

Population-Level Effects of Human Papillomavirus Vaccination Programs on Infections with Nonvaccine Genotypes

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We analyzed human papillomavirus (HPV) prevalences during prevaccination and postvaccination periods to consider possible changes in nonvaccine HPV genotypes after introduction of vaccines that confer protection against 2 high-risk types, HPV16 and HPV18. Our meta-analysis included 9 studies with data for 13,886 girls and women ≤ 19 years of age and 23,340 women 20–24 years of age. We found evidence of cross-protection for HPV31 among the younger age group after vaccine introduction but little evidence for reductions of HPV33 and HPV45. For the group this same age group, we also found slight increases in 2

nonvaccine high-risk HPV types (HPV39 and HPV52) and in 2 possible high-risk types (HPV53 and HPV73). However, results between age groups and vaccines used were inconsistent, and the increases had possible alternative explanations; consequently, these data provided no clear evidence for type replacement. Continued monitoring of these HPV genotypes is important.

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Persistent infection with a high-risk human papillomavirus (HPV) genotype is necessary for development of cervical cancer (1). Two high-risk types, HPV16 and HPV18, cause $\approx 70\%$ – 80% of cervical cancers (2–4). The HPV vaccines currently available commercially have been shown in trial settings to have $\approx 100\%$ vaccine efficacy against cervical disease caused by vaccine-specific high-risk HPV types: bivalent and quadrivalent vaccines against HPV16 and HPV18 and the new nonavalent vaccine against HPV31, HPV33, HPV45, HPV52, and HPV58 (5–7). Clinical trial data for the bivalent and quadrivalent vaccines have shown low-to-moderate protection (i.e., cross-protection) against other high-risk HPV types that are phylogenetically related to HPV16 and HPV18 (8,9).

Many countries have now introduced HPV vaccination programs (10). A recently published systematic review and meta-analysis assessed population-level effects of HPV vaccination on vaccine HPV types and showed strong evidence that HPV vaccination is highly effective against infections with these vaccine-specific high-risk types (11). The review also examined closely related HPV types as a single group and found evidence of cross-protection overall in a population-based setting (11). However, assessment of changes in the prevalence of closely related HPV types combined may not provide full evidence of the effects of a national vaccination program because examining the types as a single group potentially conceals decreases or increases in the prevalence of individual types. Grouping HPV types together limits the possibility of examining

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cross-protection provided by specific HPV types and of detecting changes in other individual nonvaccine types. For example, a theoretical concern is that reduced prevalences of infection with HPV16 and HPV18 could lead to other high-risk HPV types occupying those niches and becoming more common causes of disease. Although type replacement was not observed in the clinical trials (12), monitoring for possible type replacement in population-based settings after the introduction of national HPV vaccination programs is important. Furthermore, because nonvaccine HPV types are far less common than vaccine HPV types, a single study may have limited scope to determine whether type replacement has occurred. Combining data from several reports improves the ability to investigate type replacement. We aimed to investigate population-level effects of HPV vaccination programs that used bivalent or quadrivalent vaccines on type-specific prevalences of infection caused by individual nonvaccine high-risk HPV types.

Methods

Objectives

Using data from surveys conducted before an HPV vaccination program was introduced and data from surveys after the program was introduced, we compared HPV prevalences for similar populations within the same country. We conducted a systematic literature search to determine changes in HPV prevalence for each nonvaccine high-risk HPV type. At the time of our search, any eligible study would have considered vaccination that used bivalent or quadrivalent vaccines; consequently, high-risk HPV types used only in the nonavalent vaccine were considered nonvaccine HPV types. Each individual type was presented separately in our analysis. We included HPV types for which some cross-protection had been demonstrated in clinical trials (HPV31 and HPV33, which are phylogenetically related to HPV16, and HPV45, which is phylogenetically related to HPV18) (8,9,13); other high-risk HPV types included in the nonavalent vaccine (HPV52 and HPV58); other high-risk and probably high-risk HPV types (HPV35, HPV39, HPV51, HPV56, HPV59, and HPV68); and other possibly high-risk HPV types (HPV26, HPV53, HPV70, HPV73, and HPV82), as classified by the International Agency for Research on Cancer (14). This systematic review and meta-analysis was reported in accordance with PRISMA guidelines (15).

Search Strategy and Selection Criteria

Using Embase, Medline, LILACS, and African Index Medicus databases, we searched for eligible publications published from 2007, the year that the first HPV vaccination programs were introduced, through February 19, 2016. To identify relevant studies that mentioned both vaccination

and HPV infection or a related disease (such as HPV-related precancerous lesions, cancers, and genital warts), the search strategy incorporated MeSH terms from the PubMed database (<http://www.ncbi.nlm.nih.gov/mesh>) and relevant words found in the title or abstract (online Technical Appendix, <http://wwwnc.cdc.gov/EID/article/22/10/16-0675-Techapp1.pdf>). The search had no language restrictions.

Eligible studies were those that assessed population-level effects of HPV vaccination over time by comparing the prevalence of HPV infection (defined by the detection of HPV DNA in patient samples) during a prevaccination period with the prevalence during a postvaccination period. We excluded studies comparing HPV infection in vaccinated persons with HPV infection in unvaccinated persons as part of an individually randomized trial because such studies would not measure population-level effects. Similarly, we excluded studies in which HPV infection was compared only between unvaccinated and vaccinated persons in the postvaccination period. We also excluded studies in which only a small proportion (<2%) of the postvaccination study population was vaccinated (i.e., studies conducted in largely unvaccinated populations). One author (D.M.) initially reviewed titles and abstracts of studies for eligibility; we reviewed in full those studies that appeared to address changes in HPV prevalence after introduction of HPV vaccination programs. We also compared search results with those identified in a recent related review (11), which compared prevaccination and postvaccination periods for high-risk vaccine types (HPV16 and HPV18), cross-protected types (HPV31, HPV33, and HPV45), and all high-risk HPV nonvaccine types combined.

Data Extraction and Data Quality

For each study, we extracted data on study design and country of study. Then, for both prevaccination and postvaccination periods, we extracted data on year(s) of sample collection, study setting and population, sample size, specimen type, assay used for HPV DNA testing, HPV genotypes included in the assay, demographic and sexual behavior data collected, and the measure of effect (and method used to determine any effect). For the postvaccination period, we also extracted data on the method used to ascertain estimated vaccination coverage.

In addition, we assessed the potential bias in each study by considering the comparability of the study populations in the prevaccination versus postvaccination periods (i.e., similar setting and population demographics); the extent of adjustment for potential confounders; the suitability of the specimen type to assess HPV DNA infection; the suitability of the assay used for accurate HPV DNA testing (and whether the suitability of assays differed between the prevaccination and postvaccination periods); and the method used to estimate HPV vaccination coverage. To assess

external validity, we considered whether the study samples were population based. Each of these factors was scored as either low risk or high risk.

When published data on HPV prevalence and prevalence ratios (PRs) for individual high-risk HPV types were unavailable, we contacted authors to request the HPV type-specific prevalences during the prevaccination and postvaccination periods and the PRs for the 2 periods for each nonvaccine high-risk HPV type. We requested PRs adjusted for demographic and sexual behavior data or the unadjusted PRs if data on confounders were unavailable; we calculated unadjusted PRs if authors provided raw data. By using data from a previously conducted validation study, 1 study included adjusted odds ratios rather than PRs to adjust for the change in assay used during the prevaccination and postvaccination periods (16).

Data Analysis

We used estimates weighted to account for selection processes if that data were available from authors unweighted numbers, as shown in online Technical Appendix Table 1). We also stratified data by age group (i.e., ≤ 19 and 20–24 years of age) because of expected lower rates of vaccination coverage and lower vaccine effectiveness in those vaccinated at older ages. Consequently, for each study, we requested data from authors for the same 2 age groups. One study included data for girls < 13 years of age, so we requested data restricted to those 16–19 years of age (17).

To enable calculation of a PR for a prevalence of 0 during either the prevaccination or postvaccination period, we used a continuity correction of 0.5. When prevalence was 0 for both the prevaccination and postvaccination periods, we excluded the study from the meta-analysis for the relevant age group and HPV type. Results were further stratified by type of vaccine used (i.e., bivalent or quadrivalent). PRs within each subgroup were combined to obtain a summary PR by using a fixed-effects model if data were not shown to be heterogeneous; lack of heterogeneity was determined by a p value ≥ 0.10 calculated with the Cochrane Q test or by an I^2 value $< 25\%$ (18). Sensitivity analyses were restricted to studies that used cervical, vulval, or vaginal swabs as specimen type because urine samples have lower sensitivity for detecting HPV DNA infection (19).

