MINI-SENTINEL/CBER PROTOCOL

VACCINES ADMINISTERED IN PREGNANCY

AND BIRTH OUTCOMES:

A PROJECT TO DEVELOP DATA INFRASTRUCTURE

AND DESIGN FRAMEWORK

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Mini-Sentinel is a pilot project sponsored by the U.S. Food and Drug Administration (FDA) to inform and facilitate development of a fully operational active surveillance system, the Sentinel System, for monitoring the safety of FDA-regulated medical products. Mini-Sentinel is one piece of the Sentinel Initiative, a multi-faceted effort by the FDA to develop a national electronic system that will complement existing methods of safety surveillance. Mini-Sentinel Collaborators include Data and Academic Partners that provide access to healthcare data and ongoing scientific, technical, methodological, and organizational expertise. The Mini-Sentinel Coordinating Center is funded by the FDA through the Department of Health and Human Services (HHS) Contract number HHSF223200910006I.

History of Modifications

Version	Date	Modification	By
V2	12/5/2014	• We now distinguish between primary and pilot aims. The primary aims include (1) establishing and describing the mother-infant cohort and (2) evaluating the validity of Data Partner claims-based data for vaccine safety surveillance of adverse birth outcomes. The pilot aims include implementing the case-time-control design (CTC). Of the CTC analyses, the chart-review analysis will be considered the main pilot analysis, whereas the electronic data analysis will be considered the alternative pilot analysis. • Though we will still conduct the CTC design, we will no longer conduct a case-control design to evaluate the association between influenza vaccination and oral clefts. • We will no longer exclude deliveries that have codes for spontaneous abortion or stillbirth at the same encounter. • We now require deliveries included in the CTC design to be singleton deliveries. • We now require cases and controls in the CTC design to be from the same state and Data Partner. We also modified the criteria such that we will match on the following confounders if numbers permit: pre-gestational diabetes, gestational diabetes, 1st trimester prenatal care, urinary tract infections, respiratory tract infections, and medically attended fever. • We removed the CTC sensitivity analysis of electronic data, in which gestational age in preterm deliveries that did not have further specification, was to be randomly imputed based on the distribution in the U.S. We also deleted the sensitivity analysis in which gestational age in these deliveries was to be recalibrated based on patients with multiple sources of gestational age data. • We updated the method for estimating pregnancy start date using the American College of Obstetrics and Gynecology recommendations for best obstetric dating. • We now specify that outcomes will be identified in maternal claims or infant claims data within 30 days of the child's birth. We will also consider using longer case identification periods in infant data (e.g., up to 90 days or 365 days after birth) if case and control	Influenza vaccines and birth outcomes working group

Version	Date	Modification	By
		numbers permit. • We now specify that the CTC analyses considering alternative outcomes of CLP or CL vs. CP will be conducted if numbers permit. • We now require mothers to be linked to infants in electronic data to be included in the CTC study. • We made a modification to case criteria such that in addition to claims data, we will also use birth certificate data (when available) to identify chromosomal abnormalities for the purposes of exclusions. We also clarified that exclusion criteria based on chromosomal abnormalities will be implemented among controls. • Other minor wording modifications were made.	
V3	1/20/2017	• We changed the title to reflect applicability of this project to any vaccines administered in pregnancy. • We added a brief statement about the main goal of the study and what aspects of exposure and outcome would be useful in achieving that goal in the first part of Section I (Executive Summary) and inserted a brief rationale for the selection of influenza vaccine as the exposure and cleft lip and palate as the outcomes. • We modified aim 2 (which has three parts) so that we will no longer be estimating the sensitivity, specificity, negative predictive value, and positive predictive value of ICD9/CPT codes for confounders of interest. • For the chart review analysis, we have modified the gestational age algorithm. We will assign date of conception in the following order of preference: 1) ART-derived gestational age 2) LMP verified by ultrasound (US) dating 3) US dating, does not verify LMP 4) Gestational age as recorded on labor and delivery record 5) Gestational age as recorded on birth record 6) US, none of the other methods available 7) LMP, none of the other methods available.	

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I. EXECUTIVE SUMMARY

Developing the infrastructure to conduct routine monitoring of the safety of vaccines administered during pregnancy is an important FDA priority. This project was thus initiated to develop the data infrastructure and study design framework within the Sentinel System to investigate potential adverse birth outcomes after vaccinations during pregnancy. To do this, it was important to identify an appropriate use case, specifically a vaccine administered frequently enough during pregnancy to provide us with an adequate number of exposed women and a birth outcome that was common enough and was relatively straightforward to accurately identify in claims data.

Because of the high risk of complications from influenza during pregnancy, the Advisory Committee on Immunization Practices (ACIP) recommends influenza vaccination for women pregnant anytime during the influenza season, regardless of gestational age. This recommendation results in greater numbers of pregnant women vaccinated, making it a useful vaccine to evaluate in this pilot project. Although no safety concerns have been identified to date, prior epidemiologic studies evaluating the safety of influenza vaccines during pregnancy have been limited by the inclusion of small numbers of women receiving influenza vaccine during the 1st trimester and the comparison of vaccinated to unvaccinated women, which may have led to confounding due to important differences by vaccination status.

Mini-Sentinel is a pilot project sponsored by the FDA to inform and facilitate development of a fully operational active surveillance system, the Sentinel System, for monitoring the safety of FDA-regulated medical products. Within Mini-Sentinel, the Post-licensure Rapid Immunization Safety Monitoring (PRISM) is well-suited to address questions of vaccine safety in pregnant women because of its large size (more than 500,000 pregnancies ending in a live delivery) and well-defined study population. Building upon the existing PRISM framework, we propose to (1) augment the current PRISM data infrastructure to evaluate potential associations between vaccine exposure of pregnant women and adverse events occurring in mothers and infants and (2) develop the methodological framework for evaluating the potential risk for birth defects following vaccine exposure within PRISM.

For this study, electronic data are available from 4 national health insurance plans (henceforth referred to as “Data Partners”) and from Immunization Information Systems (IIS) in the Departments of Health in 7 states and New York City. Electronic data from Data Partners include enrollment, demographic, pharmacy dispensing, diagnosis, and procedure information. We will link mothers and infants identified in electronic Data Partner data by using administrative and claims-based data. Mother-infant pairs will then be linked to birth certificate data from Vital Events Registries in the Departments of Health in up to 10 states or cities in order to obtain additional confounder and gestational age information. Birth certificate data will also be used to form additional mother-infant linkages among mothers that remain unlinked to infants using electronic Data Partner sources alone. Chart review will be conducted to confirm vaccination, gestational age at delivery, potential confounders, and outcomes.

As mentioned, no safety concerns with regard to birth outcomes have been identified for influenza vaccines administered in pregnancy. Cleft lip and palate are easily identifiable early after birth and their corresponding ICD9 diagnosis codes have a high positive predictive value, making these outcomes suitable for evaluation in this pilot project. Using the combined outcome of cleft lip without cleft palate (CL), cleft palate without cleft lip (CP), or cleft lip with cleft palate (CLP) as a test case to evaluate the capabilities of the new data infrastructure and methodological approach, we will examine the

association between seasonal trivalent inactivated influenza vaccine (TIV) receipt during the relevant organogenesis period and risk for this particular outcome.[1]

A case-time-control design will be implemented to determine the feasibility of using this design to examine birth outcomes in the context of vaccine safety. Among cases, we will compare the odds of exposure for each case during the relevant organogenesis period to that in a self-matched comparison period. A control group matched on estimated date of conception and maternal age will be used to adjust for temporal trends in vaccination with respect to seasonality and gestational age. The major strength of the case-time-control design is implicit adjustment for between-person confounders that do not vary over time. However, the case-time-control design is subject to incomplete adjustment for time trends in exposure if controls do not represent the time trend in exposure of cases. An example of different time trends in exposure might occur if women at greater risk of having a child with a birth defect are more likely to be vaccinated earlier or later during pregnancy than women at lower risk. Additionally, the case-time-control design may have less statistical power than the nested case-control study.

Desired results and potential implications for PRISM

Prior PRISM assessments have focused on retrospective vaccine-outcome assessments within single individuals using data from Data Partners and Immunization Information Systems. This protocol describes the PRISM program's efforts to develop a large database to be used for retrospective studies of potential adverse events following vaccination in pregnant women by linking mothers with infants and by incorporating an additional data source, specifically birth certificate data. The results will be used to determine the feasibility of pregnancy outcome and birth outcome surveillance within Mini-Sentinel's PRISM program and to evaluate the novel data linkages required to conduct such surveillance.

II. BACKGROUND AND PUBLIC HEALTH IMPLICATIONS

Influenza infection has been associated with severe illness and mortality in pregnant women.[1,2] Pregnancy may increase a woman's risk of influenza-related complications through physiologic changes in heart rate, stroke volume, lung capacity, and cell-mediated immune responses.[1] During the 1918 and 1957 influenza pandemics, great numbers of excess deaths due to influenza were seen in pregnant women.[3-5] More recently, during the 2009-2010 pandemic, pregnant women infected with H1N1 influenza were at increased risk of serious illness and death and were four times more likely than the general infected population to become hospitalized.[6,7]

Pregnancy also has been associated with increased risk of influenza-related morbidity during inter-pandemic influenza seasons, with higher risk of complications at later stages of pregnancy. In a large study of Tennessee Medicaid enrollees over the course of 17 influenza seasons, women diagnosed with influenza in their first, second, and third trimesters of pregnancy had acute cardiopulmonary hospitalization rates of 6.5, 12.6, and 21.7 per 10,000 person months, respectively as compared to 6.4 per 10,000 person months in non-pregnant women diagnosed with influenza.[8]

Due to the high risk of complications from influenza infection during pregnancy, the Advisory Committee on Immunization Practices has recommended routine influenza vaccination for women pregnant during the influenza season since the 1997-1998 influenza season.[9] According to prescribing information, FluMist® (a live attenuated influenza vaccine manufactured by MedImmune) is not contraindicated for

[1] The study time period precedes licensure of quadrivalent inactivated influenza vaccine (IIV4). However, it is anticipated that the methodological approach in this protocol would apply similarly to IIV4.

use in pregnant populations.[10] However, the ACIP recommends against administering FluMist in pregnant populations due to the theoretical risk that live attenuated vaccines may pose to the fetus and instead recommends vaccination with seasonal trivalent inactivated influenza vaccine (TIV) in pregnant populations. [11] The initial ACIP recommendation for TIV in pregnant women made in 1997 was limited to the 2nd and 3rd trimesters to avoid "coincidental association with spontaneous abortion." However, the ACIP recommendation was later expanded to all 3 trimesters beginning with the 2004-2005 influenza season.[12]

Influenza vaccination rates in pregnant women are currently below full coverage levels. In the Pregnancy Risk Assessment Monitoring System (PRAMS), a collaboration between the Centers for Disease Control and Prevention (CDC) and 37 states, New York City, and a South Dakota tribal-state project, the prevalence of influenza vaccination coverage was 50.7% for seasonal vaccine and 46.6% for H1N1 vaccine during the 2009-2010 influenza season.[13] In the PRAMS study, over 45% of pregnant women cited safety concerns for their baby and/or for themselves; among those not receiving the H1N1 influenza vaccine, over 60% cited safety concerns for their baby and/or for themselves.[13] For women pregnant anytime during the 2010-11 and 2011-12 influenza seasons, the influenza vaccination coverage rates were 49% and 47%, respectively, according to Internet panel surveys conducted by the CDC at the end of each of the two seasons. [14]

