MINI-SENTINEL MEDICAL PRODUCT ASSESSMENT

EVALUATION OF THE RISK OF VENOUS THROMBOEMBOLISM AFTER GARDASIL VACCINATION

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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.

Mini-Sentinel Medical Product Assessment

Evaluation Of The Risk Of Venous Thromboembolism After Gardasil Vaccination

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I. INTRODUCTION

Gardasil is a quadrivalent vaccine indicated for the prevention of anogenital cancers, genital warts, and precancerous or dysplastic lesions caused by infection with human papillomavirus (HPV) types 6, 11, 16, and 18. Gardasil is routinely recommended for females and males aged 11–12 years in a three dose series (0, 2, and 6 months) but can be administered as young as age 9 years; catch-up vaccination is recommended for females aged 13–26 years and males aged 13-21 years who have not been previously vaccinated.[1] FDA approved Gardasil in June 2006 based on 12 randomized controlled studies involving approximately 21,000 males and females aged 9–26 years in support of its safety and efficacy.[2] In these clinical studies, injection site reactions were found to be higher among Gardasil-vaccinated persons than placebo recipients.[3,4] However, rates of systemic reactions, new onset medical conditions, serious adverse events, and deaths following vaccination were comparable between vaccine and placebo recipients. No safety issues were identified in prelicensure studies of Gardasil.

Postlicensure surveillance identified disproportional reporting of venous thromboembolism (VTE) after Gardasil vaccination. An analysis of the first 2.5 years of passive surveillance in the Vaccine Adverse Events Reporting System (VAERS) found that VTE was reported more frequently than expected compared with other vaccines.[5] The median age of reported VTE cases was 20 years (range 15–39 years) and the median onset interval was 23 days (range 0–306 days). However, 90% of the reported cases had at least one preexisting risk factor for VTE, suggesting that confounding may explain a substantial proportion of the cases. Disproportional reporting alone, in a passive surveillance system, is not sufficient to demonstrate a causal relationship between VTE and Gardasil.

To supplement passive surveillance, the Vaccine Safety Datalink (VSD) monitored 600,558 Gardasil doses administered to females aged 9–26 years for the first 3 years after licensure (August 2006 to October 2009). During this period, VSD monitored 8 outcomes using rapid cycle analyses, and no safety signals were detected based upon predefined criteria.[6,7] However, a statistically non-significant relative risk of 1.98 for VTE (defined using ICD-9 codes 415.1x and 453.x) after Gardasil administration in females aged 9–17 years was found compared with a historical comparison group of females of the same age. Eight VTE cases in females aged 9–17 years were electronically identified 1–42 days postvaccination; 5 of these cases were chart-confirmed, 2 were instances of miscoding, and 1 was ruled out after diagnostic testing. The VTE diagnosis in 4 of the 5 confirmed cases occurred within 1-7 days after vaccination; the fifth occurred on Day 32. All 5 cases had at least one known risk factor—hormonal contraceptive use, coagulation disorders, smoking, obesity, or prolonged hospitalization. No elevated risk was detected after Gardasil vaccination among adult females aged 18–26 years.

In December 2010, this information was presented to the FDA Pediatric Advisory Committee as part of a routine safety review.[8] The committee recommended that additional surveillance studies be conducted to further evaluate the risk of VTE following Gardasil vaccination. This report describes the methods and results of examining the risk of VTE after Gardasil vaccination in the Post-licensure Rapid Immunization Safety Monitoring (PRISM) program.

II. OBJECTIVES

1. To determine the existence and magnitude of any increased risk of VTE in the 1 or 4 weeks following Gardasil vaccination compared with unexposed person-time among vaccinees and to assess the role of combined hormonal contraceptives (CHCs) as a potential confounder or effect modifier. (The study was not designed to examine the risk of VTE from CHC use in its own right but rather only for the purposes of controlling for confounding of the HPV-VTE association by CHC use and assessing the possibility of effect modification of the HPV-VTE association by CHC use.)
2. To determine through medical chart review the positive predictive value of an ICD9 code based algorithm for identifying VTE

III. METHODS

A. STUDY POPULATION AND DATA SOURCES

The study population consisted of female Gardasil vaccinees 9-26 years of age from the Mini-Sentinel/PRISM Data Partners Aetna, HealthCore, Humana, Optum, or Tennessee Medicaid (Vanderbilt) during specific periods within May 2004 through June 2013:

Table 1. Periods of data used in the study, by Data Partner. "HPV-VTE" refers to data used for the main Gardasil-VTE analyses; "CHC-VTE" refers to data used for modeling the risk of VTE by duration of exposure to CHCs, which was needed to adjust one of the analyses (see Methods, Section F).

Data Partner	Start	End	No. of years
Aetna, HPV-VTE	5/2008	12/2011	~3.5
Aetna, CHC-VTE	5/2008	3/2012	~4
HealthCore, HPV-VTE	6/2006 (Gardasil licensure)	5/2011	5
HealthCore, CHC-VTE	5/2004	11/2011	7.5
Humana, HPV-VTE	10/2007	8/2011	~4
Humana, CHC-VTE	10/2007	8/2011	~4
Optum, HPV-VTE	5/2008	6/2013	~5
Optum, CHC-VTE	5/2008	6/2013	~5
Tennessee Medicaid, HPV-VTE	6/2006 (Gardasil licensure)	12/2012	~6.5
Tennessee Medicaid, CHC-VTE	1/2006	12/2010	5

(Within Data Partner, the start-date of the data used for CHC-VTE modeling is sometimes earlier than the start-date of the data used for the Gardasil-VTE analyses. This is because some Data Partners had data available from prior to Gardasil licensure, which were used to maximize the total number of VTE cases and obtain a more robust estimate of the risk of VTE based upon duration of CHC use. Data end-dates also varied within Data Partner, mostly due to the need to ensure data completeness for the main Gardasil-VTE analyses.)

Inclusion criteria specified that subjects be continuously enrolled in the health plan, with medical and pharmacy coverage, from 4 months prior to the first dose of Gardasil through at least 70 days after that

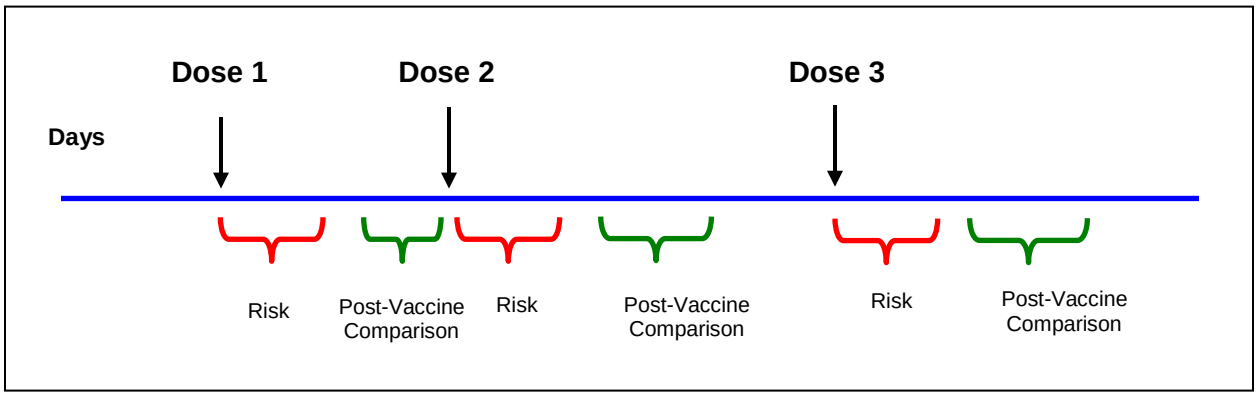
first dose. Continuously enrolled person-time was included, with the following proviso: If a vaccinee had incomplete person-time during 0-70 days after Dose 2 or 3 of Gardasil, her person-time on and after the day of that dose was excluded in order to avoid possible bias. Enrollment gaps of up to 14 days at any time in the 4 months prior to the first dose were permitted, but no such enrollment gaps were allowed from Day 0 through Day 70 after the first dose. Similarly, second and third doses were included only if there were no enrollment gaps during Days 0-70 after those doses. (Inclusion criteria for modeling VTE risk by duration of CHC use are different and are presented in Methods, Section F.)

Sources of immunization records were claims data from the Data Partners and immunization data from any of the eight participating immunization registries (also known as immunization information systems, IISs): FL, MI, MN, NYC, NYS, PA, VA, and WI. The source of VTE diagnosis records was claims data. In addition, medical record data were used to confirm both the VTE outcome and the Gardasil exposure (see Methods, Sections C, D, and H for more on chart review).

B. STUDY DESIGN AND NULL HYPOTHESIS

A self-controlled risk interval (SCRI) design[9,10] (shown schematically in Figure 1) was used. This design uses only vaccinated cases occurring in pre-specified risk or comparison intervals and controls for fixed potential confounders (e.g., genetic factors, socio-economic status), since individuals are used as their own controls.

Figure 1. Self-Controlled Risk Interval (SCRI) design



For this study, defining the risk interval following Gardasil vaccination was challenging, given the lack of a theoretical mechanism whereby the vaccine might cause VTE. We reasoned that the period of increased risk, if any, would most likely occur immediately following vaccination, be short-lived, and presumably return to baseline after each vaccination. This is consistent with the findings of the VSD Gardasil-VTE evaluation.[7] With these assumptions, we selected two risk intervals: Days 1-28 post-vaccination (primary) and Days 1-7 post-vaccination (secondary). Days 29-35 were considered a washout period. The comparison interval, considered unexposed, was Days 36-56 post-vaccination for Dose 1 and Days 36-63 for Doses 2 and 3, regardless of which risk interval was used. (The comparison interval for Dose 1 was pre-specified as one week shorter than for Doses 2 and 3 to avoid potential bias due to Dose 2 frequently being given during Days 57-63 after Dose 1. In the study population, approximately 25% of second doses were given in that 7-day period.)

The null hypothesis was that the risk of VTE onset on an average day during the defined risk interval after Gardasil was the same as the risk of VTE onset on an average day during the control interval.

In this report, the terms "risk interval," "risk window," and "RW" are used interchangeably, as are "comparison interval," "comparison window," "control interval," "control window," and "CW."

