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Efficacy, Immunogenicity, and Safety of a 9-Valent Human Papillomavirus Vaccine: Subgroup Analysis of Participants From Asian Countries

S. M. Garland,[1] P. Pitisuttithum,[2] H. Y. S. Ngan,[3] C.-H. Cho,[4] C.-Y. Lee,[5] C.-A. Chen,[6] Y. C. Yang,[7] T.-Y. Chu,[8] N.-F. Twu,[9] R. Samakoses,[10] Y. Takeuchi,[11] T. H. Cheung,[12] S. C. Kim,[13] L.-M. Huang,[14] B.-G. Kim,[15] Y.-T. Kim,[16] K.-H. Kim,[17] Y.-S. Song,[18] S. Lalwani,[19] J.-H. Kang,[20] M. Sakamoto,[21] H.-S. Ryu,[22] N. Bhatla,[23] H. Yoshikawa,[24] M. C. Ellison,[25] S. R. Han,[26] E. Moeller,[25] S. Murata,[26] M. Ritter,[25] M. Sawata,[26] C. Shields,[25] A. Walia,[25] G. Perez,[25] and A. Luxembourg[25]

[1]Western Pacific Regional HPV Labnet Reference Laboratory, Department of Infectious Disease and Microbiology, Royal Women's Hospital, Murdoch Children's Research Institute, Royal Children's Hospital and Department of Obstetrics and Gynaecology, University of Melbourne, Parkville, Victoria, Australia; [2]Vaccine Trial Centre, Mahidol University, Salaya, Thailand; [3]Department of Obstetrics and Gynaecology, the University of Hong Kong, China; [4]Department of Obstetrics and Gynecology, Keimyung University School of Medicine, Daegu, South Korea; [5]Department of Gynecology, Chang Gung Memorial Hospital, Chiayi Branch, [6]Department of Obstetrics and Gynecology, National Taiwan University Hospital, Taipei, [7]MacKay Memorial Hospital, Taipei, [8]Tzu Chi Medical Center, Hualien, and [9]Department of Obstetrics and Gynecology, Taipei Veterans General Hospital, Taipei, Taiwan; [10]Department of Pediatrics, Phramongkutklao Hospital, Bangkok, Thailand; [11]Fukui General Hospital, Japan; [12]Department of Obstetric and Gynaecology, Chinese University of Hong Kong, China; [13]Division of Gynecologic Oncology, Ewha Womans University Mokdong Hospital, School of Medicine Ewha Womans University, Seoul, South Korea; [14]Department of Pediatrics, National Taiwan University Hospital, Taipei, Taiwan; [15]Department of Obstetrics and Gynecology, Samsung Medical Center, Sungkyunkwan University School of Medicine, [16]Department of Obstetrics and Gynecology, University of Ulsan College of Medicine, Asian Medical Center, [17]Department of Pediatrics and Center for Vaccine Evaluation and Study, Ewha Womans University College of Medicine, and [18]Obstetrics and Gynecology, College of Medicine, Seoul National University, Seoul, South Korea; [19]Bharati Vidyapeeth Deemed University Medical College and Hospital, Pune, India; [20]Department of Pediatrics, Seoul St. Mary's Hospital, College of Medicine, the Catholic University of Korea, South Korea; [21]Department of Gynaecology, Sasaki Foundation Kyoundo Hospital and Department of Obstetrics and Gynaecology, School of Medicine, the Jikei University, Tokyo, Japan; [22]Department of Obstetrics and Gynecology, School of Medicine, Ajou University, Suwon, South Korea; [23]Department of Obstetrics and Gynaecology, All India Institute of Medical Sciences, New Delhi, India; [24]Ibaraki Prefectural Central Hospital, Kasama, Ibaraki, Japan; [25]Merck & Co., Inc., Kenilworth, New Jersey; and [26]MSD K.K., Tokyo, Japan

Background. A 9-valent human papillomavirus-6/11/16/18/31/33/45/52/58 (9vHPV) vaccine extends coverage to 5 next most common oncogenic types (31/33/45/52/58) in cervical cancer versus quadrivalent HPV (qHPV) vaccine. We describe efficacy, immunogenicity, and safety in Asian participants (India, Hong Kong, South Korea, Japan, Taiwan, and Thailand) from 2 international studies: a randomized, double-blinded, qHPV vaccine-controlled efficacy study (young women aged 16–26 years; NCT00543543; Study 001); and an immunogenicity study (girls and boys aged 9–15 years; NCT00943722; Study 002).

Methods. Participants (N = 2519) were vaccinated at day 1 and months 2 and 6. Gynecological samples (Study 001 only) and serum were collected for HPV DNA and antibody assessments, respectively. Injection-site and systemic adverse events (AEs) were monitored. Data were analyzed by country and vaccination group.

Results. 9vHPV vaccine prevented HPV-31/33/45/52/58–related persistent infection with 90.4%–100% efficacy across included countries. At month 7, ≥97.9% of participants seroconverted for each HPV type. Injection-site AEs occurred in 77.7%–83.1% and 81.9%–87.5% of qHPV and 9vHPV vaccine recipients in Study 001, respectively, and 62.4%–85.7% of girls/boys in Study 002; most were mild to moderate.

Conclusions. The 9vHPV vaccine is efficacious, immunogenic, and well tolerated in Asian participants. Data support 9vHPV vaccination programs in Asia.

Clinical Trials Registration. NCT00543543; NCT00943722.

Keywords. 9vHPV; Asia; cervical cancer; human papillomavirus; vaccine.

Approximately 280 000 new cervical cancers and over 140 000 related deaths occur annually in Asia (based on 2012 data [1, 2]). An additional approximately 40 000 new annual cases of other human papillomavirus (HPV)-related cancers (vaginal, vulvar, anal, penile, and oropharyngeal cancers) are estimated to affect Asian men and women [2]. Access to cervical cancer screening is highly variable in the region, and interventions for high-grade dysplasia are generally limited [1, 3–5].

Prophylactic HPV vaccination represents a unique opportunity to reduce the burden of HPV-associated disease. Bivalent HPV-16/18 and quadrivalent HPV-6/11/16/18 (qHPV) vaccines introduced over the past decade have potential to prevent the approximately 70% of cervical cancer cases attributable to HPV-16/18, both worldwide and within Asia [6]. The qHPV vaccine also protects against the approximately 90% of genital warts cases associated with HPV-6/11 [7]. Partial and inconsistent cross-protection against phylogenetically related oncogenic HPV types (31/33/45) has been observed for both vaccines in

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Correspondence: S. M. Garland, MD, The Royal Women's Hospital, Locked Bag 300, Parkville 3052, Victoria, Australia (suzanne.garland@thewomens.org.au).

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clinical studies [8]; however, its extent, duration, and public health significance remain uncertain [8–11]. The 9-valent HPV (6/11/16/18/31/33/45/52/58) vaccine (9vHPV vaccine; Gardasil 9, Merck & Co., Inc., Kenilworth, NJ, USA) extends coverage to HPV-31/33/45/52/58, which are next most commonly associated with cervical cancer globally [6, 12, 13]. Global epidemiological data indicate that the 9vHPV vaccine has potential to prevent approximately 90% of cervical cancers and HPV-related vulvar, vaginal, and anal cancers, 70%–85% of cervical precancerous lesions, and 90% of anogenital warts [7, 14–17]. Based on HPV subtype distribution across Asia, the 9vHPV vaccine may offer even greater cervical cancer protection (approximately 92% of cases) in Asia [6, 17], possibly because of the higher relative contributions of HPV-52 and HPV-58 (see Supplementary Material for more information).

In an international phase 2b/3 trial (Study 001 [18, 19]), the 9vHPV vaccine demonstrated 97% efficacy against HPV-31/33/45/52/58–related infection and disease and elicited noninferior antibody responses to HPV-6/11/16/18 compared with the qHPV vaccine in young women 16–26 years of age. In a separate phase 3 trial (Study 002), antibody responses to HPV-6/11/16/18/31/33/45/52/58 in girls and boys aged 9–15 years were noninferior to those among young women aged 16–26 years following 9vHPV vaccination, thereby supporting the bridging of efficacy findings with 9vHPV vaccine from young women to girls and boys [20].

These 2 studies included participants from multiple Asian countries (Hong Kong, India, Japan, South Korea, Taiwan, and Thailand), highlighting the regional importance of HPV-related disease in these countries. Given the specific epidemiology of HPV in East Asia (higher prevalence of HPV-52/58; see Supplementary Material for more information), it is of interest to assess the impact of the 9vHPV vaccine on the incidence of persistent infection and cervical cytological abnormalities, disease, and medical procedures related to these 2 HPV types in the subgroup of Asian participants: differences between the Asian subgroup and the overall study population may not be apparent in the overall analyses, as Asian participants represent 12% of the population enrolled in Study 001. Also, few studies have reported the incidence of cervical cytological abnormalities related to HPV-52 and HPV-58 in populations from East Asia. Subpopulation analyses of efficacy, immunogenicity, and safety in Asian participants enrolled in Study 001 and 002 were conducted to better understand the potential impact of the 9vHPV vaccine on reducing the burden of HPV-related infection and disease in the region, and help support public health decisions regarding HPV vaccination programs in Asia.

