An Overview of Quadrivalent Human Papillomavirus Vaccine Safety

2006 to 2015

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Background: A quadrivalent human papillomavirus (HPV4) type 6/11/16/18 vaccine (GARDASIL/SILGARD®) has been licensed in many countries around the world for the prevention of cervical, vulvar, vaginal, and anal cancers and precancers, as well as external genital warts causally related to HPV types 6/11/16/18. Across 7 phase 3 clinical trials involving more than 29,000 males and females ages 9–45 years, vaccination was generally well tolerated. Because of its expected public health benefit in reducing cervical cancer and other HPV-related diseases, the vaccine has been implemented in the national vaccination programs of several countries, with over 178 million doses distributed worldwide.

Methods: Extensive efforts to assess the safety of the vaccine in routine practice have been conducted over the past 9 years since licensure, including more than 15 studies in more than 1 million preadolescents, adolescents and adults from various countries. Most have been performed in the general population although there have been some in special populations (pregnant women, HIV-infected individuals and those with systemic lupus erythematosus).

Results: We present a summary of the published, postlicensure safety data from active and passive surveillance. Only syncope, and possibly skin infections were associated with vaccination in the postlicensure setting. Serious adverse events, such as adverse pregnancy outcomes, autoimmune diseases (including Guillain–Barre Syndrome and multiple sclerosis), anaphylaxis, venous thromboembolism and stroke, were extensively studied, and no increase in the incidence of these events was found compared with background rates.

Conclusions: These results, along with the safety data from the prelicensure clinical trials, confirm that the HPV4 vaccine has a favorable safety profile. Key policy, medical and regulatory organizations around the world have independently reviewed these data and continue to recommend routine HPV vaccination.

Key Words: human papillomavirus, vaccine, safety, surveillance, Gardasil

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A prophylactic quadrivalent human papillomavirus (HPV4) type 6/11/16/18 recombinant vaccine (GARDASIL/SILGARD, Merck & Co, Inc. Kenilworth, NJ) received United States (US) Food and Drug Administration (FDA) approval in June 2006 for use in girls and women ages 9–26 years based on international studies in over 20,000 girls and women.[1–4] In 2009, the vaccine was licensed by the FDA for boys and men ages 9–26 years for the prevention of genital warts, and in December 2010, the FDA approved the vaccine for the prevention of anal cancer and associated precancerous lesions due to HPV6/11/16/18 in both males and females ages 9–26 years.[5,6]

In general, vaccine safety is monitored by the manufacturer of the vaccine, public health authorities, regulatory agencies and academics in a deliberate, comprehensive manner. First, the manufacturer uses a detailed study protocol to collect data from clinical trials conducted before licensure. Once the vaccine is licensed by regulatory agencies, the manufacturer is responsible for routinely evaluating clinically significant postlicensure adverse event (AE) reports to global regulatory agencies in the form of a periodic safety report. The manufacturer may also be requested to conduct postlicensure safety surveillance studies (as a formal regulatory commitment), which can be performed by the manufacturer alone or in conjunction with academic medical centers and/or healthcare or healthcare research organizations. In addition, public health authorities and regulatory agencies also fund and conduct independent, large population-based studies, often in collaboration with academic medical centers. These studies include both passive and active surveillance studies. Active safety surveillance uses systematic procedures to identify clinically important AEs occurring within a defined period and population, by evaluating whether the temporal occurrence of these events has a potential causal association with vaccination higher than typical background rates of disease.[7,8] Passive surveillance analyses suspected AEs that are

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spontaneously identified and reported into surveillance systems by healthcare providers and the public, which are then further evaluated for any potential association with vaccination.[7,8] This collaborative approach of the many stakeholders and the availability of different lines of evidence (clinical, epidemiological and postmarketing data) ensure that vaccine safety is adequately assessed. The comprehensive, global safety surveillance program conducted for the HPV4 vaccine is one of the largest postmarketing safety databases for any vaccine and may serve as a model for evaluating other new vaccines.

The HPV4 vaccine is currently approved in 129 countries and over 183 million doses were distributed globally as of April 2015. Across 5 phase 3 clinical trials involving 21,480 females ages 9–26 and boys ages 9–16 years, vaccination was generally well tolerated and vaccine and placebo recipients reported similar incidences of systemic AEs, serious AEs (SAEs) and new medical conditions potentially consistent with autoimmune phenomena.[9] Similar results were seen in clinical trials involving 3819 women ages 24 to 45 years and 4065 men ages 16 to 26 years.[5,10] Nonetheless, rare and potentially serious safety issues related to vaccination may not emerge during clinical studies due to the low incidence rate of the medical conditions or the limited size of the population studied. These only become evident when millions of people have been vaccinated and, through the use of postlicensure safety surveillance, identifying safety signals possibly associated with the vaccine that may not have been detectable before widespread uptake.