C. EXPOSURE CODES

a. Vaccination

Gardasil vaccination was identified by means of CPT code 90649 in claims or IIS data and CVX code 62 in IIS data. For the potential VTE cases identified in claims data as occurring in the 77 days after Gardasil vaccination, medical records were sought to confirm the vaccination and its timing and dose number. (To identify potential cases for chart review, an additional 14 days was added to the 63 days in the main observation period in case of delays between the symptom onset date and the date of the VTE diagnosis according to the claims data.) Based on experience in a previous PRISM vaccine safety study,[11] neither the electronic (claims or IIS) data nor the medical record data were pre-specified to be consistently prioritized over the other, rather both were evaluated and used in establishing the timing and dose number to be used in analysis.

b. Contraceptives

CHC use is estimated to increase VTE risk by 3–6 fold due to an estrogen mediated procoagulant state.[12] Some studies have shown a higher risk in the first year of use[13,14] (especially the first 3 months). In view of the likelihood that a substantial portion of young women begin using CHCs within a few months of receiving Gardasil, we needed to control for the potentially confounding effect of CHC use. In addition, we wanted to be able to assess whether such use could be an effect modifier of the association between Gardasil and VTE. To these ends, the contraceptive use status of all cases was determined. A list of National Drug Codes (NDCs) was constructed by querying First Data Bank for the Enhanced Therapeutic Classification categories "Contraceptives Oral," "Contraceptives Intravaginal, Systemic" and "Contraceptives Transdermal." (Other contraceptives, such as emergency contraceptives, intrauterine devices, implantable devices, and injections, do not contain estrogen, the ingredient most associated with a net prothrombotic state, and therefore were not included in the query.) To ensure that this list was complete, the identified generic names were shared with the participating Data Partners, who added any missing or homegrown codes for these generic names to the list.

Because of the time-varying nature of potential confounding by duration of CHC use, we sought to characterize the CHC-associated VTE risk in weekly increments for Gardasil vaccinees using CHCs at any point between the day of vaccination and the end of the control interval (discussed further in Methods, Section F). The Mini-Sentinel Common Data Model Dispensing file was used to identify contraceptive exposure status for all potential cases, looking from up to 365 days prior to the Gardasil dose preceding a VTE code (referred to as the "dose of interest" here) through the end of the comparison interval after that dose of interest. Cases were considered exposed to contraceptives if the dispensing date + days supplied (RxDate + RxSup) included the date of the Gardasil dose of interest or any time through the comparison interval after that dose. To obtain the overall span of CHC use, consecutive overlapping dispensings were placed end to end. Suppose, for instance, there were two consecutive contraceptive

dispensings, A & B, with their respective RxDate + RxSup. If $RxDate_B$ fell within the period $RxDate_A$ + $RxSup_A$, then we assumed Dispensing B was filled early and that the actual start date for using Dispensing B was not $RxDate_B$ but instead $RxDate_A$ + $RxSup_A$ + 1. This process was repeated as needed for any number of consecutive dispensings filled early. The days supplied (RxSup) was summed for all dispensings for the same patient to determine the total duration. If a gap between one [dispensing date + days supplied] and the next [dispensing date + days supplied] was ≤ 14 days, the gap was ignored and the gap days were counted in the total duration. If the gap was >14 days, then the period covered by the prior dispensing and gap was not counted in the total duration.

Information on CHC usage found in the medical records was used to supplement the claims data in determining CHC initiation, duration, and product, although the chart data tended to be less complete and less specific about CHC dates and products than the claims data.

D. OUTCOME DEFINITION

We used ICD-9 codes 415.1x (pulmonary embolism, infarction), 451.x (phlebitis and thrombophlebitis), and 453.x (other venous embolism, thrombosis) (see Appendix 1 for detailed code list) in outpatient, ED, and inpatient settings to identify potential cases of VTE. A Mini-Sentinel review of the performance of multiple pulmonary embolism and/or deep vein thrombosis ICD-9 codes in this set reported positive predictive values ranging from 26% to 93%.[15] We excluded 415.0 (cor pulmonale), because it is not specific to VTE and can have multiple other etiologies. Although we included codes for superficial venous thrombosis because recent evidence suggested that it could be a marker for more clinically significant thromboembolic risk,[16] all analyses ultimately addressed only VTE, which consisted of either pulmonary embolism or deep vein thrombosis.

VTE diagnoses during 1-77 days following any Gardasil dose were captured. To restrict to incident cases, we considered only the first VTE diagnosis found in a patient's record since enrollment. If, upon medical record review, any of these potential cases were found to have a history of VTE, they were excluded from analyses.

Medical records of eligible VTE cases diagnosed 1-77 days following Gardasil were reviewed. VTE cases were classified using the criteria developed by the Worcester Venous Thromboembolism Study (Table 2).[17] The main analyses were conducted on the definite VTE cases. Probable and possible cases of VTE were included in some secondary analyses. In all analyses and for all categories of cases, adjudicated symptom onset dates were used rather than VTE diagnosis dates.

Table 2. VTE case validation criteria

	Pulmonary Embolism	Deep Vein Thrombosis
Definite	Confirmed by pulmonary angiography, spiral CT scan/CT pulmonary angiography, MRI scan or pathology	Confirmed by venography, compression/duplex ultrasound, CT scan or at autopsy
Probable	If above tests not performed or were indeterminate, but ventilation-perfusion scan findings were of high probability	If above tests not performed or were indeterminate, but impedance plethysomography, radionucleotide venography, or radiolabelled fibrinogen scan test results were reported as positive
Possible	If all of the above tests were not performed	If all of the above tests were not performed

	Pulmonary Embolism	Deep Vein Thrombosis
	or were indeterminate and 2 of the following criteria were satisfied: medical record indicates physician-diagnosed DVT, signs or symptoms of DVT were documented and the patient underwent therapy with anticoagulants, or an IVC filter was placed.	or were indeterminate and 2 of the following criteria were satisfied: medical record indicates physician-diagnosed DVT, signs or symptoms of DVT were documented and the patient underwent therapy with anticoagulants, or an IVC filter was placed.

E. RISK FACTORS FOR VTE

We collected data on potential cases' VTE risk factors for descriptive purposes as well as to enable exploration, in secondary statistical analyses, of their role as possible effect modifiers of the Gardasil-VTE relationship. Both claims and medical records were used to identify these risk factors. The lists of codes used to detect the risk factors for VTE in claims data are included in Appendix 2. VTE risk factors identified in medical records of definite VTE cases are listed in Appendix 3. The risk factor groups ultimately used in descriptive and statistical analyses are shown in Table 3. In addition to the 13 main groups, we created a more inclusive version of Group 5, to include long-distance travel (called 5a), and of Group 8, to include documented cases of overweight that either did not meet obesity criteria or had insufficient information to determine whether those criteria were met (called 8a). Obesity was defined as BMI ≥ 30 for adults (≥ 18)[18] and BMI ≥ 95 percentile for youth (< 18).[19]

Table 3. VTE risk factor groupings used in descriptive and secondary statistical analyses

Group no.	Risk factor group description
1	Hypercoagulable states and coagulation defects
2	Cancer, inflammatory conditions, infection
3	Cardiovascular conditions
4	Cardiac conditions
5	Transplant, surgery, venous catheterization, other immobility conditions, excluding long-distance travel
5a	As above but including recent long-distance travel, according to the medical record (more inclusive than #5)
6	Pregnancy
7	Sickle cell anemia
8	Obesity
8a	Obesity and overweight (more inclusive than #8)
9	Renal conditions
10	Tobacco use
11	Oral contraceptive CHC use
12	Thoracic outlet syndrome
13	Family history of VTE

F. STATISTICAL ANALYSES

a. SCRI analyses

Co-primary SCRI analyses. There were three co-primary analyses, all using the self-controlled risk interval design.[9,10] All the co-primary analyses used the chart-confirmed (definite) cases only. Within the three co-primary analyses, Dose 1 and all-dose analyses were pre-specified as the primary dose-specific analyses.

Analysis #1 included all Gardasil recipients with VTE onset in either the risk or the comparison interval after a Gardasil dose. It did not explicitly adjust for CHC use; however, it *implicitly* adjusted for CHC use to the extent that VTE risk from CHCs did not vary over the 63-day observation period.

Because CHC use was a potential time-varying factor that, for some vaccinees, could have caused the baseline risk of VTE to be different in the risk vs. control intervals, two additional analyses were employed. Although these analyses addressed time-varying confounding by CHC use, they were not necessarily better than Analysis #1, because Analysis #2 excluded some cases, leading to a loss of statistical power, and Analysis #3 was subject to some degree of misclassification of duration of CHC use.

Analysis #2 restricted to vaccinees whose baseline risk of VTE was unlikely to have varied between the risk and comparison intervals due to contraceptive use, i.e., (1) those vaccinees who had no record of contraceptive use as of the last day of the control window after the Gardasil dose ("never-users"), and (2) those vaccinees who had been on contraceptives continuously for at least 9 months as of the day of the Gardasil dose ("long-term users"). This restriction resulted in fewer cases being included in analysis, reducing power, but was meant to eliminate time-varying confounding related to contraceptive use.

Analysis #3 did not exclude cases and thus included the same cases as in Analysis #1, but it explicitly adjusted for the changing risk of VTE associated with the first 9 months of CHC use. In the logistic regression analysis, an offset term was used for vaccinees who initiated CHCs between 8.99 months prior to the Gardasil dose and the end of the control interval following the Gardasil dose, as determined by the medical record or inferred from the pharmacy dispensing data. The offset term was obtained by estimating the risk of VTE by duration of CHC use, which is described below:

Estimation of VTE risk by duration of CHC use. Prior to analysis, the time-varying risk of first-ever VTE was estimated from a risk curve generated from electronic claims data from 9-26 year old females in the "CHC-VTE" time periods shown in Table 1 who had a minimum of 7 months of enrolled time. (The 7-months minimum was chosen to optimize precision (compared to 13 months, for example, which would have eliminated a substantial proportion of cases and person-time and produced less stable VTE background rates) and accuracy (compared to 4 months, for example, which might have made misclassification of CHC duration somewhat more common).) Only person-days prior to the first initiation and during the first contraceptive span contributed to the risk curve. Apparent gaps in usage of ≤ 7 days were ignored. VTE cases within 1-28 days following Gardasil were excluded.

