1325 Boylston St. 11th Floor
Boston, MA 02215 USA
Telephone PPD

Post-Licensure Observational Study of the Safety of GARDASIL® in Males

Final Supplemental Report for Autoimmune Conditions

Patients Accrued: 16-October-2009 through 31-December-2016
with Follow-up through 31-May-2017

Report Date: 21-August-2020

Optum, Epidemiology Division Contacts

PPD

1325 Boylston St. 11th Floor
Boston, MA 02215

PPD

PPD

1325 Boylston St. 11th Floor
Boston, MA 02215

PPD

Table of Contents

1 EXECUTIVE SUMMARY

Title

Post-Licensure Observational Study of the Safety of GARDASIL® in Males

Rationale and Background

GARDASIL® is a quadrivalent human papillomavirus (HPV) vaccine licensed by Merck. The vaccine was approved in 2006 by the United States (US) Food and Drug Administration (FDA) for the prevention of several genital diseases caused by HPV types 6, 11, 16, and 18 in females. On 16-October-2009, the US FDA approved an additional indication for GARDASIL®: use in boys and men, ages 9 through 26 years, for the prevention of external genital warts (condyloma acuminata) caused by HPV types 6 and 11. A further indication for GARDASIL® was approved by the US FDA in December 2010: use in males and females, 9 through 26 years of age, for the prevention of anal intraepithelial neoplasia (AIN) grades 1, 2, and 3 caused by HPV types 6, 11, 16, and 18, and for the prevention of anal cancer caused by HPV types 16 and 18.[1]

On 21-October-2009, the US Centers for Disease Control and Prevention (CDC) Advisory Committee on Immunization Practices (ACIP) provided guidance that GARDASIL® may be administered to males 9 through 26 years of age to prevent acquisition of genital warts, but at that time, the vaccine was not included in the routine immunization schedule for males.[1] Two years later (25-October-2011) the ACIP recommended routine use of GARDASIL® in males aged 11 to 12 years, as well as to males aged 13 through 21 years who had either not been vaccinated previously or not completed the 3-dose series. At that time, the ACIP reiterated its permissive vaccination recommendation for males aged 22 through 26 years.[2]

Merck received approval from the US FDA to market GARDASIL®9 (a 9-valent HPV vaccine) on 10-December-2014, for use in females (ages 9-26 years) and males (ages 9-15 years) for prevention of a range of anogenital conditions caused by HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58. This vaccine was subsequently recommended for routine use by ACIP (27-March-2015) in females and males (at ages 11 or 12 years) with the ability to start as young as 9 years or as old as 26 years (females) or 21 years (males).[3] The indication for GARDASIL®9 was extended for use in males 16 to 26 years of age on 14-December-2015. GARDASIL®9 was approved by the US FDA for use as a 2-dose regimen in individuals 9 to 14 years of age on 07-October-2016; in the 2-dose schedule, the second dose should be administered 6 to

12 months after the first dose. In December 2016, ACIP provided new recommendations for use of a 2-dose schedule for those who initiate the vaccine series between the ages of 9 to 14 years, while the 3-dose series is still recommended for those who initiate at or beyond 15 years of age.[4] Starting in May 2017, quadrivalent GARDASIL® has no longer been available in the US, and has been replaced by GARDASIL®9, but remains available in other parts of the world. GARDASIL®9 has been granted additional indications by the US FDA and extended recommendations by the ACIP after May 2017, but this is beyond the scope of this study.

An observational study of the safety of GARDASIL® in males (Merck Protocol V501-070-01) was conducted by Optum using eligibility and healthcare claims data from a large US health plan (United HealthCare (UHC)). The study was a post-licensure regulatory commitment to the US FDA following the October 2009 approval of GARDASIL® use in males and was included in the risk management plan for the European Medicines Agency (EMA) and other regulatory agencies. The study includes males who received GARDASIL® in the course of routine clinical care from 16-October-2009 through 31-December-2016 and were followed for study outcomes, including autoimmune conditions through 31-May-2017 (i.e., approximately 5 months from the last potential accrual date). The Final Study Report was submitted to the FDA on 19-June-2019 and to the EMA on 22-June-2019, and included results for general safety for all vaccine doses combined (primary study objective) and 2 of the study's 3 secondary objectives: safety associated with receipt of the first vaccine dose and safety on Day 0 (day of vaccination). This Supplemental Report provides the results of planned analyses for the autoimmune condition outcomes, which is the study's remaining secondary objective.

Research Question and Objectives

This Supplemental Report presents the methods and results pertaining to the following secondary objective of the main safety study:

- to provide descriptive epidemiology of new-onset of 20 pre-specified autoimmune conditions for a period of 6 months after each dose of GARDASIL®, including comparison of incidence of these conditions to background incidence within the male population.

Study Design

The main safety study was an observational study conducted in a cohort of males who received at least one dose of GARDASIL® as part of routine care in a US health plan. The

autoimmune component of the study was conducted as an observational cohort to compare the incidence of new cases of autoimmune conditions among male GARDASIL® recipients and among males who did not receive GARDASIL®. More specifically, the autoimmune study component was conducted in male GARDASIL® recipients of the main safety study who had at least 12 months of health plan membership before receiving their first dose of GARDASIL®. This subcohort, termed the "GARDASIL® cohort" in this Supplemental Report on autoimmune outcome analyses, was matched to a cohort of males who did not receive GARDASIL®, termed the "Comparator cohort". Potential autoimmune outcomes in both the GARDASIL® and comparator cohorts were identified by diagnosis codes, and their diagnosis reviewed and adjudicated by physician specialists to determine if they were new-onset (i.e., newly diagnosed, incident) cases of autoimmune conditions. The incidence rates (IRs) of confirmed new-onset autoimmune outcomes were compared between the two cohorts. Not all males in the GARDASIL® cohort could be matched to comparators, but all autoimmune outcomes in the GARDASIL® cohort are reported, irrespective of whether GARDASIL® recipients were matched to comparators or not.

Variables and Data Source

Individuals and data were drawn from a proprietary research database containing eligibility, pharmacy, and medical claims data from a large US health plan affiliated with Optum. The Optum Research Database (ORD) contains claims and enrollment data dating back to 1993, capturing a longitudinal record of covered medical services, irrespective of treatment site. For 2016, data relating to approximately 14.6 million individuals with both medical and pharmacy benefit coverage were available, and approximately one-half were males. Medical records were retrieved from patient's healthcare providers to confirm the presence and timing of the 20 pre-specified autoimmune conditions.

Institutional Review Board

The protocol and data analysis plan (DAP) for this study were approved by the New England Institutional Review Board (NEIRB). A Waiver of Patient Authorization to access medical records for procurement purposes was obtained from The Privacy Board of the NEIRB.

Review Committees

An external Safety Review Committee (SRC) comprised of 4 experts in adolescent medicine, vaccine safety, autoimmune conditions, and pharmacoepidemiology was established prior to

the start of the study. The SRC's primary responsibility was to review and evaluate the safety data emerging from the study. The SRC also reviewed and approved the study protocol, data analysis plan (DAP), case review and adjudication procedure, methods used to conduct the study, and the study reports, including this Supplemental Report. After reviewing the data generated from the planned study analyses, the SRC was able to request and recommend further investigation or additional analyses, based upon their evaluation of safety data.

Separate from the SRC, the Case Review Committees (CRCs) were 4 independent adjudication committees composed of clinicians with expertise relevant to the autoimmune conditions being evaluated, grouped into 4 separate medical specialties. The role of the CRCs was to review copies of medical records of suspected new-onset cases of autoimmune conditions and, blinded to the vaccination status, confirm the diagnosis, and determine dates of diagnosis and of symptom onset, according to the study's pre-specified adjudication procedure.

Subjects and Study Size

Males who received at least one dose of GARDASIL® while being members of the research database between 16-October-2009 and 31-December-2016 were the source population (termed "regimen initiators") for the vaccinated cohort in the autoimmune analysis. The subset of GARDASIL® regimen initiators who had at least 12 months of health plan membership prior to their first dose of GARDASIL® were included in the analysis of autoimmune outcomes. This subcohort was named the "Autoimmune cohort" in the protocol and DAP; it is termed the "GARDASIL® cohort" in this Supplementary Report for ease of reference. The 12-month baseline period was used to identify pre-existing (i.e., prevalent) autoimmune conditions. More specifically, males with any prevalent autoimmune condition in the 12-month baseline period before receiving their first dose of GARDASIL® were not excluded from the GARDASIL® cohort. Rather, a male with evidence of a pre-existing diagnosis of a given autoimmune condition was excluded from the analyses of that specific autoimmune condition (but not from the analyses of other autoimmune conditions since that male could develop new-onset of another autoimmune condition).

A comparison group (termed "Comparator cohort") was comprised of males of similar age as the GARDASIL® cohort but who did not receive GARDASIL® prior to or during their follow-up. The comparison group was selected from the ORD and frequency matched by propensity-scores to an equal number of GARDASIL® recipients in the GARDASIL® cohort by

demographics and healthcare utilization factors. Comparators were also matched to GARDASIL® recipients in the GARDASIL® cohort by calendar time of a physician visit (cohort entry date).

Not all males in the GARDASIL® cohort could be matched. Results for the unmatched GARDASIL® recipients from the GARDASIL® cohort are also presented in this report separately.

This analysis included new-onset (i.e., incident) autoimmune outcomes identified within a 6-month risk window after each dose of the vaccine among GARDASIL® recipients in the GARDASIL® cohort, and up to 18 months following the study-specified cohort entry index date anchored on a physician visit among the males in the matched comparator cohort. To account for variations in vaccine administration schedules, the comparator cohort was followed for up to 18 months corresponding to the maximum potential follow-up among the GARDASIL® recipients - 3 doses with 6 non-overlapping months of follow-up each (549 days).

New-Onset Autoimmune Conditions

The following 20 autoimmune outcomes, identified and pre-specified based on agreement with regulatory agencies, were categorized into four condition groups (rheumatologic/hematologic, gastroenterologic, endocrinologic, and neurologic/ophthalmic) and were evaluated:

1. Rheumatologic/hematologic: Immune thrombocytopenia (ITP)*, autoimmune hemolytic anemia (AHA)*, systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), juvenile rheumatoid arthritis (JRA), psoriatic arthritis, ankylosing spondylitis (AS), reactive arthritis;
2. Gastroenterologic: Crohn's disease, ulcerative colitis (UC);
3. Endocrinologic: Type 1 diabetes, Hashimoto's disease, Graves' disease;
4. Neurologic/ophthalmic conditions: Multiple sclerosis (MS), acute disseminated encephalomyelitis (ADEM), other demyelinating diseases of the nervous system, Guillain-Barré syndrome (GBS), neuromyelitis optica, optic neuritis, and uveitis.

* ITP and AHA, 2 hematologic conditions, were included into the rheumatologic group.

Autoimmune conditions were initially identified by ICD-9 or ICD-10 diagnosis codes associated with an outpatient visit, emergency room (ER) visit, or hospitalization. For each

potential autoimmune outcome case, redacted medical records were retrieved from the healthcare site providing the service, and adjudication of the diagnosis was conducted by the CRCs according to pre-specified study procedures. Medical records of potential cases were sought for healthcare visits related to the diagnosis of the condition, to the potential condition onset (i.e., first signs or symptoms suggestive of the condition), and to the first dose for the GARDASIL® cohort (or day of physician office visit for the comparators).

The medical records were obtained and any mentions of GARDASIL® or other vaccines were redacted along with patients' protected health information (PHI). The records for every potential case were independently reviewed by 2 clinicians with appropriate expertise from the relevant CRC. Based on the medical record review, the autoimmune condition was classified as confirmed, not confirmed, or as having insufficient information, and the dates of symptom onset and of diagnosis were ascertained. Narratives were written for all potential autoimmune conditions that were adjudicated.

Statistical Analyses

Demographic characteristics and healthcare utilization factors for the matched GARDASIL® recipients in the GARDASIL® cohort, the matched comparators, and the unmatched GARDASIL® recipients in the GARDASIL® cohort were summarized. Counts of potential autoimmune cases, identified using pre-specified claim codes validated by the CRCs and the SRC, were tabulated. Adjudication results including confirmation fraction and time to symptom onset for confirmed new-onset cases were summarized. IRs of the confirmed autoimmune outcomes were estimated (number of events/1,000 person-years) for the propensity-score matched GARDASIL® cohort and the comparator cohort. Corresponding 95% confidence intervals (CIs) were calculated for IRs. Unadjusted relative rates (RRs) and 95% CIs were calculated by dividing the rates in the matched GARDASIL® cohort by the rates in the comparator cohort. Given the close matching accomplished by the propensity-score method, additional statistical adjustment of RRs was determined not to be needed and unadjusted RRs are presented.

Results

Among the 114,035 males vaccinated with GARDASIL® in the main safety study, Optum identified 65,606 males in the subcohort eligible for the autoimmune analysis who received at least one dose of GARDASIL®, including 38,347 males who received at least 2 doses of

GARDASIL®, and 21,518 males who received at least 3 doses of GARDASIL® for a total of 125,471 doses. The majority of males (89%) received their first dose between 11 to 18 years of age.

Of the 65,606 males in the GARDASIL® cohort, 55,670 (85%) were able to be propensity-score matched to an equal number (n=55,670) of comparators (males with a physician visit at which they did not receive GARDASIL®). Overall, 39,735 and 58,215 person-years of follow-up were accrued among the matched GARDASIL® cohort and matched comparator cohort, respectively. After matching, the distribution of age, geographic region, health plan membership, drugs dispensed, number of hospitalizations, number of procedures, health care visits and healthcare costs were similar among the GARDASIL® recipients and matched comparators.

Case Identification and Adjudication

All Autoimmune Conditions Combined

A total of 789 potential new-onset claims-based autoimmune cases were identified among the GARDASIL® cohort (matched and unmatched) and matched comparators. In the GARDASIL® cohort, there were 416 potential new-onset autoimmune cases (86% of medical records obtained) identified among the matched GARDASIL® recipients (**Summary Table 1**). There were 373 potential new-onset autoimmune cases (83% of medical records obtained) identified in the matched comparator cohort. Medical records were obtained from 82% (n=61) of the 74 potential new-onset autoimmune cases identified among unmatched GARDASIL recipients (data not shown).

Following adjudication, there were 96 confirmed autoimmune cases in the GARDASIL® cohort. Among those, 76 were in the matched GARDASIL® recipients (**Summary Table 1**). There were 65 confirmed autoimmune cases in the comparator cohort. The percentage of potential autoimmune cases that were confirmed as new-onset autoimmune cases through adjudication (termed “case confirmation fraction”) was 23% for the GARDASIL® cohort (21% among matched GARDASIL® recipients) and 21% among matched comparators (**Appendix E**). The case confirmation fraction for the unmatched GARDASIL® recipients was 33% (data not shown).

Following case confirmation, it was determined whether confirmed new-onset cases had a date of symptom onset occurring during the risk window for GARDASIL® recipients (within 6

months following receipt of a vaccine dose) and during the comparison window for matched comparators (within 18 months following cohort entry). Overall, there were 35 confirmed new-onset cases within the risk window among the matched GARDASIL® recipients, and 47 confirmed new-onset cases within the comparison window among the matched comparators (**Summary Table 1** and **2**). In addition, of the 20 confirmed cases among the unmatched GARDASIL® recipients, it was determined that 11 were confirmed new-onset cases within the risk window (3 Crohn's disease, 3 Hashimoto's disease, and one of each Type 1 diabetes, Graves' disease, MS, ON, and RA cases) (data not shown).

Rheumatologic/Hematologic Autoimmune Conditions

A total of 144 potential new-onset rheumatologic/hematologic claims-based autoimmune cases were identified in the GARDASIL® cohort (83% with medical records obtained). Among those, 118 (85% with medical records obtained) were in the matched GARDASIL® cohort (**Summary Table 1**). There were 96 potential new-onset rheumatologic/hematologic cases in the matched comparator cohort (85% with medical records obtained). Twenty-six (26) potential new-onset rheumatologic/hematologic cases were identified in the unmatched GARDASIL® recipients (73% with medical records obtained) (data not shown).

Following adjudication, there were 14 confirmed rheumatologic/hematologic autoimmune cases in the GARDASIL® cohort, including 11 among the matched GARDASIL® recipients (**Summary Table 1**). There were 10 confirmed cases in the comparator cohort. The case confirmation fraction was 11% for the GARDASIL® cohort (11% and 16% among the matched and unmatched GARDASIL® recipients, respectively) and 12% among matched comparators.

Following case confirmation, it was determined whether confirmed new-onset cases occurred during the relevant window for GARDASIL® recipients and matched comparators. Overall, there were 2 confirmed new-onset cases within the risk window among the matched GARDASIL® recipients, and 6 confirmed new-onset cases within the comparison window among the matched comparators (**Summary Table 1** and **2**).

Gastroenterologic Autoimmune Conditions

A total of 58 potential new-onset gastroenterologic claims-based autoimmune cases (88% with medical records obtained) were identified in the GARDASIL® cohort. Among those, 48 were matched GARDASIL® recipients (88% with medical records obtained) (**Summary Table 1**). There were 38 potential new-onset gastroenterologic cases (87% with medical records

obtained) in the matched comparator cohort. Ten (10) potential new-onset gastroenterologic claims-based cases were identified among the unmatched males in the GARDASIL® cohort (90% with medical records obtained) (data not shown).

Following adjudication, there were 30 confirmed gastroenterologic autoimmune cases in the GARDASIL® cohort, including 24 among the matched GARDASIL® recipients (**Summary Table 1**). There were 21 confirmed gastroenterologic cases in the comparator cohort. The case confirmation fraction was 59% for the GARDASIL® cohort (55% and 67% for matched and unmatched GARDASIL® recipients) and 64% among matched comparators.

Following case confirmation, it was determined that 12 confirmed new-onset cases occurred within the risk window among the matched GARDASIL® recipients, and 14 confirmed new-onset cases occurred within the comparison window among the matched comparators (**Summary Table 1** and **2**).

Endocrinologic Autoimmune Conditions

A total of 183 potential new-onset endocrinologic claims-based autoimmune cases (83% with medical records obtained) were identified in the GARDASIL® cohort. Among those, 159 were matched GARDASIL® recipients (82% with medical records obtained) (**Summary Table 1**). There were 134 potential new-onset cases (81% with medical records obtained) in the matched comparator cohort. Twenty-four (24) potential new-onset endocrinologic claims-based autoimmune cases were identified in the unmatched GARDASIL® recipients (88% with medical records obtained).

Following adjudication, there were 48 confirmed endocrinologic autoimmune cases in the GARDASIL® cohort, including 39 among matched recipients (**Summary Table 1**). There were 32 confirmed endocrinologic cases in the matched comparators. The case confirmation fractions were 32% for the GARDASIL® cohort (30% and 43% for the matched and unmatched GARDASIL® recipients) and 29% for the matched comparators.

Following case confirmation, it was determined that 19 confirmed new-onset cases occurred within the risk window among the matched GARDASIL® recipients, and 25 confirmed new-onset cases occurred within the comparison window among the matched comparators (**Summary Table 1** and **2**).

Neurologic/Ophthalmic Autoimmune Conditions

A total of 105 potential new-onset neurologic/ophthalmic claims-based autoimmune cases (91% with medical records obtained) were identified in the GARDASIL® cohort. Among those, 91 of whom were among the matched GARDASIL® recipients (92% with medical records obtained) (**Summary Table 1**). There were 105 potential new-onset cases in the matched comparator cohort (82% with medical records obtained). There were 14 potential new-onset neurologic/ophthalmic claims-based autoimmune cases among the unmatched GARDASIL® recipients (86% with medical records obtained).

Following adjudication, there were 4 confirmed neurologic/ophthalmic cases in the GARDASIL® cohort, 2 of whom were among the matched GARDASIL® recipients (**Summary Table 1**). There were 2 confirmed neurologic/ophthalmic cases in the matched comparators. The case confirmation fractions were 4% for the GARDASIL® cohort (2% for the matched and 17% for the unmatched GARDASIL® recipients) and 2% for the matched comparators.

Following case confirmation, it was determined that 2 confirmed new-onset cases occurred within the risk window among the matched GARDASIL® recipients, and 2 confirmed new-onset cases occurred within the comparison window among the matched comparators (**Summary Table 1** and **2**).

Incidence and Relative Rates

All IR (expressed per 1,000 person-years) and RR results are shown in **Summary Table 2** and **Summary Figures 1-3**.

For chart-confirmed autoimmune cases combined, the observed IR (per 1,000 person-years) was 0.88 (95% CI 0.61-1.23) in the matched GARDASIL® recipients and 0.81 (95% CI 0.59-1.07) among the matched comparators (**Summary Table 2**). The RR for all chart-confirmed autoimmune cases combined in GARDASIL® recipients vs. comparators was 1.09 (95% CI 0.70-1.69) (**Summary Table 2,** and **Summary Figures 1-3**).

For chart-confirmed rheumatologic/hematologic cases combined, the observed IR in the matched GARDASIL® recipients and comparators was 0.05 (95% CI 0.01-0.18) and 0.10 (95% CI 0.04-0.22), respectively. The RR for all chart-confirmed rheumatologic/hematologic autoimmune cases combined was 0.49 (95% CI 0.10-2.42). Relative rates were not calculated for the individual rheumatologic/hematologic outcomes (ITP, AHA, SLE, RA, JRA, psoriatic

arthritis, AS, reactive arthritis), because there were zero chart-confirmed outcomes either among the matched GARDASIL® recipients or the comparators.

For chart-confirmed gastroenterologic cases combined, the observed IR in the matched GARDASIL® recipients and comparators was 0.30 (95% CI 0.16-0.53) and 0.24 (95% CI 0.13-0.40), respectively. The RR for all chart-confirmed gastroenterologic autoimmune cases combined was 1.26 (95% CI 0.58-2.71). The RRs were not significantly increased (95% CI included 1.0) for either of the 2 specific conditions included in the gastroenterologic autoimmune category: Crohn's disease (RR 0.73, 95% CI 0.28-1.95) and UC (RR 4.39, 95% CI 0.89-21.77).

