Strong evidence of population-level impact and herd effects following human papillomavirus vaccination programs: a systematic review and meta-analysis.

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ABSTRACT

Background: Human papillomavirus (HPV) vaccination programs were first implemented in 2007. We conducted a systematic review and meta-analysis to examine the population-level impact and herd effects following female HPV vaccination programs, to verify whether the high efficacy measured in randomized controlled clinical trials are materialising under real-world conditions.

Methods: We searched Medline and Embase databases (01/2007-02/2014), and conference abstracts for time-trend studies examining changes, between the pre- and post-vaccination periods, in the incidence/prevalence of at least one HPV-related endpoint: HPV infection, anogenital warts (AGW), and high-grade cervical lesions. We derived pooled relative risk (RR) estimates using random effect models. We stratified all analyses by age and gender. We performed subgroups analysis by comparing studies according to vaccine type, vaccination coverage and years since vaccination implementation. We assessed heterogeneity across studies using I^2 and χ^2 statistics. We performed trends analysis to examine dose-response between HPV vaccination coverage and each study effect measure.

Findings: We identified 20 eligible studies, conducted in nine high-income countries, and representing >140 million person-years of follow-up. In countries with female vaccination coverage ≥50%, HPV-16/18 infections and AGW decreased significantly between the pre- and post-vaccination periods by 68% (RR=0·32, 95%CI[0·19;0·52]) and 61% (RR=0·39, 95%CI[0·22;0·71]), respectively, among females <20 years. Significant reductions in HPV-31/33/45 among females <20 years (RR=0·72, 95%CI[0·54;0·96]), and AGW among males <20 years (RR=0·66, 95%CI[0·47;0·91]) and older females (RR=0·68, 95CI[0·51;0·89]) were also observed, respectively suggesting cross-protection and herd effects. In countries with female vaccination coverage <50%, significant reductions were observed for HPV-16/18 infection (RR=0·50, 95%CI[0·34;0·74]) and AGW (RR=0·86, 95%CI[0·79;0·94]) among females <20 years, with no indication of cross-protection or herd effects.

Interpretation: Our results are promising for the long-term population-level impact of HPV vaccination programs. However, continued monitoring is essential to identify any signals of potential waning efficacy or type-replacement.

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INTRODUCTION

Since 2007, 52 out of 195 countries have implemented human papillomavirus (HPV) vaccination programs (41% of High Income (HIC) and 15% of Low and Middle Income Countries (LMIC)[1-4]). The population-level impact of HPV vaccination programs is expected to vary substantially between these countries dependant on vaccine used, implementation strategies and vaccination coverage achieved. Two HPV vaccines are currently available worldwide: the bivalent vaccine, which targets HPV types 16 and 18 (associated with 70-80% of cervical cancers globally[5]), and the quadrivalent vaccine, which additionally targets HPV types 6 and 11 (associated with 85-95% of anogenital warts (AGW) cases[6]). Most HIC are currently using the quadrivalent vaccine, whilst the picture is mixed for LMIC.[2,7] Although all HPV vaccination programs target pre-adolescent girls (including or not catch-up programs for older females), a few countries, such as the United States (U.S.) and Australia, have recently included boys.[8,9] Finally, in HIC, vaccination coverage among the younger cohorts of females ranges from nearly 90% to less than 50% depending mostly on whether the countries have school- or non-school based programs, respectively.[10]

Large international randomized controlled clinical trials have shown both HPV vaccines to be safe and well-tolerated, to be highly efficacious against vaccine-type persistent HPV infection and precancerous cervical lesions among women (Vaccine efficacy = 93%-100%),[11,12] and to provide some degree of cross-protection against three non-vaccine types (HPV-31/33/45),[12-14] associated with 10-15% of cervical cancers worldwide.[15] Current evidence from clinical trials also suggests that cross-protective vaccine efficacy estimates against infections and lesions associated with HPV-31/33/45 are higher for the bivalent vaccine than the quadrivalent.[16] Following clinical trials, mathematical models have been used to predict the long-term population-level effectiveness and cost-effectiveness of vaccination programs delivered in different settings. Modeling studies have consistently predicted that the overall burden of HPV-related diseases amongst females will substantially decline within the next decades through vaccination, and that vaccinating girls against HPV is highly cost-effective in most countries.[17-19] Despite consistency in model predictions of the direct impact of HPV vaccination among vaccinated girls, uncertainty remains about the potential population-level impact of cross-protection and herd protection (e.g., indirect impact of vaccinating girls on HPV in unvaccinated males and older females), and the vaccination coverage necessary to achieve substantial herd effects. [20-24] This information is crucial to help guide vaccine choices and inform decisions about vaccination of males.

Now that more than seven years have elapsed since the implementation of the first HPV vaccination programs in 2007 (Appendix-Table S1), it is timely to verify whether the promising results from clinical trials and model projections are materialising at the population-level. An increasing number of post-vaccination surveillance studies have recently been published using several intermediate endpoints (e.g., HPV infection, AGW, and precancerous cervical lesions). The objective of this systematic review and meta-analysis is to summarize current evidence on the population-level impact of HPV vaccination, as measured in time-trend studies among

females targeted for vaccination, and among males and older females. We focussed on the following HPV-related endpoints: 1) HPV infection; 2) AGW; and 3) high-grade cervical lesions.

METHODS

Search strategy and selection criteria

We systematically reviewed the worldwide literature and report it in accordance with the PRISMA guidelines.[25] Studies were eligible if they fulfilled the following criteria: 1) they provided data on at least one of the following endpoints: HPV infection, AGW, histopathologically confirmed high-grade cervical lesions (CIN 2 or worse); 2) the population-level impact was assessed by comparing the frequency (prevalence or incidence) of the endpoint between the pre- and post-vaccination periods (time-trend studies); 3) data from the pre- and post-vaccination periods were collected among the same population sources and using the same recruitment methodology.

We excluded studies with the following characteristics because they did not measure population-level impact: 1) HPV vaccination was administered as part of an individual-based randomized trial; or 2) HPV vaccination impact was assessed by comparing the frequency of the endpoint between vaccinated and unvaccinated individuals during the post-vaccination period.

Our search strategy involved three steps. First, we searched Medline and Embase databases between January 2007 and February 2014 using a combination of the following MeSH terms, title or abstract words, with no restriction on the language of the articles: ("papillomavirus vaccine", "papillomavirus vaccination", "HPV vaccine", or "HPV vaccination") and ("program evaluation", "population surveillance", "sentinel surveillance", "incidence", or "prevalence"), and ("papillomavirus infection", "condylomata acuminata", "anogenital warts", "cervical intraepithelial neoplasia", "cervical dysplasia", "uterine cervical neoplasm", or "HPV related diseases"). We identified eligible studies through reviewing titles and abstracts and reviewed the bibliographies of eligible articles. Second, we reviewed the abstracts of recent major conferences on HPV (EUROGIN Congress 2013, International Papillomavirus Conference 2012) to identify additional unpublished studies. Third, MD and MB contacted the authors of conference abstracts to obtain unpublished data. MD and EB independently assessed the eligibility of all studies. In addition, DM independently assessed eligibility of studies on HPV infection. If more than one publication from the same data source and research team was available, we kept the publication presenting the most recent data.

Data extraction and quality assessment

Our main outcomes were the relative risks (RR) comparing the pre- and post-vaccination periods for the: 1) prevalence of HPV infection for four HPV type subgroups: high-oncogenic risk vaccine types (HPV-16/18), three types with the greatest evidence of cross-protective efficacy (HPV-31/33/45);[16] the five potentially cross-protective types (HPV-31/33/45/52/58)[16], and all high-oncogenic risk (HR-HPV) non-vaccine types (all HR except HPV-16/18); 2) frequency (prevalence or incidence) of AGW diagnosis; and 3) frequency

(prevalence or incidence) of high-grade cervical lesions. Two authors (MD and EB) independently extracted the study characteristics and outcomes using a standardized form. MD and MB contacted authors to request supplementary extractions to standardize data stratifications between studies for comparison and pooling (e.g., same age and HPV type groupings). We also collected information on the vaccination program characteristics and vaccination coverage of the country/region of each study (Appendix–Table S1). For the HPV prevalence studies, we collected age-specific vaccination coverage directly from each study, as vaccination status was available for all study participants. Finally, the authors of each article validated the data from their study.

Prior to contacting the study investigators, MD, AM, PLM and MB assessed whether the studies had sufficient methodological quality to be included in the meta-analysis. The quality of the studies (potential for bias and confounding, and external validity) was assessed independently from the investigators of the original studies. Potential for bias and confounding within studies were assessed by reviewing the subjects' selection/recruitment procedures, endpoint definitions, algorithms used to identify cases, and potential confounders considered in the statistical analyses (Appendix-Tables S2-S4)

Data analysis

Because mostly young females (<20 years old) were vaccinated in the study populations, we decided *a priori* to stratify all our analyses by gender and age. Furthermore, because only the quadrivalent vaccine includes types HPV-6/11 (responsible for approximately 90% of AGW[6]), we decided *a priori* to stratify our analyses for AGW by the type of vaccine.

To ensure comparability of the study results included in the meta-analysis, we first defined pre- and post-vaccination periods for all studies (Appendix-Table S5). Second, for comparability, we used prevalence or incidence rate ratios as the measure of impact for all HPV-related endpoints. For HPV infection, most studies presented RR (crude and/or adjusted prevalence ratios) and 95% confidence intervals (CI). When available, we included adjusted RR in the meta-analysis. When only crude HPV prevalence over time was available, we calculated prevalence ratios by dividing the post- and pre-vaccination prevalence and estimated the 95% CI (CI approximation for prevalence ratios[26]) (Table 1). For AGW and precancerous lesions, all studies presented yearly frequency (prevalence or incidence) over time. We estimated pre-vaccination frequency by aggregating the data for up to three years prior to vaccination, and calculated RR by dividing each post-vaccination year by the pre-vaccination estimate.