No study to date has found maternal or fetal safety concerns in pregnant women receiving TIV. Of the existing post-marketing safety studies on seasonal TIV during pregnancy, few have included large numbers of women vaccinated during the first trimester. A number of studies, which do not mention manufacturer, have examined risk of pregnancy and birth outcomes following TIV in the United States. In the earliest published study, the safety of TIV was examined in more than 2,000 women who received an influenza vaccine during pregnancy and their children in the National Collaborative Perinatal Project during the early 1960's.[15] *In-utero* exposure to TIV was not associated with fetal malformations, cognitive or neurologic disabilities, or childhood cancers during the first 7 years of life. More recently, in a retrospective cohort of 252 women receiving TIV in the 2nd or 3rd trimester between July 1998 and June 2003 and 826 unvaccinated pregnant women, Munoz et al. did not find any serious adverse events within 42 days of vaccination using electronic data from a large multispecialty clinic in Texas.[16] In the same study, TIV was not associated with adverse pregnancy outcomes, including cesarean section and premature delivery, or with a number of infant medical conditions, including congenital malformations, from birth to age 6 months. In a retrospective cohort study using Georgia PRAMS data on 578 vaccinated pregnant women and 3,748 unvaccinated pregnant women experiencing a live birth between June 2004 through September 2006, TIV receipt during pregnancy was associated with *decreased* risk of preterm birth and small-for-gestational-age birth during the period of widespread influenza activity, but was not associated with either outcome during the period of pre-influenza activity.[17] In a study of 8,690 vaccinated pregnant women (439 vaccinated during the first trimester and 8,251 vaccinated during the second or third trimesters) and 76,153 unvaccinated pregnant women from a single county hospital and clinic system in Texas, TIV was not associated with increased risk of preterm delivery at 36 or less weeks gestation or at less than 32 weeks gestation, low birth weight, major malformations, stillbirth, NICU admission, neonatal death, neonatal pneumonia, or hyperbilirubinemia. TIV was associated with *decreased* risk of stillbirth, neonatal death, and preterm delivery at 36 or less weeks gestation and at less than 32 weeks gestation.

In a Vaccine Safety Datalink (VSD) retrospective cohort study of 3,707 pregnant women who received TIV during at least one of 5 influenza seasons (Fall 1997 to Spring 2002) and 45,878 unvaccinated pregnant women from a single medical care organization in California, no increased risk of cesarean section or preterm delivery was noted.[18] Two recent VSD studies incorporating data from additional

medical care organizations have also examined the safety of TIV in pregnant populations. In a retrospective cohort study that used data from 7 medical care organizations in the VSD from June 2002 through July 2009 and included 75,906 vaccinated pregnant women (21,553 during the first trimester and 54,353 during the second or third trimesters) and 147,992 unvaccinated pregnant women, no associations were found between vaccination and potential adverse events, including allergic reactions, cellulitis, and seizures in the 3 days following vaccination.[19] Furthermore, in the 42 days following TIV, no incident cases of Guillain-Barre syndrome, optic neuritis, transverse myelitis, or Bell's palsy were found and TIV was not found to be associated with thrombocytopenia or an acute neurologic event. In a matched case-control study of 243 cases and 243 controls conducted in six medical care organizations in the VSD, receipt of TIV during the 2005-2006 or 2006-2007 season was not found to be associated with spontaneous abortion in the 28 days following vaccination; furthermore, exposure defined as same-season vaccination before conception vs. vaccination post-conception was not significantly associated with spontaneous abortion when compared to no vaccination.[20] TIV in pregnant women has also been investigated in passive surveillance using data from the Vaccine Adverse Events Reporting System (VAERS). In a review of 175 VAERS reports from 1996 through 2009 in pregnant women administered seasonal influenza vaccines (148 received TIV and 27 received LAIV), the number of pregnancy complications or fetal outcomes observed was not greater than expected.

Although existing post-marketing safety data in pregnant women are reassuring, many of the existing studies have a number of limitations, including limited numbers of women receiving vaccine during the 1st trimester, potential confounding bias due to comparing vaccinated to unvaccinated women, low numbers of congenital malformation outcomes, and composite congenital malformation outcomes that combine all types of malformations.[21] Obtaining additional high quality post licensure safety data in pregnant populations is a public health priority, particularly given recent policies emphasizing the vaccination of pregnant populations in the U.S. In October 2012, the ACIP recommended for the first time that all pregnant women receive tetanus, diphtheria, and pertussis vaccine (Tdap) to provide infants protection from pertussis early in life; prior to that, in June 2011, the ACIP had voted to recommend Tdap vaccination to pregnant women, but only to those who had not previously received the vaccine.[22] Of note, repeated doses of Tdap are considered to be off-label use since Tdap vaccines are FDA-approved for one-time use in adolescents and adults.[23]

Mini-Sentinel is a pilot project sponsored by the FDA to inform and facilitate development of a fully operational active surveillance system, the Sentinel System, for monitoring the safety of FDA-regulated medical products.[24] Within Mini-Sentinel, Post-licensure Rapid Immunization Safety Monitoring (PRISM) is a collaboration between FDA, the Harvard Pilgrim HealthCare Institute (coordinating center), and four large national health insurance plans (Aetna, HealthCore, Humana, and OptumInsight, henceforth referred to as "Data Partners").[25] It is well suited to address questions of vaccine safety in pregnant women because of its large size and well-defined study population. Building upon the existing system, we propose to develop the data infrastructure and the methodological framework to evaluate potential associations between vaccine exposure of pregnant women and adverse events occurring in mothers or infants. In the present activity, mother and infant data from Data Partners will be linked with birth certificate data from Vital Events Registries in select states and cities to investigate the risk of adverse birth outcomes following influenza vaccination in pregnant women.

III. OBJECTIVES

This protocol describes the PRISM program's efforts to develop a large database to be used for retrospective studies of potential adverse events following vaccination in pregnant women. The aim is to

establish the data infrastructure and methodological framework for studying adverse birth outcomes (e.g., congenital malformations) in this system. As such, this is principally an infrastructure building and methods development activity. The results will be used to determine the feasibility of pregnancy surveillance within Mini-Sentinel's PRISM program and to evaluate the novel data linkages required to conduct such surveillance. Influenza vaccines and oral clefts are not under investigation *per se*, but are being used as test cases to fully evaluate the capabilities of the new methods and data infrastructure in anticipation of future needs.

The initial step for building the data infrastructure will be to link Data Partner data on mothers and infants using an algorithm that builds upon existing work in Data Partners. We will then use the example association of a select vaccine (i.e., TIV) and a select outcome [i.e., combined outcome of cleft lip without cleft palate (CL), cleft palate without cleft lip (CP), or cleft lip with cleft palate (CLP)]. While we will examine CL, CP, or CLP as the main outcome, we will include CL or CLP vs. CP as alternative outcomes, if numbers permit. The rationale for choosing this particular outcome in our initial work is that its corresponding ICD9 diagnosis codes have a high positive predictive value[26] and that it is typically identified within the first months of life. For Data Partner members in select states and cities with Vital Events Registries providing birth certificate data, mother-infant pairs formed using Data Partner information will also be linked to birth certificate data to obtain gestational age, confounder and outcome information. For mothers that remain unlinked to infants when using only Data Partner information to form mother-infant pairs, birth certificate data will be used to identify additional mother-infant pairs. We will conduct medical record reviews to confirm case status, confounders, and gestational age at delivery to better understand the potential strengths and limitations of using electronic data (i.e., administrative, claims-based, and birth certificate data) for surveillance.

IV. SPECIFIC AIMS

PRIMARY AIMS

AIM 1: To establish and describe a cohort of mother-infant pairs within the Sentinel database, for use in future potential studies of vaccination safety during pregnancy

a. To estimate the proportion of live deliveries (i.e., mothers) identified in Data Partner data that can be linked to infants using only Data Partner data. Furthermore, for Data Partner members in states and cities with Vital Events Registries providing birth certificate data, we will measure the incremental gain in the proportion of deliveries linked to infants using birth certificate data.

b. To compare maternal characteristics (i.e., age, race, education, and healthcare utilization) between mother-infants pairs formed using only Data Partner data vs. using birth certificate data

AIM 2: To evaluate the validity of Data Partner claims-based data for vaccine safety surveillance for adverse birth outcomes

a. To estimate the positive predictive value of ICD9 diagnosis codes for the birth outcome of interest for cases vaccinated in the risk or control intervals
b. To estimate the proportion of deliveries whose estimated date of conception using electronic claims-based data is within 7 or 14 days of the corresponding estimates based on medical records and based on birth certificate data

PILOT AIMS

AIM 3: To implement a case-time control study to evaluate the association between administration of a select vaccine (i.e., seasonal trivalent inactivated influenza vaccine [TIV]) during a risk interval corresponding to the relevant organogenesis period and a select birth outcome [i.e., combined outcome of cleft lip without cleft palate (CL), cleft palate without cleft lip (CP), or cleft lip with cleft palate (CLP)]

a. To estimate odds ratios (OR) and attributable risk (AR) estimates of CL, CP, or CLP using chart-confirmed cases (main pilot analysis) and electronic data (alternative pilot analysis using claims-based data and birth certificate data if available)

b. To evaluate the impact of the following on OR and AR estimates in the main and alternative pilot analyses:

   i. Alternative risk intervals based on the timing of exposure as defined by gestational age at vaccination
   ii. Alternative outcomes that distinguish between CLP or CL vs. CP, if numbers permit

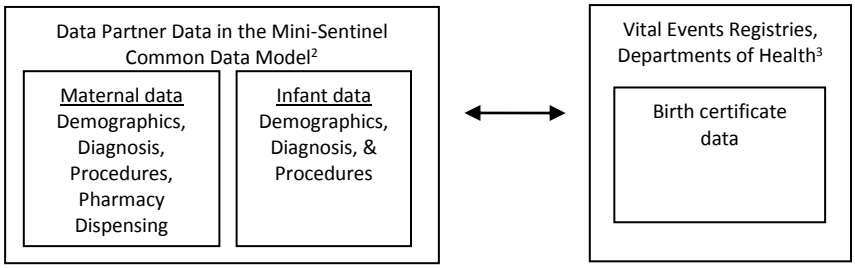
V. METHODS FOR ALL SPECIFIC AIMS

A. Study Population and Data Sources

The proposed Data Partners for participation in this activity are Aetna, HealthCore, Humana, and OptumInsight. This assessment will include data from the following sources: (1) immunization data from Immunization Information Systems (IISs) in select states and New York City, (2) administrative and claims-based data in the Mini-Sentinel Common Data Model (MSCDM, a common data format used by Data Partners), including demographic, diagnoses, procedure, and pharmacy dispensing data,[27] and (3) birth certificate data from Vital Events Registries in select cities and states. In 2012 as part of a separate PRISM activity, health plan data in three of the DPs were matched with IIS data from 2004-2011; each Data Partner matched data on health plan members (without regard to pregnancy status) with all or some of the following IIS: Florida, Michigan, Minnesota, New York City, New York state, Pennsylvania, Wisconsin, and Virginia.[28] For the present study, data from the previous IIS linkages will be used where and when available. No additional IIS linkage will be carried out for this study. Linkages of MSCDM data to birth certificate data, for select cities and states, are to be undertaken as part of the present study.

The study population will consist of women 10 through 55 years of age identified as having live deliveries and their infants. Women who have had a live delivery will be identified using demographics, diagnosis, and procedure code information in the MSCDM. Infants born to these women will be identified using demographic data in the MSCDM. As part of building the infrastructure needed to study infant outcomes following maternal vaccinations during pregnancy, the first part of this study activity will focus on forming internal linkages of these infants with mothers using MSCDM data and additional internal Data Partner information (**Figure 1**). In addition, this study will link the mother and infant pairs to birth certificate data from Vital Events Registries in select cities and states to obtain information on potential confounders. Birth certificates will also be used to form additional mother-infant pairs for those who cannot be linked using Data Partner information alone or where infants are not enrolled in the same health plan.

