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Cervical Infection With Vaccine-Associated Human Papillomavirus (HPV) Genotypes as a Predictor of Acquisition and Clearance of Other HPV Infections

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Background. Recent birth cohorts vaccinated against human papillomavirus (HPV) may be protected against up to 4 genotypes (HPV-6, -11, -16, and -18). If natural competition exists between these and other HPV types, then the prevalence of other types may increase after vaccination.

Methods. Cohort information from 3 studies was used to compare acquisition and clearance of 30 different HPV types (individually and grouped by species), according to infection status with vaccine-targeted types at baseline and the time of the index infection, respectively. Hazard ratios (HRs) were adjusted for predictors of multiple-type infection.

Results. Among 3200 females across all studies, 857 were infected with HPV at baseline, and 994 acquired new infections during follow-up. Females infected with HPV-16 were at higher risk of acquiring other α-9 HPV types (HR, 1.9; 95% confidence interval [CI], 1.2–3.0) but at similar risk of clearing existing α-9 HPV infections (HR, 0.9; 95% CI, .7–1.3). Females infected with vaccine-targeted types were generally at higher risk of acquiring additional types (HRs, > 1.0) and at equal risk of clearing existing infections. Accounting for multiple comparisons, none of the HRs of < 1.0 or >1.0 were statistically significant in our analyses of acquisition or clearance.

Conclusions. Vaccine-targeted HPV types do not appear to compete with other types, suggesting that HPV type replacement is unlikely to occur.

Keywords. human papillomavirus; vaccination; type replacement; type competition; females.

The discovery that invasive cervical cancer is caused by human papillomavirus (HPV) led to the development of 2 vaccines targeting the HPV types responsible for approximately 70% of cervical cancer cases worldwide (ie, HPV-16 and HPV-18) [1, 2]. One of these vaccines offers additional protection against HPV-6 and HPV-11, which are responsible for approximately 90% of genital warts cases [2]. But the possibility that other oncogenic HPV types may increase in prevalence following a decline in vaccine-targeted types (ie, that they will take over the ecological niche vacated by these types) remains an important concern [3]. This concept is referred to as "type replacement" [4].

HPVs are DNA viruses and are extremely stable genetically. If the hypothesis of biologic type replacement were to be true, then different HPV types must compete with one another during natural infection. Recently, we described a number of epidemiologic approaches to evaluate whether HPV type competition exists in prevaccinated cohorts, to provide insight regarding the likelihood of type replacement after introduction of vaccination [4]. One of these approaches involves the evaluation of sequential acquisition or clearance of HPV types according to infection with vaccine-targeted types; however, this approach has not been used to evaluate the potential for type replacement in females. A number of studies have evaluated the natural history and clustering patterns of HPV to determine whether acquisition or persistence varies according to infection with other types [5–11]. None of them provided evidence of HPV type competition; they all found that prior HPV infection was associated with an increased risk of acquiring additional types during follow-up, suggesting possible synergistic interactions or perhaps residual confounding due to incomplete adjustment for sexual behaviors that pose risk for acquisition.

Recently, Rositch et al [11] compared acquisition of HPV according to baseline infection status with relevant vaccine-targeted HPV types in a population of Kenyan males and found no evidence of HPV type competition. Since the natural history of HPV infection differs between males and females [12], we decided to evaluate the times to acquisition and clearance of different HPV types (individually, and grouped according

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to species) among females who were and those who were not infected with vaccine-targeted HPV types at baseline or the time of their index infection.

METHODS

Study Population and HPV DNA Detection

Subject information for the current analysis came from 3 cohort studies conducted by our McGill division: the Ludwig-McGill, McGill-Concordia, and HPV Infection and Transmission Among Couples Through Heterosexual Activity (HITCH) cohort studies. The design and methods for these studies have been described in detail elsewhere [13–15]. Below we provide a brief description of each study. All were approved by review boards or ethical committees of the participating institutions, and all participants provided written informed consent.

Ludwig-McGill Cohort Study

This study was designed to evaluate the natural history of HPV infection and cervical neoplasia [13]. Recruitment took place between 1993 and 1997 in a population of low-income women in São Paulo, Brazil. Eligible women (n = 2462) were 18–60 years of age, permanent residents of São Paulo, had an intact uterus and no referral for hysterectomy, were not pregnant or planning to become pregnant in the next 12 months, and had not been treated for cervical disease in the 6 months prior to enrollment. Participants presented for clinic visits every 4 months during their first year of follow-up and twice annually thereafter (maximum follow-up duration, 10 years). The presence of HPV DNA was determined using a polymerase chain reaction (PCR) assay with L1 consensus primers and MY09/11 amplification, followed by hybridization with individual oligonucleotide probes and by restriction fragment–length polymorphism analysis to identify 40 HPV types.

McGill-Concordia Cohort Study

This study was also designed to evaluate the natural history of HPV infection, among a younger population of university students [14]. Recruitment and follow-up took place between 1996 and 1999 and included female students attending either the McGill or Concordia University Health Clinic (Montreal, Canada). The only eligibility criteria were that participants intended to remain in Montreal for the next two years and had not been treated for cervical disease in the previous 12 months. All eligible women (n = 636) were asked to return to the clinic every 6 months over a period of 2 years. HPV DNA was detected using the L1 consensus HPV primers MY09/11 and HMB01 PCR protocol, followed by a line blot assay for the detection of 27 HPV types.

HITCH Cohort Study

This study was designed to assess HPV transmission and prevention among heterosexual couples [15]. Between 2005 and 2010, young women (aged 18–24 years) attending a university or junior college in Montreal were recruited, along with their male partners. Eligible female participants (n = 502) were currently heterosexually active with a male partner (acquired within the previous 6 months) who was also willing to enroll in the study; in addition, eligible women had an intact uterus, had no history of cervical lesions/cancer, were not currently pregnant or planning to become pregnant in the next 2 years, and were willing to comply with follow-up for at least 2 years. All eligible participants were asked to attend clinic visits every 4 months during their first year of follow-up and every 6 months during their second year of follow-up. For the current analysis, we only considered information from female participants. HPV detection and typing was done using the PGMY09/11 PCR protocol coupled with the linear array method (commercially available from Roche), which is capable of detecting 36 mucosal HPV types.

At each clinic visit, subjects were asked to complete a questionnaire to collect information on sociodemographic, lifestyle, sexual, reproductive, and contraceptive factors and to provide a cervical sample for HPV testing. Females were included in our analysis of acquisition of HPV types if valid HPV DNA results were available at baseline and at least 1 follow-up visit (Ludwig-McGill, n = 2185; McGill-Concordia, n = 578; and HITCH, n = 437). In our analysis of loss of any HPV infection (clearance), females were included if they tested positive for HPV at any visit and subsequently had a valid HPV DNA test result at at least 1 visit (Ludwig-McGill, n = 1124; McGill-Concordia, n = 279; and HITCH, n = 249). The number of females included in each of our individual type-specific analyses of HPV clearance was generally much lower because these analyses were restricted to those with the particular HPV types under study, with valid HPV testing results for at least 1 follow-up visit.