We derived summary estimates of the impact of HPV vaccination for each endpoint using random effect models on the log scale.[27,28] We performed subgroup analysis to identify potential sources of heterogeneity by comparing the summary estimates obtained from subsets of studies and/or groups within studies grouped by: vaccine type (bivalent, quadrivalent), vaccination coverage (Low<50%, High≥50%; study-specific coverage estimates for HPV infection, and country/region-level coverage for the other outcomes), age (<20, 20-24, 25-

29, 30-39 years), years since vaccination program implementation (1,2,3,4 years), source of study data (population-based, health provider/insurance-based, clinic-based), and adjustment of the impact measure (yes, no). We examined heterogeneity across studies using I^2 and χ^2 statistics[28]. I^2 values less than 50%, between 50-75%, and more than 75% represent low, substantial and considerable heterogeneity, respectively[29]. The p-value associated with the χ^2 statistic represents the statistical significance of heterogeneity. Finally, we examined dose-response between HPV vaccination coverage (independent variable) and the log RR of each study (dependent variable) by fitting a linear regression, weighted by the inverse variances of the log RR[30]. We performed all analyses using Review Manager 5.2 and SAS 9.4.

Role of the funding source

The funding source had no role in the study design, data collection, analysis and interpretation, or writing of the report. MB had full access to all the data in the study and had final responsibility for the decision to submit for publication.

RESULTS

We identified 661 articles and 29 conference abstracts, of which 20 records met the inclusion criteria (HPV infection (n=7)[31-37], AGW (n=11)[38-48], and high-grade cervical lesions[49,50] (n=2)) (Figure 1). The studies were conducted in nine HICs and examined the population-level impact of vaccination among 16,600 females for HPV infection, more than 125 million person-years of follow-up for AGW and 15 million female-years of follow-up for high-grade cervical lesions (Table 1). The vaccine used, vaccination strategy, delivery and vaccination coverage varied substantially (Table 1 and Appendix-Table S1). All studies had sufficient methodological quality to be included in the meta-analysis (Appendix-Tables S2-S4). However, because two studies examined the entire Danish population over identical time periods,[42,48] we only included the Baandrup et al. study in our main analysis (the choice of study had no impact on results, Appendix-Table S6).

HPV infections

Among females aged 14-19 years, the overall prevalence of HPV-16/18 significantly decreased, by 64% (RR=0·36, 95%CI[0·25;0·53]) compared to the pre-vaccination period (Figure 2a), with a significant dose-response with vaccination coverage (p=0·005). The overall prevalence of HPV-31/33/45 also significantly decreased post-vaccination by 28% (RR=0·72, 95%CI[0·54;0·96]), but reductions were not significantly associated with vaccination coverage. The overall prevalence of HPV-31/33/45/52/58 and non-vaccine HR types (i.e. all HR except 16/18) did not change significantly between the pre- and post-vaccination periods.

Among females aged 20-24 years, the overall prevalence of HPV-16/18 decreased by 31% (RR=0·69, 95%CI[0·47;1·01]) in the post-vaccination period (Figure 2b). Although the overall reduction in HPV-16/18 infection was not significant, a dose-response was observed with vaccination coverage (p=0·01). No significant declines in prevalence or dose-response with vaccination coverage were observed for HPV-31/33/45 or HPV-

31/33/45/52/58. Finally, there was a small non-significant increase in non-vaccine HR types (RR=1·09, 95%CI[0·98;1·22]), which was negatively associated with increasing vaccination coverage (p=0·03).

In addition to vaccination coverage, the use of adjusted or crude RRs emerged as a substantial source of heterogeneity among studies (I^2 between 50 and 75% for many endpoints, Figure 3). Interestingly, the point estimate of adjusted RRs were lower than crude RRs for HPV subgroups with substantial post-vaccination reductions (i.e., HPV-16/18 among 14-24 year olds, and HPV-31/33/45 among 14-19 year olds), but were higher for the other endpoints.

Anogenital warts diagnosis (AGW)

Among females aged 15-19 years in countries using the quadrivalent vaccine, AGW decreased significantly by 31% (RR=0·69, 95%CI[0·60;0·79]). A striking dose-response was observed between AGW reduction and increase in population-level female vaccination coverage (p=0·001) (Figure 4a). AGW were reduced by 61% (RR=0·39, 95%CI[0·22;0·71]) in studies with high vaccination coverage compared to a reduction of 14% (RR=0·86, 95%CI[0·79;0·94]) in studies with low vaccination coverage (Figure 5a). In addition to vaccination coverage, years since the start of vaccination emerged as a significant source of heterogeneity (I^2=68%, p=0·02) (Figure 5a).

Among older females (20-39 years) and young males (15-19 years) in countries using the quadrivalent vaccine, non-statistically significant decreases in AGW were observed post-vaccination (11% (RR=0·89, 95%CI[0·79;1·02] and 5% (RR=0·95, 95%CI[0·84;1·08], respectively) (Figure 4b,c). Again, there was a significant dose-response between AGW reductions among older females and young males and increase in population-level female vaccination coverage (p=0·05 and 0·005, respectively); and subgroup analyses revealed female vaccination coverage as a main source of heterogeneity (I^2=86%, p<0·008) (Figure 5b,c). In countries with high female vaccination coverage, AGW were significantly reduced by 32% (RR=0·68, 95%CI[0·51;0·89]) and 34% (RR=0·66, 95%CI[0·47;0·91]) among older females and young males, respectively. No changes in AGW were observed among older males (20-39 years) in countries using the quadrivalent vaccine.

The only study examining population-level changes in AGW following vaccination with the bivalent vaccine reported a small but significant decrease among females aged 15-19 years (RR=0·96, 95%CI[0·94;0·97]) (Figure 4a). Conversely, a small but significant increase in AGW was observed among males aged 15-19 years (Figure 4c), and there was no significant effect among older females and males (Figure 4b,d).

Figure 6 illustrates the changes over time in AGW in studies with the quadrivalent vaccine, taking into consideration the main sources of heterogeneity. Figure 6a clearly illustrates that there was a rapid and significant decline over time in AGW for females aged <30 years old in studies with high vaccination coverage. However, in studies with low vaccination coverage (Figure 6b), the decline was observed only among females <20 years old, and became significant only in the third year following vaccination implementation. There was also a rapid and significant decline over time in AGW for males aged <30 years old in studies with high female

vaccination coverage (Figure 6c). However, there was a general tendency of increasing AGW for older males in studies with low female vaccination coverage (Figure 6d).

High-grade precancerous cervical lesions

A significant decrease in high-grade lesions was observed in the only study reporting data among females aged 15-19 years (RR=0·69, 95%CI[0·66;0·73]), but there was no significant change in the two studies reporting data among older females (Appendix-Figure S1).

DISCUSSION

This systematic review and meta-analysis, representing more than 140 million person-years of follow-up data from nine HIC, reports significant population-level decreases in HPV-related outcomes up to four years after the start of HPV vaccination programs. In countries with high vaccination coverage, HPV-16/18 infection and AGW decreased by more than 60% in females younger than 20 years of age, starting after the first year of the programs. Furthermore, in these countries, our results suggest that there is evidence of vaccine cross-protection and herd effects, with significant reductions in HPV-31/33/45 infection among females younger than 20 years of age, and AGW among males and older females, respectively. In countries with low vaccination coverage, significant reductions were observed for HPV-16/18 infection and AGW among young females, but no significant reductions were observed for HPV-31/33/45 among young females or HPV-related outcomes among males and older females (i.e., no indication of cross-protection or herd effects). Our findings provide strong evidence that HPV vaccination is highly effective and can provide cross-protection outside trial settings, and reinforce the need for early vaccination and high vaccination coverage to maximize population-level effectiveness and herd effects.

Although this meta-analysis is based on time-trend ecological studies, and thus causality cannot be concluded, several factors strongly suggest that the reported reductions in population-level HPV-related outcomes can be attributed to HPV vaccination: 1) magnitude of the effect, 2) dose-response relationship between vaccination coverage and effect, and 3) consistency between the studies included in the review despite different methods and settings, and consistency with results from clinical trials and mathematical modeling. Firstly, reduction in HPV-16/18, AGW and high-grade cervical lesions were large and statistically significant in the target age groups for vaccination (females <20 years). Secondly, there was a statistically significant positive association between increases in vaccination coverage and reduction in HPV-16/18 infection among young females and AGW among both females and males. Furthermore, reductions in AGW increased over time since vaccination (as the number of vaccinated cohorts increased), especially in youngest age groups with highest vaccination coverage. Thirdly, there was consistency in results between countries with similar levels of vaccination coverage. Furthermore, in the studies where the vaccine status was available, vaccinated females had significantly lower HPV-related outcomes than unvaccinated females in the post-vaccination era.[32-34,37,41,51-54] Our results are also consistent with data from clinical trials that demonstrated a high vaccine-type efficacy,[11,12] and suggested some degree of cross-protection against HPV-31/33/45 but not against HPV-

52/58.[16] However, the higher bivalent cross-protective efficacy reported in a recent meta-analysis of clinical trial data[16] was not observed in our population-level meta-analysis (Figure 3). Finally the large herd effects observed with high vaccination coverage are consistent with predictions from dynamic model.[20-24]

The studies included in the meta-analysis possess the strengths and weaknesses inherent in ecological studies. They provide a wealth of timely information on the impact of HPV vaccination using large study populations, but are particularly vulnerable to information bias and confounding (Appendix-Tables S2-S4). However, the three most important potential sources of bias and confounding in these studies are likely to underestimate the impact of vaccination. Firstly, due to increased awareness of AGW from licensing of the HPV vaccines and the launch of the vaccination programs, there is potential for confounding related to possible increases in health seeking behaviours and information bias from increased diagnosis of AGW over time. Secondly, most studies had insufficient or no information to adequately control for sexual activity, which may have been increasing over time.[42, 55, 56] These limitations may explain the slight increase in the prevalence of non-vaccine HR types and AGW consultations in the post-vaccination period within groups with low or no vaccination coverage (e.g., older females and males) (Figures 2b and 6). Thirdly, there is potential for information bias due to masking by HPV-16/18, particularly in the pre-vaccine period.[57] That is, by preventing HPV-16/18 infection, vaccination could remove the potential masking effect of these types, producing increased detection of non-vaccine types. Conversely, the main potential source of overestimation of vaccination impact is present in clinic-based studies measuring the proportion of consultations attributable to AGW in sexual health clinics (Appendix-Table S3).[38,41] Indeed, changes in the clientele between pre- and post-vaccination periods could overestimate vaccination impact on AGW if consultations due to other causes increased (e.g., chlamydia consultations[41]). Clinic-based studies represent two thirds of the studies examining the population-level impact of vaccination on AGW in countries with high vaccination coverage, and may partly explain slight reductions in AGW among older males (Figure 6). Fourthly, the external validity of the studies was generally good (Appendix-Table S2-S4). However, because most studies were among individuals consulting the health system, HPV vaccination impact results may not be completely generalizable to groups with lower health seeking behaviour, particularly in countries where HPV vaccine is delivered in healthcare clinics. Finally, given the indirect nature of our inferences, our analysis may not have the adequate sensitivity to detect small post-vaccination effects (e.g., type-replacement, or herd effects and cross-protection when vaccination coverage is low).

