MINI-SENTINEL CBER/PRISM SURVEILLANCE PROTOCOL

INFLUENZA VACCINES AND PREGNANCY OUTCOMES

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

History of Modifications

Version	Date	Modification	By
V2	3/28/2014	• Modified specific aims so that the primary objectives focus on feasibility of the case-time-control (CTC) design, rather than its implementation, as was the case in V1 of the protocol. • Primary aims revised to include validation of SAB codes and date of SAB in electronic data, which were previously designated as secondary objectives in V1 of the protocol. • Added the following objectives: validating gestational age and validating confounders in electronic data, which are designated as primary objectives. • Modified pilot objectives (previously referred to as 'exploratory objectives' in V1 of the protocol) to include CTC implementation, which was previously included in the primary objectives in V1 of the protocol. As in v1 of the protocol, implementation of the temporal scans is still included in the pilot objectives. • Restricted exposures to 2008-09 and 2010-11 inactivated influenza vaccinations (V1 of the protocol included all seasons available). • Age range modified to 18-34 years (V1 of the protocol included 10-55 years). • Specified that a final sample of 100 cases and 100 controls will be targeted. To this end, we will attempt to obtain charts for 140 cases and 2 controls for every case. • Updated method for estimating pregnancy start date using the American College of Obstetrics and Gynecology recommendations for best obstetric dating. • Removed requirement that cases and controls be matched on method for estimating gestational age. This will be incorporated in a sensitivity analysis. • Updated method of estimating date of SAB to specify ultrasound-based date in the main analysis and all methods for assigning the date in a sensitivity analysis, (previously the converse was stated). • Removed 637*(unspecified abortion), 640.81 (other specified hemorrhage in early pregnancy), and 640.91 (unspecified hemorrhage in early pregnancy) from the case-identification algorithm. • Other minor wording modifications made.	Influenza vaccines and pregnancy outcomes working group
V3	12/30/2015	• The following edits were made to the control matching algorithm: o State will no longer be matched upon o Age will be matched upon with a +/-18 months caliper (previously the protocol specified a +/-6	Influenza vaccines and pregnancy outcomes

Mini-Sentinel CBER/PRISM Surveillance Protocol
Influenza Vaccines and Pregnancy Outcomes

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I. BACKGROUND AND PUBLIC HEALTH IMPLICATIONS

A. SPONTANEOUS ABORTION

Spontaneous abortion (SAB) is one of the most common complications of pregnancy, resulting in fetal loss prior to 20 weeks of gestational age. Between 12% to 15% of clinically recognized pregnancies result in a SAB, with the vast majority occurring prior to 12 weeks gestation.[1] When including clinically unrecognized pregnancies, the pregnancy loss rate is substantially higher, with one carefully conducted study including such pregnancies finding a loss rate of approximately 30% following implantation.[2]

Chromosomal anomalies are implicated in approximately half of all SABs, with a higher incidence of abnormal fetal karyotype at earlier gestational ages; an additional unknown proportion of SABs is due to genetic abnormalities undetected by standard karyotype analysis.[3] The etiology of SAB in apparently healthy women with chromosomally and structurally normal fetuses is unknown. One of the most important risk factors is age, with rates increasing with maternal age (9% at age 22, 20% at age 35, 55% at age 42, and 84% at age 48 years and above).[4] Other factors associated with SAB include smoking, alcohol, asthma, parity, prior history of SAB, diabetes, febrile illness, and obesity.[5-10]

B. INFLUENZA VACCINES AND RATIONALE FOR ASSESSMENT

Influenza infection has been associated with severe illness and mortality in pregnant women.[11,12] Pregnancy may increase a woman's risk of influenza-related complications through normal physiologic changes in heart rate, stroke volume, lung capacity, and cell-mediated immune responses.[11] During the 1918 and 1957 influenza pandemics, great numbers of excess deaths due to influenza were seen in pregnant women.[13-15] More recently, during the 2009-2010 influenza season, pregnant women infected with novel H1N1 influenza were at increased risk of serious illness and death and were four times more likely than the general infected population to become hospitalized.[16,17]

Pregnancy also has been associated with increased risk of influenza related morbidity during inter-pandemic influenza seasons, with higher risk of complications at later stages of pregnancy. In a large study of Tennessee Medicaid enrollees over the course of 17 influenza seasons, women diagnosed with influenza in their first, second, and third trimesters of pregnancy had acute cardiopulmonary hospitalization rates of 6.5, 12.6, and 21.7 per 10,000 person-months, respectively as compared to 6.4 per 10,000 person-months in non-pregnant women diagnosed with influenza.[18]

Due to the high risk of complications from influenza infection during pregnancy, the Advisory Committee on Immunization Practices (ACIP) has recommended routine influenza vaccination for women pregnant during the influenza season since the 1997-1998 influenza season.[19] The ACIP historically has recommended against and continues to recommend against administering live attenuated influenza vaccines in pregnant populations due to the theoretical risk that they may pose to the fetus and instead recommends vaccination with seasonal inactivated influenza vaccines in pregnant populations.[20] The initial ACIP recommendation for trivalent inactivated influenza vaccine (TIV) in pregnant women made in 1997 was limited to the second and third trimesters to avoid "coincidental association with spontaneous abortion." However, the ACIP recommendation was later expanded to all three trimesters beginning with the 2004-2005 influenza season.[21]

Influenza vaccination rates in pregnant women are currently below full coverage levels. In the Pregnancy Risk Assessment Monitoring System (PRAMS), a collaboration between the Centers for Disease Control and Prevention (CDC) and 37 states, New York City, and a South Dakota tribal-state project, the prevalence of influenza vaccination coverage was 50.7% for seasonal vaccine and 46.6% for H1N1 vaccine during the 2009-2010 influenza season.[22] In the PRAMS study, over 45% of pregnant women cited safety concerns for their baby and/or for themselves; among those not receiving the H1N1 influenza vaccine, over 60% cited safety concerns for their baby and/or for themselves.[22] For women pregnant anytime during the 2010-11 and 2011-12 influenza seasons, the influenza vaccination coverage rates were 49% and 47%, respectively, according to Internet panel surveys conducted by the CDC at the end of each of the two seasons.[23]

A number of studies, which do not mention manufacturer, have examined risk of pregnancy and birth outcomes following TIV in the United States. Of the existing postmarketing studies on seasonal vaccine during pregnancy, few have included large numbers of women vaccinated during the first trimester. No study to date has found maternal or fetal safety concerns in pregnant women receiving influenza vaccine. In the earliest published study, the safety of TIV was examined in more than 2000 women who received influenza vaccine during pregnancy and their children in the National Collaborative Perinatal Project during the early 1960's.[24] In-utero exposure to TIV was not associated with fetal malformations, cognitive or neurologic disabilities, or childhood cancers during the first 7 years of life. More recently, in a retrospective cohort of 252 women receiving TIV in the second or third trimester between July 1998 and June 2003 and 826 unvaccinated pregnant women, Munoz et al. did not find any serious adverse events within 42 days of vaccination using electronic data from a large multispecialty clinic in Texas.[25] In the same study, TIV was not associated with adverse pregnancy outcomes, including cesarean section and premature delivery, or with a number of infant medical conditions, including congenital malformations, from birth to age 6 months. In a retrospective cohort study using Georgia PRAMS data on 578 vaccinated pregnant women and 3748 unvaccinated pregnant women experiencing a live birth between June 2004 through September 2006, TIV receipt during pregnancy was associated with *decreased* risk of preterm birth and small-for-gestational-age birth during the period of widespread influenza activity, but was not associated with either outcome during the period of pre-influenza activity.[26] In a study of 8690 vaccinated pregnant women (439 vaccinated during the first trimester and 8251 vaccinated during the second or third trimesters) and 76,153 unvaccinated pregnant women from a single county hospital and clinic system in Texas, TIV was not associated with increased risk of preterm delivery at 36 or less weeks gestation or at less than 32 weeks gestation, low birth weight, major malformations, stillbirth, NICU admission, neonatal death, neonatal pneumonia, or hyperbilirubinemia; in fact, TIV was associated with *decreased* risk of stillbirth, neonatal death, and preterm delivery at 36 or less weeks gestation and at less than 32 weeks gestation. In a Vaccine Safety Datalink (VSD) retrospective cohort study of 3707 pregnant women who received TIV during at least one of 5 influenza seasons (Fall 1997 to Spring 2002) and 45,878 unvaccinated pregnant women from a single medical care organization in California, no increased risk of cesarean section or preterm delivery was noted.[27] Two recent VSD studies incorporating data from additional medical care organizations have also examined the safety of TIV in pregnant populations. In a retrospective cohort study that used data from 7 medical care organizations in the VSD from June 2002 through July 2009 and included 75,906 vaccinated pregnant women (21,553 during the first trimester and 54,353 during the second or third trimesters) and 147,992 unvaccinated pregnant women, no associations were found between vaccination and potential adverse events under investigation, including allergic reactions, cellulitis, and seizures in the 3

days following vaccination.[28] Furthermore, in the 42 days following TIV, no incident cases of Guillain-Barré syndrome, optic neuritis, transverse myelitis, or Bell's palsy were found and TIV was not found to be associated with thrombocytopenia or an acute neurologic event. In a matched case-control study of 243 cases and 243 controls conducted in six medical care organizations in the VSD, receipt of TIV during the 2005-2006 or 2006-2007 season was not found to be associated with SAB in the 28 days following vaccination; furthermore, exposure defined as same-season vaccination before conception vs. vaccination post-conception was not significantly associated with SAB when compared to no vaccination.[29] TIV in pregnant women has also been investigated in passive surveillance using data from the Vaccine Adverse Events Reporting System (VAERS). In a review of 175 VAERS reports from 1996 through 2009 in pregnant women administered seasonal influenza vaccines (148 received TIV and 27 received LAIV), the number of pregnancy complications or fetal outcomes observed was not greater than expected.[30]

The safety of 2009 H1N1 monovalent inactivated influenza vaccine (MIV) in pregnant women has been investigated in a number of studies. None of the studies has identified elevated risks of adverse pregnancy or birth outcomes following H1N1 MIV, with some studies reporting decreased risks of preterm birth, fetal death, low birth weight, or small-for-gestational-age birth following vaccination. In a review of 288 VAERS reports in pregnant women administered H1N1 MIV during the 2009-2010 influenza season, no unusual patterns of pregnancy complications or fetal outcomes were observed.[30] At least four retrospective cohort studies, none of which mention manufacturer or trade names, have been published using pregnant populations in the U.S. In a retrospective cohort study of active-duty U.S. military women that included 10,376 pregnant women receiving H1N1 MIV (4122 vaccinated during the first trimester and 6254 vaccinated during the second or third trimesters), H1N1 MIV exposure was not associated with pregnancy outcomes (including pregnancy loss and preeclampsia or eclampsia) or birth outcomes (including preterm birth, birth defects, fetal growth problems, and male-to-female sex ratio), when compared to 7560 pregnant women receiving TIV during the 2008-2009 season.[31] In another study of 3327 pregnant women enrolled in a managed care organization in Georgia, H1N1 MIV vaccination (n=1125) compared to no vaccination (n=1581) was associated with lower risk of preterm birth and higher birth weight but was not associated with small-for-gestational-age birth or low birth weight.[32]

Outside of the U.S., several studies have been conducted on the safety of 2009 H1N1 MIV in pregnant populations in countries where adjuvanted H1N1 MIV vaccines, which were not licensed in the U.S., were widely in use among those receiving H1N1 vaccination. A population-based study of 55,570 pregnant women receiving H1N1 vaccine (most of which were administered during the second or third trimesters) and 32,230 pregnant women not receiving H1N1 vaccine in Ontario, Canada found that vaccination was associated with lower risk for small-for-gestational-age birth, preterm birth at less than 32 weeks of gestation, and fetal death but was not associated with preterm birth at less than 37 weeks gestation and low Apgar score; the study did not mention the manufacturer or trade names of vaccines received.[33] A number of studies conducted in Europe have investigated risk of fetal death (SAB and stillbirth) and birth outcomes following monovalent inactivated AS03 adjuvanted split virion H1N1 vaccine (Pandemrix®, manufactured by GlaxoSmithKline Biologicals and not licensed in the U.S.) in pregnant women. The largest of these studies used a population-based registry in Norway of 25,976 pregnant women receiving Pandemrix (2431 vaccinated during first trimester and 23,545 vaccinated during the second or third trimester) and 87,335 pregnant women not receiving Pandemrix and found that vaccination was not associated with increased risk of preterm birth, term low birth weight, term low Apgar score, or fetal death (i.e., SAB or stillbirth after 12 weeks gestation); in fact, vaccination was

associated with *decreased* risk of fetal death, though the relative risk was not statistically significant.[34] Another study using a population-based registry in Sweden of 18,612 pregnant women receiving Pandemrix and 223,415 pregnant women not receiving Pandemrix found that vaccination was not associated with risk of small-for-gestational-age birth and congenital malformations but was associated with statistically significant *decreased* risks of stillbirth, preterm birth, and low birth weight.[35] Similarly, a population-based registry study in Britain that included 9161 pregnant women receiving H1N1 MIV (the majority of which was presumed to be Pandemrix by the authors and was administered during the second or third trimester)[36] and 30,418 pregnant women not receiving H1N1 MIV and another population-based registry study in Denmark that included 7062 pregnant women receiving Pandemrix and 47,523 pregnant women not receiving Pandemrix, found that vaccination was associated with decreased risk of fetal death (i.e., SAB or stillbirth).[37] Using the same population-based data sources, the Danish group found that vaccination was not associated with major congenital malformations, preterm birth, or small for gestational age in a cohort of 6989 infants exposed to Pandemrix during pregnancy (345 exposed during the first trimester and 6644 exposed during the second or third trimester) and 46,444 infants not exposed to Pandemrix during pregnancy.[38] A small manufacturer-sponsored observational cohort study conducted in the United Kingdom, which included 267 pregnant women vaccinated with Pandemrix (42 during the first trimester and 225 during the second or third trimesters), did not find an increased risk of SAB, stillbirth, major malformations, preeclampsia, prematurity, or low birth weight following vaccination, based on expected rates from other population-based studies.[39] Another small prospective cohort study conducted in Germany, which included 323 pregnant women vaccinated primarily during the second or third trimester with H1N1 MIV (of whom 90 received Pandemrix, 216 received non-adjuvanted split virion vaccine CSL H1N1 Pandemic Influenza Vaccine® (CSL Biotherapies), 2 received other H1N1 MIV vaccines, and 15 received vaccines for which manufacturer could not be ascertained) and 1329 unvaccinated pregnant women found that vaccination was not associated with major malformations, SAB, preterm delivery, preeclampsia, or birth weight.[40]

A smaller number of studies have focused on the safety of MF59-adjuvanted A/H1N1 influenza vaccine (Focetria®, manufactured by Novartis and not licensed in the United States) in pregnant populations. In a manufacturer-sponsored prospective cohort study conducted in the Netherlands, Italy, and Argentina, 2295 pregnant women receiving Focetria (92 vaccinated during the first trimester, 2195 vaccinated during the second or third trimester, and 8 for whom the gestational age at vaccination was unknown) had similar risks for gestational diabetes, preeclampsia, stillbirth low birth weight, neonatal death, or congenital malformations when compared to 2213 unvaccinated women. In that same study, no maternal deaths or SABs were observed and risk of preterm delivery was lower in pregnant women vaccinated with Focetria.[41] In another manufacturer-sponsored cohort study in Argentina that included 7293 pregnant women receiving Focetria (2874 vaccinated during the first trimester, 4281 vaccinated during the second or third trimester, and 138 for whom the gestational age at vaccination was unknown) and 23,155 unvaccinated pregnant women, vaccination was found to be associated with lower risk of preterm birth and low birth weight.[42] In that same study, vaccination was not associated with other maternal outcomes (including pregnancy induced hypertension, preclampsia, eclampsia, peripartum hemorrhage, and admission to intensive care unit) or other infant outcomes (including perinatal mortality, congenital malformations, low Apgar score, admission to neonatal intensive care unit, and non-immune jaundice).

Although existing post-marketing safety data in pregnant women are reassuring, many of the existing studies have a number of limitations, including limited numbers of women receiving vaccine during the

first1st trimester, potential confounding bias due to comparing vaccinated to unvaccinated women, or potential bias due to consideration of all person-time following vaccination as exposed rather than defining a limited time interval of increased risk.[43] Furthermore, because the pathophysiology of SAB is not well understood, studies using pre-defined risk intervals may have been biased due to misspecification of risk intervals that include days that are not at an increased risk.

Obtaining additional high quality post-licensure safety data in pregnant populations is a public health priority, particularly given recent policies emphasizing the vaccination of pregnant populations in the U.S. In October 2012, the ACIP recommended for the first time that all pregnant women receive tetanus, diphtheria, and pertussis vaccine (Tdap) to provide infants protection from pertussis early in life; prior to that, in June 2011, the ACIP had voted to recommend Tdap vaccination to pregnant women, but only to those who had not previously received the vaccine.[44] Mini-Sentinel is a pilot project sponsored by the FDA to inform and facilitate development of a fully operational active surveillance system, the Sentinel System, for monitoring the safety of FDA-regulated medical products. Within Mini-Sentinel, Post-Licensure Rapid Immunization Safety Monitoring (PRISM) is a collaboration between FDA, the Harvard Pilgrim HealthCare Institute (coordinating center), four large national health insurance plans (Aetna, HealthCore, Humana, and OptumInsight, henceforth referred to as "Data Partners") and Immunization Information Systems (i.e., IIS, immunization registries) in Departments of Health of 7 states and New York City. It is well suited to address questions of vaccine safety in pregnant women because of its large size and well-defined study population. Building upon the existing system, we propose to develop the data infrastructure and the methodological framework to evaluate potential associations between vaccine exposure of pregnant women and pregnancy-related adverse events. In addition to claims data, we will incorporate the ability to leverage birth certificate data to obtain information on gestational age and IIS data to obtain vaccine information, where available.

II. OBJECTIVES

This protocol describes the PRISM program's efforts to establish the methodological framework for studying pregnancy outcomes following exposure to vaccination during pregnancy. The results of this infrastructure building and methods development activity will be used to determine the feasibility of pregnancy surveillance within Mini-Sentinel's PRISM program and to evaluate the novel methods required to conduct such surveillance. The overarching goal of this protocol is to optimize algorithms for using claims and birth certificate data in studies of pregnancy outcomes. In addition, we will examine the feasibility of conducting a case-time-control design for examining risk of SAB following exposure to TIV using risk intervals defined by gestational age at vaccination and by the time elapsed since vaccination.

