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Safety, immunogenicity, and efficacy of quadrivalent human papillomavirus (types 6, 11, 16, 18) L1 virus-like-particle vaccine in Latin American women

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The prevalence of HPV infection in Latin America is among the highest in the world. A quadrivalent (types 6/11/16/18) human papillomavirus L1 virus-like-particle vaccine has been shown to be 95–100% effective in preventing HPV 6/11/16/18-related cervical and genital disease in women naïve to vaccine HPV types. A total of 6,004 female subjects aged 9–24 were recruited from Brazil, Mexico, Colombia, Costa Rica, Guatemala and Peru. Subjects were randomized to immunization with intramuscular (deltoid) injections of HPV vaccine or placebo at enrollment (day 1), month 2 and month 6. Among vaccinated subjects in the per-protocol population from Latin America, quadrivalent HPV vaccine was 92.8 and 100% effective in preventing cervical intraepithelial neoplasia and external genital lesions related to vaccine HPV types, respectively. These data support vaccination of adolescents and young adults in the region, which is expected to greatly reduce the burden of cervical and genital cancers, precancers and genital warts.

Key words: HPV; cervical cancer; vaccine

Infection with human papillomavirus (HPV) is considered to be an obligate step in the development of cervical cancer.[1] Human papillomavirus DNA has been isolated from more than 99% of all cases of cervical cancer.[1] Of the ~200 distinct HPV genotypes that have been identified to date, ~40 are known to be associated with genital infection, and about 30 types have been isolated from women with cervical cancer.[2] High-risk HPV types include HPV 16 and 18, and it is these types which are responsible for the majority of cervical cancers.[2] HPV types 6 and 11 can lead to anogenital condylomata acuminata (genital warts)[3]; a potentially significant medical problem.

The incidence of cervical cancer in the Latin American region is among the highest in the world[4] (33.5 cases per 100,000); even higher than other developing regions and countries such as sub-Saharan Africa (31.0 cases per 100,000) and South central and Southeast Asia (18.3 cases per 100,000).[5] The highest incidence rates are observed in Haiti (87 per 100,000), Bolivia (55 per 100,000), Peru (48 per 100,000) and Nicaragua (47 per 100,000), and the lowest rates are reported from Argentina (23 per 100,000) and Uruguay (19 per 100,000).[6] Each year near 493,000 new cases of invasive cancer of the uterine cervix are diagnosed; 83% of which (~409,000 cases) occur in developing countries and 18% (~86,000 cases) specifically in Latin America (Central America, South America and the Caribbean).[7] Acquisition of HPV infection starts with the onset of sexual activity and can be as high as 42.5% after 4 years of follow-up as was observed in a cohort of Colombian women between 15 and 19 years of age.[8]

The prevalence of HPV infection in women with normal cervical cytology in Latin America has been reported to range from 14.5 to 16.6%. Literature suggests a prevalence of HPV of 14.5% in Morelos, Mexico,[9] 14.8% in Bogotá, Colombia,[10] 14.0% in Santiago, Chile,[11] 16.6% in Concordia, Argentina[12] and 14% in Sao Paolo, Brazil.[13] These rates contrast sharply with the 3.0% prevalence of HPV infection seen in Barcelona, Spain.[14] This imbalance is further illustrated by recent literature indicating that women who had immigrated from Colombia to Spain were found to have a 27% prevalence of high-risk HPV types, compared to 8% of Spanish women living in the same region in Spain.[15] Furthermore, case–control studies of cervical cancer conducted in Brazil, Colombia, Paraguay and Peru have shown that HPV 16 and 18 are responsible for 65% of cervical squamous cell carcinoma and 84% of cervical adenocarcinomas in the countries listed above.[16,17]

Genital warts constitute a separate, yet not unimportant issue for public health systems in Latin America. The incidence of genital warts has been consistently increasing for the last decade and is a concern for several reasons.[18] Foremost, the elevated healthcare costs incurred in the course of treating recurrent genital warts can be substantial. There can also be a significant impact on a person's quality of life when dealing with genital warts, especially related to their sexuality.[19]

Screening women for cervical disease *via* Pap smear examination has been a successful cervical cancer prevention strategy for the last 50 years in developed countries. Unfortunately, the Latin American region does not have a comprehensive and organized screening strategy for prevention and detection of premalignant and malignant cervical conditions. Cervical cancer screening programs in the region can vary in their effectiveness and coverage, and are nonexistent in some places. The few relatively well-organized screening programs that do exist in Latin America are primarily located in large urban centers.[20]

The necessity of developing a primary prevention strategy to decrease the incidence of HPV infection and its consequences is evident in Latin America, as well as the rest of the world. Recent Phase III trials conduced in ~17,500 young adult women have demonstrated that a prophylactic quadrivalent (types 6/11/16/18) HPV L1 virus-like particle (VLP) vaccine was highly effective in preventing HPV 6-, 11-, 16- or 18-related cervical, vaginal and vulvar neoplasias (as well as anogenital condylomata) in women

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who were naïve to the respective vaccine HPV types at enrollment.[21,22] Durability of immune response has also been shown for at least 5 years.[23,24] To better understand the effects of the HPV vaccine on HPV-related disease in Latin America, this report presents the results of an analysis of data from subjects who received the vaccine residing in Brazil, Mexico, Colombia, Costa Rica, Guatemala and Peru.