METHODS

Study Design and Population

Study 001 (Merck & Co., Inc., Kenilworth, NJ, USA Protocol V503-001 [NCT00543543]) [18, 19, 21–23] was a randomized, double-blind, qHPV vaccine-controlled study that evaluated 9vHPV vaccine efficacy in 14 215 young women (aged 16–26 years) across 105 sites and 18 countries worldwide, including 25 sites in 5 Asian countries (Hong Kong, Japan, South Korea, Taiwan, and Thailand; N = 1717; Supplementary Table 1). All Asian participants randomized in the efficacy study were included in the subgroup analysis; those who received low or high doses of 9vHPV vaccine during the dose selection phase (69 participants from Taiwan) were not included. Data from participants from Hong Kong and Taiwan were pooled, as these individuals were considered to be part of the same ethnic group (Chinese).

Study 002 (Merck & Co., Inc., Kenilworth, NJ, USA Protocol V503-002 [NCT00943722]) [20, 24] assessed immunogenicity and safety of the 9vHPV vaccine in girls and boys (aged 9–15 years) compared with young women (aged 16–26 years) across 72 sites in 17 countries (N = 3074), including 16 sites in 4 Asian countries (India, South Korea, Taiwan, and Thailand; N = 733; Supplementary Table 1). All randomized girls and boys from these countries were included in the subgroup analysis. Data from girls and boys were pooled within each country. Because only small numbers of women from South Korea, Taiwan, and Thailand (20, 20, and 60, respectively) were enrolled in Study 002 (only 1 site enrolled young women in each of these countries) and substantial numbers of young women from these countries had participated in Study 001 (307, 531, and 465, respectively) (Supplementary Table 1), women from Study 001 were used as the comparator. Immunogenicity and safety data for Indian young women who participated in Study 002 are described, because Study 001 did not include this country. Study 002 did not include Japanese participants; a separate immunogenicity and safety study of the 9vHPV vaccine was conducted in a group of 100 Japanese girls (Study V503-008 [NCT01254643]), as reported separately [25].

Studies 001 and 002 were performed in accordance with the principles of Good Clinical Practice and were approved by the appropriate institutional review boards and regulatory agencies. All participants provided written, informed consent before study participation in accordance with local laws and regulations.

Vaccination and Follow-up

The 9vHPV vaccine (both studies) and qHPV vaccine (control arm of Study 001) were administered as a series of 3 intramuscular doses on day 1 and at months 2 and 6.

In Study 001, cervical cytology samples and cervical and external genital swabs for detection of HPV by polymerase chain reaction (PCR) assays were collected on day 1 and at months 7, 12, and every 6 months thereafter up to month 54. Participants with cervical cytological abnormalities were referred for colposcopy, based on a protocol-specified algorithm [18, 19, 22]. Tissue samples were adjudicated by a pathology panel and tested for HPV by PCR, as previously described [22, 26, 27].

Serum levels of vaccine HPV-type antibodies were assessed at day 1 and month 7 using a 9-valent competitive Luminex immunoassay (cLIA) [28]. 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.

Following each vaccination, participants recorded their oral temperature for 5 days and injection-site and systemic adverse events (AEs) for 15 days on vaccination report cards [29]. AE causality was determined by the study site investigator as previously described [29]. Serious AEs (SAEs) were prespecified as those considered life threatening by the investigator or resulted in death, significant disability or incapacity, or new or prolonged existing hospitalization, or were a congenital anomaly, cancer, or "other important medical event".

Statistical Analyses

Efficacy was evaluated in the per-protocol efficacy (PPE) population of Study 001, defined as participants who: (1) were seronegative on day 1 and PCR negative from day 1 through month 7 for the HPV type being analyzed; (2) received all 3 doses of assigned vaccine within 1 year; and (3) had no protocol violations that could interfere with the evaluation of vaccine efficacy, as judged by the study director. Supportive analyses were conducted in the HPV type-specific naïve (HNTS) population, consisting of participants who were seronegative and PCR negative on day 1 for the HPV type being analyzed, received at least 1 dose of the 9vHPV or qHPV vaccine, and had efficacy follow-up after day 1; and in the modified intention-to-treat (mITT) population, consisting of participants who received at least 1 dose of the 9vHPV or qHPV vaccine and had efficacy follow-up after day 1. Combined incidence of HPV-31/33/45/52/58–related cervical, vulvar, and vaginal disease (any grade), combined incidence of HPV-31/33/45/52/58–related cervical cytological abnormalities, and combined incidence of HPV-31/33/45/52/58–related persistent infection, as well as incidence by HPV type, are presented using incidence rates (cases per 10 000 person-years), vaccine efficacy, and 95% confidence intervals (CIs). Vaccine efficacy was calculated as 100 × (1 − 9vHPV vaccine incidence rate / qHPV vaccine incidence rate). The 95% CI of vaccine efficacy was calculated with the use of a binomial distribution-based exact method [30].

Immunogenicity was assessed in the per-protocol immunogenicity populations from each study, which included participants who: (1) were seronegative on day 1 and (for young women aged 16–26 years) PCR-negative from day 1 through month 7 for the HPV type being analyzed; (2) received all 3 vaccinations within prespecified visit intervals and had available month 7 serology results obtained within a prespecified interval; and (3) had no protocol violations that could interfere with the evaluation of the immune response to vaccine, as judged by the study director. For each HPV type, the geometric mean titer (GMT) and 95% CIs were estimated using an analysis of variance model, with log anti-HPV as the response and vaccination group as the fixed effect. Seroconversion rates and exact 95% CIs for a binomial proportion were also calculated. All of these evaluations were post hoc analyses; therefore, no statistical hypothesis tests were performed. Nonoverlapping 95% CIs were used as indicators of differences of immune response.

Safety was assessed in all participants who received at least 1 study vaccination and had follow-up data. AEs, SAEs, and AEs leading to discontinuation were summarized by vaccination group in subgroups of participants defined by country of residence.

RESULTS

Participants

Of the 14 215 young women randomized in the efficacy study (Study 001), 1717 (12.0%) were enrolled at sites in Asia. Participant baseline characteristics are shown in Table 1. Japanese participants tended to have more lifetime sexual partners than other Asian participants. Across countries, 31.0%–47.8% of participants were HPV positive at baseline (by serology or PCR), with highest rates in Japan and Thailand (Table 1). Proportions of participants testing positive for HPV by PCR or serology are shown in Supplementary Tables 2 and 3, respectively.

Of the 2604 girls and boys enrolled in Study 002, 608 (23.3%) were enrolled at sites in Asia (423 girls; 185 boys). Participant baseline characteristics are shown in Table 2.

Efficacy

In Study 001, the 9vHPV vaccine prevented HPV-31/33/45/52/58–related persistent (≥6 months) infections in Asian participants with an efficacy of 95.8% (95% CI, 87.8–98.9). Efficacy ranged from 90.4% and 94.9% among participants from Japan and Thailand, respectively, to 100% among participants from Hong Kong/Taiwan and South Korea (Table 3). Efficacy was 91.3% to 100% across the HPV types. In participants who received the qHPV vaccine, HPV-52– and HPV-58–related persistent infections were most frequent in all countries. As seen in Supplementary Table 4, the 9vHPV vaccine demonstrated efficacy against persistent infection related to HPV-52 or HPV-58 among participants from Hong Kong/Taiwan, Japan, and Thailand. No cases of HPV-52/58–related persistent infection were observed in the 9vHPV vaccine group from South Korea. The vaccine also prevented HPV-31/33/45/52/58–related persistent (≥12 months) infections with an efficacy of 93.9% (95% CI, 81.4–98.4) in Asian participants.

No cases of cervical, vulvar, or vaginal disease (any grade) related to HPV-31/33/45/52/58 were detected in the 9vHPV vaccination group, compared with 7 cases of cervical disease (4, 2, and 1 among participants from Hong Kong/Taiwan, Japan, and Thailand, respectively) in the qHPV vaccine group (Table 3).