Our results should be interpreted cautiously as they represent the short-term population-level impact of HPV vaccination programs. Firstly, the cohorts of vaccinated girls have not reached the ages with highest incidence rates of HPV infection, AGW and cervical lesions (i.e., between 20 and 35 years of age). Therefore, the direct and herd impact are expected to continue to increase over time (Figure 6) as overall population-level vaccination coverage increases. Secondly, there is currently insufficient evidence to draw conclusions about the existence of net type-replacement (e.g., no significant increase in the prevalence of HR non-vaccine types among groups with highest vaccination coverage). This may be because there is no type

replacement, or partly due to the short follow-up time or dilution of type-specific changes by grouping HPV-types. Thirdly, the time horizon was too short to examine waning of vaccine efficacy. However, randomized-control trials have shown no signs of waning vaccine efficacy after 9·5 years of follow-up.[58] Fourthly, given the long lag time between infection and cancer, there is currently no available direct evidence of the impact of vaccination on HPV-related cancers. However, given that HPV infection is the cause, and high-grade precancerous cervical lesions the precursors of cervical cancer, these intermediate outcomes have been deemed acceptable proxies for efficacy against cervical cancer by regulatory bodies worldwide.[59-62] Nevertheless, one should be careful in using reductions in precancerous cervical lesions from screening databases as proxies for cervical cancer as 1) they may reflect changes in screening recommendations and participation, and 2) they are not HPV type-specific. In addition, surveillance studies based on cervical screening registries may overestimate the population-level impact of HPV vaccination, if vaccine uptake is higher among women who get screened.[63-66] Finally, as previously shown, HPV-6/11-related disease (e.g., AGW) trends are a poor proxy of change in HPV-16/18 and its related diseases (e.g., cervical cancer).[67] This is because HPV-6/11 will be easier to eliminate and control through vaccination than HPV-16/18 due to its shorter durations of infectiousness and/or lower transmissibility.

Our overall findings are likely generalizable to HIC as most of the heterogeneity between countries disappeared once results were stratified by vaccination coverage and age (Figures 3 and 5), and given similarities in sexual behavior,[56] HPV type distribution,[68,69] age profile of HPV prevalence,[70] and cervical cancer incidence between HIC.[71] However, precise estimates of population-level impact will vary between countries according to their programmatic specificities, such as the characteristics of catch-up campaigns. Our results should be extrapolated to LMIC with caution as all studies in the meta-analysis were from HIC and given differences between HIC and LMIC in sexual behavior,[56] HPV epidemiology[70,71] and potential cofactors of HPV infection and disease, such as high HIV prevalence.[72] However, there is no evidence to suggest that vaccine efficacy would be lower in LMIC, particularly because the vaccine has been shown safe and immunogenic among HIV infected women.[73] On the other hand, herd effects may differ in LMIC with very different population-level sexual behaviour (e.g., greater mixing between older men and younger women, more concurrency in partnerships). Even in the unlikely scenario that there would be no herd effects in LMICs, a recent global modeling study has shown that HPV vaccination would be highly cost-effective, given very high cervical cancer incidence and mortality in these countries (PRIME).[19]

This first meta-analysis of the population-level impact of HPV vaccination programs shows compelling evidence of a strong and statistically significant dose-response between HPV vaccination coverage and reductions in HPV-16/18 infection and AGW among females targeted for vaccination. In addition, our study provides the first evidence of a dose-response between female vaccination coverage and reduction of AGW in older females and males. Our results have important policy implications. The sharpest declines in HPV-related outcomes in females and males were observed in countries with school-based vaccine delivery (e.g., U.K., Australia, New Zealand), suggesting that this strategy facilitates faster roll-out and higher vaccination

coverage. The study also shows population-level data supporting clinical-trial evidence of HPV vaccine cross-protection against HPV-types 31/33/45, though no dose-response was seen with vaccination coverage.

In conclusion, the results of this study are very promising for the long-term population-level impact of HPV vaccination programs on cervical cancer and other HPV-related diseases. However, it is important to continue monitoring and evaluating HPV vaccination programs to confirm these results and to remain vigilant for evidence of potential waning efficacy, type-replacement or lower vaccination coverage amongst groups at greater risk of HPV-related cancers.

PANEL: RESEARCH IN CONTEXT

Systematic review

To undertake this meta-analysis we performed a systematically review to identify all time-trend studies examining changes, between the pre- and post-vaccination periods, in the incidence/prevalence of at least one HPV-related endpoint: HPV infection, anogenital warts (AGW), and high-grade cervical lesions. We searched Medline and Embase databases between January 2007 and February 2014 using a combination of the following MeSH terms, title or abstract words, with no restriction on the language of the articles: ("papillomavirus vaccine", "papillomavirus vaccination", "HPV vaccine", or "HPV vaccination") and ("program evaluation", "population surveillance", "sentinel surveillance", "incidence", or "prevalence"), and ("papillomavirus infection", "condylomata acuminata", "anogenital warts", "cervical intraepithelial neoplasia", "cervical dysplasia", "uterine cervical neoplasm", or "HPV related diseases"). We also reviewed the abstracts of recent major conferences on HPV (EUROGIN Congress 2013, International Papillomavirus Conference 2012) to identify additional unpublished studies. Twenty records, from nine high income countries, met the inclusion criteria (HPV infection (n=7)[31-37], AGW (n=11)[38-48], and high-grade cervical lesions[49,50] (n=2))

Interpretation

This meta-analysis showed, for the first time, a strong and statistically significant dose-response between HPV vaccination coverage and population-level reductions in HPV-related outcomes among young females. In countries with high female vaccination coverage (≥50%), HPV-16/18 infection and AGW declined by more than 60% in females younger than 20 years. Furthermore, the study provides the first evidence of a dose-response between vaccination coverage and herd effects. In countries with high female vaccination coverage, AGW among young male and older females declined by 20-30%. Finally, the study showed statistically significant declines in HPV-types 31/33/45 among young females, which is suggestive of cross-protection.

CONTRIBUTORS

MD, MB and MCB conceived the study. MD and EB did the literature search and performed the analysis. MB, MCB, AM, PLM and JB participated in the analysis. MD and MB co-drafted the first version of the article. DM independently assessed eligibility of studies on HPV infection. All other authors (HA, LB, HB, SB, JMLB, TC, BD, CKF, EWF, AMJ, JAK, KK, SKK, EVK, LM, DM, LN, JO, KGP, KS, PS, SNT, CT) provided data, after having

performed supplementary analysis for the purposes of this meta-analysis. All authors interpreted the results and critically revised the manuscript for scientific content. All authors approved the final version of the article.

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CONFLICTS OF INTERESTS

MB reports unrestricted grants from Merck (herpes zoster- none are ongoing); MD has consulted for GlaxoSmithKline (herpes zoster vaccine); HA reports grant from bioCSL for the Australian genital warts surveillance network; SB, DM, KS report grant from GlaxoSmithKline for HPV testing of some samples (study number EPI-HPV-109903); JMLB reports grants from bioCSL/Merck; BD reports grants from bioCSL and speaker fees from Merck and SPMSD; CKF owns shares in CSL Biotherapies who have licensed the Gardasil vaccine to Merck, has received travel reimbursement and speaker fees from Merck; AMJ has been a Governor of the Wellcome Trust since 2011; JAK reports grant from Merck; SKK reports grants from Merck and is a member of the Scientific Advisory Board of Merck and expert lecturer for Sanofi Pasteur MSD; EVK reports grants from Merck and GlaxoSmithKline and personal fees from Merck; LN reports consulting fees from Merck; SNT reports grants from bioCSL; EB, MCB, LB, HB, JB, TC, EWF, KK, PLM, LM, AM, JO, KGP, PS, CT declare that they have no conflict of interest.

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Table 1. Characteristics of the studies included in the systematic review and meta-analysis

