PASS INFORMATION

Title	**Post-licensure Observational Safety Study of Gardasil 9®**
Version identifier of the final study report	**Version 1.0**
Date of last version of the final study report	**10-Dec-2019**
EU PAS register number	**EUPAS 13151**
Active substance	1 dose (0.5 ml): HPV Type 6 L1 protein 30 µg HPV Type 11 and 18 L1 protein 40 µg HPV Type 16 L1 protein 60 µg HPV Type 31, 33, 45, 52 and 58 L1 protein 20 µg adsorbed on amorphous aluminium hydroxyphosphate sulphate (0.5 mg Al).
Medicinal product	**Human Papillomavirus 9-valent Vaccine, (recombinant, adsorbed), ACT code J07BM03**
Joint PASS	No
Research question and objectives	The objective of this study was to describe the general safety of Gardasil 9® (9vHPV vaccine) in a population of at least 10,000 males and females who have received at least one dose of the 9vHPV vaccine by estimating the risk of health outcomes resulting in emergency room visits or hospitalizations occurring within pre-specified risk periods after a dose of the 9vHPV vaccine, and comparing to the risk of such health outcomes in a post-vaccination self-comparison reference period.
Country of study	United States (US)
Author	PPD
Merck Final Repository (RCAM) Date	**10-Dec-2019**

MARKETING AUTHORISATION HOLDER(S)

Marketing authorisation holder(s) (MAH)	US: Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc. EU: MSD VACCINS
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1 EXECUTIVE SUMMARY

Title

Post-licensure Observational Safety Study of Gardasil 9® (Gardasil 9® PLOSS)

Keywords

Gardasil 9®, Safety, Observational

Rationale and background

This observational study was conducted by Merck & Co., Inc., a subsidiary of Merck Sharp & Dohme, Corp. (hereafter referred to as Merck) as a post-licensure regulatory commitment to the United States (US) Food and Drug Administration (FDA) to monitor the general safety of Gardasil 9® (9-valent HPV vaccine, 9vHPV vaccine) when administered as part of routine health care. Clinical trials in large populations (over 16,000 individuals administered at least one dose of 9vHPV with safety follow-up) have shown that the 9vHPV vaccine is generally safe and well tolerated. The 9vHPV vaccine was approved by the FDA in December 2014 and launched in 2015 in the US as a 3-dose regimen for 9 to 26-year-old females, and 9 to 16-year-old males. In December 2015, the US indication was extended to include 16 to 26-year-old males, and in October 2016, an alternative two dose regimen was approved for 9 to 14-year-olds (males and females). In October 2018, the FDA extended the indication to include 9-45 years of age in both males and females.

Research question and objectives

The objective of this study was to describe the general safety of the 9vHPV vaccine in a population of at least 10,000 males and females who have received at least one dose of the 9vHPV vaccine by:

a) estimating the risk of health outcomes resulting in emergency room visits or hospitalizations occurring within a pre-specified risk period after a dose of the 9vHPV vaccine; and
b) comparing to the risk of such health outcomes in a post-vaccination self-comparison reference period.

There is no formal research hypothesis for this study.

Study design

This was a retrospective, observational self-controlled risk interval (SCRI) study. A risk interval after vaccination is compared with a later interval in the same vaccinee, with respect to risk of health outcome events. This self-control design reduces confounding by adjusting for time-stable covariates, such as gender and pre-vaccination medical history. The SCRI design is well-suited to studying time-limited effects of transient exposures for which periods of risk following the exposure can be validly defined.

Setting

This study was conducted at PPD a large integrated healthcare delivery system. At PPD, vaccination and medical records are computerized into databases linked by a unique identifier (electronic medical record, EMR). Therefore, the study data were collected prospectively and analyzed retrospectively. Combined with its large size, PPD healthcare system allowed for efficient accrual of a large population in a short timeframe and rapid generation of safety data on the new 9vHPV vaccine.The study work was conducted by the PPD has participated in the Centers for Disease Control and Prevention (CDC)-funded Vaccine Safety Datalink (VSD) project and has extensive experience in both CDC-funded and industry-funded studies of post-licensure vaccine safety surveillance. This surveillance took advantage of the existing computerized databases and infrastructure within PPD.

The time period covered by this study is 01 October 2015 through 30 September 2017. Accrual of study subjects and follow-up for health outcomes occurred within this timeframe. PPD used Gardasil® (4-valent HPV vaccine, 4vHPV vaccine) starting in August 2006 and began the transition to 9vHPV vaccine in July 2015 when 9vHPV vaccine became available to PPD. The transition was accomplished through using up existing stock of 4vHPV vaccine and replenishing it with 9vHPV vaccine. The two-year study period began after this transition was almost complete and at the time of the US transition of healthcare coding to the International Classification of Diseases, Version 10 (ICD-10) disease classification system. At the beginning of the study period, 9vHPV vaccine was recommended by the US Advisory Committee on Immunization Practices (ACIP) as a 3 dose series for 9 to 26-year-old females and 9 to 21-year-old males, with routine vaccination to begin at 11 to 12 years of age and a catch up schedule for females 13 to 26 years of age and males 13 to 21 years of age. Within several months after study start, the indicated age range for males was extended to include up to 26-year-olds. A 2 dose regimen for 9 to 14-year-olds was recommended by ACIP in November 2016, immediately after FDA's approval and approximately half-way through the study period.

The study protocol was approved by the PPD

Study Population

There was no active enrollment of subjects for this study. The study cohort is comprised of males and females within PPD who received at least one dose of the 9vHPV vaccine and who were 9 years of age or older and members of the health plan at the time of the dose. Males and females who received any doses of the 9vHPV vaccine outside of the health plan were excluded from this study.

The study cohorts exposed to 9vHPV vaccine in this study are as follows:

- *9vHPV-Only Cohort* – subjects who initiated the HPV vaccination and received at least one dose of 9vHPV vaccine during the study period, and who had no exposure to any other HPV vaccines.

- *Any 9vHPV Cohort* – subjects who received at least one dose of 9vHPV vaccine during the study period regardless of exposure to 4vHPV vaccine before, and who had no exposure to any HPV vaccines other than 9vHPV and 4vHPV vaccines. Of note, the *9vHPV-Only Cohort* is embedded entirely in the *Any 9vHPV Cohort*.

Safety Outcomes

Health outcomes resulting in an emergency department visit or hospitalization were grouped using pre-defined Healthcare Cost and Utilization Project (HCUP) categories. HCUP, developed by the US Agency for Healthcare Quality and Research, is a well-established diagnosis grouping structure that offers a 2-tiered pre-specified hierarchical grouping of all diagnosis codes into a manageable number of clinically meaningful categories. There are 18 categories in the top level (level 1) of the HCUP hierarchy that correspond to body systems as used in the International Classification of Diseases, Version 10 (ICD-10) disease classification system. Within the first 17 top level categories there are 135 sub-categories (i.e., level 2 categories), for a total of 152 categories. The 18th top level category (HCUP 18: "Residual codes; unclassified; all E codes"), which has no sub-categories, was excluded. It contains approximately 7,500 diverse codes that are not generally useful, nor easily categorized.

First occurrences of a health outcome in a given HCUP category in risk and comparison intervals are summed and analyzed, allowing for events in both intervals. Emergency department and hospitalization outcomes were combined for analyses, with the number and percent of these events that occurred only in the hospital reported separately.

Allergic reactions/hypersensitivity events and syncope events in the emergency department and hospital occurring on Day 0 (i.e., the date of vaccination) were identified using pre-specified ICD-10 codes rather than HCUP categories because the ICD-10 codes are more specific and allow for a more detailed accounting of allergic reactions.

Deaths among any subject in the *9vHPV-Only Cohort* or *Any 9vHPV Cohort* at any time during the study periods were also identified from medical records, state death data, social security data, and other sources, as available.

Risk and Self-Comparison Intervals

The risk interval is the time period following 9vHPV vaccination during which events were tabulated to estimate the risk of health outcomes following vaccination. Two risk intervals were evaluated: 15 days following a dose of the vaccine (Day 0–14 risk interval) and up to 60 days following a dose of the vaccine (Day 1–60 risk interval). Day 0 is defined as the date of vaccination. Risk intervals after doses 1 to 3 were combined and compared with later intervals of self-comparison time. A Dose-Specific analysis comparing incidence in risk time after each dose (1 to 3) with incidence in the self-comparison interval prior to a next dose

was also conducted. Doses included in the Dose-Specific analysis were only among subjects in the *9vHPV-Only Cohort* and included all doses administered within the study period.

Allergic reaction and syncope events on Day 0 and any deaths at any time during the study period were also evaluated, although without the use of self-comparison intervals.

No event information was collected beyond the end of the study period (30 September 2017) although a six-month period after that date was used to ensure completeness and resolution of data for the study period (i.e., final diagnoses made, non-PPD data received, etc.). All risk and self-comparison intervals stopped at 30 September 2017.

Statistical Analysis

Incidence rates and 95% confidence intervals (CIs) were estimated using the number of health outcomes divided by person-time, using the first occurrences in a given HCUP category that resulted in a hospitalization or emergency department visit during the risk and/or self-comparison interval. Odds ratios (ORs) with 95% CIs, which approximate the risk ratio of the outcome in the risk interval compared to the comparison interval, were calculated using conditional logistic regression. Intervals were designed to be comparable in length, and an offset term was used to address imbalances in risk and self-comparison intervals. A multiplicity adjustment was used to help interpret statistically significant results; however, results were flagged for significance using both unadjusted and multiplicity adjusted methods. Significantly elevated findings were further investigated. Further investigation consisted of reviewing additional details of findings, such as plotting the timing of events to look for potential clusters, performing specific diagnosis review (i.e., reviewing the diagnostic codes listed by the practitioner for the case, or reviewing the actual diagnosis codes that contributed to the HCUP category), conducting medical records review to determine a cause or time of onset, or assessing the impact of the seasonality of vaccine exposure on the findings. At the request of the eSRC (see section below), findings were investigated with consideration of their biological plausibility, clinical relevance, statistical strength, consistency, and temporality in relation to vaccination.

Rates and 95% CIs of Day 0 syncope and allergic reaction events, as well as all-cause deaths were also calculated. Medical records were reviewed and summarized to provide interpretation context for various events.

External Safety Review Committee

An external Safety Review Committee (eSRC) was assembled for this study. The eSRC was composed of 3 independent experts in relevant areas, including vaccine safety, pharmacoepidemiology, pediatrics and adolescent medicine. Committee members were independent of Merck and PPD.

The role of the eSRC was to review and evaluate the study protocol, provide ongoing input on study design and methods as needed, review and assess the study results, and request additional information needed to further evaluate any finding that may be indicative of potential safety concerns.

Results

The populations included in this final report are 140,628 *9vHPV-Only Cohort* subjects who received 239,556 doses of 9vHPV vaccine, and 215,965 *Any 9vHPV Cohort* subjects who received 330,774 doses of 9vHPV vaccine (Table 1).

Table 1. Number of doses received in *9vHPV-Only* and *Any 9vHPV* Study Cohorts within the study period, by gender

	At Least 1 Dose		At Least 2 Doses		At Least 3 Doses	
Cohort	Female	Male	Female	Male	Female	Male
9vHPV-Only (Subject N=140,628)	69,818	70,810	35,036	33,991	15,581	14,320
Any 9vHPV (Subject N=215,965)	69,818	70,810	53,719	55,336	40,690	40,401

The *9vHPV-Only Cohort* had approximately the same number of females as males (49.6% female at first dose, 50.8% female at second dose and 52.1% female at third dose) with most common age for starting the series at 11 or 12 years of age (39.0% started at 11 years of age, 13.6% started at 12 years of age, with age ranging from 9 to 86 years old). Of subjects in the *9vHPV-Only Cohort* initiating the 9vHPV vaccine series, approximately half received a second dose in the study period and 20% received a third dose during the study period. These rates were affected 1) by the end of the study period, beyond which dose information was not collected, and many of these subjects will have received additional doses; and 2) by the 2-dose regimen recommended by ACIP in November 2016, approximately half-way through the study period. On average, subjects had 83.5 days between their first and second dose of 9vHPV vaccine in the first six months of the study, whereas the average interval between first and second dose was 127.3 days in the overall study period (i.e., by the end of the study period).

The *Any 9vHPV Cohort* also had approximately the same number of females as males (49.1% female at first dose, 50.3% female at second dose and 52.1% female at third dose). Members of this cohort may have initiated their HPV vaccine series prior to the study period (e.g., initiated with 4vHPV vaccine and continued the series with 9vHPV vaccine) and age in this cohort referred to when they received their first 9vHPV vaccine dose in the study period. The most common ages at which they received their first 9vHPV vaccine study dose were 11 (28.0%) and 12 (15.2%) years of age, with age ranging from 9 to 86 years.

The months of the year with the highest 9vHPV vaccine administration were June, July and August, with December having the lowest amount administered. In the *9vHPV-Only Cohort*, August had the highest percentage with 13.6% of doses administered, then July with 10.4% and June with 9.4%; the month with the lowest percentage was December with 6.1%. In the *Any 9vHPV Cohort*, August had the highest percentage with 12.4% of doses administered, then July with 9.6%, October with 9.2% and June with 8.7%; the month with the lowest percentage was December with 6.8%.

General Safety Analyses (Self-Controlled Risk Interval Analysis)

Overall, 152 HCUP categories were analyzed, including 17 HCUP level 1 (top level) categories and 135 HCUP level 2 categories. For each HCUP category, a set of ten ORs were estimated, including a Combined Dose series analysis for each of the two study cohort and three Dose Specific analyses for the *9vHPV Only Cohort*, each using two pre-specified risk intervals, Days 0–14 and Days 1–60.

Four of the 17 analyzed HCUP level 1 categories and 14 of the 135 HCUP level 2 sub-categories had significantly elevated results in the multiplicity-unadjusted analysis (i.e., ORs with a lower confidence bound >1.0) in at least one risk interval analysis (Table 2) for a total of 18 significantly elevated results. Interval-specific OR, with 95% CIs and p-values are listed in Table 18. Significantly elevated findings were further reviewed through additional analyses and investigations, including a combination of time plots (e.g., of the time between dose receipt and outcome to look for potential time clusters), specific diagnosis of the event as given at the point of care, and in some cases medical record review. As described below, all of the statistically elevated ORs represented either events already identified at higher rates in vaccine recipients than controls in clinical studies (e.g., headache, local reactions) or events for which a cause-effect relationship with 9vHPV vaccine was implausible upon review (e.g., disorders of teeth and jaw, hernias, congenital anomalies). After multiplicity adjustment, only one of the categories remained stastically elevated, *HCUP 17.1 Symptoms; signs; and ill-defined conditions*, in the dose 1 analysis for Day 0-14 risk interval. Of note, HCUP 17.1 is a broad category containing many diverse diagnoses, with abdominal pain making up the largest subset in both the analyses of Day 0–14 and Day 1–60 risk intervals.

Table 2. HCUP Categories with Statistically Elevated Odds Ratios in at Least One Risk Interval Analysis, Before Adjustment for Multiplicity

HCUP Category*
Day 0–14 and/or Day 1–60 Risk Interval
3.2: Diabetes mellitus without complication
5.4: Delirium dementia and amnestic and other cognitive disorders
6: Diseases of the nervous system and sense organs 6.5: Headache; including migraine 6.6: Coma; stupor; and brain damage
9: Diseases of the digestive system 9.2: Disorders of teeth and jaw 9.5: Abdominal hernia 9.6: Lower gastrointestinal disorders 9.7: Biliary tract disease 9.10: Gastrointestinal hemorrhage
10.2 Diseases of male genital organs
12: Diseases of the skin and subcutaneous tissue 12.1: Skin and subcutaneous tissue infections 12.2: Other inflammatory condition of skin
14.4: Nervous system congenital anomalies
17: Symptoms; signs; and ill-defined conditions and factors influencing health status 17.1: Symptoms; signs; and ill-defined conditions

* Shaded categories indicate statistically significantly elevated ORs after multiplicity adjustment, in at least one risk interval analysis.

Ten of the 17 analyzed HCUP top-level categories and 28 of the 135 HCUP sub-categories had significantly decreased ORs in the multiplicity-unadjusted analysis (i.e., ORs with an upper confidence bound <1.0) in at least one risk interval analysis, for a total of 38 significantly decreased results in the unadjusted analysis. After multiplicity adjustment, 9 categories remained statistically decreased, 8 of which were sub-categories of the *HCUP 16: Injury and poisoning* category, with the other being *HCUP 17.2: Factors influencing health care* category. One category, *HCUP 17.1: Symptoms; signs; and ill-defined conditions*, that was not flagged as significantly decreased in the unadjusted analysis was flagged as significantly decreased after multiplicity adjustment (this was possible due to using different α thresholds for the unadjusted and adjusted methods). Overall, between both unadjusted and adjusted analyses, 10 of the 17 top-level categories and 29 of the 135 HCUP sub-categories had significantly decreased results, which were not further investigated.

Day 0 Analyses

Two sets of pre-specified outcomes occurring in the emergency room or hospitalization setting on Day 0, the day of vaccination, were examined: allergic reaction and syncope. Incidence rates were calculated based on all events, prior to review. All day 0 events were reviewed and summarized.

Among the 330,774 doses given to the *Any 9vHPV Cohort*, there were 12 allergic reaction events, with 8 events identified in the *9vHPV-Only Cohort*. Six of the 12 allergic reaction events were found on review to have onset that preceded vaccination. All of the 6 allergic reaction events with onset after vaccination were in the *9vHPV-only Cohort*. For 5 of these events, care providers noted in medical record that 9vHPV or other vaccines may have been a trigger for the event. The incidence rate of the combined dose analysis of allergic reaction was 33.4 events per million doses (95% confidence interval (CI) 14.4, 65.8) in the *9vHPV-Only Cohort* and 36.3 events per million doses (95% CI 18.7, 63.4) in the *Any 9vHPV Cohort*. All allergic events occurred after the first dose for a rate of 56.9 events per million first doses (95% CI 24.6, 112.1). The 6 allergic reactions that occurred after vaccination were among 5 subjects (i.e., one subject had two qualifying diagnoses), and 4 of the 5 subjects were female. The allergic reaction events were 2 instances of urticaria, 1 local reaction, 1 non-specific ("did not like it" mentioned in medical records) reaction accompanied with syncope (subject is also counted as a syncope event) and 1 allergic reaction event in a male diagnosed as anaphylactic in nature. One of the two urticaria events was also diagnosed as a non-specific allergic reaction (i.e., this is allergic reaction number 6). In each of these events, 9vHPV was administered with one to three other vaccines.

Among the 330,774 doses given to the *Any 9vHPV Cohort*, there were 18 syncope events with 14 events identified in *the 9vHPV-Only Cohort*. All of the syncope events were found on review to have onset after vaccination. For 5 of the 18 events, care providers noted in medical record that 9vHPV or other vaccines administered concomitantly may have been a trigger for the event (4 of these 5 were in the *9vHPV-only Cohort*). The incidence rate of the combined dose analysis was 58.4 events per million doses (95% CI 32.0, 98.1) in the *9vHPV-Only Cohort* and 54.4 events per million doses (95% CI 32.3, 86.0) in the *Any 9vHPV Cohort*. When examined by dose, most syncope events occurred after the first dose for a rate of 78.2 events per million first doses (95% CI 39.0, 140.0), with 29.0 events per million doses (95% CI 3.5, 104.7) after the second dose, and 33.4 events per million doses (95% CI 0.8, 186.3) after the third dose. In several instances lab work or other procedures were noted. In 11 of the 18 events, one to three other vaccines were administered concomitantly with 9vHPV.

Deaths

There were 37 deaths among 215,965 9vHPV vaccine recipients, or 171.3 deaths per million recipients (95% CI 120.6, 236.1), or 14.9 deaths per 100,000 person-years of follow-up (95% CI of 10.5, 20.5). The most common causes were external causes (N=22), such as suicide (N=8 of 22) and motor vehicle accidents (N=7 of 22). The second most common cause was diseases of the circulatory system (N=9), including cardiac arrest (N=4 of 9).

The most temporally proximate death relative to 9vHPV vaccination was on day 8 after vaccination; however, the individual had onset of symptoms possibly related to the death preceding the vaccination. The most temporally distant death during the study period was on day 672 after vaccination. The minimum age of death was 12 years, the maximum was 70 years, the average and median age of death were 20.7 and 20.0 years, respectively. There were 21 deaths in males (56.8%) and 16 deaths in females (43.2%), or 190.9 deaths per million male 9vHPV vaccine recipients (95% CI 118.2, 291.7) and 151.0 deaths per million female 9vHPV vaccine recipients (95% CI 86.3, 245.2).

By reviewing medical records of all deaths, none were considered by coroners, study investigators or the eSRC to be related to receipt of either 9vHPV or any other vaccines.

Conclusion

This report provides safety results associated with 9vHPV vaccination of males and females in PPD. A total of 330,774 9vHPV doses administered to 215,965 subjects was evaluated in this study.

In the general safety analysis, there were significantly elevated ORs in 18 HCUP categories (i.e. 4 top-level categories and 14 sub-categories) before any adjustment. All elevated ORs were investigated further by additional analyses and investigations, including a combination of time plots (e.g., of the time between dose receipt and outcome to look for potential time clusters), specific diagnosis of the event as given at the point of care, and in some cases medical record review. Besides a few outcomes known to be associated with the vaccine, such as headache and skin reaction, none of the statistically significant elevated ORs represented events that were plausibly caused by 9vHPV vaccine. Typically, elevated findings were either unlikely to have a plausible biological mechanism associated with the vaccine to cause the finding or were more likely to be related to follow-up care generated at clinic visits coinciding with vaccination. The findings were similar for both study cohorts (i.e., the *9vHPV-Only Cohort* of those who received 9vHPV vaccine only, and the *Any 9vHPV Cohort* of those who received 9vHPV vaccine regardless of prior exposure of 4vHPV vaccine).

Overall, no new safety signals caused by vaccination with 9vHPV vaccine were found. The study did find signals for safety concerns that were previously known to be associated with the vaccine and are already in the vaccine label (e.g., headache, allergic reaction, syncope). The observed decreased ORs in these general safety analyses, which are also unlikely to reflect beneficial vaccine effects, may represent delayed workup for possible conditions identified at the vaccine visit, a healthy vaccinee effect, or may be due to chance. Either elevations or decreases may be due to uncontrollable artifacts such as clinic and procedure scheduling practices, or seasonality of vaccination.

For the Day 0 analysis, allergic reactions and syncope were observed at rates similar to those observed in previous postmarketing observational studies of HPV vaccines or other vaccines administered to this age group (e.g., quadrivalent meningococcal conjugate vaccine (MCV4), tetanus, diphtheria, and acellular pertussis vaccine (Tdap))[1]. Half of the allergic reaction events preceded vaccination. In most instances of allergic reaction or syncope events, one to three other vaccines were administered concomitantly with 9vHPV vaccine. Due to the

possibility of syncope occurring after vaccination, the 9vHPV vaccine labeling currently advises for there to be an observation period after vaccine administration – this is not a unique concern to 9vHPV vaccine but rather is common for injected vaccines, especially when administered to adolescents[2].

All death events were reviewed and none of the deaths were plausibly caused by receipt of 9vHPV vaccine. The rates of all-cause deaths after 9vHPV vaccination appears consistent with rates cited in National Center for Health Statistics (NCHS) reporting for 2015, the closest applicable NCHS period[3].

In summary, the results of this study did not indicate any new safety concerns following immunization with 9vHPV vaccine. Where the eSRC suggested additional analyses to investigate findings, they were performed and noted. No new safety concerns were identified, but the study did find signals for safety concerns that were previously known to be associated with the vaccine and are in the vaccine label (e.g., headache, allergic reaction, syncope). The eSRC has reviewed the study data and the additional investigations, and agrees with the findings of study investigators.

Marketing Authorisation Holder(s)

US: Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.

EU: MSD VACCINS

Names and affiliations of principal investigators

PPD

2 LIST OF ABBREVIATIONS

4vHPV	Four-valent Human Papillomavirus
9vHPV	Nine-valent Human Papillomavirus
ACIP	Advisory Committee on Immunization Practices
AHRQ	Agency for Healthcare Research and Quality
CDC	Centers for Disease Control and Prevention
CI	Confidence Interval
DFDR	Double False Discovery Rate (a multiplicity adjustment)
DM	Diabetes Mellitus (DM1 = type 1, DM2 = type 2)
eSRC	External Safety Review Committee
FDA	Food and Drug Administration
HCUP	Healthcare Cost and Utilization Project
HPV	Human Papillomavirus
IR	Incidence Rate
IRB	Institutional Review Board
PPD	
MAH	Marketing Authorization Holder
MCV4	Meningococcal Conjugate Vaccine, Quadrivalent
MVA	Motor Vehicle Accident
NCHS	National Center for Health Statistics
OR	Odds Ratio
PHI	Protected Health Information
PLOSS	Post-licensure Observational Safety Study
SCRI	Self-Controlled Risk Interval
Td	Tetanus and Diphtheria Vaccine
Tdap	Tetanus, Diphtheria, and Acellular Pertussis Vaccine
US	United States
VLP	Virus-Like Particles
VSD	Vaccine Safety Datalink

3 INVESTIGATORS

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4 OTHER RESPONSIBLE PARTIES

N/A

5 MILESTONES

Milestone	Planned date	Actual date	Comments
IRB approval, final protocol dated 06 Dec 2015	05 Jan 2015	05 Jan 2015	
Start of data period	01 Oct 2015	01 Oct 2015	
End of data period	30 Sep 2017	30 Sep 2017	
Registration in the EU PAS register	25 May 2016	25 May 2016	
Final report of study results	31 Dec 2019	10 Dec 2019	

6 RATIONALE AND BACKGROUND

The human papillomavirus (HPV) 9-valent vaccine (9vHPV vaccine), Gardasil 9®, was developed to substantially increase the spectrum of protection against cancer and precancer coverage provided by Gardasil®, the quadrivalent HPV vaccine (4vHPV vaccine), while continuing to provide broad protection against genital warts. In December 2014, the Food and Drug Administration (FDA) approved 9vHPV vaccine for use in young males (9–15 years of age) and females (9–26 years of age) for prevention of cervical, vulvar, vaginal and anal cancer; precancerous or dysplastic lesions; gential warts; and persistent infections caused by the 4vHPV vaccine types (6, 11, 16, and 18), as well as 5 additional HPV types (31, 33, 45, 52 and 58). The indication for 9vHPV vaccine was extended to include males up to 26 years of age in December 2015, a few months following study start.

The 9vHPV vaccine, similar to the 4vHPV vaccine, is a recombinant vaccine prepared from the purified virus-like particles (VLPs) of the major capsid (L1) protein of HPV Types 6, 11, 16, 18, 31, 33, 45, 52, and 58. The vaccine contains a total of 270 mcg total VLP per 0.5 mL dose, consisting of 30, 40, 60, 40, 20, 20, 20, 20 and 20 mcg of HPV types 6, 11, 16, 18, 31, 33, 45, 52, 58, respectively, along with 500 mcg of aluminum (in the form of amorphous aluminum hydroxyphosphate sulfate [AAHS] adjuvant) per dose in order to have similar adjuvant-to-antigen ratios as occur in the 4vHPV vaccine.

The 9vHPV vaccine was launched in 2015 in the United States (US) as a 3-dose regimen for 9 to 26-year-old females, and 9 to 16-year-old males, administered at approximately 0, 2 and 6 months. In February 2015, the US Advisory Committee on Immunization Practices (ACIP) recommended routine vaccination to begin at 11 or 12 years of age with a catch up schedule for females 13 to 26 years of age and males 13 to 21 years of age, if the series had not yet begun or was not completed. In December 2015, the indication was extended to include 16 to 26 year old males. In October 2016, an alternative two dose regimen was approved for 9 to 14-year-old males and females. In October 2018, the FDA extended the indication to include 9-45 years of age in both men and women.

The HPV family of viruses consists of over 200 related epitheliotropic deoxyribonucleic acid (DNA) viruses[4]. Of particular concern are a small number of cancer-causing HPV types, termed high-risk HPV types, which cause cervical cancer and associated precancerous lesions, and can also cause vaginal, vulvar, penile, anal cancers and associated precancers. HPV, in particular types 6 and 11, also causes genital warts. These diseases are associated with substantial morbidity and mortality. In addition, HPV can cause benign and malignant diseases of the upper airway in both men and women, including recurrent respiratory papillomatosis and oropharyngeal cancer.

This observational study was conducted by Merck & Co., Inc., a subsidiary of Merck, Sharp & Dohme, Corp. (hereafter referred to as Merck) as a post-licensure regulatory commitment to the FDA to monitor the general safety of the 9vHPV vaccine when administered as part of routine health care. Clinical trials in large populations (over 16,000 individuals administered at least one dose of 9vHPV vaccine with safety follow-up) have shown that the 9vHPV vaccine is generally safe and well tolerated.

7 RESEARCH QUESTION AND OBJECTIVES

The objective of this study is to describe the general safety of the 9vHPV vaccine in a population of at least 10,000 males and females who have received at least one dose of the 9vHPV vaccine by:

a) estimating the risk of health outcomes resulting in emergency room visits or hospitalizations occurring within a pre-specified risk interval (as described in Risk and Self-Comparison Intervals section below) after a dose of the 9vHPV vaccine; and
b) comparing with the risk of such health outcomes in a post-vaccination self-comparison reference interval.

There is no formal research hypothesis for this study.

8 AMENDMENTS AND UPDATES

None.

9 RESEARCH METHODS

9.1 Study Design

This was a retrospective, observational self-controlled risk interval (SCRI) study whereby medical diagnoses in the risk interval after vaccination were compared in the same individual to diagnoses at a later interval. Self-control avoids confounding by time-stable covariates, and an offset term is used to adjust for time-varying confounders. The SCRI design is well-suited to studying time-limited effects of transient exposures for which periods of risk following the exposure can be validly defined.

9.2 Setting

This study was conducted at PPD a large integrated healthcare delivery system. PPD provides comprehensive health services to over 4 million residents of PPD Members are enrolled through their employer or the employer of a family member, individual prepaid plans, or state or federal programs such as Medicare. Nearly all PPD members are on a pre-paid health insurance plan for comprehensive coverage.

The study work was conducted by the PPD PPD has participated in the Centers for Disease Control and Prevention (CDC)-funded Vaccine Safety Datalink (VSD) project and has extensive experience in both CDC-funded and industry-funded studies of post-licensure vaccine safety surveillance.

