Human Papillomavirus Genotypes From Vaginal and Vulvar Intraepithelial Neoplasia in Young Women

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56 **Potential Conflicts of Interest (Appendix 1)**
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PRÉCIS

Most low- and high-grade squamous vulvar and vaginal intraepithelial lesions in young women are associated with common human papillomavirus genotypes.

ABSTRACT

Objective: To estimate the proportion of vulvar and vaginal low- and high-grade squamous intraepithelial lesions (LSILs and HSILs) in young women attributable to 14 human papillomavirus (HPV) genotypes (6, 11, 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59).

Methods: A post-hoc analysis of prospectively diagnosed vulvar and vaginal LSILs and HSILs among women 15 to 26 years of age enrolled in the placebo arms of 2 phase 3, randomized HPV vaccine trials assessed 14 prespecified HPV genotypes associated with cervical cancers or anogenital warts using a type-specific multiplex polymerase chain reaction assay. The frequency of lesions associated with specific HPV genotypes was estimated by proportional and other attribution methods.

Results: During approximately 4 years of follow-up in 8798 women, 40 vulvar LSILs and 46 vulvar HSILs were diagnosed in 68 women, and 118 vaginal LSILs and 33 vaginal HSILs were diagnosed in 107 women. Women developing vulvar (41.2%) or vaginal (49.5%) lesions also had cervical lesions, whereas 6.5% of women with cervical lesions had vaginal or vulvar lesions. At least 1 of the 14 HPV genotypes was detected in women with vulvar LSIL (72.5%), vulvar HSIL (91.3%), vaginal LSIL (61.9%), and vaginal HSIL (72.7%), and multiple genotypes were detected in 40.3%, 30.4%, 24.1%, and 45.2% of women with these HPV-positive lesions, respectively. Considering only HPV-positive lesions, the 9 most common genotypes causing cervical cancer

and anogenital warts were found in 89.4% of vulvar LSILs, 100% of vulvar HSILs, 56.0% of vaginal LSILs, and 78.3% of vaginal HSILs.

Conclusions: Most vulvar and vaginal lesions were attributable to at least 1 of the 14 HPV genotypes analyzed. Effective immunization programs could potentially prevent a substantial number of HPV-related vulvar and vaginal LSILs and HSILs.

Trial registrations: https://clinicaltrials.gov/; **Identifiers NCT00092521 and NCT00092534.**

INTRODUCTION

Many common human papillomavirus (HPV) types have been detected in vulvar and vaginal lesions typically diagnosed in women in the third to sixth decade of life.[1-8] HPV-related vulvar intraepithelial neoplasia (VIN) is divided into low-grade squamous intraepithelial lesions (LSIL, formerly VIN1) and potentially precancerous high-grade squamous intraepithelial lesions (HSIL, formerly VIN2/3).[9,10] A substantial number of untreated vulvar HSILs (87.5%) progress to cancer.[11] Low- and high-grade vaginal intraepithelial neoplasia are also classified as LSIL (formerly VaIN1) and HSIL (formerly VaIN2/3), respectively; HSILs variably progress to invasive vaginal cancer.[12] Delayed diagnosis of vulvar and vaginal cancers is common and can adversely affect prognosis.

Cervical cancer is predominately caused by 12 high-risk HPV types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59), and most anogenital warts are caused by 2 low-risk HPV types (6 and 11).[13] Three highly efficacious HPV vaccines are in widespread worldwide use against genital HPV infection and associated anogenital lesions: the bivalent (HPV16/18 [Cervarix, GlaxoSmithKline, Rixensart, Belgium]), the quadrivalent (HPV6/11/16/18 [GARDASIL; Merck & Co., Inc.,

Kenilworth, NJ, USA]), and the nonavalent vaccine (HPV6/11/16/18/31/33/45/52/58 [GARDASIL 9; Merck & Co., Inc.]).[13-15]

Estimates for the frequencies of HPV types associated with vulvovaginal lesions remain imprecise.[7,16-19] To better delineate the association of specific HPV genotypes with incident vulvovaginal abnormalities, we estimated the proportion of vulvar or vaginal lesions attributable to the 14 HPV genotypes most frequently linked to cervical cancer and anogenital warts, among women 15 to 26 years old prospectively followed in the placebo arms of 2 pivotal trials assessing the prophylactic efficacy of the quadrivalent vaccine.[20,21]

METHODS

For this post-hoc descriptive analysis, we used data from young women in the placebo arms of 2 already published, prospective, randomized, double-blind clinical trials of the quadrivalent HPV vaccine (FUTURE I, NCT00092521,[20] and FUTURE II, NCT00092534[21]) who developed vulvar or vaginal LSILs and HSILs during approximately 4 years of follow-up. Secondary objectives were to compare baseline characteristics of women with and without incident vulvar or vaginal lesions, and to explore patterns of lesion development at multiple (vulvar, vaginal, and cervical) sites in the same woman. An exploratory, but clinically informative, objective was to estimate the proportion of vulvar or vaginal LSILs or HSILs attributable to genotypes covered by current vaccines.

The study designs, protocols, and results for each study have been previously published.[20,21] Both studies were sponsored by Merck & Co., Inc., conducted in accordance with principles of Good Clinical Practice, and approved by the appropriate institutional review boards and regulatory agencies governing each site. Women reporting a history of abnormal cervical

Papanicolaou (Pap) smears or multiple sexual partners (defined as ≥4 lifetime partners by most, but not all sites) were excluded. These trials enrolled a total of 17,622 healthy, nonpregnant women aged 15 to 26 years, 8812 of whom were randomized to the placebo arms. Participants underwent pelvic examinations for cytologic testing with visual inspection of the vulvovaginal and perianal areas, and collection of cervical and anogenital swabs for HPV testing by polymerase chain reaction (PCR) assay at randomization on day 1, at months 7 and 12, and then every 6 to 12 months for up to 48 months.

The 8798 placebo recipients who received ≥1 study injection and had follow-up data were included in the current descriptive analysis.

Biopsies were obtained from all external anogenital lesions deemed possibly HPV-related on inspection. If multiple lesions were apparent, each suspicious lesion was sampled. All biopsy specimens were first read for clinical management by pathologists at a central laboratory (Diagnostic Cytology Laboratories, Indianapolis, IN, USA), then adjudicated by a panel of 4 gynecologic pathologists blinded to central laboratory and clinical diagnoses, treatment group, and HPV status. Specimens were tested for 14 prespecified HPV genotypes (6, 11, 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59) using a type-specific multiplex PCR assay developed by Merck Research Laboratories (Merck & Co, Inc.) to simultaneously amplify and detect the L1, E6, and E7 open reading frames of HPV6, 11, 16, 18, 31, 45, 52, and 58 or the E6 and E7 open reading frames of HPV33, 35, 39, 51, 56, and 59.[22,23] The adjudicated diagnoses of vaginal and vulvar LSILs (not including condylomata) and HSILs were captured for these analyses.

Baseline characteristics of women who did and did not develop vulvar or vaginal lesions were analyzed by lesion location and grade. If a woman developed >1 lesion at a site, the highest-

grade lesion was used in the analysis. To calculate age-adjusted associations between baseline characteristics and lesion development, odds ratios (ORs) and 95% confidence intervals (CIs) were computed using a nested case-control approach. Five controls per case were randomly selected from women who did not develop cervical or anogenital lesions throughout the follow-up period. The comparison group was not matched by person-time at risk.

We explored patterns of lesion development at cervical, vulvar, and vaginal sites in individual women. The proportion of women with incident lesions at a specified site who also had lesions at other sites was calculated from women with histologically confirmed cervical, vulvar, or vaginal lesions during follow-up.