Material and methods

Study design

This analysis is representative of combined data gathered from the international clinical trial program of quadrivalent HPV (types 6/11/16/18) L1 VLP vaccine (GARDASIL™, Merck, West Point, PA). In the context of several large international studies of quadrivalent HPV vaccine, a total of 6,004 female subjects aged 9–24 years old were recruited from Brazil, Mexico, Colombia, Costa Rica, Guatemala and Peru. These subjects took part in 1 of 5 blinded, placebo-controlled (with the exception of protocol 016) clinical trials (Merck protocols V501-007, -013, -015, -016 and -018) designed to analyze the efficacy, safety and immunogenicity of quadrivalent HPV (types 6, 11, 16 and 18) L1 VLP vaccine. All trials contributing data to this report enrolled nonpregnant, healthy women who had no prior abnormal (ASC-US or worse) Papanicolaou (Pap) smears, and reported a lifetime history of 4 or fewer male sex partners. Eligible subjects were randomized to immunization with intramuscular (deltoid) injections of quadrivalent HPV vaccine or placebo (no placebo arm in protocol 016) at enrollment (day 1), month 2 and month 6. Detailed methodologies of these component clinical trials have been previously reported.[21,22,25–27]

This study did not exclude subjects with prior HPV infection. Participants were asked to use effective contraception. All subjects or parents/legal guardians signed informed consents following review of the protocol procedures. Studies were conducted in conformance with applicable country or local requirements regarding ethical committee review, informed consent and other statutes or regulations regarding the protection of the rights and welfare of human subjects participating in biomedical research. No monetary compensation was allowed in some countries due to local restrictions; instead participants received compensation for travel expenses and were given the opportunity to participate in educational activities.

Study vaccine

The quadrivalent vaccine consisted of a mixture of 4 recombinant HPV type-specific VLPs composed of the L1 major capsid proteins of HPV types 6, 11, 16 and 18 synthesized in *Saccharomyces cerevisiae*.[28–30] The vaccine is composed of 20 μg of HPV 6 VLP, 40 μg of HPV 11 VLP, 40 μg of HPV 16 VLP and 20 μg of HPV 18 VLP, formulated with 225 μg of aluminum adjuvant in a total carrier volume of 0.5 mL. The 4 VLP types were purified and adsorbed onto amorphous aluminum hydroxyphosphate sulfate adjuvant (AAHS). The placebo contained the same adjuvant and was visually indistinguishable from vaccine. A small number of subjects in Colombia ($n = 43$) and Mexico ($n = 28$) received HPV 16 monovalent L1 VLP vaccine.

Clinical follow-up

Baseline demographic information was recorded from subjects at enrollment. Information regarding, sexual history, gynecologic history, pregnancy history and contraceptive use was collected only from subjects older than 15 years of age. Subjects 9–15 years of age were sexually naïve at enrollment. Smoking history, hormonal contraceptive use and lactation status was obtained only from subjects older than 15 years of age. Serology samples for the determination of HPV serostatus were gathered at enrollment and at specific times during the trials included in these analyses. Cervical and anogenital swabs were obtained for HPV DNA detection through polymerase chain reaction (PCR) testing. Mandatory tests for Chlamydia trachomatis and Neisseria Gonorrheae were performed at day 1. Testing for other reproductive tract infections was performed as indicated (at the investigators discretion).

Ascertainment of lesions

Subjects underwent routine and comprehensive anogenital examination to evaluate the presence of disease, including cervical intraepithelial neoplasia (CIN), vaginal intraepithelial neoplasia (VaIN), vulvar intraepithelial neoplasia (VIN) and genital warts. Comprehensive anogenital examination included visual inspection of the perianal area, vulva and vagina with the naked eye and a magnifying glass or colposcope. Overt lesions were photographed (protocol 013) and a clinical diagnosis recorded. Lesions considered likely HPV-related or of unknown etiology were biopsied, whereas those considered not HPV-related were not biopsied or excised for study purposes. Clinical management of cervical lesions was managed based on a colposcopy algorithm. Descriptions of the clinical management methods for cervical and other lesions have been previously described.[21,22,25–27]