The 9vHPV vaccine reduced the risk of HPV-31/33/45/52/58–related cervical cytological abnormalities by 92.1% (95% CI,

Table 1. Baseline Characteristics of Asian Participants (Young Women Aged 16–26 Years) in Study 001 by Country

	9vHPV Vaccine					qHPV Vaccine				
Characteristics	Hong Kong and Taiwan (N = 345)	Japan (N = 127)	South Korea (N = 154)	Thailand (N = 232)	Total (N = 858)	Hong Kong and Taiwan (N = 346)	Japan (N = 127)	South Korea (N = 153)	Thailand (N = 233)	Total (N = 859)
Age, y										
Mean ± SD	23.7 ± 1.9	22.9 ± 2.0	23.5 ± 1.8	22.4 ± 2.7	23.2 ± 2.2	23.8 ± 2.0	22.9 ± 2.0	23.5 ± 1.9	22.0 ± 2.6	23.1 ± 2.3
Median	24.0	23.0	24.0	23.0	24.0	24.0	23.0	24.0	22.0	23.0
Range	19–26	18–26	19–26	16–26	16–26	17–26	18–26	18–26	16–26	16–26
Age at first sexual intercourse, y										
Mean ± SD	18.9 ± 2.5	17.7 ± 1.9	20.9 ± 2.2	18.0 ± 2.7	18.8 ± 2.7	19.1 ± 2.3	17.6 ± 1.9	21.2 ± 2.2	17.7 ± 2.2	18.8 ± 2.5
Smoking status, No. (%)										
Current smoker	28 (8.1)	31 (24.4)	15 (9.7)	17 (7.3)	91 (10.6)	32 (9.2)	37 (29.1)	14 (9.2)	14 (6.0)	97 (11.3)
Former smoker	15 (4.3)	12 (9.4)	7 (4.5)	16 (6.9)	50 (5.8)	14 (4.0)	12 (9.4)	8 (5.2)	7 (3.0)	41 (4.8)
Never smoked	302 (87.5)	84 (66.1)	130 (84.4)	199 (85.8)	715 (83.3)	299 (86.4)	78 (61.4)	130 (85.0)	212 (91.0)	719 (83.7)
Unknown	0 (0.0)	0 (0.0)	2 (1.3)	0 (0.0)	2 (0.2)	1 (0.3)	0 (0.0)	1 (0.7)	0 (0.0)	2 (0.2)
Lifetime sexual partners, No. (%)[a]										
1	143 (41.4)	23 (18.1)	54 (35.1)	121 (52.2)	341 (39.7)	135 (39.0)	21 (16.5)	60 (39.5)	131 (56.2)	347 (40.4)
2	86 (24.9)	15 (11.8)	45 (29.2)	73 (31.5)	219 (25.5)	95 (27.5)	21 (16.5)	29 (19.1)	63 (27.0)	208 (24.2)
3	79 (22.9)	37 (29.1)	24 (15.6)	28 (12.1)	168 (19.6)	72 (20.8)	33 (26.0)	31 (20.4)	26 (11.2)	162 (18.9)
4	30 (8.7)	49 (38.6)	21 (13.6)	10 (4.3)	110 (12.8)	34 (9.8)	42 (33.1)	18 (11.8)	13 (5.6)	107 (12.5)
>4	6 (1.7)	0 (0.0)	1 (0.6)	0 (0.0)	7 (0.8)	10 (2.9)	0 (0.0)	3 (2.0)	0 (0.0)	13 (1.5)
Non-HPV–related cervicovaginal infections or sexually transmitted diseases, No. (%)										
Any	15 (4.3)	7 (5.5)	10 (6.5)	29 (12.5)	61 (7.1)	21 (6.1)	6 (4.7)	11 (7.2)	23 (9.9)	61 (7.1)
Chlamydia	12 (3.5)	7 (5.5)	10 (6.5)	28 (12.1)	57 (6.6)	21 (6.1)	6 (4.7)	11 (7.2)	22 (9.4)	60 (7.0)
Gonorrhea	4 (1.2)	0 (0.0)	0 (0.0)	1 (0.4)	5 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	4 (1.7)	4 (0.5)
Contraceptive use, No. (%)[b]										
Barrier	261 (75.7)	59 (46.5)	64 (41.6)	60 (25.9)	444 (51.7)	259 (74.9)	60 (47.6)	58 (38.4)	70 (30.0)	447 (52.2)
Behavior	100 (29.0)	80 (63.0)	82 (53.2)	15 (6.5)	277 (32.3)	96 (27.7)	73 (57.9)	84 (55.6)	12 (5.2)	265 (31.0)
Hormonal	41 (11.9)	11 (8.7)	5 (3.2)	140 (60.3)	197 (23.0)	40 (11.6)	8 (6.3)	6 (4.0)	143 (61.4)	197 (23.0)
Day 1 composite HPV positivity, No./total No. (%)[c]										
Serologic test	88/344 (25.6)	47/127 (37.0)	48/151 (31.8)	99/232 (42.7)	282/854 (33.0)	73/344 (21.2)	31/127 (24.4)	46/149 (30.9)	94/233 (40.3)	244/853 (28.6)
PCR assay	38/331 (11.5)	32/126 (25.4)	23/147 (15.6)	44/229 (19.2)	137/833 (16.4)	35/335 (10.4)	25/123 (20.3)	30/143 (21.0)	42/228 (18.4)	132/829 (15.9)
Serologic test or PCR assay	104/336 (31.0)	58/127 (45.7)	58/148 (39.2)	110/230 (47.8)	330/841 (39.2)	88/335 (26.3)	46/125 (36.8)	56/145 (38.6)	106/231 (45.9)	296/836 (35.4)

Abbreviations: 9vHPV, 9-valent human papillomavirus; PCR, polymerase chain reaction; SD, standard deviation; qHPV, quadrivalent human papillomavirus.

[a]The percentages for the number of lifetime sexual partners were calculated on the basis of the number of participants for whom there were data on sexual history at enrollment.

[b]Participants may have used more than 1 contraceptive method. A participant is counted once within a category and may be counted in more than 1 category. The percentages for the numbers of participants who used contraceptives were based on the number for whom this information was available.

[c]Positivity was defined as an anti-HPV titer on immunoassay of at least 30, 16, 20, 24, 10, 8, 8, 8, and 8 for HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58, respectively. The numerator in this category represents the number of HPV-positive participants, and the denominator the total number of participants with assay results that could be evaluated.

Table 2. Baseline Characteristics of Asian Participants (Girls and Boys Aged 9–15 Years) in Study 002 by Country

	9vHPV Vaccine				
Characteristics	India (N = 200)	South Korea (N = 129)	Taiwan (N = 139)	Thailand (N = 140)	Total (N = 608)
Gender, No. (%)					
Male	75 (37.5)	40 (31.0)	30 (21.6)	40 (28.6)	185 (30.4)
Female	125 (62.5)	89 (69.0)	109 (78.4)	100 (71.4)	423 (69.6)
Age					
9–12 y, No. (%)	137 (68.5)	90 (69.8)	87 (62.6)	81 (57.9)	395 (65.0)
13–15 y, No. (%)	63 (31.5)	39 (30.2)	52 (37.4)	59 (42.1)	213 (35.0)
Mean, y ± SD	11.5 ± 1.8	11.6 ± 1.8	11.7 ± 1.9	12.0 ± 1.7	11.7 ± 1.8
Median, y	11.0	12.0	11.0	12.0	12.0
Range, y	9–15	9–15	9–15	9–15	9–15
Weight, kg					
Mean ± SD	36.8 ± 9.8	47.2 ± 15.0	44.8 ± 12.6	42.6 ± 12.1	42.1 ± 12.8
Median	36.0	43.9	42.0	42.0	40.0
Range	19.0–72.0	21.5–101.1	24.5–84.0	19.0–93.5	19.0–101.1
BMI, kg/m^2					
Mean ± SD	17.7 ± 3.0	20.0 ± 4.1	19.2 ± 3.5	18.7 ± 3.8	18.8 ± 3.6
Median	17.4	19.1	18.6	18.1	18.1
Range	10.1–29.8	11.6–35.0	14.0–30.1	12.6–32.0	10.1–35.0

Abbreviations: 9vHPV, 9-valent human papillomavirus; BMI, body mass index; SD, standard deviation.

71.5–98.7) (Table 3); reduced risk of cervical cytological abnormalities related to HPV-52 or HPV-58 was also demonstrated. The incidence of HPV-31/33/45/52/58–related cervical biopsies was reduced by 100% (95% CI, 73.4–100).

Supportive analyses in the HNTS population showed reduction of HPV-31/33/45/52/58–related infection and disease endpoints (Supplementary Table 4). In the mITT analyses, efficacy was demonstrated in susceptible participants (not infected at baseline for the HPV type being analyzed); in the participants infected at baseline, incidence of infection or disease was similar between the 2 vaccine groups (Supplementary Table 4). In the qHPV vaccine group, incidence of persistent infection increased over time in the PPE, HNTS, and mITT populations. In the 9vHPV vaccine group, the incidence of persistent infection was low in the PPE and HNTS populations and started to plateau after month 24 in the mITT population (Supplementary Figure 1).

Immunogenicity

Among Asian young women from Study 001, GMTs for anti–HPV-6/11/16/18 at month 7 were generally similar between the qHPV vaccine and 9vHPV vaccine groups within each country (Table 4). Overall, ≥97.9% of participants underwent seroconversion within 1 month after the last 9vHPV vaccination (ie, study month 7) to each of the vaccine types (Table 4). Among young Indian women in Study 002 (Supplementary Table 5), GMTs were similar or higher across HPV types compared with young women in the overall Study 001 population, indicating that HPV antibody responses in young Indian women were sufficient to induce high-level protective efficacy; seroconversion rates at month 7 were 100% for all 9 HPV types (Supplementary Table 5). However, the number of young Indian women enrolled in Study 002 was limited (N = 25).

Among Asian girls and boys from Study 002, GMTs for each of the 9 HPV types were higher than in the overall population of young women (N = 6792) from Study 001 (Table 5) and the subgroups of young women from each corresponding country in Study 001 (Table 4). Overall, ≥98.8% of Asian girls and boys underwent seroconversion at month 7 to each of the 9 HPV types (Table 5). Results were similar when considering GMTs and seroconversion rates for girls only (Supplementary Table 6).

