DEVELOPING THE INFRASTRUCTURE TO CONDUCT SURVEILLANCE OF PREGNANCY OUTCOMES FOLLOWING VACCINATION:

A PROJECT UTILIZING INFLUENZA VACCINES AND SPONTANEOUS ABORTION AS A USE CASE

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I. INTRODUCTION

Maternal immunization with inactivated influenza vaccines (IIV) and tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccines (Tdap) during pregnancy is recommended by the Advisory Committee on Immunization Practices Center for Disease Control (CDC) to protect mothers and infants against influenza and pertussis related illness [1,2]. Although not contraindicated for use in pregnant women, FDA-approved labeling of influenza and Tdap vaccines note the limitations of data supporting use during pregnancy and state that these vaccines should be administered during pregnancy only if clearly needed[3-9]. Other vaccines are either contraindicated in FDA-approved labeling or not recommended by CDC for use in pregnant women, but may be inadvertently administered during early pregnancy because they are recommended for routine use in women and girls of childbearing age [2].

Pregnant women are usually excluded from pre-market trials of vaccines, and limited data are available in pregnant women inadvertently exposed prior to regulatory approval. Thus, most vaccine safety data during pregnancy have been derived from post-market studies. A number of post-market surveillance initiatives exist in the United States to evaluate the safety of vaccine use during pregnancy, including systems without internal comparators from the same study population or those without information on denominators. Some vaccine manufacturers have established pregnancy exposure registries to collect data on rates of specific outcomes of interest following exposures to vaccines during pregnancy [10,11]. The CDC and FDA co-administered Vaccine Adverse Events Reporting System (VAERS) collects provider and patient reports of adverse events following vaccination [12,13]. Both surveillance systems have limitations. The manufacturer-sponsored registries do not have internal comparators from the same population, and thus, rates are typically compared to those from other sources. VAERS collects reports of any events potentially associated with vaccination, without regard to causality, but does not collect data on the number of vaccine doses administered.

To address the limitations of post-marketing surveillance systems such as manufacturer-sponsored registries or spontaneous reporting systems, surveillance with formal epidemiologic study designs is needed. The CDC-sponsored Vaccine Safety Datalink (VSD) is a collaboration between eight medical care organizations across the United States that, among other activities, utilizes claims-based and electronic health record (EHR) data to monitor the safety of vaccine use in pregnant women [14]. The Vaccines and Medications in Pregnancy Surveillance System (VAMPSS) is coordinated by Boston University and the American Academy of Allergy, Asthma & Immunology and uses both prospective cohort and case-control surveillance methods with primary data collection to study the safety of influenza vaccine and antiviral use during pregnancy [15]. The Medication Exposure in Pregnancy Risk Evaluation Program (MEPREP), a collaboration between FDA, the Health Maintenance Organization Research Network, Kaiser Permanente Northern and Southern California, and Vanderbilt University, that conducts studies of medication use and outcomes in pregnancy with the use of claims, EHR, and birth certificate data [16].

Sentinel is an FDA-sponsored active post-marketing surveillance system developed to monitor the safety of FDA-regulated medical products in the United States. The Post-licensure Rapid Immunization Safety Monitoring (PRISM) Program is the vaccine safety component of Sentinel and includes claims data from four large national insurers. PRISM is comprised of data for over 170 million individuals, allowing for active surveillance of the safety of vaccine use during pregnancy in a large population that does not overlap with other systems. To complement other post-marketing surveillance systems, we sought to examine the feasibility of conducting safety surveillance of vaccine use during pregnancy in Sentinel, including the use of claims-based algorithms. Additionally, we explored the use of the case-time control design to conduct such surveillance. To achieve these goals, we selected a single test-use case, seasonal IIV and spontaneous abortion (SAB) risk. At the time of this activity's inception, no evidence existed for

an association between IIV and SAB. Rather, this test use case was selected based on the widespread historical use of these vaccines in pregnant women, and the reporting of SAB in passive surveillance systems such as VAERS, which together would increase the number of events on which to pilot the methods and infrastructure development. SAB is a particularly challenging outcome to study, and therefore it afforded us the opportunity to develop these methods under complex circumstances. In particular, the period for which vaccinations could potentially affect risk of SAB are largely unknown, and the risk varies substantially by gestational age, which is not readily identifiable in claims data.

The primary objectives of this activity were to:

(1) Examine the positive predictive value of claims codes for SAB through medical record review for all cases combined, and by maternal age, code, code type, and medical care setting;
(2) Examine the accuracy of gestational age in claims data for identifying pregnancy start date among live delivery controls, to be matched to confirmed cases of SAB.

Additionally, secondary objectives of the activity were to:

(1) Use a case-time control design to examine the risk of SAB following inactivated influenza vaccine in (a) the 1-28 days post vaccination or (b) any time after vaccination occurring from -4 through 4 weeks gestation, 2 through 5 weeks gestation, or 6 through 11 weeks gestation;
(2) Explore potential periods of increased risk of SAB following vaccination, without defining the risk interval *a priori* through the use of temporal scan statistics.

II. METHODS

A. DATA SOURCES

PRISM incorporates claims-based data from health plans that provide claims data to the Sentinel Distributed Database and collaborate with Sentinel as Data Partners. Claims-based data include information on demographics, diagnoses and procedure codes associated with healthcare encounters and pharmacy dispensing. Additionally, Data Partners have the capability to request medical records to confirm events recorded in claims data. For this activity, we initially identified maternal exposures and outcomes in the Sentinel Distributed Database and conducted chart review to verify them. Medical records were also used to estimate pregnancy start in SAB cases and to verify algorithm-derived pregnancy start in live delivery controls.

Prior to medical record review, we identified healthcare encounters of interest in the Sentinel Distributed Database, including visits or hospitalizations for pregnancy related care, vaccination, prenatal ultrasounds, diagnosis and treatment of SAB, and/or labor and delivery. Data Partners then identified potential encounters that were eligible for medical record review in this public health surveillance activity. Because the Data Partners were not directly connected to health care delivery systems, they requested access to these medical records through third party vendors, who requested electronic copies (i.e., pdf format) of records, which were de-identified and subsequently uploaded onto a secure server. At least three attempts via phone calls, written letters, email, or fax were made to establish contact with healthcare providers and facilities. The electronic copies of the medical records were retrieved from the Sentinel Operation Center's Secure Portal by trained SOC research assistants, who determined whether records relevant to the variables of interest (exposures, outcomes, and confounders) were received. They abstracted vaccination information as well as additional data from the charts to perform basic quality checks of data subsequently collected by clinical expert reviewers. SOC research assistants then uploaded the full text records to the SOC's Secure Portal for the clinical experts to review. Two clinical experts (obstetricians or family physicians with experience in providing obstetric care) then independently reviewed each patient's records, using a web-based questionnaire

designed specifically for the activity. The SOC's research assistants then reviewed each patient's completed questionnaires to identify any discrepancies between the two clinician reviewers. Any discrepancies that could not be readily resolved (e.g., typographical errors) were then discussed by the two clinician reviewers on regularly scheduled calls coordinated by the SOC until consensus was reached.

B. STUDY POPULATION

For all aims of the activity, we included women who were enrolled in one of two participating Data Partners, Aetna or HealthCore. We chose to focus this study on pregnant women 18 through 34 years of age because these women are considered to have a lower baseline risk for SAB. Since we planned to examine whether influenza vaccines were associated with an increased risk of SAB using a case-time control design, we further limited our study population to pregnant women who received influenza vaccines and whose pregnancy ended in either a SAB or a live delivery from September 30, 2008 through October 31, 2011. Pregnant women were considered exposed to influenza vaccines if they received a 2008-2009 or 2010-2011 IIV between 4 weeks (28 days) before pregnancy start through the SAB event or live delivery. We did not include women vaccinated during the 2009-2010 season because the pandemic H1N1 vaccine, which in theory could have a different safety profile in pregnant women, was also available during the same season. We also excluded women whose pregnancies ended in a stillbirth, elective abortion, ectopic pregnancy, or molar pregnancy.

C. STUDY DESIGN

1. Primary Aim 1: Validation of Algorithm to Identify SAB Events

Using claims data, we identified potential cases of SAB in the study population using the diagnosis and procedure codes included in Appendix 1 occurring in the inpatient, emergency department (ED), or ambulatory care setting. To avoid including follow-up visits for an SAB encounter, we excluded events with another code for SAB in the preceding 98-day period. Based on claims data, we also required cases to be enrolled for a minimum of 244 days prior to the SAB event, and to be vaccinated within 182 days preceding the SAB event. We purposefully chose a broad period for eligibility criteria for SAB cases for 2 main reasons: (1) to ensure we had the opportunity to electronically capture pre-existing conditions prior to pregnancy onset; (2) to ensure we captured all SAB cases with vaccinations during the gestational period of interest, including later occurring pregnancy losses (i.e., up to 20 weeks gestation). These criteria also facilitated the use of these cases in the exploratory case-time control design, with further explanation of eligibility criteria provided later in the report. If a woman had multiple incident SAB events with vaccinations during the study period, we selected the first chronological event in the study period to simplify the programming process. We randomly sampled 70 potential SAB cases electronically identified from each of the 2 Data Partners, for a total of 140 SAB events for medical record review.

We used de-identified full-text medical records to confirm the SAB event and estimate the dates of the SAB and pregnancy start. All cases were adjudicated by two clinician experts. SAB cases were considered confirmed if an intrauterine pregnancy and an unintentional pregnancy loss occurring prior to 20 weeks gestation were documented in the medical record. Methods to assign dates of SAB and pregnancy start, both necessary for the case-time control design, are described in sections C8 and C9.

2. Primary Aim 2: Validation of Algorithm to Identify Pregnancy Start Among Controls

In the Sentinel Distributed Database, we first identified women whose pregnancies ended in a live delivery using diagnosis and procedure codes in the inpatient setting listed in Appendix 2. To define an incident delivery, we used a washout period of 270 days. We also required controls to be enrolled in

their health care plans for a minimum of 360 days prior to the delivery and vaccinated during the gestational period of interest. These requirements helped to ensure that we had complete capture of vaccinations and confounders during pregnancy and 90 days prior to the start of pregnancy, which facilitated the use of these controls in the exploratory case-time control design.

Because we intended to match controls to cases by pregnancy start in the case-time control design, we first devised an algorithm for estimating pregnancy start followed by medical record review to confirm the pregnancy start. To initially assign pregnancy start, we used diagnosis codes assigned either to pregnant women or to their matched infants.[i] Using a slightly modified version of a previously validated algorithm used in MEPREP, we first used International Statistical Classification of Diseases (ICD-9-CM) codes for preterm delivery or post-term delivery (i.e., prolonged gestation) and assumed gestational lengths as specified in Appendix 3 [17]. If ICD-9-CM diagnosis codes for preterm or post-term deliveries were not present, we assumed a term delivery and assigned a gestational length of 270 days. We then estimated the pregnancy start by subtracting the assumed gestational length from the date of the delivery.

Up to 8 controls identified in the Sentinel Distributed Database were matched to chart confirmed SAB cases based on estimated pregnancy start date, Data Partner, and maternal age (see Sections C8 and C9). We then used medical records to confirm the pregnancy start and ensure the match was adequate (i.e., +/- 14 days of the matched case's pregnancy start). De-identified full text medical records, including prenatal records, ultrasound reports, and labor and delivery records, were sought out to validate the algorithm used to identify pregnancy start in live delivery controls. In pregnancies conceived with in-vitro fertilization or intrauterine insemination, we used the date of the procedure and embryonic age at transfer (if applicable) to assign pregnancy start. In pregnancies conceived without assisted reproductive technology, we considered both first trimester ultrasound dating and date of last menstrual period (LMP), if available. If both a first or second trimester ultrasound (i.e., up to and including 27 weeks gestation) and LMP date were documented, we used the LMP if verified by ultrasound, as defined in **Table 1**. If neither ultrasound dating nor LMP were available, then we assigned pregnancy start based on estimated gestational age (EGA) in the delivery record, if available. Patients were excluded if ultrasound, LMP, and EGA in the delivery record were unavailable.

[i] Note: Mother and infant linkages on the cohorts of pregnant women and infants identified within the Sentinel Distributed Database were performed as part of the PRISM influenza vaccines and birth defects protocol[23]

Table 1. Discrepancy between LMP and ultrasound supporting the use of each dating method to assign pregnancy onset, by gestational age at ultrasound

Gestational age at ultrasound	Discrepancy between LMP and ultrasound dating supporting use of *LMP*	Discrepancy between LMP and ultrasound dating supporting use of *ultrasound dating*
At or before 8 6/7 weeks	5 days or less	More than 5 days
9 0/7 to 13 6/7 weeks	7 days or less	More than 7 days
14 0/7 to 15 6/7 weeks	7 days or less	More than 7 days
16 0/7 to 21 6/7 weeks	10 days or less	More than 10 days
22 0/7 to 27 6/7 weeks	14 days or less	More than 14 days

3. Secondary Aim 1: Exploring the Feasibility of the Case-time Control Design

The case-time-control design was implemented as proof-of-concept in this activity, to examine the test use case association, influenza vaccine use during pregnancy, and risk of SAB. The risk interval was first defined under the assumption that risk of SAB might be increased in specific time periods following vaccination; and in separate analyses, the risk interval was defined under the assumption that the risk might be increased following IIV received at specific gestational periods, regardless of temporal proximity to the vaccination. The secondary aim utilized data collected as part of the primary validation aims, described earlier. In this next section, we describe the methods used to select cases and controls and to implement this exploratory analysis.

4. Overview of Case-time Control Design

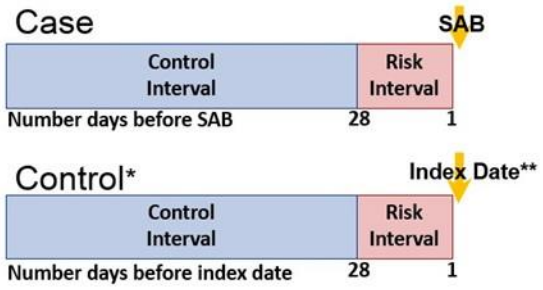
The case-time control design is a variant of a case-cross-over study (CCO) design [18,19]. The CCO study design and its variants are especially well-suited to measuring transient effects of exposures on immediate risk of illnesses with abrupt onset. In a CCO, in individuals who have experienced the outcome of interest, a comparison is made of the odds of exposure in a pre-defined risk interval to that in a self-matched comparison interval. 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 due to seasonal or gestational age patterns. As in the cases, in controls, the odds of exposure are compared in the risk vs. comparison interval to estimate the exposure trend bias. This exposure trend bias is used to adjust the odds ratio observed in cases to produce an effect estimate for the association between exposure and outcome while adjusting for time trend in exposure.

As proof-of-concept, a case-time control study design was implemented to examine whether risk of SAB is elevated in specific time periods following IIV or alternatively, following IIV received at specific gestational periods, irrespective of temporal proximity to vaccination. We identified SAB cases that were vaccinated between -4 weeks gestation until the date of the SAB. Since the likelihood of receiving an IIV differs by gestational age and calendar time, we then matched each case to a vaccinated control based on Data Partner, maternal age, and pregnancy start, where controls were initially required to have received an IIV between -4 weeks gestation and the case's gestational age at SAB. We assigned an index date in controls that corresponded to the gestational age at SAB in the case. Of note, cases and controls were informative (e.g., contributed information to odds ratio estimates, confidence intervals, and p-values) if only vaccinated in either the risk or the control interval.

5. Risk Intervals

In secondary objectives, we implemented the case-time-control design using the data collected to investigate the primary aims. First, we examined whether the risk of SAB is elevated in pre-specified periods by number of days between IIV receipt and the SAB event and then in separate analyses, following vaccination at specific gestational periods. The risk interval was first defined as receipt of IIV within 1-28 days prior to the SAB in cases or the index date in controls (Figure 1). A corresponding control interval was defined as receipt of IIV outside the risk interval [i.e., from -28 days gestation through 29 days prior to the SAB in cases or the index date in controls]. Thus, the length of the control intervals varied depending on the gestational age at SAB in the case. This risk interval was selected because previous studies suggest that antibody secreting cells increase in peripheral blood within days of vaccination with peak antibody titers occurring 2-3 weeks following administration of seasonal influenza vaccine in healthy non-pregnant individuals [20,21].