Populations and case counting

The per-protocol immunogenicity population includes all subjects aged 9–24 who were not general protocol violators; received all 3 vaccinations within acceptable day ranges; were seronegative at day 1 and (for all subjects except those <16 years old in protocols 016 and 018) negative for HPV DNA via PCR assay from day 1 through month 7 for the relevant HPV type(s); and had a month 7 serum sample collected within an acceptable day range. Analyses of efficacy against both CIN and external genital lesions (EGL; includes VIN, VaIN and Condyloma) took place in the per-protocol efficacy population (PPE). This population included all subjects aged 16–24 who received all 3 vaccinations and were seronegative and PCR-negative for the relevant HPV type(s) at enrollment (as well as PCR-negative at month 7 to the appropriate vaccine-related HPV types). Cases were counted starting 30 days after the third dose. A second analysis population was called the unrestricted susceptible population. This population included subjects who received at least 1 dose of quadrivalent HPV vaccine and were seronegative and PCR negative at enrollment for the appropriate vaccine-related HPV type. Case counting for this population began 30 days after enrollment. An intention-to-treat population analysis was also conducted and considered all subjects who received at least 1 dose of vaccine or placebo and returned for follow-up. Clinical endpoints for this population were counted from day 1. Vaccine efficacy was considered statistically significant when the lower bound of the 95% confidence interval exceeded zero.

A vaccine-HPV-type-related case of CIN or EGL was defined as a tissue sample diagnosed by the Pathology Panel as one of these abnormalities with vaccine-HPV-type DNA detected in tissue from the same lesion, as previously described.[21,22]

Immunogenicity assays

The immunogenicity of quadrivalent HPV vaccine was measured using a competitive Luminex-based immunoassay (cLIA) (developed by Merck Research Laboratories, West Point, PA, using technology from the Luminex Corporation, Austin TX).[31] Antibody titers were determined in a competitive format in which known, type-specific phycoerythrin labeled, neutralizing mAbs competed with the subject's serum antibodies for binding to conformationally sensitive, neutralizing epitopes on the VLPs. The fluorescent signals from the bound HPV-specific detection mAbs are inversely proportional to the subject's neutralizing antibody titers. Results for the assay were reported as concentration of antibody in milli-Merck Units per milliliter (mMU/mL). The high, low and negative controls used for this assay were spiked controls from heat-inactivated African Green Monkey serum diluted in antibody-depleted human sera.

Results

Mean age and weight at enrollment were similar between those groups of female subjects that received quadrivalent HPV vaccine and those that received placebo (Table I). A similar ethnic and cultural profile was also seen between vaccine and placebo cohorts, with the largest amount of subjects in both groups identifying themselves as Hispanic (importantly, the notion of "Hispanic" may be viewed differently by subjects in different countries, and therefore the percentages of subjects in ethnic categories may vary according to this). The majority of subjects in both the vaccine and placebo cohorts identified themselves as having never smoked.

At baseline, 8.0% of female subjects ages 16–24 had a non-HPV-related reproductive tract infection (RTI) or sexually transmitted disease (STD); the prevalence of RTIs and STDs in both vaccine and placebo cohorts was similar. Chlamydia trachomatis was the most common STD at enrollment.

TABLE I – SUMMARY OF LATIN AMERICAN SUBJECT CHARACTERISTICS

	Vaccine (N = 3,147)[1] n (%)	Placebo (N = 2,857)[2] n (%)
Age (years)		
Mean	19.8	20.3
Standard Deviation	3.0	2.2
Range	9–23	9–24
Weight (kg)		
Mean	56.0	56.9
Standard Deviation	11.2	10.5
Median	55	55
Race/Ethnicity		
Asian	6 (0.2)	11 (0.4)
Black	241 (7.7)	275 (9.6)
Hispanic	1,182 (37.6)	1,014 (35.5)
White	865 (27.5)	733 (25.7)
Other[3]	851 (27.0)	823 (28.8)
Smoking[4]		
Current Smoker	686 (21.8)	701 (24.5)
Ex-smoker	181 (5.8)	186 (6.5)
Never smoked	2,016 (64.1)	1,908 (66.8)

Percent is computed as [(n/N) × 100]. N = number of subjects randomized; n = number of subjects with the indicated characteristic.
[1]Brazil, N = 1,290; Colombia, N = 725; Costa Rica, N = 48; Guatemala, N = 16; Peru, N = 393; Mexico, N = 675).–[2]Brazil, N = 1,171; Colombia, N = 637; Costa Rica, N = 0; Guatemala, N = 0; Peru, N = 374; Mexico, N = 675.–[3]Includes multiracial subjects.–[4]Smoking status was not collected for adolescents in protocols 016 and 018.