Author (Country)	Vaccine used	Data source*	Study population	Population used in meta-analysis	Data collection dates†	Sample size used in meta-analysis ‡	Case definition	Effect measure in publication	Effect measure recalculated¥
HPV infection									
Cummings 2012 (U.S.)	Quadrivalent	Clinic-based	Females 14-17 yrs attending 1 of 3 urban primary care clinics in Indianapolis	Females 14-17 yrs	Prevaccine:1999-2005 Postvaccine:2010	N prevaccine:150 N postvaccine:75	HPV+ Roche Linear Array (Roche, 37 types)	OR of HPV prevalence (crude)	RR of HPV prevalence (crude)
Kahn 2012 (U.S.)	Quadrivalent	Clinic-based	Females 13-26 yrs attending 1 hospital-based adolescent clinic and 1 community health center in Cincinnati	Females 13-24 yrs, Had had sexual contact	Prevaccine:2006-2007 Postvaccine:2009-2010	N prevaccine:336 N postvaccine:383	HPV+ Roche Linear Array (Roche, 37 types)	HPV prevalence difference (adjusted)	RR of HPV prevalence (adjusted)
Tabrizi 2012 (Australia)	Quadrivalent	Clinic-based	Females 18-24 yrs attending 1 of 6 family planning clinics in Sydney, Melbourne, Perth	Females 18-24 yrs	Prevaccine:2005-2007 Postvaccine:2010-2011	N prevaccine:202 N postvaccine:1,058	HPV+ Roche Linear Array (13 types),	OR of HPV prevalence (adjusted)	RR of HPV prevalence (adjusted)
Markowitz 2013 (U.S.)	Quadrivalent	Population-based: NHANES study participants	Nationally representative sample of US females aged 14-59 yrs	Females 14-24 yrs	Prevaccine:2003-2006 Postvaccine:2007-2010	N prevaccine:1,795 N postvaccine:1,185	HPV+ Roche Linear Array (Roche, 37 types)	RR of HPV prevalence (crude)	RR of HPV prevalence (crude)
Mesher 2013 (England)	Bivalent	Clinic-based	Females 16-24 yrs undergoing chlamydia screening in community sexual health services, general practice, youth clinics in 7 regions around England	Females 16-24 yrs	Prevaccine:2008 Postvaccine:2010-2012	N prevaccine:2,354 N postvaccine:4,178	2008: Hybrid Capture 2 and Roche Linear Array 2010-2012: HPV+ In-house multiplex PCR and Luminex-based genotyping test (18 types)‖	OR of HPV prevalence (adjusted)	RR of HPV prevalence (adjusted)
Sonnenberg 2013 (England, Scotland, Wales)	Bivalent	Population-based: NATSAL study participants	Nationally representative sample of males and females aged 16-74 yrs in Britain	Females 18-24 yrs	Prevaccine:1999-2001 Postvaccine:2010-2012	N prevaccine:328 N postvaccine:795	HPV+ In-house Luminex-based genotyping assay (18 types)‖ in urine samples	OR of HPV prevalence (age-adjusted)	RR of HPV prevalence (crude)
Kavanagh 2014 (Scotland)	Bivalent	Population-based: Scottish Cervical screening Call &	Females 20-21 yrs participating in routine cervical cancer screening in	Females 20-21 yrs	Prevaccine:2009-2010 Postvaccine:2011-2012	N prevaccine:2,704 N postvaccine:1,975	HPV+ Multimetrix HPV assay (18 types)	HPV prevalence over time (no effect	RR of HPV prevalence (crude)

Author (Country)	Vaccine used	Data source*	Study population	Population used in meta-analysis	Data collection dates†	Sample size used in meta-analysis ‡	Case definition	Effect measure in publication	Effect measure recalculated¥
		Recall System	Scotland					measure)	
Anogenital warts									
Oliphant 2011 (New Zealand)	Quadrivalent	Clinic-based	New clients of 1 sexual health service in Auckland aged ≥ 10 yrs	Females and males 15-39 yrs	2007-2010 Prevaccine:2007-2008 Postvaccine:2009-2010	P-yr prevaccine: 17,517 P-yr postvaccine: 15,508	Clinical diagnosis	Annual proportion of new clients diagnosed with AGW	RR of AGW proportion (crude)
Bauer 2012 (U.S.)	Quadrivalent	Health provider /insurance-based: Clinical encounters claims data of a health program	Clients of the California Family Planning access care & treatment program aged ≥ 10 yrs (87% are females)	Females and males 15-39 yrs Program serves low-income individuals	2007-2010 Prevaccine: 2007 Postvaccine:2008-2010	P-yr prevaccine: 1,750,980 P-yr postvaccine: 5,555,420	ICD-9 codes 078.10, 078.11 OR prescription of Imiquimod or Podophyllotoxin	Annual proportion of PACT clients diagnosed with AGW	RR of AGW proportion (crude)
Kliewer 2012 (Canada)	Quadrivalent	Population-based: Medical claims and hospital discharge database	Entire population of Manitoba	Females and males 15-39 yrs	1985-2009 Prevaccine: 2006-2008 Postvaccine:2009	P-yr prevaccine: 737,366 P-yr postvaccine: 250,984	Treatments (one of 14 tariff codes for AGW treatments) OR hospitalization for AGW with ICD-9 code 078.11 OR 078.1, 078.10, 078.19 and related procedure OR ICD-10 A630 OR B07 and related procedure	Annual incidence rate of diagnosed AGW in the population	RR of AGW incidence (crude)
Leval 2012 (Sweden)	Quadrivalent	Population-based: Statistics Sweden, National Patient Register, Prescribed Drug Register	Entire population of Sweden aged ≥ 10 yrs	Females and males 15-39 yrs	2006-2010 Prevaccine: 2006 Postvaccine:2007-2010	P-yr prevaccine: 2,942,525 P-yr postvaccine: 12,043,886	ICD-10 code A63.0 OR prescription of Imiquimod or Podophyllotoxin	Annual incidence rate of diagnosed AGW in the population	RR of AGW incidence (crude)
Ali 2013 (Australia)	Quadrivalent	Clinic-based	New clients of 8 sexual health centers across Australia aged ≥ 12 yrs (Australian born)	Australian born females and males 15-39 yrs	2004-2011 Prevaccine: 2005-2007 Postvaccine:2008-2012	P-yr prevaccine: 24,147 P-yr postvaccine: 37,237	Clinical diagnosis	Annual proportion of new clients with diagnosed AGW	RR of AGW proportion (crude)
Baandrup 2013 (Denmark)	Quadrivalent	Population-based: Statistics Denmark, National Patient Registry	Entire population of Denmark ≥ 10 yrs	Females and males 15-39 yrs	2006-2011 Prevaccine: 2007-2009 Postvaccine:2010-2011	P-yr prevaccine: 5,140,633 P-yr postvaccine: 2,598,265	ICD-10 code A63.0	Annual incidence rate of diagnosed AGW in the population	RR of AGW incidence (crude)
Howell-Jones 2013 (England)	Bivalent	Population-based: Genitourinary medicine (GUM)	Entire population of England aged 15-24 yrs;	Females and males 15-24 yrs	2002-2011 Prevaccine: 2006-2008 Postvaccine:2009-2011	P-yr prevaccine: 6,790,231 P-yr postvaccine:	Clinical diagnosis	Annual incidence rate of diagnosed	RR of AGW incidence (crude)

Author (Country)	Vaccine used	Data source*	Study population	Population used in meta-analysis	Data collection dates†	Sample size used in meta-analysis ‡	Case definition	Effect measure in publication	Effect measure recalculated¥
		clinics				20,610,282		AGW in the population	
Flagg 2013 (U.S.)	Quadrivalent	Health provider /insurance-based: Truven Health Analytics Market Scan Commercial Claims and Encounters Database	Enrollees in approximately 100 health private insurance plans across the U.S. aged 10-39 yrs	Females and males 15-39 yrs, Insured employees, early retirees and their dependents	2003-2010 Prevaccine: 2004-2006 Postvaccine:2007-2010	P-yr prevaccine: 11,864,207 P-yr postvaccine: 36,000,783	1) ICD-9 codes 078.11 OR 2) ICD-9 code 078.1, 078.10, or 078.19 and therapeutic procedure or diagnosis of benign anogenital neoplasm OR 3) ≥ 1 prescription for AGW treatment and therapeutic procedure or diagnosis of benign anogenital neoplasm	Annual proportion of insured individuals with diagnosed AGW	RR of AGW proportion (crude)
Mikolajczyk 2013 (Germany)	Quadrivalent	Health provider /insurance-based: German Pharmacoepidemiological Research Database	Enrollees in 1 large health insurance company across Germany aged 10-79 yrs	Females and males 15-39 yrs	2005-2008 Prevaccine: 2005-2007 Postvaccine:2008	P-yr prevaccine: 4,439,256 P-yr postvaccine: 1,621,308	ICD-10 code A63.0	Annual incidence rate of diagnosed AGW among insured individuals	RR of AGW incidence (crude)
Nsouli-Maktabi 2013 (U.S.)	Quadrivalent	Health provider /insurance-based: Defense Medical Surveillance System	Members of the U.S. Armed Forced across the U.S. aged ≥ 17 yrs	Females and males 17-39 yrs, Member of the Forces any time between 2000-2012	2000-2012 Prevaccine: 2004-2006 Postvaccine:2007-2011	P-yr prevaccine: 3,569,823 P-yr postvaccine: 4,736,303	ICD-9 code 078.1	Annual incidence rate of diagnosed AGW among US force members	RR of AGW incidence (crude)
Sandø 2013 (Denmark)	Quadrivalent	Population-based: Statistics Denmark, National Patient Registry, Medical Products Statistics Registry	Entire population of Denmark aged 15-34 yrs	Females and males 15-34 yrs	2001-2011 Prevaccine: 2007-2009 Postvaccine:2010-2011	P-yr prevaccine: 1,326,573 P-yr postvaccine: 2,687,020	ICD-10 code A63.0, OR prescription of Podophyllotoxin	Annual proportion of the population with diagnosed AGW	RR of AGW proportion (crude)
High-grade precancerous cervical lesions									
Brotherton 2011/ Australian Institute of Health and	Quadrivalent	Health provider /insurance-based: Cervical cancer screening	Females aged <69 yrs participating in the National Cervical Screening Program	Females 15-39 yrs	2004-2011 Prevaccine:2005-2007 Postvaccine:2008-2011	P-yr prevaccine: 6,028,918 P-yr postvaccine: 7,814,102	Histopathologically confirmed CIN2+	Annual incidence of high grade cervical lesions among	RR of high grade lesion incidence (crude)

Author (Country)	Vaccine used	Data source*	Study population	Population used in meta-analysis	Data collection dates†	Sample size used in meta-analysis ‡	Case definition	Effect measure in publication	Effect measure recalculated¥
Welfare 2013 (Australia) §		program registry						screened females	
Niccolai 2013 (U.S.)	Quadrivalent	Health provider /insurance-based: Statewide surveillance (all 34 pathology laboratories report CIN2+/AIS)	Females aged 21-39 yrs from Connecticut screened for cervical cancer	Females 21-39 yrs	2008-2011 Prevaccine:2008 Postvaccine:2009-2011	P-yr prevaccine: 411,624 P-yr postvaccine: 823,248	Histopathologically confirmed CIN2+	Annual incidence of high grade lesions among females 21-39 yrs in Connecticut	RR of high grade lesion incidence (crude)

OR: Odds ratio; RR: Relative risk (Post-vaccination prevalence or incidence / Pre-vaccination prevalence or incidence)

* Data sources are considered as: 1) Population-based when the study population includes the total population of a given country/region, 2) Health provider/insurance-based when the study population is constituted of a subgroup of the total population participating in a specific health program or insurance plan, 3) Clinic-based when the study population is constituted of a limited number of clinics or hospital's clients.

