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Concurrent Infection With Multiple Human Papillomavirus Types Among Unvaccinated and Vaccinated 17-Year-Old Norwegian Girls

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Background. Whether type-specific human papillomavirus (HPV) infection influences the risk of acquiring infections with other HPV types is unclear. We studied concurrent HPV infections in 17-year-old girls from 2 birth cohorts; the first vaccine-eligible cohort in Norway and a prevaccination cohort.

Methods. Urine samples were collected and tested for 37 HPV genotypes. This study was restricted to unvaccinated girls from the prevaccination cohort (n = 5245) and vaccinated girls from the vaccine-eligible cohort (n = 4904). Risk of HPV infection was modelled using mixed-effect logistic regression. Expected frequencies of concurrent infection with each pairwise combination of the vaccine types and high-risk types (6/11/16/18/31/33/35/39/45/51/52/56/58/59) were compared to observed frequencies.

Results. Infection with multiple HPV types was more common among unvaccinated girls than vaccinated girls (9.2% vs 3.7%). HPV33 and HPV51 was the only HPV pair that was detected together more often than expected among both unvaccinated ($P = .002$) and vaccinated girls ($P < .001$). No HPV pairs were observed significantly less often than expected.

Conclusions. HPV33 and HPV51 tended to be involved in coinfection among both unvaccinated and vaccinated girls. The introduction of HPV vaccination does not seem to have had an effect on the tendency of specific HPV types to cluster together.

Keywords. human papillomavirus; HPV vaccine; HPV genotype; multiple infections; epidemiological monitoring; urine sample; Luminex assay.

Human papillomavirus (HPV) is a necessary cause of cervical cancer and contributes to a substantial proportion of cancers of the anus, vagina, penis, oropharynx, and vulva [1, 2]. Of the more than 200 HPV genotypes that so far have been identified [3], 12 types are defined as carcinogenic to humans [4]. Three vaccines to prevent HPV infection are currently licensed; a bivalent vaccine targeting HPV16 and 18, a quadrivalent vaccine targeting HPV6, 11, 16, and 18, and a nonavalent vaccine targeting HPV6, 11, 16, 18, 31, 33, 45, 52, and 58.

Women infected with HPV are often infected with more than 1 type [5–7]. Multiple HPV infections occur more frequently than expected under the assumption of independence between infections [6, 8–12]. This is not surprising because the different HPV types have the same route of transmission and common risk factors [13]. In addition, past or current infection with certain HPV types may affect the risk of acquiring infections with other types. Such interactions between HPV types could potentially also contribute to dependencies between infections.

Interactions between HPV types may have consequences for the overall effectiveness of HPV vaccination programs. In theory, type replacement may occur after HPV vaccination is introduced if competitive interactions between vaccine-targeted types and nonvaccine types exist, for example, if different types compete for the same cervical cells or if a cleared infection results in cross-protective immunity [14]. Lower prevalence of vaccine-targeted types may then lead to increased prevalence of nonvaccine types. A meta-analysis evaluating population-level effects of the bivalent and quadrivalent HPV vaccines found significantly higher prevalence of several nonvaccine types in the postvaccination period compared to the prevaccination period [15]. However, the authors concluded that their results did not provide clear evidence of type replacement and that the increase could be explained by other factors, like unmasking.

To gain insight into interactions between HPV types, several studies have investigated the combinations of types

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involved in concurrent infections [5–8, 10–12, 16–21]. Except for 1 randomized clinical trial [21], these studies included only unvaccinated individuals. Thus, whether HPV vaccination programs have had an impact on the tendency of HPV types to be involved in coinfection with other types is not known.

In Norway, 12-year-old girls have been offered HPV vaccine since 2009. The vaccine is delivered through a school-based program. The quadrivalent vaccine was used until 2017. As part of the national surveillance of the HPV vaccination program, urine samples from girls and young women are collected in a series of population-based cross-sectional studies to monitor HPV prevalence [22, 23]. We have previously studied genotype prevalence and vaccine effectiveness in 17-year-old girls [23]. In the present study, we investigated concurrent HPV infections and associations between HPV types in 17-year-old girls from a vaccine-eligible birth cohort and from a prevaccination cohort to assess the potential impact of the introduction of HPV vaccination on clustering of HPV types.

