



Practice of Epidemiology

Epidemiologic Approaches to Evaluating the Potential for Human Papillomavirus Type Replacement Postvaccination

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Currently, 2 vaccines exist that prevent infection by the genotypes of human papillomavirus (HPV) responsible for approximately 70% of cervical cancer cases worldwide. Although vaccination is expected to reduce the prevalence of these HPV types, there is concern about the effect this could have on the distribution of other oncogenic types. According to basic ecological principles, if competition exists between ≥ 2 different HPV types for niche occupation during natural infection, elimination of 1 type may lead to an increase in other type(s). Here, we discuss this issue of “type replacement” and present different epidemiologic approaches for evaluation of HPV type competition. Briefly, these approaches involve: 1) calculation of the expected frequency of coinfection under independence between HPV types for comparison with observed frequency; 2) construction of hierarchical logistic regression models for each vaccine-targeted type; and 3) construction of Kaplan-Meier curves and Cox models to evaluate sequential acquisition and clearance of HPV types according to baseline HPV status. We also discuss a related issue concerning diagnostic artifacts arising when multiple HPV types are present in specific samples (due to the inability of broad-spectrum assays to detect certain types present in lower concentrations). This may result in an apparent increase in previously undetected types postvaccination.

cervical cancer; human papillomavirus; HPV type replacement; vaccination

Abbreviations: CI, confidence interval; E, expected; HPV, human papillomavirus; O, observed; PCR, polymerase chain reaction.

The discovery of human papillomavirus (HPV) as a necessary cause of cervical cancer (1) has enormous public health implications and has already led to the establishment of 2 highly effective HPV vaccines (2, 3). Both Gardasil (Merck & Company, Whitehouse Station, New Jersey) and Cervarix (GlaxoSmithKline, London, United Kingdom) prevent infection by the 2 genotypes of HPV that cause the majority (approximately 70%) of cervical cancer cases (HPV types 16 and 18), but only Gardasil protects against additional types (HPV types 6 and 11) that are responsible for most cases (approximately 90%) of genital warts (4–6). Countries that have implemented HPV vaccination will eventually experience major reductions in the incidence of cervical cancer and other HPV-related diseases. However, the existence of other oncogenic HPV types not targeted by the vaccine raises a concern that one or more of these other types may eventually take over the ecological niches vacated by the eradication of

vaccine types; this is a concept referred to as “type replacement” (7–10). The important question that remains is: Is it possible to obtain epidemiologic insights concerning the likelihood that HPV type replacement may or may not occur?

In this article, we present different epidemiologic approaches to evaluating the potential for HPV type replacement, with examples taken from the Brazilian Ludwig-McGill cohort study (11). We also discuss another important issue related to assessing type replacement: namely, the accuracy of detecting type-specific prevalence when there is coinfection with multiple types of HPV.

HPV TYPE REPLACEMENT IN THE POSTVACCINATION ERA

Concern about type replacement is an argument against HPV vaccination that is used by some policy analysts (12),

who often cite the pneumococcal vaccine experience as evidence (13–16). However, unlike pneumococcal infection, in which the pathogen (*Streptococcus pneumoniae*) has a high rate of genetic mutation and recombination, HPVs are DNA viruses that are extremely stable genetically. In fact, the mutation rate for this virus has been estimated at only 1 base pair every 10,000 years (17). Therefore, the emergence of escape mutants that avoid vaccine immunity or entirely new HPV types is unlikely. Emergence of an existing type is also unlikely because of the relatively slower sexual infection dynamics and because the majority of the population is unexposed to specific HPV types (e.g., HPV-16 or -18), implying that any possible natural competition cannot have greatly affected the pool of susceptible persons who may acquire other types. Nonetheless, if it can be demonstrated that HPV types compete with one another during natural infection, there is still the theoretical possibility that type replacement may occur. The existence of natural type competition is a necessary condition for replacement, the other being that such natural type competition needs to be stronger than the cross-protection afforded by vaccines if type replacement is going to be possible (10).