Figure 1. Data linkages formed for PRISM Influenza Vaccines and Birth Outcomes Assessment[1]



[1] Figure not drawn to scale with respect to size of populations
[2] Mother to infant linkages of MSCDM data will be formed as part of this study. Not all mother-infant pairs will have Data Partner information available
[3] Birth Certificate data, collected as part of this study, will only be available from Vital Events Registries in Departments of Health in select states/cities.

In the population of mother-infant pairs available for analysis, we will then identify maternal vaccine exposure, potential confounders and infant birth outcomes. Unless otherwise noted, all data will be assessed from Data Partner administrative and claims data in the MSCDM. Maternal vaccine exposure information will be assessed using diagnosis, procedure, and pharmacy dispensing codes and IIS codes. Maternal age, a potential confounder, will be derived from demographic data, while concomitant medication exposure during first trimester (e.g., retinoid and folic acid antagonists) will be assessed using pharmacy dispensing codes. Maternal co-morbidities that may be confounders (e.g., diabetes, overweight, and obesity) will be assessed using diagnosis, procedure, and pharmacy dispensing codes. Gestational age at delivery will be estimated using diagnosis codes for mothers and infants while birth defect outcomes will be assessed using diagnosis and procedure codes for infants. Where available, birth certificates data will provide information on gestational age at delivery, potential confounders such as maternal race, education, prenatal smoking and alcohol use, and congenital malformation outcomes.

B. Identifying Study Populations

We will first identify female Data Partner members 10 through 55 years of age who are hospitalized for delivery of a live infant. The dates of data availability vary according to Data Partner (**Table 1**).

Table 1. Dates of Data Availability by Data Partner

Data Partner	Date Data Available in Mini-Sentinel Common Data Model
Aetna	1/1/2008 through 9/30/2012
HealthCore	1/1/2004 through 9/30/2011
Humana	6/1/2007 through 5/31/2012
OptumInsight	1/1/2008 through 3/31/2012

For women to be included, they must have continuous enrollment from at least 180 days before estimated start of pregnancy (i.e., date of last menstrual period) until 30 days after delivery. The length of the maternal enrollment requirement prior to delivery was selected to optimize our ability to capture information on exposure and confounders, while the corresponding requirement following delivery was selected because infants may not receive a unique health plan identification number until 30 days after

birth; thus, infant diagnoses and procedures may be coded in maternal claims during this time. At a minimum, we will require infants who are linked to mothers to be enrolled continuously from date of birth until 30 days of age since CL, CP, and CLP are likely diagnosed at or shortly after birth. For the case-time control design, we will consider longer infant enrollment criteria post-birth (e.g., 90 days or 180 days), if sufficient case and control numbers permit.

In future studies of malformations not diagnosed until later in life, we might consider using a longer enrollment criterion, such as requiring enrollment from birth until 90 days after birth. One prior study using Medicaid data from a single state found that 94% of malformations identified in hospitalizations in the first year of life or in birth certificates were evident in the first 90 days of life, suggesting that requiring 90 days of enrollment following birth is adequate for capturing the vast majority of birth defects.[26] Requiring enrollment for such a long period following birth may exclude a large number of infants if they are enrolled in other health plans shortly after birth. If infants with birth defects are more likely to be enrolled in other health plans shortly after birth, a loss of power may result if we use a longer minimum enrollment criterion. More importantly, if infants excluded as a result of requiring a longer enrollment are also more or less likely to have had *in utero* exposure to influenza vaccine, in addition to being more likely to have birth defects, this may lead to selection bias in case-control or cohort studies. Loss of study participants due to longer enrollment criterion for infants may also lead to lack of generalizability of findings if effect modification is present between individuals who are excluded vs. included as a result of a longer enrollment criterion. As part of building the framework for studying birth outcomes in PRISM, we will thus perform a descriptive analysis to measure the degree of study sample attrition as the required length of enrollment is increased from 0 to 90 days after birth in 10-day increments.

To identify live deliveries, we will use ICD9 diagnosis codes and ICD9 and CPT procedure codes listed in Appendix 1, which was developed using a combination of codes from the National Committee for Quality Assurance (NCQA), Healthcare Effectiveness Data and Information Set (HEDIS) Prenatal and Postpartum Care Measure, and the Medication Exposure in Pregnancy Risk Evaluation Program (MEPREP), an FDA-funded study designed to investigate the effects of medication use during pregnancy.[29] To avoid counting deliveries more than once due to capture of follow-up care, we will only consider the first delivery code (Appendix 1) in a 270 day period. Only the first delivery during the study period will be retained for the case-time-control study. Multiple pregnancies (e.g., twins, triplets, etc.) will be eligible for inclusion in descriptive analyses (i.e., Aims 1 & 2); however, only singleton pregnancies will be eligible for the case-time-control design.

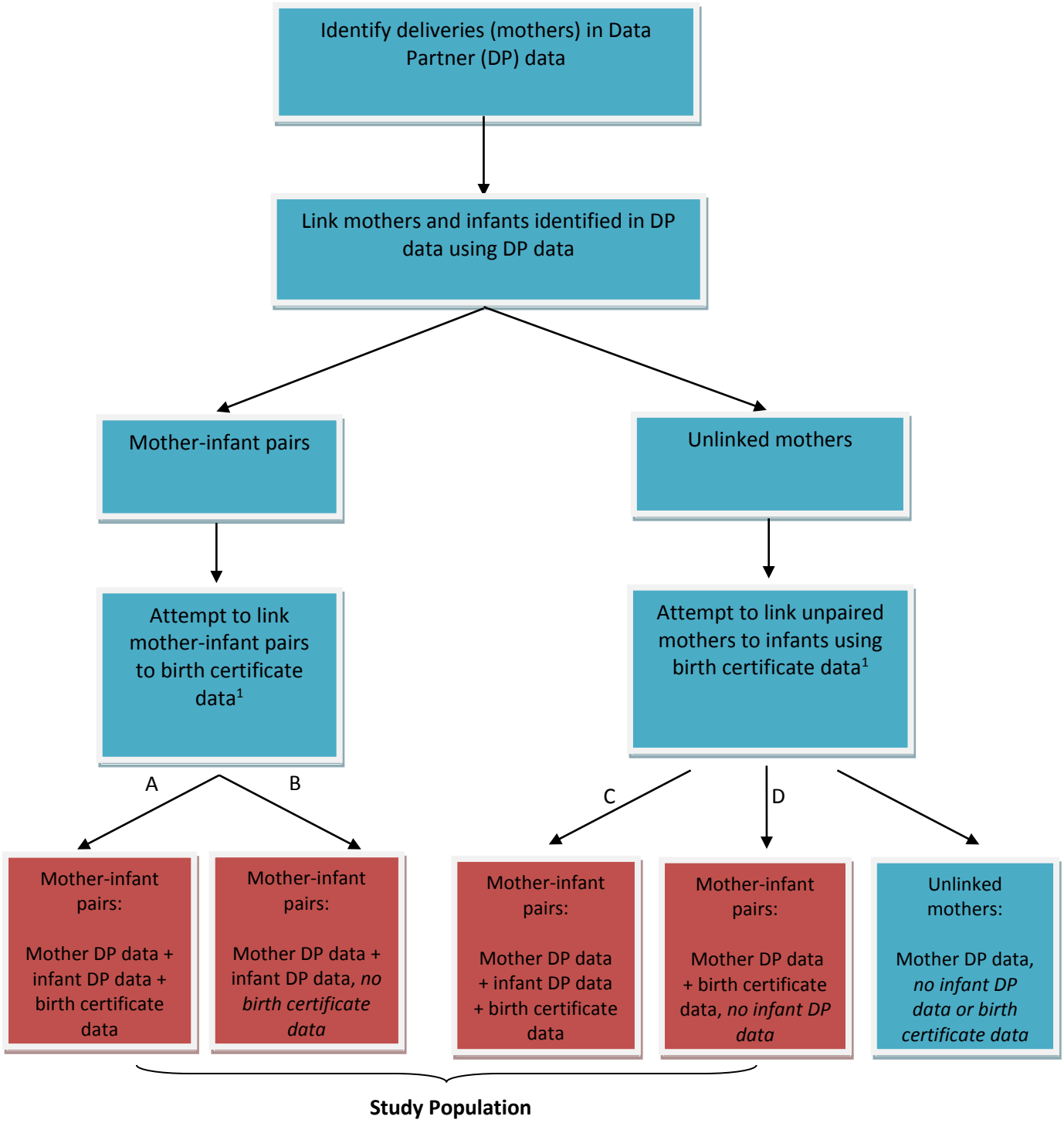
C. Linking Mothers and Infants Using Data Partner Files and Birth Certificate Data

After identifying deliveries in the MSCDM, we will identify all infants who were born during the study period using demographics data in the MSCDM (**Figure 2**). An algorithm that uses data from the MSCDM and from internal Data Partner information will then be used to link mothers and infants identified in the MSCDM. We will use the infant's date of birth and mother's dates of hospitalization for delivery, along with the mother and child's health insurance plan subscriber IDs to form mother-infant pairs. To be considered a matched pair, the mother and infant's health insurance plan subscriber IDs must match. In addition, the infant's date of birth must fall in the time period beginning with 3 days prior to the admission date and ending with the discharge date for the hospitalization for delivery (the former of which is proposed to allow for deliveries occurring prior to admission). In preliminary analyses that used data from a single PRISM Data Partner, 79% of deliveries identified in Data Partner data were linked to one or more infants using this algorithm. We will also consider using other probabilistic algorithms that may utilize variables such as last names and addresses from the Data Partners' internal sources,

depending on the potential for incremental gain in linkage rate and on feasibility, which will be investigated in the initial phases of this protocol.

For Data Partner members with deliveries in states and cities with Vital Events Registries providing birth certificate data, mother-infant pairs formed using only Data Partner data will also be linked to birth certificate data to obtain gestational age and confounder information. In addition, the use of birth certificate data may identify additional mother-infant linkages in mothers that remain unlinked using Data Partner information alone (i.e., MSCDM and internal Data Partner sources). First, additional matches may be formed if mothers and infants, both identified in MSCDM data, link independently to the same birth certificate. An example of this might occur if an infant is enrolled in the same health insurance plan as his/her mother, but under a different policy. Secondly, deliveries with no corresponding infant enrollment in the same health insurance plan may be linked to infant (and maternal) birth certificate data.

