Title: The population impact of human papillomavirus (HPV) vaccination programmes on infection with nonvaccine HPV genotypes

Running Title: Impact of HPV vaccination on nonvaccine HPV types

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Word count (Abstract): 148

Word count (Text): 3491

Abstract

We systematically identified and analysed published and unpublished data comparing HPV prevalence in prevaccination and postvaccination time periods, to consider changes in nonvaccine HPV types after vaccine introduction. Nine studies provided HPV prevalence data from 13,886 females aged ≤19 years (younger females) and 23,340 females aged 20-24 years (older females). Following vaccine introduction, there was some evidence of cross-protection for HPV31 among younger females (prevalence ratio (PR) (95%CI)=0.73(0.58-0.91)) but little evidence of a reduction in HPV33 and HPV45. There was evidence of a slight increase in two nonvaccine high-risk HPV types: HPV39 and HPV52 (younger females: PR=1.27(1.05-1.54) and 1.34(1.13-1.59) respectively), and in two possible high-risk types HPV53 and HPV73 (younger females: PR=1.51(1.10-2.06) and PR=1.36(1.03-1.80)). Given the inconsistency in findings between age groups and the vaccine used, and possible alternative explanations for the increases, there was no clear evidence for type-replacement. Continued monitoring of these HPV types is important.

Article Summary Line: Following introduction of HPV vaccination, there were some changes in the prevalence of non-vaccine HPV types, but there was no clear evidence for type-replacement

Introduction

Persistent infection with a high-risk human papillomavirus (HPV) genotype is a necessary cause of cervical cancer.*(1)* Two high-risk types (HPV16 and HPV18) cause approximately 70-80% of cervical cancers.*(2-4)* The HPV vaccines which are currently commercially available have been shown in trial settings to have close to 100% vaccine efficacy against cervical disease caused by vaccine-specific high-risk HPV types: HPV16 and 18 for the bivalent and quadrivalent vaccines; HPV31, 33, 45, 52, and 58 for the new nonavalent vaccine.*(5-7)* Clinical trial data for the bivalent and quadrivalent vaccines have also shown low to moderate protection against some of the other high-risk HPV types which are phylogenetically related to HPV16 and HPV18 (i.e. cross-protection).*(8;9)*

HPV vaccination programmes have now been introduced in many countries.[(10)] A recently published systematic review and meta-analysis assessed the population impact of HPV vaccination on the vaccine HPV types, showing strong evidence that HPV vaccination is highly effective against infection with these types.*(11)* The review also looked at closely related HPV types, but only as a single group, demonstrating some evidence of cross-protection overall in a population setting.*(11)* However, assessment of changes in the prevalence of closely related HPV types combined may not provide full evidence of the impact of vaccination, as it could potentially conceal decreases or increases in the prevalence of individual types. Grouping HPV types together limited the possibility to look at cross-protection with specific HPV types and/or changes in other individual nonvaccine types. For example, one theoretical concern is that the reductions in the prevalence of HPV16 and HPV18 infection could lead to other high-risk HPV types occupying that niche and becoming a more common cause of disease. Whilst this was not observed in the clinical trials,*(12)* it is important to monitor this potential for type replacement in population settings following the introduction of national HPV vaccination. Furthermore, since other HPV types are often far less common than the vaccine HPV types, within an individual study there is limited scope to determine whether type replacement has occurred; combining data from several reports improves the power to investigate this.

Thus, the aim of this study was to investigate the population level impact of HPV vaccination programmes, using the bivalent or quadrivalent vaccines, on the type-specific prevalence of infection of individual nonvaccine high-risk HPV types.

Methods

Objectives

We compared data on HPV prevalence from surveys conducted prior to the introduction of an HPV vaccination programme with surveys after their introduction in similar populations in the same country, to determine the change in HPV prevalence for each nonvaccine high-risk HPV type (at the time of this search, any eligible study would have considered changes following vaccination using the bivalent or quadrivalent vaccines, hence high-risk HPV types included in the nonavalent vaccine only were considered nonvaccine HPV types). Each individual type was presented separately. We included HPV types for which some cross-protection had been demonstrated in clinical trials (HPV31, HPV33, phylogenetically related to HPV16 and HPV45 phylogenetically related to HPV18),*(8;9;13)* other high-risk HPV types included in the nonavalent vaccine (HPV52 and HPV58), other high-risk and probable 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 defined 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

Embase, Medline, LILACS and African Index Medicus were searched for eligible publications from 2007 (the date the first HPV vaccination programmes were introduced) up to 19th February 2016. The search strategy incorporated MeSH terms and relevant free text words in the title/abstract to identify relevant studies which included mention of both vaccination and HPV infection or a related disease (including, but not limited to, HPV-related pre-cancerous lesions and cancers and genital warts; see Supplementary Material for full search terms). There were no language restrictions.

Eligible studies were those which assessed population-level impact of HPV vaccination over time by comparing the prevalence of HPV infection (defined by the detection of HPV DNA) in a prevaccination period to a postvaccination period. Studies which compared HPV-infection in those vaccinated and unvaccinated as part of an individually randomised trial were excluded as they would not measure a population-level effect. Similarly, studies which only compared HPV-infection between unvaccinated and vaccinated individuals in the postvaccination period were also excluded. We also excluded studies if a very small proportion (<2%) of the postvaccination study population were vaccinated (i.e. largely unvaccinated populations). Titles and abstracts were initially reviewed for eligibility by DM. Those which were deemed to consider changes in HPV prevalence following the introduction of HPV vaccination programmes were reviewed in full. Search results were also compared to those identified in the related recent review by Drolet and colleagues which compared the pre- and postvaccination periods for the high-risk vaccine types (HPV-16/18), cross-protected types (HPV-31/33/45), and all high-risk HPV nonvaccine types combined.*(11)*

Data extraction and data quality

Data were extracted by DM on study design, country of study and then (for both the pre- and postvaccination period) the year(s) of sample collection, study setting and population, sample size, the specimen type, the assay used for HPV-DNA testing, HPV genotypes included in the assay and demographic and sexual behaviour data collected, as well as the measure of effect for each study. Additionally, for the postvaccination period, data were extracted on the method used to ascertain estimated vaccination coverage.

The potential bias from each study was assessed by considering the comparability of the study populations in the pre- vs 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 this differed between the pre- and postvaccination periods) and the method used to estimate HPV vaccination coverage. External validity was assessed by considering whether the study samples were population-based. Each item was scored as either ‘low risk’ or ‘high risk’.

Published data on the prevalence and prevalence ratios for individual high-risk HPV types were not always available. Authors were contacted to request the HPV type-specific prevalence in the prevaccination and postvaccination period and the prevalence ratio comparing the two periods for each of the nonvaccine high-risk HPV types. Adjusted prevalence ratio (PR; adjusted for demographics and sexual behavior data) were requested or the unadjusted PR if no data on confounders were available; unadjusted PRs were calculated if raw data were provided. For one study (Mesher et al), adjusted odds ratios were included rather than prevalence ratios in order to additionally adjust for the change in assay between the pre- and postvaccination periods using data from a previously conducted validation study.*(16)*

Data analysis

Estimates weighted to account for selection processes were used if provided by authors (with unweighted numbers presented in Tables and Figures). Data were stratified by age-group due to expected differences in vaccination coverage and vaccine effectiveness in those vaccinated at an older age. Data were requested from authors for the same age-groups for each study (≤19 years old and 20-24 years old). Söderlund-Strand et al included data from young women aged under 13 years old hence we requested data restricted to 16-19 year olds.

To allow calculation of a prevalence ratio for a prevalence of zero (in either the prevaccination or postvaccination period), a continuity correction of 0.5 was added to all cells. When the prevalence was zero for both the prevaccination and postvaccination period, the study was omitted from the meta-analysis for the relevant age-group and HPV-type. Results were further stratified by the vaccine used (i.e. bivalent or quadrivalent). Prevalence ratios within each subgroup were combined to obtain a summary prevalence ratio using a fixed effects model if data were not shown to be heterogeneous (lack of heterogeneity was determined by a p-value≥0.10 using Cochrane's Q test and/or an I^2 value<25%).*(17)* In sensitivity analyses, analyses were restricted to studies that used cervical, vulval or vaginal swabs as the specimen type due to the lower sensitivity to detect HPV DNA infection using urine samples.*(18)*

Results

Included studies

A total of 4,648 unique papers were identified after de-duplication of searches from all four databases (Figure 1). An initial search of title and abstracts excluded 4,508 (97.0%) papers due to ineligibility. For the remaining 140 papers, a full paper search was conducted which identified ten eligible papers. Reasons for ineligibility are shown in Figure 1. One study met all eligibility criteria but the type-specific prevalence ratios were not available from authors.*(19)* Therefore, a total of nine studies were included in the systematic review and meta-analysis.*(16;20-27)* All eligible studies were repeat cross-sectional studies which compared changes in prevalence in populations prior to and after the introduction of a national HPV vaccination programme (Table 1). Only one study considered changes in HPV infection among males so only female populations were considered in the present analysis. Two studies were population-based national surveys (Markowitz et al *(25)* and Sonnenberg et al *(22)*), three studies were conducted among young women attending for chlamydia screening (Chow et al *(26)*, Mesher et al *(16)*, and Söderlund-Strand et al *(27)*), two studies comprised young women attending a primary care clinic, community health centre and/or a hospital-based adolescent clinics (Cummings et al *(20)* and Kahn et al *(21)*), and two studies comprised women attending for cervical screening (Cameron et al *(24)* and Tabrizi et al *(23)*) (Table 1).

The assessment of methodological quality is summarised in Figure 2. The majority of studies collected some demographic and sexual behaviour data to allow appropriate adjustment of the relative risks, although the number of factors collected was limited in some studies (Cameron et al *(24)*, Mesher et al *(16)*, Tabrizi et al *(23)*, and Söderlund-Strand et al *(27)*) (Figure 2). Details of which data were used for adjusted prevalence ratios are given in Table 1.

HPV types included in the nonavalent but not the bi- and quadrivalent HPV vaccines (HPV31, HPV33, HPV45, HPV52, and HPV58)

HPV types for which there is previous evidence for cross-protection (HPV31, HPV33, and HPV45): There was evidence of a reduction in the prevalence of HPV31 (Figure 3; Table 2), for females aged ≤19 years old (PR=0.73, 95% CI: 0.58-0.91). There was little evidence of a change in prevalence for HPV33 or HPV45 in the younger age-group (PR=1.04, 95%CI: 0.78-1.38 for HPV31, PR=0.96, 95%CI: 0.75-1.23 for HPV45). Results were heterogeneous for HPV31, HPV33 and HPV45 in the older age-group hence summary prevalence ratios were not calculated (Figure 3; Table 2).

