

RESEARCH ARTICLE



Immunogenicity of the 9-valent human papillomavirus vaccine: Post hoc analysis from five phase 3 studies

Anna R. Giuliano^a, Joel M. Palefsky^b, Stephen E. Goldstone^c, Jacob Bornstein^d, Ilse De Coster^e, Ana María Guevara^f, Ole Mogensen^{g,h}, Andrea Schillingⁱ, Pierre Van Damme^e, Corinne Vandermeulen^j, Misoo C. Ellison^k, Thomas Group^k, Susan Kaplan^k, Jianxin Lin^k, Rachael Bonawitz^k, and Alain Luxembourg^k

^aCenter for Immunization and Infection Research in Cancer, Moffitt Cancer Center and Research Institute, Tampa, FL, USA; ^bDepartment of Medicine, University of California at San Francisco, San Francisco, CA, USA; ^cDepartment of Surgery, Icahn School of Medicine at Mount Sinai, New York, NY, USA; ^dDepartment of Obstetrics and Gynecology, Galilee Medical Center and Azrieli Faculty of Medicine, Bar-Ilan University, Nahariya, Israel; ^eCentre for the Evaluation of Vaccination, Vaccine & Infectious Disease Institute (VAXINFECTIO), Faculty of Medicine and Health Sciences, University of Antwerp, Antwerp, Belgium; ^fResearch Unit, Pablo Tobon Uribe Hospital, Medellín, Antioquia, Colombia; ^gDepartment of Gynecology and Obstetrics, Aarhus University Hospital, Aarhus, Denmark; ^hInstitute of Clinical Medicine, Faculty of Health, Aarhus University, Aarhus, Denmark; ⁱClinical Research Center, Institute of Sciences and Innovation in Medicine, Facultad de Medicina Clínica Alemana Universidad del Desarrollo, Santiago, Chile; ^jDepartment of Public Health and Primary Care, Leuven University Vaccinology Center, KU Leuven, Leuven, Belgium; ^kMerck & Co, Inc, Rahway, NJ, USA

ABSTRACT

Post hoc analyses of 9-valent human papillomavirus (9vHPV) vaccine immunogenicity were conducted in five Phase 3 studies that enrolled males. Month 7 antibody geometric mean titers (GMTs) after three 9vHPV vaccine doses were analyzed in 10,024 males/females aged 16–26 years from studies 001 (NCT00543543), 002 (NCT00943722), 003 (NCT01651949), and 020 (NCT02114385). Covariates considered were age, gender, sexual orientation, region of residence, and race. GMTs among 2599 males/females aged 9–15 years (studies 002 and 010 [NCT01984697]) were assessed 6 months after one, two, and three 9vHPV vaccine doses. 9vHPV vaccine immunogenicity was robust across populations. Month 7 GMTs were generally higher in participants aged 16–21 versus 22–26 years. Region and race minimally impacted immunogenicity. Adjusted integrated analysis showed lower immunogenicity in men who have sex with men (MSM) versus heterosexual men (HM) for nine HPV types, and higher immunogenicity in HM versus females for seven HPV types. Among 9–15-year-olds, trends toward higher GMTs in males versus females post-Dose 3, similar GMTs post-Dose 2, and lower post-Dose 1 were observed. In conclusion, 9vHPV vaccine immunogenicity was robust in males aged 16–26 years across a range of baseline characteristics. GMT ratios for males versus females aged 9–15 years tended to increase with more doses.

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Introduction

In men, approximately 70,000 new cancers are attributable to HPV each year globally.¹ Two prophylactic HPV vaccines are widely licensed for use in males: the quadrivalent (qHPV) and the 9-valent (9vHPV) vaccines. The qHPV vaccine confers protection against high-risk HPV types 16 and 18, which cause most cases of HPV-related cancer, and HPV types 6 and 11, which cause most cases of genital warts and recurrent respiratory papillomatosis.^{2,3} The 9vHPV vaccine protects against the four HPV types covered by the qHPV vaccine, plus five additional oncogenic HPV types (HPV 31, 33, 45, 52, and 58).^{4,5} The nine HPV types targeted by the 9vHPV vaccine cause approximately 96%, 95%, and 88% of HPV-associated anal, oropharyngeal, and penile cancers, respectively (with HPV16 and HPV18 causing approximately 87%, 91%, and 77% of these cancers, respectively).⁶ HPV6 and HPV11 cause approximately 90% of genital warts and recurrent respiratory papillomatosis.^{2,3} Efficacy of the

qHPV vaccine against HPV6/11/16/18-related persistent anogenital infection (85.6% [95% CI, 73.4–92.9]), external genital disease (90.4% [95% CI, 69.2–98.1]), anal persistent infection (94.9% [95% CI, 80.4–99.4]), and anal dysplasia (77.5% [95% CI, 39.6–93.3]) was demonstrated in males aged 16–26 years in an international randomized, placebo-controlled trial,^{7,8} and in a trial conducted in Japan (85.9% efficacy [95% CI, 52.7–97.3] against HPV6/11/16/18-related persistent anogenital infection; 100% efficacy [95% CI, 49.3–100] against HPV6/11/16/18-related anal persistent infection).⁹ Long-term effectiveness was shown in an extension of the international trial, with no new cases of HPV6/11/16/18-related external genital lesions or high-grade anal intraepithelial neoplasia observed through up to 11.5 years of follow-up.¹⁰ The efficacy of the 9vHPV vaccine was established in females aged 16–26 years in a qHPV vaccine-controlled randomized clinical trial.^{11–13} Efficacy in males aged 9–26 years was inferred based on the demonstration

CONTACT Anna R. Giuliano ✉ Anna.Giuliano@moffitt.org Center for Immunization and Infection Research in Cancer, Moffitt Cancer Center and Research Institute 4117 E Fowler Ave, Tampa, Florida 33617 USA.

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of non-inferior antibody responses to vaccine-related HPV types following administration of the 9vHPV vaccine in males aged 9–15 years and 16–26 years compared with females aged 16–26 years,^{14–16} and non-inferior immunogenicity of 9vHPV vaccine versus qHPV vaccine in males aged 16–26 years.¹⁷ Long-term effectiveness was demonstrated in an extension of the immunogenicity clinical trial in males aged 9–15 years with no cases of external genital lesions related to vaccine-targeted HPV types observed through up to 10.6 years of follow-up.¹⁸

In prior analyses of trial data, an inverse relationship between age and anti-HPV antibody responses was demonstrated for qHPV vaccine in males and females aged 9–26 years and 9vHPV vaccine immunogenicity in females aged 9–26 years and males 9–15 years.^{19–21} In addition, geometric mean titers (GMTs) were lower in men who have sex with men (MSM) compared with heterosexual men (HM) after qHPV and 9vHPV vaccination.^{14,19} Also, gender, region of residence, and race were not found to substantially impact immunogenicity.^{20,21} However, in a recent meta-analysis of qHPV vaccine clinical studies, vaccine immunogenicity was observed to be higher in females than males.²² The authors suggested that vaccine dosing and scheduling for each sex could be explored further.

To further characterize these differences, we conducted an analysis of 9vHPV vaccine immunogenicity in HM, MSM, and

women aged 16–26 years based on participant characteristics at study baseline (i.e., age, region of residence, and race), and by number of doses in males and females aged 9–15 years.