† For studies on HPV infection, the pre- and post-vaccination periods were already determined in original publications (except for Kavanagh et al.). For studies on AGW and cervical lesions studies, the pre- and post-vaccination periods were determined for the purpose of this systematic review as described in the Appendix-Table S5.

‡ The sample size is restricted to the age groups used in the review. For studies on HPV infection, the pre and post-vaccination sample sizes were already determined in original studies. For studies on AGW and cervical lesions, the pre-vaccination sample size corresponds to the cumulative number of person-years up to three years pre-vaccination, including the year of the introduction of HPV vaccination. The post-vaccination sample size corresponds to the cumulative number of person-years from 1 to 4 years after the introduction of vaccination, depending on data available in each study.

§ Data from Brotherton et al. 2011[49] are restricted to the Victorian registry data. Supplementary data from the Australian Institute of Health and Welfare 2013 report [74] were provided by Dr. Brotherton. Since the report covers all regions of Australia, it was used as our main data source for the review.

ǁ 13 HR-HPV types were presented in the original publications whereas the 18 HR-HPV types available were used for the purposes of this meta-analysis

¥ For HPV infection, the investigators recalculated the RR of prevalence using the original data from their specific studies. For AGW and precancerous lesions, we estimated pre-vaccination frequency by aggregating the data for up to three years prior to vaccination, and calculated RR by dividing each post-vaccination year by the pre-vaccination estimate

Figure 1. Flowchart of study selection.

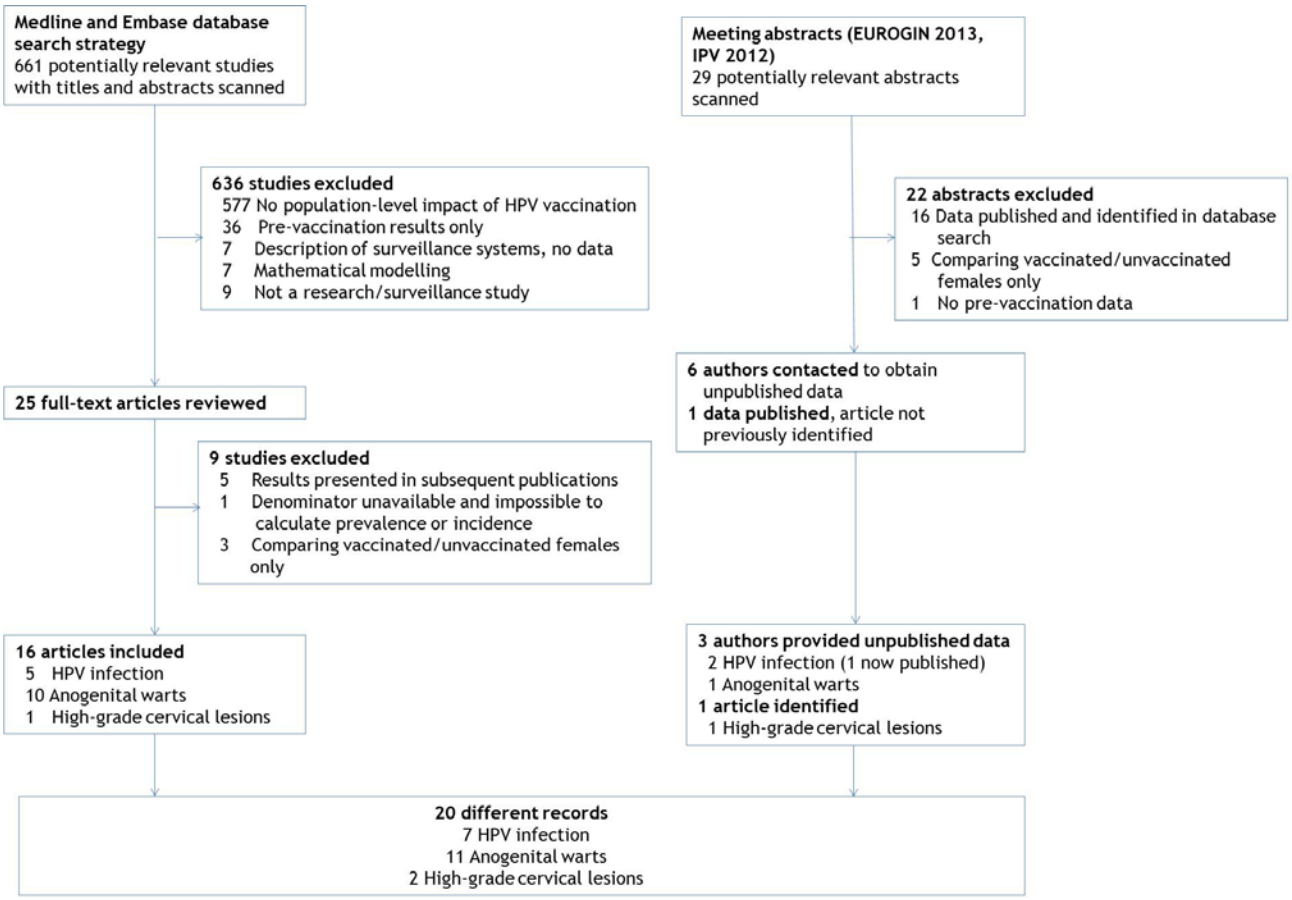
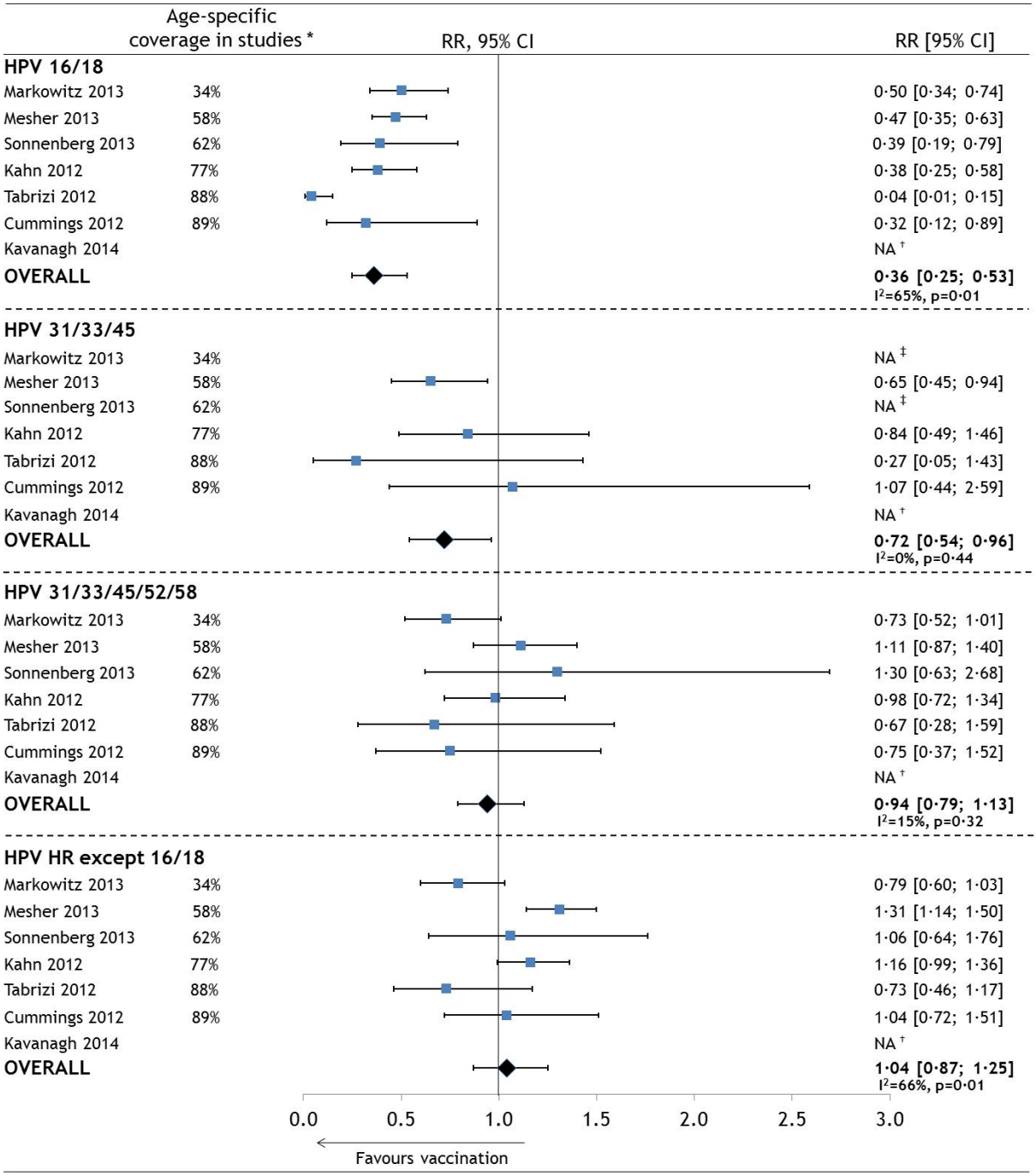
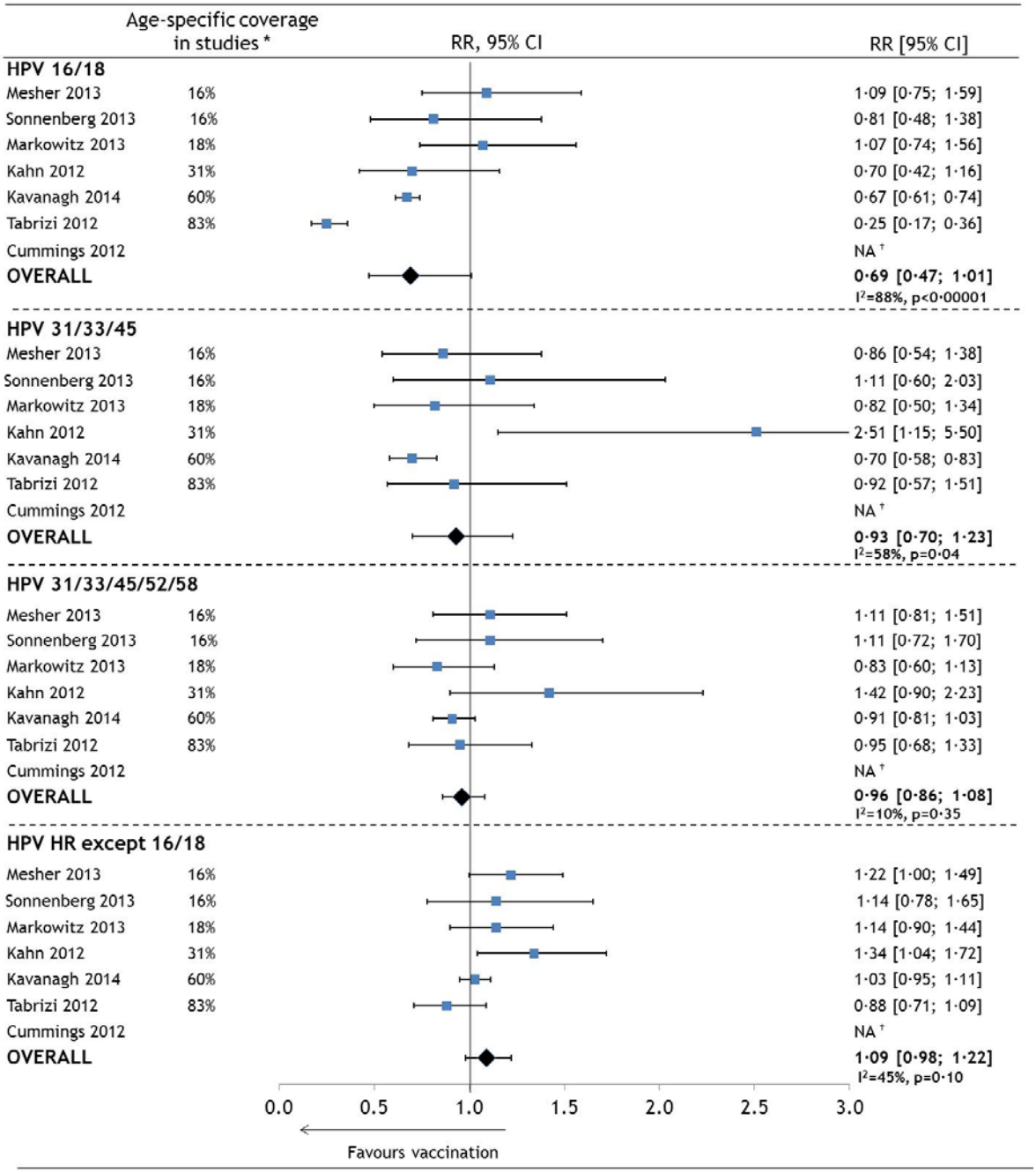