For chart-confirmed endocrinologic cases combined, the observed IR in the matched GARDASIL® recipients and comparators was 0.48 (95% CI 0.29-0.75) and 0.43 (95% CI 0.28-0.63), respectively. The RR for all chart-confirmed endocrinologic autoimmune cases combined was 1.11 (95% CI 0.61-2.02); RR were not significantly increased for any of the 3 specific conditions in the endocrinology autoimmune category: Type 1 diabetes (RR 0.98, 95% CI 0.40-2.39), Hashimoto's disease (RR 1.33, 95% CI 0.57-3.14), Graves' disease (RR 0.73, 95% CI 0.07-8.07).

For all chart-confirmed neurologic cases combined, the observed IR in the matched GARDASIL® recipients and comparators was 0.05 (95% CI 0.01-0.18) and 0.03 (95% CI 0.00-0.12), respectively. The RR for all chart-confirmed neurologic autoimmune cases combined was 1.46 (95% CI 0.21-10.40). Relative rates were not calculated for the individual neurologic outcomes (MS, ADEM, other demyelinating diseases of the nervous system, GBS, neuromyelitis optica, and optic neuritis), because there were zero chart-confirmed outcomes either among the matched GARDASIL® recipients or the comparators.

Conclusions

In this large post-marketing safety study, the incidence of new-onset of 20 pre-specified autoimmune conditions within 6 months of receipt of a dose of GARDASIL® was estimated in 55,670 males who received more than 104,000 doses of GARDASIL®, and compared to that of matched unvaccinated male comparators. Per the study protocol, the objective of these analyses was descriptive and the precision of the study is reflected in the width of the CIs of the IRs for the various autoimmune outcomes. Using a broad case detection strategy and a rigorous review and adjudication by clinical specialists following pre-specified procedures, the

number of confirmed new-onset autoimmune cases within the risk window (a total of 35 in the matched GARDASIL® recipients and 47 in the comparators) was small in both groups. The overall observed IR of new-onset autoimmune conditions was 0.88 per 1,000 person-years (95% CI 0.61-1.23) in the GARDASIL® recipients and 0.81 per 1,000 person-years (95% CI 0.59-1.07) in the comparators, a RR of 1.09 (95% CI 0.70-1.69). The estimated IRs of new-onset of the 20 pre-specified autoimmune conditions were generally similar between the GARDASIL® recipients and comparators. These estimates were generally consistent with the incidence of these conditions reported in studies looking at autoimmune conditions among both male and female GARDASIL® recipients as well as in the general male population of similar age. Finally, the findings in this study are consistent with other observational studies assessing the association of receipt of GARDASIL® and the development of autoimmune conditions in both females and males.

SRC Evaluation

After review of the study results, the SRC concluded that the study revealed no evidence of any increased risk of new-onset autoimmune conditions following receipt of GARDASIL® in males and that the results are consistent with the known safety profile of GARDASIL® (**Appendix N**).

Summary Table 1.[a] Summary of Potential and Reviewed New-Onset Autoimmune Conditions among Matched Gardasil Recipients (N= 55,670) and Comparators (N= 55,670)

Condition	Matched Gardasil Recipients							Matched Comparators						
	Potential Cases			Reviewed Cases[b]				Potential Cases			Reviewed Cases[c]			
	Total	Potential New Onset Cases[b] [N(%)]	Medical Charts Not Available [N(%)]	Not Confirmed [N(%)]	Confirmed (Overall) [N(%)]	Confirmed (New Onset and within Risk Window) [N(%)]	Insuff. Info. [N(%)]	Total	Potential New Onset Cases[c] [N(%)]	Medical Charts Not Available [N(%)]	Not Confirmed [N(%)]	Confirmed (Overall) [N(%)]	Confirmed (New Onset and within Risk Window) [N(%)]	Insuff. Info. [N(%)]
Total	**887 (100.0)**	**416 (100.0)**	**59 (100.0)**	**270 (100.0)**	**76 (100.0)**	**35 (100.0)**	**15 (100.0)**	**905 (100.0)**	**373 (100.0)**	**63 (100.0)**	**232 (100.0)**	**65 (100.0)**	**47 (100.0)**	**16 (100.0)**
Rheumatological	**173 (19.5)**	**118 (28.4)**	**18 (30.5)**	**86 (31.9)**	**11 (14.5)**	**2 (5.7)**	**3 (20.0)**	**151 (16.7)**	**96 (25.7)**	**14 (22.2)**	**69 (29.7)**	**10 (15.4)**	**6 (12.8)**	**4 (25.0)**
Immune Thrombocytopenia	10 (1.1)	4 (1.0)	0 (0.0)	2 (0.7)	2 (2.6)	0 (0.0)	0 (0.0)	12 (1.3)	7 (1.9)	1 (1.6)	2 (0.9)	4 (6.2)	3 (6.4)	0 (0.0)
Autoimmune Hemolytic Anemia	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.2)	2 (0.5)	0 (0.0)	1 (0.4)	1 (1.5)	0 (0.0)	0 (0.0)
Systemic Lupus Erythematosus	19 (2.1)	14 (3.4)	2 (3.4)	11 (4.1)	1 (1.3)	1 (2.9)	0 (0.0)	12 (1.3)	9 (2.4)	1 (1.6)	8 (3.4)	0 (0.0)	0 (0.0)	0 (0.0)
Rheumatoid Arthritis	14 (1.6)	9 (2.2)	1 (1.7)	5 (1.9)	1 (1.3)	0 (0.0)	2 (13.3)	16 (1.8)	10 (2.7)	2 (3.2)	6 (2.6)	0 (0.0)	0 (0.0)	2 (12.5)
Juvenile Rheumatoid Arthritis	19 (2.1)	8 (1.9)	2 (3.4)	1 (0.4)	5 (6.6)	0 (0.0)	0 (0.0)	22 (2.4)	8 (2.1)	0 (0.0)	3 (1.3)	4 (6.2)	3 (6.4)	2 (12.5)
Psoriatic Arthritis	6 (0.7)	2 (0.5)	0 (0.0)	2 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.3)	2 (0.5)	0 (0.0)	1 (0.4)	1 (1.5)	0 (0.0)	0 (0.0)
Ankylosing Spondylitis	91 (10.3)	68 (16.3)	12 (20.3)	54 (20.0)	1 (1.3)	1 (2.9)	1 (6.7)	76 (8.4)	53 (14.2)	9 (14.3)	44 (19.0)	0 (0.0)	0 (0.0)	0 (0.0)
Reactive Arthritis	13 (1.5)	13 (3.1)	1 (1.7)	11 (4.1)	1 (1.3)	0 (0.0)	0 (0.0)	8 (0.9)	5 (1.3)	1 (1.6)	4 (1.7)	0 (0.0)	0 (0.0)	0 (0.0)
Gastroenterological	**127 (14.3)**	**48 (11.5)**	**6 (10.2)**	**13 (4.8)**	**24 (31.6)**	**12 (34.3)**	**7 (46.7)**	**141 (15.6)**	**38 (10.2)**	**5 (7.9)**	**9 (3.9)**	**21 (32.3)**	**14 (29.8)**	**3 (18.8)**
Crohn's Disease	84 (9.5)	27 (6.5)	2 (3.4)	7 (2.6)	13 (17.1)	6 (17.1)	5 (33.3)	98 (10.8)	25 (6.7)	3 (4.8)	5 (2.2)	16 (24.6)	12 (25.5)	1 (6.3)
Ulcerative Colitis	43 (4.8)	21 (5.0)	4 (6.8)	6 (2.2)	11 (14.5)	6 (17.1)	2 (13.3)	43 (4.8)	13 (3.5)	2 (3.2)	4 (1.7)	5 (7.7)	2 (4.3)	2 (12.5)
Endocrinological	**482 (54.3)**	**159 (38.2)**	**28 (47.5)**	**89 (33.0)**	**39 (51.3)**	**19 (54.3)**	**4 (26.7)**	**483 (53.4)**	**134 (35.9)**	**25 (39.7)**	**73 (31.5)**	**32 (49.2)**	**25 (53.2)**	**6 (37.5)**
Type I Diabetes	226 (25.5)	29 (7.0)	4 (6.8)	10 (3.7)	14 (18.4)	8 (22.9)	1 (6.7)	220 (24.3)	22 (5.9)	3 (4.8)	4 (1.7)	14 (21.5)	12 (25.5)	1 (6.3)
Hashimoto's Disease	207 (23.3)	91 (21.9)	18 (30.5)	48 (17.8)	23 (30.3)	10 (28.6)	3 (20.0)	211 (23.3)	73 (19.6)	18 (28.6)	36 (15.5)	16 (24.6)	11 (23.4)	5 (31.3)
Graves' Disease	49 (5.5)	39 (9.4)	6 (10.2)	31 (11.5)	2 (2.6)	1 (2.9)	0 (0.0)	52 (5.7)	39 (10.5)	4 (6.3)	33 (14.2)	2 (3.1)	2 (4.3)	0 (0.0)

[a]Males were eligible if they had 12+ months of continuous enrollment prior to the first dose of Gardasil, or prior to the earliest healthcare visit for Comparators.
[b]Four cases (two gastroenterology; one endocrine; one neurological/ophthalmologic) were identified to have an alternative outcome by clinical reviewers during the adjudication process. Therefore, the number of potential new onset cases for the overall total and for each condition group total may not equal the sum of individual columns "Medical Charts Not Available + Not Confirmed + Confirmed + Insuff Info".
[c]Three cases (one rheumatology; two endocrinology) were identified to have an alternative outcome by clinical reviewers during the adjudication process. Therefore, the number of potential new onset cases for the overall total and for each condition group total may not equal the sum of individual columns "Medical Charts Not Available + Not Confirmed + Confirmed + Insuff Info".
[d]Total follow-up (person-years)= 121,944. Cases with no diagnosis codes for the same autoimmune condition 12 months prior to the first dose.

Summary Table 1.[a] Summary of Potential and Reviewed New-Onset Autoimmune Conditions among Matched Gardasil Recipients (N= 55,670) and Comparators (N= 55,670)

Condition	Matched Gardasil Recipients							Matched Comparators						
	Potential Cases			Reviewed Cases[b]				Potential Cases			Reviewed Cases[c]			
	Total	Potential New Onset Cases[d] [N(%)]	Medical Charts Not Available [N(%)]	Not Confirmed [N(%)]	Confirmed (Overall) [N(%)]	Confirmed (New Onset and within Risk Window) [N(%)]	Insuff. Info. [N(%)]	Total	Potential New Onset Cases[c] [N(%)]	Medical Charts Not Available [N(%)]	Not Confirmed [N(%)]	Confirmed (Overall) [N(%)]	Confirmed (New Onset and within Risk Window) [N(%)]	Insuff. Info. [N(%)]
Neurological	**105 (11.8)**	**91 (21.9)**	**7 (11.9)**	**82 (30.4)**	**2 (2.6)**	**2 (5.7)**	**1 (6.7)**	**130 (14.4)**	**105 (28.2)**	**19 (30.2)**	**81 (34.9)**	**2 (3.1)**	**2 (4.3)**	**3 (18.8)**
Multiple Sclerosis	33 (3.7)	30 (7.2)	1 (1.7)	28 (10.4)	2 (2.6)	2 (5.7)	0 (0.0)	54 (6.0)	48 (12.9)	8 (12.7)	38 (16.4)	0 (0.0)	0 (0.0)	2 (12.5)
Acute Disseminated Encephalomyelitis	13 (1.5)	10 (2.4)	0 (0.0)	10 (3.7)	0 (0.0)	0 (0.0)	0 (0.0)	5 (0.6)	5 (1.3)	0 (0.0)	5 (2.2)	0 (0.0)	0 (0.0)	0 (0.0)
Other Demyelinating Diseases of the Nervous System	3 (0.3)	3 (0.7)	0 (0.0)	3 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.2)	2 (0.5)	1 (1.6)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Guillain-Barre Syndrome	7 (0.8)	6 (1.4)	0 (0.0)	6 (2.2)	0 (0.0)	0 (0.0)	0 (0.0)	12 (1.3)	7 (1.9)	3 (4.8)	4 (1.7)	0 (0.0)	0 (0.0)	0 (0.0)
Neuromyelitis Optica	1 (0.1)	1 (0.2)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Optic Neuritis	4 (0.5)	3 (0.7)	0 (0.0)	2 (0.7)	0 (0.0)	0 (0.0)	1 (6.7)	6 (0.7)	4 (1.1)	1 (1.6)	2 (0.9)	0 (0.0)	0 (0.0)	1 (6.3)
Uveitis	44 (5.0)	38 (9.1)	6 (10.2)	32 (11.9)	0 (0.0)	0 (0.0)	0 (0.0)	51 (5.6)	39 (10.5)	6 (9.5)	31 (13.4)	2 (3.1)	2 (4.3)	0 (0.0)

[a]Males were eligible if they had 12+ months of continuous enrollment prior to the first dose of Gardasil, or prior to the earliest healthcare visit for Comparators.
[b]Four cases (two gastroenterology; one endocrine; one neurological/ophthalmologic) were identified to have an alternative outcome by clinical reviewers during the adjudication process. Therefore, the number of potential new onset cases for the overall total and for each condition group total may not equal the sum of individual columns “Medical Charts Not Available + Not Confirmed + Confirmed + Insuff Info”.
[c]Three cases (one rheumatology; two endocrinology) were identified to have an alternative outcome by clinical reviewers during the adjudication process. Therefore, the number of potential new onset cases for the overall total and for each condition group total may not equal the sum of individual columns “Medical Charts Not Available + Not Confirmed + Confirmed + Insuff Info”.
[d]Total follow-up (person-years)= 121,944. Cases with no diagnosis codes for the same autoimmune condition 12 months prior to the first dose.

Summary Table 2.[a] Relative Rates of New-Onset Autoimmune Conditions among Matched Gardasil Recipients (N= 55,670) and Comparators (N= 55,670)

Autoimmune Condition	Matched Recipients of Gardasil[c]				Matched Comparators (Unvaccinated)[d]				Relative Rate	95% CI
	Cases	Person-Years	Incidence Rate[b]	95% CI	Cases	Person-Years	Incidence Rate[c]	95%CI		
Total	**35**	**39,735**	**0.88**	**0.61 - 1.23**	**47**	**58,215**	**0.81**	**0.59 - 1.07**	**1.09**	**0.70 - 1.69**
Rheumatological	**2**	**39,756**	**0.05**	**0.01 - 0.18**	**6**	**58,211**	**0.10**	**0.04 - 0.22**	**0.49**	**0.10 - 2.42**
Immune Thrombocytopenia	0	39,757	0.00	0.00 - 0.08	3	58,213	0.05	0.01 - 0.15	NC	NC - NC
Autoimmune Hemolytic Anemia	0	39,757	0.00	0.00 - 0.08	0	58,215	0.00	0.00 - 0.05	NC	NC - NC
Systemic Lupus Erythematosus	1	39,757	0.03	0.00 - 0.14	0	58,215	0.00	0.00 - 0.05	NC	NC - NC
Rheumatoid Arthritis	0	39,757	0.00	0.00 - 0.08	0	58,215	0.00	0.00 - 0.05	NC	NC - NC
Juvenile Rheumatoid Arthritis	0	39,757	0.00	0.00 - 0.08	3	58,213	0.05	0.01 - 0.15	NC	NC - NC
Psoriatic Arthritis	0	39,757	0.00	0.00 - 0.08	0	58,215	0.00	0.00 - 0.05	NC	NC - NC
Ankylosing Spondylitis	1	39,757	0.03	0.00 - 0.14	0	58,215	0.00	0.00 - 0.05	NC	NC - NC
Reactive Arthritis	0	39,757	0.00	0.00 - 0.08	0	58,215	0.00	0.00 - 0.05	NC	NC - NC
Gastroenterological	**12**	**39,750**	**0.30**	**0.16 - 0.53**	**14**	**58,205**	**0.24**	**0.13 - 0.40**	**1.26**	**0.58 - 2.71**
Crohn's Disease	6	39,754	0.15	0.06 - 0.33	12	58,206	0.21	0.11 - 0.36	0.73	0.28 - 1.95
Ulcerative Colitis	6	39,753	0.15	0.06 - 0.33	2	58,214	0.03	0.00 - 0.12	4.39	0.89 - 21.77
Endocrinological	**19**	**39,745**	**0.48**	**0.29 - 0.75**	**25**	**58,200**	**0.43**	**0.28 - 0.63**	**1.11**	**0.61 - 2.02**
Type I Diabetes	8	39,753	0.20	0.09 - 0.40	12	58,206	0.21	0.11 - 0.36	0.98	0.40 - 2.39
Hashimoto's Disease	10	39,749	0.25	0.12 - 0.46	11	58,210	0.19	0.09 - 0.34	1.33	0.57 - 3.14
Graves' Disease	1	39,757	0.03	0.00 - 0.14	2	58,214	0.03	0.00 - 0.12	0.73	0.07 - 8.07

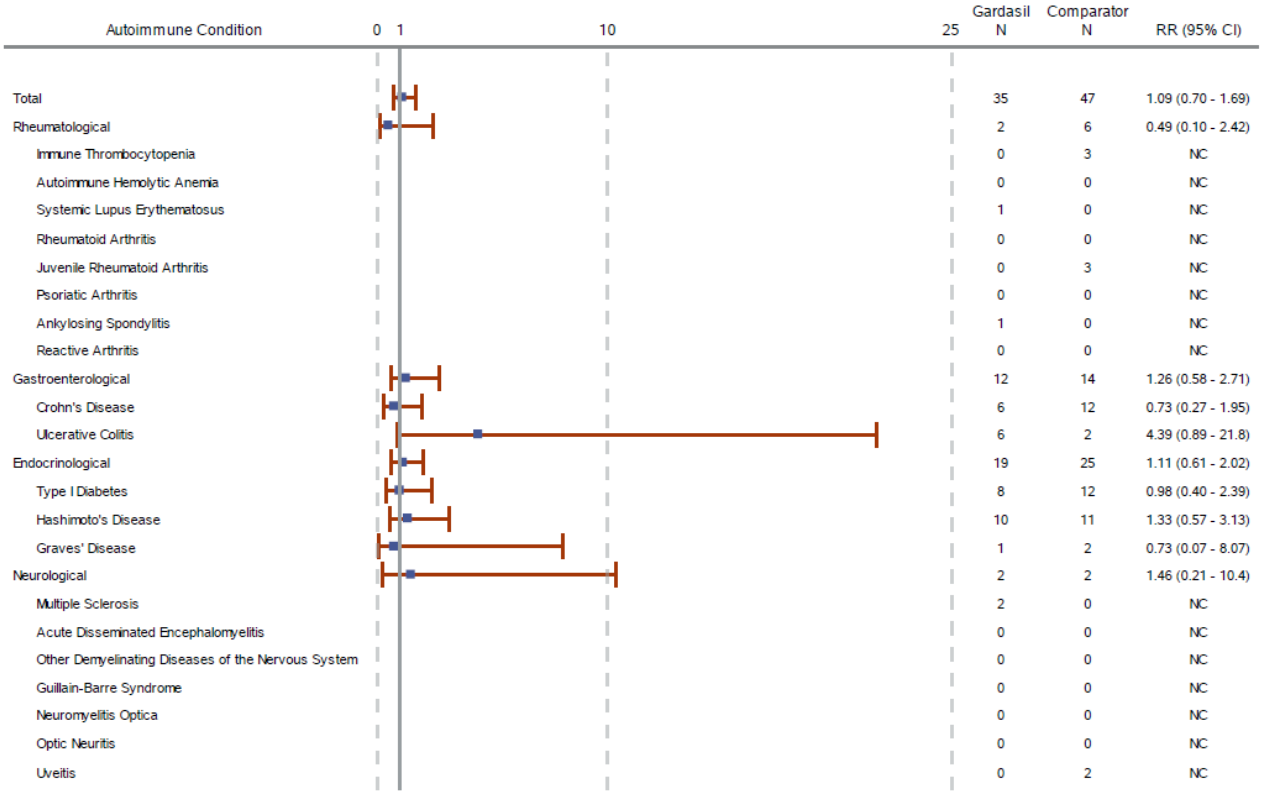
Abbreviations: CI, Confidence Interval; NC, Not Calculated
[a]Accrual 16-OCT-2009 - 31-DEC-2016
[b]Per 1,000 Person-Years
[c]Risk period consists of 6 months after each dose in follow up period
[d]Risk period consists of 18 months after index date (date of healthcare visit)

Summary Table 2.[a] Relative Rates of New-Onset Autoimmune Conditions among Matched Gardasil Recipients (N= 55,670) and Comparators (N= 55,670)

Autoimmune Condition	Matched Recipients of Gardasil[c]				Matched Comparators (Unvaccinated)[d]				Relative Rate	95% CI
	Cases	Person-Years	Incidence Rate[b]	95% CI	Cases	Person-Years	Incidence Rate[c]	95%CI		
Neurological	**2**	**39,756**	**0.05**	**0.01 - 0.18**	**2**	**58,213**	**0.03**	**0.00 - 0.12**	**1.46**	**0.21 - 10.40**
Multiple Sclerosis	2	39,756	0.05	0.01 - 0.18	0	58,215	0.00	0.00 - 0.05	NC	NC - NC
Acute Disseminated Encephalomyelitis	0	39,757	0.00	0.00 - 0.08	0	58,215	0.00	0.00 - 0.05	NC	NC - NC
Other Demyelinating Diseases of the Nervous System	0	39,757	0.00	0.00 - 0.08	0	58,215	0.00	0.00 - 0.05	NC	NC - NC
Guillain-Barre Syndrome	0	39,757	0.00	0.00 - 0.08	0	58,215	0.00	0.00 - 0.05	NC	NC - NC
Neuromyelitis Optica	0	39,757	0.00	0.00 - 0.08	0	58,215	0.00	0.00 - 0.05	NC	NC - NC
Optic Neuritis	0	39,757	0.00	0.00 - 0.08	0	58,215	0.00	0.00 - 0.05	NC	NC - NC
Uveitis	0	39,757	0.00	0.00 - 0.08	2	58,213	0.03	0.00 - 0.12	NC	NC - NC