Safety

In Study 001 (Table 6), injection-site AEs were more common within each country in young women in the 9vHPV vaccine group (85.2%, 81.9%, 87.5%, and 86.6% of participants from Hong Kong/Taiwan, Japan, South Korea, and Thailand, respectively) than in the qHPV vaccine group (77.7%, 79.5%, 82.0%, and 83.1%, respectively). The most common injection-site AEs were pain, swelling, and erythema; most were mild to moderate in intensity. The proportions of participants from Hong Kong/Taiwan, Japan, and South Korea who experienced a vaccine-related systemic AE (9vHPV, 11.8%–18.8%; qHPV, 6.3%–13.9%) were lower than in the overall study population (9vHPV, 29.5%; qHPV, 27.3 %) [18, 29]. The proportions of participants from Thailand with vaccine-related systemic AEs (9vHPV, 42.2%; qHPV, 40.3%) were significantly higher than in the overall population (Supplementary Table 7). The frequencies of severe vaccine-related systemic AEs were similar between participants from Thailand and the overall study population (Supplementary Table 7). The difference in frequency of vaccine-related systemic AEs was mainly due to a higher frequency of AEs of pyrexia among participants from Thailand (9vHPV, 16.4%; qHPV, 15.2%) versus the overall population (9vHPV, 5.0%; qHPV, 4.3%)

Table 3. Impact of the 9vHPV Vaccine on the Incidence of HPV-31/33/45/52/58–Related Persistent Infection; Cervical, Vulvar, and Vaginal Disease; Cervical Cytological Abnormalities; and Cervical Medical Procedures in Asian Participants (Young Women Aged 16–26 Years) in the PPE Population in Study 001 by Vaccination Group

	9vHPV Vaccine (N = 856)		qHPV Vaccine (N = 857)		
Endpoint	Cases / n	Rate	Cases / n	Rate	Vaccine Efficacy (95% CI)%
HPV-31/33/45/52/58–related persistent infection ≥6 months duration[a]	3 / 736	13.1	67 / 739	309.1	95.8 (87.8–98.9)
By country					
Hong Kong/Taiwan[b]	0 / 291	0.0	17 / 300	202.1	100 (78.2–100)
Japan	2 / 112	55.1	20 / 117	575.7	90.4 (62.4–98.4)
South Korea	0 / 124	0.0	11 / 113	354.0	100 (71.2–100)
Thailand	1 / 209	14.5	19 / 209	284.2	94.9 (70.9–99.8)
By HPV type					
HPV-31–related	0 / 712	0.0	7 / 702	32.5	100 (41.0–100)
HPV-33–related	0 / 707	0.0	8 / 716	36.4	100 (46.5–100)
HPV-45–related	0 / 726	0.0	1 / 725	4.5	100 (≤–999 to 100)
HPV-52–related	3 / 652	14.8	33 / 644	169.0	91.3 (74.5–97.7)
HPV-58–related	0 / 666	0.0	25 / 685	120.1	100 (86.3–100)
HPV-31/33/45/52/58–related persistent infection ≥12 months duration[c]	3 / 736	13.1	47 / 739	214.1	93.9 (81.4–98.4)
By HPV type					
HPV-31–related	0 / 712	0.0	5 / 702	23.2	100 (2.5–100)
HPV-33–related	0 / 707	0.0	8 / 716	36.4	100 (46.5–100)
HPV-45–related	0 / 726	0.0	1 / 725	4.5	100 (≤–999 to 100)
HPV-52–related	3 / 652	14.8	24 / 644	122.0	87.9 (61.1–96.9)
HPV-58–related	0 / 666	0.0	11 / 685	52.3	100 (66.5–100)
HPV-31/33/45/52/58–related cervical, vulvar, and vaginal disease (any grade)	0 / 751	0.0	7 / 745	29.4	100 (40.0–100)
By HPV type					
HPV-31–related	0 / 726	0.0	0 / 710	0.0	NA
HPV-33–related	0 / 720	0.0	2 / 722	8.7	100 (–248.2 to 100)
HPV-45–related	0 / 740	0.0	0 / 733	0.0	NA
HPV-52–related	0 / 662	0.0	4 / 650	19.2	100 (–10.1 to 100)
HPV-58–related	0 / 676	0.0	1 / 689	4.5	100 (≤–999 to 100)
By lesion type					
HPV-31/33/45/52/58–related cervical disease (any grade)	0 / 738	0.0	7 / 737	30.5	100 (39.7–100)
CIN 1	0 / 738	0.0	6 / 737	26.2	100 (33.0–100)
CIN 2/3, AIS, and cervical cancer	0 / 738	0.0	1 / 737	4.3	100 (≤–999 to 100)
HPV-31/33/45/52/58–related vulvar and vaginal disease (any grade)	0 / 751	0.0	0 / 745	0.0	NA
HPV-31/33/45/52/58–related ASC-US HR-HPV positive or worse	2 / 731	8.8	25 / 729	111.5	92.1 (71.5–98.7)
By HPV type					
HPV-31–related	0 / 708	0.0	3 / 694	13.9	100 (–68.3 to 100)
HPV-33–related	0 / 703	0.0	3 / 708	13.6	100 (–72.8 to 100)
HPV-45–related	0 / 722	0.0	2 / 717	9.0	100 (–245.6 to 100)
HPV-52–related	1 / 649	4.9	15 / 638	75.6	93.5 (58.4–99.7)
HPV-58–related	1 / 662	4.8	9 / 678	42.8	88.7 (18.8–99.5)
By lesion type					
ASC-US HR-HPV positive	1 / 731	4.4	12 / 729	53.0	91.7 (51.5–99.6)
Low-grade squamous intraepithelial lesion	1 / 731	4.4	19 / 729	84.5	94.8 (70.3–99.7)
High-grade squamous intraepithelial lesion or worse[d]	0 / 731	0.0	2 / 729	8.8	100 (–247.0 to 100)
HPV-31/33/45/52/58–related cervical biopsy	0 / 750	0.0	15 / 745	63.8	100 (73.4–100)
By HPV type					
HPV-31–related	0 / 725	0.0	0 / 710	0.0	NA
HPV-33–related	0 / 719	0.0	2 / 722	8.7	100 (–248.5 to 100)
HPV-45–related	0 / 739	0.0	0 / 733	0.0	NA
HPV-52–related	0 / 661	0.0	11 / 650	53.3	100 (67.3–100)
HPV-58–related	0 / 675	0.0	3 / 689	13.7	100 (–74.7 to 100)
HPV-31/33/45/52/58–related cervical definitive therapy	0 / 750	0.0	0 / 745	0.0	NA
HPV-31/33/45/52/58–related external genital procedures	0 / 751	0.0	0 / 745	0.0	NA

The PPE population consisted of participants who received all 3 doses of vaccine within 1 year, were seronegative at day 1, and had negative results on PCR assays for all HPV types tested from day 1 through month 7 to the vaccine HPV type being analyzed, and had no protocol violations that could interfere with the evaluation of vaccine efficacy as judged by the study director.

Table 3. Continued

Participants are counted once in each applicable endpoint category. A participant may appear in more than 1 category. Rate is the estimate of number of cases per 10000 person-years.

Abbreviations: 9vHPV, 9-valent human papillomavirus; AIS, adenocarcinoma in situ; ASC-US, atypical squamous cells of undetermined significance; CI, confidence interval; CIN, cervical intraepithelial neoplasia; HPV, human papillomavirus; HR, high risk; NA, not available (ie, not calculable); PCR, polymerase chain reaction; PPE, per-protocol efficacy; qHPV, quadrivalent human papillomavirus.

N = number of participants randomized to the respective vaccination group who received at least 1 injection. n = number of participants who have at least 1 follow-up visit after month 7.

[a]A case of persistent infection occurred if a participant, after completion of the month 7 visit, is positive for the same HPV type by the HPV-31/33/45/52/58 PCR assay to at least 1 common gene in 2 or more consecutive cervicovaginal/external genital swab, biopsy, or definitive therapy samples obtained at 2 or more consecutive visits at least 6 months (± 1 month visit windows) apart.

[b]Results for participants from Taiwan only are 0/216 and 13/228 cases in the 9vHPV and qHPV vaccine groups, respectively, representing an efficacy of 100% (95% CI, 71.7–100).

[c]A case of persistent infection occurred if a participant, after completion of the month 7 visit, is positive for the same HPV type by the HPV-31/33/45/52/58 PCR assay to at least 1 common gene in 2 or more consecutive cervicovaginal/external genital swab, biopsy, or definitive therapy samples obtained for over a period of at least 12 months (± 1 month visit windows) apart.

[d]Includes high-grade squamous intraepithelial lesion; atypical squamous cells, cannot exclude high-grade squamous intraepithelial lesion; atypical glandular cells, adenocarcinoma, and squamous cell carcinoma.

(Supplementary Table 7); AEs of pyrexia experienced by participants from Thailand were mostly mild to moderate (Supplementary Table 7), of short duration (median, 1 day) (Supplementary Table 8), and fevers were mostly low grade (Table 6). AEs of pyrexia and elevated temperatures occurred across all the study sites in Thailand (Supplementary Table 9).