To date, over 150 HPV genotypes have been identified, including more than 40 anogenital types (18–20). Based on the nucleotide sequence of the *L1* (late) capsid gene, papillomaviruses have been classified into high- and low-order clusters, referred to as genus and species, respectively. Most genital HPV types occupy a single genus, α , within which there exist 15 species (19–21). Genotypes from the same species share at least 60% of their nucleotide sequence identity, and as a result they often exhibit similar biological and pathological properties (19, 20). Among the 13 HPV types classified by the International Agency for Research on Cancer as definite or probable carcinogens, most belong to 2 species (α -7 or α -9) (22, 23). After HPVs 16 and 18, the 10 most common types implicated in cervical cancer globally (in order of decreasing prevalence) are 58, 33, 45, 31, 52, 35, 59, 39, 51, and 56 (5, 6).

According to Gause's ecological competitive exclusion principle (24), 2 species cannot stably coexist when competing for the same ecological niche. If niches overlap and one of the competing species is removed, the remaining one would then take over the available niche space and increase in prevalence. Alternatively, if a symbiotic species is removed, we would expect both species to decrease in prevalence (24). Type replacement after vaccination strongly depends on whether different HPV types interact during natural infection. Plausible competition mechanisms include generation of cross-reactive systemic or local immunity. However, it is well established that if vaccination provides cross-immunity that is at least equivalent to that of natural infection, available niche space will not be increased (25). Thus far, phase III trials of HPV vaccines have found that vaccination induces antibodies at much higher levels than natural infection. Therefore, the vaccine-induced partial cross-type protection against certain HPV types, mainly types 31, 33 (α -9), and 45 (α -7), is likely to be well above natural cross-type immunity (3, 26), implying that type replacement is unlikely to occur for these types. Although negative vaccine efficacy

(which could be misconstrued as type replacement) was reported in one of these trials for HPVs 52 and 58 (both from the α -9 species) (26), the finding could not have been due to type replacement, because this is a viral dynamics phenomenon that implies within-group transmission. Clinical trial populations do not replicate the transmission conditions seen in entire populations. As we discuss below, a diagnostic artifact is a likely explanation.

EPIDEMIOLOGIC APPROACHES TO EVALUATING HPV TYPE COMPETITION

Probabilistic approach

To gain insight into the possibility of type replacement, it is useful to evaluate competition between HPV types during natural infection. Competition of this sort may be reflected by a low probability of coinfection between 2 specific HPV types. For each pair combination involving a vaccine type and a nonvaccine type, we may calculate the expected frequency (E) of coinfection under a model of statistical independence and compare this with the observed frequency (O). This approach was first used in the late 1980s to evaluate multiple HPV infections in a Brazilian population (27) and has since been used by other investigators (7, 8, 28–35).

Table 1 presents a hypothetical example of how one can gain insights from epidemiologic studies as to whether or not any given HPV type, say type "X," could occupy the niche vacated by HPV-16. The two halves of the table show what would be a good clue if one assumes that this type competes with HPV-16 and thus would normally be observed less often than expected by chance alone. In the upper half of the table, HPV-X was found in 20 women who were also infected with HPV-16 (out of the total proportion (7%) of HPV-16-positive women among the 10,000 included in the study). Assuming independence between infections, one can calculate what the expected frequency of co-occurrence would be from the product of the two prevalences. The result is 35. In other words, the ratio of the observed number to the expected number ($O/E = 20/35 = 0.57$) is less than 1, and the 95% statistical confidence bounds indicate that this O/E ratio is statistically significant. The conclusion would be that type X tends to occur less frequently than expected in women who are infected with HPV-16. This would be cause for concern, because it suggests that HPV-X is suppressed by HPV-16 and thus its frequency could increase in the future post-HPV vaccination. Most epidemiologic studies that have examined the O/E relationship for different pairs of HPV types (30–34) have seldom found the situation in the upper portion of the table; rather, these studies have found a scenario that is comparable to the one in the lower portion of the table. The marginal distributions of HPV types are the same for type X and for type 16, but the observed frequency is now 40, indicating that HPV-X is actually detected more frequently when HPV-16 is present. However, since there are shared risk factors for HPV infection, O/E ratios greater than 1.0 do not necessarily rule out the possibility of competition between genotypes.