Visual inspection of the data together with explorations early in model-building indicated that the risk of VTE during the 9-<12 months after CHC initiation was approximately the same as the risk at ≥ 12 months. Therefore, the VTE risk was considered to plateau at 9 months of CHC usage.

The general approach taken to modeling was to use Poisson regression and fit the VTE risk by CHC duration (as well as secular month, which was the other continuous variable in the model) using progressively higher-order polynomial functions (i.e., a linear function, then linear + quadratic, then linear + quadratic + cubic, and so on, not to exceed a fifth-order polynomial function) until no statistical significance was found. Age, estrogen dosage, and Data Partner were categorical variables in the model. A number of interaction terms were introduced one by one into the modeling to check for effect modification. As specified in the protocol, goodness-of-fit was determined based on a combination of the log-likelihood ratio, p-value, Akaike information criterion (AIC), and biologic plausibility.

For Analysis #3, and prior to any analysis of the Gardasil-VTE association, two sets of offset terms were obtained from the CHC-VTE model that was ultimately selected—one for the primary, 28-day risk interval and the other for the 7-day risk interval. First, for each case, we solved the regression equation from the model to determine baseline VTE risk by week during the observation period after Gardasil vaccination. Then, using the predicted values for each week after vaccination for each case, we calculated (for each of the two risk intervals) the area under the CHC-VTE risk curve for the risk interval segment of time as a proportion of the summed areas under the curve for the risk and control interval segments of time. We then used that proportion, p (equivalent to the probability of the case being in the risk interval under the null hypothesis of no association between Gardasil and VTE), and calculated ln(p/(1-p)). This last quantity served as the offset term for the case and risk interval in question.

Secondary SCRI analyses. Four sets of secondary SCRI analyses were carried out. First, Analyses #1 and #3 were repeated including the probable and possible VTE cases. (There were no such cases to add to Analysis #2, as all three probable/possible cases had time-varying risk from CHC use.) Second, we explored the possibility of effect modification by age by repeating Analyses #1 and #3 (for all doses and both risk intervals) with age included as an interaction term in the regression model. Third, we checked for possible effect modification by VTE risk factor group by including each of the risk factor groups (dichotomous (yes/no) categorical variables) one by one as interaction terms in the model and repeating Analysis #3 (for all doses and risk intervals). Finally, we repeated Analyses #1-#3 using a Days 1-35 risk interval (and not changing control intervals), incorporating cases with onsets during the Days 29-35 washout period into the risk interval and recalculating offset terms. The decision to conduct this last set of analyses was a post hoc one whose purpose was to address uncertainty regarding the most appropriate risk interval.

b. Temporal scan statistical analyses

To check for possible clustering of VTE onsets in the observation period after Gardasil vaccination, we used the temporal scan statistic,[20,21] a self-controlled design. For the Dose 1 and all-doses analyses, we used the definite VTE cases with onset of symptoms 1-56 days after vaccination. For the analyses of Doses 2 and 3, we used the definite cases with onsets 1-63 days after vaccination. We evaluated all potential intervals of increased risk up to 50% of the respective periods (56 or 63 days), with adjustment for the multiple testing involved in evaluating the many different intervals of potential clustering. The test statistic is the maximum likelihood obtained among the various intervals. Analyses were conducted using the SaTScan software.[22]

G. DATASET CREATION AND REGISTRY MAPPING

PRISM uses Mini-Sentinel's distributed Common Data Model, by which the Data Partners maintain control over patient-level data. Data Partners periodically extract and organize data from their systems into eight files of standard format, of which the relevant ones for this study were: enrollment, demographics, encounter, diagnosis, procedure, and dispensing. To obtain immunization data from state immunization registries, Aetna, HealthCore, and Humana (not Optum or Vanderbilt, which joined the study later) provided them with member identification information to allow the registries to match Data Partner members with registry immunization records. The registries returned immunization data for members to the Data Partners, including vaccination date, vaccine code, and (when available) manufacturer and lot number, from which the Data Partners populated a uniform-format state vaccine file linkable by means of a patient identification number to the other files. Immunization data from the claims-based procedure and state vaccine files were combined into an intermediate file, eliminating duplicates, by means of a program provided by PRISM programmers.

PRISM programmers provided the Data Partners with programs to run on the standard-format patient-level files, which produced aggregate data on Gardasil vaccination and VTE organized in strata defined by such variables as date of vaccination, type of vaccine, dose number, age, length of contraceptive use, and presence of other VTE risk factors, with a count of patients conforming to the stratum's values of those variables. For example, the aggregate data file on vaccination might have a stratum for 13-year-old current contraceptive users of 0-3.99 months duration with no other VTE risk factors vaccinated with Gardasil Dose 1 on 10/25/2009. The Data Partners returned the aggregate data for analysis, using Mini-Sentinel's secure file transport methods.

H. VTE CASE AND GARDASIL EXPOSURE VALIDATION / POSITIVE PREDICTIVE VALUE CALCULATION

In order to identify the cases and obtain the medical charts, we sent programs to the Data Partners to run on their uniform-format patient-level files. These programs produced a report of the number and characteristics (e.g., age) of the cases with first-ever VTE diagnoses occurring 1-77 days after a dose of Gardasil and, for each case, a report listing all the health care encounters with a VTE diagnosis code. The case-specific reports included information on clinical setting, actual diagnosis, date of the diagnosis, and Gardasil doses.

Charts for both vaccination as well as VTE visits were sought. To confirm the vaccination timing, dose number, and type/manufacturer in the claims/IIS data, the chart associated with the most recent dose prior to the VTE index date was sought. If no such chart was available, the chart associated with the subsequent dose was sought, and so on. Immunization *history* was explicitly requested and extracted to help identify the number of the dose received prior to the VTE diagnosis. To validate VTE diagnoses and determine onset dates, clinical investigators ranked the VTE-related encounters of each case, based on which seemed likely to produce the most definitive diagnostic information, and returned the ranked lists to the Data Partners. The Data Partners attached patient name, member number, and provider name and address to the visits for which records were to be requested.

Each Data Partner identified a preferred vendor to create chart extracts. These chart extracts consisted of specific items photocopied or scanned by the vendor. For example, VTE chart extracts included, when available, the admission note, hospitalization progress notes, discharge summary, surgical reports where

epidural or general anesthesia lasted for at least 30 minutes occurring within 3 months after the index date (defined as the date of the first eligible code for VTE), and all diagnostic procedures. The chart review vendor notified the facilities, obtained the charts, photocopied or scanned the appropriate pages, and redacted the record of all personal identifiers. Data Partners had the option of reviewing the redacted records to ensure that redaction was complete. Redacted records were sent to the Mini-Sentinel Coordinating Center for abstraction and review.

A board-certified pediatric hematologist served as the VTE case adjudicator. She reviewed all medical records and classified all VTE cases as definite, probable, possible, or not-VTE. To ensure uniform application of the case definition and enable refinement of the classification rules, this adjudicator and a general pediatrician independently reviewed 20 charts, blinded to the timing of vaccination and to the other reviewer's decision. Discrepancies were discussed and resolved, and review by the adjudicator continued for the remainder of cases. All cases classified as "probable" or "possible" were double-adjudicated.

The positive predictive value of the VTE identification algorithm was determined by dividing the number of VTE cases classified as definite first-ever VTE by the total number of potential cases identified electronically for which VTE charts were obtained. Additional analysis of some of the components (i.e., settings, ICD-9 codes) of the algorithm was carried out to inform future studies of VTE.

IV. RESULTS

A. GARDASIL VACCINE DOSES ADMINISTERED

The study included 1,423,399 doses of Gardasil vaccine administered, of which 650,475 (46%) were first doses, 489,737 (34%) were second doses, and 283,187 (20%) were third doses.

B. MEDICAL RECORD CONFIRMATION OF VTE OUTCOME AND GARDASIL EXPOSURE

The total number of potential first-ever VTE cases diagnosed within 77 days after a dose of Gardasil vaccine, as ascertained in the electronic claims data, was 279. Charts to confirm/rule out VTE were obtained for 225 of these. Ninety-seven of the 225 were ruled out without being sent for adjudication. There were two general reasons for this. One reason was negative results from any of the tests listed in the "Definite" row of Table 2. The other reason was miscoding. Examples of miscoding were instances of no evidence of a VTE event in the appropriate chart; sometimes these involved a patient undergoing blood-work related to clotting disorders, e.g., when preparing to start oral contraceptives where a family history of VTE or other VTE risk factor existed. The remaining 128 cases were reviewed by the adjudicator. Of the 128 adjudicated potential cases, 53, 1, and 6 were classified as definite, probable, and possible first-ever VTE, respectively, 2 other cases were determined to have had a history of VTE, and 66 were ruled out as VTE (Figure 2). Of the 66 ruled out cases, 47 did not meet the criteria for VTE, while 19 had insufficient information to make case determination. Of the 53 definite VTE cases, 5 were found by the adjudicator to have had onset of VTE symptoms prior to Gardasil vaccination (in spite of the fact that their first VTE diagnosis code appeared after their Gardasil vaccination in the claims data) and 12 had onset beyond the control interval. Thirty had adjudicated onset of symptoms in the risk or control interval after a Gardasil dose. These were included in the main SCRI analyses. An additional 3 probable or possible cases had onset in risk or control intervals and were included in sensitivity SCRI

analyses. Six of the 53 definite cases had onset of symptoms in the Days 29-35 washout period. These were included in sensitivity SCRI analyses as well as in the temporal scan statistical analyses.

