Clinical Trial and Post-Licensure Safety Profile of a Prophylactic Human Papillomavirus (Types 6, 11, 16, and 18) L1 Virus-Like Particle Vaccine

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Background: We describe the safety of the human papillomavirus (HPV)-6/11/16/18 vaccine using updated clinical trial data (median follow-up time of 3.6 years) and summarize up to 3 years of post-licensure surveillance.
Methods: In 5 clinical trials, 21,480 girls/women aged 9 to 26 years and boys aged 9 to 16 years received ≥1 dose of HPV-6/11/16/18 vaccine or placebo. All serious and nonserious adverse experiences (AEs) and new medical conditions were recorded for the entire study period(s). As of June 2009, >25 million doses of HPV-6/11/16/18 vaccine had been distributed in the United States with >50 million doses globally. Post-licensure safety as summarized by the Centers for Disease Control and Prevention using the United States Vaccine Adverse Event Reporting System database is also reported.
Results: Eight subjects experienced a treatment-related serious AE (0.05% vaccine; 0.02% placebo). Of 18 deaths (0.1% vaccine; 0.1% placebo), all were considered unrelated to study treatment. New medical conditions which were potentially consistent with autoimmune phenomena were reported in 2.4% of both vaccine and placebo recipients. Pain, the most common injection-site AE, occurred more frequently with vaccine (81% vaccine; 75% placeboaluminum; 45% placebo-saline). No differences were seen in the incidence of the most common nonserious AEs–headache and pyrexia. The Vaccine Adverse Event Reporting System has received 14,072 reports for the HPV-6/11/16/18 vaccine since licensure, with only 7% being serious AEs, about half the average reported for licensed vaccines in general.
Conclusions: HPV-6/11/16/18 vaccination was associated with more injection-site pain than placebo but similar incidences of systemic and serious AEs and new medical conditions potentially consistent with autoimmune phenomena. Based on review of post-licensure safety information, the benefits of vaccination to prevent the majority of genital tract precancers and cancers continue to far outweigh its risks.

Key Words: human papillomavirus, prophylactic vaccine, cervical cancer, genital warts, safety

(*Pediatr Infect Dis J* 2010;29: 95–101)

Human papillomavirus (HPV) is the most prevalent of all sexually transmitted diseases and the well-established cause of virtually all cervical cancers and precancers.[1,2] Other manifestations include vulvar, vaginal and head/neck carcinomas, genital warts, and recurrent respiratory papillomatosis.[3,4] As many as 50% of sexually active individuals acquire HPV during their lifetime, although it results in disease in only a minority of them.[5,6]

A prophylactic quadrivalent HPV-6/11/16/18 vaccine (Gardasil/Silgard, Merck & Co, Inc., Whitehouse Station, NJ) was developed for the prevention of diseases associated with the 4 HPV types most commonly found in clinical HPV disease. The HPV-6/11/16/18 vaccine received Food and Drug Administration (FDA) approval in the United States in June 2006 for use in girls and women aged 9 to 26 years. It has since then been approved in more than 100 countries including Australia, Canada, and several European, African, and Asian countries. In the United States, it has been recommended by the Advisory Committee on Immunization Practice[7] and incorporated into the Vaccines for Children Program. Worldwide, it is part of the public vaccination schedule recommendation of several countries. It is produced by recombinantly expressing the major HPV capsid protein (L1) for each of the 4 HPV types in yeast but contains no viral DNA and is therefore noninfectious. The adjuvant used is amorphous aluminum hydroxyphosphate sulfate.

Phase IIb/III efficacy trials of the HPV-6/11/16/18 vaccine were conducted in females aged 16 to 26 years, the age range when peak exposure to HPV occurs.[8–11] Evaluating participants naive to the vaccine-HPV-type(s) throughout completion of the 3-dose regimen, good vaccine efficacy was demonstrated up to 5 years for HPV-6/11/16/18-related cancerous precursors (98% for cervical intraepithelial neoplasia 2/3 or adenocarcinoma in situ[12]; 100% for vulvar/vaginal intraepithelial neoplasia 2/3[13]) and 99% for genital warts.[8–11,14] Adolescent immunogenicity studies documented good anti-HPV type specific responses in girls/boys aged 10 to 15 years.[15,16] Hence, the adult efficacy data were "bridged" to preadolescent/adolescent girls, thereby covering the period preceding typical sexual debut.[15]