Statistical Analysis

We used the Kaplan–Meier method to present and compare times to acquisition or clearance of HPV (both individually and grouped by species) according to presence of vaccine-targeted types (HPV-6, -11, -16, and -18) at baseline or the time of the index infection. Cox proportional hazards regression was used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for analyses of both infection acquisition and clearance. By categorizing individuals with vaccine types as the exposed group, HRs of < 1.0 (acquisition analysis) indicate that the risk of becoming infected with a specific non–vaccine-associated HPV type is lower among individuals infected with a particular vaccine HPV type, thus implying potential type competition between these types. In our clearance analysis, the hypothesized direction is the opposite: HRs of > 1.0 signal accelerated clearance of certain HPV types among those infected with vaccine types and possible type competition. In total, there were 720 preplanned statistical tests (ie, all type-type interactions involving HPV-6/-11, HPV-16, and HPV-18 with each of the other HPV types tested for in each of the 3 studies (range, 27–32 types/species groups) in both our clearance and

acquisition analyses, as well as in our pooled analyses; therefore, in addition to presenting 95% CIs to assess statistical significance, to account for multiple comparisons we also used more-conservative *P* value thresholds of .01 and .00007 (.05/720, after Bonferroni correction) and used the log-rank method for analyses.

Owing to our inability to distinguish between HPV-6 and HPV-11 infections in the Ludwig-McGill cohort study and to the low number of HPV-11 infections observed in the McGill-Concordia and HITCH cohort studies (<10), we decided it was appropriate to group these phylogenetically related types together in all subsequent analyses. Two years was the maximum follow-up duration (ie, from the baseline visit or the first visit at which the index infection was detected) we allowed for evaluation of acquisition and clearance. If HPV DNA results were missing for visit(s) prior to the first visit at which HPV was detected (or, for evaluation of clearance, the first visit at which HPV was not detected), then the acquisition or clearance interval was assumed to span the time from the last visit at which HPV was not detected (or was detected) to the first visit at which HPV was detected (or was not detected). To investigate this assumption, we changed missing values for our acquisition and clearance analyses from negative to positive and from positive to negative, respectively, but this did not materially change our results (data not shown). We also conducted separate analyses to evaluate whether results differed according to prevalent versus incident HPV infections in comparing time to clearance (ie, infections detected at baseline vs those detected during follow-up only). Despite sparse data for some comparisons, results were very similar, and therefore we decided to combine baseline/incident infections in our analysis for this objective (data not shown). Finally, we also explored whether results varied according to definition of baseline status with HPV vaccine-targeted types (ie, those with infection present at the first 2 visits [persistent infection] vs those with infection at baseline but not at the second visit [transient infection]) but observed only minor differences according to these 2 definitions (data not shown).

Important predictors of multiple-type HPV infection (assessed using binary logistic regression), which we adjusted for in both our acquisition and clearance analyses, included age and lifetime number of sex partners. The possibility of confounding by other factors (eg, marital status, age at sexual debut, parity, smoking, oral contraceptive use, and condom use) was also evaluated empirically; however, additional adjustment for these variables generally did not have an important effect on our parameter estimates (<10% change).

Pooling was conducted to improve our precision for both our acquisition and clearance analyses. Since we expected HPV type competition (if it exists) to be a biological phenomenon (ie, consistent across populations), we also reported estimates from fixed-effects models to evaluate both objectives, assuming that results would be similar to estimates generated from random-effects models (ie, that no important residual differences exist across studies). Prior to pooling, the heterogeneity of effects was compared across studies, and the Q test statistic and Hausman specification test were used to compare estimates from fixed-effects and random-effects models (data not shown). Some very rare HPV types (ie, those with <1% cumulative incidence across all studies; HPV-26, -32, -34, -57, -69, -71, -72, and -81) were excluded from our study specific and pooled analyses because they resulted in HRs that were either very imprecise or not estimable.

RESULTS

The average age of participants at baseline in the Ludwig-McGill, McGill-Concordia, and HITCH cohort studies was 32.7, 22.5, and 21.0 years, respectively. The majority in the Ludwig-McGill study (81%) reported that they were married, but the majority in the McGill-Concordia study (77.8%) and the HITCH study (84.7%) reported that they were single. Compared with the latter 2 studies, a smaller proportion of females in the Ludwig-McGill study reported ≥5 lifetime sex partners (12.9% vs 43.6% and 60.4%, respectively) and regularly/always using condoms (3.7% vs 56.9% and 59.6%, respectively), but many more reported at least 1 pregnancy (97.3% vs 16.2% and 9.8%, respectively).

Prevalence of HPV infection (any type) at baseline was 16.4% (403 of 2462) in the Ludwig-McGill study, 27.2% (173 of 636) in the McGill-Concordia study, and 62.2% (281 of 452) in the HITCH study (Table 1). Among these females with baseline infection, the proportion with multiple HPV infections in each study was 18.4% (74), 41.0% (71), and 68.0% (191), respectively. Across these studies, the baseline prevalence of HPV-6/-11, HPV-16, and HPV-18 ranged from 1.1% to 4.0%, 2.6% to 18.1%, and 1.1% to 4.0%, respectively. Similarly, the (2-year) cumulative incidence of any new HPV infection ranged across these studies from 18.3% (in the HITCH study) to 27.0% (in the McGill-Concordia study), with HPV types belonging to the α-9 species being most common, followed by types from the α-7 and α-10 species, respectively. Clearance patterns varied across studies, but in general, high oncogenic risk types cleared less frequently compared with other types (Supplementary Table 1) [16].

In our study specific analyses of acquisition, baseline infection with vaccine-targeted HPV types (either HPV-6/-11, HPV-16, or HPV-18) was not associated with a statistically significant reduced risk of acquiring other HPV types, individually or grouped by species (Table 2). Even after adjustment for risk factors of multiple infection, the hazards of acquiring other HPV types was generally higher among females infected with vaccine-targeted HPV types, compared with those who were not. Similarly, in our study-specific analyses of clearance, coinfection with a vaccine-targeted HPV type at the time of the index infection was not associated with a statistically significant elevated risk of clearing other types after accounting for multiple

Table 1. Prevalence of Human Papillomavirus (HPV) Infection at Baseline and Cumulative Incidence During Follow-up Among Female Participants in 3 Epidemiologic Cohort Studies