Figure 2. Changes in the prevalence of HPV infections between the pre- and post-vaccination periods among females aged 13-24 years old, ranked by age-specific vaccination coverage (≥ 1 dose) reported in studies.

A) Females 13-19 years old[§]



B) Females 20-24 years old



NA: Not available; RR: Relative risk; CI: Confidence interval; HR: High-risk

p-value for trends obtained by fitting a linear regression between the log RR and the age-specific coverage of each study, weighted by the inverse variances of the log RR: Females 13-19 years old, HPV16/18 p=0.005; HPV 31/33/45 p=0.14; HPV31/33/45/52/58 p= 0.69; HPV HR except 16/18 p=0.60, Females 20-24 years old, HPV16/18 p=0.01; HPV 31/33/45 p=0.63; HPV31/33/45/52/58 p= 0.46; HPV HR except 16/18 p=0.03

§ The minimum age of participants varied between studies (see Table 1)

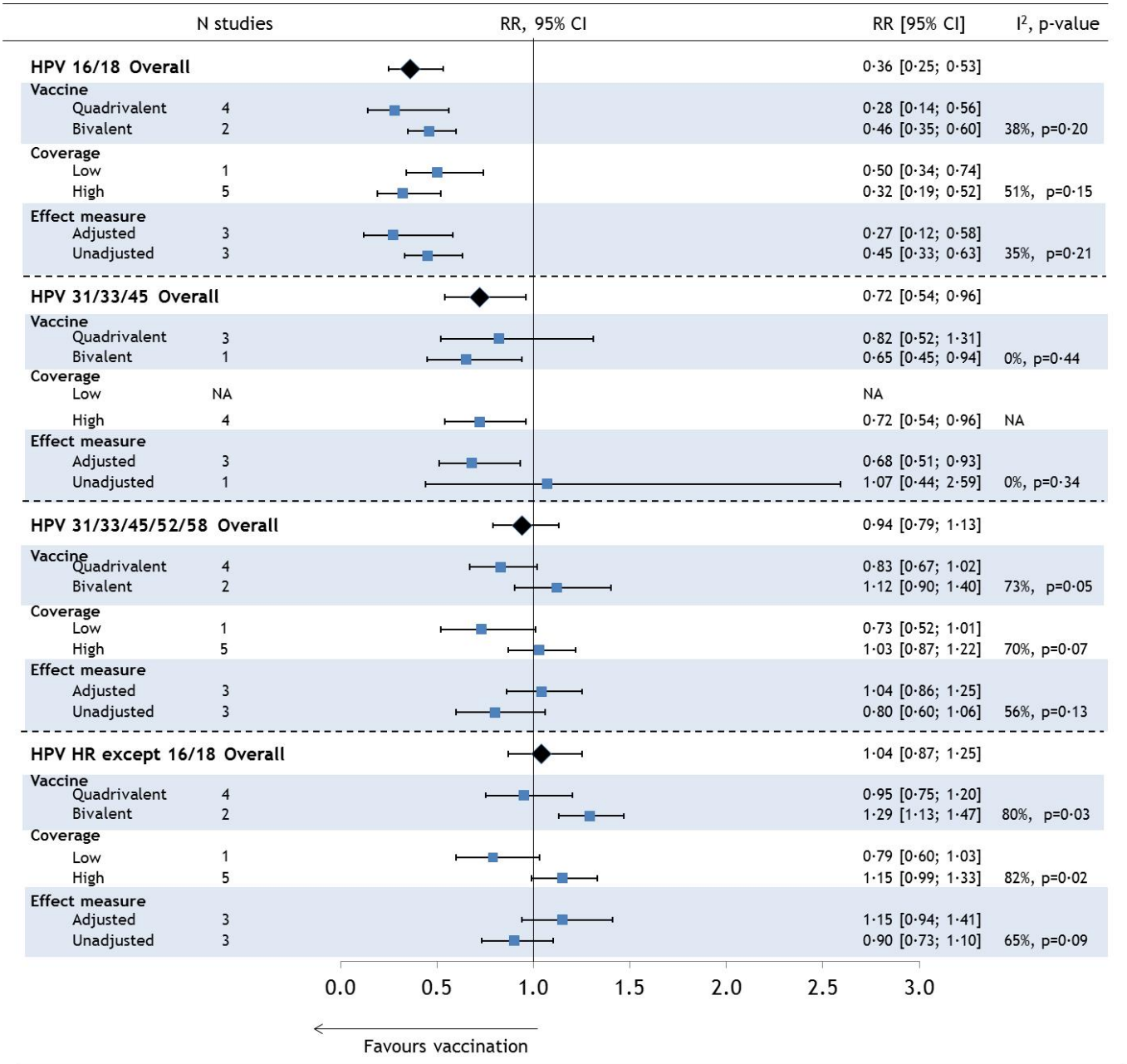
* Age-specific proportion of females, included in the analysis of each study, who received ≥1 dose of the HPV vaccine.

† Data not available for females 13-19 years old in Kavanagh et al., and for females 20-24 years old in Cummings et al.

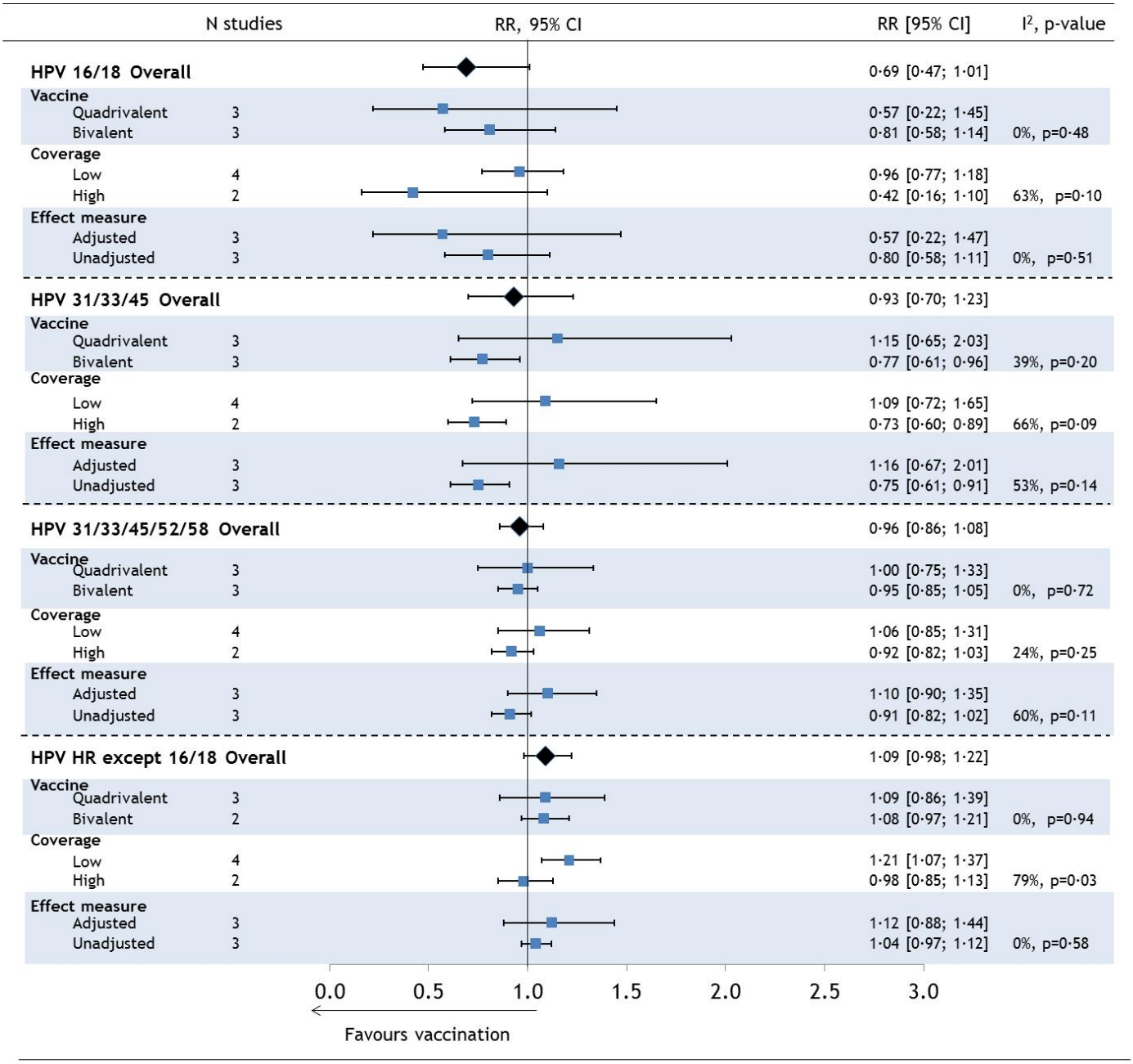
‡ Data not provided because they were considered as potentially unreliable according to NHANES analytic guidelines[70]: Prevalence estimates had a relative standard error (RSE) of >30% and the sample size was below the recommended sample size for analyses of complex survey data, by design effect and specified proportion. To be consistent throughout the studies using complex survey designs, we excluded data not meeting the recommended sample size for analyses of complex survey data, by design effect and specified proportion. The only data excluded was for HPV31-33-45 from NATSAL: unweighted pre-vaccination prevalence: 3/85; unweighted post-vaccination:16/215; weighted prevalence ratio: 3.50 (0.97-12.67).