This surveillance used existing computerized databases and infrastructure within PPD. PPD maintains comprehensive computerized records for members on emergency room visits, hospitalizations, and outpatient visits, including vaccinations, diagnoses, laboratory tests, medications, procedures, demographics and membership information, including deaths.

Among PPD members, approximately 95% of hospitalizations and emergency room visits occur within the PPD system. The remainder of the medical encounters, i.e., encounters occurring outside PPD, are still usually captured in the database through claims and record sharing. Although capture of outside medical care may sometimes be delayed by several months (i.e., with scanned, hard-copy records) many practices such as PPD allow direct linkages and immediate record sharing. Final data were collected 6 months after the study period in order to ensure that the encounter and diagnostic data were as complete as possible for the study period, however no new vaccine or event information was included after the study period (01 October 2015 to 30 September 2017).

The final study protocol (Gardasil 9® Protocol 028-00) was approved by the PPD Institutional Review Board (IRB) on 5 January 2016 (protocol version dated 06 Dec 2015). The IRB approval was renewed every year until the completion of the study. The IRB waived the requirement that written Privacy Rule authorization be obtained from study participants under the Health Insurance Portability & Accountability Act requirements for this study. At PPD, informed consent is not required for study personnel to conduct computer database searches for vaccine safety or to examine patient records for medical care provided by the institutions, as long as individual patient confidentiality is maintained, as was done in this surveillance study.

9.3 Study Population

There was no active enrollment of subjects for this study. The study cohorts were comprised of males and females within PPD who received at least one dose of the 9vHPV vaccine during the study period, who were 9 years of age or older, and members of the health plan at the time of the dose. The PPD was used to identify the study population and the date of vaccination with 9vHPV vaccine. Males and females who received any doses of the 9vHPV vaccine outside of the health plan were excluded from this study.

The study cohorts exposed to 9vHPV vaccine in this study were as follows:

- *9vHPV-Only Cohort* –subjects who initiated the HPV vaccination and received at least one dose of 9vHPV vaccine during the study period (01 Oct 2015 – 30 Sep 2017) and who had no exposure to any other HPV vaccines.

- *Any 9vHPV Cohort* – subjects who received at least one dose of 9vHPV vaccine during the study period (01 Oct 2015 – 30 Sep 2017) regardless of exposure to 4vHPV vaccine and who had no exposure to any HPV vaccines other than 9vHPV vaccine and 4vHPV vaccine.

9.4 General Safety Analysis (SCRI Analysis)

9.4.1 Safety Outcomes

Health outcomes resulting in a hospitalization or emergency room visit during the period of interest were included in the analysis. Events were categorized using the Clinical Classification Software for ICD-10-CM mapping as obtained from the Agency for Healthcare Research and Quality (AHRQ) website on 02 Feb 2017. This software was used to map thousands of ICD-10 diagnosis codes into a smaller number of clinically meaningful categories, according to body system and outcome type. These tools were developed as part of the Healthcare Cost and Utilization Project (HCUP), a Federal-State-Industry partnership sponsored by AHRQ (https://www.hcup-us.ahrq.gov/) so the event categories are referred to as HCUP categories. HCUP can be used as either a single level schema where all 70,000+ ICD-10 diagnosis codes are grouped into 285 mutually exclusive categories, or a multilevel schema where all diagnosis codes are classified into 18 categories with 135 sub-categories, with the 18 top level categories numbered 1 to 18, and the sub-categories being placed after a decimal. For example, HCUP 1 is “Infectious and parasitic diseases” (which corresponds to the first section of codes for International Classification of Diseases, Version 10 (ICD-10) and consists of sub-categories “1.1 Bacterial infection”, “1.2 Mycoses”, “1.3 Viral infection”, etc.

In this study, the multilevel, hierarchical HCUP categories were used to categorize all observed diagnoses except for those in top-level category HCUP 18, “Residual codes; unclassified” which were not analyzed. The category HCUP 18 contains approximately 7,500 ICD-10 diverse codes that are not generally useful, and not easily categorized. All of the categories that were analyzed are shown in *Annex 1. The list of HCUP categories analyzed*.

Hospitalizations and emergency room visits were tabulated by HCUP category with incidence rates and 95% confidence intervals (CIs) for each of the risk and self-comparison intervals (Section 9.4.2). Events were combined to sum first occurrences of a given outcome in each category resulting in a hospitalization or emergency department visit during the interval of interest. Thus, for analyses, emergency department visits and hospitalizations are combined such that an emergency department visit resulting in a hospitalization for the same outcome will only be counted once, avoiding duplication. An event could occur in both a risk and self-comparison interval.

As a potential indication of severity, the number and percent of events in the combined analysis that were “hospitalizations” were also recorded next to the combined figure. For example, a category may have had 100 events in the combined emergency department and hospitalization setting, of which 10 (10%) resulted in hospitalization.

For a small number of HCUP categories, the incidence rates were pre-specified to be assessed for females or males only, in which case the person-time of only that sex was used. These categories were included in the main analyses. An example is a listing of events in the categories HCUPs *2.8 Cancer of male genital organs* and *10.2 Diseases of male genital organs.* These listings included only male subjects and corresponding person-time

denominators. Similarly, there were outcomes such as *2.6 Cancer of uterus and cervix* or related to pregnancy that only included females.

9.4.2 Risk and Self-Comparison Intervals

Risk Interval

The risk interval was the time period immediately following 9vHPV vaccination. Two risk intervals were pre-specified for this study:

1) 15 days immediately following a dose of 9vHPV vaccine (Days 0-14) and;

2) up to 60 days immediately following a dose of 9vHPV vaccine, not including the day of vaccination (Days 1-60).

Day 0 was the day of vaccination, Day 1 was the first day following vaccination, and so forth.

Selected pre-specified Day 0 events were evaluated as described in Section 9.5.

Self-Comparison Interval

The self-comparison post-vaccination interval was the time period more remote from the dose of 9vHPV vaccine during which those same persons vaccinated with the 9vHPV vaccine were followed for health outcome events.

The self-comparison interval for each subject began at the end of the longest risk interval used for the study, i.e., it started 61 days after each dose. For example, the self-comparison interval for the 15-day risk interval was days 61–75 after each dose (i.e., self-comparison interval started 61 days after each 9vHPV vaccine dose).

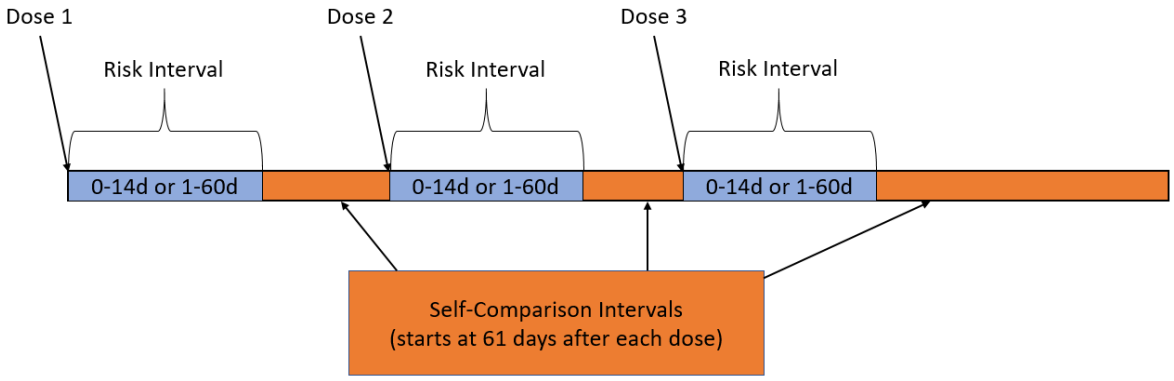
If a subsequent dose was administered during either the risk or self-comparison interval for the prior dose, the subject began a new risk interval associated with the subsequent dose.

When a risk interval was truncated due to a subsequent dose, the risk interval was shortened. However, when a self-comparison interval was truncated, the unused days of the shortened self-comparison interval were “added” to the next self-comparison interval to ensure that the total number of days of self-comparison time was maintained.

Outcomes were analyzed separately in risk and comparison intervals by either combining outcomes across doses (Section 9.4.3 Combined Dose Analysis), or by individual doses (Section 9.4.4 Dose-Specific Analysis). The same concepts applied for subjects who only received 1 or 2 doses, except that they only had 1 or 2 risk intervals.

Events during the risk interval were tabulated and compared with events during the self-comparison interval to estimate the relative risk of health outcomes following 9vHPV vaccine. A graphical depiction of the risk and self-comparison intervals is shown in Figure 1.

Figure 1. Risk & Self-Comparison Intervals for Study Population (1–3 doses)



9.4.3 Combined Dose Analysis

In the combined dose analysis, risk intervals after a subjects' first, second and third doses of 9vHPV vaccine were combined, as were self-comparison intervals of comparable length, depending on the number of doses.

The total length of the risk interval for each study subject depended on the number of doses of 9vHPV vaccine received. In the 60-day risk interval analysis, the total risk interval time was up to 60 days after 1 dose, 120 after 2 dose and 180 among subjects with exactly or >3 doses. Similarly, in the 15-day risk interval analysis, the total risk interval time was up to 15, 30, and 45 days in length among subjects with exactly 1, 2, or 3 doses of the 9vHPV vaccine, respectively.

For each study subject, the length of risk interval following dose 1 or dose 2 varied depending upon the timing of next dose of the HPV vaccine. If a subject received his or her second or third dose of the HPV vaccine prior to the end of a risk interval associated with a previous dose, the risk interval associated with the previous dose was truncated on the day prior to receipt of the next dose. However, given the recommended schedule with at least 2 months between doses, this was expected to occur only rarely.

For purposes of calculating person-time, the day of vaccination is treated as a half day so the risk interval Day 0–14 counts as 14.5 days, whereas the Day 1–60 risk interval counts 60 full days.

As discussed above, risk interval time was truncated if the next dose was administered within the 60-day risk interval. As an example, a subject that received the second dose 55 days after the first dose only had 54 days of risk time (the 55th day would be the day of vaccination for the second dose). However, for this same subject, self-comparison time was captured later, starting day 61 after the second dose. In this example, the subject had 114 (54 + 60) days of risk interval time and 120 days of self-comparison interval time.

Risk or self-comparison intervals were also truncated due to death, end of surveillance, and occurrence of an event of interest for a particular HCUP category, and subjects only accrued person-time up to the first event in a given individual HCUP category.

9.4.4 Dose-Specific Analysis

In the dose-specific analysis, events during the risk intervals after a subject's first, second, and third doses of 9vHPV vaccine were compared separately with self-comparison time after each dose. These analyses were only conducted in the *9vHPV-Only Cohort* to ensure comparability of exposure experience (i.e., all subjects in the 9vHPV vaccine dose 2 analyses had 9vHPV vaccine as dose 1, and all subjects in the dose 3 analyses had 9vHPV vaccine as doses 1 and 2).

The by-dose 60-day risk interval analysis compared events during the risk interval with days 61–120 after that same dose, if the self-comparison interval was not censored for reasons discussed above.

In the example given above (in Section 9.4.3 Combined Dose Analysis), in the Dose 1 analysis, the subject had 54 days of risk time and no self-comparison interval time. Similarly, the 14-day risk interval would be complete and would have 14.5 days of risk time, and there would be no self-comparison interval time. Imbalances in time between the risk and comparison intervals are addressed in the next section.

9.4.5 Conditional Logistic Regression

Conditional logistic regression was used to estimate odds ratios (ORs) and 95% CIs for the relative risk of health outcomes. Risk and self-comparison intervals were designed to be comparable in length. Where necessary, an offset term was used to address imbalances in risk and self-comparison intervals. A significance level (α) of 0.05 was used for the unadjusted analysis.

This study pre-specified use of the double false discovery rate (DFDR) method[5] multiplicity adjustment to aid in interpretation of statistically significant unadjusted ORs. The DFDR method determines statistical significance based on the p-values of HCUP sub-categories. Unadjusted ORs and CIs were presented to the external Safety Review Committee (eSRC) and are included in this report. A significance level (α) of 0.1 was used for the DFDR adjusted analysis. The 0.1 threshold was recommended by the developers of the DFDR method given the expectation of rare events (i.e. <5 cases) for some HCUP categories during the study period. Thus, with unadjusted findings flagged for significance at $\alpha = 0.05$ and adjusted findings flagged at $\alpha = 0.1$ there is the rare possibility that a finding may be flagged after adjustment that was not flagged in unadjusted analyses. In that case, the result will be presented as such (i.e., not significant in the unadjusted analysis but flagged after DFDR adjustment).

9.4.6 Follow-up Investigation of Elevated Categories

All categories with significant elevations were further investigated by reviewing additional detail of the corresponding conditions. For some of these categories, additional investigations and analyses were performed, as suggested by the eSRC (e.g., seasonality of vaccine exposure and diagnosis of *Diabetes mellitus without complication*), and where such investigations were requested it is noted in the text. In many cases, but not all, a detailed

review of events, including of medical charts, was conducted, and where this was done it is stated in the relevant section. Where sampling was used (e.g., a percentage of events were reviewed), this is also described.

Further investigation consisted of reviewing additional details of findings, such as plotting the timing of events to look for potential clusters, performing specific diagnosis review (i.e., reviewing the diagnostic codes listed by the practitioner for the case, or reviewing the actual diagnosis codes that contributed to the HCUP category), conducting medical records review to determine a cause or time of onset, or assessing the impact of the seasonality of vaccine exposure on the findings

The process of investigation of potential safety signals was consistent with the guidance pre-specified in the eSRC charter for this study. Although not limited to this list, considerations for safety signal identification included:

- Biological plausibility: Is there a potential and plausible biological mechanism for vaccination to cause the signaled event?
- Clinical relevance: Does clinical judgment indicate a likely (or unlikely) association between vaccination and the signaled event?
- Statistical strength: Is there a strong statistical association? A weak association may require more evidence to suggest causality.
- Consistent pattern across different comparisons: Does the finding appear in more than one comparison, cohort or dose? Of note, there is overlap between cohorts and analyses, so some overlap is built-in.
- Temporal relationship: Do the events precede vaccination? Is there clustering of events after vaccination, or does the timing seem random? Upon review, are the events found to be follow-up care that was arranged at the outpatient visit where vaccines were administered?
- Others, as deemed appropriate.

9.5 Analysis of Day 0 Events

Syncope and allergic reaction events which occurred on the day of vaccination were specifically evaluated in Day 0 analyses. Syncope and allergic reaction events were identified using ICD-10 codes (Table 3) rather than HCUP categories because the ICD-10 codes were more specific and allowed for a more detailed accounting of allergic reactions (Section 9.4.1 Safety Outcomes). Analyses included event rate calculations and medical chart review of all study subjects with an ICD-10 code for allergic reactions. Rates are presented as events per million doses, with a 95% CI around the rate.

Table 3. Outcomes Pre-Specified for Day 0 Analysis

Category	ICD10	Diagnosis Terms Included
Syncope	R55	Syncope, Near Syncope, Syncope and Collapse, Transient Syncope, Vasovagal Syncope
	I95.1	Syncope due to Orthostatic Hypotension
Allergic Reactions (including Immediate Hypersensitivity)	J98.01	Acute bronchospasm
	L27.0 L27.1	Dermatitis due to drugs and medicines taken internally
	L50.0	Allergic urticaria
	L50.6 L50.8	Other specified urticaria
	L50.9	Unspecified urticaria
	T78.2XXA T88.6XXA	Other anaphylactic shock not elsewhere classified, includes adverse effect of medicinal substance
	T78.3XXA	Angioneurotic edema, Quincke's edema
	T50.905A	Other and unspecified adverse effect of drug, medicinal and biological substance, includes allergic reaction
	T78.40XA T78.49XA	Allergy, unspecified not elsewhere classified
	T80.52XA	Anaphylactic reaction due to vaccination

9.6 Analysis of Deaths

Deaths among 9vHPV vaccine recipients were identified in PPD databases starting at the date of the first 9vHPV vaccine in the study period through the end of the study period (i.e., deaths can occur between 01 Oct 2015 through 30 Sep 2017). Deaths were identified from all available sources including the medical record, state death data and social security data. Deaths were confirmed by medical record review, were tabulated by cause and time since most recent vaccination, and were described using short narratives which included information regarding the medical history, timing of vaccination and death, and the cause of death (as available from all available sources including medical records and death certificates). These event summaries are provided in *Annex 4. Deaths, Listing / Summaries*. Dates were presented only with month and year to protect subject identities, although relative time intervals were included (e.g., "Expired 74 days after most recent vaccination in January 2017") and all available dose history is provided there. Rates with 100,000 person-year denominators and 95% confidence intervals were calculated; no statistical comparisons were made.

Any indication in subject's medical records that a death could be related, or possibly related, to receipt of 9vHPV vaccine or any other Merck product, such as a statement from a treating physician, or study principal investigator assessment upon review, required expedited reporting to Merck's pharmacovigilance team and to the eSRC.

9.7 External Safety Review Committee (eSRC)

An external Safety Review Committee (eSRC) was assembled for this study. The eSRC was composed of 3 independent experts with expertise in vaccine safety, pharmacoepidemiology and pediatric and adolescent medicine. Committee members were independent of Merck and PPD .

The role of the eSRC was to review and evaluate the study protocol, provide ongoing input on study design and methods as needed, review and assess the study results, and request additional information needed to further evaluate any finding that may be indicative of potential safety concerns. The eSRC has reviewed the results contained in this study report, including the analysis results per protocol as well as additional analyses and investigations requested by the eSRC.

9.8 Data Management and Quality Control

Data validation occurred throughout the data management and analysis process. Data quality checks included internal dataset consistency; consistency between datasets; external checks with other available databases for verification of items such as birthdates and vaccination dates; and checks to ensure that protocol and data analysis plan criteria were met. If validation checks were not satisfied, then an examination of the problem was performed on the dataset(s) in question and the problem was resolved. Where changes have been made to presented results or locked datasets, a change documentation process was followed, noting the identified issue and resolution.

PPD managed study data using the SAS system (version 9.2 or greater). Programs used for this study were like other PPD programs which are used repeatedly, however were updated as needed to reflect this study's specifications. Programming and data management for this study adhered to good quality standards including preservation of code, logs, and listings, as well as transparency in methodology. Study code was appropriately annotated with descriptive notes. PPD data elements (e.g., HCUP data files) were documented as to source and access date and archived versions are stored. Although source datasets are live and cannot be archived, intermediate datasets have been archived as appropriate.

10 RESULTS

10.1 Study Population and Vaccine Exposure

There were 236,453 *potential* subjects identified in the PPD system during the two-year study period from 01 October 2015, through 30 September 2017. After applying the following exclusion criteria (Table 4), 215,965 subjects were included in this study who received 330,774 doses.

Table 4. Reasons for Exclusion from Study Population

Criteria	N*	%
Non-Merck HPV vaccines or inadequate information to identify Merck HPV vaccines	13,971	5.91%
Not a member at time of vaccination	8,792	3.72%
9vHPV vaccine began at fourth dose or more after 01-Oct-2015	722	0.31%
4vHPV follows 9vHPV vaccine within vaccination sequence	95	0.04%
Gender unknown	89	0.04%
9vHPV vaccine dose occurred prior to 15-July-2015	64	0.03%
Less than 9 years old at receipt of 9vHPVvaccine	33	0.01%
Interval between any vaccine sequence < 14 days	10	<0.01%
Redundant medical record numbers (duplication, bad records)	4	<0.01%

* Subjects can be included in more than one row. The percentages represent the portion ineligible of the 236,453 *potential* subjects with HPV vaccine in the study period.

10.1.1 9vHPV-Only Cohort

The *9vHPV-Only Cohort* was composed of 140,628 subjects who initiated the HPV vaccination and received at least one dose of 9vHPV vaccine during the study period, and did not have exposure to any other HPV vaccines. About 40% of the subjects of the *9vHPV-Only Cohort* initiated the 9vHPV vaccine series at 11 or 12 years of age, with 39.0% starting at 11 years of age and 13.6% starting at 12 years of age (Figure 2, Table 5). This cohort received 239,556 doses of 9vHPV vaccine. The accrual by age was similar between males and females.

Figure 2. Cumulative Study Population Accrual by Age at First Dose and Gender, *9vHPV-Only Cohort*

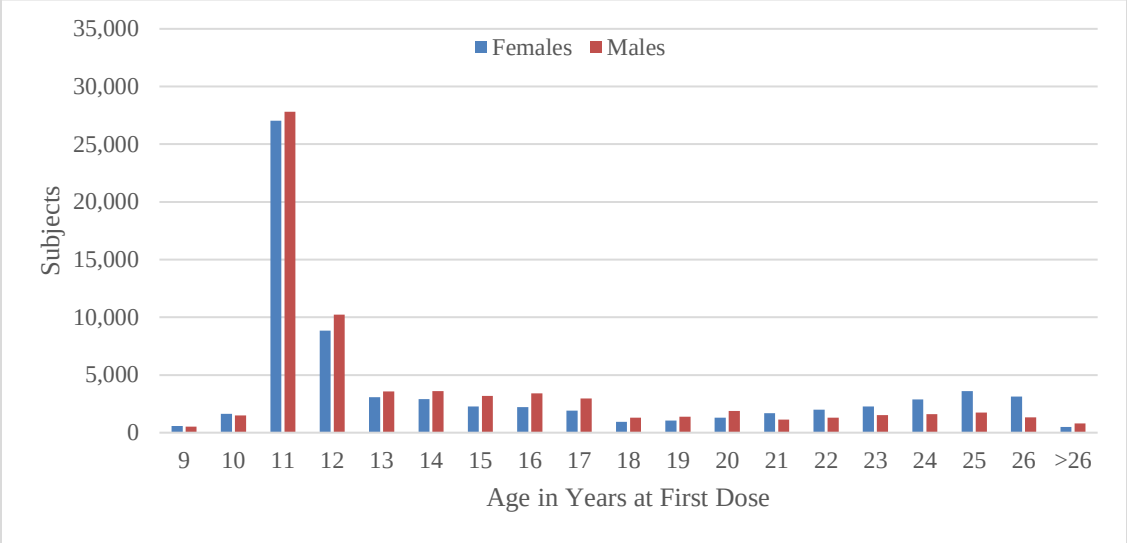


Table 5. Cumulative Study Population Accrual by Age at First Dose of 9vHPV Vaccine, Number of Doses, and Gender, *9vHPV-Only Cohort*

Age at First Dose of 9vHPV in Study Period (Years)	*9vHPV-Only Cohort*					
	At least 1 Dose of 9vHPV		At least 2 Doses of 9vHPV		At least 3 Doses of 9vHPV	
	(N = 140,628)		(N = 69,027)		(N = 29,901)	
	Female	Male	Female	Male	Female	Male
9	583	523	246	228	92	71
10	1,634	1,499	766	649	313	214
11	27,041	27,816	14,583	14,661	6,561	6,282
12	8,833	10,244	4,086	4,563	1,809	1,870
13	3,079	3,569	1,548	1,734	656	683
14	2,916	3,612	1,391	1,797	539	667
15	2,276	3,197	1,344	1,832	700	920
16	2,205	3,411	1,255	1,782	615	833
17	1,919	2,962	1,011	1,355	446	573
18	937	1,287	406	473	165	153
19	1,063	1,384	435	488	169	172
20	1,300	1,873	586	572	259	203
21	1,676	1,134	719	395	296	146
22	1,983	1,307	913	464	406	189
23	2,265	1,508	1,033	569	441	243
24	2,875	1,597	1,349	649	630	289
25	3,615	1,753	1,728	673	751	274
26	3,128	1,328	1,363	570	588	258
>26*	490	806	274	537	145	280
Subtotal	69,818	70,810	35,036	33,991	15,581	14,320

* The upper range of this age category is 86 years.

Of subjects in this cohort initiating the 9vHPV vaccine series, approximately 50% received a second dose in the study period and approximately 20% received a third dose in the study period. These rates were affected by 1) the end of the study period, beyond which dose information was not collected, and many of these subjects will have received additional doses; and 2) the 2-dose regimen recommended by ACIP in November 2016, approcimately half-way through the study period. On average, subjects had 83.5 days between their first and second dose of 9vHPV vaccine in the first six months of the study, whereas the average interval between first and second dose was 127.3 days in the overall study period (i.e., by the end of the study period). These percentages were very similar by age at series initiation and by sex (Table 6). The completion information in Table 6 used all subjects who initiated the series in the *9vHPV-Only Cohort* as denominator for completion percentages for both dose 2 and dose 3. Table 7 used subjects who received dose 2 as denominator for the dose 3 completion percentage.

Table 6.Vaccination Completion Percentages of 9vHPV Vaccine Series in *9vHPV-Only Cohort*, Overall, by Age and Gender*

Age at First Dose of 9vHPV in Study Period (Years)	Subjects Initiating Series in *9vHPV-Only Cohort* Receiving Dose 2 (%)			Subjects Initiating Series in *9vHPV-Only Cohort* Receiving Dose 3 (%)		
	Overall	Females	Males	Overall	Females	Males
All Ages	49.1%	50.2%	48.0%	21.3%	22.3%	20.2%
9-14	50.6%	51.3%	50.0%	21.6%	22.6%	20.7%
15+	46.2%	48.3%	44.0%	20.6%	21.8%	19.3%

* The completion percentage was calculated using all subjects who initiated the series in the *9vHPV-Only Cohort* as denominator for both dose 2 and dose 3.

Table 7. Completion Percentages from Second to Third Dose of 9vHPV Vaccine in *9vHPV-Only Cohort*, Overall, by Age and Gender*

Age at First Dose of 9vHPV in Study Period (Years)	Subjects in *9vHPV-Only Cohort* with Dose 2 Receiving Dose 3 (%)		
	Overall	Females	Males
All Ages	43.3%	44.5%	42.1%
9-14	42.7%	44.1%	41.4%
15+	44.5%	45.2%	43.8%

* The completion percentage was calculated using subjects who received dose 2 in the *9vHPV-Only Cohort* as the denominator.

10.1.2 Any 9vHPV Cohort

The *Any 9vHPV Cohort* was composed of 215,965 subjects who received at least one dose of 9vHPV vaccine during the study period and did not have exposure to any other HPV vaccines than 9vHPV during the study period (i.e., this cohort allowed for a 9vHPV or 4vHPV vaccine series to have initiated prior to the study start). Again as a reminder, the *9vHPV-Only Cohort* is included in this broader cohort and represents 65% (140,628/215,965) of the *Any 9vHPV Cohort*. In the *Any 9vHPV Cohort*, the most common ages for 9vHPV vaccine initiation are 11 or 12 years of age, but there were slightly more 12 years of age and older subjects getting their first dose of 9vHPV vaccine in this cohort than in the *9vHPV-Only Cohort* (28.0% of the subjects received their first 9vHPV vaccine dose at 11 years of age and 15.2% at 12 years of age), because approximately 75,000 subjects in this cohort started their HPV vaccine series prior to the study period (Figure 3, Table 8). The *Any 9vHPV Cohort* received 330,774 doses of 9vHPV vaccine.

The cumulative study population accrual of *Any 9vHPV Cohort* by dose number of 9vHPV vaccine within study period, and gender is shown in Table 9.

Many subjects in the *Any 9vHPV Cohort* started the HPV series prior to licensure or wide availability of 9vHPV vaccine at PPD Subjects with a mixed series of 4vHPV and 9vHPV are shown here (Table 10). For example, subjects in this table with 4vHPV 4vHPV 9vHPV

(i.e., two doses of 4vHPV vaccine prior to 9vHPV vaccine in the study period) are included in Table 8 in the "At least 1 dose" group and in Table 9 in the "Dose 3" group.

Among the 215,965 subjects in the *Any 9vHPV Cohort*, approximately one third were subjects with mixed series and are shown in Table 10 below. Subjects with mixed schedule were similar by gender.

Figure 3. Number of Subjects by Age at First Dose of 9vHPV Vaccine in the Study Period and Gender, *Any 9vHPV Cohort*

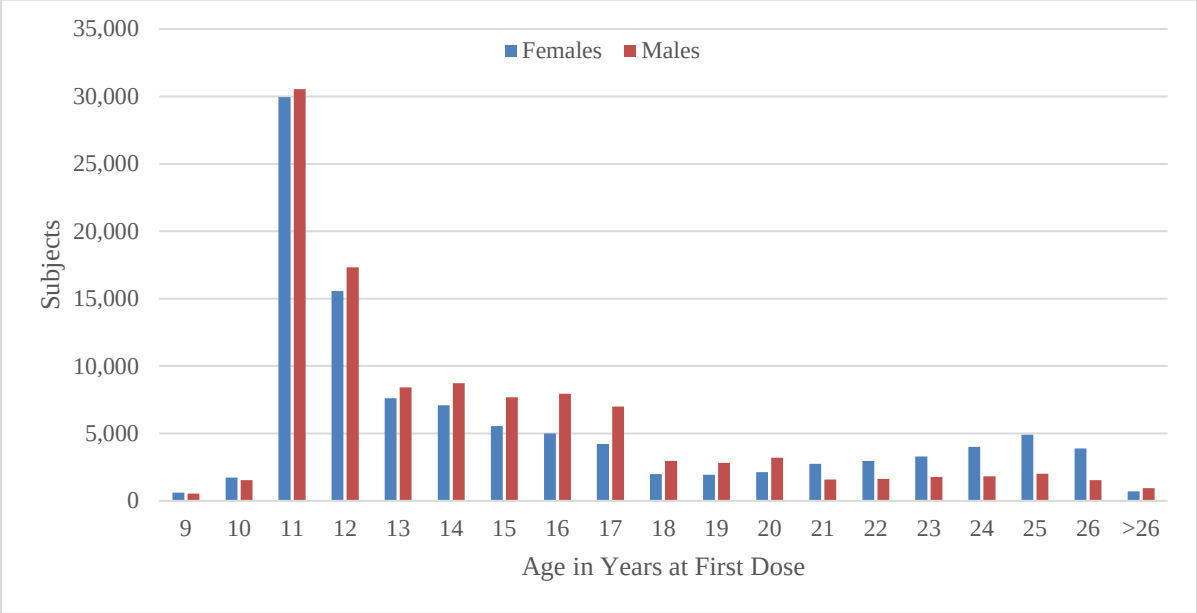


Table 8. Cumulative Study Population Accrual by Age at First Dose of 9vHPV Vaccine in Study Period, Number of Doses within the Study Period, and Gender, *Any 9vHPV Cohort*

Age at First Dose of 9vHPV in Study Period (Years)	***Any 9vHPV Cohort***					
	At least 1 Dose of 9vHPV		**At least 2 Doses of 9vHPV**		**At least 3 Doses of 9vHPV**	
	(N = 215,965)		(N = 84,908)		(N = 29,901)	
	Female	**Male**	**Female**	**Male**	**Female**	**Male**
9	604	528	259	233	92	71
10	1,736	1,543	809	671	313	214
11	29,951	30,545	16,125	16,164	6,561	6,282
12	15,568	17,324	5,917	6,474	1,809	1,870
13	7,623	8,432	2,187	2,464	656	683
14	7,099	8,727	1,942	2,538	539	667
15	5,547	7,689	1,854	2,550	700	920
16	5,007	7,957	1,741	2,687	615	833
17	4,221	7,004	1,387	2,032	446	573
18	1,993	2,959	556	680	165	153
19	1,950	2,826	563	685	169	172
20	2,136	3,202	720	728	259	203
21	2,737	1,591	902	483	296	146
22	2,964	1,634	1,115	537	406	189
23	3,295	1,766	1,238	633	441	243
24	4,007	1,810	1,587	704	630	289
25	4,915	2,008	1,990	742	751	274
26	3,892	1,539	1,502	627	588	258
>26*	696	940	311	571	145	280
Subtotal	105,941	110,024	42,705	42,203	15,581	14,320

* The upper range of this age category is 86 years.