In 2009, we presented a summary of the extensive postlicensure safety and effectiveness studies of the HPV4 vaccine conducted in collaboration with the vaccine's manufacturer (Merck & Co., Inc) and Sanofi Pasteur MSD (Merck's European joint venture with Sanofi Pasteur – Sanofi Pasteur MSD is the marketing authorization holder of the HPV4 vaccine in Europe), as well as other independent initiatives in Europe, Canada and Australia.[11] We now present available data from active and passive postlicensure safety surveillance published through 2015 (Table 1). Active and passive surveillance studies in special populations (HIV-infected, and those with systemic lupus erythematosus) are described in the Appendix, Supplemental Digital Content 1, http://links.lww.com/INF/C173.

ACTIVE SAFETY SURVEILLANCE OF THE HPV4 VACCINE

Postlicensure Safety Studies Sponsored by Health Authorities or Research Organizations

Vaccine Safety Datalink

The safety of the HPV4 vaccine has been evaluated by the US Centers for Disease Control and Prevention (CDC) using the Vaccine Safety Datalink (VSD), a highly developed, active surveillance system for vaccines in the US.[12] The VSD collects medical information from a large, nationally representative population of >9 million people from seven different integrated healthcare delivery systems each year.[13,14]

From August 2006 to October 2009, females ages 9–26 years from the VSD sites were evaluated for prespecified conditions based on safety data from prelicensure clinical trials and reports to the Vaccine Adverse Events Reporting System (VAERS), a passive reporting system in the US. A historical comparison group not vaccinated with the HPV4 vaccine was used for the less common outcomes (Guillain–Barre Syndrome [GBS], venous thromboembolism [VTE], stroke and appendicitis). A concurrent comparison group not vaccinated with the HPV4 vaccine was used to assess rates for the more common outcomes (allergic reactions, syncope and seizures).

In these analyses which included 600,558 doses of the HPV4 vaccine, there was no statistically significant increased risk between receipt of the HPV4 vaccine and any of the monitored conditions.[13] A nonstatistically significant relative risk of 1.98 for VTE following vaccination was detected among females ages 9–17 years. Five of the eight cases reported met the standard case definition for VTE, all had known risk factors for VTE (oral contraceptive use, coagulation disorders, smoking, obesity or prolonged hospitalization), and all were ages 14–17 years. The authors concluded that further study of a possible association with VTE following HPV vaccination was warranted.[13]

Register-based Safety Studies in Denmark and Sweden

To date, three studies of HPV safety in Denmark and Sweden have been published. In the first study, national cohort registries from Denmark and Sweden[16] were assessed for the safety of the HPV4 vaccine administered to adolescent girls. The study was sponsored by the Swedish Foundation for Strategic Research and the Danish Medical Research Council. The cohort included 997,585 girls ages 10–17 years, among whom 296,826 (30%) had been vaccinated with 696,420 doses of the HPV4 vaccine from October 2006 to December 2010. A total of 53 prespecified conditions were evaluated, including incident autoimmune, neurologic and VTE events up to 6 months after each vaccine dose. Significantly increased rate ratios were initially observed for three outcomes: Bechet's disease (rate ratio 3.37), Raynaud's disease (rate ratio 1.67), and type 1 diabetes (rate ratio 1.29). For these three outcomes, the authors utilized three criteria as signal strengthening: analysis based on 20 or more vaccine exposed cases (reliability), rate ratio of 3.0 or more (strength) and significantly increased rate ratio in country-specific analyses (consistency). Each of these three outcomes fulfilled only one of the three predefined signal strengthening criteria. In addition, no distinct temporal pattern between vaccine exposure and outcome was evident. The authors of this large cohort study of almost 1 million adolescent girls found no evidence between exposure to the HPV4 vaccine and autoimmune conditions, neurological conditions or VTE.