	Ludwig-McGill Study[a] (n = 2462)			McGill-Concordia Study (n = 636)		HITCH Study (n = 452)	
Variable	Baseline	Follow-up[b]	Follow-up[b] 2-year	Baseline	Follow-up[b]	Baseline	Follow-up[b]
Any HPV	403 (16.4)	758 (34.7)	516 (23.6)	173 (27.2)	156 (27.0)	281 (62.2)	80 (18.3)
Multiple HPV types	74 (3.0)	247 (11.3)	106 (4.9)	71 (11.2)	103 (17.8)	191 (42.2)	33 (7.5)
HPV types, no.[c]	1 (1–5)	1 (1–9)	1 (1–5)	1 (1–8)	2 (2–6)	2 (1–11)	1 (1–9)
HPV-6 (or -6/-11)	28 (1.1)	71 (3.2)	35 (1.6)	15 (2.4)	29 (5.0)	18 (4.0)	39 (8.9)
HPV-11	NE	NE	NE	5 (0.8)	4 (0.7)	3 (0.7)	4 (0.9)
HPV-16	64 (2.6)	215 (9.8)	108 (4.9)	43 (6.8)	61 (10.6)	82 (18.1)	29 (6.6)
HPV-18	26 (1.1)	60 (2.7)	32 (1.5)	18 (2.8)	25 (4.3)	18 (4.0)	11 (2.5)
Other α-10 HPV types[d]	13 (0.5)	84 (3.8)	63 (2.9)	3 (0.5)	11 (1.9)	10 (2.2)	10 (2.3)
Other α-9 HPV types[e]	86 (3.5)	295 (13.5)	133 (6.1)	48 (7.5)	53 (9.2)	97 (21.5)	68 (15.6)
Other α-7 HPV types[f]	62 (2.5)	197 (9.0)	83 (3.8)	20 (3.1)	46 (8.0)	76 (16.8)	42 (9.6)

Data are no. (%) of participants, unless otherwise indicated.

Abbreviations: HITCH, HPV Infection and Transmission Among Couples Through Heterosexual Activity; NE, not able to estimate.

[a] The HPV test used in the Ludwig-McGill cohort study was unable to discriminate between HPV-6 and HPV-11.

[b] The subject was counted as having given HPV type(s) if it was acquired at any time during follow-up. The number of subjects in the Ludwig-McGill, McGill-Concordia, and HITCH cohort studies with available HPV DNA testing results for at least 1 follow-up visit were 2185, 578, and 437, respectively. Subject follow-up in the Ludwig-McGill study was truncated after 7 years, at which point the sample size was reduced to approximately one quarter. Subject follow-up in both McGill-Concordia and HITCH studies was 2 years.

[c] Data are median (range) among women with detectable HPV infection.

[d] Other α-10 types include HPV-44 and HPV-55 (HPV-44 was not typed in the McGill-Concordia study; HPV-55 was only typed in the McGill-Concordia study).

[e] Other α-9 types include HPV-31, -33, -35, -52, -58, and -67 (HPV-67 was not typed in the McGill-Concordia study).

[f] Other α-7 types include HPV-39, -45, -59, -68, and -70 (HPV-70 was not typed in the McGill-Concordia study).

comparisons (Table 3). However, there were some types that cleared more rapidly (when prevalent as a coinfecting type with either HPV-6/-11, HPV-16, or HPV-18), which supports the competition hypothesis; these were significant at less conservative levels than specified a priori. Among those coinfected with HPV-16, these types included HPV-6/-11 and HPV-45 in the McGill-Concordia and HITCH studies, respectively (Table 3). Results for acquisition and clearance were similar between our study-specific and pooled analyses (Table 4). In addition to HPV-6/-11 and HPV-45, HPV-18 was also found to clear more rapidly among those coinfected with HPV-16 in our pooled analysis (Table 4). Among those coinfected with HPV-18, HPV-16 and HPV-66 cleared more rapidly among HITCH participants and HPV-6/-11 cleared more rapidly among McGill-Concordia participants. In our pooled analysis, HPV-66 plus some additional types (HPV-44, HPV-33, and HPV-61) were found to clear more rapidly among those infected with HPV-18. In our pooled analysis only, clearance of HPV-61 was positively associated with HPV-6/-11 infection. No clear evidence of type competition between HPV-6/-11, HPV-16, and HPV-18 was observed at the species level with phylogenetically related types (α-10, α-9, and α-7, respectively) in our evaluations of acquisition or clearance (Figure 1).

DISCUSSION

To our knowledge, this is the first study among females of type competition and the potential for replacement that specifically evaluates acquisition and clearance of HPV types according to infection with current (first-generation) vaccine-targeted types. Among 3200 females from Canada and Brazil, baseline infection with vaccine-targeted HPV types (HPV-6/-11, HPV-16, or HPV-18) was generally associated with a similar or shorter time to acquisition of other HPV types, providing no evidence of HPV type competition. In our evaluation of clearance (study-specific and pooled analyses), many positive associations were observed between vaccine-targeted HPVs and other types, some of which included other vaccine-protected types. Among the 8 different HPV types that were statistically significant at less conservative thresholds, HPV-66 is the only (possible) oncogenic type [16] not being targeted by current HPV vaccines [1, 2, 17] and has been implicated in approximately 0.4% of invasive cervical cancer cases globally [18]. None of these associations remained statistically significant after accounting for multiple comparisons.

The ability to pool information from 3 large cohort studies greatly enhanced our precision and allowed us to estimate associations that were previously not possible owing to sparse data in individual studies. Focusing on results from our pooled analysis, we identified 9 negative associations (defined as an HR of < 1.0; 8 had an HR of < 0.9) between baseline infection with either HPV-6/-11, HPV-16, or HPV-18 and acquisition of other types (all 95% CIs included 1.0). In our pooled analysis of clearance, we identified 41 positive associations (defined as an HR of > 1.0; 33 had an HR of > 1.1; 8 had 95% CIs excluding 1.0). Because HPV types belonging to the same species share at least 60% of their nucleotide sequence identity and exhibit similar biological and pathological properties [19–21], we expected that

Table 2. Association Between Human Papillomavirus 6/11 (HPV-6/-11), HPV-16, and HPV-18 Infection at Baseline and Future Acquisition of Other HPV Types, Adjusted for Age and Lifetime Number of Sex Partners, in 3 Epidemiologic Cohort Studies