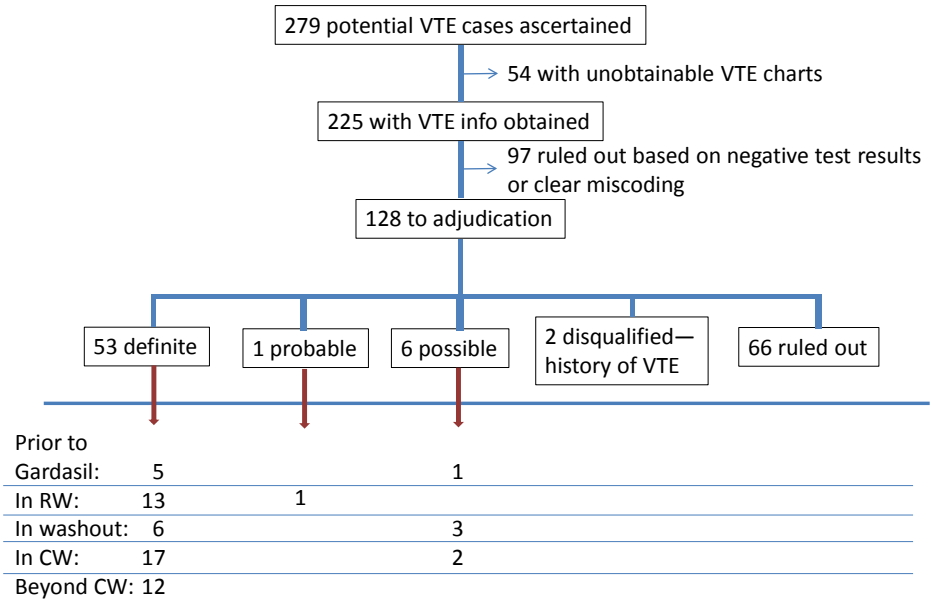


Figure 2. Disposition of potential first-ever VTE cases within 77 days of Gardasil, as ascertained in electronic claims data. The numbers below the red arrows show the temporal distribution of onsets of the respective type of case (definite, etc.) with respect to Gardasil vaccination. "RW" refers to the post-vaccination Days 1-28 risk window. The "washout" period is Days 29-35. "CW" refers to the comparison window, Days 36-56 after Dose 1 and Days 36-63 after Doses 2 and 3.

The positive predictive value of the case-finding algorithm was calculated as the number of definite first-ever VTE cases divided by the number of potential cases for which VTE-related medical records were obtained, 53/225=24%. The positive predictive values for definite first-ever VTE by setting associated with the initial VTE claim code were 8/136=6% for the outpatient setting, 10/34=29% for ED, and 35/55=64% for inpatient. Of the three-digit ICD-9 codes in the algorithm (415.1x (Pulmonary embolism, infarction), 451.x (Phlebitis and thrombophlebitis), and 453.x (Other venous embolism, thrombosis)), 451.x had low positive predictive value. Eighty-one potential cases were ascertained using that three-digit code unaccompanied by either of the other two, of which only 5 were confirmed as definite VTE, for a positive predictive value of only 6%. The positive predictive value was increased by excluding cases in the ambulatory care setting, but only to 9%.

Table 4 shows the case counts and positive predictive values, broken out by setting, for the original algorithm and for an alternative algorithm excluding ICD-9 code 451.x, which should be considered for future studies of VTE. The positive predictive value would have increased from 24% to 51% if the ambulatory care setting had not been included in the original algorithm; it would have increased from

24% to 33% if code 451.x had not been part of the algorithm. Leaving both the ambulatory care setting and code 451.x out of the algorithm would have given a positive predictive value of 65%.

Table 4. Case counts and positive predictive values (PPV) of the original algorithm (415.x, 451.x, or 453.x in any setting) and of alternative algorithms using different subsets of ICD-9 codes and/or settings. IP=inpatient, ED=emergency department, AV=ambulatory care (visit).

	Original: 415.x, 451.x, or 453.x				Excluding 451.x from algorithm			
	IP	ED	AV	Total	IP	ED	AV	Total
Definite	35	10	8	53	34	9	5	48
Possible	2	2	2	6	2	2	2	6
Probable	1	0	0	1	1	0	0	1
Ruled out	16	22	125	163	8	9	71	88
Hx of VTE	1	0	1	2	1	0	0	1
Total	55	34	136	225	46	20	78	144
PPV	64%	29%	6%	**24%**	74%	45%	6%	**33%**
PPV, IP&ED	**51%**				**65%**			

Table 5 presents the savings in chart review and the costs in terms of definite VTE cases missed for three alternative algorithms—one without the ambulatory care setting, one without the 451.x code, and one without either. In addition, the last column—containing the reciprocal of the positive predictive value—shows the cost, in terms of chart review, of each definite VTE case ascertained using the respective algorithm element (ambulatory care setting and/or 451.x code). For example, in the ambulatory care setting, 17 charts were reviewed for every definite case obtained.

Table 5. Effect of three possible alterations of VTE case-finding algorithm on positive predictive value, chart review, and number and proportion of cases that would be missed. The last column shows the cost, in terms of chart review, of each definite VTE case that was found using the respective algorithm element(s) proposed for exclusion (ambulatory care (AV) setting, 451.x code).

Change to algorithm	Positive predictive value (PPV)	Chart review saved	Definite cases missed	Proportion of missed cases	Reviewed cases/ definite cases
No AV setting	51%	136	8	8/53 = 15%	136/8 = 17
No 451.x code	33%	81	5	5/53 = 9%	81/5 = 16
Neither AV nor 451.x	65%	159	10	10/53 = 19%	159/10 = 16

Of the 60 definite, probable, or possible cases, medical records to confirm details of the Gardasil exposure were obtained for 35 (58%). Claims data appeared to under-represent the dose number in some instances: Of 12 doses appearing as the first dose in claims data, one was Dose 2 and one was Dose 3 according to chart data (Table 6). Of 18 doses appearing as the second dose in claims, 6 were Dose 3 according to charts. Where discrepancies in dose number existed, the dose number from charts was used in analysis, as it was considered more plausible for a data source (in this case, claims) to have

missed a dose than for a data source to have inserted a spurious extra dose. Concordance between electronic claims data and medical record data regarding the date of the index Gardasil vaccination was complete for all cases where Gardasil information from both sources was available.

Table 6. Comparison of electronic (claims and IIS) data and medical record data on Gardasil vaccination

Subset for whom relevant Gardasil information was *not* obtained from medical records				
According to electronic data →	Dose 1	Dose 2	Dose 3	Total
	12	7	6	25
Subset for whom relevant Gardasil information *was* obtained from medical records				
According to electronic data → According to chart data ↓	Dose 1	Dose 2	Dose 3	Total
Dose 1	10			10
Dose 2	**1**	12		13
Dose 3	**1**	**6**	5	12
Total	12	18	5	35

C. VTE RISK FACTORS

The frequencies of the 15 VTE risk factor categories, among the 30 definite VTE cases included in the main analyses, are shown in Table 7. The most frequent were oral contraceptive use (23); hypercoagulable states and coagulation defects (16); and transplant, surgery, venous catheterization, and other immobility conditions, including long-distance travel (16).

Table 7. VTE risk factors exhibited among the 30 definite VTE cases in the main SCRI analyses, according to claims and/or medical record data

Group no.	Risk factor group description	No. of definite VTE cases with risk factor
1	Hypercoagulable states and coagulation defects	16
2	Cancer, inflammatory conditions, infection	7
3	Cardiovascular conditions	4
4	Cardiac conditions	0
5	Transplant, surgery, venous catheterization, other immobility conditions, excluding long-distance travel	12
5a	As above but including recent long-distance travel, according to the medical record (more inclusive than #5)	16
6	Pregnancy	0
7	Sickle cell anemia	1
8	Obesity	10
8a	Obesity and overweight (more inclusive than #8)	14
9	Renal conditions	1
10	Tobacco use	3
11	Oral contraceptive (CHC) use	23

Group no.	Risk factor group description	No. of definite VTE cases with risk factor
12	Thoracic outlet syndrome	2
13	Family history of VTE	4

The number of risk factor groups in the 30 patients with definite VTE ranged from 1 to 5 per patient; most patients had 2 or 3 (Table 8). (These numbers exclude Categories 5a and 8a, which are supersets of Categories 5 and 8, respectively.)

Table 8. Frequency of risk factors (excluding Groups 5a and 8a) among the 30 definite VTE cases in the main SCRI analyses

No. of risk factor groups	No. of patients
0	0
1	3
2	10
3	10
4	5
5	2

The risk factor groups and other characteristics of the 33 definite, probable, or possible cases are shown in Table 9.

Table 9. Risk factor groups and other characteristics of the 33 definite, probable, or possible cases in risk and control intervals

Case #	Age group	Case status	Gardasil dose preceding VTE onset	Number of days from Gardasil dose to VTE onset	VTE risk factor groups*	CHC use	Gardasil vaccination date minus CHC start date**	CHC time-varying risk
1	12-14	Definite	3	16	1, 2, 5	No	(No CHCs)	No
2	12-14	Definite	3	36	1, 5	No	(No CHCs)	No
3	15-17	Definite	1	25	1, 2, 8, 13	Yes	12	Yes
4	15-17	Definite	1	26	8, 13	Yes	0	Yes
5	15-17	Definite	1	43	1	Yes	47	Yes
6	15-17	Definite	1	51	5	No	(No CHCs)	No
7	15-17	Definite	2	49	1, 3, 8	Yes	60	Yes
8	15-17	Definite	2	62	1, 12	Yes	259	Yes
9	15-17	Definite	3	26	1, 8	Yes	(Long-term)	No
10	15-17	Definite	3	48	1, 2, 3, 5, 9	No	(No CHCs)	No
11	18-20	Definite	1	37	5, 8, 10	Yes	Unknown	Unknown
12	18-20	Definite	2	5		Yes	71	Yes
13	18-20	Definite	2	10	5	Yes	(Long-term)	No
14	18-20	Definite	2	21	1, 8a	Yes	62	Yes
15	18-20	Definite	2	21	1, 5a, 8a	Yes	94	Yes
16	18-20	Definite	2	43	1, 5a	Yes	75	Yes
17	18-20	Definite	2	60	2, 5, 8a	No	(No CHCs)	No

Case #	Age group	Case status	Gardasil dose preceding VTE onset	Number of days from Gardasil dose to VTE onset	VTE risk factor groups*	CHC use	Gardasil vaccination date minus CHC start date**	CHC time-varying risk
18	18-20	Definite	2	63	3, 8	Yes	Unknown	Unknown
19	18-20	Definite	3	3	5, 13	Yes	-3	Yes
20	18-20	Definite	3	57	5, 12	Yes	-3	Yes
21	21-23	Definite	1	17	1, 5, 8	Yes	26	Yes
22	21-23	Definite	1	41	2, 5, 8	Yes	(Long-term)	No
23	21-23	Definite	1	48	1, 2, 3, 7	No	(No CHCs)	No
24	21-23	Definite	2	47	2, 10	Yes	(Long-term)	No
25	21-23	Definite	2	58	1, 5a, 8a	Yes	101	Yes
26	24-26	Definite	1	17	5, 8	Yes	226	Yes
27	24-26	Definite	2	49	1, 13	Yes	166	Yes
28	24-26	Definite	3	15	8	No	(No CHCs)	No
29	24-26	Definite	3	17	10	Yes	(Long-term)	No
30	24-26	Definite	3	48	1, 5a	Yes	Unknown	Unknown
31	21-23	Probable	2	24	8a	Yes	-1	Yes
32	15-17	Possible	3	63		Yes	-15	Yes
33	21-23	Possible	3	36	5, 8	Yes	181	Yes

* Key to risk factor groups is in Table 3 and Table 7. Contraceptive use is not shown in this column. Groups 5a and 8a are shown only if patient did not also have Group 5 or 8, respectively.