A. PRIMARY OBJECTIVES

1. To examine the positive predictive value of computerized CPT or ICD9 codes for SAB through medical record review for all cases combined and by maternal age and by code
2. To examine the accuracy of gestational age data in claims and in birth certificate data for the purposes of identifying pregnancy start among live delivery controls, who will be matched to chart-confirmed SAB cases

3. To examine the accuracy of potential confounders in claims data for the purposes of matching SAB cases and live delivery controls

B. PILOT OBJECTIVES

Using a case-time-control design, to examine risk of SAB following TIV using the following risk intervals:

4. In the 1-28 days post-TIV
5. After TIV received between -4 and 4 weeks gestation, 2 and 6 weeks gestation, or 6 and 11 weeks gestation

To explore potential periods for increased risk of SAB without defining the risk interval a priori:

6. Within a specific time interval defined by number of days post-TIV
7. After TIV received during a specific gestational period
8. Within a specific time interval defined by number of days post-TIV and gestational period at vaccination

III. STUDY DESIGN

A. OVERVIEW OF CASE-TIME-CONTROL DESIGN

In this protocol, our main objective is to optimize algorithms for using claims and birth certificate data for studies of pregnancy outcomes. As proof-of-concept, we will also determine the feasibility of implementing a case-time-control design to examine whether risk of SAB is elevated within 1-28 days post-TIV or whether the risk is increased after TIV received between -4 to 4 weeks gestation, between 2 to 6 weeks gestation, or between 6 to 11 weeks gestation. We will match cases and controls (at least two controls per case, up to a maximum of 6) on Data Partner, maternal age, and pregnancy start date (i.e.., date of last menstrual period (LMP), pregnancy start based on ultrasound dating, or pregnancy start based on assisted reproductive technology; see methods for determination). Matching on pregnancy start in cases and controls will address temporal patterns in vaccination by seasonality and gestational age. If feasible, we will also attempt to match cases and controls on comorbidities, infections, and other potential confounders, which will maximize the comparability between cases and controls with respect to underlying time trends in exposure.

The case-time-control design is a variant of a case-cross-over study (CCO). The CCO study and its variants are especially well-suited to measuring transient effects of exposures on immediate risk of illnesses with abrupt onset.[45] In a CCO study, in individuals who have experienced the outcome of interest, a comparison is made between the odds of exposure in a predefined risk interval to that in a self-matched comparison interval. In addition to using cases as the CCO study does, the case-time-control design also uses an external group of controls sampled from the same population that produced the cases to adjust for time trends in exposure (e.g., seasonality or gestational age at vaccination). As in the cases, in the controls, the odds of exposure is compared between the predefined risk and self-matched control interval to estimate the exposure trend bias; the odds ratio in cases is divided by the odds ratio in controls to produce an effect estimate for the association between exposure and outcome while adjusting for time trends in exposure.

In the pilot objectives, we will utilize a case-time-control design to examine whether risk of SAB is elevated in pre-specified periods by number of days between TIV receipt and SAB event and by gestational age at receipt of TIV. For defining exposure by number of days prior to SAB event, we propose to use the risk interval of 1-28 days prior to SAB. 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.[46,47] Furthermore, inflammatory immune responses in pregnant women following TIV, as measured by C-reactive protein and tumor necrosis factor-alpha, have been shown to peak at 2 days post vaccination and return to baseline levels within one week post-vaccination.[48] From a biologic plausibility standpoint, one may hypothesize that the period of risk corresponds with this approximately 4-week long period of heightened immunologic activity if immune mediated reactions are the cause of potential adverse events.

When defining exposure by gestational age, we will examine risk intervals of -4 through 4 weeks gestation, 2 through 6 weeks gestation, and 6 through 11 weeks gestation. The -4 through 4 weeks gestation risk interval was selected because immune-mediated processes resulting from vaccination in the weeks surrounding conception and the early pregnancy period may lead to increased risk of SAB**.** Previously, Wacholder et al. found a small increase in risk of SAB following receipt of bivalent vaccine against human papillomavirus types 16 and 18 (Cervarix®, manufactured by GlaxoSmithKline) in the subgroup of pregnancies conceived within 90 days prior to vaccination, though the authors concluded that this result was consistent with statistical noise.[49] Furthermore, in the VSD, a non-statistically significant increase in risk of SAB was found among women receiving TIV in the 14 days preceding conception (OR 2.3, 95% CI 0.9, 6.3), compared to women not receiving TIV.[29] For the present protocol, we selected an additional risk interval of 2 to 6 weeks gestation to reflect the period of early pregnancy, based on the rationale that inflammatory markers, systemic, and local reactions could potentially manifest and end within a shorter period following vaccination. We also selected an additional risk interval of 6 to 11 weeks gestation to correspond to the period of the highest incidence of SAB,[50] which could reflect an increased period of susceptibility.

For each of the pilot case-time-control analyses, the control interval will be defined as vaccination outside each of the risk intervals. One advantage of the case-time-control design is that it adjusts for between-person confounders that do not vary over time. However, a disadvantage is that the design will not completely adjust for time trends in exposure if controls have different time trends in exposure than cases. This might occur if women at greater risk of SAB are more likely to be vaccinated at an earlier or later gestational age than those at lower risk. Furthermore, a major disadvantage of this approach is that the risk interval must be defined a priori.

B. OVERVIEW OF TEMPORAL SCAN FOR IDENTIFICATION OF RISK INTERVALS

In vaccine safety studies, the risk interval should correspond with the true period of increased risk following vaccination. If the risk interval contains days in which there is no true increase in risk, the magnitude of an increased risk could be underestimated or completely missed.[51] Conversely, using too short of a risk interval could lead to a loss of power for relative incidence estimates. The specific choice of risk interval in vaccine studies should be informed by biologic plausibility to avoid bias and loss of power. However, because the pathophysiology of SAB is largely unknown, the case-time-control design may be susceptible to bias due to incorrectly specifying the risk interval.

To address the limitation of pre-defining the risk interval in the case-time-control approach, we propose to explore additional techniques that do not define the specific risk intervals a priori. Specifically, we propose to use temporal scan methodology to identify potential risk periods of interest in relation to vaccine receipt. The temporal scan approach has been used in prior studies in order to more precisely define the risk interval in signal refinement within a longer post-vaccination observation period. In this protocol, a temporal scan approach will be used to detect and evaluate temporal clusters of vaccination among women with SAB who have received TIV in the period of interest, adjusted for underlying temporal patterns in vaccination by gestational age and calendar week. Because the pathophysiology of SAB is not well understood, we will examine for clusters by timing of TIV receipt in several ways: (1) number of days prior to SAB event, (2) gestational age at receipt of TIV, and (3) a combination of number of days prior to SAB event and gestational age at receipt of TIV. We will use women who have had live deliveries as controls to adjust for temporal trends in TIV receipt by gestational age and calendar time.

C. DATA SOURCES

The PRISM data sources currently consist of claims-based and administrative data from Data Partners and immunization registry data from Immunization Information Systems (IIs) in Departments of Health in 7 states and New York City.[52] Claims-based and administrative data from Data Partners include data on demographics, diagnoses, procedures, and pharmacy dispensings. Under the protocol of a separate activity entitled "PRISM Influenza Vaccines and Birth Outcomes", methods are being developed to link maternal and infant Data Partner records and to link maternal Data Partner records and birth certificate data from Vital Events Registries in select cities and states.[53] For the current protocol, infant claims-based data and birth certificate data will be used, if available, in the process of matching controls (i.e. deliveries) to cases (i.e., SABs) on pregnancy start date since these data sources provide more precise estimates of gestational age than maternal claims-based counterparts. Electronic data (claims-based, administrative, and birth certificate data, where available) will be used for identifying cases and controls. However, only chart-confirmed cases and controls, as well as chart-confirmed gestational age and date of SAB will be used in the final analysis.

D. STUDY POPULATION

The participating Data Partners in this protocol are Aetna and HealthCore. The dates of data availability differ by Data Partner (Table 1). The study population will consist of females ages 18 through 34 years who received TIV in the 4 weeks prior to or during pregnancy, and whose pregnancies have ended in an SAB (cases) or live delivery (controls). Women whose pregnancies have ended in a therapeutic abortion, ectopic or molar pregnancy, or stillbirth will not be used as controls since we will not be able to accurately assess gestational age using claims-based data. The study population will be further restricted to women with continuous enrollment from 90 days prior to pregnancy start through the SAB date in cases or index date in controls. Though we do not anticipate this to occur frequently, cases and controls who receive an additional influenza vaccine in the 90 days prior to the start of the study period of interest (i.e., -4 weeks gestation) will be excluded.

Table 1: Dates of Data Availability by Data Partner

Data Partner	Date Data Available in Mini-Sentinel Common Data Model	Requirements for Data Used in Protocol[1]
Data Partner A	1/1/2008 through 10/31/2012	Vaccinations occurring in 2008-09 and 2010-11 influenza seasons
Data Partner B	1/1/2004 through 11/30/2011	Vaccinations occurring in 2008-09 and 2010-11 influenza seasons

[1]Influenza season defined as September 1 through April 30 of the following year. 2009-10 influenza season not included due to the availability of H1N1 influenza vaccine in the same season.

E. OVERVIEW OF SELECTION OF CASES AND CONTROLS

Vaccinated cases (SAB) and controls (deliveries) for this protocol will be selected in a 4-phase process (Figure 1), with a targeted final sample of 100 cases, with each case matched to at least 1 control in the final analysis. In phase 1, 140 potential cases will be initially identified in claims-based and administrative data. Also in phase 1, the initial step of identifying deliveries and estimating their pregnancy start will occur using claims-based and administrative data. If more than 140 potential cases are identified in electronic data, we will randomly sample 70 cases from each Data Partner. In phase 2, chart review will be conducted on potential cases to confirm SAB, date of SAB, and obtain pregnancy start date; potential cases will only be retained if vaccination occurred during the gestational period of interest (-4 weeks gestation to SAB event date). In phase 3, for each chart-confirmed case, we will identify 2 potential controls with the same age, pregnancy start, and vaccination between -6 weeks gestation and 2 weeks past the case's gestational age at SAB, based upon electronic data. Potential cases and controls will also be matched on other potential confounders using electronic data. We will randomly sample a minimum of 2 controls for each case. In the final phase, we will chart review potential controls to confirm pregnancy start, vaccination, and gestational age at vaccination.

F. IDENTIFYING POTENTIAL CASES AND CONTROLS IN CLAIMS-BASED AND ADMINISTRATIVE DATA (PHASE 1)

1. Cases

The inclusion criteria for cases and controls are summarized in Appendix 1. Using claims and administrative data, women who have experienced a SAB will be initially identified using the codes in Appendix 2 occurring in the inpatient, emergency department, or ambulatory care setting. To avoid including follow-up visits, a 98-day (i.e., 14 week) washout period will be used to identify incident SAB events. If there are multiple incident SAB events for a given patient, we will select the first chronological event in the study period. Though the average gestational length of pregnancies ending in miscarriage is shorter (i.e., 10 weeks), we chose the 14-week washout period to enhance the specificity for detecting incident SAB events. Initially, inclusion based on period of enrollment will be conducted through the use of administrative and claims-based data; women whose pregnancies have ended in a SAB will only be considered a potential case if based on claims-based and administrative data, they are enrolled continuously for the 244 days prior to their medical encounter for SAB. The 244-day pre-SAB enrollment criterion for potential cases incorporates a 90-day period prior to pregnancy start, 140-day period for the maximum gestational length for a pregnancy ending in SAB, and a 14-day period to allow for delays in seeking medical attention for SAB.

We will also initially require, based on electronic data, potential cases to have received TIV within the 1-182 days prior to the SAB code. This 182-day (i.e., 26 week) period was selected to enhance our ability to detect vaccinations during the gestational period of interest (-4 weeks gestation through SAB event date) and incorporates a 20-week period corresponding to the latest gestational age at which a SAB may occur, a 4-week period corresponding to the pre-gestational period of interest, and a 2-week period to allow for delays in seeking medical care for miscarriage. After the SAB event date is confirmed, we will ensure that cases are enrolled for a minimum of 90 days prior to pregnancy start through the SAB event date and will only retain cases with TIV in the period of interest (-4 weeks gestation through SAB event date). While we will use claims data to initially identify potential cases, we will limit our analysis to chart-confirmed cases and will use medical record data to identify the start of pregnancy and the date of SAB to reduce misclassification of timing of exposure with respect to gestational age and days in relation to SAB. The process of medical record review will be described later in the protocol.

2. Controls

We will identify live deliveries in claims-based and administrative data using codes in Appendix 3. To avoid including post-partum care visits, we will use a washout period of 270 days to define an incident delivery. For women who have both a SAB and live delivery during the study period, the SAB will be retained, while the live delivery will be discarded; this will be done to retain the SAB in instances where multiple pregnancies result in one or more miscarriages, and the remaining fetus(es) results in a live delivery. Initially, inclusion based on period of enrollment will be conducted with administrative and claims-based data; women whose pregnancies have ended in a delivery will only be considered for inclusion as a potential control if based on claims-based and administrative data, they are enrolled continuously for the 360 days prior to delivery hospitalization. The 360-day pre-delivery enrollment criterion for potential controls incorporates a 90-day period prior to pregnancy start and a 270-day period, the average length of term pregnancy. After chart review is conducted, we will ensure that controls are enrolled for a minimum of 90 days prior to pregnancy start through the index event date in

the matched case and will only retain controls with TIV in the period of interest (-4 weeks gestation through index event in the matched case). While we will use claims data to initially identify potential controls and estimate gestational age, we will use medical record data to confirm the gestational age to reduce misclassification of timing of exposure.

G. CHART REVIEW OF POTENTIAL CASES IDENTIFIED IN CLAIMS-BASED AND ADMINISTRATIVE DATA (PHASE 2)

Once potential SAB cases are identified using computerized data, we will conduct medical record review to confirm the SAB event and estimate the dates of SAB and pregnancy start, which will be used to calculate gestational age at vaccination and timing of vaccination (in days) in relation to SAB. We will exclude naturally conceived pregnancies ending in a miscarriage (i.e., SAB cases) that do not have LMP since we will be unable to estimate gestational age at vaccination. Following chart review, we will only retain those potential cases that have TIV occurring in the gestational period of interest (-4 weeks gestation through the date of SAB). Details on the types of data needed to validate the date of the SAB event and pregnancy start will be described later in the protocol.

H. MATCHING POTENTIAL CONTROLS TO CHART-CONFIRMED CASES (PHASE 3)

After chart review of potential cases, we will identify 1 or more potential controls (up to a maximum of 6 controls) for every case to pursue medical charts. Controls will be matched to cases on Data Partner, age, and pregnancy start (+/- 14 days), with pregnancy start estimated initially in electronic data and chart-confirmed at a later stage. Matching on pregnancy start will 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, matching on Data Partner and, maternal age will address confounding, which might occur if these factors are associated both with SAB and with timing of vaccination. If sufficient controls are available, we will also attempt to match on other important confounding factors, including comorbidities and infections, further described later in the protocol. Conditional logistic regression will be used to account for the matching and to allow for a different underlying time trend in exposure for each case:control set, which addresses the possibility of effect modification of the exposure-period association by confounders matched upon.

The matching criteria are described in more details as follows. We will match cases to controls on pregnancy start, Data Partner, and maternal age within +/-18 months. Among potential controls, we will initially estimate pregnancy start date based on an algorithm that utilizes electronic data and that is further described in the PRISM Influenza Vaccines and Birth Outcomes Protocol. Because birth certificate data and infant claims-based codes for gestational age provide more precise estimates of gestational age than their maternal claims-based counterparts, we will link potential controls identified in Data Partner records to infant Data Partner records and/or birth certificate data. We will use claims-based codes for infants born preterm, post-term, or after a prolonged gestation (Appendix 4). If claims-based codes for gestational age for infants in Appendix 4 are not evident, we will assume a gestational length of 270 days.

If there are sufficient control numbers, we will consider matching controls to cases on diagnoses of diabetes, obesity, asthma, and multiparity based on CPT and ICD9-coded data. Finally, where information on particular time-varying confounders is available in claims-based data, we will attempt to match cases and controls on such factors if sufficient controls exist. We will attempt to match cases and controls on the presence of urinary tract infections, respiratory infections, gastrointestinal infections, sexually transmitted infections, and medically attended fever within a 1-28 day period prior to SAB/index date, identified using ICD9-coded data (Appendix 5). Finally, we will collect information from the medical record on factors not matched upon in the design phase, such as smoking, alcohol, and substance abuse, and adjust for them in regression models if feasible.

Multiparity will be identified using codes listed in Appendix 5. The algorithms for identifying obesity and diabetes are described in the PRISM Influenza Vaccines and Birth Outcomes Protocol. Asthma will be identified using an algorithm validated and developed by the Medication Exposure in Pregnancy Risk Evaluation Program (MEPREP), an FDA-sponsored collaboration between 11 health plans. To be considered asthmatic, a woman must have one of the following during the 90 days prior to pregnancy through end of pregnancy: (1)>=2 outpatient visits at least 30 days apart with ICD9 diagnosis code 493*, (2) >=1 inpatient visit with ICD9 diagnosis code 493*, or (3) >=1 outpatient visit with ICD9 diagnosis code 493* and >=1 dispensing of an asthma medication (short- or long-acting beta-agonist, inhaled corticosteroid, leukotriene receptor antagonist, mast cell stabilizer, methylxanthine). This algorithm was shown to have a positive-predictive value of 95% in MEPREP.[54]

Among potential controls meeting matching and enrollment criteria, TIV identified in claims or IIS data must be received between -6 weeks gestation and 2 weeks past the case's gestational age at SAB, with gestational age estimates from birth certificate or infant-claims based estimates. A 2-week margin before and after the gestational period of interest will be initially incorporated to allow for misclassification of gestational age in live delivery controls due to use of claims and birth certificate data for gestational age estimates.

I. IDENTIFYING POTENTIAL CONTROLS IN CLAIMS-BASED AND ADMINISTRATIVE DATA (PHASE 3 AND 4)

After 2 or more potential controls are identified in electronic data for each chart confirmed case, we will then conduct a second round of chart review to confirm that these controls have vaccine exposure in the gestational period of interest (i.e., 4 weeks before pregnancy start to the index date). These potential controls will proceed to full chart review to confirm live delivery, gestational age at delivery, pregnancy start date, TIV exposure, and gestational age at vaccination. Controls will only be retained if they received TIV between -4 weeks gestation and the index date. Initially we will require controls to be continuously enrolled in the 360 days prior to delivery. This 360-day period incorporates a 90-day period prior to pregnancy start and a 270-day period, the average gestational length of a term pregnancy. Following chart review, controls will only be retained if they are determined to have enrollment 90 days prior to pregnancy start through the index date. Following chart review, if both controls in a given case-control set do not meet inclusion criteria, we will attempt to match the case to an unmatched control from a different case-control set, if available. If cases remain unmatched despite these attempts, they will only be included in analyses for Objectives 1 and 2. If both controls in a given case-control set meet inclusion criteria, we will randomly select one control.