Results

Included Studies

After we eliminated duplications, we identified 4,648 unique articles in searches from all 4 databases (Figure 1). An initial search of title and abstracts of these articles excluded 4,508 (97.0%) because of ineligibility. For the

remaining 140 articles, we examined the full text to determine compliance with eligibility criteria and identified 10 eligible studies (Figure 1). Of these 10 studies, 1 met all eligibility criteria, but the type-specific PRs were unavailable from authors (20). Therefore, we included 9 studies in the systematic review and meta-analysis (16,17,21–27). All eligible studies were repeat cross-sectional studies that compared changes in prevalence in populations before and after introduction of a national HPV vaccination program (online Technical Appendix Table 1). Because only 1 study considered changes in HPV infection among male and female populations, we considered only female populations in the analysis. Two studies were population-based national surveys (23,26); 3 studies were conducted among young women obtaining chlamydia screening (16,17,27); 2 studies comprised young women attending a primary care clinic, community health center, or hospital-based adolescent clinic (21,22); and 2 studies comprised women obtaining cervical screening (24,25) (online Technical Appendix Table 1). The included studies contained data on 13,886 girls and women ≤ 19 years of age and 23,340 women 20–24 years of age.

The studies varied in methodologic quality on the basis of potential bias (Table 1). Most studies collected some demographic and sexual behavior data to enable appropriate

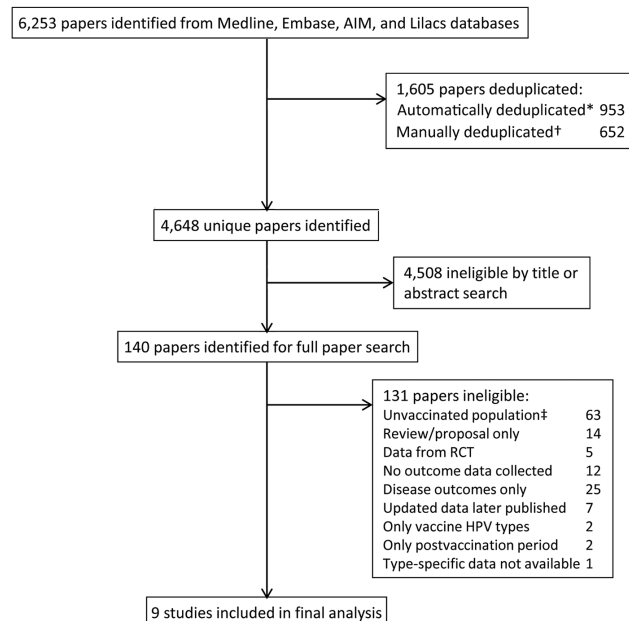


Figure 1. Flowchart for eligible studies included in systematic review and meta-analysis of changes in prevalences of nonvaccine human papillomavirus (HPV) genotypes after introduction of HPV vaccination. *100% title match, author's surname and initial, publication year, and periodical; †85% title match, and author surname; ‡includes studies in which the vast majority of the population were unvaccinated. RCT, randomized controlled trials.

Table 1. Potential bias and external validity of studies included in meta-analysis of changes in prevalences of nonvaccine HPV genotypes*

Potential bias factors	Study, authors (reference no.)								
	Meshner et al. (16)	Söderlund-Strand et al. (17)	Cummings et al. (21)	Kahn et al. (22)	Sonnenberg et al. (23)	Tabrizi et al. (24)	Cameron et al. (25)	Markowitz et al. (26)	Chow et al. (27)
Population-based samples†	H	H	H	H	L	L	L	L	H
Comparative populations†	H	H	L	L	L	L	L	L	H
Risk factor data collected and adjusted for	H	H	L	L	L	H	H	L	L
Samples suitable for assessing HPV	L	L	L	L	H	L	L	L	L
Assay with suitable accuracy	L	L	L	L	L	L	L	L	L
Identical HPV assays†	H	L	L	L	L	L	L	L	L
Vaccination status collected	H	H	L	L	H	L	L	H	H

*HPV, human papillomavirus; H (in bold), high risk of bias; L, low risk of bias.
†For both prevaccination and postvaccination periods.

adjustment of the relative risks, although the number of factors collected was limited in some studies (16,17,24,25) (Table 1; online Technical Appendix Table 1).

HPV Types Included in Nonavalent HPV Vaccines

HPV Types with Prior Evidence for Cross-Protection

We found evidence of reduced prevalence of HPV31 (Figure 2; Table 2) among girls and women ≤ 19 years of age (PR 0.73, 95% CI 0.58–0.91) but found little evidence of changed prevalences for HPV33 or HPV45 among this age group (PR 1.04, 95% CI 0.78–1.38 for HPV33; PR 0.96, 95% CI 0.75–1.23 for HPV45). Results were heterogeneous for HPV31, HPV33, and HPV45 in women 20–24 years of age; consequently, we did not calculate summary PRs (Figure 2; Table 2).

Other HPV Types

We found evidence of increased prevalence of HPV52 in those ≤ 19 years of age (PR 1.34, 95% CI 1.13–1.59) (Figure 3; Table 2), but because of heterogeneity, we did not calculate summary PRs for those 20–24 years of age. We found no evidence of a changed prevalence for HPV58 among the younger age group (PR 1.01, 95% CI 0.80–1.26) but found borderline evidence of an increase for those 20–24 years of age (PR 1.14, 95% CI 0.99–1.31).

Other High-Risk and Possibly High-Risk HPV Types

No consistent patterns appeared across the studies for other HPV vaccine types not used in the nonavalent vaccine (Table 2; online Technical Appendix Figure 1). We found evidence of increased prevalences from the prevaccination period to the postvaccination period in those ≤ 19 years of age for HPV39 (PR 1.27, 95% CI 1.05–1.54), HPV53 (PR 1.51, 95% CI 1.10–2.06), and HPV73 (PR 1.36, 95% CI 1.03–1.80). For women 20–24 years of age, evidence

indicated increased prevalence for HPV39 (PR 1.13, 95% CI 1.00–1.28).

Sensitivity Analysis

As a sensitivity analysis, we performed 3 additional analyses, all stratified by age group: by type of vaccine used (i.e., bivalent or quadrivalent); by potential bias of the original study (i.e., relatively low potential bias, defined as < 3 factors indicating high risk of bias; or relatively high potential bias, defined ≥ 3 factors indicating high risk of bias) (Table 1); and by vaccination coverage (i.e., low $< 50\%$; high $\geq 50\%$). For studies in settings that used the bivalent vaccine, we found evidence of increased prevalence between the prevaccination period and postvaccination periods among those ≤ 19 years of age for HPV52, HPV53, HPV56, and HPV70 (online Technical Appendix Table 2, Figures 2–4). Prevalence of HPV53 among women 20–24 years of age also increased. For the quadrivalent vaccine, evidence showed increased prevalences of HPV39, HPV51, and HPV59 for those ≤ 19 years of age. Among those 20–24 years of age, evidence indicated increased prevalence of HPV52 and HPV70 (online Technical Appendix Table 2, Figures 2–4).

Many of our analyses that were stratified by potential bias of the included studies had results similar to those in the unstratified analyses (online Technical Appendix Table 3). However, among those ≤ 19 years of age, studies with a relatively low potential bias showed no evidence of increased prevalence for HPV52 or HPV39, although evidence existed when the studies were unstratified. For studies with relatively high potential bias, among this younger age group, evidence showed increased prevalences of HPV51 and HPV70, although these increases were not present in the unstratified analysis. In women 20–24 years of age, evidence showed decreased prevalence for HPV33 in those studies with a relatively low potential bias. No