METHODS

Sample Collection and HPV Genotyping

In the current study, we included girls born in 1994 and 1997. The 1997 cohort was the first birth cohort offered HPV vaccine through the national immunization program. Girls born prior to 1997 were not offered free-of-charge HPV vaccine before November 2016. The National Registry was used to identify girls who were eligible for participation. All girls born in 1994 or 1997 residing in Norway on 1 February the year they turned 17 were invited, except for 5260 girls born at the end of 1994 who were not invited due to a lapse in procedures. In total, 25 811 girls born in 1994 and 31 389 girls born in 1997 were invited. Invitations were sent by mail around the girls' 17th birthday, that is in 2011 and 2014, respectively. The study was approved by the Regional Committee for Medical and Health Research Ethics, Southeast Norway. Written informed consent was obtained from all participants.

The participants received a urine sampling kit and were asked to return a first-void urine sample by mail to the Norwegian Institute of Public Health. Samples were analyzed for HPV at the Norwegian HPV Reference Laboratory. The DNA extraction and HPV genotyping protocols have been described in detail previously [22]. Briefly, a modified GP5+/GP6+ polymerase chain reaction (PCR) protocol [24] followed by a Luminex-based genotyping test [25] was used.

The method detects 37 HPV genotypes: 12 carcinogenic types, referred to as high-risk (HR) types (HPV 16/18/31/33/35/39/45/51/52/56/58/59); 1 probably HR type (HPV68); 9 possibly HR types (HPV 26/30/53/66/67/69/70/73/82); and 15 types with limited evidence of carcinogenic potential (HPV 6/11/40/42/43/54/61/74//81/83/86/87/89/90/91) [4].

Genetic Similarity of HPV Types

HPV L1 nucleotide gene sequences of the 37 genotypes were retrieved from the Human Papillomavirus Database [26]. All sequences were aligned with Mafft version 7.266 [27] employing the G-INS-i algorithm. Alignment uncertainty was reduced by removing poorly aligned and gapped regions using TrimAl version 1.4.rev15 [28] with the strict settings, producing a final alignment size of 1301 base pairs. The alignment was then visualized in AliView version 1.26 [29]. The number of differences between each pair of sequences was computed using Mega version 10.1.1 [30]. Percent identity was then calculated for all sequence pairs in the L1 alignment.

HPV Vaccination

The participants were linked to their records in the Norwegian Immunization Registry by use of the unique identification number assigned to all residents of Norway. Health professionals are required to notify the immunization registry of all vaccinations given within the childhood immunization program [31]. Girls who had not received any doses of HPV vaccine were considered unvaccinated. Girls were considered vaccinated if they had received all 3 doses of HPV vaccine. Vaccine doses received <15 days prior to urine sampling were not taken into account.

Study Sample

HPV results were available for 5468 girls born in 1994 and 6360 girls born in 1997. Because we wanted to assess the impact of HPV vaccination, we excluded vaccinated girls born in 1994 (n = 135) and unvaccinated girls born in 1997 (n = 1321). We also excluded 79 girls born in 1994 and 135 girls born in 1997 who were partially vaccinated. Finally, we excluded 9 girls with missing information on region of residence. In total, 5245 unvaccinated girls born in 1994 and 4904 vaccinated girls born in 1997 were included in the analyses.

Statistical Analyses

The analyses were restricted to 35 HPV types, because types with a prevalence of 0% in either unvaccinated or vaccinated girls (HPV26 and HPV69) were not included. All analyses were done separately for each birth cohort. Prevalence of infection among vaccinated and unvaccinated girls was compared with a Fisher mid-*P* test [32]. If HPV infections are independent events, the number of concurrent infections in an individual will follow a Poisson binomial distribution [33] with number of trials equal to the number of HPV types and success probabilities equal to the type-specific prevalences. We calculated observed to expected (O/E) ratios with exact Poisson 95% confidence intervals (CIs). O/E ratios far from unity were interpreted as indications of discrepancies between the model and the data. To account for dependencies between infections, we used mixed-effect logistic regression to model the risk of infection [34]. The model included an individual-level random intercept representing between-subject variation

in risk due to unmeasured factors and indicator variables for HPV type and region of residence. (Details are provided in the Supplementary Material.) We also analyzed both birth cohorts combined with mixed effect logistic regression. We used the model to calculate expected probabilities of concurrent infection with each of the 91 possible pairwise combinations of vaccine types and HR types (Supplementary Material). The observed proportions were compared to the expected probabilities with a mid-*P* binomial test [32]. In addition, we used alternating logistic regression (ALR) to assess associations between HPV types [35]. ALR is an implementation of generalized estimating equations where pairwise associations are modelled as odds ratios (ORs). First, we assessed whether the association between 2 types differed with genetic similarity. Pairwise combinations of the 35 types were categorized according to percent identity in the L1 region as follows: <70% (203 pairs), 70%–75% (323 pairs), and >75% (69 pairs). Percent identity <70% defines different species within alphapapilloma viruses [36]. We specified common ORs for any pair within the same category. Furthermore, we estimated associations between types according to carcinogenicity. In this model, we specified common ORs for pairs with 2 HR types, 1 non-HR type and 1 HR type, and 2 non-HR types. All tests were 2-sided and $P < .05$ was considered statistically significant. The analyses were performed with R 3.4.3.

