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Invited Commentary

Invited Commentary: Multiple Human Papillomavirus Infections and Type Replacement—Anticipating the Future After Human Papillomavirus Vaccination

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Prophylactic human papillomavirus (HPV) vaccination with 3 doses of either of 2 commercially available vaccines is highly efficacious in preventing infections with the most carcinogenic types of HPV (HPV 16 and HPV 18) at the cervix and other anatomical sites at which HPV-related cancers develop. Concern has been raised that eradicating the most virulent HPV types, 16 and 18, could result in 1 or more of the types that are not targeted by the vaccine occupying the ecological niche created by the elimination of these types, referred to as type replacement. In this issue of the *Journal*, Yang et al. (*Am J Epidemiol*. 2014;180(11):1066–1075) report on concurrent infections with multiple HPV types in unvaccinated women who underwent cervical screening in New Mexico (December 2007–April 2009) to identify possible interactions between HPV types, which if present could suggest the possibility of type replacement. Consistent with previous reports, they show minimal type-specific interactions among women with normal cytology, which they consider an indication that type replacement of HPV 16/18 is unlikely to be an issue in the general population postvaccination. Type replacement may be of less concern with the introduction of multivalent vaccines that include most of the carcinogenic HPV types; continued surveillance postvaccination should improve our understanding of the impact of HPV vaccination on type distribution and screening performance.

human papillomavirus; multiple infections; type replacement; vaccines

Abbreviations: CIN, cervical intraepithelial neoplasia; HPV, human papillomavirus.

During the last 30 years, laboratory and epidemiologic studies have established persistent carcinogenic human papillomavirus (HPV) infection as the causal agent for nearly all cervical cancers and, more recently, for other anogenital cancers and a subset of head and neck cancers (1). The etiological association of HPV with cancer has resulted in the realization of its utility in improved screening with more clinically valid and robust methods that use HPV type detection and in primary prevention with either of 2 efficacious, US Food and Drug Administration–approved vaccines that prevent a significant proportion of precancerous lesions or infections in the cervix, vagina, vulva, anus, penis, and oropharynx (2–8).

With the introduction of the HPV vaccines, concern has been raised about HPV virus "type replacement" as an emergent cause of future HPV-associated morbidity. In theory, eradicating the more virulent vaccine-targeted HPV types, types 16 and 18, raises the possibility of having 1 or more of the other HPV types not targeted by the vaccine occupy the ecological niche created by elimination of the vaccine types (9). Type replacement has been observed in some regions after the introduction of conjugated pneumococcal and *Haemophilus influenzae* type b vaccines (10–12). However, thus far, there is little biological evidence of a competitive interaction between HPV strains (13, 14); moreover, at the infection level, similarly high clearance and low persistence and progression proportions have been reported for both single and concurrent infections (15, 16). However, from a public health perspective, type replacement with carcinogenic HPV types is relevant because over time it could result in reduction in the expected impact of vaccination on cervical cancer incidence. Additionally, type replacement with noncarcinogenic types could lead to increases in morbidity, such as genital warts.

Because of the common exposure route and shared risk factors, assessing HPV type replacement is challenging. Ideal settings may be existing randomized vaccine trials with long follow-up, where confounding of HPV acquisition by sexual behavior can be minimized. This could be difficult, however, and may require pooling of data from different trials. Other epidemiologic approaches include 1) examining HPV coinfection patterns in natural history studies, ideally with information on HPV cofactors, which would allow for adjustment of potential confounders and more accurate estimates, and 2) surveillance of initially unvaccinated cohorts, especially among those without disease (i.e., persons without cervical intraepithelial neoplasia (CIN) grade 2 (CIN2), grade 3 (CIN3), or worse lesions), ideally with follow-up spanning the periods before and after introduction of vaccination programs, to allow for comparison of HPV concurrence patterns in the pre- and postvaccination periods. The latter approach was used by Yang et al. (17), with data available before the introduction of HPV vaccination.

