CBER SENTINEL ASSESSMENT

DEVELOPING THE INFRASTRUCTURE TO CONDUCT SURVEILLANCE OF BIRTH OUTCOMES FOLLOWING MATERNAL VACCINATION: A PROJECT USING INFLUENZA VACCINES AND BIRTH OUTCOMES AS A USE CASE

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The Sentinel System is sponsored by the U.S. Food and Drug Administration (FDA) to proactively monitor the safety of FDA-regulated medical products and complements other existing FDA safety surveillance capabilities. The Sentinel System is one piece of FDA's Sentinel Initiative, a long-term, multi-faceted effort to develop a national electronic system. Sentinel Collaborators include Data and Academic Partners that provide access to healthcare data and ongoing scientific, technical, methodological, and organizational expertise. The Sentinel Coordinating Center is funded by the FDA through the Department of Health and Human Services (HHS) Contract number HHSF223201400030I. This project was funded by the FDA through HHS Mini-Sentinel contract number HHSF223200910006

History of Modifications

Version	Date	Modification	By
V2	2/6/2019	Removed original Figure 3 and original Appendix B due to data error and replaced related text with corrected data.	Influenza vaccines and birth outcomes working group

CBER Sentinel Product Assessment

Developing the Infrastructure to Conduct Surveillance of Birth Outcomes Following Maternal Vaccination: A Project Using Influenza Vaccines and Birth Outcomes as a Use Case

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I. INTRODUCTION

Maternal vaccination with inactivated influenza vaccines (IIV) and pertussis-containing vaccines during pregnancy is recommended to protect mothers and infants against influenza and pertussis related illness. Clinical trials typically exclude pregnant populations, and post-marketing data on the safety of vaccine use during pregnancy are scarce or subject to limitations. These limitations include that they may lack information on population denominators or that they only assess outcomes in exposed individuals, without formal comparators. To address some of these limitations, several large scale epidemiologic surveillance systems within the United States have been established. The Vaccine Safety Datalink is sponsored by the CDC and is a collaboration between nine medical care organizations that uses claims and electronic health records from several regional health plans. The Vaccines and Medications in Pregnancy Surveillance System (VAMPSS) is coordinated by the Boston University and the American Academy of Allergy Asthma and Immunology and conducts prospective cohort and case-control surveillance using data collected for research purposes.

The FDA-sponsored Sentinel System is a large-scale active surveillance system developed to monitor the safety of marketed medical products. The Post-Licensure Rapid Immunization Safety Monitoring (PRISM) system conducts vaccine-related surveillance within Sentinel and is a partnership between FDA, six Data Partners, and Harvard Pilgrim Health Care Institute, which acts as the Sentinel Coordinating Center. PRISM uses claims data that are updated on an approximately quarterly schedule. Strengths of Sentinel include its large population size (>500,000 live births) and that it includes members from several national health insurers across the United States.

To complement other post-marketing safety surveillance systems, we assessed the feasibility of conducting safety surveillance of vaccine use during pregnancy within Sentinel's PRISM program. For this activity, we focused on developing capabilities to assess infant birth outcomes following maternal vaccination exposure during pregnancy. We assessed the feasibility of developing data infrastructure and identifying key data elements for an exposure-outcome pair selected as an example for methods development ("use case"), maternal influenza vaccination during pregnancy and cleft lip/palate in the infant. The use case was selected based on the universal recommendation for influenza vaccination in all pregnant women, and the early and relative ease of identifying cleft lip/palate at birth in the Sentinel database. The selection of cleft lip/palate as the use case was not based on any concern or evidence regarding an association between influenza vaccine and cleft lip/palate. Other malformations (e.g., cardiac defects) might not be identified until months or years following birth. We also explored the feasibility of utilizing the case-time-control study design to assess the use case association.

The specific aims of the project were the following:

A. PRIMARY AIMS

Aim 1: To establish and describe a cohort of mother-infant pairs within the Sentinel Distributed Database, as infrastructure for use in future potential studies of vaccination safety during pregnancy

Aim 2: To evaluate the validity of claims-based algorithms for gestational age and the use case outcome (cleft lip/palate), through retrospective medical record review

B. EXPLORATORY AIM

Aim 3: To explore the feasibility of using a case-time control study design to evaluate the use case association (maternal influenza vaccination during pregnancy and cleft lip/palate in the infant)

II. AIM 1: ESTABLISHING A COHORT OF MOTHER-INFANT PAIRS

A. METHODS

1. Study population and data sources

The study population for establishing the cohort of mother-infant pairs consisted of females 10 through 55 years of age with pregnancies ending in a live birth delivery, and their offspring. Live births were included if the mother had a minimum of 180 days of continuous enrollment prior to the estimated start of pregnancy through 30 days after the delivery, to maximize capture of confounders prior to the start of pregnancy and exposures during pregnancy. Infants were included if they were born during the period of interest and had at least one day of enrollment.

Four large Sentinel partners ("Data Partners") who provide claims data to the Sentinel Distributed Database participated in all aims of the project: Aetna, Health Core, Humana, and Optum. The dates of availability varied between Data Partners, but overall, we included live births occurring from 2005 through 2012.

We included claims data on mothers and infants available in the Sentinel Common Data Model, including demographic, diagnosis, procedure, and pharmacy dispensing data [1]. To develop capabilities to assess infant outcomes following maternal exposures during pregnancy, the Data Partners linked live births identified in maternal records in the Sentinel Distributed Database to infants.

Additionally, birth certificate data from select vital events registries from 9 states (**Table 1**) were linked to the maternal and infant claims data. One of the 4 participating Data Partners developed the processes for matching mothers to birth certificate data and completed the matches in pilot work prior to the start of this activity. The remaining 3 Data Partners completed the matches of mothers to birth certificate data as part of this activity. Descriptive results on birth certificate matches from all 4 Data Partners are included in this report.

Table 1. States for birth certificate matching*

Data Partner	States for birth certificate matching
Data Partner 1	Colorado, Florida, Georgia, Pennsylvania, Virginia
Data Partner 2	California, Georgia, Missouri, Virginia
Data Partner 3	Colorado, Florida, Georgia, Louisiana, Utah
Data Partner 4	Colorado, Georgia

*States for birth certificate matching varied by Data Partner; in total, there were 16 unique matches between Data Partners and states

2. Identifying and linking live deliveries identified in maternal records to infants

The Sentinel Coordinating Center distributed a program to the Data Partners to identify live births within the Sentinel Distributed Database. Live births were identified using ICD-9-CM diagnosis and procedure codes and CPT codes listed in Appendix A. To avoid capturing post-partum visits, delivery codes were excluded if they were preceded by another delivery code in the prior 273 days.

Infants with at least one day of enrollment were identified in the Sentinel Distributed Database. Of note, we later required continued infant enrollment following birth, as not all congenital anomalies are diagnosed at birth. After the Data Partners executed the distributed program to identify live births, the information from the Sentinel Distributed Database was re-linked to the Data Partner's administrative

source data (not included in the Sentinel Distributed Database) to determine patient's names, addresses, facility of delivery, and subscriber IDs. (The subscriber ID indicates the primary insured individual, so that all family members under the same health insurance policy have the same subscriber ID). These identifiers were used to link the mothers to infants that were delivered, and to create files to transfer to state Departments of Health for linkage to birth certificates. The linkage and transfer of information was conducted by Data Partners, who followed procedures for assuring patient confidentiality.

The deliveries identified in maternal records were linked to infants using computer code written and executed locally by the Data Partners. The code was written based on written guidance from the Sentinel Coordinating Center as follows. First, the Data Partners attempted to link mothers and infants based on a match on (1) the subscriber ID and (2) the infant's date of birth and mother's dates for the delivery hospitalization (i.e., the infant's date of birth was within the period 3 days prior to the date of admission through the date of discharge). Next, for the remaining unlinked mothers and infants, the Data Partners attempted to form linkages by requiring a match on (1) last names and addresses, and (2) the infant's date of birth and mother's dates for the delivery hospitalization (i.e., the infant's date of birth was within the period 3 days prior to the date of admission through the date of discharge).

As part of the mother-to-infant linkage process, each Data Partner created a standardized linkage table that was retained locally for analyses of the mother-infant cohort. The table included the following information: the mother and child's patient identifiers, the admission and discharge dates for the delivery, the child's date of birth, the method for linkage, and whether the delivery was a singleton or a multiple birth.

3. Linking administrative data to birth certificate data

After the internal mother to infant linkage process using the Data Partner administrative source data, linked mother-infant pairs were matched to birth certificate data (only applicable for the subset of states for which matches to birth certificates were conducted) to obtain data not completely captured in health plan data (e.g., gestational age at birth, race/ethnicity, tobacco use). Unlinked mothers and unlinked infants were also matched to birth certificate data in attempts to form additional mother to infant linkages (if they both matched to the same birth certificate).

Each Data Partner submitted applications to request birth certificate data from the state Departments of Health. Separate applications were required by each Data Partner for each state. After the applications were approved, the Data Partners and Departments of Health signed legal and/or data use agreements to protect personal health information, specify a secure data transfer mechanism, and define the appropriate use of pregnancy and birth data. Two possible pathways were used to match the health plan data with birth certificate data. For all but one state, demographic data were provided to the Departments of Health to perform the matching. In one state (California), the Department of Health provided the birth certificate data to the Data Partners to perform the matching. The linkage algorithms varied by state. Matching keys included a combination of one or more of the following: child's first and last name, date of birth, and/or sex; and/or mother's first and last name, social security number, maiden name, date of birth, and/or maternal age at delivery.

The Data Partners worked with the Departments of Health to determine the process for data transfer, file type, and content. Sentinel investigators and staff translated and mapped the coding in the data formats received from the states into a common format. The Data Partners executed a set of distributed programs to quality check the data, and the output was reviewed by the Sentinel Coordinating Center for basic elements of data quality.

4. Analysis

We calculated the proportion of live births identified in the Sentinel Distributed Database that could be linked to an infant overall and by Data Partner. For descriptive purposes, we identified maternal age, gestational age at birth, and multiple gestation pregnancies in the cohort of live births linked to infants (i.e., the "mother-infant cohort"). Gestational age at birth and multiple gestation status were identified using the ICD-9-CM diagnosis codes listed in Appendix B and Appendix C.

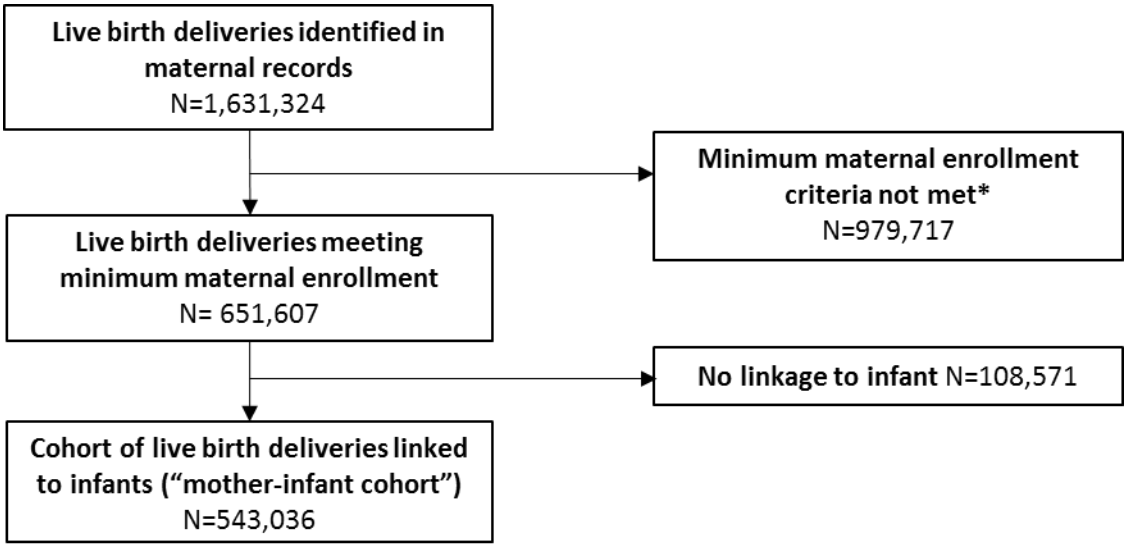
To adequately assess congenital malformations in the infant, it is generally necessary to require a period of enrollment following birth, since not all congenital malformations are diagnosed at birth. To inform the feasibility of assessing a range of outcomes, we therefore calculated the proportion of the mother-infant cohort based upon varying infant enrollment criteria (ranging between birth to 30 days of age, and birth to 360 days of age).

B. RESULTS

1. Identification of live deliveries in maternal records and linkage to infants

We identified over 1.6 million live births in maternal records in the Sentinel Distributed Database (**Figure 1**). Of the identified live births, 651,607 met minimum enrollment eligibility criteria (180 days prior to pregnancy start through 30 days after delivery). Overall 543,036 (83%) of live births identified in maternal records were linked to infants either using health plan source administrative data or by matching to the same birth certificate.