In a second nationwide study from Denmark using a self-controlled case series design, the association between VTE and HPV was investigated. Among 1,613,798 girls and women ages 10–45 years between 2006 and 2013, 4375 incident cases of VTE were identified and 889 occurred in persons vaccinated during the study period. No association between VTE and HPV4 vaccination was found overall [incidence rate ratio (IRR) for VTE = 0.77, 95% confidence interval (CI): 0.53–1.11] or in subanalyses stratified by age, anticoagulant use or oral contraceptive use.[17]

In another nationwide study from Denmark and Sweden, the association between HPV4 vaccine and multiple sclerosis (MS) and other demyelinating diseases was investigated using both a cohort analysis and a self-controlled case series analysis.[18] Among 3,983,824 girls and women ages 10–44 years between 2006 and 2012 (Sweden) or 2013 (Denmark), 789,082 received a total of 1,927,581 HPV4 vaccine doses. No association between MS or other demyelinating disease and HPV4 vaccination was found in the cohort analysis [with respective adjusted rate ratios of 0.90 (95% CI: 0.70–1.15) and 1.00 (95% CI: 0.80–1.26)], nor in the case series analysis [with respective adjusted incidence ratios of 1.05 (95% CI: 0.79–1.38) and 1.14 (95% CI: 0.88–1.47)].

Case–control Study from a Large Managed Care Organization (Kaiser Permanente)

In a nested case–control study conducted at Kaiser Permanente Southern California, the association between HPV4 vaccination central nervous system (CNS) demyelinating diseases, including MS, was assessed among females aged 9 to 26 years old

TABLE 1. Summary of Postlicensure Safety Studies of the HPV4 Vaccine

A. Active surveillance studies	Description	Number of Subjects (if Known)	Number of Doses Evaluated (if Known)	Methods	Findings
Postlicensure safety studies sponsored by health authorities or Research Organizations	Vaccine Safety Data Link[12–14]	-	600,558	Cohort design with weekly sequential analyses of electronic medical data	No statistically significant increase in risk for the outcomes monitored[15]
	Register-based nationwide cohort study in Denmark and Sweden[16]	997,585 (296,826 received at least 1 dose of HPV4 vaccine)	696,420	Register-based cohort study based on individual level data	No evidence of association between HPV4 vaccine and autoimmune or neurological conditions, or VTE
	Register-based nationwide cohort study in Denmark and Sweden[17]	1,613,798 (500,345 received at least 1 dose of HPV4 vaccine)	-	Register-based cohort study based on individual level data	No evidence of association between HPV4 vaccine and VTE
	Register-based cohort study in Denmark and Sweden[18]	3,983,824 (789,082 received at least 1 dose of HPV4 vaccine)	1,927,581	Register-based cohort study based on individual level data	No evidence of association between HPV4 vaccine and MS or other demyelinating diseases of the CNS
	Study of CNS demyelinating diseases in large managed care organization[19]	92 cases; 459 controls	36 cases; 175 controls	Nested case–control study	No evidence of association between HPV4 vaccination and MS or other demyelinating diseases of the CNS
Postlicensure safety studies sponsored by Merck and SPMSD	Protocol V501-031 - General study assessment of HPV4 vaccine after routine administration at two large managed care organizations[20]	189,629	346,972	Self-controlled risk interval design, supplemented with medical record review	HPV4 vaccine associated with syncope on the day of vaccination and possibly skin infections in 2 weeks after vaccination; no other vaccine safety signals detected[15]
	Protocol V501-031- Assessment of 16 prespecified autoimmune conditions after routine use of HPV4 vaccine at two large managed-care organizations[21]	189,629	346,972	Retrospective cohort using electronic medical data, supplemented with medical record review	No confirmed safety signals for the outcomes monitored[15]
	Pharmacoepidemiologic General Research eXtension (PGRx) Information System[22]	1974	-	Systematic case–control study utilizing ongoing research platform	No evidence of an association between HPV4 and the studied autoimmune disorders
	Protocol V501-015, LTFU in Nordic Women[2,23,24] (see Appendix, Supplemental Digital Content 1, http://links.lww.com/INF/C173)	4800	-	Long-term extension of Phase 3 clinical trial	No safety signal, up to 8 years postvaccination
	Protocol V501-018, 10 year follow-up of adolescents aged 9 to 15[22]	1661	-	Long-term extension of Phase 3 clinical trial	No safety signal through 8 years following vaccination
	Protocol V501-019, 10 year follow-up of women aged 24 to 45[10,25]	684	-	Long-term extension of Phase 3 clinical trial	No safety signal through 6 years following vaccination
	Protocol V501-020, 10 year follow-up of males aged 16 to 26[5,6,26] (see Appendix, Supplemental Digital Content 1, http://links.lww.com/INF/C173)	1085	-	Long-term extension of Phase 3 clinical trial	No safety signal through 6 years following vaccination