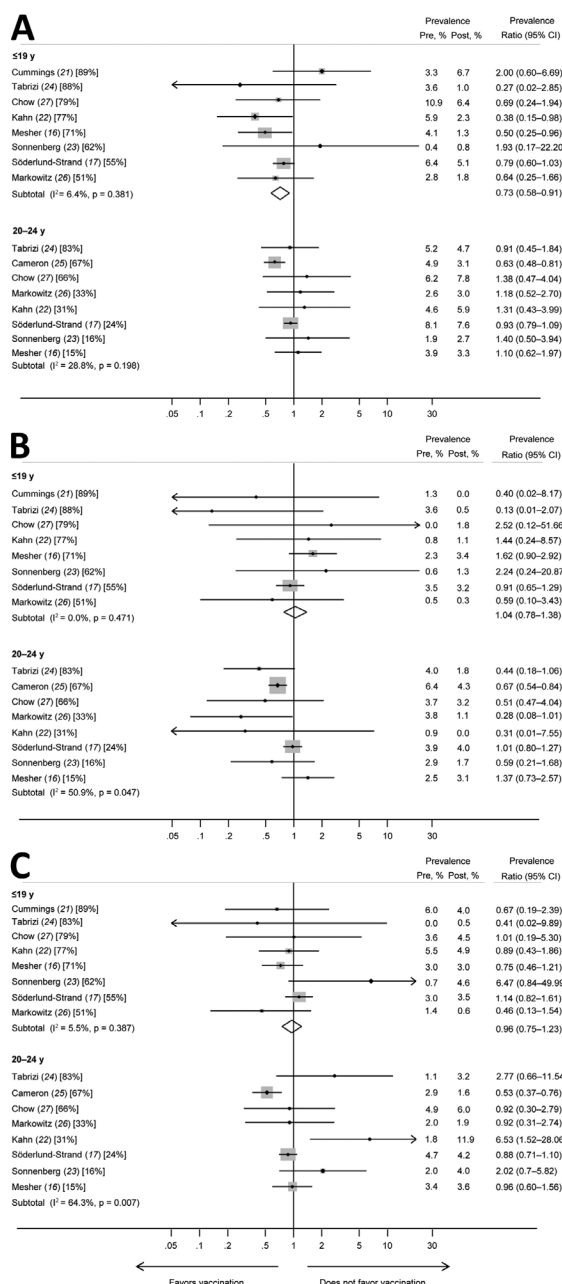


Figure 2. Prevalence ratios and 95% CIs for high-risk human papillomavirus (HPV) types (HPV31, HPV33, and HPV45) that had evidence of cross-protection for girls and women ≤19 years of age and women 20–24 years of age in studies included in a meta-analysis of changes in prevalences of nonvaccine HPV genotypes after introduction of HPV vaccination. A) HPV31; B) HPV33; C) HPV45. Percentages in brackets represent vaccination coverage (≥1 dose) for each study and age group. The size of the gray boxes around the plot points indicates the relative weight given to each study in the calculation of the summary estimate. The study by Cameron et al. (25) is omitted from analyses for the younger age group because this study included no data for the group ≤19 years of age. The study by Cummings et al. (21) is omitted from analyses for women 20–24 years of age because this study included no data for this age group. Pre, prevaccination; post, postvaccination.

summary estimate was provided in the unstratified analysis because of heterogeneity of data. Studies with a relatively high potential bias showed evidence of increased prevalences of HPV52 and HPV58 among women 20–24 years of age. Among this older age group, evidence existed for decreased prevalence of HPV82 in those studies with both relatively high potential bias and relatively low potential bias, although those studies with relatively high potential bias had a larger decrease. Again, no summary estimate was provided in the unstratified analysis because of heterogeneity.

Vaccination coverage was high for the younger age group in all studies (online Technical Appendix Table 4). For the older age group, studies with high vaccination coverage showed decreased prevalence for HPV31. No summary estimate was provided for the unstratified analysis because of heterogeneity. For the older age group, we found evidence of increased prevalences for HPV39 and HPV58 (similar to results from the unstratified analysis) but only in studies with low vaccination coverage. Although not seen in the unstratified analysis, we also found evidence of an increased prevalence for HPV70 in low-coverage studies and borderline evidence of an increased prevalence for HPV26 in high-coverage studies. No summary estimates were provided for the unstratified analyses because of heterogeneity.

Discussion

Comprehensive postvaccination surveillance should not only consider reductions of vaccine type-specific infection and associated disease but should also assess any other potential effects of reductions of targeted infections. We assessed changes in nonvaccine HPV types to determine evidence of cross-protection for individual HPV types and to investigate the potential concern that reductions in certain HPV types after the introduction of HPV vaccination in a population could create a niche that enables other nonvaccine high-risk HPV types to become more common (i.e., type replacement). We found evidence of a reduction in the prevalence of HPV31 among girls and women ≤19 years of age. Our main analysis showed increases in other nonvaccine HPV types (HPV39, HPV52, HPV53, HPV58, and HPV73), but these increases were inconsistent for the 2 age groups examined and the vaccines used.

A previous systematic review evaluated changes in high-risk HPV types combined and found evidence of a reduction in the prevalence of HPV types closely related to vaccine types (HPV31, HPV33, and HPV45) when they were considered as a single group (PR 0.72, 95% CI 0.54–0.96 for girls and women 13–19 years of age) (11). Our review provides evidence of reduced prevalence for HPV31 but little evidence of reduced prevalence for HPV33 or HPV45.

Table 2. Summary prevalence ratios for meta-analysis of changes in nonvaccine high-risk HPV types among girls and women, by age group*

Population age group, y, and HPV type	No. studies†	Heterogeneity		Prevalence ratio (95% CI)
		I ² , %	p value	
≤19				
HPV types in nonavalent vaccine	8			
HPV31		6.4	0.381	0.73 (0.58–0.91)
HPV33		0	0.471	1.04 (0.78–1.38)
HPV45		5.5	0.387	0.96 (0.75–1.23)
HPV52		24.0	0.238	1.34 (1.13–1.59)
HPV58		0	0.727	1.01 (0.80–1.26)
Other high-risk HPV types	8			
HPV35		25.1	0.229	–
HPV39		0	0.984	1.27 (1.05–1.54)
HPV51		43.6	0.088	–
HPV56		74.3	<0.001	–
HPV59		66.8	0.004	–
HPV68		0	0.690	1.26 (0.88–1.81)
Other possibly high-risk HPV types	6			
HPV26		0	0.478	1.63 (0.84–3.16)
HPV53		3.6	0.394	1.51 (1.10–2.06)
HPV70		23.6	0.257	1.34 (0.75–2.39)
HPV73		0	0.961	1.36 (1.03–1.80)
HPV82		49.0	0.081	–
20–24				
HPV types in nonavalent vaccine	8			
HPV31		28.8	0.198	–
HPV33		50.9	0.047	–
HPV45		64.3	0.007	–
HPV52		31.0	0.180	–
HPV58		0	0.806	1.14 (0.99–1.31)
Other high-risk HPV types	8			
HPV35		7.9	0.369	1.07 (0.85–1.34)
HPV39		0	0.522	1.13 (1.00–1.28)
HPV51		49.8	0.052	–
HPV56		82.6	<0.001	–
HPV59		63.6	0.007	–
HPV68		35.6	0.145	–
Other possibly high-risk HPV types	6			
HPV26		44.3	0.110	–
HPV53		30.8	0.204	–
HPV70		25.1	0.246	–
HPV73		59.2	0.032	–
HPV82		38.3	0.151	–

*HPV, human papillomavirus; –, prevalence ratio not calculated because of heterogeneity of data.

†Number of studies was the same for all HPV types within each category.

Comparing HPV prevalence in a prevaccination period to prevalence in a similar population in a postvaccination period enables consideration of population-level effects of HPV vaccination on HPV prevalence. However, these repeat cross-sectional study designs have limitations. Although all studies addressed similar populations in the prevaccination and postvaccination periods, these populations may have undergone temporal changes that are independent of HPV vaccination over time and that possibly affect HPV prevalence. For example, increases in diagnoses of other sexually transmitted infections have occurred during the same period as that of HPV vaccination programs (28). Furthermore, incidence of genital warts increased in many countries before vaccine introduction (29–31) and has continued to increase postvaccination in persons ineligible for vaccination (11). Such findings suggest that the increases we observed in some HPV types are possibly associated

with broad increases in sexual risk over time. We considered changes in demographics and sexual behavior for the populations over time when information was available, but unrecorded population changes or other temporal changes affecting the relative proportions of high-risk HPV types likely occurred over time (32,33). Also, more geographic variation exists in the relative frequency of nonvaccine HPV types in populations compared with the prevalence of HPV16, which, before the vaccination programs, was the most frequent high-risk type observed in almost all populations (34).

Furthermore, the change in assay used during the prevaccination and postvaccination periods was a potential source of bias in 1 study (16), which calculated odds ratios (ORs) adjusted for differences in diagnostic accuracy. This adjusted OR could not be converted to a PR by using the log-binomial model and was included as an OR. However,

given the low prevalence of individual HPV types, the use of an OR instead of a PR for this study was unlikely to have affected the results substantially.

Another limitation is that the broad-spectrum assays used in these studies (and in baseline prevaccination

evaluations globally) can lack sensitivity for detecting individual HPV types when multiple types are present, particularly if another HPV type with a higher viral load is present. In the postvaccination period, in the absence of HPV16 and HPV18, this lack of sensitivity could lead to an apparent but artificial increase in nonvaccine types because these types were underestimated in the prevaccine period because of the predominance of HPV16 or HPV18. Studies have shown this potential unmasking effect (35,36); some increases in nonvaccine types that we observed could result from unmasking.

Given the low prevalence of some nonvaccine HPV types, assessing changes in prevalence for individual types since the introduction of HPV vaccination has been challenging. By combining data from several studies, we enhanced our power to consider changes in individual HPV types. However, even with data from 13,886 girls and women ≤19 years of age and 23,340 women 20–24 years of age, we still had limited power to consider changes in very rare HPV types or to investigate reasons for the heterogeneity in findings for some HPV types because of inconsistent evidence for increases of specific nonvaccine types between age groups and the 2 (i.e., bivalent and quadrivalent) vaccines. Conversely, type 1 errors can occur with multiple testing, so modest evidence for increases should be interpreted with caution.