In Study 002 (Table 7), 62.4%, 74.4%, 71.2%, and 85.7% of girls and boys from India, South Korea, Taiwan, and Thailand, respectively, experienced an injection-site AE. The most common injection-site AEs were pain, swelling, and erythema; most were mild to moderate in intensity. Similar results were observed when considering only girls (Supplementary Table 10). The 9vHPV vaccine was generally well tolerated in young Indian women (Supplementary Table 11). Vaccine-related systemic AEs were more common among girls and boys from Thailand (26.4%) than those from India, South Korea, and Taiwan (4.3%–10.8%) (Table 7) but comparable with girls and boys from the overall study population (21.1%) (Supplementary Table 12). The most common vaccine-related AEs were headache and pyrexia. The frequency of vaccine-related pyrexia was higher in girls and boys from Thailand (13.6%) compared with the overall study population (7.2%) (Supplementary Table 12); vaccine-related systemic AEs were mild to moderate (Supplementary Table 12) and generally of short duration (median, 1 day) in girls and boys from Thailand (Supplementary Table 13). AEs of pyrexia occurred at both study sites in Thailand (Supplementary Table 14).

In both studies, discontinuations due to AEs were rare (9vHPV, n = 2; qHPV, n = 1; see Supplementary Material for details). No serious vaccine-related AEs were reported among Asian participants for the entire study duration. Three Asian participants (all from Study 001) died during the entire course of the study (see the Supplementary Material for more information); none of the deaths were considered vaccine related.

DISCUSSION

The 9vHPV vaccine markedly reduced the risk of HPV-31/33/45/52/58–related persistent infection, cervical cytological abnormalities, disease, and medical procedures in Asian participants. Consistent with the HPV type distribution observed in epidemiological studies in Asia, HPV-52 and HPV-58 were most commonly associated with persistent infections and cervical cytological abnormalities in participants who received the qHPV vaccine [1, 6, 31]. In the mITT analyses, nearly all cases of persistent infection and cervical cytological abnormalities and disease occurred among participants who were infected with HPV before vaccination, which highlights the value of implementing vaccination before exposure to HPV. The 9vHPV vaccine induced robust anti–HPV-6/11/16/18/31/33/45/52/58 antibody responses, with seroconversion rates ≥97.9%. GMTs to HPV-6/11/16/18 were generally comparable between 9vHPV and qHPV vaccine recipients, although GMTs for HPV-11 tended to be lower with 9vHPV vaccine. This is similar to observations in the overall study population and may not be clinically meaningful, as robust HPV-11 antibody responses were observed with both vaccines and no cases of HPV-11–related persistent infection or disease were observed in per-protocol analyses [18, 19]. GMTs to all 9 included HPV types were higher in girls and boys compared with young women from the same country, similar to previous reports in other regions (including Europe, Latin America, and North America [32], and Japan [25]). The 9vHPV vaccine was generally well tolerated in all subgroups. Injection-site AEs were generally more frequent with the 9vHPV vaccine than the qHPV vaccine, as previously observed in the overall study population [18]. Rates of vaccine-related systemic AEs were generally lower among Asian participants than in the overall population. Participants from Thailand, however, were more likely to experience vaccine-related AEs, due to a higher frequency of low-grade, short-lived fevers. The reasons for these differences are unknown; however, their impact is limited, and they do not appear to represent a clinical concern. Overall, the efficacy, immunogenicity, and safety profile of the 9vHPV vaccine was generally consistent with published results from the overall study populations [18–20].

Real-world experience in the 10 years following introduction of qHPV and bivalent HPV vaccines has demonstrated that vaccination prevents HPV infections and HPV-related disease and supports the favorable safety profile of HPV vaccines [9, 33, 34]. A recent meta-analysis found that HPV

Table 4. Summary of Anti-HPV cLIA GMTs and Seropositivity at Month 7 in Asian Participants (Young Women Aged 16–26 Years) in the PPI Population in Study 001 by Vaccination Group and Country

	9vHPV Vaccine		qHPV Vaccine		9vHPV Vaccine		qHPV Vaccine	
Assay (cLIA)	n	GMT (95% CI), mMU/mL	n	GMT (95% CI), mMU/mL	m	Seropositive (95% CI), %	m	Seropositive (95% CI), %
Hong Kong and Taiwan	N = 313		N = 312		N = 313		N = 312	
Anti–HPV-6	229	734.6 (660.0–817.7)	237	718.0 (646.2–797.7)	227	99.1 (96.9–99.9)	235	99.2 (97.0–99.9)
Anti–HPV-11	230	496.5 (443.1–556.2)	237	616.5 (551.2–689.5)	229	99.6 (97.6–100)	236	99.6 (97.7–100)
Anti–HPV-16	237	2654.6 (2394.3–2943.1)	245	2579.9 (2330.9–2855.5)	237	100 (98.5–100)	244	99.6 (97.7–100)
Anti–HPV-18	245	790.6 (698.5–894.7)	259	669.4 (593.4–755.0)	244	99.6 (97.7–100)	258	99.6 (97.9–100)
Anti–HPV-31	247	607.4 (524.1–703.9)	260	8.5 (7.3–9.8)	245	99.2 (97.1–99.9)	126	48.5 (42.2–54.7)
Anti–HPV-33	245	383.5 (339.2–433.6)	260	<4 (<4 to <4)	242	98.8 (96.5–99.7)	29	11.2 (7.6–15.6)
Anti–HPV-45	250	234.6 (206.7–266.2)	264	<3 (<3 to <3)	246	98.4 (96.0–99.6)	24	9.1 (5.9–13.2)
Anti–HPV-52	231	313.4 (279.0–352.1)	238	<3 (<3 to <3)	229	99.1 (96.9–99.9)	10	4.2 (2.0–7.6)
Anti–HPV-58	236	487.2 (429.4–552.8)	257	<4 (<4 to <4)	234	99.2 (97.0, 99.9)	39	15.2 (11.0–20.2)
Japan	N = 127		N = 127		N = 127		N = 127	
Anti–HPV-6	93	839.7 (696.3–1012.7)	100	621.2 (518.5–744.1)	93	100 (96.1–100)	98	98.0 (93.0–99.8)
Anti–HPV-11	93	611.1 (516.4–723.3)	100	607.3 (516.2–714.5)	93	100 (96.1–100)	100	100 (96.4–100)
Anti–HPV-16	96	2672.7 (2269.6–3147.3)	103	2223.4 (1898.7–2603.5)	96	100 (96.2–100)	103	100 (96.5–100)
Anti–HPV-18	99	688.7 (563.3–842.0)	109	471.9 (389.6–571.5)	99	100 (96.3–100)	106	97.2 (92.2–99.4)
Anti–HPV-31	104	672.3 (552.4–818.2)	109	5.9 (4.9–7.2)	104	100 (96.5–100)	37	33.9 (25.1–43.6)
Anti–HPV-33	109	398.3 (344.8–460.2)	111	<4 (<4 to <4)	109	100 (96.7–100)	11	9.9 (5.1–17.0)
Anti–HPV-45	111	258.5 (224.8–297.3)	111	<3 (<3 to <3)	111	100 (96.7–100)	6	5.4 (2.0–11.4)
Anti–HPV-52	98	306.3 (267.5–350.7)	96	<3 (<3 to <3)	98	100 (96.3–100)	4	4.2 (1.1–10.3)
Anti–HPV-58	95	459.6 (399.9–528.3)	99	<4 (<4 to <4)	95	100 (96.2–100)	12	12.1 (6.4–20.2)
South Korea	N = 152		N = 151		N = 152		N = 151	
Anti–HPV-6	94	820.1 (684.3–982.8)	88	801.9 (665.1–966.9)	92	97.9 (92.5–99.7)	88	100 (95.9–100)
Anti–HPV-11	94	613.0 (518.3–724.9)	88	658.2 (553.5–782.8)	94	100 (96.2–100)	88	100 (95.9–100)
Anti–HPV-16	103	2641.6 (2323.2–3003.7)	99	2691.6 (2361.0–3068.3)	103	100 (96.5–100)	99	100 (96.3–100)
Anti–HPV-18	109	634.9 (531.0–759.1)	104	627.0 (522.2–752.8)	108	99.1 (95.0–100)	104	100 (96.5–100)
Anti–HPV-31	113	553.9 (455.4–673.8)	99	7.6 (6.2–9.4)	112	99.1 (95.2–100)	45	45.5 (35.4–55.8)
Anti–HPV-33	112	337.2 (297.1–382.6)	102	<4 (<4 to <4)	112	100 (96.8–100)	5	4.9 (1.6–11.1)
Anti–HPV-45	114	213.8 (183.0–249.6)	102	<3 (<3 to <3)	113	99.1 (95.2–100)	5	4.9 (1.6–11.1)
Anti–HPV-52	100	310.5 (262.0–368.0)	93	<3 (<3 to <3)	100	100 (96.4–100)	3	3.2 (0.7–9.1)
Anti–HPV-58	104	420.1 (361.3–488.5)	99	<4 (<4 to <4)	104	100 (96.5–100)	15	15.2 (8.7–23.8)
Thailand	N = 232		N = 233		N = 232		N = 233	
Anti–HPV-6	158	910.5 (806.4–1028.0)	168	832.5 (740.0–936.5)	158	100 (97.7–100)	168	100 (97.8–100)
Anti–HPV-11	158	668.1 (586.2–761.4)	168	736.7 (649.0–836.3)	158	100 (97.7–100)	168	100 (97.8–100)
Anti–HPV-16	172	3479.4 (3125.1–3873.9)	182	3371.3 (3037.1–3742.3)	172	100 (97.9–100)	182	100 (98.0–100)
Anti–HPV-18	181	1095.5 (960.7–1249.2)	183	890.7 (781.7–1014.9)	181	100 (98.0–100)	183	100 (98.0–100)
Anti–HPV-31	195	809.1 (687.0–952.9)	189	14.2 (12.0–16.8)	194	99.5 (97.2–100)	117	61.9 (54.6–68.9)
Anti–HPV-33	189	473.3 (415.1–539.7)	196	<4 (<4 to <4)	188	99.5 (97.1–100)	28	14.3 (9.7–20.0)
Anti–HPV-45	200	357.8 (313.7–408.0)	201	<3 (<3 to <3)	199	99.5 (97.2–100)	24	11.9 (7.8–17.2)
Anti–HPV-52	172	387.7 (343.1–438.2)	174	<3 (<3 to <3)	171	99.4 (96.8–100)	8	4.6 (2.0–8.9)
Anti–HPV-58	177	545.0 (481.8–616.4)	184	<4 (<4 to 4.2)	177	100 (97.9–100)	39	21.2 (15.5–27.8)
Total	N = 824		N = 823		N = 824		N = 823	
Anti–HPV-6	574	810.9 (756.9–868.7)	593	742.7 (694.1–794.8)	570	99.3 (98.2–99.8)	589	99.3 (98.3–99.8)
Anti–HPV-11	575	576.6 (537.7–618.3)	593	653.1 (609.7–699.6)	574	99.8 (99.0–100)	592	99.8 (99.1–100)
Anti–HPV-16	608	2866.4 (2695.9–3047.8)	629	2738.7 (2578.4–2908.9)	608	100 (99.4–100)	628	99.8 (99.1–100)
Anti–HPV-18	634	817.8 (757.7–882.7)	655	676.9 (628.0–729.7)	632	99.7 (98.9–100)	651	99.4 (98.4–99.8)
Anti–HPV-31	659	661.3 (605.5–722.2)	657	9.1 (8.3–10.0)	655	99.4 (98.5–99.8)	325	49.5 (45.6–53.4)
Anti–HPV-33	655	401.2 (374.8–429.5)	669	< 4 (<4 to <4)	651	99.4 (98.4–99.8)	73	10.9 (8.7–13.5)
Anti–HPV-45	675	265.9 (247.7–285.5)	678	< 3 (<3 to <3)	669	99.1 (98.1–99.7)	59	8.7 (6.7–11.1)
Anti–HPV-52	601	331.3 (309.8–354.3)	601	< 3 (<3 to <3)	598	99.5 (98.5–99.9)	25	4.2 (2.7–6.1)
Anti–HPV-58	612	486.3 (453.8–521.1)	639	< 4 (<4 to <4)	610	99.7 (98.8–100)	105	16.4 (13.6–19.5)

