enumeration in studies of maternal vaccine safety

| Organ system | Defects | ICD-9 codes |
|---|---|---|
| Central nervous system | Encephalocele, cranial meningocele, encephalomyelocele | 742.0 |
| | Spina bifida | 741.0, 741.9 |
| | Holoprosencephaly | 742.2 |
| | Hydrocephalus (with or without Dandy–Walker or other structural lesion)—*excluded from final list* | 742.3 |
| | Microcephalus | 742.1 |
| Eye | Anophthalmia, microphthalmia | 743.00, 743.10−743.12 |
| | Cataracts and other lens defects | 743.30−743.36 |
| | Glaucoma and anterior segment defects without aniridia | 743.2x |
| Ear | Anotia, microtia | 744.01, 744.23 |
| Heart | Laterality defects—heterotaxy | 759.3 |
| | Septal heart defects | 745.4, 745.8, 745.9 |
| | Severe cardiac defects: single ventricle, tricuspid atresia, ebstein anomaly, hypoplastic left heart, hypoplastic right heart, common truncus, transposition of great vessels, atrioventricular septal defects, tetralogy of fallot, pulmonary stenosis—*excluded from final list*, aortic atresia/stenosis, coarctation, total anomalous pulmonary venous return, anomalous coronary artery | 745.0, 745.1, 745.2−745.3, 745.6, 746.00, 746.1−746.3, 746.7, 746.85, 747.1, 747.41 |
| Orofacial/respiratory | Choanal atresia/stenosis | 748.0 |
| | Cleft lip ± palate | 749.1, 749.10−749.14, 749.2, 749.20−749.25 |
| | Cleft palate | 749.0, 749.00−749.04 |
| Gastrointestinal | Biliary atresia | 751.61 |
| | Esophageal atresia ± tracheoesophageal fistula | 750.3 |
| | Intestinal atresia/stenosis | 751.1, 751.2 |
| | Pyloric stenosis | 750.5 |
| Genitourinary/renal | Exstrophy, bladder | 753.5 |
| | Exstrophy, cloacal—*excluded from final list* | 751.5 |
| | Hypospadias—second or third segree | 752.61 |
| | Renal agenesis/hypoplasia | 753.0x |
| | Renal dysplasia | 753.16 |
| | Congenital hydronephrosis | 753.20 |
| | Posterior urethral valve and/or prune belly | 753.60, 756.71 |
| Musculoskeletal | Gastroschisis or omphalocele | 756.72, 756.73, 756.79 |

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| Organ system | Defects | ICD-9 codes |
|---|---|---|
| | Diaphragmatic hernia | 756.6 |
| | Limb deficiency | 755.2–755.9 |
| | Amniotic bands—*excluded from final list* | 762.8 |
| | Sacral agenesis | 756.13 |
| | Craniosynostosis—*excluded from final list* | 756.0 |

**Table 2.**

Characteristics of the Vaccine Safety Datalink live birth cohort

| **Characteristic** | ***N* = 497 894** | |
|---|---|---|
| | ***N*** | **%** |
| Birth year | | |
| 2004 | 39 362 | 7.9 |
| 2005 | 50 653 | 10.2 |
| 2006 | 51 806 | 10.4 |
| 2007 | 52 881 | 10.6 |
| 2008 | 53 411 | 10.7 |
| 2009 | 53 090 | 10.7 |
| 2010 | 52 863 | 10.6 |
| 2011 | 52 963 | 10.6 |
| 2012 | 54 237 | 10.9 |
| 2013 | 36 655 | 7.4* |
| Infant race/ethnicity | | |
| Asian | 77 212 | 15.5 |
| African American | 36 685 | 7.4 |
| Hispanic | 145 535 | 29.2 |
| White, non-Hispanic | 195 088 | 39.2 |
| Other | 43 374 | 8.7 |
| Maternal age (years) | | |
| <18 | 6492 | 1.3 |
| 18–24 | 64 637 | 13.0 |
| 25–34 | 305 813 | 61.4 |
| ≥35 | 120 952 | 24.3 |
| Prenatal care in first trimester | 450 000 | 90.4 |
| APNCU index | | |
| Adequate/plus | 355 065 | 71.3 |
| Intermediate | 100 080 | 20.1 |
| Inadequate | 42 749 | 8.6 |
| Maternal prepregnancy diabetes | 6052 | 1.2 |
| Maternal neoplasm | 1530 | 0.3 |
| Maternal use of teratogenic medication† | 11 501 | 2.3 |
| Infant chromosomal syndrome‡ | 1497 | 0.3 |
| Infant congenital infection§ | 177 | <0.1 |

APNCU, Kotelchuck Adequacy of Prenatal Care Utilization Index; VSD, Vaccine Safety Datalink.

*2013 Live births in 2013 were limited to those between 2013 January 1 to 30 September 2013.

†Maternal medication use identified from pharmacy claims.

‡Chromosomal syndromes identified from ICD-9-CM codes (758.0–758.3, 758.6, 758.7, 279.11).

[§]Infant congenital infections identified from ICD-9-CM codes for rubella, syphilis, varicella, cytomegalovirus, and toxoplasmosis (052.x, 056.x, 078.5x, 090.x, 091.x-097.x, 130.x, 771.0–771.2).