Figure 1. Formation of a mother-infant cohort in Sentinel's PRISM program



*Minimum maternal enrollment eligibility requirement was 180 days prior to pregnancy start through 30 days after delivery

2. Characteristics of mother-infant cohort

Table 2 shows the characteristics of deliveries identified in maternal records that were and were not linked to infants. Most mother-infant pairs (i.e., deliveries that were linked to infants) consisted of mothers between the ages of 25 and 39. Approximately 10% of the total mother-infant pairs were preterm deliveries, and approximately 4.5% were multiple gestation pregnancies. Compared to deliveries that were linked to infants, unlinked deliveries were more likely to occur in women under the age of 25 (31.6% vs. 7.2%), and less likely to occur following a multiple gestation pregnancy (2.7% vs. 4.5%).

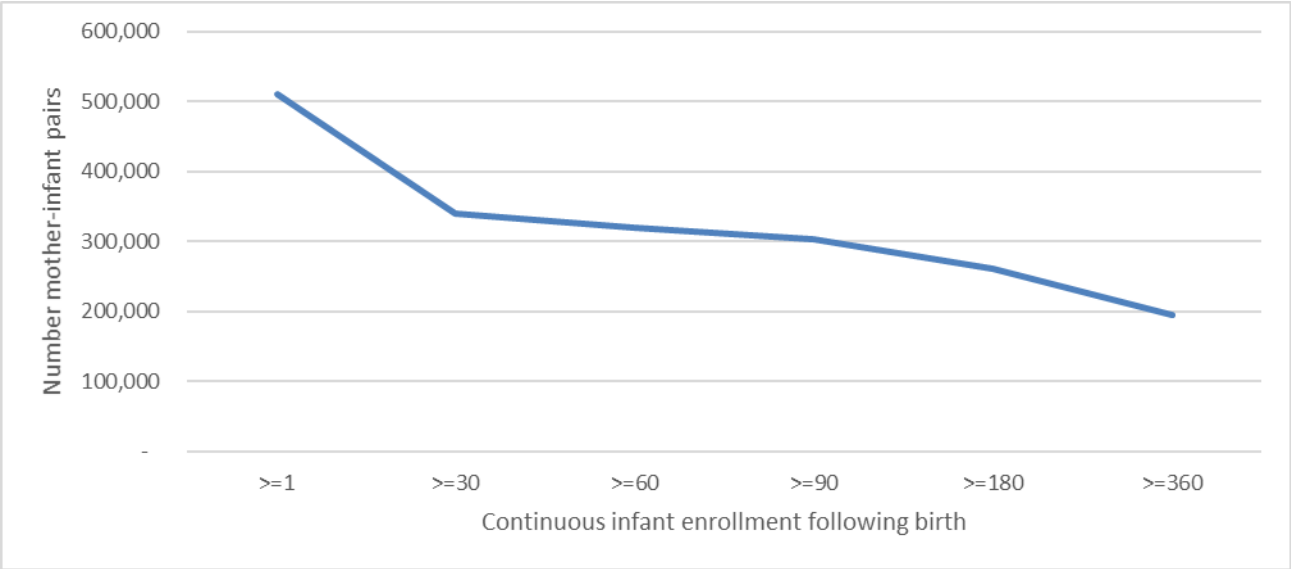
Table 2. Characteristics of live births that were and were not linked to infants (N=651,607)

Characteristic	Number live births linked to infants (%) N=543,036	Number live births NOT linked to infants (%) N=108,571
Age		
10-19	4,903 (0.9%)	13,989 (12.9%)
20-24	33,973 (6.3%)	20,267 (18.7%)
25-29	149,325 (27.5%)	25,461 (23.5%)
30-34	207,920 (38.3%)	27,979 (25.8%)
35-39	117,937 (21.7%)	15,713 (14.5%)
>=40	28,978 (5.3%)	5,162 (4.8%)
Gestational age		
Preterm delivery	56,130 (10.3%)	10,206 (9.4%)
Post-term delivery	71,373 (13.1%)	15,540 (14.3%)
Multiple gestation	24,666 (4.5%)	2,601 (2.4%)

3. Size of mother-infant cohort by infant enrollment criteria

We also assessed the feasibility of examining congenital anomalies that are not diagnosed at the birth hospitalization, which may require several months of infant enrollment following birth. **Figure 2** shows the size of the mother-infant cohort, calculated by infants' length of continuous enrollment since birth. For this analysis, we excluded from the full mother-infant cohort (N=543,036) mother-infant pairs that were multiple gestation pregnancies and where infants had a chromosomal anomaly (based on claims and birth certificate codes in Appendix D). We initially identified more than 510,973 mother-infant pairs based on these eligibility criteria, prior to requiring specified periods of infant enrollment after birth. There were 320,036 (63%) mother-infant pairs with a minimum of 60 days infant enrollment, and approximately 195,373 (38%) mother-infant pairs with a minimum of 360 days infant enrollment.

Figure 2. Size of mother-infant cohort, by infant enrollment requirement



4. Proportion of deliveries identified in maternal records linked to infants, by Data Partner and method

Each Data Partner linked more than 81% of their deliveries to infants. Each of the Data Partners was able to link over 80% of the deliveries using subscriber/family IDs, and fewer than 3% additional deliveries were linked to infants using last names and addresses or using birth certificates (when subscriber ID was not available). Birth certificate linkage only applied in states and Data Partners where birth certificate matches were attempted.

5. Proportion of deliveries identified in claims data linked to birth certificates

A total of 202,751 deliveries (31% of the total) identified in maternal records in the Sentinel Distributed Database occurred in the states and Data Partners for which birth certificate matching was accomplished. Of the 202,751 deliveries, 167,750 (83%) were linked to infants using Data Partner administrative source data. Of the 167,750 deliveries that were linked to infants using Data Partner administrative source data, 112,131 (67%) were linked to birth certificates. For individual Data Partner to state birth registry matches, birth certificate linkage rates ranged from 29% to 98%.

Of the 35,001 live births not linked to infants using Data Partner administrative source data, 10,583 (30%) were linked to birth certificates. Seven hundred and fifty-eight (2%) deliveries identified in health plan data were linked to birth certificate data and could also be linked to infant health plan data (i.e., mother and infant were linked via matches to the same birth certificate).

III. AIM 2: EVALUATING THE VALIDITY OF CLAIMS-BASED ALGORITHMS FOR VACCINE SAFETY SURVEILLANCE OF ADVERSE BIRTH OUTCOMES

A. METHODS

1. Study population

The study population for assessing the feasibility of utilizing claims-based algorithms to identify pregnancy start and the use case outcome (cleft lip/palate) was a subset of the mother-infant cohort described previously in Aim 1 of this report. From the population of linked mother-infant pairs that were linked using Data Partner source administrative data (N=542,278), mothers were required to be enrolled from 180 days prior to pregnancy start through 30 days after delivery. Infants were required to be enrolled from birth through 60 days of age (to identify cases of cleft lip/palate not diagnosed at birth). We excluded infants who died in the first 60 days of life. We incorporated a 15-day grace period in infant enrollment, as not all newborns are enrolled immediately following birth. We excluded multiple gestation pregnancies, as they have a greater risk for congenital malformations compared to singletons.

2. Algorithms

a. Identification of potential cases of cleft lip/palate and matched controls

Cases of cleft lip/palate in infants were identified using ICD-9-CM diagnosis codes 749.1* (cleft lip), 749.2* (cleft lip with cleft palate), and 749.0* (cleft palate), and birth certificate codes for cleft lip/palate (where linkage to birth certificate was available). We identified diagnosis codes in infant data within the first 60 days of life and in maternal data within 30 days of the delivery. We excluded cases in which the infant had evidence of a chromosomal anomaly, based on either ICD-9-CM codes in maternal or infant data (identified within 30 days of the delivery in maternal data or within 60 days of the birth in infant data), or birth certificate data (Appendix D), if available. For example, infants with ICD-9-CM or birth certificate codes for trisomy 13, trisomy 18, and trisomy 21 were excluded.

In potential cases, we required influenza vaccination, as identified using ICD-9-CM, CPT, HCPCS, and NDC codes (Appendix E), in one of the following intervals: (1) 2 weeks before pregnancy start through 14 weeks gestation or (2) 15 through 25 weeks gestation. This was done to facilitate the use of these cases in a pilot aim to implement a case-time-control study design (Aim 3, described in further detail in section IV of this report). These requirements were used to ultimately target vaccinations between 0 through 12 weeks gestation and 17 through 23 weeks gestation (risk and control intervals, respectively), with gestational age confirmed via chart review.

Mother-infant case pairs were matched up to a maximum of 7 (in 1 Data Partner) or 15 (in 3 Data Partners) mother-infant control pairs. Cases and controls were matched on Data Partner, maternal age (+/-24 months), and pregnancy start (+/-14 days, based on claims initially and confirmed via chart review). To be eligible as controls, mothers had to be vaccinated in the risk or control intervals of interest and lack evidence of a cleft lip/palate in claims data and birth certificate data, if available. Controls were excluded if they had evidence of a chromosomal anomaly.

b. Pregnancy start algorithm

An algorithm based on ICD-9-CM diagnosis codes was used to identify pregnancy start in mother-infant pairs who met the eligibility criteria (cases of cleft lip/palate and matched controls). We first assigned an

assumed gestational age at delivery. We then subtracted the assumed gestational age from the date of delivery (i.e., the child's date of birth) to assign pregnancy start.

Assumed gestational age at delivery was assigned using the following order of preference: (1) ICD-9-CM diagnosis codes for ranges of gestational length for preterm infants, which are coded in 2-week intervals from 25-26 through 36-37 weeks gestation (2) ICD-9-CM diagnosis codes for preterm infant of unspecified gestational length or for preterm delivery (3) ICD-9-CM diagnosis codes for post-term infant or post-term delivery (4) ICD-9-CM diagnosis codes for prolonged gestation of infant or for prolonged pregnancy, delivered, and (5) none of the above.

Gestational age assumptions for priorities 1 through 4 are listed in Appendix B. If codes for preterm, post-term, or prolonged gestation (priorities 1 through 4) were not identified, we assumed a gestational length of 273 days. A similar algorithm was validated within the Medication Exposure in Pregnancy Risk Evaluation Program (MEPREP), yielding a 2-week agreement between the algorithm and birth certificate estimates of 77%.

3. Medical record review

a. Chart retrieval, abstraction, and adjudication

To validate the case-finding and pregnancy start algorithms, we used retrospective medical record review in mothers and infants. Maternal records for prenatal care, vaccination, and the delivery hospitalization were requested. For case and control infants, we requested the birth record, and for case infants, we requested records for the diagnosis of cleft lip/palate.

Vendors contracted by each of the Data Partners attempted to contact health care providers and facilities through letters, faxes, emails, and phone calls, with a minimum of 5 attempts. Charts obtained by each Data Partner were redacted of protected health information and transferred to the Sentinel Coordinating Center through a secure portal. Next, carefully trained Sentinel research assistants reviewed the charts to abstract key information for quality control of the validation data. Finally, the medical charts were transferred to clinical reviewers using a secure portal. Two physicians with experience in perinatal research (KC, EL) reviewed the charts with structured forms to abstract information to calculate gestational age (described later in Section IIIA3c), and to identify other key clinical information. Finally, each potential case of cleft lip/palate was reviewed separately by a clinical geneticist (TW) to validate the cleft lip/palate diagnosis.

b. Case validation definition

The clinical geneticist (TW) reviewed cases using National Birth Defects Prevention Study criteria [2]. Cases were included if they had evidence of cleft lip with cleft palate, cleft palate alone, or cleft lip alone (collectively termed "cleft lip/palate"). Cases were also further classified as cleft lip with or without cleft palate, and cleft palate alone.

Cases were considered cleft lip with or without cleft palate if the defect extended through the entire lip into the floor of the nose (complete cleft lip) or if the defect extended through part of the lip but not into the floor of the nose (incomplete cleft lip). We excluded cases if they were pseudocleft lip or oblique facial cleft, which was done in accordance to the National Birth Defects Prevention Network case guidelines [2]. Cases were considered cleft palate alone if they were bifid or cleft uvula, cleft palate, type not specified, cleft hard palate, cleft soft palate, or submucous cleft palate.

We also assessed the feasibility of further classifying chart-confirmed cases of cleft lip/palate into "isolated vs multiple". Cases were classified as isolated if they (1) occurred without any major defects,

(2) occurred with one or more major defects of the same organ, organ system, or body part, or (3) occurred with other major defects that were not of the same organ, organ system, or body part but all defects were pathogenetically related. Cases were classified as multiple if they occurred with other major defects that were not of the same organ, organ system, or body part and all defects were not pathogenetically related.

c. Validation of pregnancy start algorithm

Clinical reviewers used medical records and rules based upon the American College of Obstetricians and Gynecologists(ACOG) guidelines for dating of pregnancies to validate the pregnancy start algorithm [3]. If *in-vitro* fertilization (IVF) or intrauterine insemination (IUI) was documented, then the assisted reproductive technology (ART)-derived estimated date of delivery (EDD) was used.

In pregnancies not conceived with ART, we estimated pregnancy start using last menstrual period (LMP), ultrasound (U/S) dating, the labor and delivery record, or the birth record, in the following order of preference:

(1) If both a first or second trimester U/S (up to and including 27 weeks gestation) and LMP were documented, we used the LMP if verified by U/S. Otherwise we used the U/S if discrepant from the LMP.
(2) Labor and delivery record or birth record, in that order of preference.
(3) First or second trimester ultrasound (This priority differs from priority 1 in that it was applied when LMP was not available).
(4) LMP (This priority differs from priority 1 in that it was applied when U/S dating was not available).
(5) If none of the above methods was available, we excluded the mother-infant pair from the analysis.