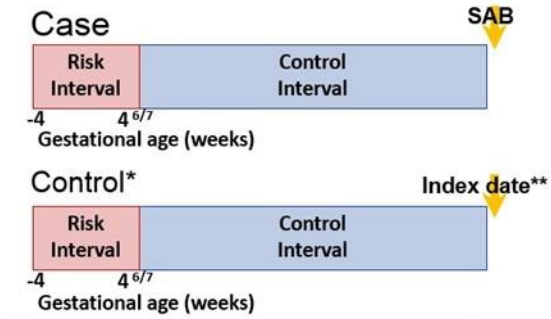
Figure 1. Example case and control for case-time control design with the risk interval defined as 1-28 day before SAB



*Controls are matched to cases on pregnancy start
**Control index date set to correspond to gestational age at matched case's event

Next, a case-time control design with the same cases and controls was used. In contrast to the preceding risk interval definition, the risk interval was defined by gestational age at exposure, which conceptually examines whether the risk of SAB is elevated following IIV received at specific gestational age periods, irrespective of temporal proximity to vaccination. For each case and control, we assessed the gestational age at IIV receipt, irrespective of timing of vaccination in relation to the SAB event or index date (Figure 2). Among women receiving IIV during the period of interest, the likelihood of receiving IIV at a gestational age hypothesized to carry a higher risk for vaccine-associated SAB was compared to that outside the period of interest. We considered three different risk intervals defined by gestational age: -4 through 4 weeks gestation, 2 through 5 weeks gestation, and 6 through 11 weeks gestation. Each of the risk intervals was analyzed separately, with the control interval consisting of all person time outside of the risk interval but within the gestational period of study (-4 weeks gestation through date of the SAB in cases or index date in controls). The -4 through 4 weeks gestation risk interval was selected to investigate whether inflammatory and immune-mediated processes resulting from vaccination near the time of conception or during early pregnancy may lead to increased risk of SAB. [22]. The interval of 2 through 5 weeks gestation was selected to investigate whether immune-mediated processes resulting from vaccination in early pregnancy might affect rates of SAB. Finally, the risk interval of 6 through 11 weeks gestation corresponds to the period of the highest incidence of SAB, which could reflect an increased period of susceptibility.

Figure 2. Example case and control for case-time control design with the risk interval defined as -4 through 4 weeks gestation



*Controls are matched to cases on pregnancy start
**Control index date set to correspond to gestational age at matched case's event

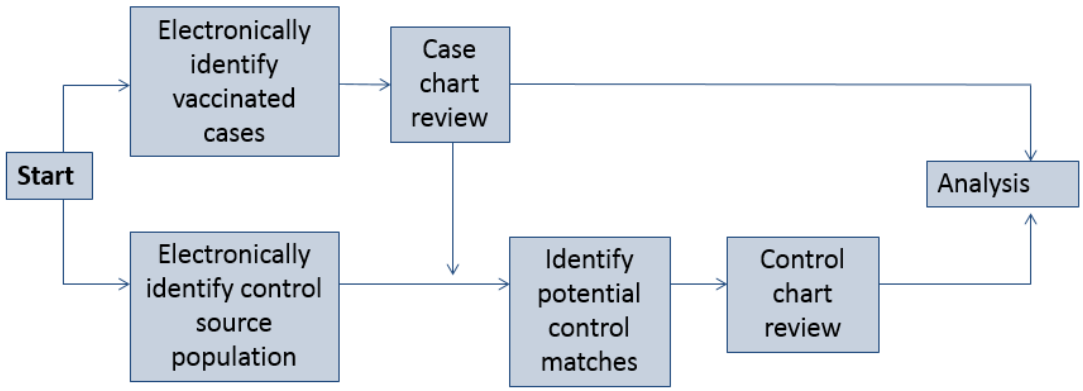
6. Study Population (Case-time-control Design)

The study population for the case-time-control design was derived from that of the primary validation aims. The study population included women who were enrolled in one of two participating Data Partners, Aetna or HealthCore. We included females 18 through 34 years of age whose pregnancy ended in either the outcome of interest, SAB, or the control outcome, live delivery from September 30, 2008 through October 31, 2011. Women whose pregnancies ended in a stillbirth, elective abortion, ectopic pregnancy, or molar pregnancy were excluded from the study population. We further restricted the study population to those receiving a 2008-2009 or 2010-2011 IIV between 4 weeks before pregnancy start through the end of pregnancy. We did not include the 2009-2010 season because the pandemic H1N1 vaccine was also available during the same season. To enhance capture of exposures during the gestational period of interest, we required enrollment between 90 days before pregnancy start through the SAB date in cases, or date of delivery in controls. For the case-time control design, we excluded multiple gestation pregnancies and pregnancies without dating information in the medical records.

7. Overview of Selection of Cases and Controls

Vaccinated SAB cases and live delivery controls were identified in a 4-phase process (Figure 3) with a targeted final sample of 100 SAB cases, each matched to at least 1 control (up to a maximum of 6) in the final analysis, after chart validation was complete. First, 140 potential cases (70 from each Data Partner) were identified in the Sentinel Distributed Database; in parallel, we identified a cohort of live deliveries within the Sentinel Distributed Database to serve as the source population for controls. Second, we reviewed the medical records of potential cases to confirm SAB, date of SAB, and obtain pregnancy start date. Third, for each chart-confirmed case, we identified up to 8 potential controls in the Sentinel Distributed Database of the same Data Partner, similar maternal age (+/-18 months), pregnancy start (+/-14 days), with vaccination between -6 weeks gestation and 2 weeks past the case's gestational age at SAB based on electronic data. Fourth, we reviewed the medical records of potential controls to confirm pregnancy start and exclude controls whose pregnancy start was not within +/-14 days of the case's pregnancy start, or whose vaccinations occurred past the index date or prior to 4 weeks before pregnancy start.

Figure 3. Case and control selection



8. Identification and Chart Confirmation of Cases

Cases were initially identified in electronic claims data as described earlier in Section C1 and confirmed with medical record review. Initial identification criteria (based on electronic data) included women who met algorithm criteria for SAB, were enrolled continuously for a minimum of 244 days prior to the SAB, and who received IIV in the 182 days preceding the SAB event (rationale further elaborated in Appendix 4).

For inclusion in the final analysis, we confirmed SAB cases with medical records, using criteria described earlier in this report. All SAB events indicated by chart review to occur prior to 6 weeks gestation were excluded since recognition of pregnancy loss prior to this point is uncommon, which makes it difficult to establish date of pregnancy start and date of SAB. Furthermore, we excluded multiple gestation pregnancies based on medical record documentation.

Medical records were used to assign date of SAB and pregnancy start among cases. We used the date of SAB diagnosis or date of ultrasound confirming SAB as recorded in the medical record, for assigning the number of days of the case event relative to vaccination and gestational age of the case event. We considered incorporating ultrasound fetal dating and symptom onset to assign date of SAB but opted against using them due to their limitations, which are described in Appendix 5. Pregnancy start in cases was assigned using the date of procedure and age at embryo transfer (if applicable) in pregnancies conceived using in-vitro-fertilization or intrauterine insemination. In cases whose pregnancies were conceived without assisted reproductive technologies, we used the date of the LMP to estimate pregnancy start. The rationale for choice of method to assign date of pregnancy start in cases and controls is described in Appendix 6.

Following chart review, we excluded cases in which chart-derived pregnancy start and SAB dates indicated that pregnant women had not received IIV between -4 weeks gestation and the SAB date. Based on these chart-derived dates, we also required continuous enrollment between 90 days before pregnancy start through the SAB date to enhance capture of exposures during the gestational period of interest and capture of pre-pregnancy confounder information.

9. Identification and Chart Confirmation of Matched Controls: Identifying Control Matches in Electronic Data

After completing chart review of potential cases, we identified 1 or more potential controls (up to a maximum of 8 controls) in the Sentinel Distributed Database for every case. Controls were identified from the source population of live deliveries (identified using the same algorithm as described earlier). Patients previously selected as cases were not eligible to be controls. Controls were matched to cases on Data Partner, age (+/-18 months), and pregnancy start (+/- 14 days), with pregnancy start estimated initially using the algorithm described earlier, and later chart-confirmed. Additional inclusion criteria for controls are described in Appendix 4. Matching on pregnancy start was implemented to address temporal trends in exposure by gestational age and calendar time, by maximizing the comparability between cases and controls with respect to the gestational and calendar periods covered by the risk and control intervals. Furthermore, we matched on Data Partner and maternal age to address potential confounding, which might occur if they were associated both with SAB and with timing of vaccination.

Among potential controls meeting matching and enrollment criteria, we identified those with IIV in the period from 42 days prior to pregnancy onset through 14 days past the matched case's gestational age at SAB. For the purposes of identifying control matches, pregnancy start in controls was based on the algorithm described earlier in section C2. A 14-day margin before and after the gestational period of interest was initially incorporated to allow for misclassification of gestational age in live delivery controls due to use of claims data for gestational age estimates.

10. Chart Review of Matched Controls

After 1 or more potential controls were identified in electronic data for each chart confirmed case, we conducted a second round of chart review to confirm that potential controls had vaccine exposure in the gestational period of interest and that they met pregnancy start matching criteria (+/-14 days of the case's pregnancy start). Controls were excluded if a pregnancy outcome other than live delivery was recorded in the medical record or if pregnancy start was more than 14 days before or after the matched case's pregnancy start. Gestational age based on medical records, using the algorithm described earlier in the validation aims, was used for the case-time control analysis. Following chart review, controls were only retained if based on chart-derived gestational age estimates, they received an IIV between -4 weeks gestation and the index date. We also required continuous enrollment from 90 days before pregnancy start through the index date to facilitate capture of exposures during the gestational period of interest and confounders prior to pregnancy onset. We also excluded multiple gestation pregnancies based on medical record documentation.

11. Clinical Information Abstracted from Medical Charts

For both cases and controls, we abstracted from medical records information on potential risk factors for SAB, including asthma, gravidity, hypertension, prior history of SAB, diabetes, febrile illness, medically attended infections, obesity, tobacco use, and alcohol use. We also assessed asthma, diabetes, and medically attended infections in claims data, via algorithms described previously in the protocol for this activity[23].

12. IIV Exposure

IIV was identified in claims-based data using National Drug Codes (NDC), Current Procedural Terminology (CPT), Healthcare Common Procedure Coding System (HCPCS) and International Statistical Classification of Diseases (ICD-9-CM) codes (Appendix 7). The main secondary analysis included vaccinations identified in electronic data, while a sensitivity analysis was restricted to vaccinations later confirmed via chart review.

III. ANALYSIS

A. PRIMARY AIMS 1 AND 2 (VALIDATION AIMS)

We first examined the positive predictive value of claims codes for SAB, using chart review as the "gold standard". We estimated the positive predictive value (i.e., chart confirmed SAB cases divided by all potential SAB cases identified in claims data with charts available) overall, and by maternal age group (18-24.999, 25-29.999, and 30-34.999 years), claims codes (i.e., specific ICD-9-CM or CPT code), type of claims code (i.e., procedure vs. diagnosis code), and medical care setting (i.e., inpatient, emergency department, or ambulatory care). Additionally, based on chart-derived pregnancy start estimates, we estimated the proportion of cases that was excluded because vaccination occurred prior to the period of interest (i.e., prior to 4 weeks before pregnancy start). To identify the optimal look-back period for vaccine codes relative to SAB codes in electronic data, we tabulated the number of cases with IIV administration occurring prior to 4 weeks before pregnancy start, stratified by the number of days that vaccination preceded the SAB event in electronic data.

In addition to validating SAB events and identifying the optimal look-back period for vaccine codes in electronic data, we examined the accuracy of gestational age information in claims data for the purposes of identifying pregnancy start among live delivery controls. We estimated the proportion of controls that were discarded because their chart-derived pregnancy start estimate indicated that vaccination had occurred prior to 4 weeks before pregnancy start, or because the pregnancy start match to the case was inadequate (more than 14 days before or after the case's pregnancy start). We also estimated the proportion of controls discarded due to vaccination occurring after the index date, per chart review data. Finally, we characterized the distribution of controls by number of days between pregnancy start when comparing electronic vs. chart review data.

B. SECONDARY AIM 1 (CASE-TIME CONTROL DESIGN)

The case-time-control design analysis required cases to have chart-confirmation of a SAB, and excluded controls with outcomes other than live delivery (i.e., ectopic pregnancy, molar pregnancy, elective abortion, SAB, or stillbirth) documented in medical records. The analysis used pregnancy start information only from medical records and incorporated both electronic and medical record information on potential confounders.

To analyze data from the case-time control design, conditional logistic regression stratified by case: control set was used. The use of conditional logistic regression, in contrast to standard logistic regression, allowed 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 was 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 was case vs. control status (1=case; 0=control), with the corresponding coefficient estimating the final odds ratio estimate, adjusted for time trend in exposure.

A series of models for each of the risk intervals was implemented, unadjusted and adjusted for hypertension, diabetes, asthma, obesity, tobacco and alcohol use, urinary tract infection, and respiratory tract infection. First, we analyzed the data with exposure defined as vaccination in the 1-28 day period prior to the SAB in cases and the index date in controls. Next, we considered risk intervals defined by gestational age at vaccination, regardless of temporal proximity to the SAB event. The risk interval was first defined as -4 through 4 weeks gestation, while the control interval was defined as 5 weeks gestation through the SAB in cases or the index date in controls. Next, the risk interval was defined as 2 through 5 weeks gestation, while the control interval was defined as the combined period of -4 through 1 week gestation and 7 weeks gestation to the SAB in cases or index date in controls. Finally, the risk interval was defined as 6 through 11 weeks gestation, while the control interval was defined as the combined period of -4 through 5 weeks gestation and 12 weeks gestation to the SAB in cases or the index date in controls.

C. SENSITIVITY ANALYSIS FOR SECONDARY CASE-TIME CONTROL DESIGN AIMS

We conducted a number of sensitivity analyses for the exploratory case-time control design analysis. The first set of sensitivity analyses was performed to address the possibility that earlier pregnancy losses may be more likely to be due to chromosomal anomalies or other genetic factors, which could make medical product exposures irrelevant to causes of the SAB. First, we excluded cases with medical record documentation of a blighted ovum (anembryonic gestation) and their matched controls. Second, we restricted the analysis to cases with detection of a fetal heart beat prior to the pregnancy loss, and third, we restricted the analysis to cases that occurred at or after 12 weeks gestation.

The second set of sensitivity analyses was performed to address the possible influence of incomplete medical record documentation on odds ratio estimates. First, because we were unable to obtain medical records to confirm vaccination on all patients, we analyzed cases and controls for whom vaccinations were confirmed in medical records. Second, because we were unable to obtain the delivery record from all patients, in addition to requiring chart confirmation of SAB in all cases (which was required in the main analysis), we also required chart confirmation of a live delivery in all controls.

D. EXPLORATORY AIM 2 (TEMPORAL SCAN STATISTICS)

An important limitation of the case-time control design is that the risk interval must be defined before the analysis is conducted. Because the pathophysiology of SAB is largely unknown, it is difficult to know the appropriate periods of risk to assign. By contrast, with temporal scan statistics, it is not necessary to define the risk interval *a priori*. Furthermore, the scan statistic evaluates multiple overlapping time windows, adjusting statistical analyses for the multiple testing.

In exploratory analyses, we used a two-dimensional scan statistic to explore whether the risk of SAB is elevated in a particular period following vaccination at a particular gestational age.

The temporal analysis compared the timing of vaccination among vaccinated cases to that among vaccinated controls using a Bernoulli model. We first randomly sampled one control per case. For each location and size of the scanning window, the alternative hypothesis was that there was an elevated risk within the risk interval as compared to outside. Because analytical formulas are not available to estimate the variances of scan statistics, we used Monte Carlo simulation to obtain p-values, based on 9,999 randomly generated datasets. The calculations were performed using SAS version 9.4 and the free SaTScan software for the spatial and space-time scan statistics (www.satscan.org). For each scan statistic analysis, we report the start and end time of the most likely cluster and the corresponding p-value.