Methods

Study population

Immunogenicity data from five Phase 3 clinical studies of the 9vHPV vaccine were used for these post hoc analyses. The studies, which enrolled approximately 13,000 participants (2578 males; 10,433 females) are summarized in Table 1. Primary trial data have been previously published.^{11,12,14–17,23} Four studies from the 9vHPV vaccine clinical program (001, 002, 003, and 020) contributed to the analysis of immunogenicity by baseline covariates in males (HM and MSM) aged 16–26 years compared with females aged 16–26 years, and two studies from the 9vHPV vaccine clinical program (002 and 010) contributed to the analysis of immunogenicity following 1, 2, and 3 doses in males aged 9–15 years compared with females aged 9–15 years. This analysis included male and female participants in study 010 who received 2 doses of 9vHPV vaccine 6 months apart.

Each study was conducted in accordance with the principles of Good Clinical Practice and approved by the appropriate institutional review boards and regulatory agencies. Written informed

Table 1. Phase 3 studies of the 9vHPV vaccine included in the current post hoc immunogenicity analyses.

Study	Key Objectives	Study Population	Included in Analyses ^a	
			Males and Females (aged 16–26 years)	Males and Females (aged 9–15 years)
001	Immunogenicity and efficacy of 9vHPV vaccine vs qHPV vaccine in females	Females aged 16–26 years randomized to qHPV or 9vHPV vaccine (each $N = 6799$) ^b	$N = 6792$ females (9vHPV) $N = 6795$ females (qHPV)	N/A
002	Immunogenicity of 9vHPV vaccine in adolescents vs females	Females ($N = 1935$) and males ($N = 669$) aged 9–15 years and females aged 16–26 years ($N = 470$) enrolled to receive 3 doses of 9vHPV vaccine	$N = 468$ females (9vHPV)	$N = 1933$ females (9vHPV) $N = 666$ males (9vHPV)
003	Immunogenicity of 9vHPV vaccine in males vs females	HM aged 16–26 years ($N = 1106$), MSM aged 16–26 years ($N = 313$), and females aged 16–26 years ($N = 1101$) enrolled to receive 3 doses of 9vHPV vaccine	$N = 1103$ HM (9vHPV) $N = 313$ MSM (9vHPV) $N = 1099$ females (9vHPV)	N/A
020	Immunogenicity of 9vHPV vaccine vs qHPV vaccine in males	HM aged 16–26 years randomized to qHPV ($N = 251$) or 9vHPV vaccine ($N = 249$)	$N = 249$ HM (9vHPV) $N = 251$ HM (qHPV)	N/A
010	Immunogenicity of 2-dose vs 3-dose 9vHPV vaccine regimens in adolescents vs females	Females aged 9–14 years randomized to 2 doses of 9vHPV vaccine at Months 0 and 6 ($N = 301$) or Months 0 and 12 ($N = 151$) or 3 doses of 9vHPV vaccine ($N = 301$) Males aged 9–14 randomized to 9vHPV vaccine at Months 0 and 6 ($N = 301$) or Months 0 and 12 ($N = 150$) Females aged 16–26 received 3 doses of 9vHPV vaccine ($N = 314$)	N/A	$N = 301$ females (2-dose 9vHPV at Months 0 and 6) $N = 301$ males (2-dose 9vHPV at Months 0 and 6)

Study 001: NCT00543543.^{11,12}

Study 002: NCT00943722.¹⁵

Study 003: NCT01651949.¹⁴

Study 020: NCT02114385.¹⁷

Study 010: NCT01984697.^{16,23}

^aParticipants who received at least one dose of 9vHPV vaccine. In each study, most (>95%) participants completed the assigned dosing regimen.

^bParticipants who received the low-dose, mid-dose, or high-dose formulation of 9vHPV vaccine during the dose selection portion of the study^{11,24} are not included; immunogenicity results in these participants are reported elsewhere.²⁵

Abbreviations: 9vHPV, 9-valent human papillomavirus; HM, heterosexual men; MSM, men who have sex with men; N/A, not applicable; PPI, per-protocol immunogenicity; qHPV, quadrivalent human papillomavirus.

consent was provided by all adult participants, or by a legally acceptable representative for participants who were minors.

Vaccine administration

Participants in studies 001 and 020 received 0.5-mL doses of 9vHPV or qHPV vaccine; participants in studies 002, 003, and 010 received 0.5-mL doses of 9vHPV vaccine (Merck & Co., Inc., Rahway, New Jersey, USA). Vaccines were administered as an intramuscular injection on Day 1, Month 2, and Month 6 (studies 001, 002, 003, and 020); or Day 1 and Month 6 (study 010).^{11–12,14–17,23}

Immunogenicity evaluation

Analyses in males and females aged 16–26 years were based on serum samples collected on Day 1 and Month 7 (1 month post-Dose 3).^{11,12,14,15,17} Analyses in males and females aged 9–15 years were based on serum samples collected at Day 1 and 6 months post-last dose.^{15,16,23} Serum samples were assessed for antibodies against HPV 6/11/16/18/31/33/45/52/58 using the 9-valent competitive Luminex immunoassay (cLIA).²⁶

Statistical analysis

Immunogenicity was assessed in the relevant per-protocol immunogenicity (PPI) population, comprising those who had no protocol violations that could interfere with immunogenicity evaluation, received the number of doses of qHPV or 9vHPV vaccine required by the protocol, had a Month 7 sample collected within acceptable day ranges, and were seronegative at Day 1 and (for participants 16–26 years of age in study 001 and study 002) PCR-negative Day 1 through Month 7 for the HPV type(s) being analyzed. To be included in the PPI analysis for HPV 6 and 11, participants were required to be negative for both HPV 6 and 11.

For each HPV type, GMTs, GMT ratios, and associated 95% CIs were estimated using an analysis of variance model with log anti-HPV as the response and vaccination group as the fixed

effect. In addition, analysis of covariance (ANCOVA) model of log anti-HPV titers via a mixed effects model methodology was used to estimate GMTs, GMT ratios, and associated 95% CIs after controlling for age and geographic region. Study number was included as a random effect to account for variability among studies. Baseline covariates included in the analysis were age, gender, sexual orientation, region of residence, and race, whereby sexual orientation and race were based on self-reporting. Region of residence was considered to be a surrogate for race in adjusted analyses. All analyses were exploratory in nature, with no statistical hypothesis testing performed.

Results

Immunogenicity in men and women by baseline characteristics

Four trials conducted in young adults (studies 001, 002, 003, and 020 from the 9vHPV vaccine clinical program; Table 1) are included in these analyses. Table 2 presents a summary of the baseline characteristics by age, world region of residence, and race among young adult HM, MSM, and females across these four trials.

Most HM and all MSM were enrolled in study 003. As previously reported, study 003 enrolled 2520 participants 16–26 years of age (1106 HM, 313 MSM, and 1001 females) from five regions (Africa, Asia-Pacific, Europe, Latin America, North America).¹⁴ The 9vHPV vaccine was highly immunogenic in all three groups of participants, with anti-HPV GMTs at Month 7 generally highest in HM, followed by females, and lowest in MSM.¹⁴ Baseline characteristics of the males and females aged 9–15 years who received 9vHPV vaccine in studies 002 and 010 are reported elsewhere.^{15,16}

Overall, higher GMTs were observed in younger (16–21 years of age) versus older (22–26 years of age) males (HM, MSM) and females, with statistically significant differences (non-overlapping 95% CIs) between age strata observed only among HM (Supplementary Table S1). GMT differences across the three populations were more pronounced among young

Table 2. Baseline characteristics of 9vHPV vaccine recipients aged 16–26 years in four studies by gender and sexual orientation^a.

