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Impact of baseline covariates on the immunogenicity of the 9-valent HPV vaccine – A combined analysis of five phase III clinical trials

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ABSTRACT

Background: The immunogenicity profile of the 9-valent HPV (9vHPV) vaccine was evaluated across five phase III clinical studies conducted in girls and boys 9–15 years of age and young women 16–26 years of age. The effect of baseline characteristics of subjects on vaccine-induced HPV antibody responses was assessed.

Methods: Immunogenicity data from 11,304 subjects who received ≥1 dose of 9vHPV vaccine in five Phase III studies were analyzed. Vaccine was administered as a 3-dose regimen. HPV antibody titers were assessed 1 month after dose 3 using a competitive Luminex immunoassay and summarized as geometric mean titers (GMTs). Covariates examined were age, gender, race, region of residence, and HPV serostatus and PCR status at day 1.

Results: GMTs to all 9 vaccine HPV types decreased with age at vaccination initiation, and were otherwise generally similar among the demographic subgroups defined by gender, race and region of residence. For all subgroups defined by race or region of residence, GMTs were higher in girls and boys than in young women. Vaccination of subjects who were seropositive at day 1 to a vaccine HPV type resulted in higher GMTs to that type, compared with those in subjects who were seronegative for that type at day 1.

Conclusions: 9vHPV vaccine immunogenicity was robust among subjects with differing baseline characteristics. It was generally comparable across subjects of different races and from different regions. Greater immunogenicity in girls and boys versus young women (the population used to establish 9vHPV vaccine efficacy in clinical studies) indicates that the anti-HPV responses generated by the vaccine in adolescents from all races or

Abbreviations: HPV, human papillomavirus; VLP, virus-like particle; 9vHPV, 9-valent human papillomavirus; cLIA, competitive Luminex immunoassay; GMTs, geometric mean titers; CI, confidence interval; mMU/mL, milli-Merck units per milliliter; qHPV, quadrivalent human papillomavirus

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regions were sufficient to induce high-level protective efficacy. This immunogenicity profile supports a widespread 9vHPV vaccination program and early vaccination.

1. Introduction

Human papillomavirus (HPV) is the cause of nearly all cervical cancers and a substantial proportion of anal, vulvar, vaginal, penile and oropharyngeal cancers; thus, it is responsible of approximately 5% of the global cancer burden [1]. The identification of HPV as a primary cause of anogenital cancers created an opportunity for cancer prevention through vaccination. First generation HPV vaccines, including the quadrivalent HPV (types 6/11/16/18) (qHPV) vaccine and the bivalent HPV (types 16/18) vaccine were initially developed [2]. A 9-valent HPV (types 6/11/16/18/31/33/45/52/58) (9vHPV) vaccine (Gardasil 9, Merck & Co., Inc., Kenilworth, NJ) was subsequently developed to provide protection against the HPV types already covered by the qHPV vaccine and the next five most common oncogenic types associated with cervical cancer worldwide (types 31/33/45/52/58) [3]. The 9vHPV vaccine could potentially prevent approximately 90% of cervical cancers, HPV-related vulvar, vaginal and anal cancers and genital warts worldwide [4–9]. The 9vHPV vaccine was licensed in 2014 in the US, in 2015 in Canada, the EU and Australia, and in 2015 and 2016 in other countries.

In a clinical trial conducted in women 16–26 years of age, the 9vHPV vaccine prevented infection and disease caused by HPV 31/33/45/52/58. It also induced anti-HPV 6/11/16/18 antibody responses that were non-inferior to responses induced by the qHPV vaccine; efficacy of the 9vHPV vaccine against infection and disease caused by HPV 6/11/16/18 was inferred based on these results [10–12]. In another clinical trial, the 9vHPV vaccine induced non-inferior antibody responses to HPV 6/11/16/18/31/33/45/52/58 in girls and boys 9–15 years of age vs. women 16–26 years of age; efficacy of the 9vHPV vaccine against infection and disease caused by the 9 vaccine HPV types in girls and boys 9–15 years of age was inferred based on these results [13].

HPV infection is a global health concern; prophylactic HPV vaccination is included in the national immunization programs of at least 80 countries [14], and used in diverse settings worldwide. It is anticipated that the 9vHPV vaccine will be widely licensed and recommended. Thus, it is useful to evaluate the impact of demographic parameters on the immunogenicity of the 9vHPV vaccine. Of relevant note, a similar study examining the impact of demographic parameters on the immunogenicity of the qHPV vaccine was published shortly after the initial licensure of the qHPV vaccine [15]. This report summarizes a combined analysis of five Phase III clinical trials conducted in girls and boys 9–15 years of age and women 16–26 years of age to examine antibody responses in subgroups for which individual studies may have had limited sample size. Thus, these analyses are novel and may be of interest to many as the 9vHPV vaccine becomes more widely available. Immunogenicity of the 9vHPV vaccine in young men 16–26 years of age was not included in these analyses; it will be the topic of another report so that the additional complexities specific to that population (i.e., lower HPV antibody responses in men having sex with men than in heterosexual men [16,17]) can be fully explored.

2. Materials and methods

2.1. Enrollment and vaccination

An analysis of the combined immunogenicity database of Phase III studies submitted to regulatory agencies in support of the licensure of the 9vHPV vaccine was conducted. This analysis included 11,304 subjects who received 9vHPV vaccine in five Phase III studies (Table 1). These studies contained three separate populations: virginal girls 9–15 years of age, virginal boys 9–15 years of age, and young women 16–26 years of age, most of whom were sexually active. Eligible subjects received a 3-dose vaccination regimen given as intramuscular injections at day 1, month 2 and month 6. Each study was conducted in accordance with principles of Good Clinical Practice and was approved by the institutional review board at each participating institution and by regulatory agencies. Written informed consent was provided by all adult subjects and by a parent or legal guardian of subjects who were minors, assent was also obtained from minors in conformity with

Table 1
Phase III studies of the 9vHPV vaccine contributing to the combined immunogenicity analysis.