	Adjusted Hazard Ratio[a] (95% CI), by Baseline Vaccine-Associated HPV Type Infection								
	Ludwig-McGill Study[b]			McGill-Concordia Study			HITCH Study		
HPV Type Acquired	HPV-6/11 (n = 28)	HPV-16 (n = 64)	HPV-18 (n = 26)	HPV-6/11 (n = 20)	HPV-16 (n = 43)	HPV-18 (n = 18)	HPV-6/11 (n = 21)	HPV-16 (n = 82)	HPV-18 (n = 18)
α-10 species	NE	1.2 (.3. 5.0)	NE	1.7 (.2, 14.2)	0.8 (.3, 2.1)	0.6 (.2, 1.9)	7.7 (1.4, 41.0)	1.5 (.7, 3.1)	1.3 (.3, 5.4)
HPV-6/11	NA	NE	NE	NA	0.7 (.2, 2.9)	NE	NA	1.8 (.9, 3.8)	1.9 (.6, 6.1)
HPV-44	NE	3.1 (.7, 13.1)	NE	ND	ND	ND	7.7 (1.4, 41.0)	0.6 (.1, 4.6)	2.5 (.3, 21.0)
HPV-55	ND	ND	ND	1.7 (.2, 14.2)	NE	2.9 (.4, 23.4)	ND	ND	ND
α-9 species	3.8 (1.7, 8.6)	2.2 (1.0, 4.7)	2.1 (.7, 6.7)	0.4 (.1, 2.6)	0.9 (.3, 2.6)	1.2 (.4, 3.9)	1.8 (.6, 5.8)	1.7 (.9, 3.5)	0.6 (.1, 4.6)
HPV-16	1.3 (.3, 5.1)	NA	0.8 (.1, 5.7)	0.8 (.2, 3.3)	NA	2.1 (.6, 6.6)	NE	NA	NE
HPV-31	4.8 (1.3, 16.9)	5.2 (1.8, 14.8)	NE	1.3 (.2, 9.7)	0.5 (.1, 4.1)	2.8 (.6, 12.1)	3.1 (.7, 14.0)	1.7 (.6, 5.0)	NE
HPV-33	3.6 (.5, 27.4)	4.8 (1.1, 20.9)	3.9 (.5, 31.0)	7.0 (1.5, 33.4)	1.2 (.2, 9.7)	NE	5.9 (.6, 53.8)	0.9 (.1, 8.0)	NE
HPV-35	4.3 (.9, 20.8)	1.9 (.3, 14.4)	NE	NE	NE	NE	4.1 (.4, 39.9)	NE	3.5 (.4, 34.0)
HPV-52	4.9 (1.2, 20.7)	1.2 (.2, 8.9)	4.2 (1.0, 18.5)	5.4 (1.5, 18.9)	3.1 (1.0, 9.5)	NE	NE	3.2 (1.4, 7.4)	2.6 (.6, 11.2)
HPV-58	NE	2.2 (.5, 9.4)	2.7 (.4, 20.2)	1.5 (.2, 11.9)	1.6 (.3, 7.2)	NE	NE	0.7 (.2, 3.1)	1.7 (.2, 13.3)
HPV-67	NE	NE	NE	ND	ND	ND	2.3 (.5, 10.0)	2.0 (.9, 4.8)	NE
α-7 species	2.5 (.9, 6.7)	0.7 (.2, 2.7)	NE	0.8 (.2, 3.2)	1.6 (.7, 3.6)	1.5 (.4, 6.2)	2.2 (.7, 7.4)	1.8 (.9, 3.6)	2.4 (.7, 8.0)
HPV-18	NE	NE	NA	0.9 (.1, 6.6)	1.1 (.2, 4.6)	NA	NE	1.9 (.5, 7.4)	NA
HPV-39	5.0 (.6, 39.4)	2.8 (.4, 21.8)	NE	1.7 (.4, 7.5)	2.1 (.7, 6.2)	2.5 (.6, 10.8)	2.5 (.6, 10.7)	1.2 (.5, 3.2)	2.0 (.5, 8.6)
HPV-45	3.4 (.4, 26.3)	2.0 (.3, 15.2)	NE	NE	NE	NE	NE	2.3 (.7, 7.7)	NE
HPV-59	2.9 (.4, 22.0)	1.8 (.2, 13.6)	NE	NE	3.0 (.6, 14.2)	NE	3.6 (.8, 16.0)	0.9 (.3, 3.4)	2.7 (.6, 12.0)
HPV-68	NE	NE	NE	NE	NE	NE	NE	2.3 (.4, 12.7)	4.7 (.5, 40.6)
HPV-70	4.4 (.6, 34.4)	NE	NE	ND	ND	ND	6.1 (.6, 61.0)	1.0 (.1, 9.7)	5.3 (.5, 51.5)
Other types									
HPV-40	7.2 (.9, 57.9)	NE	NE	NE	NE	NE	1.4 (.2, 10.8)	1.4 (.4, 4.2)	2.3 (.5, 10.4)
HPV-42	NE	NE	NE	8.3 (.8, 83.8)	2.8 (.3, 25.9)	NE	0.6 (.1, 4.7)	2.5 (1.3, 4.9)	0.5 (.1, 3.7)
HPV-51	1.0 (.1, 7.4)	NE	NE	2.5 (.9, 7.0)	0.5 (.1, 2.2)	NE	NE	0.6 (.2, 1.8)	0.7 (.1, 5.3)
HPV-53	2.4 (.6, 9.8)	1.4 (.4, 5.9)	1.3 (.2, 9.2)	0.7 (.1, 5.3)	1.8 (.6, 5.2)	NE	NE	1.6 (.7, 3.7)	0.6 (.1, 4.6)
HPV-54	NE	8.5 (3.2, 22.3)	NE	1.9 (.4, 7.9)	0.7 (.2, 3.1)	2.0 (.5, 8.4)	NE	1.0 (.7, 5.3)	2.5 (.5, 11.6)
HPV-56	NE	2.2 (.3, 16.8)	NE	1.0 (.1, 7.8)	NE	1.4 (.2, 10.9)	4.2 (1.2, 14.5)	2.8 (1.1, 6.9)	1.2 (.2, 8.7)
HPV-61	NE	2.0 (.3, 15.1)	8.7 (2.0, 38.1)	ND	ND	ND	1.8 (.4, 7.9)	1.9 (.7, 4.9)	1.9 (.4, 8.4)
HPV-62	3.7 (.5, 28.1)	1.9 (.2, 13.9)	NE	ND	ND	ND	1.8 (.4, 7.6)	2.1 (.9, 4.7)	3.8 (1.1, 12.9)
HPV-66	NE	8.0 (1.7, 37.4)	NE	1.3 (.2, 10.0)	1.2 (.3, 5.3)	1.4 (.2, 10.5)	1.3 (.3, 5.3)	1.0 (.4, 2.2)	2.5 (.9, 7.1)
HPV-73	2.9 (.4, 21.7)	NE	NE	1.6 (.2, 12.5)	0.8 (.1, 6.4)	6.6 (1.8, 23.3)	NE	3.5 (1.5, 7.8)	1.6 (.4, 6.7)
HPV-82	7.5 (.9, 60.5)	4.3 (.5, 35.0)	NE	1.6 (.2, 12.7)	0.8 (.1, 6.1)	2.0 (.3, 15.9)	NE	2.0 (.5, 7.6)	2.4 (.3, 18.7)
HPV-83	NE	6.9 (1.5, 31.0)	NE	2.5 (.3, 20.8)	1.1 (.1, 8.9)	3.0 (.4, 23.9)	NE	1.8 (.3, 9.2)	NE
HPV-84	2.6 (.3, 19.2)	4.9 (1.5, 16.3)	NE	1.9 (.6, 6.3)	1.6 (.6, 4.1)	NE	0.6 (.1, 4.7)	1.3 (.6, 2.7)	2.5 (.9, 7.0)
HPV-89	NE	4.6 (.6, 37.4)	NE	ND	ND	ND	0.9 (.2, 3.8)	1.8 (1.0, 3.5)	2.8 (1.2, 6.7)

Abbreviations: CI, confidence interval; HITCH, HPV Infection and Transmission Among Couples Through Heterosexual Activity; HPV, human papillomavirus; NA, not an applicable outcome type; ND, presence of HPV type was not determined; NE, not able to estimate.