B. Passive Surveillance Programs	Description	Number of Subjects (if known)	Number of Doses Evaluated (if Known)	Methods	Findings
	Vaccine adverse event reporting system[15,27–30]	-	56,000,000 doses distributed in US	Voluntary, passive surveillance system operated by the FDA and CDC	Most AEs were not greater than background rates. Disproportional reporting of syncope and venous thromboembolic events
	Vaccine adverse event reporting system[31]	147 reports after vaccine administration to pregnant women	-	Voluntary, passive surveillance system operated by the FDA and CDC	VAERS reports, comprising ~6 years of monitoring, found no safety concern among pregnant women who received HPV4 vaccine during pregnancy, nor in their offspring
	Australian national surveillance program[32–39] - (see Appendix, Supplemental Digital Content 1, http://links.lww.com/INF/C173)		Almost 7 million Gardasil doses distributed in Australia[40]	Voluntary, passive surveillance system operated by the TGA	The TGA has identified no new safety signals

(*Continued*)

TABLE 1. (Continued)

C. Studies in Special populations	Description	Number of Subjects (if Known)	Number of Doses Evaluated (if Known)	Methods	Findings
	The HPV4 vaccine pregnancy registry[41,42]	863	-	Voluntary reports from healthcare providers or consumers about women who were given HPV4 vaccine during pregnancy	Rates of spontaneous abortions and major birth defects were not greater than the unexposed population rates
	Study in HIV-infected young women[43] (see Appendix, Supplemental Digital Content 1, http://links.lww.com/INF/C173)	319	-	International phase II, open-label, single arm study with stratification by CD4+ cell count	HPV4 vaccine was safe and immunogenic in HIV-infected women
	Study in HIV-infected children[44] (see Appendix, Supplemental Digital Content 1, http://links.lww.com/INF/C173)	126	-	Randomized, double-blind, placebo controlled trial	HPV4 vaccine was safe and immunogenic in HIV-infected children
	Study in women with SLE[45] (see Appendix, Supplemental Digital Content 1, http://links.lww.com/INF/C173)	100	-	Prospective, open-label study	HPV4 vaccine was well tolerated in patients with stable SLE
	Study in women with SLE[46] (see Appendix, Supplemental Digital Content 1, http://links.lww.com/INF/C173)	27	27, 25 and 20 subjects received one, two and three doses of HPV vaccine, respectively	Prospective, open-label study	HPV4 vaccine was generally well tolerated and immunogenic in adolescents and young women with SLE

CDC indicates Centers for Disease Control and Prevention; FDA, Food and Drug Administration; HPV4, quadrivalent human papillomavirus; SPMSD, Sanofi Pasteur MSD; LTFU, long-term follow-up; SLE, systemic lupus erythematosus.

at symptom onset (ie, the indicated age range for the HPV4 vaccine) and diagnosed between 2008 and 2011.[19] Up to 3 years after vaccination, 92 cases and 459 matched controls were identified. Of these, 36 cases and 175 matched controls had an HPV vaccination within the 3-year period before symptom onset (among cases) or index date (among controls). There was no association between HPV4 vaccination and risk of CNS demyelinating diseases up to 3 years later [adjusted odds ratio (OR): 1.05, 95% CI: 0.62–1.78].

Postlicensure Safety Studies Sponsored by Merck and Sanofi Pasteur MSD

Additional long-term follow-up (LTFU) studies for safety and effectiveness were conducted by organizations external to Merck and Sanofi Pasteur MSD, and all data were reviewed and interpreted by external expert committees.

Protocol V501-031: A Postlicensure Surveillance Program to Assess the Safety of the HPV4 Vaccine in a Managed Care Organization Setting (US)

An observational safety surveillance study of the HPV4 vaccine was conducted within Kaiser Permanente's (KP) integrated healthcare delivery systems in Northern and Southern California.[20] It assessed the safety of the HPV4 vaccine administered to females during routine clinical care by evaluating all postvaccination emergency department (ED) visits and hospitalizations. It included 189,629 females vaccinated with at least one dose of the HPV4 vaccine between August 2006 and March 2008. A total of 346,972 doses were administered; 44,001 females received all three recommended doses. The study was overseen by an independent Safety Review Committee (SRC), a group of experts external to the study team and to Merck, who evaluated all postvaccination ED visits and hospitalizations identified in the electronic medical records.