HPV types were grouped into bivalent vaccine types (16/18); quadrivalent vaccine types (6/11/16/18), nonavalent vaccine types (6/11/16/18/31/33/45/52/58), the 5 additional types included in the 9-genotype vaccine but not in the quadrivalent vaccine (31/33/45/52/58), and the most common nonvaccine high-risk types identified in the quadrivalent HPV vaccine trials (35/39/51/56/59).

Proportional attribution was the primary attribution approach.[16-19,24] The relative proportion of coinfected lesions attributed to each HPV type detected in the lesion corresponded to the relative proportion of lesions from the same population in which that HPV type had been detected as a single infection. Four other approaches[16-19,24] were used as sensitivity analyses. (**Appendix 2**)

For additional interpretative context, we also present the type-specific analyses for only the subset of lesions in which any of the 14 HPV types being tested was identified.

RESULTS

There were 8812 women aged 15 to 26 years at baseline randomized to the 2 placebo arms, but 14 women were excluded from this analysis because of missing data or cross treatment with vaccine. During approximately 4 years of follow-up in the remaining 8798 women, a total of 86 vulvar lesions (40 LSILs and 46 HSILs) were diagnosed in 68 women, and 151 vaginal lesions (118 LSILs and 33 HSILs) were diagnosed in 107 women (**Appendix Table 1**).

Women who developed vulvar or vaginal lesions during followup tended to have higher numbers of lifetime and recent (last 6 months) sex partners and also tended to test positive for at least one measured HPV genotype at baseline than women who remained lesion-free.

Women who developed vaginal lesions during followup were more likely to have a Pap abnormality at baseline compared to those with no lesions during followup (LSIL OR = 3.29, 95% CI 1.77, 6.12; HSIL OR = 2.45, 95% CI 0.94, 6.36); however, development of vulvar lesions during followup was not associated with abnormal Pap test results at baseline. (Appendix, Table 1).

By the end of the approximately 4 years of follow-up, 41.2% of women with vulvar lesions and 49.5% of women with vaginal lesions also had cervical lesions, whereas only 6.5% of women with cervical lesions had vaginal or vulvar lesions (**Table 1**). Overall, 10.3% of women with vulvar lesions had vaginal lesions, while 6.5% of women with vaginal lesions also had vulvar lesions. In 47.1% of women who developed vulvar lesions and 53.3% of women who developed vaginal lesions, abnormalities involving cervical and other sites were also present. Women who developed vulvar HSILs had the highest likelihood of having lesions at all 3 genital sites (8.33%). For women with lesions at multiple sites, no consistent pattern in the relative timing of diagnosis was observed.

In total, 72.5% of vulvar LSILs and 91.3% of vulvar HSILs tested positive for ≥1 of the 14 HPV types assayed (**Table 2, Figure 1A**), and coinfections multiple HPV types were present in 24.1% and 45.2% of the HPV-positive LSILs and HSILs, respectively. Using proportional attribution, 87.7% and 89.4% of all HPV-positive vulvar LSILs were attributable to HPV types in the quadrivalent and nonavalent vaccine, respectively. Specifically, 52.0% of all vulvar LSILs and 71.7% of HPV-positive vulvar LSILs were associated with HPV6, predominantly as single-type infections. Overall, 60.0% to 67.5% of vulvar LSILs were linked to nonavalent vaccine types, most (60.0% to 65.0%) of which were quadrivalent vaccine types (**Appendix Figure 1)**.

In vulvar HSILs, HPV16 was the predominant type detected, with proportional attribution rates of 67.9% among all lesions and 74.3% among HPV-positive lesions (**Table 2**). Using multitype adjusted attribution methods, 76.1% to 91.3% of all vulvar HSILs were attributable to nonavalent vaccine types and a smaller proportion (65.2% to 78.3%) to quadrivalent vaccine types, indicating a nontrivial contribution of types 31, 33, 45, 52, and 58 (10.9% to 14.7%) (**Appendix Figure 1**). All HPV-positive vulvar HSILs were attributable to nonavalent vaccine types (**Table 2, Figure 1A**).

In vaginal LSILs (**Table 3**), HPV31, 56, and 16 were the most prevalent types and only HPV33 went undetected. Overall, 61.9% of vaginal LSILs and 72.7% of vaginal HSILs tested positive for ≥1 of the 14 HPV types assayed, with coinfections present in 41.1% and 33.3% of the HPV-positive LSILs and HSILs, respectively (**Figure 1B**). By the proportional method, 3.9% of all vaginal LSILs (6.4% of HPV-positive vaginal LSILs) were attributable to the low-risk types [HPV6 (2.2%) and HPV11 (1.7%)]. Of all HPV-positive vaginal LSILs, 56.0% were attributable to nonavalent vaccine types by the proportional method. Adjusting for coinfections, 27.1% to

43.2% of all vaginal LSILs were attributable to the nonavalent vaccine types and 15.3% to 21.2% to quadrivalent vaccine types, revealing a substantial contribution of types 31, 33, 45, 52, and 58 (11.9% to 22.0%; **Appendix Figure 2)**. An estimated 18.6% to 26.8% of vaginal LSILs were attributable to the nonvaccine types 35, 39, 51, 56, and 59.

The most common HPV type in vaginal HSILs was HPV16, accounting for 32.5% of all lesions and 46.6% of HPV-positive lesions using the proportional method (**Table 3**). Most other HPV types tested were also detected (except 11, 45, and 39), but usually as coinfections with HPV16. For all vaginal HSILs, multitype adjusted attribution estimates ranged from 30.3% to 48.5% for quadrivalent vaccine types, from 12.1% to 21.2% for types 31, 33, 45, 52, and 58 (**Appendix Figure 2**), and from 42.4% to 60.6% for all nonavalent vaccine types. Although nonvaccine HPV types were detected in 30.3% of vaginal HSILs, 60% of these lesions were coinfected with quadrivalent HPV types; therefore, only 12.1% to 15.1% of vaginal HSILs were exclusively attributable to this group (**Table 3, Appendix Figure 2**). Of all HPV-positive vaginal HSILs, 78.3% were attributable to nonavalent vaccine types (**Table 3, Figure 1B**).

The majority of HPV-positive lesions were attributable to types targeted by the nonavalent vaccine using the proportional method, including 89.4% and 100% of vulvar LSILs and HSILs, and 56.0% and 78.3% of vaginal LSILs and HSILs, respectively (**Appendix Table 2**). These estimates compare with 87.7% and 83.9% of vulvar LSILs and HSILs and 25.2% and 57.4% of vaginal LSILs and HSILs, respectively, attributable to the 4 genotypes (6, 11, 16, and 18) in the quadrivalent vaccine. The nonvaccine high-risk types (35, 39, 51, 56, and 59) measured in the quadrivalent vaccine trials were detected in 10.6% of vulvar LSILs, no vulvar HSILs, 44.0% of vaginal LSILs, and 21.7% of vaginal HSILs.

DISCUSSION

We estimated the prevalence of 14 HPV types associated with vulvar and vaginal LSILs and HSILs in young women prospectively randomized in 2 double-blind trials, and determined the proportion of lesions attributable to genotypes covered by current HPV vaccines as well as 5 additional nonvaccine HPV genotypes. In this analysis of 8812 young women, 40 vulvar LSILs and 46 vulvar HSILs were diagnosed in 68 women, and 118 vaginal LSILs and 33 vaginal HSILs were diagnosed in 107 women during approximately 4 years of follow-up. Development of lesions was associated with a history of numerous sexual partners and HPV infection at baseline. Most HPV-positive lesions were attributable to HPV types targeted by the nonavalent vaccine using the proportional attribution method, including 89.4% and 100% of vulvar LSILs and HSILs, and 56.0% and 78.3% of vaginal LSILs and HSILs, respectively. The 5 additional HPV types in the nonavalent vaccine but not in the quadrivalent vaccine were detected in 1.7% of vulvar LSILs, 16.1% of vulvar HSILs, 30.8% of vaginal LSILs, and 20.9% of vaginal HSILs. Nonvaccine HPV types contributed more frequently to vaginal LSIL but less to vaginal HSIL, which is also seen in cervical intraepithelial neoplasia.[25] HPV6 accounted for 71.7% of HPV-positive vulvar LSILs.