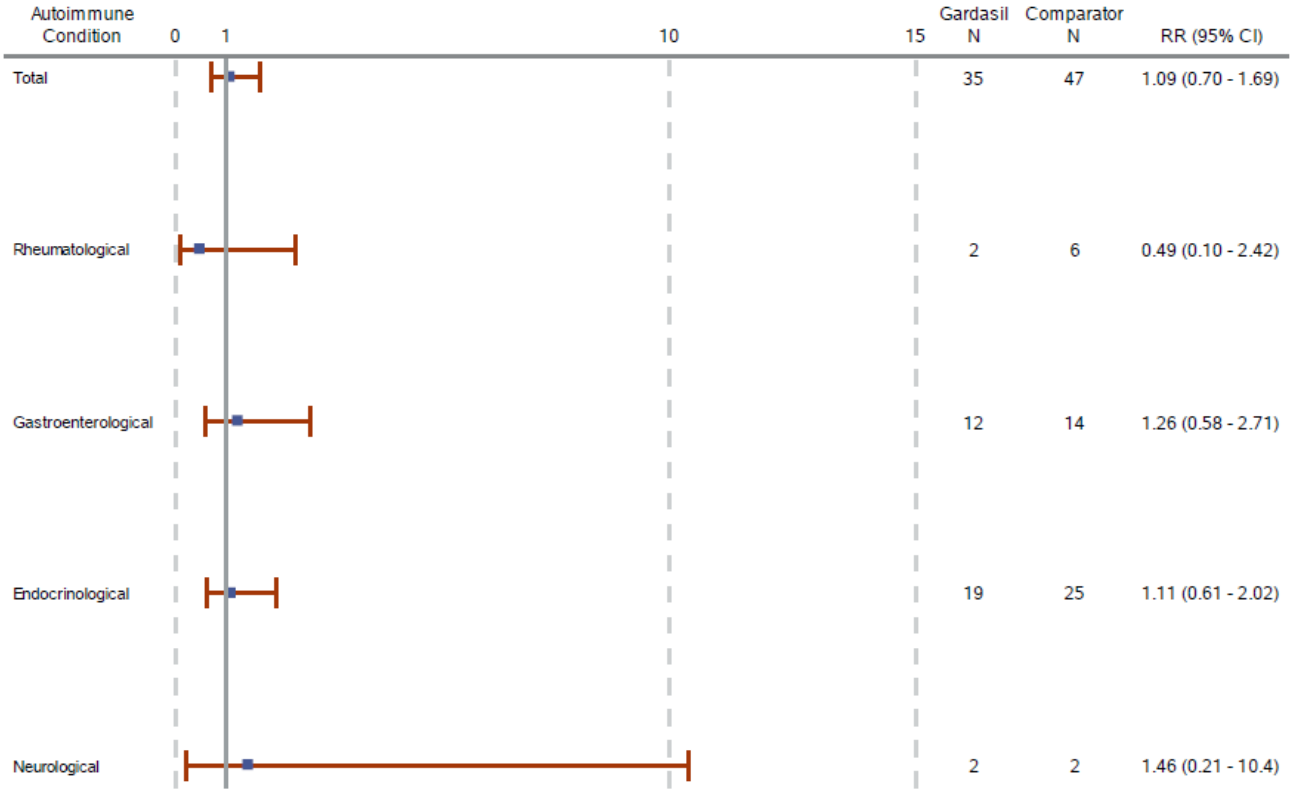
Abbreviations: CI, Confidence Interval; NC, Not Calculated
[a]Accrual 16-OCT-2009 - 31-DEC-2016
[b]Per 1,000 Person-Years
[c]Risk period consists of 6 months after each dose in follow up period
[d]Risk period consists of 18 months after index date (date of healthcare visit)

Summary Figure 1.[a] Relative Rates[b,c] of Medical Chart-Confirmed New-Onset Autoimmune Conditions among Matched Gardasil Recipients and Comparators by Autoimmune Condition Category (Forest Plot)



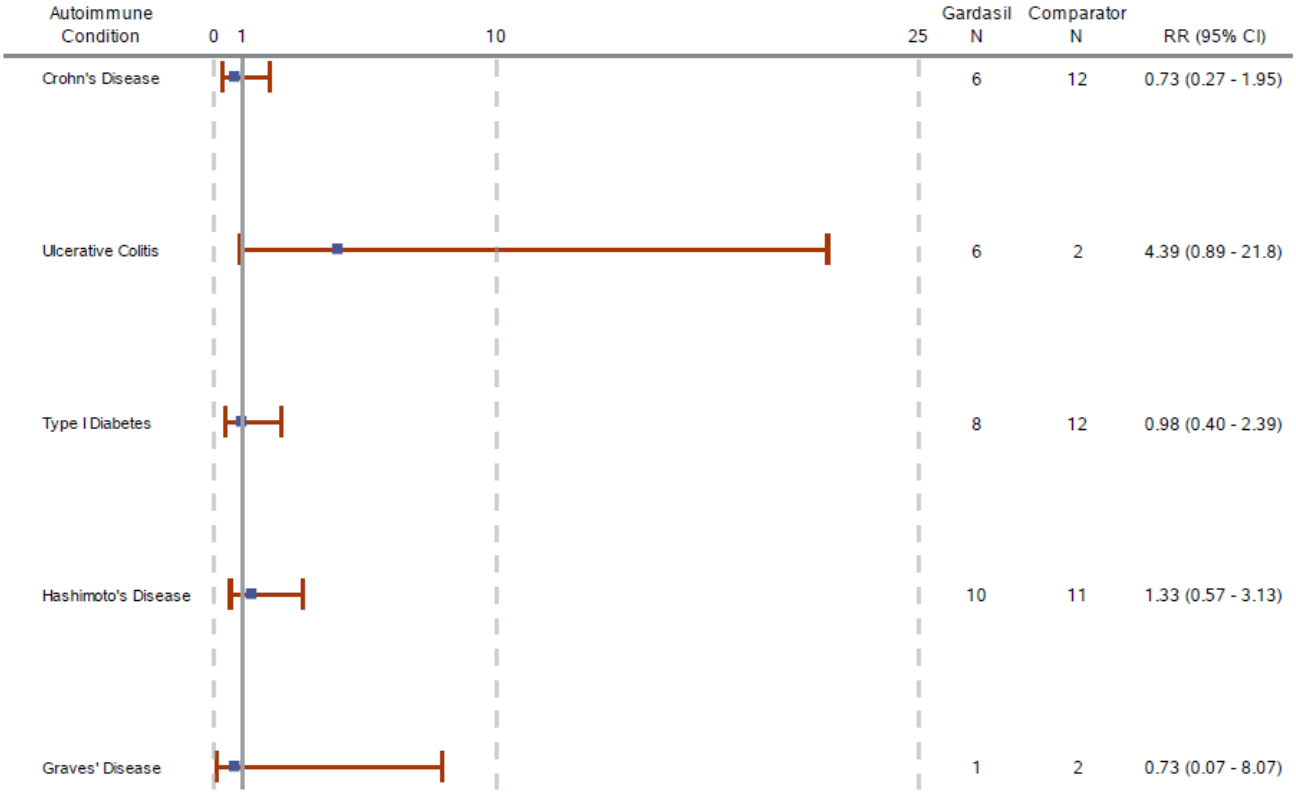
Abbreviations: CI-confidence interval; NC-not calculated.
[a]Accrual 16-OCT-2009 - 31-DEC-2016
[b]Per 1,000 Person-Years
[c]Relative rates calculated as the ratio of the incidence rate of the autoimmune condition among the matched regimen initiators divided by the incidence rate of the autoimmune condition among the matched comparators.

Summary Figure 2.[a] Relative Rates[b,c] of Medical Chart-Confirmed New-Onset Autoimmune Conditions among Matched Gardasil Recipients and Comparators by Autoimmune Condition Category



Abbreviations: CI-confidence interval
[a]Accrual 16-OCT-2009 - 31-DEC-2016
[b]Per 1,000 Person-Years
[c]Relative rates calculated as the ratio of the incidence rate of the autoimmune condition among the matched regimen initiators divided by the incidence rate of the autoimmune condition among the matched comparators.

Summary Figure 3.[a] Relative Rates[b,c] of Medical Chart-Confirmed New-Onset Autoimmune Conditions among Matched Gardasil Recipients and Comparators by Autoimmune Condition



Abbreviations: CI-confidence interval
[a]Accrual 16-OCT-2009 - 31-DEC-2016
[b]Per 1,000 Person-Years
[c]Relative rates calculated as the ratio of the incidence rate of the autoimmune condition among the matched regimen initiators divided by the incidence rate of the autoimmune condition among the matched comparators.

2 LIST OF ABBREVIATIONS

ACIP	Advisory Committee on Immunization Practices
ADEM	Acute disseminated encephalomyelitis
AHA	Autoimmune hemolytic anemia
AIN	Anal intraepithelial neoplasia
AS	Ankylosing spondylitis
CDC	Centers for Disease Control and Prevention
CI	Confidence interval
CPT	Current procedural terminology
CRC	Case Review Committee
DAP	Data analysis plan
FDA	Food and Drug Administration
GBS	Guillain-Barré syndrome
EMA	European Medicines Agency
ER	Emergency room
HCFA	Health Care Financing Agency
HCPCS	Healthcare Common Procedure Coding System
HIPAA	Health Insurance Portability and Accountability Act
HPV	Human papillomavirus
ICD-9	International Classification of Diseases, Ninth Revision
ICD-9-CM	International Classification of Diseases, Ninth Revision, Clinical Modification
ICD-10	International Classification of Diseases, Tenth Revision
ICD-10-CM	International Classification of Diseases, Tenth Revision, Clinical Modification
ITP	Immune thrombocytopenia
IR	Incidence rate
JRA	Juvenile rheumatoid arthritis
KM	Kaplan-Meier
MMWR	Morbidity and Mortality Weekly Report
MS	Multiple sclerosis
NEIRB	New England Institutional Review Board
ORD	Optum Research Database
PHI	Protected health information
RA	Rheumatoid arthritis
RR	Relative rate
SLE	Systemic lupus erythematosus
SOP	Standard operating procedure
SRC	Safety Review Committee
UHC	United HealthCare
US	United States

3 RATIONALE AND BACKGROUND

GARDASIL® is a quadrivalent human papillomavirus (HPV) vaccine manufactured by Merck & Co. Inc. The vaccine was approved in 2006 by the United States (US) Food and Drug Administration (FDA) for the prevention of several diseases caused by HPV types 6, 11, 16, and 18 in females. On 16-October-2009, the US FDA approved GARDASIL® for use in boys and men, 9 through 26 years of age, for the prevention of external genital warts (condyloma acuminata) caused by HPV types 6 and 11. Given by intramuscular injection, the HPV4 3-dose regimen included a second dose 2 months after the first, and a third dose 4 months after the second. In December 2010, the US FDA approved GARDASIL® for use in males and females, 9 through 26 years of age, for the prevention of anal intraepithelial neoplasia (AIN) grades 1, 2, and 3 caused by HPV types 6, 11, 16, and 18, and for the prevention of anal cancer caused by HPV types 16 and 18.

On 21-October-2009 the US Centers for Disease Control and Prevention (CDC) Advisory Committee on Immunization Practices (ACIP) provided guidance that GARDASIL® may be administered to males 9 through 26 years of age to prevent acquisition of genital warts, but at that time, the vaccine was not included in the routine immunization schedule for males.[1] Two years later (25-October-2011), the ACIP recommended routine use of GARDASIL® in males aged 11 or 12 years, as well as to males 13 through 21 years who had either not been vaccinated previously or not completed the 3-dose series. At that time, the ACIP reiterated its permissive vaccination recommendation for males aged 22 through 26 years.[2]

Merck received approval from the US FDA to market GARDASIL®9 (a 9-valent HPV vaccine) on 10-December-2014, for use in females (ages 9-26 years) and males (ages 9-15 years) for prevention of a range of anogenital conditions caused by HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58. This vaccine was subsequently recommended for routine use by ACIP (27-March-2015) in females and males (at ages 11 or 12 years) with the ability to start as young as 9 years or as old as 26 years (females) or 21 years (males).[3] The indication for GARDASIL®9 was extended for use in males 16 to 26 years of age on 14-December-2015. GARDASIL®9 was approved by the US FDA for use as a 2-dose regimen in individuals 9 to 14 years of age on 07-October-2016; in the 2-dose schedule, the second dose should be administered 6 to 12 months after the first dose. In December 2016, ACIP provided new recommendations for use of a 2-dose schedule for those who initiate the vaccine series between the ages of 9 to 14 years, while the 3-dose series is still recommended for those who initiate at or beyond 15 years of age.[4] Starting in May 2017, quadrivalent GARDASIL® has no longer been available

in the US, and has been replaced by GARDASIL®9, but remains available in other parts of the world. GARDASIL®9 has been granted additional indications by the US FDA and extended recommendations by the ACIP after May 2017 but this is beyond the scope of this study.

An observational study of the safety of GARDASIL® in males (Merck Protocol V501-070-01) was conducted by Optum. The study was a post-licensure regulatory commitment to the US FDA following the October 2009 approval of GARDASIL® use in males and was included in the risk management plan for the European Medicines Agency (EMA) and other regulatory agencies. The study includes males who received GARDASIL® in the course of routine clinical care from 16-October-2009 through 31-December-2016 and were followed for study outcomes, including autoimmune conditions through 31-May-2017 (i.e., approximately 5 months from the last potential accrual date). The Final Study Report was submitted to the FDA on 19-June-2019 and to the EMA on 22-June-2019, and included results for general safety for all vaccine doses combined (primary study objective) and 2 of the study's 3 secondary objectives: safety associated with receipt of the first vaccine dose and safety on Day 0 (day of vaccination). This Supplemental Report provides the results of planned analyses for the autoimmune condition outcomes, which is the study's remaining secondary objective.

4 RESEARCH QUESTION AND OBJECTIVES

4.1 Objectives

The primary objective of the main observational safety study was to describe the general safety of GARDASIL® among males within 60 days following the administration of *each dose* of the vaccine by estimating: a) the incidence of health outcomes resulting in emergency room (ER) visits or hospitalizations occurring in the combined 60-day risk periods after each dose of GARDASIL®; and b) the incidence of such health outcomes as compared to incidence in a post-vaccination self-comparison reference period (relative rate [RR]).

The 3 secondary objectives of this study were:

1. To describe the general safety of a *first dose* of GARDASIL® in males;
2. To provide descriptive epidemiology of new onset of 20 pre-specified autoimmune conditions for a period of 6 months after each dose of GARDASIL®, including comparison of incidence of these conditions to background incidence within the male population; and

3. To describe the general safety of GARDASIL® on the day of vaccination (referred to as Day 0).

This Supplemental Report describes the secondary objective related to autoimmune conditions. The occurrence of new-onset of 20 pre-specified autoimmune conditions was identified during a risk window of 6 months after each dose of GARDASIL® from the outpatient, ER, and hospital settings. The incidence of these new-onset autoimmune conditions among male GARDASIL® recipients was compared to background incidence within a male population of similar age distribution (who did not receive GARDASIL®). For ease and clarity of reference, these conditions are collectively referred to as “autoimmune conditions” in this Supplemental Report:

- Rheumatologic/hematologic: immune thrombocytopenia (ITP)*, autoimmune hemolytic anemia (AHA)*, systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), juvenile rheumatoid arthritis (JRA), psoriatic arthritis, ankylosing spondylitis (AS), reactive arthritis;
- Gastroenterologic: Crohn’s disease, ulcerative colitis (UC);
- Endocrinologic: Type 1 diabetes, Hashimoto’s disease, Graves’ disease;
- Neurologic/ophthalmic: multiple sclerosis (MS), acute disseminated encephalomyelitis (ADEM), other demyelinating diseases of the nervous system, Guillain-Barré syndrome (GBS), neuromyelitis optica, optic neuritis, uveitis.

* ITP and AHA, two hematologic conditions, were included into the rheumatologic group.

5 STUDY COMMITTEES

Safety Review Committee (SRC)

Study results were provided for review and interpretation by the SRC, an external committee comprised of 4 experts in adolescent medicine, vaccine safety, autoimmune conditions, and pharmacoepidemiology that was established at the study onset and prior to data analysis. The SRC’s primary responsibility was to review and evaluate the safety data emerging from the study. The SRC had the ability to request and recommend further investigation or additional analyses if the committee determined that a safety signal for any condition was suggested by the data, based on preliminary analysis or review. The SRC also reviewed and approved the

study protocol, data analysis plan (DAP), case review and adjudication procedure, methods used to conduct the study, and the study reports, including this Supplemental Report.

Case Review Committee (CRC)

The Case Review Committees (CRCs) were 4 independent committees of clinicians with expertise relevant to the autoimmune conditions being evaluated (i.e., rheumatologic/hematologic, gastroenterologic, endocrinologic, and neurologic/ophthalmic). The CRCs' primary responsibility was to review redacted medical records (vaccine and protected health information (PHI) was redacted) of potential new-onset cases of autoimmune conditions and to confirm or not the case diagnosis and determine dates of diagnosis and of symptom onset according to the study's pre-specified adjudication procedures.

6 RESEARCH METHODS

This analysis follows the approach described in the Study Protocol 070-01 dated 19-January-2011.

6.1 Study Design

The main safety study was an observational study conducted in a cohort of males who received at least one dose of GARDASIL® as part of routine care in a US health plan. The autoimmune component of the study was conducted as an observational cohort to compare the incidence of new cases of autoimmune conditions among male GARDASIL® recipients and among males who did not receive GARDASIL®. More specifically, the autoimmune study component was conducted in male GARDASIL® recipients of the main safety study who had at least 12 months of health plan membership before receiving their first dose of GARDASIL®. This subcohort, termed the "GARDASIL® cohort" in this Supplemental Report on autoimmune outcome analyses, was matched to a cohort of males who did not receive GARDASIL®, termed the "Comparator cohort". Potential autoimmune outcomes in both the GARDASIL® and comparator cohorts were identified by diagnosis codes, and their diagnosis reviewed and adjudicated by physician specialists to determine if they were new-onset (i.e., newly diagnosed, incident) cases of autoimmune conditions. The incidence rates (IRs) of confirmed new-onset autoimmune outcomes were compared between the two cohorts. Not all males in the GARDASIL® cohort could be matched to comparators, but all autoimmune outcomes in the GARDASIL® cohort are reported, irrespective of whether GARDASIL® recipients were matched to comparators or not.

6.2 Setting

Individuals for this study were drawn from a proprietary research database containing eligibility, pharmacy claims, and medical claims data from a large US health plan (United HealthCare (UHC)) affiliated with Optum. The Optum Research Database (ORD) (formerly known as the Life Sciences Research Database) contains claims and enrollment data dating back to 1993, capturing a longitudinal record of medical services, irrespective of treatment site. In 2017, there were approximately 14.6 million individuals within the database for whom both medical and pharmacy benefit coverage were available. The patient population in the database is geographically diverse across the US and corresponds well to the US population with respect to gender, age distribution less than 65 years of age, and census region. This data source is updated with new claims and enrollment information on a monthly basis.

Within the ORD, type and site of medical encounters may be distinguished using a combination of provider, procedure, and site of care codes. For hospitalizations, claims associated with the health outcomes were identified between the beginning and end dates of a hospitalization. Each hospitalization record contains information on up to 9 ICD-9 or ICD-10 diagnosis codes associated with inpatient services, with the primary diagnosis listed in the first position, and up to 6 procedures recorded with ICD-9 Clinical Modification (ICD-9-CM) and ICD-10 Clinical Modification (ICD-10-CM) procedure codes, current procedural terminology (CPT) codes, or Health Care Financing Agency (HCFA) Common Procedure Coding System (HCPCS) codes. The facility transactions contain each service category that the facility (e.g., hospital) listed on its claim for reimbursement, such as surgeries, radiologic procedures, laboratory tests, room and board charges, or other billed items.

The ORD provides the opportunity to link patient and physician survey data to pharmacy and medical claims, medical record data, socioeconomic measures, and clinical laboratory results. Optum research activities utilize de-identified data from the research database except in limited instances where applicable law allows the use of patient identifiable data.

6.3 Institutional Review Board and Privacy Board Approval

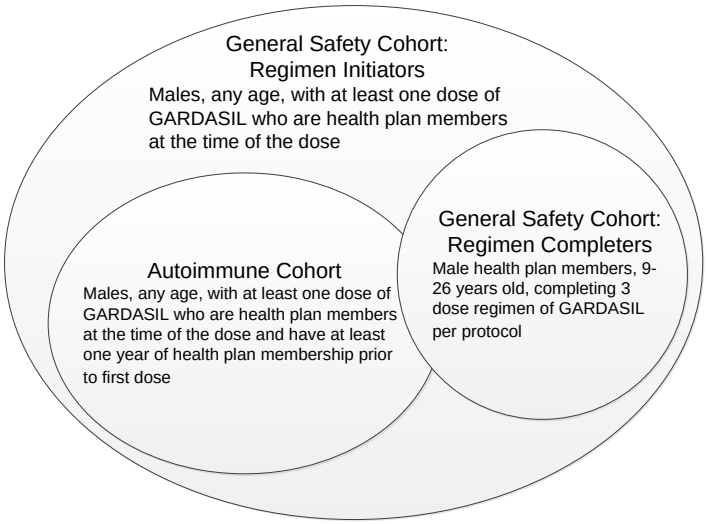
The protocol and data analysis plan (DAP) for this study were approved by the New England Institutional Review Board (NEIRB). A Waiver of Patient Authorization to access medical records for procurement purposes was obtained from The Privacy Board of the NEIRB. Confidentiality of patient records was maintained at all times. Study reports contained

aggregate data and outcome narratives and did not identify individual patients or physicians. At no time during the study did the sponsor receive patient identifying information.

6.4 Subjects

Three main cohorts of GARDASIL® recipients were created in the main safety study. Accrual of study participants took place between 16-October-2009 and 31-December-2016 with follow-up through 31-May-2017. Autoimmune conditions were monitored in the subcohort named "autoimmune cohort" in the protocol and DAP (**Figure A**). In this report, this subcohort is referred to as the "GARDASIL® cohort" for ease of reference.

Figure A. Study Cohorts with Gardasil Use



The cohort named "Autoimmune Cohort" in the above graph is referred to as "GARDASIL® cohort" in this report for ease of reference.