Figure 2. Flowchart Illustrating Mother-Infant Linkage in PRISM Influenza Vaccines and Birth Outcomes Assessment[1]



[1]Birth certificate data will only be available from Vital Events Registries in select states/cities

D. Descriptive Measures of Linked Mother-Infant Pairs for Specific Aim 1

We will calculate linkage rates, defined as the proportion of live deliveries identified in Data Partner data that can be linked to an infant. First, among all Data Partners, we will calculate the linkage rate for deliveries identified in MSCDM data linked to infants using Data Partner data alone (Groups A and B, **Figure 2**). This will measure the extent of linkage that can be achieved without use of birth certificate data. For Data Partner members delivering in states and cities with Vital Events Registries providing birth certificate data, mother-infant pairs will be subsequently linked to birth certificates to obtain confounder information. Additionally, where available, birth certificate data will be used to identify additional mother-infant pairs among mothers who remain unlinked when using only Data Partner information to form mother-infant linkages. We will calculate the linkage rate for the following: deliveries identified in maternal Data Partner data linked to infant Data Partner data using a combination of birth certificate and Data Partner data (Group C, **Figure 2**) and deliveries identified in Data Partner data linked to birth certificate data with no infant Data Partner data available (Group D, **Figure 2**). The linkage rate for Group C will provide a measure of the incremental gain in mother-infant linkage due to use of birth certificates that corresponds to mother-infant pairs *with infant Data Partner data available*, while the linkage rate for Group D will provide a measure of the incremental gain in linkage due to use of birth certificate data that corresponds to mother-infant pairs *with no infant Data Partner data* available. Together, linkage rates for Groups C and D will yield the overall incremental gain in linkage rate due to use of birth certificate data, corresponding to mother-infant pairs *with or without infant Data Partner data available.*

Mothers linked to infants using only Data Partner data may differ in important ways from those that cannot be linked to infants using Data Partner information alone. For example, if infants with birth defects are more likely to enroll in Medicaid or another health insurance plan at birth, we will unlikely be able to link these infants to mothers using Data Partner sources alone, though we may be able to identify these matches through the use of birth certificates. In Data Partner members delivering in states and cities providing birth certificate data, we will thus examine whether maternal characteristics (i.e., maternal age, race, education, and healthcare utilization) differ between mother-infants pairs formed using only Data Partner data (Groups A and B combined, **Figure 2**) vs. those formed using birth certificate data (Groups C and D combined, **Figure 2**). Since maternal race and education are not widely available in Data Partner data, birth certificate data will be used to obtain maternal characteristics for the purposes of this comparison. One limitation is that the comparison of maternal factors collected from birth certificates will need to be limited to the subset of mothers with birth certificate data available (i.e., Groups A vs. Groups C and D combined). However, we will also compare select maternal demographic and pregnancy related factors that can be obtained from claims and administrative data (i.e., maternal age, diabetes, multiple pregnancy, gestational length) using all mothers regardless of the availability of birth certificate data (i.e., Groups A and B combined vs. Groups C and D combined).

VI. METHODS FOR PRIMARY AIM 2 AND PILOT AIM 3

A. Study Population and Overview of Study Design

Using the data infrastructure developed in Specific Aim 1, we will use the vaccine-outcome pair example of TIV and CL, CP, or CLP. We propose to test the feasibility of using a case-time-control study to

examine the null hypothesis that there is no association between in-utero exposure to TIV and CL, CP, or CLP.

We will conduct a series of analyses with the case-time-control design using electronic data only (i.e., Data Partner claims-based data, currently available IIS data, and birth certificate data to identify vaccination, gestational age at vaccination, confounders, and outcomes). Additionally, our main pilot analyses will be performed following chart review of cases; chart review of cases identified in computerized data as receiving TIV within the risk or control intervals will be conducted to confirm vaccination, gestational age at vaccination, confounders, and case status.

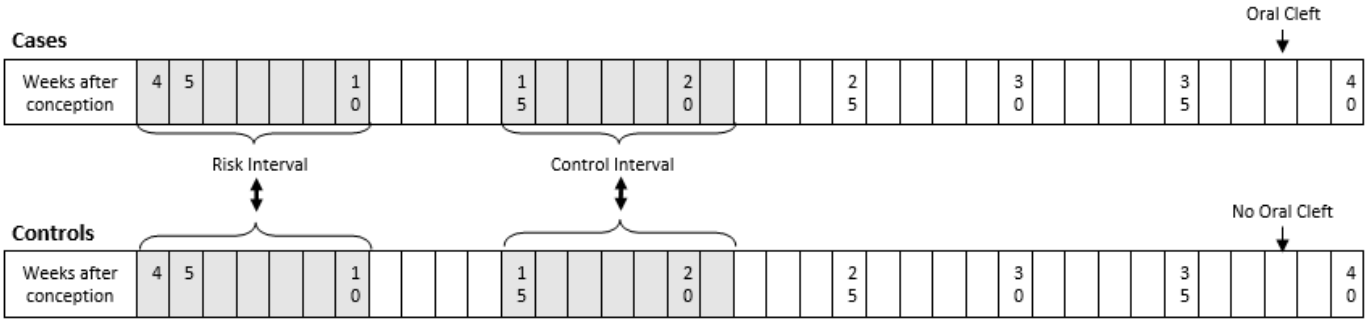
B. Case-Time-Control Design

The case-time-control study design is (**Figure 3**) an extension of the case-crossover (CCO) study. We will match cases and controls (ratio of 1:1) on maternal age, Data Partner, and state, and on estimated date of conception to adjust for seasonal patterns of vaccination. If case and control numbers permit, we will also consider matching cases and controls on pre-gestational diabetes, gestational diabetes, 1st trimester prenatal care, urinary tract infections, respiratory tract infections, and medically attended fever. Data on potential matching factors will be identified in maternal claims-based data.

The CCO study and its variants are especially well suited to measuring transient effects of exposures on immediate risk of illnesses with abrupt onset[30]. In a CCO study, in individuals who have experienced the outcome of interest, a comparison is made between the odds of exposure in a predefined risk interval to that in a self-matched comparison interval. In addition to using cases as the CCO study does, the case-time-control design also uses an external group of controls sampled from the same population that produced the cases to adjust for time trends in exposure (e.g., seasonality, or gestational age at vaccination). As in the cases, in the controls, the odds of exposure is compared between the predefined risk and self-matched control interval to estimate the exposure trend bias; the odds ratio in cases is divided by the odds ratio in controls to produce an effect estimate for the association between exposure and outcome while adjusting for time trends in exposure. A risk interval of 4 weeks through 10 weeks conceptional age (6-12 weeks gestation) will be used to correspond to the embryologic development of the lip and palate. A comparison interval of 15 through 21 weeks conceptional age (17-23 weeks gestation) will be used, allowing for a four-week washout period. We will also consider other risk intervals in alternative analyses to allow for a delay from the time of vaccine exposure until disease outcome. Only cases or controls vaccinated in either the risk or control interval (but not both intervals) will be informative for the purposes of the analysis.

One advantage of the case-time-control design is that it adjusts for between person confounders that do not vary over time.[31,32] However, a disadvantage is that the design will not completely adjust for time trends in exposure if controls have different time trends in exposure than cases,[31-33] which might occur if high risk women are more likely to be vaccinated earlier or later during pregnancy than low risk women. Another disadvantage is that relative to other designs such as a case-control design, the case-time-control design may have less statistical power[33] because the analytic modeling method for case-time control data is less restrictive and includes more degrees of freedom.

Figure 3: Case-Time-Control Design for PRISM Influenza Vaccines and Birth Outcomes Assessment



C. Exposure

For all four Data Partners participating in this activity, TIV will be identified using claims-based data throughout the study period. Additionally, for three Data Partners, vaccination data through 2011 from any of the eight IISs that participated in IIS matches as part of a prior Mini-Sentinel activity (Florida, Michigan, Minnesota, New York City, New York State, Pennsylvania, Virginia, and Wisconsin) will be included. CPT, HCPCS, NDC, and ICD9 diagnosis and procedure codes (Appendix 2) will be used to identify TIV in claims-based data. CVX codes will be used to identify TIV in IIS data. Vaccine product type will be identified via chart review of vaccine visits.

D. Estimating Gestational Age at Delivery and Date of Conception from Electronic Data

Because conception typically occurs 2 weeks following LMP, date of conception will be assigned to occur 2 weeks after LMP. LMP will be estimated using gestational age (number of weeks since LMP) at delivery and date of delivery. For the electronic data analysis, gestational age at delivery will be ascertained in birth certificates, if available. If gestational age at delivery is not available in birth certificates, the next most preferred method is maternal or infant claims-based codes. The preference order for methods to estimate gestational age using birth certificate data or claims-based codes is further described below.

In birth certificate data, the preferred estimate for gestational age will be the obstetric estimate, which was added to the U.S. birth certificate in 2003 and specifies that the estimate must not come from a neonatal examination.[34] However, not all states adopted the new version of the birth certificate. If the obstetric estimate is not available in birth certificate data, we will use the clinical estimate, which does not specify that the estimate should *not be derived* from a neonatal examination.[34] Finally, if neither an obstetric nor a clinical estimate of gestational age is available in birth certificate data, we will use the estimated date based on last menstrual period in birth certificate data to estimate gestational age at delivery. In MEPREP, the percent within-2-week agreement of gestational age in medical records with the clinical evaluation estimate in birth certificate data was 94%, while the within-2-week agreement of medical records with estimate based on LMP in birth certificates was 83%.[35] In that study, gestational age in the medical record was based on clinical evaluation in 36% of infants, on LMP in 21% of infants, and on ultrasound in 11% of infants; the method to estimate gestational age in medical charts was unavailable in 33% of infants.[35]

If birth certificate estimates of gestational age at delivery are not available, we will use the following claims-based diagnosis codes to assign gestational age at delivery in the following order of preference: (1) ICD9 diagnosis codes for ranges of gestational length for preterm infants, which are coded in two

week intervals from 25-26 through 36-37 weeks gestation (2) ICD9 codes for preterm birth of unspecified length or for preterm delivery, (3) ICD9 codes for post-term infant or for post-term delivery, (4) ICD9 codes for prolonged gestation of infant or for prolonged pregnancy delivered or (5) other diagnosis code for birth or delivery. For maternal or infant claims-based codes for preterm birth or delivery, the following gestational weeks will be assigned as outlined in Appendix 3: (1) the upper limit specified by ICD9 codes for ranges of gestational length [e.g., assumed gestational length of 28 weeks (196 days) for ICD9 code 765.24 for 27-28 weeks gestation] or (2) assign gestational length of 35 weeks (245 days) for ICD9 code 765.20 for preterm birth of unspecified gestational length or for ICD9 code 644.21 for preterm delivery. If birth certificates and maternal and infant claims-based codes for preterm birth or delivery are not available, we will use ICD9 codes for post-term pregnancy, post-term infant, prolonged pregnancy, and prolonged gestation of infant. For maternal or infant claims-based codes for post-term birth or prolonged gestation, we will make the following assumptions as outlined in Appendix 3: (1) 41 weeks (287 days) for ICD9 codes 645.1*(post-term pregnancy) or 766.21 (post-term infant) or (2) 42 weeks (294 days) for ICD9 codes 645.2* (prolonged pregnancy) or 766.22 (prolonged gestation of infant). If both prolonged pregnancy/prolonged gestation of infant and post-term pregnancy/infant codes are present for a given pregnancy, we will assume a gestational length of 42 weeks (294 days). If birth certificate data are not available and maternal and infant preterm, post-term, or prolonged gestation codes are not evident in the data, we will assume that the delivery was full-term and assume a gestational length of 270 days. In a study that used data from the British Columbia Medical Services Plan, the assumption of gestational age at delivery of 245 days for preterm births and gestational age at delivery of 273 days for non-preterm deliveries produced within-1-week agreement between the claims-based estimates and clinical estimate in the delivery discharge record of 68% for preterm deliveries and 76% for non-preterm deliveries; the corresponding within-2-week agreements were 75% for pre-term deliveries and 99% for non-preterm deliveries.[36] In the MEPREP study, an algorithm similar to the one proposed for the present PRISM assessment with the exception that it did not include post-term delivery or prolonged gestation delivery codes, found that the within-1-week agreement between the claims-based estimates and gestational age recorded in birth certificates was 61% in pre-term deliveries and 45% in non-preterm deliveries; the corresponding within-2-week agreement was 77% in both preterm and non-preterm deliveries[37]. We anticipate that using maternal and infant codes for post-term and prolonged gestation may improve the validity of gestational age estimates for these types of deliveries.

E. Estimating Gestational Age at Delivery and Date of Pregnancy Start from Chart Review Data

For the analysis based on chart-review data, we will estimate the date of conception using information from medical records. As specified by the American College of Obstetrics and Gynecology (ACOG) guidelines to assign estimated date of delivery (EDD), the assisted reproductive technology (ART)-derived gestational age will be used in instances of *in vitro* fertilization or intrauterine insemination.