Of the 40 vulvar LSILs in our study, 72.5% were positive for ≥1 of the 14 HPV types tested. These findings are consistent with several meta-analyses.[3,4] Applying the proportional method to HPV-positive vulvar LSILs, 89.4% were attributed to nonavalent vaccine types, with only 1.7% attributed to the 5 additional HPV types not in the quadrivalent vaccine. As with previous reports, the most common type in these lesions was HPV6, identified in 71.7% of HPV-positive vulvar LSILs and targeted by the quadrivalent and nonavalent vaccine.

All HPV-positive vulvar HSILs in our study were attributable to genotypes covered by the nonavalent vaccine, including HPV16 found in 74.3% of lesions by the proportional method. Nonvaccine types were unusual and only identified in coinfections with vaccine types. In close agreement with our findings, a multinational, retrospective analysis reported that 88.7% (509/587) of vulvar HSILs were HPV positive, 77.3% of the positive lesions were attributable to HPV16, and 94.2% to nonavalent vaccine types.[1] Both HPV positivity exceeding 80% and the predominance of HPV16 in vulvar HSILs have been observed previously.[3,4] HPV31, closely related to type 16[26], appeared to play a relatively modest role in vulvar HSILs (14.7% in our study using proportional attribution), whereas HPV33 was infrequently detected. In contrast, prior analyses identified HPV33 in vulvar HSILs (7.7%-9.2%), whereas type 31 was rare. Nonavalent HPV types were found in 56.0% of vaginal LSILs in this study, as also observed in cervical intraepithelial neoplasia.[25,27] Other investigators have observed mainly HPV16 associated with vaginal LSILs.[3,4,12] Non-HPV causes of vaginal LSILs may reflect past *in utero* exposure to diethylstilbestrol in women 40 years of age and above.[28,29]

Of the 33 vaginal HSILs in our study, 72.7% tested HPV positive, of which 78.3% were attributable to nonavalent vaccine types by the proportional attribution method. A nearly identical attribution of 79.0% was found in 181 HPV-positive vaginal HSILs from a recent multinational, retrospective survey.[5] In contrast to our findings, most previous reports have identified >90% of vaginal lesions as HPV positive.[30] Differences in assays to detect HPV, variations in the prevalent genotypes, sample storage and handling, age distribution of study participants, sample size, and intra-observer variability in the cytologic or histologic diagnosis may explain some differences across studies.

Approximately 41% and 50% of women with vulvar and vaginal lesions, respectively, also developed cervical lesions in our study, confirming the multifocal nature of anogenital infection and subsequent disease,[31] particularly the association of cervical disease with HPV-related vaginal and vulvar lesions.[32-34] While the coexistence of HPV-related cervical, vulvar, and vaginal cancers and precancerous lesions has not been well studied, a history of cervical cancer or CIN2/3 has been associated with an increased risk of both vulvar and vaginal cancers. About 30% of patients with vaginal cancer had previous premalignant or cancerous cervical lesions.

Our study has several important limitations. This study was a post-hoc, descriptive analysis of clinical trial data; the relatively small number of events can affect the precision of the estimated attribution fractions. Applying 5 attribution approaches may be a better measure of biologic variability as opposed to statistical variability. The ideal approach for measuring attribution is laser-capture microdissection. Because our study was limited to women 15 to 26 years of age, it is possible that older women could differ in HPV type attribution or positivity. Nonetheless, our results were consistent with those reported from recent large multinational studies of vulvar and vaginal HSILs conducted in women over a wider age range with mean (±SD) ages of 50 (±15) years for vulvar HSILs, and 50 (±14) years for vaginal HSILs.[1,2]

Vulvar and vaginal lesions are rare but increasing findings in young women.[7] HPV infections, including vaccine genotypes, cause the majority of genital abnormalities. Widespread adoption of an efficacious prophylactic vaccine has the potential to prevent a substantial fraction of HPV-related vulvar and vaginal lesions in addition to preventing the majority of cervical lesions.[20,21,24,35,36]

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Figure Legends

Figure 1. Vulvar or vaginal lesion attribution in women aged 15 to 26 years to nonavalent vaccine types (6/11, 16/18, and 31/33/45/52/58) and high-risk nonvaccine types (35/39/51/56/59). (A) Left panel: Based on the proportional attribution method. Percentage of all HPV-positive vulvar LSILs attributable to quadrivalent and nonavalent vaccine types were measured respectively. Denominator includes all lesions (n = 40 for vulvar LSILs and n = 46 for vulvar HSILs). Right panel: Using multitype adjusted attribution methods, percentage of all vulvar LSIL and HSILs attributable to all HPV vaccine types. Denominator includes HPV-positive lesions (n = 29 for vulvar LSILs and n = 42 for vulvar HSILs). (B) Left panel: Based on the proportional attribution method. Denominator includes all lesions (n = 118 for vaginal LSILs and n = 33 for vaginal HSILs). Right panel: Using multitype adjusted attribution methods, percentage of all vaginal LSILs and HSILs attributable to HPV genotypes. Denominator includes HPV-positive lesions only (n = 72 for vaginal LSILs and n = 23 for vaginal HSILs).

Appendix Figure 1. Vulvar low- and high-grade squamous intraepithelial lesions attributable to nonavalent vaccine, quadrivalent vaccine, and nonvaccine types. Percent of vulvar disease in women aged 15 to 26 years attributed to HPV type groups using 5 attribution methods. Single: Includes lesions with single-type infections only. Exclusive: Lesions attributed to the indicated HPV type group only in the absence of mixed DNA coinfection with other HPV type groups (this fraction includes coinfections between types 6/11/16/18 and 31/33/45/52/58). Proportional: Coinfected lesions allocated proportionally to the relative distribution of HPV types in lesions infected with single HPV types. Hierarchical: Lesions allocated first to group 6/11/16/18, then to 31/33/45/52/58, and then to 35/39/51/56/59. Any: Includes any lesion in which a respective HPV type was present, regardless of coinfection with other types. Denominators include all lesions (HPV positive and negative). Color highlight estimates derived from multitype adjusted attribution method.