We decided against performing random-effects meta-analyses in the presence of between-study heterogeneity because, in most instances, inconsistency occurred in the direction of effect, making a summary estimate (i.e., the average value of these opposing effects) uninformative (37). Exploring the causes of heterogeneity could provide further insight into the reasons for these increases, so we performed 3 subgroup analyses by vaccine used, potential bias, and vaccine coverage. Results of the stratification by potential bias suggested that increased PRs for some HPV types may have been reported more often in the studies with relatively high potential bias. However, for all 3 subgroup sensitivity analyses, the small number of studies in each stratum limited the interpretation of the analyses. Similarly, we were limited to only 8 studies for each age group and had insufficient ability to perform meta-regression analyses (because meta-regression should generally not be considered for <10 studies) (37). As further data accrue, a useful future analysis would be exploring the association between reductions in the HPV vaccine types and any increases (not resulting from unmasking) in nonvaccine HPV types. If increases result from type replacement, then we would expect to see increasing prevalences of nonvaccine HPV types as prevalences of vaccine HPV types decrease.

Our confirmation of reductions in a cross-protected HPV type is encouraging. However, the results of this systematic review and meta-analysis provide no clear evidence

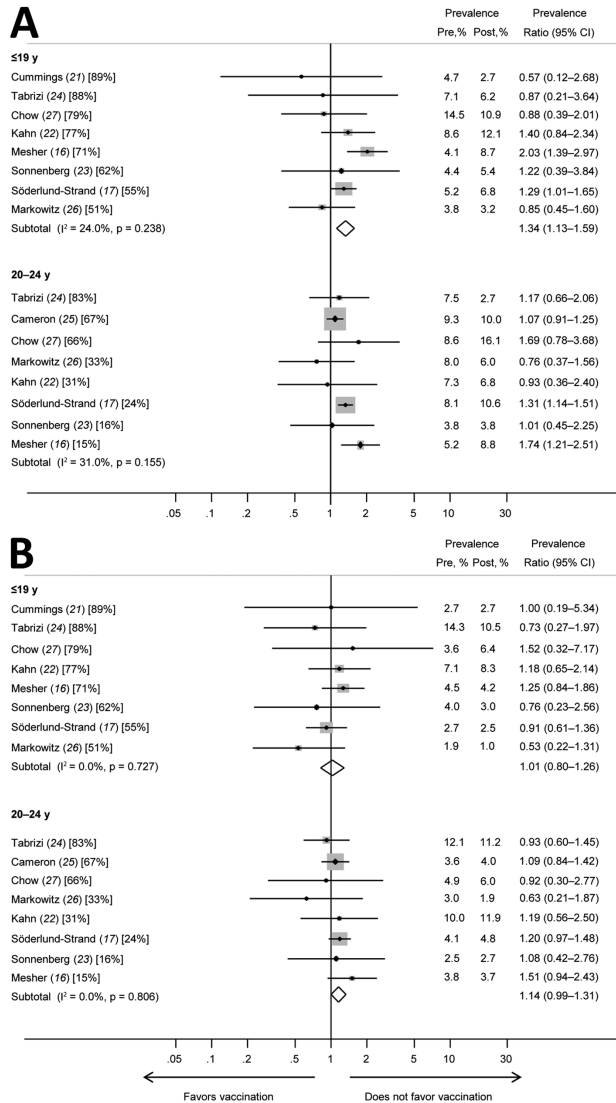


Figure 3. Prevalence ratios and 95% CIs for other high-risk human papillomavirus (HPV) types (HPV52 and HPV58) included in the nonvalent vaccine for girls and women ≤19 years of age and women 20–24 years of age in studies included in a meta-analysis of changes in prevalences of nonvaccine HPV genotypes after introduction of HPV vaccination. A) HPV52; B) HPV58. Percentages in brackets represent vaccination coverage (≥1 dose) for each study and age group. The sizes of the gray boxes around the plot points indicates the relative weight given to each study in the calculation of the summary estimate. The study by Cameron et al. (25) is omitted from analyses for the younger age group because this study included no data for persons ≤19 years of age. The study by Cummings et al. (21) is omitted from analyses for women 20–24 years of age because the study included no data for this age group. Pre, prevaccination; post, postvaccination.

for type replacement because the data are unclear about the extent to which any observed increases result from other temporal changes, changes in the study populations, or an unmasking effect of broad spectrum HPV assays. Large-scale epidemiologic analyses that use various designs have not detected evidence of any interactions between high-risk types, and the known high evolutionary stability of these viruses lessens the risk that type replacement will be a problem (38,39).

Most women included in the surveillance studies were those vaccinated at older ages (i.e., potentially vaccinated after HPV exposure), and some studies included populations with relatively low coverage, compared with nationally reported vaccination coverage for routine cohorts. Future studies should continue to monitor population-level prevalences of these HPV types. In particular, studies should consider populations vaccinated at young ages and having high vaccination coverage and, perhaps more important, should examine the absolute prevalence of cervical intraepithelial neoplasia 3 lesions attributed to each high-risk HPV type.

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Population-Level Effects of Human Papillomavirus Vaccination Programs on Infections with Nonvaccine Genotypes

Technical Appendix

Search Details, Study Details, and Prevalence Ratios

Database Search Strategies

Medline Search Strategy: identified 2,410 studies (2016 Feb 19)

1. Epidemiologic Studies/
2. exp case-control Studies/
3. (case* and control*).tw
4. exp Cohort Studies/
5. cohort*.tw
6. Cross-sectional Studies/
7. (cross* and section*).tw
8. Seroepidemiologic Studies/
9. Sentinel Surveillance/
10. Public Health Surveillance/
11. Incidence/
12. Prevalence/
13. Odds Ratio/
14. odds ratio.tw
15. risk ratio.tw
16. rate ratio.tw
17. relative risk.tw

18. screening method.tw
19. effectiveness.tw
20. observational.tw
21. (step* and wedge*).tw
22. Or/1-21
23. Human Papillomavirus DNA Tests/
24. exp Papillomavirus Infections/
25. exp Papillomaviridae/
26. (HPV or papilloma*).tw
27. Uterine Cervical Neoplasms/
28. Genital Neoplasms, Female/
29. Genital Diseases, Female/
30. Uterine Cervical Dysplasia/
31. (Penile ADJ1 wart).tw
32. (cervi* or genit*).tw
33. warts.tw
34. condyloma*.tw
35. neoplas*.tw
36. dysplas*.tw
37. lesion*.tw
38. cancer*.tw
39. carcin*.tw
40. maligna*.tw
41. disease*.tw
42. (carcinoma adj2 situ).tw
43. Or/33-42
44. And/32,43
45. Or/23-30,44

46. (Immunis* or immuniz* or vaccin*).tw

47. Papillomavirus Vaccines/

48. Or/46-47

49. Humans/

50. limit to yr=2007-2016

51. And/22,45,48,49,50

Embase search strategy: identified 3,843 studies (2016 Feb 19)

1. Epidemiology/

2. Cross-sectional study/

3. (cross\$ ADJ1 section\$.tw

4. exp case control study /

5. (case\$ ADJ1 control\$.tw

6. cohort analysis/

7. cohort\$.tw

8. exp Disease surveillance/

9. exp health survey/

10. incidence/

11. exp prevalence/

12. sentinel surveillance/

13. seroepidemiology/

14. risk/

15. infection risk/

16. population risk/

17. risk reduction/

18. observational study/

19. (odd\$ ADJ1 ratio).tw

20. (risk ADJ1 ratio).tw

21. (rate ADJ1 ratio).tw

22. (relative ADJ1 risk).tw
23. (screening ADJ1 method).tw
24. effectiveness.tw
25. observational.tw
26. (step\$ ADJ1 wedge\$).tw
27. Or/1-26
28. exp Papilloma virus /
29. hpv.tw
30. Papilloma\$.tw
31. Uterine cervix disease/
32. Uterine cervix dysplasia/
33. exp Uterine Cervix Tumor/
34. urogenital tract tumor/
35. genital tract tumor/
36. female genital tract tumor/
37. female genital tract cancer/
38. gynecologic cancer/
39. genital tract cancer/
40. female genital tract cancer/
41. Urogenital tract cancer/
42. Female genital tract cancer/
43. female genital tumor/
44. female genital tract infection/
45. genital tract infection/
46. gynecologic infection/
47. (peni\$ ADJ1 wart\$).tw
48. (cervi\$ or genit\$).tw
49. wart\$.tw

50. condyloma\$.tw
51. neoplas\$.tw
52. dysplas\$.tw
53. lesion\$.tw
54. cancer\$.tw
55. carcin\$.tw
56. maligna\$.tw
57. disease\$.tw
58. (carcinoma ADJ2 situ).tw
59. Or/49-58
60. And/48,59
61. Or/28-47,60
62. (Immunis\$ or immuniz\$ or vaccin\$).tw
63. Wart virus vaccine/
64. Or/62,63
65. Humans/
66. limit to yr=2007-2016
67. And/27,61,64,65,66