RESULTS

In total, 956 unvaccinated girls born in 1994 (18.2%) and 512 vaccinated girls born in 1997 (10.4%) were infected with at least 1 of the 35 HPV types we investigated (Table 1). The prevalence of infection with multiple types was significantly higher among unvaccinated than vaccinated girls (9.2% vs 3.7%, $P < .0001$). However, the prevalence of multiple infections without vaccine types was only slightly higher (4.2% vs 3.6%, $P = .09$). Multiple infection with at least 1 vaccine type was rare among vaccinated girls (0.1%).

For all vaccine types and most HR types, the prevalence of type-specific multiple infection (ie, type-specific infection in combination with at least 1 other HPV type) was significantly higher among unvaccinated than vaccinated girls (Figure 1 and Supplementary Table 1). The prevalence of type-specific multiple infection without vaccine types did not differ significantly for any of the (nonvaccine) HR types, except HPV31 ($P < .0001$).

Under the assumption of independence, infection with 3 types and infection with 4 or more types occurred significantly more often than expected; O/E ratios were 4.44 (95% CI, 3.66–5.34) and 57.3 (95% CI, 47.5–68.5), respectively, for unvaccinated girls and 15.9 (95% CI, 11.8–21.0) and 333.0 (95% CI, 236.8–455.2), respectively, for vaccinated girls (Table 2). No infection also occurred significantly more often than expected. In contrast, infection with 1 type occurred significantly less often than expected; the O/E ratio was 0.36 (95% CI, .33–.39) for unvaccinated girls and 0.46 (95% CI, .41–.51) for vaccinated girls.

Significant deviations were also found when taking dependencies between infections into account with mixed-effect logistic regression (Table 2). However, except for 2 infections in unvaccinated girls, the O/E ratios were all substantially closer to 1 than under the assumption of independence. For unvaccinated girls, the O/E ratios were 1.31 (95% CI, 1.08–1.58) for 3 infections and 1.32 (95% CI, 1.10–1.58) for 4 or more infections, whereas corresponding numbers for vaccinated girls were 1.62 (95% CI, 1.20–2.14) and 1.40 (95% CI, .99–1.91).

For pairs of vaccine types and HR types, the observed number of girls with concurrent infection was plotted against the expected frequency (Figure 2 and Supplementary Table 2). Among unvaccinated girls, 8 pairs were observed significantly more often than expected: 16 + 52 ($P = .049$), 18 + 51 ($P = .02$), 31 + 52 ($P = .005$), 33 + 51 ($P = .002$), 39 + 45 ($P = .04$), 39 + 52 ($P = .02$), 39 + 58 ($P = .03$), and 45 + 59 ($P = .02$) (Supplementary Table 2). These pairs were detected in 17, 19, 11, 13, 5, 9, 4, and 6 girls, respectively. Among vaccinated girls, the following 4 pairs occurred significantly more often than expected: 11 + 16 ($P = .047$), 33 + 51 ($P < .0001$), 33 + 58 ($P = .009$), and 39 + 56 ($P = .02$). They were detected in 1, 14, 3, and 5 girls, respectively. No pairs were observed significantly less often than expected in either cohort. When combining both cohorts, 6 pairs were observed significantly more often than expected: 18 + 51 ($P = .03$), 31 + 52 ($P = .009$), 33 + 51 ($P < .0001$), 33 + 58 ($P = .01$), 39 + 45 ($P = .03$), and 39 + 52 ($P = .04$).