Appendix Figure 2. Vaginal low- and high-grade squamous intraepithelial lesions attributable to nonavalent vaccine, quadrivalent vaccine, and nonvaccine types. Percent of vulvar disease in women aged 15 to 26 years attributed to HPV type groups using 5 attribution methods. Single: Includes lesions with single-type infections only. Exclusive: Lesions attributed to the indicated HPV type group only in the absence of mixed DNA coinfection with other HPV type groups (this fraction includes coinfections between types 6/11/16/18 and 31/33/45/52/58). Proportional: Coinfected lesions allocated proportionally to the relative distribution of HPV types in lesions infected with single HPV types. Hierarchical: Lesions allocated first to group 6/11/16/18, then to 31/33/45/52/58, and then to 35/39/51/56/59. Any: Includes any lesion in which a respective HPV type was present, regardless of coinfection with other types. Denominators include all

437 lesions (HPV positive and negative). Color highlight estimates derived from multitype adjusted
438 attribution method.
439
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450

451 **Table 1. Proportions[a] of young women who developed lesions at multiple sites (cervical, vulvar, or vaginal) during follow-up.**

	Subset with cervical lesions			Subset with vulvar lesions			Subset with vaginal lesions			With lesion at any other site	With lesion at both other sites
	Any cervical n (%)	LSIL n (%)	HSIL n (%)	Any vulvar n (%)	LSIL n (%)	HSIL n (%)	Any vaginal n (%)	LSIL n (%)	HSIL n (%)	n (%)	n (%)
Cervical lesions											
Any (N = 1201)	--	--	--	28 (2.33)	13 (1.08)	15 (1.25)	53 (4.41)	41 (3.41)	12 (1.00)	78 (6.49)	3 (0.25)
LSIL (N = 677)	--	--	--	16 (2.36)	8 (1.18)	8 (1.18)	36 (5.32)	28 (4.14)	8 (1.18)	50 (7.39)	2 (0.30)
HSIL (N = 524)	--	--	--	12 (2.29)	5 (0.95)	7 (1.34)	17 (3.24)	13 (2.48)	4 (0.76)	28 (5.34)	1 (0.19)
Vulvar lesions											
Any (N = 68)	28 (41.18)	16 (23.53)	12 (17.65)	--	--	--	7 (10.29)	4 (5.88)	3 (4.41)	32 (47.06)	3 (4.41)
LSIL (N = 32)	13 (40.63)	8 (25.00)	5 (15.63)	--	--	--	3 (9.38)	1 (3.13)	2 (6.25)	16 (50.00)	--
HSIL (N = 36)	15 (41.67)	8 (22.22)	7 (19.44)	--	--	--	4 (11.11)	3 (8.33)	1 (2.78)	16 (44.44)	3 (8.33)
Vaginal lesions											
Any (N = 107)	53 (49.53)	36 (33.64)	17 (15.89)	7 (6.54)	3 (2.80)	4 (3.74)	--	--	--	57 (53.27)	3 (2.80)
LSIL (N = 81)	41 (50.62)	28 (34.57)	13 (16.05)	4 (4.94)	1 (1.23)	3 (3.70)	--	--	--	43 (53.09)	2 (2.47)
HSIL (N = 26)	12 (46.15)	8 (30.77)	4 (15.38)	3 (11.54)	2 (7.69)	1 (3.85)	--	--	--	14 (53.85)	1 (3.85)

452 N,total number of women who developed the lesion type specified in the rows during the follow-up.

453 n, number of women with a specified lesion type in each row) who also developed the lesion type indicated in the columns.

454 [a]Percent (%) calculated as n/N x 100.

455

456 **Table 2. Type-specific prevalence and proportional attribution of HPV genotypes in vulvar lesions among young women.**

HPV type(s) tested	Vulvar LSIL						Vulvar HSIL					
	All lesions in denominator (N = 40)			Only HPV-positive lesions in denominator (N = 29)			All lesions in denominator (N = 46)			Only HPV-positive lesions in denominator (N = 42)		
	Any[a] n (%)	Single[b] n (%)	Prop[c] n (%)	Any[a] n (%)	Single[b] n (%)	Prop[c] n (%)	Any[a] n (%)	Single[b] n (%)	Prop[c] n (%)	Any[a] n (%)	Single[b] n (%)	Prop[c] n (%)
6	21 (52.5)	17 (42.5)	20.8 (52.0)	21 (72.4)	17 (58.6)	20.8 (71.7)	8 (17.4)	3 (6.5)	4.03 (8.8)	8 (19.0)	3 (7.1)	4.03 (9.6)
11	3 (7.5)	1 (2.5)	1.6 (3.9)	3 (10.3)	1 (3.4)	1.6 (5.4)	2 (4.3)	0 (0.0)	0.0 (0.0)	2 (4.8)	0 (0.0)	0.0 (0.0)
16	4 (10.0)	2 (5.0)	3.1 (7.8)	4 (13.8)	2 (6.9)	3.1 (10.7)	32 (69.6)	16 (34.8)	31.2 (67.9)	32 (76.2)	16 (38.1)	31.2(74.3)
18	0 (0.0)	0 (0.0)	0.0 (0.0)	0 (0.0)	0 (0.0)	0.0 (0.0)	1 (2.2)	0 (0.0)	0.0 (0.0)	1 (2.4)	0 (0.0)	0.0 (0.0)
31	1 (2.5)	0 (0.0)	0.5 (1.3)	1 (3.4)	0 (0.0)	0.5 (1.7)	8 (17.4)	4 (8.7)	6.8 (14.7)	8 (19.0)	4 (9.5)	6.8 (16.1)
33	0 (0.0)	0 (0.0)	0.0 (0.0)	0 (0.0)	0 (0.0)	0.0 (0.0)	2 (4.3)	0 (0.0)	0.0 (0.0)	2 (4.8)	0 (0.0)	0.0 (0.0)
45	0 (0.0)	0 (0.0)	0.0 (0.0)	0 (0.0)	0 (0.0)	0.0 (0.0)	0 (0.0)	0 (0.0)	0.0 (0.0)	0 (0.0)	0 (0.0)	0.0 (0.0)
52	2 (5.0)	0 (0.0)	0.0 (0.0)	2 (6.9)	0 (0.0)	0.0 (0.0)	2 (4.3)	0 (0.0)	0.0 (0.0)	2 (4.8)	0 (0.0)	0.0 (0.0)
58	0 (0.0)	0 (0.0)	0.0 (0.0)	0 (0.0)	0 (0.0)	0.0 (0.0)	2 (4.3)	0 (0.0)	0.0 (0.0)	2 (4.8)	0 (0.0)	0.0 (0.0)
35	0 (0.0)	0 (0.0)	0.0 (0.0)	0 (0.0)	0 (0.0)	0.0 (0.0)	0 (0.0)	0 (0.0)	0.0 (0.0)	0 (0.0)	0 (0.0)	0.0 (0.0)
39	3 (7.5)	1 (2.5)	1.6 (3.9)	3 (10.3)	1 (3.4)	1.6 (5.4)	0 (0.0)	0 (0.0)	0.0 (0.0)	0 (0.0)	0 (0.0)	0.0 (0.0)
51	1 (2.5)	0 (0.0)	0.5 (1.3)	1 (3.4)	0 (0.0)	0.5 (1.7)	1 (2.2)	0 (0.0)	0.0 (0.0)	1 (2.4)	0 (0.0)	0.0 (0.0)
56	1 (2.5)	1 (2.5)	1.0 (2.5)	1 (3.4)	1 (3.4)	1.0 (3.4)	6 (13.0)	0 (0.0)	0.0 (0.0)	6 (14.3)	0 (0.0)	0.0 (0.0)
59	1 (2.5)	0 (0.0)	0.0 (0.0)	1 (3.4)	0 (0.0)	0.0 (0.0)	2 (4.3)	0 (0.0)	0.0 (0.0)	2 (4.8)	0 (0.0)	0.0 (0.0)
6/11/16/18	--	--	25.4 (63.6)	--	--	25.4 (87.7)	--	--	35.2 (76.6)	--	--	35.2 (83.9)
31/33/45/52/58	--	--	0.5 (1.3)	--	--	0.5 (1.7)	--	--	6.8 (14.7)	--	--	6.8 (16.1)
6/11/16/18/31/33/45/52/58	--	--	25.9 (64.9)	--	--	25.9 (89.4)	--	--	42.0 (91.3)	--	--	42.0 (100)
35/39/51/56/59	--	--	3.1 (7.7)	--	--	3.1 (10.6)	--	--	0 (0.0)	--	--	0 (0.0)

457 N/n = number of women with indicated lesion types.

458 [a]Number (percent) of all lesions testing positive for the respective HPV type, regardless of coinfections.