J. VACCINE EXPOSURE

TIV will be initially identified in claims-based data using NDC (National Drug Codes), CPT (Current Procedural Terminology), HCPCS (Healthcare Common Procedure Coding System) and ICD9 (International Statistical Classification of Diseases) codes (Appendix 6). These include codes used by healthcare providers and insurers prior to the 2012-13 influenza season for capturing seasonal inactivated influenza vaccines for administrative and reimbursement purposes. TIV exposure will also be identified in IIS data (i.e., immunization registries, maintained by Departments of Health) using CVX (Vaccines administered) codes. We will conduct chart review to verify vaccine exposures.

K. CASE-TIME-CONTROL DESIGN

As proof-of-concept, a case-time-control study design will be implemented to examine whether risk of SAB is elevated in specific time periods following TIV or in specific gestational periods following TIV. We will identify SAB cases that were vaccinated between -4 weeks gestation until the date of the SAB. Since the likelihood of receiving TIV differs by gestational age and calendar time, we will match each case to a vaccinated control based on Data Partner, maternal age, and pregnancy start, where the control must have received TIV between -4 weeks gestation and the case's gestational age at SAB. In order to understand the feasibility of using the case-time-control design in Mini-Sentinel, we will first examine (1) the validity of claims data for identifying SAB; (2) the validity of birth certificate and claims data for identifying pregnancy start among live delivery controls for matching them to chart-confirmed cases; and (3) the validity of using claims data for matching cases to controls on confounders, if matching on factors other than DP and pregnancy start is ultimately implemented. The details of the descriptive statistics for Primary Objectives 1-3, which will be used to address each of these aims, are described further in the analytic section of the protocol.

In Pilot Objectives 4-5, we will implement the case-time-control design and analyze the resulting data. For Pilot Objective 4, we will define the risk interval as receipt of TIV within 1-28 days prior to SAB, while the control interval will be defined as receipt of TIV outside of the risk interval (i.e., between -4 weeks gestation and 29 days prior to SAB, Figure 2). Although we will strive for an exact match by pregnancy start, it is plausible that we will not identify enough controls to match to cases. If an exact pregnancy start match is not possible, we will assign an index date in controls that corresponds to the gestational age at SAB in the case. Of note, cases and controls will only be informative if vaccinated in either the risk or the control interval. In exploratory analysis, we will stratify the analysis for this objective by gestational age at SAB (less than 12 weeks gestation vs. 12 or more weeks gestation) since the etiology of SAB differs by gestational age at occurrence. In addition, because the underlying causes of SAB may differ by whether a heartbeat is detected prior to the miscarriage, we will consider stratifying by this factor, depending on whether we have sufficient case numbers. If we have sufficient case numbers, we will also consider excluding cases that have a threatened abortion identified prior to vaccination.

matched controls, if numbers permit. In addition, information on potential risk factors for SAB, including asthma, gravidity, prior history of SAB, diabetes, febrile illness, medically attended infections, and obesity, will be collected primarily for descriptive purposes. If feasible, we will adjust for smoking, alcohol, and substance abuse in regression models, using information from the medical record.

All SAB events estimated to have occurred prior to 6 weeks gestation will be excluded since recognition of pregnancy loss prior to this point is uncommon and thus it is difficult to establish date of pregnancy start and date of SAB. Potential cases or controls for whom it is determined that TIV did not occur between -4 weeks gestation and the case's gestational age at SAB event (i.e., the study period of interest) will also be excluded.

Accurate assessment of SAB date and gestational age is necessary for determining timing of vaccination in relation to SAB date/index date in controls and gestational age at vaccination, both of which define potential risk intervals in this study. Medical records will be used to assign date of SAB among cases and estimated pregnancy start among cases and controls. The American College of Obstetrics and Gynecologists (ACOG) currently includes the following indications for an ultrasound during first trimester (before 13 weeks and 6 days gestation), among others: confirmation of an intrauterine pregnancy, evaluation of a suspected ectopic or molar pregnancy, evaluation of vaginal bleeding or pelvic pain, estimation of gestational age, and confirmation of cardiac activity.[55] Among other indications, second and third trimester ultrasound is indicated for estimation of gestational age, evaluation of fetal growth, vaginal bleeding, or abdominal/pelvic pain, or evaluation of suspected fetal death, molar pregnancy, or ectopic pregnancy. Of note, ACOG recommends to use caution when estimating gestational age using third trimester ultrasound because its accuracy is only within 3-4 weeks.

We will use the date of SAB diagnosis for assigning number of days of the case event relative to vaccination and gestational age of the case event. While we considered incorporating ultrasound fetal dating and symptom onset, they have several limitations. First, there is variable capture of this information in medical records. Second, ultrasound fetal dating may be inaccurate, due to restricted fetal growth in pregnancies ending in early pregnancy loss[56]; furthermore, symptom onset may not accurately reflect onset of a miscarriage because symptoms of a normal pregnancy may overlap with that of an occurrence of a pregnancy loss. Third, related to the second point, it would likely be difficult to obtain inter-rater reliability because of the inherent challenges in capturing clinical intuition into a standard, replicable algorithm.

Among confirmed SAB cases, we will estimate pregnancy start using the date of procedure and embryo transfer (if applicable) in pregnancies conceived using in-vitro-fertilization or intrauterine insemination. Among naturally conceived pregnancies that end in miscarriage, we will use the date of the last menstrual period (LMP) to estimate pregnancy start.

Among livebirth controls, we will estimate date of pregnancy start using first or second trimester ultrasound or LMP in naturally conceived pregnancies and using date of the procedure or embryo transfer in pregnancies conceived using in-vitro-fertilization or intrauterine insemination. If ultrasound dating and LMP date are both available for naturally conceived pregnancies, we will use the LMP if the discrepancy between the expected due dates is seven days or less for first trimester ultrasounds or ten days or less for second trimester ultrasounds.[55] If more than one ultrasound is available, we will use the earliest performed. If numbers permit, we will also consider conducting a sensitivity analysis restricted to matched case and control sets where LMP was used to estimate pregnancy start.

IV. ANALYSIS

A. ANALYSIS FOR PRIMARY OBJECTIVES (OBJECTIVES 1-3)

In Primary Objective 1, we will determine the feasibility of using claims data to identify potential cases for the proposed study. We will examine the positive predictive value of claims codes for SAB, using chart review as the "gold standard". We will estimate the positive predictive value (i.e., chart confirmed SAB cases divided by all potential SAB cases identified via claims data) overall, by maternal age group (18-24, 25-29, 30-34, and 35-39 years), and by claims codes (i.e., specific ICD9 or CPT code).

In addition to validating case status in Primary Objective 1, we will estimate the proportion of cases that need to be discarded because vaccination occurs prior to the period of interest (i.e., prior to -4 weeks gestation). We will also identify the optimal look-back period for vaccine codes in relation to SAB codes in electronic data to minimize the number of cases that need to be discarded because vaccination occurred before -4 weeks gestation. To accomplish this, we will tabulate the proportion of excluded cases due to this reason by days between vaccine and SAB codes in electronic data.

In Primary Objective 2, we will examine the accuracy of gestational age data in claims and in birth certificate data for the purposes of identifying pregnancy start among live delivery controls, who will be matched to chart-confirmed cases. We will estimate the proportion of controls that must be discarded because their chart-confirmed pregnancy start date is not within the pre-specified number of days from the case date. We will estimate the proportion of controls that must be discarded because their vaccination is determined via chart review to occur after the case's gestational age at SAB. We will also examine whether the proportion of discarded controls due to each of these two reasons differs by whether birth certificates or claims data were used to estimate pregnancy start date in electronic data. Finally, we will describe the distribution of matched case-control pairs by difference in pregnancy start date in cases and controls. We will stratify by whether birth certificates or claims data were used to estimate gestational age.

In Primary Objective 3, we will determine the accuracy of claims data for matching potential cases and controls on potential confounders. We will determine the positive predictive value in cases and controls for each of the confounders matched upon. We will also determine the proportion of matched case-control pairs that have concordant status in chart data for each matching factor (i.e., confounder).

B. ANALYTIC PLAN FOR CASE-TIME-CONTROL DESIGN (PILOT OBJECTIVES 4-5)

For the case-time-control design, conditional logistic regression stratified by case:control set will be conducted. The use of conditional logistic regression, in contrast to standard logistic regression, will allow each matched case:control set to have a different odds ratio for time trend in exposure without specifying its function in the model. The outcome will be the probability that an individual's vaccination occurred in the risk interval (1=yes, vaccinated in risk interval; 0=no, vaccinated in control interval); the independent variable will be case vs. control status (1=case; 0=control), with the corresponding coefficient estimating the final odds ratio estimate, adjusted for time trend in exposure. Where

applicable, we will also adjust for time-varying confounders not matched upon by including terms in the model.

C. ANALYTIC PLAN FOR TEMPORAL SCANS (PILOT OBJECTIVES 6-8)

In exploratory analyses, we will use the temporal scan statistic to (1) evaluate whether there is a particular time period after vaccination during which there is an increased risk of SAB (Pilot Objective 6) and (2) evaluate whether there is a particular gestational period during which vaccination increases the risk of SAB (Pilot Objective 7), without defining the risk interval a priori. In Pilot Objective 8, we will also use 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. For example, an increased risk of SAB may occur in the 1-14 days following TIV only if vaccination occurs between 4-6 weeks after pregnancy start. The advantage of a scan statistic is that it is not necessary to define the risk interval a priori, which is important since the plausible period of risk following vaccination is not well known. Furthermore, an advantage is that the scan statistic is able to evaluate multiple overlapping time windows, adjusting statistical analyses for the multiple testing inherent in the risk intervals being evaluated.

We will compare the timing of vaccination among vaccinated cases to that among vaccinated controls using a Bernoulli model. For each location and size of the scanning window, the alternative hypothesis is that there is an elevated risk within the risk interval as compared to outside. For the Bernoulli model the likelihood function is the following, where C is the total number of cases, c is the observed number of cases within the window, n is the total number of cases and controls within the window, N is the combined total number of cases and controls in the data set, and $I\left(\frac{c}{n} \geq \frac{C-c}{N-n}\right)$ is an indicator equal to 1 when the window has more cases than expected under the null-hypothesis and 0 otherwise.

$$\left(\frac{c}{n}\right)^{c}\left(\frac{n-c}{n}\right)^{n-c}\left(\frac{C-c}{N-n}\right)^{C-c}\left(\frac{(N-n)-(C-c)}{N-n}\right)^{(N-n)-(C-c)} I\left(\frac{c}{n} \geq \frac{C-c}{N-n}\right)$$

The likelihood ratio (i.e., the test statistic) for each window location and size will be computed. The window with the maximum likelihood ratio will be the most likely cluster and the least likely to have occurred by chance.

Because analytical formulas are not available to estimate the variances of scan statistics, we will use Monte Carlo simulation to obtain p-values.[57] First 9999 random data sets will be generated under the null hypothesis. The null hypothesis is that the vaccination times of each case and its matched control are interchangeable and independent of the case/control status. Therefore, conditioned on the two vaccination times in each matched pair, we will randomly assign one of the two vaccination times to the case and the other to the control for each data set. For each random data set, we will calculate the most likely cluster in the same way as for the real data. The Monte Carlo p-value for the cluster in the real data set will then be calculated using the formula p= R / (1 + number of simulations) = R / (10,000), where R is the rank of the maximum likelihood from the real data set. For example, if there were only 17 random data sets with a maximum likelihood larger than the maximum likelihood from the real data set, then R=18 and p=0.0018. The calculations will be performed using SAS and the free SaTScan software for the spatial and space-time scan statistics (www.satscan.org).

For each scan statistic analysis, the result reported will be the start and end time of the most likely cluster, its p-value and it observed relative risk. However, one limitation of calculating the relative risk is that it may be overestimated if the scan is underpowered.

V. STRENGTHS AND LIMITATIONS

A. STRENGTHS

A marked strength of this proposal is that it only includes vaccinated individuals, avoiding misclassification of exposure due to receipt of influenza vaccine in non-traditional settings, thereby not appearing in claims or IIS data. Only including vaccinated individuals also avoids confounding by indication, which might occur if vaccinated and unvaccinated individuals differ by underlying comorbidities associated with risk of SAB. The use of medical record to assign gestational age will further reduce the possibility for misclassification of timing of exposure. This study design also adjusts for potential confounding by gestational age and calendar time, which may affect both timing of vaccination and risk of SAB, via matching and the use of conditional logistic regression. By requiring chart-confirmation of SAB and date of SAB onset, misclassification of outcome will be mitigated. Importantly, the use of temporal scans for exploring whether SAB may be related to timing of vaccination, gestational age at vaccination, or both, is novel. In particular, temporal scans are a useful tool for studying pregnancy-related adverse events because their pathophysiology is not well understood, thus making it difficult to identify the appropriate risk interval before conducting the analysis. The current protocol will serve as a test case and help to develop the infrastructure and methods for surveillance of pregnancy-related adverse events following vaccination.

B. LIMITATIONS

Foremost, we will have limited power to detect small or modest effect sizes in this feasibility study. For example, our target sample size of 100 cases and 100 controls corresponds to approximately 80% power to detect a relative risk of 2.4 or above for the pilot objective of examining whether there is an elevated risk with exposure during the risk interval of 2-6 weeks gestation. Of note, this power calculation may be somewhat optimistic if we obtain fewer charts than originally anticipated or if a significant portion of cases or controls do not meet study inclusion criteria (e.g., not vaccinated during the period of interest), or depending on the distribution of cases and controls in 3 different gestational age risk periods. Our power calculation may also be an overestimate if our assumptions used to calculate power, such as the gestational age distribution of SAB or the gestational distribution of vaccination among controls (both of which are based on published literature), are incorrect. However, the primary objectives of this proof-of-concept protocol are to determine optimal algorithms for using claims and birth certificate data for pregnancy related studies. As such, this study will have the capability to inform future studies on pregnancy outcomes in the Mini-Sentinel.

The current study's case definition is limited to women seeking medical care for SAB. A large percentage of miscarriages occur without medical care, particularly in those occurring early during pregnancy. A significant proportion of these early pregnancies, particularly in the first six weeks, are unrecognized by the mother, making detection difficult. Thus, results may not be applicable to the effects of vaccines on

risk of miscarriages early during pregnancy. While we will mitigate the potential for confounding by indication by only including vaccinated individuals, the case-time-control study and temporal scans may be biased if the temporal trend of exposure in controls does not represent that of cases. This may be true if a third factor is associated both with the timing of vaccination and case vs. control status (i.e., risk of SAB). We will match on maternal age, infections, and pregnancy start to minimize confounding by gestational age or calendar time and will attempt to match on diabetes, obesity, asthma, and parity if there are adequate numbers of potential controls. However, it is not possible to match on other factors not captured fully in claims-based data, including smoking, alcohol, substance abuse, environmental toxins, and prior history of SAB. While we will collect information on a number of these risk factors in medical records and conduct descriptive analyses, they are not always systematically recorded in the medical record. The control population in this study is limited to mothers that have been linked to birth certificate data and/or infant Data Partner records. If these women differ with respect to comorbidities or healthcare utilization from the general population of live deliveries, our selected group of controls may not be representative of the temporal trend in exposure in cases. We will compare the characteristics of live delivery controls by study inclusion status and consider matching to cases on comorbidities as feasible. In addition, differential misclassification of gestational age at vaccination may occur if dating accuracy differs by case status. Finally, while the temporal scan techniques overcome the limitation of pre-defining the period of risk, they may produce overestimates of relative risk if the study is underpowered. Furthermore, no confidence intervals are produced with this technique. As such, the temporal scan should be considered exploratory.

VI. APPENDICES

Appendix 1: Summary of inclusion criteria

Cases

- 1st in 98-day SAB initially identified in claims data
- Chart-confirmation of SAB and date of diagnosis
- Information available in chart to identify pregnancy start and gestational age at SAB
- Continuous enrollment from 90 days before pregnancy start through SAB date
- TIV received between -4 weeks gestation and SAB date of onset
- No influenza vaccine received in 90 days before -4 weeks gestation

Controls

- 1st in 270-day delivery initially identified in claims data
- In reference to the matched case, same Data Partner, pregnancy start date, maternal age, and if feasible, status of other confounders
- Information available in chart to confirm gestational age
- Continuous enrollment 90 days before pregnancy start through index date (date of SAB in case)
- TIV received between -4 weeks gestation and SAB date in case
- No influenza vaccine received in 90 days before -4 weeks gestation

Appendix 2: CPT and ICD9 diagnosis codes for identifying spontaneous abortion

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	ICD9	MISSED ABORTION
634	ICD9	SPONTANEOUS ABORTION
634.0	ICD9	SPONTANEOUS AB COMP GENITAL TRACT&PELVIC INF
634.00	ICD9	UNSPEC SPONT AB COMP GENITAL TRACT&PELV INF
634.01	ICD9	INCPL SPONTANEOUS AB COMP GENITAL TRACT&PELV INF
634.02	ICD9	COMPLETE SPONT AB COMP GENITAL TRACT&PELV INF
634.1	ICD9	SPONTANEOUS AB COMP DELAY/EXCESSIVE HEMORRHAGE
634.10	ICD9	UNSPEC SPONTANEOUS AB COMP DELAY/EXCESS HEMORR
634.11	ICD9	INCPL SPONTANEOUS AB COMP DELAY/EXCESS HEMORR
634.12	ICD9	COMPLETE SPONTANEOUS AB COMP DELAY/EXCESS HEMORR
634.2	ICD9	SPONTANEOUS AB COMP DAMAGE PELVIC ORGANS/TISSUES
634.20	ICD9	UNSPEC SPONT AB COMP DAMGE PELV ORGN/TISSUES
634.21	ICD9	INCPL SPONT AB COMP DAMGE PELV ORGN/TISSUES
634.22	ICD9	COMPLETE SPONT AB COMP DAMGE PELV ORGN/TISSUES
634.3	ICD9	SPONTANEOUS ABORTION COMPLICATED RENAL FAILURE
634.30	ICD9	UNSPEC SPONTANEOUS AB COMPLICATED RENAL FAILURE
634.31	ICD9	INCOMPLETE SPONTANEOUS AB COMP RENAL FAILURE
634.32	ICD9	COMPLETE SPONTANEOUS AB COMP RENAL FAILURE
634.4	ICD9	SPONTANEOUS AB COMPLICATED METABOLIC DISORDER