** Positive numbers indicate CHC use started prior to index dose of Gardasil.

An average of 11% of Gardasil first-dose recipients had a first contraceptive dispensing within 59 days before or after their first dose. The proportion was highest (22%-25% in each year of age) for 19-26 year olds, in which group the number of first doses was lowest (< 21,000 in each year of age) (Figure 3).

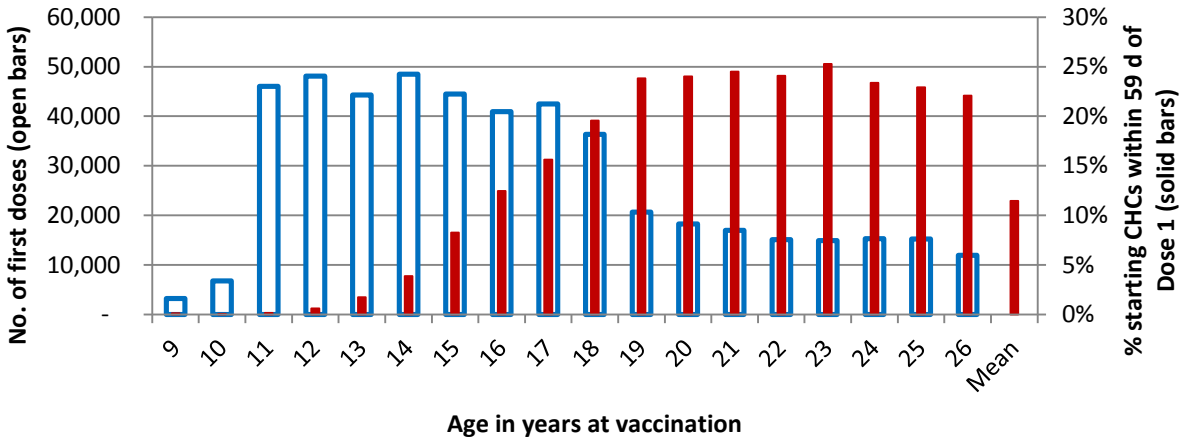


Figure 3. Number of Gardasil Dose 1 vaccinees and percentage with a first CHC dispensing within +/- 59 days of Dose 1, by age.

D. CHC-VTE RISK MODELING

Approximately 9,000 potential cases of VTE in roughly 12 million person-years were included in the CHC-VTE modeling. Ultimately, a model including Data Partner (5 levels), CHC flag (2 levels), estrogen dose indicator (high/low), age group (6 levels), secular month (continuous, modeled as a linear function), weeks on CHCs (continuous, modeled as a cubic function), and two interaction terms—age in years x CHC status and Data Partner x secular month—was selected as the most appropriate one, based on both statistical and biological criteria. The model was selected prior to any analysis of the Gardasil-VTE association.

Figure 4 shows the shape of the cubic function describing the risk of VTE by duration of CHC use from the model.

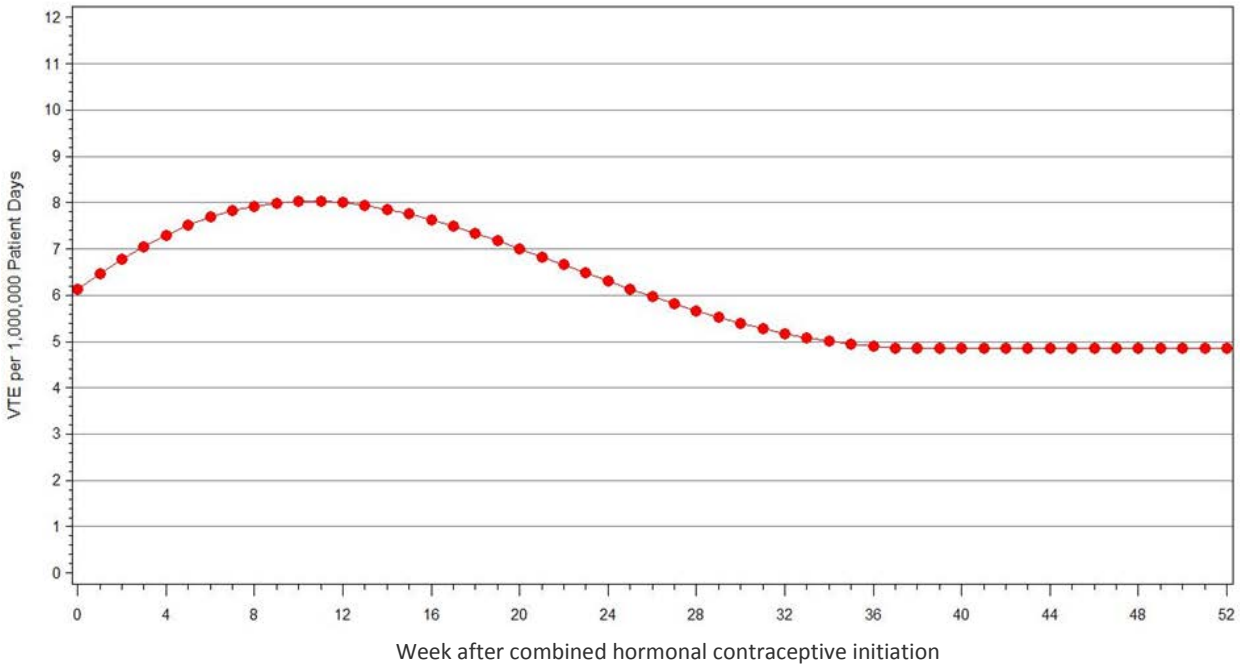


Figure 4. Predicted VTE incidence by week in the year after combined hormonal contraceptive initiation. The curve of predicted VTE incidence obtained by modeling VTE risk by duration of CHC use is a cubic function to Week 39 (9 months) of CHC duration, after which the risk was determined to plateau. The model, including the cubic function describing the risk of VTE by duration of CHC use, was used for calculating offset terms for the CHC-adjusted Analysis #3.

E. GARDASIL-VTE STATISTICAL ANALYSIS

a. SCRI analyses of Gardasil-VTE association

Table 10 shows the results of the three co-primary analysis methods—#1-unadjusted for duration of CHC use, #2- restricted to never- and long-term CHC users, and #3-CHC-adjusted, respectively—applied to the definite VTE cases. All the results were null, regardless of dose number or risk interval. The CHC-

adjusted results for the unrestricted group (bottom third of the table) were very similar to the unadjusted results for the same group (top third of the table). The second of the three approaches, which dealt with potential confounding from CHC use by restricting to patients determined to have no time-varying risk due to CHCs, had comparatively few cases (middle third of the table) and thus was less informative than we had hoped.

Table 10. Case counts and risk estimates for the three co-primary self-controlled risk interval analyses of the association between Gardasil and VTE, for all doses and both risk windows. Only definite VTE cases were included in analysis. "RW" refers to the risk window; "CW" refers to the control window.

1. Analyses with all definite VTE cases, with **no adjustment** for CHC use						
Dose	Days in RW	Cases in RW	Cases in CW	RR	95% CI lower bound	95% CI upper bound
1	1-28	4	5	0.60	0.15	2.27
2	1-28	4	8	0.50	0.13	1.59
3	1-28	5	4	1.25	0.33	5.05
All	1-28	13	17	0.70	0.33	1.44
1	1-7	0	5	0	--	--
2	1-7	1	8	0.50	0.03	2.73
3	1-7	1	4	1.00	0.05	6.76
All	1-7	2	17	0.43	0.07	1.51
2. Analyses with definite VTE cases, **restricted** to those with no time-varying risk of VTE from CHC use						
Dose	Days in RW	Cases in RW	Cases in CW	RR	CI lower bound	CI upper bound
1	1-28	0	3	0	--	--
2	1-28	1	2	0.50	0.02	5.22
3	1-28	4	2	2.00	0.39	14.42
All	1-28	5	7	0.66	0.20	2.08
1	1-7	0	3	0	--	--
2	1-7	0	2	0	--	--
3	1-7	0	2	0	--	--
All	1-7	0	7	0	--	--

3. Analyses with all definite VTE cases, with **adjustment** for CHC use						
Dose	Days in RW	Cases in RW	Cases in CW	RR	CI lower bound	CI upper bound
1	1-28	4	5	0.61	0.15	2.32
2	1-28	4	8	0.47	0.13	1.50
3	1-28	5	4	1.29	0.34	5.21
All	1-28	13	17	0.70	0.33	1.43
1	1-7	0	5	0	--	--
2	1-7	1	8	0.47	0.03	2.55
3	1-7	1	4	1.09	0.06	7.38
All	1-7	2	17	0.43	0.07	1.50

The 3 probable or possible VTE cases were included in sensitivity analyses. All had time-varying risk due to CHC use, thus there were no such cases to add to the second, restricted analysis. Results of the other two analysis methods are shown in Table 11. In these unrestricted analyses, the addition of 2 probable/ possible cases to the comparison interval of Dose 3 caused the point estimates for that dose to change from ≥ 1 to < 1 (Table 10 and Table 11). The addition of 1 case to the 28-day risk interval of Dose 2 led to a small increase in the point estimates for that dose. The altered risk estimates for Doses 2 and 3 and for all-doses combined remained statistically non-significant.