459 [b]Number (percent) of lesions testing positive for the respective HPV type only, excluding coinfections.

460 [c]Number (percent) of lesions attributable to the respective HPV type, as determined applying the proportional attribution method.

461

462 **Table 3. Type-specific prevalence and proportional attribution of HPV genotypes in vaginal lesions among young women.**

HPV type(s) tested	Vaginal LSIL						Vaginal HSIL					
	All lesions in denominator (N = 118)			Only HPV-positive lesions in denominator (N = 73[a])			All lesions in denominator (N = 33)			Only HPV-positive lesions in denominator (N = 24[a])		
	Any[b] n (%)	Single[c] n (%)	Prop[d] n (%)	Any[b] n (%)	Single[c] n (%)	Prop[d] n (%)	Any[b] n (%)	Single[c] n (%)	Prop[d] n (%)	Any[b] n (%)	Single[c] n (%)	Prop[d] n (%)
6	4 (3.4)	2 (1.7)	2.6 (2.2)	4 (5.5)	2 (2.7)	2.6 (3.6)	1 (3.0)	1 (3.0)	1.0 (3.0)	1 (4.2)	1 (4.2)	1.0 (4.3)
11	4 (3.4)	1 (0.8)	2.0 (1.7)	4 (5.5)	1 (1.4)	2.0 (2.7)	0 (0.0)	0 (0.0)	0.0 (0.0)	0 (0.0)	0 (0.0)	0.0 (0.0)
16	14 (11.9)	6 (5.1)	9.5 (8.1)	14 (19.2)	6 (8.2)	9.5 (13.2)	13 (39.4)	6 (18.2)	10.7 (32.5)	13 (54.2)	6 (25.0)	10.7 (46.6)
18	7 (5.9)	2 (1.7)	4.0 (3.4)	7 (9.6)	2 (2.7)	4.0 (5.6)	2 (6.1)	1 (3.0)	1.5 (4.5)	2 (8.3)	1 (4.2)	1.5 (6.5)
31	18 (15.3)	9 (7.6)	14.7 (12.4)	18 (24.7)	9 (12.3)	14.7 (20.4)	2 (6.1)	1 (3.0)	1.5 (4.5)	2 (8.3)	1 (4.2)	1.5 (6.5)
33	0 (0.0)	0 (0.0)	0.0 (0.0)	0 (0.0)	0 (0.0)	0.0 (0.0)	3 (9.1)	1 (3.0)	1.3 (4.0)	3 (12.5)	1 (4.2)	1.3 (5.7)
45	3 (2.5)	2 (1.7)	2.5 (2.1)	3 (4.1)	2 (2.7)	2.5 (3.5)	0 (0.0)	0 (0.0)	0.0 (0.0)	0 (0.0)	0 (0.0)	0.0 (0.0)
52	13 (11.0)	1 (0.8)	3.3 (2.8)	13 (17.8)	1 (1.4)	3.3 (4.6)	1 (3.0)	1 (3.0)	1.0 (3.0)	1 (4.2)	1 (4.2)	1.0 (4.3)
58	5 (4.2)	1 (0.8)	1.7 (1.4)	5 (6.8)	1 (1.4)	1.7 (2.4)	1 (3.0)	1 (3.0)	1.0 (3.0)	1 (4.2)	1 (4.2)	1.0 (4.3)
35	1 (0.8)	0 (0.0)	0.0 (0.0)	1 (1.4)	0 (0.0)	0.0 (0.0)	2 (6.1)	1 (3.0)	1.2 (3.5)	2 (8.3)	1 (4.2)	1.2 (5.1)
39	8 (6.8)	5 (4.2)	6.4 (5.4)	8 (11.0)	5 (6.8)	6.4 (8.9)	0 (0.0)	0 (0.0)	0.0 (0.0)	0 (0.0)	0 (0.0)	0.0 (0.0)
51	12 (10.2)	2 (1.7)	5.3 (4.5)	12 (16.4)	2 (2.7)	5.3 (7.4)	2 (6.1)	1 (3.0)	1.2 (3.5)	2 (8.3)	1 (4.2)	1.2 (5.1)
56	15 (12.7)	7 (5.9)	12.0 (10.2)	15 (20.5)	7 (9.6)	12.0 (16.7)	5 (15.2)	1 (3.0)	1.6 (5.0)	5 (20.8)	1 (4.2)	1.6 (7.1)
59	11 (9.3)	5 (4.2)	7.9 (6.7)	11 (15.1)	5 (6.8)	7.9 (10.9)	1 (3.0)	1 (3.0)	1.0 (3.0)	1 (4.2)	1 (4.2)	1.0 (4.3)
6/11/16/18	--	--	18.1 (15.4)	--	--	18.1 (25.2)	--	--	13.2 (40.0)	--	--	13.2 (57.4)
31/33/45/52/58	--	--	22.2 (18.8)	--	--	22.2 (30.8)	--	--	4.8 (14.6)	--	--	4.8 (20.9)
6/11/16/18/31/ 33/45/52/58	--	--	40.4 (34.2)	--	--	40.4 (56.0)	--	--	18.0 (54.6)	--	--	18.0 (78.3)
35/39/51/56/59	--	--	31.7 (26.8)	--	--	31.7 (44.0)	--	--	5.0 (15.1)	--	--	5.0 (21.7)

463 N/n = number of women with indicated lesion types.

464 [a]Due to incomplete data for 2 lesions (1 LSIL and 1 HSIL), these 2 cases were excluded from the proportional attribution analyses; therefore, the denominator is
465 72 for LSILs and 23 for HSILs.

466 [b]Number (percent) of all lesions testing positive for the respective HPV type, regardless of coinfections.

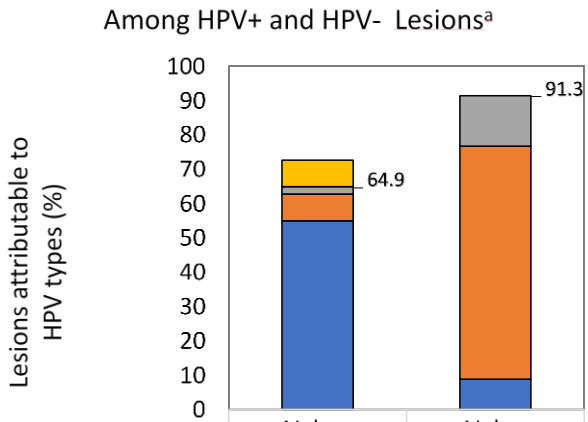
467 [c]Number (percent) of lesions testing positive for the respective HPV type only, excluding coinfections.

468 [d]Number (percent) of lesions attributable to the respective HPV type, as determined applying the proportional attribution method.