In this issue of the *American Journal of Epidemiology*, Yang et al. (17) describe a study in which they examined the distribution of concurrent occurrence of multiple HPV infections among women in New Mexico, with a special interest in identifying possible antagonistic interactions between HPV types. If present, such interactions could suggest the possibility of HPV type replacement in the postvaccination era. The study was conducted in a large cohort of women ($n = 47{,}617$) who underwent routine cytological screening from December 2007 to April 2009. Yang et al. further analyzed the extent to which these interactions varied according to age (≤30 years, 31–49 years, or ≥50 years) and cytological outcome (normal, atypical squamous cells of unknown significance (ASC-US), atypical squamous cells—cannot exclude HSIL (ASC-H), atypical glandular cells of undetermined significance (AGUS), low-grade squamous intraepithelial lesion (LSIL), or high-grade squamous intraepithelial lesion (HSIL)). Liquid-based cytological specimens (SurePath (Becton, Dickinson and Company, Franklin Close, New Jersey) or ThinPrep (Hologic, Inc., Bedford, Massachusetts)) were tested, with identification of 37 types of HPV, using the LINEAR ARRAY HPV Genotyping Test (Roche Diagnostics, Indianapolis, Indiana); 35 individual HPV types were included in the analysis. To investigate those interactions, the authors used a novel single-parameter frailty model recently developed by the same research group (18) which captures the heterogeneity in susceptibility to multiple infections at the individual level. Greater heterogeneity values indicate excess susceptibility to multiple infections, while lower values indicate lower susceptibility to multiple infections.

Concurrent infections with multiple HPV types have been reported to occur more commonly than would be expected by chance alone, ranging from 20% to over 30% of infections depending on the population and region of study (results of selected studies published over the past 5 years are presented in Table 1). The distribution of concurrent infections, regardless of the population, differs by age and cervical abnormality, being highest in persons with abnormal lesions. Risk factors for multiple infections generally mirror those associated with HPV acquisition, particularly higher number of sexual partners (13). Like other studies, the study by Yang et al. (17) showed an excess of multiple infections for women of all ages and cytology groups, especially among younger women with low-grade cytology. Yang et al. further report that heterogeneity (or susceptibility to multiple infections) was greatest among older women and those with abnormal cytology. The minimal number of type-specific interactions among women with normal cytology was considered by the authors as an indication that type replacement in women vaccinated against HPV 16/18 is unlikely to be an issue in the general population.

Yang et al. further found evidence of positive interaction between HPV 56 and 66 and between HPV 51 and 82 (17). However, as they mention in their article, such a finding could be an artifact caused by "unmasking" and cross-reaction between probes used for detection of these types by the LINEAR ARRAY assay, and biases with the use of consensus primers have been reported previously (19–22). Differential interactions resultant from test performance and typing artifacts have been reported in other studies as well (23), underscoring the need for standardization and monitoring of performance of the assays (22, 24).

Comparable results from this and other natural history studies with different statistical approaches are reassuring and support the hypothesis of a lack of competitive interaction between different HPV strains. Furthermore, a similar report on an HPV-vaccinated group of women from Finland (14) (see Table 1) corroborated the lack of evidence for HPV type replacement at the infection level—that is, no other HPV types becoming more prevalent after the introduction of HPV vaccination programs. However, considering the whole spectrum of the natural history of HPV infection and cervical neoplasia, there are outstanding questions to be resolved.

Even if HPV infection rates remained constant for carcinogenic types not directly inhibited by vaccination, in theory there is still a possibility of HPV type replacement at the precursor-lesion level in the context of screening and treatment. In the prevaccine era, most precursor cervical lesions that were excised, especially among younger women, were associated with HPV 16 or HPV 18, and a sizeable proportion of those cervices harbored concurrent infections with other carcinogenic types. Therefore, when these HPV 16- or HPV 18-associated precursor lesions are treated, the removal of the transformation zone also treats (by removal) other concurrent "passenger" or "bystander" HPV infections. As an example, if a woman was positive at the cervix for both HPV 16 and HPV 33 and had a more quickly progressing HPV 16-associated precursor lesion that was excised, both the HPV 16 and HPV 33 infections would be treated. However, in the vaccine era, because HPV 16 infections will be eradicated, the woman would only have HPV 33, which could in turn persist long enough to cause a precursor lesion. Although this scenario is plausible in theory, results from the first years of follow-up of women who participated in the phase III clinical trials where these vaccines were proven efficacious showed a significant reduction, among vaccinated women, in the proportion who were referred to colposcopy and underwent treatment (2, 3, 25), suggesting that if type replacement at the lesion level did occur, it was minimal. Nonetheless, longer follow-up of these first cohorts of vaccinated women and accumulation of additional precancer outcomes will be needed to adequately address this important question.