For both unvaccinated and vaccinated girls, the association between pairs of HPV types with the highest percent identity

Table 1. Human Papillomavirus (HPV) Infection Among Unvaccinated Girls Born in 1994 (n = 5245) and Vaccinated Girls Born in 1997 (n = 4904)

HPV Infection	Unvaccinated, No. (%)	Vaccinated, No. (%)	*P* Value[a]
Infection with at least 1 HPV type	956 (18.2)	512 (10.4)	<.0001
Infection with a single nonvaccine type	333 (6.3)	298 (6.1)	.58
Infection with a single vaccine type	143 (2.7)	32 (0.7)	<.0001
Infection with multiple HPV types	480 (9.2)	182 (3.7)	<.0001
Multiple infection with no vaccine types	222 (4.2)	175 (3.6)	.09
Multiple infection with at least 1 vaccine type	258 (4.9)	7 (0.1)	<.0001

[a]Fisher mid-*P* test was used to compare prevalence among unvaccinated and vaccinated girls.

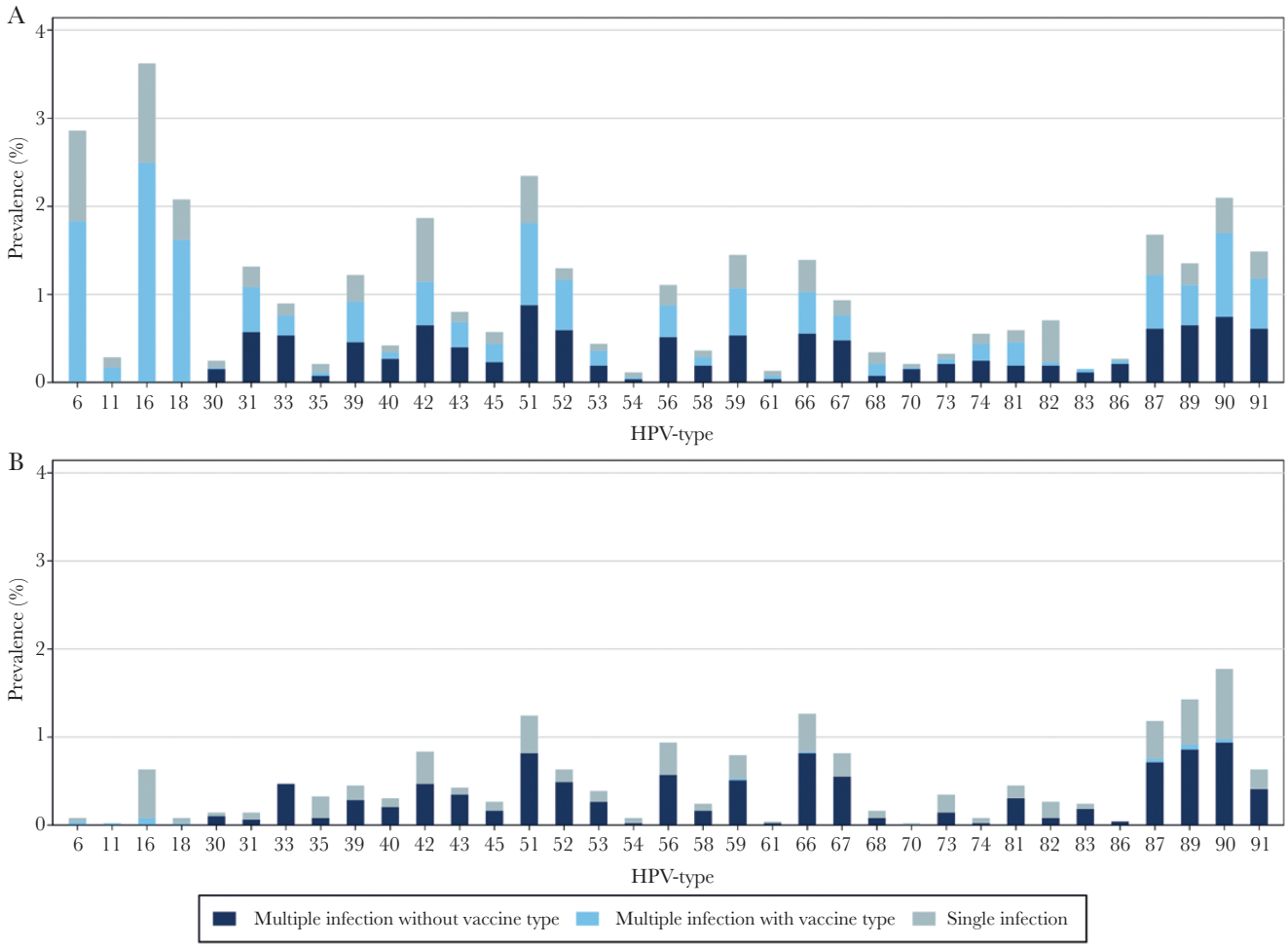

Figure 1. Type-specific human papillomavirus (HPV) prevalence among 5245 unvaccinated girls born in 1994 (*A*) and 4904 vaccinated girls born in 1997 (*B*).