Other HPV types (HPV52 and HPV58): There was evidence of an increase in the prevalence of HPV52 in ≤19 year old females (PR=1.34, 95% CI: 1.13-1.59) (Figure 4; Table 2), but a summary prevalence ratio was not calculated for the older age-group due to heterogeneity. There was no evidence of a change in the prevalence of HPV58 for the younger age-group (PR=1.01, 95%CI: 0.80-1.26) although borderline evidence of an increase among those aged 20-24 years (PR=1.14, 95%CI: 0.99-1.31).

Other high-risk and possibly high-risk HPV types

No consistent patterns across the studies were observed for the non-nonavalent vaccine HPV types (Figure S1; Table 2). There was evidence of an increased prevalence between the prevaccination period and postvaccination period in ≤19 year old females for HPV39, HPV53 and HPV73 (PR=1.27, 95%CI: 1.05-1.54, PR=1.51, 95% CI: 1.10-2.06 and PR=1.36, 95% CI: 1.03-1.80 respectively). For the 20-24 year olds, there was some evidence of an increase in HPV39 (PR=1.13, 95% CI: 1.00-1.28).

Sensitivity analyses

As a sensitivity analysis, we performed three additional stratified analyses (all stratified by age-group); (i) by vaccine used (i.e. bivalent or quadrivalent), (ii) by potential bias of study (relatively low potential bias, defined as fewer than three domains classified as high-risk of bias, or relatively high potential bias, defined as three or more domains classified as high-risk of bias) (Figure 2) and (iii) by vaccination coverage (low <50%, high ≥50%).

For studies in settings using the bivalent vaccine, there was some evidence of an increased prevalence between the prevaccination period and postvaccination period in ≤19 year old females for HPV52, HPV53, HPV56, and HPV70 (Table S1; Figures S2, S3, and S4). The prevalence of HPV53 among 20-24 year old women also increased. For the quadrivalent vaccine, there was evidence of an increase in HPV39, HPV51, and HPV59 for females ≤19 years old. Among 20-24 year olds, there was evidence of an increase in the prevalence of HPV52 and HPV70 (Table S1; Figures S2, S3, and S4).

Many of the analyses stratified by potential bias of included studies gave similar results to the unstratified analyses (Table S2). However, in the younger age-group, for studies with relatively low potential bias there was no evidence of increases in HPV52 or HPV39 (which were seen when studies were unstratified). For studies with relatively high potential bias, in the younger age-group there was evidence of an increase in the prevalence of HPV51 and HPV70 which was not seen in the unstratified analysis. In the older age-group there was evidence of a decrease in HPV 33 for those studies at a relatively low potential bias (no summary estimate was provided in the unstratified analysis due to heterogeneity). For studies with a relatively high potential bias there was evidence of an increase in the prevalence of HPV52 and HPV58. There was also evidence for a decrease in the prevalence of HPV82 for both those with relatively high potential bias and relatively low potential bias (although there was a larger decrease in those studies with relatively high potential bias; no summary estimate was provided in the unstratified analysis due to evidence for heterogeneity).

Vaccination coverage was high for all studies in the younger age-group (Table S3). For older women, there was a decrease in HPV31 for studies with high vaccination coverage (no summary estimate was provided for the unstratified analysis due to heterogeneity). There was evidence of an increase in HPV39 and HPV58 (as with the unstratified analysis) although only for the studies with low coverage. There was also evidence of increases not seen in the unstratified analysis (HPV70 for low coverage studies and borderline evidence for HPV26 for high coverage studies; both types had no summary estimate for the unstratified analysis due to heterogeneity).

Discussion

Comprehensive postvaccination surveillance should consider not just the reductions in vaccine type-specific infection and associated diseases but also evaluate any other potential impacts of the reduction of the targeted infection. Thus, we assessed changes in the nonvaccine HPV types to determine evidence of cross protection for individual types and the potential concern that the reductions seen in certain HPV types after HPV vaccine introduction could create a niche for other, nonvaccine high-risk HPV types to become more common (i.e. type-replacement). We demonstrated evidence of a reduction in the prevalence of HPV31 in the younger age-group. In our main analysis, we show increases in other nonvaccine HPV types, HPV39, HPV52, HPV53, HPV58, and HPV73 but these increases were inconsistent between age-groups and the vaccine used.

A previous systematic review evaluated changes in high-risk HPV types combined, and found some evidence of a reduction of the HPV types closely related to the vaccine types (HPV31, HPV33, and/or HPV45) when considered as a single group (PR=0.72, 95% CI:

0.54-0.96 for 13-19 year olds).*(11)* Our review provides evidence of a reduction in the prevalence of HPV31, but little evidence of a reduction in HPV33 or HPV45.

Comparing HPV prevalence in a prevaccination period to a similar population in postvaccination period allows us to consider the population-level impact of HPV vaccination on HPV prevalence. However, these repeat cross-sectional study designs have some limitations. Although all studies included similar populations in the pre- and postvaccination periods, there may have been temporal changes in these populations over time which could affect HPV prevalence, independent of HPV vaccination. For example, there have been increases in other STI diagnoses over this same time period in some countries.*(28)* Furthermore, in many countries the incidence of genital warts was increasing prior to the vaccine introduction*(29-31)* and has continued to increase postvaccination in those not eligible for vaccination.*(11)* It is therefore possible that the increases in some HPV types we observed are associated with broad increases in sexual risk over time. Changes in demographics and sexual behaviour between the populations were considered when available, but it is likely that there were some unrecorded population changes and/or other temporal changes in the relative proportions of high-risk HPV types over time.*(32;33)* There is also more geographical variation in the relative frequency of nonvaccine HPV types in populations compared with HPV16 prevalence which, prior to vaccination programs, was the most frequent high risk type observed in almost all populations.*(34)*

The change in assay between the pre- and postvaccination for one of the studies (Mesher et al) was a potential source of bias. A validation study comparing these two testing assays allowed odds ratios (ORs) to be adjusted for the differences in diagnostic accuracy. This adjusted odds ratio could not be converted to a prevalence ratio using the log-binomial model and thus was included as an OR. However, given the low prevalence of individual HPV types, the use of an OR for this study (rather than a PR) is unlikely to have affected the results substantially.

Another limitation is that the broad-spectrum assays which have been used in these studies (and in baseline prevaccination evaluations globally) can lack sensitivity to detect individual HPV types when multiple types are present, particularly in the presence of another HPV type with a higher viral load. In the postvaccination period, in the absence of HPV16 and HPV18 this could lead to an apparent, artificial increase in nonvaccine types (because they were underestimated in the pre-vaccine period due to the predominance of HPV16 and/or HPV18). This potential unmasking effect has been demonstrated in analytical studies;*(35;36)* hence some of the increases in nonvaccine types observed could be due to unmasking.

Given the low prevalence of some other nonvaccine HPV types, it is a challenge to assess changes in prevalence for individual types since the introduction of HPV vaccination. By combining data from several studies, we had enhanced power to consider changes in the individual HPV types. However, even with data from 13,886 women aged ≤19 years old and 23,340 women aged 20-24 years old, we still had limited power to consider changes in the very rare HPV types or to investigate the reasons for the heterogeneity in findings for some HPV types, with inconsistent evidence for increases of specific nonvaccine types between age-groups and the two vaccines. Conversely, type 1 errors can occur with multiple testing and 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 there was inconsistency in the direction of effect, making the summary estimate (the average value of these opposing effects) uninformative*(37)*. Exploring the causes of heterogeneity could provide some further insight into the reasons for these increases, and we carried out subgroup analyses by vaccine used, by potential bias and by vaccine coverage. The results of the stratification by potential bias suggest that increased prevalence ratios for some HPV types may have been reported more often in the studies with relative high potential bias. However, for all three sensitivity analyses the small number of studies in each stratum limited the interpretation of these analyses. Similarly, we were limited to only eight studies for each age-group and thus at present have insufficient power to perform meta-regression analyses (as meta-regression should generally not be considered when there are fewer than ten studies)*(37)*. As further data accrue, one useful future analysis would be to explore the association between the reductions in the HPV vaccine-types and any increases in nonvaccine HPV types (that are not due to unmasking) - if increases were due to type-replacement then we would expect to see increasing prevalence of nonvaccine HPV types as prevalence of vaccine HPV types decreases.

It is encouraging that we confirm the reductions in a cross-protected HPV type. The results of this systematic review and meta-analysis do not provide any clear evidence for type-replacement, as it is not clear to what extent any increases seen are due to other temporal changes, changes in the study populations, and/or an unmasking effect of broad spectrum HPV assays. Large scale epidemiological analyses using various designs have not detected evidence of any significant interactions between high-risk types; the known high evolutionary stability of these viruses, lessens the risk that type-replacement will be a problem.*(38;39)*

The majority of women included in the surveillance studies were those vaccinated at older ages (i.e. potentially vaccinated after HPV exposure) and some studies include populations with relatively low coverage compared to nationally reported vaccination coverage for routine cohorts. Future studies should continue to monitor population prevalence of these types. In particular, populations vaccinated at a younger age with higher vaccination coverage should be considered and, perhaps more importantly, the absolute prevalence of CIN3 lesions attributed to each high-risk HPV type.

Acknowledgments

The authors would like to thank Kavita Panwar who undertook the HPV testing for the data provided for Mesher et al.