Study	Key objectives	Experimental arm	Control arm	Included in analyses[a]
001	Immunogenicity, efficacy vs. qHPV	Women age 16–26 years randomized to 9vHPV vaccine (N=6799)[b]	Women age 16–26 years randomized to qHPV vaccine (N=6799)[b]	N=6792[b,c]
002	Adult-to-adolescent immunobridging	Girls and boys age 9–15 years (N=2604) enrolled to receive 9vHPV vaccine	Women age 16–26 years enrolled to receive 9vHPV vaccine (N=470)	N=3066
005	Co-administration with Menactra/Adacel	Girls and boys age 11–15 years randomized to concomitant arm (N=621)	Girls and boys age 11–15 years randomized to non-concomitant arm (N=620)	N=618[d]
007	Co-administration with Repevax	Girls and boys age 11–15 years randomized to concomitant arm (N=526)	Girls and boys age 11–15 years randomized to non-concomitant arm (N=528)	N=528[d]
009	qHPV-to-9vHPV immunobridging	Girls age 9–15 years randomized to 9vHPV vaccine (N=300)	Girls age 9–15 years randomized to qHPV vaccine (N=300)	N=300[c]

Study 001: NCT00543543 [10].
Study 002: NCT00943722 [13].
Study 005: NCT00988884 [22].
Study 007: NCT01073293 [23].
Study 009/GDS01C: NCT01304498 [12].

[a] Subjects who received at least one vaccination with 9vHPV vaccine. A total of 11,304 subjects who received at least one 9vHPV vaccination are included in these analyses. Most subjects (97.7% [11,046 of 11,304]) received the three vaccinations.

[b] Subjects who received the low-dose, mid-dose or high-dose formulation of 9vHPV vaccine during the dose selection portion of the study [10,43] are not included; immunogenicity results in these subjects are reported in [44].

[c] Subjects randomized to the 9vHPV vaccine who received ≥1 dose of vaccine.

[d] Subjects randomized to the non-concomitant arm who received ≥1 dose of 9vHPV vaccine. Subjects randomized to the concomitant arm of studies 005 and 007 are not considered in this report; immunogenicity results in these subjects are reported in [22,23].

applicable national and local requirements. Baseline characteristics for the overall population of subjects who were randomized to receive the 9vHPV vaccine are presented in Table 2.

2.2. Immunogenicity evaluation

Serum samples were obtained at day 1 and month 7 for anti-HPV antibody testing. The serum samples were assessed for antibodies to HPV VLP types 6/11/16/18/31/33/45/52/58 by a multiplexed competitive Luminex Immunoassay (cLIA; HPV-9 cLIA Version 2.0; performed by PPD Vaccines and Biologics Lab, Wayne, PA, USA), as described previously [18]. Antibody titers for each individual HPV type were determined through competition with type-specific monoclonal antibodies, so it is not possible to directly compare assay results across HPV types. In addition, cervical and external genital swabs collected at day 1 and month 7 in young women 16–26 years of age for testing by polymerase chain reaction (PCR) for type-specific detection of HPV DNA; PCR testing included the 9 vaccine types and 5 additional oncogenic HPV types (HPV 35/39/51/56/59)[19,20]. HPV seropositivity at day 1 or PCR positivity at day 1 and month 7 was not a reason for exclusion from the study; however, the results were part of the criteria to define analysis populations.

2.3. Data analysis

The serum samples from day 1 and PCR samples from day 1 and month 7 were analyzed for each vaccine HPV type prior to enrollment to identify participants who were positive to one or more HPV types, and these participants were subsequently excluded from the per-protocol immunogenicity analysis for the corresponding HPV type(s). To be included in the HPV type specific per-protocol immunogenicity analysis populations, subjects had to meet the following requirements: (1) be seronegative at day 1 and (for 16- to 26-year-old women) PCR-negative from day 1 through month 7 only for the HPV type being analyzed (for HPV 6 and HPV 11 immunogenicity analyses, because of extensive cross-reactivity due to the high amino acid sequence identity [92%] between HPV 6 and HPV 11 L1 proteins [21], subjects had to be seronegative and, for women 16–26 years of age, PCR-negative for both HPV 6 and HPV 11); (2) receive all 3 doses of the correct clinical material within acceptable day ranges; (3) have a post-dose 3 serology result within acceptable day ranges and (4) have no protocol violation that could potentially interfere with the immunogenicity evaluation as judged by the study director. Seropositive was defined as anti-HPV serum cLIA levels ≥30, 16, 20, 24, 10, 8, 8, 8, 8 milli-Merck units per milliliter (mMU/mL) for HPV types 6, 11, 16, 18, 31, 33, 45, 52 and 58 respectively. Subjects who incidentally received a concomitant vaccination in studies 001, 002 and 009, were excluded from per-protocol immunogenicity analyses as concomitant vaccination was prohibited per protocol in these studies [10,12,13]. Thus, for consistency across studies, subjects in the concomitant arm of studies 005 and 007 (studies to assess co-administration of 9vHPV vaccine with diphtheria, tetanus, pertussis, poliomyelitis and meningococcal vaccines) were also excluded from this combined immunogenicity analysis. Immunogenicity results from the concomitant and non-concomitant arms of studies 005 and 007 have been reported [22,23]. Subjects excluded from per-protocol analyses are summarized in Supplementary material Table 1. Although the per-protocol analyses excluded subjects who were HPV positive (seropositive and/or PCR positive) for vaccine HPV types at baseline, a separate analysis was performed including these subjects to elucidate the differences in immune response between baseline HPV positive and HPV negative subjects. To be included in this analysis, subjects had to meet the following requirements: (1) have a day 1 serology result and a day 1 PCR result; (2) receive all 3 doses of the correct clinical material; and (3) have a post-dose 3 serology result within acceptable day ranges. These analyses were done in subjects (women 16–26 years) enrolled in study 001.

Geometric mean titers (GMTs) with associated 95% confidence intervals were computed and compared across categories of baseline subject characteristics. Cohorts analyzed included subjects given the 9vHPV vaccine stratified into the following three age/sex groups: boys 9–15 years of age, girls 9–15 years of age, and young women 16–26 years of age. Baseline covariates analyzed included age, sex, race, region of residence, and baseline HPV seropositivity and PCR-positivity. All of these evaluations were exploratory in nature; therefore, no statistical tests of hypotheses were performed. Non overlapping 95% confidence intervals were used as indicators of differences of immune response.