Code	Type	Description
634.40	ICD9	UNSPEC SPONTANEOUS AB COMP METABOLIC DISORDER
634.41	ICD9	INCPL SPONTANEOUS AB COMP METABOLIC DISORDER
634.42	ICD9	COMPLETE SPONTANEOUS AB COMP METABOLIC DISORDER
634.5	ICD9	SPONTANEOUS ABORTION COMPLICATED BY SHOCK
634.50	ICD9	UNSPEC SPONTANEOUS ABORTION COMPLICATED SHOCK
634.51	ICD9	INCOMPLETE SPONTANEOUS AB COMPLICATED SHOCK
634.52	ICD9	COMPLETE SPONTANEOUS ABORTION COMPLICATED SHOCK
634.6	ICD9	SPONTANEOUS ABORTION COMPLICATED BY EMBOLISM
634.60	ICD9	UNSPEC SPONTANEOUS ABORTION COMPLICATED EMBOLISM
634.61	ICD9	INCOMPLETE SPONTANEOUS AB COMPLICATED EMBOLISM
634.62	ICD9	COMPLETE SPONTANEOUS AB COMPLICATED EMBOLISM
634.7	ICD9	SPONTANEOUS ABORTION W/OTHER SPEC COMPLICATIONS
634.70	ICD9	UNSPEC SPONTANEOUS AB W/OTH SPEC COMPLICATIONS
634.71	ICD9	INCOMPLETE SPONTANEOUS AB W/OTH SPEC COMPS
634.72	ICD9	COMPLETE SPONTANEOUS AB W/OTH SPEC COMPLICATIONS
634.8	ICD9	SPONTANEOUS ABORTION W/UNSPECIFIED COMPLICATION
634.80	ICD9	UNSPEC SPONTANEOUS AB W/UNSPEC COMPLICATION
634.81	ICD9	INCOMPLETE SPONTANEOUS AB W/UNSPEC COMPLICATION
634.82	ICD9	COMPLETE SPONTANEOUS AB W/UNSPEC COMPLICATION
634.9	ICD9	SPONTANEOUS AB WITHOUT MENTION COMPLICATION
634.90	ICD9	UNSPEC SPONTANEOUS AB WITHOUT MENTION COMP
634.91	ICD9	INCOMPLETE SPONTANEOUS AB WITHOUT MENTION COMP
634.92	ICD9	COMPLETE SPONTANEOUS AB WITHOUT MENTION COMP

Appendix 3: CPT and ICD9 diagnosis and procedure codes for identifying live deliveries

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	ICD9	PLACENTA PREVIA WITHOUT HEMORRHAGE WITH DELIVERY
641.11	ICD9	HEMORRHAGE FROM PLACENTA PREVIA WITH DELIVERY
641.21	ICD9	PREMATURE SEPARATION OF PLACENTA WITH DELIVERY
641.31	ICD9	ANTPRTM HEMORR ASSOC W/COAGULAT DEFEC W/DELIV
641.81	ICD9	OTHER ANTEPARTUM HEMORRHAGE WITH DELIVERY
641.91	ICD9	UNSPECIFIED ANTEPARTUM HEMORRHAGE WITH DELIVERY

Code	Type	Description
642.01	ICD9	BENIGN ESSENTIAL HYPERTENSION WITH DELIVERY
642.02	ICD9	BEN ESSENTIAL HYPERTENSION W/DELIV W/CURRENT PPC
642.11	ICD9	HYPERTENSION SEC TO RENAL DISEASE WITH DELIVERY
642.12	ICD9	HTN SEC RENAL DISEASE W/DELIV W/CURRENT PP COMPL
642.21	ICD9	OTHER PRE-EXISTING HYPERTENSION WITH DELIVERY
642.22	ICD9	OTH PRE-EXISTING HTN W/DELIV W/CURRENT PP COMPL
642.31	ICD9	TRANSIENT HYPERTENSION OF PREGNANCY W/DELIVERY
642.32	ICD9	TRANSIENT HTN PG W/DELIV W/CURRENT PP COMPL
642.41	ICD9	MILD OR UNSPECIFIED PRE-ECLAMPSIA WITH DELIVERY
642.42	ICD9	MILD/UNSPEC PRE-ECLAMPSIA W/DELIV W/CURRENT PPC
642.51	ICD9	SEVERE PRE-ECLAMPSIA, WITH DELIVERY
642.52	ICD9	SEVERE PRE-ECLAMPSIA W/DELIVERY W/CURRENT PPC
642.61	ICD9	ECLAMPSIA, WITH DELIVERY
642.62	ICD9	ECLAMPSIA W/DELIVERY W/CURRENT PPC
642.71	ICD9	PRE-ECLAMP/ECLAMPSIA SUPERIMPS PRE-XST HTN DELIV
642.72	ICD9	PRE-ECLAMPSIA/ECLMPSIA W/PRE-EXIST HTN-DEL W/PPC
642.91	ICD9	UNSPECIFIED HYPERTENSION WITH DELIVERY
642.92	ICD9	UNSPEC HYPERTENSION W/DELIVERY W/CURRENT PPC
643.01	ICD9	MILD HYPEREMESIS GRAVIDARUM DELIVERED
643.11	ICD9	HYPEREMESIS GRAVIDA W/METAB DISTURBANCE DELIV
643.21	ICD9	LATE VOMITING OF PREGNANCY DELIVERED
643.81	ICD9	OTHER VOMITING COMPLICATING PREGNANCY DELIVERED
643.91	ICD9	UNSPECIFIED VOMITING OF PREGNANCY DELIVERED
644.21	ICD9	ERLY ONSET DELIV DELIV W/WO MENTION ANTPRTM COND
645.11	ICD9	POST TERM PG DELIV W/WO MENTION ANTPRTM COND

Code	Type	Description
645.21	ICD9	PROLONGED PG DELIV W/WO MENTION ANTPRTM COND
646.01	ICD9	PAPYRACEOUS FETUS DELIV W/WO ANTPRTM COND
646.11	ICD9	EDEMA/XCESS WT GAIN PG DELIV W/WO ANTPRTM COMP
646.12	ICD9	EDEMA/EXCESS WEIGHT GAIN PG DELIV W/CURRENT PPC
646.21	ICD9	UNSPECIFIED RENAL DISEASE PREGNANCY W/DELIVERY
646.22	ICD9	UNSPEC RENAL DISEASE PG W/DELIV W/CURRENT PPC
646.31	ICD9	PREGNANCY COMP RECUR PREG LOSS W/WO ANTPRTM COND
646.41	ICD9	PERIPHERAL NEURITIS IN PREGNANCY WITH DELIVERY
646.42	ICD9	PERIPH NEURITIS PREGNANCY W/DELIV W/CURRENT PPC
646.51	ICD9	ASYMPTOMATIC BACTERIURIA IN PREGNANCY W/DELIVERY
646.52	ICD9	ASX BACTERIURIA PG W/DELIV W/CURRENT PPC
646.61	ICD9	INFECTIONS GENITOURINARY TRACT PREGNANCY W/DELIV
646.62	ICD9	INFS GU TRACT PREGNANCY W/DELIV W/CURRENT PPC
646.71	ICD9	LIVER BILIARY TRACT D/O PREG DEL W/WO ANTPRTM
646.81	ICD9	OTHER SPEC COMPLICATION PREGNANCY W/DELIVERY
646.82	ICD9	OTH SPEC COMPS PREGNANCY W/DELIV W/CURRENT PPC
646.91	ICD9	UNSPECIFIED COMPLICATION OF PREGNANCY W/DELIVERY
647.01	ICD9	MATERNAL SYPHILIS COMP PREGNANCY W/DELIVERY
647.02	ICD9	MTRN SYPHILIS COMP PG W/DELIV W/CURRENT PPC
647.11	ICD9	MATERNAL GONORRHEA WITH DELIVERY
647.12	ICD9	MATERNAL GONORRHEA W/DELIVERY W/CURRENT PPC
647.21	ICD9	OTHER MATERNAL VENEREAL DISEASES WITH DELIVERY
647.22	ICD9	OTH MATERNAL VENEREAL DZ W/DELIV W/CURRENT PPC
647.31	ICD9	MATERNAL TUBERCULOSIS WITH DELIVERY
647.32	ICD9	MATERNAL TUBERCULOSIS W/DELIVERY W/CURRENT PPC

Code	Type	Description
647.41	ICD9	MATERNAL MALARIA WITH DELIVERY
647.42	ICD9	MATERNAL MALARIA W/DELIVERY W/CURRENT PPC
647.51	ICD9	MATERNAL RUBELLA WITH DELIVERY
647.52	ICD9	MATERNAL RUBELLA W/DELIVERY W/CURRENT PPC
647.61	ICD9	OTHER MATERNAL VIRAL DISEASE WITH DELIVERY
647.62	ICD9	OTH MATERNAL VIRAL DISEASE W/DELIV W/CURRENT PPC
647.81	ICD9	OTH SPEC MATERNAL INF&PARASITIC DISEASE W/DELIV
647.82	ICD9	OTH SPEC MTRN INF&PARASITIC DZ DELIV W/CURR PPC
647.91	ICD9	UNSPEC MATERNAL INFECTION/INFESTATION W/DELIVERY
647.92	ICD9	UNSPEC MATERNAL INF/INFEST W/DELIV W/CURRENT PPC
648.01	ICD9	MATERNAL DIABETES MELLITUS WITH DELIVERY
648.02	ICD9	MATERNAL DM W/DELIVERY W/CURRENT PPC
648.11	ICD9	MTRN THYROID DYSF DELIV W/WO ANTPRTM COND
648.12	ICD9	MATERNAL THYROID DYSF W/DELIV W/CURRENT PPC
648.21	ICD9	MATERNAL ANEMIA, WITH DELIVERY
648.22	ICD9	MATERNAL ANEMIA W/DELIVERY W/CURRENT PPC
648.31	ICD9	MATERNAL DRUG DEPENDENCE WITH DELIVERY
648.32	ICD9	MATERNAL DRUG DEPENDENCE W/DELIV W/CURRENT PPC
648.41	ICD9	MATERNAL MENTAL DISORDERS WITH DELIVERY
648.42	ICD9	MATERNAL MENTAL DISORDERS W/DELIV W/CURRENT PPC
648.51	ICD9	MATERNAL CONGENITAL CV DISORDERS W/DELIVERY
648.52	ICD9	MATERNAL CONGEN CV D/O W/DELIV W/CURRENT PPC
648.61	ICD9	OTH MATERNAL CARDIOVASCULAR DISEASES W/DELIVERY
648.62	ICD9	OTH MATERNAL CV DISEASES W/DELIV W/CURRENT PPC
648.71	ICD9	BN&JNT D/O MAT BACK PELVIS&LW LMB W/DEL

Code	Type	Description
648.72	ICD9	BN&JNT D/O MAT BACK PELV&LW LMB W/DEL W/PP COMPL
648.81	ICD9	ABNORMAL MATERNAL GLUCOSE TOLERANCE W/DELIVERY
648.82	ICD9	ABNORMAL MTRN GLU TOLERNC W/DELIV W/CURRENT PPC
648.91	ICD9	OTH CURRENT MATERNAL CCE W/DELIVERY
648.92	ICD9	OTH CURRENT MATERNAL CCE W/DEL W/CURRNT PP COMPL
649.01	ICD9	TOBACCO USE D/O COMP PG CHILDBIRTH/PP DELIVERED
649.02	ICD9	TOB USE D/O COMP PG BIRTH/PP DEL W/MEN PP COMP
649.11	ICD9	OBESITY COMP PG CHILDBIRTH/THE PP DELIVERED
649.12	ICD9	OBESITY COMP PG CHILDBIRTH/THE PP DEL W/PP COMP
649.21	ICD9	BARIATRIC SURG STS COMP PG BIRTH/PP DELIVERED
649.22	ICD9	BARIATRC SURG STS COMP PG BIRTH/PP DEL W/PP COMP
649.31	ICD9	COAGULATION DEFECTS COMP PG BIRTH/THE PP DEL
649.32	ICD9	COAGULATION DEFEC COMP PG BIRTH/PP DEL W/PP COMP
649.41	ICD9	EPILEPSY COMP PG CHILDBIRTH/THE PP DELIVERED
649.42	ICD9	EPILEPSY COMP PG CHILDBIRTH/THE PP DEL W/PP COMP
649.51	ICD9	SPOTTING COMPLICATING PREGNANCY DELIVERED
649.61	ICD9	UTERINE SIZE DATE DISCREPANCY DELIVERED
649.62	ICD9	UTERINE SZ DATE DISCREPANCY DEL W/MEN PP COMPL
649.71	ICD9	CERVICAL SHORTENING DELIVERED W/WO ANTPRTM COND
649.81	ICD9	ONSET LABR AFTR 37 BEFOR 39 CMPL WK GEST C/S DEL
649.82	ICD9	ONSET LABR AFTR 37 BFOR 39 WK GEST C/S DEL W/PPC
650	ICD9	NORMAL DELIVERY
651.01	ICD9	TWIN PREGNANCY, DELIVERED
651.11	ICD9	TRIPLET PREGNANCY, DELIVERED
651.21	ICD9	QUADRUPLET PREGNANCY, DELIVERED

Code	Type	Description
651.31	ICD9	TWIN PG W/FETAL LOSS&RETENTION 1 FETUS DELIV
651.41	ICD9	TRIPLET PG W/FETAL LOSS&RETENTION 1/MORE DELIV
651.51	ICD9	QUADRUPLET PG W/FETAL LOSS&RETN 1/MORE DELIV
651.61	ICD9	OTH MX PG W/FETAL LOSS&RETN 1/MORE FETUS DELIV
651.71	ICD9	MX GEST FLW ELCTV FETAL RDUC DEL W/WO AP COND
651.81	ICD9	OTHER SPECIFIED MULTIPLE GESTATION DELIVERED
651.91	ICD9	UNSPECIFIED MULTIPLE GESTATION DELIVERED
652.01	ICD9	UNSTABLE LIE OF FETUS, DELIVERED
652.11	ICD9	BREECH/ MALPRSATION CONVRT CEPHALIC PRSATION DEL
652.21	ICD9	BREECH PRESENTATION W/O MENTION VERSION DELIV
652.31	ICD9	TRANSVERSE/OBLIQUE FETAL PRESENTATION DELIVERED
652.41	ICD9	FETAL FACE OR BROW PRESENTATION DELIVERED
652.51	ICD9	HIGH FETAL HEAD AT TERM, DELIVERED
652.61	ICD9	MX GEST W/MALPRESENTATION 1 FETUS/MORE DELIV
652.71	ICD9	PROLAPSED ARM OF FETUS, DELIVERED
652.81	ICD9	OTH SPEC MALPOSITION/MALPRESENTATION FETUS DELIV
652.91	ICD9	UNSPEC MALPOSITION/MALPRESENTATION FETUS DELIV
653.01	ICD9	MAJOR ABNORM BONY PELVIS NOT FURTHER SPEC DELIV
653.11	ICD9	GENERALLY CONTRACTED PELVIS PREGNANCY DELIVERED
653.21	ICD9	INLET CONTRACTION OF PELVIS PREGNANCY DELIVERED
653.31	ICD9	OUTLET CONTRACTION OF PELVIS PREGNANCY DELIVERED
653.41	ICD9	FETOPELVIC DISPROPORTION, DELIVERED
653.51	ICD9	UNUSUALLY LARGE FETUS CAUS DISPROPRTN DELIVERED
653.61	ICD9	HYDROCEPHALIC FETUS CAUSING DISPROPRTN DELIVERED
653.71	ICD9	OTH FETAL ABNORM CAUSING DISPROPRTN DELIVERED

Code	Type	Description
653.81	ICD9	FETAL DISPROPORTION OF OTHER ORIGIN DELIVERED
653.91	ICD9	UNSPECIFIED FETAL DISPROPORTION DELIVERED
654.01	ICD9	CONGENITAL ABNORM PREGNANT UTERUS DELIVERED
654.02	ICD9	CONGEN ABNORM PG UTERUS DELIV W/MENTION PPC
654.11	ICD9	TUMORS OF BODY OF UTERUS, DELIVERED
654.12	ICD9	TUMORS BODY UTERUS DELIVERED W/MENTION PPC
654.21	ICD9	PREV C/S DELIV DELIV W/WO MENTION ANTPRTM COND
654.31	ICD9	RETROVERTED&INCARCERATED GRAVID UTERUS DELIVERED
654.32	ICD9	RETROVRT&INCARCERAT GRAVD UTRUS DELIV W/ PPC
654.41	ICD9	OTH ABN SHAPE/PSTN GRAVD UTRUS&NGHBR STRCT DELIV
654.42	ICD9	OTH ABN SHAPE/POS GRAVID UTERUS DEL W/PP COMPL
654.51	ICD9	CERVICAL INCOMPETENCE, DELIVERED
654.52	ICD9	CERVICAL INCOMPETENCE DELIVERED W/MENTION PPC
654.61	ICD9	OTH CONGENITAL/ACQUIRED ABNORM CERVIX W/DELIVERY
654.62	ICD9	OTH CONGEN/ACQ ABNORM CERV DELIV W/MENTION PPC
654.71	ICD9	CONGENITAL/ACQUIRED ABNORM VAGINA W/DELIVERY
654.72	ICD9	CONGEN/ACQ ABNORM VAGINA DELIVERED W/MENTION PPC
654.81	ICD9	CONGENITAL/ACQUIRED ABNORMALITY VULVA W/DELIVERY
654.82	ICD9	CONGEN/ACQ ABNORM VULVA DELIVERED W/MENTION PPC
654.91	ICD9	OTH&UNSPEC ABNORM ORGN&SOFT TISSUES PELV W/DELIV
654.92	ICD9	OTH&UNS ABN ORGN&SOFT TISS PELVIS DEL W/PP COMPL
655.01	ICD9	CNTRL NERV SYS MALFORMATION IN FETUS W/DELIVERY
655.11	ICD9	CHROMOSM ABNORM FETUS AFFECT MGMT MOTH W/DELIV
655.21	ICD9	HEREDITARY DZ POSS AFFECT FETUS MGMT MOM W/DEL
655.31	ICD9	SPCT DAMGE FETUS VIRL DZ MOM AFFCT MGMT MOM DEL