Funding

Supported by Public Health England

Table 1: Characteristics of studies selected for systematic review

	Cameron et al	Chow et al	Cummings et al	Kahn et al	Markowitz et al	Mesher et al	Söderlund-Strand et al	Sonnenberg et al	Tabrizi et al
Study design	Repeat cross-sectional studies	Repeat cross-sectional studies	Repeat cross-sectional studies	Repeat cross-sectional studies	Repeat cross-sectional studies	Repeat cross-sectional studies	Repeat cross-sectional studies	Repeat cross-sectional studies	Repeat cross-sectional studies
Country of study	UK (Scotland)	Australia	USA	USA	USA	UK (England)	Sweden	UK (Britain)	Australia
Vaccine introduced	Bivalent	Quadrivalent	Quadrivalent	Quadrivalent	Quadrivalent	Bivalent	Quadrivalent	Bivalent	Quadrivalent
Year(s) of sample collection	Prevaccination: 2009-2010 Postvaccination: 2011-2013	Prevaccination: 2004-2007 Postvaccination: 2007-2014	Prevaccination: 1995-2005 Postvaccination: 2010	Prevaccination: 2006-2007 Postvaccination: 2009-2010	Prevaccination: 2003-2006 Postvaccination: 2009-2012	Prevaccination: 2008 Postvaccination: 2010-2013	Prevaccination: 2008 Postvaccination: 2012-2013	Prevaccination: 1999-2001 Postvaccination: 2010-2012	Prevaccination: 2005-2007 Postvaccination: 2010-2011
Number of specimens tested	Prevaccination: 2705 Postvaccination: 3010	Prevaccination: 136 Postvaccination: 328	Prevaccination: 150 Postvaccination: 75	Prevaccination: 365 Postvaccination: 383	Prevaccination: 1795 Postvaccination: 1209	Prevaccination: 2354 Postvaccination: 7321	Prevaccination: 11457 Postvaccination: 3555	Prevaccination: 328 Postvaccination: 795	Prevaccination: 202 Postvaccination: 1058
Study population and setting	Females (aged 20-21 years old) attending for cervical screening as part of national cervical screening programme.	Australian-born females (aged 21 years old and younger) attending for chlamydia screening at a sexual health centre in Melbourne and testing positive for chlamydia	Females (aged 14-17 years old) attending one of three primary care clinics in Indiana	Females (aged 13-26 years old) who had had sexual intercourse, recruited from hospital based adolescent clinic and a community health centre	Females (aged 14-24 years old) participating in population based NHANES survey	Sexually active females (aged 16-25 year old) attending for chlamydia screening at community sexual health settings	Females (all ages) attending for chlamydia screening in a defined region of Sweden	Sexually experienced females (aged 18-44 years old) selected via households using stratified probability sample survey (participating in Natsal survey)	Females (aged 18-24 years old) attending for cervical screening at sentinel family planning clinics in Sydney, Melbourne and Perth
Specimen type	Residual LBC* specimen	Cervical and high vaginal swab samples	Self-collected vaginal swab	Cervicovaginal swabs by clinician or self-	Self-collected cervicovaginal swab	Residual vulval vaginal swab specimen	Genital swabs (either alone or	Urine sample	Sample of exfoliated cervical cells preserved

				collected swab			immersed in urine)		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	Prevaccination: Linear Array HPV Genotyping test in those testing positive for Hybrid Capture 2 Postvaccination: 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 using L1 consensus primer set PGMY09-PGMY11). If positive for Amplicor or PCMY09/PGMY11 PCR-ELISA were genotyped using the Linear Array HPV genotyping test
Demographic and sexual behaviour data collected	Scottish Index of Multiple Deprivation, month/year of birth These data were not used to adjust the HPV prevalence ratios in	Age-stratified prevalence ratios were adjusted for by number of male partners, 100% condom use with all partners in	Samples matched on age at enrolment, clinic site and reported sexual activity. Data on ethnicity, sexual partners in previous last year,	Age, race, health care insurance, knowledge about HPV vaccines, smoking status, gynaecologic history (number of pregnancies, history	Ethnicity, poverty index and, for those reported ever having sex; age at first sex, lifetime number of partners, number of partners in the	Age stratified prevalence ratios were adjusted for age, chlamydia positivity at time specimen taken and collection venue type	All samples were anonymised (individual age was known)	Extensive demographic and sexual behaviour data collected. These data were not used to adjust the HPV prevalence ratios in	Age, current use of hormonal contraception, smoking status and postcode of residence These data were not used to adjust the

	this meta-analysis	the past 12 months status and anatomical sampling method (cervical vs high vaginal sample)	sexual partners in previous 2 months, lifetime sexual partners, instances of vaginal intercourse in previous year and instances of vaginal intercourse in the previous 2 months These data were not used to adjust the HPV prevalence ratios in this meta-analysis	of STIs), sexual behaviours (age at first sex, number of male lifetime partners, number of male partners in previous 3 months, anal sex, condom use) These data were not used to adjust the HPV prevalence ratios in this meta-analysis	previous 12 months. These data were not used to adjust the HPV prevalence ratios in this meta-analysis			this meta-analysis	HPV prevalence ratios in this meta-analysis
Vaccination status	Data linked from Scottish Immunisation call/recall system and Child Health Schools Programme system	Self-reported. Data not available for all women	Collected from medical notes	Collected from immunisation registry for 87% of women. Collected from self-administered questionnaire for remaining 13% of women.	Self-reported	Not collected for individuals	Not collected for individuals	Self-reported	Self-reported and validated against the National HPV vaccine register

* LBC = Liquid based cytology

354

Table 2: Prevalence ratio for nonvaccine high-risk HPV types stratified by age-group

Age-group / HPV type	Number of studies	Heterogeneity		Prevalence ratio* (95% CI)
		I^2	p-value	
≤19 year old females				
HPV types included in nonavalent vaccine				
HPV 31	8	6.4%	0.381	0.73 (0.58-0.91)
HPV 33	8	0.0%	0.471	1.04 (0.78-1.38)
HPV 45	8	5.5%	0.387	0.96 (0.75-1.23)
HPV 52	8	24.0%	0.238	1.34 (1.13-1.59)
HPV 58	8	0.0%	0.727	1.01 (0.80-1.26)
Other high-risk HPV types				
HPV 35	8	25.1%	0.229	-
HPV 39	8	0.0%	0.984	1.27 (1.05-1.54)
HPV 51	8	43.6%	0.088	-
HPV 56	8	74.3%	<0.001	-
HPV 59	8	66.8%	0.004	-
HPV 68	8	0.0%	0.690	1.26 (0.88-1.81)
Other possibly high-risk HPV types				
HPV 26	6	0.0%	0.478	1.63 (0.84-3.16)
HPV 53	6	3.6%	0.394	1.51 (1.10-2.06)
HPV 70	6	23.6%	0.257	1.34 (0.75-2.39)
HPV 73	6	0.0%	0.961	1.36 (1.03-1.80)
HPV 82	6	49.0%	0.081	-
20-24 year old females				
HPV types included in nonavalent vaccine				
HPV 31	8	28.8%	0.198	-
HPV 33	8	50.9%	0.047	-
HPV 45	8	64.3%	0.007	-
HPV 52	8	31.0%	0.180	-
HPV 58	8	0.0%	0.806	1.14 (0.99-1.31)
Other high-risk HPV types				
HPV 35	8	7.9%	0.369	1.07 (0.85-1.34)
HPV 39	8	0.0%	0.522	1.13 (1.00-1.28)
HPV 51	8	49.8%	0.052	-
HPV 56	8	82.6%	<0.001	-
HPV 59	8	63.6%	0.007	-
HPV 68	8	35.6%	0.145	-
Other possibly high-risk HPV types				
HPV 26	6	44.3%	0.110	-
HPV 53	6	30.8%	0.204	-
HPV 70	6	25.1%	0.246	-
HPV 73	6	59.2%	0.032	-
HPV 82	6	38.3%	0.151	-

* Summary prevalence ratio only calculated if data were not shown to be heterogeneous

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Figure Legends

Figure 1: Flow chart for eligible studies included in systematic review

Figure 2: Potential Bias and external validity of included studies

Figure 3: Prevalence ratio for high-risk HPV types with evidence of cross-protection (HPV31, HPV33, HPV45) stratified by age-group, percentages in square brackets represent vaccination coverage (at least one dose) for each study/age-group

Figure 4: Prevalence ratio for other high-risk HPV types included in the nonavalent vaccine (HPV52, HPV58) stratified by age-group, percentages in square brackets represent vaccination coverage (at least one dose) for each study/age-group

Technical Appendix Figure 1: Prevalence ratio for other probably high-risk HPV types (HPV35, HPV39, HPV51, HPV56, HPV59 and HPV68) stratified by age-group, percentages in square brackets represent vaccination coverage (at least one dose) for each study/age-group

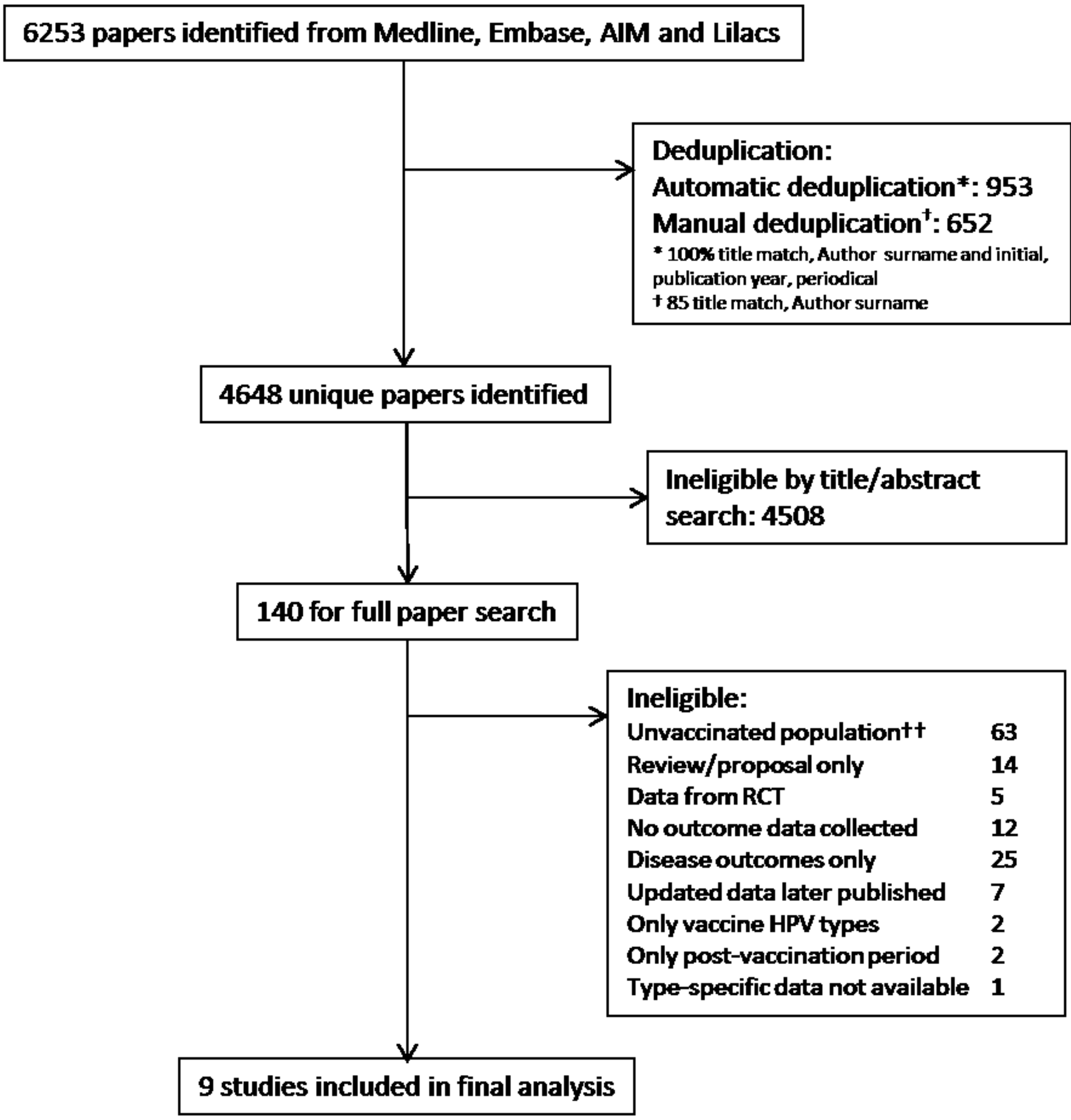
Technical Appendix Figure 2: Prevalence ratio for high-risk HPV types with evidence of cross-protection (HPV31, HPV33, HPV45) stratified by age-group and vaccine type, percentages in square brackets represent vaccination coverage (at least one dose) for each study/age-group