It has been previously observed that HPV antibody response to HPV vaccination declines with increasing age [2,13,15]. Analyses were conducted to explore whether this relationship varies with race and geographic region. Linear regression model was fitted on the logarithm (base 10) of HPV antibody titer at Month 7 as a function of age at vaccination dose 1 to model the relationship of HPV antibody response at Month 7 with age. Graphical methods were used to display the regression line representing the estimated mean $\log_{10}$-HPV antibody response as a function of age together with the 95% confidence band around the regression line. The regression line and 95% confidence band were displayed by race and geographic region to graphically compare trends of the relationship of HPV antibody response by age across race and geographic region. For each HPV type, two analyses were conducted: an analysis of mean HPV antibody response by race irrespective of geographic region (this analysis is relevant given that race is a reasonable surrogate for geographic region); a second analysis of mean HPV antibody response by race and geographic region. No formal statistical testing was done on the trends of the relationship of mean HPV antibody response by age across race or race and geographic region.

In studies 001 and 009, subjects were randomized to receive 9vHPV vaccine or qHPV vaccine [10,12]. This report considers only subjects who received the 9vHPV vaccine. Immunogenicity of qHPV vaccine by baseline covariates has already been reported [15].

Table 2
Subject characteristics (all randomized subjects).

	Females 9–15 years of age		Males 9–15 years of age		Females 16–26 years of age	
	n	(%)	n	(%)	n	(%)
Subjects in population	2809		1243		7269	
Age (years)						
Subjects with data	2809		1243		7269	
Mean	12		12		22	
SD	2		2		2	
Median	12		12		22	
Range	9 to 15		9 to 15		16 to 26	
Race						
Asian	470	(16.7)	224	(18.0)	1113	(15.3)
Black	182	(6.5)	60	(4.8)	281	(3.9)
White	1749	(62.3)	665	(53.5)	4004	(55.1)
Other[a]	408	(14.5)	294	(23.7)	1871	(25.7)
Region						
Africa	95	(3.4)	30	(2.4)	40	(0.6)
Asia-Pacific	458	(16.3)	219	(17.6)	998	(13.7)
Europe	1102	(39.2)	373	(30.0)	2531	(34.8)
Latin America	545	(19.4)	286	(23.0)	2319	(31.9)
North America	609	(21.7)	335	(27.0)	1381	(19.0)

Study participants were from 26 countries (Austria, Belgium, Brazil, Canada, Chile, Colombia, Costa Rica, Denmark, Finland, Germany, Hong Kong, India, Italy, Japan, Korea, Mexico, New Zealand, Norway, Peru, Poland, South Africa, Spain, Sweden, Taiwan, Thailand, and the United States [including Puerto Rico]).

[a] The category 'Other' for the race variable includes Multi-Racial, American Indian or Alaska Native, Native Hawaiian or Pacific Islander, Unknown and missing race information. Most subjects in that category are Multi-Racial.

3. Results

The population included in the present analysis was ethnically diverse and resided in both high-income and low- and middle-income countries. The baseline characteristics among the age/sex cohorts are shown in Table 2. Overall, 98.8% (11,304 of 11,321) of subjects randomized to 9vHPV vaccine received at least one dose of vaccine and 97.6% (11,046 of 11,321) of subjects received all three doses of vaccine. Principal reasons for exclusion from per-protocol immunogenicity analyses included seropositivity and/or PCR positivity to HPV vaccine types and missing serology samples (Supplementary material Table 1).

Table 3 summarizes the serum anti-HPV responses at month 7 in the three populations analyzed. For all subjects, seroconversion rates at month 7 ranged from 99.6% to 100%. As seen previously in study 002 [13], geometric mean titers (GMTs) at month 7 were markedly higher in girls and boys than in young women for all 9 vaccine HPV types; and among the adolescents, administration of the vaccine to boys generally resulted in marginally higher anti-HPV GMTs than girls of the same age. Fig. 1 summarizes the serum anti-HPV responses at month 7 in girls and women, stratified by age at enrollment. GMTs decreased with increasing age. Relatively large variations for ages 16 and 17 years were observed, likely representing random variations due to the limited numbers of subjects enrolled in this age range (~2% of total girls and women enrollment). Supplementary material Fig. 1 provides a similar analysis for boys. For each of the 9 HPV types, month 7 GMTs decreased as the age at first vaccination increased.

Small numeric differences in month 7 anti-HPV GMTs were observed among subpopulations of women 16–26 years of age defined by race. In particular, black women tended to have higher anti-HPV GMTs than Asian or white women or women of other races. However, no consistent pattern was demonstrated across all 9 vaccine types (Table 4). Subjects in Africa, Latin America and North America tended to have higher anti-HPV GMTs than subjects in Asia, and Europe (Table 5). Analyses of month 7 GMTs by race (Supplementary material Tables 2 and 3) and by region (Supplementary material Tables 4 and 5) in girls and boys 9–15 years of age provided similar results. Month 7 GMTs were markedly higher in girls and boys 9–15 years of age than in women 16–26 years of age for all subgroups defined by race or region for all 9 HPV types.

In exploratory analyses, the inverse relationship between mean HPV antibody responses at month 7 and age was seen regardless of race and geographic region (Supplementary material Fig. 2). Even though small differences were observed among subgroups defined by race or race and region, no consistent pattern was demonstrated across all 9 vaccine types.

Table 6 displays the anti-HPV levels at month 7 in subject groups

Table 3
Per-protocol summary of month 7 anti-HPV geometric mean titers in subjects who received 3 doses of 9vHPV vaccine.