Analysis of the composite HPV 6, 11, 16 and 18 status of female subjects 16–24 years of age by both PCR and serology assay indicated that 25.1 and 13.9% of subjects were positive to one of these vaccine HPV types at baseline by serology and PCR, respectively (Table II). Thirty-two percent of subjects were positive to a vaccine-related HPV type by either serology or PCR. The percentages of subjects who were positive to vaccine-related HPV types by PCR or serology or both were comparable between the placebo and vaccine cohorts. Serology data gathered from female subjects who were 9–24 years old at enrollment strongly illustrate the cumulative risk of acquiring HPV infection as age increases (Table III). For example, 96.5% of subjects below 12 years of age were naïve to all 4 vaccine-related HPV types at enrollment. This percentage dropped to 73.4% in those subjects who were 18 years old at enrollment and 65.1% in those subjects who were age 23 or older at enrollment. Additionally, the majority of subjects who were found to be positive to a vaccine-related HPV type were found to be positive to only one vaccine-related HPV type. Lifetime number of sexual partners at enrollment was an indirect indicator of PCR positivity to vaccine-related HPV types. Virginal subjects at enrollment were far more likely to be naïve to all 4 vaccine-related HPV types than those subjects who had 4 lifetime sexual partners (98.7 *versus* 74.4%, respectively) (data not shown). Only 2 subjects were positive to 3 vaccine-related HPV types at enrollment, and none were positive to all 4 vaccine-related HPV types at enrollment.

Subjects in the per-protocol immunogenicity population experienced large increases in anti HPV 6, 11, 16 and 18 geometric mean titer (GMT) after each successive vaccination. Geometric mean titers for both cohorts (girls 9–15 years old and women 16–24 years old) were higher than levels generally seen during natural responses to HPV infection. Subjects 9–15 years old had a stronger antibody response against vaccine-related HPV types than subjects 16–24 years old, indicated by higher GMT values at month 7 (Table IV).

Among all enrolled subjects in the PPE population, efficacy against CIN1 or worse related to HPV 6, 11, 16 or 18 was 92.8% (95% CI: 77.6, 98.6), and efficacy against CIN2 or worse was 95.3% (95% CI: 71.0, 99.9) (Table V). There was 1 case of CIN3 among subjects who received the quadrivalent HPV vaccine. In those subjects who received at least 1 dose of quadrivalent HPV vaccine and were seronegative and PCR negative at enrollment for the appropriate vaccine-related HPV type (unrestricted susceptible population), efficacy against HPV 6-, 11-, 16- or 18-related CIN was 91.2, 100, 86.4, and 93.4%, respectively (Table V). The

TABLE II – SUMMARY OF COMPOSITE HPV 6, 11, 16, AND 18 STATUS BY PCR AND/OR SEROLOGY AT ENROLLMENT; FEMALES 16–24 YEARS OLD

	Vaccine m/n (%)	Placebo m/n (%)	Total m/n (%)
Composite positivity to HPV 6, 11, 16, or 18			
By serology[1]	701/2,876 (24.4)	721/2,791 (25.8)	1,422/5,667 (25.1)
By PCR[2]	374/2,843 (13.2)	408/2,764 (14.8)	782/5,607 (13.9)
By serology or PCR	876/2,857 (30.7)	929/2,769 (33.6)	1,805/5,626 (32.1)
Positivity by PCR			
HPV 6	86/2,852 (3.0)	117/2,765 (4.2)	203/5,617 (3.6)
HPV 11	23/2,856 (0.8)	23/2,772 (0.8)	46/5,628 (0.8)
HPV 16	225/2,850 (7.9)	236/2,768 (8.5)	461/5,618 (8.2)
HPV 18	77/2,854 (2.7)	93/2,769 (3.4)	170/5,623 (3.0)
Positivity by serology			
HPV 6	284/2,874 (9.9)	292/2,790 (10.5)	576/5,664 (10.2)
HPV 11	88/2,874 (3.1)	98/2,790 (3.5)	186/5,664 (3.3)
HPV 16	386/2,874 (13.4)	407/2,790 (14.6)	793/5,664 (14.0)
HPV 18	114/2,874 (4.0)	122/2,790 (4.4)	236/5,664 (4.2)

Percentages are calculated as [(m/n) × 100]. m = number of subjects in the respective category; n = number of subjects with nonmissing data (serology, PCR, or both) at day 1 for HPV 6, 11, 16, and 18.
[1]Positive (negative) by serology is defined as an anti-HPV cLIA titer ≥ (<) the serostatus cutoff of 20, 16, 20, or 24, respectively, for HPV 6, 11, 16, or 18.–[2]Positive by PCR to a given HPV type is defined as having a positive PCR result for the respective HPV type at day 1 on at least 1 required swab or (if obtained) biopsy sample. Negative by PCR to a given HPV type is defined as having negative PCR results for the respective HPV type at day 1 on all required swabs and (if obtained) biopsy samples.