Technical Appendix Figure 3: Prevalence ratio for other high-risk HPV types included in the nonavalent vaccine (HPV52, HPV58) stratified by age-group and vaccine type, percentages in square brackets represent vaccination coverage (at least one dose) for each study/age-group

Technical Appendix Figure 4: Prevalence ratio for other probably high-risk HPV types (HPV35, HPV39, HPV51, HPV56, HPV59 and HPV68) stratified by age-group and vaccine type, percentages in square brackets represent vaccination coverage (at least one dose) for each study/age-group

Figures

Figure 1: Flow chart for eligible studies included in systematic review



†† Includes studies where the vast majority of the population were unvaccinated

Figure 2: Potential Bias and external validity of included studies

	Population-based pre- and post-vaccination sample	Comparative populations for pre- and post-vaccination	Risk factor data collected and adjusted for	Suitable sample to assess HPV	HPV assay with suitable diagnostic accuracy	HPV assay for pre- and post-vaccination identical	Collection of vaccination status
Chow et al	H	H	L	L	L	L	H
Cummings et al	H	L	L	L	L	L	L
Kahn et al	H	L	L	L	L	L	L
Kavanagh et al	L	L	H	L	L	L	L
Markowitz et al	L	L	L	L	L	L	H
Mesher et al	H	H	H	L	L	H	H
Sōderlund-Strand et al	H	H	H	L	L	L	H
Sonnenberg et al	L	L	L	H	L	L	H
Tabrizi et al	L	L	H	L	L	L	L

Key
L = Low risk of bias
H = High risk of bias

Figure 3: Prevalence ratio for high-risk HPV types with evidence of cross-protection (HPV31, HPV33, HPV45) stratified by age-group, percentages in square brackets represent vaccination coverage (at least one dose) for each study/age-group

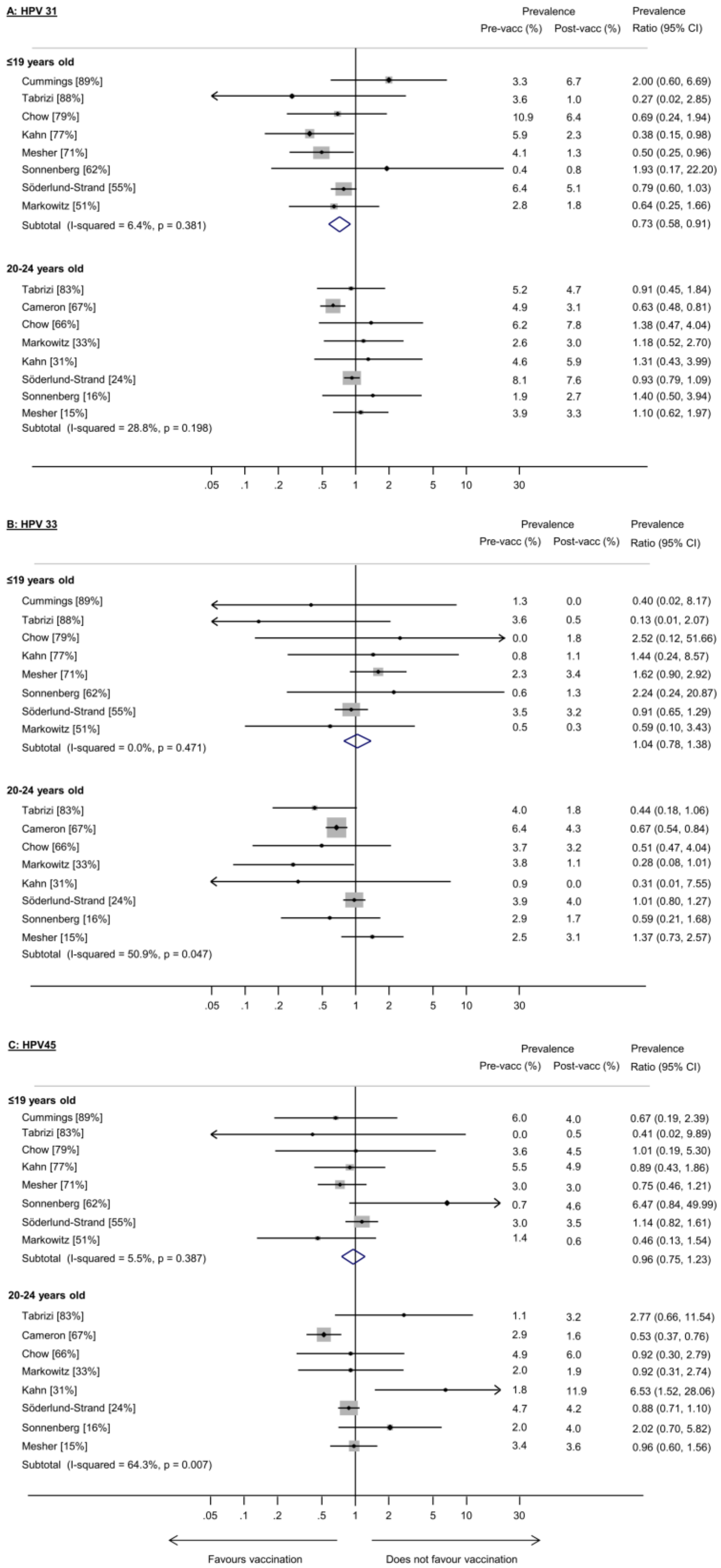
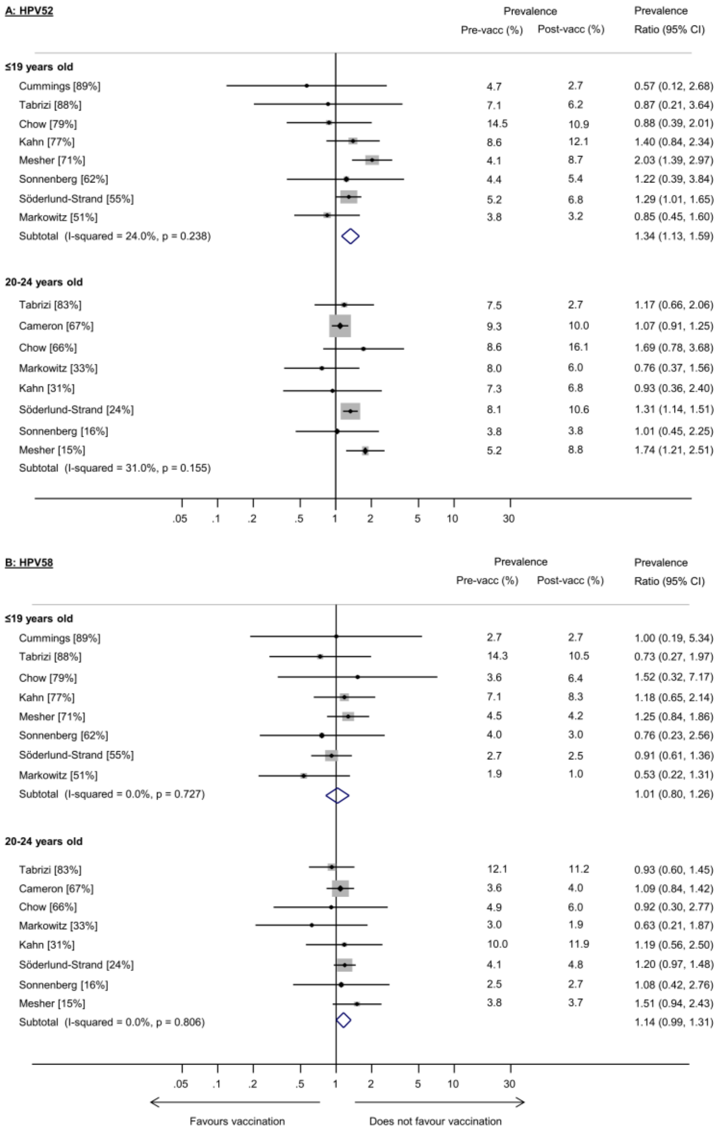


Figure 4: Prevalence ratio for other high-risk HPV types included in the nonavalent vaccine (HPV52, HPV58) stratified by age-group, percentages in square brackets represent vaccination coverage (at least one dose) for each study/age-group



Technical Appendix

Search strategies

Medline search strategy: 2410 (19 Feb 2016)

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: 3843 (19 Feb 2016)

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: *58* (19 Feb 2016)
((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 (Immuni$ 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: *17* (19 Feb 2016)
hpv OR Papilloma$

Supplementary Tables

Table S1: Prevalence ratio for non-vaccine high-risk HPV types stratified by age-group and vaccine type