6.4.1 GARDASIL® Cohort

The GARDASIL® cohort was a subset of the main study cohort eligible for autoimmune analyses. It was composed of GARDASIL® recipients identified from the regimen initiator cohort (i.e., males of any age who received at least one dose of GARDASIL® between 16-Oct-2009 and 31-December-2016 and were health plan members at the time of each dose) who also had 12 months of continuous enrollment prior to their first dose (baseline period) of GARDASIL®. The 12-month baseline period was used to identify pre-existing (i.e., prevalent) autoimmune conditions. More specifically, males with any prevalent autoimmune condition in

the 12-month baseline period before receiving their first dose of GARDASIL® were not excluded from the GARDASIL® cohort. Rather, a male with evidence of a pre-existing diagnosis of a given autoimmune condition was excluded from the analyses of that specific autoimmune condition (but not from the analyses of other autoimmune conditions since that male could develop new-onset of another autoimmune condition). Specific to the GARDASIL® cohort, the following exclusion criteria were applied:

- Males with less than 12 months of continuous enrollment prior to their first dose of GARDASIL®; and
- Males with any codes for a given pre-specified autoimmune condition in the baseline period up to and including the day of cohort entry were excluded from the analysis for that specific condition.

6.4.2 Comparator Cohort

The comparator cohort was identified from males enrolled in the health plan concurrently with the GARDASIL® recipients (i.e., between 16-October-2009 and 31-December-2016 with the potential for follow-up through 31-May-2017). The comparator cohort included:

- Any males with a physician office/outpatient visit, as defined by the presence of corresponding CPT codes; and
- A 12-month baseline period (prior to the physician/outpatient visit triggering cohort entry); and
- Complete medical coverage and pharmacy benefits to enhance comparability in access to medical care between the GARDASIL® recipients and the comparators.

The following exclusions were applied to the comparator cohort:

- Any males vaccinated with GARDASIL® during the baseline period; and
- Males with any codes for a given pre-specified autoimmune condition in the baseline period up to and including the day of cohort entry were excluded from the analysis for that specific condition.

Males in the comparator cohort could have received vaccinations other than GARDASIL®. The cohort entry date (also referred to as the index date) for the comparison group was the date of a physician office visit. The distribution of dates of cohort entry for the comparison cohort

were chosen to match the distribution of office visit dates corresponding to the dates of first dose of GARDASIL® for the vaccinated males in the GARDASIL® cohort. If a comparator received a GARDASIL® vaccination after the cohort entry date, the follow-up time for that male was censored as of the date of the GARDASIL® dose and he became eligible as a vaccinated male in the GARDASIL® cohort. To account for variations in vaccine administration schedules, males in the comparator cohort were followed for up to 18 months following cohort entry (corresponding to the maximum potential follow-up among the GARDASIL® recipients - 3 doses with 6 non-overlapping months of follow-up each).

The comparator cohort was propensity-score matched to the GARDASIL® recipients. The comparator cohort was comprised of those selected at random from potential comparators whose propensity score was sufficiently close to each GARDASIL® initiator (matched in a 1:1 ratio) using a greedy match algorithm.[5] Specifically, the algorithm matched GARDASIL® recipients and comparators iteratively, identifying the closest matches first, beginning with estimated propensity score at the 8th decimal point. If a match at the 8th digit is not identified, the algorithm iteratively matches with less precision, decreasing by one decimal point at each iteration down to the 1st decimal point until a match is found. If no matches are found, the GARDASIL® recipient remains unmatched. Separate propensity scores were developed in blocks of calendar time with different variables to accommodate changes over time in patient characteristics of individuals in the GARDASIL® and comparator cohorts. Examples of variables included in the propensity-score model were demographic variables, healthcare utilization variables, and diagnosis and procedure codes. A full list of the variables in the propensity score is included in **Appendix A**. The propensity score was estimated using an unconditional logistic regression model incorporating the predictors of GARDASIL® initiation. A stepwise selection of variables was used to increase model discrimination and to reduce the number of variables included in the model. The stepwise criteria consisted of a *p*-value of 0.2 for model entry and 0.3 for retaining variables. Where consistent with the variable type, binary variables or counts of unique claims were used for inclusion into the propensity-score model. Categorical variables with more than 2 categories were represented by indicator variables.

The propensity-score model indicated a high level of discrimination between individuals in the GARDASIL® and comparator cohorts in each yearly block (2013 c-statistic = 0.957). The c-statistic can range from 0.5 to 1.0 (with higher values indicating greater model discrimination between the groups). This high level of discrimination prompted a re-examination of the codes

selected for the propensity score and subsequent exclusion of codes associated with vaccination for administrative reasons or coding conventions (e.g., procedure codes or diagnostic codes indicating a need for vaccination) for 2014. These codes were identified as having a strong association (RR > 3.0) with vaccination and no plausible direct or indirect causal effect on any study outcome; therefore, including them in the propensity-score model may lead to greater model discrimination (as indicated by a high c-statistic) that reduces available matches without improving confounder control. The 2014 propensity-score model c-statistic was 0.917, reflecting reduced discrimination (and greater availability of matches) by the exclusion of administrative variables, and a similar propensity-score model c- statistics was observed in 2015 (0.909) and 2016 (0.880).

6.5 Variable and Outcome Definitions

6.5.1 Identification of Potential New-Onset Autoimmune Conditions

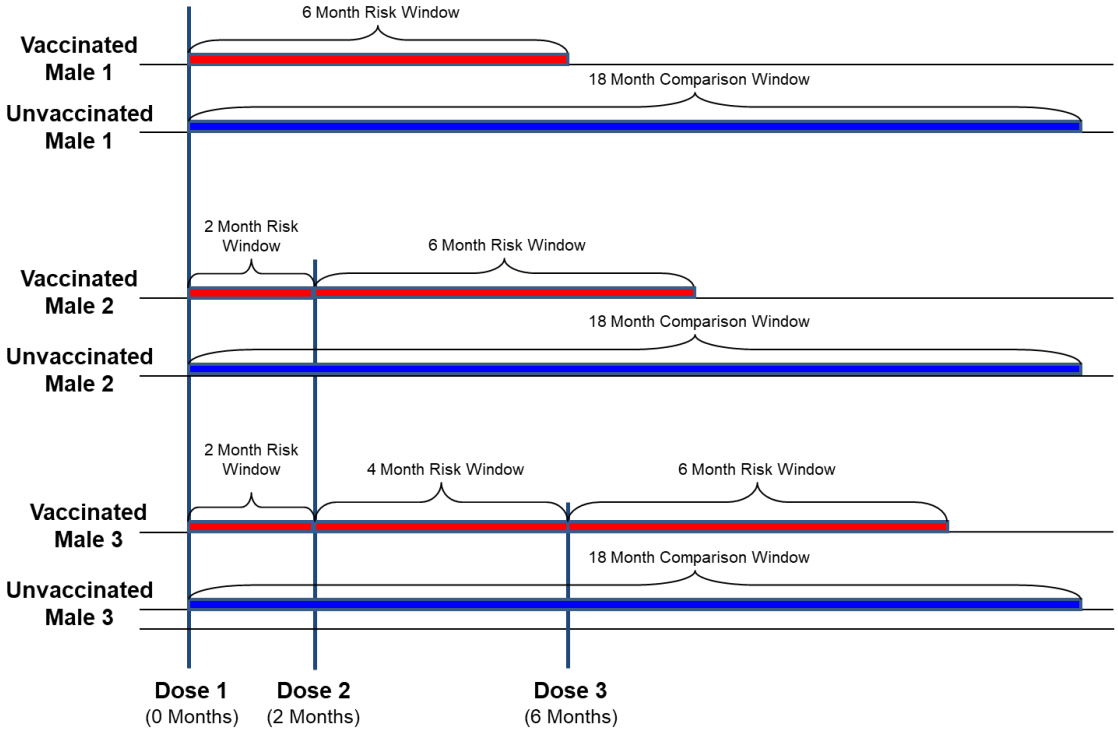
In the ORD database, the 20 pre-specified autoimmune conditions were identified by ICD-9 or ICD-10 (starting on 01-October-2015) diagnosis codes associated with an outpatient visit, ER visit, or hospitalization. Codes for identification of the autoimmune conditions are specified in study manuals, and were reviewed and approved by the CRCs and the SRC. The codes were selected to maximize the sensitivity of initial detection of potential cases in the electronic database. Although a 6-month risk window was utilized in the risk calculation for autoimmune outcomes, all potential autoimmune events occurring up to one year following the receipt of the last dose of GARDASIL® were initially identified from the underlying database to help ensure capture of all outcomes (including those initially identified outside of the 6-month risk windows).

6.6 GARDASIL® Cohort - Risk Period

The risk period used in the GARDASIL® cohort was 6 months following receipt of a GARDASIL® dose and identification of any potential new-onset autoimmune code was conducted within that 6-month risk window following receipt of each dose of GARDASIL®. This 6-month risk window represents the time following vaccination during which symptom onset of a new-onset (i.e., incident) autoimmune condition case could occur, beginning the day after a dose of GARDASIL® and continuing until 183 days (6 months) after a vaccine recipient's dose (**Figure B**). If more than one dose was administered to an individual during the study period, the risk period following each dose was evaluated for diagnosis codes of the specified autoimmune conditions. If there was less than 6 months between the doses, the risk period

associated with the earlier dose was truncated at the subsequent dose. If there was more than 6 months between doses then the risk period associated with the earlier dose was censored at 6 months. The total length of the risk period was the sum of the risk period after each dose and a maximum of 18 months.

Figure B. Risk and Comparison Periods among the GARDASIL® and Comparator cohorts[1]



[1]Figure includes possible scenarios where recipients receive 1, 2, and 3 doses.

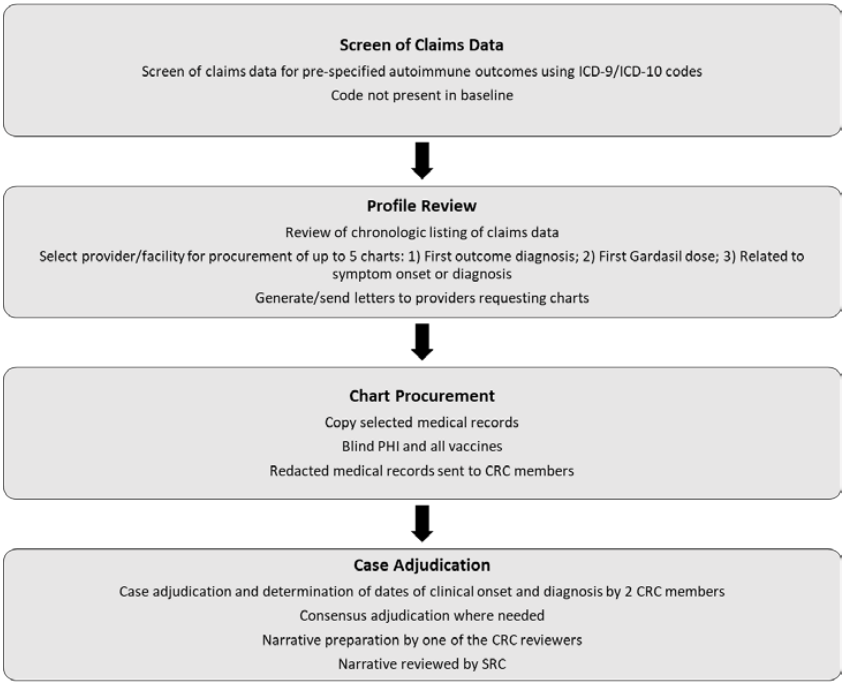
6.7 Comparator Cohort

A propensity-score matched cohort of males not vaccinated with GARDASIL® was identified as a comparison group for the GARDASIL® cohort. **Figure B** represents an illustration of potential follow-up scenarios for the GARDASIL® and comparator cohorts. To account for variations in vaccine administration schedules, males in the comparison cohort were followed for up to 18 months following cohort entry, corresponding to the maximal potential follow-up among the GARDASIL® recipients - 3 doses with 6 non-overlapping months of follow-up each (549 days). If a male in the comparator cohort received a dose of GARDASIL® then the comparison period was censored at the date of vaccination.

6.8 Medical Chart Procurement and Case Adjudication

Following the initial identification of potential cases using diagnostic codes, a pre-specified step-wise process was followed to obtain medical records and adjudicate each case to determine the outcome diagnosis, the date of symptom onset, and the date of outcome diagnosis (**Figure C** and **Appendix M**). The adjudication process was carried out by the CRCs composed of clinicians with expertise in the given autoimmune condition area. There were 4 CRCs utilized (one each for rheumatologic/hematologic, gastroenterologic, endocrinologic, and neurologic/ophthalmic conditions, respectively). Of note, "outcome" is used interchangeably with "autoimmune condition" in this section.

Figure C. Case Identification and Chart Procurement Process



6.8.1 Claims-Profile Review

Following the initial identification of potential new-onset autoimmune conditions based on a screen of the claims data, the electronic claims record for each potential case was examined (claims-profile review). For each potential case, the claims-profile included claims from up to 12 months prior to the cohort entry date through 12 months after the outcome date. For patients with potential outcomes, chronologic listings of their electronic health claims including medical and pharmacy claims were examined by a clinical consultant (a nurse with experience

reviewing claims profiles) in order to determine the medical sites of care most likely to yield medical records with the necessary information for adjudication. For each potential new-onset autoimmune condition, up to 5 medical records from at least 3 different sources were requested: those related to the diagnosis of the condition, to the potential condition onset (i.e., first signs or symptoms suggestive of the condition), and to the first dose of GARDASIL® for the GARDASIL® recipients (or day of the matched physician office visit for the comparators). Additional details of the claims-profile review and medical chart procurement processes are specified in study manuals.

6.8.2 Procurement of Medical Chart Data for Potential Autoimmune Condition Cases

Medical records marked for retrieval during the claims-profile review were sought from healthcare providers to confirm or refute the diagnosis of autoimmune condition outcomes identified electronically. A chart procurement vendor contacted the locations of the patient's care and requested copies of necessary, relevant documents from the medical records such as physician office visit notes, hospital discharge summaries, and laboratory results. The chart procurement vendor reviewed the photocopied records for completeness and redacted PHI and any vaccine information. Electronic photocopies of the redacted medical records were provided to Optum. As a quality control step, Optum staff reviewed a subset of the medical records to ensure the completeness of the records and the redaction of vaccines and PHI. The photocopied redacted medical charts were provided electronically to the CRC members for adjudication. The CRC members conducted their adjudication of the potential autoimmune cases in a manner that was blinded to the GARDASIL® vaccination status.

6.8.3 Case Adjudication

The CRC members reviewed available case medical documentation for potential new-onset autoimmune conditions. For each autoimmune condition, a set of diagnosis criteria was provided to the CRC members as guidance, based on published and professional association guidelines. Using the study- and condition-specific adjudication guidelines provided in the study manuals and their clinical knowledge and judgment, the CRC members adjudicated the diagnosis and determined the date of clinical onset of the condition (i.e., date of first signs or symptoms suggestive of the condition found in the medical record) as well as the date of clinical diagnosis (i.e., first date when the diagnosis was considered likely in the medical records). Each potential new-onset autoimmune case was reviewed independently by 2 CRC adjudicators. Consensus was required if there was disagreement on (1) case status/diagnosis, and/or (2) date of clinical onset, and/or (3) date of diagnosis. If the

adjudicators were unable to reach a consensus, a third CRC member of the same CRC would serve as a tie-breaker. However, a tie-breaker was not needed during the adjudication process for autoimmune conditions.

As a result of the adjudication, each potential case of autoimmune condition was classified as:

1. A confirmed case:
    - If, based on the clinical information in the medical record, the CRC adjudicator determined that the potential case had the autoimmune condition of interest.
2. Not a confirmed case:
    - If the potential case did not have the autoimmune condition of interest. Based on his/her clinical judgment, the adjudicator then provided his/her best assessment of an alternative diagnosis, if available.
3. Insufficient information:
    - If determination of case status was not possible given the available medical chart information. Optum sought additional medical records if available, and provided them to the original 2 members (when possible) for case review.

If, during the adjudication process, the potential case was considered by either of the adjudicators to have one of the alternative autoimmune conditions that was one of the study outcomes, then two analytic checks were performed by Optum to 1) determine if the alternative autoimmune condition of interest was pre-existing, i.e., if there was a diagnosis code(s) for it in the 12-month baseline period; and 2) determine if the alternative autoimmune condition had already been flagged as a stand-alone outcome. If the alternative autoimmune condition was determined to be a pre-existing condition or it was a separate outcome already identified then re-adjudication was not required. If the alternative autoimmune condition was not a pre-existing condition and was not already identified then the alternative autoimmune condition was re-adjudicated by the appropriate CRC.

Optum used the adjudicated date of clinical onset and vaccination date to determine if confirmed new-onset cases occurred during or outside the risk period (for GARDASIL® recipients) or the comparison period (for comparators).

6.8.4 Narratives for Adjudicated Autoimmune Condition Cases

For each potential autoimmune outcome adjudicated, a narrative was prepared by one of the CRC members who reviewed the case, and included relevant information from the subject's medical history as obtained from the medical chart. The data elements included in the autoimmune case narratives were dependent upon an internal Optum data disclosure review and approval.

Following authoring by a CRC member, the narratives were reviewed by a clinical consultant who was not part of any CRC. The objective of this review was to confirm inclusion of important clinical elements in the narrative as well as to verify that the information presented was consistent with clinical expectation, and that the narratives were consistent with relevant case dates provided by Optum. Narratives for each adjudicated case are provided in **Appendix F-I**.

6.9 Statistical Analysis

6.9.1 Demographic Characteristics and Healthcare Utilization Factors

Demographics and baseline attributes (defined using available data from the 12-month baseline period prior to cohort entry) among the GARDASIL® cohort, the matched subset of the GARDASIL® cohort and comparator cohort, and the unmatched subset of the GARDASIL® cohort were tabulated. These characteristics include:

- Demographics (as identified on date of cohort entry)
  - Age category in years [<9, 9-10, 11-12, 13-14, 15-17, 18-20, 21-23, 24-26, >26]
  - Geographic region [Northeast, Midwest, South, West]
  - Duration of preceding continuous health plan membership in months [mean, SD]
- Measures of health care service utilization during the baseline period [mean, SD]
  - Number of 3-digit ICD-9/ICD-10 diagnostic codes (including inpatient and outpatient)
  - Number of outpatient visits (a count of claims coming from a physician that applied specific CPT code (992XX or 993XX) indicating it was an office visit)
  - Number of hospitalizations (a count of claims based on facility claims)
  - Number of days hospitalized (among those with hospitalizations, number of days between the beginning and end dates of a hospitalization)

- Number of preventive medicine outpatient visits (a count of claims from specific CPT, ICD-9 and ICD-10 codes (max 1 per day))
- Number of outpatient primary care or pediatrician physician visits (a count of claims from visits with a provider specialty of family practice, internal medicine or pediatrics (max 1 per day))
- Number of ER visits (a count of claims with ER as the site of service (max 1 per day))
- Number of procedures (a count of claims for surgical procedures (max 1 per day))
- Number of laboratory tests (a count of claims for laboratory tests from CPT codes)
- Total healthcare utilization costs ($US) (the sum of medications, hospital and doctor costs)
- Number of drug classes dispensed (a count of claims based on drug codes)
- Number of all drugs dispensings including unique and refill dispensings (a count of claims based on drug codes)

Annual household income and household net worth measures were identified in the ORD Consumer Database. These income measures were estimated with income models that included multiple sources of data such as national income data, income from consumer survey information, zip code level income, as well as census income distribution data at the state level.

In order to illustrate the length of follow-up of males in the GARDASIL® and comparator cohorts, a Kaplan-Meier (KM) curve for time to disenrollment for the matched GARDASIL® cohort and propensity-score matched comparator cohort was created (**Figure 1**). The curve depicts the time from the index date (date of first dose for GARDASIL® recipients or date of physician office visit for comparators) and the proportion of males remaining enrolled in the health care plan.

6.9.2 Claims-Identified Autoimmune Cases

The number of claims-identified potential new-onset autoimmune cases among the GARDASIL® recipients (matched and unmatched) and the matched comparator cohort were tabulated.

6.9.3 Chart-Confirmed Autoimmune Cases

Following receipt of medical records and adjudication, the number of chart-confirmed cases were tabulated. The confirmation fraction was estimated (number of confirmed cases / number of adjudicated cases) overall, by condition category (rheumatologic/hematologic, gastroenterologic, endocrinologic, neurologic/ophthalmic), and for the individual autoimmune conditions.

For the autoimmune chart-confirmed cases among all GARDASIL® recipients in the GARDASIL® cohort and propensity-score matched comparators, bar graphs were created depicting the number of days since most recent vaccination (or index date for matched comparators) to the date of clinical onset as determined by the clinical adjudicators. Plots were created separately for each autoimmune outcome within the separate condition groups: rheumatologic/hematologic, gastroenterologic, endocrinologic, neurologic/ophthalmic. Median age at onset, median number of days from most recent dose and from the first dose (or index date for comparators) to date of clinical onset were also calculated.

6.9.4 Incidence Rates

Incidence rates (IRs) of chart-confirmed autoimmune outcome cases were estimated among the matched GARDASIL® recipients in the GARDASIL® cohort and compared to the matched comparators using the adjudicated clinical onset date as the outcome date. Corresponding 95% confidence intervals (CIs) were calculated for IRs using Poisson regression. To calculate IRs (number of confirmed events/1,000 person-years), all eligible days in each risk and comparison period were summed separately for the matched GARDASIL® cohort and for the comparator cohort, respectively. Censoring of person-time occurred upon receipt of GARDASIL® among individuals in the comparator cohort, disenrollment from the health plan, death, occurrence of the new-onset autoimmune outcome of interest, or if the risk period overlapped with the end of the study. Incidence rates are presented for all autoimmune conditions combined using cases identified across healthcare settings (outpatient, ER, and inpatient settings combined), by outcome category (rheumatologic/hematologic, gastroenterologic, endocrinologic, neurologic/ophthalmic) and by individual autoimmune conditions.