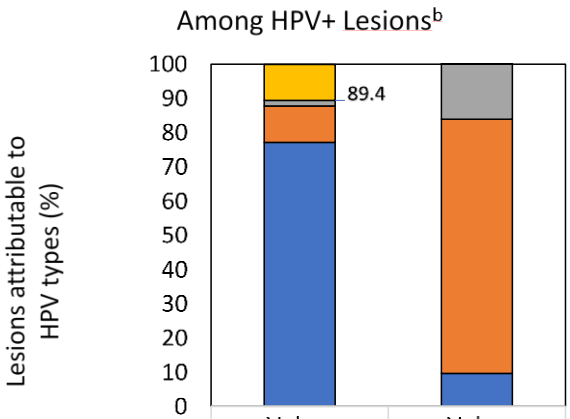
469

470 **Figure 1.**

A



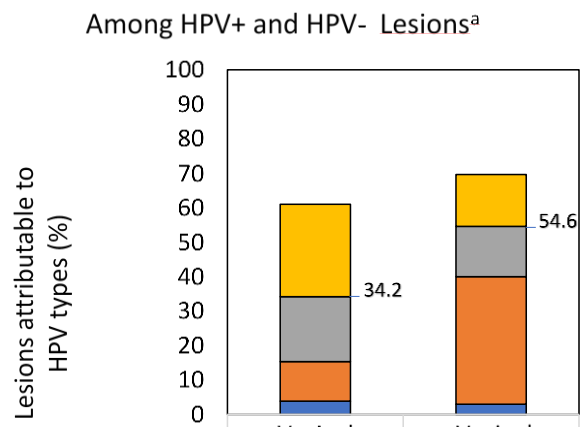
	Vulvar LSIL	Vulvar HSIL
35/39/51/56/59	7.7	0
31/33/45/52/58	2.1	14.7
16/18	7.8	67.9
6/11	55	8.8



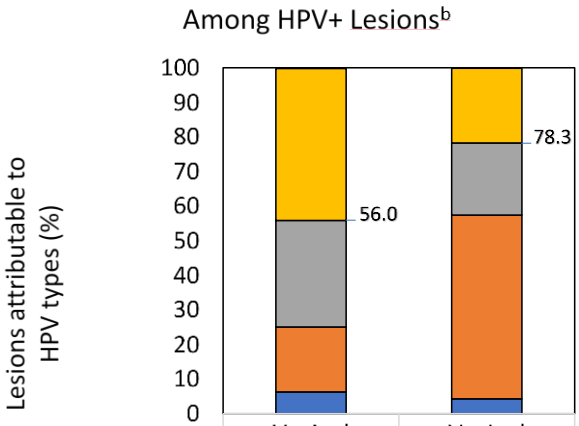
	Vulvar LSIL	Vulvar HSIL
35/39/51/56/59	10.5	0.3
31/33/45/52/58	1.6	16.1
16/18	10.7	74.3
6/11	77.1	9.6

471

B



	Vaginal LSIL	Vaginal HSIL
35/39/51/56/59	26.8	15
31/33/45/52/58	18.8	14.6
16/18	11.5	37
6/11	3.9	3



	Vaginal LSIL	Vaginal HSIL
35/39/51/56/59	43.9	21.6
31/33/45/52/58	30.8	20.9
16/18	18.8	53.1
6/11	6.3	4.3

[a]Based on proportional attribution method. Denominator includes all lesions.

[b]Using multiple-type adjusted attribution methods. Denominator includes HPV-positive lesions.

472

Appendix 1. Potential Conflicts of Interests

All academic authors have been investigators for Merck & Co., Inc., Kenilworth, NJ, USA.

Suzanne M. Garland reports having received funding through her institution to perform HPV vaccine studies for Merck & Co., Inc., CSL Limited, and GlaxoSmithKline; received payment for board membership on the Merck Global Advisory Board; and received honoraria for lectures including services on a speakers' bureau conducted during her personal time; she also serves as co-chair of the PATRICIA publication steering committee.

Kevin A. Ault reports having received grants to his institution from Merck & Co., Inc. and the National Institutes of Health, and advisory committee fees from the American College of Obstetricians and Gynecologists. He also serves on the editorial board for the National Cancer Institute (USA).

Xavier Bosch reports having received institutional research and educational grants from Sanofi Pasteur MSD and GlaxoSmithKline and personal travel grant and speaker's honorarium from Sanofi Pasteur MSD and GlaxoSmithKline.

Darron R. Brown has served on an advisory board at Merck & Co., Inc. and has lectured on the quadrivalent HPV vaccine (honoraria received from Merck & Co., Inc. are donated to charities). His laboratory has received research funding from Merck & Co., Inc. Indiana University and Merck &Co., Inc. have an agreement that pays the university, based on certain landmarks related to vaccine development. Darron Brown receives a portion of these funds as income.

Xavier Castellsagué (deceased) had reported receiving institutional research and educational grants from Sanofi Pasteur MSD, Merck & Co., Inc., GlaxoSmithKline, and Genticel, and occasional personal travel grant and speaker's honorarium from Sanofi Pasteur MSD and Vianex.

Alex Ferenczy reports being a member of Pathology Panel for Merck & Co., Inc. randomized controlled vaccine trials.

Daron G. Ferris reports having received grants to his institution and lecture fees from Merck Sharp & Dohme, a subsidiary of Merck & Co., Inc., and advisory board and consultant fees from Merck & Co., Inc.

Elmar A. Joura reports having received grant support paid to his institution from Merck & Co., Inc. and GlaxoSmithKline; advisory board fees from Merck & Co., Inc. and Sanofi Pasteur MSD, and lecture fees from Sanofi Pasteur MSD, Merck & Co., Inc., GlaxoSmithKline, and Roche.

Anna R. Giuliano reports having received grant support and advisory board member fees to her institution from Merck & Co., Inc.

Mauricio Hernandez-Avila reports nothing to disclose.

Warner K. Huh reports having received honoraria for advisory board participation with Merck & Co., Inc.

Ole-Erik Iversen reports having received compensation from Merck & Co., Inc. and GlaxoSmithKline to conduct vaccine clinical trials as well as scientific advisory board fees from Merck & Co., Inc.

Susanne K. Kjaer reports having received scientific advisory board and speaker's fees from Sanofi Pasteur MSD and Merck & Co., Inc., and unrestricted research grants through her institution from Merck & Co., Inc., and scientific advisory board fees from Becton Dickinson.

Robert J. Kurman reports being a member of the Pathology Panel for Merck & Co., Inc. randomized controlled vaccine trials.

Joaquin Luna reports nothing to disclose.

Joseph Monsonego reports having received an honorarium as a member of the scientific advisory board of Sanofi Pasteur MSD, Merck & Co., Inc., Roche Diagnostics, Genprobe, and Genticel, and compensation from Merck & Co., Inc. and GlaxoSmithKline to conduct vaccine trials.

Nubia Muñoz reports having received an honorarium from Merck & Co., Inc. for being a member of the HPV Global Advisory Board.

Jorma Paavonen reports having received research funding from Merck & Co., Inc. and GlaxoSmithKline through his institution.

Punnee Pitisuttihum reports having received research funding from Merck & Co., Inc. through her institution.

Brigitte M. Ronnett reports consulting for Merck & Co., Inc as a member of the Pathology Panel for Merck & Co., Inc. randomized controlled vaccine trials.

Marc Steben reports having received grants and personal fees from Merck & Co., Inc., BD Diagnostics, Hologic/Gen-Probe, Roche Diagnostics, and Valeant as well as personal fees from Cepheid, Inovio, and Paladin.

Mark H. Stoler has served or is serving as a consultant in clinical trial design and as an expert pathologist for HPV vaccine and diagnostic trials for Roche, Ventana Medical Systems, Hologic/Gen-Probe, Becton Dickinson, Cepheid, Qiagen, Inovio, and Merck & Co., Inc.

Cosette M. Wheeler reports having received equipment and reagents for HPV genotyping from Roche Molecular Systems and contracts for HPV vaccine studies from GlaxoSmithKline and Merck & Co., Inc. through her institution, the University of New Mexico.

Monika Wagner is a senior consultant with LASER Analytica, contracted to participate in the analysis, design, and reporting of study findings.

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Appendix 2. Attribution approaches used in the sensitivity methods

Single-type attribution included only lesions in which a single HPV type was detected, yielding a minimum estimate of attribution. **Multitype: exclusive**-group attribution included only lesions in which the HPV types belonging to a prespecified group were detected, whether as mono- or coinfection, in the absence of HPV types included in other groupings, yielding the lowest estimate of attribution for a group of HPV types. For the **hierarchical** attribution estimate, lesions were first attributed to quadrivalent vaccine types regardless of coinfections. The remaining HPV-positive lesions were then stepwise attributed to the additional nonavalent vaccine types, followed by the remainder to the nonvaccine high-risk types. For the final group in this hierarchy, hierarchical and exclusive-group estimates become identical. The estimation of **any**-type attribution was calculated by including in the numerator any lesion in which a given HPV type was present, regardless of coinfection with other types, generating a maximum estimate of attribution.