[a] Hazard ratios <1.0 indicate that the risk of becoming infected with a specific non–vaccine-associated HPV type is lower among individuals infected with a particular vaccine HPV type, thus implying potential type competition between these types.

[b] Subject follow-up was truncated after 2 years (from baseline) in the Ludwig-McGill study.

types from the same species may be more likely to compete with one another; however, this was generally not the case in our study. Although we would have preferred to evaluate HPV-6 and HPV-11 separately, this probably would not have made much of a difference, considering that these are among the 2 most closely related HPV types with indistinguishable biological and pathological properties [19]. Plummer et al compared time to acquisition/clearance of other HPV types according to infection with HPV-16 and also found no evidence of competition according to degree of phylogenetic relatedness (α-9 species types). However, they did find a slight decrease in incidence of α-7 species types, particularly HPV-59 and HPV-68 [10].

Despite the large sample size of this study, we were still unable to accurately evaluate HPV acquisition/clearance for rare HPV types, which is reflected by wide CIs for some comparisons. Also, despite the use of well-established consensus primer PCR assays to detect a broad spectrum of HPV types [22], these assays have been documented to have reduced sensitivity in cases of multiple infection and low viral DNA load

Table 3. Association Between Human Papillomavirus 6/11 (HPV-6/-11), HPV-16, and HPV-18 Infection at the Time of Index Infection and Clearance of Other HPV Types, Adjusted for Age and Lifetime Number of Sex Partners, in 3 Epidemiologic Cohort Studies

	Adjusted Hazard Ratio[a] (95% CI), by Index Vaccine-Type HPV Infection								
	Ludwig-McGill Study[b]			McGill-Concordia Study			HITCH Study		
HPV Type Cleared	HPV-6/11 (n = 103)	HPV-16 (n = 276)	HPV-18 (n = 87)	HPV-6/11 (n = 42)	HPV-16 (n = 81)	HPV-18 (n = 39)	HPV-6/11 (n = 49)	HPV-16 (n = 96)	HPV-18 (n = 25)
α-10 species	3.0 (.4, 23.7)	1.8 (.8, 3.9)	0.7 (.2, 2.3)	22.3 (.8, 662.1)	1.7 (.8, 3.8)	5.8 (.7, 48.8)	NE	0.6 (.3, 1.4)	2.8 (.7, 11.3)
HPV-6/11	NA	1.6 (.6, 4.1)	0.5 (.1, 1.9)	NA	3.6 (1.4, 8.9)[c]	5.4 (1.1, 27.3)[c]	NA	1.3 (.6, 2.9)	3.0 (.7, 13.3)
HPV-44	3.0 (.4, 23.7)	2.1 (.5, 9.2)	4.3 (.5, 34.8)	ND	ND	ND	NE	0.9 (.1, 5.2)	8.3 (.1, 532.9)
HPV-55	ND	ND	ND	22.3 (.8, 662.1)	0.5 (.1, 2.6)	22.3 (.8, 662.1)	ND	ND	ND
α-9 species	0.6 (.2, 1.9)	0.8 (.4, 1.5)	1.1 (.4, 3.6)	NE	0.8 (.4, 1.5)	1.0 (.4, 2.9)	1.7 (.8, 3.4)	1.3 (.7, 2.4)	0.6 (.3, 1.2)
HPV-16	0.6 (.1, 4.1)	NA	0.8 (.2, 3.3)	NE	NA	2.1 (.5, 10.1)	1.4 (.6, 3.1)	NA	19.5 (1.7, 216.9)[c]
HPV-31	0.4 (.1, 1.6)	1.5 (.6, 3.6)	0.9 (.1, 6.4)	3.6 (.6, 20.1)	0.6 (.1, 4.4)	0.8 (.2, 3.0)	1.4 (.5, 4.3)	0.7 (.3, 1.7)	0.6 (.1, 2.4)
HPV-33	NE	2.7 (.6, 11.5)	6.8 (.5, 42.3)	NE	NE	NE	1.4 (.1, 17.2)	1.4 (.1, 17.2)	NE
HPV-35	NE	0.1 (.0, 0.7)	0.7 (.1, 5.6)	NE	NE	NE	NE	NE	NE
HPV-52	1.8 (.2, 13.3)	0.6 (.1, 2.5)	1.8 (.2, 13.3)	NE	0.8 (.3, 2.4)	2.5 (.3, 21.2)	0.9 (.3, 2.9)	1.8 (.8, 3.9)	0.5 (.2, 1.3)
HPV-58	0.6 (.1, 2.3)	0.7 (.2, 3.1)	NE	NE	0.6 (.1, 2.9)	1.0 (.2, 5.4)	NE	0.8 (.2, 2.9)	1.2 (.1, 11.3)
HPV-67	NE	NE	NE	ND	ND	ND	1.2 (.5, 2.7)	1.2 (.5, 2.8)	1.4 (.5, 3.8)
α-7 species	0.9 (.3, 2.8)	1.8 (.7, 4.6)	0.5 (.1, 3.7)	0.3 (.1, 1.1)	1.8 (.7, 4.6)	2.0 (.5, 8.9)	1.9 (.9, 4.1)	0.8 (.5, 1.6)	0.6 (.1, 2.1)
HPV-18	1.3 (.2, 10.0)	2.3 (.7, 7.2)	NA	0.5 (.1, 5.2)	3.3 (1.0, 11.0)	NA	0.9 (.1, 8.1)	0.4 (.1, 1.5)	NA
HPV-39	1.5 (.2, 12.4)	1.3 (.2, 10.2)	NE	NE	0.6 (.1, 3.2)	1.0 (.1, 9.2)	1.5 (.4, 5.2)	0.8 (.4, 1.7)	0.3 (.1, 1.4)
HPV-45	NE	2.1 (.3, 16.1)	NE	1.2 (.2, 6.1)	0.8 (.1, 3.4)	4.9 (.5, 52.1)	0.7 (.2, 2.9)	49.6 (3.0, 811.6)[d]	1.3 (.1, 29.3)
HPV-59	NE	0.4 (.1, 2.9)	0.4 (.1, 3.4)	NE	NE	NE	0.9 (.2, 3.0)	1.2 (.4, 3.5)	0.9 (.1, 6.7)
HPV-68	0.6 (.1, 2.4)	0.4 (.1, 1.7)	NE	NE	NE	NE	0.7 (.1, 7.5)	0.3 (.1, 2.5)	0.7 (.0, 50.7)
HPV-70	1.5 (.2, 12.5)	1.5 (.2, 12.5)	NE	ND	ND	ND	NE	0.7 (.1, 26.9)	NE
Other types									
HPV-40	3.8 (.5, 31.1)	1.0 (.2, 4.4)	0.8 (.1, 6.3)	NE	NE	NE	NE	2.1 (.6, 7.2)	0.2 (.0, 1.8)
HPV-42	0.3 (.0, 22.9)	0.3 (.0, 22.9)	NE	NE	NE	NE	0.7 (.2, 2.0)	0.9 (.4, 1.9)	1.3 (.4, 4.7)
HPV-51	0.7 (.3, 1.9)	0.8 (.4, 1.8)	1.2 (.3, 5.0)	2.5 (.8, 7.4)	0.3 (.1, 1.1)	1.4 (.5, 4.0)	2.1 (.8, 5.3)	1.8 (.5, 6.1)	NE
HPV-53	0.8 (.2, 2.4)	0.6 (.3, 1.3)	0.8 (.1, 5.6)	NE	0.6 (.2, 1.6)	2.6 (.3, 20.5)	0.4 (.1, 2.0)	1.3 (.5, 3.0)	12.1 (.9, 156.9)
HPV-54	0.7 (.1, 3.3)	0.7 (.2, 2.5)	NE	1.1 (.1, 9.5)	1.6 (.5, 5.2)	NE	0.4 (.1, 1.8)	0.5 (.2, 1.4)	0.8 (.2, 3.0)
HPV-56	NE	0.9 (.3, 2.6)	3.5 (.5, 26.5)	6.2 (.6, 62.3)	1.5 (.4, 5.4)	NE	3.5 (.4, 34.6)	0.5 (.1, 2.6)	0.7 (.1, 3.7)
HPV-61	3.3 (.4, 26.8)	3.0 (.4, 22.4)	5.0 (.5, 51.7)	ND	ND	ND	4.7 (.4, 52.8)	0.3 (.1, 1.4)	NE
HPV-62	NE	1.9 (.5, 6.8)	NE	ND	ND	ND	2.0 (.6, 6.8)	0.8 (.3, 1.9)	0.4 (.1, 2.0)
HPV-66	NE	0.8 (.2, 2.7)	NE	NE	0.7 (.2, 2.2)	NE	0.8 (.3, 1.8)	0.8 (.4, 1.7)	6.1 (1.3, 29.5)[d]
HPV-73	1.5 (.3, 6.3)	0.8 (.1, 6.1)	NE	NE	0.2 (.0, 1.6)	0.7 (.1, 24.8)	0.8 (.1, 6.8)	0.8 (.3, 2.1)	0.3 (.0, 2.2)
HPV-82	NE	1.5 (.2, 13.6)	1.7 (.4, 8.4)	6.3 (.5, 76.9)	0.4 (.1, 1.6)	NE	NE	0.5 (.2, 1.3)	1.2 (.2, 5.5)
HPV-83	NE	2.9 (.6, 13.8)	NE	NE	19.9 (1.9, 207.0)[c]	NE	0.5 (.0, 10.6)	0.1 (.0, 1.3)	2.4 (.1, 42.7)
HPV-84	0.7 (.2, 2.3)	0.9 (.3, 2.6)	1.3 (.2, 9.4)	2.2 (.6, 8.0)	0.8 (.4, 1.6)	NE	0.9 (.3, 2.2)	0.7 (.3, 1.6)	0.6 (.1, 2.4)
HPV-89	NE	NE	NE	ND	ND	ND	1.3 (.6, 3.2)	1.1 (.6, 1.8)	1.3 (.5, 3.7)