LILACS search strategy: identified 58 studies (2016 Feb 19)

((cross\$ AND section\$) OR (case\$ AND control\$) OR (cohort\$) OR (odd\$ AND ratio) OR (risk AND ratio) OR (rate AND ratio) OR (relative AND risk) OR effectiveness OR observational OR (“step wedge” OR “step-wedge” OR stepwedge)) AND (hpv OR Papilloma\$ OR ((cervi\$ or genit\$) AND (wart\$ OR neoplas\$ OR dysplas\$ OR lesion\$ OR cancer\$ OR carcin\$ OR adeno\$ OR squamous\$ OR disease\$ OR (carcinoma AND situ)))) AND (Immunis\$ or vaccin\$) AND (PD 2007 OR PD 2008 OR PD 2009 OR PD 2010 OR PD 2011 OR PD 2012 OR PD 2013 OR PD 2014 OR PD 2015 OR PD 2016)

AIM search strategy: identified 17 studies (2016 Feb 19)

hpv OR Papilloma\$

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Technical Appendix Table 1. Characteristics of studies selected for systematic review and meta-analysis of changes in prevalence of nonvaccine HPV genotypes*

Characteristic	Study (reference no.)								
	Cameron et al. (1)	Chow et al. (2)	Cummings et al. (3)	Kahn et al. (4)	Markowitz et al. (5)	Mesher et al. (6)	Söderlund-Strand et al. (7)	Sonnenberg et al. (8)	Tabrizi et al. (9)
Country of study	Scotland UK	Australia	USA	USA	USA	England, UK	Sweden	Great Britain, UK	Australia
Vaccine introduced	Bivalent	Quadrivalent	Quadrivalent	Quadrivalent	Quadrivalent	Bivalent	Quadrivalent	Bivalent	Quadrivalent
Sample collection, y									
Prevac	2009–2010	2004–2007	1995–2005	2006–2007	2003–2006	2008	2008	1999–2001	2005–2007
Postvac	2011–2013	2007–2014	2010	2009–2010	2009–2012	2010–2013	2012–2013	2010–2012	2010–2011
Specimens tested, no.									
Prevac	2,705	136	150	365	1,795	2,354	11,457	328	202
Postvac	3,010	328	75	383	1,209	7,321	3,555	795	1,058
Study population, † age, y (additional detail)	20–21	≤ 21 (Australian born)	14–17	13–26 (had had sexual intercourse)	14–24	16–25 (sexually active)	All ages	18–44 (sexually experienced)	18–24
Setting for recruiting participants	Cervical screening as part of national cervical screening program	Chlamydia screening at sexual health center in Melbourne, Australia (tested positive)	1 of 3 primary care clinics in Indiana	Hospital-based adolescent clinic and a community health center	Population-based NHANES survey	Chlamydia screening at community sexual health settings	Chlamydia screening in a defined region of Sweden	Households participating in Natsal survey (selected with a stratified probability sample survey)	Cervical screening at sentinel family planning clinics in Sydney, Melbourne, and Perth
Specimen type	Residual LBC	Cervical and high vaginal swab	Self-collected vaginal swab	Cervicovaginal swabs by clinician or self-collected swab	Self-collected cervicovaginal swab	Residual vulval vaginal swab	Genital swabs (alone or immersed in urine)	Urine	Exfoliated cervical cells preserved in PreservCyt‡
Assay for HPV DNA testing	Multimetrix HPV assay	PapType HPV assay	Linear Array HPV Genotyping test	Linear Array HPV Genotyping test	Linear Array HPV Genotyping test	Prevac: Linear Array HPV Genotyping test in those testing positive for Hybrid Capture 2 Postvac: In-house multiplex PCR- and Luminex-based genotyping system	PCR testing with genotyping by matrix-assisted laser desorption ionization time-of-flight (MALDI-TOF) mass spectrometry	In-house multiplex PCR- and Luminex-based genotyping system	Amplicor DNA test for 13 high-risk types (if negative, tested for presence of mucosal DNA by using L1 consensus primer set PGMY09-PGMY11). If positive for Amplicor or PCMY09/PGMY11, PCR-ELISA were genotyped by using the Linear Array HPV genotyping test
Demographic and sexual behavior data collected	Scottish Index of Multiple Deprivation, mo/y of birth§	Age-stratified PRs were adjusted for by no. male partners, 100%	Samples matched on basis of age at enrollment, clinic site,	Age, race, health care insurance, knowledge of HPV vaccines,	Ethnicity, poverty index, and for those reporting ever having sex, age at first sex,	Age- stratified PRs were adjusted for age, chlamydia positivity at	All samples were anonymised (individual age was known)	Extensive demographic and sexual behavior data collected‡	Age, current use of hormonal contraception, smoking status and postal code

Characteristic	Study (reference no.)								
	Cameron et al. (1)	Chow et al. (2)	Cummings et al. (3)	Kahn et al. (4)	Markowitz et al. (5)	Meshher et al. (6)	Söderlund-Strand et al. (7)	Sonnenberg et al. (8)	Tabrizi et al. (9)
		condom use with all partners in the past 12 mo status, and anatomic sampling method (cervical vs. high vaginal sample)	and reported sexual activity. Data on ethnicity, no. sexual partners in last year and in last 2 mo, no. lifetime sexual partners, no. instances of vaginal intercourse in last year and in the last 2 mo§	smoking status, gynecologic history (no. pregnancies, history of STIs), sexual behaviors (i.e., age at first sex, no. male lifetime partners, no. male partners in last 3 mo, anal sex, condom use)§	lifetime no. partners in last 12 mo§	time specimen taken, and collection venue type			of residence§
Vaccination information	Linked from Scottish Immunisation call/recall system and Child Health Schools Programme system	Self-reported; not available for all women	Collected from medical notes	Collected from immunisation registry for 87% of women; collected from self-administered questionnaire for others	Self-reported	Not collected for individuals	Not collected for individuals	Self-reported	Self-reported and validated against the National HPV vaccine register

*Study design for all studies was repeat cross-sectional. HPV, human papillomavirus; LBC, liquid-based cytology; Prevac, prevaccination period; Postvac, postvaccination period; PRs, prevalence ratios.

†Population in all studies were female.

‡Cytoc Corporation, Marlborough, MA, USA.

§These data were not used to adjust the HPV prevalence ratios in this meta-analysis.

Technical Appendix Table 2. Prevalence ratios for nonvaccine high-risk HPV types for female adolescents and women in systemic review and meta-analysis, by age group and vaccine type*

Age group, y/HPV type	Bivalent vaccine				Quadrivalent vaccine			
	No. of studies†	Heterogeneity		Prevalence ratio (95% CI)	No. studies†	Heterogeneity		Prevalence ratio (95% CI)
		I ² , %	p value			I ² , %	p value	
≤19								
Nonavalent vaccine HPV types	2				6			
HPV 31		10.4	0.291	0.54 (0.29–1.03)		8.7	0.36	0.75 (0.60–0.96)
HPV 33		0	0.785	1.66 (0.94–2.92)		0	0.687	0.89 (0.64–1.24)
HPV 45		75.4	0.044	–		0	0.716	1.01 (0.76–1.34)
HPV 52		0	0.408	1.93 (1.34–2.77)		0	0.627	1.20 (0.99–1.47)
HPV 58		0	0.445	1.19 (0.81–1.73)		0	0.742	0.92 (0.69–1.22)
Other high-risk HPV types	2				6			
HPV 35		85.2	0.009	–		0	0.914	0.91 (0.58–1.42)
HPV 39		0	0.755	1.30 (0.89–1.91)		0	0.932	1.26 (1.01–1.58)
HPV 51		74.9	0.046	–		35.2	0.172	1.16 (1.00–1.36)
HPV 56		18.3	0.269	2.08 (1.43–3.04)		64.9	0.014	–
HPV 59		51.9	0.149	–		0	0.478	1.27 (1.03–1.57)
HPV 68		0	0.444	1.84 (0.62–5.47)		0	0.601	1.20 (0.82–1.76)
Other possibly high-risk types	2				4			
HPV 26		0	0.873	1.89 (0.84–4.26)		26.8	0.251	1.21 (0.38–3.81)
HPV 53		0	0.894	2.22 (1.25–3.94)		0	0.445	1.28 (0.88–1.85)
HPV 70		0	0.957	4.07 (1.43–11.55)		0	0.97	0.82 (0.41–1.64)
HPV 73		0	0.926	1.39 (0.98–1.98)		0	0.806	1.32 (0.83–2.07)
HPV 82		0	0.998	2.00 (0.50–7.95)		65.1	0.035	–
20–24								
Nonavalent vaccine HPV types	3				5			
HPV 31		57.8	0.094	–		0	0.889	0.95 (0.81–1.10)
HPV 33		55.0	0.108	–		48.1	0.103	–
HPV 45		74.2	0.021	–		56.9	0.055	–
HPV 52		65.6	0.055	1.26 (0.87–1.83)		0	0.53	1.28 (1.12–1.46)
HPV 58		0	0.499	1.17 (0.94–1.46)		0	0.684	1.12 (0.93–1.34)
Other high-risk HPV types	3				5			
HPV 35		0	0.968	1.22 (0.79–1.87)		43.1	0.134	–
HPV 39		44.8	0.163	1.32 (0.93, 1.88)		0	0.743	1.09 (0.93–1.28)
HPV 51		0	0.57	1.37 (1.16–1.62)		47.0	0.11	1.19 (0.88–1.61)
HPV 56		75.4	0.017	1.45 (0.82–2.59)		87.5	<0.001	–
HPV 59		86.1	0.001	–		0	0.604	1.13 (0.94–1.37)
HPV 68		67.4	0.046	–		0	0.842	0.99 (0.72–1.37)
Other possibly high-risk types	3				3			
HPV 26		69.0	0.04	–		21.1	0.282	1.35 (0.28–6.47)
HPV 53		0.3	0.367	1.23 (1.05–1.45)		16.9	0.3	0.90 (0.64–1.25)
HPV 70		0	0.382	1.11 (0.81–1.51)		0	0.811	2.47 (1.24–4.94)
HPV 73		43.8	0.169	–		76.3	0.015	–
HPV 82		73.7	0.022	–		0	0.989	0.94 (0.39–2.26)