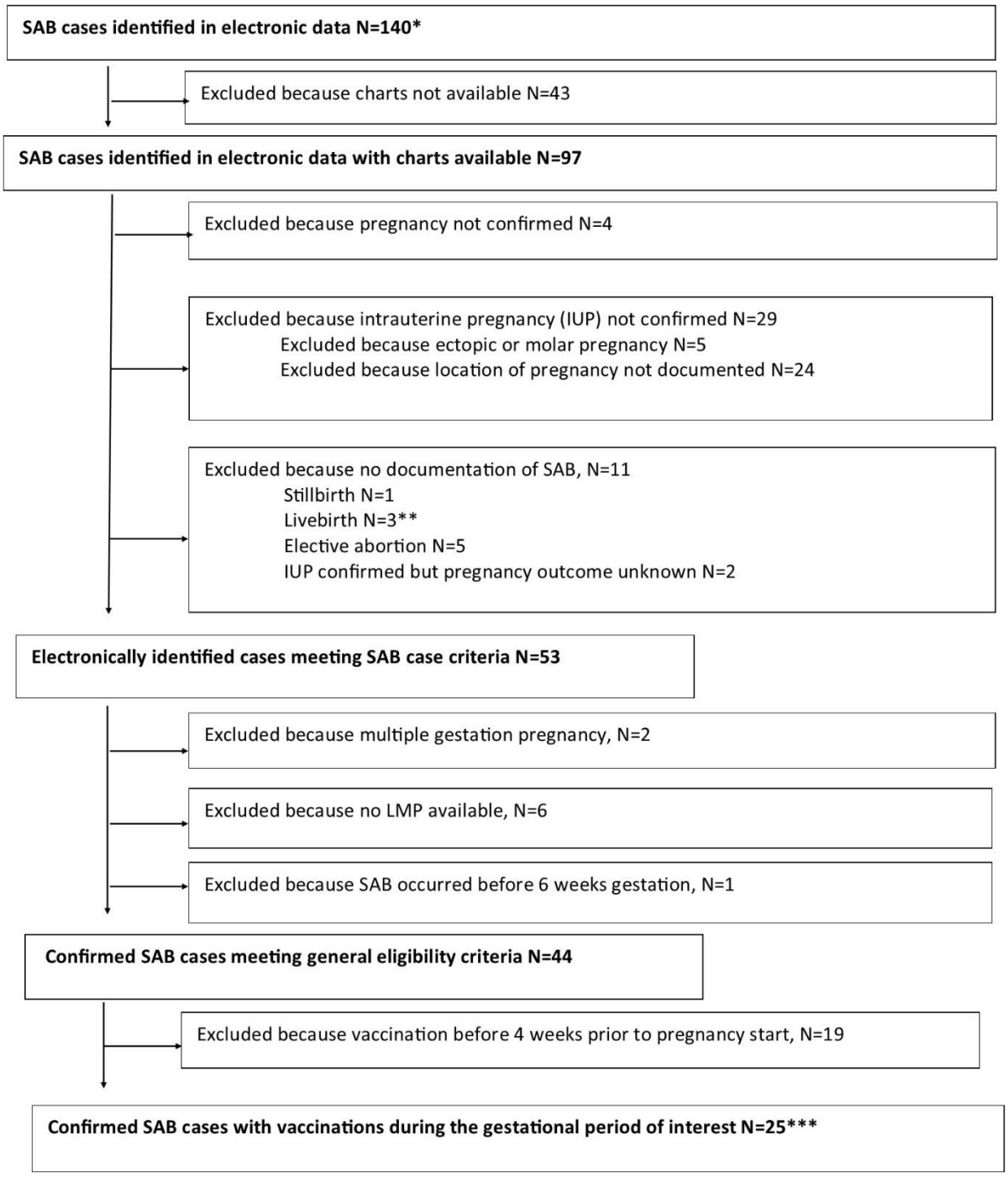
IV. RESULTS

A. PRIMARY AIM 1: VALIDATION OF ALGORITHM TO IDENTIFY SAB EVENTS

Of the 140 cases identified in electronic data (**Figure 4**), we obtained medical charts for 97 (69%). Based on medical record review by clinical experts, we determined that 53 (55%) of the electronically identified cases with charts available met case confirmation criteria, specifically documentation of an intrauterine pregnancy (IUP) and subsequent pregnancy loss before 20 weeks gestation. The most common reason for failing to meet case confirmation criteria was lack of documentation of the location of the pregnancy (and therefore an IUP), applicable to 24 of the 44 (55%) unconfirmed cases with charts available. Less common reasons for failure to meet case confirmation criteria include lack of documentation of pregnancy (n=4), documentation of an ectopic or molar pregnancy (and therefore absence of documentation of an IUP, n=5), IUP with pregnancy outcome other than SAB (stillbirth. livebirth, or elective abortion, n=9), and IUP with unknown pregnancy outcome (n=2).

Of the 53 confirmed cases of SAB, we further excluded 9 cases due to occurrence prior to 6 weeks gestation, multiple gestation pregnancy, or absence of LMP in medical records. Of the 44 remaining confirmed cases, we further excluded 19 patients whose vaccination occurred prior to 4 weeks before pregnancy start, leaving 25 eligible SAB cases with vaccinations during the gestational period of interest.

Figure 4. Chart confirmation of spontaneous abortion cases identified in the Sentinel Distributed Database



* Randomly sampled from a total of 1586 potential cases identified in electronic data
** Includes patients undergoing a postpartum dilation and curettage for retained placenta
*** From the 25 eligible SAB cases with vaccinations during the gestational period of interest, 6 were excluded because we were unable to identify control matches. Thus, a total of 19 cases were eligible for the case-time control design analysis.

Table 2 shows the positive predictive value of claims algorithms for SAB, overall, and by age, code type, diagnosis code, and medical care setting. The majority of cases were identified in women 30-34.999 years of age, with ICD-9-CM diagnosis code 632 (missed abortion) or 634 (spontaneous abortion) alone, and in the ambulatory visit setting. Confidence intervals were wide and overlapped between each of the subgroups examined.

Table 2. Positive predictive value of claims algorithms for SAB

	Chart-confirmed cases	Cases with medical charts available	Positive predictive value (95% CI)
Total cases	53	97	54.6% (44.2 to 64.8%)
Maternal age			
18-24.999 years	10	17	58.8% (32.9 to 81.6%)
25-29.999 years	13	29	44.8% (26.5 to 64.3%)
30-34.999 years	30	51	58.8% (44.2 to 72.4%)
Code type			
Procedure code	0	1	0 -----
Diagnosis code	50	87	57.5% (46.4 to 68.0%)
Diagnosis and procedure code	3	9	33.3% (7.5 to 70.0%)
Diagnosis code[i]			
632 (missed abortion) and 634* (spontaneous abortion)	6	9	66.7% (29.9 to 92.5%)
632 without 634*	28	43	65.1% (49.1 to 79.0%)
634* without 632	19	44	43.2% (28.4 to 59.0%)
No diagnosis codes	0	1	0 -----
Setting			
Ambulatory visit + emergency department (ED)	2	2	100% (15.8 to 100%)
Ambulatory visit only	44	80	55.0% (43.5 to 66.2%)
ED only	5	11	45.5% (16.8 to 76.6%)
Inpatient	2	4	50% (6.8 to 93.2%)

[i]634* refers to 634, and 634.0x-634.9x

B. IDENTIFYING OPTIMAL LOOK-BACK PERIOD FOR IIV RELATIVE TO SAB IN ELECTRONIC DATA

To fully capture SAB cases with IIV exposures within the gestational period of interest (4 weeks prior to pregnancy start until the day prior to the SAB), we had purposefully identified vaccinations within a wide range prior to SAB (1 to 182 days before) in electronic data. This wider look-back period targeted capture of late occurring SABs (through 20 weeks gestation) with vaccinations during the periconceptional period. This approach resulted in discarding a large proportion of cases that were vaccinated prior to the gestational period of interest. The intent was to maximize sensitivity in this initial activity, towards the goal of identifying narrower criteria for future surveillance efforts. **Table 3** shows the number of cases that were excluded following chart review validation due to vaccination occurring prior to 4 weeks before pregnancy start, stratified by potential look-back periods for vaccinations relative to SAB events in electronic data. The 90-day look-back period was optimal because it captured all cases meeting study criteria, while reducing the number of potential cases identified (and therefore charts that needed to be reviewed) from 97 to 56, a decrease of 42%.

Table 3. Proportion of cases meeting study inclusion criteria by identification period for IIV relative to SAB event in claims data

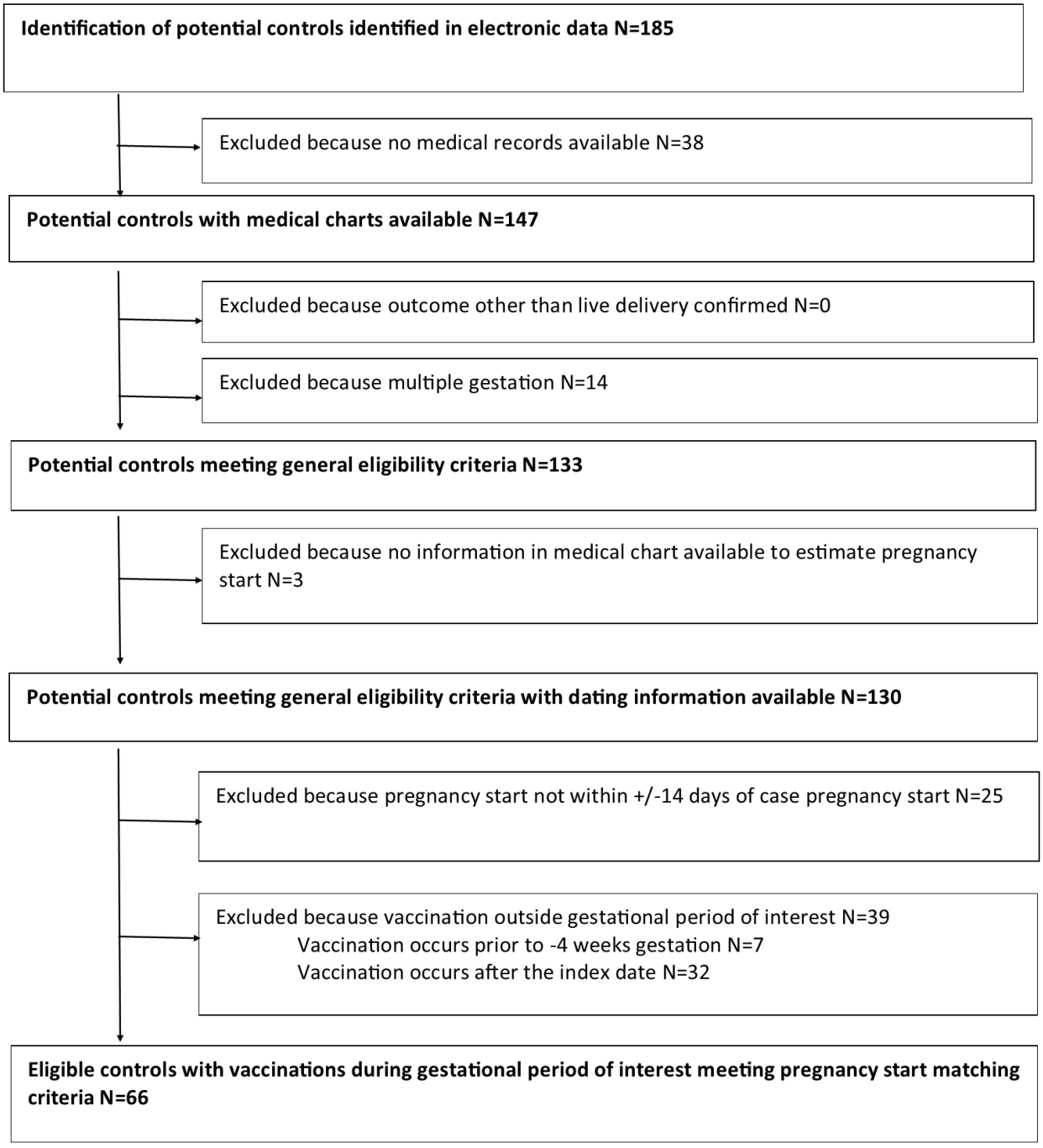
Timing (days) between vaccine and SAB date in electronic data	Number confirmed cases meeting inclusion criteria*/Total number cases identified in electronic data with charts available (%)	% study-eligible cases missed by using shorter look-back period
1-182	25/97 (26%)	-------
1-100	25/60 (42%)	0/25 (0%)
1-90	25/56 (45%)	0/25 (0%)
1-60	24/44 (55%)	1/25 (4%)

*Confirmed cases with vaccinations during the gestational period of interest

C. PRIMARY AIM 2: VALIDATION OF PREGNANCY START ALGORITHM AMONG CONTROLS

Of the 185 controls identified in the Sentinel Distributed Database, we obtained pregnancy related medical charts for 147 (79%, Figure 5). One hundred thirty eligible controls had dating information (i.e., LMP, ultrasound dating, or gestational age from the delivery record) available in medical records. Altogether, we excluded 64 controls (34% of controls identified in electronic data) due to use of the gestational age algorithm to identify eligible controls. Among these 64 controls, 25 were excluded for failing to meet pregnancy start match criteria (i.e., within +/-14 days of the matched case's pregnancy start). Also 7 controls were excluded whose vaccination occurred prior to -4 weeks gestation, and 32 controls were excluded because vaccination occurred after the index date (i.e., gestational age at the matched case's SAB). Following these exclusions, a total of 66 controls remained.

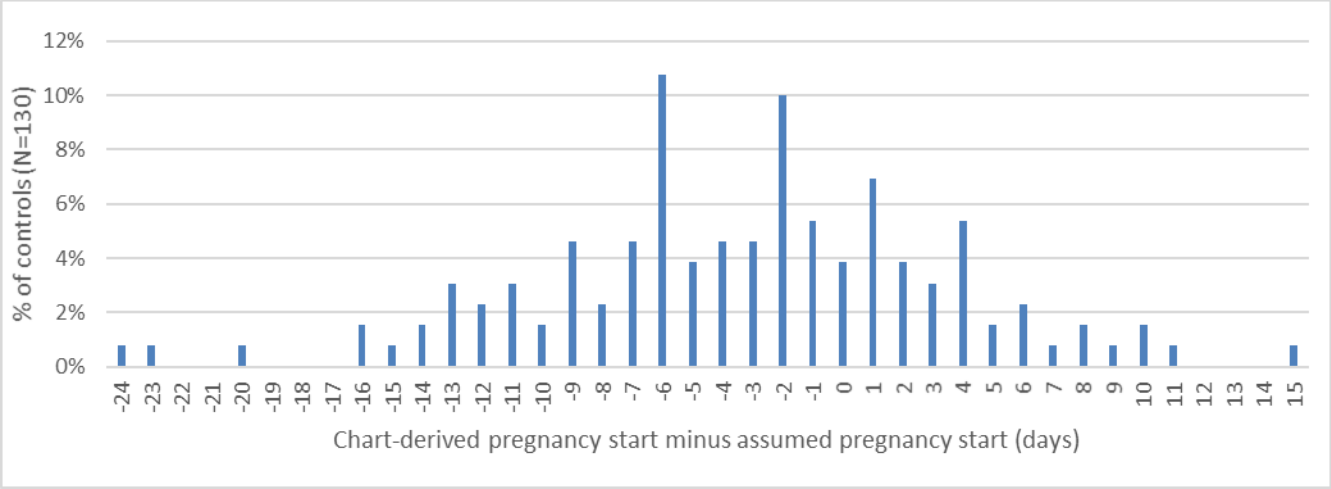
Figure 5. Chart confirmation of controls identified in the Sentinel Distributed Database



D. COMPARING ASSUMED PREGNANCY START TO CHART-DERIVED ESTIMATES

We compared assumed pregnancy start (based on the algorithm) to chart review estimates in the 130 eligible livebirth controls with dating information in charts available (Figure 6). We observed that 124 (95%) of the deliveries had an algorithm-derived pregnancy start that was within 14 days before or after their "gold standard" (chart-derived) estimate. Furthermore, 93 (72%) of the deliveries had an algorithm-derived pregnancy start that was within 7 days before or after the chart-derived estimate. More specifically, 5 (4%) controls had the same pregnancy start estimates, while 31 (24%) had chart-derived estimates within 1-7 days *after* electronic-derived estimates and 57 (44%) had chart-derived estimates within 1-7 days *before* electronic-derived estimates. Seven controls (5%) had chart-derived estimates within 8-14 days *after* electronic-derived estimates, and 24 controls (18%) had chart-derived estimates within 8-14 days *before* electronic-derived estimates.