The OR was significantly elevated for 50 event categories during at least one risk interval. As expected in a study conducting multiple comparisons, many events showed statistically significantly decreased ORs (79 event categories). After multiplicity adjustment, the ORs for 10 event categories remained significantly increased, while 12 categories remained significantly decreased. The study did not exclude preexisting conditions, and further medical record review by the SRC revealed that most diagnoses were present before vaccination or that the diagnostic workups had been initiated at the vaccination visit. After complete analysis, only skin infections during days 1 to 14 (all doses combined, OR: 1.8; 95% CI: 1.3–2.4) and syncope on the day of vaccination (all doses combined, OR: 6.0; 95% CI: 3.9–9.2) were noted by the independent SRC as likely associations with HPV4 vaccination. More detailed review of skin infection diagnoses suggested that some may have been local injection site reactions, despite insufficient detail to exclude acute noninjection site infections. The SRC and investigators identified no other safety concerns, including neurological events and VTE.

This study also monitored for new-onset (ie, not preexisting) cases of autoimmune conditions within 6 months after receipt of a dose of the HPV4 vaccine in any healthcare setting (outpatient, ED and hospital).[21] Prespecified autoimmune conditions of interest were composed of three groups: rheumatologic/autoimmune disorders, including immune thrombocytopenia, autoimmune hemolytic anemia, systemic lupus erythematosus, rheumatoid arthritis and juvenile rheumatoid arthritis; autoimmune endocrine conditions, including type 1 diabetes, Hashimoto's disease and Graves' disease; and autoimmune neurologic/ophthalmic conditions, including MS, acute disseminated encephalomyelitis, other demyelinating diseases of the CNS, vaccine-associated demyelination, GBS, neuromyelitis optica, optic neuritis and uveitis. Case reviews by independent

expert committees were conducted to confirm autoimmune diagnoses. To interpret the findings of the study, using the population at KP Southern California only, the background incidence rates of the autoimmune conditions in the unvaccinated female population ages 9–26 years were estimated for comparison with the observed incidence in the vaccinated women.

This study showed no conditions for which the estimated IRR was significantly higher in the vaccinated population than in the background population, except for Hashimoto's disease (IRR: 1.29, 95% CI: 1.08–1.56), a relatively common autoimmune condition in young women.[21] The SRC and the investigator team interpreted the observed IRR for Hashimoto disease as unlikely a true signal, based on the lack of consistent evidence for a safety signal for all autoimmune thyroid conditions [IRR = 0.72 (0.50–1.01) for Graves' disease]. In addition, disease onset was randomly distributed in relation to the vaccination timing, and several confirmed new-onset autoimmune thyroid condition cases were also likely pre-existing cases at the time of vaccination. Overall, the SRC and the investigators identified no autoimmune safety concerns in this study.

HPV4 Vaccine Relationship to Autoimmune Diseases Using the Pharmacoepidemiologic General Research eXtension Information System (France)

This case–control study of French females ages 14–26 years[22] was conducted by a private organization, LA-SER, using the Pharmacoepidemiologic General Research eXtension (PGRx) information system. This system collects cases of diseases and a reference pool of controls, independent of exposure to drugs or vaccines. This study assessed whether HPV4 vaccine was associated with a modified risk of prespecified autoimmune conditions (central demyelination, GBS, lupus, rheumatoid arthritis, undifferentiated connectivitis, myositis and dermatomyositis, type 1 diabetes, autoimmune thyroiditis and idiopathic thrombocytopenic purpura). Between 2007 and 2011, 321 cases with potential autoimmune conditions were recruited from medical specialty centers and 1653 controls (ie, people without the autoimmune condition of interest) were recruited from general practices. A total of 26 of 248 (10.5%) definite autoimmune cases and 232 of 1001 (23.2%) matched controls had confirmed prior exposure to the HPV4 vaccine in the relevant time window at risk. Using unconditional logistic regression, the odds of exposure to the HPV4 vaccine in the cases was compared with matched controls. No evidence of an increased risk of the studied autoimmune disorders was observed following HPV4 vaccination. However, small sample sizes for the individual disorders limited the statistical power to determine any differences. The study observed no unusual accrual of incident autoimmune conditions.

Long-term Extensions of Clinical Trials of the HPV4 Vaccine

Four long-term extension studies were designed to investigate the safety, immunogenicity and effectiveness of the HPV4 vaccine in different populations of females and males. The safety data from two of these studies are described below. Data from Protocols V501-015 and V501-020 are described in the Appendix, Supplemental Digital Content 1, http://links.lww.com/INF/C173.