in the L1 region was similar to the association between pairs of types with the lowest percent identity (Figure 3). Among unvaccinated girls, OR was 5.76 (95% CI, 5.11–6.50) for pairs with percent identity <70% and 6.41 (95% CI, 5.36–7.66) for pairs with percent identity >75%. Among vaccinated girls, corresponding ORs were 8.73 (95% CI, 7.24–10.5) and 8.34 (95% CI, 6.17–11.3), respectively. In each category of percent identity, the OR was higher for vaccinated girls than for unvaccinated girls.

We observed a slightly stronger association between 2 HR types than between 2 non-HR types among unvaccinated girls; ORs were 6.55 (95% CI, 5.55–7.72) and 5.16 (95% CI, 4.51–5.89), respectively (Figure 4). Among vaccinated girls, the association between 2 HR types was similar to the association between 2 non-HR types; ORs were 9.32 (95% CI, 7.07–12.3) and 9.36 (95% CI, 7.56–11.6), respectively. Again, higher ORs were found for vaccinated girls.

DISCUSSION

In this study, we investigated concurrent HPV infections among 17-year-old Norwegian girls from the first birth cohort offered HPV vaccine and from a prevaccination birth cohort. Infection with multiple types was more common among unvaccinated girls in the prevaccination cohort than among vaccinated girls in the vaccine-eligible cohort. This was mainly attributable to a reduction in multiple infections with at least 1 vaccine type. Several pairs of HPV-types were involved in coinfection more often than expected, but HPV33 and HPV51 was the only pair observed more often than expected in both unvaccinated and vaccinated girls. The association between pairs of HPV types did not become stronger with increasing percent identity in the L1 region. In unvaccinated girls, the association between HR types was somewhat stronger than between non-HR types.

In both birth cohorts, the observed frequencies of no infection and infection with 3 or more types were higher than expected under the assumption of independence. Our results correspond well with findings from previous studies [6, 8, 10–12] and support that infections with different HPV types do not occur independently. Previous studies on concurrent HPV infections have found positive associations between several pairs of HPV types [5–7, 10–12, 16]. Some negative associations have

Table 2. Observed and Expected Frequencies of Infection With Multiple Types of Human Papillomavirus (HPV) Among Unvaccinated Girls Born in 1994 (n = 5245) and Vaccinated Girls Born in 1997 (n = 4904)

	Poisson Binomial[a]			Mixed Effect Model[b]	
Number of HPV Types	Observed, No. (%)	Expected, No. (%)	Observed/Expected (95% CI)	Expected, No. (%)	Observed/Expected (95% CI)
Unvaccinated					
0	4289 (81.8)	3657.9 (69.7)	1.17 (1.14–1.21)	4094.8 (78.1)	1.05 (1.02–1.08)
1	476 (9.1)	1329.7 (25.4)	0.36 (.33–.39)	781.0 (14.9)	0.61 (.56–.67)
2	248 (4.7)	230.0 (4.4)	1.08 (.95–1.22)	193.5 (3.7)	1.28 (1.13–1.45)
3	112 (2.1)	25.2 (0.5)	4.44 (3.66–5.34)	85.2 (1.6)	1.31 (1.08–1.58)
≥4	120 (2.3)	2.1 (0.04)	57.3 (47.5–68.5)	90.6 (1.7)	1.32 (1.10–1.58)
Vaccinated					
0	4392 (89.6)	4123.7 (84.1)	1.07 (1.03–1.10)	4305.8 (87.8)	1.02 (.99–1.05)
1	330 (6.7)	717.8 (14.6)	0.46 (.41–.51)	461.1 (9.4)	0.72 (.64–.80)
2	94 (1.9)	59.2 (1.2)	1.59 (1.28–1.94)	78.8 (1.6)	1.19 (.96–1.46)
3	49 (1.0)	3.1 (0.06)	15.9 (11.8–21.0)	30.3 (0.6)	1.62 (1.20–2.14)
≥4	39 (0.8)	0.1 (0.002)	333.0 (236.8–455.2)	27.9 (0.6)	1.40 (.99–1.91)

Abbreviation: CI, confidence interval.

[a]Independence between infections with different HPV types is assumed. Success probabilities are equal to the type-specific prevalences.