	Study 001, Study 002, Study 003, and Study 020 (N = 10,038) ^b		
	HM (N = 1355)	MSM (N = 313)	Women (N = 8370)
Age, years			
Mean (SD)	20.8 (2.9)	22.2 (2.4)	21.8 (2.5)
Median	21	22	22
Range	16–26	16–26	16–26
Region, n (%)			
Africa	20 (1.5)	10 (3.2)	60 (0.7)
Asia-Pacific	131 (9.7)	40 (12.8)	1128 (13.5)
Europe	641 (47.3)	105 (33.5)	2923 (34.9)
Latin America	236 (17.4)	74 (23.6)	2553 (30.5)
North America	327 (24.1)	84 (26.8)	1706 (20.4)
Race ^a , n (%)			
Asian	107 (7.9)	34 (10.9)	1223 (14.6)
Black	51 (3.8)	27 (8.6)	346 (4.1)
White	944 (69.7)	178 (56.9)	4670 (55.8)
Other ^c	253 (18.7)	74 (23.6)	2131 (25.5)

^aSexual orientation and race were based on self-reporting.

^bPopulation includes all randomized participants.

^cThis category is mostly comprised of multi-racial participants.

Abbreviations: 9vHPV, 9-valent human papillomavirus; HM, heterosexual men; MSM, men who have sex with men; SD, standard deviation.

adults aged 16–21 years compared with aged 22–26 years for each of the 9 HPV types that the vaccine is directed against. Among 16–21-year-olds, GMTs were significantly higher for each of the 9vHPV vaccine types among HM compared with females or MSM and tended to be higher in females versus MSM. Among 22–26-year-olds, HM and females had similar

GMT responses to the vaccine, with lower GMTs observed among MSM. Small differences in GMTs (mostly non-statistically significant) were observed among males (HM, MSM) and females across groups defined by region of residence (Table 3) or race (Supplementary Table S2). MSM from Asia-Pacific and North America tended to have higher GMTs than

Table 3. Anti-HPV GMTs by region of residence at Month 7 in HM, MSM, and women aged 16–26 years who received 9vHPV vaccine in study 003 (PPI population^a).

Assay (cLIA)	HM			MSM			Women		
	n	GMT, mMU/mL	(95% CI)	n	GMT, mMU/mL	(95% CI)	n	GMT, mMU/mL	(95% CI)
Africa									
		(N = 20)			(N = 10)			(N = 20)	
Anti-HPV 6	15	929.8	(587.4, 1471.6)	5	305.2	(137.8, 676.1)	11	675.7	(395.3, 1155.2)
Anti-HPV 11	15	746.3	(478.4, 1164.0)	5	207.2	(95.9, 447.4)	11	573.0	(341.0, 963.0)
Anti-HPV 16	18	3919.6	(2615.5, 5874.1)	8	1434.8	(782.1, 2632.2)	15	3744.5	(2404.0, 5832.6)
Anti-HPV 18	18	1132.7	(742.4, 1728.2)	8	193.5	(102.7, 364.7)	17	1109.3	(718.2, 1713.4)
Anti-HPV 31	19	823.9	(559.7, 1212.8)	9	248.5	(141.7, 435.8)	16	673.4	(441.9, 1026.3)
Anti-HPV 33	18	403.7	(264.0, 617.4)	9	141.9	(77.8, 258.8)	17	289.6	(187.1, 448.4)
Anti-HPV 45	19	324.1	(202.9, 517.7)	9	84.0	(42.5, 165.9)	18	265.2	(163.9, 429.2)
Anti-HPV 52	18	504.4	(320.9, 793.1)	8	137.3	(69.6, 270.6)	17	341.0	(214.1, 543.2)
Anti-HPV 58	19	611.4	(409.5, 913.0)	8	148.2	(79.9, 275.0)	15	360.1	(229.3, 565.4)
Asia-Pacific									
		(N = 129)			(N = 40)			(N = 130)	
Anti-HPV 6	95	620.5	(516.5, 745.5)	26	688.3	(484.7, 977.4)	96	623.3	(519.3, 748.1)
Anti-HPV 11	96	496.1	(417.9, 588.8)	26	474.8	(341.6, 660.1)	96	512.6	(431.9, 608.5)
Anti-HPV 16	105	2916.3	(2466.2, 3448.5)	32	2914.1	(2151.0, 3948.0)	112	2647.6	(2251.0, 3114.2)
Anti-HPV 18	107	689.1	(563.6, 842.6)	33	693.9	(483.1, 996.5)	108	644.3	(527.5, 787.0)
Anti-HPV 31	106	673.0	(554.6, 816.7)	35	509.8	(364.0, 713.8)	112	624.7	(517.5, 754.1)
Anti-HPV 33	105	341.2	(286.4, 406.4)	34	263.2	(193.5, 357.9)	111	315.9	(266.5, 374.5)
Anti-HPV 45	107	228.3	(184.2, 283.1)	33	206.4	(140.2, 304.0)	112	209.5	(169.8, 258.5)
Anti-HPV 52	106	305.4	(256.3, 363.9)	35	242.9	(179.0, 329.5)	112	327.8	(276.4, 388.8)
Anti-HPV 58	106	475.0	(397.2, 568.1)	34	389.2	(283.8, 533.8)	112	443.2	(372.4, 527.5)
Europe									
		(N = 392)			(N = 105)			(N = 389)	
Anti-HPV 6	303	770.9	(702.4, 846.0)	49	502.6	(398.9, 633.4)	278	658.5	(597.6, 725.7)
Anti-HPV 11	304	614.0	(558.8, 674.6)	50	414.9	(328.9, 523.3)	281	537.0	(486.9, 592.2)
Anti-HPV 16	314	3241.2	(2960.5, 3548.6)	63	2046.1	(1671.4, 2504.8)	296	2592.1	(2361.1, 2845.6)
Anti-HPV 18	313	784.4	(698.9, 880.3)	64	496.7	(384.8, 641.1)	308	625.9	(557.1, 703.1)
Anti-HPV 31	312	683.8	(611.9, 764.1)	66	383.5	(301.2, 488.3)	306	508.2	(454.3, 568.6)
Anti-HPV 33	311	382.5	(347.1, 421.5)	68	242.3	(196.9, 298.1)	309	309.3	(280.6, 340.9)
Anti-HPV 45	314	215.3	(190.6, 243.2)	67	127.4	(97.8, 165.9)	318	172.9	(153.2, 195.2)
Anti-HPV 52	312	396.2	(358.1, 438.4)	68	223.7	(180.1, 277.7)	312	320.7	(289.9, 354.8)
Anti-HPV 58	308	513.6	(465.2, 567.0)	64	300.0	(241.5, 372.8)	306	399.3	(361.6, 441.0)
Latin America									
		(N = 236)			(N = 74)			(N = 234)	
Anti-HPV 6	181	770.8	(675.5, 879.5)	37	482.9	(360.7, 646.6)	158	667.5	(579.6, 768.8)
Anti-HPV 11	182	576.9	(511.0, 651.4)	37	386.4	(295.1, 505.7)	159	508.7	(446.8, 579.3)
Anti-HPV 16	200	3432.7	(3032.3, 3885.9)	53	1,992.2	(1565.7, 2535.0)	184	2662.3	(2339.4, 3029.8)
Anti-HPV 18	202	807.3	(700.0, 931.0)	58	615.3	(471.5, 802.9)	198	631.6	(546.9, 729.4)
Anti-HPV 31	205	716.6	(621.0, 827.0)	58	370.5	(283.0, 485.0)	191	548.3	(472.6, 636.0)
Anti-HPV 33	201	378.2	(332.5, 430.3)	58	228.4	(179.6, 290.4)	204	301.5	(265.2, 342.6)
Anti-HPV 45	201	228.7	(195.9, 267.1)	63	145.2	(110.1, 191.5)	203	176.4	(151.2, 205.8)
Anti-HPV 52	203	356.8	(311.2, 409.0)	61	202.9	(158.1, 260.3)	196	290.6	(252.9, 334.0)
Anti-HPV 58	199	472.6	(413.9, 539.6)	58	289.0	(226.1, 369.5)	194	362.2	(316.7, 414.3)
North America									
		(N = 326)			(N = 84)			(N = 326)	
Anti-HPV 6	253	868.0	(783.8, 961.3)	47	708.1	(558.8, 897.3)	165	891.6	(785.7, 1011.7)
Anti-HPV 11	254	698.3	(627.9, 776.5)	47	529.3	(413.6, 677.5)	165	720.0	(631.2, 821.4)
Anti-HPV 16	262	3562.9	(3178.6, 3993.6)	56	2781.0	(2172.7, 3559.7)	174	3,341.1	(2904.5, 3843.4)
Anti-HPV 18	266	873.3	(769.0, 991.8)	57	820.4	(623.3, 1079.9)	200	820.1	(708.2, 949.7)
Anti-HPV 31	266	739.5	(650.4, 840.7)	59	511.0	(389.2, 671.1)	201	660.7	(570.1, 765.8)
Anti-HPV 33	266	410.3	(366.2, 459.6)	61	308.4	(243.3, 390.8)	212	370.7	(326.4, 421.0)
Anti-HPV 45	268	265.2	(230.6, 305.1)	60	206.0	(153.2, 277.0)	220	197.2	(168.9, 230.1)
Anti-HPV 52	268	431.1	(383.0, 485.3)	60	294.7	(229.4, 378.4)	212	412.6	(361.2, 471.4)
Anti-HPV 58	265	543.4	(485.2, 608.6)	59	375.1	(295.0, 476.8)	212	458.9	(404.3, 520.8)