*HPV, human papillomavirus; –, prevalence ratios were not calculated because of heterogeneity of data.

†Number of studies were the same for all HPV types within each category.

Technical Appendix Table 3. Prevalence ratios for nonvaccine high-risk HPV types for female adolescents and women in systemic review and meta-analysis, by age group and potential bias*

Age group, y/HPV type	Relatively low potential bias†				Relatively high potential bias‡			
	No. studies§	Heterogeneity		Prevalence ratio (95% CI)	No. studies§	Heterogeneity		Prevalence ratio (95% CI)
		I ² , %	p value			I ² , %	p value	
≤19								
Nonavalent vaccine HPV types	5				3			
HPV 31		31.2	0.213	–		0	0.447	0.73 (0.58–0.93)
HPV 33		0	0.526	0.79 (0.30–2.06)		34.4	0.218	–
HPV 45		21.5	0.278	0.84 (0.49–1.44)		0.6	0.366	0.99 (0.76–1.31)
HPV 52		0	0.681	1.09 (0.77–1.56)		61.9	0.072	–
HPV 58		0	0.672	0.87 (0.58–1.30)		0	0.505	1.08 (0.82–1.42)
Other high-risk HPV types	5				3			
HPV 35		0	0.424	0.85 (0.46–1.58)		60.6	0.079	–
HPV 39		0	0.907	1.21 (0.83–1.78)		0	0.846	1.30 (1.04–1.61)
HPV 51		45.3	0.120	–		0	0.433	1.28 (1.09–1.50)
HPV 56		69.3	0.011	–		79.9	0.007	–
HPV 59		0	0.465	1.29 (0.94–1.76)		85.9	0.001	–
HPV 68		12.6	0.333	1.21 (0.76–1.93)		0	0.948	1.33 (0.75–2.36)
Other possibly high-risk types	5				1			
HPV 26		3.3	0.388	1.27 (0.45–3.58)		–	–	1.93 (0.82–4.59)
HPV 53		0	0.514	1.32 (0.92–1.90)		–	–	2.19 (1.18–4.04)
HPV 70		0	0.831	0.90 (0.45–1.76)		–	–	4.02 (1.31–12.32)
HPV 73		0	0.909	1.33 (0.87–2.05)		–	–	1.39 (0.96–2.00)
HPV 82		55.0	0.064	–		–	–	2.00 (0.42–9.44)
20–24								
Nonavalent vaccine HPV types	5				3			
HPV 31		27.7	0.237	–		0	0.670	0.95 (0.81–1.11)
HPV 33		0	0.599	0.64 (0.52–0.78)		0	0.424	1.03 (0.83–1.27)
HPV 45		78.5	0.001	–		0	0.948	0.90 (0.74–1.10)
HPV 52		0	0.905	1.06 (0.91–1.22)		11.8	0.322	1.37 (1.20–1.56)
HPV 58		0	0.859	1.04 (0.85–1.28)		0	0.600	1.23 (1.02–1.50)
Other high-risk HPV types	5				3			
HPV 35		0	0.754	1.42 (0.97–2.08)		10.7	0.326	0.90 (0.67–1.21)
HPV 39		8.3	0.359	1.12 (0.94–1.34)		0	0.415	1.14 (0.97–1.34)
HPV 51		32.5	0.205	–		46.9	0.152	–
HPV 56		0	0.914	1.03 (0.89–1.21)		94.5	0.000	–
HPV 59		0	0.443	1.08 (0.91–1.28)		86.4	0.001	–
HPV 68		0	0.692	1.04 (0.72–1.49)		72.5	0.026	–
Other possibly high-risk types	5				1			
HPV 26		54.8	0.065	–		–	–	1.14 (0.37–3.50)
HPV 53		36.3	0.179	–		–	–	1.52 (0.86–2.69)
HPV 70		34.5	0.191	–		–	–	1.64 (0.79–3.37)
HPV 73		56.0	0.059	–		–	–	1.92 (1.04–3.53)
HPV 82		0	0.984	0.75 (0.60–0.94)		–	–	0.22 (0.10–0.51)

*HPV, human papillomavirus; –, prevalence ratios were not calculated because of heterogeneity of data.

†Average-low potential bias includes 6 studies (1, 3–5, 8, 9).

‡Average-high potential bias includes 3 studies (2,6,7).

§Number of studies were the same for all HPV types within each category.

Technical Appendix Table 4. Prevalence ratio for nonvaccine high-risk HPV types for female adolescents and women in systemic review and meta-analysis, by age group and vaccination coverage*