Figure 6. Comparison of assumed pregnancy start to gold standard (chart review) estimates of pregnancy start*



*Positive quantities indicate that the chart derived ("gold standard") pregnancy start occurred after the algorithm-derived pregnancy start and that the algorithm *overestimated* gestational age. Negative quantities indicate that the algorithm *underestimated* gestational age.

E. SECONDARY AIM 1: CASE-TIME CONTROL DESIGN ANALYSIS

Cases and controls

As described earlier, 53 cases identified in the Sentinel Distributed Database met SAB confirmation criteria (Figure 4). After excluding multiple gestation pregnancies, cases without pregnancy dating information, and cases with vaccinations occurring outside the gestational period of interest (before -4 weeks gestation or after the case SAB date), a total of 25 cases remained. We further excluded 4 cases without eligible control matches identified in electronic data (i.e., a live delivery of the same Data Partner, maternal age, pregnancy start, and with vaccinations between 6 weeks prior to pregnancy start and 2 weeks after the index date). We also excluded 2 cases for whom subsequent clinical expert adjudication revealed that none of the potential control matches identified in electronic data met pregnancy start matching criteria with the case (+/-14 days). Thus, a total of 19 cases were eligible for the case-time control design analysis. Characteristics of cases included in the case-time control design are presented in **Table 4**.

The 19 eligible cases were matched to a total of 66 controls that ultimately met eligibility criteria, including pregnancy start within +/-14 days of the matched case, singleton pregnancy, and vaccination during the gestational period of interest. The final control to case matching ratio was variable and ranged from 1:1 to 6:1. Sixteen of the 19 cases had two or more matched controls.

Table 4. Characteristics of cases included in case-time control design analysis (N=19)

Characteristic	N	(%)
Maternal age at pregnancy start (years)		
18-24.999	3	15.8%
25-29.999	5	26.3%
30-34.999	11	57.9%
Gravidity		
1	11	57.9%
2 or more	7	36.8%
Unknown	1	5.3%
History of prior SAB*		
Yes	0	0.0%
No	11	57.9%
Unknown**	8	42.1%
Smoked during pregnancy*	0	0.0%
Alcohol*	2	10.5%
Diabetes***	1	5.3%
Asthma***	2	10.5%
Hypertension*	1	5.3%
Obesity*	3	15.8%
Respiratory tract infection***	2	10.5%
Gastrointestinal infection***	1	5.3%
Urinary tract infection*	0	0.0%
Febrile illness*	0	0.0%

*Based upon medical record data

**Unknown status for history of SAB includes patients whose gravidity and parity notation indicated that an abortus had occurred but there was no further indication whether it was an induced or spontaneous abortion.

***Based upon claims or medical record data

F. CASE-TIME CONTROL DESIGN ODDS RATIO ESTIMATES

Table 5 presents the odds ratio estimates from the case-time control design analysis, which inherently adjusts for time trends in exposure by gestational age and calendar time, Data Partner, and maternal age. In unadjusted and adjusted models, we found no evidence for an association between vaccination with IIV during pregnancy and SAB, regardless of whether the risk interval was defined by time since vaccination or gestational age at vaccination (**Table 5**). However, all confidence intervals were wide due to small case numbers.

Table 5. Case-time control design odds ratio estimates by risk interval*

Risk interval definition	Cases	Controls	Unadjusted OR (95% CI)**	Adjusted OR (95% CI) ***
Time since vaccination				
1-28 days	15	53	0.68 (0.17, 2.79)	0.49 (0.15, 1.60)
Gestational age at vaccination				
-4 through 4 weeks gestation	8	33	0.53 (0.09, 3.11)	0.42 (0.05, 3.61)
2 through 5 weeks gestation	11	42	0.68 (0.17, 2.79)	0.84 (0.19, 3.79)
6 through 11 weeks gestation	13	56	1.96 (0.55, 7.04)	1.74 (0.46, 6.63)

* The case-time control odds ratio was estimated by dividing the odds ratio in controls by the odds ratio in cases, the former of which estimates the time trend in exposure.
**All odds ratio estimates are inherently adjusted for calendar time, gestational age, Data Partner, and maternal age, due to two reasons: (1) cases and controls were matched on the latter two factors and pregnancy start; and (2) conditional logistic regression was used.
***Odds ratio additionally adjusted for asthma, hypertension, alcohol use, respiratory tract infection, and urinary tract infection. Tobacco use, gravidity, diabetes, and obesity not adjusted for in models because their associated standard errors were large.

G. CASE-TIME CONTROL DESIGN SENSITIVITY ANALYSIS

The first three sensitivity analyses, which are restricted to cases without a diagnosis of blighted ovum, cases with documentation of a fetal heartbeat, and cases occurring at or after 12 weeks gestation, were proposed to address the possibility that later occurring pregnancy losses are less likely due to chromosomal anomalies and other genetic causes. If true, including earlier occurring losses could potentially bias odds ratio estimates towards the null. We were unable to conduct sensitivity analyses restricted to cases without diagnosis of a blighted ovum or those occurring at or after 12 weeks gestation due to limited numbers of eligible cases (n=8, n=4, respectively). When restricting to the 15 cases without a diagnosis of blighted ovum, unadjusted results were similar to those observed in the main secondary analysis (**Table 5**). We did not perform adjusted analyses due to limited case numbers.

The fourth and fifth sensitivity analyses, which separately required (1) documentation of vaccination for all patients and (2) documentation of a live delivery for all controls, were proposed to assess the potential impact of missing medical record documentation on odds ratio estimates. The unadjusted results for both sensitivity analyses addressing incomplete medical record documentation were similar to those observed in the main secondary analysis (**Table 6**). We did not perform adjusted analyses due to limited case numbers.

Table 6. Sensitivity analyses of case-time control design

Sensitivity analysis	Cases	Controls	Unadjusted OR (95% CI)
Restrict to SAB cases without blighted ovum diagnosis (and their matched controls)			
Time since vaccination			
1-28 days	11	45	0.82 (0.24, 2.83)
Gestational age at vaccination			
-4 through 4 weeks gestation	7	29	0.22 (0.02, 2.37)
2 through 5 weeks gestation	10	41	0.86 (0.20, 3.64)
6 through 11 weeks gestation	12	52	2.83 (0.69, 11.62)
Restrict to SAB cases and live delivery controls with chart documentation of vaccination			
Time since vaccination			
1-28 days	7	16	0.55 (0.11, 2.69)
Gestational age at vaccination			
-4 through 4 weeks gestation	5	13	0.22 (0.02, 2.31)
2 through 5 weeks gestation	6	14	1.72 (0.32, 9.34)
6 through 11 weeks gestation	8	20	1.67 (0.36, 7.68)
Restrict to livebirth controls with chart confirmation of live delivery (and their matched cases)*			
Time since vaccination			
1-28 days	15	46	0.53 (0.18, 1.57)
Gestational age at vaccination			
-4 through 4 weeks gestation	8	27	0.41 (0.07, 2.30)
2 through 5 weeks gestation	10	34	0.77 (0.18, 3.22)
6 through 11 weeks gestation	13	47	2.08 (0.58, 7.44)

*The main analysis did not require controls to have confirmation of a live delivery. Though not all controls had their pregnancy outcome documented, none had a pregnancy outcome other than a live delivery documented in medical records.

H. SECONDARY TEMPORAL SCAN ANALYSIS

The two-dimensional temporal scan did not identify any clusters that met statistical significance. The two-dimensional temporal scan identified two potential clusters: (1) risk interval defined by 45 to 65 days gestation and 7 to 21 days prior to SAB and (2) risk interval defined by 24 to 43 days gestation and 33 to 39 days prior to SAB. Neither cluster was statistically significant (p=0.58, 0.99, respectively).

V. DISCUSSION

This activity demonstrated that with Sentinel it is feasible to conduct surveillance of pregnancy outcomes following vaccination. For this proof-of-concept activity, we chose to study SAB, one of the most challenging pregnancy outcomes, since it is relatively common, and there are limited pre- and post-market safety data available in pregnant populations. While the ability to conduct large-scale, population-based surveillance is an important strength of Sentinel, the use of retrospective healthcare data to identify and evaluate potential safety signals in pregnant women requires rigorous evaluation of the data and methods needed for these surveillance activities.

The principal objective of this exploratory activity was to validate and refine electronic algorithms for conducting surveillance of pregnancy outcomes following vaccination within Sentinel, using influenza vaccines and SAB as a test use case. Our claims-based algorithm for SAB in Sentinel's PRISM program yielded an overall positive predictive value (PPV) of 55%, which was lower than the PPV (92%) observed in prior validation work in the Vaccine Safety Datalink [24]. The lower PPV in Sentinel's PRISM program highlights the importance of incorporating medical record reviews for surveillance of this outcome and may be due to several reasons. First, we required documentation of an intrauterine pregnancy as part of our case definition. The majority of ineligible cases did not meet our case definition due to the absence of this type of documentation, which is one of the challenges of working with national health insurers that do not have direct electronic access to the medical records of patients. Our Data Partners work with vendors to acquire medical records from healthcare facilities (hospitals and outpatient clinics) throughout the U.S. and to electronically scan relevant portions of the medical record for centralized review by our clinical adjudicators. Information about the presence of an intrauterine pregnancy and confirmation of a SAB event may occur over several visits to different healthcare facilities. A less common reason for not meeting the case definition is miscoding of pregnancy outcomes, such as the occurrence of an induced abortion or stillbirth. We deliberately used a wide look-back period to identify vaccinations prior to SAB events in electronic data to consistently capture exposures during the periconceptional period in late occurring SABs. A sizeable proportion of cases was vaccinated prior to the gestational period of interest and therefore excluded. We anticipated this finding would occur given our intent to maximize sensitivity in this feasibility project to understand the data available for future pregnancy safety surveillance. Given our findings, we propose that future work use a shorter look-back period of 1 to 90 days for vaccinations relative to SAB events, as we anticipate this time period will be sufficient to identify cases vaccinated during the gestational period of interest.

Compared to the "gold standard" chart-derived estimates, our algorithm to assign pregnancy start in pregnancies ending in a live delivery was accurate within +/- 7 days in 72% of deliveries and within +/-14 days in 95% of deliveries, similar to, or better than, other published algorithms. For example, in MEPREP, investigators observed that 46% of deliveries had algorithm-derived gestational estimates that were within +/-7 days of gestational age estimates recorded on birth certificates [17]. In contrast, the VSD observed that 90% of assumed and medical-record derived gestational ages agreed within +/- 7 days [24]. The VSD derives pregnancy start from electronic medical records, which contain more precise information (e.g., LMP or expected date of delivery) than ICD-9-CM codes. Given the lack of specificity of some ICD-9-CM codes for gestational age, we anticipated significant challenges matching potential

controls to cases using only electronic algorithms. While we did lose a substantial proportion of controls due to the algorithm's assumptions about gestational age, we were able to match 76% of our eligible SAB cases to one or more controls by pregnancy start. In future surveillance efforts, requiring a tighter pregnancy start match between cases and controls in electronic data (e.g., +/-7 days) than the final desired match based on chart review data (e.g., +/-14 days) will greatly increase efficiency in study designs that require matching by pregnancy start. Additionally, in the future, ICD-10-CM codes may provide more accurate estimates of gestational age.

Our approach of conducting surveillance of SAB following vaccination during pregnancy has some limitations. First, the case-time control design required a two-phase approach for chart reviews, because gestational age estimates were not available in electronic data for pregnancies ending in SABs. Second, our analysis was underpowered due to the small number of cases, limited by the number of charts that we could review with available resources, particularly given that this was principally an infrastructure building activity with the primary aim to validate key algorithms needed for surveillance. In the future if conducting surveillance, we anticipate that the chart review burden would decrease based on the lessons learned from this activity, therefore increasing the number of cases retained for analyses. However, it may be necessary to begin with larger sample sizes before proceeding to chart review to maintain adequate power. Of note, the ICD-10-CM may make it possible to estimate gestational age in pregnancies ending in SABs, therefore making a two-stage chart review approach unnecessary.

A prior study in the Vaccine Safety Datalink reported that exposure to IIV during pregnancy in the 2010-11 and 2011-12 seasons was associated with an increased risk of SAB in the 1-28 days following vaccination (adjusted odds ratio 2.0, 95% CI 1.1-3.6)[20]. By contrast, consistent with systematic reviews (which did not include the VSD study just described), we found no evidence to suggest an association between inactivated influenza vaccine during pregnancy and SAB [25,26]. This surveillance activity is the first to examine the association using a case-time control design, whose major strength is inclusion of only vaccinated individuals, which reduces the likelihood of confounding due to differences between vaccinated and unvaccinated individuals. An additional strength of our approach is that we considered a wide range of risk intervals, defined by temporal proximity of vaccination to the event, and gestational age at vaccination independent of temporal proximity to event. Furthermore, the use of the two-dimensional temporal scan to explore whether SAB may be related to timing of vaccination and gestational age at vaccination, is novel.

In conclusion, surveillance of pregnancy outcomes following vaccination is feasible in Sentinel, which has the strength of an active surveillance in a large study population. The use of a retrospective healthcare utilization database to identify and evaluate potential adverse events following vaccinations during pregnancy requires rigorous validation of relevant electronic data elements. To further inform future surveillance of pregnancy outcomes of specific regulatory interest in Sentinel, validation of additional electronic data elements, including ICD-10-CM based algorithms and algorithms for other pregnancy outcomes, will be needed.

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VII. APPENDICES

A. APPENDIX 1: CODES TO IDENTIFY SAB CASES

Code	Type	Description
01965	CPT	ANESTHESIA INCOMPLETE/MISSED ABORTION
59812	CPT	TX INCOMPLETE ABORTION ANY TRIMESTER SURGICAL
59820	CPT	TX MISSED ABORTION FIRST TRIMESTER SURGICAL
59821	CPT	TX MISSED ABORTION SECOND TRIMESTER SURGICAL
632	ICD-9-CM	MISSED ABORTION
634	ICD-9-CM	SPONTANEOUS ABORTION
634.0	ICD-9-CM	SPONTANEOUS AB COMP GENITAL TRACT&PELVIC INF
634.00	ICD-9-CM	UNSPEC SPONT AB COMP GENITAL TRACT&PELV INF
634.01	ICD-9-CM	INCPL SPONTANEOUS AB COMP GENITAL TRACT&PELV INF
634.02	ICD-9-CM	COMPLETE SPONT AB COMP GENITAL TRACT&PELV INF
634.1	ICD-9-CM	SPONTANEOUS AB COMP DELAY/EXCESSIVE HEMORRHAGE
634.10	ICD-9-CM	UNSPEC SPONTANEOUS AB COMP DELAY/EXCESS HEMORR
634.11	ICD-9-CM	INCPL SPONTANEOUS AB COMP DELAY/EXCESS HEMORR
634.12	ICD-9-CM	COMPLETE SPONTANEOUS AB COMP DELAY/EXCESS HEMORR
634.2	ICD-9-CM	SPONTANEOUS AB COMP DAMAGE PELVIC ORGANS/TISSUES
634.20	ICD-9-CM	UNSPEC SPONT AB COMP DAMGE PELV ORGN/TISSUES
634.21	ICD-9-CM	INCPL SPONT AB COMP DAMGE PELV ORGN/TISSUES
634.22	ICD-9-CM	COMPLETE SPONT AB COMP DAMGE PELV ORGN/TISSUES
634.3	ICD-9-CM	SPONTANEOUS ABORTION COMPLICATED RENAL FAILURE
634.30	ICD-9-CM	UNSPEC SPONTANEOUS AB COMPLICATED RENAL FAILURE
634.31	ICD-9-CM	INCOMPLETE SPONTANEOUS AB COMP RENAL FAILURE
634.32	ICD-9-CM	COMPLETE SPONTANEOUS AB COMP RENAL FAILURE
634.4	ICD-9-CM	SPONTANEOUS AB COMPLICATED METABOLIC DISORDER
634.40	ICD-9-CM	UNSPEC SPONTANEOUS AB COMP METABOLIC DISORDER
634.41	ICD-9-CM	INCPL SPONTANEOUS AB COMP METABOLIC DISORDER
634.42	ICD-9-CM	COMPLETE SPONTANEOUS AB COMP METABOLIC DISORDER
634.5	ICD-9-CM	SPONTANEOUS ABORTION COMPLICATED BY SHOCK
634.50	ICD-9-CM	UNSPEC SPONTANEOUS ABORTION COMPLICATED SHOCK
634.51	ICD-9-CM	INCOMPLETE SPONTANEOUS AB COMPLICATED SHOCK
634.52	ICD-9-CM	COMPLETE SPONTANEOUS ABORTION COMPLICATED SHOCK
634.6	ICD-9-CM	SPONTANEOUS ABORTION COMPLICATED BY EMBOLISM
634.60	ICD-9-CM	UNSPEC SPONTANEOUS ABORTION COMPLICATED EMBOLISM
634.61	ICD-9-CM	INCOMPLETE SPONTANEOUS AB COMPLICATED EMBOLISM
634.62	ICD-9-CM	COMPLETE SPONTANEOUS AB COMPLICATED EMBOLISM
634.7	ICD-9-CM	SPONTANEOUS ABORTION W/OTHER SPEC COMPLICATIONS
634.70	ICD-9-CM	UNSPEC SPONTANEOUS AB W/OTH SPEC COMPLICATIONS
634.71	ICD-9-CM	INCOMPLETE SPONTANEOUS AB W/OTH SPEC COMPS
634.72	ICD-9-CM	COMPLETE SPONTANEOUS AB W/OTH SPEC COMPLICATIONS
634.8	ICD-9-CM	SPONTANEOUS ABORTION W/UNSPECIFIED COMPLICATION