In pregnancies not conceived with ART, we will estimate date of conception using LMP, ultrasound dating, the labor and delivery record, or the birth record, in the following order of preference:

(1) As specified by the ACOG guidelines, if both a first or second trimester ultrasound (i.e., up to and including 27 weeks gestation) and LMP date are documented:
    - We will use the LMP if verified by ultrasound. Specifically, we will use LMP if the discrepancy between the EDD is

    - *five* days or less for ultrasounds up to and including 8 weeks gestation[2]
    - *seven* days or less for ultrasounds from 9 weeks up to and including 15 weeks gestation
    - *10* days or less for ultrasounds from 16 weeks up to and including 21 weeks gestation
    - *14* days or less for ultrasounds from 22 weeks up to and including 27 weeks gestation.[38]
  - If the discrepancy between LMP and ultrasound dating is greater than the amounts specified in the bullet point proceeding, we will use ultrasound dating.
  - If more than one ultrasound is available, we will use the earliest performed.

(2) If LMP AND/OR first or second trimester ultrasound is unavailable, we will use gestational age as recorded on the labor and delivery record.
(3) If LMP AND/OR first or second trimester ultrasound, AND the labor and delivery record are unavailable, we will use gestational age as recorded on the birth record.
(4) If the labor and delivery record, birth record, AND LMP are unavailable, we will use first or second trimester ultrasound dating.
(5) If the labor and delivery record, birth record, AND first or second trimester US dating are unavailable, we will use LMP.
(6) If none of the above methods is available, we will exclude the patient from the chart-review analysis.

Of note, we will implement the ACOG guidelines to handle discrepancies between LMP and US dating if both are documented in the available records. We anticipate that the absence of either LMP or US dating in the available documentation could indicate that we have received incomplete records, as occurs, to varying degrees, in all retrospective medical chart review studies. In those instances, we will opt to use the gestational age estimate recorded on the labor and delivery or birth records (rather than LMP or US dating) since the treating physician would presumably make clinical judgements using all dating information, even if we do not receive all of the data elements.

F. Exposure Window (i.e., Risk Interval)

For the analysis based on electronic data (alternative pilot analysis) and based on chart-review data (main pilot analysis), we propose to use a main risk interval of 4 through 10 weeks conceptional age, which corresponds to the embryologic period of lip and palatal development.[39] This exposure window makes the assumption that influenza vaccination only affects risk of cleft lip and palate during this period of development, presumably because vaccination has a relatively immediate impact. However, a delay between the exposure's action until disease initiation (i.e., a latency period) might potentially exist. Thus, to incorporate latency periods, separate analyses with alternative exposure windows of (1) 0-10 weeks conceptional age (2-12 weeks gestation) and (2) -2-10 weeks conceptional age (0-12 weeks gestation) will be conducted.

[2] The ACOG guidelines state that mean sac diameter measurements are not recommended for estimating the due date. Crown-rump length should be used up to and through 13 weeks gestation. A composite of biparietal diameter, head circumference, abdominal circumference, and femur length should be used from 14 weeks up to and including 27 weeks gestation.

G. Confounders

Potential confounders will be assessed from electronic Data Partner sources (including demographic data and ICD9, CPT, and NDC codes) and from birth certificate data, where available (**Table 2**). At the minimum, we will collect potential confounder information from the initial prenatal visit and the birth and delivery medical records. Depending on our ability to obtain complete prenatal records, we will also consider using information beyond the prenatal initial visit to obtain additional confounder information.

Table 2. Data Used for Ascertaining Confounder Information

Confounder	Demographics from Administrative Data	ICD9 and CPT Codes in Claims-Based Data	Pharmacy Dispensing Codes in Claims-Based Data	Chart Review (Initial Prenatal Visit to End of 2nd Trimester)	Birth Certificate Data
Timing of first prenatal care visit		X		X	X
Maternal demographics	X				X
Prenatal smoking and alcohol use		X		X	X
Folic acid supplementation and multivitamin use			X	X	
Retinoid and folic acid antagonist medications			X	X	
Overweight and obesity		X		X	
Pre-gestational diabetes		X	X	X	
Gestational diabetes		X	X		
Urinary tract infections		X		X	
Respiratory tract infections		X		X	
Medically attended fever		X		X	

H. Healthcare Utilization

We will ascertain 1st trimester prenatal care receipt [yes vs. no] in maternal claims using CPT codes for standard laboratory tests (e.g., obstetric panel, antibody screen, ABO/Rh blood typing, syphilis screen, Hepatitis B virus surface antigen, or rubella antibody/titer) or ultrasounds (Appendix 4). We will also collect information on timing of 1st prenatal care visit from the medical record.

I. Comorbidities

Maternal diabetes during pregnancy (i.e., pre-gestational diabetes, which predates pregnancy, or gestational diabetes, which is diagnosed or has onset during pregnancy) and maternal pre-pregnancy overweight and obesity have both been associated with elevated risk of oral clefts in infants.[40,41] Pre-gestational diabetes and gestational diabetes will be assessed using a modified version of a previously used algorithm (**Table 3**).[42] Women will be considered to have gestational diabetes if they meet at least one criterion for diabetes during pregnancy (Criteria A) and at least one criterion for gestational diabetes (Criteria B). Women will be considered to have pre-gestational diabetes if they meet at least one criterion for diabetes during pregnancy but do not meet any of the criteria for gestational diabetes. This algorithm [which differs slightly from our proposed code list in that it did not include V58.67, long-term (current) use of insulin] has been shown to have moderate to high positive predictive values for gestational diabetes (82%) and pre-gestational diabetes (74%).[42] We also propose to collect information on pre-gestational diabetes from the medical record corresponding to the mother's first prenatal visit. We will not collect information on gestational diabetes from the medical record because it is frequently not diagnosed until the 3rd trimester.

Table 3. Algorithm Used to Define Pre-Gestational Diabetes and Gestational Diabetes[42]

Criteria A: Criteria to Identify Diabetes During Pregnancy Using Codes in Appendix 5 and 6	Criteria B: Criteria to Further Classify Diabetes During Pregnancy as Gestational Diabetes
(a) ≥2 outpatient diagnosis codes for gestational diabetes (GDM)/diabetes during pregnancy that occurred on different dates (b) ≥1 outpatient diagnosis code and ≥1 procedure code for diabetes management or training during pregnancy (c) ≥1 outpatient diagnosis code for GDM/diabetes and ≥1 antidiabetic medication dispensing during pregnancy (d) ≥1 inpatient diagnosis code for GDM/diabetes during pregnancy	(a) Glucose tolerance test during the defined pregnancy period (the algorithm assumes that women would not be administered a glucose tolerance test to detect gestational diabetes if they had previously been diagnosed with pre-gestational diabetes) (b) Diagnosis code for gestational diabetes during pregnancy period WITHOUT antidiabetic drug dispensing or diagnosis code for pre-gestational diabetes between 365 and 190 days prior to date of delivery

Overweight and obesity will be identified using ICD9 diagnosis codes for obesity or overweight in the 180 days prior through 90 days after estimated date of conception (Appendix 7). In one prior study of 3 health plans in the HMO Research Health Network that used these same codes, with the exception of V85.2-V85.4, body mass index ranges, the sensitivity for ICD9 codes for obesity was low (33%), but the specificity was high (99%).[42] Among women who were morbidly obese, ICD9 codes for obesity/morbid obesity were sensitive (sensitivity of 70%). Because the overall sensitivity of ICD9 codes for capturing overweight and obesity is relatively low, we will also collect this information in medical record reviews at the initial prenatal visit (**Table 2**). Furthermore, many women may not seek out healthcare for routine preventive healthcare prior to pregnancy, further decreasing our ability to detect overweight or obesity in claims data.

J. Medications and Folic Acid and Multivitamin Supplements

Prenatal use of folic acid antagonists (e.g., dihydrofolate reductase inhibitors and antiepileptic medications[43-46]) and retinoid medications (e.g., isotretinoin, acitretin, tretinoin, bexarotene[47]), have been associated with increased risk of oral clefts in offspring. We will identify folic acid antagonist medications during the 1st and 2nd trimesters from dispensing dates and days supplied using NDC codes in pharmacy dispensing data. One limitation of using pharmacy dispensing data is that this information may not necessarily reflect ingestion of medications.

Maternal multivitamin use has been consistently associated with lower risk of oral facial clefts, though it is unclear which specific component may be responsible for the decrease in risk.[48] It has been hypothesized that folic acid supplementation, which is one of many components typically included in multivitamins, may lead to decreased risk, but studies are inconsistent.[48] NDC codes in pharmacy dispensing data will be used to collect information on maternal multivitamin use and folic acid supplementation during pre-defined risk and control interval. Because multivitamins and folic acid supplements are often times purchased over the counter, we will also propose to collect information on these supplements in review of the medical record from the first prenatal care visit through the end of 2nd trimester, if the results of our pilot study demonstrate feasibility and usefulness of collecting information from all of these charts.

One limitation of using medical records or diagnosis and procedure codes for folic acid supplements is that there may be underreporting of folic acid supplement use. We will thus compare the prevalence of 1st trimester folic acid use in PRISM study controls to national population based estimates. We will also compare the prevalence of 1st trimester folic acid use in PRISM study oral cleft cases to that would be expected based on the national population biased estimates and relative risk estimates from published studies. If the prevalence estimates from the literature for cases and/or controls differ greatly from those found in the present assessment, we will consider applying multiple imputation techniques to randomly assign folic acid exposure to cases and controls while imposing prevalence estimates from the literature. We will repeat this simulation process multiple times to incorporate the uncertainty in the random assignment and combine estimates from the multiple replications to produce results for this sensitivity analysis.

K. Prenatal Smoking and Alcohol Use

Maternal smoking use has been consistently associated with an increased risk of oral clefts, with a comprehensive systematic review and meta-analysis reporting a RR of 1.2 (95% CI 1.1, 1.4).[49] The literature on maternal alcohol use is less consistent.[50-54] To adjust for prenatal alcohol and smoking, we will use ICD9 diagnosis codes for smoking and alcohol use and CPT codes for counseling for cessation of smoking and alcohol associated with encounter dates between 4 weeks prior to conception through the end of the 2nd trimester (Appendix 8). Because ICD9 and CPT codes could potentially lack sensitivity for capturing maternal smoking and alcohol use, we also propose to collect information on prenatal smoking and alcohol use in review of the medical record from the first prenatal care visit through end of 2nd trimester, if the results of our pilot study demonstrate feasibility and usefulness.

We propose to bin prenatal smoking obtained from medical record review into the following categories: 0 cigarettes per day, ≤5 cigarettes per day, and >5 cigarettes per day during the risk and control intervals and to bin prenatal alcohol use into the following categories: <1 drink per week, 1-2 drinks per week, and 3+ drinks per week during the risk and control intervals.[54] Because it is anticipated that the

granularity of these two confounders in medical records with respect to amount and frequency of use will differ from provider to provider, we will consider using alternative categorizations of alcohol use and smoking after reviewing the degree of detail in medical charts.

One limitation of using medical records or ICD9/CPT codes for alcohol and smoking information is that women who have an underlying greater risk of developing birth defects due to lifestyle or other factors may be less like likely to seek out medical care early during pregnancy, leading to substantially incomplete capture of confounder information in the risk interval for cases relative to controls. The direction of bias for the TIV-oral clefts association will depend on (1) the direction of the association between the confounder and oral clefts, and (2) the direction of the association between the confounder and TIV. For example, for the case-control design, under the null hypothesis of no association between TIV exposure and oral clefts, assume there is a positive association between alcohol and oral clefts and a negative association between TIV and alcohol (because patients who consume alcohol during pregnancy may be less likely to have prenatal care, including recommended influenza vaccination). If there is systematic under-ascertainment of alcohol use for cases relative to controls, then, the true positive association between *alcohol* and oral clefts would be underestimated, and the true null association for *TIV*-oral cleft would be biased toward a *protective* association.