	Bivalent vaccine				Quadrivalent vaccine			
Age-group / HPV type	Number of studies	Heterogeneity I^2	Heterogeneity p-value	Prevalence ratio* (95% CI)	Number of studies	Heterogeneity I^2	Heterogeneity p-value	Prevalence ratio* (95% CI)
≤19 year old females								
HPV types included in nonavalent vaccine								
HPV 31	2	10.4%	0.291	0.54 (0.29-1.03)	6	8.7%	0.36	0.75 (0.60-0.96)
HPV 33	2	0.0%	0.785	1.66 (0.94-2.92)	6	0.0%	0.687	0.89 (0.64-1.24)
HPV 45	2	75.4%	0.044	-	6	0.0%	0.716	1.01 (0.76-1.34)
HPV 52	2	0.0%	0.408	1.93 (1.34-2.77)	6	0.0%	0.627	1.20 (0.99-1.47)
HPV 58	2	0.0%	0.445	1.19 (0.81-1.73)	6	0.0%	0.742	0.92 (0.69-1.22)
Other high-risk HPV types								
HPV 35	2	85.2%	0.009	-	6	0.0%	0.914	0.91 (0.58-1.42)
HPV 39	2	0.0%	0.755	1.30 (0.89-1.91)	6	0.0%	0.932	1.26 (1.01-1.58)
HPV 51	2	74.9%	0.046	-	6	35.2%	0.172	1.16 (1.00-1.36)
HPV 56	2	18.3%	0.269	2.08 (1.43-3.04)	6	64.9%	0.014	-
HPV 59	2	51.9%	0.149	-	6	0.0%	0.478	1.27 (1.03-1.57)
HPV 68	2	0.0%	0.444	1.84 (0.62-5.47)	6	0.0%	0.601	1.20 (0.82-1.76)
Other possibly high-risk HPV types								
HPV 26	2	0.0%	0.873	1.89 (0.84-4.26)	4	26.8%	0.251	1.21 (0.38-3.81)
HPV 53	2	0.0%	0.894	2.22 (1.25-3.94)	4	0.0%	0.445	1.28 (0.88-1.85)
HPV 70	2	0.0%	0.957	4.07 (1.43-11.55)	4	0.0%	0.97	0.82 (0.41-1.64)
HPV 73	2	0.0%	0.926	1.39 (0.98-1.98)	4	0.0%	0.806	1.32 (0.83-2.07)
HPV 82	2	0.0%	0.998	2.00 (0.50-7.95)	4	65.1%	0.035	-
20-24 year old females								
HPV types included in nonavalent vaccine								
HPV 31	3	57.8%	0.094	-	5	0.0%	0.889	0.95 (0.81-1.10)
HPV 33	3	55.0%	0.108	-	5	48.1%	0.103	-
HPV 45	3	74.2%	0.021	-	5	56.9%	0.055	-
HPV 52	3	65.6%	0.055	1.26 (0.87, 1.83)	5	0.0%	0.53	1.28 (1.12-1.46)
HPV 58	3	0.0%	0.499	1.17 (0.94-1.46)	5	0.0%	0.684	1.12 (0.93-1.34)
Other high-risk HPV types								
HPV 35	3	0.0%	0.968	1.22 (0.79-1.87)	5	43.1%	0.134	-
HPV 39	3	44.8%	0.163	1.32 (0.93, 1.88)	5	0.0%	0.743	1.09 (0.93-1.28)
HPV 51	3	0.0%	0.57	1.37 (1.16-1.62)	5	47.0%	0.11	1.19 (0.88, 1.61)
HPV 56	3	75.4%	0.017	1.45 (0.82, 2.59)	5	87.5%	<0.001	-
HPV 59	3	86.1%	0.001	-	5	0.0%	0.604	1.13 (0.94-1.37)

HPV 68	3	67.4%	0.046	-	5	0.0%	0.842	0.99 (0.72-1.37)
Other possibly high-risk HPV types								
HPV 26	3	69.0%	0.04	-	3	21.1%	0.282	1.35 (0.28-6.47)
HPV 53	3	0.3%	0.367	1.23 (1.05-1.45)	3	16.9%	0.3	0.90 (0.64-1.25)
HPV 70	3	0.0%	0.382	1.11 (0.81-1.51)	3	0.0%	0.811	2.47 (1.24-4.94)
HPV 73	3	43.8%	0.169	-	3	76.3%	0.015	-
HPV 82	3	73.7%	0.022	-	3	0.0%	0.989	0.94 (0.39-2.26)

* Summary prevalence ratio only calculated if data were not shown to be heterogeneous

Table S2: Prevalence ratio for non-vaccine high-risk HPV types stratified by age-group and potential bias

Age-group / HPV type	Relatively low potential bias[1]				Relatively high potential bias[2]			
	Number of studies	Heterogeneity		Prevalence ratio[3] (95% CI)	Number of studies	Heterogeneity		Prevalence ratio[3] (95% CI)
		I^2	p-value			I^2	p-value	
≤19 year old females								
Nonavalent HPV types								
HPV 31	5	31.2 %	0.213	-	3	0.0%	0.447	0.73 (0.58-0.93)
HPV 33	5	0.0%	0.526	0.79 (0.30-2.06)	3	34.4 %	0.218	-
HPV 45	5	21.5 %	0.278	0.84 (0.49-1.44)	3	0.6%	0.366	0.99 (0.76-1.31)
HPV 52	5	0.0%	0.681	1.09 (0.77-1.56)	3	61.9 %	0.072	-
HPV 58	5	0.0%	0.672	0.87 (0.58-1.30)	3	0.0%	0.505	1.08 (0.82-1.42)
Other high-risk HPV types								
HPV 35	5	0.0%	0.424	0.85 (0.46-1.58)	3	60.6 %	0.079	-
HPV 39	5	0.0%	0.907	1.21 (0.83-1.78)	3	0.0%	0.846	1.30 (1.04-1.61)
HPV 51	5	45.3 %	0.120	-	3	0.0%	0.433	1.28 (1.09-1.50)
HPV 56	5	69.3 %	0.011	-	3	79.9 %	0.007	-
HPV 59	5	0.0%	0.465	1.29 (0.94-1.76)	3	85.9 %	0.001	-
HPV 68	5	12.6 %	0.333	1.21 (0.76-1.93)	3	0.0%	0.948	1.33 (0.75-2.36)
Other possibly high-risk HPV types								
HPV 26	5	3.3%	0.388	1.27 (0.45-3.58)	1	-	-	1.93 (0.82, 4.59)
HPV 53	5	0.0%	0.514	1.32 (0.92-1.90)	1	-	-	2.19 (1.18, 4.04)
HPV 70	5	0.0%	0.831	0.90 (0.45-1.76)	1	-	-	4.02 (1.31, 12.32)
HPV 73	5	0.0%	0.909	1.33 (0.87-2.05)	1	-	-	1.39 (0.96, 2.00)
HPV 82	5	55.0 %	0.064	-	1	-	-	2.00 (0.42, 9.44)
20-24 year old females								
Nonavalent HPV types								
HPV 31	5	27.7 %	0.237	-	3	0.0%	0.670	0.95 (0.81-1.11)
HPV 33	5	0.0%	0.599	0.64 (0.52-0.78)	3	0.0%	0.424	1.03 (0.83-1.27)
HPV 45	5	78.5 %	0.001	-	3	0.0%	0.948	0.90 (0.74-1.10)
HPV 52	5	0.0%	0.905	1.06 (0.91-1.22)	3	11.8 %	0.322	1.37 (1.20-1.56)
HPV 58	5	0.0%	0.859	1.04 (0.85-1.28)	3	0.0%	0.600	1.23 (1.02-1.50)
Other high-risk HPV types								
HPV 35	5	0.0%	0.754	1.42 (0.97-2.08)	3	10.7 %	0.326	0.90 (0.67-1.21)
HPV 39	5	8.3%	0.359	1.12 (0.94-1.34)	3	0.0%	0.415	1.14 (0.97-1.34)
HPV 51	5	32.5 %	0.205	-	3	46.9 %	0.152	-
HPV 56	5	0.0%	0.914	1.03 (0.89-1.21)	3	94.5 %	0.000	-
HPV 59	5	0.0%	0.443	1.08 (0.91-1.28)	3	86.4 %	0.001	-
HPV 68	5	0.0%	0.692	1.04 (0.72-1.49)	3	72.5 %	0.026	-
Other possibly high-risk HPV types								

HPV 26	5	54.8 %	0.065	-	1	-	-	1.14 (0.37, 3.50)
HPV 53	5	36.3 %	0.179	-	1	-	-	1.52 (0.86, 2.69)
HPV 70	5	34.5 %	0.191	-	1	-	-	1.64 (0.79, 3.37)
HPV 73	5	56.0 %	0.059	-	1	-	-	1.92 (1.04, 3.53)
HPV 82	5	0.0%	0.984	0.75 (0.60-0.94)	1	-	-	0.22 (0.10, 0.51)

1 Average-low potential bias includes studies; Cameron et al, Cummings et al, Kahn et al, Markowitz et al, Sonnenberg et al and Tabrizi et al

2 Average-high potential bias includes studies; Chow et al, Mesher et al and Söderlund-Strand et al

3 Summary prevalence ratio only calculated if data were not shown to be heterogeneous

Table S3: Prevalence ratio for non-vaccine high-risk HPV types stratified by age-group and vaccination coverage

	Low vaccination coverage (<50%)				High vaccination coverage (≥50%)			
Age-group / HPV type	Number of studies	Heterogeneity I^2	Heterogeneity p-value	Prevalence ratio[1] (95% CI)	Number of studies	Heterogeneity I^2	Heterogeneity p-value	Prevalence ratio[1] (95% CI)
≤19 year old females								
Nonavalent HPV types								
HPV 31	0		-		8	6.4%	0.381	0.73 (0.58-0.91)
HPV 33	0		-		8	0.0%	0.471	1.04 (0.78-1.38)
HPV 45	0		-		8	5.5%	0.387	0.96 (0.75-1.23)
HPV 52	0		-		8	24.0 %	0.238	1.34 (1.13-1.59)
HPV 58	0		-		8	0.0%	0.727	1.01 (0.80-1.26)
Other high-risk HPV types								
HPV 35	0		-		8	25.1 %	0.229	-
HPV 39	0		-		8	0.0%	0.984	1.27 (1.05-1.54)
HPV 51	0		-		8	43.6 %	0.088	-
HPV 56	0		-		8	74.3 %	<0.001	-
HPV 59	0		-		8	66.8 %	0.004	-
HPV 68	0		-		8	0.0%	0.690	1.26 (0.88-1.81)
Other possibly high-risk HPV types								
HPV 26	0		-		6	0.0%	0.478	1.63 (0.84-3.16)
HPV 53	0		-		6	3.6%	0.394	1.51 (1.10-2.06)
HPV 70	0		-		6	23.6 %	0.257	1.34 (0.75-2.39)
HPV 73	0		-		6	0.0%	0.961	1.36 (1.03-1.80)
HPV 82	0		-		6	49.0 %	0.081	-
20-24 year old females								
Nonavalent HPV types								
HPV 31	5	0.0%	0.838	0.96 (0.83-1.12)	3	25.5 %	0.261	-
HPV 33	5	36.3 %	0.179	-	3	0.0%	0.618	0.65 (0.53-0.81)
HPV 45	5	55.9 %	0.06	-	3	62.7 %	0.068	-
HPV 52	5	26.1 %	0.248	-	3	0.0%	0.513	1.10 (0.94-1.27)
HPV 58	5	0.0%	0.689	1.21 (1.01-1.45)	3	0.0%	0.807	1.04 (0.83-1.30)
Other high-risk HPV types								
HPV 35	5	30.4 %	0.219	-	3	0.0%	0.590	1.29 (0.80-2.07)
HPV 39	5	5.3%	0.377	1.17 (1.00-1.37)	3	0.0%	0.482	1.08 (0.89-1.30)
HPV 51	5	56.7 %	0.056	-	3	37.8 %	0.201	-
HPV 56	5	30.5 %	0.218	-	3	91.7 %	<0.001	-
HPV 59	5	73.5 %	0.004	-	3	0.0%	0.673	1.15 (0.96-1.37)
HPV 68	5	61.7 %	0.034	-	3	0.0%	0.810	1.20 (0.78-1.85)
Other possibly high-risk HPV types								