^aIncludes all participants who were not general protocol violators, received all three vaccinations within acceptable day ranges, were seronegative at Day 1 for the relevant HPV type(s), and had a Month 7 serum sample collected within an acceptable day range.

N = Number of participants randomized to the respective vaccination group who received at least 1 injection.

n = Number of participants contributing to the analysis.

Abbreviations: 9vHPV, 9-valent human papillomavirus; CI, confidence interval; cLIA, competitive Luminex immunoassay; GMT, geometric mean titer; HM, heterosexual men; HPV, human papillomavirus; mMU, milli Merck units; MSM, men who have sex with men; PPI, per-protocol immunogenicity.

MSM from Europe and Latin America. MSM from Africa had the lowest observed GMTs, although the sample size for this population was small ($n = 10$). Conversely, HM from Africa ($n = 20$) had the highest observed GMTs compared with HM from other regions. The differences in GMTs between HM and MSM for each of the 9vHPV vaccine types were most pronounced in participants from Africa and Latin America. Females from North America tended to have higher GMTs than women from Europe. Analysis by race showed that Asian MSM tended to have higher GMTs than White MSM or MSM of other races.

Further analyses were conducted by integrating the immunogenicity results of studies 001, 002, 003, and 020. After adjustment for age and region of residence, GMTs at Month 7 (1 month post-Dose 3 of 9vHPV vaccine) were significantly lower (i.e., all 95% CIs for GMT ratios excluded 1.0) among MSM compared with HM for all nine HPV types (Table 4). GMT ratios (MSM/HM) ranged from 0.64 to 0.79 (depending on the HPV type). GMTs were also lower in MSM compared with females with GMT ratios (MSM/females) ranging from 0.72 to 0.92. The 95% CIs of the GMT ratios did not cross 1 for seven HPV types but included 1 for HPV18 and HPV45 (the upper bound of the 95% CI was 1.05 for HPV18 and 1.01 for HPV45).

Analyses by region of residence integrating the immunogenicity results of studies 003 and 020 were conducted in HM and MSM. After adjustment for age, GMTs at Month 7 were significantly lower (i.e., all 95% CIs for GMT ratios excluded 1.0) among MSM compared with HM for all nine HPV types in participants from Africa, Europe, and Latin America (except

for HPV18 in Latin America: upper bound of 95% CI of GMT ratio = 1.01). They were similar (i.e., all 95% CIs for GMT ratios included 1.0) among MSM compared with HM for all nine HPV types in participants from Asia-Pacific. And they were lower or similar among MSM compared with HM depending on the HPV type in participants from North America (Table 5).

GMTs across the nine vaccine-targeted HPV types were generally higher in HM compared with women, with estimated GMT ratios (HM/women) ranging from 1.06 to 1.22. The 95% CIs of the GMT ratios excluded 1.0 for all HPV types except for HPV6 and HPV11, where the lower bound of the 95% CI was 0.99 for HPV6 and 0.98 for HPV11.

Analogous analyses conducted in HM, MSM, and women who received qHPV vaccine in the qHPV vaccine clinical program (including HM and MSM participants in studies 020 and 122 from the qHPV vaccine clinical program, and women participants in studies 007, 013, 015, and 016 from the qHPV vaccine clinical program) showed lower anti-HPV6, 11, 16, and 18 GMTs in MSM than in HM or women, with estimated GMT ratios ranging from 0.60 to 0.74 (MSM/HM) and 0.52 to 0.66 (MSM/women). In these analyses, anti-HPV6, 11, and 18 GMT ratios (HM/women) ranged from 0.84 to 0.89 (with the 95% CIs of the GMT ratio including 1.0 for HPV 18) and anti-HPV16 GMT ratio (HM/women) was 1.07 (95% CI of the GMT ratio included 1.0) (Supplementary Table S3). Analogous analyses conducted in HM and women who received qHPV vaccine in studies 020 and 001 from the 9vHPV

Table 4. Integrated analysis of anti-HPV adjusted^a GMTs at Month 7 in HM, MSM, and females aged 16–26 years who received 9vHPV vaccine in studies 001, 002, 003, and 020 (PPI population^b).