Cases designated as “insufficient information” were classified as non-cases (i.e., not confirmed cases).

6.9.5 Relative Rates

For the matched GARDASIL® recipients and the matched comparators, relative rates (RRs) of each new-onset autoimmune condition within 6 months (Day 0-183) after receipt of any dose of GARDASIL® were estimated based on confirmed new-onset cases. The RRs (IRs in the matched GARDASIL® cohort divided by IR in the comparator cohort) and 95% CIs were calculated. Plots of the RRs for the confirmed new-onset autoimmune outcomes are presented overall, by autoimmune condition category (rheumatologic/hematologic, endocrinologic, gastroenterologic, and neurologic/ophthalmic), and by individual autoimmune condition when available. Given the close matching accomplished by the propensity-score method, additional statistical adjustment of RRs was determined not to be needed and unadjusted RRs are presented.

6.9.6 Other Analyses

Although a 6-month risk window was utilized in the risk calculation for autoimmune outcomes, all potential autoimmune events occurring (during health plan enrolled period) up to one year following the receipt of the third dose of GARDASIL® were initially identified and adjudicated to help ensure capture of all outcomes (including those initially identified outside of the 6-month risk windows). Among the chart-confirmed autoimmune cases with symptom onset within the 6-month risk windows, the proportion with a diagnosis claim within 6 months only as compared to those with a claim more than 6 months following the date of vaccination was calculated overall and separately by autoimmune condition category (rheumatologic/ hematologic, endocrinologic, gastroenterologic, and neurologic/ophthalmic).

SAS version 9.4 (SAS Institute, Cary, NC) was used for all analyses.

7 PRIVACY AND CONFIDENTIALITY

Confidentiality of individual records was maintained at all times. All analyses were performed in accordance with applicable laws and regulations. This Final Report contains aggregate results and outcome narratives and does not identify individuals or physicians. The Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule [45 CRF 164.512(i)(2)] permits protected health information (PHI) to be used or disclosed for research, without individual authorization if certain criteria are met. At no time during the study did Merck, the CRCs, or the SRC receive data that was considered to provide identifying information.

8 QUALITY ASSURANCE

The study was carried out according to Optum's internal procedures that are consistent with the International Society for Pharmacoepidemiology's Guidelines for Good Pharmacoepidemiology Practices (http://www.pharmacoepi.org). In particular, the internal procedures in place at Optum specify that processes and deliverables are documented, reviewed, and validated in sufficient detail to allow for subsequent re-examination or replication.

9 RESULTS

9.1 Participants

Among the 114,035 males vaccinated with GARDASIL® in the main safety study, Optum identified 65,606 males in the subcohort eligible for the autoimmune analyses (the "GARDASIL® cohort") who received at least one dose of GARDASIL®, including 38,347 males who received at least 2 doses of GARDASIL®, and 21,518 males who received at least 3 doses of GARDASIL® for a total of 125,471 doses (**Table 1**). The majority of males (89%) received the first dose between 11 to 18 years of age. Of the 65,606 males in the GARDASIL® cohort, 55,670 (85%) were propensity-score matched to an equal number (n=55,670) of comparators (males with a physician visit at which they did not receive GARDASIL®). Among the matched GARDASIL® recipients, a total of 104,763 doses were received (data not shown). Overall, 39,735 and 58,215 person-years of follow-up were accrued among matched GARDASIL® recipients and matched comparators, respectively.

9.2 Demographic Characteristics Among Matched and Unmatched Cohorts

Characteristics were measured in the 12-month baseline period and they are presented for all individuals in the GARDASIL® and comparator cohorts, matched GARDASIL® and comparator cohort members, and the unmatched GARDASIL® cohort members (**Table 2**). After matching, the distribution of age, geographic region, health plan membership, drugs dispensed, number of hospitalizations, number of procedures, health care visits and healthcare costs were similar among the GARDASIL® recipients and comparators. Compared to the matched GARDASIL® recipients, the demographic characteristics among unmatched GARDASIL® recipients were similarly distributed. However, the proportion of males ages 11 or 12 years was lower in the unmatched subset of GARDASIL® recipients compared to the matched GARDASIL® recipients (9.71% vs 28.65%) and lower in the oldest age category (> 26 years) (0.02% vs 1.01%).

9.3 Healthcare Utilization and Health Plan Enrollment Among Matched Cohorts

Healthcare utilization factors and socioeconomic status (SES) measures (annual household income and net worth) were measured in the 12-month baseline period (**Table 3**). The mean number of physician visits, ER visits, hospitalizations, procedures, laboratory tests, total health care costs, and number of drugs dispensed were similar among the matched cohorts. The GARDASIL® recipients had a slightly higher number of mean hospitalization days as compared to the matched comparators (6.18 versus 5.54 days). The distribution of annual household income and net worth was similar among the matched GARDASIL® recipients and comparators.

To explore the duration of health plan enrollment among the matched GARDASIL® recipients and matched comparators, a Kaplan-Meier (KM) curve was constructed (**Figure 1**) and includes the time in months from cohort entry date through disenrollment from the health plan or censoring at the end of the study period, and percent remaining enrolled in the health plan. Among GARDASIL® recipients, 67% remained in the health plan 12 months after the first dose; 47% remained for 24 months; 34% remained for 36 months; and 25% remained for 48 months. Similar proportions were observed for the matched comparators at 12 (64%), 24 (45%), 36 (34%), and 48 (27%) months.

9.4 Autoimmune Condition Identification and Case Adjudication

A summary of potential new-onset autoimmune conditions by adjudication outcome among matched GARDASIL® and comparator cohort members is provided in **Table 4** (background data provided in **Appendices C-D** and **J-L**). Detailed summaries of the adjudication outcomes of potential new-onset autoimmune conditions for all members of the GARDASIL® cohort (matched and unmatched) are provided in **Appendix B** and **Appendix J**. Confirmation fractions are included in **Appendix E**. Following adjudication, for each claims-based potential autoimmune outcome case, a narrative was prepared by one of the CRC members who reviewed the case (irrespective of the adjudication outcome, i.e., confirmed, not confirmed or insufficient information). The narratives are included in **Appendices F-I**.

A total of 490 potential new-onset claims-based autoimmune cases were identified among all members of the GARDASIL® cohort, 416 and 74 among the matched and unmatched GARDASIL® recipients respectively (**Table 4** (background data provided in **Appendix B**)). Among individuals in the matched comparator cohort, 373 were identified with potential new-onset autoimmune cases. Medical records were obtained for 85% of the potential autoimmune

cases among the GARDASIL® recipients (86% and 82% among the matched and unmatched recipients, respectively) and 84% among the matched comparators.

Following adjudication, there were 96 confirmed cases in the GARDASIL® cohort, including 76 among the matched GARDASIL® recipients and 20 among the unmatched GARDASIL® recipients. Among the matched comparators, there were 65 confirmed cases. The case confirmation fraction among potential cases with medical records received was 23% (96/418) for all GARDASIL® recipients (21% and 33% among the matched and unmatched recipients, respectively) and 21% (65/310) among the matched comparators (**Appendix E**).

Following case confirmation, it was determined whether confirmed new-onset cases had a date of symptom onset occurring during the risk window for GARDASIL® recipients (within 6 months following receipt of a vaccine dose) and during the comparison window for matched comparators (within 18 months following cohort entry). Overall, there were 35 confirmed new-onset cases within the risk window among the matched GARDASIL® recipients, and 47 confirmed new-onset cases within the comparison window among the comparators (**Table 4**). In addition, of the 20 confirmed cases among the unmatched GARDASIL® recipients, it was determined that 11 were confirmed new-onset cases within the risk window (3 Crohn's disease, 3 Hashimoto's disease, and one of each Type 1 diabetes, Graves' disease, MS, ON, and RA cases) (details provided below with each condition group).

Rheumatologic/Hematologic Conditions

A total of 144 potential new-onset rheumatologic/hematologic claims-based autoimmune cases were identified in the GARDASIL® cohort, including 118 among the matched GARDASIL® recipients (**Table 4** (background data provided in **Appendix B** and **Appendix E**)). Medical records were obtained for 83% (119/144) of the potential autoimmune cases among GARDASIL® recipients, including 85% (n=100) of the matched GARDASIL® recipients.

Following adjudication, there were 14 confirmed cases among the GARDASIL® recipients, including 11 among the matched GARDASIL® recipients. Among the matched GARDASIL® recipients potential cases with medical records received, the confirmation fraction was 11% (11/100). Of the 11 confirmed cases, 2 were confirmed as new-onset and within the risk window (one case of SLE and one case of AS). No cases of ITP, AHA, RA, psoriatic arthritis, or reactive arthritis were confirmed as new-onset. There were 9 confirmed rheumatologic cases that were not within the risk window.

A total of 96 potential new-onset rheumatologic/hematologic claims-based autoimmune cases were identified among the matched comparators (**Table 4** and more details in **Appendix D**). Medical records were obtained for 85% (n=82) of them. There were 10 confirmed cases among the matched comparators with medical information available, for a confirmation fraction of 12% (10/82). No cases of AHA, SLE, RA, psoriatic arthritis, AS, or reactive arthritis were confirmed as new-onset in the comparison window. During the adjudication process, it was noted that one case reviewed for potential RA had an alternative diagnosis of potential JRA, and the CRC determined that it was new-onset JRA; that JRA case was within the comparison window. Of the 10 confirmed cases, 6 were confirmed as new-onset and within the comparison window (3 ITP cases and 3 JRA cases). There were 4 confirmed cases that were not within the comparison window.

A total of 26 potential new-onset rheumatologic/hematologic claims-based autoimmune cases were identified among the unmatched GARDASIL® recipients (data not shown). Medical records were obtained for 73% (n=19) of them. There were 3 rheumatologic/hematologic confirmed new-onset cases among the unmatched GARDASIL® recipients with medical information available (2 cases of RA and one case of ITP). Only one of the 3 confirmed cases was within the risk window (a case of RA).

For rheumatologic/hematologic conditions, a similar pattern of the distribution of time from most recent dose (or the index date) to clinical onset was observed for all GARDASIL® recipients and the comparators (**Figure 2A**). The median time from index date to clinical onset for the chart-confirmed cases among the matched GARDASIL® recipients was 147 days (range 130-164) (data not shown). The median time from index date to clinical onset for the chart-confirmed cases among the matched comparators was 137 days (range 64-535) (data not shown).

Gastroenterologic Conditions

A total of 58 potential new-onset gastroenterologic claims-based autoimmune cases were identified in the GARDASIL® cohort, including 48 among the matched GARDASIL® recipients (**Table 4** and more details in **Appendix B** and **Appendix E**). Medical records were obtained for 88% (51/58) of the potential autoimmune cases among GARDASIL® recipients, including 88% (n=42) among the matched GARDASIL® recipients.

Following adjudication, there were 30 confirmed cases among the GARDASIL® recipients, including 24 among the matched GARDASIL® recipients. Among the matched GARDASIL® recipients potential cases with medical records received, the case confirmation fraction was 57% (24/42). During the adjudication process, it was noted that two cases of potential Crohn's disease had an alternative diagnosis of potential ulcerative colitis (UC). The CRC confirmed both UC conditions, although only one was new-onset within the risk window. Of the 24 confirmed cases, 12 were confirmed as new-onset and within the risk window. There were 12 confirmed cases that were not within the risk window.

A total of 38 potential new-onset gastroenterologic claims-based autoimmune cases were identified among the matched comparators (**Appendix D**). Medical records were obtained for 87% (n=33) of them. Overall, 21 of the 33 potential cases (64%) with medical information available were confirmed among the matched comparators. Of the 21 confirmed cases, 14 were confirmed as new-onset and within the comparison window (12 Crohn's disease and 2 UC). There were 7 confirmed cases that were not within the comparison window.

A total of 10 potential new-onset gastroenterologic claims-based autoimmune cases were identified among the unmatched GARDASIL® recipients (data not shown). Medical records were obtained for 90% (n=9) of the potential cases. There were 6 gastroenterologic confirmed new-onset cases among the unmatched GARDASIL® recipients (3 cases of Crohn's disease and 3 cases of UC). Three of the 6 confirmed cases were within the risk window (3 cases of Crohn's disease).

For gastroenterologic conditions, a similar pattern of the distribution of time from most recent dose (or the index date) to clinical onset was observed for GARDASIL® recipients and the comparators (**Figure 2B**). The median time from index date to clinical onset for the chart-confirmed cases among the matched GARDASIL® recipients was 168 days (range 37-596) (data not shown). The median time from index date to clinical onset for the chart-confirmed cases among the matched comparators was 220 days (range 21-451) (data not shown).

Endocrinologic Conditions

A total of 183 potential new-onset endocrinologic claims-based autoimmune cases were identified in the GARDASIL® cohort, including 159 among the matched GARDASIL® recipients (**Table 4** with more details in **Appendix B** and **Appendix E**). Medical records were obtained

for 83% (152/183) of the potential autoimmune cases among GARDASIL® recipients, including 82% (n=131) among the matched GARDASIL® recipients.

After adjudication, there were 48 confirmed cases among the GARDASIL® recipients, including 39 among the matched GARDASIL® recipients. Among the matched GARDASIL® recipients potential cases with medical records received, the confirmation fraction was 30% (39/131). During the adjudication process, it was noted that one case of potential Graves' disease had an alternative diagnosis of potential Hashimoto's disease, but the CRC determined that there was insufficient information to adjudicate the Hashimoto's outcome. Of the 39 confirmed cases among the matched GARDASIL® recipients with medical information available, 19 were confirmed as new-onset and within the risk window (8 Type 1 diabetes, 10 Hashimoto's disease, and 1 Graves' disease). Twenty confirmed cases were not within the risk window.

A total of 134 potential new-onset endocrinologic claims-based autoimmune cases were identified among the matched comparators (**Table 4** with more details in **Appendix D**). Medical records were obtained for 81% (n=109) of them. Among the matched comparators with medical information available, 29% (32/109) of the potential cases were confirmed. During the adjudication process, it was noted that two cases of potential Graves' disease had an alternative diagnosis of potential Hashimoto's disease. The CRC confirmed both Hashimoto's outcomes, although only one was new-onset within the comparison window. Of the 32 confirmed cases, 25 were confirmed as new-onset and within the comparison window (12 Type 1 diabetes, 11 Hashimoto's disease, and 2 Graves' disease). Seven confirmed cases were not within the comparison window.

A total of 24 potential new-onset endocrinologic claims-based autoimmune cases were identified among the unmatched GARDASIL® recipients (data not shown). Medical records were obtained for 88% (n=21) of the potential cases. There were 9 endocrinologic confirmed new-onset cases among the unmatched GARDASIL® recipients with medical information available (2 cases of Type 1 diabetes, 2 cases of Graves' disease, and 5 cases of Hashimoto's disease). Five of the 9 confirmed cases were within the risk window (one case of Type 1 diabetes, one case of Graves' disease, and 3 cases of Hashimoto's disease); 4 confirmed cases were not within the risk window.

For endocrinologic conditions, a similar pattern of the distribution of time from most recent dose (or the index date) to clinical onset was observed for all GARDASIL® recipients and the comparators (**Figure 2C**). The median time from index date to clinical onset for the chart-confirmed cases among the matched GARDASIL® recipients was 124 days (range 1-508) (data not shown). The median time from index date to clinical onset for the chart-confirmed cases among the matched comparators was 239 days (range 2-528) (data not shown).

Neurologic/Ophthalmic Conditions

A total of 105 potential new-onset neurologic claims-based autoimmune cases were identified in the GARDASIL® cohort, including 91 among the matched GARDASIL® recipients (**Table 4** and more details in **Appendix B** and **Appendix E**). Medical records were obtained for 91% (96/105) of the potential autoimmune cases among GARDASIL® recipients, including 92% (n=84) among the matched GARDASIL® recipients.

Following adjudication, there were 4 confirmed cases among the GARDASIL® recipients, including 2 among the matched GARDASIL® recipients. Among the matched GARDASIL® recipients potential cases with medical records received, 2% (2/84) were confirmed. During the adjudication process, it was noted that one case of potential other demyelinating diseases of the nervous system had an alternative diagnosis of potential MS, and the CRC confirmed that it was new-onset; the case was within the risk window. Of the 2 confirmed cases (both MS), both were confirmed as new-onset and within the risk window. No cases of ADEM, other demyelinating diseases of the nervous system, GBS, neuromyelitis optica, optic neuritis, or uveitis were confirmed as new-onset and in the risk window among matched GARDASIL® recipients.

A total of 105 potential new-onset neurologic claims-based autoimmune cases were identified among the matched comparators (**Table 4** and more details in **Appendix D**). Medical records were obtained for 82% (n=86) of them. Overall, 2 of 86 potential cases with medical information available (2%) were confirmed (both uveitis). Of the 2 confirmed cases of uveitis, both were confirmed as new-onset and within the comparison window. No cases of MS, ADEM, other demyelinating diseases of the nervous system, GBS, neuromyelitis optica, or optic neuritis were confirmed as new-onset among the matched comparators.

A total of 14 potential new-onset neurologic claims-based autoimmune cases were identified among the unmatched GARDASIL® recipients (data not shown). Medical records were

obtained for 86% (n=12) of the potential cases. There were 2 neurologic confirmed new-onset cases among the unmatched GARDASIL® recipients (one case of MS and one case of optic neuritis), and both were within the risk window.

A similar pattern of the distribution of time from most recent dose (or the index date) to clinical onset was observed for all GARDASIL® recipients and the comparators for neurologic conditions (**Figure 2D**). The median time from index date to clinical onset for the chart-confirmed cases among the matched GARDASIL® recipients was 181 days (range 133-228) (data not shown). The median time from index date to clinical onset for the chart-confirmed cases among the matched comparators was 162 days (range 144-179) (data not shown).

Other Analyses

Among the chart-confirmed autoimmune cases with symptom onset within risk window in the matched GARDASIL® recipients, 83% had a claim indicating the diagnosis within 6 months (the risk window) while the remaining 17% had a first diagnosis code more than 6 months following the date of vaccination. By condition category, among confirmed new-onset cases with onset of symptoms within the 6-month risk window following receipt of a dose of GARDASIL®, 50% of confirmed rheumatologic cases, 83% of gastroenterologic cases, 84% of endocrinologic cases, and 100% of neurologic cases had a claim indicating the diagnosis claim within the 6-month risk window.

9.5 Incidence and Relative Rates of Autoimmune Conditions

There were 55,670 matched GARDASIL® recipients who accrued 39,735 person-years and 55,670 matched comparators who accrued 58,215 person-years (**Table 5**). Analyses were conducted on all chart-confirmed cases within the risk window (35 individuals in the matched GARDASIL® cohort and 47 in the matched comparator cohort) and by condition category: rheumatologic/hematologic (2 chart-confirmed cases in the GARDASIL® recipients and 6 in the comparators); gastroenterologic (12 chart-confirmed cases in the GARDASIL® recipients and 14 in the comparators); endocrinologic (19 chart-confirmed cases in the GARDASIL® recipients and 25 in the comparators); and neurologic (2 chart-confirmed cases in the GARDASIL® recipients and 2 in the comparators).

For all matched chart-confirmed cases combined, the observed IR was 0.88 per 1,000 person-years (95% CI 0.61-1.23) in the GARDASIL® recipients and 0.81 (95% CI 0.59-1.07) in the matched comparators (**Table 5**). For the matched GARDASIL® recipients and comparators

respectively, the IRs (per 1000 person-years) of chart-confirmed cases by condition category were: for rheumatologic conditions 0.05 (95%CI 0.01-0.18) versus 0.10 (95% CI 0.04-0.22); for gastroenterologic conditions 0.30 (95%CI 0.16-0.53) versus 0.24 (95% CI 0.13-0.40); for endocrinologic conditions 0.48 (95%CI 0.29-0.75) versus 0.43 (95% CI 0.28-0.63); and for neurologic conditions 0.05 (95%CI 0.01-0.18) versus 0.03 (95% CI 0.00-0.12).

The RR for all confirmed new-onset autoimmune conditions combined was 1.09 (95% CI 0.70-1.69) (**Table 5** and **Figures 3A-C**). The estimated RRs by autoimmune category were: rheumatologic/hematologic (RR 0.49, 95% CI 0.10-2.42); gastroenterologic (RR 1.26, 95% CI 0.58-2.71); endocrinologic (1.11, 95% CI 0.61-2.02); and neurologic/ophthalmic (RR 1.46, 95% CI 0.21-10.40). Lastly, the RRs for individual autoimmune conditions were: Crohn's disease (RR 0.73, 95% CI 0.28-1.95); UC (RR 4.39, 95% CI 0.89-21.77); Type I diabetes (RR 0.98, 95% CI 0.40-2.39); Hashimoto's disease (RR 1.33, 95% CI 0.57-3.14); and Graves' disease (RR 0.73, 95% CI 0.07-8.07). When the number of confirmed cases was zero in either the matched GARDASIL® recipients or comparators, the RR was not calculated.

10 DISCUSSION

Using a US commercial health insurance claims database, this study assessed and reviewed all potential autoimmune cases with available medical records among males following vaccination with GARDASIL® during routine clinical care and among an equal number of males not vaccinated with GARDASIL®. This study observed no difference in the incidence of new-onset of 20 pre-specified autoimmune conditions among males in the GARDASIL® cohort and males in a matched comparator cohort. Although this study was large, some autoimmune conditions had few or no outcomes, resulting in IR & RR estimates with wide confidence intervals reflecting limited power to assess differences in risk for the rarest conditions. However, the point estimates for the incidence rates generated from this study are consistent with other large observational studies measuring the relationship of GARDASIL® use with the development of specific autoimmune conditions.

Regarding the analysis of individual autoimmune conditions, three conditions (Crohn's disease, Type 1 diabetes, and Graves' disease) had RR point estimates below 1, and two conditions (ulcerative colitis and Hashimoto's disease) had RR point estimates greater than 1; for all 5 conditions, the RR 95% CIs included 1.0, suggesting that the findings were consistent with a null association. Details on ulcerative colitis and Hashimoto's disease, the 2 conditions with slightly elevated RRs, are discussed below. In addition, there were 2 cases of

MS in the matched GARDASIL® cohort and none in the comparator cohort, which is also discussed, although an RR could not be calculated.