HPV 26	4	53.8 %	0.09	-	2	0.0%	0.862	1.76 (1.00-3.12)
HPV 53	4	0.0%	0.522	1.31 (0.95-1.81)	2	76.6 %	0.039	-
HPV 70	4	11.8 %	0.334	1.72 (1.06-2.79)	2	0.0%	0.335	1.08 (0.76-1.53)
HPV 73	4	52.5 %	0.097	-	2	0.0%	0.503	1.02 (0.82-1.26)
HPV 82	4	33.7 %	0.21	-	2	0.0%	0.675	0.75 (0.59-0.94)

1 Summary prevalence ratio only calculated if data were not shown to be heterogeneous

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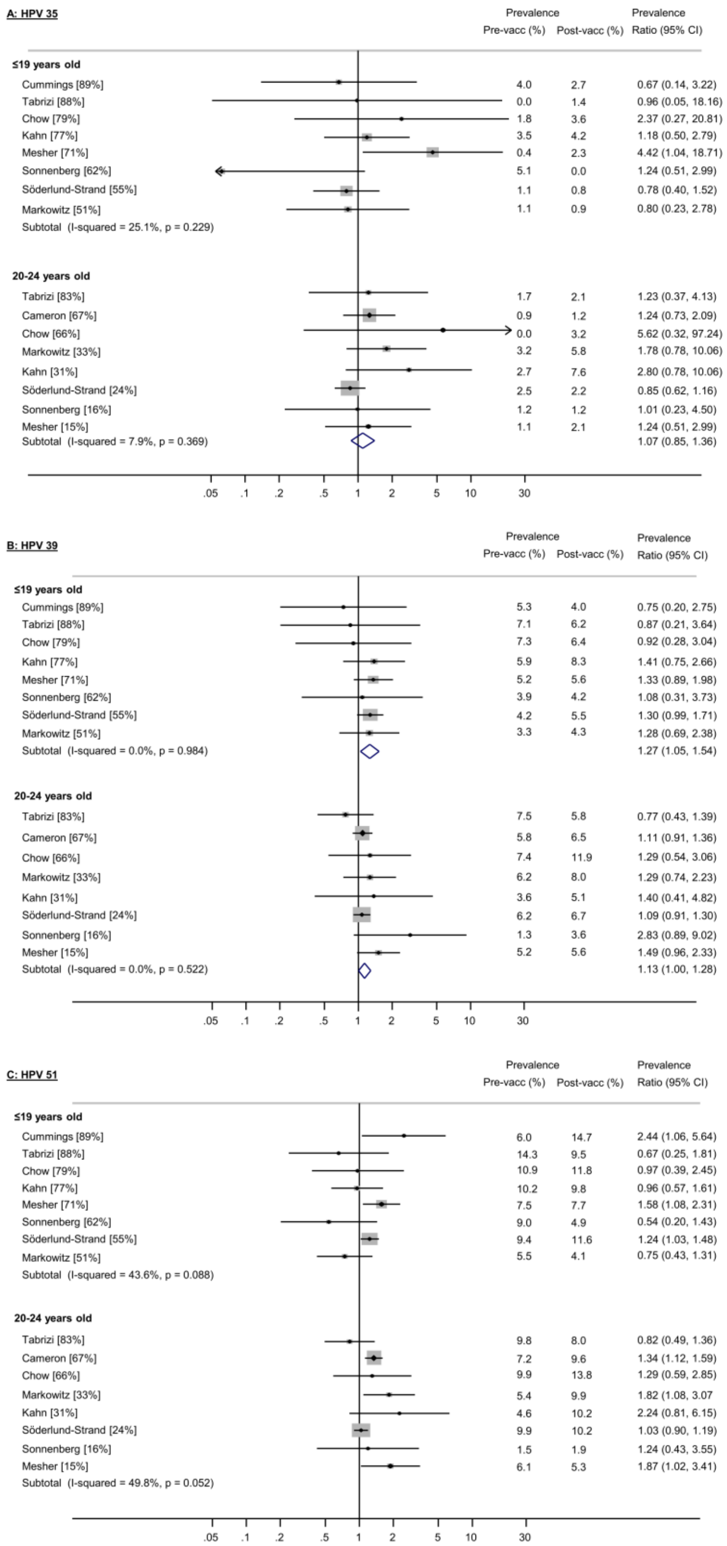
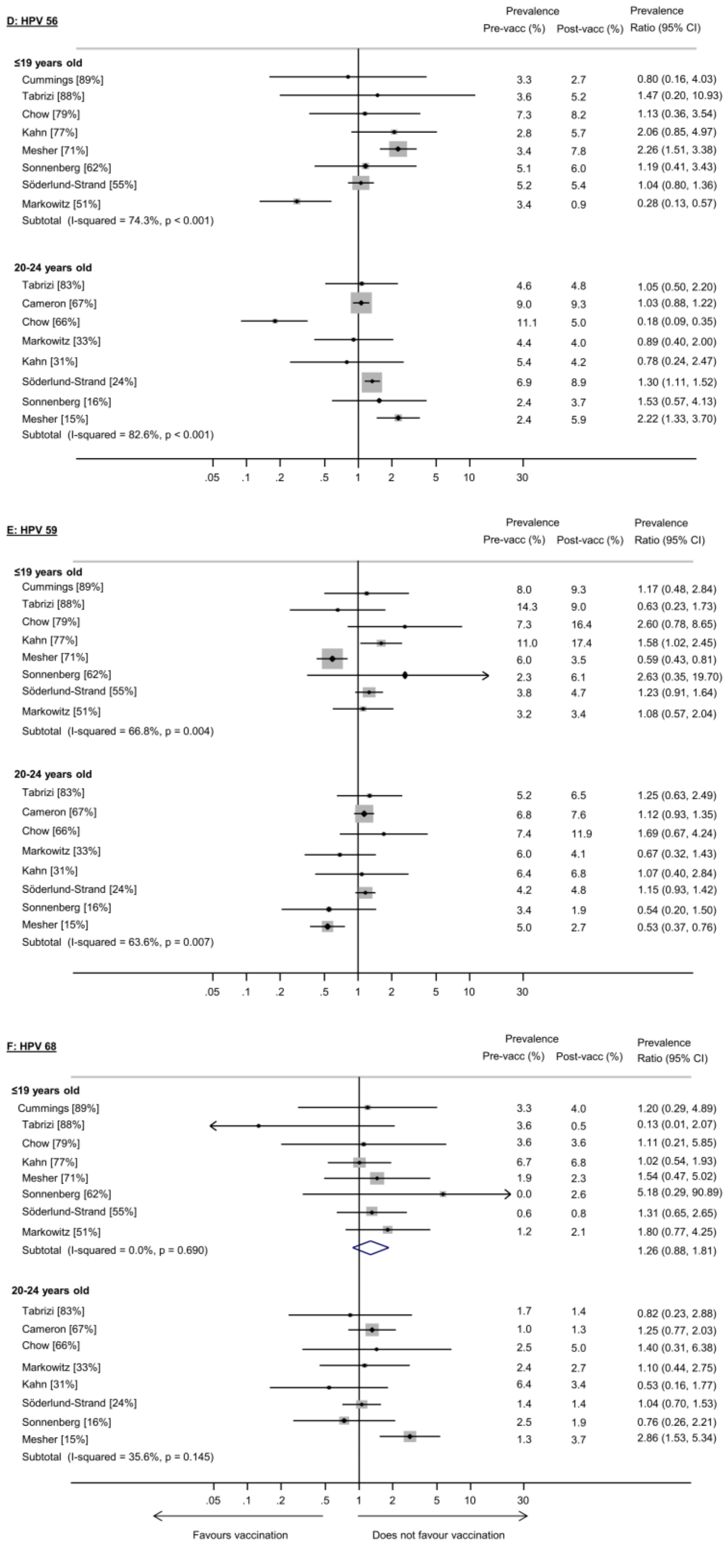
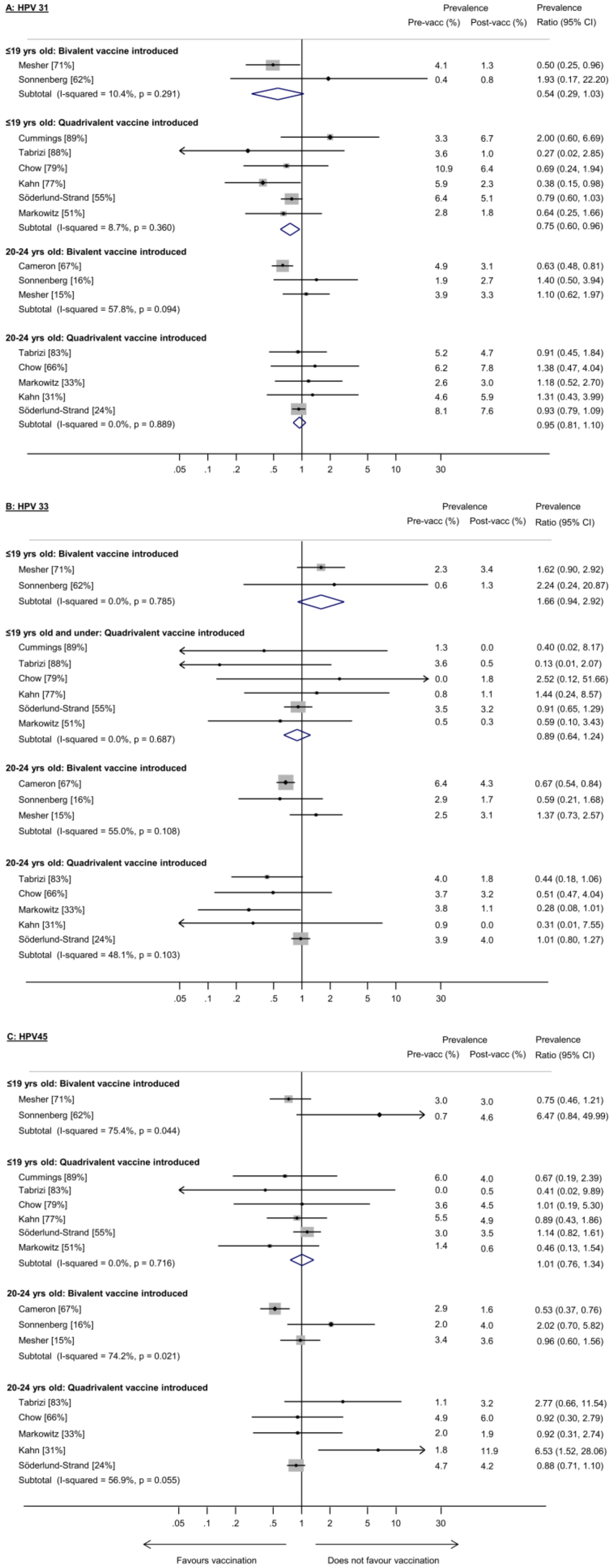
Supplementary Figures