Assay (cLIA)	Study 003, Study 020		Study 003		Study 001, Study 002, Study 003		Estimated GMT Ratio (95% CI)		
	HM (N = 1352)		MSM (N = 313)		Females (N = 8359)		HM/Females	MSM/Females	MSM/HM
	n	GMT, mMU/mL (95% CI)	n	GMT, mMU/mL (95% CI)	n	GMT, mMU/mL (95% CI)			
Anti-HPV 6	1075	862.6 (739.1, 1006.7)	164	665.8 (549.4, 806.8)	5029	803.2 (691.6, 932.9)	1.07 (0.99, 1.16)	0.83 (0.72, 0.95)	0.77 (0.68, 0.88)
Anti-HPV 11	1079	672.3 (591.3, 764.3)	165	510.6 (429.7, 606.6)	5039	636.8 (563.7, 719.4)	1.06 (0.98, 1.14)	0.80 (0.70, 0.92)	0.76 (0.66, 0.87)
Anti-HPV 16	1133	3889.5 (3406.6, 4440.8)	212	2804.8 (2377.9, 3308.4)	5142	3313.4 (2918.3, 3761.9)	1.17 (1.09, 1.26)	0.85 (0.75, 0.95)	0.72 (0.64, 0.81)
Anti-HPV 18	1140	957.7 (831.8, 1102.6)	220	761.2 (634.1, 913.8)	5715	831.4 (728.0, 949.6)	1.15 (1.06, 1.26)	0.92 (0.79, 1.05)	0.79 (0.69, 0.92)
Anti-HPV 31	1142	822.4 (708.2, 954.9)	227	525.5 (435.4, 634.1)	5632	683.2 (592.7, 787.7)	1.20 (1.10, 1.31)	0.77 (0.67, 0.88)	0.64 (0.56, 0.73)
Anti-HPV 33	1137	449.9 (377.0, 536.7)	230	316.0 (257.8, 387.4)	5909	388.2 (326.9, 460.9)	1.16 (1.07, 1.25)	0.81 (0.72, 0.92)	0.70 (0.62, 0.80)
Anti-HPV 45	1141	309.8 (255.5, 375.7)	232	220.6 (175.3, 277.5)	6031	253.7 (210.6, 305.7)	1.22 (1.11, 1.34)	0.87 (0.75, 1.01)	0.71 (0.61, 0.83)
Anti-HPV 52	1142	425.1 (375.0, 481.8)	232	275.5 (233.8, 324.5)	5641	381.9 (339.7, 429.4)	1.11 (1.03, 1.21)	0.72 (0.63, 0.82)	0.65 (0.57, 0.74)
Anti-HPV 58	1129	608.4 (506.0, 731.7)	223	410.5 (332.0, 507.5)	5657	501.3 (418.7, 600.1)	1.21 (1.12, 1.32)	0.82 (0.72, 0.93)	0.67 (0.59, 0.77)

^aThe adjusted GMTs, GMT ratios, and associated 95% CIs were estimated using an ANCOVA model of the natural logarithm of anti-HPV titers via a mixed model methodology. Age and region of residence were included in the model as covariates, and study (or protocol) as a random effect.

^bIncludes all participants who were not general protocol violators, received all three vaccinations within acceptable day ranges, were seronegative at Day 1 for the relevant HPV type(s), and had a Month 7 serum sample collected within an acceptable day range.

N = Number of participants randomized to the respective vaccination group who received at least 1 injection.

n = Number of participants contributing to the analysis.

Abbreviations: 9vHPV, 9-valent human papillomavirus; ANCOVA, analysis of covariance; CI, confidence interval; cLIA, competitive Luminex immunoassay; GMT, geometric mean titer; HM, heterosexual men; HPV, human papillomavirus; mMU, milli Merck units; MSM, men who have sex with men; PPI, per-protocol immunogenicity.

Table 5. Integrated analysis by region of residence of anti-HPV adjusted^a GMTs at Month 7 in HM and MSM aged 16–26 years who received 9vHPV vaccine in studies 003 and 020 (PPI population^b).

	HM		MSM		
Assay (cLIA)	n	GMT, mMU/mL (95% CI)	n	GMT, mMU/mL (95% CI)	GMT ratio (MSM/HM) (95% CI)
Africa					
Anti-HPV 6	15	1041.6 (599.3, 1810.4)	5	388.3 (159.6, 944.8)	0.37 (0.15, 0.91)
Anti-HPV 11	15	752.9 (489.1, 1159.0)	5	236.0 (100.6, 553.5)	0.31 (0.12, 0.80)
Anti-HPV 16	18	4188.8 (2588.9, 6777.4)	8	1770.5 (896.7, 3496.0)	0.42 (0.20, 0.88)
Anti-HPV 18	18	1121.5 (749.5, 1678.1)	8	233.6 (126.2, 432.2)	0.21 (0.10, 0.43)
Anti-HPV 31	19	978.1 (550.1, 1739.1)	9	403.0 (200.3, 811.1)	0.41 (0.22, 0.77)
Anti-HPV 33	18	461.9 (258.6, 825.0)	9	191.2 (91.9, 397.9)	0.41 (0.20, 0.85)
Anti-HPV 45	19	436.3 (185.0, 1029.0)	9	136.6 (50.6, 368.8)	0.31 (0.14, 0.69)
Anti-HPV 52	18	591.6 (320.9, 1090.5)	8	209.6 (93.3, 470.7)	0.35 (0.16, 0.79)
Anti-HPV 58	19	777.0 (369.2, 1635.4)	8	206.4 (84.0, 507.0)	0.27 (0.12, 0.57)
Asia-Pacific					
Anti-HPV 6	95	708.1 (524.1, 956.9)	26	794.1 (529.2, 1191.8)	1.12 (0.78, 1.61)
Anti-HPV 11	96	511.9 (404.1, 648.5)	26	494.8 (345.0, 709.6)	0.97 (0.67, 1.39)
Anti-HPV 16	105	3184.1 (2445.0, 4146.7)	32	3204.0 (2262.0, 4538.1)	1.01 (0.74, 1.37)
Anti-HPV 18	107	796.5 (564.5, 1123.8)	33	808.4 (520.2, 1256.3)	1.01 (0.69, 1.48)
Anti-HPV 31	106	682.6 (528.0, 882.4)	35	526.3 (365.5, 757.7)	0.77 (0.54, 1.11)
Anti-HPV 33	105	398.3 (289.2, 548.6)	34	310.6 (207.7, 464.5)	0.78 (0.55, 1.10)
Anti-HPV 45	107	262.1 (183.2, 374.8)	33	238.1 (149.3, 379.7)	0.91 (0.60, 1.37)
Anti-HPV 52	106	285.5 (238.6, 341.5)	35	230.4 (169.6, 313.0)	0.81 (0.57, 1.15)
Anti-HPV 58	106	498.7 (390.4, 637.1)	34	413.1 (293.7, 581.2)	0.83 (0.59, 1.15)
Europe					
Anti-HPV 6	531	824.9 (704.3, 966.3)	49	593.1 (455.0, 773.1)	0.72 (0.57, 0.91)
Anti-HPV 11	532	663.0 (581.0, 756.7)	50	497.2 (387.5, 637.9)	0.75 (0.59, 0.95)
Anti-HPV 16	548	3535.6 (3134.1, 3988.5)	63	2414.5 (1940.9, 3003.6)	0.68 (0.55, 0.84)
Anti-HPV 18	547	821.2 (727.3, 927.2)	64	567.8 (438.3, 735.5)	0.69 (0.53, 0.90)
Anti-HPV 31	546	720.7 (633.1, 820.4)	66	462.8 (359.1, 596.3)	0.64 (0.50, 0.82)
Anti-HPV 33	547	436.8 (371.6, 513.4)	68	307.7 (240.2, 394.2)	0.70 (0.57, 0.88)
Anti-HPV 45	546	234.0 (200.7, 272.7)	67	154.7 (116.4, 205.6)	0.66 (0.50, 0.87)
Anti-HPV 52	547	409.6 (366.4, 457.8)	68	256.5 (203.9, 322.7)	0.63 (0.50, 0.79)
Anti-HPV 58	540	586.6 (496.4, 693.2)	64	384.7 (297.1, 498.3)	0.66 (0.52, 0.82)
Latin America					
Anti-HPV 6	181	969.9 (724.2, 1298.9)	37	617.5 (429.5, 887.7)	0.64 (0.49, 0.83)
Anti-HPV 11	182	718.5 (534.9, 965.2)	37	489.8 (337.5, 710.9)	0.68 (0.52, 0.90)
Anti-HPV 16	200	3859.7 (3136.5, 4749.7)	53	2297.8 (1749.5, 3017.9)	0.60 (0.47, 0.75)
Anti-HPV 18	202	972.4 (740.6, 1276.7)	58	758.6 (544.0, 1057.8)	0.78 (0.60, 1.01)
Anti-HPV 31	205	851.0 (646.4, 1120.5)	58	455.0 (323.6, 639.8)	0.53 (0.41, 0.70)
Anti-HPV 33	201	469.0 (349.6, 629.1)	58	291.1 (205.6, 412.0)	0.62 (0.48, 0.80)
Anti-HPV 45	201	307.4 (210.0, 450.0)	63	201.8 (130.9, 311.1)	0.66 (0.49, 0.87)
Anti-HPV 52	203	447.1 (326.4, 612.5)	61	261.3 (181.3, 376.5)	0.58 (0.45, 0.75)
Anti-HPV 58	199	630.0 (417.1, 951.7)	58	399.2 (253.8, 628.0)	0.63 (0.49, 0.82)
North America					
Anti-HPV 6	253	860.2 (776.5, 952.9)	47	749.6 (590.3, 951.8)	0.87 (0.67, 1.13)
Anti-HPV 11	254	691.0 (623.8, 765.5)	47	565.2 (445.0, 718.0)	0.82 (0.63, 1.06)
Anti-HPV 16	262	3513.2 (3165.1, 3899.6)	56	2997.5 (2388.0, 3762.5)	0.85 (0.66, 1.10)
Anti-HPV 18	266	944.4 (701.7, 1271.0)	57	996.1 (683.3, 1452.3)	1.05 (0.79, 1.41)
Anti-HPV 31	266	726.1 (642.8, 820.1)	59	558.4 (430.5, 724.2)	0.77 (0.58, 1.03)
Anti-HPV 33	266	489.0 (363.1, 658.5)	61	401.8 (281.7, 573.2)	0.82 (0.64, 1.05)
Anti-HPV 45	268	335.2 (232.1, 484.2)	60	295.8 (189.6, 461.6)	0.88 (0.64, 1.21)
Anti-HPV 52	268	422.5 (378.4, 471.7)	60	318.8 (252.4, 402.8)	0.75 (0.58, 0.98)
Anti-HPV 58	265	576.7 (482.5, 689.3)	59	437.5 (333.0, 574.6)	0.76 (0.59, 0.98)