Accepted for publication July 15, 2009.
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Supported by Merck Research Laboratories. S.B. and K.R. have received research support from and are consultants for Merck and Co., Inc. S.B. and K.R. have also received research grants from GlaxoSmithKline. M.G. has received research support from Merck and Co. Inc., GenProbe, GlaxoSmithKline, MediSpectra, MGI Pharma, sanofi aventis, 3M, ARIAD, Precision Therapeutics, and Tigris Pharmaceuticals, and honoraria from Merck and Co. Inc., GlaxoSmithKline, MGI Pharma, and Monogen.
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Authors are responsible for the work described in this article. All authors were involved in at least one of the following: conception, design, acquisition, statistical analysis, interpretation of data, drafting the manuscript, and/or revising the manuscript for important intellectual content.
D.R.B. has received lecture fees, advisory board fees, and intellectual property fees from Merck and Co., Inc. A.C. has received lecture fees, grant support and consulting fees from Merck and Co., Inc and GlaxoSmithKline.
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Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Web site (www.pidj.com).

ISSN: 0891-3668/10/2902-0095
DOI: 10.1097/INF.0b013e3181b77906

Updated safety results have been generated for the HPV-6/11/16/18 vaccine, which now include more complete data for 3 of the aforementioned trials that were ongoing at the time of the original application. These safety outcomes include injection-site, systemic and serious AEs, deaths, and new medical conditions (including detailed information on autoimmune disorders). Safety data reported to the US FDA through the Vaccine Adverse Event Reporting System (VAERS) since licensure are also summarized.[17,18]

MATERIALS AND METHODS–CLINICAL TRIALS

Enrollment

The 5 Phase IIb/III clinical trials of the HPV-6/11/16/18 vaccine are summarized in Table, Supplemental Digital Content 1, http://links.lww.com/INF/A205. Detailed protocol descriptions and the primary results have been published previously.[8–10,15,16] The 2 largest studies, FUTURE I and FUTURE II, were designed to be of 4 years duration; however, the independent Data and Safety Monitoring Board recommended vaccination of women in the placebo group earlier than planned due to the high vaccine efficacy and safety seen in these studies. The cumulative data reported here reflect 36,447 person-years-at-risk in the HPV-6/11/16/18 vaccine group (median follow-up time of 3.6 years, upper range = 5.8, 25th–75th percentiles = 2.8–3.8) and 34,220 person-years-at-risk in the placebo group (median follow-up time of 3.6 years, upper range = 5.9, 25th–75th percentiles = 3.5–3.9).

All study design, conduct, and analytic aspects, including safety assessment, were in accordance with established practices for conducting vaccine clinical studies and followed existing Good Clinical Practice guidelines and considerations for the ethical treatment of human subjects.

Vaccination

All studies evaluated a 3-dose vaccination series, given at day 1, month 2, and month 6. In the 3 efficacy trials, eligible subjects were randomized to receive HPV-6/11/16/18 vaccine or aluminum-containing placebo. All participants in Protocol 016 (an immunogenicity study designed to compare age groups) received HPV-6/11/16/18 vaccine, and subjects in Protocol 018 (a safety and immunogenicity study in preadolescent and adolescent boys and girls) were randomized to receive either HPV-6/11/16/18 vaccine or nonaluminum-containing (saline) placebo.[15,16]

Safety Evaluations

All trials evaluated safety by observing subjects for at least 30 minutes while sitting or lying down after each injection, followed by vaccination report card (VRC)-aided surveillance to collect AEs (serious and nonserious) and any use of concomitant vaccines or medications on days 1 to 15 postvaccination. Although all AEs may have been recorded by study subjects or their caregivers for the entire 15-day postvaccination period, the VRCs for all studies prompted the recording of numeric temperatures and injection-site AEs of pain, redness, and swelling on days 1 to 5 only. In addition, in Protocol 018, systemic AEs of sore or aching muscles, sore or aching joints, headaches, hives or other rash, and diarrhea were prompted on the VRC for 15 days. The investigator was responsible for determining seriousness, action taken, and relationship to study vaccine for any VRC-recorded AE. The following criteria were used to assess the relationship between vaccination and the AE: (1) exposure, (2) time course, (3) likely cause, and (4) rechallenge. Only a subset of Protocol 015 subjects (n = 911) was followed using VRC-aided surveillance, whereas the remaining subjects were evaluated using a general surveillance method in which questions were asked at each visit to determine if any serious AEs had occurred.

Serious AEs were to be recorded at any time during the studies if the event resulted in death or was considered by the investigator to be related to vaccine/placebo (ie, treatment-related) or a study procedure. Mandatory worksheets were completed to ensure that no serious AEs went unreported.