**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) | One inpatient diagnosis *or two* outpatient diagnoses *or* one outpatient diagnosis *and* death in first year |
| | Holoprosencephaly (742.2) | Two outpatient diagnoses *or* one 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) | Two outpatient diagnosis *or* one outpatient diagnosis *and* death in first year |
| Ear | Anotia, microtia (744.01, 744.23) | Two outpatient diagnoses *or* one diagnosis *and* death in first year |
| Cardiac | Severe cardiac defects: single ventricle, tricuspid atresia, ebstein 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) | Two inpatient diagnoses *or* one inpatient *and* one outpatient diagnosis *or* one diagnosis (inpatient or outpatient) *and* death in first year |
| | Other cardiac defects: septal defects, heterotaxy, papvr (745.4, 745.8, 745.9, 747.42, 759.3) | Two diagnoses (inpatient or outpatient) *or* one diagnosis *and* death in first year |
| Orofacial/respiratory | Choanal atresia/stenosis (748.0) | Two outpatient diagnoses *or* one 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) | One inpatient diagnosis *or two* outpatient diagnoses *or* one outpatient diagnoses *and* death in first year |
| Gastrointestinal | Biliary atresia (751.61); intestinal atresia/stenosis (751.1, 751.2) | One inpatient diagnosis *or two* outpatient diagnoses *or* one outpatient diagnosis *and* death in first year |
| | Esophageal atresia ± tracheoesophageal fistula (750.3) | Two outpatient diagnoses *or* one inpatient *and* one outpatient diagnosis *or* one inpatient *or* outpatient diagnosis *and* death in first year |
| | Pyloric stenosis (750.5) | One inpatient diagnosis *or* one outpatient diagnosis *and* death in first year |
| | Exstrophy, bladder (753.5) | One inpatient diagnosis by 3 months of age *and* one outpatient diagnosis by 1 year *or* one inpatient diagnosis *and* death in the first year |
| Genitourinary/renal | Hypospadias—second or third degree (752.61); renal dysplasia (753.15) | Two outpatient diagnoses *or* one outpatient diagnosis *and* death in first year; hypospadias limited to males |
| | Renal agenesis/hypoplasia (753.0) | One inpatient diagnosis *and* one outpatient diagnosis *or* one diagnosis (inpatient or outpatient) *and* death in first year |
| | Congenital hydronephrosis (753.2x); posterior urethral valve and/or prune belly (753.60, 756.71) | Two outpatient diagnoses *or* one diagnosis (inpatient or outpatient) *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) | One inpatient diagnosis by 3 months of age *or* one inpatient diagnosis *and* death in first year |
| | Limb deficiency (755.2–755.9) | One inpatient *or two* outpatient diagnoses *and* one diagnosis within 3 months *or* one inpatient *or* outpatient diagnosis *and* death in first year |
| | Sacral agenesis (756.13) | One inpatient diagnosis *or two* outpatient diagnoses *or* one diagnosis (inpatient or outpatient) *and* death in first year |

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**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 Iowa's surveillance program* per 10 000 live births (2007–2011) | Rates in EUROCAT per 10 000 live births† (2004–2012) |
|---|---|---|---|
| Encephalocele, cranial meningocele, encephalomyelocele (742.0) | 0.64 | 1.0 | 0.23–0.44 |
| Spina bifida (741.0x, 741.9x) | 1.89 | 4.3 | 1.68–2.0 |
| Microcephalus (742.1) | 12.9 | NA | 2.12–2.96 |
| Holoprosencephaly (742.2) | 3.29 | 1.7 | 0.23–0.40 |
| Anophthalmia, microphthalmia (743.00, 743.10–743.12) | 0.82 | 2.2 | 0.61–0.96 |
| Cataracts and other lens defects (743.30–743.36, 743.2x) | 3.76 | 2.7 | 1.3–1.7 |
| Anotia, microtia (744.01, 744.23) | 2.5 | 2.4 | 0.20–0.45 |
| Severe cardiac defects: single ventricle, tricuspid atresia, ebstein 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) | 16.9 | 34.9‡ | 16.6–20.0 |
| Choanal atresia/stenosis (748.0) | 0.52 | 1.6 | 0.6–1.0 |
| Cleft lip and/or cleft palate (749.1, 749.10–749.14, 749.2, 749.20– 749.25, 749.0, 749.00–749.04) | 14.5 | 16.9 | 12.1–14.7 |
| Biliary atresia (751.61) | 1.16 | 0.5 | NA |
| Intestinal atresia/stenosis (751.1, 751.2) | 7.75 | 8.4 | 4.1–4.9 |
| Esophageal atresia tracheoesophageal fistula (750.3) | 1.39 | 2.6 | 1.9–2.6 |
| Exstrophy, bladder (753.5) | 0.26 | 0.2 | 0.3–0.8 |
| Hypospadias—second or third degree (752.61) | 59.2§ | 56.0§ | 16.2−19.9 |
| Renal dysplasia (753.15) | 0.74 | NA | 2.2–2.8 |
| Renal agenesis/hypoplasia (753.0) | 1.63 | 6.1 | 0.2−0.4 |
| Congenital hydronephrosis (753.2x) | 39.7 | NA | 9.0−10.9 |
| Posterior urethral valve and/or prune belly (753.60, 756.71) | 0.51 | 1.2 | 0.4–1.0 |
| Gastroschisis or omphalocele (756.72, 756.73, 756.79) | 5.12 | 8.6 | 3.5−3.9 |
| Diaphragmatic hernia (756.6) | 1.67 | 2.8 | 1.8−2.1 |
| Limb deficiency (755.2–755.9) | 1.53 | 6.2 | 3.2−4.3 |
| Sacral agenesis (756.13) | 0.22 | NA | NA |

*US-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.