Code	Type	Description
655.41	ICD9	SPCT DAMGE FETUS OTH DZ MOM AFFCT MGMT MOM DEL
655.51	ICD9	SPCT DAMGE FETUS FROM RX AFFECT MGMT MOTH DELIV
655.61	ICD9	SPCT DAMGE FETUS FROM RAD AFFECT MGMT MOTH DELIV
655.71	ICD9	DECR FETAL MOVEMENTS AFFECT MGMT MOTH DELIV
655.81	ICD9	OTH KNOWN/SPCT FETAL ABNORM NEC MGMT MOTH DELIV
655.91	ICD9	UNSPEC FETAL ABNORM AFFECT MANAGEMENT MOTH DELIV
656.01	ICD9	FETAL-MATERNAL HEMORRHAGE WITH DELIVERY
656.11	ICD9	RHESUS ISOIMMUNIZATION AFFECT MGMT MOTH DELIV
656.21	ICD9	ISOIMMU OTH&UNS BLD-GRP INCOMPAT MGMT MOTH DELIV
656.31	ICD9	FETAL DISTRESS AFFECT MANAGEMENT MOTH DELIVERED
656.41	ICD9	INTRAUTERINE DEATH AFFECT MANAGEMENT MOTH DELIV
656.51	ICD9	POOR FETAL GROWTH AFFECT MANAGEMENT MOTH DELIV
656.61	ICD9	EXCESS FETAL GROWTH AFFECT MANAGEMENT MOTH DELIV
656.71	ICD9	OTH PLACENTAL CONDS AFFECT MANAGEMENT MOTH DELIV
656.81	ICD9	OTH SPEC FETAL&PLACNTL PROBS MGMT MOTH DELIV
656.91	ICD9	UNSPEC FETAL&PLACNTL PROB AFFECT MGMT MOTH DELIV
657.01	ICD9	POLYHYDRAMNIOS, WITH DELIVERY
658.01	ICD9	OLIGOHYDRAMNIOS, DELIVERED
658.11	ICD9	PREMATURE RUPTURE MEMBRANES PREGNANCY DELIVERED
658.21	ICD9	DELAY DELIV AFTER SPONT/UNSPEC RUP MEMB DELIV
658.31	ICD9	DELAY DELIV AFTER ARTFICL RUPTURE MEMB DELIV
658.41	ICD9	INFECTION OF AMNIOTIC CAVITY DELIVERED
658.81	ICD9	OTH PROBLEM ASSOC W/AMNIOTIC CAVITY&MEMB DELIV
658.91	ICD9	UNSPEC PROB ASSOC W/AMNIOTIC CAVITY&MEMB DELIV
659.01	ICD9	FAILED MECHANICAL INDUCTION OF LABOR DELIVERED

Code	Type	Description
659.11	ICD9	FAILED MEDICAL/UNSPEC INDUCTION LABOR DELIVERED
659.21	ICD9	UNSPEC MATERNAL PYREXIA DURING LABOR DELIVERED
659.31	ICD9	GENERALIZED INFECTION DURING LABOR DELIVERED
659.41	ICD9	GRAND MULTIPARITY DELIV W/WO ANTPRTM COND
659.51	ICD9	ELDERLY PRIMIGRAVIDA, DELIVERED
659.61	ICD9	ELDER MULTIGRAVIDA DELIV W/MENTION ANTPRTM COND
659.71	ICD9	ABN FETL HRT RATE/RHYTHM DELIV W/WO ANTPRTM COND
659.81	ICD9	OTH SPEC INDICAT CARE/INTERVEN RELATED L&D DELIV
659.91	ICD9	UNSPEC INDICAT CARE/INTERVEN RELATED L&D DELIV
660.01	ICD9	OBST CAUS MALPOSITION FETUS@ONSET LABR DELIV
660.11	ICD9	OBSTRUCTION BY BONY PELVIS DURING L&D DELIVERED
660.21	ICD9	OBST ABN PELV SFT TISS DUR LABRAND DELIV DELIV
660.31	ICD9	DEEP TRNSVRSE ARREST-OCCIPITOPOSTER-DEL-UNS APC
660.41	ICD9	SHOULDER DYSTOCIA DURING LABOR&DELIVER DELIVERED
660.51	ICD9	LOCKED TWINS, DELIVERED
660.61	ICD9	UNSPECIFIED FAILED TRIAL OF LABOR DELIVERED
660.71	ICD9	UNSPEC FAILED FORCEPS/VACUUM EXTRACTOR DELIVERED
660.81	ICD9	OTHER CAUSES OF OBSTRUCTED LABOR DELIVERED
660.91	ICD9	UNSPECIFIED OBSTRUCTED LABOR WITH DELIVERY
661.01	ICD9	PRIMARY UTERINE INERTIA WITH DELIVERY
661.11	ICD9	SECONDARY UTERINE INERTIA WITH DELIVERY
661.21	ICD9	OTHER AND UNSPECIFIED UTERINE INERTIA W/DELIVERY
661.31	ICD9	PRECIPITATE LABOR, WITH DELIVERY
661.41	ICD9	HYPERTON INCOORD/PROLONG UTERINE CONTRACS DELIV
661.91	ICD9	UNSPECIFIED ABNORMALITY OF LABOR WITH DELIVERY

Code	Type	Description
662.01	ICD9	PROLONGED FIRST STAGE OF LABOR DELIVERED
662.11	ICD9	UNSPECIFIED PROLONGED LABOR DELIVERED
662.21	ICD9	PROLONGED SECOND STAGE OF LABOR DELIVERED
662.31	ICD9	DELAYED DELIVERY 2 TWIN TRIPLET ETC DELIVERED
663.01	ICD9	PROLAPSE OF CORD COMPLICATING L&D DELIVERED
663.11	ICD9	CORD AROUND NECK W/COMPRS COMP L&D DELIVERED
663.21	ICD9	OTH&UNSPEC CORD ENTANGL W/COMPRS COMP L&D DELIV
663.31	ICD9	OTH&UNS CRD ENTANGL W/O COMPRS COMP L&D DELIV
663.41	ICD9	SHORT CORD COMPLICATING L&D DELIVERED
663.51	ICD9	VASA PREVIA COMPLICATING L&D DELIVERED
663.61	ICD9	VASCULAR LESIONS CORD COMPLICATING L&D DELIVERED
663.81	ICD9	OTH UMBILICAL CORD COMPS DURING L&D DELIVERED
663.91	ICD9	UNSPEC UMBILICAL CORD COMP DURING L&D DELIVERED
664.01	ICD9	FIRST-DEGREE PERINEAL LACERATION WITH DELIVERY
664.11	ICD9	SECOND-DEGREE PERINEAL LACERATION WITH DELIVERY
664.21	ICD9	THIRD-DEGREE PERINEAL LACERATION WITH DELIVERY
664.31	ICD9	FOURTH-DEGREE PERINEAL LACERATION WITH DELIVERY
664.41	ICD9	UNSPECIFIED PERINEAL LACERATION WITH DELIVERY
664.51	ICD9	VULVAR AND PERINEAL HEMATOMA WITH DELIVERY
664.61	ICD9	ANAL SPHINCT TEAR COMP DELIVERY W OR W/O AP COND
664.81	ICD9	OTHER SPECIFIED TRAUMA PERINEUM&VULVA W/DELIVERY
664.91	ICD9	UNSPECIFIED TRAUMA TO PERINEUM&VULVA W/DELIVERY
665.01	ICD9	RUPTURE UTERUS BEFORE ONSET LABOR W/DELIVERY
665.11	ICD9	RUPTURE OF UTERUS DURING LABOR WITH DELIVERY
665.22	ICD9	INVERSION UTERUS DELIVERED W/PPC

Code	Type	Description
665.31	ICD9	LACERATION OF CERVIX, WITH DELIVERY
665.41	ICD9	HIGH VAGINAL LACERATION WITH DELIVERY
665.51	ICD9	OTHER INJURY TO PELVIC ORGANS WITH DELIVERY
665.61	ICD9	DAMAGE TO PELVIC JOINTS AND LIGAMENTS W/DELIVERY
665.71	ICD9	PELVIC HEMATOMA, WITH DELIVERY
665.72	ICD9	PELVIC HEMATOMA DELIVERED W/PPC
665.81	ICD9	OTHER SPECIFIED OBSTETRICAL TRAUMA WITH DELIVERY
665.82	ICD9	OTH SPEC OBSTETRICAL TRAUMA DELIV W/POSTPARTUM
665.91	ICD9	UNSPECIFIED OBSTETRICAL TRAUMA WITH DELIVERY
665.92	ICD9	UNSPECIFIED OBSTETRICAL TRAUMA DELIVERED W/PPC
666.02	ICD9	THIRD-STAGE POSTPARTUM HEMORRHAGE WITH DELIVERY
666.12	ICD9	OTHER IMMEDIATE POSTPARTUM HEMORRHAGE W/DELIVERY
666.22	ICD9	DELAYED AND SEC POSTPARTUM HEMORRHAGE W/DELIVERY
666.32	ICD9	POSTPARTUM COAGULATION DEFECTS WITH DELIVERY
667.02	ICD9	RETN PLACNTA W/O HEMORR DEL W/MENTION PP COMPL
667.12	ICD9	RETN PORTIONS PLCNTA/MEMB W/O HEMORR DEL W/COMPL
668.01	ICD9	PULM COMPL ADMIN ANES/OTH SEDATION L&D DEL
668.02	ICD9	PULM COMPL ADMIN ANES/OTH SEDAT DEL W/PP COMPL
668.11	ICD9	CARD COMPL ADMIN ANES/OTH SEDATION L&D DEL
668.12	ICD9	CARD COMPL ADMIN ANES/SEDAT L&D-DEL W/PP COMPL
668.21	ICD9	CNA COMPL ADMIN ANES/OTH SEDATION L&D DEL
668.22	ICD9	CNA COMPL ADMIN ANES/SEDAT L&D DEL W/PP COMPL
668.81	ICD9	OTH COMPL ADMIN ANES/OTH SEDATION L&D DEL
668.82	ICD9	OTH COMPL ADMN ANES/OTH SEDAT DEL W/PP COMPL
668.91	ICD9	UNS COMPL ADMIN ANES/OTH SEDATION L&D DEL

Code	Type	Description
668.92	ICD9	UNS COMP ADMN ANESTHESIA/OTH SEDAT L&D DEL W/PPC
669.01	ICD9	MTRN DISTRESS W/DELIV W/WO MENTION ANTPRTM COND
669.02	ICD9	MATERNAL DISTRESS W/DELIVERY W/MENTION PPC
669.11	ICD9	SHOCK DURING/FOLLOW L&D W/DEL W/W/O ANTPRTM COND
669.12	ICD9	SHOCK DURING/FOLLOWING L&D W/DELIV W/MENTION PPC
669.21	ICD9	MAT HYPOTENSION SYND W/DEL W/W/O ANTPRTM COND
669.22	ICD9	MATERNAL HYPOTENS SYNDROME W/DELIV W/MENTION PPC
669.32	ICD9	ACUTE KIDNEY FAILURE FOLLOW L&D DELIV W/MEN PPC
669.41	ICD9	OTH COMPL OB SURG&PROC DELIV W/WO ANTPRTM COND
669.42	ICD9	OTH COMPL OB SURG&PROC W/DEL W/MENTION PP COMPL
669.51	ICD9	FORCEPS/EXTRACTOR DEL W/O INDICATION-DELIVERED
669.61	ICD9	BREECH XTRAC W/O INDICAT DELIV W/WO ANTPRTM COND
669.71	ICD9	C/S DELIV W/O INDICAT DELIV W/WO ANTPRTM COND
669.81	ICD9	OTH COMP L&D DELIVERED W/WO MENTION ANTPRTM COND
669.82	ICD9	OTHER COMPLICATION L&D DELIVERED W/MENTION PPC
669.91	ICD9	UNSPEC COMP L&D DELIV W/WO MENTION ANTPRTM COND
669.92	ICD9	UNSPEC COMPLICATION L&D W/DELIVERY W/MENTION PPC
670.02	ICD9	MAJOR PUERPERAL INFECTION, UNSPECIFIED, DELIVERE
670.12	ICD9	PUERPERAL ENDOMETRITIS DELIVERED W/MEN PP COMP
670.22	ICD9	PUERPERAL SEPSIS DELIVERED W/MENTION OF PP COMP
670.32	ICD9	PUERPERAL SEPTIC THROMBOPHLEBITS DEL MEN PP COMP
670.82	ICD9	OTHER MAJOR PUERPERAL INFECTION DEL MEN PP COMP
671.01	ICD9	VARICOSE VNS LEGS DELIV W/WO ANTPRTM COND
671.02	ICD9	VARICOSE VEINS LEGS W/DELIVERY W/MENTION PPC
671.11	ICD9	VARICOSE VNS VULVA&PERIN DELIV W/WO ANTPRTM COND

Code	Type	Description
671.12	ICD9	VARICOSE VEINS VULVA&PERIN W/DELIV W/MENTION PPC
671.21	ICD9	SUP THROMBOPHLEB DELIV W/WO MENTION ANTPRTM COND
671.22	ICD9	SUP THROMBOPHLEBITIS W/DELIV W/MENTION PPC
671.31	ICD9	DEEP PHLEBOTHROMBOSIS ANTEPARTUM WITH DELIVERY
671.42	ICD9	DEEP PHLEBOTHROMBOSIS POSTPARTUM WITH DELIVERY
671.51	ICD9	OTH PHLEBITIS&THROMB DELIV W/WO ANTPRTM COND
671.52	ICD9	OTH PHLEBITIS&THROMBOSIS W/DELIV W/MENTION PPC
671.81	ICD9	OTH VENOUS COMP DELIV W/WO MENTION ANTPRTM COND
671.82	ICD9	OTH VENOUS COMPLICATION W/DELIVERY W/MENTION PPC
671.91	ICD9	UNS VENOUS COMP DELIV W/WO MENTION ANTPRTM COND
671.92	ICD9	UNSPEC VENOUS COMP W/DELIVERY W/MENTION PPC
672.02	ICD9	PUERPERAL PYREXIA UNKN ORIGIN DELIV W/ PPC
673.01	ICD9	OB AIR EMBO W/DELIV W/WO MENTION ANTPRTM COND
673.02	ICD9	OBSTETRICAL AIR EMBOLISM W/DELIV W/MENTION PPC
673.11	ICD9	AMNIOTIC FLUID EMBOLISM DEL W/WO ANTEPARTUM COND
673.12	ICD9	AMNIOTIC FLUID EMBOLISM W/DELIVERY W/MENTION PPC
673.21	ICD9	OB BLD-CLOT EMBOLISM DEL W/WO ANTEPARTUM COND
673.22	ICD9	OBSTETRICAL BLOOD-CLOT EMBOLISM W/MENTION PPC
673.31	ICD9	OB PYEMIC&SEPTIC EMBOLISM DEL W/WO ANTPRTM COND
673.32	ICD9	OB PYEMIC&SEPTIC EMBOLISM DELIVERY W/PP COMPL
673.81	ICD9	OTH OB PULMARY EMBOLSIM DEL W/WO ANTEPARTUM COND
673.82	ICD9	OTH OB PULMONARY EMBO W/DELIV W/MENTION PPC
674.01	ICD9	CERBROVASC D/O DELIV W/WO MENTION ANTPRTM COND
674.02	ICD9	CEREBRVASC DISORDER W/DELIVERY W/MENTION PPC
674.12	ICD9	DISRUPTION C-SECT WOUND W/DELIVERY W/MENTION PPC

Code	Type	Description
674.22	ICD9	DISRUPTRUPT PERINL WOUND W/DEL W/PP COMPLICATON
674.32	ICD9	OTH COMP OB SURG WOUNDS W/DELIV W/MENTION PPC
674.42	ICD9	PLACENTAL POLYP W/DELIVERY W/MENTION PPC
674.51	ICD9	PERIPARTUM CARDIOMYPATH DELIV W/WO ANTPRTM COND
674.52	ICD9	PERIPARTUM CARDIOMYPATH DELIV W/MENTION PP COND
674.82	ICD9	OTH COMP PUERPERIUM W/DELIVERY W/MENTION PPC
674.92	ICD9	UNSPEC COMPS PUERPERIUM W/DELIVERY W/MENTION PPC
675.01	ICD9	INF NIPPLE W/CHLDBRTH DEL W/WO ANTEPARTUM COND
675.02	ICD9	INF NIPPLE ASSOC W/CHILDBRTH DELIV W/MENTION PPC
675.11	ICD9	ABSCESS BREAST W/CHLDBRTH DEL W/WO ANTPRTM COND
675.12	ICD9	ABSC BRST ASSOC W/CHILDBIRTH DELIV W/MENTION PPC
675.21	ICD9	NONPURULENT MASTITIS DELIV W/WO ANTPRTM COND
675.22	ICD9	NONPURULENT MASTITIS DELIVERED W/MENTION PPC
675.81	ICD9	OTH SPEC BREAST-NIPPLE INFECT ASSOC W/CB DELIVER
675.82	ICD9	OTH INF BRST&NIPPLE W/CHLDBRTH DEL W/PP COMPL
675.91	ICD9	UNS INF BRST&NIPPLE DELIV W/WO ANTPRTM COND
675.92	ICD9	UNSPEC INF BREAST&NIPPLE DELIV W/MENTION PPC
676.01	ICD9	RETRACTED NIPPLE DELIV W/WO MENTION ANTPRTM COND
676.02	ICD9	RETRACTED NIPPLE DELIVERED W/MENTION PPC
676.11	ICD9	CRACKED NIPPLE DELIV W/WO MENTION ANTPRTM COND
676.12	ICD9	CRACKED NIPPLE DELIVERED W/MENTION PPC
676.21	ICD9	ENGORGEMENT BREASTS DEL W/WO ANTEPARTUM COND
676.22	ICD9	ENGORGEMENT BREASTS DELIVERED W/MENTION PPC
676.31	ICD9	UNS D/O BREAST W/CHLDBRTH DEL W/WO ANTPRTM COND
676.32	ICD9	OTH&UNS D/O BREAST W/CHILDBIRTH DEL W/PP COMPL

Code	Type	Description
676.41	ICD9	FAILED LACTATION W/DEL W/WO MENTION ANTPRTM COND
676.42	ICD9	FAILURE LACTATION W/DELIVERY W/MENTION PPC
676.51	ICD9	SUPPRESSED LACTATION DELIV W/WO ANTPRTM COND
676.52	ICD9	SUPPRESSED LACTATION W/DELIVERY W/MENTION PPC
676.61	ICD9	GALACTORRHEA W/DELIV W/WO MENTION ANTPRTM COND
676.62	ICD9	GALACTORRHEA W/DELIVERY W/MENTION PPC
676.81	ICD9	OTH D/O LACTATION DELIV W/WO ANTPRTM COND
676.82	ICD9	OTH DISORDER LACTATION W/DELIVERY W/MENTION PPC
676.91	ICD9	UNS D/O LACTATION DELIV W/WO ANTPRTM COND
676.92	ICD9	UNSPEC DISORDER LACTATION W/DELIV W/MENTION PPC
678.01	ICD9	FETAL HEMATOLOGIC COND DELIV W/WO ANTPRTM COND
678.11	ICD9	FETAL CONJOINED TWINS DELIV W/WO ANTPRTM COND
679.01	ICD9	MATERNAL COMP FROM IU PROC DEL W/WO ANTPRTM COND
679.02	ICD9	MATERNAL COMP FROM IN UTERO PROC DEL W/PP COMP
679.11	ICD9	FETAL COMP FROM IN UTERO PROCEDURE DELIVERED
679.12	ICD9	FETAL COMP FROM IN UTERO PROC DELIVERY W/PP COMP
72	ICD9	FORCEPS VACUUM AND BREECH DELIVERY
72.0	ICD9	LOW FORCEPS OPERATION
72.1	ICD9	LOW FORCEPS OPERATION WITH EPISIOTOMY
72.2	ICD9	MID FORCEPS OPERATION
72.21	ICD9	MID FORCEPS OPERATION WITH EPISIOTOMY
72.29	ICD9	OTHER MID FORCEPS OPERATION
72.3	ICD9	HIGH FORCEPS OPERATION
72.31	ICD9	HIGH FORCEPS OPERATION WITH EPISIOTOMY
72.39	ICD9	OTHER HIGH FORCEPS OPERATION