Table 9. Cumulative Study Population Accrual by Age at First Dose and Dose Number of 9vHPV Vaccine in Study Period, and Gender, *Any 9vHPV Cohort*

Age at First Dose of 9vHPV in Study Period (Years)	*Any 9vHPV Cohort*					
	Dose 1		Dose 2		Dose 3	
	(N = 140,628)		(N = 109,055)		(N = 81,091)	
	Female	Male	Female	Male	Female	Male
9	583	523	262	233	110	76
10	1,634	1,499	842	682	382	247
11	27,041	27,816	16,479	16,499	9,117	8,676
12	8,833	10,244	7,683	8,581	6,778	6,843
13	3,079	3,569	3,778	4,258	3,609	3,752
14	2,916	3,612	3,501	4,463	3,163	3,857
15	2,276	3,197	2,958	4,082	2,867	3,880
16	2,205	3,411	2,555	4,174	2,603	3,892
17	1,919	2,962	2,095	3,380	2,040	3,267
18	937	1,287	887	1,280	890	1,225
19	1,063	1,384	848	1,217	771	1,082
20	1,300	1,873	974	1,353	841	907
21	1,676	1,134	1,248	684	1,011	402
22	1,983	1,307	1,429	693	1,073	360
23	2,265	1,508	1,593	752	1,116	382
24	2,875	1,597	1,972	800	1,377	406
25	3,615	1,753	2,434	863	1,607	408
26	3,128	1,328	1,803	724	1,051	372
>26*	490	806	378	618	284	367
Subtotal	69,818	70,810	53,719	55,336	40,690	40,401

* The upper range of this age category is 86 years.

Table 10. Mixed Schedule of 9vHPV Vaccine and 4vHPV Vaccine in *Any 9vHPV Cohort*

Vaccine Series	Female	Male	Overall
4vHPV 4vHPV 9vHPV	13,608	13,934	27,542
4vHPV 4vHPV 9vHPV 9vHPV	55	22	77
4vHPV 4vHPV 9vHPV 9vHPV 9vHPV	8	5	13
4vHPV 9vHPV	9,049	10,817	19,866
4vHPV 9vHPV 9vHPV	8,422	9,283	17,705
4vHPV 9vHPV 9vHPV 9vHPV	62	39	101
Grand Total	31,204	34,100	65,304

Because all subjects receiving dose 1 in the study period were by definition in the *9vHPV-Only Cohort* and *Any 9vHPV Cohort*, the percentage of subjects initiating the series who received dose 2 is the same as for the *9vHPV-Only Cohort* reported above in Table 6. The percentage of subjects in the *Any 9vHPV Cohort* with a dose 2 who received dose 3 (comparable to the figures in Table 7 above) is shown here in Table 11.

Table 11. Completion Percentages from Second to Third Dose of 9vHPV Vaccine in *Any 9vHPV Cohort**, Overall, by Age and Gender

Age at First Dose of 9vHPV in Study Period (Years)	Subjects in *Any 9vHPV Cohort* with Dose 2 Receiving Dose 3 (%)		
	Overall	Females	Males
All Ages	45.8%	47.0%	44.6%
9-14	47.4%	48.9%	46.1%
15+	43.2%	44.1%	42.2%

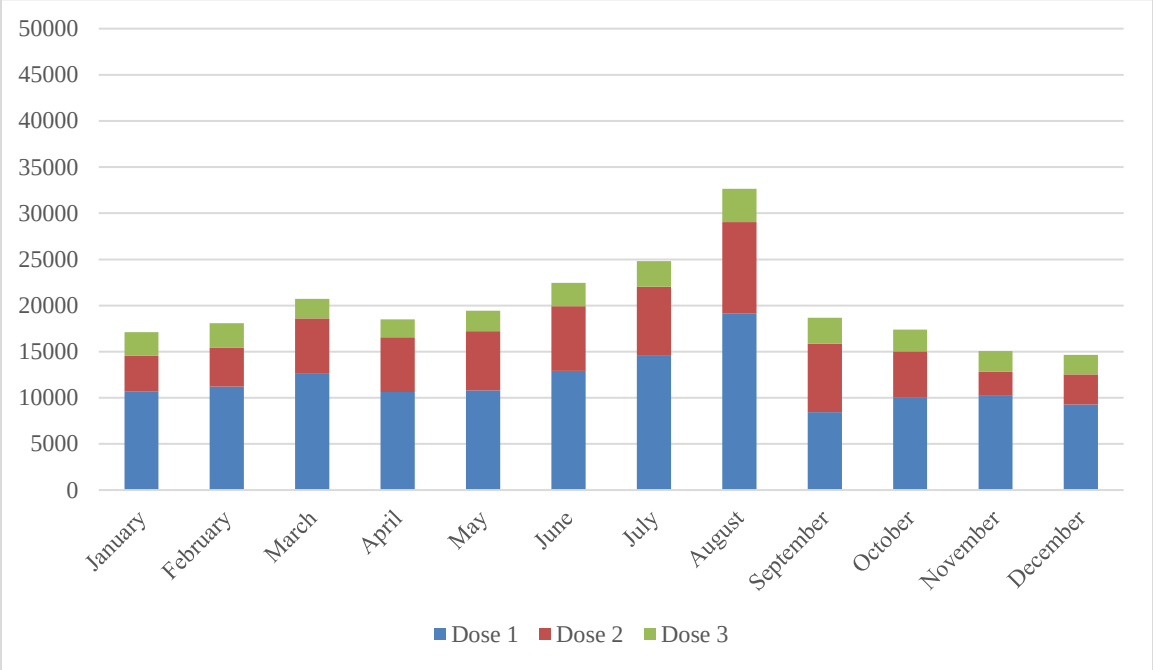
* The completion percentage was calculated using subjects who received dose 2 in the *Any 9vHPV-Cohort* as the denominator.

10.1.3 Seasonality of Vaccination

Overall, the peak month of 9vHPV vaccine administration in both the *9vHPV-Only Cohort* (Figure 4) and the *Any 9vHPV Cohort* (Figure 5) was August, with the second highest being July, and December having the lowest amount administered.

In the *9vHPV-Only Cohort* (Figure 4), the uptake of 9vHPV vaccine was higher during the summer months: June (9.4%), July (10.4%), and August (13.6%), with December having the fewest doses administered (6.1%).

Figure 4. Doses in *9vHPV-Only Cohort* by Dose Number and Calendar Month



In the *Any 9vHPV Cohort* (Figure 5), the overall vaccine uptake pattern is similar to the *9vHPV-Only Cohort*, with the peak of 9vHPV vaccine administration in the summer: June

(8.7%), July (9.6%), and August (12.4%), with October also being a peak month (9.2%). December had the fewest doses administered (6.8%).

Figure 5. Doses in *Any 9vHPV Cohort* by Dose Number and Calendar Month

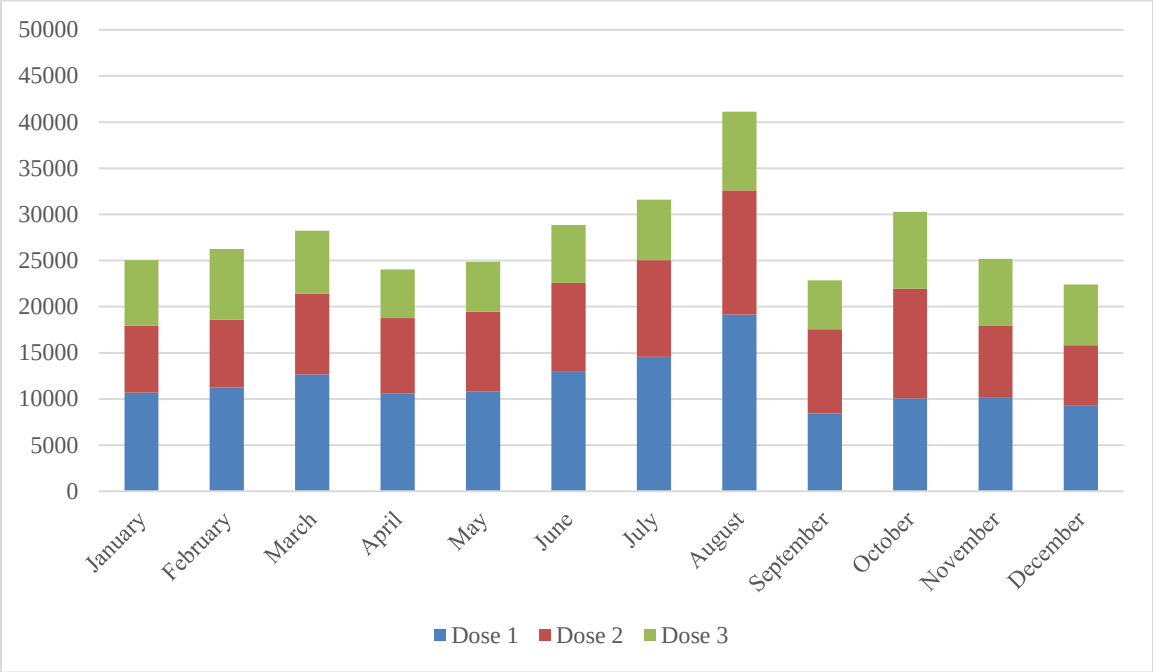


Figure 6 and Figure 7 show administration of 9vHPV by dose number and by month for each cohort across the entire study period also showing peaks in August for both cohorts.

Figure 6. Doses in *9vHPV-Only Cohort* by Dose Number and Study Month

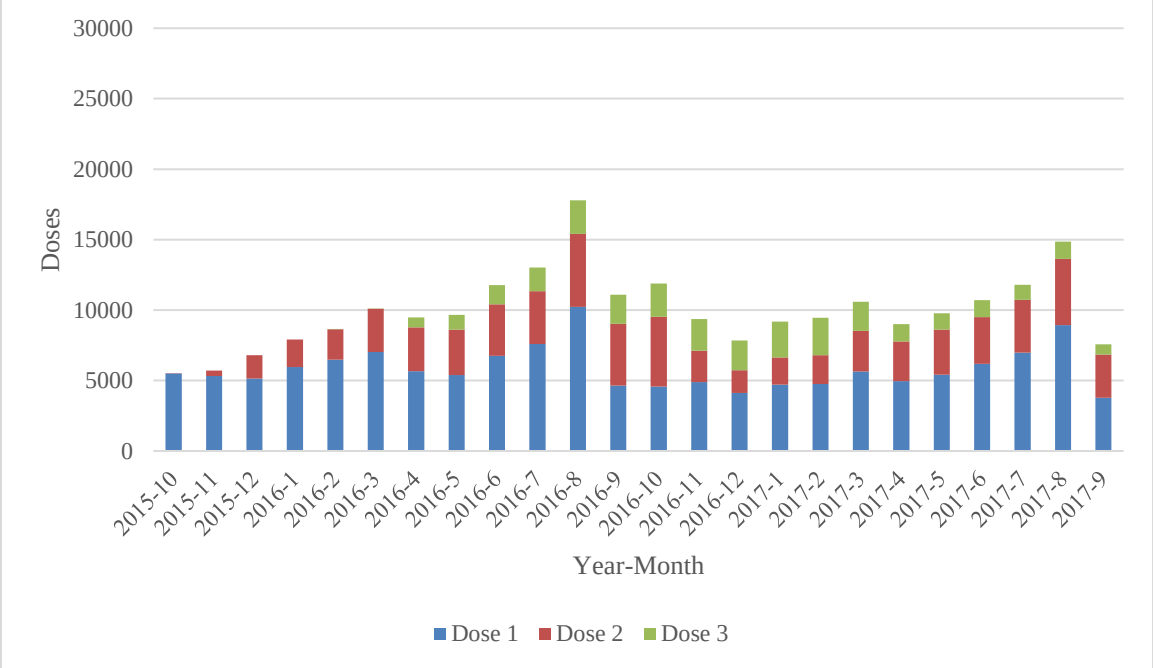
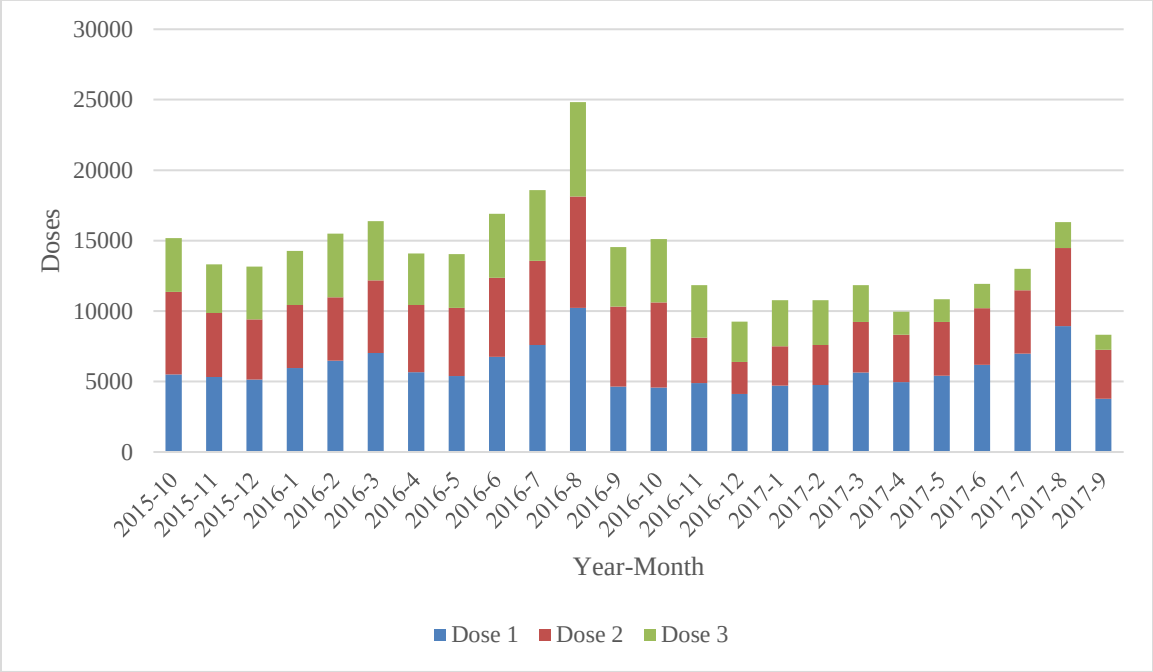


Figure 7. Doses in *Any 9vHPV Cohort* by Dose Number and Study Month



10.1.4 Concomitant Vaccine Use

Most study subjects received concomitant vaccines along with a first dose of 9vHPV, while fewer received concomitant vaccines with the second and third doses. In the *9vHPV-Only Cohort*, 77.1% of dose 1 vaccinees received concomitant vaccines, while only 19.5% of dose 2 and 22.2% dose 3 vaccinees received concomitant vaccines (data shown in Annex 2, Table 6a, with additional detail by all observed concomitant vaccine types). Similarly, in the *Any 9vHPV Cohort* 30.1% of dose 2 and 32.1% of dose 3 vaccinees received concomitant vaccines (data shown in Annex 2, Table 6b, with additional detail by all observed concomitant vaccine types). Note that dose 1 9vHPV vaccinees are the same in both cohorts, so the percent receiving concomitant vaccines was identical (i.e., everyone who has 9vHPV vaccine as dose 1 in the study period is by definition in both cohorts).

The most common concomitant vaccines given with the first dose of 9vHPV vaccine were quadrivalent meningococcal conjugate vaccine (MCV4) (58.0%) and tetanus, diphtheria and/or acellular pertussis vaccines (Tdap or Td) (52.4%). In *9vHPV-Only Cohort*, only 3.7% of dose 2 and 2.9% of dose 3 recipients received MCV4, while 1.9% of dose 2 and 1.2% of dose 3 vaccinees received Tdap/Td vaccine (Figure 8). In the *Any 9vHPV Cohort*, 7.6% of dose 2 and 7.9% of dose 3 vaccinees received MCV4 and 2.1% of dose 2 and 1.4% of dose 3 recipients received Tdap/Td vaccine (Figure 9). The most common concomitant vaccine given with dose 2 and dose 3 was influenza vaccine in both cohorts, at rates ranging approximately between 10% and 20%.

Concomitant vaccination at each study dose was very similar between the two cohorts.

Figure 8. Concomitant Vaccine Use, *9vHPV-Only Cohort*

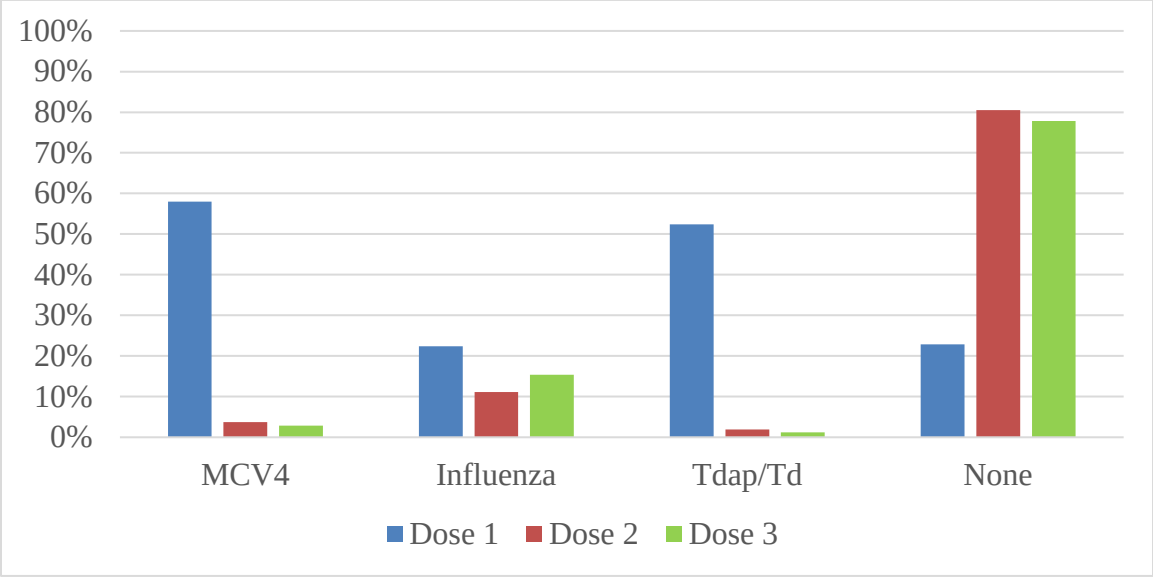
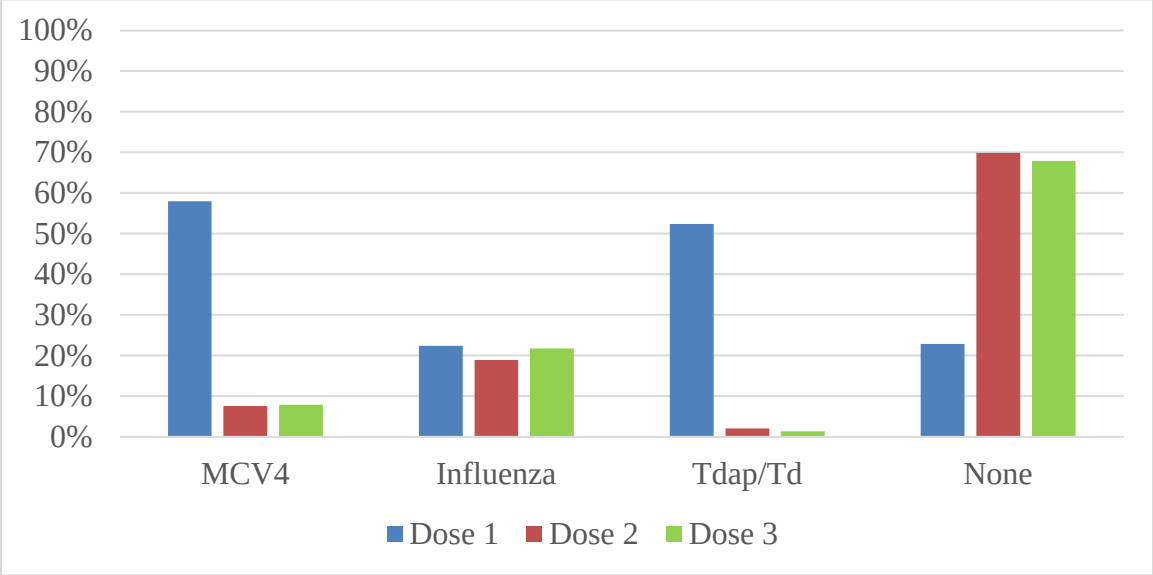


Figure 9. Concomitant Vaccine Use, *Any 9vHPV Cohort*



10.2 Population Characteristics

Both the *9vHPV-Only Cohort* and *Any 9vHPV Cohort* were balanced by sex, with approximately half of each cohort being female. In each cohort, the largest race group was white at approximately 34%, and then unknown race (race information unavailable). In each group approximately 30% specified Hispanic ethnicity. The two study cohorts were very similar to each other by all measured population characteristics (Table 12) which is not unexpected due to the overlap between cohorts.

The population and household demographic characteristics of each study cohort are also presented in this table. The household demographic characteristics of the two cohorts were characterized based on household income and education from most recent census tract information and extrapolated from subjects' addresses.

The number of months of membership in the prior year of each study subject was also assessed. The mean length of membership was 10.5 months for subjects in the *9vHPV-Only Cohort* and 10.9 months in the *Any 9vHPV Cohort*.

Table 12. Demographic Characteristics of Study Populations

	9vHPV-Only Cohort **N = 140,628**	***Any 9vHPV Cohort*** **N = 215,965**
	N (%)	**N (%)**
Gender		
Female	69,918 (49.6)	105,941 (49.1)
Male	70,810 (50.4)	110,024 (50.9)
Race		
White	48,069 (34.2)	73,231 (33.9)
Asian	29,335 (20.9)	43,413 (20.1)
Black	10,740 (7.6)	17,895 (8.3)
Multiracial	9,064 (6.4)	14,086 (6.5)
Pacific Islander	1,159 (0.8)	1,827 (0.8)
Native American	708 (0.5)	1,072 (0.5)
Unknown/Other	41,553 (29.5)	64,441 (29.8)
Ethnicity		
Hispanic	41,674 (29.6)	65,596 (30.4)
Non-Hispanic	30,781 (21.9)	50,707 (23.5)
Unknown Ethnicity	68,173 (48.5)	99,662 (46.1)
Household Income (%)*		
<$29,999	19.3%	19.4%
$30,000–49,999	11.6%	11.7%
$50,000–99,999	31.4%	31.5%
$100,000–149,999	18.2%	18.2%
$150,000–199,999	8.3%	8.2%
$200,000+	7.6%	7.5%
Household Education (%)*		
12th grade or less	15.1%	15.2%
High School Graduate	21.1%	21.2%
Some College, No Degree	22.2%	22.3%
Associate or bachelor's degree	29.9%	29.7%
Graduate or Professional Degree	10.2%	10.0%
Doctorate Degree	1.5%	1.5%

* Data were calculated based on census tract information

Each study cohort's propensity to utilize health care in the year prior to this study was characterized using several measures. Approximately half received influenza vaccine in the prior year (47% in the *9vHPV-Only Cohort* and 49% in the *Any 9vHPV Cohort)*. Additionally, the number of weeks in the year prior to a subject's first 9vHPV vaccine dose in which there was at least one type of healthcare visit (Table 13) was examined. For example, the row "Ambulatory, with 1-3 weeks of encounters" = 67,369 (47.9%), can be read as "There were 67,369 subjects (47.9% of the *9vHPV-Only Cohort*) who had either 1, 2 or 3 weeks with at least 1 ambulatory encounter." For both measures, receipt of influenza vaccine in the prior year and weeks with health care utilization in the prior year, the two study cohorts are very similar.

Table 13. Number and Proportion of Subjects with Prior Year Encounters, by Cohort

Health care encounter type	***9vHPV-Only Cohort*** (N = 140,628)	***Any 9vHPV Cohort*** (N = 215,965)
Ambulatory		
with no encounters	48,639 (34.6%)	65,014 (30.1%)
with 1-3 weeks of encounters	67,369 (47.9%)	108,436 (50.2%)
with 4-6 weeks of encounters	14,998 (10.7%)	26,200 (12.1%)
with ≥7 weeks of encounters	9,622 (6.8%)	16,315 (7.6%)
Emergency		
with no encounters	122,141 (86.9%)	185,700 (86.0%)
with 1-3 weeks of encounters	17,973 (12.8%)	29,422 (13.6%)
with 4-6 weeks of encounters	433 (0.3%)	710 (0.3%)
with ≥7 weeks of encounters	81 (0.1%)	133 (0.1%)
Inpatient		
with no encounters	139,098 (98.9%)	213,390 (98.8%)
with 1-3 weeks of encounters	1,492 (1.1%)	2,514 (1.2%)
with 4-6 weeks of encounters	31 (<0.1%)	53 (<0.1%)
with ≥7 weeks of encounters	7 (<0.1%)	8 (<0.1%)
Lab Encounters		
with no encounters	105,305 (74.9%)	158,461 (73.4%)
with 1-3 weeks of encounters	32,744 (23.3%)	53,195 (24.6%)
with 4-6 weeks of encounters	1,947 (1.4%)	3,242 (1.5%)
with ≥7 weeks of encounters	632 (0.4%)	1,067 (0.5%)
Radiology		
with no encounters	120,719 (85.8%)	183,152 (84.8%)
with 1-3 weeks of encounters	19,090 (13.6%)	31,439 (14.6%)
with 4-6 weeks of encounters	747 (0.5%)	1,260 (0.6%)
with ≥7 weeks of encounters	72 (0.1%)	114 (0.1%)
Telephone		
with no encounters	112,772 (80.2%)	171,748 (79.5%)
with 1-3 weeks of encounters	25,510 (18.1%)	40,421 (18.7%)
with 4-6 weeks of encounters	1,822 (1.3%)	2,935 (1.4%)
with ≥7 weeks of encounters	524 (0.4%)	861 (0.4%)
Other		
with no encounters	136,192 (96.8%)	202,922 (94.0%)
with 1-3 weeks of encounters	4,274 (3.0%)	12,830 (5.9%)
with 4-6 weeks of encounters	115 (0.1%)	156 (0.1%)
with ≥7 weeks of encounters	47 (<0.1%)	57 (<0.1%)

Ambulatory includes visits at outpatient clinics, same day surgeries, urgent care visits, and other same-day ambulatory hospital encounters, but excludes emergency department encounters and observation beds.
Emergency encounters include those that became inpatient stays. The inpatient stays would be a separate encounter. Excludes urgent care visits.
Inpatient is acute inpatient hospital stays, including all inpatient stays, same-day hospital discharges, hospital transfers, observation bed, and acute hospital care where the discharge is after the admission date.
Lab and radiology encounters only in that setting that are not linked to other encounter types (e.g., not linked to an ambulatory encounter).

Telephone encounters are appointments that take place over the phone.
Other encounters are non-overnight encounters that don't fit into the above categories, such as: hospice visits, home health visits, visits to a skilled nursing facility, and other non-hospital visits.

10.3 General Safety Results

Overall, 152 HCUP categories were analyzed, including 17 HCUP level 1 categories and 135 HCUP level 2 sub-categories. Nine body systems/level 1 HCUP categories did not have any statistically significant elevations (Table 14).

Table 14. HCUP Categories without Statistically Increased Odds Ratios in Any Risk Interval Analyses

HCUP Category
1: Infectious and parasitic diseases
2: Neoplasms
4: Diseases of the blood and blood-forming organs
7: Diseases of the circulatory system
8: Diseases of the respiratory system
11: Complications of pregnancy; childbirth; and the puerperium
13: Diseases of the musculoskeletal system and connective tissue
15: Certain conditions originating in the perinatal period
16: Injury and poisoning

Among the rest of the HCUP categories, 18 HCUP categories, including 4 HCUP level 1 categories and 14 HCUP level 2 categories, had significantly elevated results (i.e., a lower confidence limit > 1.0) in at least one risk interval (0–14 or 1–60 days) in either study cohort analysis. Table 15 shows a summary overview of all HCUP categories that had a significantly elevated OR before multiplicity adjustment. After DFDR multiplicity adjustment, one HCUP category (*HCUP 17.1 Symptoms; signs; and ill-defined conditions*) remained statistically significant and is shaded in this table.

Interval-specific ORs and 95% CIs are presented in Table 18 and Table 19. Table 18 is a summary of outcomes with significantly elevated ORs and Table 19 is a summary of outcomes with significantly decreased ORs.