The non-significant increase in the RR of UC observed in this study is consistent with two other large population-based studies looking at the relationship of GARDASIL® vaccination with autoimmune conditions. A population-based study of males in Olmsted County, Minnesota reported an age-specific adjusted IR of UC of 5.2 to 12.9 cases per 100,000 person-years, which was similar to incidence rates of 0.03 and 0.15 per 1,000 person-years among GARDASIL® recipients and comparators observed in the current study.[6] A national population-based safety study of GARDASIL® among males 10 to 17 years of age in Denmark found no significant risk for the autoimmune conditions assessed, including UC (RR 0.68, 95% CI 0.30-1.15) or Crohn's disease (RR 0.63, 95% CI 0.28-1.41) associated with GARDASIL® administration.[7] In addition, a retrospective cohort study of girls aged 12 to 17 years in Ontario found no association between UC and vaccination (RR 0.23, 95% CI 0.05-1.03).[8]

The incidence rate of Hashimoto's disease, a common autoimmune condition among young males and adolescents, was slightly higher among GARDASIL® recipients vs comparators, resulting in a non-significant RR of 1.33, 95% CI 0.57-3.14. Similar non-significant differences in the incidence of this condition have been found previously in a population-based safety study of GARDASIL® administration among boys in Denmark which found no association between GARDASIL® vaccination and hypothyroidism (RR 1.77, 95% CI 0.73-4.31).[7] That study observed 5 Hashimoto's events over 24,115 person-years of follow-up time among vaccinated individuals, for a crude IR of 0.21 per 1,000 person-years, which is similar to the estimate in the current study (0.25 cases per 1,000 person-years). In addition, a safety study of GARDASIL® administration in women 9 to 26 years of age reported an elevated incidence rate ratio for Hashimoto's disease which was not confirmed as a safety signal after further investigation, based on a lack of consistent evidence of the timing of disease onset in relation to vaccination timing, potential cases possibly pre-existing, and no consistent elevated incidence of autoimmune thyroid conditions in the vaccinated cohort.[9]

There were 2 MS outcomes that were adjudicated as confirmed outcomes among the matched GARDASIL® recipients and none among the matched comparators, and as such, a RR was not calculated. The IR of MS in the current study (0.05 per 1,000 person years) is consistent with the incidence reported in an observational safety study of GARDASIL® in females.[9] In that study, the authors reported the incidence of MS as 3.4 per 100,000 person-years. Three

recent reviews evaluated the role of HPV vaccines on risk of MS and also found no association. First, in a systematic review of HPV vaccination and MS, the authors found no significant association between the two.[10] Second, a meta-analysis of 6 observational studies among females reported a non-significant pooled odds ratio of 0.98.[11] Lastly, a meta-analysis and systematic review of 22 post-licensure observational studies among females found no significant association between GARDASIL® and risk of MS (pooled odds ratio 0.96).[12]

Strengths

This post-licensure safety study included a large number of males who received GARDASIL® as part of routine clinical care in the US and examined the subsequent risk of several autoimmune conditions. A concurrent cohort of matched males who did not receive GARDASIL® was used as a comparator to put the IRs of confirmed cases of new-onset autoimmune conditions into context. The propensity-score matching served to reduce differences between GARDASIL® recipients and comparators that might confound the association between GARDASIL® and the autoimmune conditions. As a result, any proposed alternate explanation for the observed lack of association would need to also explain how it could operate in the face of so many variables that were well balanced between the cohorts. The concurrent matched comparator cohort that was used provided additional control of potential changes in diagnostic and treatment modalities over calendar time.

The autoimmune analysis utilized a rigorous case detection, review and adjudication process designed to maximize both the sensitivity of case detection in the electronic healthcare database and the specificity of confirmation of case status and timing of autoimmune symptom onset and clinical diagnosis. A sensitive screening approach that used a wide range of diagnosis codes was applied to maximize the identification of individuals with potential autoimmune conditions during study follow-up. Following this initial broad screen, up to 5 medical records were sought for each potential case from a variety of healthcare sources including the individual's primary care provider as well as specialists in order to maximize the breadth and scope of clinical information available for case adjudication. Following medical record retrieval, each potential case was reviewed independently by two clinician specialists with distinct backgrounds and training relevant to the outcome to confirm both the diagnosis and the date of clinical onset, following pre-specified adjudication procedures. The clinical adjudication was guided by a set of diagnosis criteria that was provided to the CRC members.

These diagnosis criteria were derived from published and professional association guidelines. This case review process underwent extensive validation and testing over the course of the study.

The study design accommodated substantial lag time (up to several years) between clinical onset of a potential autoimmune outcome and clinical recognition of the diagnosis that might lead to the assignment of a code reflecting the diagnosis. This was important since some of the autoimmune conditions of interest could take several months or even years to be diagnosed. Finally, the source database is geographically diverse across the US and corresponds well to the US population with respect to gender, age distribution, and census region, so that the results represent the routine care of a broadly distributed population of males vaccinated with GARDASIL®.

Limitations

The study design aimed to address certain limitations of the use of healthcare claims databases. This study involved the description and follow-up of individuals who received GARDASIL® (and matched comparators) in routine patient care settings, and reflects the interactions between patients and the health care system represented by transactions for payment of services rendered. The translation from the sequence of insurance claims present in the data into a patient's medical history at a particular point in time involved the application of rules and judgment. The complexity of this data source that arises from administrative capture of routine healthcare provides a strength in that the study results will be most generalizable to routine use of GARDASIL® permitting direct inferences to patients. However, this complexity is also associated with challenges, including uncertain diagnoses and timing of those diagnoses, and potentially incomplete recording of medical services, including receipt of vaccinations outside of the health plan.[13-15] This study included several features that aimed to address these uncertainties, including confirmation of both the diagnosis and timing of autoimmune outcomes through select profile review and medical record confirmation, and the use of a propensity-score matched cohort design. Although up to 5 medical records were sought for review and adjudication, the median number of charts received was 2 for both the GARDASIL® recipients and the comparators.

In this real-world study, case adjudication of autoimmune outcomes was conducted using medical information collected as part of routine healthcare where routine work-up and evaluation requires consultation with multiple healthcare providers and specialists, as well as

multiple laboratory and imaging tests. As such, the study narratives reflect the level of detail and timing of the clinical course using these real-world data.

Comparators were required to have a healthcare contact at cohort entry. Because most the GARDASIL® recipients received several doses of the vaccine, they may have had more opportunity for autoimmune condition diagnosis during the study follow-up than comparators. However, the propensity score was balanced on healthcare utilization factors, and follow-up time was accounted for in the analysis.

Analyses for many of the autoimmune conditions were based on a small number of chart-confirmed new-onset cases, which gave the study limited power in estimating RRs for these conditions. The case confirmation fractions overall and by condition category tended to be low, but are generally consistent with those observed in the Vaccine Safety Datalink [16] and may be driven by the relatively broad range of diagnosis codes used to initially identify, with high sensitivity, potential autoimmune cases in the ORD. For example, many of the codes used to identify potential ankylosing spondylitis cases were related to injury, strain or overuse rather than a diagnosis of ankylosing spondylitis.

Conclusions

In this large post-marketing safety study, the incidence of new-onset of 20 pre-specified autoimmune conditions within 6 months of receipt of a dose of GARDASIL® was estimated in 55,670 males who received more than 104,000 doses GARDASIL®, and compared to that of matched unvaccinated male comparators. Using a broad case detection strategy and a rigorous review and adjudication by clinical specialists following pre-specified procedures, the number of confirmed new-onset autoimmune cases within the risk window was small in both groups (a total of 35 in the matched GARDASIL® recipients and 47 in the comparators). Per the study protocol, the objective of these analyses was descriptive and the precision of the study is reflected in the width of the CIs of the IRs for the various autoimmune outcomes. The estimated IRs of the 20 pre-specified autoimmune conditions overall and across each condition were generally similar between the GARDASIL® recipients and comparators. They were also generally consistent with the incidence of these conditions reported in studies looking at autoimmune conditions among GARDASIL® recipients or in the general male population of the same age. Finally, the findings in this study are consistent with other observational studies assessing the association of receipt of GARDASIL® and the development of autoimmune conditions in both females and males.

The SRC reviewed the methods and the adjudication process of the autoimmune study component. After review of the study results, the SRC concluded that the study revealed no evidence of any increased risk of new-onset autoimmune conditions following receipt of GARDASIL® in males and that the results are consistent with the known safety profile of GARDASIL® (**Appendix N**).

11 REFERENCES

1. CDC. *Morbidity and Mortality Weekly*. 2010 [cited 2020 29 Jan]; Available from: https://www.cdc.gov/mmwr/preview/mmwrhtml/mm5920a5.htm.
2. CDC. *Morbidity and Mortality Weekly*. 2011 [cited 2020 05 Feb]; Available from: https://www.cdc.gov/mmwr/preview/mmwrhtml/mm6050a3.htm.
3. CDC. *Morbidity and Mortality Weekly*. 2015 [cited 2020 29 Jan]; Available from: https://www.cdc.gov/mmwr/preview/mmwrhtml/mm6411a3.htm.
4. CDC. *Morbity and Mortality Weekly*. 2016 [cited 2020 29 Jan]; Available from: https://www.cdc.gov/mmwr/volumes/65/wr/mm6549a5.htm.
5. Parsons L. *Reducing Bias in a Propesity Score Matched-Pair Sample Using Greedy Matching Techniques*. [cited 2020 14 Feb]; Available from: https://support.sas.com/resources/papers/proceedings/proceedings/sugi26/p214-26.pdf.
6. Loftus, C.G., et al., *Update on the incidence and prevalence of Crohn's disease and ulcerative colitis in Olmsted County, Minnesota, 1940-2000.* Inflamm Bowel Dis, 2007. **13**(3): p. 254-61.
7. Frisch, M., et al., *Quadrivalent human papillomavirus vaccination in boys and risk of autoimmune diseases, neurological diseases and venous thromboembolism.* Int J Epidemiol, 2018. **47**(2): p. 634-641.
8. Liu, E.Y., et al., *Quadrivalent human papillomavirus vaccination in girls and the risk of autoimmune disorders: the Ontario Grade 8 HPV Vaccine Cohort Study.* CMAJ, 2018. **190**(21): p. E648-E655.
9. Chao, C., et al., *Surveillance of autoimmune conditions following routine use of quadrivalent human papillomavirus vaccine.* J Intern Med, 2012. **271**(2): p. 193-203.
10. Meggiolaro, A., G. Migliara, and G. La Torre, *Association between Human Papilloma Virus (HPV) vaccination and risk of Multiple Sclerosis: A systematic review.* Hum Vaccin Immunother, 2018. **14**(5): p. 1266-1274.
11. Mouchet, J., et al., *Human papillomavirus vaccine and demyelinating diseases-A systematic review and meta-analysis.* Pharmacol Res, 2018. **132**: p. 108-118.
12. Willame, C., et al., *Systematic Review and Meta-analysis of Postlicensure Observational Studies on Human Papillomavirus Vaccination and Autoimmune and Other Rare Adverse Events.* Pediatr Infect Dis J, 2019.
13. Schneeweiss, S. and J. Avorn, *A review of uses of health care utilization databases for epidemiologic research on therapeutics.* J Clin Epidemiol, 2005. **58**(4): p. 323-37.
14. Seeger, J.D., *Commercial Databases*, in *Pharmacoepidemiology 5th Edition*, S. B, Editor. 2012, Wiley: Chicester, UK. p. 189-208.
15. Ferver K. *The Use of Claims Data in Healthcare Research*. 2009 [cited 2020 30 January]; Available from: https://benthamopen.com/contents/pdf/TOPHJ/TOPHJ-2-11.pdf.
16. Gee, J., et al., *Monitoring the safety of quadrivalent human papillomavirus vaccine: findings from the Vaccine Safety Datalink.* Vaccine, 2011. **29**(46): p. 8279-84.

12 TABLES AND FIGURES

Table 1. Cumulative[a] Gardasil Cohort by Age at First Dose of Gardasil and Dose Number Accrual Through Q42016, Protocol 070

Age at First Gardasil Dose (Years)	Dose 1 (N= 65,606)	Dose 2 (N= 38,347)	Dose 3 (N= 21,518)
9	250	153	84
10	603	359	204
11	8,744	5,067	2,737
12	8,170	4,759	2,654
13	7,436	4,554	2,613
14	8,179	5,059	2,923
15	7,220	4,647	2,804
16	7,039	4,271	2,467
17	6,776	3,924	2,221
18	4,979	2,589	1,342
19	1,693	852	436
20	1,175	548	293
21	734	340	168
22	523	259	131
23	438	233	107
24	369	202	96
25	401	195	76
26	234	128	71
< 9	79	10	6
> 26	564	198	85
Total	65,606	38,347	21,518

[a]Accrual 16-OCT-2009 - 31-DEC-2016

Table 2.[a] Demographic Characteristics among the Gardasil Cohort and Comparators, Matched Gardasil Recipients and Comparators, and Unmatched Recipients During the Baseline Period

Characteristic	All Gardasil Cohort and Comparators				Matched Gardasil Recipients and Comparators				Unmatched Gardasil Recipients (N= 9,936)	
	Gardasil Recipients (N= 65,606)		Comparators (N= 1,322,978)		Gardasil Recipients (N= 55,670)		Comparators (N= 55,670)			
	N	%	N	%	N	%	N	%	N	%
Age (years) [Count,%]										
< 9	78	0.12	93,407	7.06	78	0.14	101	0.18	0	0.00
9-10	853	1.30	71,984	5.44	833	1.50	813	1.46	20	0.20
11-12	16,914	25.78	129,326	9.78	15,949	28.65	16,855	30.28	965	9.71
13-14	15,614	23.80	94,471	7.14	13,013	23.38	13,113	23.55	2,601	26.18
15-17	21,039	32.07	139,636	10.55	16,516	29.67	15,989	28.72	4,523	45.52
18-20	7,845	11.96	120,924	9.14	6,463	11.61	6,219	11.17	1,382	13.91
21-23	1,695	2.58	57,837	4.37	1,363	2.45	1,231	2.21	332	3.34
24-26	1,004	1.53	80,371	6.08	893	1.60	810	1.46	111	1.12
> 26	564	0.86	535,022	40.44	562	1.01	539	0.97	2	0.02
Geographic area [Count,%]										
Northeast	7,145	10.89	110,685	8.37	5,945	10.68	5,990	10.76	1,200	12.08
Midwest	16,468	25.10	343,318	25.95	13,873	24.92	14,080	25.29	2,595	26.12
South	30,348	46.26	657,316	49.68	26,024	46.75	25,964	46.64	4,324	43.52
West	11,645	17.75	211,659	16.00	9,828	17.65	9,636	17.31	1,817	18.29

Abbreviations: SD, Standard Deviation; ICD, International Classification of Disease; ER, Emergency Room
[a]Accrual 16-OCT-2009 - 31-DEC-2016

Table 2.[a] Demographic Characteristics among the Gardasil Cohort and Comparators, Matched Gardasil Recipients and Comparators, and Unmatched Recipients During the Baseline Period

Characteristic	All Gardasil Cohort and Comparators				Matched Gardasil Recipients and Comparators				Unmatched Gardasil Recipients (N= 9,936)	
	Gardasil Recipients (N= 65,606)		Comparators (N= 1,322,978)		Gardasil Recipients (N= 55,670)		Comparators (N= 55,670)			
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Duration of preceding continuous health plan membership months	34.46	18.42	23.15	14.29	34.00	19.01	33.77	19.33	37.02	14.48
Number of drug classes dispensed	1.95	2.30	2.85	3.20	1.94	2.30	1.93	2.29	2.04	2.29
Number of different drugs dispensed	4.64	7.91	8.52	14.86	4.59	7.92	4.65	8.21	4.95	7.82
Number of hospitalizations	0.02	0.16	0.04	0.28	0.02	0.16	0.02	0.16	0.02	0.17
Number of inpatient hospital days (among those hospitalized)	6.47	14.82	6.35	13.82	6.18	14.37	5.54	9.60	7.94	16.83
Number of 3-digit ICD-9/ICD-10 diagnostic codes	7.06	4.77	7.52	6.52	7.01	4.83	7.03	4.96	7.35	4.46
Number of physician visits	3.92	3.42	4.22	4.43	3.92	3.46	3.94	3.30	3.93	3.20
Number of ER visits	0.35	1.70	0.59	2.40	0.35	1.65	0.33	1.57	0.35	1.94
Number of procedures	0.62	1.18	1.01	1.94	0.61	1.18	0.61	1.21	0.66	1.17
Total healthcare utilization costs ($US)	2,872.83	9,052.40	4,407.08	21,281.00	2,833.24	8,972.60	2,852.05	19,145.00	3,094.62	9,484.70

Abbreviations: SD, Standard Deviation; ICD, International Classification of Disease; ER, Emergency Room
[a]Accrual 16-OCT-2009 - 31-DEC-2016

Table 3.[a] Healthcare Utilization Factors among the Matched Gardasil Cohort and Comparators not Vaccinated with Gardasil in the Optum Research Database During the Baseline Period

Characteristic	Matched Gardasil Recipients[b] (N= 55,670)			Matched Comparators (N= 55,670)		
	Mean	SD	Median (IQR)	Mean	SD	Median (IQR)
Number of outpatient physician visits	3.92	3.46	3.00 (2.00-5.00)	3.94	3.30	3.00 (2.00-5.00)
Number of outpatient primary care/pediatrician physician visits	1.88	2.1	1.00 (0.00-3.00)	1.91	2.11	1.00 (0.00-3.00)
Number of preventive medicine outpatient visits	1.02	0.5	1.00 (1.00-1.00)	1.04	0.53	1.00 (1.00-1.00)
Number of emergency room visits	0.35	1.65	0.00 (0.00-0.00)	0.33	1.57	0.00 (0.00-0.00)
Number of hospitalizations	0.02	0.16	0.00 (0.00-0.00)	0.02	0.16	0.00 (0.00-0.00)
Number of inpatient hospital days (among those hospitalized)	6.18	14.37	3.00 (2.00-6.00)	5.54	9.60	3.00 (1.00-6.00)
Number of procedures	0.61	1.18	0.00 (0.00-1.00)	0.61	1.21	0.00 (0.00-1.00)
Number of laboratory tests	2.84	7.25	1.00 (0.00-3.00)	2.89	7.13	1.00 (0.00-3.00)
Number of different drugs dispensed (including unique and refill dispensing)	4.59	7.92	2.00 (0.00-6.00)	4.65	8.21	2.00 (0.00-6.00)

Abbreviations: SD, Standard Deviation; IQR, Interquartile Range
[a]Accrual 16-OCT-2009 through 31-DEC-2016
[b]Gardasil recipients with at least 12+ months continuous enrollment prior to dose 1

Table 3.[a] Healthcare Utilization Factors among the Matched Gardasil Cohort and Comparators not Vaccinated with Gardasil in the Optum Research Database During the Baseline Period

Characteristic	Matched Gardasil Recipients[b] (N= 55,670)		Matched Comparators (N= 55,670)	
	N	%	N	%
Annual Household Income				
< $40,000	3,303	5.93	2,541	4.56
$40,000 – $49,999	1,985	3.57	1,697	3.05
$50,000 - $59,999	2,339	4.20	2,117	3.80
$60,000 - $74,999	3,748	6.73	3,542	6.36
$75,000 - $99,999	6,276	11.27	6,776	12.17
$100,000 +	31,829	57.17	33,459	60.10
Missing/Unknown	6,190	11.12	5,538	9.95
Net Worth				
< $25,000	6,258	11.24	5,160	9.27
$25,000 - $149,999	10,313	18.53	10,156	18.24
$150,000 - $249,999	6,950	12.48	7,577	13.61
$250,000 - $499,999	13,117	23.56	14,558	26.15
$500,000 +	14,873	26.72	14,605	26.23
Missing/Unknown	4,159	7.47	3,614	6.49

Abbreviations: SD, Standard Deviation; IQR, Interquartile Range
[a]Accrual 16-OCT-2009 through 31-DEC-2016
[b]Gardasil recipients with at least 12+ months continuous enrollment prior to dose 1

Table 4.[a] Summary of Potential and Reviewed New-Onset Autoimmune Conditions among Matched Gardasil Recipients (N= 55,670) and Comparators (N= 55,670)