Regarding the order of preference, we implemented ACOG guidelines to handle discrepancies between LMP and U/S dating if and only if both were documented in the available records. We did not use LMP or U/S dating if only one of these methods was available in the records received, because we may have received incomplete records, as this occurs to varying degrees, in all retrospective medical chart review studies. When only LMP or only U/S was available, we therefore opted to use the gestational age estimate recorded on the labor and delivery or birth records when available, since the clinician attending the birth would presumably make clinical judgements to provide the best obstetric estimate using all dating information available.

4. Analysis

a. Validation of cleft lip/palate algorithm

To validate the algorithm for cleft lip/palate, we calculated the positive predictive value as the proportion of potential cases of cleft lip/palate that met the case definition on the basis of medical record data.

b. Validation of pregnancy start algorithm

To validate the algorithm for pregnancy start, we calculated the proportion of total deliveries identified in electronic data with charts available, by number of days between the algorithm-derived and chart-derived pregnancy start.

Next, using the exposure status determined by the chart-derived gestational age as the true exposure status, we calculated the positive predictive value of influenza vaccine exposure during the first trimester of pregnancy (0 through 12 weeks gestation). We identified the exposure status in claims data in the following intervals (1) 2 weeks before pregnancy start through 14 weeks gestation, (2) 1 week before pregnancy start through 13 weeks gestation, and (3) 0 through 12 weeks gestation. The purpose of using the different identification periods was to determine the optimal time period for identifying vaccinations in claims data, with the understanding that a wider identification period could enhance capture at the cost of including more false positives (i.e., vaccinations that occurred outside first trimester, the interval of interest).

B. RESULTS

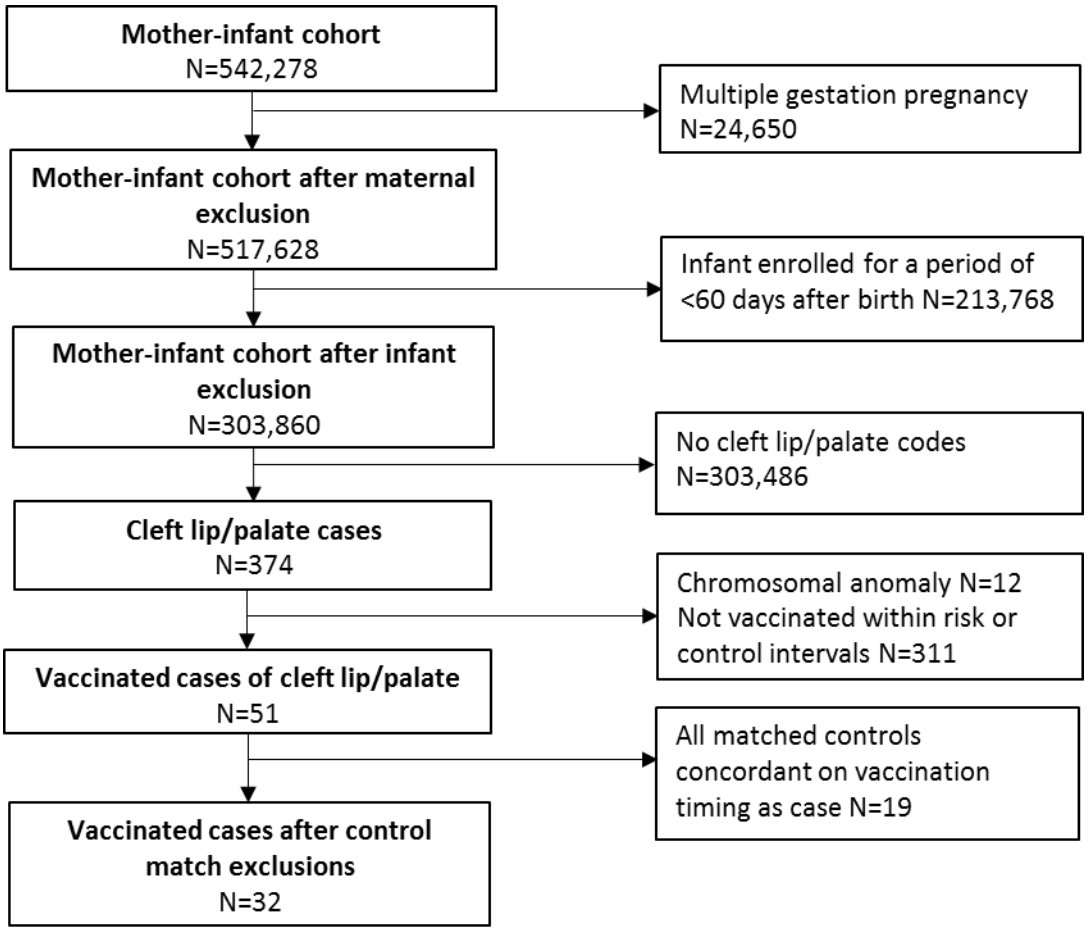
1. Study population

Figure 3 shows the identification of the study population and potential cases of cleft lip/palate. We identified a total of 303,860 mother-infant pairs meeting initial eligibility criteria. These included singleton deliveries identified in mothers with enrollment from 180 days prior to pregnancy start through 30 days after the delivery, who were linked to infants with enrollment from birth until 60 days of age. We allowed a 15-day grace period for infant enrollment. We excluded infants who died before 60 days of age.

2. Identification of cleft lip/palate cases and matched controls

Of the total 303,860 mother infant-pairs that were linked using Data Partner administrative source data, 374 had an infant diagnosis code for cleft lip/palate in the Sentinel Distributed Database or birth certificates, for an unconfirmed prevalence of 12.3 per 10,000 live birth in claims data (**Figure 3**). A total of 51 cleft lip/palate cases were potentially vaccinated in the risk or control intervals. After excluding cases that were concordant with all matched controls on vaccination timing, we identified 32 discordant cases that were potentially informative to conduct chart reviews to validate cleft lip/palate and gestational age.

Figure 3. Identification of study population and potential cases of cleft lip/palate



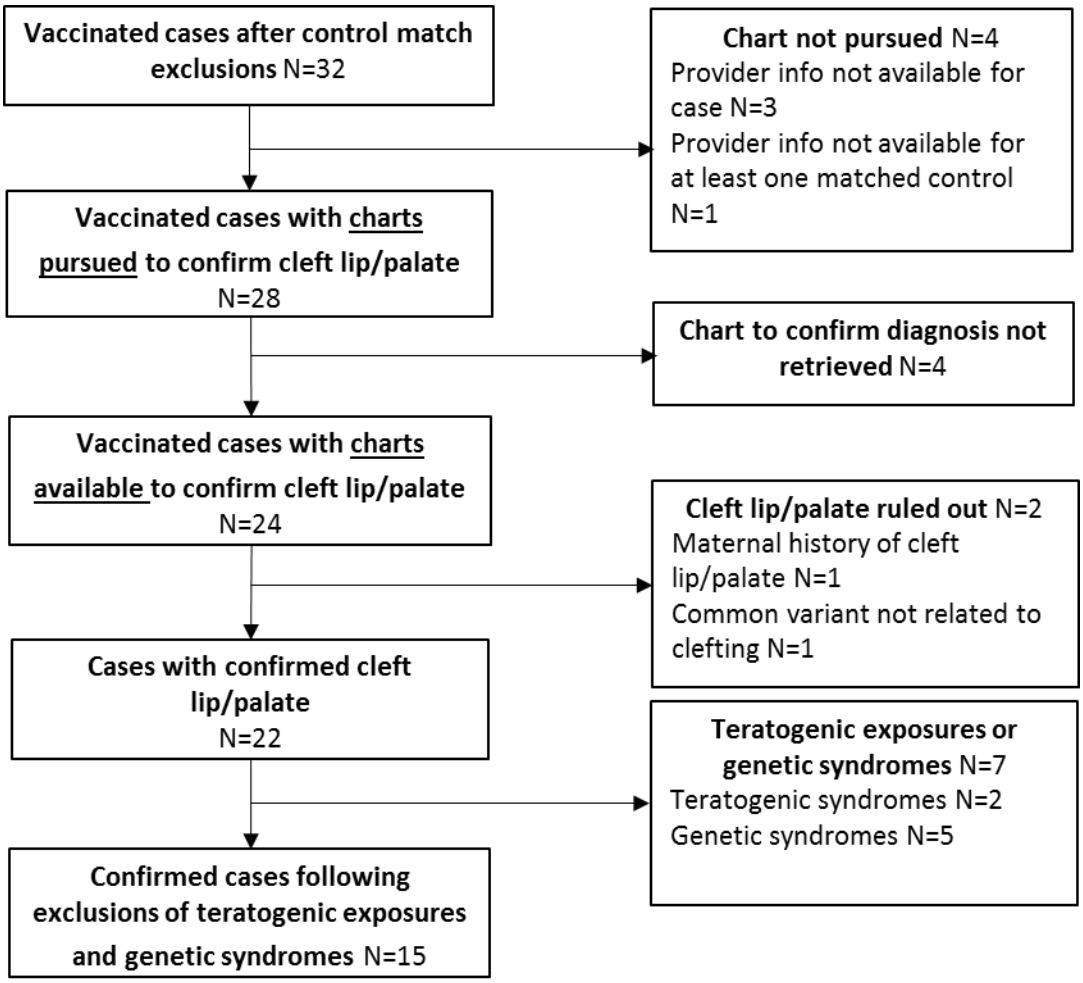
*Mother-infant cohort includes deliveries linked to infants using Data Partner administrative source data

The 32 potential cases were matched to 326 controls (mother-infant pairs without evidence of cleft lip/palate). We excluded 45 controls because they were matched to a case for which we could not pursue charts (This exclusion criterion was implemented to maximize the proportion of controls that would be informative for the exploratory aim 3, the case-time-control design analysis). Therefore, a total of 281 controls proceeded to chart review.

3. Chart validation of potential cases of cleft lip/palate

Figure 4 shows chart validation of the 32 potential cases of cleft lip/palate identified in the Sentinel Distributed Database. Of the 32 vaccinated cases, 24 (75%) had medical records available to confirm the cleft lip/palate in the infant. Of the 24 cases with medical records available, 22 (92%) were confirmed to have a cleft lip/palate. After excluding 5 patients with a genetic syndrome and 2 cases with a teratogenic syndrome, 15 cases of cleft lip/palate remained. Examples of genetic syndromes included Pierre Robin sequence, Stickler syndrome, and FGFR2-associated disorder, while teratogenic syndromes included hyperglycemia and substance use.

Figure 4. Validation of potential cases of cleft lip/palate identified in the Sentinel Distributed Database



Of the 15 confirmed cases of cleft lip/palate, 11 were cases of cleft lip with or without cleft palate and 4 were cases of cleft palate alone.

4. Chart validation of pregnancy start algorithm

a. Availability of pregnancy start information in medical records

Table 3 shows the medical record data elements used to validate pregnancy start. Overall 223 (71% of the total 313 mother-infant pairs for whom chart review was attempted) had medical records available to confirm pregnancy start.

Of the 223 mother-infant pairs for whom we had dating information from charts, 197 (88%) had one of three scenarios preferred to estimate pregnancy start: (1) IVF or IUI-derived EDD was used to estimate pregnancy start, N=2, or in instances where IVF or IUI was not documented, (2) both U/S and LMP were available, N=138, or (3) the labor and delivery or birth record was available, N=57.

Table 3. Medical record elements used to validate pregnancy start

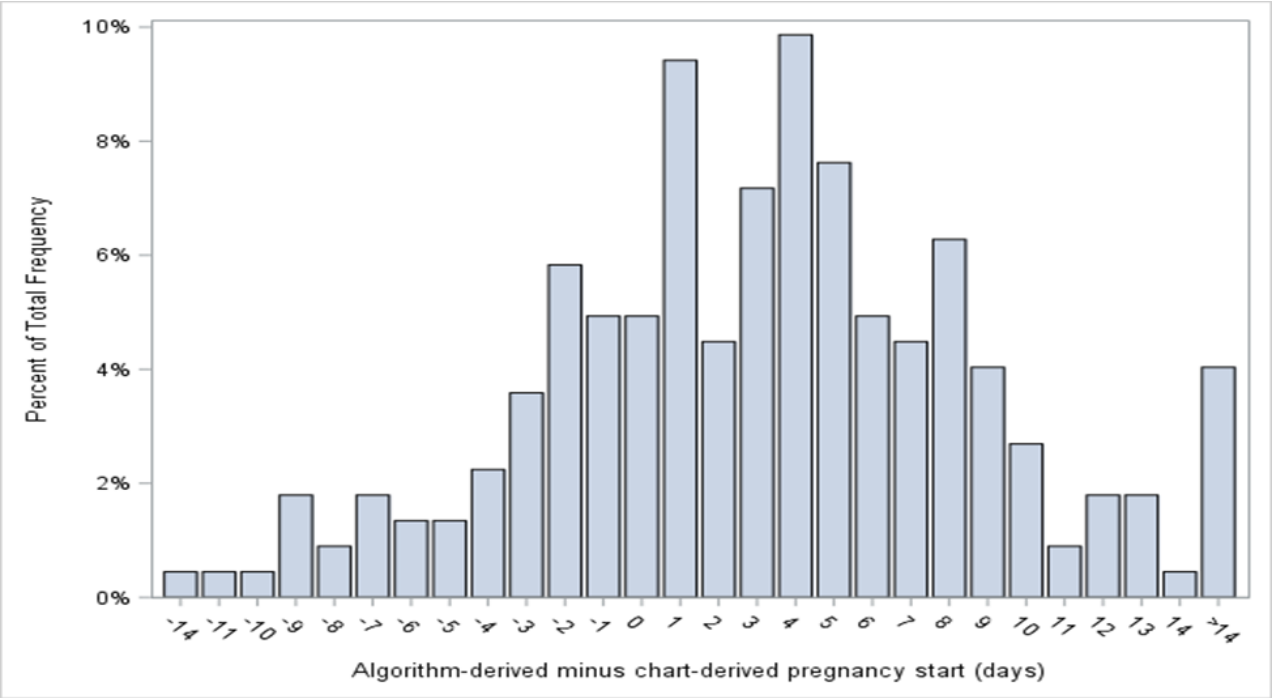
Medical record elements used to validate pregnancy start	Number of mother-infant pairs (N=313)
Information available and used to estimate pregnancy start*	223
IVF or IUI derived EDD	2
First Trimester U/S and LMP	117
Second Trimester U/S and LMP	21
Labor and delivery and/or birth record	57
First trimester U/S	1
LMP	25
No information available to confirm pregnancy start	90

*Methods were applied sequentially as listed to validate pregnancy start. See section IIIA3c for rationale.

b. Comparison of pregnancy start algorithm to dating information in medical records

Figure 5 shows the proportion of mother-infant pairs by agreement between the algorithm-derived and chart-derived pregnancy start. Of the 223 mother-infant pairs with pregnancy start available in medical records, 214 (96%) had within 2-week agreement between the algorithm and the medical record. In 165 (74%) of the mother-infant pairs, there was within 1-week agreement between the algorithm and the medical record.