Population	N	n	% Seropositive (95% CI)	GMT (95% CI)
Anti-HPV 6				
9- through 15-year-old girls	2805	2349	99.7 (99.4, 99.9)	1744.6 (1684.7, 1806.7)
9- through 15-year-old boys	1239	1055	99.9 (99.5, 100)	2085.3 (1984.2, 2191.6)
16- through 26-year-old women	7260	4321	99.8 (99.6, 99.9)	893.7 (873.5, 914.3)
Anti-HPV 11				
9- through 15-year-old girls	2805	2350	99.9 (99.7, 100)	1289.7 (1244.3, 1336.8)
9- through 15-year-old boys	1239	1055	100 (99.7, 100)	1469.2 (1397.7, 1544.4)
16- through 26-year-old women	7260	4327	100 (99.9, 100)	669.3 (653.6, 685.4)
Anti-HPV 16				
9- through 15-year-old girls	2805	2405	99.9 (99.7, 100)	7159.9 (6919.7, 7408.5)
9- through 15-year-old boys	1239	1076	100 (99.7, 100)	8444.9 (8054.2, 8854.5)
16- through 26-year-old women	7260	4361	100 (99.9, 100)	3159.0 (3088.6, 3231.1)
Anti-HPV 18				
9- through 15-year-old girls	2805	2420	99.9 (99.6, 100)	2085.5 (2002.2, 2172.3)
9- through 15-year-old boys	1239	1074	100 (99.7, 100)	2620.4 (2474.3, 2775.2)
16- through 26-year-old women	7260	4884	99.8 (99.7, 99.9)	809.9 (789.2, 831.1)
Anti-HPV 31				
9- through 15-year-old girls	2805	2397	100 (99.8, 100)	1883.3 (1811.3, 1958.1)
9- through 15-year-old boys	1239	1069	100 (99.7, 100)	2173.5 (2057.0, 2296.6)
16- through 26-year-old women	7260	4806	99.8 (99.6, 99.9)	664.8 (647.4, 682.6)
Anti-HPV 33				
9- through 15-year-old girls	2805	2418	99.9 (99.7, 100)	960.6 (927.5, 994.9)
9- through 15-year-old boys	1239	1076	100 (99.7, 100)	1178.6 (1120.9, 1239.4)
16- through 26-year-old women	7260	5056	99.7 (99.5, 99.8)	419.2 (409.6, 429.1)
Anti-HPV 45				
9- through 15-year-old girls	2805	2430	99.8 (99.6, 100)	728.7 (697.6, 761.2)
9- through 15-year-old boys	1239	1079	100 (99.7, 100)	841.7 (790.0, 896.7)
16- through 26-year-old women	7260	5160	99.6 (99.4, 99.7)	254.1 (247.0, 261.5)
Anti-HPV 52				
9- through 15-year-old girls	2805	2426	99.9 (99.7, 100)	978.2 (942.8, 1015.0)
9- through 15-year-old boys	1239	1077	100 (99.7, 100)	1062.2 (1007.2, 1120.2)
16- through 26-year-old women	7260	4792	99.8 (99.6, 99.9)	382.4 (373.0, 392.0)
Anti-HPV 58				
9- through 15-year-old girls	2805	2397	99.9 (99.7, 100)	1306.0 (1259.8, 1354.0)
9- through 15-year-old boys	1239	1072	100 (99.7, 100)	1545.8 (1470.6, 1624.8)
16- through 26-year-old women	7260	4818	99.8 (99.6, 99.9)	489.2 (477.5, 501.2)

N=number of individuals randomized to the respective vaccination group who received at least 1 injection.
n=number of individuals contributing to the analysis.
mMU=milli-Merck units.
CI=confidence interval.
GMT=geometric mean titers (given in milli-Merck units per milliliter).