TABLE III – POSITIVITY TO VACCINE HPV TYPES AT ENROLLMENT AMONG FEMALE SUBJECTS AGED 9–24[1]

Age at enrollment (years)	Subjects *N*	*n* (%)				
		0[2]	≥1[2]	≥2[2]	≥3[2]	4[2]
Below 12	142	137 (96.5)	5 (3.5)	0 (0.0)	0 (0.0)	0 (0.0)
12	54	52 (96.3)	2 (3.7)	0 (0.0)	0 (0.0)	0 (0.0)
13	40	40 (100)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
14	54	48 (88.9)	6 (11.1)	1 (1.9)	0 (0.0)	0 (0.0)
15	36	36 (100)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
16	99	65 (65.7)	34 (34.3)	7 (7.1)	1 (1.0)	0 (0.0)
17	200	130 (65.0)	70 (35.0)	25 (12.5)	3 (1.5)	0 (0.0)
18	632	464 (73.4)	168 (26.6)	32 (5.1)	4 (0.6)	1 (0.2)
19	808	587 (72.6)	221 (27.4)	41 (5.1)	6 (0.7)	0 (0.0)
20	972	668 (68.7)	304 (31.3)	71 (7.3)	12 (1.2)	0 (0.0)
21	1049	686 (65.4)	363 (34.6)	101 (9.6)	17 (1.6)	2 (0.2)
22	1040	703 (67.6)	337 (32.4)	92 (8.8)	13 (1.3)	0 (0.0)
23 and up	869	566 (65.1)	303 (34.9)	71 (8.2)	20 (2.3)	2 (0.2)

N = number of subjects who received ≥1 vaccination in the indicated age category with nonmissing serology and/or PCR data for all 4 HPV types.

[1]Subjects aged 9–15 enrolled in protocol 016 and protocol 018 did not undergo cervicovaginal sampling for HPV detection. In these subjects, enrollment HPV status is based on anti-HPV serostatus.–[2]Positivity to vaccine HPV types.

TABLE IV – MONTH 7 HPV cLIA GEOMETRIC MEAN TITERS AMONG GIRLS/WOMEN RECEIVING VACCINE ENROLLED IN LATIN AMERICAN COUNTRIES; PER-PROTOCOL IMMUNOGENICITY POPULATION[1]

HPV type	Girls 9–15 years old			Women 16–24 years old		
	n	GMT	95% CI	*n*	GMT	95% CI
HPV 6	233	982.9	(872.4, 1,107.5)	1,159	525.0	(502.6, 548.4)
HPV 11	233	1,242.7	(1,094.4, 1,411.3)	1,167	730.9	(695.7, 767.8)
HPV 16	235	5,163.9	(4,449.8, 5,992.7)	1,131	2,540.3	(2,379.5, 2,711.9)
HPV 18	237	1,036.5	(890.1, 1,207.0)	1,237	473.7	(448.0, 500.8)

CI = confidence interval; cLIA = competitive luminex immunoassay; GMT = geometric mean titer (mMU = milli Merck units). *n* = number of subjects contributing to the analysis. Confidence intervals for GMT and seroconversion rate are not provided if $n < 10$.

[1]The per-protocol immunogenicity population includes all subjects who were not general protocol violators; received all 3 vaccinations within acceptable day ranges; were seronegative at day 1 and (for all subjects except those <16 years old in protocols 016 and 018) PCR negative day 1 through month 7 for the relevant HPV type(s); and had a month 7 serum sample collected within an acceptable day range.

majority (5 out of 7) of cases of CIN in the vaccine cohort were related to HPV 16. There were no cases of cervical cancer in either the placebo or vaccine cohorts; however, there were 5 cases of adenocarcinoma *in situ*, all in the placebo cohort. An additional analysis was conducted in all randomized subjects regardless of baseline HPV or disease status—the intention-to-treat population. Efficacy against CIN or worse in this population of women with and without prevalent cervical intraepithelial neoplasia and infection due to vaccine and nonvaccine HPV types at enrollment was 51.3% (95% CI: 33.5, 64.7).

Efficacy in the prevention of any HPV 6-, 11-, 16- or 18-related external genital lesions (VIN, VaIN, Condyloma) was 100% (95% CI: 93.3, 100) for subjects in the PPE population (Table VI). In those subjects in the unrestricted susceptible population, the efficacy against EGL related to both HPV 16 and HPV 18 was 100%, while efficacy against EGL related to HPV 6 and 11 was 94.8 and 86.1%, respectively (Table VI). There were 4 subjects who became cases of EGL in the vaccine group among subjects in the unrestricted susceptible population, and all became cases of Condyloma. No cases of VIN 2/3 or VaIN 2/3 were seen in subjects in either the unrestricted susceptible or PPE populations who received quadrivalent HPV vaccine. Efficacy against any HPV 6-, 11-, 16- or 18-related EGL in the intention-to-treat population of all enrolled subjects was 78.5% (95% CI: 65.7, 87.1). Most EGL disease cases were Condyloma.

The majority of subjects enrolled in the quadrivalent HPV vaccine clinical program from Latin American countries reported at least 1 adverse experience (91.7% for subjects who received vaccine versus 86.1% for subjects who received aluminum-containing placebo) (Table VII). More vaccine-related adverse experiences were reported by subjects who received quadrivalent HPV vaccine compared to those subjects who received placebo. An increased occurrence of injection-site adverse experiences was primarily responsible for the increase in adverse experiences seen in subjects receiving quadrivalent vaccine. Common vaccine-related injection-site adverse experiences included pain (81.7% for vaccine *versus* 71.8% for placebo), swelling (22.3% for vaccine *versus* 15.5% for placebo) and erythema (14.9% for vaccine *versus* 10.4% for placebo).