^aThe adjusted GMTs, GMT ratios, and associated 95% CIs were estimated using an ANCOVA model of the natural logarithm of anti-HPV titers via a mixed model methodology. Age was included in the model as a covariate, and study (or protocol) as a random effect.

^bIncludes all participants who were not general protocol violators, received all three vaccinations within acceptable day ranges, were seronegative at Day 1 for the relevant HPV type(s), and had a Month 7 serum sample collected within an acceptable day range.

N = Number of participants randomized to the respective vaccination group who received at least 1 injection.

n = Number of participants contributing to the analysis.

Abbreviations: 9vHPV, 9-valent human papillomavirus; ANCOVA, analysis of covariance; CI, confidence interval; cLIA, competitive Luminex immunoassay; GMT, geometric mean titer; HM, heterosexual men; HPV, human papillomavirus; mMU, milli Merck units; MSM, men who have sex with men; PPI, per-protocol immunogenicity.

Table 6. HPV GMTs at 6 months post-last dose in males and females aged 9–15 years who received 9vHPV vaccine (PPI population^a).

Study 002 (9–15 years)						Study 010 (9–14 years)				
Assay (cLIA)	n	GMT, mMU/mL (95% CI) Males 3 doses (N = 612)	n	GMT, mMU/mL (95% CI) Females 3 doses (N = 1773)	GMT Ratio, (95% CI) Male 3 doses/ Females 3 doses	n	GMT, mMU/mL (95% CI) Males 2 doses (N = 301)	n	GMT, mMU/mL (95% CI) Females 2 doses (N = 301)	GMT ratio (95% CI) Male 2 doses/ Females 2 doses
Anti-HPV 6	456	700.5 (648.0, 757.3)	404	625.7 (576.0, 679.8)	1.12 (1.00, 1.25)	261	474.5 (422.9, 532.5)	256	498.8 (444.0, 560.3)	0.95 (0.81, 1.12)
Anti-HPV 11	459	455.2 (417.2, 496.6)	406	396.4 (361.4, 434.9)	1.15 (1.01, 1.30)	265	367.5 (326.1, 414.1)	257	383.2 (339.4, 432.6)	0.96 (0.81, 1.14)
Anti-HPV 16	467	2873.8 (2665.9, 3097.9)	411	2450.2 (2261.7, 2654.4)	1.17 (1.05, 1.31)	274	2198.4 (1956.5, 2470.2)	270	2204.9 (1960.6, 2479.6)	1.00 (0.84, 1.18)
Anti-HPV 18	465	784.1 (710.1, 865.7)	413	497.7 (448.1, 552.9)	1.58 (1.36, 1.82)	273	393.0 (344.6, 448.1)	270	416.5 (364.9, 475.3)	0.94 (0.78, 1.14)
Anti-HPV 31	462	702.8 (639.1, 773.0)	411	579.6 (524.0, 641.1)	1.21 (1.06, 1.39)	272	343.0 (300.8, 391.1)	270	345.2 (302.6, 393.8)	0.99 (0.82, 1.20)
Anti-HPV 33	465	375.0 (344.1, 408.6)	408	281.5 (256.8, 308.5)	1.33 (1.18, 1.51)	272	284.7 (250.8, 323.3)	271	285.5 (251.4, 324.3)	1.00 (0.83, 1.19)
Anti-HPV 45	468	259.3 (232.0, 289.7)	415	197.7 (175.7, 222.4)	1.31 (1.12, 1.54)	274	67.5 (59.1, 77.1)	272	72.7 (63.6, 83.2)	0.93 (0.77, 1.12)
Anti-HPV 52	467	316.6 (288.8, 347.0)	415	297.2 (269.6, 327.6)	1.07 (0.93, 1.22)	274	157.9 (140.6, 177.4)	270	148.6 (132.2, 167.0)	1.06 (0.90, 1.25)
Anti-HPV 58	464	539.8 (495.4, 588.0)	413	431.6 (394.2, 472.7)	1.25 (1.10, 1.42)	271	392.9 (351.3, 439.4)	268	370.3 (330.9, 414.4)	1.06 (0.91, 1.24)
Study 010 (9–14 years)						Study 001 (16–26 years)				
Assay (cLIA)	n	GMT, mMU/mL (95% CI) Males 1 dose (N = 301)	n	GMT, mMU/mL (95% CI) Females 1 dose (N = 301)	GMT Ratio, (95% CI) Males 1 dose/ Females 1 dose	GMT Ratio, (95% CI) Males 2 dose/ Males 1 dose	GMT Ratio, (95% CI) Females 2 dose/ Females 1 dose	n	GMT, mMU/mL (95% CI) Females Day 1 Seropositive and PCR-Negative ^b	
Anti-HPV 6	261	67.1 (60.6, 74.3)	251	75.2 (67.8, 83.4)	0.89 (0.77, 1.03)	7.07 (6.11, 8.18)	6.63 (5.63, 7.81)	917	108.1 (102.2, 114.3)	
Anti-HPV 11	263	43.0 (38.3, 48.3)	256	50.1 (44.5, 56.4)	0.86 (0.73, 1.01)	8.54 (7.23, 10.10)	7.64 (6.45, 9.06)	208	44.6 (39.2, 50.8)	
Anti-HPV 16	272	140.3 (124.1, 158.5)	269	160.2 (141.7, 181.1)	0.88 (0.74, 1.04)	15.67 (13.18, 18.63)	13.76 (11.66, 16.25)	564	126.6 (115.1, 139.3)	
Anti-HPV 18	271	29.5 (25.8, 33.6)	269	36.5 (32.0, 41.7)	0.81 (0.67, 0.97)	13.34 (11.11, 16.02)	11.41 (9.42, 13.82)	296	83.0 (74.3, 92.8)	
Anti-HPV 31	270	21.7 (19.0, 24.8)	269	30.0 (26.3, 34.2)	0.72 (0.60, 0.87)	15.79 (13.04, 19.12)	11.50 (9.60, 13.78)	373	38.7 (35.0, 42.6)	
Anti-HPV 33	270	18.5 (16.3, 20.9)	270	22.8 (20.1, 25.9)	0.81 (0.68, 0.97)	15.41 (12.93, 18.37)	12.51 (10.44, 15.01)	248	24.9 (22.1, 28.0)	
Anti-HPV 45	272	4.6 (4.0, 5.2)	271	5.9 (5.2, 6.8)	0.77 (0.64, 0.93)	14.82 (12.32, 17.83)	12.25 (10.11, 14.84)	97	23.7 (20.2, 27.9)	
Anti-HPV 52	272	19.2 (16.7, 22.1)	269	27.2 (23.6, 31.3)	0.71 (0.58, 0.86)	8.21 (6.89, 9.80)	5.47 (4.52, 6.61)	244	22.3 (20.3, 24.6)	
Anti-HPV 58	269	37.6 (33.4, 42.3)	267	46.1 (41.0, 52.0)	0.81 (0.69, 0.96)	10.46 (8.87, 12.33)	8.03 (6.83, 9.44)	419	21.7 (19.9, 23.8)	