Code	Type	Description
634.80	ICD-9-CM	UNSPEC SPONTANEOUS AB W/UNSPEC COMPLICATION
634.81	ICD-9-CM	INCOMPLETE SPONTANEOUS AB W/UNSPEC COMPLICATION
634.82	ICD-9-CM	COMPLETE SPONTANEOUS AB W/UNSPEC COMPLICATION
634.9	ICD-9-CM	SPONTANEOUS AB WITHOUT MENTION COMPLICATION
634.90	ICD-9-CM	UNSPEC SPONTANEOUS AB WITHOUT MENTION COMP
634.91	ICD-9-CM	INCOMPLETE SPONTANEOUS AB WITHOUT MENTION COMP
634.92	ICD-9-CM	COMPLETE SPONTANEOUS AB WITHOUT MENTION COMP

B. APPENDIX 2: CODES TO IDENTIFY LIVE DELIVERY CONTROLS

Code	Type	Description
01960	CPT	ANESTHESIA VAGINAL DELIVERY ONLY
01961	CPT	ANESTHESIA CESAREAN DELIVERY ONLY
01962	CPT	ANES URGENT HYSTERECTOMY FOLLOWING DELIVERY
01963	CPT	ANESTHESIA C HYST W/O ANY LABOR ANALG/ANES CARE
01967	CPT	NEURAXIAL LABOR ANALG/ANES PLND VAGINAL DELIVERY
01968	CPT	ANES CESARN DLVR FLWG NEURAXIAL LABOR ANALG/ANES
01969	CPT	ANES CESARN HYST FLWG NEURAXIAL LABOR ANALG/ANES
59400	CPT	OB CARE ANTEPARTUM VAG DLVR & POSTPARTUM
59409	CPT	VAGINAL DELIVERY ONLY
59410	CPT	VAGINAL DELIVERY ONLY W/POSTPARTUM CARE
59514	CPT	CESAREAN DELIVERY ONLY
59515	CPT	CESAREAN DELIVERY ONLY W/POSTPARTUM CARE
59610	CPT	ROUTINE OB CARE VAG DLVRY & POSTPARTUM CARE VB
59612	CPT	VAGINAL DELIVERY AFTER CESAREAN DELIVERY
59614	CPT	VAGINAL DELIVERY & POSTPARTUM CARE VBAC
59618	CPT	ROUTINE OBSTETRICAL CARE ATTEMPTED VBAC
59620	CPT	CESAREAN DELIVERY ATTEMPTED VBAC
59622	CPT	CESAREAN DLVRY & POSTPARTUM CARE ATTEMPTED VBA
641.01	ICD-9-CM	PLACENTA PREVIA WITHOUT HEMORRHAGE WITH DELIVERY
641.11	ICD-9-CM	HEMORRHAGE FROM PLACENTA PREVIA WITH DELIVERY
641.21	ICD-9-CM	PREMATURE SEPARATION OF PLACENTA WITH DELIVERY
641.31	ICD-9-CM	ANTPRTM HEMORR ASSOC W/COAGULAT DEFEC W/DELIV
641.81	ICD-9-CM	OTHER ANTEPARTUM HEMORRHAGE WITH DELIVERY
641.91	ICD-9-CM	UNSPECIFIED ANTEPARTUM HEMORRHAGE WITH DELIVERY
642.01	ICD-9-CM	BENIGN ESSENTIAL HYPERTENSION WITH DELIVERY
642.02	ICD-9-CM	BEN ESSENTIAL HYPERTENSION W/DELIV W/CURRENT PPC
642.11	ICD-9-CM	HYPERTENSION SEC TO RENAL DISEASE WITH DELIVERY
642.12	ICD-9-CM	HTN SEC RENAL DISEASE W/DELIV W/CURRENT PP COMPL
642.21	ICD-9-CM	OTHER PRE-EXISTING HYPERTENSION WITH DELIVERY
642.22	ICD-9-CM	OTH PRE-EXISTING HTN W/DELIV W/CURRENT PP COMPL
642.31	ICD-9-CM	TRANSIENT HYPERTENSION OF PREGNANCY W/DELIVERY

Code	Type	Description
642.32	ICD-9-CM	TRANSIENT HTN PG W/DELIV W/CURRENT PP COMPL
642.41	ICD-9-CM	MILD OR UNSPECIFIED PRE-ECLAMPSIA WITH DELIVERY
642.42	ICD-9-CM	MILD/UNSPEC PRE-ECLAMPSIA W/DELIV W/CURRENT PPC
642.51	ICD-9-CM	SEVERE PRE-ECLAMPSIA, WITH DELIVERY
642.52	ICD-9-CM	SEVERE PRE-ECLAMPSIA W/DELIVERY W/CURRENT PPC
642.61	ICD-9-CM	ECLAMPSIA, WITH DELIVERY
642.62	ICD-9-CM	ECLAMPSIA W/DELIVERY W/CURRENT PPC
642.71	ICD-9-CM	PRE-ECLAMP/ECLAMPSIA SUPERIMPS PRE-XST HTN DELIV
642.72	ICD-9-CM	PRE-ECLAMPSIA/ECLMPSIA W/PRE-EXIST HTN-DEL W/PPC
642.91	ICD-9-CM	UNSPECIFIED HYPERTENSION WITH DELIVERY
642.92	ICD-9-CM	UNSPEC HYPERTENSION W/DELIVERY W/CURRENT PPC
643.01	ICD-9-CM	MILD HYPEREMESIS GRAVIDARUM DELIVERED
643.11	ICD-9-CM	HYPEREMESIS GRAVIDA W/METAB DISTURBANCE DELIV
643.21	ICD-9-CM	LATE VOMITING OF PREGNANCY DELIVERED
643.81	ICD-9-CM	OTHER VOMITING COMPLICATING PREGNANCY DELIVERED
643.91	ICD-9-CM	UNSPECIFIED VOMITING OF PREGNANCY DELIVERED
644.21	ICD-9-CM	ERLY ONSET DELIV DELIV W/WO MENTION ANTPRTM COND
645.11	ICD-9-CM	POST TERM PG DELIV W/WO MENTION ANTPRTM COND
645.21	ICD-9-CM	PROLONGED PG DELIV W/WO MENTION ANTPRTM COND
646.01	ICD-9-CM	PAPYRACEOUS FETUS DELIV W/WO ANTPRTM COND
646.11	ICD-9-CM	EDEMA/XCESS WT GAIN PG DELIV W/WO ANTPRTM COMP
646.12	ICD-9-CM	EDEMA/EXCESS WEIGHT GAIN PG DELIV W/CURRENT PPC
646.21	ICD-9-CM	UNSPECIFIED RENAL DISEASE PREGNANCY W/DELIVERY
646.22	ICD-9-CM	UNSPEC RENAL DISEASE PG W/DELIV W/CURRENT PPC
646.31	ICD-9-CM	PREGNANCY COMP RECUR PREG LOSS W/WO ANTPRTM COND
646.41	ICD-9-CM	PERIPHERAL NEURITIS IN PREGNANCY WITH DELIVERY
646.42	ICD-9-CM	PERIPH NEURITIS PREGNANCY W/DELIV W/CURRENT PPC
646.51	ICD-9-CM	ASYMPTOMATIC BACTERIURIA IN PREGNANCY W/DELIVERY
646.52	ICD-9-CM	ASX BACTERIURIA PG W/DELIV W/CURRENT PPC
646.61	ICD-9-CM	INFECTIONS GENITOURINARY TRACT PREGNANCY W/DELIV
646.62	ICD-9-CM	INFS GU TRACT PREGNANCY W/DELIV W/CURRENT PPC
646.71	ICD-9-CM	LIVER BILIARY TRACT D/O PREG DEL W/WO ANTPRTM
646.81	ICD-9-CM	OTHER SPEC COMPLICATION PREGNANCY W/DELIVERY
646.82	ICD-9-CM	OTH SPEC COMPS PREGNANCY W/DELIV W/CURRENT PPC
646.91	ICD-9-CM	UNSPECIFIED COMPLICATION OF PREGNANCY W/DELIVERY
647.01	ICD-9-CM	MATERNAL SYPHILIS COMP PREGNANCY W/DELIVERY
647.02	ICD-9-CM	MTRN SYPHILIS COMP PG W/DELIV W/CURRENT PPC
647.11	ICD-9-CM	MATERNAL GONORRHEA WITH DELIVERY
647.12	ICD-9-CM	MATERNAL GONORRHEA W/DELIVERY W/CURRENT PPC
647.21	ICD-9-CM	OTHER MATERNAL VENEREAL DISEASES WITH DELIVERY
647.22	ICD-9-CM	OTH MATERNAL VENEREAL DZ W/DELIV W/CURRENT PPC

Code	Type	Description
647.31	ICD-9-CM	MATERNAL TUBERCULOSIS WITH DELIVERY
647.32	ICD-9-CM	MATERNAL TUBERCULOSIS W/DELIVERY W/CURRENT PPC
647.41	ICD-9-CM	MATERNAL MALARIA WITH DELIVERY
647.42	ICD-9-CM	MATERNAL MALARIA W/DELIVERY W/CURRENT PPC
647.51	ICD-9-CM	MATERNAL RUBELLA WITH DELIVERY
647.52	ICD-9-CM	MATERNAL RUBELLA W/DELIVERY W/CURRENT PPC
647.61	ICD-9-CM	OTHER MATERNAL VIRAL DISEASE WITH DELIVERY
647.62	ICD-9-CM	OTH MATERNAL VIRAL DISEASE W/DELIV W/CURRENT PPC
647.81	ICD-9-CM	OTH SPEC MATERNAL INF&PARASITIC DISEASE W/DELIV
647.82	ICD-9-CM	OTH SPEC MTRN INF&PARASITIC DZ DELIV W/CURR PPC
647.91	ICD-9-CM	UNSPEC MATERNAL INFECTION/INFESTATION W/DELIVERY
647.92	ICD-9-CM	UNSPEC MATERNAL INF/INFEST W/DELIV W/CURRENT PPC
648.01	ICD-9-CM	MATERNAL DIABETES MELLITUS WITH DELIVERY
648.02	ICD-9-CM	MATERNAL DM W/DELIVERY W/CURRENT PPC
648.11	ICD-9-CM	MTRN THYROID DYSF DELIV W/WO ANTPRTM COND
648.12	ICD-9-CM	MATERNAL THYROID DYSF W/DELIV W/CURRENT PPC
648.21	ICD-9-CM	MATERNAL ANEMIA, WITH DELIVERY
648.22	ICD-9-CM	MATERNAL ANEMIA W/DELIVERY W/CURRENT PPC
648.31	ICD-9-CM	MATERNAL DRUG DEPENDENCE WITH DELIVERY
648.32	ICD-9-CM	MATERNAL DRUG DEPENDENCE W/DELIV W/CURRENT PPC
648.41	ICD-9-CM	MATERNAL MENTAL DISORDERS WITH DELIVERY
648.42	ICD-9-CM	MATERNAL MENTAL DISORDERS W/DELIV W/CURRENT PPC
648.51	ICD-9-CM	MATERNAL CONGENITAL CV DISORDERS W/DELIVERY
648.52	ICD-9-CM	MATERNAL CONGEN CV D/O W/DELIV W/CURRENT PPC
648.61	ICD-9-CM	OTH MATERNAL CARDIOVASCULAR DISEASES W/DELIVERY
648.62	ICD-9-CM	OTH MATERNAL CV DISEASES W/DELIV W/CURRENT PPC
648.71	ICD-9-CM	BN&JNT D/O MAT BACK PELVIS&LW LMB W/DEL
648.72	ICD-9-CM	BN&JNT D/O MAT BACK PELV&LW LMB W/DEL W/PP COMPL
648.81	ICD-9-CM	ABNORMAL MATERNAL GLUCOSE TOLERANCE W/DELIVERY
648.82	ICD-9-CM	ABNORMAL MTRN GLU TOLERNC W/DELIV W/CURRENT PPC
648.91	ICD-9-CM	OTH CURRENT MATERNAL CCE W/DELIVERY
648.92	ICD-9-CM	OTH CURRENT MATERNAL CCE W/DEL W/CURRNT PP COMPL
649.01	ICD-9-CM	TOBACCO USE D/O COMP PG CHILDBIRTH/PP DELIVERED
649.02	ICD-9-CM	TOB USE D/O COMP PG BIRTH/PP DEL W/MEN PP COMP
649.11	ICD-9-CM	OBESITY COMP PG CHILDBIRTH/THE PP DELIVERED
649.12	ICD-9-CM	OBESITY COMP PG CHILDBIRTH/THE PP DEL W/PP COMP
649.21	ICD-9-CM	BARIATRIC SURG STS COMP PG BIRTH/PP DELIVERED
649.22	ICD-9-CM	BARIATRC SURG STS COMP PG BIRTH/PP DEL W/PP COMP
649.31	ICD-9-CM	COAGULATION DEFECTS COMP PG BIRTH/THE PP DEL
649.32	ICD-9-CM	COAGULATION DEFEC COMP PG BIRTH/PP DEL W/PP COMP
649.41	ICD-9-CM	EPILEPSY COMP PG CHILDBIRTH/THE PP DELIVERED