A nonavalent vaccine (manufactured by Merck and Company, Inc. (West Point, Pennsylvania)) that is effective against

Table 1. Findings of Studies That Evaluated Interactions Between Different Types of Human Papillomavirus in the Context of Multiple-Type Infections in the Past 5 Years

First Author, Year (Reference No.)	Study Population	Study Location	Study Sample	HPV Vaccination Status	Age, years	HPV Detection Method	No. of HPV Types Detected	Results/Conclusions
Wentzensen, 2014 (32)	Population-based study	New Mexico, United States	59,664 women	Unvaccinated	≤30 vs. >30	LINEAR ARRAY HPV Genotyping Test (Roche Diagnostics, Indianapolis, Indiana)	37	Observed additive effects of HPV types on risk of high-grade squamous intraepithelial lesions in multiply infected women
Mollers, 2014 (33)	Self-collected vaginal samples from 3 cross-sectional studies; high-risk setting	The Netherlands	3,874 women	Unvaccinated	16–29	SPF_{10}-DEIA/$HPVLiPA_{25}$, version 1 (Labo Bio-Medical Products B.V., Rijswijk, the Netherlands)	25	No evidence for particular type-type interaction found; findings suggested that clustering differs among HPV types and varies across risk groups
Querec, 2013 (34)	Immune-competent women, self- and clinician-collected cervicovaginal samples; mostly routine screening population	Pooled data from 6 different studies, United States	32,245 women	Unvaccinated	11–83	LINEAR ARRAY HPV Genotyping Test	37	Infections with multiple HPV types were detected more often than expected; negative associations were few and less significant, supporting the expectation of no type replacement with vaccination
Rositch, 2012 (35)	HIV-negative uncircumcised men	Kenya	1,097 men	Unvaccinated	18–24	GP5+/GP6+ primers and EIA	44	No evidence of potential for type replacement and competition
Campos, 2011 (15)	Guanacaste HPV Natural History Study	Costa Rica	980 women, 1,646 infections	Unvaccinated	18–>47	MY09/MY11 polymerase chain reaction	>40	Concurrent, prevalent detection of additional HPV types did not change the likelihood of viral persistence
Chaturvedi, 2011 (13)	Costa Rica HPV16/18 Vaccine Trial	Costa Rica	5,871 women	Unvaccinated	18–25	SPF_{10}-DEIA/$HPVLiPA_{25}$	25	Coinfecting HPV genotypes occur at random and lead to cervical disease independently
Carozzi, 2012 (36)	NTCC cohort	Multiple countries in Europe	36,778 women	Unvaccinated	25–60	GP5+/GP6+ primers and RLB	13	24% of Hybrid Capture 2–positive women (Digene Corporation, Gaithersburg, Maryland) were multiply infected; coinfections occurred more frequently than expected by chance