Condition	Matched Gardasil Recipients							Matched Comparators						
	Potential Cases			Reviewed Cases[b]				Potential Cases			Reviewed Cases[c]			
	Total	Potential New Onset Cases[d] [N(%)]	Medical Charts Not Available [N(%)]	Not Confirmed [N(%)]	Confirmed (Overall) [N(%)]	Confirmed (New Onset and within Risk Window) [N(%)]	Insuff. Info. [N(%)]	Total	Potential New Onset Cases[b] [N(%)]	Medical Charts Not Available [N(%)]	Not Confirmed [N(%)]	Confirmed (Overall) [N(%)]	Confirmed (New Onset and within Risk Window) [N(%)]	Insuff. Info. [N(%)]
Total	**887 (100.0)**	**416 (100.0)**	**59 (100.0)**	**270 (100.0)**	**76 (100.0)**	**35 (100.0)**	**15 (100.0)**	**905 (100.0)**	**373 (100.0)**	**63 (100.0)**	**232 (100.0)**	**65 (100.0)**	**47 (100.0)**	**16 (100.0)**
Rheumatological	**173 (19.5)**	**118 (28.4)**	**18 (30.5)**	**86 (31.9)**	**11 (14.5)**	**2 (5.7)**	**3 (20.0)**	**151 (16.7)**	**96 (25.7)**	**14 (22.2)**	**69 (29.7)**	**10 (15.4)**	**6 (12.8)**	**4 (25.0)**
Immune Thrombocytopenia	10 (1.1)	4 (1.0)	0 (0.0)	2 (0.7)	2 (2.6)	0 (0.0)	0 (0.0)	12 (1.3)	7 (1.9)	1 (1.6)	2 (0.9)	4 (6.2)	3 (6.4)	0 (0.0)
Autoimmune Hemolytic Anemia	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.2)	2 (0.5)	0 (0.0)	1 (0.4)	1 (1.5)	0 (0.0)	0 (0.0)
Systemic Lupus Erythematosus	19 (2.1)	14 (3.4)	2 (3.4)	11 (4.1)	1 (1.3)	1 (2.9)	0 (0.0)	12 (1.3)	9 (2.4)	1 (1.6)	8 (3.4)	0 (0.0)	0 (0.0)	0 (0.0)
Rheumatoid Arthritis	14 (1.6)	9 (2.2)	1 (1.7)	5 (1.9)	1 (1.3)	0 (0.0)	2 (13.3)	16 (1.8)	10 (2.7)	2 (3.2)	6 (2.6)	0 (0.0)	0 (0.0)	2 (12.5)
Juvenile Rheumatoid Arthritis	19 (2.1)	8 (1.9)	2 (3.4)	1 (0.4)	5 (6.6)	0 (0.0)	0 (0.0)	22 (2.4)	8 (2.1)	0 (0.0)	3 (1.3)	4 (6.2)	3 (6.4)	2 (12.5)
Psoriatic Arthritis	6 (0.7)	2 (0.5)	0 (0.0)	2 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.3)	2 (0.5)	0 (0.0)	1 (0.4)	1 (1.5)	0 (0.0)	0 (0.0)
Ankylosing Spondylitis	91 (10.3)	68 (16.3)	12 (20.3)	54 (20.0)	1 (1.3)	1 (2.9)	1 (6.7)	76 (8.4)	53 (14.2)	9 (14.3)	44 (19.0)	0 (0.0)	0 (0.0)	0 (0.0)
Reactive Arthritis	13 (1.5)	13 (3.1)	1 (1.7)	11 (4.1)	1 (1.3)	0 (0.0)	0 (0.0)	8 (0.9)	5 (1.3)	1 (1.6)	4 (1.7)	0 (0.0)	0 (0.0)	0 (0.0)
Gastroenterological	**127 (14.3)**	**48 (11.5)**	**6 (10.2)**	**13 (4.8)**	**24 (31.6)**	**12 (34.3)**	**7 (46.7)**	**141 (15.6)**	**38 (10.2)**	**5 (7.9)**	**9 (3.9)**	**21 (32.3)**	**14 (29.8)**	**3 (18.8)**
Crohn's Disease	84 (9.5)	27 (6.5)	2 (3.4)	7 (2.6)	13 (17.1)	6 (17.1)	5 (33.3)	98 (10.8)	25 (6.7)	3 (4.8)	5 (2.2)	16 (24.6)	12 (25.5)	1 (6.3)
Ulcerative Colitis	43 (4.8)	21 (5.0)	4 (6.8)	6 (2.2)	11 (14.5)	6 (17.1)	2 (13.3)	43 (4.8)	13 (3.5)	2 (3.2)	4 (1.7)	5 (7.7)	2 (4.3)	2 (12.5)
Endocrinological	**482 (54.3)**	**159 (38.2)**	**28 (47.5)**	**89 (33.0)**	**39 (51.3)**	**19 (54.3)**	**4 (26.7)**	**483 (53.4)**	**134 (35.9)**	**25 (39.7)**	**73 (31.5)**	**32 (49.2)**	**25 (53.2)**	**6 (37.5)**
Type I Diabetes	226 (25.5)	29 (7.0)	4 (6.8)	10 (3.7)	14 (18.4)	8 (22.9)	1 (6.7)	220 (24.3)	22 (5.9)	3 (4.8)	4 (1.7)	14 (21.5)	12 (25.5)	1 (6.3)
Hashimoto's Disease	207 (23.3)	91 (21.9)	18 (30.5)	48 (17.8)	23 (30.3)	10 (28.6)	3 (20.0)	211 (23.3)	73 (19.6)	18 (28.6)	36 (15.5)	16 (24.6)	11 (23.4)	5 (31.3)
Graves' Disease	49 (5.5)	39 (9.4)	6 (10.2)	31 (11.5)	2 (2.6)	1 (2.9)	0 (0.0)	52 (5.7)	39 (10.5)	4 (6.3)	33 (14.2)	2 (3.1)	2 (4.3)	0 (0.0)

[a]Males were eligible if they had 12+ months of continuous enrollment prior to the first dose of Gardasil, or prior to the earliest healthcare visit for Comparators.
[b]Four cases (two gastroenterology; one endocrine; one neurological/ophthalmologic) were identified to have an alternative outcome by clinical reviewers during the adjudication process. Therefore, the number of potential new onset cases for the overall total and for each condition group total may not equal the sum of individual columns "Medical Charts Not Available + Not Confirmed + Confirmed + Insuff Info".
[c]Three cases (one rheumatology; two endocrinology) were identified to have an alternative outcome by clinical reviewers during the adjudication process. Therefore, the number of potential new onset cases for the overall total and for each condition group total may not equal the sum of individual columns "Medical Charts Not Available + Not Confirmed + Confirmed + Insuff Info".
[d]Total follow-up (person-years)= 121,944. Cases with no diagnosis codes for the same autoimmune condition 12 months prior to the first dose.

Table 4.[a] Summary of Potential and Reviewed New-Onset Autoimmune Conditions among Matched Gardasil Recipients (N= 55,670) and Comparators (N= 55,670)

Condition	Matched Gardasil Recipients							Matched Comparators						
	Potential Cases			Reviewed Cases[b]				Potential Cases			Reviewed Cases[c]			
	Total	Potential New Onset Cases[d] [N(%)]	Medical Charts Not Available [N(%)]	Not Confirmed [N(%)]	Confirmed (Overall) [N(%)]	Confirmed (New Onset and within Risk Window) [N(%)]	Insuff. Info. [N(%)]	Total	Potential New Onset Cases[b] [N(%)]	Medical Charts Not Available [N(%)]	Not Confirmed [N(%)]	Confirmed (Overall) [N(%)]	Confirmed (New Onset and within Risk Window) [N(%)]	Insuff. Info. [N(%)]
Neurological	**105 (11.8)**	**91 (21.9)**	**7 (11.9)**	**82 (30.4)**	**2 (2.6)**	**2 (5.7)**	**1 (6.7)**	**130 (14.4)**	**105 (28.2)**	**19 (30.2)**	**81 (34.9)**	**2 (3.1)**	**2 (4.3)**	**3 (18.8)**
Multiple Sclerosis	33 (3.7)	30 (7.2)	1 (1.7)	28 (10.4)	2 (2.6)	2 (5.7)	0 (0.0)	54 (6.0)	48 (12.9)	8 (12.7)	38 (16.4)	0 (0.0)	0 (0.0)	2 (12.5)
Acute Disseminated Encephalomyelitis	13 (1.5)	10 (2.4)	0 (0.0)	10 (3.7)	0 (0.0)	0 (0.0)	0 (0.0)	5 (0.6)	5 (1.3)	0 (0.0)	5 (2.2)	0 (0.0)	0 (0.0)	0 (0.0)
Other Demyelinating Diseases of the Nervous System	3 (0.3)	3 (0.7)	0 (0.0)	3 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.2)	2 (0.5)	1 (1.6)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Guillain-Barre Syndrome	7 (0.8)	6 (1.4)	0 (0.0)	6 (2.2)	0 (0.0)	0 (0.0)	0 (0.0)	12 (1.3)	7 (1.9)	3 (4.8)	4 (1.7)	0 (0.0)	0 (0.0)	0 (0.0)
Neuromyelitis Optica	1 (0.1)	1 (0.2)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Optic Neuritis	4 (0.5)	3 (0.7)	0 (0.0)	2 (0.7)	0 (0.0)	0 (0.0)	1 (6.7)	6 (0.7)	4 (1.1)	1 (1.6)	2 (0.9)	0 (0.0)	0 (0.0)	1 (6.3)
Uveitis	44 (5.0)	38 (9.1)	6 (10.2)	32 (11.9)	0 (0.0)	0 (0.0)	0 (0.0)	51 (5.6)	39 (10.5)	6 (9.5)	31 (13.4)	2 (3.1)	2 (4.3)	0 (0.0)

[a]Males were eligible if they had 12+ months of continuous enrollment prior to the first dose of Gardasil, or prior to the earliest healthcare visit for Comparators.
[b]Four cases (two gastroenterology; one endocrine; one neurological/ophthalmologic) were identified to have an alternative outcome by clinical reviewers during the adjudication process. Therefore, the number of potential new onset cases for the overall total and for each condition group total may not equal the sum of individual columns "Medical Charts Not Available + Not Confirmed + Confirmed + Insuff Info".
[c]Three cases (one rheumatology; two endocrinology) were identified to have an alternative outcome by clinical reviewers during the adjudication process. Therefore, the number of potential new onset cases for the overall total and for each condition group total may not equal the sum of individual columns "Medical Charts Not Available + Not Confirmed + Confirmed + Insuff Info".
[d]Total follow-up (person-years)= 121,944. Cases with no diagnosis codes for the same autoimmune condition 12 months prior to the first dose.

Table 5.[a] Relative Rates of New-Onset Autoimmune Conditions among Matched Gardasil Recipients (N= 55,670) and Comparators (N= 55,670)

Autoimmune Condition	Matched Recipients of Gardasil[c]				Matched Comparators (Unvaccinated)[d]				Relative Rate	95% CI
	Cases	Person-Years	Incidence Rate[b]	95% CI	Cases	Person-Years	Incidence Rate[c]	95%CI		
Total	**35**	**39,735**	**0.88**	**0.61 - 1.23**	**47**	**58,215**	**0.81**	**0.59 - 1.07**	**1.09**	**0.70 - 1.69**
Rheumatological	**2**	**39,756**	**0.05**	**0.01 - 0.18**	**6**	**58,211**	**0.10**	**0.04 - 0.22**	**0.49**	**0.10 - 2.42**
Immune Thrombocytopenia	0	39,757	0.00	0.00 - 0.08	3	58,213	0.05	0.01 - 0.15	NC	NC - NC
Autoimmune Hemolytic Anemia	0	39,757	0.00	0.00 - 0.08	0	58,215	0.00	0.00 - 0.05	NC	NC - NC
Systemic Lupus Erythematosus	1	39,757	0.03	0.00 - 0.14	0	58,215	0.00	0.00 - 0.05	NC	NC - NC
Rheumatoid Arthritis	0	39,757	0.00	0.00 - 0.08	0	58,215	0.00	0.00 - 0.05	NC	NC - NC
Juvenile Rheumatoid Arthritis	0	39,757	0.00	0.00 - 0.08	3	58,213	0.05	0.01 - 0.15	NC	NC - NC
Psoriatic Arthritis	0	39,757	0.00	0.00 - 0.08	0	58,215	0.00	0.00 - 0.05	NC	NC - NC
Ankylosing Spondylitis	1	39,757	0.03	0.00 - 0.14	0	58,215	0.00	0.00 - 0.05	NC	NC - NC
Reactive Arthritis	0	39,757	0.00	0.00 - 0.08	0	58,215	0.00	0.00 - 0.05	NC	NC - NC
Gastroenterological	**12**	**39,750**	**0.30**	**0.16 - 0.53**	**14**	**58,205**	**0.24**	**0.13 - 0.40**	**1.26**	**0.58 - 2.71**
Crohn's Disease	6	39,754	0.15	0.06 - 0.33	12	58,206	0.21	0.11 - 0.36	0.73	0.28 - 1.95
Ulcerative Colitis	6	39,753	0.15	0.06 - 0.33	2	58,214	0.03	0.00 - 0.12	4.39	0.89 - 21.77
Endocrinological	**19**	**39,745**	**0.48**	**0.29 - 0.75**	**25**	**58,200**	**0.43**	**0.28 - 0.63**	**1.11**	**0.61 - 2.02**
Type I Diabetes	8	39,753	0.20	0.09 - 0.40	12	58,206	0.21	0.11 - 0.36	0.98	0.40 - 2.39
Hashimoto's Disease	10	39,749	0.25	0.12 - 0.46	11	58,210	0.19	0.09 - 0.34	1.33	0.57 - 3.14
Graves' Disease	1	39,757	0.03	0.00 - 0.14	2	58,214	0.03	0.00 - 0.12	0.73	0.07 - 8.07

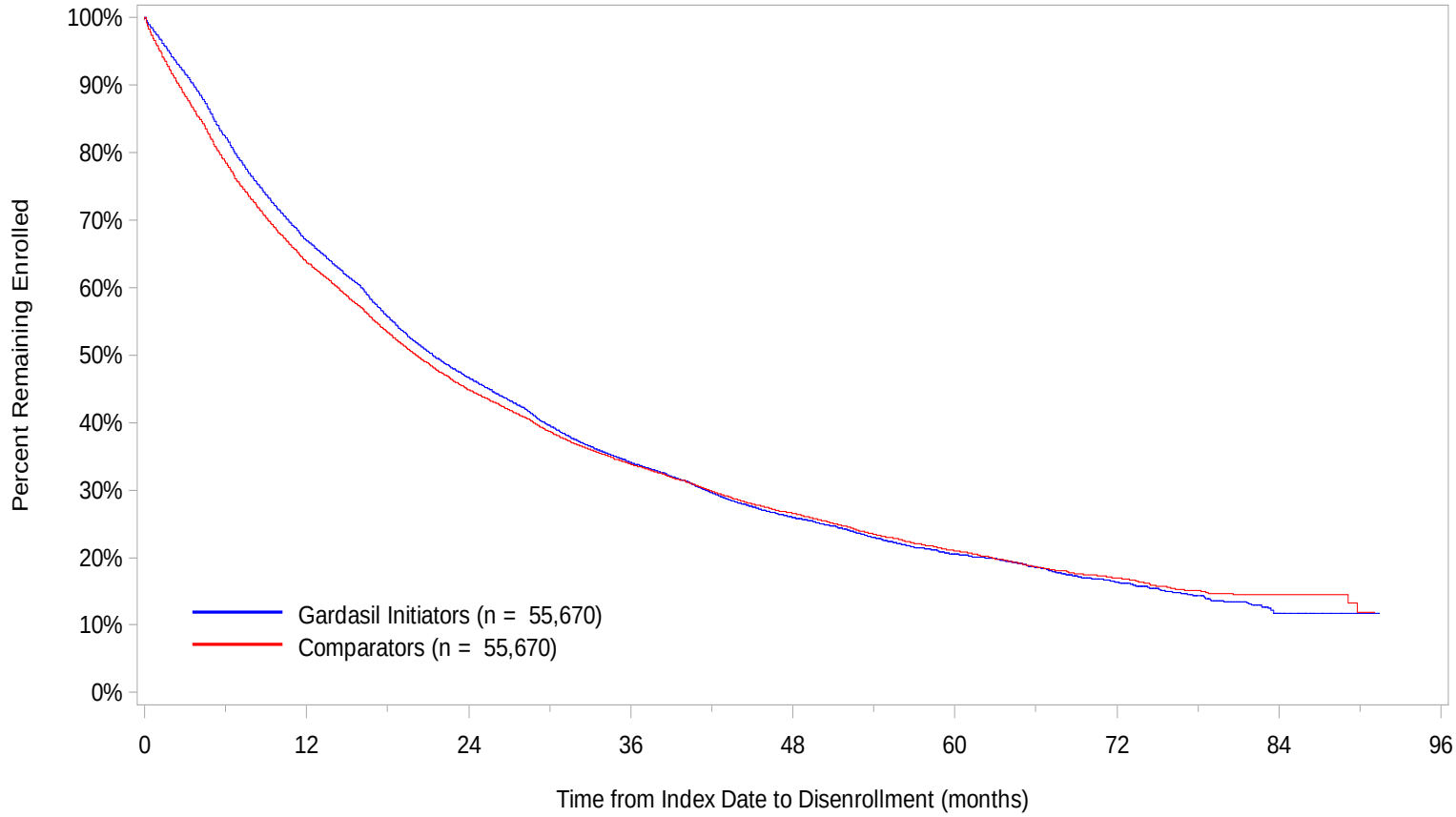
Abbreviations: CI, Confidence Interval; NC, Not Calculated
[a]Accrual 16-OCT-2009 - 31-DEC-2016
[b]Per 1,000 Person-Years
[c]Risk period consists of 6 months after each dose in follow up period
[d]Risk period consists of 18 months after index date (date of healthcare visit)

Table 5.[a] Relative Rates of New-Onset Autoimmune Conditions among Matched Gardasil Recipients (N= 55,670) and Comparators (N= 55,670)

Autoimmune Condition	Matched Recipients of Gardasil[c]				Matched Comparators (Unvaccinated)[d]				Relative Rate	95% CI
	Cases	Person-Years	Incidence Rate[b]	95% CI	Cases	Person-Years	Incidence Rate[c]	95%CI		
Neurological	**2**	**39,756**	**0.05**	**0.01 - 0.18**	**2**	**58,213**	**0.03**	**0.00 - 0.12**	**1.46**	**0.21 - 10.40**
Multiple Sclerosis	2	39,756	0.05	0.01 - 0.18	0	58,215	0.00	0.00 - 0.05	NC	NC - NC
Acute Disseminated Encephalomyelitis	0	39,757	0.00	0.00 - 0.08	0	58,215	0.00	0.00 - 0.05	NC	NC - NC
Other Demyelinating Diseases of the Nervous System	0	39,757	0.00	0.00 - 0.08	0	58,215	0.00	0.00 - 0.05	NC	NC - NC
Guillain-Barre Syndrome	0	39,757	0.00	0.00 - 0.08	0	58,215	0.00	0.00 - 0.05	NC	NC - NC
Neuromyelitis Optica	0	39,757	0.00	0.00 - 0.08	0	58,215	0.00	0.00 - 0.05	NC	NC - NC
Optic Neuritis	0	39,757	0.00	0.00 - 0.08	0	58,215	0.00	0.00 - 0.05	NC	NC - NC
Uveitis	0	39,757	0.00	0.00 - 0.08	2	58,213	0.03	0.00 - 0.12	NC	NC - NC

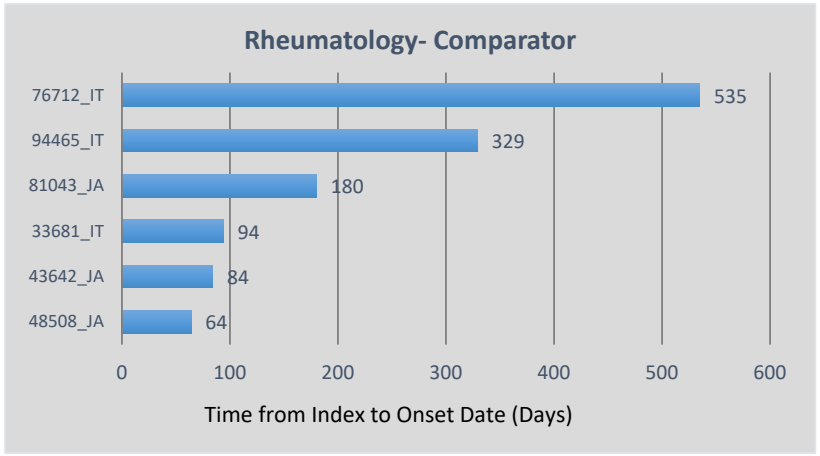
Abbreviations: CI, Confidence Interval; NC, Not Calculated
[a]Accrual 16-OCT-2009 - 31-DEC-2016
[b]Per 1,000 Person-Years
[c]Risk period consists of 6 months after each dose in follow up period
[d]Risk period consists of 18 months after index date (date of healthcare visit)

Figure 1. Kaplan Meier Curve of Follow-up Time Ending at Disenrollment or End of Study Period for Propensity-Score Matched Gardasil Recipients[a,b] and Comparators[c] with at Least 12 Months of Enrollment Prior to Cohort Initiation



[a]Males any age with at least one dose of Gardasil (Index Date = 1st Dose)
[b]Accrual 16-OCT-2009 - 31-DEC-2016
[c]Males any age not vaccinated with Gardasil (Index Date = Earliest health service visit)

Figure 2A. Time from Most Recent Dose for All Gardasil Recipients or Index Date for Comparators to Onset for Chart-Confirmed Rheumatology Conditions Within the Risk Window



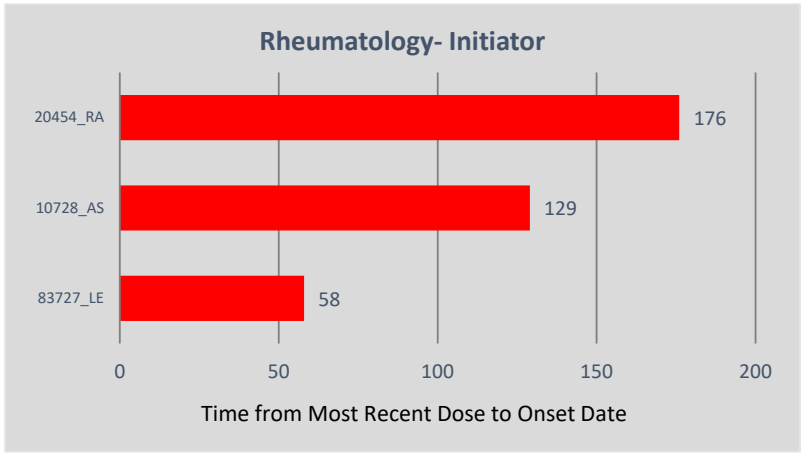
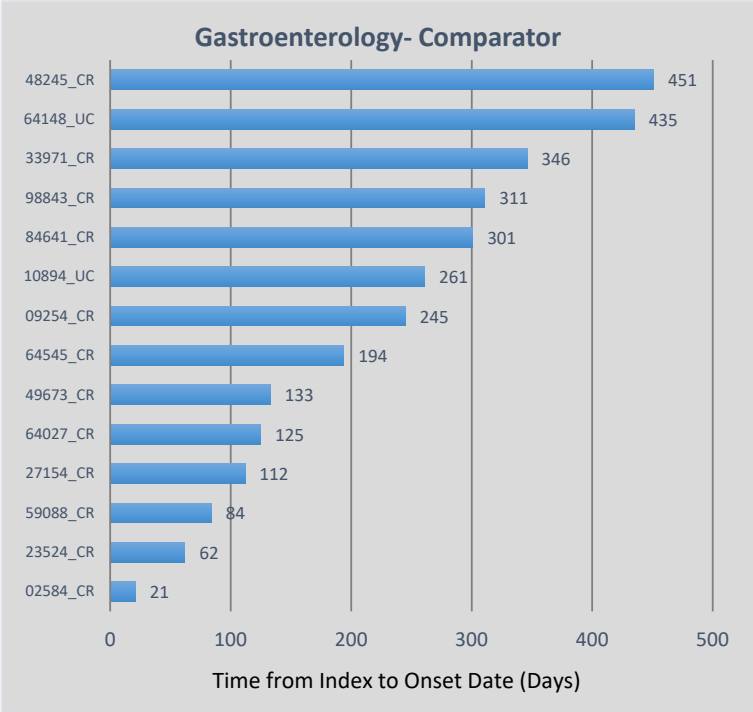