Code	Type	Description
649.42	ICD-9-CM	EPILEPSY COMP PG CHILDBIRTH/THE PP DEL W/PP COMP
649.51	ICD-9-CM	SPOTTING COMPLICATING PREGNANCY DELIVERED
649.61	ICD-9-CM	UTERINE SIZE DATE DISCREPANCY DELIVERED
649.62	ICD-9-CM	UTERINE SZ DATE DISCREPANCY DEL W/MEN PP COMPL
649.71	ICD-9-CM	CERVICAL SHORTENING DELIVERED W/WO ANTPRTM COND
649.81	ICD-9-CM	ONSET LABR AFTR 37 BEFOR 39 CMPL WK GEST C/S DEL
649.82	ICD-9-CM	ONSET LABR AFTR 37 BFOR 39 WK GEST C/S DEL W/PPC
650	ICD-9-CM	NORMAL DELIVERY
651.01	ICD-9-CM	TWIN PREGNANCY, DELIVERED
651.11	ICD-9-CM	TRIPLET PREGNANCY, DELIVERED
651.21	ICD-9-CM	QUADRUPLET PREGNANCY, DELIVERED
651.31	ICD-9-CM	TWIN PG W/FETAL LOSS&RETENTION 1 FETUS DELIV
651.41	ICD-9-CM	TRIPLET PG W/FETAL LOSS&RETENTION 1/MORE DELIV
651.51	ICD-9-CM	QUADRUPLET PG W/FETAL LOSS&RETN 1/MORE DELIV
651.61	ICD-9-CM	OTH MX PG W/FETAL LOSS&RETN 1/MORE FETUS DELIV
651.71	ICD-9-CM	MX GEST FLW ELCTV FETAL RDUC DEL W/WO AP COND
651.81	ICD-9-CM	OTHER SPECIFIED MULTIPLE GESTATION DELIVERED
651.91	ICD-9-CM	UNSPECIFIED MULTIPLE GESTATION DELIVERED
652.01	ICD-9-CM	UNSTABLE LIE OF FETUS, DELIVERED
652.11	ICD-9-CM	BREECH/ MALPRSATION CONVRT CEPHALIC PRSATION DEL
652.21	ICD-9-CM	BREECH PRESENTATION W/O MENTION VERSION DELIV
652.31	ICD-9-CM	TRANSVERSE/OBLIQUE FETAL PRESENTATION DELIVERED
652.41	ICD-9-CM	FETAL FACE OR BROW PRESENTATION DELIVERED
652.51	ICD-9-CM	HIGH FETAL HEAD AT TERM, DELIVERED
652.61	ICD-9-CM	MX GEST W/MALPRESENTATION 1 FETUS/MORE DELIV
652.71	ICD-9-CM	PROLAPSED ARM OF FETUS, DELIVERED
652.81	ICD-9-CM	OTH SPEC MALPOSITION/MALPRESENTATION FETUS DELIV
652.91	ICD-9-CM	UNSPEC MALPOSITION/MALPRESENTATION FETUS DELIV
653.01	ICD-9-CM	MAJOR ABNORM BONY PELVIS NOT FURTHER SPEC DELIV
653.11	ICD-9-CM	GENERALLY CONTRACTED PELVIS PREGNANCY DELIVERED
653.21	ICD-9-CM	INLET CONTRACTION OF PELVIS PREGNANCY DELIVERED
653.31	ICD-9-CM	OUTLET CONTRACTION OF PELVIS PREGNANCY DELIVERED
653.41	ICD-9-CM	FETOPELVIC DISPROPORTION, DELIVERED
653.51	ICD-9-CM	UNUSUALLY LARGE FETUS CAUS DISPROPRTN DELIVERED
653.61	ICD-9-CM	HYDROCEPHALIC FETUS CAUSING DISPROPRTN DELIVERED
653.71	ICD-9-CM	OTH FETAL ABNORM CAUSING DISPROPRTN DELIVERED
653.81	ICD-9-CM	FETAL DISPROPORTION OF OTHER ORIGIN DELIVERED
653.91	ICD-9-CM	UNSPECIFIED FETAL DISPROPORTION DELIVERED
654.01	ICD-9-CM	CONGENITAL ABNORM PREGNANT UTERUS DELIVERED
654.02	ICD-9-CM	CONGEN ABNORM PG UTERUS DELIV W/MENTION PPC
654.11	ICD-9-CM	TUMORS OF BODY OF UTERUS, DELIVERED

Code	Type	Description
654.12	ICD-9-CM	TUMORS BODY UTERUS DELIVERED W/MENTION PPC
654.21	ICD-9-CM	PREV C/S DELIV DELIV W/WO MENTION ANTPRTM COND
654.31	ICD-9-CM	RETROVERTED&INCARCERATED GRAVID UTERUS DELIVERED
654.32	ICD-9-CM	RETROVRT&INCARCERAT GRAVD UTRUS DELIV W/ PPC
654.41	ICD-9-CM	OTH ABN SHAPE/PSTN GRAVD UTRUS&NGHBR STRCT DELIV
654.42	ICD-9-CM	OTH ABN SHAPE/POS GRAVID UTERUS DEL W/PP COMPL
654.51	ICD-9-CM	CERVICAL INCOMPETENCE, DELIVERED
654.52	ICD-9-CM	CERVICAL INCOMPETENCE DELIVERED W/MENTION PPC
654.61	ICD-9-CM	OTH CONGENITAL/ACQUIRED ABNORM CERVIX W/DELIVERY
654.62	ICD-9-CM	OTH CONGEN/ACQ ABNORM CERV DELIV W/MENTION PPC
654.71	ICD-9-CM	CONGENITAL/ACQUIRED ABNORM VAGINA W/DELIVERY
654.72	ICD-9-CM	CONGEN/ACQ ABNORM VAGINA DELIVERED W/MENTION PPC
654.81	ICD-9-CM	CONGENITAL/ACQUIRED ABNORMALITY VULVA W/DELIVERY
654.82	ICD-9-CM	CONGEN/ACQ ABNORM VULVA DELIVERED W/MENTION PPC
654.91	ICD-9-CM	OTH&UNSPEC ABNORM ORGN&SOFT TISSUES PELV W/DELIV
654.92	ICD-9-CM	OTH&UNS ABN ORGN&SOFT TISS PELVIS DEL W/PP COMPL
655.01	ICD-9-CM	CNTRL NERV SYS MALFORMATION IN FETUS W/DELIVERY
655.11	ICD-9-CM	CHROMOSM ABNORM FETUS AFFECT MGMT MOTH W/DELIV
655.21	ICD-9-CM	HEREDITARY DZ POSS AFFECT FETUS MGMT MOM W/DEL
655.31	ICD-9-CM	SPCT DAMGE FETUS VIRL DZ MOM AFFCT MGMT MOM DEL
655.41	ICD-9-CM	SPCT DAMGE FETUS OTH DZ MOM AFFCT MGMT MOM DEL
655.51	ICD-9-CM	SPCT DAMGE FETUS FROM RX AFFECT MGMT MOTH DELIV
655.61	ICD-9-CM	SPCT DAMGE FETUS FROM RAD AFFECT MGMT MOTH DELIV
655.71	ICD-9-CM	DECR FETAL MOVEMENTS AFFECT MGMT MOTH DELIV
655.81	ICD-9-CM	OTH KNOWN/SPCT FETAL ABNORM NEC MGMT MOTH DELIV
655.91	ICD-9-CM	UNSPEC FETAL ABNORM AFFECT MANAGEMENT MOTH DELIV
656.01	ICD-9-CM	FETAL-MATERNAL HEMORRHAGE WITH DELIVERY
656.11	ICD-9-CM	RHESUS ISOIMMUNIZATION AFFECT MGMT MOTH DELIV
656.21	ICD-9-CM	ISOIMMU OTH&UNS BLD-GRP INCOMPAT MGMT MOTH DELIV
656.31	ICD-9-CM	FETAL DISTRESS AFFECT MANAGEMENT MOTH DELIVERED
656.41	ICD-9-CM	INTRAUTERINE DEATH AFFECT MANAGEMENT MOTH DELIV
656.51	ICD-9-CM	POOR FETAL GROWTH AFFECT MANAGEMENT MOTH DELIV
656.61	ICD-9-CM	EXCESS FETAL GROWTH AFFECT MANAGEMENT MOTH DELIV
656.71	ICD-9-CM	OTH PLACENTAL CONDS AFFECT MANAGEMENT MOTH DELIV
656.81	ICD-9-CM	OTH SPEC FETAL&PLACNTL PROBS MGMT MOTH DELIV
656.91	ICD-9-CM	UNSPEC FETAL&PLACNTL PROB AFFECT MGMT MOTH DELIV
657.01	ICD-9-CM	POLYHYDRAMNIOS, WITH DELIVERY
658.01	ICD-9-CM	OLIGOHYDRAMNIOS, DELIVERED
658.11	ICD-9-CM	PREMATURE RUPTURE MEMBRANES PREGNANCY DELIVERED
658.21	ICD-9-CM	DELAY DELIV AFTER SPONT/UNSPEC RUP MEMB DELIV
658.31	ICD-9-CM	DELAY DELIV AFTER ARTFICL RUPTURE MEMB DELIV

Code	Type	Description
658.41	ICD-9-CM	INFECTION OF AMNIOTIC CAVITY DELIVERED
658.81	ICD-9-CM	OTH PROBLEM ASSOC W/AMNIOTIC CAVITY&MEMB DELIV
658.91	ICD-9-CM	UNSPEC PROB ASSOC W/AMNIOTIC CAVITY&MEMB DELIV
659.01	ICD-9-CM	FAILED MECHANICAL INDUCTION OF LABOR DELIVERED
659.11	ICD-9-CM	FAILED MEDICAL/UNSPEC INDUCTION LABOR DELIVERED
659.21	ICD-9-CM	UNSPEC MATERNAL PYREXIA DURING LABOR DELIVERED
659.31	ICD-9-CM	GENERALIZED INFECTION DURING LABOR DELIVERED
659.41	ICD-9-CM	GRAND MULTIPARITY DELIV W/WO ANTPRTM COND
659.51	ICD-9-CM	ELDERLY PRIMIGRAVIDA, DELIVERED
659.61	ICD-9-CM	ELDER MULTIGRAVIDA DELIV W/MENTION ANTPRTM COND
659.71	ICD-9-CM	ABN FETL HRT RATE/RHYTHM DELIV W/WO ANTPRTM COND
659.81	ICD-9-CM	OTH SPEC INDICAT CARE/INTERVEN RELATED L&D DELIV
659.91	ICD-9-CM	UNSPEC INDICAT CARE/INTERVEN RELATED L&D DELIV
660.01	ICD-9-CM	OBST CAUS MALPOSITION FETUS@ONSET LABR DELIV
660.11	ICD-9-CM	OBSTRUCTION BY BONY PELVIS DURING L&D DELIVERED
660.21	ICD-9-CM	OBST ABN PELV SFT TISS DUR LABRAND DELIV DELIV
660.31	ICD-9-CM	DEEP TRNSVRSE ARREST-OCCIPITOPOSTER-DEL-UNS APC
660.41	ICD-9-CM	SHOULDER DYSTOCIA DURING LABOR&DELIVER DELIVERED
660.51	ICD-9-CM	LOCKED TWINS, DELIVERED
660.61	ICD-9-CM	UNSPECIFIED FAILED TRIAL OF LABOR DELIVERED
660.71	ICD-9-CM	UNSPEC FAILED FORCEPS/VACUUM EXTRACTOR DELIVERED
660.81	ICD-9-CM	OTHER CAUSES OF OBSTRUCTED LABOR DELIVERED
660.91	ICD-9-CM	UNSPECIFIED OBSTRUCTED LABOR WITH DELIVERY
661.01	ICD-9-CM	PRIMARY UTERINE INERTIA WITH DELIVERY
661.11	ICD-9-CM	SECONDARY UTERINE INERTIA WITH DELIVERY
661.21	ICD-9-CM	OTHER AND UNSPECIFIED UTERINE INERTIA W/DELIVERY
661.31	ICD-9-CM	PRECIPITATE LABOR, WITH DELIVERY
661.41	ICD-9-CM	HYPERTON INCOORD/PROLONG UTERINE CONTRACS DELIV
661.91	ICD-9-CM	UNSPECIFIED ABNORMALITY OF LABOR WITH DELIVERY
662.01	ICD-9-CM	PROLONGED FIRST STAGE OF LABOR DELIVERED
662.11	ICD-9-CM	UNSPECIFIED PROLONGED LABOR DELIVERED
662.21	ICD-9-CM	PROLONGED SECOND STAGE OF LABOR DELIVERED
662.31	ICD-9-CM	DELAYED DELIVERY 2 TWIN TRIPLET ETC DELIVERED
663.01	ICD-9-CM	PROLAPSE OF CORD COMPLICATING L&D DELIVERED
663.11	ICD-9-CM	CORD AROUND NECK W/COMPRS COMP L&D DELIVERED
663.21	ICD-9-CM	OTH&UNSPEC CORD ENTANGL W/COMPRS COMP L&D DELIV
663.31	ICD-9-CM	OTH&UNS CRD ENTANGL W/O COMPRS COMP L&D DELIV
663.41	ICD-9-CM	SHORT CORD COMPLICATING L&D DELIVERED
663.51	ICD-9-CM	VASA PREVIA COMPLICATING L&D DELIVERED
663.61	ICD-9-CM	VASCULAR LESIONS CORD COMPLICATING L&D DELIVERED
663.81	ICD-9-CM	OTH UMBILICAL CORD COMPS DURING L&D DELIVERED

Code	Type	Description
663.91	ICD-9-CM	UNSPEC UMBILICAL CORD COMP DURING L&D DELIVERED
664.01	ICD-9-CM	FIRST-DEGREE PERINEAL LACERATION WITH DELIVERY
664.11	ICD-9-CM	SECOND-DEGREE PERINEAL LACERATION WITH DELIVERY
664.21	ICD-9-CM	THIRD-DEGREE PERINEAL LACERATION WITH DELIVERY
664.31	ICD-9-CM	FOURTH-DEGREE PERINEAL LACERATION WITH DELIVERY
664.41	ICD-9-CM	UNSPECIFIED PERINEAL LACERATION WITH DELIVERY
664.51	ICD-9-CM	VULVAR AND PERINEAL HEMATOMA WITH DELIVERY
664.61	ICD-9-CM	ANAL SPHINCT TEAR COMP DELIVERY W OR W/O AP COND
664.81	ICD-9-CM	OTHER SPECIFIED TRAUMA PERINEUM&VULVA W/DELIVERY
664.91	ICD-9-CM	UNSPECIFIED TRAUMA TO PERINEUM&VULVA W/DELIVERY
665.01	ICD-9-CM	RUPTURE UTERUS BEFORE ONSET LABOR W/DELIVERY
665.11	ICD-9-CM	RUPTURE OF UTERUS DURING LABOR WITH DELIVERY
665.22	ICD-9-CM	INVERSION UTERUS DELIVERED W/PPC
665.31	ICD-9-CM	LACERATION OF CERVIX, WITH DELIVERY
665.41	ICD-9-CM	HIGH VAGINAL LACERATION WITH DELIVERY
665.51	ICD-9-CM	OTHER INJURY TO PELVIC ORGANS WITH DELIVERY
665.61	ICD-9-CM	DAMAGE TO PELVIC JOINTS AND LIGAMENTS W/DELIVERY
665.71	ICD-9-CM	PELVIC HEMATOMA, WITH DELIVERY
665.72	ICD-9-CM	PELVIC HEMATOMA DELIVERED W/PPC
665.81	ICD-9-CM	OTHER SPECIFIED OBSTETRICAL TRAUMA WITH DELIVERY
665.82	ICD-9-CM	OTH SPEC OBSTETRICAL TRAUMA DELIV W/POSTPARTUM
665.91	ICD-9-CM	UNSPECIFIED OBSTETRICAL TRAUMA WITH DELIVERY
665.92	ICD-9-CM	UNSPECIFIED OBSTETRICAL TRAUMA DELIVERED W/PPC
666.02	ICD-9-CM	THIRD-STAGE POSTPARTUM HEMORRHAGE WITH DELIVERY
666.12	ICD-9-CM	OTHER IMMEDIATE POSTPARTUM HEMORRHAGE W/DELIVERY
666.22	ICD-9-CM	DELAYED AND SEC POSTPARTUM HEMORRHAGE W/DELIVERY
666.32	ICD-9-CM	POSTPARTUM COAGULATION DEFECTS WITH DELIVERY
667.02	ICD-9-CM	RETN PLACNTA W/O HEMORR DEL W/MENTION PP COMPL
667.12	ICD-9-CM	RETN PORTIONS PLCNTA/MEMB W/O HEMORR DEL W/COMPL
668.01	ICD-9-CM	PULM COMPL ADMIN ANES/OTH SEDATION L&D DEL
668.02	ICD-9-CM	PULM COMPL ADMIN ANES/OTH SEDAT DEL W/PP COMPL
668.11	ICD-9-CM	CARD COMPL ADMIN ANES/OTH SEDATION L&D DEL
668.12	ICD-9-CM	CARD COMPL ADMIN ANES/SEDAT L&D-DEL W/PP COMPL
668.21	ICD-9-CM	CNA COMPL ADMIN ANES/OTH SEDATION L&D DEL
668.22	ICD-9-CM	CNA COMPL ADMIN ANES/SEDAT L&D DEL W/PP COMPL
668.81	ICD-9-CM	OTH COMPL ADMIN ANES/OTH SEDATION L&D DEL
668.82	ICD-9-CM	OTH COMPL ADMN ANES/OTH SEDAT DEL W/PP COMPL
668.91	ICD-9-CM	UNS COMPL ADMIN ANES/OTH SEDATION L&D DEL
668.92	ICD-9-CM	UNS COMP ADMN ANESTHESIA/OTH SEDAT L&D DEL W/PPC
669.01	ICD-9-CM	MTRN DISTRESS W/DELIV W/WO MENTION ANTPRTM COND
669.02	ICD-9-CM	MATERNAL DISTRESS W/DELIVERY W/MENTION PPC