In all trials, subjects were evaluated for new medical conditions during the entire course of follow-up. Each subject's medical history was recorded at day 1, including any acute or chronic medical conditions that occurred during the year before study entry and any previous gynecologic conditions or procedures. After day 1, any medical/gynecologic conditions or procedures that occurred since the last study visit were recorded. New medical conditions were not considered AEs if they occurred post month 7 or were not considered by the investigators to be vaccine/placebo- or procedure-related.

Data Analysis

Two populations were considered for evaluations of safety: (1) the overall safety population, which comprised all enrolled subjects regardless of method of surveillance, and (2) the detailed safety population, which comprised only those subjects who were followed using the VRC-aided surveillance method.

AEs and new medical conditions were summarized as frequencies and percentages according to study group and the type of AE reported, considering all visits for the administration of a dose of vaccine or placebo. The incidences of these events in the vaccine and placebo groups were compared through the calculation of risk differences and associated 95% confidence intervals (CIs) and nominal *P*-values for the difference in incidence rates using the method of Miettinen and Nurminen.[19] Formal hypothesis testing was not prespecified, and no adjustments for multiplicity were made. Nominal *P*-values should be interpreted cautiously, as 1 of every 20 comparisons would be expected to be significant ($P < 0.05$) by chance.

Post-Liscensure Surveillance

The FDA and the CDC closely monitor the safety of all vaccines through VAERS, available at http://www.cdc.gov/vaccinesafety/vaers/. VAERS is a national passive reporting system that accepts reports from the public on AEs occurring after vaccination with vaccines licensed in the United States. Approximately 30,000 VAERS reports are filed annually, with 10% to 15% classified as serious (causing disability, hospitalization, life-threatening illness, or death). Anyone can file a VAERS report, including health care providers, vaccine recipients or their parents or guardians, or other members of the public. Recently, the CDC published 2 years of post-licensure safety surveillance that had been reported to the US FDA through VAERS, covering the period from licensure (June 1, 2006) through December 31, 2008.[17] Here we summarize the published information regarding syncope, Guillain-Barré syndrome, and venous thromboembolic events,[17] and provide updated information regarding overall AEs,[18] and deaths that was available as of June 1, 2009.[18] A detailed review of VAERS can be found in reference 20.

RESULTS

Selected baseline characteristics are presented in Table, Supplemental Digital Content 2, http://links.lww.com/INF/A206. Given that only 1 of the 2 trials that enrolled boys had a placebo arm, there was a slight imbalance between the HPV-6/11/16/18 vaccine and placebo groups with respect to gender. Other demographic characteristics were well balanced between the 2 groups.

Of the 21,514 randomized subjects, 21,464 and 10,224 were included in the overall and detailed safety populations, respectively (Fig. 1). Approximately 47% of subjects in the overall safety population were aged 19 years or younger and 24% were in the 9 to 17-year-old age range.

Overall Safety Population

AE-Related Study Discontinuations

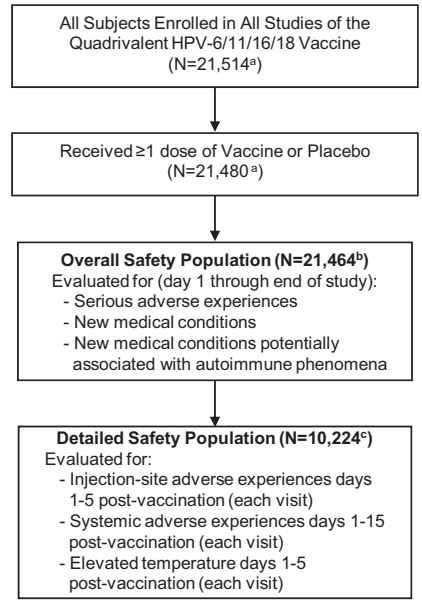
Forty-two subjects (n = 24 vaccine [0.2%]; n = 18 placebo [0.2%]) in the overall safety population had early study discontinuations because of an AE. As seen in Table, Supplemental Digital Content 3, http://links.lww.com/INF/A207, 17 of these discontinuations were attributed to a treatment-related AE (n = 10 vaccine [0.1%]; n = 7 placebo [0.1%]). Twenty early discontinuations were due to a serious AE (n = 11 vaccine [0.1%]; n = 9 placebo [0.1%]), with one deemed treatment-related (hypersensitivity/placebo group).