Table 15. HCUP Categories with Statistically Increased Odds Ratios in at Least One Risk Interval Analysis

HCUP Category*
Day 0–14 and/or Day 1–60 Risk Interval
3.2: Diabetes mellitus without complication
5.4: Delirium dementia and amnestic and other cognitive disorders
6: Diseases of the nervous system and sense organs 6.5: Headache; including migraine 6.6: Coma; stupor; and brain damage
9: Diseases of the digestive system 9.2: Disorders of teeth and jaw 9.5: Abdominal hernia 9.6: Lower gastrointestinal disorders 9.7: Biliary tract disease 9.10: Gastrointestinal hemorrhage
10.2 Diseases of male genital organs
12: Diseases of the skin and subcutaneous tissue 12.1: Skin and subcutaneous tissue infections 12.2: Other inflammatory condition of skin
14.4: Nervous system congenital anomalies
17: Symptoms; signs; and ill-defined conditions and factors influencing health status 17.1: Symptoms; signs; and ill-defined conditions

* Shaded categories indicate statistically significantly elevated ORs after multiplicity adjustment, in at least one analysis.

10.3.1 Summary of Significant Elevations or Decreases in Odds Ratios

10.3.1.1 Summary of Significantly Elevated Odds Ratios

In all, there were 18 elevated HCUP categories as shown above in Table 15, and they are enumerated in Section 10.3.2 (“Detail of Significantly Elevated Safety Results”) below, and explored more fully in the Section 10.3.4 (“Follow-up Investigation of Categories with Elevated ORs”).

These elevated findings are across both cohorts, in the combined dose series and dose-specific analyses.

For 3 HCUP categories, there were elevated findings in both the Day 0–14 and the Day 1–60 analyses (Table 16).

Table 16. HCUP Categories that were Significantly Elevated in Both Day 0–14 and Day 1–60 Risk Interval Analyses

HCUP Category*
9.10: Gastrointestinal hemorrhage
17: Symptoms; signs; and ill-defined conditions and factors influencing health status
17.1: Symptoms; signs; and ill-defined conditions

* Shaded category indicates statistically significantly elevated ORs after multiplicity adjustment, in at least one analysis.

Combined Dose Series Analyses

In the combined dose series analysis for the Day 1-60 risk interval, there were 4 HCUP categories that had statistically significant elevations in either the *9vHPV-Only Cohort* or *Any 9vHPV Cohort*. One of these categories, HCUP 9.10: *Gastrointestinal hemorrhage,* was significantly elevated in both study cohorts, with the OR being 2.18 (95% CI: 1.19, 4.00) in the *9vHPV-Only Cohort* and 1.70 (95% CI: 1.04, 2.78) in the *Any 9vHPV Cohort*. No categories remained significant after multiplicity adjustment.

In the combined dose series analysis for the Day 0-14 risk interval, there were 6 HCUP categories that had statistically significant elevations in either the *9vHPV-Only Cohort* or *Any 9vHPV Cohort*. Two of these categories, HCUP 12: *Diseases of the skin and subcutaneous tissue* and its sub-category HCUP 12.1: *Skin and subcutaneous tissue infections*, were significantly elevated in both study cohorts. The ORs for HCUP 12: *Diseases of the skin and subcutaneous tissue* were 1.40 (95% CI: 1.02, 1.92) and 1.44 (95% CI: 1.12, 1.87) for the *9vHPV-Only Cohort* and the *Any 9vHPV Cohort*, respectively, and for the category HCUP 12.1: *Skin and subcutaneous tissue infections* they were 1.86 (95% CI: 1.15, 3.01) and 1.84 (95% CI: 1.25, 2.70) for the *9vHPV-Only Cohort* and the *Any 9vHPV Cohort*, respectively. No categories remained significant after multiplicity adjustment.

Dose-Specific Analyses

The Dose-Specific analyses were only conducted in the *9vHPV-Only Cohort*. This was to ensure comparability of exposure experience (i.e., all subjects in the 9vHPV vaccine dose 2 analyses had 9vHPV vaccine as dose 1, all during the study period, and all subjects in the dose 3 analyses had 9vHPV vaccine as doses 1 and 2, all during the study period as well).

In the analysis of dose 1 for the Day 1-60 risk interval, there were 9 categories that had statistically significant elevations and in the analysis of dose 1 for the Day 0-14 risk interval, there were 4 categories that had statistically significant elevations. Two categories were significant in both Day 1-60 and Day 0-14 risk interval analyses: HCUP 17: *Symptoms; signs; and ill-defined conditions and factors influencing health status* and its sub-category HCUP 17.1: *Symptoms; signs; and ill-defined conditions*. HCUP 17: *Symptoms; signs; and ill-defined conditions and factors influencing health status* had an OR of 1.13 (95% CI: 1.02, 1.26) in the Day 1-60 risk interval analysis and 1.36 (95% CI: 1.13, 1.64) in the Day 0-14 risk interval analysis. The category HCUP 17.1: *Symptoms; signs; and ill-defined conditions* had an OR of 1.16 (95% CI: 1.03, 1.30) in the Day 0-60 risk interval and 1.47 (95% CI: 1.20,

1.80) in the Day 0-14 risk interval, the latter of which remained significant after multiplicity adjustment.

In the analysis of dose 2 for the Day 1-60 risk interval, there were 2 categories that had statistically significant elevations and in the analysis of the Day 0-14 risk interval, there were 3 categories that had statistically significant elevations, with one category, HCUP 9.10: *Gastrointestinal hemorrhage*, being significant in both risk interval analyses. The ORs for this category were 3.80 (95% CI: 1.07, 13.46) in the Day 1-60 risk interval analysis and undefined in the Day 0-14 risk interval analysis due to there being no comparison events, but the lower bound of the CI was 1.70. No categories remained significant after multiplicity adjustment.

In the analysis of dose 3 for the Day 1-60 risk interval, there was 1 category with a statistically significant elevation: HCUP 5.04: *Delirium dementia and amnestic and other cognitive disorders*. It had an incalculable odds ratio (95% CI: 1.11, incalculable upper bound) and did not remain significant after multiplicity adjustment. The odds ratio and upper bound are mathematically incalculable when there are 0 cases in the comparison interval. In the Day 0-14 risk interval analysis, there were no categories that had statistically significant elevations.

All significantly elevated safety results are shown in Table 18.

10.3.1.2 Summary of Significantly Decreased Odds Ratios

There were also several statistically significantly decreased ORs (i.e., unadjusted ORs with an upper confidence bound <1.0) and overall, there were more significantly decreased ORs (n=38) than there were increased (n=18), both prior to and after multiplicity adjustment. Across both risk intervals in the unadjusted analysis, there were 10 decreased HCUP level 1 categories and 27 decreased HCUP level 2 categories, with multiplicity adjustment flagging an additional level 2 category.

In the Day 0–14 analyses, 5 HCUP level 1 categories and 11 HCUP level 2 categories had outcomes with significantly decreased ORs in the unadjusted analysis, none of which remained significant after multiplicity adjustment. One level 2 HCUP category that was not significantly decreased in the unadjusted analysis was found to be significant after multiplicity adjustment. In the Day 1–60 analyses, 9 HCUP level 1 categories and 26 HCUP level 2 categories had outcomes with significantly decreased ORs, 9 of which were significant after multiplicity adjustment. For 12 decreased categories, the decrease was observed in both the Day 0–14 and Day 1–60 risk interval analyses (Table 17).

Table 17. HCUP Categories that were Significantly Decreased in Both Day 0–14 and Day 1–60 Risk Interval Analyses

HCUP Category*
1: Infectious and parasitic diseases
5.3: Attention deficit conduct and disruptive behavior disorders
7: Diseases of the circulatory system
9.12: Other gastrointestinal disorders
11: Complications of pregnancy; childbirth; and the puerperium
13.6: Acquired deformities
16: Injury and poisoning 16.4: Intracranial injury 16.8: Superficial injury; contusion 16.11: Poisoning 16.12: Other injuries and conditions due to external causes
17.2: Factors influencing health care

* Shaded categories indicate statistically significantly decreased ORs after multiplicity adjustment, in at least one risk interval analysis.

All significantly decreased safety results are shown in Table 19.

10.3.2 Detail of Significantly Elevated Safety Results

The full listing of the safety results by population and risk interval is provided in *Annex 2. General Safety Results* (see Section "All Safety Tables"). The study results were grouped by cohort and doses, and further displayed by risk window and gender. All tables contain the number of events, the number and percent of events that were identified from in-patient hospitalizations, incidence rates with 95% CIs, and ORs regardless of statistical significance.

Table 18 shows the number of events, incidence rates, and ORs for each HCUP category with a significant elevation. In addition, for context, the table shows the results across both cohorts and all analyses for that category. Findings in Table 18 are formatted to indicate significantly elevated findings: elevated statistically significant unadjusted ORs on this table are ***bolded and italicized*** and shading indicates ORs which were statistically significant after multiplicity adjustment (p values are not shown). Additional information, specifically the number and percent of subjects who were hospitalized, the number of events in the comparison interval, and incidence rates with 95% CIs, can be found in *Annex 2. General Safety Results*. Incidence rates for all sex-specific listings can also be found in that annex.

The significantly elevated findings in Table 18 prompted additional investigations recommended by the eSRC and conducted by PPD staff and the study principal investigator, which are described in Section 10.3.4.

Table 18. Summary of HCUP Categories with Significantly Elevated Odds Ratios

HCUP Code	Cohort*/ Dose	Day 1-60 Risk Interval					Day 0-14 Risk Interval				
		Risk Period		Self-Comparison Period		Risk vs Self-Comparison Period	Risk Period		Self-Comparison Period		Risk vs Self-Comparison Period
		N	IR	N	IR	OR (95% CI)	N	IR	N	IR	OR (95% CI)
3.2: Diabetes mellitus without complication	9v-Only	55	1.58	27	0.84	***1.66 (1.01, 2.74)***	22	2.34	9	1.05	1.64 (0.72, 3.71)
	- Dose 1	37	1.73	14	0.99	1.69 (0.88, 3.25)	17	3.07	6	1.48	1.89 (0.70, 5.07)
	- Dose 2	14	1.31	6	0.67	2.20 (0.84, 5.74)	3	1.11	2	0.82	1.55 (0.26, 9.29)
	- Dose 3	7	1.48	3	0.70	2.64 (0.52, 13.32)	2	1.70	1	0.89	1.90 (0.14, 56.15)
	Any 9v	83	1.67	54	1.19	1.32 (0.92, 1.90)	30	2.31	16	1.31	1.39 (0.74, 2.63)
5.4: Delirium dementia and amnestic and other cognitive disorders	9v-Only	22	0.60	10	0.31	1.77 (0.79, 3.96)	8	0.85	1	0.12	7.82 (0.98, 62.73)
	- Dose 1	9	0.42	3	0.21	1.89 (0.47, 7.55)	3	0.54	0	0.00	. (0.43, .)
	- Dose 2	8	0.75	5	0.55	1.16 (0.36, 3.73)	3	1.11	1	0.41	2.72 (0.29, 71.55)
	- Dose 3	5	1.06	0	0.00	***. (1.11, .)***	2	1.70	0	0.00	. (0.27, .)
	Any 9v	28	0.54	16	0.35	1.41 (0.73, 2.70)	10	0.77	1	0.08	***8.93 (1.13, 70.53)***
6: Diseases of the nervous system and sense organs	9v-Only	909	25.37	807	25.46	*0.86 (0.78, 0.96)*	274	29.46	234	27.22	0.94 (0.78, 1.13)
	- Dose 1	540	25.36	383	27.24	0.96 (0.83, 1.11)	166	30.03	100	24.74	***1.33 (1.02, 1.72)***
	- Dose 2	275	25.83	226	25.11	1.04 (0.87, 1.26)	81	30.01	71	29.04	1.13 (0.82, 1.57)
	- Dose 3	115	24.35	100	23.27	1.00 (0.76, 1.33)	30	25.51	38	33.95	0.74 (0.45, 1.21)
	Any 9v	1320	26.17	1171	25.65	0.92 (0.85, 1.00)	373	28.91	315	25.87	1.00 (0.86, 1.17)
6.5: Headache; including migraine	9v-Only	308	8.61	282	8.89	*0.80 (0.67, 0.95)*	109	11.69	87	10.12	0.99 (0.74, 1.33)
	- Dose 1	186	8.72	131	9.30	0.90 (0.70, 1.15)	70	12.66	30	7.42	***1.82 (1.17, 2.85)***
	- Dose 2	81	7.60	81	8.99	0.84 (0.61, 1.17)	28	10.37	29	11.86	0.97 (0.57, 1.65)
	- Dose 3	49	10.36	38	8.83	1.17 (0.77, 1.80)	12	10.20	15	13.39	0.77 (0.35, 1.66)
	Any 9v	480	9.51	417	9.11	0.92 (0.80, 1.06)	145	11.22	117	9.61	1.03 (0.80, 1.32)

Table 18. Summary of HCUP Categories with Significantly Elevated Odds Ratios (continued)

HCUP Code	Cohort*/ Dose	Day 1-60 Risk Interval					Day 0-14 Risk Interval				
		Risk Period		Self-Comparison Period		Risk vs Self-Comparison Period	Risk Period		Self-Comparison Period		Risk vs Self-Comparison Period
		N	IR	N	IR	OR (95% CI)	N	IR	N	IR	OR (95% CI)
6.6: Coma; stupor; and brain damage	9v-Only	14	0.38	4	0.12	2.48 (0.80, 7.72)	4	0.43	1	0.12	4.14 (0.46, 37.02)
	- Dose 1	9	0.42	0	0.00	***. (1.67, .)***	3	0.54	0	0.00	. (0.43, .)
	- Dose 2	3	0.28	1	0.11	2.54 (0.27, 66.77)	1	0.37	0	0.00	. (0.05, .)
	- Dose 3	2	0.42	1	0.23	1.82 (0.14, 53.67)	0	0.00	0	0.00	--
	Any 9v	17	0.33	8	0.17	1.49 (0.62, 3.53)	4	0.31	3	0.25	1.38 (0.31, 6.16)
9: Diseases of the digestive system	9v-Only	852	23.70	646	20.54	0.99 (0.88, 1.10)	245	26.16	190	22.22	0.99 (0.81, 1.22)
	- Dose 1	526	24.70	290	20.61	***1.21 (1.03, 1.41)***	146	26.41	91	22.51	1.19 (0.90, 1.57)
	- Dose 2	245	23.00	175	19.43	1.21 (0.99, 1.49)	73	27.04	54	22.08	1.25 (0.87, 1.80)
	- Dose 3	98	20.75	97	22.58	0.92 (0.69, 1.24)	27	22.95	31	27.69	0.81 (0.47, 1.38)
	Any 9v	1193	23.63	938	20.62	1.01 (0.92, 1.11)	338	26.06	278	22.91	1.00 (0.85, 1.18)
9.2: Disorders of teeth and jaw	9v-Only	83	2.26	61	1.89	0.94 (0.66, 1.34)	30	3.19	15	1.74	1.35 (0.70, 2.62)
	- Dose 1	55	2.58	33	2.34	0.97 (0.60, 1.56)	25	4.52	12	2.97	1.40 (0.67, 2.94)
	- Dose 2	24	2.25	10	1.11	***2.38 (1.14, 4.98)***	3	1.11	2	0.82	1.55 (0.26, 9.29)
	- Dose 3	4	0.85	7	1.63	0.52 (0.15, 1.78)	2	1.70	1	0.89	1.90 (0.14, 56.15)
	Any 9v	120	2.33	87	1.88	1.06 (0.79, 1.42)	42	3.23	17	1.40	***1.86 (1.03, 3.34)***
9.5: Abdominal hernia	9v-Only	56	1.52	25	0.78	***1.73 (1.06, 2.80)***	7	0.74	8	0.93	0.62 (0.21, 1.80)
	- Dose 1	36	1.69	10	0.71	***2.63 (1.28, 5.42)***	6	1.08	4	0.99	1.15 (0.31, 4.34)
	- Dose 2	16	1.50	8	0.89	1.72 (0.73, 4.05)	1	0.37	4	1.64	0.26 (0.03, 2.31)
	- Dose 3	4	0.85	2	0.46	1.51 (0.25, 9.00)	0	0.00	0	0.00	--
	Any 9v	71	1.38	31	0.67	***1.82 (1.18, 2.80)***	8	0.61	9	0.74	0.66 (0.24, 1.79)
9.6: Lower gastrointestinal disorders	9v-Only	136	3.84	109	3.51	0.97 (0.74, 1.28)	40	4.36	29	3.49	1.19 (0.71, 1.99)
	- Dose 1	83	3.89	42	2.98	***1.53 (1.01, 2.32)***	21	3.80	15	3.71	1.12 (0.56, 2.24)
	- Dose 2	44	4.12	37	4.10	1.03 (0.64, 1.64)	14	5.18	8	3.27	1.66 (0.65, 4.26)
	- Dose 3	14	2.96	16	3.72	0.74 (0.33, 1.69)	6	5.10	5	4.46	1.06 (0.31, 3.61)
	Any 9v	183	3.68	157	3.48	0.95 (0.76, 1.19)	53	4.15	42	3.53	1.14 (0.74, 1.74)

Table 18. Summary of HCUP Categories with Significantly Elevated Odds Ratios (continued)

HCUP Code	Cohort*/ Dose	Day 1-60 Risk Interval					Day 0-14 Risk Interval				
		Risk Period		Self-Comparison Period		Risk vs Self-Comparison Period	Risk Period		Self-Comparison Period		Risk vs Self-Comparison Period
		N	IR	N	IR	OR (95% CI)	N	IR	N	IR	OR (95% CI)
9.7: Biliary tract disease	9v-Only	52	1.47	37	1.15	1.13 (0.69, 1.85)	20	2.13	8	0.93	1.93 (0.83, 4.48)
	- Dose 1	35	1.64	18	1.28	1.43 (0.74, 2.74)	11	1.99	4	0.99	2.12 (0.64, 6.97)
	- Dose 2	13	1.22	9	1.00	1.31 (0.52, 3.27)	5	1.85	3	1.23	1.38 (0.31, 6.16)
	- Dose 3	6	1.27	2	0.46	1.77 (0.33, 9.59)	4	3.40	1	0.89	2.26 (0.22, 23.44)
	Any 9v	74	1.48	47	1.02	1.40 (0.92, 2.13)	29	2.23	12	0.98	***2.06 (1.04, 4.09)***
9.10: Gastrointestinal hemorrhage	9v-Only	44	1.20	16	0.50	***2.18 (1.19, 4.00)***	16	1.70	5	0.58	2.50 (0.89, 7.02)
	- Dose 1	27	1.27	8	0.57	***2.32 (1.02, 5.29)***	9	1.63	3	0.74	2.10 (0.53, 8.35)
	- Dose 2	14	1.31	3	0.33	***3.80 (1.07, 13.46)***	7	2.59	0	0.00	***. (1.70, .)***
	- Dose 3	3	0.63	2	0.46	2.00 (0.18, 22.06)	0	0.00	1	0.89	. (., 18.08)
	Any 9v	55	1.07	26	0.56	***1.70 (1.04, 2.78)***	20	1.54	10	0.82	1.58 (0.72, 3.48)
10.2: Diseases of male genital organs	9v-Only	124	3.38	65	2.02	***1.44 (1.04, 1.98)***	38	4.04	19	2.21	1.57 (0.89, 2.78)
	- Dose 1	81	3.80	35	2.48	***1.60 (1.04, 2.46)***	26	4.70	12	2.97	1.61 (0.78, 3.29)
	- Dose 2	28	2.62	15	1.66	1.67 (0.88, 3.15)	8	2.96	3	1.23	2.65 (0.70, 10.00)
	- Dose 3	15	3.17	9	2.09	1.58 (0.69, 3.63)	4	3.40	2	1.79	2.07 (0.38, 11.30)
	Any 9v	170	3.31	108	2.33	1.28 (0.99, 1.64)	50	3.84	31	2.54	1.38 (0.86, 2.20)
12: Diseases of the skin and subcutaneous tissue	9v-Only	369	10.13	263	8.20	1.04 (0.88, 1.23)	122	12.97	66	7.67	***1.40 (1.02, 1.92)***
	- Dose 1	235	11.02	134	9.52	1.16 (0.94, 1.43)	82	14.83	39	9.64	1.47 (0.98, 2.20)
	- Dose 2	96	9.00	62	6.88	1.31 (0.94, 1.83)	30	11.11	15	6.13	***1.88 (1.00, 3.53)***
	- Dose 3	41	8.67	29	6.74	1.27 (0.78, 2.08)	10	8.50	9	8.04	0.82 (0.31, 2.14)
	Any 9v	526	10.29	388	8.44	1.08 (0.94, 1.24)	177	13.60	100	8.21	***1.44 (1.12, 1.87)***
12.1: Skin and subcutaneous tissue infections	9v-Only	180	4.96	123	3.85	1.09 (0.85, 1.39)	64	6.80	26	3.02	***1.86 (1.15, 3.01)***
	- Dose 1	117	5.49	70	4.97	1.07 (0.78, 1.49)	42	7.59	19	4.70	1.53 (0.86, 2.72)
	- Dose 2	43	4.03	29	3.22	1.33 (0.82, 2.16)	14	5.18	5	2.04	***2.90 (1.04, 8.04)***
	- Dose 3	22	4.65	9	2.09	2.03 (0.92, 4.49)	8	6.80	1	0.89	4.96 (0.59, 41.96)
	Any 9v	257	5.04	190	4.15	1.06 (0.87, 1.30)	93	7.15	41	3.37	***1.84 (1.25, 2.70)***

Table 18. Summary of HCUP Categories with Significantly Elevated Odds Ratios (continued)

HCUP Code	Cohort*/ Dose	Day 1-60 Risk Interval					Day 0-14 Risk Interval				
		Risk Period		Self-Comparison Period		Risk vs Self-Comparison Period	Risk Period		Self-Comparison Period		Risk vs Self-Comparison Period
		N	IR	N	IR	OR (95% CI)	N	IR	N	IR	OR (95% CI)
12.2: Other inflammatory condition of skin	9v-Only	27	0.73	18	0.56	1.14 (0.60, 2.14)	9	0.96	5	0.58	1.39 (0.44, 4.40)
	- Dose 1	15	0.70	7	0.50	1.43 (0.56, 3.67)	6	1.08	3	0.74	1.37 (0.31, 6.10)
	- Dose 2	8	0.75	4	0.44	1.75 (0.52, 5.87)	3	1.11	0	0.00	. (0.53, .)
	- Dose 3	4	0.85	4	0.93	0.96 (0.24, 3.84)	0	0.00	1	0.89	. (., 18.08)
	Any 9v	43	0.84	25	0.54	1.46 (0.87, 2.43)	16	1.23	5	0.41	***2.83 (1.02, 7.86)***
14.4: Nervous system congenital anomalies	9v-Only	18	0.54	9	0.31	1.86 (0.75, 4.63)	4	0.43	2	0.23	1.19 (0.19, 7.30)
	- Dose 1	14	0.66	2	0.14	***5.01 (1.10, 22.83)***	3	0.54	0	0.00	. (0.43, .)
	- Dose 2	4	0.37	4	0.44	0.98 (0.25, 3.94)	1	0.37	1	0.41	0.91 (0.02, 35.32)
	- Dose 3	2	0.42	2	0.46	0.91 (0.09, 8.74)	0	0.00	0	0.00	--
	Any 9v	22	0.47	11	0.26	1.84 (0.83, 4.12)	6	0.46	2	0.16	2.17 (0.41, 11.34)
17: Symptoms; signs; and ill-defined conditions and factors influencing health status	9v-Only	1722	48.39	1449	45.89	*0.90 (0.83, 0.97)*	564	60.76	434	50.98	1.03 (0.90, 1.18)
	- Dose 1	1041	48.98	633	45.08	***1.13 (1.02, 1.26)***	341	61.73	195	48.26	***1.36 (1.13, 1.64)***
	- Dose 2	514	48.36	417	46.40	1.07 (0.93, 1.22)	162	60.05	133	54.42	1.14 (0.90, 1.44)
	- Dose 3	216	45.83	216	50.37	0.88 (0.72, 1.08)	68	57.85	63	56.30	1.00 (0.70, 1.43)
	Any 9v	2450	48.84	2139	46.98	*0.93 (0.87, 0.99)*	793	61.63	630	52.10	1.07 (0.96, 1.20)

Table 18. Summary of HCUP Categories with Significantly Elevated Odds Ratios (continued)

HCUP Code	Cohort*/ Dose	Day 1-60 Risk Interval					Day 0-14 Risk Interval				
		Risk Period		Self-Comparison Period		Risk vs Self-Comparison Period	Risk Period		Self-Comparison Period		Risk vs Self-Comparison Period
		N	IR	N	IR	OR (95% CI)	N	IR	N	IR	OR (95% CI)
17.1: Symptoms; signs; and ill-defined conditions	9v-Only	1509	42.28	1233	39.03	0.93 (0.85, 1.01)**	500	53.73	365	42.94	1.09 (0.95, 1.26)
	- Dose 1	911	42.84	543	38.65	***1.16 (1.03, 1.30)***	302	54.66	162	40.08	***1.47 (1.20, 1.80)***
	- Dose 2	448	42.13	353	39.26	1.09 (0.94, 1.27)	144	53.37	115	47.05	1.16 (0.90, 1.49)
	- Dose 3	189	40.08	187	43.59	0.90 (0.73, 1.12)	59	50.19	54	48.25	1.02 (0.70, 1.50)
	Any 9v	2139	42.53	1825	40.07	0.95 (0.89, 1.02)	706	54.70	543	44.94	1.12 (0.99, 1.25)

* Cohort Ns: *9vHPV-Only* = 140,628. Dose 1 = 140,628. Dose 2 = 69,027. Dose 3 = 29,901. *Any 9vHPV* = 215,965.
** There is one instance (HCUP Code 17.1) where an unadjusted finding was not flagged as significant (i.e., it had p>0.05 in the unadjusted analysis) but after multiplicity adjustment the finding was flagged as significant (i.e., it had p<0.10 after multiplicity adjustment).

Note: There are a small number of findings that are not flagged as significant but due to rounding appear that they could be. When the finding is not flagged, it is because the unrounded confidence intervals do not span 1. In these instances, the lower-bound may round to 1.00 but be less than 1 (e.g., 0.9964), or the upper-bound rounds to 1.00 but is greater than 1 (e.g., 1.0007).

Key: "9v-Only" = *9-Valent HPV-Only Cohort*, "Any 9v" = *Any 9-Valent HPV Cohort*. CI = Confidence Interval. HCUP = Healthcare Cost and Utilization Project. IR = Incidence rate in 1000 person-years. OR=Odds Ratio.

Statistically significant decreased unadjusted ORs on this table are *italicized*.
Elevated statistically significant unadjusted ORs on this table are ***bolded and italicized***.
Shading indicates ORs which were statistically significant after multiplicity adjustment (p value not shown).
A dash ("-") indicates an incalculable value due to not having comparison interval events.

10.3.3 Detail of Significantly Decreased Safety Results

Table 19 shows the number of events, incidence rates, and ORs for each HCUP category with a significant decrease. In addition, for context, the table shows the results across both cohorts and all analyses. Findings in Table 19 are formatted to indicate significantly decreased findings: decreased statistically significant unadjusted ORs on this table are ***bolded and italicized*** and shading indicates ORs which were statistically significant after multiplicity adjustment (p values are not shown). Additional information, specifically the number and percent that were hospitalized, the number of events in the comparison interval, and incidence rates with 95% CIs, can be found in *Annex 2. General Safety Results*. Incidence rates for all sex-specific listings can also be found in the same annex.