Code	Type	Description
72.4	ICD9	FORCEPS ROTATION OF FETAL HEAD
72.5	ICD9	BREECH EXTRACTION
72.51	ICD9	PART BREECH EXTRAC W/FORCEPS AFTERCOMING HEAD
72.52	ICD9	OTHER PARTIAL BREECH EXTRACTION
72.53	ICD9	TOTAL BREECH EXTRAC W/FORCEPS AFTERCOMING HEAD
72.54	ICD9	OTHER TOTAL BREECH EXTRACTION
72.6	ICD9	FORCEPS APPLICATION TO AFTERCOMING HEAD
72.7	ICD9	VACUUM EXTRACTION
72.71	ICD9	VACUUM EXTRACTION WITH EPISIOTOMY
72.79	ICD9	OTHER VACUUM EXTRACTION
72.8	ICD9	OTHER SPECIFIED INSTRUMENTAL DELIVERY
72.9	ICD9	UNSPECIFIED INSTRUMENTAL DELIVERY
73	ICD9	OTHER PROCEDURES INDUCING OR ASSISTING DELIVERY
73.0	ICD9	ARTIFICIAL RUPTURE OF MEMBRANES
73.01	ICD9	INDUCTION LABOR ARTIFICIAL RUPTURE MEMBRANES
73.09	ICD9	OTHER ARTIFICIAL RUPTURE OF MEMBRANES
73.1	ICD9	OTHER SURGICAL INDUCTION OF LABOR
73.2	ICD9	INTERNAL AND COMBINED VERSION AND EXTRACTION
73.21	ICD9	INTERNAL AND COMBINED VERSION WITHOUT EXTRACTION
73.22	ICD9	INTERNAL AND COMBINED VERSION WITH EXTRACTION
73.3	ICD9	FAILED FORCEPS
73.4	ICD9	MEDICAL INDUCTION OF LABOR
73.5	ICD9	MANUALLY ASSISTED DELIVERY
73.51	ICD9	MANUAL ROTATION OF FETAL HEAD
73.59	ICD9	OTHER MANUALLY ASSISTED DELIVERY

Code	Type	Description
73.6	ICD9	EPISIOTOMY
73.8	ICD9	OPERATIONS ON FETUS TO FACILITATE DELIVERY
73.9	ICD9	OTHER OPERATIONS ASSISTING DELIVERY
73.91	ICD9	EXTERNAL VERSION TO ASSIST DELIVERY
73.92	ICD9	REPLACEMENT OF PROLAPSED UMBILICAL CORD
73.93	ICD9	INCISION OF CERVIX TO ASSIST DELIVERY
73.94	ICD9	PUBIOTOMY TO ASSIST DELIVERY
73.99	ICD9	OTHER OPERATIONS TO ASSIST DELIVERY
74.0	ICD9	CLASSICAL CESAREAN SECTION
74.1	ICD9	LOW CERVICAL CESAREAN SECTION
74.2	ICD9	EXTRAPERITONEAL CESAREAN SECTION
74.4	ICD9	CESAREAN SECTION OF OTHER SPECIFIED TYPE
74.9	ICD9	CESAREAN SECTION OF UNSPECIFIED TYPE
74.99	ICD9	OTHER CESAREAN SECTION OF UNSPECIFIED TYPE
763.0	ICD9	FETUS/NEWBORN AFFECTED BREECH DELIV&EXTRACTION
763.2	ICD9	FETUS OR NEWBORN AFFECTED BY FORCEPS DELIVERY
763.3	ICD9	FETUS/NEWBORN AFFECTED DELIVERY VACUUM EXTRACTOR
763.4	ICD9	FETUS OR NEWBORN AFFECTED BY CESAREAN DELIVERY
763.6	ICD9	FETUS OR NEWBORN AFFECTED PRECIPITATE DELIVERY
768.0	ICD9	FETAL DEATH D/T ASPHYX/ANOXIA BFOR LABR/UNS TIME
768.1	ICD9	FETAL DEATH FROM ASPHYXIA OR ANOXIA DURING LABOR
V27	ICD9	OUTCOME OF DELIVERY
V27.0	ICD9	OUTCOME OF DELIVERY SINGLE LIVEBORN
V27.1	ICD9	OUTCOME OF DELIVERY SINGLE STILLBORN
V27.2	ICD9	OUTCOME OF DELIVERY TWINS BOTH LIVEBORN

Code	Type	Description
V27.3	ICD9	OUTCOME DELIVERY TWINS 1 LIVEBORN& 1 STILLBORN
V27.4	ICD9	OUTCOME OF DELIVERY TWINS BOTH STILLBORN
V27.5	ICD9	OUTCOME DELIVERY OTH MULTIPLE BIRTH ALL LIVEBORN
V27.6	ICD9	OUTCOME DELIV OTH MULTIPLE BIRTH SOME LIVEBORN
V27.7	ICD9	OUTCOME DELIV OTH MULTIPLE BIRTH ALL STILLBORN
V27.9	ICD9	OUTCOME OF DELIVERY, UNSPECIFIED
V30	ICD9	SINGLE LIVEBORN
V30.0	ICD9	SINGLE LIVEBORN, BORN IN HOSPITAL
V30.00	ICD9	SINGLE LIVEBORN HOSPITAL W/O C-SECTION
V30.01	ICD9	SINGLE LIVEBORN HOSPITAL DELIV BY C-SECTION
V30.1	ICD9	SINGLE LIVEBORN BORN BEFORE ADMISSION HOSPITAL
V30.2	ICD9	SINGLE LIVEBORN BORN OUTSIDE HOSPITAL&NOT HOSP
V31	ICD9	LIVEBORN TWIN BIRTH MATE LIVEBORN
V31.0	ICD9	LIVEBORN TWIN-MATE LIVEBORN IN HOSPITAL
V31.00	ICD9	LIVEBORN TWIN-MATE LIVEBORN HOSP W/O C-SEC
V31.01	ICD9	LIVEBORN TWIN-MATE LIVEBORN HOSP C-SEC
V31.1	ICD9	LIVEBORN TWIN-MATE LIVEBORN BEFORE ADMISS
V31.2	ICD9	LIVEBORN TWIN-MATE LIVEBORN OUTSIDE HOSP
V32	ICD9	LIVEBORN TWIN- MATE STILLBORN
V32.0	ICD9	LIVEBORN TWIN-MATE STILLBORN HOSPITAL
V32.00	ICD9	LIVEBORN TWIN-MATE STILLBORN HOSP W/O C-SEC
V32.01	ICD9	LIVEBORN TWIN-MATE STILLBORN HOSPITAL C-SEC
V32.1	ICD9	LIVEBORN TWIN-MATE STILLBORN BEFORE ADMISS
V32.2	ICD9	LIVEBORN TWIN-MATE STILLB OUTSIDE HOSP&NOT HOSP
V33	ICD9	LIVEBORN TWIN UNS WHETHER MATE LIVEBORN/STILLB

Code	Type	Description
V33.0	ICD9	LIVEBORN TWIN-UNS MATE LIVEBORN/STILLB HOSP
V33.00	ICD9	LIVEB TWIN-UNS MATE LIVEB/STILLB-HOSP W/O C-SEC
V33.01	ICD9	TWIN UNS MATE STILLB/LIVEB BORN HOS DEL C/S DEL
V33.1	ICD9	LIVB TWIN-UNS MATE LIVEB/STILLB-BEFORE ADMISS
V33.2	ICD9	LIVEB TWIN-UNS MATE LIVEB/STILLB OUTSIDE HOSP
V34	ICD9	LIVEBORN OTH MULTIPLE MATES ALL LIVEBORN
V34.0	ICD9	LIVEBORN OTH MULTIPLE-MATES LIVEBORN HOSPITAL
V34.00	ICD9	OTH MX MATES ALL LIVEB BORN HOS DEL W/O C/S DEL
V34.01	ICD9	LIVEBORN OTH MX-MATES LIVEBORN HOSP C-SEC
V34.1	ICD9	LIVEBORN OTH MX-MATES LIVEBORN BEFOR ADMISSION
V34.2	ICD9	LIVEBORN OTH MX-MATES LIVEBORN OUTSIDE HOSP
V35	ICD9	LIVEBORN OTHER MULTIPLE MATES ALL STILLBORN
V35.0	ICD9	LIVEBORN OTH MX-MATES ALL STILLBORN HOSPITAL
V35.00	ICD9	LIVEBORN OTH MX-MATES STILLB HOSP W/O C-SEC
V35.01	ICD9	LIVEBORN OTH MX-MATES STILLBORN HOSP C-SEC
V35.1	ICD9	LIVEBORN OTH MX-MATES STILLB BEFORE ADMISSION
V35.2	ICD9	LIVEBORN OTH MX-MATES STILLB OUTSIDE HOSP
V36	ICD9	LIVEBORN OTH MULTIPLE-MATES LIVEBORN&STILLBORN
V36.0	ICD9	LIVEBORN OTH MX-MATES LIVEB&STILLB IN HOSPITAL
V36.00	ICD9	LIVEB OTH MX-MATES LIVEB&STILLB HOSP W/O C-SEC
V36.01	ICD9	LIVEBORN OTH MX-MATES LIVEB&STILLB HOSP C-SEC
V36.1	ICD9	LIVEB OTH MX-MATES LIVEB&STILLB BEFORE ADMISS
V36.2	ICD9	LIVEB OTH MX-MATES LIVEB&STILLB OUTSIDE HOSP
V37	ICD9	LIVEBORN OTH MX-UNS WHETHER MATES LIVEB/STILLB
V37.0	ICD9	LIVEBORN OTH MX-UNS MATES STILLB/LIVEB IN HOSP

Code	Type	Description
V37.00	ICD9	LIVEB OTH MX-UNS MATE LIVEB/STILLB-HOSP WO C-SEC
V37.01	ICD9	LIVEB OTH MX-UNS MATES LIVEB/STILLB HOSP C-SEC
V37.1	ICD9	LIVEB OTH MX-UNS MATES LIVEB/STILLB BEFOR ADMISS
V37.2	ICD9	LIVEB OTH MX-UNS MATES LIVEB/STILLB OUTSIDE HOSP
V39	ICD9	LIVEBORN UNSPEC WHETHER SINGLE TWIN/MULTIPLE
V39.0	ICD9	LIVEBORN UNSPEC SINGLE TWIN/MX BORN HOSPITAL
V39.00	ICD9	LIVEBORN UNS SINGLE TWIN/MX IN HOSP W/O C-SEC
V39.01	ICD9	LIVEBORN UNS SINGLE TWIN/MX IN HOSP C-SEC
V39.1	ICD9	LIVEBORN UNS SINGLE TWIN/MX BEFORE ADMISSION
V39.2	ICD9	LIVEBORN UNS SINGLE TWIN/MX OUTSIDE HOSP

Appendix 4: ICD9 codes used to estimate gestational age at delivery

Code	Description	Assumed gestational age at delivery in weeks	Assumed gestational age at delivery in days
765.21	Less than 24 completed weeks of gestation	24	168
765.22	24 completed weeks of gestation	24	168
765.23	25-26 completed weeks of gestation	26	182
765.24	27-28 completed weeks of gestation	28	196
765.0*	Disorders relating to extreme immaturity of infant	28	196
765.25	29-30 completed weeks gestation	30	210
765.26	31-32 completed weeks gestation	32	224
765.27	33-34 completed weeks gestation	34	238
765.28	35-36 completed weeks gestation	36	252
765.1*	Disorders related to other preterm infants	35	245
765.20	Preterm with unspecified weeks of gestation	35	245
766.21	Post-term infant	41	287
766.22	Prolonged gestation of infant	42	294

Appendix 5: ICD9 codes used for identifying confounders

Confounder	Code	Description
Fever	780.6	FEVER & OTH PHYSIOLOGIC DISTURBANCES TEMP REG
Fever	780.60	FEVER UNSPECIFIED
Fever	780.61	FEVER PRESENTING CONDITIONS CLASSIFIED ELSEWHERE
Fever	780.62	POSTPROCEDURAL FEVER
Fever	780.63	POSTVACCINATION FEVER
Gastrointestinal infection	001	CHOLERA
Gastrointestinal infection	001.0	CHOLERA DUE TO VIBRIO CHOLERAE
Gastrointestinal infection	001.1	CHOLERA DUE TO VIBRIO CHOLERAE EL TOR
Gastrointestinal infection	001.9	UNSPECIFIED CHOLERA
Gastrointestinal infection	002.0	TYPHOID FEVER
Gastrointestinal infection	002.1	PARATYPHOID FEVER A
Gastrointestinal infection	002.2	PARATYPHOID FEVER B
Gastrointestinal infection	002.3	PARATYPHOID FEVER C
Gastrointestinal infection	002.9	UNSPECIFIED PARATYPHOID FEVER
Gastrointestinal infection	003.0	SALMONELLA GASTROENTERITIS
Gastrointestinal infection	003.8	OTHER SPECIFIED SALMONELLA INFECTIONS
Gastrointestinal infection	004.0	SHIGELLA DYSENTERIAE
Gastrointestinal infection	004.1	SHIGELLA FLEXNERI
Gastrointestinal infection	004.2	SHIGELLA BOYDII
Gastrointestinal infection	004.3	SHIGELLA SONNEI
Gastrointestinal infection	004.8	OTHER SPECIFIED SHIGELLA INFECTIONS
Gastrointestinal infection	004.9	UNSPECIFIED SHIGELLOSIS
Gastrointestinal infection	005	OTHER FOOD POISONING
Gastrointestinal infection	005.0	STAPHYLOCOCCAL FOOD POISONING
Gastrointestinal infection	005.1	BOTULISM FOOD POISONING
Gastrointestinal infection	005.2	FOOD POISONING DUE TO CLOSTRIDIUM PERFRINGENS
Gastrointestinal infection	005.3	FOOD POISONING DUE TO OTHER CLOSTRIDIA
Gastrointestinal infection	005.4	FOOD POISONING DUE TO VIBRIO PARAHAEMOLYTICUS

Confounder	Code	Description
Gastrointestinal infection	005.8	OTHER BACTERIAL FOOD POISONING
Gastrointestinal infection	005.81	FOOD POISONING DUE TO VIBRIO VULNIFICUS
Gastrointestinal infection	005.89	OTHER BACTERIAL FOOD POISONING
Gastrointestinal infection	005.9	UNSPECIFIED FOOD POISONING
Gastrointestinal infection	006.0	ACUTE AMEBIC DYSENTERY WITHOUT MENTION ABSCESS
Gastrointestinal infection	006.1	CHRONIC INTEST AMEBIASIS WITHOUT MENTION ABSC
Gastrointestinal infection	006.2	AMEBIC NONDYSENTERIC COLITIS
Gastrointestinal infection	007	OTHER PROTOZOAL INTESTINAL DISEASES
Gastrointestinal infection	007.0	BALANTIDIASIS
Gastrointestinal infection	007.1	GASTROINTESTINAL INFECTIONARDIASIS
Gastrointestinal infection	007.2	COCCIDIOSIS
Gastrointestinal infection	007.3	INTESTINAL TRICHOMONIASIS
Gastrointestinal infection	007.4	CRYPTOSPORIDIOSIS
Gastrointestinal infection	007.5	CYCLOSPORIASIS
Gastrointestinal infection	007.8	OTHER SPECIFIED PROTOZOAL INTESTINAL DISEASES
Gastrointestinal infection	007.9	UNSPECIFIED PROTOZOAL INTESTINAL DISEASE
Gastrointestinal infection	008	INTESTINAL INFECTIONS DUE TO OTHER ORGANISMS
Gastrointestinal infection	008.0	INTESTINAL INFECTION DUE TO ESCHERICHIA COLI
Gastrointestinal infection	008.00	INTESTINAL INFECTION DUE TO UNSPECIFIED E COLI
Gastrointestinal infection	008.01	INTESTINAL INFECTION DUE ENTEROPATHOGENIC E COLI
Gastrointestinal infection	008.02	INTESTINAL INFECTION DUE ENTEROTOXIGENIC E COLI
Gastrointestinal infection	008.03	INTESTINAL INFECTION DUE ENTEROINVASIVE E COLI
Gastrointestinal infection	008.04	INTESTINAL INF DUE ENTEROHEMORRHAGIC E COLI
Gastrointestinal infection	008.09	INTESTINAL INF DUE OTH INTESTINAL E COLI INFS
Gastrointestinal infection	008.1	INTEST INF DUE ARIZONA GROUP PARACOLON BACILLI
Gastrointestinal infection	008.2	INTESTINAL INFECTION DUE TO AEROBACTER AEROGENES
Gastrointestinal infection	008.3	INTESTINAL INFECTIONS DUE TO PROTEUS
Gastrointestinal infection	008.4	INTESTINAL INFECTIONS DUE OTHER SPEC BACTERIA

Confounder	Code	Description
Gastrointestinal infection	008.41	INTESTINAL INFECTIONS DUE TO STAPHYLOCOCCUS
Gastrointestinal infection	008.42	INTESTINAL INFECTIONS DUE TO PSEUDOMONAS
Gastrointestinal infection	008.43	INTESTINAL INFECTIONS DUE TO CAMPYLOBACTER
Gastrointestinal infection	008.44	INTESTINAL INFS DUE YERSINIA ENTEROCOLITICA
Gastrointestinal infection	008.45	INTESTINAL INFECTIONS DUE CLOSTRIDIUM DIFFICILE
Gastrointestinal infection	008.46	INTESTINAL INFECTIONS DUE TO OTHER ANEROBES
Gastrointestinal infection	008.47	INTESTINAL INFECTIONS DUE OTH GM-NEGATIVE BACTER
Gastrointestinal infection	008.49	INTESTINAL INFECTION DUE TO OTHER ORGANISMS
Gastrointestinal infection	008.5	INTESTINAL INF DUE UNSPEC BACTERL ENTERITIS
Gastrointestinal infection	008.6	INTESTINAL INFECTION ENTERITIS DUE SPEC VIRUS
Gastrointestinal infection	008.61	INTESTINAL INFECTION ENTERITIS DUE TO ROTAVIRUS
Gastrointestinal infection	008.62	INTESTINAL INFECTION ENTERITIS DUE TO ADENOVIRUS
Gastrointestinal infection	008.63	INTESTINAL INFECTION ENTERITIS DUE NORWALK VIRUS
Gastrointestinal infection	008.64	INTEST INF ENTERITIS DUE OTH SMALL ROUND VIRUSES
Gastrointestinal infection	008.65	ENTERITIS DUE TO CALICIVIRUS
Gastrointestinal infection	008.66	INTESTINAL INFECTION ENTERITIS DUE TO ASTROVIRUS
Gastrointestinal infection	008.67	INTESTINAL INFECTION ENTERITIS DUE ENTRVRUS NEC
Gastrointestinal infection	008.69	INTESTINAL INF ENTERITIS DUE OTH VIRAL ENTERITIS
Gastrointestinal infection	008.8	INTESTINAL INFECTION DUE TO OTHER ORGANISM NEC
Gastrointestinal infection	009	ILL-DEFINED INTESTINAL INFECTIONS
Gastrointestinal infection	009.0	INFECTIOUS COLITIS ENTERITIS AND GASTROENTERITIS
Gastrointestinal infection	009.1	COLITIS ENTERIT&GASTROENTERIT INF ORIGIN
Gastrointestinal infection	009.2	INFECTIOUS DIARRHEA
Gastrointestinal infection	009.3	DIARRHEA OF PRESUMED INFECTIOUS ORIGIN
Multiparity	659.4	GRAND MULTIPARITY WITH CURRENT PREGNANCY
Multiparity	659.6	ELDERLY MULTIGRAVIDA
Multiparity	V23.3	PREGNANCY WITH GRAND MULTIPARITY
Multiparity	V23.82	SUPERVISION HIGH-RISK PG ELDER MULTIGRAVIDA