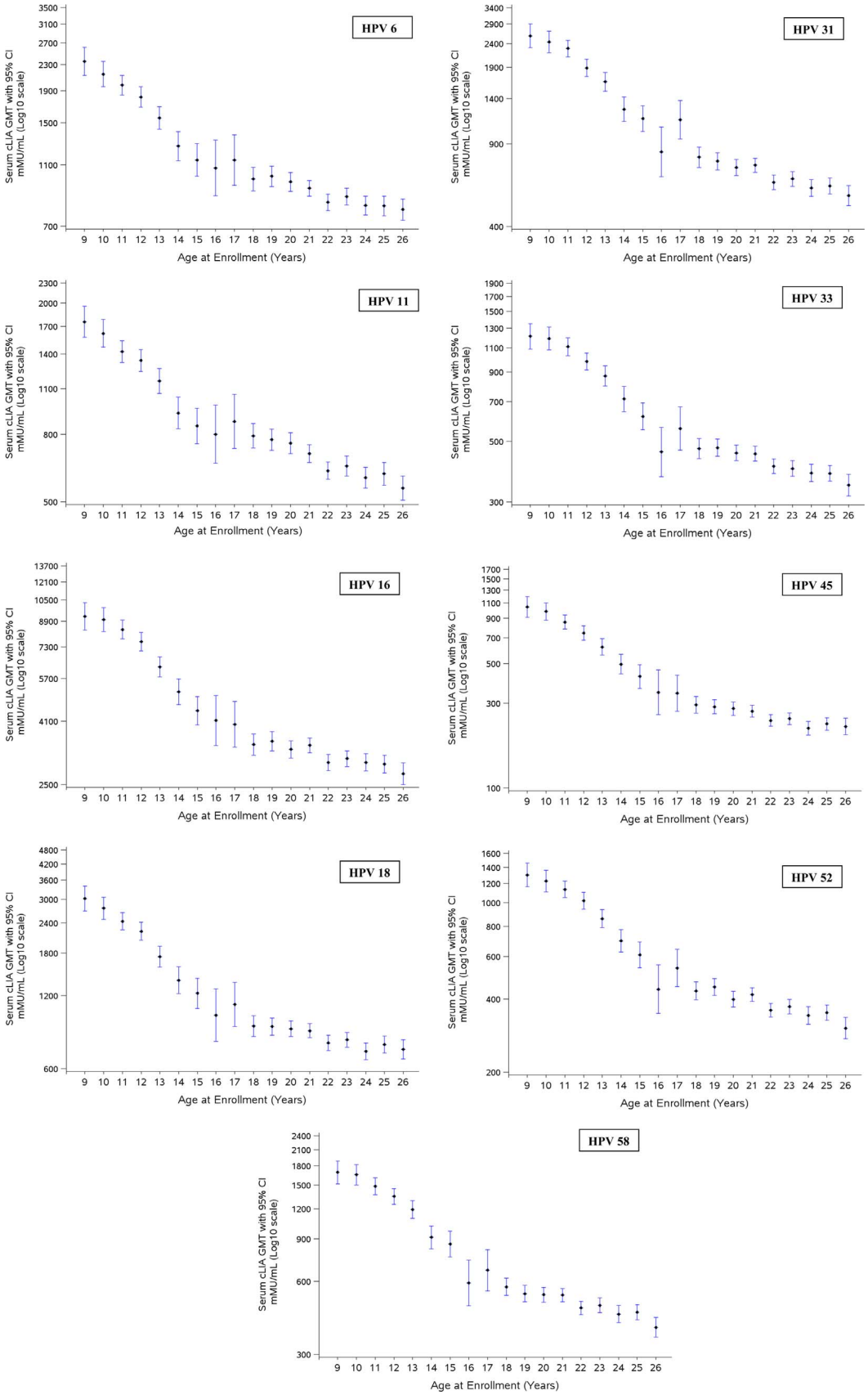

Fig. 1. Plots of month 7 anti-HPV geometric mean titers (GMTs) responses in females to component human papillomavirus (HPV) vaccine types, by age at enrollment. GMTs with associated 95% confidence intervals are presented for the per-protocol immunogenicity population. cLIA, competitive Luminex-based immunoassay; mMU, milli-Merck units.

Table 4
Per-protocol summary of anti-HPV geometric mean titers at month 7 by race in women 16–26 years of age who received 3 doses of 9vHPV vaccine.

	Race							
	Asian		Black		White		Other	
Assay	n	GMT (95% CI)	n	GMT (95% CI)	n	GMT (95% CI)	n	GMT (95% CI)
HPV 6	763	837.4 (793.1, 884.0)	123	935.3 (817.1, 1070.6)	2415	895.4 (868.5, 923.1)	1020	929.0 (886.5, 973.7)
HPV 11	764	594.5 (561.9, 629.0)	122	670.1 (581.8, 771.7)	2421	691.1 (669.5, 713.3)	1020	677.7 (645.4, 711.6)
HPV 16	792	3071.2 (2913.4, 3237.7)	152	3983.9 (3531.7, 4493.9)	2361	3077.8 (2985.2, 3173.4)	1056	3307.7 (3159.9, 3462.3)
HPV 18	831	850.9 (799.4, 905.7)	170	995.0 (866.8, 1142.3)	2669	755.6 (729.7, 782.3)	1214	886.2 (841.6, 933.2)
HPV 31	858	710.7 (667.6, 756.6)	169	786.4 (683.0, 905.5)	2631	619.5 (597.8, 642.1)	1148	725.1 (686.9, 765.4)
HPV 33	856	420.2 (397.1, 444.6)	189	414.6 (367.6, 467.5)	2733	417.1 (404.1, 430.5)	1278	424.0 (404.8, 444.0)
HPV 45	885	281.4 (262.9, 301.3)	190	345.0 (297.9, 399.6)	2824	227.3 (218.8, 236.1)	1261	290.1 (274.1, 307.2)
HPV 52	788	353.8 (332.7, 376.1)	166	444.0 (388.4, 507.5)	2690	388.2 (375.6, 401.4)	1148	381.0 (362.1, 400.8)
HPV 58	814	520.3 (490.5, 551.9)	161	493.1 (431.9, 562.9)	2720	483.6 (468.2, 499.4)	1123	480.8 (457.2, 505.5)

GMT, geometric mean titer (given in milli-Merck units per milliliter). CI, confidence interval.

defined by day 1 HPV serostatus and PCR status. Inclusion of subjects regardless of baseline HPV status permitted a comparison of vaccine-induced immune responses with those generated in response to an HPV infection. Robust antibody responses were observed in all groups for all HPV types. GMTs appeared to be the highest in the group which was seropositive and PCR negative on day 1 (i.e., subjects who were seropositive at enrollment likely due to a prior exposure to HPV).

GMTs were analyzed over time in the per-protocol population and in subjects seropositive and PCR negative at day 1 in study 001. Table 7 enumerates anti-HPV GMTs at all time- points from month 3 (1 month post-dose 2) and month 7 (1 month post-dose 3) to month 42 in subjects that were seropositive and PCR negative at day 1. Notably, in

Table 5
Per-protocol summary of month 7 anti-HPV geometric mean titers by region in women 16–26 years of age who received 3 doses of 9vHPV vaccine.

	Region									
	Africa		Asia-Pacific		Europe		Latin America		North America	
Assay	n	GMT (95% CI)	n	GMT (95% CI)	n	GMT (95% CI)	n	GMT (95% CI)	n	GMT (95% CI)
HPV 6	16	1029.5 (708.5, 1496.1)	691	817.9 (772.7, 865.8)	1454	850.9 (818.2, 884.9)	1292	946.6 (908.1, 986.8)	868	953.2 (906.1, 1002.8)
HPV 11	15	764.4 (511.2, 1142.9)	692	588.9 (555.0, 624.8)	1458	660.0 (633.7, 687.5)	1292	686.0 (656.9, 716.4)	870	729.5 (692.0, 769.1)
HPV 16	20	5218.2 (3746.9, 7267.3)	722	2943.1 (2785.2, 3109.8)	1412	2929.3 (2816.1, 3047.1)	1336	3355.0 (3221.8, 3493.8)	871	3412.8 (3245.7, 3588.5)
HPV 18	21	1376.9 (930.3, 2037.7)	758	827.4 (775.1, 883.2)	1604	714.2 (682.9, 747.0)	1537	887.6 (847.9, 929.2)	964	838.4 (791.3, 888.3)
HPV 31	23	986.1 (673.5, 1443.9)	785	673.6 (631.0, 719.0)	1584	578.7 (552.7, 605.9)	1454	725.5 (691.6, 761.2)	960	717.3 (676.1, 760.9)
HPV 33	18	442.9 (300.3, 653.3)	782	407.1 (383.8, 431.9)	1635	396.9 (381.1, 413.4)	1616	429.3 (412.0, 447.3)	1005	450.9 (428.1, 475.0)
HPV 45	24	518.1 (343.1, 782.3)	810	267.7 (249.4, 287.4)	1714	207.8 (197.9, 218.2)	1604	291.0 (276.7, 306.1)	1008	272.0 (255.2, 289.8)
HPV 52	20	552.8 (376.5, 811.7)	717	340.6 (319.4, 363.2)	1620	365.1 (349.8, 381.0)	1465	390.8 (373.7, 408.8)	970	432.1 (409.0, 456.7)
HPV 58	15	706.9 (458.1, 1090.8)	743	497.3 (467.5, 528.9)	1647	468.2 (449.2, 487.9)	1425	482.8 (461.7, 504.7)	988	527.2 (499.8, 556.1)

GMT, geometric mean titer (given in milli-Merck units per milliliter). CI, confidence interval.