Table 11. Case counts and risk estimates for self-controlled risk interval sensitivity analyses of the association between Gardasil and VTE including definite, probable, and possible VTE cases. "RW" refers to the risk window; "CW" refers to the control window. Rows identical to the corresponding rows in Table 10 (because there were no probable or possible VTE cases for the respective dose number and risk window) are in blue.

1a. Analyses with all definite, probable, or possible VTE cases, with **no adjustment** for CHC use						
Dose	Days in RW	Cases in RW	Cases in CW	RR	95% CI lower bound	95% CI upper bound
1	1-28	4	5	0.60	0.15	2.27
2	1-28	5	8	0.63	0.19	1.87
3	1-28	5	6	0.83	0.24	2.77
All	1-28	14	19	0.68	0.33	1.35
1	1-7	0	5	0	--	--
2	1-7	1	8	0.50	0.03	2.73
3	1-7	1	6	0.67	0.04	3.90
All	1-7	2	19	0.39	0.06	1.35

3a. Analyses with all definite, probable, or possible VTE cases, with **adjustment** for CHC use						
Dose	Days in RW	Cases in RW	Cases in CW	RR	CI lower bound	CI upper bound
1	1-28	4	5	0.61	0.15	2.32
2	1-28	5	8	0.60	0.18	1.80
3	1-28	5	6	0.89	0.25	2.95
All	1-28	14	19	0.69	0.34	1.37
1	1-7	0	5	0	--	--
2	1-7	1	8	0.47	0.03	2.57
3	1-7	1	6	0.78	0.04	4.65
All	1-7	2	19	0.40	0.06	1.37

None of the analyses of effect modification by age or by VTE risk factor produced statistically significant results, nor did any of the analyses using the Days 1-35 risk interval (Table 12).

Table 12. Case counts and risk estimates for self-controlled risk interval sensitivity analyses of the association between Gardasil and VTE, using a risk window of Days 1-35 post-vaccination. Only definite VTE cases were included in analysis. "RW" refers to the risk window; "CW" refers to the control window.

1. Analyses with all definite VTE cases, with **no adjustment** for CHC use						
Dose	Days in RW	Cases in RW	Cases in CW	RR	95% CI lower bound	95% CI upper bound
1	1-35	5	5	0.60	0.17	2.16
2	1-35	6	8	0.60	0.20	1.73
3	1-35	8	4	1.60	0.50	5.99
All	1-35	19	17	0.83	0.43	1.61
2. Analyses with definite VTE cases, **restricted** to those with no time-varying risk of VTE from CHC use						
Dose	Days in RW	Cases in RW	Cases in CW	RR	CI lower bound	CI upper bound
1	1-35	1	3	0.20	0.01	1.56
2	1-35	2	2	0.80	0.10	6.66
3	1-35	5	2	2.00	0.43	13.96
All	1-35	8	7	0.85	0.30	2.42
3. Analyses with all definite VTE cases, with **adjustment** for CHC use						
Dose	Days in RW	Cases in RW	Cases in CW	RR	CI lower bound	CI upper bound
1	1-35	5	5	0.61	0.17	2.20
2	1-35	6	8	0.58	0.19	1.66
3	1-35	8	4	1.60	0.50	5.99
All	1-35	19	17	0.82	0.42	1.59

b. Temporal scan statistics

The temporal distribution of onsets of definite VTE cases from Day 1 post-vaccination through the last day of the respective control interval is shown for Doses 1, 2, and 3 in Figure 5. Of the temporal scan statistical tests conducted on the onsets of the definite VTE cases after Doses 1, 2, 3, and all doses combined, none detected any statistically significant clustering of post-vaccination onset timing.

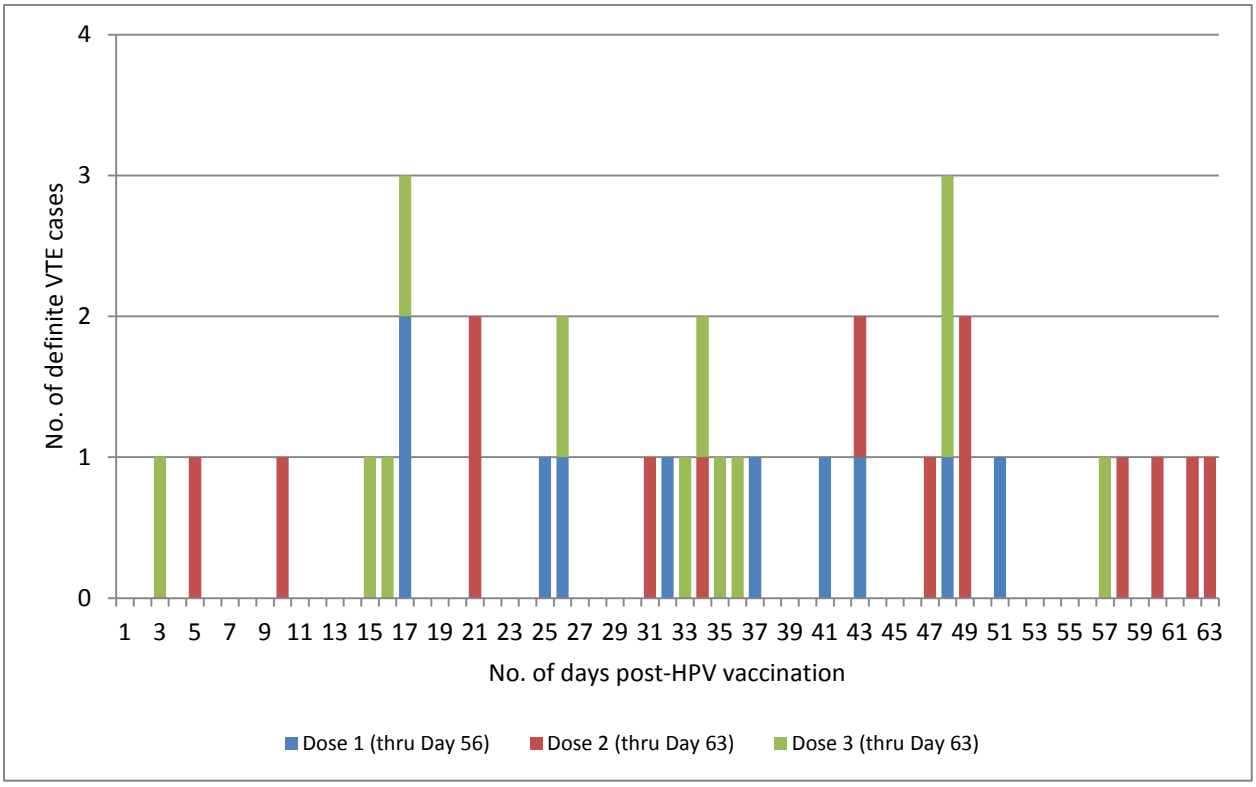


Figure 5. Temporal distribution of onsets of definite VTE cases from Day 1 post-vaccination through the last day of the respective control interval for Gardasil Doses 1, 2, and 3

V. DISCUSSION

In December 2010, FDA presented a review of the postlicensure safety data to FDA's Pediatric Advisory Committee.[8] Data from VAERS and VSD were presented that suggested that more VTE cases were being observed than expected after vaccination with Gardasil. Because these data were inconclusive, FDA launched this Sentinel study to further investigate the risk in a larger population. The main results that shaped our investigation were from the VSD, which included 600,558 doses of Gardasil administered to females aged 9-26 years.[6,7] During prospective surveillance, the VSD researchers found an elevated, although not statistically significant, point estimate of risk of VTE among Gardasil vaccinees aged 9-17 years compared with a historical comparison group of girls of the same age (relative risk based on 8 potential cases identified in electronic data at end of surveillance: 1.98). No elevated risk was detected after Gardasil vaccination among women aged 18–26 years. Medical records of the 8 potential VTE cases found in the electronic data 1–42 days after vaccination were reviewed, and 5 of the cases were confirmed. All 5 confirmed cases had at least one known VTE risk factor. The VTE diagnosis in 4 of the 5 confirmed cases occurred within 1-7 days after vaccination.

The VSD's findings of acute-onset VTE and the presence of known VTE risk factors in the VTE cases (which could have produced confounding) informed our choice of study design and risk intervals. In view of the prevalence of known VTE risk factors among the VSD cases, we used a self-controlled design,

which served to control completely for time-invariant confounders such as genetically determined coagulation disorders. Regarding risk intervals, there is no clear consensus about what the true risk period for VTE after vaccination might be (assuming vaccination is linked to thrombosis at all). Based on the onset intervals of the 5 VTE cases in the VSD study, we selected Days 1-28 as the primary risk interval. We chose Days 1-7 as a secondary risk interval because of VSD's finding that 4 of the 5 confirmed cases had VTE diagnosed within Days 1-7 after vaccination. (Regarding control intervals, we selected a post-vaccination one instead of a pre-vaccination one in order to avoid the bias that would have been present if a VTE event were to influence the occurrence and/or timing of subsequent Gardasil vaccination in a patient.[23,24])

In our self-controlled study comprising more than 1.4 million doses of Gardasil among more than 650,000 9-26 year old females in the U.S., we found no evidence of an increased risk of VTE. None of the self-controlled risk interval analyses produced statistically significant results for any of the doses or risk intervals. Likewise, the temporal scan statistical test did not detect any temporal clustering of VTE onsets in the 8-9 weeks after Gardasil vaccination, providing reassurance that we did not miss an increased risk that might have existed even in the few weeks beyond our primary 28-day interval. Two key sensitivity analyses were also conducted: (a) one that included all levels of diagnostic certainty ("probable" or "possible" VTE cases) and (b) another that extended the risk window to include the washout period (a change from 1-28 days to 1-35 days post-vaccination). Neither sensitivity analysis revealed evidence of an association.