The PPI population included all participants who had no protocol violation that could interfere with the evaluation of the immune response to vaccine as judged by the study director, received all 3 vaccinations within acceptable day ranges, were seronegative at day 1 and 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.

Seropositive percent represents proportion of participants with anti-HPV serum levels ≥30, 16, 20, 24, 10, 8, 8, 8, and 8 mMU/mL for HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58, respectively.

Abbreviations: 9vHPV, 9-valent human papillomavirus; CI, confidence interval; cLIA, competitive Luminex immunoassay; GMT, geometric mean titer; mMU, milli-Merck units; PPI, per-protocol immunogenicity; qHPV, quadrivalent human papillomavirus.

N = number of participants randomized to the respective vaccination group who received at least 1 injection. n = number of participants contributing to the analysis. m = number of participants who had seroconversion.

Table 5. Summary of Anti-HPV cLIA GMTs and Seropositivity at Month 7 in the PPI Population of Asian Girls and Boys (Aged 9–15 Years) in Study 002, by Country, and the Overall Population of Young Women (Aged 16–26 Years) From Study 001

	Study 002										Study 001[a]	
	9vHPV Vaccine (Girls and Boys Aged 9–15 y)										9vHPV Vaccine (Women Aged 16–26 y)	
	India (N = 200)		South Korea (N = 129)		Taiwan (N = 139)		Thailand (N = 140)		Total (N = 608)		Overall Study Population (N = 6792)	
Assay (cLIA)	n	GMT (95% CI), mMU/mL	n	GMT (95% CI), mMU/mL	n	GMT (95% CI), mMU/mL	n	GMT (95% CI), mMU/mL	n	GMT (95% CI), mMU/mL	n	GMT (95% CI), mMU/mL
Anti–HPV-6	170	1641.2 (1428.0–1886.2)	120	2226.3 (1931.8–2565.6)	134	1308.8 (1129.9–1516.0)	131	1464.8 (1277.5–1679.6)	555	1615.9 (1503.3–1736.8)	3993	893.1 (871.7–915.1)
Anti–HPV-11	170	1180.0 (1024.2–1359.5)	120	1524.0 (1318.2–1761.9)	134	956.6 (836.9–1093.5)	131	1024.5 (888.4–1181.5)	555	1146.6 (1067.2–1231.9)	3995	666.3 (649.6–683.4)
Anti–HPV-16	175	7061.4 (6125.2–8140.8)	121	8265.5 (7182.8–9511.5)	135	5804.4 (5142.0–6552.1)	135	6598.6 (5742.3–7582.6)	566	6857.8 (6399.4–7349.0)	4032	3131.1 (3057.1–3206.9)
Anti–HPV-18	178	2118.5 (1798.9–2494.9)	120	2530.4 (2147.5–2981.7)	137	1688.0 (1469.3–1939.3)	132	2433.7 (2081.7–2845.1)	567	2150.5 (1986.0–2328.8)	4539	804.6 (782.7–827.1)
Anti–HPV-31	171	1666.0 (1453.4–1909.7)	119	2177.4 (1864.5–2542.9)	136	1636.2 (1424.7–1879.1)	133	1748.3 (1518.0–2013.7)	559	1776.3 (1654.0–1907.6)	4466	658.4 (636.7–680.9)
Anti–HPV-33	175	855.0 (736.9–992.0)	121	1053.1 (907.2–1222.4)	137	796.4 (696.6–910.5)	134	891.4 (777.0–1022.6)	567	887.4 (825.7–953.7)	4702	415.9 (405.6–426.4)
Anti–HPV-45	179	742.0 (627.4–877.5)	121	900.1 (746.6–1085.2)	137	715.2 (602.4–849.0)	134	787.2 (675.7–917.1)	571	776.9 (713.6–845.9)	4792	252.8 (246.2–259.6)
Anti–HPV-52	176	827.0 (708.2–965.8)	121	1005.9 (866.0–1168.5)	136	779.0 (668.6–907.7)	134	753.8 (657.1–864.8)	567	831.6 (771.1–896.9)	4455	379.7 (371.6–388.0)
Anti–HPV-58	173	1198.1 (1030.5–1393.0)	121	1572.7 (1362.8–1814.9)	136	1152.8 (1006.3–1320.7)	133	1209.3 (1045.5–1398.9)	563	1261.2 (1172.3–1357.0)	4486	482.5 (469.9–495.3)
Assay (cLIA)	m	Seropositive (95% CI), %	m	Seropositive (95% CI), %	m	Seropositive (95% CI), %	m	Seropositive (95% CI), %	m	Seropositive (95% CI), %	m	Seropositive (95% CI), %
Anti–HPV-6	168	98.8 (95.8–99.9)	120	100 (97.0–100)	133	99.3 (95.9–100)	131	100 (97.2–100)	552	99.5 (98.4–99.9)	3985	99.8 (99.6–99.9)
Anti–HPV-11	169	99.4 (96.8–100)	120	100 (97.0–100)	134	100 (97.3–100)	131	100 (97.2–100)	554	99.8 (99.0–100)	3994	100 (99.9–100)
Anti–HPV-16	174	99.4 (96.9–100)	121	100 (97.0–100)	135	100 (97.3–100)	135	100 (97.3–100)	565	99.8 (99.0–100)	4031	100 (99.9–100)
Anti–HPV-18	177	99.4 (96.9–100)	120	100 (97.0–100)	137	100 (97.3–100)	132	100 (97.2–100)	566	99.8 (99.0–100)	4532	99.8 (99.7–99.9)
Anti–HPV-31	171	100 (97.9–100)	119	100 (96.9–100)	136	100 (97.3–100)	133	100 (97.3–100)	559	100 (99.3–100)	4457	99.8 (99.6–99.9)
Anti–HPV-33	174	99.4 (96.9–100)	121	100 (97.0–100)	137	100 (97.3–100)	134	100 (97.3–100)	566	99.8 (99.0–100)	4689	99.7 (99.5–99.9)
Anti–HPV-45	178	99.4 (96.9–100)	121	100 (97.0–100)	137	100 (97.3–100)	134	100 (97.3–100)	570	99.8 (99.0–100)	4773	99.6 (99.4–99.8)
Anti–HPV-52	175	99.4 (96.9–100)	121	100 (97.0–100)	136	100 (97.3–100)	134	100 (97.3–100)	566	99.8 (99.0–100)	4446	99.8 (99.6–99.9)
Anti–HPV-58	172	99.4 (96.8–100)	121	100 (97.0–100)	136	100 (97.3–100)	133	100 (97.3–100)	562	99.8 (99.0–100)	4476	99.8 (99.6–99.9)

The PPI population included all participants who had no protocol violation that could interfere with the evaluation of the immune response to vaccine as judged by the study director, received all 3 vaccinations within acceptable day ranges, were seronegative at day 1 and (16 to 26-year-old women only) 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.