Figure 5. Proportion of mother-infant pairs by agreement between algorithm-derived and chart-derived pregnancy start



c. Prenatal vaccination exposure status

Table 4 shows the proportion of exposures confirmed within the first trimester of pregnancy (0 through 12 weeks gestation), by period of identification of exposures in claims data. We used the following identification periods: -2 through 14 weeks, -1 through 13 weeks, and 0 through 12 weeks gestation. We observed the highest confirmation rate, 73%, when we restricted the observation period to the targeted period (0 through 12 weeks gestation). Using this shorter period, we identified 74 of 75 (99%) of the total exposures that were identified using the widest identification period (-2 through 14 weeks) and confirmed as occurring in first trimester.

Table 4. Proportion of exposures confirmed to occur during first trimester of pregnancy (0 through 12 weeks gestation), by period of identification of exposures in claims data*

	Cases and controls combined	
Period of identification of exposures in Sentinel Distributed Database	**Exposure identified****	**Exposure confirmed (% of total identified)**
2 weeks before pregnancy start through 14 weeks gestation	158	75 (47%)
1 week before pregnancy start through 13 weeks gestation	129	74 (57%)
0 through 12 weeks gestation	101	74 (73%)

*Exposures identified using diagnosis, procedure, and dispensing codes for influenza vaccine; gestational age at exposure initially identified based on claims-based algorithm and confirmed based on medical record data

**Analysis includes all potential vaccinated cases of cleft lip/palate and vaccinated controls meeting the exposure identification criteria listed for that table row.

IV. EXPLORATORY AIM 3: EXAMINING THE FEASIBILITY OF USING A CASE-TIME-CONTROL DESIGN

A. METHODS

1. Study population

We included mother-infant pairs that were linked using Data Partner administrative source data, as described in Aim 2. Mothers with singleton pregnancies ending in a live birth delivery were included if they were enrolled from 180 days prior to pregnancy start through 30 days after delivery. Infants were required to be enrolled for a minimum of 60 days following birth to capture cleft lip/palate diagnoses, which may not be made immediately following birth. We excluded infants who died before 60 days of age.

From the mother-infant cohort, the study population for this aim included cases (mother-infant pairs with evidence of cleft/lip palate) and matched controls (mother-infant pairs without evidence of cleft lip/palate), who received influenza vaccination during pre-defined time intervals during pregnancy. Additional requirements for cases and controls are described further in section IVA3 below.

2. Study design

We explored the feasibility of using a case-time-control study design to evaluate the use case association (maternal influenza vaccination during pregnancy and risk of cleft lip/palate in the infant). The selection of cleft lip/palate as the use case was not based on any concern or evidence regarding an association between the influenza vaccine and cleft lip/palate.

Strengths of the case-time-control design include that it adjusts for between person confounders that do not vary over time, adjusts for time trends in exposure, and avoids confounding that results from comparing vaccinated to unvaccinated persons.

The case-time-control design is an extension of the case-crossover design. The case-crossover design and its variants are especially well-suited to measuring transient effects of exposures on immediate risk of illnesses with abrupt onset. In a case-crossover study, in individuals who have experienced the outcome of interest (e.g., cleft lip/palate), a comparison is made between the odds of exposure in a pre-defined risk interval (during which exposure is thought to increase the risk of the outcome) and a self-matched control interval. The case-time-control design expands upon the case-crossover design by using an external group of control patients (e.g., mother-infant pairs without evidence of cleft lip/palate) sampled from the same population that produced the cases to adjust for time trends in exposure (e.g., seasonality, or gestational age at vaccination).

We defined the risk interval as 6 through 12 weeks gestation (corresponding to the period of lip and palate development) and used a control interval of 17 through 23 weeks gestation, which allowed for a 5-week washout period. In additional analyses, we defined the risk interval as 0 through 12 weeks gestation, allowing for an induction period of the vaccine prior to the period of lip and palate development.

The study included cases that were vaccinated in either the risk or control interval. We matched each case with up to 15 controls (for 3 of the 4 Data Partners) or up to 7 controls (for the 4th Data Partner). Controls were matched to cases on Data Partner, pregnancy start (+/- 14 days; based initially on claims data and later chart-confirmed), and maternal age at pregnancy start (+/-24 months).

3. Identifying vaccinated cases and vaccinated controls

Potential cases and controls were identified in the Sentinel Distributed Database before proceeding to a single round of chart review for both cases and controls. We first identified cases (mother-infant pairs with evidence of cleft lip/palate and vaccinated during the risk or control intervals of interest during pregnancy) and then identified up to 15 control matches per case (mother-infant pairs without evidence of cleft lip/palate and vaccinated during the risk or control intervals of interest during pregnancy) using the algorithms for case-finding and gestational age described in Aim 2. Vaccinations were identified using ICD-9-CM, HCPCS, CPT, and NDC codes in the Sentinel Distributed Database (Appendix E).

We then chart-confirmed cleft lip/palate in cases and gestational age in cases and controls using the criteria described in Aim 2. Following chart reviews, the eligible population included confirmed cases of cleft lip/palate and matched controls, both required to be vaccinated either in the risk or control interval. In the final analysis, only case-control sets in which the case was discordant from at least one matched control on timing of vaccination (i.e., risk vs. control interval) were included.

4. Analysis

Due to the low number of informative cases, we did not calculate an odds ratio for the primary risk interval (6 through 10 weeks gestation). However, we used conditional logistic regression to calculate an unadjusted odds ratio for the association between vaccination in additional analyses using the alternative risk interval of 0 through 12 weeks gestation. An offset term was used to adjust for the unequal length of the risk and control intervals. Of note, the unadjusted analysis inherently adjusts for time trends in exposure due to seasonality and gestational age, due to matching cases to controls on pregnancy start.

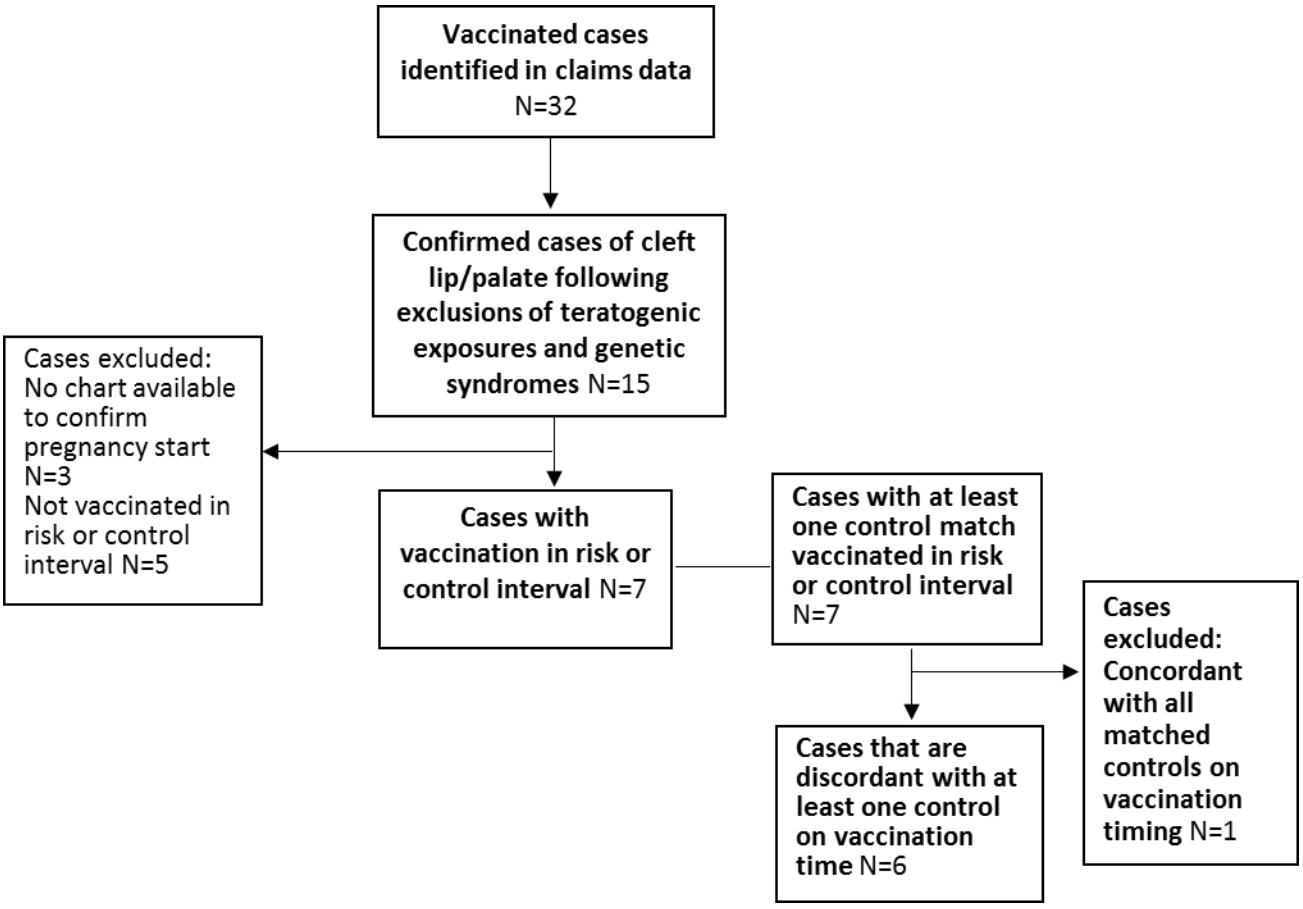
B. RESULTS

1. Alternative risk interval

The alternative risk interval analysis incorporated a risk interval of 0 through 12 weeks gestation and a control interval of 17 through 23 weeks gestation. Due to anticipated imprecision of gestational age in claims data, we used wider observation periods in electronic data (2 weeks prior to pregnancy start through 12 weeks gestation and 15 through 25 weeks gestation) than would be included in the final analysis following chart reviews. As described earlier in section IIIB7, based on these initial inclusion criteria, we identified a total of 32 potential cases in claims data.

Of these cases, 15 met case confirmation criteria, and further exclusions were made based on chart reviews of gestational age (**Figure 6**). We identified a total of 7 cases that were vaccinated in the risk or control interval, matched to 34 controls. After excluding 1 case that was concordant with all 4 controls on vaccinating timing, 6 confirmed cases and 30 matched controls remained. We observed an unadjusted odds ratio of 0.27, 95% CI 0.05 to 1.5.

Figure 6. Case disposition for case-time-control design analysis, alternative risk interval of 0 through 12 weeks gestation



2. Primary risk interval

Based on chart review data, we identified 5 confirmed cases that were vaccinated in the primary risk interval (6 through 12 weeks gestation) or the control interval (17 through 23 weeks gestation). These 5 cases were matched to 16 controls. After excluding case-control matched sets in which the case was concordant with all matched controls on timing of vaccination, 3 confirmed cases and 9 matched controls remained. As noted earlier, we did not calculate an odds ratio due to the low number of informative cases.

V. DISCUSSION

In this activity, we demonstrated the feasibility of conducting surveillance of infant outcomes following maternal vaccinations within Sentinel. Strengths of Sentinel include its large population size, the ability to assess denominators and therefore conduct formal epidemiologic analyses, and the use of claims data, which minimizes recall bias present in studies with self-reported data. We successfully linked more than 80% of deliveries identified in maternal records in the Sentinel Distributed Database to infants. In doing so, we formed a large cohort of more than 500,000 mother-infant pairs. We also demonstrated the feasibility of identifying key data elements needed to study birth outcomes following maternal vaccination through a use case, influenza vaccines and cleft lip/palate.