Table continues

Table 1. Continued

First Author, Year (Reference No.)	Study Population	Study Location	Study Sample	HPV Vaccination Status	Age, years	HPV Detection Method	No. of HPV Types Detected	Results/Conclusions
Vaccarella, 2011 (37)	Guanacaste HPV Natural History Study	Costa Rica	8,424 women	Unvaccinated	18–84; mean ≈ 40	MY09/MY11 primers	>40	Prevalence of multiple infection was 7.3% overall and 33% among HPV-positive women; coinfection occurred more often than expected by chance; degree of clustering increased with genetic similarity of L1 region
Vaccarella, 2010 (23)	IARC HPV prevalence surveys (15 studies)	Multiple countries, worldwide	14,176 women	Unvaccinated	≥15; mean ≈ 41	GP5+/GP6+ primers; typing by either RLB or EIA	36	Prevalence of coinfection was 3% overall and 26% among HPV-positive women (15 types); some of the observed excess differed by genotyping method (only in EIA, not in RLB)
Palmroth, 2012 (14)	HPV vaccine trial participants	Finland	4,808 (approximately 2,400 HPV-vaccinated and, in the control arm, HAV-vaccinated) women	Vaccinated and unvaccinated	16–17	SPF_{10}-DEIA/ $HPVLiPA_{25}$	25	No excess risk of either low-risk or high-risk HPVs in vaccinated women; in the control (HAV) arm, HPV 18-positive women had increased likelihood of α7 types
Wentzensen, 2009 (16)	Women referred to colposcopy for abnormal cytology	Oklahoma, United States	1,670 women	Unvaccinated	18–81; median, approximately 25	LINEAR ARRAY HPV Genotyping Test	37	Younger women were more likely to have multiple infections; results did not show synergistic or antagonistic clustering of genotypes

Abbreviations: EIA, enzyme immunoassay; HAV, hepatitis A virus; HIV, human immunodeficiency virus; HPV, human papillomavirus; IARC, International Agency for Research on Cancer; NTCC, New Technologies in Cervical Cancer; RLB, reverse line blot.

7 carcinogenic types of HPV (types 16, 18, 31, 35, 45, 52, and 58), plus the noncarcinogenic types 6 and 11, is under regulatory review for licensure (26) and could theoretically prevent up to 90% of cervical cancers. Additionally, the bivalent vaccine (manufactured by GlaxoSmithKline Vaccines (Rixensart, Belgium)) has demonstrated cross-protection against HPV 16/18-related types, including HPV 31, 33, 51, and 45, among women who receive 3 doses (27). Thus, even higher protection is expected to occur due to cross-protection against other HPV types with current vaccines and the approval of a vaccine that targets 7 carcinogenic types in the near future, thus making type replacement less relevant.

In recent years, several countries have introduced the use of molecular HPV detection tests, alone or in conjunction with cytological analysis, as the primary method of screening for cervical cancer. Because of the high negative predictive value and thus the heightened ability of these new tests to identify women with very low risk of having a CIN3 or worse lesion detected following a negative test result, screening guidelines were recently reviewed in several countries, and new guidelines allow for extended screening intervals in comparison with cytology alone (28, 29). While current screening guidelines do not differentiate between vaccinated and unvaccinated individuals, the implementation of vaccination programs using one of the 2 approved vaccines may warrant a new review of the screening guidelines in the not-so-distant future, since a decrease in the performance of current screening methods is expected among vaccinated women based on mathematical models (30, 31). The vaccination programs mainly target girls aged 9–12 years, to obtain the most benefit from the vaccine; thus, highly vaccinated cohorts are not expected to reach cervical cancer screening age until 5–10 years from now (given the introduction of the vaccine in approximately 2007–2009). However, in some countries, like Australia, vaccine uptake was considerable among women in the catch-up age groups (up to age 26 years), who are already reaching cervical cancer screening age. New models of the risk of developing CIN3 or worse lesions will have to be developed that take into account possible modifications of the natural history of HPV infection and cervical neoplasia introduced by vaccination. Policy-makers will need this information when defining screening and management guidelines that incorporate HPV testing and vaccination, to avoid excessive screening and (especially) overtreatment of young women with slower-growing CIN2/CIN3 lesions and possible higher lesion regression potential.

This report by Yang et al. outlines the baseline distribution of HPV types before the introduction of HPV vaccination in New Mexico in 2006–2007 (17). Given this unique resource, we look forward to continued reports, from this cohort and others, on the distribution of HPV types after introduction of the HPV vaccine, to further improve our understanding of the impact of HPV vaccination on the HPV type distribution and screening performance.

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