Serious AEs and Deaths

No significant difference in the rates of serious systemic AEs (Table 1) were noted between vaccine and placebo recipients (risk difference = −0.16, 95% CI = −0.44 to 0.12, $P = 0.253$). No significant differences between the vaccine and placebo groups were found across the system organ classes listed in Table 1 ($P > 0.05$ for all comparisons). For those categories where the number of serious AEs was greater than 5 in either the vaccine or placebo group, a numerically higher percentage of HPV-6/11/16/18 vaccine recipients reported infections.

Six serious systemic AEs among 5 recipients of HPV-6/11/16/18 vaccine were determined by the investigator to be vaccine-related (Table 1). The serious systemic AEs were recurrent vaginal hemorrhage, bronchospasm, gastroenteritis, ulcerative colitis, and a combination of hypertension and headache. Two placebo subjects reported serious systemic AEs determined to be possibly treatment-related: hypersensitivity, and chills/headache/fever. Each of these subjects recovered from the serious AE(s) except for the subject who developed ulcerative colitis, which was reportedly ongoing at the end of the study. For detailed narratives please see Table, Supplemental Digital Content 4, http://links.lww.com/INF/A208. One subject in the HPV-6/11/16/18 vaccine group had a serious injection-site AE that was deemed probably vaccine-related: injection-site joint movement impairment and pain (onset 1 day postdose 2 and lasting 5 months). One serious AE of anaphylactic reaction occurred in the placebo group which was attributed to administration of ceftriaxone (not treatment related).

Eighteen study subjects who received ≥1 dose of vaccine (n = 11 [0.1%]) or placebo (n = 7 [0.1%]) died during the 5 studies (note: there were 5 additional deaths reported in ongoing studies that are not included in this report and 1 death that was reported after the completion of Protocol 018). All deaths were classified by the investigator as not related to study treatment/procedures. Road traffic accidents (n = 7) and suicide (n = 3) accounted for over half of the deaths. The causes of the remaining 8 fatalities were as follows (treatment group/relative day of onset following the last dose): pneumonia/sepsis (vaccine/625 days),



[a] Including only the approved formulation (GARDASIL), thereby excluding Protocol 007 subjects who received quadrivalent HPV vaccine with higher virus-like particle or aluminum doses than the approved formulation (n=552) or Protocol 016 subjects who received quadrivalent HPV vaccine with lower virus-like particle doses than the approved formulation (n=1524).

[b] 16 subjects randomized to vaccine (n=14) or placebo (n=2) who received non-compliant vaccination regimens (mixed regimens of vaccine and placebo) were excluded from the overall safety analysis population.

[c] Includes subjects who used a vaccination report card to record adverse experiences occurring after each vaccination visit; this surveillance method was used in all studies but only at selected sites in Protocol 015 (spontaneous reporting was used by the 11,240 Protocol 015 participants who were not given vaccination report cards).

FIGURE 1. Safety populations: detailed safety and overall safety.

TABLE 1. Serious AEs* by System Organ Class: Overall Safety Population

	HPV-6/11/16/18 Vaccine (N = 11,778)				Placebo Nonaluminum Containing + Aluminum-Containing (N = 9686)			
	All Serious AEs		Treatment-Related†		All Serious AEs		Treatment-Related†	
	n	(%)	n	(%)	n	(%)	n	(%)
No. of subjects with follow-up	11,641				9578			
System organ class								
Blood/lymphatic system	3	(0.03)			0	(0.0)		
Cardiac	3	(0.03)			1	(0.01)		
Gastrointestinal	4	(0.03)	1	(0.01)	2	(0.02)		
General	0	(0.0)			2	(0.02)	1	(0.01)
Hepatobiliary	2	(0.02)			0	(0.0)		
Immune system	0	(0.0)			2	(0.02)	1	(0.01)
Infections/infestations	22	(0.2)	1	(0.01)	14	(0.1)		
Injury/poisoning/procedural	26	(0.2)			32	(0.3)		
Metabolism/nutrition	2	(0.02)			0	(0.0)		
Musculoskeletal/connective tissue	1	(0.01)			2	(0.02)		
Neoplasms benign malignant, unspecified (including cysts and polyps)	1	(0.01)			1	(0.01)		
Nervous system	5	(0.04)	1	(0.01)	5	(0.05)	1	(0.01)
Pregnancy/puerperium/perinatal	34	(0.3)			38	(0.4)		
Psychiatric	3	(0.03)			2	(0.02)		
Renal/urinary	2	(0.02)			2	(0.02)		
Reproductive system/breast	4	(0.03)	1	(0.01)	4	(0.04)		
Respiratory/thoracic/mediastinal	5	(0.04)	1	(0.01)	4	(0.04)		
Skin/subcutaneous tissue	1	(0.01)			1	(0.01)		
Vascular	4	(0.03)	1	(0.01)	2	(0.02)		
Total number of subjects with a serious systemic AE	107	(0.9)	5	(0.04)	103	(1.1)	2	(0.02)
Total number of subjects with a serious injection site AE	1	(0.01)	1	(0.01)	0	(0.0)	0	(0.0)