Confounder	Code	Description
Multiparity	V23.84	SUPERVISION HIGH-RISK PG YOUNG MULTIGRAVIDA
Multiparity	V61.5	MULTIPARITY
Respiratory tract infection	052.1	VARICELLA PNEUMONITIS
Respiratory tract infection	055.1	POSTMEASLES PNEUMONIA
Respiratory tract infection	073.0	ORNITHOSIS WITH PNEUMONIA
Respiratory tract infection	114.4	CHRONIC PULMONARY COCCIDIOIDOMYCOSIS
Respiratory tract infection	114.5	UNSPECIFIED PULMONARY COCCIDIOIDOMYCOSIS
Respiratory tract infection	115.05	HISTOPLASMA CAPSULATUM PNEUMONIA
Respiratory tract infection	115.15	HISTOPLASMA DUBOISII PNEUMONIA
Respiratory tract infection	115.95	UNSPECIFIED HISTOPLASMOSIS PNEUMONIA
Respiratory tract infection	130.4	PNEUMONITIS DUE TO TOXOPLASMOSIS
Respiratory tract infection	136.3	PNEUMOCYSTOSIS
Respiratory tract infection	460	ACUTE NASOPHARYNGITIS
Respiratory tract infection	461.0	ACUTE MAXILLARY SINUSITIS
Respiratory tract infection	461.1	ACUTE FRONTAL SINUSITIS
Respiratory tract infection	461.2	ACUTE ETHMOIDAL SINUSITIS
Respiratory tract infection	461.3	ACUTE SPHENOIDAL SINUSITIS
Respiratory tract infection	461.8	OTHER ACUTE SINUSITIS
Respiratory tract infection	461.9	ACUTE SINUSITIS, UNSPECIFIED
Respiratory tract infection	462	ACUTE PHARYNGITIS
Respiratory tract infection	463	ACUTE TONSILLITIS
Respiratory tract infection	464.0	ACUTE LARYNGITIS
Respiratory tract infection	464.00	ACUTE LARYNGITIS, WITHOUT MENTION OF OBSTRUCTIO
Respiratory tract infection	464.01	ACUTE LARYNGITIS, WITH OBSTRUCTION
Respiratory tract infection	464.10	ACUTE TRACHEITIS WITHOUT MENTION OF OBSTRUCTION
Respiratory tract infection	464.11	ACUTE TRACHEITIS WITH OBSTRUCTION
Respiratory tract infection	464.20	ACUTE LARYNGOTRACHEITIS W/O MENTION OBSTRUCTION
Respiratory tract infection	464.21	ACUTE LARYNGOTRACHEITIS WITH OBSTRUCTION

Confounder	Code	Description
Respiratory tract infection	464.30	ACUTE EPIGLOTTITIS WITHOUT MENTION OBSTRUCTION
Respiratory tract infection	464.31	ACUTE EPIGLOTTITIS WITH OBSTRUCTION
Respiratory tract infection	464.4	CROUP
Respiratory tract infection	464.50	UNSPEC SUPRAGLOTTIS WITHOUT MENTION OBSTRUCTION
Respiratory tract infection	464.51	UNSPECIFIED SUPRAGLOTTIS, WITH OBSTRUCTION
Respiratory tract infection	465.0	ACUTE LARYNGOPHARYNGITIS
Respiratory tract infection	465.8	ACUTE URIS OF OTHER MULTIPLE SITES
Respiratory tract infection	465.9	ACUTE URIS OF UNSPECIFIED SITE
Respiratory tract infection	466.0	ACUTE BRONCHITIS
Respiratory tract infection	466.1	ACUTE BRONCHIOLITIS
Respiratory tract infection	466.11	ACUTE BRONCHIOLITIS DUE TO RSV
Respiratory tract infection	466.19	ACUTE BRONCHIOLITIS DUE OTH INFECTIOUS ORGANISMS
Respiratory tract infection	473.0	CHRONIC MAXILLARY SINUSITIS
Respiratory tract infection	473.1	CHRONIC FRONTAL SINUSITIS
Respiratory tract infection	473.2	CHRONIC ETHMOIDAL SINUSITIS
Respiratory tract infection	473.3	CHRONIC SPHENOIDAL SINUSITIS
Respiratory tract infection	473.8	OTHER CHRONIC SINUSITIS
Respiratory tract infection	473.9	UNSPECIFIED SINUSITIS
Respiratory tract infection	474.0	CHRONIC TONSILLITIS AND ADENOIDITIS
Respiratory tract infection	474.00	CHRONIC TONSILLITIS
Respiratory tract infection	474.01	CHRONIC ADENOIDITIS
Respiratory tract infection	474.02	CHRONIC TONSILLITIS AND ADENOIDITIS
Respiratory tract infection	475	PERITONSILLAR ABSCESS
Respiratory tract infection	480.0	PNEUMONIA DUE TO ADENOVIRUS
Respiratory tract infection	480.1	PNEUMONIA DUE TO RESPIRATORY SYNCYTIAL VIRUS
Respiratory tract infection	480.2	PNEUMONIA DUE TO PARAINFLUENZA VIRUS
Respiratory tract infection	480.3	PNEUMONIA DUE TO SARS-ASSOCIATED CORONAVIRUS
Respiratory tract infection	480.8	PNEUMONIA DUE TO OTHER VIRUS NEC

Confounder	Code	Description
Respiratory tract infection	480.9	UNSPECIFIED VIRAL PNEUMONIA
Respiratory tract infection	481	PNEUMOCOCCAL PNEUMONIA
Respiratory tract infection	482.0	PNEUMONIA DUE TO KLEBSIELLA PNEUMONIAE
Respiratory tract infection	482.1	PNEUMONIA DUE TO PSEUDOMONAS
Respiratory tract infection	482.2	PNEUMONIA DUE TO HEMOPHILUS INFLUENZAE
Respiratory tract infection	482.3	PNEUMONIA DUE TO STREPTOCOCCUS
Respiratory tract infection	482.30	PNEUMONIA DUE TO UNSPECIFIED STREPTOCOCCUS
Respiratory tract infection	482.31	PNEUMONIA DUE TO STREPTOCOCCUS GROUP A
Respiratory tract infection	482.32	PNEUMONIA DUE TO STREPTOCOCCUS GROUP B
Respiratory tract infection	482.39	PNEUMONIA DUE TO OTHER STREPTOCOCCUS
Respiratory tract infection	482.4	PNEUMONIA DUE TO STAPHYLOCOCCUS
Respiratory tract infection	482.40	PNEUMONIA DUE TO STAPHYLOCOCCUS UNSPECIFIED
Respiratory tract infection	482.41	METHICILLIN SUSECPTIBLE PNEUMONIA STAPH AUREUS
Respiratory tract infection	482.42	METHICILLIN RESISTANT PNEUMONIA D/T STAPH AUREUS
Respiratory tract infection	482.49	OTHER STAPHYLOCOCCUS PNEUMONIA
Respiratory tract infection	482.8	PNEUMONIA DUE TO OTHER SPECIFIED BACTERIA
Respiratory tract infection	482.81	PNEUMONIA DUE TO ANAEROBES
Respiratory tract infection	482.82	PNEUMONIA DUE TO ESCHERICHIA COLI
Respiratory tract infection	482.83	PNEUMONIA DUE TO OTHER GRAM-NEGATIVE BACTERIA
Respiratory tract infection	482.84	LEGIONNAIRES+ DISEASE
Respiratory tract infection	482.89	PNEUMONIA DUE TO OTHER SPECIFIED BACTERIA
Respiratory tract infection	482.9	UNSPECIFIED BACTERIAL PNEUMONIA
Respiratory tract infection	483	PNEUMONIA DUE TO OTHER SPECIFIED ORGANISM
Respiratory tract infection	483.0	PNEUMONIA DUE TO MYCOPLASMA PNEUMONIAE
Respiratory tract infection	483.1	PNEUMONIA DUE TO CHLAMYDIA
Respiratory tract infection	483.8	PNEUMONIA DUE TO OTHER SPECIFIED ORGANISM
Respiratory tract infection	484.1	PNEUMONIA IN CYTOMEGALIC INCLUSION DISEASE
Respiratory tract infection	484.3	PNEUMONIA IN WHOOPING COUGH

Confounder	Code	Description
Respiratory tract infection	484.5	PNEUMONIA IN ANTHRAX
Respiratory tract infection	484.6	PNEUMONIA IN ASPERGILLOSIS
Respiratory tract infection	484.7	PNEUMONIA IN OTHER SYSTEMIC MYCOSES
Respiratory tract infection	484.8	PNEUMONIA OTH INFECTIOUS DISEASES CLASS ELSW
Respiratory tract infection	485	BRONCHOPNEUMONIA ORGANISM UNSPECIFIED
Respiratory tract infection	486	PNEUMONIA, ORGANISM UNSPECIFIED
Respiratory tract infection	487.0	INFLUENZA WITH PNEUMONIA
Respiratory tract infection	487.1	INFLUENZA WITH OTHER RESPIRATORY MANIFESTATIONS
Respiratory tract infection	487.8	INFLUENZA WITH OTHER MANIFESTATIONS
Respiratory tract infection	488	INFLUENZA D/T CERTN IDENTIFIED INFLUENZA VIRUSES
Respiratory tract infection	488.0	INFLUENZA DUE TO IDENTIFID AVIAN INFLUENZA VIRUS
Respiratory tract infection	488.01	INFLUENZA D/T ID AVIAN INFLUENZA VIRUS PNEUMONIA
Respiratory tract infection	488.02	INFLUENZA D/T ID AVIAN FLU VIRUS OTH RESP MANIF
Respiratory tract infection	488.09	INFLUENZA D/T ID AVIAN FLU VIRUS W/OTH MANIF
Respiratory tract infection	488.1	INFLUENZA D/T ID 2009 H1N1 INFLUENZA VIRUS
Respiratory tract infection	488.11	FLU D/T ID 2009 NOVEL H1N1 VIRUS W/PNEUMONIA
Respiratory tract infection	488.12	FLU D/T ID 2009 H1N1 VIRUS OTH RESP MANIF
Respiratory tract infection	488.19	FLU D/T ID 2009 H1N1 VIRUS W/OTH MANIF
Respiratory tract infection	488.8	INFLUENZA DUE TO NOVEL INFLUENZA A
Respiratory tract infection	488.81	INFLUENZA IDENT NOVEL INFLUENZA A W/PNEUMONIA
Respiratory tract infection	488.82	INFLUENZA IDENT NOVEL INFLUENZA A RESP MANIFEST
Respiratory tract infection	488.89	INFLUENZA IDENT NOVEL INFLUENZA A OTH MANIFEST
Respiratory tract infection	513.0	ABSCESS OF LUNG
Sexually transmitted infection	090	CONGENITAL SYPHILIS
Sexually transmitted infection	090.0	EARLY CONGENITAL SYPHILIS SYMPTOMATIC
Sexually transmitted infection	090.1	EARLY CONGENITAL SYPHILIS, LATENT
Sexually transmitted infection	090.2	UNSPECIFIED EARLY CONGENITAL SYPHILIS
Sexually transmitted infection	090.3	SYPHILITIC INTERSTITIAL KERATITIS

Confounder	Code	Description
Sexually transmitted infection	090.4	JUVENILE NEUROSYPHILIS
Sexually transmitted infection	090.40	UNSPECIFIED JUVENILE NEUROSYPHILIS
Sexually transmitted infection	090.41	CONGENITAL SYPHILITIC ENCEPHALITIS
Sexually transmitted infection	090.42	CONGENITAL SYPHILITIC MENINGITIS
Sexually transmitted infection	090.49	OTHER JUVENILE NEUROSYPHILIS
Sexually transmitted infection	090.5	OTHER LATE CONGENITAL SYPHILIS SYMPTOMATIC
Sexually transmitted infection	090.6	LATE CONGENITAL SYPHILIS, LATENT
Sexually transmitted infection	090.7	LATE CONGENITAL SYPHILIS UNSPECIFIED
Sexually transmitted infection	090.9	CONGENITAL SYPHILIS, UNSPECIFIED
Sexually transmitted infection	091	EARLY SYPHILIS, SYMPTOMATIC
Sexually transmitted infection	091.0	GENITAL SYPHILIS
Sexually transmitted infection	091.1	PRIMARY ANAL SYPHILIS
Sexually transmitted infection	091.2	OTHER PRIMARY SYPHILIS
Sexually transmitted infection	091.3	SECONDARY SYPHILIS OF SKIN OR MUCOUS MEMBRANES
Sexually transmitted infection	091.4	ADENOPATHY DUE TO SECONDARY SYPHILIS
Sexually transmitted infection	091.5	EARLY SYPHILIS UVEITIS DUE TO SECONDARY SYPHILIS
Sexually transmitted infection	091.50	EARLY SYPHILIS SYPHILITIC UVEITIS UNSPECIFIED
Sexually transmitted infection	091.51	EARLY SYPHILIS SYPHILITIC CHORIORETINITIS
Sexually transmitted infection	091.52	EARLY SYPHILIS SYPHILITIC IRIDOCYCLITIS
Sexually transmitted infection	091.6	EARLY SYPHILIS SEC SYPHILIS OF VISCERA AND BONE
Sexually transmitted infection	091.61	EARLY SYPHILIS SECONDARY SYPHILITIC PERIOSTITIS
Sexually transmitted infection	091.62	EARLY SYPHILIS SECONDARY SYPHILITIC HEPATITIS
Sexually transmitted infection	091.69	EARLY SYPHILIS SEC SYPHILIS OF OTHER VISCERA
Sexually transmitted infection	091.7	EARLY SYPHILIS SECONDARY SYPHILIS RELAPSE
Sexually transmitted infection	091.8	EARLY SYPHILIS OTHER FORMS OF SECONDARY SYPHILIS
Sexually transmitted infection	091.81	EARLY SYPHILIS ACUTE SYPHILITIC MENINGITIS
Sexually transmitted infection	091.82	EARLY SYPHILIS, SYPHILITIC ALOPECIA
Sexually transmitted infection	091.89	EARLY SYPHILIS OTHER FORMS OF SECONDARY SYPHILIS

Confounder	Code	Description
Sexually transmitted infection	091.9	EARLY SYPHILIS UNSPECIFIED SECONDARY SYPHILIS
Sexually transmitted infection	092	EARLY SYPHILIS, LATENT
Sexually transmitted infection	092.0	EARLY SYPH LATENT SEROLOGICAL RELAPSE AFTER TX
Sexually transmitted infection	092.9	EARLY SYPHILIS, LATENT, UNSPECIFIED
Sexually transmitted infection	093	CARDIOVASCULAR SYPHILIS
Sexually transmitted infection	093.0	ANEURYSM OF AORTA SPECIFIED AS SYPHILITIC
Sexually transmitted infection	093.1	SYPHILITIC AORTITIS
Sexually transmitted infection	093.2	SYPHILITIC ENDOCARDITIS
Sexually transmitted infection	093.20	UNSPECIFIED SYPHILITIC ENDOCARDITIS OF VALVE
Sexually transmitted infection	093.21	SYPHILITIC ENDOCARDITIS MITRAL VALVE
Sexually transmitted infection	093.22	SYPHILITIC ENDOCARDITIS AORTIC VALVE
Sexually transmitted infection	093.23	SYPHILITIC ENDOCARDITIS TRICUSPID VALVE
Sexually transmitted infection	093.24	SYPHILITIC ENDOCARDITIS PULMONARY VALVE
Sexually transmitted infection	093.8	OTHER SPECIFIED CARDIOVASCULAR SYPHILIS
Sexually transmitted infection	093.81	SYPHILITIC PERICARDITIS
Sexually transmitted infection	093.82	SYPHILITIC MYOCARDITIS
Sexually transmitted infection	093.89	OTHER SPECIFIED CARDIOVASCULAR SYPHILIS
Sexually transmitted infection	093.9	UNSPECIFIED CARDIOVASCULAR SYPHILIS
Sexually transmitted infection	094	NEUROSYPHILIS
Sexually transmitted infection	094.0	TABES DORSALIS
Sexually transmitted infection	094.1	GENERAL PARESIS
Sexually transmitted infection	094.2	SYPHILITIC MENINGITIS
Sexually transmitted infection	094.3	ASYMPTOMATIC NEUROSYPHILIS
Sexually transmitted infection	094.8	OTHER SPECIFIED NEUROSYPHILIS
Sexually transmitted infection	094.81	SYPHILITIC ENCEPHALITIS
Sexually transmitted infection	094.82	SYPHILITIC PARKINSONISM
Sexually transmitted infection	094.83	SYPHILITIC DISSEMINATED RETINOCHOROIDITIS
Sexually transmitted infection	094.84	SYPHILITIC OPTIC ATROPHY