^aIncludes all participants who received the number of vaccination doses required by the protocol within acceptable day ranges, had a 4-week post-last dose serum sample collected within an acceptable day range, were seronegative at baseline to the relevant HPV type, and had no other protocol violations that could interfere with immunogenicity evaluation.

^bIncludes participants from Study 001 who were seropositive and PCR-negative at Day 1 to the relevant HPV type(s), completed the three-dose regimen, and had a post-Dose 3 serology result within acceptable day range as described.²⁰

N = Number of participants randomized to the respective vaccination group who received at least one injection of 9vHPV vaccine.

n = Number of participants contributing to the analysis.

Abbreviations: 9vHPV, 9-valent human papillomavirus; ANCOVA, analysis of covariance; CI, confidence interval; cLIA, competitive Luminex immunoassay; GMT, geometric mean titer; HM, heterosexual men; HPV, human papillomavirus; mMU, milli Merck units; MSM, men who have sex with men; PPI, per-protocol immunogenicity.

vaccine clinical program revealed generally higher HPV6 and 11 GMTs in women, and generally higher HPV16 and 18 GMTs in men (Supplementary Table S4).

Immunogenicity in young adolescents by gender and number of 9vHPV vaccine doses

GMTs at 6 months post-last dose were analyzed in males and females aged 9–15 years who received three doses of 9vHPV vaccine in study 002 and in males and females aged 9–14 years who received one or two doses in study 010. Similar to the

observation among young adults, GMTs after three doses were generally higher in males compared with females (GMT ratios [male/female]: 1.07 to 1.58; lower bound of 95% CI for male/female ratio below 1 for HPV52 and ranging from 1.00 to 1.36 for the other HPV types; Table 6). However, GMTs were similar between males and females after two doses (GMT ratios [male/female]: 0.93 to 1.06; all 95% CIs for male/female GMT ratios crossing 1) and GMTs tended to be lower in males versus females after one dose (GMT ratios [male/female]: 0.71 to 0.89; upper bound of the 95% CI for male/female GMT ratio slightly above 1 [1.01 to 1.04] for HPV6, 11, and 16, and

ranging from 0.86 to 0.97 for the other HPV types). GMTs after two doses were generally higher than GMTs after one dose, with GMT ratios (males two doses/males one dose) ranging from 7.07 to 15.79 and GMT ratios (females two doses/females one dose) ranging from 5.47 to 13.76 (all 95% CIs for GMT ratios crossing 1).

Antibody levels after HPV infection were assessed by measuring Day 1 (pre-9vHPV vaccination) GMTs in females aged 16–26 years enrolled in study 001 with serologic evidence of prior HPV infection at any time before Day 1 (seropositive at Day 1), but without active infection (PCR negative at Day 1) at baseline for a given HPV type.²⁰ After two or three doses of 9vHPV vaccine, GMTs in both males and females aged 9–15 years were higher than those observed among women after HPV infection. In contrast, after a single 9vHPV vaccine dose GMTs in males and females 9–15 years of age were similar to (i.e., HPV11, 16, 52, and 58), or lower than (i.e., HPV6, 18, 31, 33, and 45) those observed among women subsequent to HPV infection (Table 6).

Discussion

We previously reported that the 9vHPV vaccine elicited strong HPV antibody responses in females aged 9–26 years and males aged 9–15 years in study participants from various regions and races.²⁰ The present analyses show that the 9vHPV vaccine also induces robust HPV antibody responses in males aged 16–26 years with only small differences in GMTs observed across world regions and races. Previous analyses in females aged 9–26 years showed a decrease in GMT responses to qHPV and 9vHPV vaccines with increasing age at time of vaccination. The present analyses confirm this trend in males, with higher GMTs observed in younger (aged 16–21 years) versus older (aged 22–26 years) males.