Protocols V501-018 and V501-019

These two, 10-year studies provide the first long-term safety data among adolescent girls and boys (Protocol-018), and adult women (Protocol-019). As each of the original studies was of 4 years duration, the total follow-up will be approximately 14 years when the studies are completed. The long-term safety data analyzed the incidence of SAEs that a study investigator considered as possibly, probably, or definitely related to prior administration of the HPV4 vaccine or to a study procedure; incidence of death; and incidence of pregnancy, including pregnancy outcomes and fetal or infant condition.

Among the 1781 preadolescent and adolescent girls and boys ages 9–15 who participated in Protocol-018, 1661 (93%) participated in the LTFU study. Three SAEs occurred during the LTFU study: a fatal road traffic accident (4.7 years postdose 3); one case of tonic–clonic movements of 3 minutes duration postphlebotomy (7 years postdose 3) and one case of cranial nerve VII paralysis of 2.7 weeks duration (131 days postdose 3), the last case was reported by the investigator to be vaccine-related. The subject was treated with prednisolone and fully recovered. No significant pregnancy-related adverse outcome trends were observed.[47]

Among the 3817 women ages 24–45 years who participated in Protocol-019,[10] 684 vaccine recipients and 651 placebo recipients from five sites in Colombia participated in the LTFU study.[25] An interim analysis through 6 years postvaccination found no SAEs and approximately 13% of all subjects reported at least one new medical condition—most commonly bacterial vaginitis, hypothyroidism and uterine leiomyoma. None was considered to be vaccine-related.

PASSIVE SAFETY SURVEILLANCE PROGRAMS

Several countries have passive reporting systems for AEs related to medicines and vaccines whereby information is spontaneously reported by health practitioners or the public, rather than systematically collected, as is the case with active surveillance.[48] For example, for vaccines, this includes US VAERS,[27,28] the Canadian Adverse Events Following Immunisation Surveillance System (CAEFISS), the Australian National surveillance program, and the pregnancy registry in the US, Canada and France.[49] Published passive surveillance data for HPV4 vaccine are available from the US[27–29] and Australia,[32–39] as described below. EudraVigilance, a central computer database created by the EMA in December 2001 to capture AE reports for medicines and vaccines licensed across the European Union (EU) is described in the Appendix, Supplemental Digital Content 1, http://links.lww.com/INF/C173.[50]

US VAERS

The US CDC and FDA maintain VAERS.[27,28] Although manufacturers are required to report to VAERS, most information comes from healthcare providers, patients or others.[27,28] When VAERS identifies potential safety concerns, more controlled systems are used to further evaluate them.[29]

The first 2 years (June 2006 to December 2008) of VAERS data following HPV4 vaccine licensure have been published.[30] The safety profile described by these data is consistent with prelicensure data,[9] except for a possible increase in risk of VTE and syncope. The most recent review of VAERS assessed all 25,176 AEs reported among females who received the HPV4 vaccine between June 2006 and March 2014, at which time 67 million doses of HPV4 vaccine had been distributed in the US.[40] Of these, 7.6% were classified as serious (ie, defined as associated with disability, hospitalization, life-threatening illness or death). Reporting peaked in 2008 and decreased each year thereafter—the proportion of reports to VAERS that were classified as serious peaked in 2009 at 12.8% and decreased annually thereafter to 7.4%.[15] Throughout the 7 years of on-going postlicensure surveillance, no previously reported or new medical conditions were identified as safety signals which would require further evaluation.[30]

Another study to examine the safety of the HPV4 vaccine in pregnancy was performed via a search of the VAERS database for

nonmanufacturer reports of AEs in pregnant women who received the vaccine between June 1 2006 and December 31 2013.[31] A total of 147 reports after vaccine administration to pregnant women were evaluated by a review of clinical reports and available medical records. The most frequent pregnancy-specific AE was spontaneous abortion in 15 (10.2%) reports, followed by elective terminations in six (4.1%). Maternal fever was the most frequent nonpregnancy-specific AE in three reports. Two reports of major birth defects were received, and no maternal deaths were noted. One hundred and three (70.1%) reports did not describe an AE. The authors concluded that this review of VAERS reports, comprising more than 6 years of monitoring, found no safety concern among pregnant women who received this vaccine during pregnancy, nor in their offspring.