Table 1. Hypothetical Example of Analysis of Co-occurrence of Different Types of Human Papillomavirus in Epidemiologic Studies^a

HPV-X Status	HPV-16 Status			O ^b	E ^c	O/E Ratio	95% CI
	No. of HPV-16+ Women	No. of HPV-16- Women	Total No. of Women				
<i>Type X Co-occurs With HPV-16 Less Frequently Than Expected</i>							
No. of HPV-X+ women	20	480	500	20	35	0.57 ^d	0.35, 0.88
No. of HPV-X- women	680	8,820	9,500				
Total no. of women	700	9,300	10,000				
<i>Type X Co-occurs With HPV-16 More Frequently Than Expected</i>							
No. of HPV-X+ women	40	460	500	40	35	1.14 ^e	0.82, 1.56
No. of HPV-X- women	660	8,840	9,500				
Total no. of women	700	9,300	10,000				

Abbreviations: CI, confidence interval; E, expected; HPV, human papillomavirus virus; O, observed.

^a Concomitant (cross-sectional) or sequential (cohort) acquisition.

^b Observed frequency of coinfection with HPV-16 and HPV-X.

^c Expected frequency of coinfection with HPV-16 and HPV-X.

^d Interpretation: HPV type X is under "suspicion" for replacement.

^e Interpretation: HPV type X is not "suspected" for replacement.

Using period prevalence data for the first year of subject follow-up from the Ludwig-McGill cohort study ($n = 2,462$ women), we compared the observed and expected numbers of coinfections, focusing on HPV-16 for this example. The Ludwig-McGill study has been described in detail elsewhere (11). Briefly, it included an average of 10 follow-up visits per woman (every 4 months during the first year and twice annually in subsequent years), with questionnaire administration, Papanicolaou cytology, and HPV testing performed at each visit. In Figure 1, the majority of log(O/E) ratios were above the null. The average weighted log(O/E) ratio was 0.87 (95% confidence interval (CI): 0.67, 1.06). For some types, the O/E ratios were zero because those types were not observed in coinfection with HPV-16. These types were included in our calculation of the average weighted O/E ratio. Previously, other investigators who have evaluated HPV type interactions have restricted their analysis to positive women (i.e., women with ≥ 1 HPV infection) to ensure that they have focused on a population with sufficient HPV exposure opportunity (27, 29, 30, 36). This approach leads to higher expected frequencies (reduced O/E ratios) for all pairwise combinations, making results difficult to compare.

Considering that mucosotropic HPV infections share a common route of transmission and many risk factors (37, 38), it is not surprising that infection with multiple HPV types occurs often, in up to 50% of infected women (38, 39) and more frequently than expected by chance (7, 8, 28, 30, 32–34, 40). Thus, in calculating the expected frequency of coinfection, our assumption that infections occur independently is a major limitation, leading to biased estimates of the O/E ratio away from zero. Therefore, to account for correlation between HPV infections, we should attempt to adjust for common risk factors in evaluating pairwise interactions (41), which would reduce most positive associations, thus improving our ability to detect competition between HPV types.

Regression approach

Another approach to evaluating type competition is to construct logistic regression models for each vaccine type separately and calculate the odds ratio for each pairwise association involving nonvaccine types. Conceptually, the interpretation of odds ratios is the same as for O/E ratios; that is, odds ratios less than 1.0 would indicate that the odds of being infected with a particular nonvaccine HPV type are lower among persons with a vaccine type than among those without a vaccine type, and vice versa for odds ratios greater than 1.0. A benefit of this approach is that confounding, as described above, may be addressed by the addition of relevant covariates to the model. In particular, factors such as age and number of sexual partners, which are normally predictive of multiple HPV infections, should be included (29, 38, 42–45). Positive associations that persist after adjustment may indicate synergistic effects between specific HPV types, but more likely indicate either residual confounding or polymerase chain reaction (PCR) cross-reactivity.

In a recent pooled analysis of International Agency for Research on Cancer HPV prevalence surveys, Vaccarella et al. (32) evaluated clustering patterns between all HPV types via hierarchical regression models with woman-level random effects, which presumably should have accounted for any residual variation in HPV infection risk not captured by covariates in their model. Although only a single statistically significant negative association was observed (between HPV-16 and HPV-81), multiple positive associations were observed (between HPV types 33 and 35, 33 and 58, 33 and 39, 18 and 45, and 31 and 35). Because results from this study differed by genotyping method, the authors attributed clustering of these HPV types to a diagnostic artifact and not true biological interaction.