Previous analyses of qHPV and 9vHPV clinical trials in males 16–26 years of age revealed a lower GMT response in MSM compared with HM.^{14,19} This analysis assessed whether these differences may have been caused by imbalances between groups in terms of age and/or region of residence. The integrated analysis of immunogenicity in HM, MSM, and females aged 16–26 years showed that the lower immune response to 9vHPV vaccine among MSM compared with HM is unlikely to be explained by differences in participant age, world region of residence, or variability across studies. Differences are also unlikely to be explained by variability in laboratory testing since all samples were tested using the same validated immunoassay in the clinical trials that supported licensure of the 9vHPV vaccine. Lower antibody responses to hepatitis A and hepatitis B vaccinations have been reported among MSM previously infected with HIV.^{27–29} However, MSM included in the present immunogenicity analyses were HIV negative at enrollment. Therefore, it remains unclear why lower anti-HPV GMTs were observed in MSM compared with HM following HPV vaccination. MSM is a population with generally wider exposure to HPV compared with HM (see for instance higher baseline HPV seropositivity in MSM vs HM in study 003¹⁴). Thus, immune imprinting (a phenomenon also known as “original antigenic sin”), whereby prior antigenic encounters may influence subsequent responses to related antigens, has

been proposed as a potential explanation for the lower observed anti-HPV GMTs in this population.¹⁴ This may reinforce the importance of adolescent vaccination prior to sexual debut and potential exposure to HPV. Differences by region of residence were observed. GMTs were lower in MSM compared with HM in Africa, Europe, and Latin America for all nine HPV types, and were similar or lower in MSM compared with HM in North America. An exception to the general trend of lower immunogenicity was observed in MSM from Asia, who had similar GMTs for the nine vaccine-targeted HPV types compared with HM. In a qHPV vaccine study among Japanese males 16–26 years of age, GMT point estimates at Month 7 were lower among Japanese MSM compared with HM, although 95% CIs were overlapping.⁹ Since the prevalence of anogenital HPV infection is generally lower in Asian countries relative to non-Asian countries,³⁰ one could speculate that there may be less immune imprinting in Asian MSM. The most dramatic differences in GMTs between MSM and HM were observed in participants from Africa. However, these results should be interpreted with caution due to the limited numbers of participants from this region.

The integrated analysis also showed a higher immunogenicity of 9vHPV vaccine in HM compared with women with respect to the seven high-risk HPV types (HPV16/18/31/33/45/52/58), and similar immunogenicity in HM and women for the two low-risk HPV types (HPV6/11). This contrasts with previous observations of lower humoral responses in males versus females with other vaccines.³¹ For the qHPV vaccine, immunogenicity was higher in HM versus females for the two high-risk HPV types (HPV16/18) and lower in HM versus women for the two low-risk HPV types (HPV6/11). Trends of lower immunogenicity in men versus women for HPV6, 11, and 18 have also been noted in a meta-analysis of 18 clinical trials of the qHPV vaccine.²² Any differences in HPV vaccine immunogenicity after three doses between MSM, HM, and females described in this report are unlikely to have clinical significance, as similar differences have been reported after administration of three doses of the qHPV vaccine, which is highly effective and provides durable protection against HPV-related disease in these three populations.^{7,8,10,19,32,33}

Comparative analysis of immunogenicity in adolescents indicated potential differences in HPV antibody responses due to gender and the number of 9vHPV vaccine doses received. As seen in older adolescents and young adults, immunogenicity was generally higher in males aged 9–15 years than in females aged 9–15 years following three doses of 9vHPV vaccine. In contrast, we observed that immunogenicity was similar for males and females aged 9–14 years who received two doses of 9vHPV vaccine 6 months apart and tended to be lower in males compared with females aged 9–14 years following one dose of 9vHPV vaccine for most HPV types; the clinical significance of this lower immunogenicity is unknown. These results suggest that the immunogenicity profiles after one, two, or three doses established in one demographic group are not necessarily applicable to another demographic group.

GMTs after a single dose in males and females aged 9–14 years in this study were similar to, or lower than, those observed previously in young women with evidence of prior HPV infection. While antibody response to HPV infection provides only partial protection,^{34–36} one cannot infer based on these findings that one dose of 9vHPV vaccine may also only provide partial protection. Active research is being conducted on HPV vaccine doses and timing of doses. This includes studies to assess extended interval two-dose regimens³⁷ as well as a single-dose schedule.^{38,39} The present results show that GMTs after one dose of 9vHPV vaccine are similar or lower than GMTs after HPV infection. Results of a previously reported trial in 9–14-year-olds²³ showed lower immunogenicity and incomplete seroconversion observed after a single dose of 9vHPV vaccine compared with two- and three-dose regimens (56–98% after one dose depending on the HPV type and 99–100% after two or three doses). Since the minimum level of antibody needed for protection is unknown, it will be important to assess the long-term effectiveness of single-dose HPV vaccination against HPV-related disease in randomized, controlled efficacy trials that include years of follow-up. Notably, while several randomized clinical trials are ongoing to assess efficacy of single-dose HPV vaccination to prevent persistent infection,^{38,39} they do not include assessment of efficacy of single-dose HPV vaccination in males, nor efficacy against HPV-related diseases. One ongoing cluster-randomized study is assessing the population-level impact of adding male single-dose HPV vaccination to a female vaccination program (NCT04953130).

The post hoc nature of this study should be considered when interpreting these findings. Another potential limitation was the low number of MSM participants, which precluded analysis of smaller groups within this population. A strength of this analysis is that it utilized data generated by a validated immunoassay and standard procedures spanning multiple clinical studies, allowing for comparison across data sets. Furthermore, the included studies were international, multi-country clinical trials, supporting the generalizability of the data.

Further studies of 9vHPV vaccine efficacy and immunogenicity in males are underway, including two randomized clinical trials assessing 9vHPV vaccination efficacy toward prevention of oral HPV infection in males 20–45 years of age (NCT04199689)⁴⁰ and males 20–50 years of age living with HIV (NCT04255849); two randomized clinical trials (NCT04635423 and NCT05285826) assessing 9vHPV vaccine efficacy against anogenital HPV persistent infection and disease in males 16–26 years of age and 20–45 years of age, respectively; and one clinical trial (NCT04708041) assessing 9vHPV vaccine immunogenicity of extended interval dosing regimens (two doses administered 1–5 years apart) in adolescents 9–15 years of age.³⁷

In conclusion, this post hoc analysis of 9vHPV vaccine immunogenicity confirmed that robust antibody responses are induced for all nine HPV types across a range of baseline characteristics. Although there were differences in immune responses to a three-dose regimen between HM, MSM, and females, this has not translated to decreased protection in any of these demographic groups in efficacy studies. Moreover, the 9vHPV vaccine has been demonstrated to be well tolerated in both males and females.^{41–43} These findings reinforce the benefits of HPV vaccination for

males and support the adoption of gender-neutral and catch-up vaccination programs. Gender-neutral HPV vaccination programs, which have become more common in recent years, are advantageous as they provide gender equity, greater individual and herd protection against HPV infection and disease, and increased program resilience should vaccination coverage change, such as occurred recently during the COVID-19 pandemic.^{44–47}

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Disclosure statement

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

ARG reports grant support from, and is an advisory board member for, Merck & Co., Inc., Rahway, NJ, USA.

JMP is a scientific advisory board member for Merck & Co., Inc. and Inovio and reports travel support from Merck & Co., Inc., personal fees and grants from Vir Biotech, and stock options from Virion Therapeutics, outside the submitted work.

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AS reports personal fees from MSD and has written chapters about human papillomavirus vaccines in a pediatric and adolescent gynecology book, a book for parents of adolescents, an infectious disease journal, and a vaccines journal.

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Data availability statement

The data sharing policy, including restrictions, of Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA is available at http://engagezone.msd.com/ds_documentation.php. Requests for access to the clinical study data can be submitted through the EngageZone site or via e-mail to dataaccess@msd.com.

Corresponding Author's Biographical Notes

Anna R. Giuliano, PhD, is the founding director of the Center for Immunization and Infection Research in Cancer (CIIRC) at the Moffitt Cancer Center. Her work has contributed significantly to our understanding of the rate at which HPV infections are acquired and cleared, the proportion that progress to disease, and also to HPV vaccine protection against multiple diseases in women and men.

ORCID

Anna R. Giuliano  <http://orcid.org/0000-0002-5440-8859>

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