Australian National Surveillance Program

The Australian government funded a school-based program utilizing the HPV4 vaccine from April 2007 as an ongoing program in 12- to 13-year-old girls, with a catch-up program to 26 years of age until December 2009.[32] All vaccines given in schools are reported through the National HPV Vaccination Program Register, whereas HPV4 vaccines administered in the community are reported to the Register on a voluntary basis. To date, the vaccine coverage rate reported by the Registry has been high, with figures nationally for 12–17 year olds being 83% for dose 1, 78% for dose 2 and 70% for dose 3.[51] Beginning in February 2013, Australia extended the program to include routine male vaccination of first year high school males ages 12–13 years, with a catch-up program extending to the end of 2014 for males ages 14–15 years.[34]

AEs following immunization have been monitored through passive surveillance. In Victoria, the State government established a new central reporting system in April 2007 named Surveillance of AEs Following Vaccination in the Community (SAEFVIC), to capture any significant AEs following any immunizations (AEFI). Physicians expert in vaccination and safety perform clinical review of cases of AEFI (adult and children), and administer further doses of vaccine under supervision where appropriate. AEs that have specifically been addressed by SAFEVIC include syncope, seizures, anaphylaxis and anaphylactoid reactions, as described in the Appendix, Supplemental Digital Content 1, http://links.lww.com/INF/C173.

PREGNANCY REGISTRY FOR THE HPV4 VACCINE

The HPV4 vaccine is not recommended for use during pregnancy since no adequate and well-controlled studies in pregnant women have been performed. Clinical trial data from inadvertent vaccination of pregnant women are described in Ref 15.[41] As a postlicensure commitment to the FDA, the EMA and Canadian health authorities, Merck and Sanofi Pasteur MSD maintained a pregnancy registry for the HPV4 vaccine from 2006 to 2012.[52] The main goals of the registry were to acquire information on pregnancy exposures and outcomes, to identify safety signals and to provide information to healthcare providers, regulators and women about exposures during pregnancy. The registry is a passive surveillance system, based on voluntary postlicensure reports. Women were enrolled if the exposure was reported from the US, Canada or France; there was a unique patient identifier; a healthcare provider was identified; and the exposure occurred within 1 month before the date of onset of the last menstrual period or at any time during pregnancy.

Prospective reports received before the outcome of the pregnancy was known comprised the primary cohort for rate calculations. The primary outcomes of interest were birth defects and pregnancy outcomes including elective and spontaneous abortions (before week 20), fetal deaths (after week 20) and live births. Birth defects were defined as previously described.

As of May 31, 2012, 2802 women exposed to the HPV4 vaccine during pregnancy were enrolled in the Pregnancy Registry. An analysis of this registry covering the first 2 years after licensure (from June 1, 2006 to May 31, 2008) has been reported.[52] The overall rate of spontaneous abortion (6.9 per 100 outcomes, 95% CI: 4.8–9.6) was comparable with that reported in the literature. In the general population, the rate of fetal deaths is approximately 0.62–1 per 100 outcomes, which is slightly lower than the findings of 1.5 per 100 outcomes (95% CI: 0.60–3.09). However, the number of fetal deaths was small (seven reports), and the CI was wide. The overall rate of major birth defects [2.2 per 100 live-born neonates, 95% CI: 1.05–4.05] was similar to the expected prevalence of 2.67%. The congenital anomalies identified varied in type, etiology and gestational age at exposure and did not reveal any consistent pattern. The data did not support a causal relationship between the HPV4 vaccine and birth defects or other adverse pregnancy outcomes.[52]

REVIEW OF SAFETY STATEMENTS BY REGULATORY AND RECOMMENDING ORGANIZATIONS

The safety data for the HPV4 vaccine have been reviewed by numerous global health authorities and regulatory agencies (see Table, Supplemental Digital Content 2, http://links.lww.com/INF/C174). The Global Advisory Committee on Vaccine Safety (GACVS) of the WHO has reviewed the safety of the vaccine on five separate occasions and continues to affirm that the benefit/risk profile of the vaccine remains favorable.[53–57] In addition, the US President's Cancer Panel 2014 report[58] stated that "HPV vaccines are safe and effective similar to other licensed adolescent vaccines." The FDA, CDC and health authorities from other countries continue to monitor the safety of HPV vaccines and follow-up on individual reports of SAEs in both genders.