Chaturvedi et al. (33) also examined HPV coinfection patterns among women from a vaccine study in Costa Rica. To

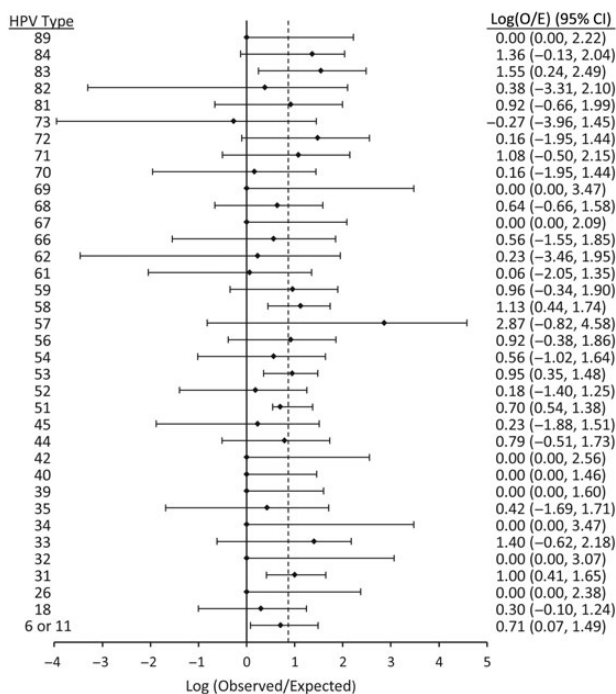


Figure 1. Log(observed/expected) ratios ($\log(O/E)$) and 95% confidence intervals (CI) for coinfections involving human papillomavirus (HPV) type 16 and other HPV types. Ratios were calculated using 1-year period prevalence information. The dashed line represents the average weighted $\log(O/E)$ of 0.87 (95% CI: 0.67, 1.06). HPV types belonging to the same species as HPV-16 (α -9) include types 31, 33, 35, 52, 58, and 67. For HPV types with an O/E ratio of 0 (types 26, 32, 34, 39, 40, 42, 67, 69, and 89), 0 was listed for the log and lower range of the 95% CI.

account for positive correlation between HPV infections, they adjusted for predictors of multiple infection but also calculated a pooled odds ratio by averaging across all pair-specific odds ratios (separately for HPV types 6, 11, 16, and 18) and used this to represent the underlying affinity of each of these vaccine types for being involved in coinfection. They calculated the difference between the pair-specific odds ratio and the pooled odds ratio (log scale) to assess whether any particular pair of genotypes deviated from the pooled odds ratio. This procedure was repeated for a total of 300 type-type combinations (25 HPV types), and statistically significant negative associations were observed between HPVs 44 and 68, 44 and 73, and 18 and 33, whereas HPVs 11 and 53, 31 and 33, 34 and 42, 45 and 68, and 45 and 73 were found to be positively associated. In general, HPV genotypes occurred independently, and phylogenetic relatedness had no influence.

The 2 studies described above did not account for the presence of other HPV types in evaluation of pairwise interactions, which according to Rositch et al. (36) may lead to confounding. Another issue is that for rare HPV types, few or no coinfections may be observed, which could lead to non-positivity or wide confidence intervals and extremely limited

power to detect competition with these types. Rositch et al. (36) addressed some of these issues using data from a randomized controlled trial of Kenyan males through a semi-Bayesian regression approach. Multivariate hierarchical logistic models for 4 outcome types (HPVs 6, 11, 16, and 18) included variables identified a priori as predictors of multiple HPV infection, as well as all other HPV types. The hierarchical component was introduced through prior means for type-specific estimates, obtained by calculating the crude average log odds of coinfection for each type. By intentionally introducing some bias using priors, this produces a shrinkage effect that reduces the overall error across estimates and improves the precision of each estimate (46). A mix of null and positive associations, but no negative associations, was reported in this study.