Code	Type	Description
669.11	ICD-9-CM	SHOCK DURING/FOLLOW L&D W/DEL W/W/O ANTPRTM COND
669.12	ICD-9-CM	SHOCK DURING/FOLLOWING L&D W/DELIV W/MENTION PPC
669.21	ICD-9-CM	MAT HYPOTENSION SYND W/DEL W/W/O ANTPRTM COND
669.22	ICD-9-CM	MATERNAL HYPOTENS SYNDROME W/DELIV W/MENTION PPC
669.32	ICD-9-CM	ACUTE KIDNEY FAILURE FOLLOW L&D DELIV W/MEN PPC
669.41	ICD-9-CM	OTH COMPL OB SURG&PROC DELIV W/WO ANTPRTM COND
669.42	ICD-9-CM	OTH COMPL OB SURG&PROC W/DEL W/MENTION PP COMPL
669.51	ICD-9-CM	FORCEPS/EXTRACTOR DEL W/O INDICATION-DELIVERED
669.61	ICD-9-CM	BREECH XTRAC W/O INDICAT DELIV W/WO ANTPRTM COND
669.71	ICD-9-CM	C/S DELIV W/O INDICAT DELIV W/WO ANTPRTM COND
669.81	ICD-9-CM	OTH COMP L&D DELIVERED W/WO MENTION ANTPRTM COND
669.82	ICD-9-CM	OTHER COMPLICATION L&D DELIVERED W/MENTION PPC
669.91	ICD-9-CM	UNSPEC COMP L&D DELIV W/WO MENTION ANTPRTM COND
669.92	ICD-9-CM	UNSPEC COMPLICATION L&D W/DELIVERY W/MENTION PPC
670.02	ICD-9-CM	MAJOR PUERPERAL INFECTION, UNSPECIFIED, DELIVERE
670.12	ICD-9-CM	PUERPERAL ENDOMETRITIS DELIVERED W/MEN PP COMP
670.22	ICD-9-CM	PUERPERAL SEPSIS DELIVERED W/MENTION OF PP COMP
670.32	ICD-9-CM	PUERPERAL SEPTIC THROMBOPHLEBITS DEL MEN PP COMP
670.82	ICD-9-CM	OTHER MAJOR PUERPERAL INFECTION DEL MEN PP COMP
671.01	ICD-9-CM	VARICOSE VNS LEGS DELIV W/WO ANTPRTM COND
671.02	ICD-9-CM	VARICOSE VEINS LEGS W/DELIVERY W/MENTION PPC
671.11	ICD-9-CM	VARICOSE VNS VULVA&PERIN DELIV W/WO ANTPRTM COND
671.12	ICD-9-CM	VARICOSE VEINS VULVA&PERIN W/DELIV W/MENTION PPC
671.21	ICD-9-CM	SUP THROMBOPHLEB DELIV W/WO MENTION ANTPRTM COND
671.22	ICD-9-CM	SUP THROMBOPHLEBITIS W/DELIV W/MENTION PPC
671.31	ICD-9-CM	DEEP PHLEBOTHROMBOSIS ANTEPARTUM WITH DELIVERY
671.42	ICD-9-CM	DEEP PHLEBOTHROMBOSIS POSTPARTUM WITH DELIVERY
671.51	ICD-9-CM	OTH PHLEBITIS&THROMB DELIV W/WO ANTPRTM COND
671.52	ICD-9-CM	OTH PHLEBITIS&THROMBOSIS W/DELIV W/MENTION PPC
671.81	ICD-9-CM	OTH VENOUS COMP DELIV W/WO MENTION ANTPRTM COND
671.82	ICD-9-CM	OTH VENOUS COMPLICATION W/DELIVERY W/MENTION PPC
671.91	ICD-9-CM	UNS VENOUS COMP DELIV W/WO MENTION ANTPRTM COND
671.92	ICD-9-CM	UNSPEC VENOUS COMP W/DELIVERY W/MENTION PPC
672.02	ICD-9-CM	PUERPERAL PYREXIA UNKN ORIGIN DELIV W/ PPC
673.01	ICD-9-CM	OB AIR EMBO W/DELIV W/WO MENTION ANTPRTM COND
673.02	ICD-9-CM	OBSTETRICAL AIR EMBOLISM W/DELIV W/MENTION PPC
673.11	ICD-9-CM	AMNIOTIC FLUID EMBOLISM DEL W/WO ANTEPARTUM COND
673.12	ICD-9-CM	AMNIOTIC FLUID EMBOLISM W/DELIVERY W/MENTION PPC
673.21	ICD-9-CM	OB BLD-CLOT EMBOLISM DEL W/WO ANTEPARTUM COND
673.22	ICD-9-CM	OBSTETRICAL BLOOD-CLOT EMBOLISM W/MENTION PPC
673.31	ICD-9-CM	OB PYEMIC&SEPTIC EMBOLISM DEL W/WO ANTPRTM COND

Code	Type	Description
673.32	ICD-9-CM	OB PYEMIC&SEPTIC EMBOLISM DELIVERY W/PP COMPL
673.81	ICD-9-CM	OTH OB PULMARY EMBOLSIM DEL W/WO ANTEPARTUM COND
673.82	ICD-9-CM	OTH OB PULMONARY EMBO W/DELIV W/MENTION PPC
674.01	ICD-9-CM	CERBROVASC D/O DELIV W/WO MENTION ANTPRTM COND
674.02	ICD-9-CM	CEREBRVASC DISORDER W/DELIVERY W/MENTION PPC
674.12	ICD-9-CM	DISRUPTION C-SECT WOUND W/DELIVERY W/MENTION PPC
674.22	ICD-9-CM	DISRUPTRUPT PERINL WOUND W/DEL W/PP COMPLICATON
674.32	ICD-9-CM	OTH COMP OB SURG WOUNDS W/DELIV W/MENTION PPC
674.42	ICD-9-CM	PLACENTAL POLYP W/DELIVERY W/MENTION PPC
674.51	ICD-9-CM	PERIPARTUM CARDIOMYPATH DELIV W/WO ANTPRTM COND
674.52	ICD-9-CM	PERIPARTUM CARDIOMYPATH DELIV W/MENTION PP COND
674.82	ICD-9-CM	OTH COMP PUERPERIUM W/DELIVERY W/MENTION PPC
674.92	ICD-9-CM	UNSPEC COMPS PUERPERIUM W/DELIVERY W/MENTION PPC
675.01	ICD-9-CM	INF NIPPLE W/CHLDBRTH DEL W/WO ANTEPARTUM COND
675.02	ICD-9-CM	INF NIPPLE ASSOC W/CHILDBRTH DELIV W/MENTION PPC
675.11	ICD-9-CM	ABSCESS BREAST W/CHLDBRTH DEL W/WO ANTPRTM COND
675.12	ICD-9-CM	ABSC BRST ASSOC W/CHILDBIRTH DELIV W/MENTION PPC
675.21	ICD-9-CM	NONPURULENT MASTITIS DELIV W/WO ANTPRTM COND
675.22	ICD-9-CM	NONPURULENT MASTITIS DELIVERED W/MENTION PPC
675.81	ICD-9-CM	OTH SPEC BREAST-NIPPLE INFECT ASSOC W/CB DELIVER
675.82	ICD-9-CM	OTH INF BRST&NIPPLE W/CHLDBRTH DEL W/PP COMPL
675.91	ICD-9-CM	UNS INF BRST&NIPPLE DELIV W/WO ANTPRTM COND
675.92	ICD-9-CM	UNSPEC INF BREAST&NIPPLE DELIV W/MENTION PPC
676.01	ICD-9-CM	RETRACTED NIPPLE DELIV W/WO MENTION ANTPRTM COND
676.02	ICD-9-CM	RETRACTED NIPPLE DELIVERED W/MENTION PPC
676.11	ICD-9-CM	CRACKED NIPPLE DELIV W/WO MENTION ANTPRTM COND
676.12	ICD-9-CM	CRACKED NIPPLE DELIVERED W/MENTION PPC
676.21	ICD-9-CM	ENGORGEMENT BREASTS DEL W/WO ANTEPARTUM COND
676.22	ICD-9-CM	ENGORGEMENT BREASTS DELIVERED W/MENTION PPC
676.31	ICD-9-CM	UNS D/O BREAST W/CHLDBRTH DEL W/WO ANTPRTM COND
676.32	ICD-9-CM	OTH&UNS D/O BREAST W/CHILDBIRTH DEL W/PP COMPL
676.41	ICD-9-CM	FAILED LACTATION W/DEL W/WO MENTION ANTPRTM COND
676.42	ICD-9-CM	FAILURE LACTATION W/DELIVERY W/MENTION PPC
676.51	ICD-9-CM	SUPPRESSED LACTATION DELIV W/WO ANTPRTM COND
676.52	ICD-9-CM	SUPPRESSED LACTATION W/DELIVERY W/MENTION PPC
676.61	ICD-9-CM	GALACTORRHEA W/DELIV W/WO MENTION ANTPRTM COND
676.62	ICD-9-CM	GALACTORRHEA W/DELIVERY W/MENTION PPC
676.81	ICD-9-CM	OTH D/O LACTATION DELIV W/WO ANTPRTM COND
676.82	ICD-9-CM	OTH DISORDER LACTATION W/DELIVERY W/MENTION PPC
676.91	ICD-9-CM	UNS D/O LACTATION DELIV W/WO ANTPRTM COND
676.92	ICD-9-CM	UNSPEC DISORDER LACTATION W/DELIV W/MENTION PPC

Code	Type	Description
678.01	ICD-9-CM	FETAL HEMATOLOGIC COND DELIV W/WO ANTPRTM COND
678.11	ICD-9-CM	FETAL CONJOINED TWINS DELIV W/WO ANTPRTM COND
679.01	ICD-9-CM	MATERNAL COMP FROM IU PROC DEL W/WO ANTPRTM COND
679.02	ICD-9-CM	MATERNAL COMP FROM IN UTERO PROC DEL W/PP COMP
679.11	ICD-9-CM	FETAL COMP FROM IN UTERO PROCEDURE DELIVERED
679.12	ICD-9-CM	FETAL COMP FROM IN UTERO PROC DELIVERY W/PP COMP
72	ICD-9-CM	FORCEPS VACUUM AND BREECH DELIVERY
72.0	ICD-9-CM	LOW FORCEPS OPERATION
72.1	ICD-9-CM	LOW FORCEPS OPERATION WITH EPISIOTOMY
72.2	ICD-9-CM	MID FORCEPS OPERATION
72.21	ICD-9-CM	MID FORCEPS OPERATION WITH EPISIOTOMY
72.29	ICD-9-CM	OTHER MID FORCEPS OPERATION
72.3	ICD-9-CM	HIGH FORCEPS OPERATION
72.31	ICD-9-CM	HIGH FORCEPS OPERATION WITH EPISIOTOMY
72.39	ICD-9-CM	OTHER HIGH FORCEPS OPERATION
72.4	ICD-9-CM	FORCEPS ROTATION OF FETAL HEAD
72.5	ICD-9-CM	BREECH EXTRACTION
72.51	ICD-9-CM	PART BREECH EXTRAC W/FORCEPS AFTERCOMING HEAD
72.52	ICD-9-CM	OTHER PARTIAL BREECH EXTRACTION
72.53	ICD-9-CM	TOTAL BREECH EXTRAC W/FORCEPS AFTERCOMING HEAD
72.54	ICD-9-CM	OTHER TOTAL BREECH EXTRACTION
72.6	ICD-9-CM	FORCEPS APPLICATION TO AFTERCOMING HEAD
72.7	ICD-9-CM	VACUUM EXTRACTION
72.71	ICD-9-CM	VACUUM EXTRACTION WITH EPISIOTOMY
72.79	ICD-9-CM	OTHER VACUUM EXTRACTION
72.8	ICD-9-CM	OTHER SPECIFIED INSTRUMENTAL DELIVERY
72.9	ICD-9-CM	UNSPECIFIED INSTRUMENTAL DELIVERY
73	ICD-9-CM	OTHER PROCEDURES INDUCING OR ASSISTING DELIVERY
73.0	ICD-9-CM	ARTIFICIAL RUPTURE OF MEMBRANES
73.01	ICD-9-CM	INDUCTION LABOR ARTIFICIAL RUPTURE MEMBRANES
73.09	ICD-9-CM	OTHER ARTIFICIAL RUPTURE OF MEMBRANES
73.1	ICD-9-CM	OTHER SURGICAL INDUCTION OF LABOR
73.2	ICD-9-CM	INTERNAL AND COMBINED VERSION AND EXTRACTION
73.21	ICD-9-CM	INTERNAL AND COMBINED VERSION WITHOUT EXTRACTION
73.22	ICD-9-CM	INTERNAL AND COMBINED VERSION WITH EXTRACTION
73.3	ICD-9-CM	FAILED FORCEPS
73.4	ICD-9-CM	MEDICAL INDUCTION OF LABOR
73.5	ICD-9-CM	MANUALLY ASSISTED DELIVERY
73.51	ICD-9-CM	MANUAL ROTATION OF FETAL HEAD
73.59	ICD-9-CM	OTHER MANUALLY ASSISTED DELIVERY
73.6	ICD-9-CM	EPISIOTOMY

Code	Type	Description
73.8	ICD-9-CM	OPERATIONS ON FETUS TO FACILITATE DELIVERY
73.9	ICD-9-CM	OTHER OPERATIONS ASSISTING DELIVERY
73.91	ICD-9-CM	EXTERNAL VERSION TO ASSIST DELIVERY
73.92	ICD-9-CM	REPLACEMENT OF PROLAPSED UMBILICAL CORD
73.93	ICD-9-CM	INCISION OF CERVIX TO ASSIST DELIVERY
73.94	ICD-9-CM	PUBIOTOMY TO ASSIST DELIVERY
73.99	ICD-9-CM	OTHER OPERATIONS TO ASSIST DELIVERY
74.0	ICD-9-CM	CLASSICAL CESAREAN SECTION
74.1	ICD-9-CM	LOW CERVICAL CESAREAN SECTION
74.2	ICD-9-CM	EXTRAPERITONEAL CESAREAN SECTION
74.4	ICD-9-CM	CESAREAN SECTION OF OTHER SPECIFIED TYPE
74.9	ICD-9-CM	CESAREAN SECTION OF UNSPECIFIED TYPE
74.99	ICD-9-CM	OTHER CESAREAN SECTION OF UNSPECIFIED TYPE
763.0	ICD-9-CM	FETUS/NEWBORN AFFECTED BREECH DELIV&EXTRACTION
763.2	ICD-9-CM	FETUS OR NEWBORN AFFECTED BY FORCEPS DELIVERY
763.3	ICD-9-CM	FETUS/NEWBORN AFFECTED DELIVERY VACUUM EXTRACTOR
763.4	ICD-9-CM	FETUS OR NEWBORN AFFECTED BY CESAREAN DELIVERY
763.6	ICD-9-CM	FETUS OR NEWBORN AFFECTED PRECIPITATE DELIVERY
768.0	ICD-9-CM	FETAL DEATH D/T ASPHYX/ANOXIA BFOR LABR/UNS TIME
768.1	ICD-9-CM	FETAL DEATH FROM ASPHYXIA OR ANOXIA DURING LABOR
V27	ICD-9-CM	OUTCOME OF DELIVERY
V27.0	ICD-9-CM	OUTCOME OF DELIVERY SINGLE LIVEBORN
V27.1	ICD-9-CM	OUTCOME OF DELIVERY SINGLE STILLBORN
V27.2	ICD-9-CM	OUTCOME OF DELIVERY TWINS BOTH LIVEBORN
V27.3	ICD-9-CM	OUTCOME DELIVERY TWINS 1 LIVEBORN& 1 STILLBORN
V27.4	ICD-9-CM	OUTCOME OF DELIVERY TWINS BOTH STILLBORN
V27.5	ICD-9-CM	OUTCOME DELIVERY OTH MULTIPLE BIRTH ALL LIVEBORN
V27.6	ICD-9-CM	OUTCOME DELIV OTH MULTIPLE BIRTH SOME LIVEBORN
V27.7	ICD-9-CM	OUTCOME DELIV OTH MULTIPLE BIRTH ALL STILLBORN
V27.9	ICD-9-CM	OUTCOME OF DELIVERY, UNSPECIFIED
V30	ICD-9-CM	SINGLE LIVEBORN
V30.0	ICD-9-CM	SINGLE LIVEBORN, BORN IN HOSPITAL
V30.00	ICD-9-CM	SINGLE LIVEBORN HOSPITAL W/O C-SECTION
V30.01	ICD-9-CM	SINGLE LIVEBORN HOSPITAL DELIV BY C-SECTION
V30.1	ICD-9-CM	SINGLE LIVEBORN BORN BEFORE ADMISSION HOSPITAL
V30.2	ICD-9-CM	SINGLE LIVEBORN BORN OUTSIDE HOSPITAL&NOT HOSP
V31	ICD-9-CM	LIVEBORN TWIN BIRTH MATE LIVEBORN
V31.0	ICD-9-CM	LIVEBORN TWIN-MATE LIVEBORN IN HOSPITAL
V31.00	ICD-9-CM	LIVEBORN TWIN-MATE LIVEBORN HOSP W/O C-SEC
V31.01	ICD-9-CM	LIVEBORN TWIN-MATE LIVEBORN HOSP C-SEC
V31.1	ICD-9-CM	LIVEBORN TWIN-MATE LIVEBORN BEFORE ADMISS