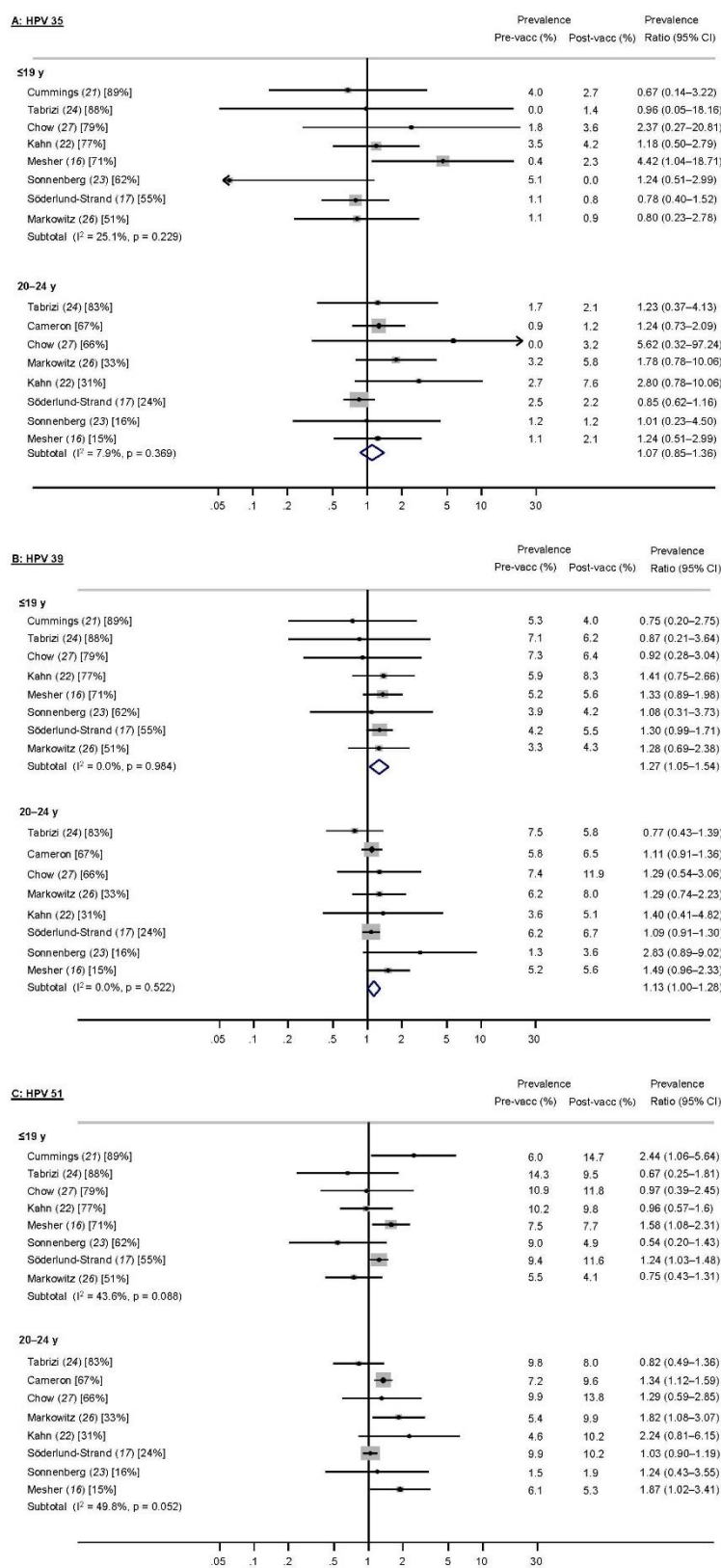
Age group, y/ HPV type	Low vaccination coverage (<50%)				High vaccination coverage (≥50%)			
	No. studies†	I ² , %	Heterogeneity p value	Prevalence ratio (95% CI)	No. studies†	I ² , %	Heterogeneity p value	Prevalence ratio (95% CI)
≤19								
Nonavalent HPV types	0				8			
HPV 31		–	–	–	6.4	0.381		0.73 (0.58–0.91)
HPV 33		–	–	–	0	0.471		1.04 (0.78–1.38)
HPV 45		–	–	–	5.5	0.387		0.96 (0.75–1.23)
HPV 52		–	–	–	24.0	0.238		1.34 (1.13–1.59)
HPV 58		–	–	–	0	0.727		1.01 (0.80–1.26)
Other high-risk HPV types	0				8			
HPV 35		–	–	–	25.1	0.229		–
HPV 39		–	–	–	0	0.984		1.27 (1.05–1.54)
HPV 51		–	–	–	43.6	0.088		–
HPV 56		–	–	–	74.3	<0.001		–
HPV 59		–	–	–	66.8	0.004		–
HPV 68		–	–	–	0	0.690		1.26 (0.88–1.81)
Other possibly high-risk types	0				6			
HPV 26		–	–	–	0	0.478		1.63 (0.84–3.16)
HPV 53		–	–	–	3.6	0.394		1.51 (1.10–2.06)
HPV 70		–	–	–	23.6	0.257		1.34 (0.75–2.39)
HPV 73		–	–	–	0	0.961		1.36 (1.03–1.80)
HPV 82		–	–	–	49.0	0.081		–
20–24								
Nonavalent HPV types	5				3			
HPV 31		0	0.838	0.96 (0.83–1.12)	25.5	0.261		–
HPV 33		36.3	0.179	–	0	0.618		0.65 (0.53–0.81)
HPV 45		55.9	0.06	–	62.7	0.068		–
HPV 52		26.1	0.248	–	0	0.513		1.10 (0.94–1.27)
HPV 58		0	0.689	1.21 (1.01–1.45)	0	0.807		1.04 (0.83–1.30)
Other high-risk HPV types	5				3			
HPV 35		30.4	0.219	–	0	0.590		1.29 (0.80–2.07)
HPV 39		5.3	0.377	1.17 (1.00–1.37)	0	0.482		1.08 (0.89–1.30)
HPV 51		56.7	0.056	–	37.8	0.201		–
HPV 56		30.5	0.218	–	91.7	<0.001		–
HPV 59		73.5	0.004	–	0	0.673		1.15 (0.96–1.37)
HPV 68		61.7	0.034	–	0	0.810		1.20 (0.78–1.85)
Other possibly high-risk types	4				2			
HPV 26		53.8	0.09	–	0	0.862		1.76 (1.00–3.12)
HPV 53		0	0.522	1.31 (0.95–1.81)	76.6	0.039		–
HPV 70		11.8	0.334	1.72 (1.06–2.79)	0	0.335		1.08 (0.76–1.53)
HPV 73		52.5	0.097	–	0	0.503		1.02 (0.82–1.26)
HPV 82		33.7	0.21	–	0	0.675		0.75 (0.59–0.94)

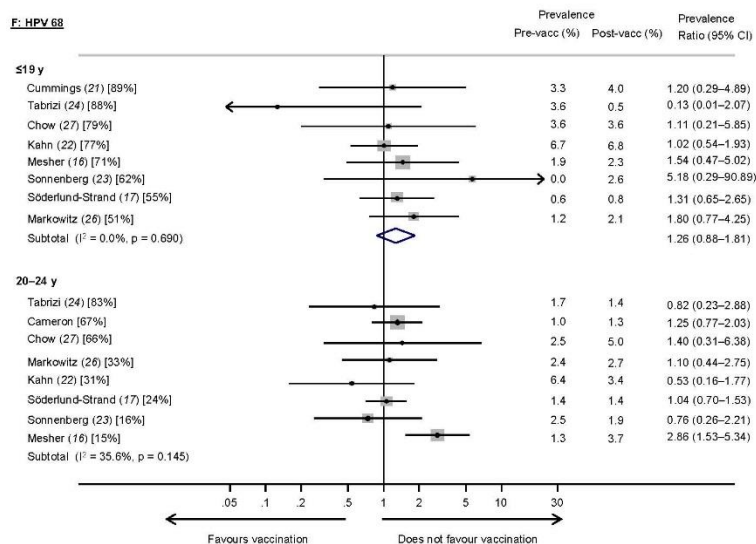
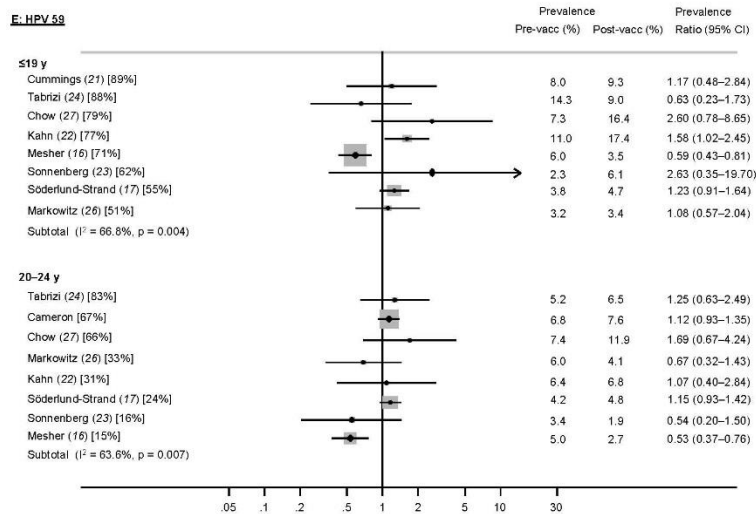
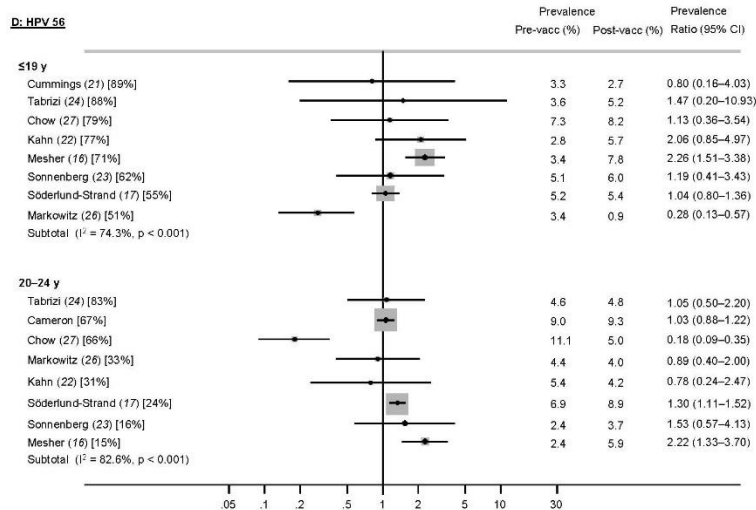
*HPV, human papillomavirus; –, prevalence ratios were not calculated because of heterogeneity of data.

†Number of studies were the same for all HPV types within each category.