Using Ludwig-McGill data, we illustrate the effects of shrinkage and adjustment for confounding in Figure 2. Panel A presents results from a multivariate logistic regression model with HPV-16 as the outcome and all other types as predictor variables. Woman-level clustering was accounted for with woman-specific intercepts. The odds ratio estimates for some rare HPV types were highly unstable, and these types were excluded from the model. Panel B presents the results from a similar model, with the addition of age and lifetime number of sexual partners at baseline as covariates. The average weighted log odds ratio appeared to be only slightly reduced by adjustment, from 0.38 (95% CI: 0.10, 0.62) to 0.37 (95% CI: 0.12, 0.58), possibly because these variables were not strong predictors of coinfection in the Ludwig-McGill data set. Panel C results are from a model similar to that in panel B, with the addition of a fully Bayesian approach to shrinkage, where the prior distribution for type-specific odds ratio estimates was centered around the pooled estimate. Shrinkage reduced the problem of non-positivity, since unstable estimates were pulled (shrunk) more closely towards the overall mean, which enabled us to include rare types in the model. The confidence intervals were also narrower in comparison with panels A and B. The pooled log odds ratio from the shrinkage model was 0.53 (95% CI: 0.21, 0.77).

By addressing issues of sparse data and confounding by a common route of transmission, regression approaches that employ shrinkage to stabilize estimates and include adjustment for confounders may be useful in this context for evaluation of HPV type competition (47).

Cohort approach

When cohort information is available, comparison of sequential acquisition and clearance of HPV types according to infection with vaccine types is another useful approach to evaluating type competition. For acquisition, time to incident HPV infection(s) may be assessed for each of the non-vaccine types separately (or grouped together by species) according to baseline infection with one of the vaccine types. For evaluation of clearance, the approach is similar except that eligible women must be positive for the specific type(s) under study at baseline. Using Cox regression with adjustment for important confounding factors, we may calculate hazard ratios and associated confidence intervals. If