[b]Expected numbers are based on mixed effect logistic regression. The model included an individual-level random intercept and indicator variables for HPV type and region of residence.

also been observed [5–7, 16]. However, the pairs of HPV types that are associated differ between studies, possibly because of substantial variation in type-specific prevalences due to different geographical settings and differences in the age distribution of the participants. No previous studies have observed an association between HPV33 and HPV51.

The sensitivity of PCR assays using consensus or general primers for detecting individual HPV types may decrease when other types with a higher viral load are present because of competition for the primers [14]. Although we would expect the potentially lower sensitivity to result in a negative bias, no HPV pairs were observed significantly less often than expected. The sensitivity for detecting pairs of HPV types may have been higher among the vaccinated girls, because we would expect less masking in the PCR detection of nonvaccine types by vaccine types due to the low prevalence of vaccine types among

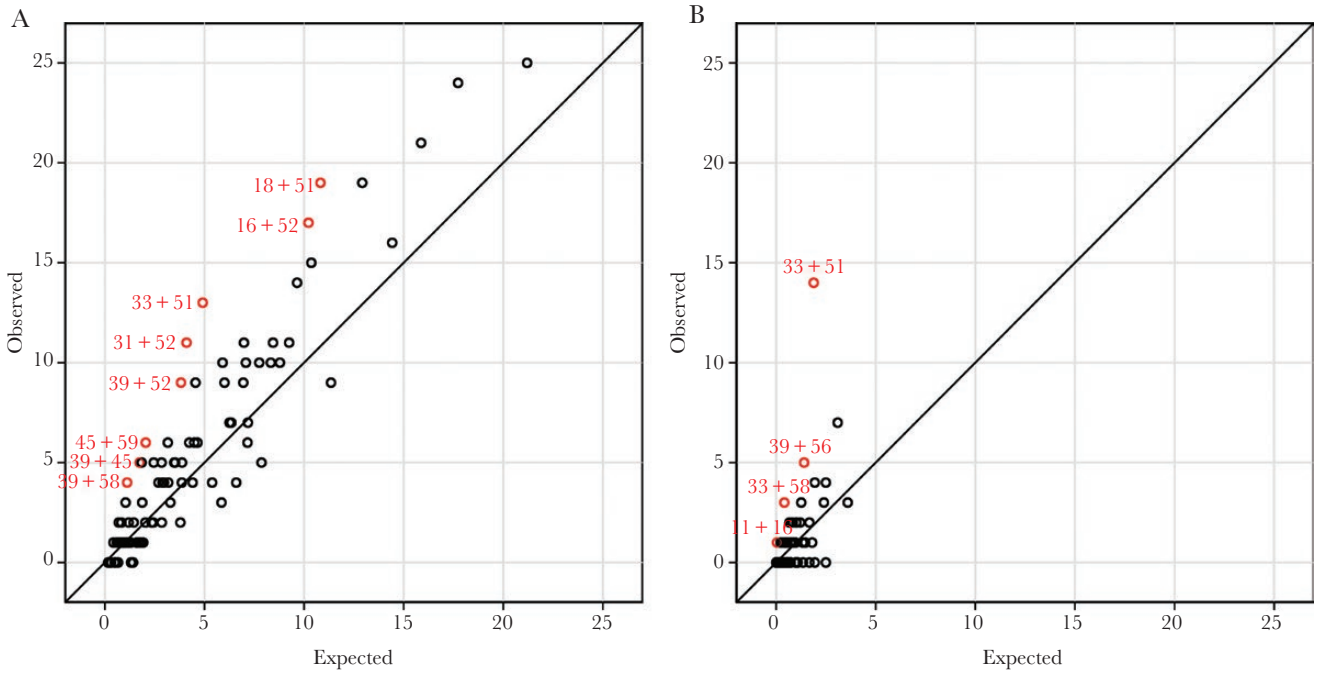

Figure 2. Occurrence of concurrent infection with each possible pairwise combination of high-risk and vaccine human papillomavirus types (6, 11, 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59) among 5245 unvaccinated girls born in 1994 (*A*) and 4904 vaccinated girls born in 1997 (*B*). Mixed-effect logistic regression was used to calculate expected number of girls. Pairs with a significant deviation between the observed and expected number ($P < .05$) are represented in red.