556 **Appendix Table 1. Baseline characteristics of young women with no cervical or genital lesions during follow-up and young women**
557 **who developed vulvar or vaginal lesions.[a]**

	No cervical or genital lesions (N = 7294)	Women who developed vulvar lesions (N = 68)				Women who developed vaginal lesions (N = 107)			
		Vulvar LSIL (n = 32)		Vulvar HSIL (n = 36)		Vaginal LSIL (n = 81)		Vaginal HSIL (n = 26)	
Age, mean ± SD	20.1 ± 2.0	19.2 ± 2.0		19.6 ± 2.1		19.6 ± 2.2		19.6 ± 1.9	
	n (%)	n (%)	Age-adjusted OR (95% CI)[b]	n (%)	Age-adjusted OR (95% CI)[b]	n (%)	Age-adjusted OR (95% CI)[b]	n (%)	Age-adjusted OR (95% CI)[b]
Lifetime number of sex partners									
1	2486 (36.6)	9 (30.0)	1.00	10 (27.8)	1.00	17 (23.0)	1.00	6 (24.0)	1.00
2-3	3107 (45.7)	13 (43.3)	1.20 (0.49, 2.94)	18 (50.0)	1.51 (0.66, 3.45)	39 (52.7)	2.04 (1.11, 3.76)	17 (68.0)	2.58 (1.00, 6.63)
≥4	1201 (17.7)	8 (26.7)	1.17 (0.42, 3.31)	8 (22.2)	1.39 (0.53, 3.62)	18 (24.3)	1.95 (0.97, 3.92)	2 (8.0)	0.49 (0.10, 2.47)
Number of new sex partners in past 6 months									
0	4848 (71.4)	19 (63.3)	1.00	20 (55.6)	1.00	39 (52.7)	1.00	12 (48.0)	1.00
1	1672 (24.6)	7 (23.3)	0.64 (0.25, 1.67)	10 (27.8)	1.73 (0.78, 3.85)	28 (37.8)	2.02 (1.19, 3.44)	9 (36.0)	1.48 (0.61, 3.58)
≥2	275 (4.1)	4 (13.4)	1.04 (0.28, 3.85)	6 (16.7)	3.01 (0.93, 9.79)	7 (9.5)	2.44 (0.94, 6.35)	4 (16.0)	3.59 (1.03, 12.54)
Pap results at study entry									
Negative	6476 (91.6)	28 (93.3)	1.00	32 (94.1)	1.00	62 (77.5)	1.00	19 (76.0)	1.00
ASC-US or worse	594 (8.4)	2 (6.7)	0.83 (0.18, 3.81)	2 (5.9)	1.11 (0.30, 4.05)	18 (22.5)	3.29 (1.77, 6.12)	6 (24.0)	2.45 (0.94, 6.36)
Baseline HPV anogenital infection[c]									
6/11	263 (3.6)	4 (12.5)	2.51 (0.74, 8.49)	4 (11.1)	3.51 (1.19, 10.32)	6 (7.4)	1.84 (0.75, 4.51)	3 (11.5)	3.24 (1.04, 10.10)
16/18	672 (9.2)	5 (15.6)	1.64 (0.57, 4.74)	4 (11.1)	1.65 (0.62, 4.41)	16 (19.8)	2.08 (1.13, 3.85)	4 (15.4)	1.53 (0.56, 4.19)
6/11/16/18	863 (11.8)	8 (25.0)	2.04 (0.83, 5.03)	7 (19.4)	2.18 (0.95, 5.01)	19 (23.5)	2.04 (1.16, 3.58)	5 (19.2)	1.43 (0.56, 3.65)
31/33/45/52/58 no 6/11/16/18	602 (8.3)	3 (9.4)	0.85 (0.24, 3.03)	5 (13.9)	1.89 (0.70, 5.11)	14 (17.3)	2.30 (1.20, 4.42)	5 (19.2)	1.97 (0.71, 5.40)
35/39/51/56/59	1162 (15.9)	6 (18.8)	1.08 (0.42, 2.81)	6 (16.7)	0.90 (0.35, 2.30)	29 (35.8)	2.61 (1.56, 4.38)	5 (19.2)	0.85 (0.32, 2.30)
16/18/31/33/45/52/58	1333 (18.3)	8 (25.0)	1.09 (0.46, 2.57)	12 (33.3)	2.88 (1.39, 5.95)	32 (39.5)	2.80 (1.71, 4.60)	10 (38.5)	2.08 (0.95, 4.56)
6/11/16/18/31/33/45/52/58	1465 (20.1)	11 (34.4)	1.56 (0.71, 3.45)	12 (33.3)	2.39 (1.17, 4.90)	33 (40.7)	2.56 (1.57, 4.18)	10 (38.5)	1.84 (0.84, 4.02)

[a]Women with only cervical lesions without vulvar or vaginal lesions are not shown in the table. Only highest-grade lesions are reported.

[b]Age-adjusted OR (95% CI) calculated using a case-control design with all cases and control group (5 controls per case) randomly sampled from women without cervical or genital lesions after follow-up.

[c]The reference groups of these analyses are the women who are negative to the HPV types tested in the particular analysis (eg, the reference group for women infected with HPV6/11 at baseline is the rest of women negative to HPV6/11.

ASC-US, atypical squamous cells of undetermined significance; n, number of the specified lesion type in the subset of women; N, number of women who developed the specified lesion type during the follow-up

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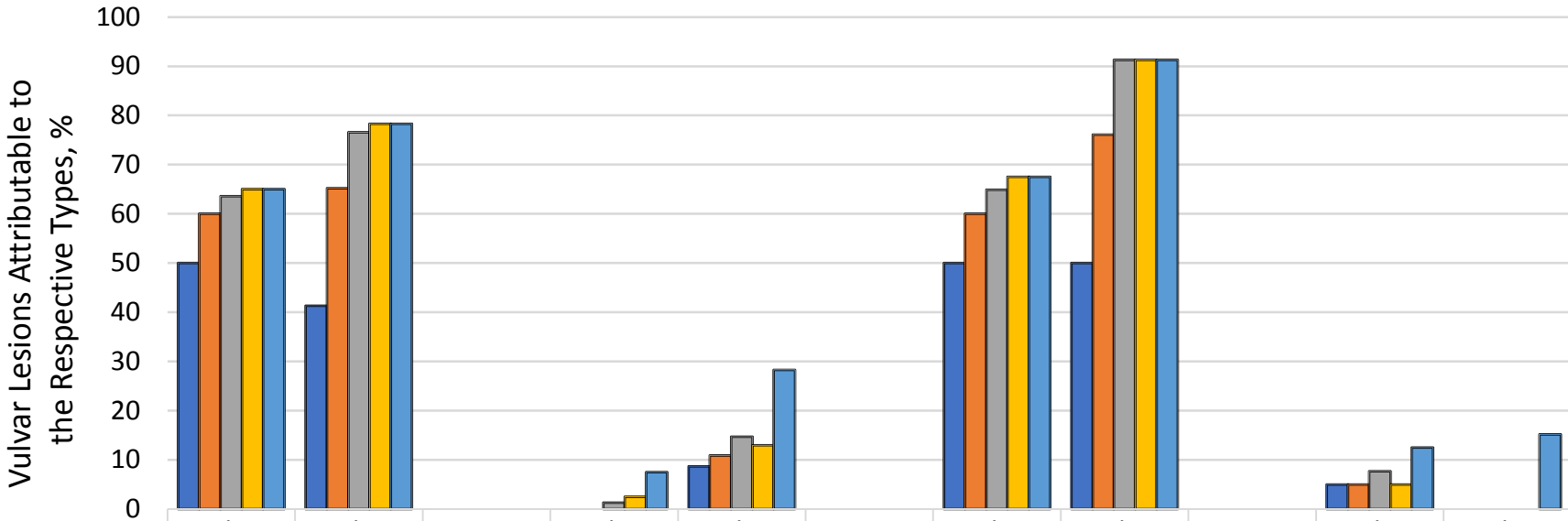
559 **Appendix Table 2. Proportion of potentially preventable HPV-related[a] vaginal or vulvar lesions by the 3 most commonly used**
560 **vaccines (assessed by the proportional attribution method).**