We will thus conduct a number of analyses to test the sensitivity of our results to incomplete capture of alcohol and smoking in medical records and claims data. For the case-time control design, we will assume a range of prevalence of exposure to alcohol/smoking and use multiple imputation techniques to randomly reassign cases unexposed (with respect to alcohol/smoking) in the risk interval to being exposed in the risk interval. Furthermore, for the case-time control design, for the smoking and alcohol sensitivity analyses, under the range of prevalence of exposure to alcohol/smoking in the risk interval, we will conduct separate analyses that (1) represent the scenario in which all of the cases exposed to alcohol/smoking in the risk interval are assumed to continue to be exposed in the control interval and (2) represent the scenario in which all of the cases exposed to alcohol/smoking in the risk interval are assumed to be no longer exposed in the control interval. We will repeat this simulation process multiple times to incorporate the uncertainty in the random assignment and combine estimates from the multiple replications to produce results for this sensitivity analysis. Finally, in the standard U.S. birth certificate format, the number of cigarettes smoked daily during 1st trimester, 2nd trimester, and 3rd trimester is recorded, along with number of drinks consumed per week. If birth certificate data for smoking and alcohol use are consistently populated across all states, we will consider supplementing chart review and claims-based data of smoking and alcohol with birth certificate information where maternal data have been linked with birth certificates.

L. Respiratory Tract Infection, Medically Attended Fever, and Urinary Tract Infection

A handful of studies have found modest associations of, respiratory tract infections and febrile illness with increased risks of CL, CP, or CLP.[55,56] We will identify these conditions and urinary tract infections using maternal-claims based codes listed in the PRISM Influenza Vaccines and SAB Protocol.[57]

VII. OUTCOMES

A. Electronic Data

Potential cases of CL or CLP will be identified using ICD9 diagnosis codes 749.1* (cleft lip) and 749.2* (cleft lip with cleft palate), while potential cases of CP will be identified using 749.0* (cleft palate). Outcomes will be identified in maternal claims or infant claims data within 30 days of the child's birth. We will also consider using longer case identification periods in infant data (e.g., up to 90 days or 365 days after birth) if case and control numbers permit. One potential limitation is that continuous infant enrollment until the upper age limit would also be required to ensure complete capture of outcomes during the case identification period, leading to a decrease in study population size. A study using Medicaid data from a single U.S. state found that the positive predictive value for ICD9 diagnosis codes for CL, CP, or CLP was 93%.[26] The positive predictive value improved to 100% in that study when both diagnosis and procedure codes were used. However, the number of cases with both types of codes was only 59%.[26] Thus, we will not require both diagnosis and procedure codes in our case definition. In future studies of other birth defects with low positive predictive value requiring both diagnosis and procedure codes could potentially increase the positive predictive value of outcomes substantially. However, we will explore whether the use of CPT or ICD9 procedure codes for cleft lip repair and/or cleft palate repair in the first year and half of life (Appendix 9) might capture additional cases of CL, CP, or CLP not captured by ICD9 diagnosis codes. However, one limitation of including such codes is that we will only have complete data for the first year and a half of life in a subset of infants.

For descriptive purposes, the prevalence estimates of CL or CLP and CP based on electronic data in the current assessment will be compared to estimates in the United States, such as the National Birth Defects Prevention (NBDPS) Study[58,59] and the Metropolitan Atlanta Congenital Defects Program (MACDP)[60]. The NBDPS and MACDP are two population-based birth defects surveillance systems that have collected data since 1997 and 1967, respectively.

Case definitions will be based on the NBDPS criteria [61,62], which exclude potential cases that (1) occur as part of a genetic syndrome or other syndrome of known etiology (e.g., single gene disorders or chromosome abnormalities such as trisomy 13, 18, or 21) or that (2) occur secondary to other major malformations (e.g., holoprosencephaly or amniotic band sequence), using ICD9 codes and birth certificate data where possible. For example, potential cases with additional ICD9 codes for trisomy 13 (758.1), trisomy 18 (758.2), and trisomy 21 (758.0) or birth certificate codes for Down's syndrome or other chromosomal anomalies will not be considered cases. Similar exclusions will be made among controls to maximize their similarity with cases.

B. Medical Record Review Data

Potential cases identified as potentially having been vaccinated in the risk or control intervals in claims data will undergo medical record review and will be further adjudicated and classified according to NBDPS criteria. We currently have resources available to chart review a total of 200 cases and controls combined. If the total number of case:control sets exceeds 100, we will randomly select 100 case:control sets for chart review. Because of the potential for misclassification of gestational age using claims-based algorithms, we will also chart review potential cases identified in computerized data as receiving TIV within 2 weeks before and after the risk and control intervals to help identify additional

cases that were misclassified as receiving TIV outside those intervals; these additional cases will be included in the analysis using chart review data. For the analysis using chart review data, cases identified in computerized data that are later reclassified as receiving TIV outside these intervals will be excluded.

In addition to using ICD9 coded data to exclude potential cases that occur as part of a genetic or other syndrome or as secondary to other major malformations, we will also use medical record data for this purpose. Using chart review data, all potential cases will be considered to be CL or CLP if the defect extends through the entire lip into the floor of the nose (complete cleft lip) or if the defect extends through part of the lip but not into the floor of the nose (incomplete cleft lip). Potential cases will not be considered to be CL or CLP if they are pseudocleft lip, oblique facial cleft, or cleft palate without an associated cleft lip. Potential cases will be considered to be CP if they are bifid or cleft uvula, cleft palate, type not specified, cleft hard palate, cleft soft palate, or submucous cleft palate. Cases will not be considered to be cleft palate without cleft lip if the cleft palate coexists with a cleft lip.

We will also assess the feasibility of further classifying chart-confirmed cases of CL or CLP and CP into "isolated vs. multiple."[61] If feasible, cases would be 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 are not of the same organ, organ system, or body part but all defects are pathogenetically related. If feasible, cases would be classified as multiple if they occur with other major defects that are not of the same organ, organ system, or body part and all defects are not pathogenetically related.

VIII. STATISTICAL ANALYSIS

A. Analytic Plan for Electronic Data (i.e., Alternative Pilot Analysis)

For the electronic data analysis (**Table 4**), we will require mothers to be linked to infant DP records. Where available, we will use birth certificate data to estimate gestational age; otherwise claims data will be used. We will use both birth certificate data and claims data to assess CL, CP, or CLP status. First, the main risk interval of 4-10 weeks conceptional age (6-12 weeks gestational age) and the main outcome of CL, CP, or CLP will be examined.

We will also examine the main outcome (CL, CP, or CLP) but with alternative risk intervals of 0-10 and -2-10 weeks conceptional age (2-12 and 0 -12 weeks gestation) to incorporate a latency period. We will next examine the main risk interval as described above (4-10 weeks conceptional age) but with CL or CLP vs. CP as alternative outcomes, if numbers permit. Cases coded both as CL or CLP and as CP in electronic data will be categorized as CL or CLP.

Finally, in sensitivity analyses, we will examine the potential impact of incomplete capture of alcohol and smoking in ICD9/CPT data on our results. For separate analyses for each of these confounders, we will assume a range of exposure prevalence of alcohol/smoking in the risk interval for cases. We will also conduct sensitivity analyses, under the range of prevalence of exposure to alcohol/smoking in the risk interval, for which we will assume either (1) that all cases exposed (with respect to alcohol/smoking) in the risk interval continue to be exposed in the control interval or (2) that all cases exposed in the risk interval become unexposed to alcohol/smoking in the control interval.

Table 4. Analytic Plan for Alternative Pilot Analysis using Electronic Data

Analysis Plan	Linkages required	Notes	Rationale for Alternative Analysis	Risk Interval in Weeks Conceptional Age	Control Interval for in Weeks Conceptional Age	Outcomes	Data Source, Outcomes	Data Source, Gestational Age[1]
A	Maternal claims + infant claims +/- birth certificates	Main risk interval and outcome	----------	4-10	15-21	CL, CP, or CLP	Claims-based or birth certificate data	Claims-based or birth certificate data
B	Maternal claims + infant claims +/- birth certificates	Alternative risk interval	To allow for induction period	0-10	15-21	CL, CP, or CLP	Claims-based or birth certificate data	Claims-based or birth certificate data
C	Maternal claims + infant claims +/- birth certificates	Alternative risk interval	To allow for induction period	-2-10	15-21	CL, CP, or CLP	Claims-based or birth certificate data	Claims-based or birth certificate data
D	Maternal claims + infant claims +/- birth certificates	Alternative outcomes of CLP or CL vs. CP, if numbers permit	Lip and primary palate have distinct developmental origins from the secondary palate[39]	4-10	15-21	CLP or CL CP	Claims-based or birth certificate data	Claims-based or birth certificate data

[1]Preferred method for estimating gestational age in the following order: (1) obstetric estimate in birth certificate data, if available (2) clinical estimate in birth certificate data, if available (3) last menstrual period in birth certificate data, if available or (4) claims data, if birth certificate estimate not available.

B. Analytic Plan for Chart Review Data (i.e., Main Pilot Analysis)

Using the case-time-control design, we will conduct analyses using chart review-based estimates of gestational age and where available, confounders as noted in chart review. For gestational diabetes as a potential confounder, we will use Data Partner and birth certificate data (**Table 5**).

We will use the main risk interval of 4-10 weeks conceptional age (6-12 weeks gestation) and examine CL, CP, or CLP as a main outcome. We will also consider alternative risk intervals of 0 to 10 weeks and -2-10 weeks conceptional age (2-12 and 0-12 weeks gestation) to allow for a latency period. Next, we will consider CLP or CL vs. CP as alternative outcomes, if case numbers permit. Another analysis will examine the alternative outcomes of isolated CLP or CL vs. multiple CLP or CL vs. isolated CP vs. multiple CP, if numbers permit.

Finally, in sensitivity analyses, we will examine the potential impact of incomplete capture of alcohol and smoking in medical record data on our results. In separate analyses for each confounder, we will assume a range of exposure prevalence of alcohol/smoking in the risk interval for cases. We will also conduct additional sensitivity analyses, under the range of prevalence of exposure to alcohol/smoking in the risk interval, we will assume either (1) that all cases exposed (with respect to alcohol/smoking) in the risk interval continue to be exposed in the control interval or (2) that all cases exposed in the risk interval become unexposed to alcohol/smoking in the control interval.

Table 5. Analytic Plan for Main Pilot Analysis, Using Chart Confirmed Cases and Gestational Age Estimates from Medical Record[1]

Analysis Plan	Notes	Rationale for Alternative Analysis	Risk Interval in Weeks Conceptional Age	Control Interval in Weeks Conceptional Age	Outcomes
F	Main risk interval and outcome	----------	4-10	15-21	CL, CP, or CLP
G	Alternative risk interval	Allow for possible induction period	0-10	15-21	CL, CP, or CLP
H	Alternative risk interval	Allow for possible induction period	-2-10	15-21	CL, CP, or CLP
I	Alternative outcomes of CLP or CL vs. CP, if numbers permit	Lip and primary palate have distinct developmental origins from the secondary palate[39]	4-10	15-21	CLP or CL CP

[1]We will estimate date of conception using 1st or 2nd trimester ultrasound or LMP in naturally conceived pregnancies and using the date of the procedure in pregnancies conceived using in-vitro-fertilization or intrauterine insemination. If ultrasound dating and LMP date are both available for naturally conceived pregnancies, we will use the LMP if the discrepancy between the expected due dates is seven days or less for 1st trimester ultrasounds or ten days or less for 2nd trimester ultrasounds[63]. If more than one ultrasound is available, we will use the earliest performed.