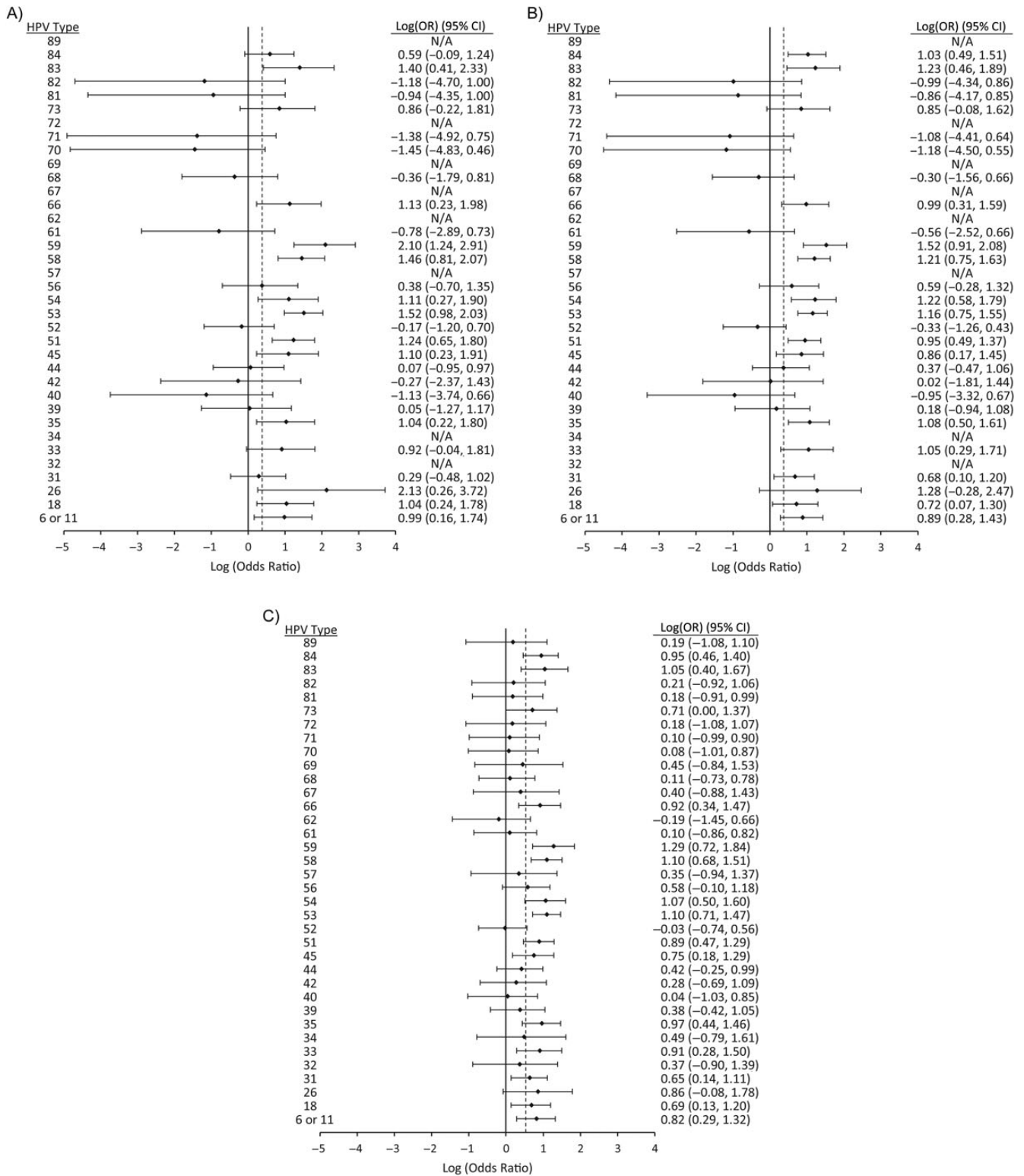


Figure 2. Log(odds ratios) (log(OR)) and 95% confidence intervals (CI) for human papillomavirus (HPV) type 16 for coinfection with other HPV types. Estimates were obtained from logistic regression models adjusting for all other HPV types (A); adjusted for all other types, age, and lifetime number of sexual partners at baseline (B); and adjusted for all other types, age, lifetime number of sexual partners, and shrinkage (C). Dashed lines represent the average weighted log(OR) in panels A and B, which were 0.38 (95% CI: 0.10, 0.62) and 0.37 (95% CI: 0.12, 0.58), respectively, and the pooled log(OR) from hierarchical logistic regression in panel C, which was 0.53 (95% CI: 0.21, 0.77). HPV types belonging to the same species as HPV-16 (α -9) include types 31, 33, 35, 52, 58, and 67. In panels A and B, rare HPV types (types 32, 34, 57, 62, 67, 69, 72, and 89) were excluded from the model because they caused model instability. These types were included in the model shown in panel C because the hierarchical model is able to stabilize estimates. N/A, not applicable.

we categorize women with a vaccine type as the exposed group, hazard ratios less than 1.0 would indicate that the risk of becoming infected with a particular nonvaccine HPV type was lower among those infected with a vaccine type than among those without a vaccine type, and vice versa for hazard ratios greater than 1.0. Our interpretation is similar to what we described for O/E ratios and odds ratios, except that for clearance it is the opposite; that is, hazard ratios greater than 1.0 indicate accelerated clearance of certain HPV types among persons with a vaccine genotype and thus potential type competition.

Previous studies examining the natural history of HPV did not suggest that prior infection with one or more HPV types inhibits acquisition of other types or facilitates clearance of prevalent types in women (7, 8, 28, 29, 40, 48). Rather, the majority of studies found that the presence of preexisting HPV infection actually increased a woman's risk of acquiring other types, including those from the same species (8, 28, 40). Although these studies did not focus specifically on vaccine target types, they still provided valuable insights concerning type competition in general.

Using Ludwig-McGill cohort data, we prepared Kaplan-Meier curves to compare acquisition and clearance of HPV infection with α -9 genotypes (excluding HPV-16) between women with and without HPV-16 infection at baseline (Figure 3). Despite adjustment for important risk factors for multiple infection (e.g., age, lifetime number of sexual partners), women infected with HPV-16 still appeared more likely to acquire other phylogenetically related HPV types and less likely to clear infections with these genotypes.