The numbers of VTE cases following Doses 1, 2, and 3 of Gardasil in the temporal scan analysis look somewhat similar (10, 14, and 12 cases in the weeks after Dose 1, 2, and 3, respectively) despite the apparently progressively fewer people receiving Doses 2 and 3 compared to Dose 1 according to the claims data. This might suggest to some that there is a greater risk after Dose 2 or 3 than after Dose 1. However, it is likely a consequence of three circumstances: (a) The claims data were not always accurate regarding the dose number—chart review revealed that later doses were sometimes misclassified as earlier doses in the claims data (Table 6). Thus, the *true* distribution of Gardasil doses is less skewed toward first doses than it appears to be according to the claims data. (b) The follow-up period for Dose 1 was 1 week shorter than the follow-up period for Doses 2 and 3. (c) Finally, with numbers as low as those observed, chance could have played a role in producing differences from the expected distribution of cases among the three doses. In any case, neither the SCRI analyses nor the temporal scan statistical analysis identified an increased risk of VTE after any of the three doses, and, unlike inferences based on comparing VTE incidence among claims-based dose numbers, these findings are all based on chart-confirmed cases and chart-confirmed dose numbers as well as self-controlled methods.

The strengths of our study are its size, the self-controlled design used to control for time-invariant confounding, the adjustment for time-varying confounding from CHC use, the checks for possible effect modification by age and VTE risk factors, the use of chart review to validate both cases and exposures, and the use of the temporal scan statistic to supplement the main analyses. The shape of the risk curve of VTE by CHC duration obtained from modeling and used for the adjustment of the Gardasil-VTE analysis (Analysis #3) was consistent with what has been reported in the literature.[13]

Because of the control for confounding and other strengths of our study, we consider our null results to be more credible than the association suggested by the VAERS study that found disproportional

reporting of venous thromboembolic events using data mining methods.[5] Considering that VSD saw an elevated (albeit not statistically significant) risk estimate for 9-17 year olds but not for 18-26 year olds,[6,7] we checked to see if the risk of VTE after Gardasil vaccination varied with age at vaccination and found no evidence of such effect modification by age. Indeed, the definite cases aged 9-17 years did not fall predominantly in the risk interval, but rather 4 occurred in the risk interval and 6 in the control interval (Cases 1-10 in Table 9).

The lack of association we found agrees with the results of three studies published more recently than the VAERS and VSD studies. The first, an FDA postmarket commitment study, used a SCRI design with two alternative risk intervals, Days 1-14 and Days 1-60, and included approximately 190,000 females in Kaiser Permanente of Northern and Southern California who had received at least one dose of Gardasil. No increased risk of venous embolism, thromboembolic events, or other clotting disorders or dysfunction was observed.[25] The second was a cohort study comprising more than 696,000 doses of Gardasil administered to females in Denmark and Sweden. No increased risk of VTE was seen using a risk window of 1-90 days after vaccination (rate ratio 0.86 (95% CI: 0.55-1.36)).[26] The third used a self-controlled case series design to eliminate time-invariant confounding and studied a population of Danish females; 500,345 of these had received Gardasil. Using a post-vaccination risk window of 1-42 days, the investigators found an incidence ratio of 0.77 (95% CI: 0.53-1.11).[27]

We found that the positive predictive value of our VTE case-finding algorithm, 24%, could have been increased by not including the ambulatory care setting and/or the 451.x phlebitis and thrombophlebitis ICD-9 code. Those algorithm elements led to a cost of 16-17 charts reviewed for every definite case identified. However, excluding those elements from the algorithm would have meant missing 9%-19% of the definite cases identified by means of the full algorithm. This information, together with a sense of the relative importance of sensitivity (to maximize statistical power) and specificity (to minimize chart review burden) for a particular study, may be helpful in selecting case-finding algorithms in future studies of VTE.

One limitation of our study was the possible existence of some misclassification of CHC duration in the CHC-adjusted analysis (Analysis #3). Such misclassification could have occurred as a result of: 1) failure of claims data to capture complete information on CHC use (if, for example, a patient obtained contraceptives from a Planned Parenthood organization), 2) the RxDate not necessarily being the true CHC initiation date, 3) our ignoring of any apparent *discontinuation* of CHC use during the observation period, and 4) the use of a minimum enrollment requirement of 4 months instead of longer, which theoretically could have led to longer-term CHC use being misclassified as shorter-term use. But given the variability in the period of time between CHC initiation and Gardasil vaccination observed, it seems unlikely for any consistent bias to have been introduced by such misclassification.

Another limitation was that charts could not be obtained for approximately one-fifth of the potential cases identified by the algorithm. This is similar to the proportion of cases with unobtainable charts in other recent PRISM studies—22% in the rotavirus vaccine-intussusception study[11] and 14% in the influenza vaccine-febrile seizures study,[28] for example. The fact that charts were not obtained for all cases reduced statistical power.

Finally, in light of the fact that there were only 30 definite VTE cases in risk and control intervals, the analyses of effect modification by age and VTE risk factors, which all produced null results, may have had limited power to detect true effect modification of the Gardasil-VTE relationship by these factors.

VI. CONCLUSIONS

In this study comprising more than 1.4 million doses of Gardasil administered, we found no evidence of an increased risk of VTE among 9-26 year old females. These results agree with those of three recent studies. Particular strengths of our study were the self-controlled design, which controlled for time-invariant confounding, and the adjustment for time-varying confounding from CHC use.

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VIII. APPENDICES

Appendix 1: Codes used to identify VTE

ICD9	Description
415.1*	(This would include all codes beginning with these 4 digits.)
415.1	Pulmonary embolism and infarction
415.11	Iatrogenic pulmonary embolism and infarction
415.12	Septic pulmonary embolism
415.19	Other pulmonary embolism and infarction
451.*	(This would include all codes beginning with these 3 digits.)
451	Phlebitis and thrombophlebitis
451.0	Phlebitis and thrombophlebitis of superficial vessels of lower extremities
451.1	Phlebitis and thrombophlebitis of deep veins of lower extremities
451.11	Phlebitis and thrombophlebitis of femoral vein (deep) (superficial)
451.19	Phlebitis and thrombophlebitis of other
451.2	Phlebitis and thrombophlebitis of lower extremities unspecified
451.8	Phlebitis and thrombophlebitis of other sites
451.81	Phlebitis and thrombophlebitis of iliac vein
451.82	Phlebitis and thrombophlebitis of superficial veins of upper extremities
451.83	Phlebitis and thrombophlebitis of deep veins of upper extremities
451.84	Phlebitis and thrombophlebitis of upper extremities unspecified
451.89	Phlebitis and thrombophlebitis of other sites
451.9	Phlebitis and thrombophlebitis of unspecified site
453.*	(This would include all codes beginning with these 3 digits.)
453	Other venous embolism and thrombosis
453.0	Budd-Chiari syndrome
453.1	Thrombophlebitis migrans
453.2	Embolism and thrombosis of inferior vena cava
453.3	Embolism and thrombosis of renal vein
453.4	Acute venous embolism and thrombosis of deep vessels of lower extremity
453.40	Acute venous embolism and thrombosis of unspecified deep vessels of lower extremity
453.41	Acute venous embolism and thrombosis of deep vessels of proximal lower extremity
453.42	Acute venous embolism and thrombosis of deep vessels of distal lower extremity
453.5	Chronic venous embolism and thrombosis of deep vessels of lower extremity
453.50	Chronic venous embolism and thrombosis of unspecified deep vessels of lower extremity
453.51	Chronic venous embolism and thrombosis of deep vessels of proximal lower extremity
453.52	Chronic venous embolism and thrombosis of deep vessels of distal lower extremity
453.6	Venous embolism and thrombosis of superficial vessels of lower extremity

ICD9	Description
453.7	Chronic venous embolism and thrombosis of other specified vessels
453.71	Chronic venous embolism and thrombosis of superficial veins of upper extremity
453.72	Chronic venous embolism and thrombosis of deep veins of upper extremity
453.73	Chronic venous embolism and thrombosis of upper extremity, unspecified
453.74	Chronic venous embolism and thrombosis axillary veins
453.75	Chronic venous embolism and thrombosis of subclavian veins
453.76	Chronic venous embolism and thrombosis of internal jugular veins
453.77	Chronic venous embolism and thrombosis of other thoracic veins
453.79	Chronic venous embolism and thrombosis of other specified veins
453.8	Acute venous embolism and thrombosis of other specified veins
453.81	Acute venous embolism and thrombosis of superficial veins of upper extremity
453.82	Acute venous embolism and thrombosis of deep veins of upper extremity
453.83	Acute venous embolism and thrombosis of upper extremity, unspecified
453.84	Acute venous embolism and thrombosis of axillary veins
453.85	Acute venous embolism and thrombosis of subclavian veins
453.86	Acute venous embolism and thrombosis of internal jugular veins
453.87	Acute venous embolism and thrombosis of other thoracic veins
453.89	Acute venous embolism and thrombosis of other specified veins
453.9	Embolism and thrombosis of unspecified site

Appendix 2: Codes used to identify select VTE risk factors

Group	Category	Condition	Look back from VTE diagnosis	Code type	Codes
1	**Primary hypercoagulable state**	Primary hypercoagulable state	Since enrolled	ICD9DX	289.81
		Sulfur bearing amino acid metabolism disturbances	Since enrolled	ICD9DX	270.4
	Coagulation defects	Congenital deficiency of clotting factors (dysfibrinogenemia)	Since enrolled	ICD9DX	286.3
	Secondary hypercoagulable state	Secondary hypercoagulable state	90 days	ICD9DX	289.82
2	**Cancer**	Malignancy (except skin)	183 days	ICD9DX	140.x–171.x, 174.x–208.x,
		Chemotherapy	183 days	ICD9PX	99.25
			183 days	ICD9DX	V58.1x
		Radiation therapy	183 days	ICD9DX	V58.0
				CPT4PX	20555
	Inflammatory conditions	Inflammatory bowel disease	Since enrolled	ICD9DX	555.x, 556.x
		Rheumatoid arthritis	Since enrolled	ICD9DX CPTP2	714.x 0540F, 3455F – 3476F, 4187F, 4192F – 4196F
		Systemic lupus erythematosis	Since enrolled	ICD9DX	695.4
	Infection	Sepsis	60 days	ICD9DX	003.1, 020.2, 022.3, 036.2, 038.x, 054.5, 449, 785.52, 995.91, 995.92
		Osteomyelitis	60 days	ICD9DX	003.24, 730.0x - 730.2x
3	**Cardiovascular conditions**	Metabolic syndrome	Since enrolled	ICD9DX	277.7
		Hyperlipidemia	Since enrolled	ICD9DX	272.0-272.4
		Diabetes mellitus	Since enrolled	ICD9DX	250.x
		Hypertension	Since enrolled	ICD9DX	401.x – 405.x
4	**Cardiac**	Congenital heart disease	Since enrolled	ICD9DX	745.x – 747.x
		Congestive heart failure	Since enrolled	ICD9DX	428.0
5	**Venous catheterization**	Central venous catheter	90 days	CPT4PX	36481, 36500, 36556, 36558, 36561, 36563, 36565, 36566, 36569, 36571, 36575–36598
		Peripherally inserted central catheter	90 days	ICD9PX	38.93