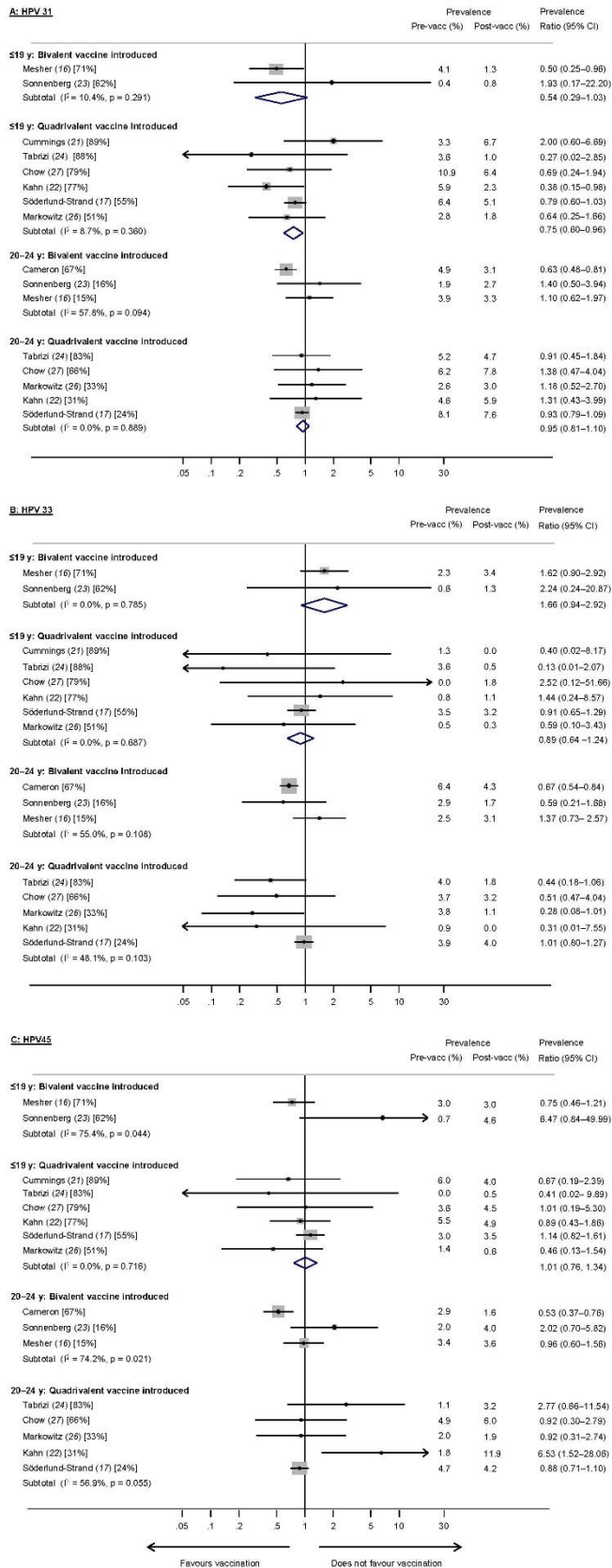
Technical Appendix Figure 1.

Prevalence ratios for meta-analysis of changes in other probable high-risk human papillomavirus (HPV) types (HPV35, HPV39, HPV51, HPV56, HPV59, and HPV68) for girls and women, by age group (≤ 19 and 20–24 years of age). Percentages in square brackets represent vaccination coverage (at least 1 dose) for each study and age group. The size of the dark boxes around the plot points indicates the relative weight given to each study in calculation of the summary estimate. The study by Cameron et al. (25) is omitted from analyses for the younger age group because this study included no data for those ≤ 19 years of age. The study by Cummings et al. (21) is omitted from analyses for women 20–24 years of age because this study included no data for this age group. Pre, prevaccination; post, postvaccination.

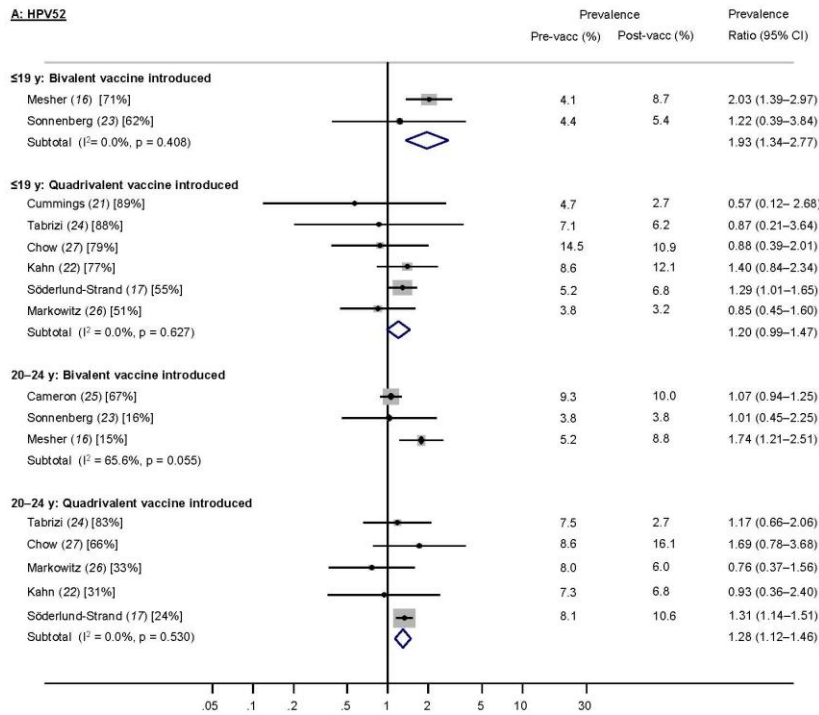




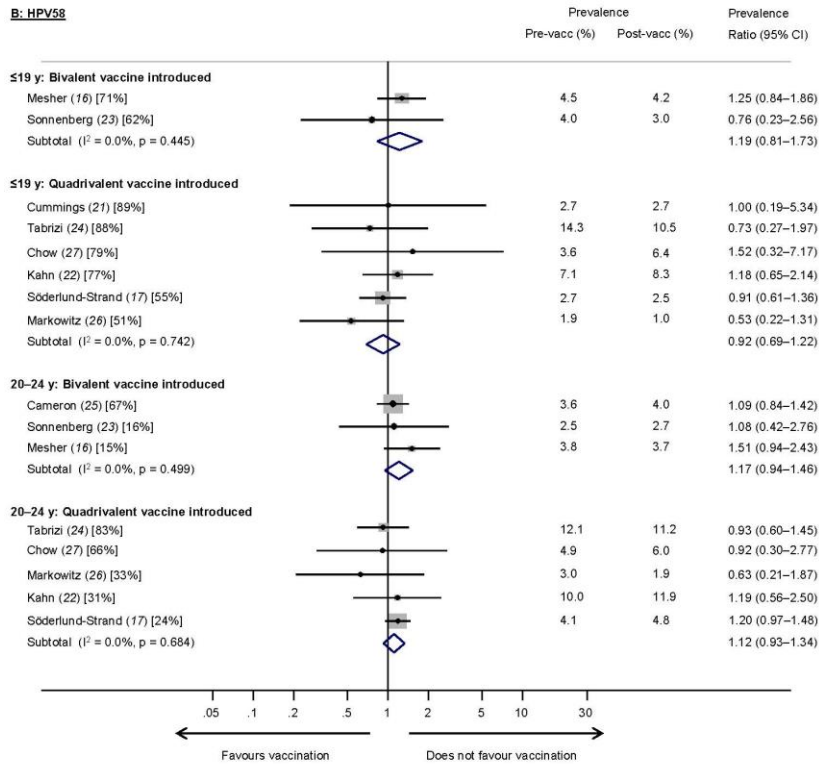
Technical Appendix Figure 2. Prevalence ratios for meta-analysis of changes in high-risk human papillomavirus (HPV) types (HPV31, HPV33, and HPV45) with evidence of cross-protection for girls and women, by age group (≤ 19 and 20–24 years of age) and vaccine type. Percentages in square brackets represent vaccination coverage (at least 1 dose) for each study and age group. The size of the dark boxes around the plot points indicates the relative weight given to each study in the calculation of the summary estimate. The study by Cameron et al. (25) is omitted from analyses for the younger age group because this study included no data for the group ≤ 19 years of age. The study by Cummings et al. (21) is omitted from analyses for women 20–24 years of age because this study included no data for this age group. Pre, prevaccination; post, postvaccination.



A: HPV52



B: HPV58



Technical Appendix Figure 3.

Prevalence ratios for meta-analysis of changes in other high-risk human papillomavirus (HPV) types (HPV52 and HPV58) included in the nonavalent vaccine for girls and women, by age group (≤ 19 and 20–24 years of age) and vaccine type. Percentages in square brackets represent vaccination coverage (at least 1 dose) for each study and age group. The size of the dark boxes around the plot points indicates the relative weight given to each study in the calculation of the summary estimate. The study by Cameron et al. (25) is omitted from analyses for the younger age group because this study included no data for the group ≤ 19 years of age. The study by Cummings et al. (21) is omitted from analyses for women 20–24 years of age because this study included no data for this age group. Pre, prevaccination; post, postvaccination.

Technical Appendix Figure 4. Prevalence ratios for meta-analysis of changes in other probably high-risk HPV types (HPV35, HPV39, HPV51, HPV56, HPV59, and HPV68) for girls and women, by age-group (≤ 19 and 20–24 years of age) and vaccine type. Percentages in square brackets represent vaccination coverage (at least 1 dose) for each study and age group. The size of the dark boxes around the plot points indicates the relative weight given to each study in the calculation of the summary estimate. The study by Cameron et al. (25) is omitted from analyses for the younger age group because this study included no data for the group ≤ 19 years of age. The study by Cummings et al. (21) is omitted from analyses for women 20–24 years of age because this study included no data for this age group. Pre, prevaccination; post, postvaccination.