Table 6
Month 7 anti-HPV geometric mean titers by day 1 serostatus and PCR status in women, 16–26 years of age who completed the 3-dose 9vHPV vaccine regimen[a].

			Females 16–26 years of age (N=7260)		
HPV type	**Day 1 serostatus**	**Day 1 PCR status**	**n**	**GMT (mMU/mL)**	**(95% CI)**
HPV 6	Negative	Negative	4720	901.4	(881.8, 921.4)
	Negative	Positive	113	1025.2	(881.8, 1192.0)
	Positive	Negative	807	1876.0	(1742.2, 2020.1)
	Positive	Positive	109	1509.5	(1287.3, 1770.1)
HPV 11	Negative	Negative	4723	675.7	(660.3, 691.4)
	Negative	Positive	13	618.4	(331.1, 1155.3)
	Positive	Negative	188	1065.9	(935.0, 1215.0)
	Positive	Positive	14	1110.9	(652.9, 1890.2)
HPV 16	Negative	Negative	4799	3177.3	(3109.4, 3246.7)
	Negative	Positive	323	2941.4	(2676.1, 3233.1)
	Positive	Negative	492	5248.6	(4848.6, 5681.5)
	Positive	Positive	260	4374.0	(3968.9, 4820.6)
HPV 18	Negative	Negative	5334	815.9	(796.0, 836.3)
	Negative	Positive	178	941.2	(829.7, 1067.7)
	Positive	Negative	266	1917.2	(1714.3, 2144.0)
	Positive	Positive	86	1472.5	(1236.3, 1753.8)
HPV 31	Negative	Negative	5254	668.2	(651.5, 685.3)
	Negative	Positive	184	625.3	(553.5, 706.4)
	Positive	Negative	327	964.4	(877.3, 1060.1)
	Positive	Positive	112	798.5	(690.3, 923.7)
HPV 33	Negative	Negative	5503	424.1	(414.8, 433.7)
	Negative	Positive	101	443.3	(375.7, 523.1)
	Positive	Negative	215	665.7	(582.5, 760.7)
	Positive	Positive	59	616.0	(482.4, 786.7)
HPV 45	Negative	Negative	5620	255.0	(248.1, 262.0)
	Negative	Positive	130	256.9	(216.8, 304.4)
	Positive	Negative	82	354.0	(279.1, 449.1)
	Positive	Positive	29	285.8	(195.7, 417.4)
HPV 52	Negative	Negative	5259	385.1	(376.1, 394.3)
	Negative	Positive	275	303.5	(272.8, 337.5)
	Positive	Negative	220	547.1	(488.5, 612.7)
	Positive	Positive	121	319.8	(271.4, 376.7)
HPV 58	Negative	Negative	5267	493.8	(482.5, 505.4)
	Negative	Positive	158	423.3	(376.1, 476.3)
	Positive	Negative	373	618.9	(559.6, 684.6)
	Positive	Positive	82	669.8	(548.4, 818.0)

N=number of subjects who received at least 1 injection of 9vHPV vaccine; n=number of subjects contributing to the analysis.
GMT, geometric mean titer (given in milli-Merck units per milliliter). CI, confidence interval.
[a] This analysis population includes subjects who received all 3 doses of correct clinical material, had serology & PCR results at day 1 for the relevant HPV type and had a post-dose 3 or month 7 serology result within acceptable day ranges.

this population, the anti-HPV GMTs generated by the 9vHPV vaccine were dramatically increased after 2 doses (month 3) or 3 doses (month 7), and were substantially higher (as evidenced by non-overlapping 95% CI) than GMTs observed in the per-protocol population for all time points from month 3 to month 42.

4. Discussion

A combined analysis of the immunogenicity in five Phase III clinical studies showed that a 3-dose regimen of the 9vHPV vaccine was highly immunogenic in girls and boys 9–15 years of age and young women 16–26 years of age, with seroconversion rates at 1 month post-dose 3 > 99% in these three populations. GMTs at 1 month post-dose 3 in the combined database were higher in girls and boys than in young women, a finding consistent with results previously seen in study 002 [13]. Moreover, the 9vHPV vaccine induced robust HPV antibody responses to all 9 vaccine HPV types in all subgroups of subjects defined by age, race, and geographic region of residence. GMTs at 1 month post-dose 3 steadily decreased with increasing age at the start of vaccination. Small numeric differences in GMTs were observed among subpopulations defined by race and region of residence. In groups of subjects who were seropositive and PCR negative for a given HPV type at day 1, higher GMTs were seen for this HPV type compared with groups of subjects who were seronegative for this HPV type at day 1. HPV seropositivity at baseline likely reflects a humoral immune response following prior infection with HPV; PCR negativity likely indicates the absence of ongoing infection with HPV. The higher GMTs in this population are suggestive of an anamnestic response following 9vHPV vaccine administration [24]. Recently, Scherer et al. reported that a single dose of the qHPV vaccine improved the B cell memory of persons with pre-existing antibodies to HPV 16. In this study, a single dose of qHPV vaccine administered to HPV 16-seropositive women boosted antibody levels 24- to 930-fold at one month post-vaccination and elicited HPV 16-specific memory B cells that expressed type specific neutralizing antibodies [25]. These data indicate that vaccination augments natural HPV immunity by not only boosting antibody levels but also eliciting a quantitatively and qualitatively superior memory B cell response. Of note, the qHPV vaccine has been shown to protect seropositive women against subsequent disease due to the corresponding vaccine HPV type [26]. Taken together these results indicate that in subjects previously infected with certain HPV vaccine types and who have cleared infection, vaccination could potentially prevent reinfection and disease due to these types. It must be noted though, regardless of the HPV seropositivity status prior to vaccination, all subjects exhibited a robust boost in GMTs post-vaccination.