The linkage of a large number of mothers to infants serves as the foundation for conducting surveillance on infant outcomes following maternal exposures during pregnancy. Our mother-to-infant linkage rate of 83% is similar to MEPREP (86%) and higher than a study that utilized nationwide Medicaid data on inpatient deliveries (56%) [4, 5]. We anticipate that not all mothers were linked to infants because the infant was not enrolled in the mother's health plan after birth, which might occur if the parent's insurance coverage changed or if the infant was covered under a different insurance plan than the mother (e.g., the infant was covered under the father's insurance plan and the mother was not, or the infant was adopted).

Because some health insurers assign infants temporary IDs in the neonatal period before a permanent ID takes effect, more than one ID of the same patient may be present in health plan enrollment data if additional data management is not done. Without understanding these processes, one might falsely assume that different patient IDs necessarily represent distinct patients, which could lead to mistaken inferences, for example that a delivery linked to more than one infant patient id necessarily represents a multiple birth (linkage to separate infants) when it in fact is a singleton delivery. Prior to data cleaning the linked mother-infant cohort, we observed duplicate enrollment records in approximately 5% of infants in preliminary analysis for one Data Partner.

To address this, we opted to keep all mother-infant linkages (including those in which infants had multiple IDs) and subsequently limit the mother-infant cohort to deliveries that linked to only one infant patient id. Alternative data management approaches include: (1) for each infant, combining all claims data captured under both the temporary and permanent IDs or (2) for each infant, selecting a single patient ID and claims data associated with it (and therefore excluding claims data associated with the other patient ID for the patient). These alternative approaches are more challenging for multiple births and are only possible for a select subset of mother-baby pairs, that is when the pregnancy is determined to be a singleton delivery (via maternal administrative codes) or when the pregnancy is a twin birth with infants of different sexes.

We successfully completed several matches of health plan administrative data with birth certificates. However, there were some limitations. First, the process was time- and resource-intensive and required separate applications from each Data Partner to each state. Linkage rates were variable among the individual Data Partner to state matches, likely due to differences in matching algorithms at the vital events registries. This activity demonstrates that it is possible to pursue linkages to birth certificates to obtain specific clinical elements that are not available in the Sentinel Distributed Database, or to obtain more accurate data on gestational age if needed, to address specific surveillance questions. However, linkage to birth certificates on a routine basis (for example, on a yearly basis) would remain challenging, given the number of individual Data Partner to state matches that need to occur, and the need to ensure that all data are quality checked. If birth certificate matches are pursued, we recommend that

overall processes and matching algorithms be standardized to ensure quality and maximize matching rates.

We demonstrated the ability to capture key variables needed to assess birth outcomes following vaccination, including vaccination, outcomes, and gestational age, through a use case, influenza vaccines and cleft lip/palate. First, we observed a prevalence of cleft lip/palate of 12.3 per 10,000 live births in electronic data (e.g. unconfirmed cases), similar to other active surveillance systems. Other estimates of cleft lip/palate range from 12.2 per 10,000 in the National Birth Defects Prevention Study [6] to 14.5 per 10,000 in the Vaccine Safety Datalink [7]. Further, we confirmed a cleft lip/palate diagnosis in 92% of infants with charts available. This positive predictive value is comparable to another validation study that included Tennessee Medicaid claims data and reported a positive predictive value of 93% [8].

Though we initially hypothesized that claims data on gestational age might lack adequate precision for the purposes of conducting safety surveillance of infant birth outcomes, we found the level of agreement between claims data and medical records to be sufficient to support the use of claims data to assign timing of exposure with respect to risk windows of at least a few weeks long. We found a within 2-week agreement of 96% when comparing gestational age estimates based on the claims-based algorithm vs. medical record data. By comparison, MEPREP observed a 2-week agreement of 77% between a similar claims-based algorithm and birth certificate data [9]. Assuming that vaccination exposures and associated dates identified in claims data were valid, the positive predictive value for exposure to influenza vaccines during the first trimester of pregnancy based on algorithm-derived gestational age was 73%. With ICD-9 coded data, we anticipate that Sentinel has capabilities to examine point exposures during relatively long risk intervals defined by gestational age. We anticipate that exposures that are used for long periods of time (treatments for chronic conditions, in contrast to acute exposures like vaccines) will have an even higher positive predictive value for identifying exposures during a relatively long risk interval. In MEPREP, the positive predictive value for exposure to fluoxetine (an antidepressant) during first trimester, based on algorithm-derived gestational age, was 97% [9]. Furthermore, we anticipate that ICD-10-CM based algorithms for gestational age will have improved performance over ICD-9-CM based algorithms, given that codes are more specific. Notably, maternal codes for weeks gestation (<8, 8, 9, 10,…40, 41, 42, >42 weeks gestation) have been added in the ICD-10-CM.

We observed that 3% of pregnant women enrolled in the participating Data Partners of Sentinel received influenza vaccination between 6 and 12 weeks gestation. In comparison, the VSD previously found that the proportion of pregnant women who received influenza vaccination during the first trimester of pregnancy (0-14 weeks gestation) was 12% from 2004-2013 [10]. We may have observed a lower exposure prevalence because the VSD study required that pregnant women have at least a 1-week overlap during their first trimester and the influenza season, which we did not require; this enrollment requirement would and which increase the likelihood that women would receive influenza vaccine.

In the exploratory aim, we sought to assess the feasibility of implementing a case-time-control study design for the use case, influenza vaccines and risk of cleft lip/palate. The design was chosen to limit bias due to comparing vaccinated to unvaccinated individuals and bias due to incomplete capture of vaccinations in claims data (e.g., vaccinations occurring in the workplace that were not submitted for reimbursement). Our finding of no increased risk of cleft lip/palate following maternal vaccination during the first trimester of pregnancy (OR 0.27, 95% CI 0.05 to 1.55) is consistent with results from other surveillance systems, including the VSD (PR 0.97, 95% CI 0.74, 1.30) and VAMPSS (OR 0.87, 95% CI 0.58, 1.29) [10, 11].

Our case-time control analysis of the association between influenza vaccine exposure during pregnancy and cleft lip/palate in the infant had a few limitations. First, requiring enrollment from birth through 60 days of age –which was done to maximize capture of outcomes not identified at birth—had the consequence of excluding children who died before that age, since death leads to disenrollment from health insurance plans. Hypothetically speaking, if a medical product under study is associated with one or more lethal syndrome(s) that cause a congenital malformation under study, excluding early life deaths could potentially bias results towards the null. However, this exclusion is unlikely to result in any significant bias, as the lethal syndromes that include cleft lip/palate are exceedingly rare. Second, despite the large size of the PRISM mother-infant cohort, the case-time-control design had limited power and confidence intervals were wide. The analysis of the primary risk interval (6 through 12 weeks gestation) had too few cases to warrant calculating an odds ratio. We identified more than 30 vaccinated cases in the Sentinel Distributed Database and confirmed a diagnosis of cleft lip/palate in more than 20 cases. However, we excluded approximately half of the chart-confirmed cases due to documentation of genetic/teratogenic syndromes in charts, and approximately one third due to misclassification of exposure timing. A large proportion of these exclusions were made because we used a period longer than the targeted risk interval to identify vaccinations in claims data.

The benefits of the case-time-control study design include that it avoids confounding that arises when comparing vaccinated and unvaccinated individuals [12]. Another benefit is that if chart review is needed to confirm outcomes or other clinical information, the design reduces the number chart reviews of mothers and infants. It remains theoretically possible to use the case-time-control study design with reasonable statistical power to examine outcomes that have greater exposure or outcome prevalence than our use case (e.g., composite outcome that includes select structural birth defects; prevalence of 150 per 10,000 live births). For rare outcomes, we suggest that investigators consider using alternative study designs that are likely to have greater statistical power, such as a cohort design with adjustments for confounding using standard methods and/or propensity scores. However, this approach may be infeasible if chart reviews are needed in all patients. This approach could be more feasible if only a subset of the full cohort, or only a limited amount of information needs to be chart reviewed.

Conclusions

Surveillance of infant birth outcomes following maternal vaccination is feasible in Sentinel. This surveillance requires linkage of mothers to infants, which we successfully demonstrated in more than 80% of deliveries identified in maternal records, resulting in a large cohort of more than 500,000 mother-infant pairs. The use of claims databases to identify and evaluate potential adverse events in infants following maternal vaccination requires rigorous validation of relevant algorithms. While we demonstrated high validity of ICD-9-CM algorithms for gestational age and a use case outcome (cleft lip/palate), validated algorithms would be needed to assess other birth outcomes. To further inform future assessments of birth outcomes after exposure to vaccines, additional validation of certain data elements (e.g., ICD-10 based algorithms for gestational age, and ICD-9 and ICD-10-based algorithms for outcomes of interest) is needed to support such surveillance.

VI. APPENDICES

A. CODES TO IDENTIFY LIVE BIRTHS

Code	Description
650	Normal delivery
V27.0	Single newborn
V27.2	Twins, both liveborn
V27.3	Twins, one liveborn
V27.5	Other multiple birth, all liveborn
V27.6	Other multiple birth, some liveborn
V30.0	Single newborn, born in hospital
V30.00	Single newborn, born in hospital
V30.01	Single newborn, born in hospital, cesarean
V30.1	Single liveborn, born before admission to hospital
V31.0	Twin, born in hospital
V31.00	Twin, born in hospital
V31.01	Twin, born in hospital, cesarean
V31.1	Twin birth, mate liveborn, born before admission to hospital
V31.2	Twin birth, mate liveborn, born outside hospital and not hospitalized
V32.0	Twin, born in hospital, mate stillborn
V32.00	Twin birth mate stillborn born in hospital, delivered without mention of cesarean section
V32.01	Twin, born in hospital, cesarean, mate stillborn
V32.1	Twin birth, mate stillborn, born before admission to hospital
V32.2	Twin birth, mate stillborn, born outside hospital and not hospitalized
V33.0	Twin, born in hospital
V33.00	Twin birth, unspecified whether mate liveborn or stillborn, born in hospital, delivered without mention of cesarean section
V33.01	Twin, born in hospital, cesarean
V33.1	Twin birth, unspecified whether mate liveborn or stillborn, born before admission to hospital
V34.0	Other multiple, born in hospital
V34.00	Other multiple, born in hospital
V34.01	Other multiple, born in hospital, cesarean
V34.1	Other multiple birth (three or more), mates all liveborn, born before admission to hospital
V35.0	Other multiple, born in hospital, mates stillborn
V35.00	Other multiple, born in hospital, mates stillborn
V35.01	Other multiple, born in hospital, cesarean, mates stillborn
V35.1	Other multiple birth (three or more), mates all stillborn, born before admission to hospital
V36.0	Other multiple, born in hospital, mates liveborn and stillborn
V36.00	Other multiple, born in hospital, mates liveborn and stillborn
V36.01	Other multiple, born in hospital, cesarean, mates liveborn and stillborn
V36.1	Other multiple birth (three or more), mates liveborn and stillborn, born before admission to hospital
V37.0	Other multiple, born in hospital
V37.00	Other multiple, born in hospital

Code	Description
V37.01	Other multiple, born in hospital, cesarean
V37.1	Other multiple birth (three or more), unspecified whether mates liveborn or stillborn, born before admission to hospital
V39.0	Unspecified, born in hospital
V39.00	Unspecified, born in hospital
V39.01	Unspecified, born in hospital, cesarean
V39.1	Liveborn, unspecified whether single, twin or multiple, born before admission to hospital
01960	Anesthesia for vaginal delivery only
01961	Anesthesia for cesarean delivery only
01962	Anesthesia for urgent hysterectomy following delivery
01967	Neuraxial labor anesthesia/analgesia for planned vaginal delivery
01968	Anesthesia for cesarean delivery following neuraxial labor analgesia/anesthesia
01969	Anesthesia for cesarean hysterectomy following neuraxial labor analgesia/anesthesia
59400	Routine ob care incl antepartum car, vaginal delivery, postpartum care
59409	Vaginal delivery only
59410	Vaginal delivery including postpartum care
59510	Routine ob care including antepartum care, cesarean delivery, postpartum care
59514	Cesarean delivery only
59515	Cesarean delivery, including postpartum care
59610	Obstetrical care including antepartum care, vaginal delivery, postpartum care, after previous c-section
59612	Vaginal delivery only after previous c-section
59614	Vaginal delivery after previous c-section, including postpartum care
59618	Obstetrical care including antepartum care, cesarean delivery, postpartum care, after previous c-section
59620	Cesarean delivery only after previous c-section
59622	Cesarean delivery after previous c-section, including postpartum care
641.01	Placenta previa without hemorrhage, with delivery, with or without mention of antepartum condition
641.11	Hemorrhage from placenta previa, with delivery, with or without mention of antepartum condition
641.21	Premature separation of placenta, with delivery, with or without mention of antepartum condition
641.31	Antepartum hemorrhage associated with coagulation defect, with delivery, with or without mention of antepartum condition
641.81	Other antepartum hemorrhage, with delivery, with or without mention of antepartum condition
641.91	Unspecified antepartum hemorrhage, with delivery, with or without mention of antepartum condition
642.01	Benign essential hypertension with delivery, with or without mention of antepartum condition
642.02	Benign essential hypertension, with delivery, with mention of post-partum complication
642.11	Hypertension secondary to renal disease, with delivery, with or without mention of antepartum condition