A number of descriptive histograms and tables will be used to characterize the TIV and oral cleft data in order to better understand the prevalence of confounders and vaccinations among cases and controls for both designs.

Conditional logistic regression stratified by case:control set will be conducted. The use of conditional logistic regression, in contrast to standard logistic regression, will allow each matched case:control set to have a different odds ratio for time trend in exposure without specifying its function in the model. The outcome will be the probability that an individual's vaccination occurred in the risk interval (1=yes, vaccinated in risk interval; 0=no, vaccinated in control interval); the independent variable will be case vs. control status (1=case; 0=control), with the corresponding coefficient estimating the final odds ratio estimate, adjusted for time trend in exposure. An offset term will be used to account for differences in lengths between risk and control intervals. Where applicable, we will also adjust for confounders not matched upon by including terms in the model.
To calculate attributable risks for the main CTC analysis, we will calculate OR*p0/(OR*p0+1-p0) - p0, where p0 is the prevalence at birth of cleft lip and cleft palate combined, calculated using ICD9 codes in the cohort for this assessment. The baseline birth prevalence, p0 will be corrected based on chart review results.

For aim 3, we will first calculate the proportion of cases of CL, CP, or CLP identified in claims-based data that are chart-confirmed. Similarly, we will also calculate the positive predictive value for potential cases of CLP or CL and for potential cases of CP identified by claims-based data, using medical record review as the "gold standard." To validate our claims-based algorithm to estimate gestational age at delivery, we will calculate the proportion of deliveries whose estimated gestational age at delivery using ICD9 codes is within 7 and 14 days of the corresponding estimates based on (1) medical records and (2) birth certificates.

C. Data Set Creation and Registry Mapping

PRISM uses the MSCDM, which allows Data Partners to maintain control over patient-level data. Data Partners extract and output data into ten files of standard format. The files relevant for the present study are: Enrollment, Demographic, Encounter, Dispensing, Procedure, Diagnosis, and MS_State_Vaccine.

To obtain immunization data on all vaccines from IISs to populate the MS_State_Vaccine table, Data Partners will provide the IISs with member identification information for mothers to allow them to match Data Partner members with IIS immunization records. In addition, in some instances, Data Partners will provide member identification information for mothers and for infants to Vital Events Registries to link with birth certificate data. In other instances, Vital Events Registries will provide birth certificate data to Data Partners to perform the birth certificate linkages with Data Partner sources. When applicable, the separate registries will return immunization data (e.g., vaccination date, vaccine code, and manufacturer and lot number when available) and/or birth certificate data (e.g., gestational age at delivery, prenatal smoking and alcohol use) for Data Partner members to the Data Partners. The Data Partners will then populate the appropriate MS_State_Vaccine and/or birth certificate files, which will then both be linked to the other files by the patient identifier. Duplicate records will be combined using methods to be developed by PRISM programmers.

PRISM programmers will provide Data Partners with programs to be run on the study-specific patient-level files, which will combine information from all data sources. The programs will produce data sets for each Data Partner pregnancy cohort with information on influenza vaccination status (i.e., vaccination in the risk intervals, vaccination in the control intervals, no vaccination during the defined period of pregnancy), calendar week of vaccination, calendar week of estimated date of conception, estimated gestational age at vaccination, estimated gestational age at delivery, vaccine manufacturer, age group,

confounders (i.e., alcohol use during the risk and control intervals, smoking during the risk and control intervals, medication use during the risk and control intervals, prenatal healthcare utilization, diabetes, overweight, and obesity), and outcomes for the infant cohort (CL or CLP and CP). Data Partners will return the data sets for analysis at Harvard, using Mini-Sentinel's secure file transport methods.

IX. FURTHER ANALYSIS TO BE CONDUCTED FOR STATISTICALLY SIGNIFICANT ASSOCIATIONS

We do not anticipate finding any significant associations between influenza vaccine and CL, CLP, or CP as this is an infrastructure building and methods development activity rather than a formal exposure-outcome pair assessment. However, should any statistically significant result arise, we will do the following investigations:

- Use a temporal scan to identify where the peak period of risk is within the risk interval
- Stratify results by Data Partner and influenza season
- Consider alternative case definitions if PPV is low
- Stratify results by maternal age and other potential effect modifiers

X. INSTITUTIONAL REVIEW BOARD APPROVAL AND OTHER AUTHORIZATIONS

Per the privacy section on the Mini-Sentinel policies and procedures manual:
4.1 Mini-Sentinel Activities Are Public Health Practice, Not Research
The HHS Office of Human Research Protections (OHRP) determined that the regulations administered by OHRP (45 CFR Part 46, "Common Rule") do not apply to the activities that are included in the FDA's Sentinel Initiative. FDA stated that this assessment also applies to Mini-Sentinel, as it is part of the Sentinel Initiative.

XI. APPENDICES

Appendix 1. ICD9 diagnosis codes for identifying live deliveries

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

Code	Description
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
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

Code	Description
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

Code	Description
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
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

Code	Description
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
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

Code	Description
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
647.91	Unspecified infection or infestation of mother, with delivery, with or without mention of antepartum condition

Code	Description
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

Code	Description
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
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

Code	Description
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
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

Code	Description
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
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

Code	Description
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
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

Code	Description
	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

Code	Description
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
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

Code	Description
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
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

Code	Description
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
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

Code	Description
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
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

Code	Description
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

Code	Description
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
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

Code	Description
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

Code	Description
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
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

Code	Description
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

Appendix 2. CVX, CPT, and ICD9 codes used to identify TIV. NDC codes will also be used to identify TIV

Code	Type	Description
140	CVX	Influenza, seasonal, injectable, preservative free
141	CVX	Influenza, seasonal, injectable
135	CVX	Influenza, high dose seasonal
15	CVX	Influenza, split (incl. Purified surface antigen)
16	CVX	Influenza, whole
88	CVX	Influenza, unspecified formulation
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

Code	Type	Description
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

Appendix 3. ICD9 codes used to estimate gestational age at delivery

Code	Description	Assumed gestational age at delivery in weeks	Assumed gestational age at delivery in days
765.21	Less than 24 completed weeks of gestation	24	168
765.22	24 completed weeks of gestation	24	168
765.23	25-26 completed weeks of gestation	26	182
765.24	27-28 completed weeks of gestation	28	196
765.0*	Disorders relating to extreme immaturity of infant	28	196
765.25	29-30 completed weeks gestation	30	210
765.26	31-32 completed weeks gestation	32	224
765.27	33-34 completed weeks gestation	34	238
765.28	35-36 completed weeks gestation	36	252
765.1*	Disorders related to other preterm infants	35	245
765.20	Preterm with unspecified weeks of gestation	35	245
644.21	Early onset of delivery, delivered, with or without mention of antepartum condition	35	245
645.1*	Post-term pregnancy	41	287
766.21	Post-term infant	41	287
645.2*	Prolonged pregnancy	42	287
766.22	Prolonged gestation of infant	42	294

Appendix 4. ICD9 and CPT codes used to identify 1st trimester prenatal care

Code	Type	Description
80055	CPT	Obstetric panel
85025	CPT	Blood count, complete (CBC), automated and automated differential WBC count
85027	CPT	Blood count, complete (CBC), automated
85004	CPT	Blood count, automated differential WBC count
85007	CPT	Blood count, blood smear, microscopic examination with manual differential WBC count
85009	CPT	Blood count, manual differential WBC count, buffy coat
87340	CPT	Infectious agent antigen detection by immunofluorescent technique; hepatitis B surface antigen
86762	CPT	Antibody; rubella
86780	CPT	Antibody; treponema pallidum
86592	CPT	Syphilis test, non-treponemal antibody; qualitative
86850	CPT	Antibody screen, RBC, each serum technique
86900	CPT	Blood typing; ABO
86901	CPT	Blood typing; Rh (D)
76801	CPT	Ultrasound, pregnant uterus, real time with image documentation, fetal and maternal evaluation, first trimester (< 14 weeks, 0 days), transabdominal approach; single or first gestation
76802	CPT	Ultrasound, pregnant uterus, real time with image documentation, fetal and maternal evaluation, first trimester (< 14 weeks, 0 days), transabdominal approach; each additional gestation
76805	CPT	Ultrasound, pregnant uterus, real time with image documentation, fetal and maternal evaluation, after first trimester (> 14 weeks 0 days), transabdominal approach; single or first gestation
76810	CPT	Ultrasound, pregnant uterus, real time with image documentation, fetal and maternal evaluation, after first trimester (> 14 weeks 0 days), transabdominal approach; each additional gestation
76811-76812	CPT	Ultrasound, pregnant uterus, real time with image documentation, fetal and maternal evaluation plus detailed fetal anatomic examination, transabdominal approach
76813-76814	CPT	Ultrasound, pregnant uterus, real time with image documentation, first trimester fetal nuchal translucency measurement, transabdominal or transvaginal approach

Code	Type	Description
76815	CPT	Ultrasound, pregnant uterus, real time with image documentation, limited (eg, fetal heart beat, placental location, fetal position and/or qualitative amniotic fluid volume), 1 or more fetuses
76816	CPT	Ultrasound, pregnant uterus, real time with image documentation, follow-up (eg, re-evaluation of fetal size by measuring standard growth parameters and amniotic fluid volume, re-evaluation of organ system(s) suspected or confirmed to be abnormal on a previous scan), transabdominal approach, per fetus
76817	CPT	Ultrasound, pregnant uterus, real time with image documentation, transvaginal

Appendix 5. ICD9 and CPT codes used to identify diabetes during pregnancy

Code	Type	Category	Description
250	ICD9	Diabetes diagnosis	Diabetes mellitus
250.0	ICD9	Diabetes diagnosis	Diabetes mellitus without mention of complication
250.00	ICD9	Diabetes diagnosis	Diabetes mellitus without complication type ii or unspecified type not stated as uncontrolled
250.01	ICD9	Diabetes diagnosis	Diabetes mellitus without complication type i not stated as uncontrolled
250.02	ICD9	Diabetes diagnosis	Diabetes mellitus without complication type ii or unspecified type uncontrolled
250.03	ICD9	Diabetes diagnosis	Diabetes mellitus without complication type i uncontrolled
250.1	ICD9	Diabetes diagnosis	Diabetes with ketoacidosis
250.10	ICD9	Diabetes diagnosis	Diabetes mellitus with ketoacidosis type ii or unspecified type not stated as uncontrolled
250.11	ICD9	Diabetes diagnosis	Diabetes mellitus with ketoacidosis type i not stated as uncontrolled
250.12	ICD9	Diabetes diagnosis	Diabetes mellitus with ketoacidosis type ii or unspecified type uncontrolled
250.13	ICD9	Diabetes diagnosis	DMI ketoacd uncontrold
250.2	ICD9	Diabetes diagnosis	Diabetes with hyperosmolarity
250.20	ICD9	Diabetes diagnosis	Diabetes mellitus with hyperosmolarity type ii or unspecified type not stated as uncontrolled
250.21	ICD9	Diabetes diagnosis	Diabetes mellitus with hyperosmolarity type i not stated as uncontrolled
250.22	ICD9	Diabetes diagnosis	Diabetes mellitus with hyperosmolarity type ii or unspecified type uncontrolled
250.23	ICD9	Diabetes diagnosis	Diabetes mellitus with hyperosmolarity type i uncontrolled
250.3	ICD9	Diabetes diagnosis	Diabetes mellitus with other coma