Table 19. Summary of HCUP Categories with Significantly Decreased Odds Ratios

HCUP Code	Cohort*/ Dose	Day 1-60 Risk Interval					Day 0-14 Risk Interval				
		Risk Period		Self-Comparison Period		Risk vs Self-Comparison Period	Risk Period		Self-Comparison Period		Risk vs Self-Comparison Period
		N	IR	N	IR	OR (95% CI)	N	IR	N	IR	OR (95% CI)
1: Infectious and parasitic diseases	9v-Only	285	7.82	261	8.24	0.95 (0.80, 1.12)	74	7.87	86	10.00	0.79 (0.58, 1.07)
	- Dose 1	167	7.83	120	8.52	0.87 (0.67, 1.13)	41	7.41	43	10.63	0.71 (0.45, 1.13)
	- Dose 2	94	8.82	81	8.99	0.98 (0.71, 1.35)	28	10.37	27	11.04	0.95 (0.55, 1.66)
	- Dose 3	26	5.50	28	6.51	0.79 (0.44, 1.40)	5	4.25	7	6.25	0.39 (0.10, 1.47)
	Any 9v	394	7.70	370	8.11	***0.82 (0.70, 0.96)***	99	7.61	111	9.11	***0.74 (0.56, 0.98)***
1.3: Viral infection	9v-Only	182	5.01	174	5.44	***0.73 (0.58, 0.92)***	48	5.10	55	6.39	0.68 (0.45, 1.03)
	- Dose 1	103	4.83	81	5.75	0.79 (0.57, 1.10)	27	4.88	28	6.92	0.73 (0.42, 1.28)
	- Dose 2	65	6.09	51	5.66	1.11 (0.75, 1.64)	17	6.29	17	6.95	0.95 (0.47, 1.92)
	- Dose 3	16	3.38	19	4.41	0.83 (0.42, 1.64)	4	3.40	3	2.68	1.08 (0.22, 5.18)
	Any 9v	246	4.82	245	5.34	***0.77 (0.64, 0.93)***	62	4.76	68	5.58	0.76 (0.53, 1.09)
1.5: Immunizations and screening for infectious disease	9v-Only	32	0.87	35	1.09	***0.54 (0.31, 0.96)***	6	0.64	10	1.16	0.40 (0.14, 1.19)
	- Dose 1	19	0.89	15	1.06	0.63 (0.29, 1.39)	3	0.54	4	0.99	0.45 (0.08, 2.50)
	- Dose 2	8	0.75	14	1.55	0.45 (0.18, 1.14)	2	0.74	4	1.63	0.32 (0.05, 2.17)
	- Dose 3	5	1.06	3	0.70	0.76 (0.10, 5.50)	1	0.85	1	0.89	0.95 (0.02, 37.12)
	Any 9v	44	0.86	41	0.89	0.75 (0.47, 1.21)	8	0.61	12	0.98	0.50 (0.19, 1.27)
2.11: Cancer; other primary	9v-Only	13	0.41	16	0.53	0.50 (0.19, 1.30)	2	0.21	7	0.81	0.15 (0.02, 1.28)
	- Dose 1	8	0.37	7	0.50	0.27 (0.05, 1.58)	0	0.00	4	0.99	***. (., 0.82)***
	- Dose 2	5	0.47	5	0.55	0.94 (0.27, 3.26)	1	0.37	0	0.00	. (0.05, .)
	- Dose 3	2	0.42	3	0.70	0.61 (0.07, 4.08)	1	0.85	2	1.79	0.48 (0.02, 6.26)
	Any 9v	16	0.35	24	0.54	***0.42 (0.19, 0.95)***	2	0.15	8	0.66	0.13 (0.02, 1.09)

Table 19. Summary of HCUP Categories with Significantly Decreased Odds Ratios (continued)

HCUP Code	Cohort*/ Dose	Day 1-60 Risk Interval					Day 0-14 Risk Interval				
		Risk Period		Self-Comparison Period		Risk vs Self-Comparison Period	Risk Period		Self-Comparison Period		Risk vs Self-Comparison Period
		N	IR	N	IR	OR (95% CI)	N	IR	N	IR	OR (95% CI)
2.15: Maintenance chemotherapy; radiotherapy	9v-Only	3	0.08	4	0.12	0.66 (0.12, 3.18)	0	0.00	4	0.47	. (0.00, 1.02)
	- Dose 1	2	0.09	2	0.14	0.66 (0.07, 6.34)	0	0.00	2	0.49	. (., 2.54)
	- Dose 2	0	0.00	1	0.11	. (., 16.06)	0	0.00	1	0.41	. (., 17.21)
	- Dose 3	1	0.21	1	0.23	0.91 (0.02, 35.48)	0	0.00	1	0.89	. (., 18.08)
	Any 9v	4	0.08	5	0.11	0.72 (0.17, 2.84)	0	0.00	5	0.41	***. (0.00, 0.77)***
5: Mental Illness	9v-Only	756	21.40	658	20.88	***0.89 (0.79, 1.00)***	219	23.60	201	23.50	0.86 (0.71, 1.06)
	- Dose 1	458	21.50	300	21.33	1.08 (0.92, 1.28)	128	23.15	97	23.99	1.04 (0.78, 1.37)
	- Dose 2	228	21.40	196	21.77	1.01 (0.82, 1.24)	69	25.56	57	23.31	1.08 (0.76, 1.55)
	- Dose 3	99	20.96	90	20.94	0.94 (0.69, 1.28)	25	21.25	24	21.44	0.98 (0.55, 1.73)
	Any 9v	1131	22.65	1011	22.24	0.92 (0.84, 1.01)	338	26.22	290	23.98	1.00 (0.85, 1.18)
5.3: Attention deficit conduct and disruptive behavior disorders	9v-Only	113	3.10	110	3.51	0.78 (0.59, 1.04)	31	3.29	38	4.42	0.62 (0.37, 1.01)
	- Dose 1	63	2.95	46	3.27	0.95 (0.63, 1.44)	19	3.44	19	4.70	0.74 (0.38, 1.48)
	- Dose 2	35	3.28	41	4.55	0.78 (0.49, 1.24)	9	3.33	10	4.09	0.87 (0.35, 2.17)
	- Dose 3	16	3.38	14	3.25	1.02 (0.49, 2.12)	3	2.55	6	5.36	0.52 (0.13, 2.07)
	Any 9v	167	3.27	170	3.74	***0.79 (0.63, 1.00)***	46	3.53	57	4.68	***0.65 (0.43, 0.98)***
5.8: Mood disorders	9v-Only	271	7.63	249	7.83	***0.82 (0.67, 1.00)***	85	9.04	65	7.56	1.00 (0.71, 1.41)
	- Dose 1	167	7.83	102	7.24	1.17 (0.88, 1.54)	48	8.68	32	7.91	1.15 (0.71, 1.86)
	- Dose 2	77	7.22	72	7.99	0.89 (0.63, 1.26)	26	9.63	19	7.77	1.17 (0.63, 2.16)
	- Dose 3	36	7.61	40	9.30	0.77 (0.47, 1.26)	11	9.35	8	7.14	1.31 (0.52, 3.30)
	Any 9v	425	8.46	405	8.85	0.86 (0.74, 1.00)	126	9.68	111	9.11	0.96 (0.74, 1.25)
5.13: Suicide and intentional self-inflicted injury	9v-Only	168	4.68	166	5.25	***0.75 (0.58, 0.95)***	47	5.00	46	5.35	0.83 (0.54, 1.26)
	- Dose 1	94	4.41	76	5.40	0.83 (0.59, 1.17)	22	3.98	26	6.43	0.66 (0.36, 1.21)
	- Dose 2	53	4.97	39	4.32	1.15 (0.76, 1.75)	17	6.29	8	3.27	1.84 (0.78, 4.35)
	- Dose 3	25	5.29	32	7.44	0.63 (0.35, 1.14)	8	6.80	7	6.25	0.97 (0.34, 2.77)
	Any 9v	269	5.33	266	5.84	***0.82 (0.68, 0.99)***	71	5.46	70	5.75	0.88 (0.63, 1.24)

Table 19. Summary of HCUP Categories with Significantly Decreased Odds Ratios (continued)

HCUP Code	Cohort*/ Dose	Day 1-60 Risk Interval					Day 0-14 Risk Interval				
		Risk Period		Self-Comparison Period		Risk vs Self-Comparison Period	Risk Period		Self-Comparison Period		Risk vs Self-Comparison Period
		N	IR	N	IR	OR (95% CI)	N	IR	N	IR	OR (95% CI)
6: Diseases of the nervous system and sense organs	9v-Only	909	25.37	807	25.46	***0.86 (0.78, 0.96)***	274	29.46	234	27.22	0.94 (0.78, 1.13)
	- Dose 1	540	25.36	383	27.24	0.96 (0.83, 1.11)	166	30.03	100	24.74	*1.33 (1.02, 1.72)*
	- Dose 2	275	25.83	226	25.11	1.04 (0.87, 1.26)	81	30.01	71	29.04	1.13 (0.82, 1.57)
	- Dose 3	115	24.35	100	23.27	1.00 (0.76, 1.33)	30	25.51	38	33.95	0.74 (0.45, 1.21)
	Any 9v	1320	26.17	1171	25.65	0.92 (0.85, 1.00)	373	28.91	315	25.87	1.00 (0.86, 1.17)
6.5: Headache; including migraine	9v-Only	308	8.61	282	8.89	***0.80 (0.67, 0.95)***	109	11.69	87	10.12	0.99 (0.74, 1.33)
	- Dose 1	186	8.72	131	9.30	0.90 (0.70, 1.15)	70	12.66	30	7.42	*1.82 (1.17, 2.85)*
	- Dose 2	81	7.60	81	8.99	0.84 (0.61, 1.17)	28	10.37	29	11.86	0.97 (0.57, 1.65)
	- Dose 3	49	10.36	38	8.83	1.17 (0.77, 1.80)	12	10.20	15	13.39	0.77 (0.35, 1.66)
	Any 9v	480	9.51	417	9.11	0.92 (0.80, 1.06)	145	11.22	117	9.61	1.03 (0.80, 1.32)
7: Diseases of the circulatory system	9v-Only	369	10.21	336	10.63	***0.82 (0.70, 0.97)***	104	11.06	106	12.33	***0.73 (0.55, 0.98)***
	- Dose 1	216	10.13	148	10.51	1.01 (0.81, 1.27)	64	11.57	53	13.11	0.87 (0.59, 1.30)
	- Dose 2	119	11.16	101	11.21	1.00 (0.76, 1.33)	28	10.37	23	9.40	1.17 (0.66, 2.06)
	- Dose 3	40	8.46	46	10.69	0.78 (0.50, 1.21)	12	10.20	16	14.29	0.66 (0.30, 1.44)
	Any 9v	525	10.33	494	10.84	***0.85 (0.74, 0.96)***	153	11.76	158	12.97	***0.79 (0.63, 1.00)***
7.2: Diseases of the heart	9v-Only	287	7.92	261	8.20	***0.82 (0.68, 0.98)***	80	8.50	80	9.30	0.74 (0.53, 1.03)
	- Dose 1	162	7.60	117	8.31	0.91 (0.70, 1.18)	46	8.32	38	9.40	0.84 (0.53, 1.34)
	- Dose 2	97	9.10	72	7.99	1.14 (0.84, 1.55)	25	9.26	19	7.77	1.26 (0.68, 2.34)
	- Dose 3	32	6.77	34	7.90	0.88 (0.54, 1.43)	9	7.65	10	8.93	0.83 (0.33, 2.10)
	Any 9v	414	8.13	392	8.57	***0.84 (0.72, 0.97)***	121	9.30	123	10.10	0.81 (0.62, 1.05)
7.3: Cerebrovascular disease	9v-Only	5	0.14	8	0.25	0.51 (0.16, 1.59)	2	0.21	3	0.35	0.41 (0.05, 2.99)
	- Dose 1	0	0.00	4	0.28	***. (., 0.74)***	0	0.00	1	0.25	. (., 13.89)
	- Dose 2	3	0.28	3	0.33	0.66 (0.11, 3.86)	1	0.37	1	0.41	0.91 (0.02, 35.32)
	- Dose 3	2	0.42	0	0.00	. (0.26, .)	1	0.85	0	0.00	. (0.05, .)
	Any 9v	9	0.17	10	0.22	0.65 (0.25, 1.68)	3	0.23	5	0.41	0.30 (0.06, 1.60)

Table 19. Summary of HCUP Categories with Significantly Decreased Odds Ratios (continued)

HCUP Code	Cohort*/ Dose	Day 1-60 Risk Interval					Day 0-14 Risk Interval				
		Risk Period		Self-Comparison Period		Risk vs Self-Comparison Period	Risk Period		Self-Comparison Period		Risk vs Self-Comparison Period
		N	IR	N	IR	OR (95% CI)	N	IR	N	IR	OR (95% CI)
8: Diseases of the respiratory system	9v-Only	1250	34.88	1052	33.08	***0.90 (0.82, 0.98)***	340	36.48	294	34.32	0.92 (0.78, 1.09)
	- Dose 1	769	36.14	505	35.94	1.04 (0.92, 1.18)	208	37.63	152	37.61	1.09 (0.88, 1.36)
	- Dose 2	371	34.86	278	30.90	1.16 (0.99, 1.37)	99	36.68	84	34.36	1.05 (0.78, 1.42)
	- Dose 3	138	29.23	126	29.34	0.96 (0.74, 1.23)	36	30.61	35	31.27	0.92 (0.57, 1.48)
	Any 9v	1770	35.17	1526	33.45	0.94 (0.87, 1.01)	473	36.60	407	33.60	0.99 (0.86, 1.13)
8.5: Pleurisy; pneumothorax; pulmonary collapse	9v-Only	19	0.52	22	0.68	0.55 (0.27, 1.12)	3	0.32	6	0.70	0.39 (0.10, 1.58)
	- Dose 1	13	0.61	8	0.57	0.98 (0.37, 2.57)	2	0.36	1	0.25	1.46 (0.11,
	- Dose 2	5	0.47	8	0.89	0.50 (0.13, 2.00)	1	0.37	3	1.23	43.14)
	- Dose 3	1	0.21	3	0.70	0.30 (0.01, 2.85)	0	0.00	2	1.79	0.30 (0.01, 2.83)
	Any 9v	25	0.49	32	0.69	***0.56 (0.31, 0.99)***	5	0.38	9	0.74	. (., 3.30)
											0.48 (0.16, 1.44)
8.9: Other upper respiratory disease	9v-Only	185	5.12	189	5.87	0.87 (0.71, 1.07)	43	4.57	50	5.81	0.68 (0.45, 1.04)
	- Dose 1	116	5.44	99	7.03	0.82 (0.61, 1.10)	31	5.61	27	6.68	0.96 (0.56, 1.65)
	- Dose 2	50	4.69	44	4.88	0.97 (0.64, 1.48)	7	2.59	12	4.91	0.40 (0.14, 1.12)
	- Dose 3	22	4.65	24	5.58	0.86 (0.48, 1.57)	5	4.25	9	8.04	0.54 (0.18, 1.61)
	Any 9v	264	5.19	264	5.73	***0.81 (0.68, 0.97)***	61	4.69	71	5.83	0.74 (0.52, 1.05)
9.12: Other gastrointestinal disorders	9v-Only	287	7.90	248	7.80	0.85 (0.71, 1.02)	72	7.65	76	8.84	0.87 (0.63, 1.20)
	- Dose 1	175	8.21	100	7.10	1.16 (0.89, 1.51)	40	7.23	31	7.67	1.02 (0.62, 1.66)
	- Dose 2	80	7.50	74	8.21	0.93 (0.67, 1.30)	24	8.89	25	10.22	0.88 (0.49, 1.58)
	- Dose 3	35	7.40	41	9.53	0.75 (0.47, 1.20)	8	6.80	14	12.50	0.53 (0.22, 1.30)
	Any 9v	397	7.80	360	7.85	***0.85 (0.73, 0.99)***	96	7.38	111	9.11	***0.70 (0.53, 0.94)***
10: Diseases of the genitourinary system	9v-Only	464	12.83	354	11.25	0.96 (0.82, 1.12)	123	13.18	120	13.96	***0.76 (0.58, 0.99)***
	- Dose 1	280	13.13	162	11.51	1.17 (0.95, 1.46)	71	12.84	56	13.85	0.91 (0.62, 1.34)
	- Dose 2	134	12.57	113	12.54	1.01 (0.77, 1.31)	39	14.44	34	13.90	1.06 (0.66, 1.69)
	- Dose 3	57	12.06	47	10.93	1.04 (0.69, 1.57)	14	11.90	15	13.40	0.75 (0.35, 1.62)
	Any 9v	676	13.35	553	12.20	0.98 (0.86, 1.10)	183	14.14	167	13.71	0.90 (0.72, 1.13)

Table 19. Summary of HCUP Categories with Significantly Decreased Odds Ratios (continued)

HCUP Code	Cohort*/ Dose	Day 1-60 Risk Interval					Day 0-14 Risk Interval				
		Risk Period		Self-Comparison Period		Risk vs Self-Comparison Period	Risk Period		Self-Comparison Period		Risk vs Self-Comparison Period
		N	IR	N	IR	OR (95% CI)	N	IR	N	IR	OR (95% CI)
10.1: Diseases of the urinary system	9v-Only	232	6.43	201	6.40	0.82 (0.66, 1.00)	56	5.95	69	8.02	***0.55 (0.37, 0.81)***
	- Dose 1	140	6.56	86	6.11	1.10 (0.82, 1.47)	30	5.42	31	7.67	0.62 (0.35, 1.10)
	- Dose 2	69	6.47	67	7.43	0.85 (0.60, 1.22)	21	7.78	22	8.99	0.84 (0.45, 1.56)
	- Dose 3	27	5.71	25	5.81	0.78 (0.43, 1.42)	5	4.25	7	6.25	0.32 (0.08, 1.28)
	Any 9v	337	6.67	305	6.77	0.86 (0.73, 1.02)	85	6.53	97	7.96	***0.67 (0.49, 0.92)***
11: Complications of pregnancy; childbirth; and the puerperium	9v-Only	60	1.63	74	2.33	***0.54 (0.36, 0.80)***	14	1.49	23	2.67	***0.45 (0.22, 0.90)***
	- Dose 1	36	1.69	34	2.41	0.70 (0.40, 1.22)	7	1.27	14	3.46	***0.35 (0.13, 0.96)***
	- Dose 2	16	1.50	22	2.44	0.59 (0.28, 1.25)	6	2.22	3	1.23	2.04 (0.51, 8.15)
	- Dose 3	8	1.69	8	1.86	0.73 (0.26, 2.04)	1	0.85	3	2.68	0.32 (0.01, 2.98)
	Any 9v	84	1.63	109	2.38	***0.57 (0.42, 0.79)***	22	1.69	34	2.79	***0.53 (0.30, 0.93)***
11.3: Complications mainly related to pregnancy	9v-Only	36	0.98	53	1.68	***0.49 (0.30, 0.79)***	10	1.06	16	1.86	0.53 (0.24, 1.19)
	- Dose 1	21	0.98	25	1.77	0.64 (0.34, 1.23)	5	0.90	11	2.72	0.42 (0.14, 1.23)
	- Dose 2	11	1.03	14	1.55	0.60 (0.23, 1.55)	5	1.85	2	0.82	2.54 (0.49, 13.07)
	- Dose 3	4	0.85	6	1.39	0.50 (0.14, 1.86)	0	0.00	1	0.89	. (., 18.08)
	Any 9v	44	0.86	67	1.47	***0.50 (0.33, 0.76)***	13	1.00	21	1.72	0.54 (0.27, 1.09)
11.4: Indications for care in pregnancy; labor; and delivery	9v-Only	0	0.00	5	0.16	***. (0.00, 0.72)***	0	0.00	0	0.00	--
	- Dose 1	0	0.00	1	0.07	. (., 12.54)	0	0.00	0	0.00	--
	- Dose 2	0	0.00	2	0.22	. (., 2.94)	0	0.00	0	0.00	--
	- Dose 3	0	0.00	0	0.00	--	0	0.00	0	0.00	--
	Any 9v	0	0.00	5	0.11	***. (0.00, 0.74)***	0	0.00	0	0.00	--
11.5: Complications during labor	9v-Only	0	0.00	4	0.12	***. (0.00, 0.98)***	0	0.00	1	0.12	. (0.00, 17.37)
	- Dose 1	0	0.00	1	0.07	. (., 12.54)	0	0.00	1	0.25	. (., 13.89)
	- Dose 2	0	0.00	1	0.11	. (., 16.06)	0	0.00	0	0.00	--
	- Dose 3	0	0.00	1	0.23	. (., 17.28)	0	0.00	0	0.00	--
	Any 9v	0	0.00	4	0.09	. (0.00, 1.00)	0	0.00	1	0.08	. (0.00, 17.79)

Table 19. Summary of HCUP Categories with Significantly Decreased Odds Ratios (continued)

HCUP Code	Cohort*/ Dose	Day 1-60 Risk Interval					Day 0-14 Risk Interval				
		Risk Period		Self-Comparison Period		Risk vs Self-Comparison Period	Risk Period		Self-Comparison Period		Risk vs Self-Comparison Period
		N	IR	N	IR	OR (95% CI)	N	IR	N	IR	OR (95% CI)
13: Diseases of the musculoskeletal system and connective tissue	9v-Only	626	17.31	525	16.48	***0.87 (0.77, 0.99)***	161	17.12	139	16.28	0.84 (0.66, 1.07)
	- Dose 1	371	17.41	236	16.77	1.02 (0.85, 1.22)	94	17.00	68	16.82	0.92 (0.65, 1.30)
	- Dose 2	180	16.89	135	14.98	1.14 (0.90, 1.45)	46	17.04	39	15.95	1.13 (0.73, 1.74)
	- Dose 3	84	17.78	72	16.75	1.02 (0.73, 1.42)	21	17.85	22	19.65	0.88 (0.47, 1.65)
	Any 9v	912	17.95	799	17.43	0.91 (0.82, 1.01)	225	17.30	218	17.98	0.82 (0.68, 1.00)
13.2: Non-traumatic joint disorders	9v-Only	185	5.12	176	5.50	***0.74 (0.59, 0.92)***	51	5.42	36	4.19	0.97 (0.61, 1.52)
	- Dose 1	112	5.25	79	5.61	0.88 (0.64, 1.21)	31	5.60	18	4.45	1.00 (0.52, 1.90)
	- Dose 2	52	4.87	36	3.99	1.19 (0.77, 1.85)	15	5.55	6	2.45	2.27 (0.87, 5.96)
	- Dose 3	24	5.07	25	5.81	0.75 (0.41, 1.37)	5	4.25	7	6.25	0.61 (0.18, 2.04)
	Any 9v	282	5.56	281	6.10	***0.79 (0.66, 0.94)***	76	5.84	68	5.58	0.88 (0.62, 1.24)
13.6: Acquired deformities	9v-Only	30	0.82	38	1.21	***0.59 (0.34, 1.00)***	5	0.53	18	2.09	***0.20 (0.07, 0.60)***
	- Dose 1	13	0.61	18	1.28	0.48 (0.22, 1.05)	2	0.36	9	2.23	***0.11 (0.01, 0.84)***
	- Dose 2	12	1.12	6	0.67	2.46 (0.77, 7.85)	2	0.74	3	1.23	0.69 (0.12, 4.13)
	- Dose 3	5	1.06	9	2.09	0.51 (0.17, 1.54)	1	0.85	6	5.36	0.17 (0.02, 1.43)
	Any 9v	50	0.97	56	1.23	0.72 (0.48, 1.09)	9	0.69	25	2.05	***0.30 (0.14, 0.67)***
16: Injury and poisoning	9v-Only	2592	71.95	2342	74.26	***0.80 (0.75, 0.85)***	691	73.86	659	77.09	***0.81 (0.72, 0.91)***
	- Dose 1	1580	74.46	1156	82.54	***0.88 (0.81, 0.96)***	407	73.68	331	81.95	0.89 (0.76, 1.04)
	- Dose 2	737	69.45	617	68.77	1.00 (0.89, 1.12)	202	74.89	192	78.59	0.97 (0.79, 1.19)
	- Dose 3	312	66.30	306	71.47	0.91 (0.77, 1.07)	85	72.33	84	75.11	0.94 (0.69, 1.28)
	Any 9v	3806	75.35	3524	77.59	***0.86 (0.82, 0.90)***	992	76.57	971	80.24	***0.86 (0.78, 0.94)***
16.1: Joint disorders and dislocations; trauma-related	9v-Only	83	2.29	87	2.73	***0.68 (0.49, 0.94)***	23	2.44	24	2.91	0.77 (0.43, 1.39)
	- Dose 1	44	2.06	40	2.84	0.62 (0.38, 1.02)	10	1.81	8	1.98	0.97 (0.36, 2.57)
	- Dose 2	30	2.81	28	3.10	0.94 (0.55, 1.58)	9	3.33	11	4.50	0.76 (0.31, 1.87)
	- Dose 3	10	2.11	10	2.32	0.62 (0.24, 1.61)	4	3.40	3	2.68	1.08 (0.22, 5.18)
	Any 9v	129	2.53	142	3.09	0.82 (0.64, 1.04)	37	2.84	37	3.12	0.84 (0.53, 1.35)

Table 19. Summary of HCUP Categories with Significantly Decreased Odds Ratios (continued)

HCUP Code	Cohort*/ Dose	Day 1-60 Risk Interval					Day 0-14 Risk Interval				
		Risk Period		Self-Comparison Period		Risk vs Self-Comparison Period	Risk Period		Self-Comparison Period		Risk vs Self-Comparison Period
		N	IR	N	IR	OR (95% CI)	N	IR	N	IR	OR (95% CI)
16.2: Fractures	9v-Only	520	14.22	441	13.74	***0.81 (0.70, 0.93)***	147	15.63	135	15.70	1.00 (0.79, 1.26)
	- Dose 1	305	14.31	224	15.92	***0.79 (0.65, 0.96)***	86	15.55	71	17.56	0.79 (0.56, 1.11)
	- Dose 2	152	14.26	114	12.65	1.08 (0.84, 1.39)	43	15.92	36	14.72	1.10 (0.70, 1.73)
	- Dose 3	65	13.75	57	13.25	1.03 (0.72, 1.49)	18	15.30	21	18.76	0.88 (0.47, 1.65)
	Any 9v	748	14.62	665	14.41	***0.86 (0.77, 0.97)***	204	15.68	195	16.01	0.86 (0.70, 1.05)
16.4: Intracranial injury	9v-Only	116	3.16	118	3.67	***0.68 (0.52, 0.90)***	25	2.66	35	4.07	***0.55 (0.32, 0.96)***
	- Dose 1	60	2.81	50	3.55	0.72 (0.47, 1.09)	10	1.81	14	3.46	0.40 (0.16, 1.03)
	- Dose 2	39	3.66	39	4.33	0.77 (0.48, 1.23)	12	4.44	11	4.50	1.05 (0.46, 2.41)
	- Dose 3	17	3.59	16	3.72	0.86 (0.41, 1.80)	3	2.55	4	3.57	0.69 (0.12, 4.13)
	Any 9v	183	3.56	188	4.06	***0.76 (0.61, 0.94)***	43	3.30	57	4.68	***0.63 (0.42, 0.96)***
16.6: Open wounds	9v-Only	448	12.23	400	12.47	***0.82 (0.71, 0.95)***	117	12.44	98	11.40	0.98 (0.74, 1.30)
	- Dose 1	286	13.42	195	13.85	1.00 (0.82, 1.22)	70	12.66	52	12.86	1.10 (0.76, 1.61)
	- Dose 2	116	10.88	90	9.99	1.17 (0.88, 1.55)	35	12.96	24	9.81	1.48 (0.87, 2.52)
	- Dose 3	47	9.94	61	14.18	***0.67 (0.45, 1.00)***	12	10.20	11	9.82	1.02 (0.44, 2.34)
	Any 9v	640	12.47	567	12.29	0.90 (0.80, 1.02)	161	12.37	137	11.25	1.03 (0.81, 1.30)
16.7: Sprains and strains	9v-Only	679	18.56	604	19.01	***0.84 (0.75, 0.95)***	168	17.86	155	18.14	0.85 (0.68, 1.07)
	- Dose 1	413	19.38	302	21.47	0.94 (0.80, 1.10)	91	16.46	81	20.03	0.81 (0.59, 1.12)
	- Dose 2	185	17.36	144	15.98	1.08 (0.86, 1.36)	54	20.00	41	16.76	1.19 (0.80, 1.80)
	- Dose 3	83	17.57	78	18.14	0.99 (0.71, 1.38)	23	19.55	20	17.86	1.14 (0.63, 2.09)
	Any 9v	1002	19.55	944	20.61	***0.86 (0.78, 0.94)***	246	18.91	243	20.04	0.87 (0.72, 1.04)
16.8: Superficial injury; contusion	9v-Only	587	16.00	535	16.73	***0.79 (0.70, 0.90)***	150	15.95	167	19.54	***0.72 (0.57, 0.90)***
	- Dose 1	344	16.14	257	18.26	0.87 (0.73, 1.03)	82	14.83	84	20.77	0.76 (0.55, 1.05)
	- Dose 2	170	15.95	146	16.21	0.97 (0.77, 1.23)	44	16.30	50	20.45	0.76 (0.50, 1.16)
	- Dose 3	73	15.45	76	17.68	0.87 (0.63, 1.22)	24	20.40	21	18.76	1.01 (0.55, 1.85)
	Any 9v	885	17.23	794	17.27	***0.89 (0.80, 0.98)***	222	17.06	231	19.13	***0.82 (0.68, 0.99)***

Table 19. Summary of HCUP Categories with Significantly Decreased Odds Ratios (continued)

HCUP Code	Cohort*/ Dose	Day 1-60 Risk Interval					Day 0-14 Risk Interval				
		Risk Period		Self-Comparison Period		Risk vs Self-Comparison Period	Risk Period		Self-Comparison Period		Risk vs Self-Comparison Period
		N	IR	N	IR	OR (95% CI)	N	IR	N	IR	OR (95% CI)
16.11: Poisoning	9v-Only	35	0.95	63	1.96	***0.40 (0.26, 0.62)***	9	0.96	17	1.98	***0.38 (0.16, 0.90)***
	- Dose 1	17	0.80	26	1.85	***0.45 (0.23, 0.88)***	6	1.08	9	2.23	0.50 (0.17, 1.51)
	- Dose 2	16	1.50	20	2.22	0.65 (0.33, 1.29)	3	1.11	6	2.45	0.46 (0.11, 1.88)
	- Dose 3	2	0.42	7	1.63	0.25 (0.05, 1.22)	0	0.00	2	1.79	. (., 3.30)
	Any 9v	66	1.28	93	2.01	***0.58 (0.42, 0.80)***	14	1.08	26	2.13	***0.44 (0.23, 0.87)***
16.12: Other injuries and conditions due to external causes	9v-Only	446	12.18	421	13.09	***0.75 (0.65, 0.86)***	113	12.01	111	12.91	0.77 (0.59, 1.02)
	- Dose 1	270	12.66	210	14.92	0.82 (0.67, 1.00)	69	12.48	57	14.10	0.89 (0.61, 1.29)
	- Dose 2	131	12.29	103	11.43	1.07 (0.82, 1.40)	32	11.85	32	13.08	0.87 (0.52, 1.47)
	- Dose 3	46	9.73	47	10.93	0.79 (0.51, 1.20)	12	10.20	13	11.61	0.73 (0.32, 1.68)
	Any 9v	651	12.69	611	13.22	***0.83 (0.74, 0.93)***	153	11.76	159	13.05	***0.79 (0.63, 1.00)***
17: Symptoms; signs; and ill-defined conditions and factors influencing health status	9v-Only	1722	48.39	1449	45.89	***0.90 (0.83, 0.97)***	564	60.76	434	50.98	1.03 (0.90, 1.18)
	- Dose 1	1041	48.98	633	45.08	*1.13 (1.02, 1.26)*	341	61.73	195	48.26	*1.36 (1.13, 1.64)*
	- Dose 2	514	48.36	417	46.40	1.07 (0.93, 1.22)	162	60.05	133	54.42	1.14 (0.90, 1.44)
	- Dose 3	216	45.83	216	50.37	0.88 (0.72, 1.08)	68	57.85	63	56.30	1.00 (0.70, 1.43)
	Any 9v	2450	48.84	2139	46.98	***0.93 (0.87, 0.99)***	793	61.63	630	52.10	1.07 (0.96, 1.20)
17.1: Symptoms; signs; and ill-defined conditions	9v-Only	1509	42.28	1233	39.03	0.93 (0.85, 1.01)**	500	53.73	365	42.94	1.09 (0.95, 1.26)
	- Dose 1	911	42.84	543	38.65	*1.16 (1.03, 1.30)*	302	54.66	162	40.08	*1.47 (1.20, 1.80)*
	- Dose 2	448	42.13	353	39.26	1.09 (0.94, 1.27)	144	53.37	115	47.05	1.16 (0.90, 1.49)
	- Dose 3	189	40.08	187	43.59	0.90 (0.73, 1.12)	59	50.19	54	48.25	1.02 (0.70, 1.50)
	Any 9v	2139	42.53	1825	40.07	0.95 (0.89, 1.02)	706	54.70	543	44.94	1.12 (0.99, 1.25)

Table 19. Summary of HCUP Categories with Significantly Decreased Odds Ratios (continued)

HCUP Code	Cohort*/ Dose	Day 1-60 Risk Interval					Day 0-14 Risk Interval				
		Risk Period		Self-Comparison Period		Risk vs Self-Comparison Period	Risk Period		Self-Comparison Period		Risk vs Self-Comparison Period
		N	IR	N	IR	OR (95% CI)	N	IR	N	IR	OR (95% CI)
17.2: Factors influencing health care	9v-Only	310	8.55	294	9.17	***0.77 (0.65, 0.92)***	87	9.25	89	10.35	***0.72 (0.53, 0.99)***
	- Dose 1	187	8.77	124	8.81	1.02 (0.79, 1.30)	51	9.22	44	10.88	0.80 (0.52, 1.24)
	- Dose 2	91	8.53	84	9.32	0.97 (0.71, 1.32)	25	9.26	22	8.99	1.13 (0.64, 2.02)
	- Dose 3	36	7.61	42	9.76	0.71 (0.45, 1.14)	11	9.35	12	10.72	0.75 (0.32, 1.77)
	Any 9v	439	8.62	428	9.28	***0.81 (0.71, 0.94)***	116	8.91	121	9.93	***0.76 (0.58, 0.99)***

* Cohort Ns: *9vHPV-Only* = 140,628. Dose 1 = 140,628. Dose 2 = 69,027. Dose 3 = 29,901. *Any 9vHPV* = 215,965.
** There is one instance (HCUP Code 17.1) where an unadjusted finding was not flagged as significant (i.e., it had p>0.05 in the unadjusted analysis) but after multiplicity adjustment the finding was flagged as significant (i.e., it had p<0.10 after multiplicity adjustment).