*Denominator indicates number of subjects with follow-up. A subject may have had >1 serious AE but is counted only once in each row. $P > 0.05$ for all comparisons.
†Determined by the investigator to be possibly, probably, or definitely related to the vaccine/placebo.

pancreatic cancer (vaccine/578 days), infective thrombosis/myocarditis/septic shock (vaccine/359 days), arrhythmia (vaccine/27 days), pulmonary embolism (vaccine/20 days), convulsion/overdose from nonstudy medication (vaccine/4 days), asphyxia (placebo/256 days), and pulmonary embolism (placebo/202 days).

New Medical Conditions

New medical conditions were not considered AEs if they occurred post month 7 or were not determined by the investigators to be vaccine/placebo- or procedure-related. The proportions of subjects reporting new medical conditions by system organ class are shown in Table, Supplemental Digital Content 5, http://links.lww.com/INF/A209. Differences (nominal $P < 0.05$) were noted for 9 categories with a higher incidence observed in the placebo group for 8 of the 9 categories. The single category where the vaccine group had a higher incidence was injury/poisoning/procedural conditions and the specific condition that was reported with the highest frequency was joint sprain (0.82% vaccine; 0.56% placebo). Overall, the most common specific medical conditions were all of an infectious nature, namely vaginal candidiasis (11% vaccine; 14% placebo), bacterial vaginosis (10% vaccine; 12% placebo), nasopharyngitis (9% vaccine; 9% placebo), and urinary tract infection (9% vaccine; 11% placebo). Additional specific medical conditions with an incidence ≥5% were influenza (5% vaccine; 6% placebo), headache (6% vaccine; 5% placebo), and vaginal discharge (6% vaccine; 8% placebo). The vaccine group had one case of 6th cranial nerve paralysis of unknown cause (reported 18 months after dose 3); and one case of pseudoparalysis of 24 hours duration (reported 30 months after dose 3). Tongue paralysis which was attributed to metoclopramide, occurred in one placebo recipient (reported 18 months after dose 3).

Anaphylactic reaction and anaphylactic shock were reported as a new medical condition in 7 subjects (5 vaccine; 2 placebo) and 2 subjects (2 vaccine), respectively. In the 7 vaccine recipients, 5 had attributable causes: ibuprofen (6 months postdose 3), naproxen sodium (12 months postdose 3), gentamicin (18 months postdose 3), nuts (42 months postdose 3), and buckwheat (30 months postdose 3). The remaining 2 cases had unknown causes (21 months and 42 months postdose 3). Of the 2 reported events of anaphylactic reaction in the placebo group, each was due to an unknown cause (both 18 months postdose 3).

The proportions of subjects who reported new medical conditions potentially indicative of an autoimmune phenomenon after day 1 was 2.4% in both vaccination groups (Table, Supplemental Digital Content 6, http://links.lww.com/INF/A210). The most common autoimmune conditions were arthralgia (1.0% vaccine; 1.0% placebo), hypothyroidism (0.3% vaccine; 0.4% placebo), and psoriasis (0.1% vaccine; 0.2% placebo). Differences (nominal $P < 0.05$) were noted between the vaccine and placebo groups for thyroiditis (8 vaccine; 1 placebo), rheumatoid arthritis (5 vaccine; 0 placebo), and proteinuria (9 vaccine; 1 placebo). Rates for each of these conditions in the vaccine group were <0.1%.

Detailed Safety Population

Temperature Elevations

A higher proportion of vaccine recipients compared with placebo recipients (11% vs. 10%) recorded a maximum temperature of ≥37.8°C (≥100°F) oral or oral equivalent ($P < 0.05$). Temperature elevations of ≥38.9°C (≥102°F) were reported by 1.5% and 1.0% of vaccine and placebo recipients, respectively.

Injection-Site and Systemic AEs

In both vaccine and placebo recipients, pain, swelling, and erythema were the most commonly reported injection-site AEs (Table 2). The proportion of subjects reporting an injection-site AE within 5 days after any vaccination was higher in vaccine recipients compared with aluminum- (83% vs. 77%, $P < 0.05$) or nonaluminum-containing (83% vs. 49%, $P < 0.05$) placebo recipients. Most injection-site AEs reported in vaccine recipients were mild-to-moderate in intensity (78%). Across all 3 doses, vaccine recipients were more likely to report injection-site AEs of severe intensity compared with placebo recipients (4% vs. 2%, $P < 0.05$).