DISCUSSION

In the 9 years of post-licensure vaccine safety monitoring and evaluation conducted following the initial licensure of HPV4 in the US, no serious safety concerns have been identified in any study conducted worldwide. The safety profile of the HPV4 vaccine has been studied for 13 years including the evaluations made during the clinical trials and in the postlicensure setting. In the post-licensure setting alone, the vaccine has been studied extensively for 9 years in different countries using active and passive surveillance methods. The active safety surveillance studies in Denmark, Sweden, and the US (VSD and KP) alone included more than 1.6 million doses of the HPV4 vaccine. The studies were conducted in diverse populations across the world using different methodologies. It is important to know the background rates of medical conditions in the pre-vaccination era, to allow a rapid distinction between real vaccine-induced AE and alleged concerns. As noted by others, temporal relationship of an AE to a vaccine does not mean causality.[59,60] Importantly, SAEs, such as adverse pregnancy outcomes, autoimmune conditions, MS, VTE, GBS, anaphylaxis and stroke were extensively studied and showed no increase in the incidence of these AEs compared with background rates. Overall, the findings of these postlicensure studies confirm the safety results of the prelicensure clinical studies. Together, these pre- and postlicensure data demonstrate that the HPV4 vaccine has a favorable safety profile.

The first 2 years of VAERS data following HPV4 vaccine licensure found disproportional reporting VTE.[30] The possible association of HPV4 vaccine with VTE was subsequently evaluated in three active surveillance studies. Neither the VSD,[12–14] the KP study,[20,21] nor the Danish/Swedish cohort studies[16,17] found any association between vaccination and VTE. Of all the non-SAEs

reported and reviewed, only syncope and possibly skin infections were found to be associated with vaccination. Syncope was first identified in the VAERS database in 2006, whereby the CDC noted an increased reporting of syncope compared with other vaccines given to females of the same age.[30] Syncope immediately after vaccination is thought to be related to vagal nerve stimulation resulting in bradycardia and transient hypotension, which occurs commonly in adolescents after injections or venipuncture.[37] Since 2006, the Advisory Committee on Immunization Practice has recommended that a 15-minute postvaccination observation period be strongly considered for this patient population, regardless of the type of vaccine being administered.[61] A more recent review of VAERS data has shown that the rate of syncope has declined significantly since this recommendation was instituted.[15]

The studies presented here have limitations. Safety signals from spontaneous passive reporting require further investigation, as the information gathered is often incomplete, and the information is rarely sufficient to establish a causal relationship between vaccine administration and a particular health outcome. Although spontaneous reporting is a valuable tool for providing safety signals in a continuous manner, passive surveillance must be complemented with more formal approaches to confirm, characterize or quantify possible safety concerns.[7,8,62]

Given these limitations and reporting biases, potential causal relationships are tested through the use of appropriate epidemiologic methods, including active surveillance studies. The strengths of the active surveillance studies described here are numerous. The studies included ethnically diverse global populations and the large sample size of most studies allowed for the detection of rare AEs. In most of the active surveillance studies, the AEs of interest were prespecified and the events were adjudicated by an independent review committee. This combination of both active and passive safety surveillance systems provides a comprehensive means of monitoring HPV4 vaccine safety globally, and represents one of the most extensive safety evaluations of any licensed vaccine.

A study published in 2013 examined reasons parents do not have their teens immunized. The intent to not vaccinate for HPV increased from 39.8% in 2008 to 43.9% in 2010 (OR for trend: 1.08, 95% CI: 1.04–1.13). Concern about the safety of HPV vaccine has grown annually.[63] The CDC recently published a systematic review of the literature on the barriers to HPV vaccination of US adolescents.[64] For healthcare professionals, concerns about safety were rarely identified as a barrier to vaccination; by contrast, concerns about vaccine AEs, safety and newness were a key barrier to vaccination for parents. Thus, several resources have been developed by CDC including a dedicated website for healthcare professionals (http://www.cdc.gov/vaccines/youarethekey). In addition, the GACVS have stated that allegations of harm based on incomplete information may lead to vaccine underutilization.[65]

In summary, the data presented here, reflecting experiences with the HPV4 vaccine in hundreds of thousands of recipients, and the reviews by global health experts and organizations, reinforce the favorable safety profile of the vaccine. The HPV4 vaccine has also been shown to be highly effective at the population level, with marked reductions in the prevalence of HPV vaccine-type-related infection and disease.[66–84] The extensive information presented here can be used by healthcare providers to help address questions regarding the safety of the HPV4 vaccine and improve vaccination rates so that patients may benefit from the protection afforded by the vaccine.

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