Technical Appendix Figure 1: Prevalence ratio for other probably high-risk HPV types (HPV35, HPV39, HPV51, HPV56, HPV59 and HPV68) stratified by age-group, percentages in square brackets represent vaccination coverage (at least one dose) for each study/age-group



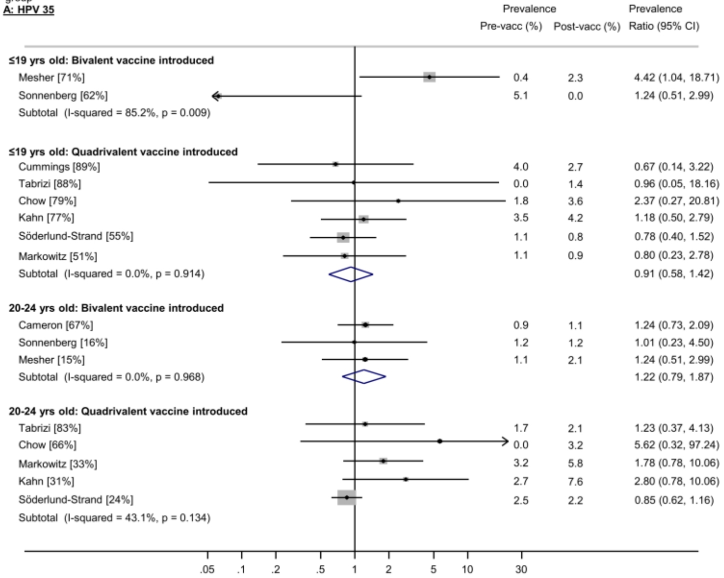

D: HPV 56
Prevalence
Pre-vacc (%) Post-vacc (%)
Prevalence Ratio (95% CI)
≤19 years old
Cummings [89%] 3.3 2.7 0.80 (0.16, 4.03)
Tabrizi [88%] 3.6 5.2 1.47 (0.20, 10.93)
Chow [79%] 7.3 8.2 1.13 (0.36, 3.54)
Kahn [77%] 2.8 5.7 2.06 (0.85, 4.97)
Mesher [71%] 3.4 7.8 2.26 (1.51, 3.38)
Sonnenberg [62%] 5.1 6.0 1.19 (0.41, 3.43)
Söderlund-Strand [55%] 5.2 5.4 1.04 (0.80, 1.36)
Markowitz [51%] 3.4 0.9 0.28 (0.13, 0.57)
Subtotal (I-squared = 74.3%, p < 0.001)
20-24 years old
Tabrizi [83%] 4.6 4.8 1.05 (0.50, 2.20)
Cameron [67%] 9.0 9.3 1.03 (0.88, 1.22)
Chow [66%] 11.1 5.0 0.18 (0.09, 0.35)
Markowitz [33%] 4.4 4.0 0.89 (0.40, 2.00)
Kahn [31%] 5.4 4.2 0.78 (0.24, 2.47)
Söderlund-Strand [24%] 6.9 8.9 1.30 (1.11, 1.52)
Sonnenberg [16%] 2.4 3.7 1.53 (0.57, 4.13)
Mesher [15%] 2.4 5.9 2.22 (1.33, 3.70)
Subtotal (I-squared = 82.6%, p < 0.001)
.05 .1 .2 .5 1 2 5 10 30
E: HPV 59
Prevalence
Pre-vacc (%) Post-vacc (%)
Prevalence Ratio (95% CI)
≤19 years old
Cummings [89%] 8.0 9.3 1.17 (0.48, 2.84)
Tabrizi [88%] 14.3 9.0 0.63 (0.23, 1.73)
Chow [79%] 7.3 16.4 2.60 (0.78, 8.65)
Kahn [77%] 11.0 17.4 1.58 (1.02, 2.45)
Mesher [71%] 6.0 3.5 0.59 (0.43, 0.81)
Sonnenberg [62%] 2.3 6.1 2.63 (0.35, 19.70)
Söderlund-Strand [55%] 3.8 4.7 1.23 (0.91, 1.64)
Markowitz [51%] 3.2 3.4 1.08 (0.57, 2.04)
Subtotal (I-squared = 66.8%, p = 0.004)
20-24 years old
Tabrizi [83%] 5.2 6.5 1.25 (0.63, 2.49)
Cameron [67%] 6.8 7.6 1.12 (0.93, 1.35)
Chow [66%] 7.4 11.9 1.69 (0.67, 4.24)
Markowitz [33%] 6.0 4.1 0.67 (0.32, 1.43)
Kahn [31%] 6.4 6.8 1.07 (0.40, 2.84)
Söderlund-Strand [24%] 4.2 4.8 1.15 (0.93, 1.42)
Sonnenberg [16%] 3.4 1.9 0.54 (0.20, 1.50)
Mesher [15%] 5.0 2.7 0.53 (0.37, 0.76)
Subtotal (I-squared = 63.6%, p = 0.007)
.05 .1 .2 .5 1 2 5 10 30
F: HPV 68
Prevalence
Pre-vacc (%) Post-vacc (%)
Prevalence Ratio (95% CI)
≤19 years old
Cummings [89%] 3.3 4.0 1.20 (0.29, 4.89)
Tabrizi [88%] 3.6 0.5 0.13 (0.01, 2.07)
Chow [79%] 3.6 3.6 1.11 (0.21, 5.85)
Kahn [77%] 6.7 6.8 1.02 (0.54, 1.93)
Mesher [71%] 1.9 2.3 1.54 (0.47, 5.02)
Sonnenberg [62%] 0.0 2.6 5.18 (0.29, 90.89)
Söderlund-Strand [55%] 0.6 0.8 1.31 (0.65, 2.65)
Markowitz [51%] 1.2 2.1 1.80 (0.77, 4.25)
Subtotal (I-squared = 0.0%, p = 0.690) 1.26 (0.88, 1.81)
20-24 years old
Tabrizi [83%] 1.7 1.4 0.82 (0.23, 2.88)
Cameron [67%] 1.0 1.3 1.25 (0.77, 2.03)
Chow [66%] 2.5 5.0 1.40 (0.31, 6.38)
Markowitz [33%] 2.4 2.7 1.10 (0.44, 2.75)
Kahn [31%] 6.4 3.4 0.53 (0.16, 1.77)
Söderlund-Strand [24%] 1.4 1.4 1.04 (0.70, 1.53)
Sonnenberg [16%] 2.5 1.9 0.76 (0.26, 2.21)
Mesher [15%] 1.3 3.7 2.86 (1.53, 5.34)
Subtotal (I-squared = 35.6%, p = 0.145)
.05 .1 .2 .5 1 2 5 10 30
Favours vaccination
Does not favour vaccination

Technical Appendix Figure 2: Prevalence ratio for high-risk HPV types with evidence of cross-protection (HPV31, HPV33, HPV45) stratified by age-group and vaccine type, percentages in square brackets represent vaccination coverage (at least one dose) for each study/age-group

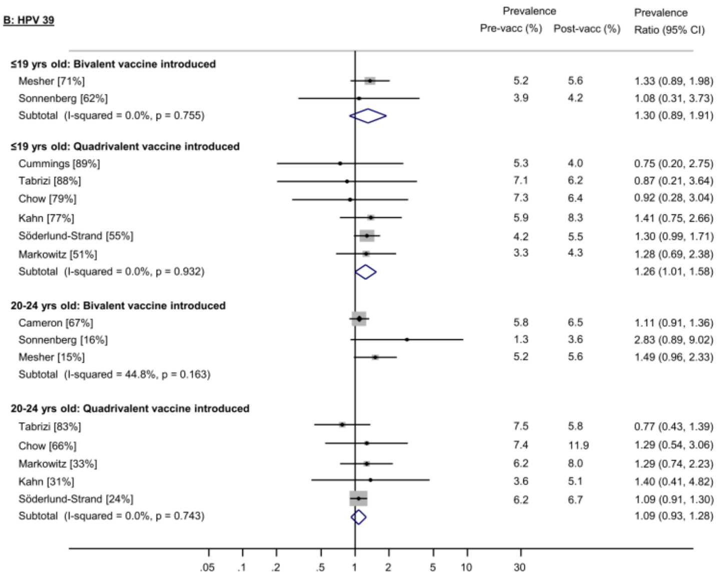


Technical Appendix Figure 4: Prevalence ratio for other probably high-risk HPV types (HPV35, HPV39, HPV51, HPV56, HPV59 and HPV68) stratified by age-group and vaccine type, percentages in square brackets represent vaccination coverage (at least one dose) for each study/age-group