Table, Supplemental Digital Content 7, http://links.lww.com/INF/A211, presents the number and percentage of subjects with any systemic clinical adverse experience (incidence ≥1% in one or more vaccination groups) reported within 15 days after any vaccination visit, categorized by system organ class. The proportions of subjects who reported a systemic adverse experience were comparable among the vaccination groups. Comparing vaccine with placebo, the most common systemic adverse experiences were headache (26% vs. 28%), pyrexia (13% vs. 11%), and nausea (6% vs. 6%). Syncope was reported in 0.3% versus 0.4% of vaccine and placebo recipients, respectively, of which 0.1% versus 0.2% was considered vaccine-related. Three subjects in the vaccine group and 2 subjects in the placebo group had nontreatment related vasovagal syncope. One subject in the placebo had treatment-related vasovagal syncope.

VAERS Post-Licensure Surveillance Summary

As of June 1, 2009, more than 25 million doses of HPV-6/11/16/18 vaccine had been distributed in the United States. Since June 8, 2006 (date of US vaccine licensure) and June 1, 2009,

TABLE 2. Injection-Site AEs* With Incidence ≥1% (Days 1 to 5 Following Any Vaccination, Detailed Safety Population)

	HPV-6/11/16/18 Vaccine (n = 6160)		Placebo (Nonaluminum Containing) (n = 594)		Placebo (Aluminum-Containing) (n = 3470)	
	n	(%)	n	(%)	n	(%)
≥1 injection site AE	5030/6069	(82.9)	289/584	(49.5)	2638/3410	(77.4)
Bruising	156/6069	(2.6)	13/584	(2.2)	110/3410	(3.2)
Mild	132/6069	(2.2)	11/584	(1.9)	99/3410	(2.9)
Moderate	20/6069	(0.3)	2/584	(0.3)	11/3410	(0.3)
Severe	4/6069	(0.1)	0/584	(0.0)	0/3410	(0.0)
Postdose 1	2/6068	(<0.1)	—	—	—	—
Postdose 2	0/5961	(0.0)	—	—	—	—
Postdose 3	2/5837	(<0.1)	—	—	—	—
Erythema†‡§	1432/6069	(23.6)	77/584	(13.2)	629/3410	(18.4)
Mild	1201/6069	(19.8)	71/584	(12.2)	556/3410	(16.3)
Moderate	171/6069	(2.8)	6/584	(1.0)	59/3410	(1.7)
Severe	53/6069	(0.9)	0/584	(0.0)	14/3410	(0.4)
Postdose 1	15/6068	(0.2)	—	—	9/3410	(0.3)
Postdose 2	17/5961	(0.3)	—	—	2/3351	(<0.1)
Postdose 3	24/5837	(0.4)	—	—	3/3295	(<0.1)
Pain†‡¶	4935/6069	(81.3)	265/584	(45.4)	2572/3410	(75.4)
Mild	3259/6069	(53.7)	229/584	(39.2)	1903/3410	(55.8)
Moderate	1523/6069	(25.1)	33/584	(5.7)	623/3410	(18.3)
Severe	152/6069	(2.5)	3/584	(0.5)	46/3410	(1.3)
Postdose 1	47/6068	(0.8)	1/584	(0.2)	12/3410	(0.4)
Postdose 2	57/5961	(1.0)	1/564	(0.2)	18/3351	(0.5)
Postdose 3	75/5837	(1.3)	1/559	(0.2)	21/3295	(0.6)
Paraesthesia†	22/6069	(0.4)	10/584	(1.7)	5/3410	(0.1)
Mild	19/6069	(0.3)	10/584	(1.7)	4/3410	(0.1)
Moderate	3/6069	(<0.1)	0/584	(0.0)	1/3410	(<0.1)
Severe	0/6069	(0.0)	0/584	(0.0)	0/3410	(0.0)
Pruritus†	167/6069	(2.8)	5/584	(0.9)	97/3410	(2.8)
Mild	136/6069	(2.2)	5/584	(0.9)	81/3410	(2.4)
Moderate	30/6069	(0.5)	0/584	(0.0)	13/3410	(0.4)
Severe	1/6069	(<0.1)	0/584	(0.0)	3/3410	(0.1)
Postdose 1	1/6068	(<0.1)	—	—	2/3410	(0.1)
Postdose 2	0/5961	(0.0)	—	—	0/3351	(0.0)
Postdose 3	0/5837	(0.0)	—	—	1/3295	(<0.1)
Swelling†‡‖	1469/6069	(24.2)	45/584	(7.7)	540/3410	(15.8)
Mild	1086/6069	(17.9)	39/584	(6.7)	444/3410	(13.0)
Moderate	261/6069	(4.3)	5/584	(0.9)	75/3410	(2.2)
Severe	116/6069	(1.9)	1/584	(0.2)	21/3410	(0.6)
Postdose 1	32/6068	(0.5)	0/584	(0.0)	6/3410	(0.2)
Postdose 2	48/5961	(0.8)	0/564	(0.0)	8/3351	(0.2)
Postdose 3	52/5837	(0.9)	1/559	(0.2)	8/3295	(0.2)