Discussion

The information presented in this report is interesting in that it is derived solely from a cohort of Latin American subjects. Data from subjects such as those living in areas of high HPV prevalence can help in the better understanding of HPV-related diseases in the region, which can aid the decision-making process related to the prevention of these diseases. Antibody titers from the vaccinated population indicated a robust immune response at month 7 in both girls and women. High efficacy of the quadrivalent HPV vaccine was seen in both the PPE and unrestricted susceptible population of Latin American subjects in the prevention of CIN 2/3, AIS, VIN 2/3, VaIN 2/3 and genital warts. Analyses of efficacy in the intention-to-treat population, though informative, must be viewed in the context of the intended prophylactic use of the quadrivalent HPV vaccine. Subjects with infection or disease related to vaccine HPV types at enrollment will not benefit from vaccination with a prophylactic quadrivalent vaccine. Thus, the importance of vaccination prior to HPV exposure is evident.

Comparisons of the baseline data in this report to the population of the Latin American region as a whole are difficult. Much data exist, however, on the prevalence of HPV infection in individual Latin American countries. Comparison of these data to the prevalence of HPV exposure at baseline in the current report is interest-

TABLE V – ANALYSIS OF EFFICACY AGAINST HPV 6/11/16/18-RELATED CERVICAL DISEASE BY POPULATION; WOMEN 16–24 YEARS OF AGE[1]

Population	Vaccine			Placebo			Efficacy (%)	95% CI
	n	Cases	Rate	*n*	Cases	Rate		
Per-protocol								
HPV 6	2,075	0	0.0	1,976	8	0.2	100.0	(44.5, 100.0)
HPV 11	2,075	0	0.0	1,976	1	0.0	100.0	(<0.0, 100.0)
HPV 16	1,990	3	0.1	1,880	25	0.6	88.7	(62.9, 97.8)
HPV 18	2,265	0	0.0	2,201	10	0.2	100.0	(56.9, 100.0)
CIN 1 or worse[2]	2,415	3	0.1	2,377	41	0.7	92.8	(77.6, 98.6)
CIN 1	2,415	2	0.0	2,377	29	0.5	93.3	(73.3, 99.2)
CIN 2 or worse	2,415	1	0.0	2,377	21	0.4	95.3	(71.0, 99.9)
CIN 2	2,415	0	0.0	2,377	16	0.3	100.0	(74.6, 100.0)
CIN 3	2,415	1	0.0	2,377	13	0.2	92.5	(49.8, 99.8)
AIS	2,415	0	0.0	2,377	5	0.1	100.0	(<0.0, 100.0)
Cervical cancer	2,415	0	0.0	2,377	0	0.0	NA	NA
Unrestricted susceptible								
HPV 6	2,321	1	0.0	2,262	11	0.2	91.2	(39.6, 99.8)
HPV 11	2,321	0	0.0	2,262	2	0.0	100.0	(<0.0, 100.0)
HPV 16	2,212	5	0.1	2,173	36	0.6	86.4	(65.3, 95.8)
HPV 18	2,521	1	0.0	2,511	15	0.2	93.4	(57.2, 99.8)
CIN 1 or worse[2]	2,671	7	0.1	2,681	59	0.8	88.2	(74.2, 95.5)
CIN 1	2,671	4	0.1	2,681	45	0.6	91.2	(75.8, 97.7)
CIN 2 or worse	2,671	3	0.0	2,681	26	0.3	88.5	(62.5, 97.8)
CIN 2	2,671	1	0.0	2,681	19	0.3	94.8	(67.0, 99.9)
CIN 3	2,671	2	0.0	2,681	18	0.2	88.9	(53.8, 98.8)
AIS	2,671	0	0.0	2,681	5	0.1	100.0	(<0.0, 100.0)
Cervical cancer	2,671	0	0.0	2,681	0	0.0	NA	NA
Intention-to-treat								
HPV 6	2,718	4	0.0	2,725	19	0.2	79.1	(37.1, 94.8)
HPV 11	2,718	0	0.0	2,725	5	0.1	100.0	(<0.0, 100.0)
HPV 16	2,718	55	0.7	2,725	92	1.2	40.6	(16.2, 58.3)
HPV 18	2,718	5	0.1	2,725	22	0.3	77.4	(38.9, 93.3)
CIN 1 or worse[2]	2,718	62	0.8	2,725	126	1.6	51.3	(33.5, 64.7)
CIN 1	2,718	34	0.4	2,725	93	1.2	63.8	(45.9, 76.3)
CIN 2 or worse	2,718	45	0.6	2,725	67	0.8	33.1	(1.0, 55.2)
CIN 2	2,718	27	0.3	2,725	41	0.5	34.5	(<0.0, 61.2)
CIN 3	2,718	34	0.4	2,725	45	0.6	24.8	(<0.0, 53.3)
AIS	2,718	0	0.0	2,725	5	0.1	100.0	(<0.0, 100.0)
Cervical cancer	2,718	0	0.0	2,725	0	0.0	NA	NA