Code	Description
642.12	Hypertension secondary to renal disease, with delivery, with mention of post-partum complication
642.21	Other pre-existing hypertension, with delivery, with or without mention of antepartum condition
642.22	Other pre-existing hypertension, with delivery, with mention of post-partum complication
642.31	Transient hypertension of pregnancy, with delivery, with or without mention of antepartum condition
642.32	Transient hypertension of pregnancy, with delivery, with mention of post-partum complication
642.41	Mild or unspecified pre-eclampsia, with delivery, with or without mention of antepartum condition
642.42	Mild or unspecified pre-eclampsia, with delivery, with mention of post-partum complication
642.51	Severe pre-eclampsia, with delivery, with or without mention of antepartum condition
642.52	Severe pre-eclampsia, with delivery, with mention of post-partum complication
642.61	Eclampsia, with delivery, with or without mention of antepartum condition
642.62	Eclampsia, with delivery, with mention of post-partum complication
642.71	Pre-eclampsia or eclampsia superimposed on pre-existing hypertension, with delivery, with or without mention of antepartum condition
642.72	Pre-eclampsia or eclampsia superimposed on pre-existing hypertension, with delivery, with mention of post-partum complication
642.91	Unspecified hypertension, with delivery, with or without mention of antepartum condition
642.92	Unspecified hypertension, with delivery, with mention of post-partum complication
643.01	Mild hyperemesis gravidarum, with delivery, with or without mention of antepartum condition
643.11	Hyperemesis gravidarum with metabolic disturbance, with delivery, with or without mention of antepartum condition
643.21	Late vomiting of pregnancy, with delivery, with or without mention of antepartum condition
643.81	Other vomiting complicating pregnancy, with delivery, with or without mention of antepartum condition
643.91	Unspecified vomiting of pregnancy, with delivery, with or without mention of antepartum condition
644.21	Early onset of delivery, delivered, with or without mention of antepartum condition
645.01	Prolonged pregnancy, with delivery
645.11	Post term pregnancy, delivered, with or without mention of antepartum condition
645.21	Prolonged pregnancy, delivered, with or without mention of antepartum condition
645.22	Prolonged pregnancy, with delivery, with mention of post-partum complication
646.01	Papyraceous fetus, delivered, with or without mention of antepartum condition
646.11	Edema or excessive weight gain in pregnancy, with delivery, with or without mention of antepartum condition
646.12	Edema or excessive weight gain in pregnancy, with delivery, with mention of post-partum complication
646.21	Unspecified renal disease in pregnancy, with delivery, with or without mention of antepartum condition

Code	Description
646.22	Unspecified renal disease in pregnancy, with delivery, with mention of post-partum complication
646.31	Habitual aborter, with delivery, with or without mention of antepartum condition
646.41	Peripheral neuritis in pregnancy, with delivery, with or without mention of antepartum condition
646.42	Peripheral neuritis in pregnancy, with delivery, with mention of post-partum complication
646.51	Asymptomatic bacteriuria in pregnancy, with delivery, with or without mention of antepartum condition
646.52	Asymptomatic bacteriuria in pregnancy, with delivery, with mention of post-partum complication
646.61	Infections of genitourinary tract in pregnancy, with delivery, with or without mention of antepartum condition
646.62	Infections of genitourinary tract in pregnancy, with delivery, with mention of post-partum complication
646.71	Liver disorders in pregnancy, with delivery, with or without mention of antepartum condition
646.81	Other specified complications of pregnancy, with delivery, with or without mention of antepartum condition
646.82	Other specified complications of pregnancy, with delivery, with mention of post-partum complication
646.91	Unspecified complication of pregnancy, with delivery, with or without mention of antepartum condition
647.01	Syphilis of mother, complicating pregnancy, with delivery, with or without mention of antepartum condition
647.02	Syphilis of mother, complicating pregnancy, with delivery, with mention of post-partum complication
647.11	Gonorrhea of mother, with delivery, with or without mention of antepartum condition
647.12	Gonorrhea of mother, with delivery, with mention of post-partum complication
647.21	Other venereal diseases of mother, with delivery, with or without mention of antepartum condition
647.22	Other venereal diseases of mother, with delivery, with mention of post-partum complication
647.31	Tuberculosis of mother, with delivery, with or without mention of antepartum condition
647.32	Tuberculosis of mother, with delivery, with mention of post-partum complication
647.41	Malaria of mother, with delivery, with or without mention of antepartum condition
647.42	Malaria of mother, with delivery, with mention of post-partum complication
647.51	Rubella of mother, with delivery, with or without mention of antepartum condition
647.52	Rubella of mother, with delivery, with mention of post-partum complication
647.61	Other viral diseases of mother, with delivery, with or without mention of antepartum condition
647.62	Other viral diseases of mother, with delivery, with mention of post-partum complication
647.81	Other specified infectious and parasitic diseases of mother, with delivery, with or without mention of antepartum condition
647.82	Other specified infectious and parasitic diseases of mother, with delivery, with mention of post-partum complication

Code	Description
647.91	Unspecified infection or infestation of mother, with delivery, with or without mention of antepartum condition
647.92	Unspecified infection or infestation of mother, with delivery, with mention of post-partum complication
648.01	Diabetes mellitus of mother, with delivery, with or without mention of antepartum condition
648.02	Diabetes mellitus of mother, with delivery, with mention of post-partum complication
648.11	Thyroid dysfunction of mother, with delivery, with or without mention of antepartum condition
648.12	Thyroid dysfunction of mother, with delivery, with mention of post-partum complication
648.21	Anemia of mother, with delivery, with or without mention of antepartum condition
648.22	Anemia of mother, with delivery, with delivery, with mention of post-partum complication
648.31	Drug dependence of mother, with delivery, with or without mention of antepartum condition
648.32	Drug dependence of mother, with delivery, with mention of post-partum complication
648.41	Mental disorders of mother, with delivery, with or without mention of antepartum condition
648.42	Mental disorders of mother, with delivery, with mention of post-partum complication
648.51	Congenital cardiovascular disorders of mother, with delivery, with or without mention of antepartum condition
648.52	Congenital cardiovascular disorders of mother, with delivery, with mention of post-partum complication
648.61	Other cardiovascular diseases of mother, with delivery, with or without mention of antepartum condition
648.62	Other cardiovascular diseases of mother, with delivery, with mention of post-partum complication
648.71	Bone and joint disorders of back, pelvis, and lower limbs, with delivery, with or without mention of antepartum condition
648.72	Bone and joint disorders of back, pelvis, and lower limbs, with delivery, with mention of post-partum complication
648.81	Abnormal glucose tolerance of mother, with delivery, with or without mention of antepartum condition
648.82	Abnormal glucose tolerance of mother, with delivery, with mention of post-partum complication
648.91	Other current conditions classifiable elsewhere of mother, with delivery, with or without mention of antepartum condition
648.92	Other current conditions classifiable elsewhere of mother, with delivery, with mention of post-partum complication
649.01	Tobacco use disorder complicating pregnancy, childbirth, or the puerperium, delivered, with or without mention of antepartum condition
649.02	Tobacco use disorder complicating pregnancy, childbirth, or the puerperium, with delivery, with mention of post-partum complication
649.11	Obesity complicating pregnancy, childbirth, or the puerperium, delivered, with or without mention of antepartum condition

Code	Description
649.12	Obesity complicating pregnancy, childbirth, or the puerperium, with delivery, with mention of post-partum complication
649.21	Bariatric surgery status complicating pregnancy, childbirth, or the puerperium, delivered, with or without mention of antepartum condition
649.22	Bariatric surgery status complicating pregnancy, childbirth, or the puerperium, with delivery, with mention of post-partum complication
649.31	Coagulation defects complicating pregnancy, childbirth, or the puerperium, delivered, with or without mention of antepartum condition
649.32	Coagulation defects complicating pregnancy, childbirth, or the puerperium, with delivery, with mention of post-partum complication
649.41	Epilepsy complicating pregnancy, childbirth, or the puerperium, delivered, with or without mention of antepartum condition
649.42	Epilepsy complicating pregnancy, childbirth, or the puerperium, delivered, with mention of postpartum complication
649.51	Spotting complicating pregnancy, delivered, with or without mention of antepartum condition
649.61	Uterine size date discrepancy, delivered, with or without mention of antepartum condition
649.62	Uterine size date discrepancy, delivered, with mention of postpartum complication
649.71	Cervical shortening, delivered, with or without mention of antepartum condition
649.81	Onset (spontaneous) of labor after 37 completed weeks of gestation but before 39 completed weeks gestation, with delivery by (planned) cesarean section, delivered, with or without mention of antepartum condition
649.82	Onset (spontaneous) of labor after 37 completed weeks of gestation but before 39 completed weeks gestation, with delivery by (planned) cesarean section, delivered, with mention of postpartum complication
651.01	Twin pregnancy, delivered, with or without mention of antepartum condition
651.11	Triplet pregnancy, with or without mention of antepartum condition
651.21	Quadruplet pregnancy, delivered
651.31	Twin pregnancy with fetal loss and retention of one fetus, delivered, with or without mention of antepartum condition
651.41	Triplet pregnancy with fetal loss and retention of one or more fetus(es), delivered, with or without mention of antepartum condition
651.51	Quadruplet pregnancy with fetal loss and retention of one or more fetus(es), delivered, with or without mention of antepartum condition
651.61	Other multiple pregnancy with fetal loss and retention of one or more fetus(es), delivered, with or without mention of antepartum condition
651.71	Multiple gestation following (elective) fetal reduction, delivered, with or without mention of antepartum condition
651.81	Other specified multiple gestation, delivered, with or without mention of antepartum condition
651.91	Unspecified multiple gestation, delivered, with or without mention of antepartum condition
652.01	Unstable lie, delivered, with or without mention of antepartum condition
652.11	Breech or other malpresentation successfully converted to

Code	Description
652.21	Breech presentation without mention of version, delivered, with or without mention of antepartum condition
652.31	Transverse or oblique presentation, delivered, with or without mention of antepartum condition
652.41	Face or brow presentation, delivered, with or without mention of antepartum condition
652.51	High head at term, delivered, with or without mention of antepartum condition
652.61	Multiple gestation with malpresentation of one fetus or more, delivered, with or without mention of antepartum condition
652.71	Prolapsed arm of fetus, delivered, with or without mention of antepartum condition
652.81	Other specified malposition or malpresentation, delivered, with or without mention of antepartum condition
652.91	Unspecified malposition or malpresentation, delivered, with or without mention of antepartum condition
653.01	Major abnormality of bony pelvis, not further specified, delivered, with or without mention of antepartum condition
653.11	Generally contracted pelvis, delivered, with or without mention of antepartum condition
653.21	Inlet contraction of pelvis, delivered, with or without mention of antepartum condition
653.31	Outlet contraction of pelvis, delivered, with or without mention of antepartum condition
653.41	Fetopelvic disproportion, delivered, with or without mention of antepartum condition
653.51	Unusually large fetus causing disproportion, delivered, with or without mention of antepartum condition
653.61	Hydrocephalic fetus causing disproportion, delivered, with or without mention of antepartum condition
653.71	Other fetal abnormality causing disproportion, delivered, with or without mention of antepartum condition
653.81	Disproportion of other origin, delivered, with or without mention of antepartum condition
653.91	Unspecified disproportion, delivered, with or without mention of antepartum condition
654.01	Congenital abnormalities of uterus, delivered, with or without mention of antepartum condition
654.02	Congenital abnormalities of uterus, delivered, with mention of post-partum complication
654.11	Tumors of body of uterus, delivered, with or without mention of antepartum condition
654.12	Tumors of body of uterus, delivered, with mention of post-partum complication
654.21	Previous cesarean delivery, delivered, with or without mention of antepartum condition
654.31	Retroverted and incarcerated gravid uterus, delivered, with or without mention of antepartum condition
654.32	Retroverted and incarcerated gravid uterus, delivered, with mention of post-partum complication
654.41	Other abnormalities in shape or position of gravid uterus, delivered, with or without mention of antepartum condition
654.42	Other abnormalities in shape or position of gravid uterus, delivered, with mention of post-partum complication
654.51	Cervical incompetence, delivered, with or without mention of antepartum condition
654.52	Cervical incompetence, delivered, with mention of post-partum complication
654.61	Other congenital or acquired abnormality of cervix, delivered, with or without mention of antepartum condition