Comparing approaches

Based on results presented here from the Ludwig-McGill study, type competition does not appear to exist between HPV-16 and other genotypes; that is, estimates less than 1.0 (O/E ratios, odds ratios, and hazard ratios for incidence) or greater than 1.0 (hazard ratios for clearance) were not statistically significant. Although the probabilistic approach is arguably the most intuitive, it does not permit adjustment for confounding and is more likely to produce biased estimates, making it more difficult to reliably assess type competition. We therefore recommend using regression and cohort approaches. Evidence of type competition that is consistently reported across approaches and studies should be a strong signal to investigators that type replacement is more likely to occur for the flagged HPV type(s).

DIAGNOSTIC ARTIFACTS

An additional concern related to HPV type replacement postvaccination is the possibility of diagnostic artifacts. Currently, the most common HPV DNA tests being used for research and surveillance are consensus (or general) primer PCR assays with MY09/11 or GP5+/6+ primer sets. By targeting sequences in the *L1* gene of HPV, these assays amplify and detect a broad spectrum of mucosotropic HPV types (49). However, there may be competition for reagents (e.g., primers) between at least 1 of the current HPV vaccine types and other prevalent types in consensus PCR assays.

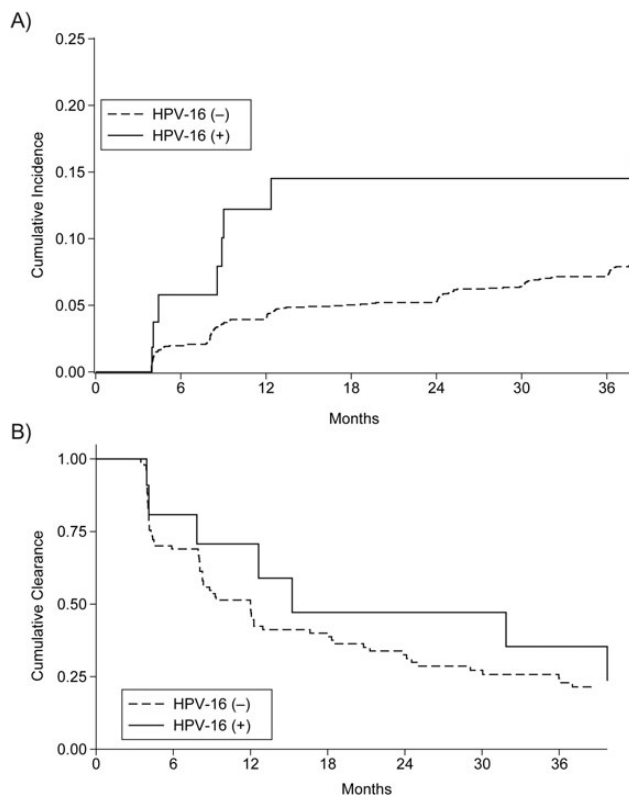


Figure 3. Kaplan-Meier curves showing time to incident human papillomavirus (HPV) infection (A) and clearance of existing HPV infection (α -9 genotypes, excluding HPV-16) (B) according to HPV-16 status at baseline, adjusted for age and lifetime number of sexual partners. Hazard ratios and associated 95% confidence intervals (CI) for panels A and B were 1.49 (95% CI: 0.82, 2.73) and 0.79 (95% CI: 0.38, 1.64), respectively.

The impact of this may be that in the presence of vaccine types, other prevalent HPV types are being missed (50). For instance, if a specimen contains 1,000,000 HPV-16 genome copies but only 1,000 HPV-31 genome copies, then during amplification the HPV-16 sequences will overwhelm the minority type during the exponential phase of replication, and the resulting signal for HPV-16 will be revealed at the expense of HPV-31. Hence, this specimen may be erroneously labeled as an HPV-16 monoinfection. However, if HPV-16 is removed, the existing 1,000 molecules will have the entire reagent mixture for their amplification to proceed unhindered, and the specimen will be HPV-31-positive.

In the postvaccination era, surveillance will be necessary to monitor trends in the distribution of HPV types. If an increase in nonvaccine types is observed, it will be important to distinguish whether this results from true type replacement or represents a diagnostic artifact. For example, if we observe an increase in the prevalence of HPV-31 postvaccination, an alternative explanation to type replacement is that HPV-31 had always been present but was underestimated in the presence of vaccine types that were eliminated. In HPV vaccine trials, a differential increase in prevalence may

occur in the intervention arm, since this group would be protected against future infection by vaccine types, whereas the placebo arm would not. By ignoring this possibility, one may arrive at erroneous conclusions when interpreting vaccine efficacy against nonvaccine HPV types.