Code	Type	Description
V31.2	ICD-9-CM	LIVEBORN TWIN-MATE LIVEBORN OUTSIDE HOSP
V32	ICD-9-CM	LIVEBORN TWIN- MATE STILLBORN
V32.0	ICD-9-CM	LIVEBORN TWIN-MATE STILLBORN HOSPITAL
V32.00	ICD-9-CM	LIVEBORN TWIN-MATE STILLBORN HOSP W/O C-SEC
V32.01	ICD-9-CM	LIVEBORN TWIN-MATE STILLBORN HOSPITAL C-SEC
V32.1	ICD-9-CM	LIVEBORN TWIN-MATE STILLBORN BEFORE ADMISS
V32.2	ICD-9-CM	LIVEBORN TWIN-MATE STILLB OUTSIDE HOSP&NOT HOSP
V33	ICD-9-CM	LIVEBORN TWIN UNS WHETHER MATE LIVEBORN/STILLB
V33.0	ICD-9-CM	LIVEBORN TWIN-UNS MATE LIVEBORN/STILLB HOSP
V33.00	ICD-9-CM	LIVEB TWIN-UNS MATE LIVEB/STILLB-HOSP W/O C-SEC
V33.01	ICD-9-CM	TWIN UNS MATE STILLB/LIVEB BORN HOS DEL C/S DEL
V33.1	ICD-9-CM	LIVB TWIN-UNS MATE LIVEB/STILLB-BEFORE ADMISS
V33.2	ICD-9-CM	LIVEB TWIN-UNS MATE LIVEB/STILLB OUTSIDE HOSP
V34	ICD-9-CM	LIVEBORN OTH MULTIPLE MATES ALL LIVEBORN
V34.0	ICD-9-CM	LIVEBORN OTH MULTIPLE-MATES LIVEBORN HOSPITAL
V34.00	ICD-9-CM	OTH MX MATES ALL LIVEB BORN HOS DEL W/O C/S DEL
V34.01	ICD-9-CM	LIVEBORN OTH MX-MATES LIVEBORN HOSP C-SEC
V34.1	ICD-9-CM	LIVEBORN OTH MX-MATES LIVEBORN BEFOR ADMISSION
V34.2	ICD-9-CM	LIVEBORN OTH MX-MATES LIVEBORN OUTSIDE HOSP
V35	ICD-9-CM	LIVEBORN OTHER MULTIPLE MATES ALL STILLBORN
V35.0	ICD-9-CM	LIVEBORN OTH MX-MATES ALL STILLBORN HOSPITAL
V35.00	ICD-9-CM	LIVEBORN OTH MX-MATES STILLB HOSP W/O C-SEC
V35.01	ICD-9-CM	LIVEBORN OTH MX-MATES STILLBORN HOSP C-SEC
V35.1	ICD-9-CM	LIVEBORN OTH MX-MATES STILLB BEFORE ADMISSION
V35.2	ICD-9-CM	LIVEBORN OTH MX-MATES STILLB OUTSIDE HOSP
V36	ICD-9-CM	LIVEBORN OTH MULTIPLE-MATES LIVEBORN&STILLBORN
V36.0	ICD-9-CM	LIVEBORN OTH MX-MATES LIVEB&STILLB IN HOSPITAL
V36.00	ICD-9-CM	LIVEB OTH MX-MATES LIVEB&STILLB HOSP W/O C-SEC
V36.01	ICD-9-CM	LIVEBORN OTH MX-MATES LIVEB&STILLB HOSP C-SEC
V36.1	ICD-9-CM	LIVEB OTH MX-MATES LIVEB&STILLB BEFORE ADMISS
V36.2	ICD-9-CM	LIVEB OTH MX-MATES LIVEB&STILLB OUTSIDE HOSP
V37	ICD-9-CM	LIVEBORN OTH MX-UNS WHETHER MATES LIVEB/STILLB
V37.0	ICD-9-CM	LIVEBORN OTH MX-UNS MATES STILLB/LIVEB IN HOSP
V37.00	ICD-9-CM	LIVEB OTH MX-UNS MATE LIVEB/STILLB-HOSP WO C-SEC
V37.01	ICD-9-CM	LIVEB OTH MX-UNS MATES LIVEB/STILLB HOSP C-SEC
V37.1	ICD-9-CM	LIVEB OTH MX-UNS MATES LIVEB/STILLB BEFOR ADMISS
V37.2	ICD-9-CM	LIVEB OTH MX-UNS MATES LIVEB/STILLB OUTSIDE HOSP
V39	ICD-9-CM	LIVEBORN UNSPEC WHETHER SINGLE TWIN/MULTIPLE
V39.0	ICD-9-CM	LIVEBORN UNSPEC SINGLE TWIN/MX BORN HOSPITAL
V39.00	ICD-9-CM	LIVEBORN UNS SINGLE TWIN/MX IN HOSP W/O C-SEC
V39.01	ICD-9-CM	LIVEBORN UNS SINGLE TWIN/MX IN HOSP C-SEC

Code	Type	Description
V39.1	ICD-9-CM	LIVEBORN UNS SINGLE TWIN/MX BEFORE ADMISSION
V39.2	ICD-9-CM	LIVEBORN UNS SINGLE TWIN/MX OUTSIDE HOSP

C. APPENDIX 3: ICD-9-CM 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
766.21	Post-term infant	41	287
766.22	Prolonged gestation of infant	42	294

D. APPENDIX 4: RATIONALE FOR ELECTRONIC CASE AND CONTROL ENROLLMENT INCLUSION CRITERIA

Cases

Our final analysis required spontaneous abortion events with continuous enrollment from 90 days before pregnancy start until the date of spontaneous abortion and with vaccinations between 4 weeks before pregnancy start and the date of the SAB. Because we were unable to identify pregnancy start in claims data, we maximized capture of cases meeting the enrollment criteria by requiring initially that cases be enrolled 244 days prior to the SAB event identified in claims data. Similarly, to maximize the number of cases meeting the criteria for vaccinations during the gestational period of interest, we required that potential cases have vaccine codes within the 182 days preceding the SAB event. Both of these criteria incorporated a 140-day period, the maximum gestational length for a pregnancy ending in SAB, and a 14-day period to allow for delays in seeking medical attention for a SAB.

Controls

Our final analysis required control patients (whose pregnancies ended in a livebirth) to be continuously enrolled between 90 days before pregnancy start until the gestational age at the matched case's SAB. Because there is some inherent uncertainty in claims-derived pregnancy start in claims data, we maximized capture of controls meeting the enrollment criteria by requiring initially that controls be enrolled 360 days prior to the delivery. The 360-day pre-delivery enrollment criterion incorporates a 270-day period, the average length of term pregnancy.

E. APPENDIX 5: LIMITATIONS OF USING ULTRASOUND DATING AND SYMPTOM ONSET TO ASSIGN SAB EVENT DATE

We considered using gestational age based on ultrasound confirming SAB or clinical diagnosis (symptoms or clinical events documented in the medical record such as hemorrhaging or vaginal bleeding) to assign date of SAB if available. However, in the midst of adjudicating SAB dates, our clinical experts advised us of the limitations of using ultrasound dating, specifically that it may be subject to substantial underestimates of gestational age due to poor fetal growth. Furthermore, they advised that there are major limitations of using clinical diagnosis to assign date of SAB, because normal symptoms of pregnancy (e.g., vaginal bleeding) might overlap with symptoms of a miscarriage. In such instances we might mistakenly classify the onset earlier relative to the true onset.

The use of gestational age based on ultrasound confirming SAB or use of symptom onset could potentially assign earlier dates of SAB relative to the truth. Conversely, use of date of ultrasound confirming SAB or the date of diagnosis would likely assign later dates of SAB, relative to the truth. It is not possible to determine the presence/absence or direction of potential bias on relative risk estimates with the use of each of these SAB date estimation methods.

However, we determined that if the primary analysis were to use more conservative dates (i.e., date of visit or date of ultrasound confirming SAB), a sensitivity analysis could be implemented using less conservative dates (i.e., symptom onset and/or gestational estimates based on ultrasound). Yet the converse (i.e., primary analysis incorporating symptom onset and/or gestational estimates on ultrasound; secondary analysis only using date of visit or ultrasound confirming SAB) would not be feasible because person time is censored following the date of SAB among cases, and we would be unable to sample new controls to allow for vaccinations beyond original index dates. We thus opted to use the date of ultrasound or visit to allow flexibility in using alternative SAB date algorithms if needed. This decision is also consistent with our pregnancy start algorithm among cases, which was formed on the principle that gestational age estimates based on ultrasound in pregnancies that end in a loss are systematically biased.

F. APPENDIX 6: RATIONALE FOR METHODS TO DETERMINE PREGNANCY START IN CASES AND CONTROLS

Pregnancy start among live delivery controls: Use of medical record-based ultrasound and LMP

We assigned pregnancy start in live delivery controls using the latest clinical guidelines available at the time for dating, established by the American College of Obstetricians and Gynecologists (ACOG)[2]. The guidelines state that when both date of last menstrual period (LMP) and ultrasound are available, the ultrasound-based date should be used when it is more than 7 days from the LMP-based date for a first trimester ultrasound and more than 10 days from the LMP-based date for a second trimester ultrasound (i.e., the accepted margins of error in ultrasound dating). However, if the LMP and US-based dates are within 7 or 10 days (depending on the trimester of the ultrasound), the LMP should be defaulted to. Furthermore, our study protocol[3] specified that fetal dating ultrasound be used if no LMP is documented in the record; similarly, LMP was to be used if no fetal ultrasound was available. Of note, ACOG guidelines for dating of pregnancies were developed with the objective of guiding key clinical decisions such as obstetric management.

Pregnancy start in SAB cases: Use of medical record-based LMP

We considered assigning pregnancy start among SAB cases using clinical guidelines for dating established by ACOG. However, study clinicians advised that ultrasound might not be accurate because pregnancies ending in failure are more likely to be subject to poor fetal growth than pregnancies with continuing viability, upon which fetal growth curves are based. Mukri et al.[4] previously found that viable pregnancies that later ended in losses were smaller in size (as measured by crown rump length) than expected based on gestational age. Furthermore, they observed that the viable pregnancies that eventually miscarried had smaller crown-rump-length than those that continued to be viable past first trimester. Because of delayed fetal growth, the gestational age at vaccination could be substantially underestimated by using ultrasound dating in this study.

Our working group acknowledged that it is appropriate to incorporate ultrasound dating into estimating pregnancy start in pregnancies ending in live births (i.e., *controls)*. However, we considered whether the use of LMP alone might be a better approach than incorporating both LMP and ultrasound into the pregnancy start algorithm in *cases*. Our working group also acknowledged that each of the approaches for pregnancy dating in cases has its own limitations. Yet given the lack of other alternatives, it was necessary for the group to weigh the potential implications of each of the two available approaches, LMP alone vs. incorporating both LMP and ultrasound.

Potential implications on study results

The working group discussed that both LMP and ultrasound are subject to measurement error. The direction and magnitude of any potential bias on IIV-SAB associations cannot be predicted with each of

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[2] American College of Obstetricians and Gynecologists. ACOG Practice Bulletin No. 101: Ultrasonography in pregnancy. Obstet Gynecol. 2009 Feb;113(2 Pt 1):451-61. doi: 10.1097/AOG.0b013e31819930b0.

[3] Kawai, A.K., et al. Mini-Sentinel CBER /PRISM Surveillance Protocol: Influenza Vaccines and Pregnancy Outcomes. December 30, 2015. https://www.sentinelinitiative.org/sites/default/files/PRISM/Mini-Sentinel_PRISM_Influenza-Vaccines-and-Pregnancy-Outcomes-Protocol_0.pdf

[4] Mukri F, Bourne T, Bottomley C, Schoeb C, Kirk E, Papageorghiou AT. Evidence of early first-trimester growth restriction in pregnancies that subsequently end in miscarriage. BJOG. 2008 Sep;115(10):1273-8. doi: 10.1111/j.1471-0528.2008.01833.x.

the methods available to estimate pregnancy start in SAB cases. However, LMP is likely to be subject to bi-directional measurement error, with respect to the true pregnancy start date, thereby leading to both underestimates and overestimates of gestational age. These errors might be introduced due to recall bias, bleeding not associated with menses, and delayed ovulation, among other causes[5]. In contrast and as described earlier, ultrasound dating is skewed towards underestimates of gestational age in pregnancies ending in losses, as compared with overestimates of gestational age.

Some studies suggest that historically, women were more likely to be vaccinated during later stages of pregnancy. For example, a prior Vaccine Safety Datalink study that included data between 2002 and 2009 found the following rates of influenza vaccinations by trimester[6]:

- 1st trimester: 49 per 1000 pregnancies
- 2nd trimester: 88 per 1000 pregnancies
- 3rd trimester: 79 per 1000 pregnancies

In deciding which method to use for estimating pregnancy start, we considered the implications on relative risk estimates. Under the null hypothesis of no association between vaccination and SAB, one might expect the distribution of true timing of vaccination to be the same in cases and controls. That is, if there is no association between vaccination and risk of SAB, both cases and controls would, to an equal extent, tend to have later vaccinations than earlier vaccinations, with respect to gestational age.

Potential bias with the use of ultrasound

We first considered the theoretical implications on bias of relative risk estimates if we used ultrasound dating among cases, assuming minimal or no measurement error of pregnancy start among controls since LMP could be corrected with ultrasound dating among controls. The use of ultrasound among cases and their subsequent systematic underestimation of gestational age could falsely elevate the frequency of vaccination within each of the risk intervals based on gestational age (i.e., -4 to 4, 2 to 6, or 6 to 11 weeks gestation). In turn, this would cause a falsely elevated prevalence of vaccination in the gestational-based risk interval among cases, when compared to controls (OR falsely elevated >1), even when the true distribution of timing of vaccination is similar between the two groups.

Potential bias with the use of LMP alone

In a different scenario, we then considered the theoretical implications on bias if we instead used only LMP among cases, again assuming little to no measurement error of pregnancy start among controls and under the null hypothesis. The use of LMP among cases would falsely cause both later and earlier dates, relative to the true pregnancy start date. It is acknowledged that with smaller numbers and increased uncertainty of LMP dates, an IIV-SAB association could be found by chance. However, from a theoretical standpoint, relative to the scenario described with the use of ultrasound dating, the bi-directional measurement error in gestational age caused by the use of LMP would less likely bias the results in one direction.

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[5] Lynch CD1, Zhang J. The research implications of the selection of a gestational age estimation method. Paediatr Perinat Epidemiol. 2007 Sep;21 Suppl 2:86-96.

[6] Naleway AL, Kurosky S, Henninger ML, Gold R, Nordin JD, Kharbanda EO, Irving S, Craig Cheetham T, Nakasato C, Glanz JM, Hambidge SJ, Davis RL, Klein NP, McCarthy NL, Weintraub E. Vaccinations given during pregnancy, 2002-2009: a descriptive study. Am J Prev Med. 2014 Feb;46(2):150-7. doi: 10.1016/j.amepre.2013.10.010.

The direction and magnitude of any potential bias on IIV-SAB associations cannot be predicted with each of the methods available to estimate pregnancy start in SAB cases. However, given that the use of ultrasound is more likely to be associated with unidirectional bias in the absence of an IIV-SAB association, the working group determined that the better of the two options for estimating pregnancy start was to use LMP. While the use of LMP is also subject to measurement error, the results are anticipated to be less subject to systematic bias, when compared to using ultrasound in conjunction with LMP.