Code	Description
654.62	Other congenital or acquired abnormality of cervix, delivered, with mention of post-partum complication
654.71	Congenital or acquired abnormality of vagina, delivered, with or without mention of antepartum condition
654.72	Congenital or acquired abnormality of vagina, delivered, with mention of post-partum complication
654.81	Congenital or acquired abnormality of vulva, delivered, with or without mention of antepartum condition
654.82	Congenital or acquired abnormality of vulva, delivered, with mention of post-partum complication
654.91	Other and unspecified abnormality of organs and soft tissues of pelvis, delivered, with or without mention of antepartum condition
654.92	Other and unspecified abnormality of organs and soft tissues of pelvis, delivered, with mention of post-partum complication
655.01	Central nervous system malformation in fetus, affecting management of mother, delivered, with or without mention of antepartum condition
655.11	Chromosomal abnormality in fetus, affecting management of mother, delivered, with or without mention of antepartum condition
655.21	Hereditary disease in family possibly affecting fetus, affecting management of mother, delivered, with or without mention of antepartum condition
655.31	Suspected damage to fetus from viral disease in the mother, affecting management of mother, delivered, with or without mention of antepartum condition
655.41	Suspected damage to fetus from other disease in the mother, affecting management of mother, delivered, with or without mention of antepartum condition
655.51	Suspected damage to fetus from drugs, affecting management of mother, delivered, with or without mention of antepartum condition
655.61	Suspected damage to fetus from radiation, affecting management of mother, delivered, with or without mention of antepartum condition
655.71	Decreased fetal movements, affecting management of mother, delivered, with or without mention of antepartum condition
655.81	Other known or suspected fetal abnormality, not elsewhere classified, affecting management of mother, delivered, with or without mention of antepartum condition
655.91	Unspecified suspected fetal abnormality, affecting management of mother, delivered, with or without mention of antepartum condition
656.01	Fetal-maternal hemorrhage, affecting management of mother, delivered, with or without mention of antepartum condition
656.11	Rhesus isoimmunization, affecting management of mother, delivered, with or without mention of antepartum condition
656.21	Isoimmunization from other and unspecified blood-group, affecting management of mother, delivered, with or without mention of antepartum condition
656.31	Fetal distress, affecting management of mother, delivered, with or without mention of antepartum condition
656.51	Poor fetal growth, affecting management of mother, delivered, with or without mention of antepartum condition

Code	Description
656.61	Excessive fetal growth, affecting management of mother, delivered, with or without mention of antepartum condition
656.71	Other placental conditions, affecting management of mother, delivered, with or without mention of antepartum condition
656.81	Other specified fetal and placental problems, affecting management mother, delivered, with or without mention of antepartum condition
656.91	Unspecified fetal and placental problem, affecting management of mother, delivered, with or without mention of antepartum condition
657.01	Polyhydramnios, delivered, with or without mention of antepartum condition
658.01	Oligohydramnios, delivered, with or without mention of antepartum condition
658.11	Premature rupture of membranes, delivered, with or without mention of antepartum condition
658.21	Delayed delivery after spontaneous or unspecified rupture, delivered, with or without mention of antepartum condition
658.31	Delayed delivery after artificial rupture of membranes, delivered, with or without mention of antepartum condition
658.41	Infection of amniotic cavity, delivered, with or without mention of antepartum condition
658.81	Other problems associated with amniotic cavity and membrane, delivered, with or without mention of antepartum condition
658.91	Unspecified problem associated with amniotic cavity and membrane, delivered, with or without mention of antepartum condition
659.01	Failed mechanical induction of labor, delivered, with or without mention of antepartum condition
659.11	Failed medical or unspecified induction of labor, delivered, with or without mention of antepartum condition
659.21	Unspecified type maternal pyrexia during labor, delivered, with or without mention of antepartum condition
659.31	Generalized infection during labor, delivered, with or without mention of antepartum condition
659.41	Grand multiparity, with current pregnancy, delivered, with or without mention of antepartum condition
659.51	Elderly primigravida, delivered, with or without mention of antepartum condition
659.61	Elderly multigravida, delivered, with or without mention of antepartum condition
659.71	Abnormality in fetal heart rate/rhythm, delivered, with or without mention of antepartum condition
659.81	Other specified indications for care or intervention related to labor and delivery, delivered, with or without mention of antepartum condition
659.91	Unspecified indication for care or intervention related to labor and delivery, delivered, with or without mention of antepartum condition
660.01	Obstruction caused by malposition of fetus at onset of labor, delivered, with or without mention of antepartum condition
660.11	Obstruction by bony pelvis during labor, delivered, with or without mention of antepartum condition
660.21	Obstruction by abnormal pelvic soft tissues during labor, delivered, with or without mention of antepartum condition

Code	Description
660.31	Deep transverse arrest and persistent occipitoposterior position, delivered, with or without mention of antepartum condition
660.41	Shoulder (girdle) dystocia, delivered, with or without mention of antepartum condition
660.51	Locked twins, delivered, with or without mention of antepartum condition
660.61	Failed trial of labor, unspecified, delivered, with or without mention of antepartum condition
660.71	Failed forceps or vacuum extractor, unspecified, delivered, with or without mention of antepartum condition
660.81	Other causes of obstructed labor, delivered, with or without mention of antepartum condition
660.91	Unspecified obstructed labor, delivered, with or without mention of antepartum condition
661.01	Primary uterine inertia, delivered, with or without mention of antepartum condition
661.11	Secondary uterine inertia, delivered, with or without mention of antepartum condition
661.21	Other and unspecified uterine inertia, delivered, with or without mention of antepartum condition
661.31	Precipitate labor, delivered, with or without mention of antepartum condition
661.41	Hypertonic, incoordinate, or prolonged uterine contractions, delivered, with or without mention of antepartum condition
661.91	Unspecified abnormality of labor, delivered, with or without mention of antepartum condition
662.01	Prolonged first stage of labor, delivered, with or without mention of antepartum condition
662.11	Prolonged labor, unspecified type, delivered, with or without mention of antepartum condition
662.21	Prolonged second stage of labor, delivered, with or without mention of antepartum condition
662.31	Delayed delivery of second twin, triplet, etc., delivered, with or without mention of antepartum condition
663.01	Prolapse of cord complicating labor and delivery, delivered, with or without mention of antepartum condition
663.11	Cord around neck, with compression, complicating labor and deliver, delivered, with or without mention of antepartum condition
663.21	Other and unspecified cord entanglement, with compression, delivered, with or without mention of antepartum condition
663.31	Other and unspecified cord entanglement, without mention
663.41	Short cord complicating labor and delivery, delivered, with or without mention of antepartum condition
663.51	Vasa previa complicating labor and delivery, delivered, with or without mention of antepartum condition
663.61	Vascular lesions of cord complicating labor and delivery, delivered, with or without mention of antepartum condition
663.81	Other umbilical cord complications during labor and delivery, delivered, with or without mention of antepartum condition
663.91	Unspecified umbilical cord complication during labor and delivery, delivered, with or without mention of antepartum condition

Code	Description
664.01	First-degree perineal laceration, delivered, with or without mention of antepartum condition
664.11	Second-degree perineal laceration, delivered, with or without mention of antepartum condition
664.21	Third-degree perineal laceration, delivered, with or without mention of antepartum condition
664.31	Fourth-degree perineal laceration, delivered, with or without mention of antepartum condition
664.41	Unspecified perineal laceration, delivered, with or without mention of antepartum condition
664.51	Vulvar and perineal hematoma, delivered, with or without mention of antepartum condition
664.61	Anal sphincter tear complicating delivery, not associated with third-degree perineal laceration, delivered, with or without mention of antepartum condition
664.81	Other specified trauma to perineum and vulva, delivered, with or without mention of antepartum condition
664.91	Unspecified trauma to perineum and vulva, delivered, with or without mention of antepartum condition
665.01	Rupture of uterus before onset of labor, delivered, with or without mention of antepartum condition
665.11	Rupture of uterus during labor, delivered, with or without mention of antepartum condition
665.22	Inversion of uterus, delivered, with mention of postpartum complication
665.31	Laceration of cervix, delivered, with or without mention of antepartum condition
665.41	High vaginal laceration, delivered, with or without mention of antepartum condition
665.51	Other injury to pelvic organs, delivered, with or without mention of antepartum condition
665.61	Damage to pelvic joints and ligaments, delivered, with or without mention of antepartum condition
665.71	Pelvic hematoma, delivered, with or without mention of antepartum condition
665.72	Pelvic hematoma, delivered with mention of postpartum complication
665.81	Other specified obstetrical trauma, delivered, with or without mention of antepartum condition
665.82	Other specified obstetrical trauma, delivered, with mention of postpartum complication
665.91	Unspecified obstetrical trauma, delivered, with or without mention of antepartum condition
665.92	Unspecified obstetrical trauma, delivered, with mention of postpartum complication
666.02	Third-stage postpartum hemorrhage, delivered, with mention of postpartum complication
666.12	Other immediate postpartum hemorrhage, delivered, with mention of postpartum complication
666.22	Delayed and secondary postpartum hemorrhage, delivered, with mention of postpartum complication
666.32	Postpartum coagulation defects, delivered, with mention of postpartum complication
667.02	Retained placenta without hemorrhage, delivered, with mention of postpartum complication

Code	Description
667.12	Retained portions of placenta or membranes, without hemorrhage, delivered, with mention of postpartum complication
668.01	Pulmonary complications of anesthesia or other sedation in labor and delivery, delivered, with or without mention of antepartum condition
668.02	Pulmonary complications of anesthesia or other sedation in labor and delivery, delivered, with mention of postpartum complication
668.11	Cardiac complications of anesthesia or other sedation in labor and delivery, delivered, with or without mention of antepartum condition
668.12	Cardiac complications of anesthesia or other sedation in labor and delivery, delivered, with mention of postpartum complication
668.21	Central nervous system complications of anesthesia or other sedation in labor and delivery, delivered, with or without mention of antepartum condition
668.22	Central nervous system complications of anesthesia or other sedation in labor and delivery, delivered, with mention of postpartum complication
668.81	Other complications of anesthesia or other sedation in labor and delivery, delivered, with or without mention of antepartum condition
668.82	Other complications of anesthesia or other sedation in labor and delivery, delivered, with mention of postpartum complication
668.91	Unspecified complication of anesthesia or other sedation in labor and delivery, delivered, with or without mention of antepartum condition
668.92	Unspecified complication of anesthesia or other sedation in labor and delivery, delivered, with mention of postpartum complication
669.01	Maternal distress, delivered, with or without mention of antepartum condition
669.02	Maternal distress, delivered, with mention of postpartum complication
669.11	Shock during or following labor and delivery, delivered, with or without mention of antepartum condition
669.12	Shock during or following labor and delivery, delivered, with mention of postpartum complication
669.21	Maternal hypotension syndrome, delivered, with or without mention of antepartum condition
669.22	Maternal hypotension syndrome, delivered, with mention of postpartum complication
669.32	Acute renal failure, delivered, with mention of postpartum complication
669.41	Other complications of obstetrical surgery and procedures, delivered, with or without mention of antepartum condition
669.42	Other complications of obstetrical surgery and procedures, delivered, with mention of postpartum complication
669.51	Forceps or vacuum extractor delivery without mention of indication, delivered, with or without mention of antepartum condition
669.61	Breech extraction, without mention of indication, delivered, with or without mention of antepartum condition
669.71	Cesarean delivery, without mention of indication, delivered, with or without mention of antepartum condition
669.81	Other complications of labor and delivery, delivered, with or without mention of antepartum condition

Code	Description
669.82	Other complication of labor and delivery, delivered, with mention of postpartum complication
669.91	Unspecified complication of labor and delivery, delivered, with or without mention of antepartum condition
669.92	Unspecified complication of labor and delivery, delivered, with mention of postpartum complication
670.02	Major puerperal infection, delivered, with mention of postpartum complication
670.12	Puerperal endometritis, delivered, with mention of postpartum complication
670.22	Puerperal sepsis, delivered, with mention of postpartum complication
670.32	Puerperal septic thrombophlebitis, delivered, with mention of postpartum complication
670.82	Other major puerperal infection, delivered, with mention of postpartum complication
671.01	Varicose veins of legs, delivered, with or without mention of antepartum condition
671.02	Varicose veins of legs, delivered, with mention of postpartum complication
671.11	Varicose veins of vulva and perineum, delivered, with or without mention of antepartum condition
671.12	Varicose veins of vulva and perineum, delivered, with mention of postpartum complication
671.21	Superficial thrombophlebitis, delivered, with or without mention of antepartum condition
671.22	Superficial thrombophlebitis, delivered, with mention of postpartum complication
671.31	Deep phlebothrombosis, antepartum, delivered, with or without mention of antepartum condition
671.42	Deep phlebothrombosis, postpartum, delivered, with mention of postpartum complication
671.51	Other phlebitis and thrombosis, delivered, with or without mention of antepartum condition
671.52	Other phlebitis and thrombosis, delivered, with mention of postpartum complication
671.81	Other venous complications, delivered, with or without mention of antepartum condition
671.82	Other venous complications, delivered, with mention of postpartum complication
671.91	Unspecified venous complication, delivered, with or without mention of antepartum condition
671.92	Unspecified venous complication, delivered, with mention of postpartum complication
672.02	Pyrexia of unknown origin, delivered, with mention of postpartum complication
673.01	Obstetrical air embolism, delivered, with or without mention of antepartum condition
673.02	Obstetrical air embolism, delivered, with mention of postpartum complication
673.11	Amniotic fluid embolism, delivered, with or without mention of antepartum condition
673.12	Amniotic fluid embolism, delivered, with mention of postpartum complication
673.21	Obstetrical blood-clot embolism, delivered, with or without mention of antepartum condition
673.22	Obstetrical blood-clot embolism, delivered, with mention of postpartum complication
673.31	Obstetrical pyemic and septic embolism, delivered, with or without mention of antepartum condition
673.32	Obstetrical pyemic and septic embolism, delivered, with mention of postpartum complication
673.81	Other obstetrical pulmonary embolism, delivered, with or without mention of antepartum condition
673.82	Other obstetrical pulmonary embolism, delivered, with mention of postpartum complication