Code	Type	Category	Description
250.30	ICD9	Diabetes diagnosis	Diabetes mellitus with other coma type ii or unspecified type not stated as uncontrolled
250.31	ICD9	Diabetes diagnosis	Diabetes mellitus with other coma type i not stated as uncontrolled
250.32	ICD9	Diabetes diagnosis	Diabetes mellitus with other coma type ii or unspecified type uncontrolled
250.33	ICD9	Diabetes diagnosis	Diabetes mellitus with other coma type i uncontrolled
250.4	ICD9	Diabetes diagnosis	Diabetes with renal manifestations
250.40	ICD9	Diabetes diagnosis	Diabetes mellitus with renal manifestations type ii or unspecified type not stated as uncontrolled
250.41	ICD9	Diabetes diagnosis	Diabetes mellitus with renal manifestations type i not stated as uncontrolled
250.42	ICD9	Diabetes diagnosis	Diabetes mellitus with renal manifestations type ii or unspecified type uncontrolled
250.43	ICD9	Diabetes diagnosis	Diabetes mellitus with renal manifestations type i uncontrolled
250.5	ICD9	Diabetes diagnosis	Diabetes with ophthalmic manifestations
250.50	ICD9	Diabetes diagnosis	Diabetes mellitus with ophthalmic manifestations type ii or unspecified type not stated as uncontrolled
250.51	ICD9	Diabetes diagnosis	Diabetes mellitus with ophthalmic manifestations type i not stated as uncontrolled
250.52	ICD9	Diabetes diagnosis	Diabetes mellitus with ophthalmic manifestations type ii or unspecified type uncontrolled
250.53	ICD9	Diabetes diagnosis	Diabetes mellitus with ophthalmic manifestations type i uncontrolled
250.6	ICD9	Diabetes diagnosis	Diabetes with neurological manifestations
250.60	ICD9	Diabetes diagnosis	Diabetes mellitus with neurological manifestations type ii or unspecified type not stated as uncontrolled
250.61	ICD9	Diabetes diagnosis	Diabetes mellitus with neurological manifestations type i not stated as uncontrolled
250.62	ICD9	Diabetes diagnosis	Diabetes mellitus with neurological manifestations type ii or unspecified type uncontrolled
250.63	ICD9	Diabetes diagnosis	Diabetes mellitus with neurological manifestations type i uncontrolled
250.7	ICD9	Diabetes diagnosis	Diabetes with peripheral circulatory disorders
250.70	ICD9	Diabetes diagnosis	Diabetes mellitus with peripheral circulatory disorders type ii or unspecified type not stated as uncontrolled
250.71	ICD9	Diabetes diagnosis	Diabetes mellitus with peripheral circulatory disorders type i not stated as uncontrolled
250.72	ICD9	Diabetes diagnosis	Diabetes mellitus with peripheral circulatory disorders type ii or unspecified type uncontrolled

Code	Type	Category	Description
250.73	ICD9	Diabetes diagnosis	Diabetes mellitus with peripheral circulatory disorders type i uncontrolled
250.8	ICD9	Diabetes diagnosis	Diabetes with other specified manifestations
250.80	ICD9	Diabetes diagnosis	Diabetes mellitus with other specified manifestations type ii or unspecified type not stated as uncontrolled
250.81	ICD9	Diabetes diagnosis	Diabetes mellitus with other specified manifestations type i not stated as uncontrolled
250.82	ICD9	Diabetes diagnosis	Diabetes mellitus with other specified manifestations type ii or unspecified type uncontrolled
250.83	ICD9	Diabetes diagnosis	Diabetes mellitus with other specified manifestations type i uncontrolled
250.9	ICD9	Diabetes diagnosis	Diabetes with unspecified complication
250.90	ICD9	Diabetes diagnosis	Diabetes mellitus with unspecified complication type ii or unspecified type not stated as uncontrolled
250.91	ICD9	Diabetes diagnosis	Diabetes mellitus with unspecified complication type i not stated as uncontrolled
250.92	ICD9	Diabetes diagnosis	Diabetes mellitus with unspecified complication type ii or unspecified type uncontrolled
250.93	ICD9	Diabetes diagnosis	Diabetes mellitus with unspecified complication type i uncontrolled
648.0	ICD9	Gestational diabetes diagnosis	Diabetes mellitus complicating pregnancy childbirth or the puerperium
648.00	ICD9	Gestational diabetes diagnosis	Diabetes mellitus of mother, complicating pregnancy, childbirth, or the puerperium, unspecified as to episode of care or not applicable
648.01	ICD9	Gestational diabetes diagnosis	Diabetes mellitus of mother, complicating pregnancy, childbirth, or the puerperium, delivered, with or without mention of antepartum condition
648.02	ICD9	Gestational diabetes diagnosis	Diabetes mellitus of mother, complicating pregnancy, childbirth, or the puerperium, delivered, with mention of postpartum complication
648.03	ICD9	Gestational diabetes diagnosis	Diabetes mellitus of mother, complicating pregnancy, childbirth, or the puerperium, antepartum condition or complication
648.04	ICD9	Gestational diabetes diagnosis	Diabetes mellitus of mother, complicating pregnancy, childbirth, or the puerperium, postpartum condition or complication
648.8	ICD9	Gestational diabetes diagnosis	Abnormal glucose tolerance of mother complicating pregnancy childbirth or the puerperium
648.80	ICD9	Gestational diabetes diagnosis	Abnormal glucose tolerance of mother, unspecified as to episode of care or not applicable

Code	Type	Category	Description
648.81	ICD9	Gestational diabetes diagnosis	Abnormal glucose tolerance of mother, delivered, with or without mention of antepartum condition
648.82	ICD9	Gestational diabetes diagnosis	Abnormal glucose tolerance of mother, delivered, with mention of postpartum complication
648.83	ICD9	Gestational diabetes diagnosis	Abnormal glucose tolerance of mother, antepartum condition or complication
648.84	ICD9	Gestational diabetes diagnosis	Abnormal glucose tolerance of mother, postpartum condition or complication
G0108	CPT	Procedure code for diabetes management	Diabetes outpatient self-management training services, individual, per 30 minutes
G0109	CPT	Procedure code for diabetes management	Diabetes outpatient self-management training services, group session, per 30 minutes
S9214	CPT	Procedure code for diabetes management	Home management of gestation diabetes
S9140	CPT	Procedure code for diabetes management	Diabetic management program, follow-up visit to non-MD provider
S9141	CPT	Procedure code for diabetes management	Diabetic management program, follow-up visit to provider
S9455	CPT	Procedure code for diabetes management	Diabetic management program, group session
S9460	CPT	Procedure code for diabetes management	Diabetic management program, nurse visit
S9465	CPT	Procedure code for diabetes management	Diabetic management program, dietitian visit
82951	CPT	Glucose tolerance test	Glucose tolerance test, 3 specimens
82951	CPT	Glucose tolerance test	Glucose tolerance test, each test beyond 3 specimens
V58.67	ICD9	Diabetes medication	Long-term (current use) of insulin

Appendix 6. Diabetes medications used to identify diabetes during pregnancy

Medications to Identify Diabetes During Pregnancy
Acarbose
Chlorpropamide
Exenatide
Glimepiride
Glipizide
Glipizide/Metformin HCL
Glyburide
Glyburide, Micro/Metformin HCL
Glyburide,Micronized
Insulin
Metformin Hcl
Miglitol
Nateglinide
Pioglitazone HCL
Pioglitazone Hcl/Metformin HCL
Pioglitazone/Glimepiride
Pramlintide Acetate
Repaglinide
Repaglinide/Metformin HCL
Rosiglitazone Maleate
Rosiglitazone/Glimepiride
Rosiglitazone/Metformin HCL
Saxagliptin Hydrochloride
Sitagliptin Phos/Metformin HCL
Sitagliptin Phosphate
Tolazamide
Tolbutamide

Appendix 7. Codes used to identify overweight/obesity and receipt of 1st trimester prenatal care

Code	Type	Description
278	ICD9	Overweight, obesity and other hyperalimentation
278.0	ICD9	Overweight and obesity
278.00	ICD9	Obesity, unspecified
278.01	ICD9	Morbid obesity
278.02	ICD9	Overweight
278.03	ICD9	Obesity hypoventilation syndrome
649.1	ICD9	Obesity complicating pregnancy, childbirth, or the puerperium
649.10	ICD9	Obesity complicating pregnancy, childbirth, or the puerperium. unspecified as to episode of care or not applicable
649.11	ICD9	Obesity complicating pregnancy, childbirth, or the puerperium. delivered, with or without mention of antepartum condition
649.12	ICD9	Obesity complicating pregnancy, childbirth, or the puerperium. delivered, with mention of postpartum complication
649.13	ICD9	Obesity complicating pregnancy, childbirth, or the puerperium. antepartum condition or complication
649.14	ICD9	Obesity complicating pregnancy, childbirth, or the puerperium. postpartum condition or complication
V85.2*	ICD9	Body mass index between 25-29, adult
V85.3*	ICD9	Body mass index between 30-39, adult
V85.4*	ICD9	Body mass index 40 and over, adult

Appendix 8. ICD9 and CPT codes used to identify smoking and alcohol use

Code	Type	Description
99406	CPT	Counseling /risk factor reduction for smoking and tobacco use
99407	CPT	Counseling /risk factor reduction for smoking and tobacco use
1034F	CPT	Current tobacco smoker
1035F	CPT	Current smokeless tobacco user
4000F	CPT	Tobacco use cessation intervention, counseling or pharmacologic therapy
4001F	CPT	Tobacco use cessation intervention, pharmacologic therapy
D1320	CPT	Tobacco counseling for the control and prevention of oral disease
G0436, G0437	CPT	Smoking and tobacco cessation counseling visit for the asymptomatic patient
G8688	CPT	Currently a smokeless tobacco user and no exposure to secondhand smoke
G8692	CPT	Current smokeless tobacco user and no exposure to secondhand smoke
4004F	CPT	Patient screened for tobacco use and received tobacco cessation counseling, if identified as a tobacco user
4009F	CPT	Pharmacologic therapy for cessation of tobacco use
V15.82	ICD9	Tobacco use disorder, unspecified drug dependence
V15.82	ICD9	History of tobacco use
305.1	ICD9	Tobacco use disorder
303*	ICD9	Alcohol abuse syndrome
305.0*	ICD9	Non-dependent alcohol abuse

Appendix 9. CPT Codes used to identify CL, CP, or CLP

Code	Type	Description
00102	CPT	Anesthesia for procedures on plastic repair of cleft lip
00172	CPT	Anesthesia for intraoral procedures, including biopsy; not otherwise specified; repair of cleft palate
40700	CPT	Plastic repair of cleft lip/nasal deformity; primary, partial or complete, unilateral
40701	CPT	Plastic repair of cleft lip/nasal deformity; primary bilateral, 1-stage procedure
40702	CPT	Plastic repair of cleft lip/nasal deformity; primary bilateral, 1 of 2 stages
40720	CPT	Plastic repair of cleft lip/nasal deformity; secondary, by recreation of defect band re-closure
40761	CPT	Plastic repair of cleft lip/nasal deformity with cross lip pedicle flap (Abbe-Estlander type), including sectioning and inserting of pedicle
42200	CPT	Palatoplasty for cleft palate, soft and/or hard palate only
42205	CPT	Palatoplasty for cleft palate, with closure of alveolar ridge; soft tissue only
42210	CPT	Palatoplasty for cleft palate, with bone graft to alveolar ridge (includes obtaining graft)
42215	CPT	Palatoplasty for cleft palate; major revision
42220	CPT	Palatoplasty for cleft palate; secondary lengthening procedure
42225	CPT	Palatoplasty for cleft palate; attachment pharyngeal flap
27.54	ICD9	Repair of cleft lip
27.62	ICD9	Correction of cleft palate
27.63	ICD9	Revision of cleft palate repair

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