Note: There are a small number of findings that are not flagged as significant but due to rounding appear that they could be. When the finding is not flagged, it is because the unrounded confidence intervals do not span 1. In these instances, the lower-bound may round to 1.00 but be less than 1 (e.g., 0.9964), or the upper-bound rounds to 1.00 but is greater than 1 (e.g., 1.0007).

Key: "9v-Only" = *9-Valent HPV-Only Cohort*, "Any 9v" = *Any 9-Valent HPV Cohort*. CI = Confidence Interval. HCUP = Healthcare Cost and Utilization Project. IR = Incidence rate in 1000 person-years. OR=Odds Ratio.

Statistically significant elevated unadjusted ORs on this table are *italicized*.
Decreased statistically significant unadjusted ORs on this table are ***bolded and italicized***.
Shading indicates ORs which were statistically significant after multiplicity adjustment (p value not shown).
A dash ("-") indicates an incalculable value due to not having comparison interval events.

10.3.4 Follow-up Investigation of Categories with Elevated ORs

In this section, 18 HCUP categories (4 level 1 categories and 14 sub-categories) with significant elevations were further investigated by reviewing additional details of the corresponding conditions. In some of these categories, additional investigations were performed, as suggested by the eSRC (e.g., association between seasonality of vaccine exposure and *HCUP 3.2 Diabetes mellitus without complication*) and where this was requested, it is noted in the text. In many cases, but not all, medical record review of events was conducted, and where this was done it is stated in the relevant section. Where sampling was used (e.g., a percentage of events were reviewed) this is also described.

10.3.4.1 Exploration of finding in HCUP 3.2: *Diabetes mellitus without complication*

The category *HCUP 3.2: Diabetes mellitus without complication* was significantly elevated in the combined dose series Day 1–60 analysis for *9vHPV-Only Cohort* (OR 1.66, 95% CI 1.01, 2.74) (Table 18). There were 55 events in the risk interval of the Day 1-60 analysis, approximately half (50.9%) of which were diagnosed in the inpatient setting. The specific diagnoses are listed in Table 20.

Table 20. Detail for HCUP 3.2: *Diabetes Mellitus without Complication*, Combined Dose Series, 1–60 Day Risk Interval

Diagnosis	N = 55
Type 1 diabetes without complications	17
Hyperglycemia	10
Prediabetes	10
Type 2 diabetes mellitus without complications	10
Other abnormal glucose	7
Impaired fasting glucose	1

All above events were further characterized regarding timing of onset and seasonality of vaccine exposure, as suggested by eSRC. Of these 55 events, 40 had onset prior to vaccination, 11 were diagnoses for conditions other than new diabetes mellitus (DM) (5 were hyperglycemia diagnoses, 2 were “other abnormal glucose”, 4 were prediabetes codes), and 4 DM events were new onset. Of the new onset events, 3 were diagnosed with Type 1 DM and 1 with Type 2 DM. There were 27 DM events in the comparison interval (not shown), and of these, 23 had onset prior to vaccination. Of the 4 new onset DM events in the comparison interval, 1 was a diagnosis of new onset Type 2 DM, 2 were hyperglycemia diagnoses and 1 was a new prediabetes diagnosis.

In response to eSRC suggestion, we conducted *post hoc* statistical comparisons of confirmed new onset cases of DM. There were 4 new onset DM events (both Type 1 and Type 2 combined) during the risk interval as compared with 1 new onset DM event during the

comparison interval for an incidence rate ratio of 3.51 (95% CI 0.35, 172.68). There were 3 new onset Type 1 DM events in the risk interval as compared with 0 events during the comparison interval. Due to no events in the comparison interval, an incidence rate ratio was not calculable while the lower bound of the 95% CI was 0.36 (the upper bound was not calculable). There was 1 new onset Type 2 DM event during the risk interval as compared with 1 event during the comparison interval for an incidence rate ratio 0.88 (95% CI 0.01, 68.81). None of these *post hoc* analyses were statistically significant (these *post hoc* calculations were made using Stata, Version 11).

Seasonality with regard to onset of DM after vaccination was explored by examining when subjects were diagnosed with DM. The 15 subjects with new onset diagnoses (11 non-DM and 4 DM) were diagnosed throughout the year and there was not clear seasonality [January (N=2), February (N=4), March (N=3), and April, May, June, July, August and October each with 1 event; no events were diagnosed in September, November or December]. Of the 40 subjects with prior DM diagnoses, 11 were diagnosed in October, while the remaining months generally averaged less than 3 diagnoses per month (February, July and November had 4 each, January had 3, April, May, June, September, December had 2 each and August had 1). No specific seasonality was observed. Given the small number of events, no inference could be drawn from this analysis of seasonality.

The finding here has only a small number of events without prior onset of DM (N=4) which are unlikely to be causally related to receipt of 9vHPV vaccine and are not the cause of this association (i.e., 93% of the diagnoses in the risk window are DM with prior onset or not DM). Although the odds ratio was increased across all the analyses here (both *9vHPV-Only Cohort*, *Any 9vHPV Cohort* combined dose series analyses, and at each dose), this finding likely is due to follow-up care generated at clinic visits coinciding with vaccination. This finding was not explored further.

Of note, type 1 DM after HPV vaccination has been investigated specifically by PPD with the VSD[6], comparing HPV vaccinated subjects with unvaccinated subjects and adjusting for age, sex, race, Medicaid status, years of membership at PPD and calendar timeline, and no increased risk for development of Type 1 DM was associated with HPV vaccine receipt. Another study evaluated the risk of autoimmune diseases, including Type 1 DM, after HPV vaccine in female adolescents and young adults in France between 2008 and 2014. This case-referent surveillance study reported a point estimate that was significantly protective for the combined autoimmune disease category (a combination of central demyelination/multiple sclerosis, connective tissue disease, Guillain-Barré syndrome, Type 1 DM, autoimmune thyroiditis, and idiopathic thrombocytopenia). This study further reported a point estimate that was protective for Type 1 DM specifically, but it was not statistically significant[7].

10.3.4.2 Exploration of finding in HCUP 5.4: *Delirium dementia and amnestic and other cognitive disorders*

The HCUP category *5.4: Delirium dementia and amnestic and other cognitive disorders* was significantly elevated in two different analyses: combined dose series Day 0-14 analysis for the *Any 9vHPV Cohort* (OR 8.93, 95% CI 1.13, 70.53) and dose 3 Day 1-60 analysis for the

9vHPV-Only Cohort (OR not calculable due to no self-comparison events, 95% CI lower bound of 1.11, no upper bound) (Table 18).

Medical record review revealed that all the events were due to injuries. There were 10 events in the Day 0–14 risk interval of the *Any 9vHPV Cohort* analysis, 9 of which were postconcussion syndrome diagnoses after sports or play related injuries: football (N=3), fighting (N=2), hit by stick, ran into window, etc. The one non-postconcussion event was a delirium diagnosis in a subject who had a scooter accident while not wearing a helmet.

There were 5 events in the Day 1–60 risk interval of the *9vHPV-Only Cohort* dose 3 analysis. These events were also related to postconcussion syndrome due to similar causes: fighting, wrestling, a trampoline injury, a soccer injury, and a mosh pit injury.

Medical record review showed that these cognitive disorder diagnoses were due to sporting and play injuries, which makes it implausible that they were caused by vaccination. This finding was not explored further.

10.3.4.3 Exploration of finding in HCUP 6: *Diseases of the nervous system and sense organs*

This level 1 HCUP category, *Diseases of the nervous system and sense organs*, was significantly elevated in the *9vHPV-Only Cohort* analysis of the Day 0–14 risk interval after Dose 1 (OR 1.33, 95% CI 1.02, 1.72) (Table 18). There were 166 events in the risk interval which are further detailed in Table 21.

For context, this category was significantly *decreased* in the *9vHPV-Only Cohort* analysis of the combined dose series for the Day 1–60 risk interval (OR 0.86, 95% CI 0.78, 0.96).

Table 21. Detail for HCUP 6: *Diseases of the Nervous System and Sense Organs*, Dose 1, Day 0–14 Risk Interval

Diagnosis	**N** N=166
Headache; including migraine (discussed in report Section 10.3.4.4 below*)	67
Ear conditions: otitis media (16), otitis externa (8), dizziness (5), vertigo (4), lightheadedness (2), other ear conditions (4)	41
Eye disorders: conjunctivitis (9), eye pain (3), hordeolum (3), swelling (2), visual disturbance (2), other various individual disorders (11)	30
Epilepsy; convulsions	13
Hereditary and degenerative nervous system conditions (1 prior onset, 1 overdose)	2
Paralysis (both pre-existing)	2
Central nervous system infection (diagnosed with unspecified viral encephalitis with seizure, day 13)	1
Coma; stupor; and brain damage (post motor vehicle accident)	1
Other: pain (5), planned MRI, paresthesia, tingling, ataxia	9

Of the above categories, headache is investigated in the next section, Section 10.3.4.4, and "Epilepsy; convulsions" is further discussed in the next paragraph. The other categories in Table 21 were found to be conditions unlikely to be caused by vaccination, such as otitis media or conjunctivitis, or were diagnoses more likely to be related to follow-up care generated at clinic visits coinciding with vaccination.

The *Epilepsy; convulsions* category was further examined. Of the 13 events, 4 were seizures on post-vaccination days 1, 3, 9, 10 in subjects with prior history of seizures, 1 event was a possible seizure in a subject with factitious disorder (Munchausen syndrome) and substance abuse history, 1 event was a nonspecific paroxysmal spell that was determined to be possibly anaphylactic in nature, 4 events were planned procedures or workups in subjects where a history of epilepsy is noted but these were not seizures, and 3 were new diagnoses of seizures that occurred in subjects on post-vaccination days 1, 9, and 11. The day 1 event was a new diagnosis of seizure in a subject who was eventually diagnosed with epilepsy; however, there were questions as to whether or not it was a new condition PPD PPD This event PPD so was considered to be a serious adverse event. The day 9 event was in a subject who had a first seizure while playing a video game; during the neurologic workup he was found to have an abnormal EEG, was prescribed levetiracetam, and has had at least one additional similar seizure after missing two doses of the medication. The day 11 event was diagnosed as idiopathic complex partial seizures in a subject who was found to have an incidental pineal mass, and who said he had experienced similar events in the past but had not told his family.

Of note, two of the events in the *Epilepsy; convulsions* category were considered by care providers to have potential relation to receipt of 9vHPV vaccine. The first event was a new seizure on the day after vaccination and is described above (the subject with the PPD . The second was the nonspecific paroxysmal spell, possible anaphylactic

event on the day of vaccination. This event, despite a diagnosis of "nonspecific paroxysmal spell" appears to have more likely been an allergic reaction. In this event, the subject had a scratchy throat, cough sensation and shakiness approximately 5–10 minutes after vaccination. Providers administered 1 mg of epinephrine and PPD where the symptoms appeared to be resolved, with no physical findings suggestive of allergic reaction per the examining clinician.

Two sub-categories, HCUP 6.5 and HCUP 6.6, were further explored and are discussed below. The remaining diagnoses in the category HCUP 6: *Diseases of the Nervous System and Sense Organs* were more likely to be related to follow-up care generated at clinic visits coinciding with vaccination than to be effects of vaccination, and not explored further.

10.3.4.4 Exploration of finding in HCUP 6.5: *Headache; including migraine*

The HCUP category *6.5: Headache; including migraine* was significantly elevated in the dose 1 analysis of the Day 0–14 risk interval in the *9vHPV-Only Cohort* (OR 1.82, 95% CI 1.17, 2.85) (Table 18). The types of headache and/or migraine as diagnosed are further characterized (Table 22). Headache is commonly listed as a side effect of HPV vaccine[8,9].

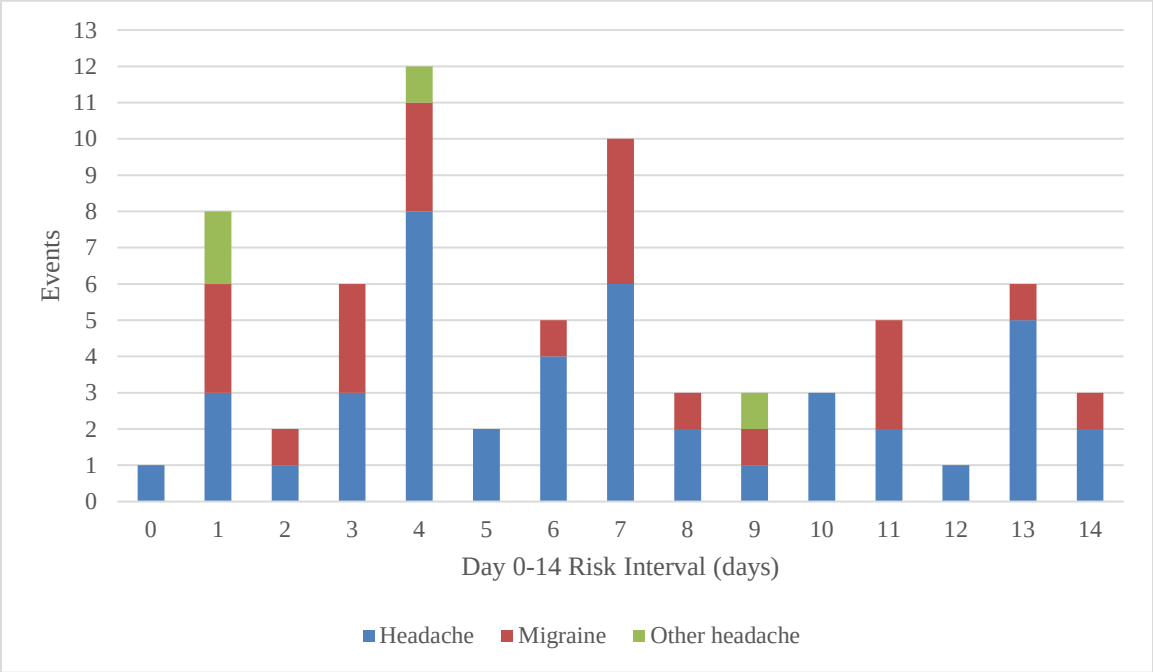
Table 22. Detail for HCUP 6.5: *Headache; including migraine*, Dose 1, Day 0–14 Risk Interval

Diagnosis	Count (N=70*)	Percent
Headache	44	63%
Migraine	22	32%
Other specified headache (cluster, tension)	3	4%

* Table 22 shows 70 events whereas Table 21 shows 67 for the category "Headache; including migraine". In the Table 21 for top-level category HCUP 6: *Diseases of the Nervous System and Sense Organs*, three events are counted in rows other than headache. Subjects are only counted once for the HCUP 6 category despite the possibility of having events in more than one sub-category.

The events were mostly spread across the Days 0-14 risk interval, with more in the first week after vaccination (Figure 10). The peak number of headaches occurred on post-vaccination day 4 with smaller peaks on days 1 and 7.

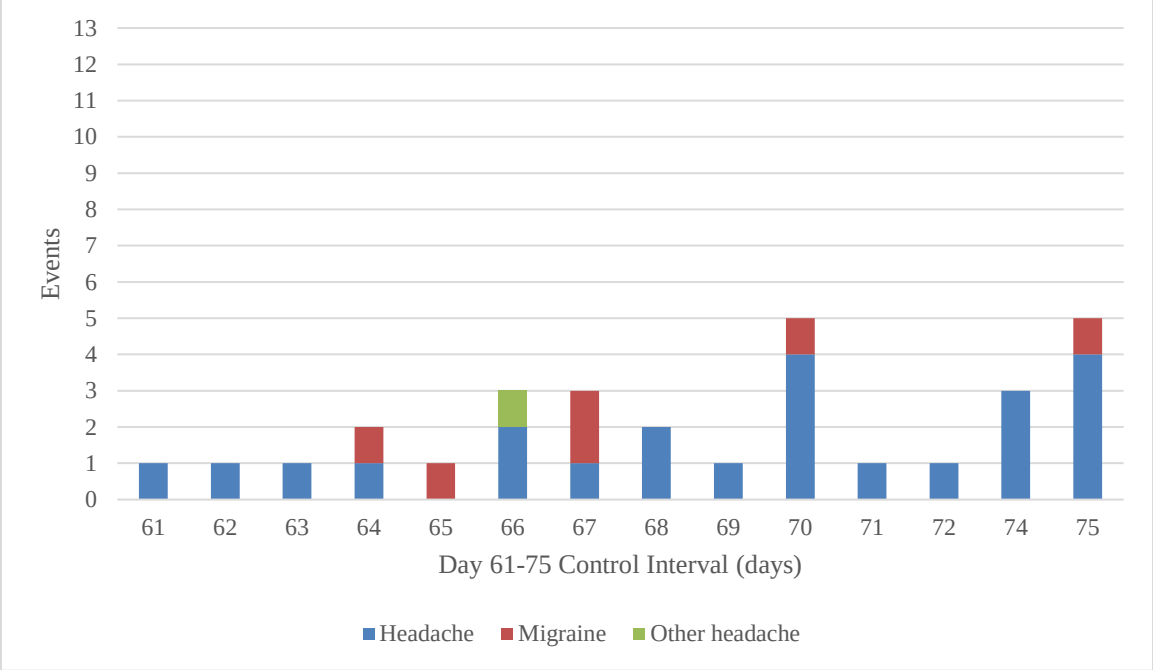
Figure 10. Detail for Timing of HCUP 6.5: *Headache; including migraine*, Dose 1, Day 0–14 Risk Interval



Headaches occurring during the self-comparison interval were also characterized (N= 30) and they were similar in distribution to those during the risk interval shown in Table 22, with most being headache (N=23, 77%) and migraines (N=6, 20%), and only one other specific type of headache (N=1, tension headache, 3%). The detail of their timing is shown in Figure 11, showing equal peaks on days 70 and 75.

A 10% sample review was conducted among the 70 events in Table 22 so 7 events were reviewed. Four of the 7 had onset that preceded vaccination (e.g., presenting on day 1 after vaccination with “four days of headache and low fever”) and the other three had prior medical history of headaches (“chronic daily headache”, discussion of headaches at vaccination visit that were “likely due to poor sleep hygiene” and “became ill [day 4] with stomach ache, nausea and vomiting accompanied with headache” in a patient with several prior instances of same).

Figure 11. Detail for Timing of HCUP 6.5: *Headache; including migraine*, Dose 1, Day 61-75 Control Interval



As with the level 1 category HCUP 6: *Diseases of the nervous system and sense organs*, the finding in HCUP 6.5: *Headache; including migraine* is more likely based on follow-up care generated at clinic visits coinciding with vaccination or pre-existing medical history, than based on effects of vaccination. This finding was not explored further.

10.3.4.5 Exploration of finding in HCUP 6.6: *Coma; stupor; and brain damage*

The HCUP category *6.6: Coma; stupor; and brain damage* was significantly elevated in the dose 1 analysis of the Day 1–60 risk interval in the *9vHPV-Only Cohort* (OR not calculable due to no self-comparison events, 95% CI lower bound of 1.67, no upper bound) (Table 18).

There were 9 events in the risk interval, none of which were considered related to vaccination.

Of these 9 events, 2 were evaluations for anoxic brain damage. The first of these was a hospitalization for a study subject on day 21 after vaccination for acute hypoxic respiratory failure, suspected due to status asthmaticus and acute community acquired pneumonia who was found to have an anomalous coronary artery. The second was a subject hospitalized approximately 7 weeks after vaccination for chronic bronchiectasis with recent worsening after a viral illness.

Of the remaining events, two of the 9 were evaluations for somnolence and in both subjects the symptoms were present prior to, or noted at, the vaccination visit. The remaining 5 of the 9 events were related to trauma evaluations (3 motor vehicle accidents, a football injury and a fall while intoxicated).

This finding was not explored further as on review, it is implausible that these events were caused by vaccination.

10.3.4.6 Exploration of finding in HCUP 9: *Diseases of the digestive system*

The HCUP category *9: Diseases of the digestive system* was significantly elevated in dose 1 Day 1–60 analysis in the *9vHPV-Only Cohort* (OR 1.21, 95% CI 1.03, 1.41) (Table 18). There were many events identified in the risk interval (N=526) and just under half of those were hospitalizations (42.4%).

This level 1 category HCUP 9: *Diseases of the digestive system* was not explored further except for its sub-categories HCUP 9.2, 9.5, 9.6, 9.7 and 9.10 (Table 23), which were also significantly elevated in one or more analyses, and are further discussed later. Please see Sections 10.3.4.7, 10.3.4.8, 10.3.4.9, 10.3.4.10, and 10.3.4.11. The remaining sub-categories had small numbers of events and the diagnoses were implausibly caused by vaccination.

Table 23. Detail for HCUP 9: *Diseases of the digestive system*, Dose 1, Day 1–60 Risk Interval

Sub-categories of HCUP 9	**N= 526**
9.1 Intestinal infection	5
9.2 Disorders of teeth and jaw (mostly dental: caries, toothaches)*	54
9.3 Diseases of mouth, excluding dental (e.g. parotitis, stomatitis)	11
9.4 Upper GI disorders (2/3 GERD, 1/3 gastritis or esophagitis)	95
9.5 Abdominal hernia*	27
9.6 Lower gastrointestinal disorders*	75
9.7 Biliary tract disease (23/27 cholelithiasis, 4/27 cysts)*	27
9.8 Liver disease (hepatitis, fatty liver, jaundice, abnormal labs)	17
9.9 Pancreatic disorders (not diabetes) (pancreatitis – reviewed, none related)	4
9.10 Gastrointestinal hemorrhage*	22
9.11 Noninfectious gastroenteritis (all gastroenteritis)	53
9.12 Other gastrointestinal disorders (83 nausea, vomiting & diarrhea. 37 constipation. The rest are: gastrostomy status (3), dysphagia (3), swelling (3), celiac disease (2), abdominal distension, ascites, change in bowel habit, foreign body sensation, and peritoneal adhesions)	136

* Asterisks mark HCUP sub-categories that were significant and are explored further in sections 10.3.4.7, 10.3.4.8, 10.3.4.9, 10.3.4.10, and 10.3.4.11 below. Fewer events are shown in this top-level category due to overlap (i.e., someone that has an event in 9.5 and 9.10 will count towards each sub-category when examined individually but will only be counted once in Table 23).

10.3.4.7 Exploration of finding in HCUP 9.2: *Disorders of teeth and jaw*

The HCUP category *9.2 Disorders of teeth and jaw* was significantly elevated in the dose 2 Day 1–60 risk interval analysis in the *9vHPV-Only Cohort* (OR 2.38, 95% CI 1.14, 4.98) and in the combined dose series Day 0–14 risk interval analysis in the *Any 9vHPV Cohort* (OR 1.86, 95% CI 1.03, 3.34) (Table 18).

In the dose 2 analysis, 24 events were identified in the Day 1–60 risk interval of the *9vHPV only Cohort*, with 70.8% of the diagnoses coming from hospitalizations. Diagnoses consisted of dental caries (N=10), toothache (N=6), dentofacial anomalies (N=5), other jaw disease (N=2) and dental abscess (N=1).

In the combined dose series analysis, 42 events in the Day 0–14 risk interval of the *Any 9vHPV Cohort*, with 52.4% of these being hospitalizations. Diagnoses consisted of dental caries (N=13), toothache (N=12), dentofacial anomalies (N=6), dental abscess or cysts (N=6), impacted teeth (N=2), other jaw disease (N=2), and gingivitis (N=1).

This finding was not explored further as these disorders of the teeth and jaw events are implausibly caused by vaccination and more likely based on follow-up care generated at clinic visits coinciding with vaccination.

10.3.4.8 Exploration of finding in HCUP 9.5: *Abdominal hernia*

The HCUP category *9.5: Abdominal hernia* was significantly elevated in 3 different analyses. This outcome was elevated in the combined dose series for both the *9vHPV-Only Cohort* (OR 1.73, 95% CI 1.06, 2.80) and the *Any 9vHPV Cohort* (OR 1.82, 95% CI 1.18, 2.80) and the Dose 1 analysis in the *9vHPV-Only Cohort* (OR 2.63, 95% CI 1.28, 5.42) (Table 18). All of these findings were in Day 1–60 risk interval analyses.

The diagnoses of all 71 subjects in the combined dose series of the *Any 9vHPV Cohort* were reviewed. The 56 events in the *9vHPV-Only Cohort* were a subset of the 71 (78.9%), as were the 36 events after dose 1.

The 36 events of abdominal hernia after dose 1, 97.2% of which were hospitalizations, were inguinal (N=20), umbilical (N=8), diaphragmatic (N=4), ventral (N=3) and femoral (N=1) hernias.

Most (95.8%) of the 71 events in the combined dose series risk interval were hospitalizations, and were inguinal (N=29), umbilical (N=14), diaphragmatic (N=9), ventral (N=5), other (N=4) hernias.

This finding was not explored further due to the implausibility of abdominal hernias being caused by vaccination.

10.3.4.9 Exploration of finding in HCUP 9.6: *Lower gastrointestinal disorders*

The HCUP category *9.6: Lower gastrointestinal disorders* was significantly elevated in the dose 1 Day 1–60 risk interval analysis in *9vHPV-Only Cohort* (OR 1.53, 95% CI 1.01, 2.32) (Table 18).

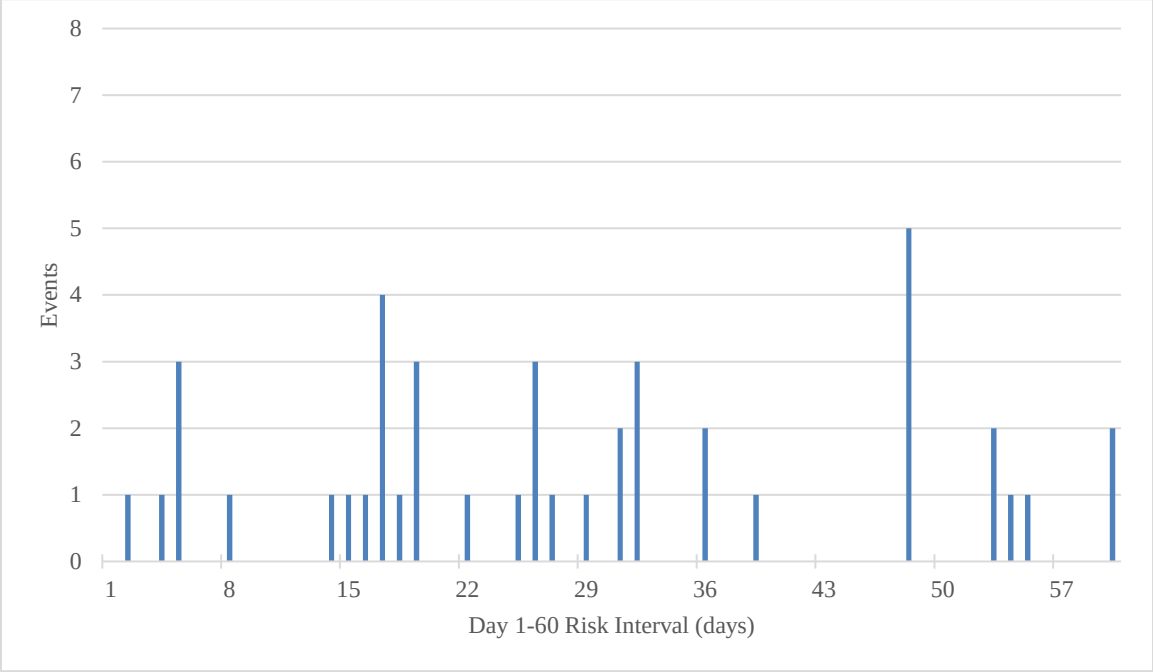
This category consisted of 83 events, 73.5% of which were hospitalizations (Table 24).

Table 24. Detail for HCUP 9.6: *Lower Gastrointestinal Disorders*, Dose 1, Day 1–60 Risk Interval

Diagnosis	**N = 83**
Appendicitis (acute 41, unspecified 2)	43
Crohn's disease	11
Ulcerative colitis	9
Abscess of anal or rectal region	5
Anal fissure or fistula	5
Diverticular disease of intestine	4
Other disease of anus or rectum (polyp, pain, prolapse)	3
Paralytic ileus and intestinal obstruction	3

The most common diagnosis was appendicitis, for which the average onset was on post-vaccination day 28. The time distribution of events during the risk interval are shown in Figure 12 and does not suggest a temporal association with vaccination.

Figure 12. Appendicitis Events in HCUP 9.6: Lower Gastrointestinal Disorders, Dose 1, Day 1–60 Risk Interval



Appendicitis events were not reviewed further due to the unlikely possibility of a causal relationship with vaccination.