Group	Category	Condition	Look back from VTE diagnosis	Code type	Codes
		Central venous catheter placement with guidance	90 days	ICD9PX	38.97
	Transplant	Lung, heart, liver, bone marrow or hematopoietic stem cell, kidney, pancreas, intestine	90 days	ICD9PX ICD9DX	33.5, 33.6, 37.51, 41.0x, 50.5x, 52.8x, 55.6x V42.0, V42.1, V42.6, V42.7, V42.81-V42.83
			90 days	CPT4PX	32851 – 32854, 33935, 33945, 38340, 44133-44137, 47135, 48554, 50360, 50365, 50380
		Complications of transplanted organ	90 days	ICD9DX	996.81 – 996.86
	Immobility conditions	Fracture of skull, spine and trunk, lower limb	90 days	ICD9DX	800.x – 809.x, 820.x – 829.x, V54.13- V54.17, V54.23-V54.27
		Extracranial injury	90 days	ICD9DX	851.x-854.x, 861.x-869.x
		Crushing injury	90 days	ICD9DX	925.x – 929.x
		Burns (>10% body surface)	30 days	ICD9DX	948.1 – 948.9
		Spinal cord injury	90 days	ICD9DX	952.x
		Spina bifida	Since enrolled	ICD9DX	741.x
		Paralysis	Since enrolled	ICD9DX	342.x- 344.x
		Casting: halo, hip spica, long leg	90 days	CPT4PX	29000, 29305, 29325, 29345, 29365
	Open Urologic Surgery	Renal exploration or drainage	90 days	CPT4PX	50010–50045
		Repair of anomalous vessels of kidney			50100
		Procedures of renal pelvis			50100–50135
		Nephrectomy			50220-50240
		Open surgical procedures of the kidney			50400-50540
		Open repairs urinary system			51800–51980
		Nephrectomy	90 days	ICD9PX	55.4-55.5x
	Open Gynecologic Surgery	Myomectomy	90 days	CPT4PX	58140-58146
		Open procedures fallopian tubes with/without ovaries			58700-58770
		Open procedure ovary			58800-58925
		Removal ovary with/without multiple procedures for malignancy			58940-58960

Group	Category	Condition	Look back from VTE diagnosis	Code type	Codes
		Tubal pregnancy, hysterotomy procedures			59100-59140
	Bariatric Surgery	Anesthesia for intraperitoneal procedures in upper abdomen including laparoscopy; gastric restrictive procedure for morbid obesity	90 days	CPT4PX	00797
		Laparoscopic gastric bypass with small bowel resection			43644, 43645
		Laparoscopic bariatric procedures			43770–43775
		Open bariatric procedure for morbid obesity			43842–43865
		Bariatric procedures: removal, replacement, revision port components			43886-43888
		Bariatric procedures	90 days	ICD9PX	43.7, 43.82, 43.89, 44.31, 44.38, 44.39, 44.5, 44.68, 44.69, 44.95-44.99, 45.51, 45.91
	Open Gastrointestinal surgery	Enterolysis, enterectomy	90 days	CPT4PX	44005, 44120-44128
		Colon resection			44139-44160
		Open repair procedures of intestine			44602-44680
		Open and transrectal procedures of rectum			45000-45190
		Resection of anal fistula			46270-46320
		Anal repairs			46700-46947
		Hepatectomy			47120-47130
		Open repair of liver			47300-47362
		Open procedures of the pancreas			48000-48548
		Exploratory and drainage procedures: abdomen and peritoneum			49000-49081

Group	Category	Condition	Look back from VTE diagnosis	Code type	Codes
		Resection of presacreal/sacrrococcygeal tumor			49215
		Surgical repair abdominal wall			49900
		Open excision of large and small intestine, total abdominal colectomy, intestinal anastomosis	90 days	ICD9PX	45.6-45.9x
		Other repair of intestine			46.7x
		Resection or repair of rectum, repair of fistula			48.4-48.99
		Hepatectomy, repair of liver			50.22, 50.3, 50.4, 50.6x
		Exploratory laparotomy			54.11
	Intracranial neurosurgery	Craniectomy/craniotomy	90 days	CPT4PX	61304-61323, 61340-61530, 61566, 61567
		Lobectomy, hemispherectomy			61537-61543
		Craniotomy for hypophysectomy, pituitary tumor			61546
		Removal of foreign body from brain			61570, 61571
		Surgical treatment of arteriovenous malformation			61680-61692, 61705
		Surgical treatment brain aneurysm			61697, 61700
		Craniotomy, craniectomy	90 days	ICD9PX	01.2x
	Hip or lower extremity surgery	Incision, bone cortex, pelvis and/or hip (e.g. osteomyelitis or bone abscess)	90 days	CPT4PX	26992
		Procedures of bones and joints of hip and pelvis			27050-27071
		Radical resection of bone tumor of hip/pelvis			27075-27078
		Revision/reconstruction of hip and pelvis (e.g. slipped femoral epiphysis, hip arthroplasty)			01214, 01215, 27097-27187

Group	Category	Condition	Look back from VTE diagnosis	Code type	Codes
		Open treatment of fracture/dislocation of hip/pelvis			27202, 27215, 27217, 27218, 27226-27228, 27236, 27248, 27253, 27254, 27258, 27269
		Knee arthroplasty			01402, 27437-27447, 27486, 27487
		Open treatment of fracture/dislocation of femur/knee			27506, 27507, 27511, 27513, 27514, 27519, 27524, 27535, 27540, 27556, 27566
		Revision of hip and knee replacement	90 days	ICD9PX	00.7–00.87
		Application of external fixator device (pins/wires, screws into bone), internal fixation			78.15, 78.17, 78.55, 78.57, 79.15, 79.16, 79.26, 79.35, 79.36, 79.5, 84.7x
		Open reduction of dislocation of hip or knee			79.85, 79.86
		Joint replacement lower extremity			81.5x
	Spinal cord surgery	Partial resection vertebral component	90 days	CPT4PX	22100-22103
		Spinal fusion: lateral extracavitary approach			22532-22534
		Spinal fusion: anterior and posterior approach			22548-22632
		Procedures to correct anomalous spinal vertebrae			22800-22819
		Spinal instrumentation: segmental/non-segmental			22840-22855
		Vertebral corpectomy			63081-63091, 63101-63103, 63300-63308
		Exploration and decompression of spinal canal structures	90 days	ICD9PX	03.0x
		Meningocele and myelomeningocele repair			03.5x
		Spinal fusion			81.0x, 81.6 –81.64
6	**Pregnancy**	Pregnancy and postpartum	Variable		See protocol: http://www.mini-sentinel.org/assessments/medical_events/details.aspx?ID=123

Group	Category	Condition	Look back from VTE diagnosis	Code type	Codes
7	**Sickle cell anemia**	Sickle cell anemia	Since enrolled	ICD9DX	282.6, 282.41, 282.42
8	**Overweight**	Overweight and obesity	365 days	ICD9DX	278.0*, V85.3*, V85.4*, V85.54
			365 days	ICD9DX	278.02-278.09
9	**Renal**	Nephrotic syndrome	Since enrolled	ICD9DX	581.x
10	**Tobacco use**	Tobacco use	Since enrolled	ICD9DX	V15.82
				CPT2	4004F
			Since enrolled	ICD9DX	305.1, 649.0x, 989.84
				CPT4PX	99406, 99407
				CPT2	1034F, 1035F, 4000F, 4001F
				HCPCS	D1320, G0436 – G0437, G8688, G8692, G9016, S4995, S9075, S9453

Appendix 3: Risk factors identified in medical records of the 30 definite VTE cases in the main SCRI analyses

	Description	Risk factor group no.	No. of definite VTE cases with condition
1	Activated protein C resistance	1	1
2	Factor V Leiden (FVL) mutation	1	1
3	Prothrombin 20210 gene mutation	1	1
4	Antithrombin III deficiency	1	2
5	Protein C deficiency	1	2
6	Protein S deficiency	1	3
7	Methylene tetrahydrofolate reductase (MTHFR) mutation	1	4
8	Elevated homocysteine	1	2
9	Other thrombophilic risk factors	1	3
10	Anticardiolipin antibodies/antiphospholipid syndrome/ lupus anticoagulant	1	3
11	Other secondary hypercoagulable state	1	1
12	Systemic lupus erythematosis	2	1
13	Any recent serious infections	2	5
14	Diabetes mellitus, type I or II	3	1
15	Hypertension	3	1
16	Venous catheterization (past 90 days)	5	3
17	Musculoskeletal fracture or injury	5	4
18	Recently bedridden for more than 3 days	5	2
19	Recent surgeries	5	6
20	Recent international or cross-country travel	5a	4
21	Sickle cell anemia	7	1
22	Obesity	8	10
23	Obesity/overweight	8a	14
24	Tobacco use status on date of VTE diagnosis	10	3
25	Oral contraceptive (CHC) use	11	23
26	Thoracic outlet syndrome	12	2
27	Family history of VTE	13	4

Appendix 4. Racial and ethnic composition of potential first-ever VTE cases within 77 days of Gardasil (all female)

Age group in years	9-11	12-14	15-17	18-20	21-23	24-26	Total	Percentage of total
Total in age group	6	26	72	61	56	58	279	
American Indian/Alaska Native	0	0	0	1	0	1	2	0.7%
Black/African American	1	2	7	4	5	5	24	8.6%
White	2	14	30	19	19	18	102	36.6%
Race unknown	3	10	35	37	32	34	151	54.1%
Hispanic	0	2	0	3	1	4	10	3.6%
Not Hispanic	3	11	27	19	13	16	89	31.9%
Hispanic ethnicity unknown	3	13	45	39	42	38	180	64.5%

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