Confounder	Code	Description
Sexually transmitted infection	094.85	SYPHILITIC RETROBULBAR NEURITIS
Sexually transmitted infection	094.86	SYPHILITIC ACOUSTIC NEURITIS
Sexually transmitted infection	094.87	SYPHILITIC RUPTURED CEREBRAL ANEURYSM
Sexually transmitted infection	094.89	OTHER SPECIFIED NEUROSYPHILIS
Sexually transmitted infection	094.9	UNSPECIFIED NEUROSYPHILIS
Sexually transmitted infection	095	OTHER FORMS OF LATE SYPHILIS WITH SYMPTOMS
Sexually transmitted infection	095.0	SYPHILITIC EPISCLERITIS
Sexually transmitted infection	095.1	SYPHILIS OF LUNG
Sexually transmitted infection	095.2	SYPHILITIC PERITONITIS
Sexually transmitted infection	095.3	SYPHILIS OF LIVER
Sexually transmitted infection	095.4	SYPHILIS OF KIDNEY
Sexually transmitted infection	095.5	SYPHILIS OF BONE
Sexually transmitted infection	095.6	SYPHILIS OF MUSCLE
Sexually transmitted infection	095.7	SYPHILIS OF SYNOVIUM TENDON AND BURSA
Sexually transmitted infection	095.8	OTHER SPECIFIED FORMS LATE SYMPTOMATIC SYPHILIS
Sexually transmitted infection	095.9	UNSPECIFIED LATE SYMPTOMATIC SYPHILIS
Sexually transmitted infection	096	LATE SYPHILIS, LATENT
Sexually transmitted infection	097	OTHER AND UNSPECIFIED SYPHILIS
Sexually transmitted infection	097.0	UNSPECIFIED LATE SYPHILIS
Sexually transmitted infection	097.1	UNSPECIFIED LATENT SYPHILIS
Sexually transmitted infection	097.9	UNSPECIFIED SYPHILIS
Sexually transmitted infection	098	GONOCOCCAL INFECTIONS
Sexually transmitted infection	098.0	GONOCOCCAL INFECTION LOWER GENITOURINARY TRACT
Sexually transmitted infection	098.10	GONOCOCCAL INFECTION UPPER GU TRACT SITE UNSPEC
Sexually transmitted infection	098.11	GONOCOCCAL CYSTITIS
Sexually transmitted infection	098.12	GONOCOCCAL PROSTATITIS
Sexually transmitted infection	098.13	GONOCOCCAL EPIDIDYMO-ORCHITIS
Sexually transmitted infection	098.14	GONOCOCCAL SEMINAL VESICULITIS

Confounder	Code	Description
Sexually transmitted infection	098.15	GONOCOCCAL CERVICITIS
Sexually transmitted infection	098.16	GONOCOCCAL ENDOMETRITIS
Sexually transmitted infection	098.17	GONOCOCCAL SALPINGITIS SPECIFIED AS ACUTE
Sexually transmitted infection	098.19	OTH GONOCOCCAL INFECTIONS UPPER GU TRACT
Sexually transmitted infection	098.2	GONOCOCCAL INFECTIONS CHRONIC LOWER GU TRACT
Sexually transmitted infection	098.30	CHRONIC GONOCCL INF UPPER GU TRACT SITE UNSPEC
Sexually transmitted infection	098.31	GONOCOCCAL CYSTITIS, CHRONIC
Sexually transmitted infection	098.32	GONOCOCCAL PROSTATITIS, CHRONIC
Sexually transmitted infection	098.33	GONOCOCCAL EPIDIDYMO-ORCHITIS CHRONIC
Sexually transmitted infection	098.34	GONOCOCCAL SEMINAL VESICULITIS CHRONIC
Sexually transmitted infection	098.35	GONOCOCCAL CERVICITIS, CHRONIC
Sexually transmitted infection	098.36	GONOCOCCAL ENDOMETRITIS, CHRONIC
Sexually transmitted infection	098.37	GONOCOCCAL SALPINGITIS
Sexually transmitted infection	098.39	OTH CHRONIC GONOCOCCAL INFECTIONS UPPER GU TRACT
Sexually transmitted infection	098.40	GONOCOCCAL CONJUNCTIVITIS
Sexually transmitted infection	098.41	GONOCOCCAL IRIDOCYCLITIS
Sexually transmitted infection	098.42	GONOCOCCAL ENDOPHTHALMIA
Sexually transmitted infection	098.43	GONOCOCCAL KERATITIS
Sexually transmitted infection	098.49	OTHER GONOCOCCAL INFECTION OF EYE
Sexually transmitted infection	098.50	GONOCOCCAL ARTHRITIS
Sexually transmitted infection	098.51	GONOCOCCAL SYNOVITIS AND TENOSYNOVITIS
Sexually transmitted infection	098.52	GONOCOCCAL BURSITIS
Sexually transmitted infection	098.53	GONOCOCCAL SPONDYLITIS
Sexually transmitted infection	098.59	OTHER GONOCOCCAL INFECTION OF JOINT
Sexually transmitted infection	098.6	GONOCOCCAL INFECTION OF PHARYNX
Sexually transmitted infection	098.7	GONOCOCCAL INFECTION OF ANUS AND RECTUM
Sexually transmitted infection	098.81	GONOCOCCAL KERATOSIS
Sexually transmitted infection	098.82	GONOCOCCAL MENINGITIS

Confounder	Code	Description
Sexually transmitted infection	098.83	GONOCOCCAL PERICARDITIS
Sexually transmitted infection	098.84	GONOCOCCAL ENDOCARDITIS
Sexually transmitted infection	098.85	OTHER GONOCOCCAL HEART DISEASE
Sexually transmitted infection	098.86	GONOCOCCAL PERITONITIS
Sexually transmitted infection	098.89	GONOCOCCAL INFECTION OF OTHER SPECIFIED SITES
Sexually transmitted infection	099.0	CHANCROID
Sexually transmitted infection	099.1	LYMPHOGRANULOMA VENEREUM
Sexually transmitted infection	099.2	GRANULOMA INGUINALE
Sexually transmitted infection	099.3	REITERS DISEASE
Sexually transmitted infection	099.4	OTHER NONGONOCOCCAL URETHRITIS
Sexually transmitted infection	099.40	UNSPECIFIED NONGONOCOCCAL URETHRITIS
Sexually transmitted infection	099.41	NONGONOCOCCAL URETHRITIS DUE CHLAMYDTRACHOMATIS
Sexually transmitted infection	099.49	NONGONOCOCCAL URETHRITIS DUE OTHER SPEC ORGANISM
Sexually transmitted infection	099.50	CHLAMYDIA TRACHOMATIS INFECTION UNSPECIFIED SITE
Sexually transmitted infection	099.51	CHLAMYDIA TRACHOMATIS INFECTION OF PHARYNX
Sexually transmitted infection	099.52	CHLAMYDIA TRACHOMATIS INFECTION OF ANUS&RECTUM
Sexually transmitted infection	099.53	CHLAMYDTRACHOMATIS INFECTION LOWER GU SITES
Sexually transmitted infection	099.54	CHLAMYDTRACHOMATIS INFECTION OTH GU SITES
Sexually transmitted infection	099.55	CHLAMYDTRACHOMATIS INFECTION UNSPEC GU SITE
Sexually transmitted infection	099.56	CHLAMYDIA TRACHOMATIS INFECTION OF PERITONEUM
Sexually transmitted infection	099.59	CHLAMYDIA TRACHOMATIS INFECTION OTHER SPEC SITE
Sexually transmitted infection	099.8	OTHER SPECIFIED VENEREAL DISEASES
Sexually transmitted infection	099.9	UNSPECIFIED VENEREAL DISEASE
Sexually transmitted infection	647.00	MATERNAL SYPHILIS-COMPLICATING PC/P-UNS EOC
Sexually transmitted infection	647.01	MATERNAL SYPHILIS COMP PREGNANCY W/DELIVERY
Sexually transmitted infection	647.02	MTRN SYPHILIS COMP PG W/DELIV W/CURRENT PPC
Sexually transmitted infection	647.03	MATERNAL SYPHILIS, ANTEPARTUM
Sexually transmitted infection	647.04	MATERNAL SYPHILIS POSTPARTUM CONDITION/COMPLICAT

Confounder	Code	Description
Sexually transmitted infection	647.1	MTRN GONORRHEA COMP PG CHILDBIRTH/THE PUERPERIUM
Sexually transmitted infection	647.10	MATERNAL GONORRHEA-COMPLICATING PC/P-UNS EOC
Sexually transmitted infection	647.11	MATERNAL GONORRHEA WITH DELIVERY
Sexually transmitted infection	647.12	MATERNAL GONORRHEA W/DELIVERY W/CURRENT PPC
Sexually transmitted infection	647.13	MATERNAL GONORRHEA, ANTEPARTUM
Sexually transmitted infection	647.14	MATERNAL GONORRHEA POSTPART CONDITION/COMPLICAT
Sexually transmitted infection	647.20	OTH MATERNAL VENEREAL DZ-COMPLICAT PC/P-UNS EOC
Sexually transmitted infection	647.21	OTHER MATERNAL VENEREAL DISEASES WITH DELIVERY
Sexually transmitted infection	647.22	OTH MATERNAL VENEREAL DZ W/DELIV W/CURRENT PPC
Sexually transmitted infection	647.23	OTH MATERNAL VENEREAL DISEASE ANTPRTM COND/COMPL
Sexually transmitted infection	647.24	OTHER VENEREAL DISEASES POSTPARTUM COND/COMPL
Urinary tract infection	590.0	CHRONIC PYELONEPHRITIS
Urinary tract infection	590.00	CHRON PYELONEPHRITIS W/O LES RENL MEDULRY NECROS
Urinary tract infection	590.01	CHRON PYELONEPHRITIS W/LES RENAL MEDULRY NECROS
Urinary tract infection	590.1	ACUTE PYELONEPHRITIS
Urinary tract infection	590.10	ACUT PYELONEPHRITIS W/O LES RENAL MEDULRY NECROS
Urinary tract infection	590.11	ACUT PYELONEPHRITIS W/LES RENAL MEDULRY NECROS
Urinary tract infection	590.2	RENAL AND PERINEPHRIC ABSCESS
Urinary tract infection	590.3	PYELOURETERITIS CYSTICA
Urinary tract infection	590.80	UNSPECIFIED PYELONEPHRITIS
Urinary tract infection	590.81	PYELITIS/PYELONEPHRITIS DISEASES CLASSIFIED ELSW
Urinary tract infection	590.9	UNSPECIFIED INFECTION OF KIDNEY
Urinary tract infection	59000	AMNIOCENTESIS DIAGNOSIC
Urinary tract infection	59001	AMNIOCENTESISS THER AMNIOTIC FLUID RDCTJ US GID
Urinary tract infection	595.0	ACUTE CYSTITIS
Urinary tract infection	595.1	CHRONIC INTERSTITIAL CYSTITIS
Urinary tract infection	595.2	OTHER CHRONIC CYSTITIS
Urinary tract infection	595.4	CYSTITIS IN DISEASES CLASSIFIED ELSEWHERE

Confounder	Code	Description
Urinary tract infection	595.89	OTHER SPECIFIED TYPES OF CYSTITIS
Urinary tract infection	595.9	UNSPECIFIED CYSTITIS
Urinary tract infection	597.0	URETHRAL ABSCESS
Urinary tract infection	597.80	UNSPECIFIED URETHRITIS
Urinary tract infection	597.89	OTHER URETHRITIS
Urinary tract infection	599.0	URINARY TRACT INFECTION SITE NOT SPECIFIED
Urinary tract infection	646	OTHER COMPLICATIONS OF PREGNANCY NEC
Urinary tract infection	646.60	INFS GU TRACT PREGNANCY UNSPEC AS EPIS CARE
Urinary tract infection	646.61	INFECTIONS GENITOURINARY TRACT PREGNANCY W/DELIV
Urinary tract infection	646.62	INFS GU TRACT PREGNANCY W/DELIV W/CURRENT PPC
Urinary tract infection	646.63	INFECTIONS OF GENITOURINARY TRACT ANTEPARTUM
Urinary tract infection	646.64	INFECTIONS GU TRACT POSTPARTUM COND/COMPL
Urinary tract infection	647.0	MTRN SYPHILIS COMP PG CHILDBIRTH/THE PUERPERIUM

Appendix 6: CPT, CVX, and HCPCS codes for identifying exposure to trivalent influenza vaccine prior to the 2013-14 season

Code	Type	Description[1]
90655	CPT	INFLUENZA VIRUS VACCINE, SPLIT VIRUS, PRESERVATIVE FREE, FOR CHILDREN 6-35 MONTHS OF AGE, FOR INTRAMUSCULAR USE
90656	CPT	INFLUENZA VIRUS VACCINE, SPLIT VIRUS, PRESERVATIVE FREE, FOR USE IN INDIVIDUALS 3 YEARS OF AGE AND ABOVE, FOR INTRAMUSCULAR USE
90657	CPT	INFLUENZA VIRUS VACCINE, SPLIT VIRUS, FOR CHILDREN 6-35 MONTHS OF AGE, FOR INTRAMUSCULAR USE
90658	CPT	INFLUENZA VIRUS VACCINE, SPLIT VIRUS, FOR USE IN INDIVIDUALS 3 YEARS OF AGE AND ABOVE, FOR INTRAMUSCULAR USE
90659	CPT	INFLUENZA VIRUS VACCINE, WHOLE VIRUS, FOR INTRAMUSCULAR OR JET INJECTION USE
90662	CPT	INFLUENZA VIRUS VACCINE, SPLIT VIRUS, PRESERVATIVE FREE, ENHANCED IMMUNOGENICITY VIA INCREASED ANTIGEN CONTENT, FOR INTRAMUSCULAR USE
15	CVX	INFLUENZA, SPLIT (INCL. PURIFIED SURFACE ANTIGEN)
16	CVX	INFLUENZA, WHOLE
135	CVX	INFLUENZA, HIGH DOSE SEASONAL
140	CVX	INFLUENZA, SEASONAL, INJECTABLE, PRESERVATIVE FREE
141	CVX	INFLUENZA, SEASONAL, INJECTABLE
Q2034	HCPCS	INFLUENZA VIRUS VACCINE, SPLIT VIRUS, FOR INTRAMUSCULAR USE (AGRIFLU)
Q2035	HCPCS	INFLUENZA VIRUS VACCINE, SPLIT VIRUS, WHEN ADMINISTERED TO INDIVIDUALS 3 YEARS OF AGE AND OLDER, FOR INTRAMUSCULAR USE (AFLURIA)
Q2036	HCPCS	INFLUENZA VIRUS VACCINE, SPLIT VIRUS, WHEN ADMINISTERED TO INDIVIDUALS 3 YEARS OF AGE AND OLDER, FOR INTRAMUSCULAR USE (FLULAVAL)
Q2037	HCPCS	INFLUENZA VIRUS VACCINE, SPLIT VIRUS, WHEN ADMINISTERED TO INDIVIDUALS 3 YEARS OF AGE AND OLDER, FOR INTRAMUSCULAR USE (FLUVIRIN)
Q2038	HCPCS	INFLUENZA VIRUS VACCINE, SPLIT VIRUS, WHEN ADMINISTERED TO INDIVIDUALS 3 YEARS OF AGE AND OLDER, FOR INTRAMUSCULAR USE (FLUZONE)
Q2039	HCPCS	INFLUENZA VIRUS VACCINE, SPLIT VIRUS, WHEN ADMINISTERED TO INDIVIDUALS 3 YEARS OF AGE AND OLDER, FOR INTRAMUSCULAR USE (NOT OTHERWISE SPECIFIED)

[1]The descriptions of the codes in this table are verbatim from the following sources: (1) "HL7 Table 0292, Vaccine Administered (CVX)", available on the CDC website[58], (2) *Health Care Procedure Coding System: National Level II Medicare Codes*[59], (3) *CPT Plus! A Comprehensive Guide to Current Procedural Terminology*[60] and (4) *International Classification of Diseases, 9th Revision, Clinical Modification*[61]. Of note, NDCs (National Dispensing Codes) will also be used to identify TIV exposure.

Appendix 7: Considerations for choice of case-time-control design, as compared to the self-controlled case series approach

In developing this protocol, several key factors were considered in selecting the study design. At the forefront of the design choice were the case-time-control design and the self-controlled case series because of their inherent ability to control for confounding by time-constant or relatively time constant factors such as race/ethnicity and age (the latter since this is an adolescent/adult population). Several considerations were made in selecting the case-time-control design for the primary analysis, as outlined below.

1. **Time scale and addressing confounding by calendar time and gestational age**

For this evaluation, exposure is defined on two time scales: time since vaccination and gestational age at vaccination. With a SCCS design, it is possible to examine the TIV-SAB association if defining the risk interval as time since vaccination and simultaneously adjusting for time-varying gestational age and calendar time in regression models. However, residual confounding by gestational age and calendar time might remain due to low case numbers in each stratum. Furthermore, because a woman's likelihood of vaccination could potentially decrease after a miscarriage, the key assumption of the SCCS of no change in probability of exposure across follow-up time is violated, such that additional methodological techniques would need to be used. With a SCCS, it is not possible to examine the TIV-SAB association if exposed person-time is defined by gestational age at vaccination.

In contrast, the case-time-control design allows one to examine the TIV-SAB association while defining exposed person-time by time since vaccination and by gestational age at vaccination in two iterations of the design. For both time scales, matching cases to controls on date of LMP adjusts for time trends in vaccination by calendar time and gestational age. Thus, the key reason that we chose the case-time-control design over the self-controlled case series is that it allows us to examine both exposure time scales (i.e., time since vaccination and gestational age at vaccination) while adjusting for seasonality and gestational age by matching, thereby avoiding residual confounding due to model misspecification.

2. **Exposure and outcome misclassification**

A SCCS design avoids bias due to misclassification of exposure, but only if restricted to vaccinated cases. Similarly, a case-time-control design avoids bias due to misclassification of exposure by only including vaccinated cases and controls. To correctly classify the timing of exposure, both the SCCS and the case-time-control design can be conducted such that medical record information is required to assign gestational age.

The SCCS and case-time-control design can both be specified to minimize misclassification of outcome by requiring that all SAB cases and their date of onset be confirmed via medical record review.

3. Control selection

No controls are used in an SCCS study, though unvaccinated cases could be included to contribute information to adjustments for confounding by gestational age and calendar time. No selection bias would be introduced by including such individuals.

In a case-time-control design, all individuals are vaccinated, thus making them comparable with respect to vaccination status. Controls are used to estimate the time trend in exposure in the source population that gave rise to the cases. If controls are not representative of the time trend in exposure, bias may be introduced. However, we have maximized the comparability of cases and controls with respect to time trends in exposure by matching on Data Partner, maternal age, and pregnancy start (the latter of which addresses seasonality). We will also consider matching on other confounders if there are sufficient control matches. By using conditional logistic regression, we will allow a different time-trend in exposure for each matched case:control set, which addresses the possibility of effect modification of the exposure-period association by confounders matched upon.

As a result of the matching process, one potential source of control exclusion bias, as stated in the protocol, is the requirement that all controls be linked to infants so that we can obtain more accurate estimates of claims-based gestational age, which are needed for matching controls to cases before proceeding to chart review of controls. In doing so, mothers whose infants are not enrolled in the same health plan policy are excluded from the study. If control exclusion is related to factors that are associated with timing of vaccination, such as SES or healthcare utilization, bias may be introduced. However, such differences between excluded and included individuals are expected to be minimal, even if they exist.

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