All the Crohn's disease events above (N=11) were reviewed to determine onset date. The subjects either had a Crohn's disease diagnosis prior to their first 9vHPV vaccine (9 of the 11) or reported symptoms at the clinic visit coinciding with their first 9vHPV vaccine dose, which on workup led to the Crohn's disease diagnosis (2 of the 11).

This finding was not explored further due to the implausibility of a causal relationship with vaccination for appendicitis, the prior onset of Crohn's disease, and the smaller numbers for the other outcomes, most of which also likely pre-existed vaccination.

10.3.4.10 Exploration of finding in HCUP 9.7: *Biliary tract disease*

The HCUP category *9.7 Biliary tract disease* was significantly elevated in the analysis of the Day 0–14 risk interval in the combined dose series in the *Any 9vHPV Cohort* (OR 2.06, 95% CI 1.04, 4.09) (Table 18).

There were 29 events in this finding, approximately 2/3 of which were hospitalizations. Most were calculus of the gallbladder (16/29, 55%), with smaller numbers of cholecystitis (N=4, 14%) which were reviewed and found to be present at vaccination, biliary colic (N=3, 10%), calculus of gallbladder and bile duct (N=3, 10%), or other biliary tract disease (N=3, 10%).

This finding was not explored further due to the implausibility of vaccination causing biliary tract diseases – they likely were already present at vaccination.

10.3.4.11 Exploration of finding in HCUP 9.10: *Gastrointestinal hemorrhage*

The HCUP category *9.10: Gastrointestinal hemorrhage* was significantly elevated in 5 different analyses. Four of these elevations were in analyses of the Day 1–60 risk interval and one was in the Day 0–14 risk interval analysis.

In the Day 1–60 risk interval analyses, there were significant elevations in the combined dose series analyses in both the *9vHPV-Only Cohort* (OR 2.18, 95% CI 1.19, 4.00) and the *Any 9vHPV Cohort* (OR 1.70, 95% CI 1.04, 2.78), and in the dose 1 analysis (OR 2.32, 95% CI 1.02, 5.29) and the dose 2 analysis (OR 3.80, 95% CI 1.07, 13.46) of the *9vHPV-Only Cohort* (Table 18).

In the analysis of the Day 0–14 risk interval, the significant finding was after dose 2 in *9vHPV-Only Cohort* (OR not calculable due to no self-comparison events, 95% CI lower bound of 1.70, no upper bound) (Table 18).

In the combined dose series Day 1-60 analysis, 55 events were identified in the risk intervals of the *Any 9vHPV Cohort*, and the diagnoses of these events were reviewed (Table 25). Of those, 44 events (80%) were from the *9vHPV-Only Cohort*.

Separate review of diagnoses was also performed for the events in the Day 1-60 risk interval after dose 1 (Table 26) and dose 2 (Table 27), as well as the events in the Day 0–14 risk interval after dose 1 (Table 28).

Table 25. Detail for HCUP 9.10: *Gastrointestinal Hemorrhage*, Combined Dose Series, Day 1–60 Risk Interval

Diagnosis*	**N = 55**
Hemorrhage of anus and rectum	32
Gastrointestinal hemorrhage, unspecified	10
Hematemesis	7
Melena	6

* 36.4% were diagnoses in the inpatient setting

Table 26. Detail for HCUP 9.10: *Gastrointestinal Hemorrhage*, Dose 1, Day 1–60 Risk Interval

Diagnosis*	**N = 27**
Hemorrhage of anus and rectum	18
Gastrointestinal hemorrhage, unspecified	4
Hematemesis	3
Melena	2

* 22.2% were diagnoses in the inpatient setting

Table 27. Detail for HCUP 9.10: *Gastrointestinal Hemorrhage*, Dose 2, Day 1–60 Risk Interval

Diagnosis / Day 1–60 Risk Interval*	**N = 14**
Hemorrhage of anus and rectum	7
Gastrointestinal hemorrhage, unspecified	3
Melena	3
Hematemesis	1

* 57.1% were diagnoses in the inpatient setting

Table 28. Detail for HCUP 9.10: *Gastrointestinal Hemorrhage*, Dose 2, Day 0–14 Risk Interval

Diagnosis*	**N = 7**
Hemorrhage of anus and rectum	4
Gastrointestinal hemorrhage, unspecified	1
Hematemesis	1
Melena	1

* 57.1% were diagnoses in the inpatient setting

Many of the findings in this category were likely based on follow-up care generated at clinic visits coinciding with vaccination, and where this was not the case (i.e., acute events in the

post-vaccination period), reviewed events do not appear to be plausibly caused by vaccination. A 10% sample of the events from the broadest category (randomly sampled from the 55 events shown in Table 25) confirmed this, with 4 of the 6 events reviewed being prior onset and the other 2 being blood in stool with a contributing cause (one after straining due to constipation, the other bleeding after diarrhea well after vaccination). The 10 "Gastrointestinal hemorrhage, unspecified" events, 7 hematemesis events and 6 melena events in Table 25 above (the broadest of the tables in this section) were each reviewed, most of which were acute; they were varying in nature, and almost all of them had a likely etiology (e.g., constipation, hemorrhoids, alcohol use, diarrhea, other illness).

10.3.4.12 Exploration of finding in HCUP 10.2: *Diseases of male genital organs*

The HCUP category *10.2: Diseases of male genital organs* was significantly elevated in both combined dose series Day 1–60 risk interval analysis (OR 1.44, 95% CI 1.04, 1.98) and dose 1 Day1–60 risk interval analysis (OR 1.60, 95% CI 1.04, 2.46) in the *9vHPV-Only Cohort* (Table 18). The diagnoses of all events in the Day 1-60 risk interval were summarized for each analysis in Table 29 and Table 30 respectively.

Table 29. Detail for HCUP 10.2: *Diseases of Male Genital Organs*, Combined Dose Series, *9vHPV-Only Cohort*, Day 1–60 Risk Interval

Diagnosis*	**N = 124**
Prepuce disorder (phimosis, balanoposthitis, etc.)	37
Testicular pain	26
Epididymitis	13
Hydrocele	9
Testicular torsion	6
Other disorder of penis, e.g., irritation	5
13 other categories, each with N of 4 or less	28

* 55.6% were diagnoses in the inpatient setting

Table 30. Detail for HCUP 10.2: *Diseases of Male Genital Organs*, Dose 1, *9vHPV-Only Cohort*, Day 1–60 Risk Interval

Diagnosis*	**N = 81**
Prepuce disorder (phimosis, balanoposthitis, etc.)	36
Testicular pain	21
Epididymitis	9
Hydrocele	6
Other disorder of penis, e.g., irritation	5
Testicular torsion	3
Erectile dysfunction	1

* 59.3% were diagnoses in the inpatient setting

This finding was not explored further due to the implausibility of 9vHPV vaccine causing disorders of the prepuce or testes; rather these were more likely to be follow-up care generated at clinic visits coinciding with vaccination.

10.3.4.13 Exploration of finding in HCUP 12: *Diseases of the skin and subcutaneous tissue*

The HCUP category *12: Diseases of the skin and subcutaneous tissue* was significantly elevated in 3 analyses: the combined dose series Day 0–14 risk interval analysis (OR 1.40, 95% CI 1.02, 1.92) and dose 2 Day 0–14 risk interval analysis (OR 1.88, 95% CI 1.00, 3.53), both for the *9vHPV-Only Cohort*, and then for the combined dose series Day 0–14 risk interval analysis for the *Any 9vHPV Cohort* (OR 1.44, 95% CI 1.12, 1.87) (Table 18).

HCUP category 12 is a level 1 category consisting of four sub-categories 12.1 to 12.4 (Table 31). The broadest analysis with a significant finding in this category was the *Any 9vHPV Cohort* combined dose series analysis which had N=177 events in the risk window, 25.4% of which were hospitalizations. There were 122 events in the *9vHPV-Only Cohort*, which is a subset of the *Any 9vHPV Cohort*, so these 122 events made up a subset of the 177 events. The broader cohort of 177 events was investigated.

In the broader cohort, the first two sub-categories, 12.1 and 12.2, are discussed in the next two sections. Of the 67 events in category 12.4, the only events that were further examined were the 20 rashes. These rash events occurred on a mean of 6.1 days after vaccination, with a standard deviation of 4.6 days. The median of occurrence since vaccination is 4 days, with a range of 0 to 14 days. These 20 events were reviewed and were nonspecific in nature (e.g., shingles, tinea, contact dermatitis, urticaria, insect bites, localized, diffuse, etc.), with discussion of vaccination as a potential cause in 5 of the 20 events.

Table 31. Detail for HCUP 12: *Diseases of the Skin and Subcutaneous Tissue*, Combined Dose Series, Days 0-14, *Any 9vHPV Cohort*

Diagnosis	**N=177**
12.1 Skin and subcutaneous tissue infections (see 10.3.4.14 below)	**93**
12.2 Other inflammatory condition of skin (see 10.3.4.15 below)	**16**
12.3 Chronic ulcer of skin (subject with a pressure ulcer)	**1**
12.4 Other skin disorders, which consisted of:	**67**
Rash (mean day 6.1, median 4, SD 4.6, min 0, max 14)	*20/67*
Nail related (e.g., paronychia, ingrowing)	*14/67*
Acne	*11/67*
Various*	*22/67*

* Various: acanthosis nigricans (3); folliculitis (2); localized swelling, leg (2); pigmentation disorder (2); alopecia; epidermal cyst; epidermal thickening; follicular cyst; hidradenitis suppurativa; hyperhidrosis; localized scleroderma (morphea); localized swelling, forearm; localized swelling, hand; localized swelling, neck; other skin changes; skin mass of back; and one unspecified skin disorder.

In the dose 2 Days 0–14 analysis, there were 30 events identified in the risk period after dose 2, of which 26.7% were hospitalizations, the detail of which is shown in Table 32.

Table 32. Detail for HCUP 12: *Diseases of the Skin and Subcutaneous Tissue*, Dose 2, Days 0-14, *9vHPV-Only Cohort*

Diagnosis	**N=30**
12.1 Skin and subcutaneous tissue infections	**14**
12.2 Other inflammatory condition of skin	**3**
12.3 Chronic ulcer of skin	**0**
12.4 Other skin disorders, which consisted of:	**13**
Rash (days 0, 4, 11 and 11)	*4/13*
Nail related (both ingrowing)	*2/13*
Acne	*3/13*
Various: folliculitis; localized scleroderma (morphea); skin mass of back; and other skin changes	*4/13*

To further breakdown the 30 events above, review of the diagnosis detail showed that the events could be broken down into three categories: Cellulitis, Abscess, and various that were neither cellulitis nor abscess. All the events determined to be cellulitis or abscess were from the *12.1 Skin and subcutaneous tissue infections* category; of the N=14 in that category, 4 were cellulitis, 3 were abscess and the remaining 7 were neither and consisted of various other tissue infections implausibly caused by vaccination (e.g., pilonidal cyst, foreign body). The 7 cellulitis and abscess events are detailed in Table 33 and further described below.

Table 33. Detail for Cellulitis and Abscess Events in HCUP 12: *Diseases of the Skin and Subcutaneous Tissue*, Dose 2, *9vHPV-Only Cohort*

Diagnosis	
Cellulitis	**4**
Specified location: left arm, days 2, 3, 14	*3/4*
Location not specified: day 13	*1/4*
Abscess	**3**
Specified location: thigh on day 2, groin on day 13	*2/3*
Location not specified: day 8	*1/3*

The four cellulitis events were as follows, based on medical record review:

- The day 2 cellulitis on “left arm” event was in a subject vaccinated with 9vHPV vaccine on the right arm – PPD received two other vaccines on her left arm.
- The day 3 cellulitis on “left arm” event was in a subject who received 9vHPV vaccine in their left deltoid. They were reported to have a slightly painful rash to their left forearm and left upper arm “starting 3 days ago”, but vaccination is not noted as a precipitating event. The rash was constant but worsening at the time of examination, getting larger, more painful when scratched and was itchy. The patient had a history of smaller rashes prior to this that would usually resolve on their own. No further follow-up was done.
- The cellulitis coded with “location not specified” on day 13 was found on review to be a right thigh pimple (not where 9vHPV vaccine was administered).

- The cellulitis on "left arm" on day 14 was a two-day history of forearm swelling and redness, potentially due to an insect bite.

The three abscess events were as follows, based on medical record review. None were at vaccination sites. These were:

- Small pimple-like abscess on the thigh on day 2, suspected mosquito bite.
- Right thigh abscess on day 8, suspected insect bite.
- Groin abscess on day 13 in a patient with a history of recurrent superficial boils.

The findings in this category were explored further through examination of the significantly elevated sub-categories below (i.e., HCUP 12.1 and HCUP 12.2).

10.3.4.14 Exploration of finding in HCUP 12.1: *Skin and subcutaneous tissue infections*

The HCUP category *12.1 Skin and subcutaneous tissue infections* was significantly elevated in 3 analyses, including the combined dose series analysis (OR 1.86, 95% CI 1.15, 3.01) and dose 2 analysis (OR 2.90, 95% CI 1.04, 8.04) in the *9vHPV-Only Cohort*, and in the combined dose series analysis in the *Any 9vHPV Cohort* (OR 1.84, 95% CI 1.25, 2.70) (Table 18). All these findings were in Day 0-14 risk interval analyses.

The diagnoses of all 93 events in the combined dose series of the *Any 9vHPV Cohort* (15.1% hospitalized) were reviewed. As with the HCUP category 12 findings described in the section above, HCUP category 12.1 is generally comprised of events in three categories: cellulitis, abscess, and "other" (Table 34).

The 64 events in the *9vHPV-Only Cohort* were a large subset of those 93 in the *Any 9vHPV Cohort* (15.6% of the 64 were hospitalized) and a separate review of this subset alone was not done as it would be redundant to do so.

There were 14 events in the dose 2 analysis of HCUP 12.1 and, as they are a subset of the combined dose series events, they are included in Table 34, although not identified specifically by dose there. These are the same events described in the preceding section, i.e., the four cellulitis events (3 on the left arm, 1 on the thigh), three abscesses (2 on the thigh, 1 on the groin), and the other 7 were neither abscess nor cellulitis and were unrelated to vaccination.

Of the cellulitis events that were in specified locations shown in Table 34, four are specified in the arm. Three of these are the "left arm" events described in the previous section and the fourth is a child seen for arm swelling and redness on the left arm with two vaccines given there, however 9vHPV vaccine was given in the right deltoid. Thus, of these four cellulitis of the arm events, two are on the opposite side from 9vHPV vaccine injection site, one was likely an insect bite, and one was an itchy rash over the entire arm starting on the day of vaccination with vaccination not mentioned as a precipitating factor.

Table 34. Detail for HCUP 12.1: *Skin and subcutaneous tissue infections*, Combined Dose Series, Day 0–14 Risk Interval, *Any 9vHPV Cohort*

Diagnosis	**N = 93**
Overall stats: mean day 6, median 5, SD 4.4, range 0–14	
Cellulitis: mean day 5, median 3, SD 4.7, range 0–14	**40**
Specified location: face (5), arm (4), hand (3), elbow, finger, foot, knee, lower limb, periorbital	*18/40*
Location not specified: mean day 4, median 2, SD 4.1, range 0–13	*22/40*
Abscess: mean day 6, median 6, SD 3.7, range 0–13	**28**
Specified location: thigh (3), abdominal wall (2), axilla (2), face, groin, hand, lower limb	*11/28*
Location not specified: mean day 5, median 5, SD 3.6, range 0–12	*17/28*
Other: pilonidal cyst (11), paronychia (6), impetigo (2), lymphangitis (2), foreign body of ear, furuncle, insect bite, pustule	**25**

Overall, the timing of HCUP 12.1 events in the Day 0–14 risk interval had a mean of 6 days, a median of 5 days, and a standard deviation of 4.4 days.

Cellulitis events specifically occurred at a mean of 5 days, with median of 3 days and standard deviation of 4.7 days. Where location was specified, only 4 were in a potential vaccination location and of these, only one was potentially related to receipt of 9vHPV vaccine upon medical record review. Cellulitis events in unspecified locations were not reviewed further but had a mean of day 4, median of day 2 with a standard deviation of 4.1 days. Some of these cellulitis events in unspecified locations could potentially have been related to receipt of 9vHPV or other vaccines.

Abscess events specifically occurred at a mean of 6 days with a median of 3 and a standard deviation of 3.7. Where location was specified, none were specified as arm, but 2 were specified as axilla with neither being discussed as related to receipt of vaccines upon medical record review (one same side as 9vHPVvaccination, one opposite side). Abscess events in unspecified locations were not reviewed further but had a mean and median occurrence of 5 days and a standard deviation of 3.6 days; and some of these potentially could have been related to receipt of 9vHPV or other vaccines.

Where cases were reviewed, they were found to be various in nature and generally not due to vaccination; however when due to vaccination they appeared to be common local reactions likely misdiagnosed/miscoded as cellulitis or abscess, and were commonly found to be at injection sites for vaccines other than 9vHPV. This finding was not explored further.

10.3.4.15 Exploration of finding in HCUP 12.2: *Other inflammatory condition of skin*

The HCUP category *12.2: Other inflammatory condition of skin* was significantly elevated in analysis of the Day 0–14 risk interval in the *Any 9vHPV Cohort* (OR 2.83, 95% CI 1.02, 7.86) (Table 18).

The diagnoses of all 16 subjects for this finding (43.8% hospitalized) were reviewed. Events were comprised of pruritus (N=6) all of which were reviewed and unrelated to vaccination, psoriasis (N=5), and one each of perioral dermatitis, pityriasis rosea, rosacea, Stevens-Johnson syndrome, and sunburn. The Stevens-Johnson syndrome event was chart reviewed and preceded vaccination.

This finding was not explored further due to the implausibility of these inflammatory condition of the skin events being caused by vaccination, and more likely to be follow-up care generated at clinic visits coinciding with vaccination and pre-existing conditions.

10.3.4.16 Exploration of finding in HCUP 14.4: *Nervous system congenital anomalies*

The HCUP category *14.4: Nervous system congenital anomalies* was significantly elevated in analysis of the Day 1–60 risk interval after dose 1 (OR 5.01, 95% CI 1.10, 22.83) (Table 18).

There were 14 nervous system congenital anomaly events in the risk interval, most of which were hospitalizations (85.7%). Diagnoses consisted of microcephaly (N=5), congenital hydrocephalus (N=4), congenital malformation of the nervous system (N=2), neurofibromatosis (N=2), and congenital malformation of the brain (N=1).

This finding was not explored further due to their being congenital conditions preceding vaccination.

10.3.4.17 Exploration of finding in HCUP 17: *Symptoms; signs; and ill-defined conditions and factors influencing health status*

The HCUP category *17: Symptoms; signs; and ill-defined conditions and factors influencing health status* was significantly elevated after dose 1 in both the Day 0–14 risk interval analysis (OR 1.36, 95% CI 1.13, 1.64) and Day 1–60 risk interval analysis (OR 1.13, 95% CI 1.02, 1.26) of the *9vHPV-Only Cohort* (Table 18). All diagnoses of all events identified in risk interval of dose 1 Day 0-14 risk interval analysis, and dose 1 Day 1-60 risk interval analysis are reviewed and summarized in Table 35 and Table 36 respectively.

For context, this category was significantly decreased in combined dose series Day1-60 risk interval analysis in both the *9vHPV-Only Cohort* (OR 0.90, 95% CI 0.83, 0.97) and the *Any 9vHPV Cohort* (OR 0.93, 95% CI 0.87, 0.99).

Table 35. Detail in HCUP 17: *Symptoms; Signs; and Ill-Defined Conditions and Factors Influencing Health Status*, Dose 1, Day 0–14 Risk Interval

Diagnosis	**N=341**
Abdominal pain (multiple types)	102
Allergic reaction (35 non-specific, 7 specified, 6 anaphylaxis, 4 food)	52
Nausea and/or vomiting	41
Syncope (including vasovagal, near)	27
Fever	22
Urticaria	19
Dermatitis	9
40 other categories, each with counts of 6 or fewer	69

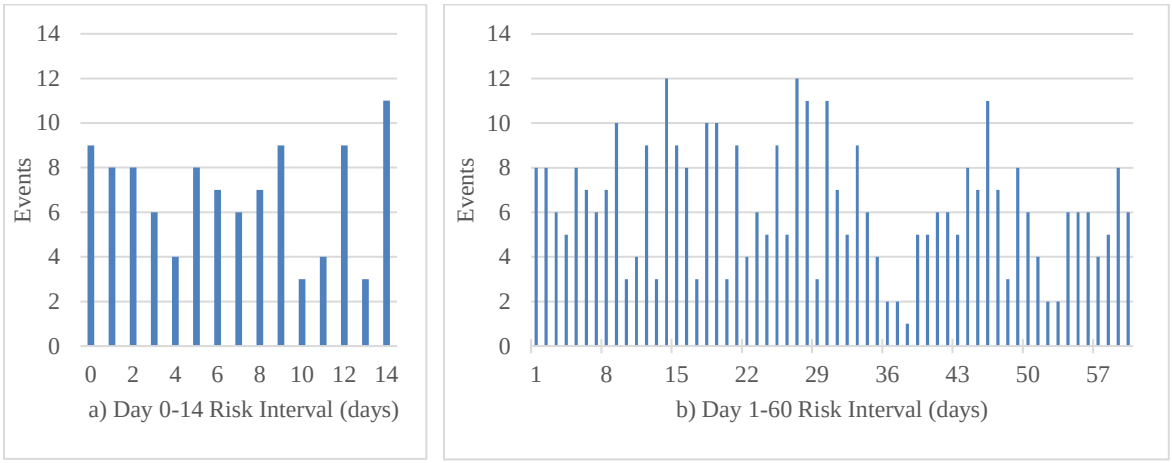
Table 36. Detail for HCUP 17: *Symptoms; Signs; and Ill-Defined Conditions and Factors Influencing Health Status*, Dose 1, Day 1–60 Risk Interval

Diagnosis	**N = 1041**
Abdominal pain (multiple types)	376
Nausea and/or vomiting	140
Allergic reactions (75 non-specific, 25 specified, 6 anaphylaxis, 11 food)	117
Syncope (including vasovagal, near)	67
Fever	61
Urticaria	38
Dermatitis	34
Other long term (current) drug therapy	21
Long term (current) use of inhaled steroids	17
Pelvic pain	15
Other (75 categories, each with N<10)	155

The most common diagnosis groups in Day 0-14 and Day 1-60 risk interval analyses were further investigated by examining the distribution of the events across the risk interval.

Abdominal pain is the largest sub-category of events in the Day 0–14 risk interval after dose 1, as well as the largest in the Day 1–60 risk interval. As shown in Figure 13, the events are relatively evenly distributed across both the Day 0-14 risk interval (Figure 13a) and the Day 1-60 risk interval (Figure 13b) without apparent clustering, although there were more events during days 1–30 (N=214) than during days 31–60 (N=162) in Day 1-60 risk interval analysis.

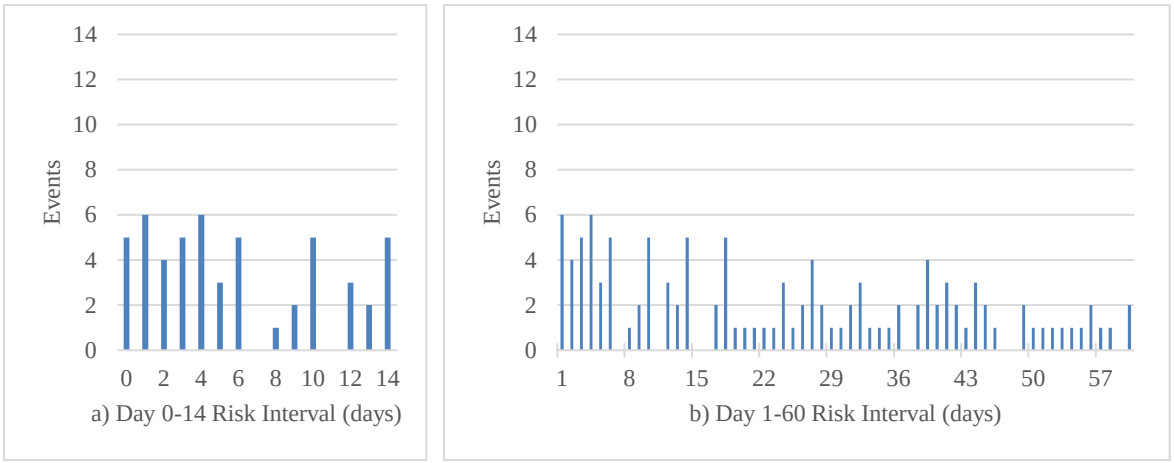
Figure 13. Abdominal Pain Events in HCUP 17, Dose 1



Note: Figure 13a and Figure 13b include multiple variations of abdominal pain, e.g., unspecified, upper, epigastric, right upper quadrant, right lower quadrant, general, etc.

Allergic reactions (Figure 14) occurred more commonly in the week after vaccination than in the second week (Figure 14a); beyond the first two weeks, they were rare and evenly distributed across the rest of the Day 1–60 risk interval (Figure 14b).

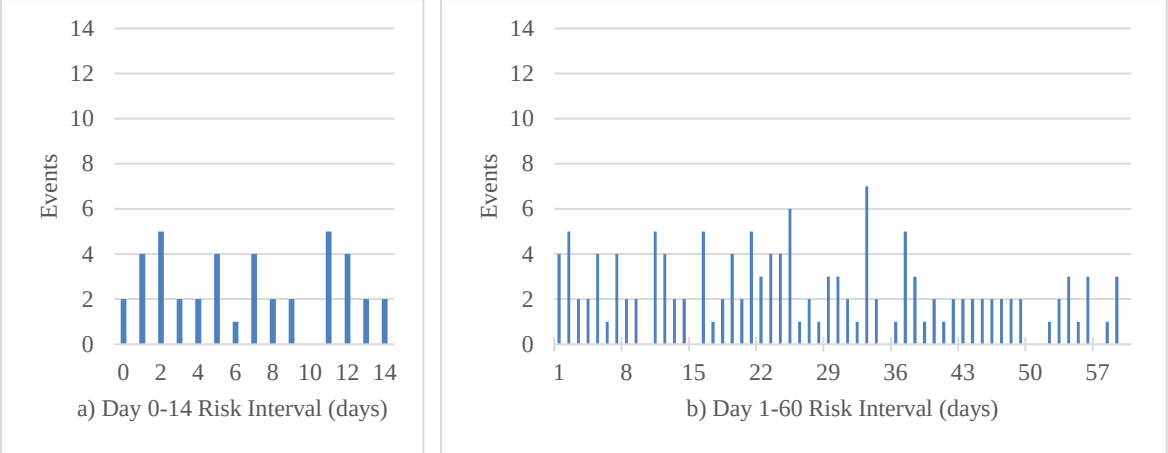
Figure 14. Allergic Reaction Events in HCUP 17, Dose 1



Note: Figure 14a and Figure 14b include multiple variations of allergic reaction, such as unspecified allergic reaction, unspecified anaphylaxis, allergy to specified food, drug, bees, etc.

Nausea and/or vomiting events (Figure 15) appeared evenly dispersed across the Day 0–14 risk interval (Figure 15a). Although there was no clear distribution pattern of nausea and/or vomiting events in the Day 1–60 risk interval, there were more events in the first month (N=85) than in the second month (N=55).

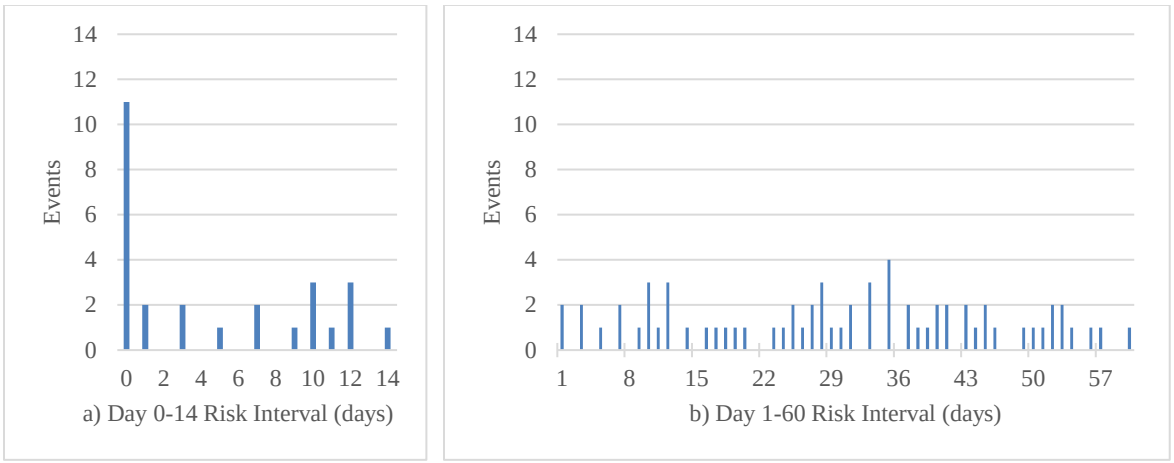
Figure 15. Nausea and/or Vomiting Events in HCUP 17, Dose 1



Note: These figures (Figure 15) include multiple variations of nausea and/or vomiting, such as nausea and vomiting; nausea; nausea, vomiting and diarrhea; etc.

Most of the syncope events (Figure 16) are on the day of vaccination. Syncope is discussed more in the examination of Day 0 events (Section 10.4). Chart review found that several of the events referred to patients being walked by staff to the emergency department either from clinic where they experienced syncope after vaccination or from the laboratory where phlebotomy occurred. Syncope events were evenly distributed across the Day 1–60 risk interval (which does not include Day 0), with approximately the same number of events in the first 30 days (N=33) as in the second 30 days (N=34).