Code	Description
674.01	Cerebrovascular disorders, with delivery, delivered, with or without mention of antepartum condition
674.02	Cerebrovascular disorders, delivered, with mention of postpartum complication
674.12	Disruption of cesarean wound, delivered, with mention of postpartum complication
674.22	Disruption of perineal wound, delivered, with mention of postpartum complication
674.32	Other complic of obstet surg wounds, delivered, with mention of postpartum complication
674.42	Placental polyp, delivered, with mention of postpartum complication
674.51	Peripartum cardiomyopathy, delivered, with or without mention of antepartum condition
674.52	Peripartum cardiomyopathy, delivered, with mention of postpartum condition
674.82	Other complications of puerperium, delivered, with mention of postpartum complication
674.92	Unspecified complications of puerperium, delivered, with mention of postpartum complication
675.01	Infection of nipple, delivered, with or without mention of antepartum condition
675.02	Infection of nipple, delivered, with mention of postpartum complication
675.11	Abscess of breast, delivered, with or without mention of antepartum condition
675.12	Abscess of breast, delivered, with mention of postpartum complication
675.21	Nonpurulent mastitis, delivered, with or without mention of antepartum condition
675.22	Nonpurulent mastitis, delivered, with mention of postpartum complication
675.81	Other spec infect of breast, with delivery, with or without mention of antepartum condition
675.82	Other spec infect of breast, delivered, with mention of postpartum complication
675.91	Unspec infect of breast, with delivery, with or without mention of antepartum condition
675.92	Unspec infect of breast, delivered, with mention of postpartum complication
676.01	Retracted nipple, delivered, with or without mention of antepartum condition
676.02	Retracted nipple, delivered, with mention of postpartum complication
676.11	Cracked nipple, delivered, with or without mention of antepartum condition
676.12	Cracked nipple, delivered, with mention of postpartum complication
676.21	Engorgement of breasts, delivered, with or without mention of antepartum condition
676.22	Engorgement of breasts, delivered, with mention of postpartum complication
676.31	Other disorder of breasts, delivered, with or without mention of antepartum condition
676.32	Other disorder of breasts, delivered, with mention of postpartum complication
676.41	Failure of lactation, delivered, with or without mention of antepartum condition
676.42	Failure of lactation, delivered, with mention of postpartum complication
676.51	Suppressed lactation, delivered, with or without mention of antepartum condition
676.52	Suppressed lactation, delivered, with mention of postpartum complication
676.61	Galactorrhea, delivered, with or without mention of antepartum condition
676.62	Galactorrhea, delivered, with mention of postpartum complication
676.81	Other disorders of lactation, delivered, with or without mention of antepartum condition
676.82	Other disorders of lactation, delivered, with mention of postpartum complication
676.91	Unspecified disorder of lactation, delivered, with or without mention of antepartum condition
676.92	Unspecified disorder of lactation, delivered, with mention of postpartum complication
678.01	Fetal hematologic conditions, delivered, with or without mention of antepartum condition
678.11	Fetal conjoined twins, delivered, with or without mention of antepartum condition

Code	Description
679.01	Maternal complications from in utero procedure, delivered with or without mention of antepartum condition
679.02	Maternal complications from in utero procedure, delivered with mention of postpartum condition
679.11	Fetal complications from in utero procedure, delivered, with or without mention of antepartum condition
679.12	Fetal complications from in utero procedure, delivered with mention of postpartum condition
72	Forceps, vacuum, and breech delivery
72.0	Low forceps operation
72.1	Low forceps operation with episiotomy
72.2	Mid forceps operation
72.21	Mid forceps operation with episiotomy
72.29	Other mid forceps operation
72.3	High forceps operation
72.31	High forceps operation with episiotomy
72.39	Other high forceps operation
72.4	Forceps rotation of fetal head
72.5	Breech extraction
72.51	Partial breech extraction with forceps to aftercoming head
72.52	Other partial breech extraction
72.53	Total breech extraction with forceps to aftercoming head
72.54	Other total breech extraction
72.6	Forceps application to aftercoming head
72.7	Vacuum extraction
72.71	Vacuum extraction with episiotomy
72.79	Other vacuum extraction
72.8	Other specified instrumental delivery
72.9	Unspecified instrumental delivery
73	Other procedures inducing or assisting delivery
73.0	Artificial rupture of membranes
73.01	Induction of labor by artificial rupture of membranes
73.09	Other artificial rupture of membranes
73.1	Other surgical induction of labor
73.2	Internal and combined version and extraction
73.21	Internal and combined version without extraction
73.22	Internal and combined version with extraction
73.3	Failed forceps
73.4	Medical induction of labor
73.5	Manually assisted delivery

Code	Description
73.51	Manual rotation of fetal head
73.59	Other manually assisted delivery
73.6	Episiotomy
73.8	Operations on fetus to facilitate delivery
73.9	Other operations assisting delivery
73.91	External version
73.92	Replacement of prolapsed umbilical cord
73.93	Incision of cervix to assist delivery
73.94	Pubiotomy to assist delivery
73.99	Other operations assisting delivery
74.0	Classical cesarean section
74.1	Low cervical cesarean section
74.2	Extraperitoneal cesarean section
74.4	Cesarean section of other specified type
74.9	Cesarean section of unspecified type
74.99	Other cesarean section of unspecified type
763.0	Breech delivery and extraction affecting fetus or newborn
763.2	Forceps delivery affecting fetus or newborn
763.3	Delivery by vacuum extractor affecting fetus or newborn
763.4	Cesarean delivery affecting fetus or newborn
763.6	Precipitate delivery affecting fetus or newborn
V27	Outcome of delivery
V27.1	Single stillborn
V27.4	Twins, stillborn
V27.7	Other multiple birth, all stillborn
V27.9	Mother with unspecified outcome of delivery

B. CODES TO IDENTIFY GESTATIONAL AGE AT BIRTH

Code	Description	Assumed gestational age at delivery in weeks
765.21	Less than 24 completed weeks of gestation	24
765.22	24 completed weeks of gestation	24
765.23	25-26 completed weeks of gestation	26
765.24	27-28 completed weeks of gestation	28
765.0*	Disorders relating to extreme immaturity of infant	28
765.25	29-30 completed weeks gestation	30
765.26	31-32 completed weeks gestation	32
765.27	33-34 completed weeks gestation	34
765.28	35-36 completed weeks gestation	36
765.1*	Disorders related to other preterm infants	35
765.20	Preterm with unspecified weeks of gestation	35
644.21	Early onset of delivery, delivered, with or without mention of antepartum condition	35
645.1*	Post-term pregnancy	41
766.21	Post-term infant	41
645.2*	Prolonged pregnancy	42
766.22	Prolonged gestation of infant	42

C. CODES TO IDENTIFY MULTIPLE GESTATION PREGNANCY

Code	Description
6512	QUADRUPLET PREGNANCY
65120	QUADRUPLET PG UNSPEC AS EPIS CARE
65121	QUADRUPLET PREGNANCY DELIVERED
65123	QUADRUPLET PREGNANCY ANTEPARTUM
6515	QUAD PG W/FETL LOSS&RETAIN 1/MOR
65150	QUAD PG-FETL LOSS&RETN 1/>UNS EOC
65151	QUAD PG W/FETAL LOSS&RETN 1/> DEL
65153	QUAD PG-FETL LOSS&RETN 1/> ANTPRTM
6511	TRIPLET PREGNANCY
65110	TRIPLET PG UNSPEC AS EPIS CARE
65111	TRIPLET PREGNANCY DELIVERED
65113	TRIPLET PREGNANCY ANTEPARTUM
6514	TRIPLET PG W/FETAL LOSS&RETN 1/MORE
65140	TRIPLT PG-FETL LOSS&RETN 1/>UNS EOC
65141	TRIPLET PG W/FETL LOSS&RETN 1/> DEL
65143	TRIPLT PG-FETL LOSS&RETN 1/>ANTPRTM
6510	TWIN PREGNANCY
65100	TWIN PREGNANCY UNSPEC AS EPIS CARE
65101	TWIN PREGNANCY DELIVERED
65103	TWIN PREGNANCY ANTEPARTUM
6513	TWIN PG W/FETAL LOSS&RETN 1 FETUS
65130	TWIN PG-FETAL LOSS&RETAIN 1-UNS EOC
65131	TWIN PG-FETAL LOSS&RETN 1 FETUS DEL
65133	TWIN PG-FETAL LOSS&RETAIN 1 ANTPRTM
V31	LIVEBORN TWIN MATE LIVEBORN
V32	LIVEBORN TWIN-MATE STILLBORN
V33	LIVEBORN TWIN-UNS MATE LIVEB/STILLB
651	MULTIPLE GESTATION
6516	OTH MX PG W/FETAL LOSS&RETN 1/MORE
65160	OTH MX PG-FETL LOSS&RETN 1/>UNS EOC
65161	OTH MX PG-FETAL LOSS&RETAIN 1/>DEL
65163	OTH MX PG-FETL LOSS&RETN 1/>ANTPRTM
6517	MX GEST FLW ELEC FETAL REDUCTION
65170	MX GEST FLW FETL RDUC UNS EPIS CARE
65171	MX GEST FETL RDUC DEL W/WO AP COND
65173	MX GEST FLW FETL RDUC AP COND/COMPL
6518	OTHER SPECIFIED MULTIPLE GESTATION
65180	OTH SPEC MX GEST UNS AS EPIS CARE
65181	OTH SPEC MULTIPLE GESTATION DELIV
65183	OTH SPEC MULTIPLE GESTATION ANTPRTM
6519	UNSPECIFIED MULTIPLE GESTATION

Code	Description
65190	UNSPEC MX GEST UNSPEC AS EPIS CARE
65191	UNSPEC MULTIPLE GESTATION DELIVERED
65193	UNSPEC MULTIPLE GESTATION ANTPRTM
V34	LIVEBORN OTH MX MATES ALL LIVEBORN
V35	LIVEBORN OTH MX MATES ALL STILLBORN
V36	LIVEBORN OTH MX-MATES LIVEB&STILLB
V37	LIVEB OTH MX-UNS MATES LIVEB/STILLB

D. CODES USED TO IDENTIFY CHROMOSOMAL ANOMALIES

Code	Code Type	Description
758	DX	CHROMOSOMAL ANOMALIES
758.0	DX	DOWNS SYNDROME
758.1	DX	PATAUS SYNDROME
758.2	DX	EDWARDS SYNDROME
758.3	DX	AUTOSOMAL DELETION SYNDROMES
758.31	DX	CRI-DU-CHAT SYNDROME
758.32	DX	VELO-CARDIO-FACIAL SYNDROME
758.33	DX	AUTOSOMAL DEL SYND OTH MICRODEL
758.39	DX	AUTOSOMAL DEL SYND OTH AUTOSOML DEL
758.4	DX	BAL AUTOSOM TRNSLOCAT NORMAL INDIVD
758.5	DX	OTHER CONDS DUE AUTOSOMAL ANOMALIES
758.6	DX	GONADAL DYSGENESIS
758.7	DX	KLINEFELTERS SYNDROME
758.8	DX	OTH COND D/T CHROMOSOME ANOMALIES
758.81	DX	OTH COND DUE SEX CHROMOSM ANOMALIES
758.89	DX	OTH COND D/T CHROMOSOME ANOMAL OTH
758.9	DX	CONDS DUE ANOMALY UNSPEC CHROMOSOME
279.11	DX	DIGEORGES SYNDROME
DOWNS	Birth certificate	Down's syndrome
OTHERCHR	Birth certificate	Other chromosomal anomaly

E. CODES TO IDENTIFY INFLUENZA VACCINATION

Code	Type	Description
Q2035	HCPCS	Influenza virus vaccine, split virus, when administered to individuals 3 years of age and older, for intramuscular use (Afluria)
Q2036	HCPCS	Influenza virus vaccine, split virus, when administered to individuals 3 years of age and older, for intramuscular use (FluLaval)
Q2037	HCPCS	Influenza virus vaccine, split virus, when administered to individuals 3 years of age and older, for intramuscular use (Fluvirin)
Q2038	HCPCS	Influenza virus vaccine, split virus, when administered to individuals 3 years of age and older, for intramuscular use (Fluzone)
Q2039	HCPCS	Influenza virus vaccine, split virus, when administered to individuals 3 years of age and older, for intramuscular use (not otherwise specified)
Q2034	HCPCS	Influenza virus vaccine, split virus, for intramuscular use (Agriflu)
G0008	HCPCS	Administration of influenza virus vaccine
90655	CPT	Influenza virus vaccine, split virus, preservative free, for children 6-35 months of age, for intramuscular use
90657	CPT	Influenza virus vaccine, split virus, for children 6-35 months of age, for intramuscular use
90656	CPT	Influenza virus vaccine, split virus, preservative free, for use in individuals 3 years of age and above, for intramuscular use
90658	CPT	Influenza virus vaccine, split virus, for use in individuals 3 years of age and above, for intramuscular use
90662	CPT	Influenza virus vaccine, split virus, preservative free, enhanced immunogenicity via increased antigen content, for intramuscular use
90659	CPT	Influenza virus vaccine, whole virus, for intramuscular or jet injection use
90724	CPT	Influenza virus vaccine
99.52	ICD9	Prophylactic vaccination against influenza
V04.81	ICD9	Need for prophylactic vaccination and inoculation against influenza
V06.6	ICD9	Need for prophylactic vaccination and inoculation against streptococcus pneumoniae (pneumococcus) and influenza

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