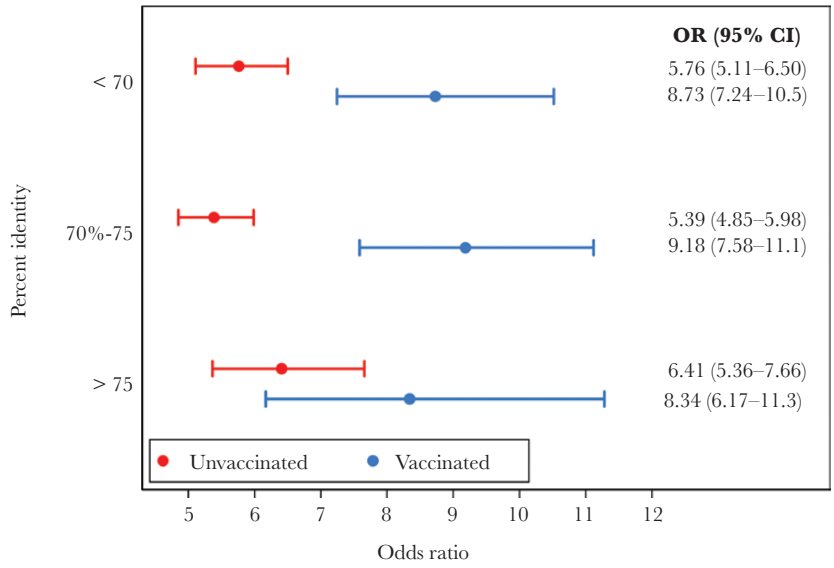

Figure 3. Associations between pairs of human papillomavirus types according to percent identity in the L1 region. Abbreviations: CI, confidence interval; OR, odds ratio.

the vaccinated girls. This may have led to differences between unvaccinated and vaccinated girls regarding the HPV pairs that were detected.

Two closely related HPV types may be detected together even if only 1 of the types is present as a result of cross-hybridization. This may explain why the 2 most similar types in our study, HPV33 and HVP58, were observed together significantly more often than expected among vaccinated girls. Two previous studies evaluating concurrent infections have also found a positive association between HPV33 and HPV58 [5, 11]. Percent identity was >70% for all the pairs that were observed significantly more often than expected, but it was only 70.5% for HPV33 and HPV51, the only pair that was significant in both cohorts. Overall, the association between the most similar pairs did not differ from the association between the least similar pairs. This is in agreement with results from a Costa Rican study [16]. In contrast, Vaccarella et al found that the most similar pairs were the most likely to be detected together [5]. However, the findings depended on genotyping method. The authors therefore concluded that the clustering of similar types was a result of a diagnostic artefact.

Among unvaccinated girls, we observed a slightly stronger association between HR types than between non-HR types. This is in agreement with results from a Dutch study [12]. HR types may have a higher probability of being detected together because infections with HR types generally have longer durations

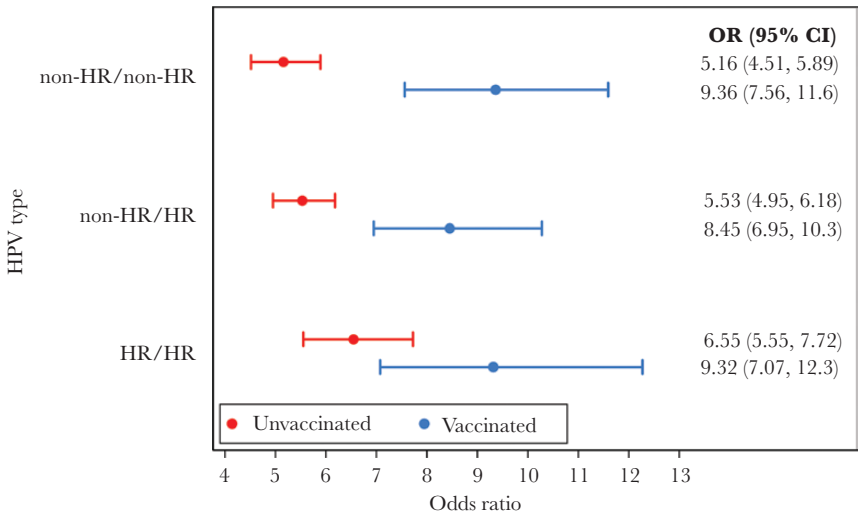

Figure 4. Associations between pairs of HPV types according to carcinogenicity. HR types: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59; non-HR types: 6, 11, 30, 40, 42, 43, 53, 54, 61, 66, 67, 68, 70, 73, 74, 81, 82, 83, 86, 87, 89, 90, and 91. Abbreviations: CI, confidence interval; HPV, human papillomavirus; HR, high risk; OR, odds ratio.