Figure 3. Subgroup analyses of the changes in the prevalence of HPV infections between the pre- and post-vaccination periods among females.

A) Females 13-19 years old



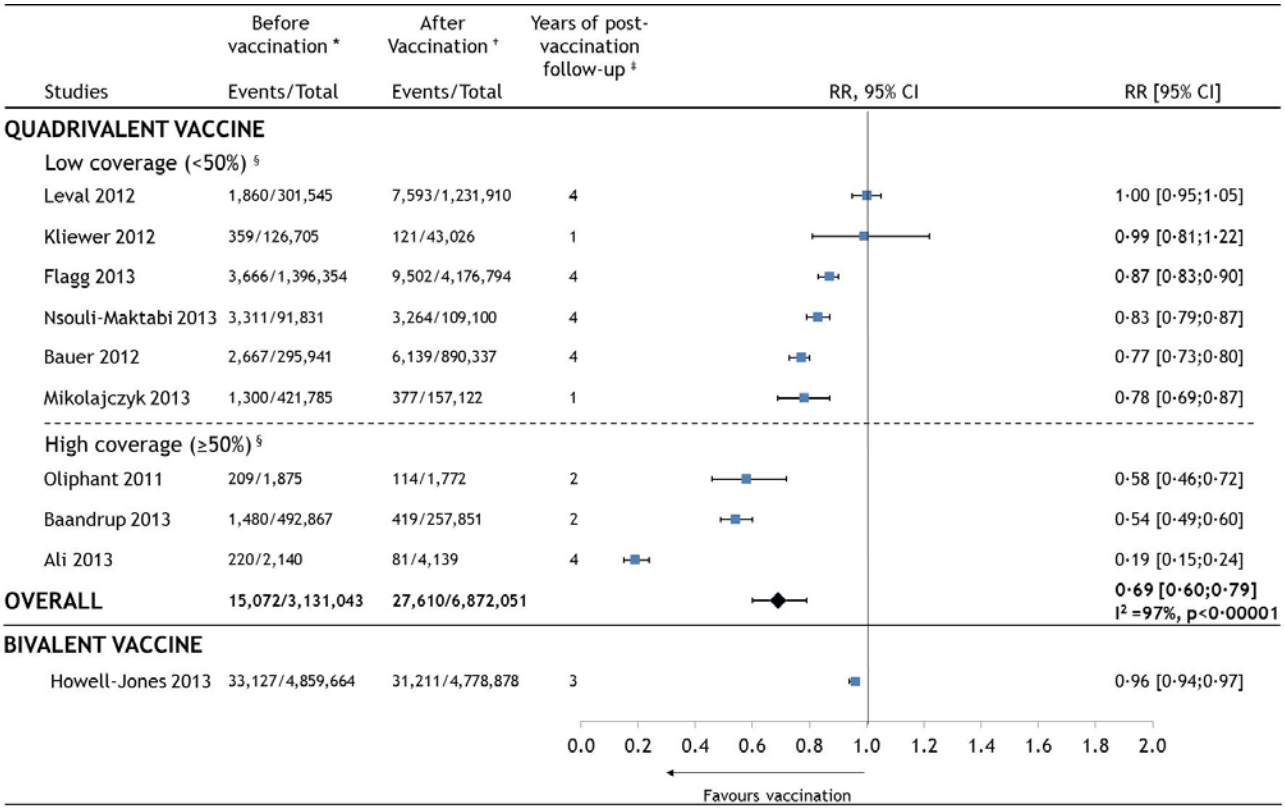
B) Females 20-24 years old



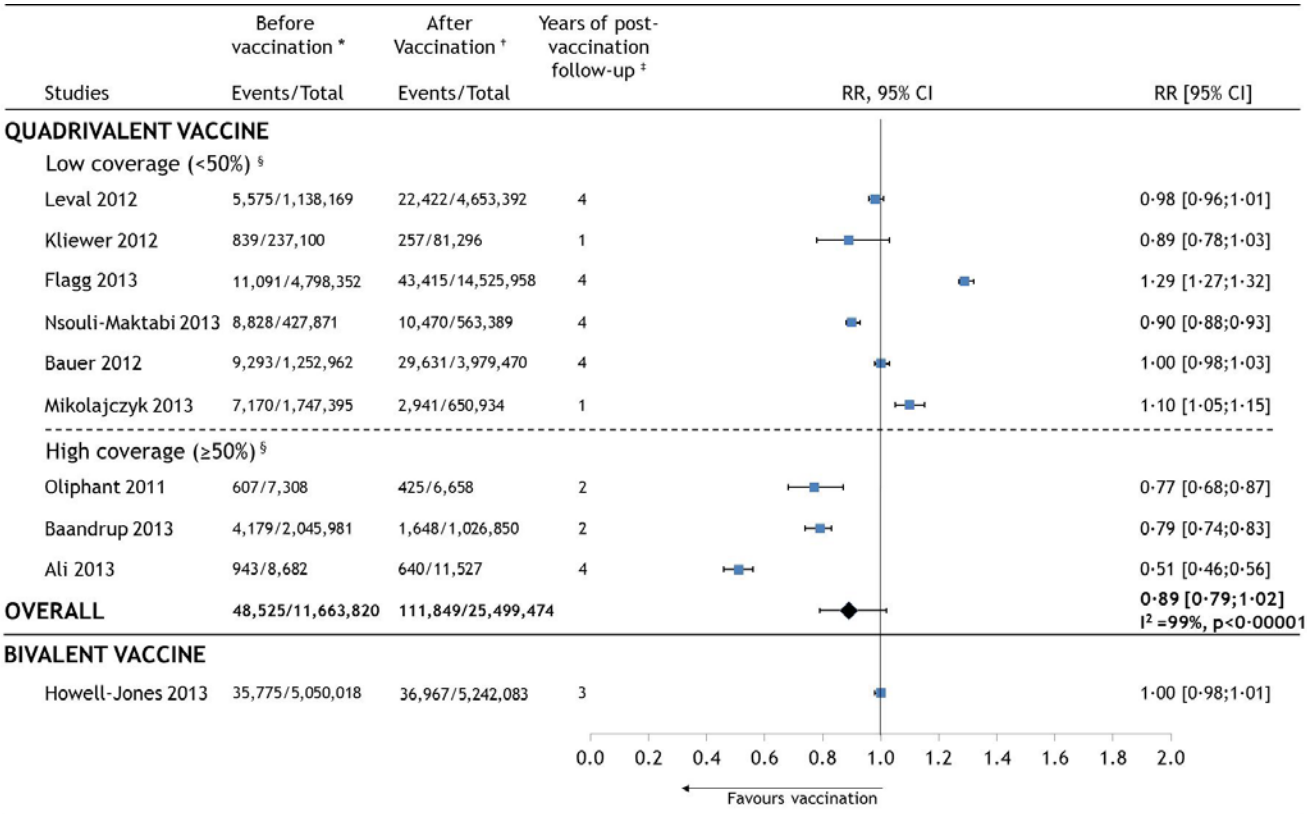
NA: Not available; RR: Relative risk; CI: Confidence interval; HR: High-risk

Figure 4. Changes in AGW diagnosis between the pre- and post-vaccination periods among females and males aged 15-39 years old, ranked by the national/setting-specific females' vaccination coverage.