In a Phase III clinical study (study 001), the 9vHPV vaccine prevented infection and disease related to HPV 31/33/45/52/58 in young women 16–26 years of age from multiple races and regions [10]. In the same study, the efficacy findings established with qHPV vaccine for HPV 6/11/16/18 in earlier clinical studies [27–29] were extended

Table 7
Month 7 anti-HPV geometric mean titers in women, 16–26 years of age who completed the 3-dose 9vHPV vaccine regimen in study 001.

	Per protocol immunogenicity population		Day 1 seropositive and PCR-negative	
Assay time point	**n**	**GMT (95% CI)**	**n**	**GMT (95% CI)**
HPV 6				
Day 1	3993	< 16 (< 16, < 16)	917	108.1 (102.2, 114.3)
Month 3	788	734.0 (692.8, 777.7)	188	2384.0 (1982.9, 2866.1)
Month 7	3993	893.1 (871.7, 915.1)	752	1874.8 (1737.6, 2022.8)
Month 12	800	330.6 (312.2, 350.1)	213	951.9 (807.3, 1122.3)
Month 24	715	208.6 (195.5, 222.7)	182	634.3 (529.6, 759.8)
Month 36	685	163.9 (153.0, 175.6)	155	462.9 (382.5, 560.2)
Month 42	692	147.2 (137.3, 157.8)	163	444.1 (369.2, 534.3)
HPV 11				
Day 1	3995	< 6 (< 6, < 6)	208	44.6 (39.2, 50.8)
Month 3	790	529.1 (499.7, 560.1)	44	1666.4 (1229.9, 2257.9)
Month 7	3995	666.3 (649.6, 683.4)	175	1050.2 (914.9, 1205.6)
Month 12	810	212.4 (200.1, 225.6)	49	609.9 (465.7, 798.9)
Month 24	763	123.3 (115.8, 131.2)	40	360.7 (264.9, 491.0)
Month 36	690	89.6 (83.3, 96.3)	35	214.4 (149.4, 307.7)
Month 42	696	84.9 (79.0, 91.3)	34	201.9, (140.6, 289.8)
HPV 16				
Day 1	4032	< 12 (< 12, < 12)	564	126.6 (115.1, 139.3)
Month 3	794	2435.8 (2303.5, 2575.6)	104	7064.1 (5775.9, 8639.7)
Month 7	4032	3131.1 (3057.1, 3206.9)	458	5149.6 (4752.9, 5579.5)
Month 12	819	1041.7 (979.9, 1107.4)	134	3079.9 (2582.1, 3673.6)
Month 24	778	520.7 (484.7, 559.4)	98	1824.4 (1436.6, 2316.9)
Month 36	695	386.5 (356.3, 419.4)	82	1228.6 (939.5, 1606.6)
Month 42	709	346.8 (319.3, 376.7)	90	1186.7 (934.8, 1506.4)
HPV 18				
Day 1	4539	< 8 (< 8, < 8)	296	83.0 (74.3, 92.8)
Month 3	908	470.8 (442.8, 500.7)	58	1920.1 (1464.2, 2517.9)
Month 7	4539	804.6 (782.7, 827.1)	241	1883.4 (1670.6, 2123.4)
Month 12	929	198.6 (184.9, 213.4)	72	1012.7 (773.7, 1325.6)
Month 24	886	86.0 (79.0, 93.6)	52	537.2 (390.1, 739.8)
Month 36	789	78.5 (71.9, 85.6)	48	397.0 (285.8, 551.5)
Month 42	806	70.8 (64.8, 77.3)	47	374.9 (268.6, 523.2)
HPV 31				
Day 1	4466	< 4 (< 4, < 4)	373	38.7 (35.0, 42.6)
Month 3	881	437.6 (406.7, 470.8)	83	825.6 (609.4, 1118.4)
Month 7	4466	658.4 (636.7, 680.9)	295	952.8 (831.5, 1091.8)
Month 12	909	196.5 (183.5, 210.4)	90	452.2 (340.3, 600.8)
Month 24	863	101.9 (94.9, 109.5)	71	242.0 (174.5, 335.6)
Month 36	772	72.7 (67.5, 78.4)	62	182.1 (128.4, 258.4)
Month 42	783	70.4 (65.3, 75.9)	68	163.7 (119.9, 223.4)
HPV 33				
Day 1	4702	< 4 (< 4, < 4)	248	24.9 (22.1, 28.0)
Month 3	937	287.8 (272.9, 303.5)	50	647.0 (459.2, 911.4)
Month 7	4702	415.9 (405.6, 426.4)	196	660.4 (550.1, 792.9)
Month 12	958	126.2 (119.9, 132.9)	68	372.9 (276.8, 502.4)
Month 24	909	65.3 (61.7, 69.0)	52	243.3 (169.1, 349.8)
Month 36	813	46.8 (44.0, 49.8)	45	184.0 (124.1, 272.9)
Month 42	835	44.3 (41.6, 47.1)	39	172.6 (111.8, 266.5)
HPV 45				
Day 1	4792	< 3 (< 3, < 3)	97	23.7 (20.2, 27.9)
Month 3	956	160.4 (151.7, 169.7)	14	389.1 (197.5, 766.4)
Month 7	4792	252.8 (246.2, 259.6)	76	346.8 (244.3, 492.4)
Month 12	976	69.2 (65.4, 73.3)	18	203.5 (105.3, 393.5)
Month 24	928	33.0 (31.0, 35.0)	13	115.5 (51.6, 258.2)
Month 36	835	22.9 (21.4, 24.4)	11	60.8 (23.7, 155.8)
Month 42	846	21.1 (19.8, 22.5)	13	87.7 (36.9, 208.3)
HPV 52				
Day 1	4455	< 3 (< 3, < 3)	244	22.3 (20.3, 24.6)
Month 3	895	241.3 (229.7, 253.4)	41	877.2 (543.0, 1417.0)
Month 7	4455	379.7 (371.6, 388.0)	199	534.7 (447.2, 639.3)
Month 12	916	118.9 (113.0, 125.0)	53	450.3 (320.3, 633.0)
Month 24	867	57.9 (54.7, 61.2)	40	265.6 (175.1, 402.8)
Month 36	777	47.9 (45.0, 50.9)	34	177.7 (120.2, 262.8)
Month 42	791	43.2 (40.6, 46.0)	33	178.0 (120.8, 262.3)

(continued on next page)