Abbreviations: CI, confidence interval; HITCH, HPV Infection and Transmission Among Couples Through Heterosexual Activity; HPV, human papillomavirus; NA, not an applicable outcome type; ND, presence of HPV type was not determined; NE, not able to estimate.

[a] Hazard ratios >1.0 indicate accelerated clearance of specific HPV types among individuals infected with a particular vaccine HPV type, thus implying potential type competition between these types.

[b] Subject follow-up was truncated after 2 years (from the time of index HPV infection) in the Ludwig-McGill study.

[c] Not statistically significant at the .01 level of testing.

[d] Not statistically significant at the .00007 level of testing (Bonferroni corrected *P* value threshold).

[23–32]. In the context of our investigation, this may explain why those coinfected with vaccine-targeted HPV types appeared to clear certain other types more rapidly; that is, differences in clearance may be attributed to differential PCR sensitivity ("masking") as a result of competition for reagents (eg, primers) among those coinfected with vaccine-targeted HPV types [32]. Because of this same masking phenomenon, those infected with vaccine-targeted HPV types may be at even greater risk of acquiring other HPV types than what our results suggest.

There is a strong possibility that adjustment for shared HPV risk factors (predictors of multiple infection) was not sufficient and that some unmeasured variables (eg, behavioral, biological, or host immunity factors) led to residual confounding, which would explain why those infected with vaccine-targeted HPV types were generally at higher risk of acquiring other HPV types in our analyses [12]. Although we should expect there to be some degree of misclassification in the self report of lifetime number of sex partners, condom use, and other suspected

Table 4. Association Between Human Papillomavirus 6/11 (HPV-6/-11), HPV-16, and HPV-18 Infection at Baseline or the Time of Index Infection and Acquisition or Clearance of Other HPV Types, Adjusted for Age, Lifetime Number of Sex Partners, and Study, in the Pooled Analysis of 3 Cohort Studies