Seropositive percent represents the proportion of participants with anti-HPV serum levels ≥30, 16, 20, 24, 10, 8, 8, 8, and 8 mMU/mL for HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58, respectively.

Abbreviations: 9vHPV, 9-valent human papillomavirus; CI, confidence interval; cLIA, competitive Luminex immunoassay; GMT, geometric mean titer; mMU, milli-Merck units; PPI, per-protocol immunogenicity.

N = number of participants randomized to the respective vaccination group who received at least 1 injection. n = number of participants contributing to the analysis. m = number of participants who had seroconversion.

[a]Based on [19].

Table 6. AEs in Asian Young Women (Aged 16–26 Years) from Study 001 by Vaccination Group and Country

	9vHPV Vaccine					qHPV Vaccine				
	Hong Kong and Taiwan (N = 345)	Japan (N = 127)	South Korea (N = 152)	Thailand (N = 232)	Total (N = 856)	Hong Kong and Taiwan (N = 346)	Japan (N = 127)	South Korea (N = 150)	Thailand (N = 231)	Total (N = 854)
Event	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Participants with 1 or more AE[a]	304 (88.1)	108 (85.0)	137 (90.1)	211 (90.9)	760 (88.8)	297 (85.8)	103 (81.1)	130 (86.7)	206 (89.2)	736 (86.2)
Injection-site event[b]	294 (85.2)	104 (81.9)	133 (87.5)	201 (86.6)	732 (85.5)	269 (77.7)	101 (79.5)	123 (82.0)	192 (83.1)	685 (80.2)
Pain[c]	286 (82.9)	104 (81.9)	131 (86.2)	199 (85.8)	720 (84.1)	260 (75.1)	100 (78.7)	119 (79.3)	189 (81.8)	668 (78.2)
Mild	216 (62.6)	63 (49.6)	76 (50.0)	103 (44.4)	458 (53.5)	217 (62.7)	76 (59.8)	86 (57.3)	93 (40.3)	472 (55.3)
Moderate	68 (19.7)	41 (32.3)	42 (27.6)	86 (37.1)	237 (27.7)	37 (10.7)	23 (18.1)	27 (18.0)	91 (39.4)	178 (20.8)
Severe	2 (0.6)	0	13 (8.6)	10 (4.3)	25 (2.9)	6 (1.7)	1 (0.8)	6 (4.0)	5 (2.2)	18 (2.1)
Swelling	160 (46.4)	57 (44.9)	79 (52.0)	71 (30.6)	367 (42.9)	99 (28.6)	53 (41.7)	53 (35.3)	63 (27.3)	268 (31.4)
Mild: 0 to ≤2.5 cm	121 (35.1)	36 (28.3)	57 (37.5)	51 (22.0)	265 (31.0)	84 (24.3)	46 (36.2)	43 (28.7)	50 (21.6)	223 (26.1)
Moderate: >2.5 cm to ≤5.0 cm	27 (7.8)	14 (11.0)	11 (7.2)	15 (6.5)	67 (7.8)	12 (3.5)	5 (3.9)	6 (4.0)	11 (4.8)	34 (4.0)
Severe: >5.0 cm	11 (3.2)	7 (5.5)	11 (7.2)	5 (2.2)	34 (4.0)	3 (0.9)	2 (1.6)	4 (2.7)	2 (0.9)	11 (1.3)
Unknown	1 (0.3)	0	0	0	1 (0.1)	0	0	0	0	0
Erythema	126 (36.5)	51 (40.2)	59 (38.8)	26 (11.2)	262 (30.6)	88 (25.4)	48 (37.8)	36 (24.0)	15 (6.5)	187 (21.9)
Mild: 0 to ≤2.5 cm	108 (31.3)	35 (27.6)	42 (27.6)	20 (8.6)	205 (23.9)	78 (22.5)	44 (34.6)	29 (19.3)	13 (5.6)	164 (19.2)
Moderate: >2.5 cm to ≤5.0 cm	13 (3.8)	11 (8.7)	10 (6.6)	5 (2.2)	39 (4.6)	9 (2.6)	3 (2.4)	5 (3.3)	2 (0.9)	19 (2.2)
Severe: >5.0 cm	5 (1.4)	5 (3.9)	7 (4.6)	1 (0.4)	18 (2.1)	1 (0.3)	1 (0.8)	2 (1.3)	0	4 (0.5)
Pruritus[c]	16 (4.6)	12 (9.4)	15 (9.9)	10 (4.3)	53 (6.2)	4 (1.2)	14 (11.0)	7 (4.7)	7 (3.0)	32 (3.7)
Mild	13 (3.8)	11 (8.7)	12 (7.9)	7 (3.0)	43 (5.0)	4 (1.2)	14 (11.0)	5 (3.3)	5 (2.2)	28 (3.3)
Moderate	3 (0.9)	1 (0.8)	2 (1.3)	3 (1.3)	9 (1.1)	0	0	2 (1.3)	2 (0.9)	4 (0.5)
Severe	0	0	1 (0.7)	0	1 (0.1)	0	0	0	0	0
Systemic event[d]	136 (39.4)	41 (32.3)	70 (46.1)	128 (55.2)	375 (43.8)	141 (40.8)	38 (29.9)	72 (48.0)	139 (60.2)	390 (45.7)
Any vaccine-related systemic event	65 (18.8)	15 (11.8)	19 (12.5)	98 (42.2)	197 (23.0)	48 (13.9)	8 (6.3)	19 (12.7)	93 (40.3)	168 (19.7)
Headache	10 (2.9)	5 (3.9)	4 (2.6)	40 (17.2)	59 (6.9)	9 (2.6)	4 (3.1)	3 (2.0)	41 (17.7)	57 (6.7)
Pyrexia	9 (2.6)	4 (3.1)	2 (1.3)	38 (16.4)	53 (6.2)	6 (1.7)	0	1 (0.7)	35 (15.2)	42 (4.9)
Serious event	2 (0.6)	1 (0.8)	1 (0.7)	2 (0.9)	6 (0.7)	2 (0.6)	2 (1.6)	1 (0.7)	2 (0.9)	7 (0.8)
Vaccine-related event	0	0	0	0	0	0	0	0	0	0
Death	0	0	0	0	0	0	0	0	0	0
Discontinuation due to AE[e]	0	0	0	1 (0.4)	1 (0.1)	0	0	1 (0.7)	0	1 (0.1)
Vaccine-related event	0	0	0	1 (0.4)	1 (0.1)	0	0	1 (0.7)	0	1 (0.1)
Serious event	0	0	0	0	0	0	0	0	0	0
Serious vaccine-related event	0	0	0	0	0	0	0	0	0	0
Participants with temperature data (N)	344	127	148	231	850	346	126	148	231	851
Maximum temperatures (oral)[f]										
≥37.8°C	13 (3.8)	4 (3.1)	2 (1.4)	38 (16.5)	57 (6.7)	12 (3.5)	1 (0.8)	3 (2.0)	38 (16.5)	54 (6.3)
≥38.9°C	1 (0.3)	0	0	8 (3.5)	9 (1.1)	0	0	0	4 (1.7)	4 (0.5)

Every participant is counted a single time for each applicable specific AE.

Abbreviations: 9vHPV, 9-valent human papillomavirus; AE, adverse event; qHPV, quadrivalent human papillomavirus.

N = number of participants who underwent randomization, received at least 1 dose of vaccine, and had at least 1 follow-up visit related to the AE. n = number of participants contributing to the analysis.

[a]AEs that were reported within 1 to 15 days after any vaccination.

[b]Injection-site events were AEs that were reported within 1 to 5 days after any vaccination. A specific AE appears on this table only if its incidence in 1 or more of the columns is ≥5% incidence after rounding.

[c]Intensities of pain and itching were defined as: mild if there was an awareness of the sign or symptom but it did not interfere with usual activities; as moderate if there was enough discomfort to cause interference with usual activity; and as severe if the pain or discomfort was incapacitating, rendering the participant unable to work or carry out usual activities.

[d]Systemic events were AEs that were reported within 1 to 15 days after any vaccination. A specific AE appears on this table only if its incidence in 1 or more of the columns is ≥5% incidence after rounding.

[e]Discontinuation due to AE was reported within 1 to 15 days after any vaccination.

[f]Temperatures were recorded within 1 to 5 days after any vaccination.