Numerous studies that have compared PCR methods have noted deficiencies in the sensitivity of consensus PCR versus type-specific or multiple-primer PCR systems (e.g., PGMY09/11 and modified GP5+/6+), particularly in cases of multiple infection and low viral DNA load (51–59). Recently, Mori et al. (59) found that in samples containing HPV-16 and either HPV-18, -51, -52, or -58, these latter types were not sufficiently amplified by consensus PCR at lower viral loads. Consistent with previous reports (51, 53, 57), sensitivity was most severely affected for types 51 and 52. Therefore, negative vaccine efficacy against certain HPV types (26) may simply be a consequence of inadequate test performance, and just as it is important to identify types that should be monitored for replacement, it is equally important to evaluate the test used and ensure that it performs adequately. The World Health Organization HPV LabNet provides blinded “proficiency panels” designed to evaluate whether the assays used can detect a mono-infection equally well in the presence of other HPV types. Comparison of results from more than 100 laboratories worldwide that have used a variety of HPV assays has shown that underestimation of some HPV types when other types are present in the same sample is a definite problem for some assays, but not for others (60, 61). In this regard, continued monitoring for adequate performance of assays used for surveillance will be of critical importance.

OTHER ISSUES TO CONSIDER IN THE EVALUATION OF HPV TYPE REPLACEMENT

The term *unmasking* has previously been used in the pneumococcal vaccine literature to describe detection of apparent type replacement resulting from misattribution of a strain of microorganism causing disease when multiple strains are present (62, 63). Because multiple infection with oncogenic HPV types is also common in evaluating cases of cervical cancer, assigning causality to a particular HPV type is often difficult and may also lead to misclassification in this scenario (64). When investigators are faced with this situation, they often will apply an oncogenic hierarchy in which the lesion is attributed to the HPV type present that usually progresses most rapidly to cause cancer. Often, this will either be HPV-16 or HPV-18, which may or may not be present in the actual lesion (65). When multiple HPVs are present, there could also be different lesions individually caused by different types. Cervical excisional treatment may remove multiple lesions and HPV types simultaneously. However, when excisional procedures for vaccine types detectable by screening are no longer performed in the future, the number of women at risk for disease caused by nonvaccine types may seem to increase. van der Marel et al. (66) used genotyping and laser-capture microdissection PCR analysis to evaluate high-grade cervical lesions with multiple HPV infections (including HPV-16) and found that HPV-16 was the causal type in all cases. We therefore

expect that type replacement observed as a consequence of errors in assigning causality or reduced rates of excisional treatment will be low.

The possibility that HPV vaccination could lead to an increase in risky sexual behavior (i.e., “risk compensation”) (67) due to a perceived lower risk of sexually transmitted infections among young vaccinees also has important implications for HPV type replacement. To investigate this, Liddon et al. (68) recently evaluated data from a large national US survey and found no association between HPV vaccination and reported risky sexual behaviors. Although these results may provide comfort to concerned parents and health officials, only prospective follow-up studies can provide a definitive answer to this question.

So far, there are no indications that the biological prerequisites for type replacement are present in the HPV field. Diagnostic laboratory artifacts may explain some deviations from random effects. Furthermore, the significant cross-protection seen after vaccination is likely to dwarf possible tendencies for replacement that may not have been possible to detect because of insufficient statistical power. Moreover, even if type replacement is observed, unless it leads to disease, it may not have important public health implications. Because HPV-16 and HPV-18 pose much higher cancer risks than any other HPV type, replacement by a non-oncogenic type or an oncogenic type that entails much lower risk of cancer may not have any major consequences. Results from long-term surveillance studies comparing the prevalences of different HPV types implicated in cervical cancer or high-grade lesions (pre- vs. postvaccination) will eventually provide a clearer estimate of the population-level impact of current vaccines. Until then, we may gain valuable insight through evaluation of type competition to identify HPV types considered suspicious for replacement. In the unlikely event that such signals were to be found, types that were flagged could then be included in the new generation of multivalent vaccines (69, 70).

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