	Adjusted Hazard Ratio (95% CI), by Baseline/Index Infection Status					
	Vaccine-Targeted Type Acquisition[a]			Vaccine-Targeted Type Clearance[b]		
HPV Type Outcome	HPV-6/11 (n = 69)	HPV-16 (n = 189)	HPV-18 (n = 62)	HPV-6/11 (n = 187)	HPV-16 (n = 453)	HPV-18 (n = 151)
α-10 species	1.1 (.3, 4.1)	1.7 (1.0, 2.7)	0.8 (.3, 2.0)	2.3 (.8, 6.6)	1.4 (.8, 2.3)	2.5 (.8, 7.6)
HPV-6/11	NA	1.7 (.9, 3.3)	1.1 (.4, 3.5)	NA	1.7 (1.1, 2.6)[c]	0.9 (.4, 2.0)
HPV-44	1.8 (.2, 13.1)	2.0 (.6, 6.7)	2.6 (.3, 21.1)	2.9 (.3, 31.3)	1.7 (.4, 3.8)	6.7 (1.1, 42.4)[c]
HPV-55	1.7 (.2, 14.2)	NE	2.9 (.4, 23.4)	22.3 (.8, 662.1)	0.5 (.1, 2.6)	22.3 (.8, 662.1)
α-9 species	1.9 (1.0, 3.9)	1.9 (1.2, 3.0)	1.5 (.6, 3.6)	1.1 (.6, 1.8)	0.9 (.7, 1.3)	0.8 (.5, 1.3)
HPV-16	0.9 (.4, 2.7)	NA	1.1 (.4, 3.1)	1.1 (.6, 2.0)	NA	1.4 (.7, 3.0)
HPV-31	3.1 (1.3, 7.2)	2.3 (1.2, 4.6)	1.0 (.3, 4.2)	1.0 (.5, 2.1)	0.9 (.5, 1.5)	0.8 (.4, 1.7)
HPV-33	5.2 (1.8, 14.8)	2.0 (.7, 5.8)	1.2 (.1, 8.6)	0.9 (.2, 3.7)	1.3 (.4, 2.5)	9.5 (1.1, 80.2)[c]
HPV-35	4.3 (1.2, 15.4)	0.7 (.1, 5.0)	1.7 (.2, 12.5)	NE	0.6 (.3, 1.4)	0.9 (.3, 2.6)
HPV-52	3.6 (1.4, 9.0)	3.8 (2.1, 7.0)	2.6 (.9, 7.2)	0.8 (.3, 2.3)	1.0 (.6, 1.7)	0.8 (.4, 1.8)
HPV-58	0.7 (.1, 5.0)	1.7 (.7, 4.1)	1.6 (.4, 6.5)	0.6 (.1, 2.4)	0.7 (.4, 1.4)	1.0 (.3, 3.1)
HPV-67	2.6 (.6, 11.0)	2.8 (1.2, 6.7)	NE	1.0 (.4, 2.2)	1.1 (.5, 2.5)	1.3 (.5, 3.4)
α-7 species	1.8 (.9, 3.6)	1.6 (1.0, 2.7)	1.7 (.8, 3.9)	0.9 (.5, 1.6)	1.4 (.9, 2.1)	1.0 (.4, 2.2)
HPV-18	0.6 (.1, 4.4)	1.3 (.5, 3.4)	NA	1.1 (.3, 3.4)	2.0 (1.1, 3.7)[c]	NA
HPV-39	2.6 (.9, 7.2)	2.3 (1.1, 4.7)	2.7 (1.0, 7.3)	0.7 (.2, 1.9)	1.0 (.5, 1.8)	0.8 (.3, 2.3)
HPV-45	1.3 (.2, 9.3)	2.2 (.8, 6.4)	NE	1.1 (.4, 3.3)	2.7 (1.2, 5.8)[c]	0.7 (.1, 4.9)
HPV-59	2.6 (.8, 8.4)	2.2 (.9, 5.2)	1.7 (.4, 7.0)	1.4 (.4, 4.8)	1.1 (.4, 3.2)	0.7 (.2, 3.1)
HPV-68	NE	0.8 (.2, 3.1)	2.1 (.5, 8.8)	0.9 (.3, 2.9)	0.5 (.2, 1.4)	2.0 (.1, 27.6)
HPV-70	5.5 (1.3, 24.4)	1.0 (.1, 7.9)	2.6 (.3, 19.7)	1.9 (.5, 6.7)	2.1 (.6, 7.7)	NE
Other types						
HPV-40	3.1 (.7, 13.3)	2.6 (.9, 7.6)	1.5 (.2, 11.1)	6.9 (.9, 54.9)	1.3 (.6, 3.0)	0.5 (.2, 1.7)
HPV-42	1.6 (.4, 6.5)	6.0 (3.2, 11.6)	0.7 (.1, 5.4)	0.8 (.4, 2.0)	0.9 (.5, 1.8)	1.3 (.3, 5.5)
HPV-51	1.6 (.7, 4.0)	0.5 (.2, 1.3)	0.3 (.1, 2.2)	1.2 (.7, 2.0)	0.9 (.5, 1.5)	1.3 (.6, 2.9)
HPV-53	1.2 (.4, 3.6)	2.2 (1.2, 3.9)	0.8 (.2, 3.1)	0.7 (.3, 1.8)	0.7 (.4, 1.1)	1.3 (.4, 4.1)
HPV-54	1.4 (.3, 5.9)	2.6 (1.2, 5.9)	1.6 (.4, 6.5)	0.9 (.3, 3.1)	1.1 (.6, 2.2)	0.8 (.3, 3.2)
HPV-56	2.8 (1.0, 7.7)	2.6 (1.3, 5.4)	1.5 (.4, 6.1)	1.6 (.4, 6.8)	0.7 (.4, 1.4)	0.5 (.2, 1.4)
HPV-61	1.8 (.4, 8.0)	1.7 (.6, 5.0)	5.6 (2.0, 16.0)	4.9 (1.1, 22.3)[c]	0.8 (.2, 2.7)	17.0 (3.3, 86.5)[d]
HPV-62	3.4 (1.0, 10.9)	3.8 (1.8, 8.0)	3.6 (1.1, 11.7)	1.6 (.5, 5.1)	0.9 (.4, 1.7)	0.3 (.1, 1.3)
HPV-66	1.6 (.5, 5.1)	2.0 (1.0, 3.9)	3.3 (1.4, 7.7)	0.8 (.4, 1.8)	0.9 (.6, 1.5)	12.0 (2.6, 54.7)[d]
HPV-73	1.3 (.3, 5.2)	3.0 (1.5, 5.9)	2.7 (1.0, 7.5)	1.4 (.4, 4.6)	0.9 (.5, 1.7)	0.7 (.2, 2.3)
HPV-82	2.5 (.6, 10.5)	2.3 (.9, 6.2)	2.5 (.6, 10.4)	1.4 (.2, 10.6)	0.9 (.5, 1.9)	1.1 (.4, 3.1)
HPV-83	1.4 (.2, 10.5)	3.2 (1.2, 8.4)	1.6 (.2, 11.4)	1.9 (.4, 8.2)	1.5 (.6, 3.6)	2.0 (.6, 6.6)
HPV-84	1.6 (.6, 4.2)	2.5 (1.4, 4.3)	1.5 (.5, 4.0)	1.0 (.5, 1.8)	1.0 (.6, 1.5)	0.7 (.2, 2.2)
HPV-89	1.6 (.4, 6.5)	3.6 (1.9, 7.2)	4.4 (1.9, 10.2)	1.4 (.6, 3.2)	1.0 (.6, 1.7)	2.4 (.5, 3.9)

Subject follow-up was truncated after 2 years (from the time of index HPV infection) in the Ludwig-McGill study.

Abbreviations: CI, confidence interval; HPV, human papillomavirus; NA, not an applicable outcome type; NE, not able to estimate.

[a] Hazard ratios <1.0 indicate that the risk of becoming infected with a specific non–vaccine-associated HPV type is lower among individuals infected with a particular vaccine HPV type (left side of table), thus implying potential type competition between these types.

[b] Hazard ratios >1.0 indicate accelerated clearance of specific HPV types among individuals infected with a particular vaccine HPV type (right side of table), thus implying potential type competition between these types.

[c] Not statistically significant at the .01 level of testing.