Table 7. AEs in Asian Girls and Boys (Aged 9–15 Years) in Study 002 by Country

	9vHPV Vaccine				
	India (N = 194)	South Korea (N = 129)	Taiwan (N = 139)	Thailand (N = 140)	Total (N = 602)
Event	n (%)	n (%)	n (%)	n (%)	n (%)
Participants with 1 or more AE[a]	127 (65.5)	99 (76.7)	104 (74.8)	126 (90.0)	456 (75.7)
Injection-site event[b]	121 (62.4)	96 (74.4)	99 (71.2)	120 (85.7)	436 (72.4)
Pain[c]	117 (60.3)	91 (70.5)	96 (69.1)	118 (84.3)	422 (70.1)
Mild	62 (32.0)	72 (55.8)	77 (55.4)	74 (52.9)	285 (47.3)
Moderate	46 (23.7)	17 (13.2)	17 (12.2)	39 (27.9)	119 (19.8)
Severe	9 (4.6)	2 (1.6)	2 (1.4)	5 (3.6)	18 (3.0)
Swelling	46 (23.7)	26 (20.2)	40 (28.8)	35 (25.0)	147 (24.4)
Mild: 0 to ≤2.5 cm	35 (18.0)	12 (9.3)	29 (20.9)	23 (16.4)	99 (16.4)
Moderate: >2.5 cm to ≤5.0 cm	8 (4.1)	8 (6.2)	8 (5.8)	8 (5.7)	32 (5.3)
Severe: >5.0 cm	3 (1.5)	6 (4.7)	3 (2.2)	4 (2.9)	16 (2.7)
Erythema	36 (18.6)	34 (26.4)	39 (28.1)	13 (9.3)	122 (20.3)
Mild: 0 to ≤2.5 cm	31 (16.0)	27 (20.9)	33 (23.7)	9 (6.4)	100 (16.6)
Moderate: >2.5 cm to ≤5.0 cm	4 (2.1)	3 (2.3)	4 (2.9)	3 (2.1)	14 (2.3)
Severe: >5.0 cm	1 (0.5)	4 (3.1)	2 (1.4)	1 (0.7)	8 (1.3)
Pruritus[c]	1 (0.5)	11 (8.5)	6 (4.3)	1 (0.7)	19 (3.2)
Mild	1 (0.5)	11 (8.5)	3 (2.2)	1 (0.7)	16 (2.7)
Moderate	0	0	3 (2.2)	0	3 (0.5)
Severe	0	0	0	0	0
Edema[d]	0	19 (14.7)	0	0	19 (3.2)
Mild	0	12 (9.3)	0	0	12 (2.0)
Moderate	0	4 (3.1)	0	0	4 (0.7)
Severe	0	3 (2.3)	0	0	3 (0.5)
Systemic event[e]	34 (17.5)	35 (27.1)	25 (18.0)	69 (49.3)	163 (27.1)
Any vaccine-related systemic event	21 (10.8)	6 (4.7)	6 (4.3)	37 (26.4)	70 (11.6)
Headache	1 (0.5)	2 (1.6)	2 (1.4)	15 (10.7)	20 (3.3)
Pyrexia	19 (9.8)	0	3 (2.2)	19 (13.6)	41 (6.8)
Serious event	0	2 (1.6)	0	0	2 (0.3)
Vaccine-related event	0	0	0	0	0
Death	0	0	0	0	0
Discontinuation due to AE[f]	0	0	0	0	0
Participants with temperature data (N)	194	129	139	140	602
Maximum temperatures (oral)[g]					
≥37.8°C	20 (10.3)	2 (1.6)	4 (2.9)	24 (17.1)	50 (8.3)
≥38.9°C	0	0	1 (0.7)	5 (3.6)	6 (1.0)

Every participant is counted a single time for each applicable specific AE.

Abbreviations: 9vHPV, 9-valent human papillomavirus; AE, adverse event.

N = number of participants who underwent randomization, received at least 1 dose of vaccine, and had at least 1 follow-up visit related to the AE. n = number of participants contributing to the analysis.

[a]AEs that were reported within 1 to 15 days after any vaccination.

[b]Injection-site events were AEs that were reported within 1 to 5 days after any vaccination. A specific AE appears on this table only if its incidence in 1 or more of the columns is ≥5% incidence after rounding.

[c]Intensities of pain and itching were defined as: mild if there was an awareness of the sign or symptom but it did not interfere with usual activities; as moderate if there was enough discomfort to cause interference with usual activity; and as severe if the pain or discomfort was incapacitating, rendering the participant unable to work or carry out usual activities.

[d]Injection-site edema was reported in 19 girls and boys from a single study site in South Korea in Study 002. Edema was not reported as an AE at other study sites in South Korea or other countries; moreover, this particular study site did not report any event of injection-site swelling, even though this would have been anticipated because injection-site swelling is one of the most common AEs following vaccination. Reports of injection-site AE of edema at this study site may be due to language-related misinterpretation (ie, even though there are 2 distinct Korean words for swelling and edema, respectively, there is also another word for both swelling and edema).

[e]Systemic events were AEs that were reported within 1 to 15 days after any vaccination. A specific AE appears on this table only if its incidence in 1 or more of the columns is ≥5% incidence after rounding.

[f]Discontinuation due to AE was reported within 1 to 15 days after any vaccination.

[g]Temperatures were recorded within 1 to 5 days after any vaccination.

vaccines were highly immunogenic and well tolerated in Asian populations, consistent with international HPV vaccination studies [35].

Vaccination programs may represent the most effective prevention strategies in countries without organized cervical cancer screening programs [3, 36]. This is relevant to Asia, which

contributes over half of the global cervical cancer burden, and where comprehensive, organized screening programs have not been widely implemented [4]. The 9vHPV vaccine can provide additional benefits over bivalent and quadrivalent HPV vaccines by expanding coverage to HPV-31/33/45/52/58. The expansion of vaccine coverage to HPV-52/58 is of particular importance in Asia due to the relatively high prevalence of these types (see Supplementary Material) [1, 12]. The robust reduction of HPV-52– and HPV-58–related persistent infection and cervical cytological abnormalities in 9vHPV vaccine recipients should inform cervical screening algorithms in vaccinated populations in Asia.

HPV vaccination is considered likely to be cost effective in preventing HPV-associated cancers, particularly in developing countries with limited access to other forms of cervical cancer prevention and control [37–39]. Based on studies using Japanese, US and Austrian data, a vaccination program for 9vHPV is expected to improve health outcomes and be cost effective compared with programs implemented with bivalent or qHPV vaccines [40–43].

Although several Asian countries have licensed bivalent or qHPV vaccines, few have implemented national HPV vaccination programs to date [3–5], and only approximately 0.2% of Asian women have received a full course of HPV vaccination, compared with 1.4% worldwide [3]. In Malaysia, a national school-based HPV vaccination program has been in place since 2010 and achieved a high degree of coverage [3–5]. Pilot programs had been implemented in India and Thailand as of 2015 [3]. Issues related to loss of public confidence in vaccination and misperceptions surrounding vaccine safety have emerged in some regions [44–46], despite data from large epidemiological studies and active surveillance programs by national and international organizations, which overwhelmingly support the safety of HPV vaccination [47–49]. As misperceptions regarding vaccine safety and clusters of anxiety-related immunization reactions can have damaging consequences for vaccination programs [46, 50], health care professionals and authorities must be prepared to respond to these challenges in implementing successful vaccination programs [50].

In conclusion, the 9vHPV vaccine is efficacious, immunogenic, and generally well tolerated in clinical studies in Asian girls, boys, and young women, consistent with findings in the global clinical program. These data support widespread vaccination programs in Asia. This information may represent valuable insight for decision-making purposes regarding implementation of vaccination programs/HPV-related disease prevention.

Supplementary Data

Supplementary materials are available at *The Journal of Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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Primary Investigators in Asia, Study V503-001: *Hong-Kong*: Tak-Hong Cheung, Yuen-Sheung Hextan Ngan; *Japan*: Hideki Hanashi, Masaru Sakamoto, Nobuhiro Takeshima, Yuzuru Takeuchi, Wataru Tsunezawa; *South Korea*: Chi-Heum Cho, Byoung Gie Kim, Seung Cheol Kim, Young Tak Kim, Hee-Sug Ryu, Yong Sang Song; *Taiwan*: Chi-An Chen, Hung-Hsueh Chou, Tang-Yuan Chu, Chung-Yuan Lee, Nae-Fang Twu, Yuh-Cheng Yang, Mu-Hsien Yu; *Thailand*: Nipon Khemapech, Sompong Koonlerkit, Sutham Pinjaroen, Punnee Pitisuttithum, Sarikapan Wilailak.

Study V503-002: *India*: Amaresh Adyar, Neerja Bhatla, Sukanta Chatterjee, Hemant Jain, Sanjay Lalwani, Sudha Marwah, Daljit Singh; *Korea*: Chi-Heum Cho, Jin Han Kang, Dongsoo Kim, Kyung-Hyo Kim; *Taiwan*: Li-Min Huang, Tzou-Yien Liu, Horng-Der Tsai; *Thailand*: Punnee Pitisuttithum, Rudiwilai Samakoses.

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