*Denominator indicates number of subjects with follow-up for the specific adverse experience. A subject may have had >1 injection site AE, or >1 severe injection site AE, but is counted only once in each row.

†Vaccine versus nonaluminum containing placebo, P value <0.05, unadjusted for multiple comparisons.

‡Vaccine versus Aluminum containing placebo, P value <0.05, unadjusted for multiple comparisons.

§For erythema, the severity was unknown for 7 vaccine recipients. Intensity was measured in size (inches): mild (0 to ≤1), moderate (>1 to ≤2), severe (>2).

¶For pain, the severity was unknown for 1 vaccine recipient.

‖For swelling, the severity was unknown for 6 vaccine recipients. Intensity was measured in size (inches): mild (0 to ≤1), moderate (>1 to ≤2), severe (>2).

VAERS had received 14,072 reports of AEs after HPV-6/11/16/18 vaccination.[18] Of these, 93% were nonserious reports, including fainting, pain, and swelling at the injection site, headache, nausea, and fever.

Serious AEs were defined by the Code of Federal Regulations as hospitalization, death, permanent disability, life threatening illness, or certain other medically important conditions. A confirmed case was defined as a report that met the case definition, but was not necessarily associated with the vaccination. The serious AEs which were summarized included deaths, Guillain-Barré Syndrome (GBS), and blood clots. VAERS had received 43 US reports of death following HPV-6/11/16/18 vaccination as of June 1, 2009 (26 confirmed, 9 still under investigation and 8 unconfirmed due to no identifiable patient information). In the 26 reports confirmed, the CDC noted no unusual pattern or clustering of the deaths to suggest vaccine causality.[18] The time of death after vaccination ranged from 2 to 405 days.[17]

GBS is a rare disorder that occurs in 1 to 2 out of every 100,000 adolescents per year.[18] VAERS had received 42 reports of GBS after HPV-6/11/16/18 vaccination.[17] Most of the reports could not be confirmed or did not meet the case definition.[17] Of the 12 cases that met the Brighton case definition, 6 reported concomitant vaccination with meningococcal conjugate vaccine, and 6 were administered HPV-6/11/16/18 vaccine alone.[21] The CDC reports show a temporal association only, without evidence to support a causal relationship to vaccination. As of December 31, 2008, there were 56 reports of venous thromboembolism (VTE) after vaccination with 31 reports with sufficient information for clinical review.[17] The CDC reported that there is increased reporting of VTE compared with what has been found for other vaccines, but noted that 28 of the 31 cases (90%) had a known risk factor for blood clots, such as taking oral contraceptives. The background rates of venous thromboembolism among oral contraceptive users (aged 14–29 years) is 21 to 31 per 100,000 woman years.[22]

As of December 31, 2008, VAERS has received 1896 reports of syncope with 5% of reports coded as serious.[17] The most commonly associated symptoms in serious reports of syncope were loss of consciousness, dizziness, headache, nausea, vomiting, fall, and head injury.

DISCUSSION

This report summarizes the available data from clinical trials of more than 20,000 male and female adolescents and women aged 9 to 26 years with up to 5.8 years (median = 3.6 years) of follow-up. In addition, passive surveillance is reported for up to 3 years post-licensure with more than 25 million doses distributed in the United States. HPV-6/11/16/18 vaccination was generally well tolerated in the clinical trials. Among the serious AEs reported, the vaccine and placebo groups were comparable with respect to the overall incidence and types of serious AEs. The proportions of subjects reporting new medical conditions were comparable between vaccine and placebo recipients, with no safety signals identified regarding allergic reactions or other immune-mediated conditions. Vaccine was associated with higher incidences of injection-site AEs and transient low-grade fevers than aluminum-containing placebo, but few subjects discontinued vaccination due to an AE in the clinical trials. Based on review of the available post-licensure safety information, the FDA and CDC concluded the vaccine continues to be safe and effective, and its benefits continue to outweigh its risks.[23]