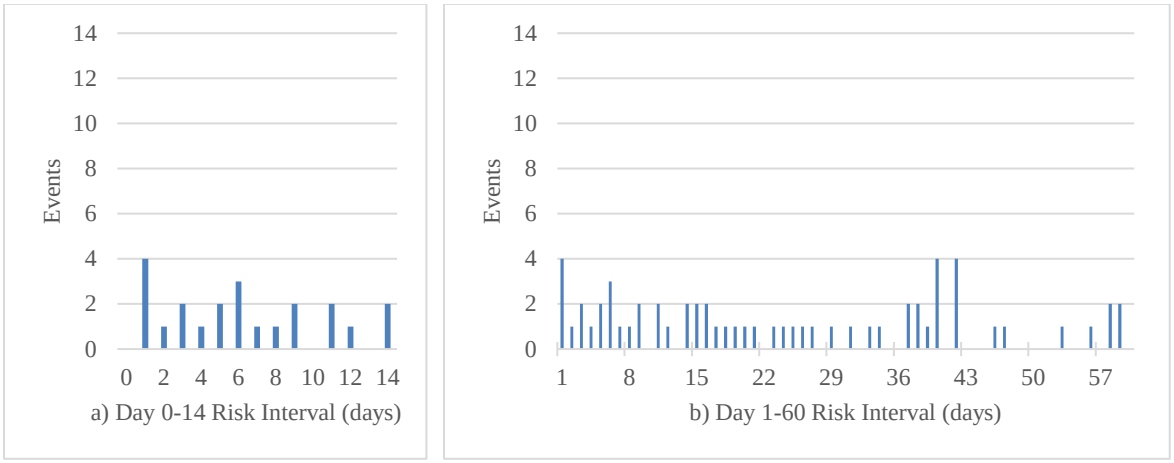
Figure 16. Syncope Events in HCUP 17, Dose 1



Note: These figures (Figure 16) include multiple variations such as syncope, near syncope, syncope & collapse, vasovagal syncope.

Fever events (Figure 17) appeared relatively evenly dispersed across the Day 0–14 risk interval, with a slight peak occurring on the day after vaccination (Figure 17a). Fever occurred throughout the Day 1–60 risk interval (Figure 17b). Like for the Day 0–14 risk interval analyses, there was a peak on day 1 after vaccination, as well as on days 40 and 42. There were more events in the first 30 days (N=37) than in the second 30 days (N=24); however number of events were small and there were no other obvious patterns.

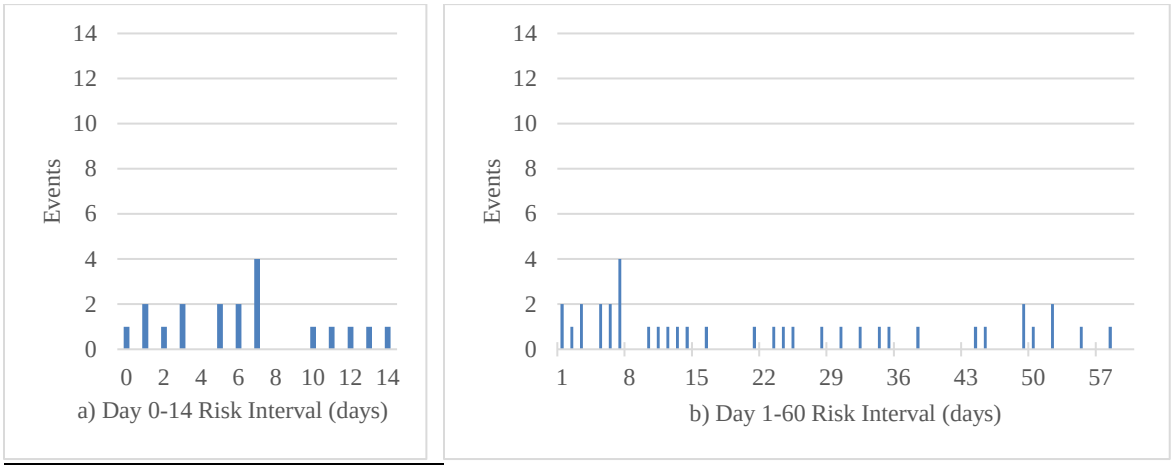
Figure 17. Fever Events in HCUP 17, Dose 1



Note: This figure (Figure 17), unlike other figures in this section, did not have multiple terms.

Urticaria events in the Day 0–14 risk interval (Figure 18a) appeared evenly distributed across the interval, with a slight peak on day 7. For the Day 1–60 risk interval analysis, there were more urticaria events during the first 30 days than in the second 30 days, with more events occurring during the first week than in later weeks (Figure 18b).

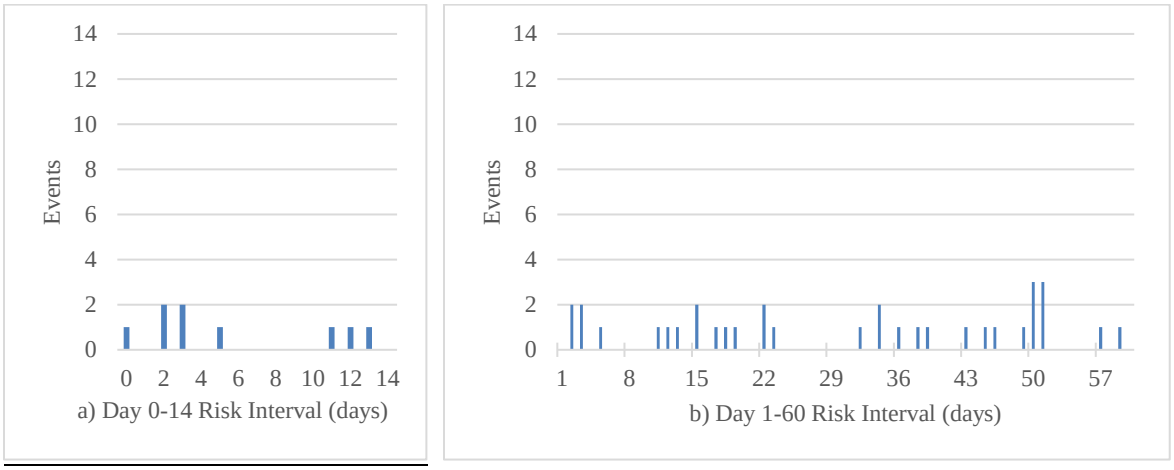
Figure 18. Urticaria Events in HCUP 17, Dose 1



Note: Figure 18a and Figure 18b include the terms urticaria, unspecified urticaria, allergic urticaria and recurrent periodic urticaria.

There was a small number of dermatitis events in the Day 0-14 risk interval, with more in the first week than in the second (Figure 19a); the dermatitis events appeared to be evenly dispersed across the Day 1–60 risk interval, with a similar number of events in days 0–30 (N=16) versus days 31–60 (N=18) (Figure 19b).

Figure 19. Dermatitis Events in HCUP 17, Dose 1



Dermatitis events shown here contains similar diagnoses, including atopic dermatitis, contact dermatitis, contact dermatitis due to poison oak, unspecified dermatitis, etc.

This broad category was not explored beyond the enumeration of contributing diagnosis categories and exploration of the timing of the events comprising the category, as shown in figures above (Figure 19a and Figure 19b). Some findings in this category may be related to

receipt of vaccines when close to vaccination, but similar outcomes, upon chart review (e.g., HCUP 9: *Diseases of the digestive system*, cellulitis and abscess as explored in HCUP 12.1, etc.) showed a mix of events that are various in nature. Some of these events could potentially be related to vaccination and some are implausibly caused by vaccination. Many events were more likely to be based on follow-up care generated at clinic visits coinciding with vaccination. The fact that this finding is significantly elevated at dose 1 for the Day 1-60 and Day 0-14 risk intervals analyses, yet significantly reduced across the combined dose series analyses for Day 1-60 risk intervals supports this hypothesis, i.e., care was generated at the well care visit for dose 1 – a visit more likely to be associated with pent-up healthcare needs – then, when mixed with care generated at doses 2 and 3, returns to normal or even reduced levels.

10.3.4.18 Exploration of finding in HCUP 17.1: *Symptoms; signs; and ill-defined conditions*

The HCUP category 17.1: *Symptoms; signs; and ill-defined conditions* was significantly elevated both in the examination of the Day 0–14 risk interval (OR 1.47, 95% CI 1.20, 1.80, remains significant after DFDR adjustment) and the Day 1–60 risk interval after dose 1 (OR 1.16, 95% CI 1.03, 1.30) in *9vHPV-Only Cohort* (Table 18).

For context, this category was significantly decreased in the DFDR adjusted analysis of the combined dose series for the Day 1–60 risk interval in the *9vHPV-Only Cohort* (OR 0.93, 95% CI 0.85, 1.01). As described in methods Section 9.4.5, the DFDR adjustment uses an alpha of 0.1 whereas the calculation of the 95% CI uses an alpha of 0.05. This finding is an unusual instance where the unadjusted finding is not significant (upper bound is just over 1) but the finding is flagged as being significant after multiplicity adjustment.

For the Day 0–14 risk interval after dose 1, there were 341 level 1 HCUP category 17 events, 302 of which (89%) were in HCUP sub-category 17.1.

For the Day 1–60 risk interval after dose 1, there were 1041 level 1 HCUP category 17 events 911 of which (88%) were in HCUP sub-category 17.1.

As HCUP category 17.1: *Symptoms; signs; and ill-defined conditions* made up most (approximately 90%) of HCUP category 17 *Symptoms; signs; and ill-defined conditions and factors influencing health status*, explored in the previous section (10.3.4.17), HCUP category 17.1 was not explored on its own as it would be redundant to do so.

10.4 Analysis of Day 0 Events

Incidence rates were calculated for pre-specified Day 0 outcomes of allergic reactions and syncope in the combined hospitalization and emergency room setting. A total of 30 events (12 allergic reaction and 18 syncope events) were identified after administration of 330,774 doses in the *Any 9vHPV Cohort*. A total of 22 events (8 allergic reaction and 14 syncope events) were from the *9vHPV-Only Cohort* (a subset of the *Any 9vHPV Cohort*) who were administered a total of 239,556 doses. Event descriptions from medical record review are provided in *Annex 3. Day 0 Results, Listing / Summaries.*

In the *9vHPV-Only Cohort*, incidence rates of allergic reactions after 9vHPV vaccination were 33.4 per million doses (95% CI 14.4, 65.8) and 58.4 per million doses (95% CI 32.0, 98.1) for syncope (Table 37) in the combined dose series analysis. Additional allergic reaction and syncope categories were pre-specified but did not contain events. There were no events in these pre-specified allergic reaction sub-categories: anaphylactic reaction due to vaccination, angioneurotic or Quincke's edema, allergic or other specified urticaria, or dermatitis due to drugs and medicines taken internally. There were no events in a pre-specified Syncope (including collapse) sub-category: Syncope due to Orthostatic Hypotension. Of note, allergic reactions were mostly observed in females (7/8, or 87.5%).

Table 37. Counts and Incidence Rates for Pre-Selected Day 0 Events in Combined Dose Series for *9vHPV-Only Cohort*, Combined Emergency Room and Hospital Settings

Outcome	N	Female	Male	Incidence per 1 million doses*, with 95% CI
Allergic reactions	8	7	1	33.4 (14.4, 65.8)
- Acute bronchospasm	1	1	0	4.2 (0.1, 23.3)
- Allergy, unspecified, not classified elsewhere	4	4	0	16.7 (4.5, 42.8)
- Other anaphylactic shock, not classified elsewhere	1	0	1	4.2 (0.1, 23.3)
- Other and unspecified adverse effect of drug	1	1	0	4.2 (0.1, 23.3)
- Unspecified urticaria	1	1	0	4.2 (0.1, 23.3)
Syncope (including collapse)	14	6	8	58.4 (32.0, 98.1)

*Denominator used to calculate incidence rate was 239,556 doses.

When the analysis is presented by dose (Table 38), the Day 0 events occurred more often after first administration of the vaccine compared to the rest of the series. There were no allergic events after doses 2 or 3, and there were 2 syncope events after dose 2 and 1 event after dose 3. As all of the allergic reaction events above in Table 37 are the same as those after dose 1 in Table 38, the same gender difference is observed for that outcome here.

Table 38. Counts and Incidence Rate for Pre-Selected Day 0 Events, By Dose, *9vHPV-Only Cohort*, Combined Emergency Room and Hospital Settings

	Outcome	N	Female	Male	Number of Doses	Incidence per 1 million doses, with 95% CI
Dose 1	Allergic reactions	8	7	1	140,628	56.9 (24.6, 112.1)
	Syncope (incl. collapse)	11	5	6		78.2 (39.0, 140.0)
Dose 2	Allergic reactions	0	0	0	69,027	0.0 (0.0, 53.4)
	Syncope (incl. collapse)	2	0	2		29.0 (3.5, 104.7)
Dose 3	Allergic reactions	0	0	0	29,901	0.0 (0.0, 123.4)
	Syncope (incl. collapse)	1	1	0		33.4 (0.8, 186.3)

In the *Any 9vHPV Cohort*, incidence rate of allergic reactions after 9vHPV vaccination was 36.3 per million doses (95% CI 18.7, 63.4) and 54.4 per million doses (95% CI 32.3, 86.0) for syncope (Table 39). Similar to the results in the *9vHPV-Only Cohort*, no events were identified in the following pre-specified sub-categories: anaphylactic reaction due to vaccination, angioneurotic or Quincke's edema, allergic or other specified urticaria, dermatitis due to drugs and medicines taken internally, or Syncope due to Orthostatic Hypotension. Also like the results in the *9vHPV-Only Cohort*, the allergic reactions were almost all in females (11/12, or 91.6%).

Table 39. Counts and Incidence Rates for Pre-Selected Day 0 Events in Combined Dose Series for *Any 9vHPV Cohort*, Combined Emergency Room and Hospital Settings

Outcome	N	Female	Male	Incidence per 1 million doses, with 95% CI
Allergic reactions	12	11	1	36.3 (18.7, 63.4)
- Acute bronchospasm	1	1	0	3.0 (0.1, 16.8)
- Allergy, unspecified, not classified elsewhere	6	6	0	18.1 (6.7, 39.5)
- Other anaphylactic shock, not classified elsewhere	1	0	1	3.0 (0.1, 16.8)
- Other and unspecified adverse effect of drug	1	1	0	3.0 (0.1, 16.8)
- Unspecified urticaria	3	3	3	9.1 (1.9, 26.5)
Syncope (including collapse)	18	8	10	54.4 (32.3, 86.0)

*Denominator used to calculate incidence rate was 330,774 doses.

Of the 12 allergic reaction events, 6 preceded vaccination upon chart review. The other 6 were among 5 subjects (i.e., one subject had two qualifying diagnoses) and providers noted that these may potentially be related to vaccination with 9vHPV or other vaccines. Two of these were instances of urticaria, 1 was a local reaction, 1 was a non-specific ("did not like it" mentioned in medical records) reaction accompanied with syncope (subject is also counted as a syncope event), and 1 of the allergic reaction events was diagnosed in a male as anaphylactic in nature. One of the two urticaria events was also diagnosed as a non-specific

allergic reaction (i.e., this is allergic reaction number 6). In each of these events, 9vHPV vaccine was administered with one to three other vaccines. These 5 subjects consisted of 4 females and a male, therefore the observed incidence of post-vaccination allergic reaction events per million doses was 24.4 (95% CI 6.6, 62.4) for females and 6.0 (95% CI 0.2, 33.5) for males. Thus, after review of onset, there was still a gender imbalance and, although it would not be statistically significant (p = 0.216, calculation performed using Stata, Version 11), literature supports that there are increased rates of allergic reactions following vaccination in females[10,11].

Of the 18 syncope events, 5 were noted by providers to be possibly associated with vaccination. In several instances, lab work or other procedures were noted. In 11 of the 18 events, one to three other vaccines were administered concomitantly with 9vHPV vaccine.

10.5 Analysis of Deaths

In all, there were 37 deaths among 215,965 9vHPV vaccine recipients across the entire study period (Table 43), or 171.3 deaths per million recipients (95% CI 120.6, 236.1), or 14.9 deaths per 100,000 person-years of follow-up (95% CI 10.5, 20.5). The most common causes were external causes (N=22), such as suicide (N=8 of 22) and motor vehicle accidents (N=7 of 22). The largest non-external cause was diseases of the circulatory system for which there were 9 deaths (Table 40), for a rate of 3.63 deaths per 100,000 person-years of follow-up (95% CI 1.66, 6.90) or 41.7 deaths per million recipients (95% CI 19.1, 79.1).

All deaths were reviewed for cause and time-since-vaccination. None were considered by investigators or coroners or the eSRC to be related to receipt of 9vHPV or other vaccines. Details regarding all deaths are contained in *Annex 4. Deaths, Listing / Summaries*. The most temporally proximate death relative to 9vHPV vaccination was on day 8 after vaccination; however, the individual had onset symptoms possibly related to the death preceding the vaccination. The most temporally distant death during the study period was on day 672 after vaccination. The average number of days between vaccination and death was 201 days, with a median interval of 188 days. The minimum age of death was 12 years, the maximum was 70 years, the average and median age of death were 20.7 and 20 years, respectively.

There were slightly more deaths in males than in females, with 21 in males (56.8%) and 16 deaths in females (43.2%), as shown in Table 40.

Table 40. Causes of Deaths in Study Population, in Total and by Gender

Cause (including counts)	N	Female	Male
External cause: Suicide (8), motor vehicle accident (MVA) (7), complications of medical care (2), drowning (2), overdose (2), homicide	22	9	13
Disease of the circulatory system: Cardiac arrest (4), cardiovascular collapse, cerebral ischemia, embolism and thrombosis, nontraumatic subarachnoid hemorrhage, unknown circulatory disease	9	4	5
Disease of the nervous system: Encephalitis (2)	2	1	1
Neoplasm: Malignant neoplasm, metastatic cancer	2	1	1
Endocrine, nutritional or metabolic disease: Diabetes mellitus	1	0	1
Infectious or parasitic disease: Viral myocarditis	1	1	0

Although all deaths were reviewed and summarized, deaths within the immediate post-vaccination period are summarized more fully here (we have defined the immediate post-vaccination period as 90 days which was not pre-specified in the study protocol). Excluding 6 deaths due to external causes (4 suicides, MVA, drowning), there were 7 subjects who died within 90 days; additional information regarding the time interval between vaccination and death is shown in Table 41. See *Annex 4. Deaths, Listing / Summaries* for further details.

Table 41. Brief Narratives for Non-External Cause Deaths Within 90 Days

Category and Cause	Age at 9vHPV Vaccination	Sex	Interval (Days) 9vHPV to Onset	Interval (Days) 9vHPV to Death
Disease of the nervous system: Encephalitis	12	M	Precedes	8
Disease of the circulatory system: Nontraumatic subarachnoid hemorrhage	25	F	10	10
Disease of the circulatory system: Cardiovascular collapse	25	M	42	48
Disease of the circulatory system: Embolism and thrombosis	26	M	Unknown	50
Neoplasm: Metastatic cancer	70	M	Precedes	58
Disease of the circulatory system: Cerebral ischemia	24	F	66	78
Disease of the circulatory system: Cardiac arrest	22	M	75	*98*

10.6 Adverse Events/Adverse Reactions Reporting

Adverse events were not actively solicited in this study, however some events were pre-specified for review (Day 0 syncope or allergic reaction events, deaths, signal investigation). On review, if a notation in the medical record explicitly indicated that a health care provider suspected any adverse event (serious or non-serious) to be causally related to the 9vHPV vaccine, the event was to be reported to Merck Global Safety.

All study deaths were reviewed, and none had such a notation.

On review of syncope and allergic reaction events, 10 events of the 30 reviewed noted that a provider believed that the event may have been associated with receipt of 9vHPV vaccine (6 of the 10 were syncope events, 5 of the 10 were allergic reaction events, with one event overlapping both categories). None were determined by study investigators to qualify as serious adverse events. These 10 events were reported to Merck Global Safety.

Two additional events where providers stated a potential relation to 9vHPV vaccine were discovered during follow-up investigations of elevated findings. One of these events was considered a serious adverse event since it resulted in overnight hospitalization for new diagnosis of seizure in a subject who was eventually diagnosed with epilepsy; in this event,

timing of event onset was unclear and may have preceded vaccination. Both of these additional events are described in more detail in Section 10.3.4.3 above. These 2 events were also reported to Merck Global Safety.

11 DISCUSSION

11.1 Key Results

This report provides safety results following vaccination of males and females with 9vHPV vaccine in PPD between 01 October 2015 and 30 September 2017. A total of 330,774 9vHPV vaccine doses administered to 215,965 subjects was evaluated in this study. The two study cohorts, the *9vHPV-Only Cohort* and the *Any 9vHPV Cohort*, were intended to represent a "purely defined" 9vHPV vaccination cohort, and a more "broadly defined" 9vHPV vaccination cohort, respectively. They overlapped greatly due to the *9vHPV-Only Cohort* being entirely included in, and comprising approximately two thirds of, the *Any 9vHPV Cohort*. Thus, the results between the two populations are often similar.

In October 2016, the ACIP changed their recommendation regarding HPV vaccination from 3 doses to 2 doses, with the second dose being administered 6-12 months after the first dose[12]. The recommendation was for immunocompetent girls and boys who initiate the HPV series between ages 9 through 14 years. For immunocompromised individuals as well as all for individuals who initiate the series at ages 15 through 26 years, the recommendations were unchanged from previous, that is to receive three doses of HPV on a 0, 1-2 and 6 months schedule.

In November 2016, PPD implemented the ACIP recommended 2-dose HPV vaccine schedule. The change in schedule resulted in there being fewer 9 through 14 year-olds in the study who received third doses than was originally anticipated when the study started in October 2015. The change also resulted in vaccinees having longer time intervals between first and second doses during the later part of the study period. In the *9vHPV-Only Cohort*, subjects averaged 83.5 days between their first and second dose of 9vHPV vaccines in the first six months of the study, whereas the average interval between first and second dose was 127.3 days in the overall study period (i.e., by the end of the study period).

In the general safety analyses using Days 0-14 and Days 1-60 as risk intervals, there were significantly elevated ORs in 18 HCUP categories, some of which included overlapping HCUP sub-categories. The elevated ORs were investigated further, and the individual events did not appear to be caused by 9vHPV vaccine, or had been previously reported as safety concerns with 9vHPV vaccine and are currently listed in the package insert as common local or system adverse reactions (e.g., allergic reaction, headache, injection site reaction)[9]. Where further investigation was conducted, it consisted of reviewing additional details of findings, such as plotting the timing of events to look for potential clusters, performing specific diagnosis review (i.e., reviewing the diagnostic codes listed by the practitioner for the case, or reviewing the actual diagnosis codes that contributed to the HCUP category), conducting medical records review to determine a cause or time of onset, or assessing the impact of the seasonality of vaccine exposure on the findings. In addition, findings were investigated with consideration of their biological plausibility, clinical relevance, statistical strength,

consistency, and temporality in relation to vaccination. In most cases, the additional investigation led to rule out the vaccine as being causally related to the event. For example, most cases of diabetes mellitus had onset prior to 9vHPV vaccination and many were not actually visits for diabetes mellitus but instead were for related conditions (e.g., hyperglycemia). Similarly, the events contributing to the cognitive disorders finding were all due to sport or play injuries. As another example, the HCUP category with the most elevated sub-category findings was HCUP 9: *Diseases of the digestive system*, which had several significantly elevated sub-categories such as disorders of teeth, hernias, lower gastrointestinal disorders (most of which were appendicitis), biliary tract disease, or gastrointestinal hemorrhage; upon review, most were found to either precede vaccination or were implausibly caused by vaccination (e.g., dental caries, inguinal hernias, calculus of the gallbladder, etc.). This was typical of elevated findings throughout the study, where the events contributing to the findings were either unlikely to have a plausible biological mechanism causally related to the vaccine and/or were more likely to be related to follow-up care generated at clinic visits coinciding with vaccination. The findings were similar in populations who received either a 9vHPV vaccine-only series or those who received 4vHPV vaccine prior to receiving 9vHPV vaccine.

In the general safety analysis using Days 0–14 and Days 1-60 as risk intervals, there were 39 decreased ORs which were not investigated further. Similar to the significantly elevated findings, the observed decreased ORs were unlikely to reflect vaccine effects, and may represent delayed workup for possible conditions identified at the vaccine visit, a healthy vaccinee effect (i.e., vaccinations are typically given when recipients are relatively symptom-free while later they may revert to a more usual state of health which is not necessarily symptom-free, resulting in an apparent lower risk of events around the time of vaccination than at later time), or may be due to chance.

In the Day 0 analysis, allergic reactions and syncope were observed at rates similar to those observed in previous postmarketing observational studies of HPV or other vaccines administered to this age group (e.g., MCV4, Tdap)[1]. Half of the allergic reaction events preceded vaccination and those after vaccination were considered by providers (6 events in 5 subjects) to be possibly associated with vaccination. The remaining allergic reaction events and the syncope events were generally routine and consistent with a population of this size and composition. In most instances of allergic reaction or syncope events, one to three other vaccines were administered concomitantly with 9vHPV vaccine. Of the 18 syncope events, 5 were noted by providers to be possibly associated with vaccination. Due to the possibility of syncope occurring after vaccination, the 9vHPV vaccine product labeling currently advises for there to be an observation period after vaccine administration – this is not a unique concern to 9vHPV vaccine but rather is common for injected vaccines, especially when administered in adolescents[2].

There were 14.94 deaths per 100,000 person-years (95% CI 10.52, 20.50) in the study overall. This rate is consistent with death rates by age groups cited in National Center for Health Statistics (NCHS) 2015 report[3], the closest applicable NCHS period (see 5–14, 15–24, and 25–34 year NCHS age categories, Table 42).

Table 42. All Cause Deaths in 9vHPV Vaccine PLOSS as Compared to 2015 NCHS Rates

	9vHPV Vaccine PLOSS		NCHS
NCHS Age Categories*	N	Rate per 100,000 PY (95% CI)	Rate per 100,000 PY
5–14	6	4.20 (1.54, 9.14)	13.2
15–24	24	27.25 (17.46, 40.54)	69.5
25–34	6	36.03 (13.22, 78.41)	116.7

* This study only includes 9+ year-olds so the age categories are not exactly comparable to NCHS rates. One death in a 70-year-old was excluded from Table 42 due to being an extreme outlier in the study.

There were 9 deaths in this study due to cardiovascular disease which, per eSRC request, was compared with national death rates dues to cardiovascular disease in 15–24 and 25–34 year-olds in NCHS data. The rates observed were the same or higher than those reported by NCHS (Table 43), but NCHS rates are contained within the calculated 95% CIs of the observed study rates.

Table 43. Deaths Due to Cardiovascular Disease in 9vHPV Vaccine PLOSS as Compared to 2015 NCHS Rates

	9vHPV Vaccine PLOSS		NCHS
NCHS Age Categories*	N	Rate per 100,000 PY (95% CI)	Rate per 100,000 PY
5–14	1	0.70 (0.02, 3.90)	0.7
15–24	5	5.68 (1.84, 13.25)	2.8
25–34	3	18.02 (3.72, 52.64)	9.9

* This current study only includes 9+ year-olds, thus the age categories are not precisely comparable.

11.2 Limitations

This safety analysis utilized PPD electronic databases to assess health outcomes in a large population vaccinated with 9vHPV vaccine. General analyses included all events in pre-defined risk and control intervals without regard to whether a condition was pre-existing. Thus, it is possible that some outcomes included events in both risk and self-comparison intervals that preceded vaccination. Review of several outcomes with statistically significant elevations (e.g., diabetes mellitus, gastrointestinal disorders) revealed that, for most, onset preceded vaccination.

In addition, many vaccinations occurred on the same day as a medical and/or laboratory test, which at times led to subsequent referral to specialists and new diagnoses. Thus, the interval closest to vaccination, even in the absence of attributable safety events, can have increased medical activity which has the potential to appear as increased odds of medical utilization by HCUP categorized events.

Similarly, the observed decreased ORs for the general safety analyses, which are also unlikely to reflect vaccine effects, may represent delayed workup for possible conditions identified at the vaccine visit, a healthy vaccinee effect (i.e., vaccinations are typically given when recipients are relatively symptom-free; later they may revert to a more usual state of health which is not necessarily symptom-free, resulting in an apparent lower risk of events around the time of vaccination than at later time), or may be due to chance.

Either elevations or decreases in the general safety comparisons may be due to uncontrollable artifacts such as clinic and procedure scheduling practices, or seasonality of vaccination (i.e., more vaccination in the summer than in other periods of the year).

Even though the uptake of 9vHPV vaccine during the study period was robust, safety follow-up after over 330,000 doses of 9vHPV vaccine may not be sufficient to assess the risk of rare safety outcomes, especially after a second or third dose of which there were fewer. The ACIP recommendation to move younger recipients to a 2-dose series likely resulted also in fewer third doses being given than initially anticipated, which limited our ability to assess the safety of a third dose specifically.

The safety analysis examined hospital and emergency room information from 0-14 and 1-60 day risk intervals after 1 to 3 doses of 9vHPVvaccine. As such, the study was unable to examine the safety of 9vHPV vaccine beyond these pre-defined, time-limited intervals for these settings. Deaths were examined during the entire study period.

Finally, due to resource constraints, investigators were not able to conduct medical chart review for all events and all findings, and investigation was often limited to reviewing diagnosis codes as given by providers at the point of care.

11.3 Generalizability

Although PPD , a single integrated healthcare delivery system, consists of a large racially and geographically diverse population, it may not perfectly represent the national population of recipients of the same age and gender. However, due to its size and diversity, the findings of this study should be broadly applicable.

12 CONCLUSION

In summary, in this study of over 330,000 doses of 9vHPV vaccine administered to about 216,000 males and females at PPD , no new safety signals associated with 9vHPV vaccination were identified to be of concern. The significantly elevated results were further investigated and were generally unlikely to have plausible biological mechanisms for the

vaccine to cause the finding, were often likely to be related to follow-up care generated at clinic visits coinciding with vaccination, or were common reactions already included in the product labeling. The Day 0 analysis of allergic reaction and syncope events showed rates similar to those observed in previous postmarketing observational studies of HPV vaccines as well as other vaccines administered to this age group; they were generally routine and consistent with a population of this size and composition. All deaths were reviewed and none were associated with receipt of 9vHPV vaccine; the rate of deaths also appeared consistent with national data for a comparable period and population.

Overall, the results of this study did not indicate any new safety concerns following immunization with 9vHPV vaccine. Where the eSRC suggested additional analyses to investigate findings, they were performed and noted. No new safety concerns were identified, but the study did find signals for safety concerns that were previously known to be associated with the vaccine and are in the vaccine label (e.g., headache, allergic reaction, syncope). The eSRC has reviewed the study data and the additional investigations, and agrees with the findings of study investigators (see eSRC approval letter in Annex 5).

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