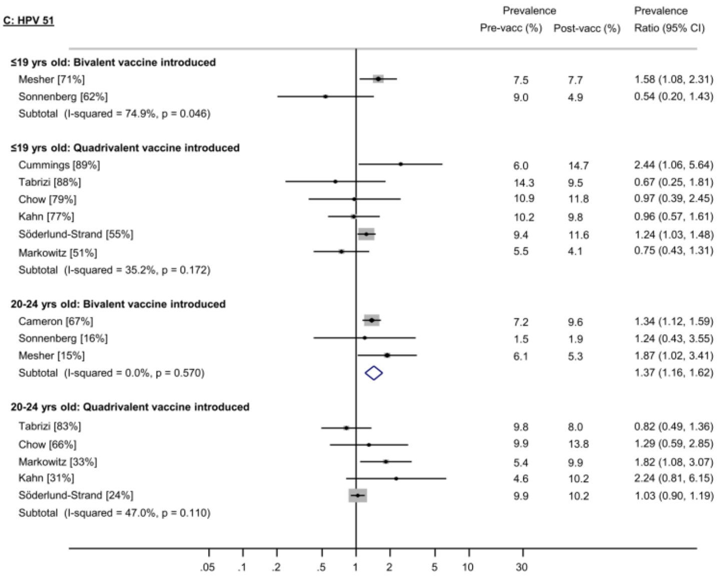
A: HPV 35



B: HPV 39



C: HPV 51



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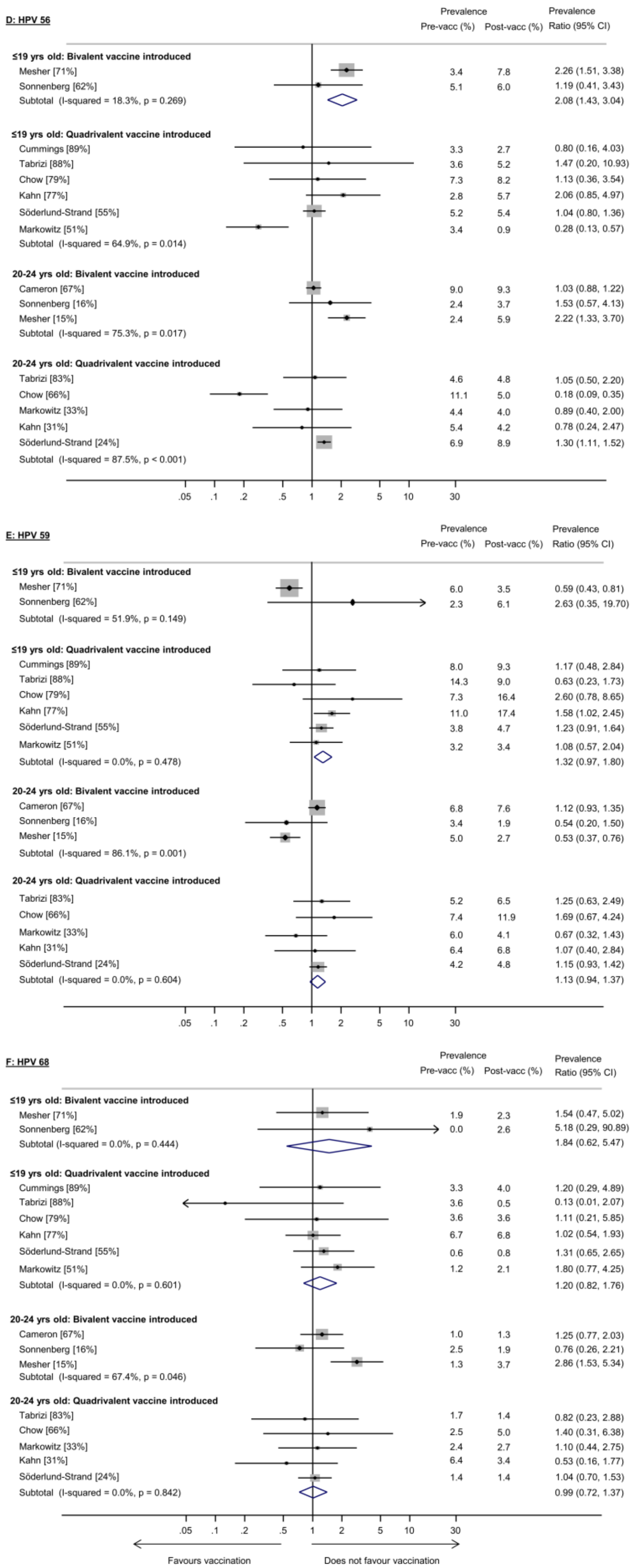
D: HPV 56
Prevalence
Pre-vacc (%)
Post-vacc (%)
Prevalence Ratio (95% CI)
≤19 yrs old: Bivalent vaccine introduced
Mesher [71%] 3.4 7.8 2.26 (1.51, 3.38)
Sonnenberg [62%] 5.1 6.0 1.19 (0.41, 3.43)
Subtotal (I-squared = 18.3%, p = 0.269) 2.08 (1.43, 3.04)
≤19 yrs old: Quadrivalent vaccine introduced
Cummings [89%] 3.3 2.7 0.80 (0.16, 4.03)
Tabrizi [88%] 3.6 5.2 1.47 (0.20, 10.93)
Chow [79%] 7.3 8.2 1.13 (0.36, 3.54)
Kahn [77%] 2.8 5.7 2.06 (0.85, 4.97)
Söderlund-Strand [55%] 5.2 5.4 1.04 (0.80, 1.36)
Markowitz [51%] 3.4 0.9 0.28 (0.13, 0.57)
Subtotal (I-squared = 64.9%, p = 0.014)
20-24 yrs old: Bivalent vaccine introduced
Cameron [67%] 9.0 9.3 1.03 (0.88, 1.22)
Sonnenberg [16%] 2.4 3.7 1.53 (0.57, 4.13)
Mesher [15%] 2.4 5.9 2.22 (1.33, 3.70)
Subtotal (I-squared = 75.3%, p = 0.017)
20-24 yrs old: Quadrivalent vaccine introduced
Tabrizi [83%] 4.6 4.8 1.05 (0.50, 2.20)
Chow [66%] 11.1 5.0 0.18 (0.09, 0.35)
Markowitz [33%] 4.4 4.0 0.89 (0.40, 2.00)
Kahn [31%] 5.4 4.2 0.78 (0.24, 2.47)
Söderlund-Strand [24%] 6.9 8.9 1.30 (1.11, 1.52)
Subtotal (I-squared = 87.5%, p < 0.001)
.05 .1 .2 .5 1 2 5 10 30
E: HPV 59
Prevalence
Pre-vacc (%)
Post-vacc (%)
Prevalence Ratio (95% CI)
≤19 yrs old: Bivalent vaccine introduced
Mesher [71%] 6.0 3.5 0.59 (0.43, 0.81)
Sonnenberg [62%] 2.3 6.1 2.63 (0.35, 19.70)
Subtotal (I-squared = 51.9%, p = 0.149)
≤19 yrs old: Quadrivalent vaccine introduced
Cummings [89%] 8.0 9.3 1.17 (0.48, 2.84)
Tabrizi [88%] 14.3 9.0 0.63 (0.23, 1.73)
Chow [79%] 7.3 16.4 2.60 (0.78, 8.65)
Kahn [77%] 11.0 17.4 1.58 (1.02, 2.45)
Söderlund-Strand [55%] 3.8 4.7 1.23 (0.91, 1.64)
Markowitz [51%] 3.2 3.4 1.08 (0.57, 2.04)
Subtotal (I-squared = 0.0%, p = 0.478) 1.32 (0.97, 1.80)
20-24 yrs old: Bivalent vaccine introduced
Cameron [67%] 6.8 7.6 1.12 (0.93, 1.35)
Sonnenberg [16%] 3.4 1.9 0.54 (0.20, 1.50)
Mesher [15%] 5.0 2.7 0.53 (0.37, 0.76)
Subtotal (I-squared = 86.1%, p = 0.001)
20-24 yrs old: Quadrivalent vaccine introduced
Tabrizi [83%] 5.2 6.5 1.25 (0.63, 2.49)
Chow [66%] 7.4 11.9 1.69 (0.67, 4.24)
Markowitz [33%] 6.0 4.1 0.67 (0.32, 1.43)
Kahn [31%] 6.4 6.8 1.07 (0.40, 2.84)
Söderlund-Strand [24%] 4.2 4.8 1.15 (0.93, 1.42)
Subtotal (I-squared = 0.0%, p = 0.604) 1.13 (0.94, 1.37)
.05 .1 .2 .5 1 2 5 10 30
F: HPV 68
Prevalence
Pre-vacc (%)
Post-vacc (%)
Prevalence Ratio (95% CI)
≤19 yrs old: Bivalent vaccine introduced
Mesher [71%] 1.9 2.3 1.54 (0.47, 5.02)
Sonnenberg [62%] 0.0 2.6 5.18 (0.29, 90.89)
Subtotal (I-squared = 0.0%, p = 0.444) 1.84 (0.62, 5.47)
≤19 yrs old: Quadrivalent vaccine introduced
Cummings [89%] 3.3 4.0 1.20 (0.29, 4.89)
Tabrizi [88%] 3.6 0.5 0.13 (0.01, 2.07)
Chow [79%] 3.6 3.6 1.11 (0.21, 5.85)
Kahn [77%] 6.7 6.8 1.02 (0.54, 1.93)
Söderlund-Strand [55%] 0.6 0.8 1.31 (0.65, 2.65)
Markowitz [51%] 1.2 2.1 1.80 (0.77, 4.25)
Subtotal (I-squared = 0.0%, p = 0.601) 1.20 (0.82, 1.76)
20-24 yrs old: Bivalent vaccine introduced
Cameron [67%] 1.0 1.3 1.25 (0.77, 2.03)
Sonnenberg [16%] 2.5 1.9 0.76 (0.26, 2.21)
Mesher [15%] 1.3 3.7 2.86 (1.53, 5.34)
Subtotal (I-squared = 67.4%, p = 0.046)
20-24 yrs old: Quadrivalent vaccine introduced
Tabrizi [83%] 1.7 1.4 0.82 (0.23, 2.88)
Chow [66%] 2.5 5.0 1.40 (0.31, 6.38)
Markowitz [33%] 2.4 2.7 1.10 (0.44, 2.75)
Kahn [31%] 6.4 3.4 0.53 (0.16, 1.77)
Söderlund-Strand [24%] 1.4 1.4 1.04 (0.70, 1.53)
Subtotal (I-squared = 0.0%, p = 0.842) 0.99 (0.72, 1.37)
.05 .1 .2 .5 1 2 5 10 30
Favours vaccination
Does not favour vaccination

8