Our data confirms that aluminum-based adjuvants are associated with higher rates of transient injection site AEs—shortcomings which are offset by their benefits in priming the immune system.[24] The HPV-6/11/16/18 vaccine contains a proprietary adjuvant which is currently used in other vaccines (ie, COMVAX, PedvaxHIB, and VAQTA) which have been distributed globally in over 300 million doses. Based on the notable relative differences in injection-site AE incidences between nonaluminum placebo recipients and the aluminum placebo recipients, particularly with respect to pain and swelling, a high proportion of the injection-site reactions observed with the HPV-6/11/16/18 vaccine clearly stem from the aluminum adjuvant.

Pediatric and adolescent episodes of postvaccination syncope, including cases associated with convulsion, have been described in the literature for several vaccines.[25–29] In the clinical trials, we observed syncope in equal rates in the vaccine (0.1%) and placebo (0.2%) arms although it should be noted that in clinical trials, patients were observed for 30 minutes postvaccination and generally remained in a seated position during this time. In Australia, a mass hysterical response to vaccination in school-aged girls has been reported.[30] In the post-licensure surveillance using VAERS, the CDC noted an increased reporting of syncope compared with other vaccines given to females of the same age.[17] Recognizing a heightened propensity for immediate postvaccination syncope among adolescents and young adults, 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.[28]

Rare and potentially serious AEs may not emerge during clinical trial experiences involving a limited number of people. Pharmacoviligance relies on the collection, management, and assessment of safety data by regulatory authorities such as the FDA and the European Medicines Agency. Of the 14,072 reports that VAERS has received for the HPV-6/11/16/18 vaccine since licensure, 7% were reports of serious AEs, about half of the average for individual vaccines overall. In Australia, where vaccine uptake is more than 80%, rare cases of anaphylaxis (2.6 events per 100,000 doses) and no cases of anaphylactic shock have been observed.[31] Others analyses have provided further support for the rareness of anaphylaxis and other serious AEs after administration of millions of doses of this vaccine.[31,32]

The clinical trial and postmarketing safety analyses were accompanied by some limitations. VRC-aided surveillance was not applied to subjects outside of North America in the largest clinical trial (FUTURE II). Hypotheses regarding specific systemic clinical adverse experiences or new medical conditions were not specified a priori. Nominal *P*-values, which were not adjusted for multiplicity, should be interpreted cautiously as 1 of every 20 comparisons would be expected to be significant ($P < 0.05$) by chance. As noted, for 8 of the 9 new medical conditions system organ classes for which the nominal P value was <0.05, the incidence was higher in the placebo group than in the vaccine group, indicating that the differences were likely due to chance. Passive post-licensure surveillance systems such as VAERS provide useful information on trends in vaccine safety. However, because the US does not have a national registry for immunization and vaccination, VAERS cannot report the total number of people who have received the HPV-6/11/16/18 vaccine. In addition, judgments about causality (whether the vaccine was truly responsible for an AE) cannot be made from VAERS reports because of incomplete information and lack of a control group. This is exemplified by a recent large-scale cohort study which was undertaken to anticipate events that might be mistakenly assumed to be caused by HPV immunization.[33] Using a database of female adolescents (n = 214,896) and young adults (n = 221,472) followed in the pre-HPV vaccine era (2005), Siegrist et al[33] identified the most frequent immune-mediated conditions, ie, those most likely to be tempo-

rally associated with a putative HPV vaccine administration. They found immune-mediated conditions to be a frequent cause (10.3%) of emergency room consultation by adolescent girls. Such use of population-based data allows for the rapid assessment of vaccine-safety issues that may compromise vaccine programs.

In conclusion, in clinical trials conducted in the 9 to 26-year-old age range, vaccination was generally well tolerated with no apparent adverse health impact following completion of the vaccination regimen. The pharmacovigilance plan for the HPV-6/11/16/18 vaccine is ongoing, with continuous monitoring as the postmarketing experience becomes more prolonged and widespread.

ACKNOWLEDGMENTS

The authors thank all the participating investigators and subjects, as well as the following individuals for their specific contributions to this report: Mark J. Johnson, Kathy Harkins, Mary Anne Rutkowski, Carolyn Maass, Laurie Orloski, and Mary Anne Goss.

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