Table 7 *(continued)*

Assay time point	Per protocol immunogenicity population		Day 1 seropositive and PCR-negative	
	n	GMT (95% CI)	n	GMT (95% CI)
HPV 58				
Day 1	4486	< 4 (< 4, < 4)	419	21.7 (19.9, 23.8)
Month 3	884	281.1 (265.3, 297.7)	85	546.2 (436.4, 729.4)
Month 7	4486	482.5 (469.9, 495.3)	342	606.2 (539.3, 681.5)
Month 12	905	153.3 (145.5, 161.6)	108	273.4 (219.0, 341.2)
Month 24	852	80.3 (75.7, 85.3)	84	147.4 (114.8, 189.3)
Month 36	765	55.0 (51.4, 58.8)	79	101.3 (78.0, 131.6)
Month 42	784	52.0 (48.7, 55.6)	76	95.1 (73.6, 122.9)

n=number of subjects contributing to the analysis.
GMT, geometric mean titer (given in milli-Merck units per milliliter).
CI, confidence interval.

to the 9vHPV vaccine based on the demonstration of non-inferior HPV 6/11/16/18 antibody responses. In additional analyses, both qHPV and 9vHPV vaccine were found to be highly efficacious against infection and disease in subgroups of young women 16–26 years of age differing by age, race, and region of residence [29–35] . Therefore, the small differences in 9vHPV vaccine immunogenicity by age, race or region of residence shown in this report in young women 16–26 years of age are unlikely to have a clinical significance.

As seen in this report, anti-HPV GMTs at month 7 are substantially higher in all subgroups of girls and boys 9–15 years of age defined by age, race, and region of residence compared with HPV antibody responses in young women 16–26 years of age in the combined database (Table 3) or previously reported in study 001 [10]. As previously reported, prophylactic administration of the 9vHPV vaccine to 16–26-year-olds was highly effective in preventing infection and disease due to vaccine HPV types [10]. Thus, the anti-HPV responses generated by the vaccine in adolescents were sufficient to induce high-level protective efficacy. Overall, 9vHPV vaccine efficacy can be inferred in all subgroups and the small differences in 9vHPV vaccine immunogenicity by age, race or region of residence shown in this report are unlikely to have a clinical significance in girls and boys 9–15 years of age.

There are several limitations to this combined analysis of immunogenicity. Even though the studies included in these analyses enrolled subjects from six continents, they enrolled only a limited number of subjects from Africa and South Asia. Therefore, it will be important to further evaluate the immunogenicity of the 9vHPV vaccine in these regions, especially given the prevalence of HIV infection or other co-infections and malnutrition in these regions which may impact immune response to the vaccine. Of note, studies of the qHPV vaccine in sub-Saharan Africa, India, and Vietnam, and a study in HIV-infected children demonstrated robust immunogenicity in these populations [36–39]. Given that the 9vHPV vaccine and qHPV vaccine have comparable immunogenicity profiles [10–12], similar results are expected with the 9vHPV vaccine.

This combined analysis assessed the immunogenicity of a 3-dose regimen of 9vHPV vaccine. The use of an alternative 2-dose regimen for HPV vaccines has been recommended in 2014 by the World Health Organization in 9- to 14-year-olds [40]. The 2-dose schedule for the previously developed bivalent and quadrivalent HPV vaccines has been implemented in several countries [41]. A Phase III study to assess a 2-dose regimen of the 9vHPV vaccine in girls and boys 9–14 years of age has recently provided relevant immunogenicity data [42].

In summary, the 9vHPV vaccine induced robust HPV antibody responses to all 9 vaccine HPV types in subjects from all ages, races, and geographic regions represented in the aforementioned five Phase III studies of the vaccine. This comprehensive immunogenicity profile provides compelling evidence for administration of the 9vHPV vaccine at an early age (i.e., before exposure to HPV) and supports a widespread 9vHPV vaccination program regardless of race or region of residence.

5. Conclusion

In clinical trials, the 9vHPV vaccine was highly immunogenic in subjects aged 9–26 years. The 9vHPV vaccine immunogenicity was robust among subjects with differing baseline characteristics (age, gender, race, region of residence, and HPV serostatus and PCR status at day 1). Its immunogenicity profile was similar to that of the qHPV vaccine. The demonstrated efficacy, safety and immunogenicity profile of the 9vHPV vaccine supports widespread vaccination programs.

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Author contribution

Study concept and design: RM, EM, AL.
Acquisition of data: LKP, EDM, OEI, PP, PVD, EAJ, S-EO, DF, SB, ARG.
Analysis and interpretation of data: All authors.
Manuscript Preparation: All Authors.
Statistical analysis: OMB, DH, RM.

Conflicts of interest

LKP: was advisory board member for Sanofi Pasteur and investigator at the vaccine trials funded by MSD.
JAR: Nothing to disclose.
EDM: has received research grants from and is a member of a speaker's bureau for Merck & Co., Inc, Kenilworth, NJ, USA.
O-EI: has received compensation from Merck to conduct vaccine clinical trials and scientific advisory board fees.
PP: No potential conflicts of interest to disclose.
PVD: Acts as chief and principal investigator for vaccine trials conducted on behalf of the University of Antwerp, for which the University obtains research grants from vaccine manufacturers; speak-

ers fees for presentations on vaccines are paid directly to an educational fund held by the University of Antwerp. PVD receives no personal remuneration for this work.

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SB: has received research grants from and is a member of a speaker's bureau for Merck & Co., Inc., Kenilworth, NJ, USA and has served as a paid expert witness and consultant for Merck.

ARG: has received fees for serving on an advisory board and grant support through her institution from Merck.

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SP: has received travel expenses from Sanofi Pasteur MSD.

JC: has received fees for serving on advisory boards from Merck, Abbott, Gen-Probe Hologic, and Becton Dickinson, lecture fees from GlaxoSmithKline, and grant support from Roche, Abbott, Gen- Probe Hologic, Becton Dickinson, and Qiagen.

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WH: has received fees for serving on advisory board from Merck.

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OMB, DH, EM, HQ, AL: are employees of Merck & Co., Inc., Kenilworth, NJ, USA.

RM, CR: were employees of Merck & Co., Inc., Kenilworth, NJ, USA at the time of the study.

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Appendix A. Supplementary material

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