n = number of subjects evaluable; CI = confidence interval; CIN = cervical intraepithelial neoplasia; AIS = adenocarcinoma in situ.
[1]Per-protocol included all subjects who received 3 doses of vaccine or placebo and were seronegative and PCR negative for the relevant HPV type(s) at day 1 (and PCR negative for the relevant HPV types at month 7) – case counting began at month 7; unrestricted susceptible included subjects who received at least 1 dose of vaccine or placebo and were seronegative and PCR negative at enrollment for the appropriate vaccine-related HPV type – case counting began 30 days after enrollment; intention-to-treat included all subjects who received at least 1 dose of vaccine and returned for follow-up – case counting began at day 1. Two subjects under age 16 were included in the analysis; both in the placebo group—neither became a case.–[2]Subjects are counted once per row, but could be included in more than 1 row.

ing. As previously stated, the prevalence of HPV is generally accepted to be between 14 and 17% among women aged 18–65 with normal cervical cytology in Latin America; however, for women under 25 years of age the prevalence is over 30%.[9–12,20] We report a prevalence of HPV 6/11/16/18 infection at enrollment of 13.9%, although only for the 4 vaccine-related HPV types. When positive results by serology are considered, the prevalence of HPV exposure rises to 32.1%, highlighting the transient nature of most HPV infections.

While the percentage of the population in the current report who was exposed to vaccine-related HPV types at enrollment rises with age, it is clear that this is not a region-specific phenomenon, vaccination of adolescents/young adults before exposure to HPV will likely provide the maximal vaccine benefit. Given the relatively high prevalence of HPV in the trial population, the confirmatory results presented herein are encouraging, as a substantial proportion of the population had been previously exposed to vaccine HPV types. Additionally, while the vaccine was more immunogenic in younger subjects, this result is not totally unexpected. While younger people usually have more robust immune responses against protein antigens, the significance of a more intense immune response in the case of the younger quadrivalent HPV vaccine recipients is unclear, as a protective level of anti-HPV antibodies has not yet been calculated.

In most Latin American countries, the rates of cervical cancer have remained stable during the last 4–5 decades; exceptions are Colombia and Chile where declines in both incidence and mortality rates have been reported.[5] These declines are probably partially explained by a decline in parity. High parity has been shown to be an important cofactor increasing the risk of progression from chronic HPV infection to cervical cancer.[2] The high rates of HPV infection and disease in most countries in Latin America and the absence of an overall decline in these rates most likely reflect the lack of well organized and effective screening programs.

Despite the obvious barriers, preliminary Pap screening program evaluations are becoming more numerous in Latin American countries, specifically in remote, low-resource settings, in an attempt to create an effective rural coordinated screening network where previously there was none. A cervical cancer prevention and screening program in rural Nicaragua is one example of this strategy.[32] Another large ongoing study, the Latin American Screening Study or LAMS, has enrolled over 12,000 women from low-resource areas of Brazil and Argentina.[20] Together with these exploratory studies using traditional Pap smear, recent experiences

TABLE VI – ANALYSIS OF EFFICACY AGAINST HPV 6/11/16/18-RELATED EXTERNAL GENITAL DISEASE BY POPULATION; WOMEN 16–24 YEARS OF AGE[1]

	Vaccine			Placebo			Efficacy (%)	95% CI
	n	Cases	Rate	*n*	Cases	Rate		
Per-protocol								
HPV 6	2,088	0	0.0	1,990	42	0.9	100.0	(91.3, 100.0)
HPV 11	2,088	0	0.0	1,990	5	0.1	100.0	(<0.0, 100.0)
HPV 16	1,993	0	0.0	1,885	14	0.3	100.0	(71.4, 100.0)
HPV 18	2,278	0	0.0	2,215	2	0.0	100.0	(<0.0, 100.0)
Any EGL[2]	2,429	0	0.0	2,396	56	1.0	100.0	(93.3, 100.0)
Condyloma	2,429	0	0.0	2,396	45	0.8	100.0	(91.6, 100.0)
VIN 1 or VaIN 1	2,429	0	0.0	2,396	6	0.1	100.0	(16.1, 100.0)
VIN 2/3, VaIN 2/3 or worse	2,429	0	0.0	2,396	9	0.2	100.0	(49.9, 100.0)
Unrestricted susceptible								
HPV 6	2,345	3	0.0	2,283	56	0.9	94.8	(84.0, 99.0)
HPV 11	2,345	1	0.0	2,283	7	0.1	86.1	(<0.0, 99.7)
HPV 16	2,237	0	0.0	2,193	19	0.3	100.0	(78.9, 100.0)
HPV 18	2,546	0	0.0	2,535	5	0.1	100.0	(<0.0, 100.0)
Any EGL[2]	2,699	4	0.1	2,705	79	1.0	95.0	(86.6, 98.7)
Condyloma	2,699	4	0.1	2,705	62	0.8	93.6	(82.7, 98.3)
VIN 1 or VaIN 1	2,699	1	0.0	2,705	12	0.2	91.6	(43.5, 99.8)
VIN 2/3, VaIN 2/3 or worse	2,699	0	0.0	2,705	13	0.2	100.0	(67.0, 100.0)
Intention-to-treat								
HPV 6	2,745	14	0.2	2,748	73	0.9	80.9	(65.8, 90.0)
HPV 11	2,745	3	0.0	2,748	10	0.1	69.8	(<0.0, 94.7)
HPV 16	2,745	7	0.1	2,748	26	0.3	73.0	(36.1, 90.1)
HPV 18	2,745	0	0.0	2,748	5	0.1	100.0	(<0.0, 100.0)
Any EGL[2]	2,745	22	0.3	2,748	102	1.2	78.5	(65.7, 87.1)
Condyloma	2,745	16	0.2	2,748	82	1.0	80.5	(66.5, 89.4)
VIN 1 or VaIN 1	2,745	7	0.1	2,748	16	0.2	56.0	(<0.0, 84.7)
VIN 2/3, VaIN 2/3 or worse	2,745	5	0.1	2,748	16	0.2	68.6	(10.3, 91.0)