[d] Not statistically significant at the .00007 level of testing (Bonferroni corrected *P* value threshold).

risk factors of multiple-type HPV infection, self-reported condom use has previously been shown to be a valid indicator of sexually transmitted disease risk [33, 34], and in our Ludwig-McGill study, approximately 90% of females reported the same number of lifetime sex partners at their baseline and first follow-up visits. Another approach that others have used to reduce confounding in cross-sectional comparisons of HPV type interactions is to restrict their analyses to HPV-positive women, which ensures that the included population all had sufficient HPV exposure opportunity [35–37]. In addition to adjusting for important measured predictors of multiple infection, we also performed analyses restricted to 1652 females with incident HPV infection. This approach led to attenuated risk associations in our acquisition analysis (generally estimates slightly above or below 1.0), but they were not meaningfully different for our purpose of evaluating type competition (Supplementary Table 2).

In our analyses of acquisition and clearance, the interval between visits ranged between 4 and 6 months. This may have led to slight

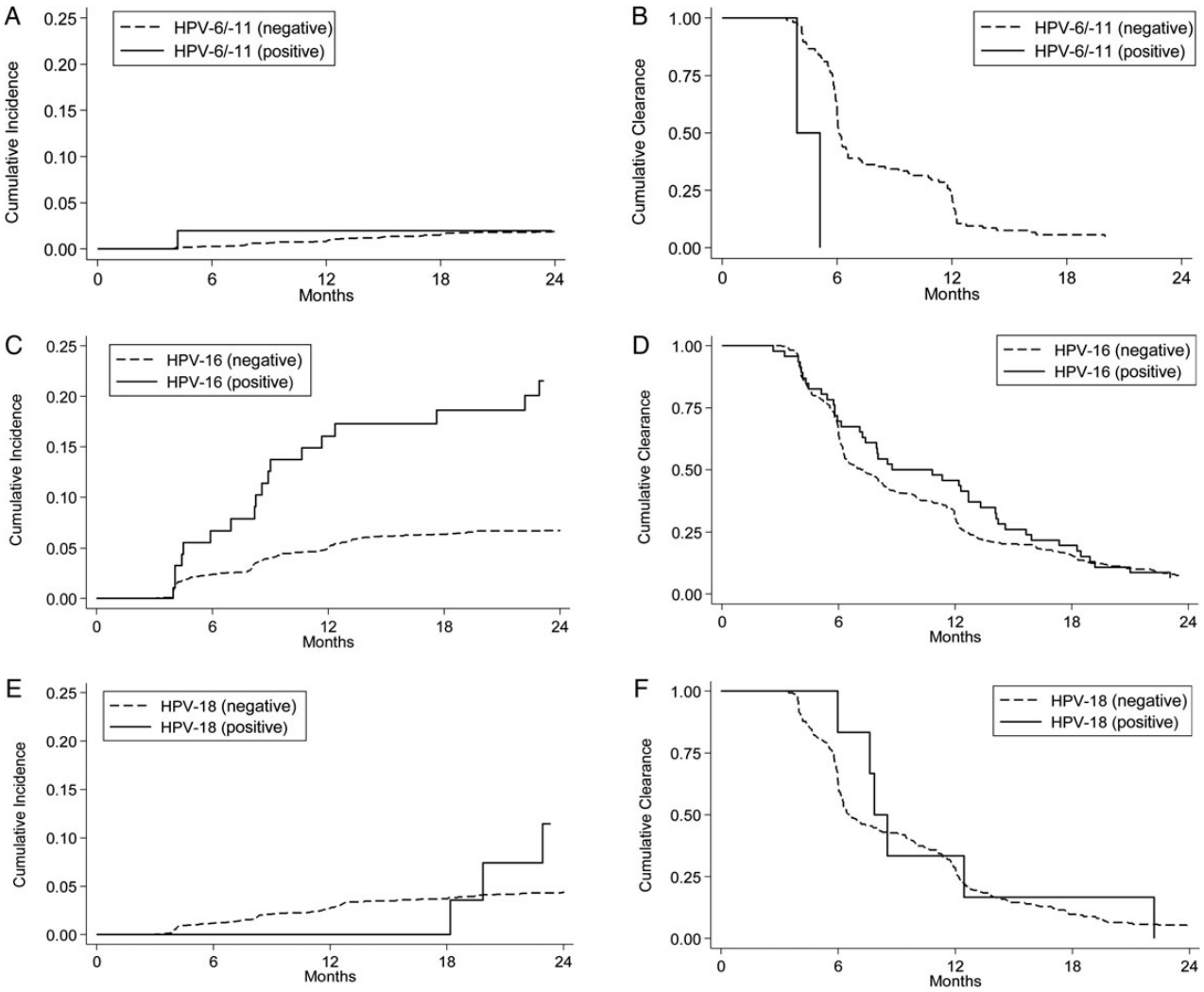

Figure 1. Kaplan–Meier curves showing the times to incidence and clearance of human papillomavirus (HPV) infection with α-10 types (*A* and *B*; excluding HPV-6/-11), α-9 types (*C* and *D*; excluding HPV-16), and α-7 types (*E* and *F*; excluding HPV-18), according to HPV-6/-11, HPV-16, and HPV-18 status at baseline or the time of index infection. All analyses included pooled results from the Ludwig-McGill, McGill-Concordia, and HPV Infection and Transmission Among Couples Through Heterosexual Activity (HITCH) cohort studies and were adjusted for age, lifetime number of sex partners, and study. Hazard ratios were 1.1 (95% confidence interval [CI], .4–4.1; *A*), 2.3 (95% CI, .8–6.6; *B*), 1.9 (95% CI, 1.2–3.0; *C*), 0.9 (95% CI, .7–1.3; *D*), 1.7 (95% CI, .8–3.9; *E*), and 1.0 (95% CI, .4–2.2; *F*).

overestimation of acquisition or clearance time; however, since our objective was to compare groups according to their infection status with vaccine-targeted HPV types (not to estimate the time to an event), we do not suspect any bias was introduced. In addition, we assumed type competition (if it exists) to be a consistent phenomenon, across populations and women of different ages; therefore, despite known differences in risk of HPV acquisition and persistence due to acquired immunity or other factors [12, 38], pooling was considered appropriate. We also explored the possibility of effect modification according to age in the Ludwig-McGill study, stratifying females into 2 age groups (<25 years vs ≥25 years at enrollment) but found no difference (data not shown).

No consistent or strong evidence of type competition between specific HPV types was observed across our analyses of acquisition and clearance. Although some types were flagged as possible candidates in our clearance analysis, this may have resulted from the high number of statistical comparisons or from PCR detection issues. In summary, our study provides no clear evidence to suggest that type replacement may occur following vaccination. While we cannot definitively rule out the existence of type competition, it is reassuring that most studies on this topic have arrived at the same conclusion. Ultimately, the population-level impact of vaccines will be determined by comparing the prevalence (before vs after vaccination) of different HPV types involved in cancerous/precancerous cervical lesions, using long-term surveillance data. Until these data become available, results from studies like ours that evaluate natural HPV type competition may

provide the best clues regarding the likelihood of HPV type replacement.

Supplementary Data

Supplementary materials are available at http://jid.oxfordjournals.org. Consisting of data provided by the author to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the author, so questions or comments should be addressed to the author.

Notes

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