Vaccine		Bivalent vaccine (%)	Quadrivalent vaccine (%)	Nonavalent vaccine (%)	Incremental gain in HPV type-specific coverage with the 9-valent vaccine versus the quadrivalent vaccine (%)	None[b] (%)
Targeted HPV genotypes[a]		16/18	6/11/16/18	6/11/16/18/31/33/45/ 52/58	31/33/45/52/58	35/39/51/56/59
Vaginal	LSIL	18.8	25.2	56.0	30.8	44.0
	HSIL	53.1	57.4	78.3	20.9	21.7
Vulvar	LSIL	10.7	87.7	89.4	1.7	10.6
	HSIL	74.3	83.9	≤100.0	16.1	0.0

[a]A total of 14 HPV types were assessed. Some lesions not categorized as HPV-related could have been caused by other HPV types for which genotyping was not performed. Other nonassayed HPV types could have also been present in the lesions categorized in this analysis as HPV-related. The 12 high-risk HPV types in the assay are among the most commonly detected HPV types in lesions.

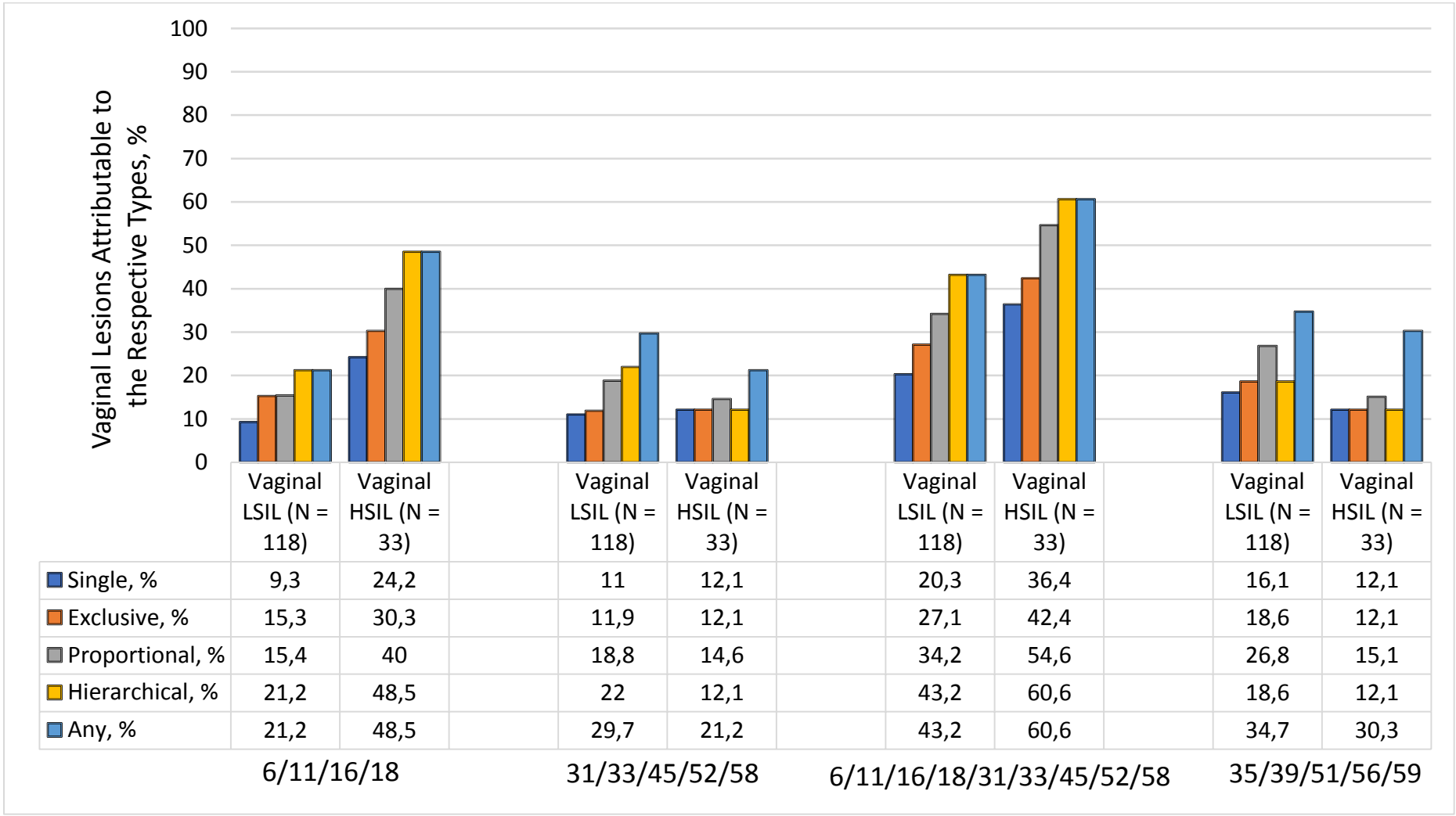
[b]Not covered by any of the 3 vaccines in widespread use.

Appendix Figure 1.



	Vulvar LSIL (N=40)	Vulvar HSIL (N=46)	Vulvar LSIL (N=40)	Vulvar HSIL (N=46)	Vulvar LSIL (N=40)	Vulvar HSIL (N=46)	Vulvar LSIL (N=40)	Vulvar HSIL (N=46)
Single, %	50	41,3	0	8,7	50	50	5	0
Exclusive, %	60	65,2	0	10,9	60	76,1	5	0
Proportional, %	63,6	76,6	1,3	14,7	64,9	91,3	7,7	0
Hierarchical, %	65	78,3	2,5	13	67,5	91,3	5	0
Any, %	65	78,3	7,5	28,3	67,5	91,3	12,5	15,2
	6/11/16/18		31/33/45/52/58		6/11/16/18/31/33/45/52/58		35/39/51/56/59	

Appendix Figure 2.



	Vaginal LSIL (N = 118)	Vaginal HSIL (N = 33)	Vaginal LSIL (N = 118)	Vaginal HSIL (N = 33)	Vaginal LSIL (N = 118)	Vaginal HSIL (N = 33)	Vaginal LSIL (N = 118)	Vaginal HSIL (N = 33)
Single, %	9,3	24,2	11	12,1	20,3	36,4	16,1	12,1
Exclusive, %	15,3	30,3	11,9	12,1	27,1	42,4	18,6	12,1
Proportional, %	15,4	40	18,8	14,6	34,2	54,6	26,8	15,1
Hierarchical, %	21,2	48,5	22	12,1	43,2	60,6	18,6	12,1
Any, %	21,2	48,5	29,7	21,2	43,2	60,6	34,7	30,3
	6/11/16/18		31/33/45/52/58		6/11/16/18/31/33/45/52/58		35/39/51/56/59	

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