n = number of subjects evaluable; CI = confidence interval; EGL = external genital lesions; VaIN = vaginal intraepithelial neoplasia; VIN = vulvar intraepithelial neoplasia.

[1]Per-protocol included all subjects who received 3 doses of vaccine or placebo and were seronegative and PCR negative for the relevant HPV type(s) at day 1 (and PCR negative for the relevant HPV types at month 7) – case counting began at month 7; unrestricted susceptible included subjects who received at least 1 dose of vaccine or placebo and were seronegative and PCR negative at enrollment for the appropriate vaccine-related HPV type – case counting began 30 days after enrollment; intention-to-treat included all subjects who received at least 1 dose of vaccine and returned for follow-up – case counting began at day 1. Two subjects under age 16 were included in the analysis; both in the placebo group—neither became a case.–[2]Subjects are counted once per row, but could be included in more than 1 row.

TABLE VII – ADVERSE EXPERIENCE SUMMARY

	Vaccine		Placebo	
	n/m	%	*n/m*	%
Number (%) of subjects				
with 1 or more adverse experiences[1]	1,398/1,525	91.7	1,067/1,239	86.1
injection-site adverse experiences	1,289/1,525	84.5	896/1,239	72.3
systemic adverse experiences	1,001/1,525	65.6	800/1,239	64.6
with vaccine-related[2] adverse experiences[1]	1,362/1,525	89.3	993/1,239	80.1
injection-site adverse experiences	1,289/1,525	84.5	896/1,239	72.3
systemic adverse experiences	706/1,525	46.3	550/1,239	44.4
with serious adverse experiences	12/3,099	0.4	12/2,814	0.4
with serious vaccine-related adverse experiences	2/3,099	0.1	1/2,814	0.0
who died	0/3,099	0.0	0/2,814	0.0

n = number of subjects with the indicated characteristic; *m* = number of subjects with follow-up. Percentages are calculated based on the number of subjects with follow-up.

[1]These adverse experience categories were calculated from the detailed safety population, a subgroup of the overall safety population who filled out adverse event diary cards.–[2]Determined by the investigator to be possibly, probably, or definitely related to the vaccine.

with alternatives for secondary HPV detection and prevention of cervical cancer in Latin America have garnered attention. These alternatives include direct visualization of lesions with acetic acid and Lugol's iodine,[33] aided visual inspection, screening colposcopy, and cervicography.[34]

The current analysis has several important limitations. First, while the efficacy trials included a broad representation of Latin American, 16- to 24-year-old women with high numbers of sex partners or with poor access to health care were under-represented. Thus, the findings of this study cannot be extrapolated to all segments of the Latin American population. Second, because only 50–70% of HPV infections result in detectable anti-HPV responses, the baseline serology test may have underestimated prior exposure to HPV-6/11/16/18 in the study population. However, given the large numbers of subjects who were naïve to vaccine-HPV-types, and the substantial clinical impact of the vaccine in the population, the overall conclusions of this study are likely to be applicable. Finally, the duration of efficacy of the quadrivalent HPV vaccine has not been determined. While the risk of HPV infection remains throughout life, high efficacy without breakthrough infections due to waning immunity has been demonstrated through 5 years post-vaccination.[24] In addition, immune memory

has been seen in response to antigen challenge at 5 years post-vaccination in those previously receiving quadrivalent vaccine, which is considered a marker for long lasting protection.[23]

In summary, we have shown that a quadrivalent HPV vaccine formulated on proprietary AAHS aluminum adjuvant is highly efficacious, tolerable and immunogenic in a population of Latin American subjects. These data support vaccination of adolescents and young adults in the region, which is expected to greatly reduce the burden of cervical and genital cancers, precancers and genital warts.

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