[37]. HPV16 was the most prevalent type among unvaccinated girls, but rare among vaccinated girls. The substantial decline may explain why we did not observe a stronger association between HR types among vaccinated girls, because HPV16 is one of the most persistent types.

For most pairs with a significant deviation between the expected and observed number, the *P* values were close to .05. Some of these findings may have occurred by chance. Thus, no strong evidence was found of interactions between vaccine types and nonvaccine types, a requirement of type replacement. However, for HPV33 and HPV51, the *P* value was substantially smaller among both unvaccinated and vaccinated girls. The positive association between HPV33 and HPV51 is therefore less likely to be due to chance, especially considering that it was found in both cohorts. The long duration of HPV33 infections [37] might explain why coinfections involving HPV33 may occur more frequently than expected. However, the duration of HPV51 infections is much shorter. It is possible that our findings are a result of interaction between HPV33 and HPV51. Potential biological mechanisms that could specifically cause HPV33 and HPV51 to interact have not been identified. However, longitudinal studies with regular HPV testing of the participants might clarify whether potential interactions between HPV33 and HPV51 are immediate or delayed [38] and whether they operate through acquisition or clearance.

An underlying assumption when studying concurrent HPV infections is that synergistic interactions result in positive associations between types, whereas competitive interactions result in negative associations. Whether this is a valid assumption has been questioned [38–40]. Even when there is no interaction between 2 types, a positive effect estimate may be observed. Confounding due to unobserved risk factors shared by multiple HPV types and correlation between the times an individual is at risk for infection with different types will lead to a bias in a positive direction [39, 40]. Moreover, competitive interaction can also lead to a positive association. A positive association can occur in the case of cross-immunity, that is when immunity after a cleared infection with one type reduces the risk of acquiring the other type [38–40]. However, it is unlikely that interactions that operate after an infection has been cleared have had an effect on our results. We expect few girls to be immune after past infections. Median duration of HPV infections is about 10 months [37], and the participants were only 17 years old. In a recent national survey, only 24% of girls in the last year of upper secondary school reported that they were younger than 16 years at the time of first sexual intercourse [41].

An important limitation is the lack of information on sexual behavior. Although unmeasured risk factors that are common to all HPV types are accounted for in the mixed-effect model, confounding due to insufficient adjustment for this important risk factor cannot be ruled out. This might explain why the model underestimated the number of girls infected with 3 or more types. However, studies from Norway do not indicate that sexual behavior changed during the study period [41–43]. Moreover, no association has been observed between HPV vaccination and sexual behavior [44–46]. Thus, we have no reason to believe that comparisons between unvaccinated and vaccinated girls are confounded by sexual behavior. Furthermore, we have not been able to control for correlation between times at risk for infection [39]. This may have resulted in a positive bias and could explain why no negative associations were found. The times-at-risk bias could also explain why associations were stronger among vaccinated girls. Because vaccinated girls spend more time not at risk than unvaccinated girls, the correlation between times at risk for infection with different HPV types tends to be higher in vaccinated girls, which may lead to a more pronounced bias. However, controlling for time at risk is usually not feasible [39]. Another potential limitation is that multiple HPV types detected together in urine may reflect infections at different anatomical sites. Interaction between such infections is unlikely to occur. However, testing of first-void urine samples for HPV, as was done in our study, has a high sensitivity and specificity for detection of cervical HPV [47]. Moreover, agreement between type-specific HPV detection in urine samples and cervical samples is good [48, 49]. Finally, the low prevalence of type-specific infections in the vaccinated cohort may have precluded detection of interactions.

Strengths of our study include the population-based design and large number of both unvaccinated and vaccinated participants. To our knowledge, concurrent HPV infections in vaccinated individuals has not previously been assessed in a population-based study. Through linkage with the immunization registry, we were able to obtain accurate information on the participants' HPV vaccination status.

In conclusion, vaccinated girls were less likely than unvaccinated girls to be infected with multiple HPV types. Furthermore, HPV33 and HPV51 tended to be involved in coinfection among both unvaccinated and vaccinated girls. This may be an indication of interaction between these types. However, we cannot rule out other explanations for this finding, for example, correlation between times at risk for infection with different HPV types. We did not find indications of interaction between any other pairs. Moreover, our results do not indicate that the introduction of HPV vaccine has had an effect on the tendency of specific pairs of HPV types to occur in coinfection.

Supplementary Data

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

Notes

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Potential conflicts of interest. All authors: No reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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