Figure 2B. Time from Most Recent Dose for All Gardasil Recipients or Index Date for Comparators to Onset for Chart-Confirmed Gastroenterology Conditions Within the Risk Window



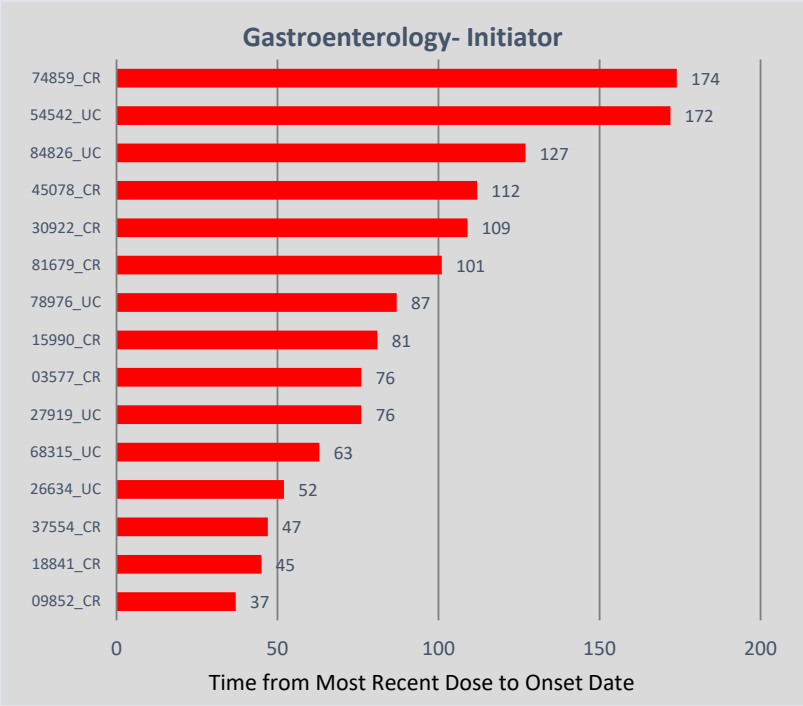
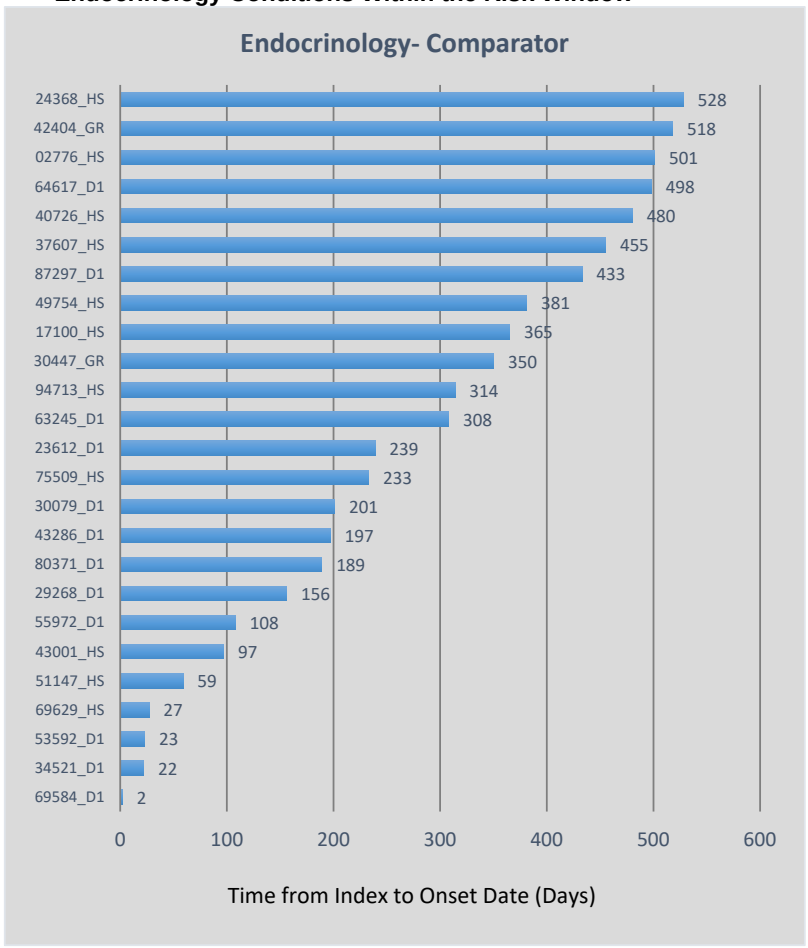


Figure 2C. Time from Most Recent Dose for All Gardasil Recipients or Index Date for Comparators to Onset for Chart-Confirmed Endocrinology Conditions Within the Risk Window



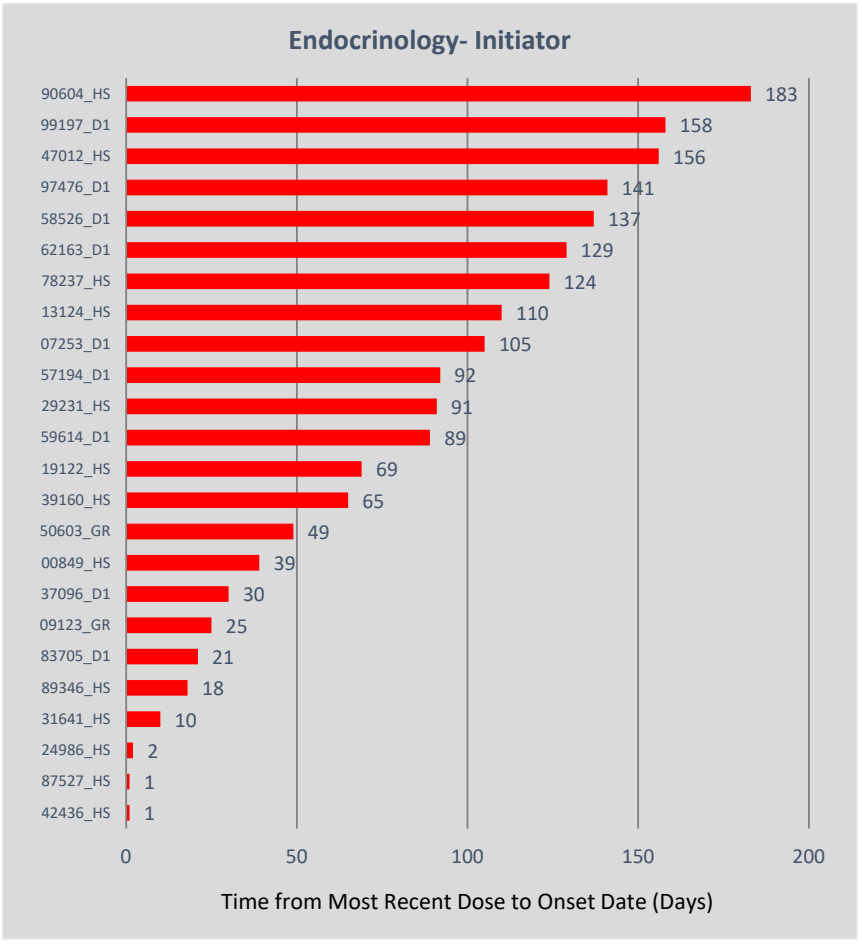
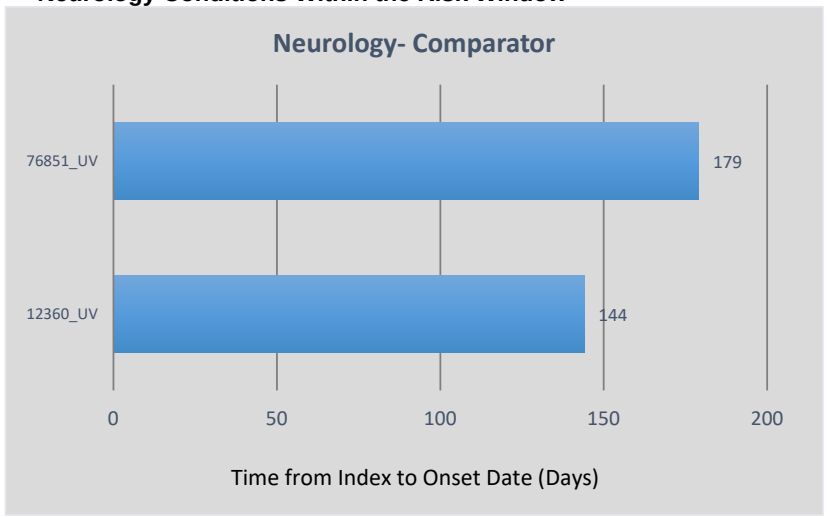


Figure 2D. Time from Most Recent Dose for All Gardasil Recipients or Index Date for Comparators to Onset for Chart-Confirmed Neurology Conditions Within the Risk Window



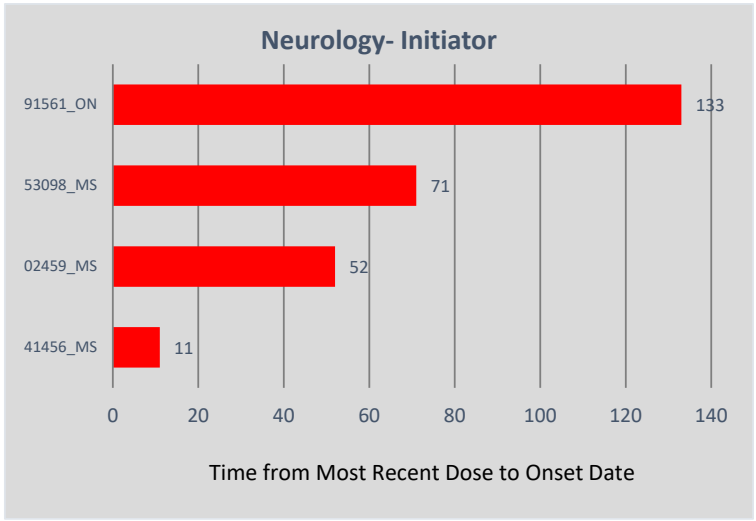
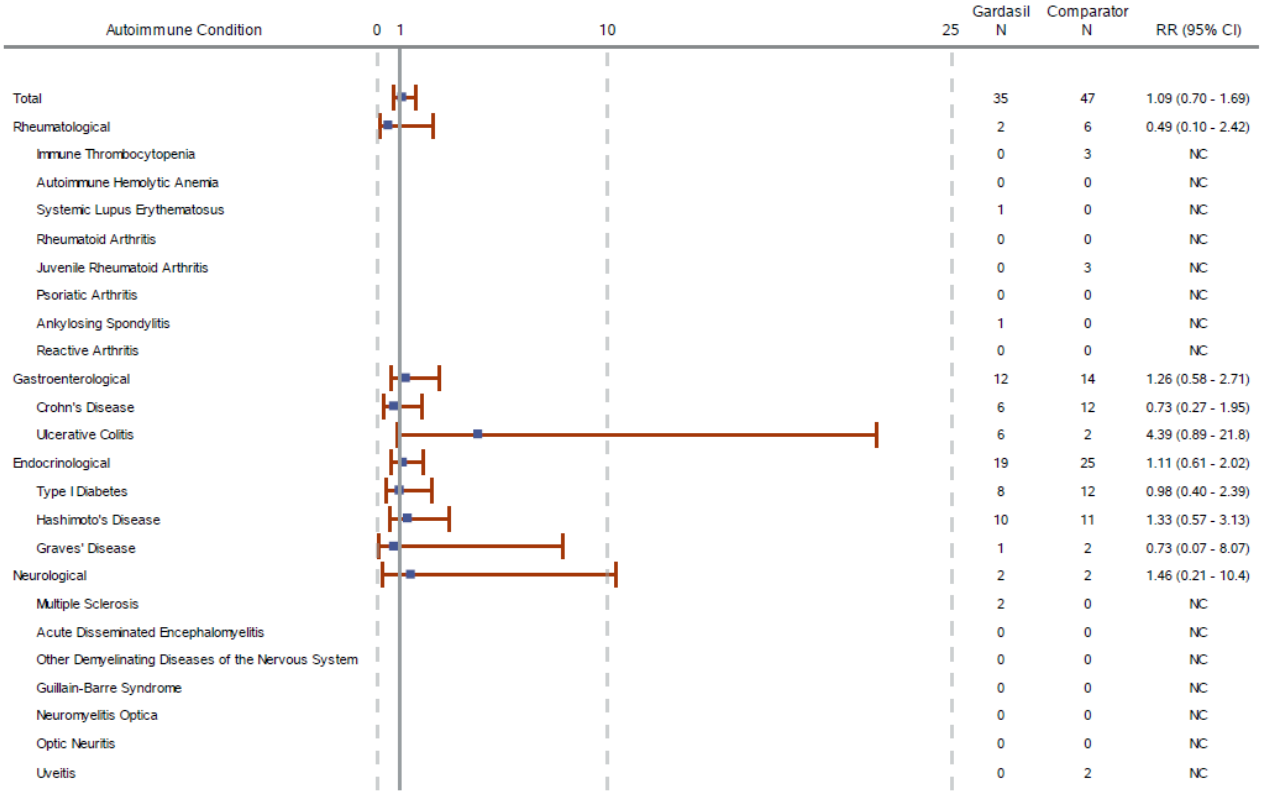
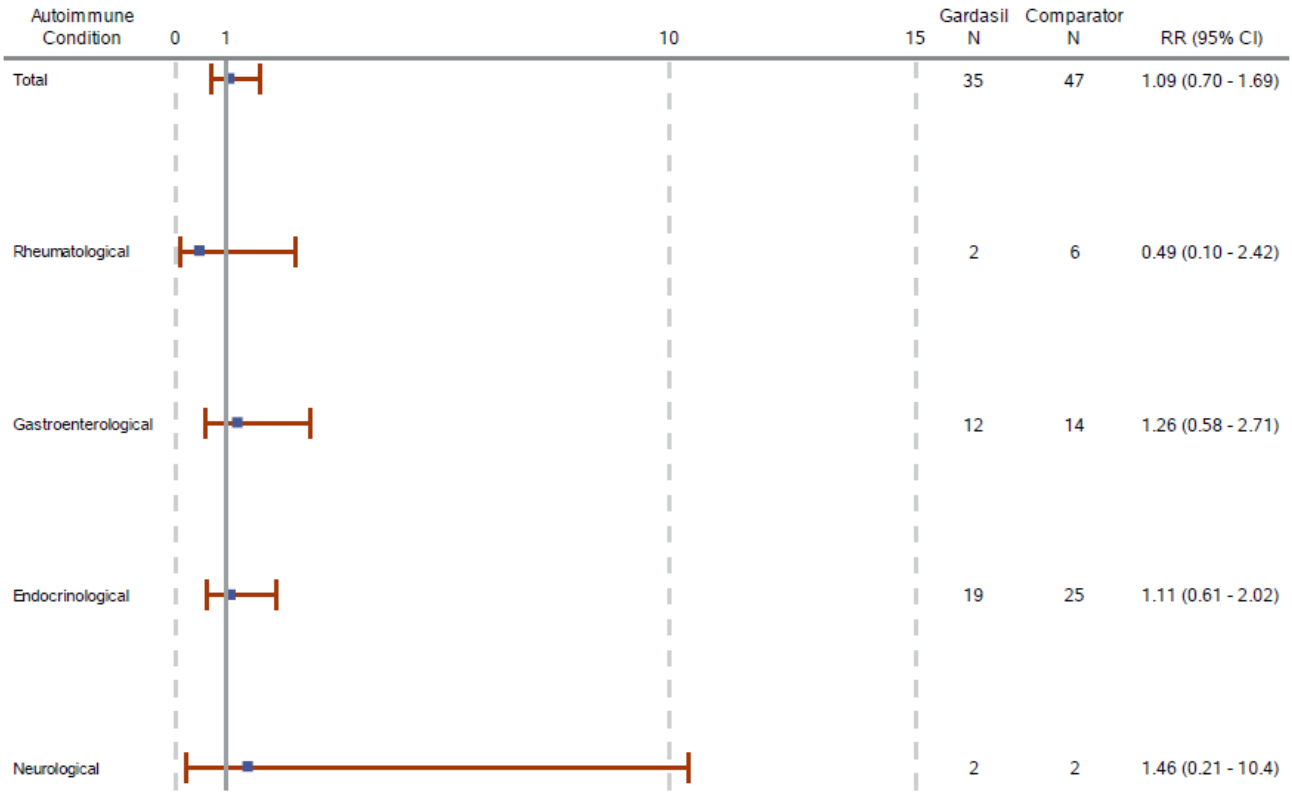


Figure 3A.[a] Relative Rates[b,c] of Medical Chart-Confirmed New-Onset Autoimmune Conditions among Matched Gardasil Recipients and Comparators by Autoimmune Condition Category (Forest Plot)



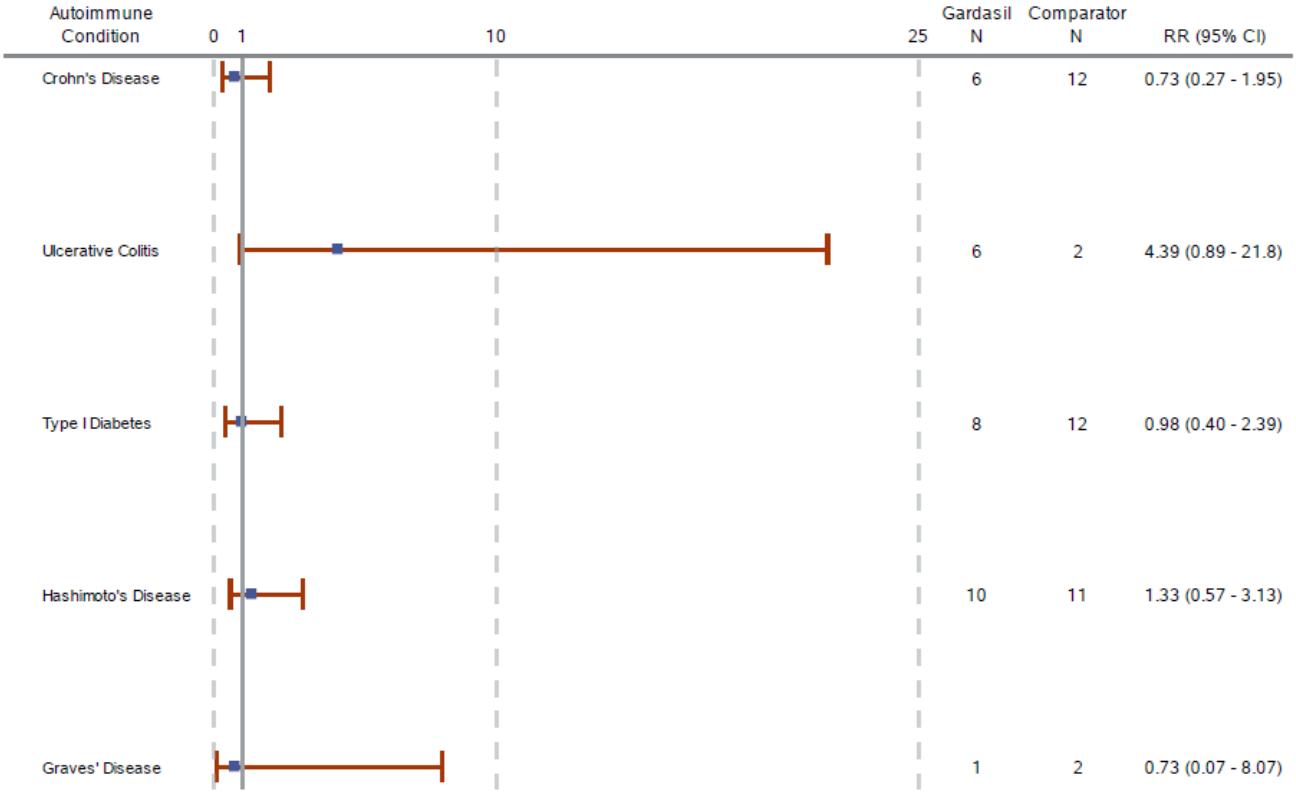
Abbreviations: CI-confidence interval; NC-not calculated.
[a]Accrual 16-OCT-2009 - 31-DEC-2016
[b]Per 1,000 Person-Years
[c]Relative rates calculated as the ratio of the incidence rate of the autoimmune condition among the matched regimen initiators divided by the incidence rate of the autoimmune condition among the matched comparators.

Figure 3B.[a] Relative Rates[b,c] of Medical Chart-Confirmed New-Onset Autoimmune Conditions among Matched Gardasil Recipients and Comparators by Autoimmune Condition Category



Abbreviations: CI-confidence interval
[a]Accrual 16-OCT-2009 - 31-DEC-2016
[b]Per 1,000 Person-Years
[c]Relative rates calculated as the ratio of the incidence rate of the autoimmune condition among the matched regimen initiators divided by the incidence rate of the autoimmune condition among the matched comparators.

Figure 3C.[a] Relative Rates[b,c] of Medical Chart-Confirmed New-Onset Autoimmune Conditions among Matched Gardasil Recipients and Comparators by Autoimmune Condition



Abbreviations: CI-confidence interval
[a]Accrual 16-OCT-2009 - 31-DEC-2016
[b]Per 1,000 Person-Years
[c]Relative rates calculated as the ratio of the incidence rate of the autoimmune condition among the matched regimen initiators divided by the incidence rate of the autoimmune condition among the matched comparators.