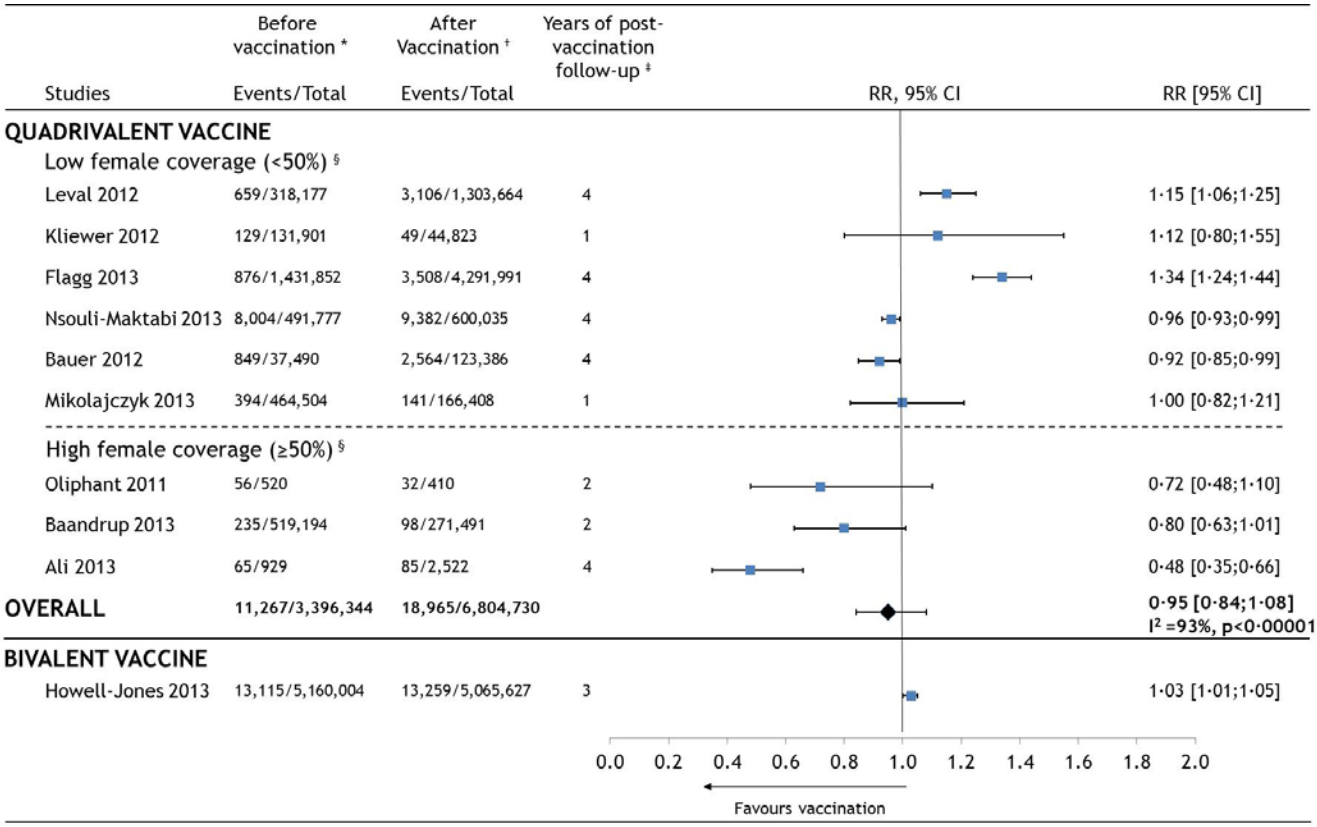
A) Females 15-19 years old



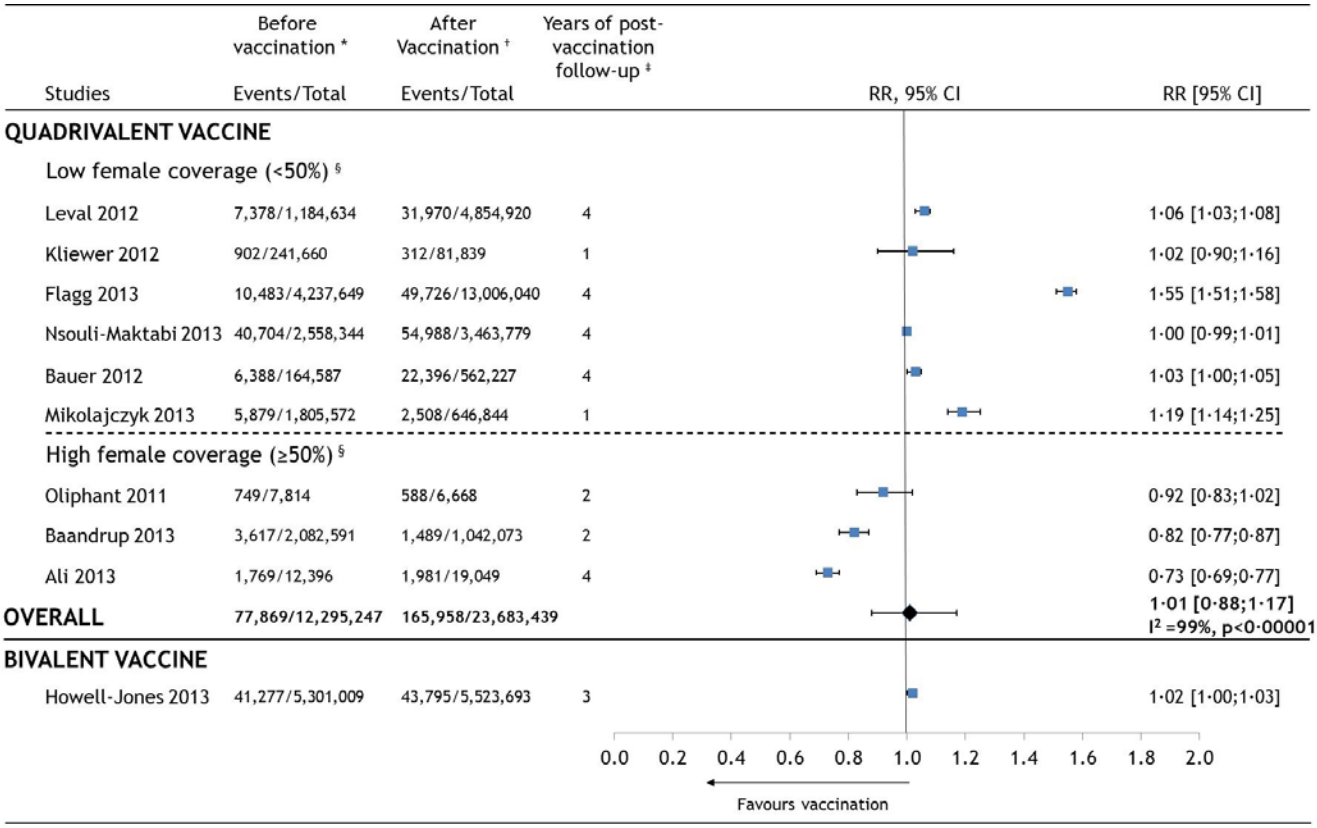
B) Females 20-39 years old



C) Males 15-19 years old



D) Males 20-39 years old

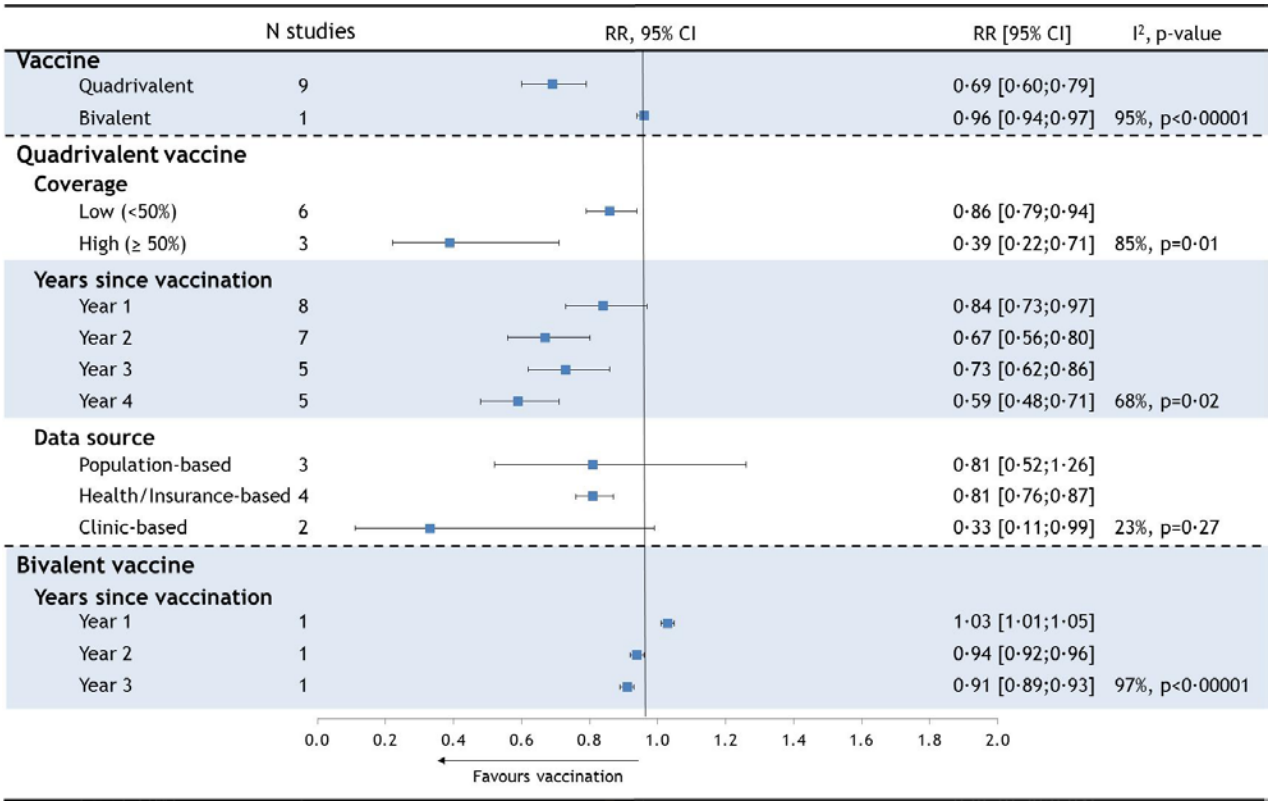


RR: Relative risk; CI: Confidence interval
p-value for trends obtained by fitting a linear regression between the log RR and the rank of vaccination coverage of each study, weighted by the inverse variances of the log RR : Females 15-19 years old: p=0.001; Females 20-39 years old: p=0.05; Males 15-19 years old: p=0.005; Males 20-39 years old: p=0.06

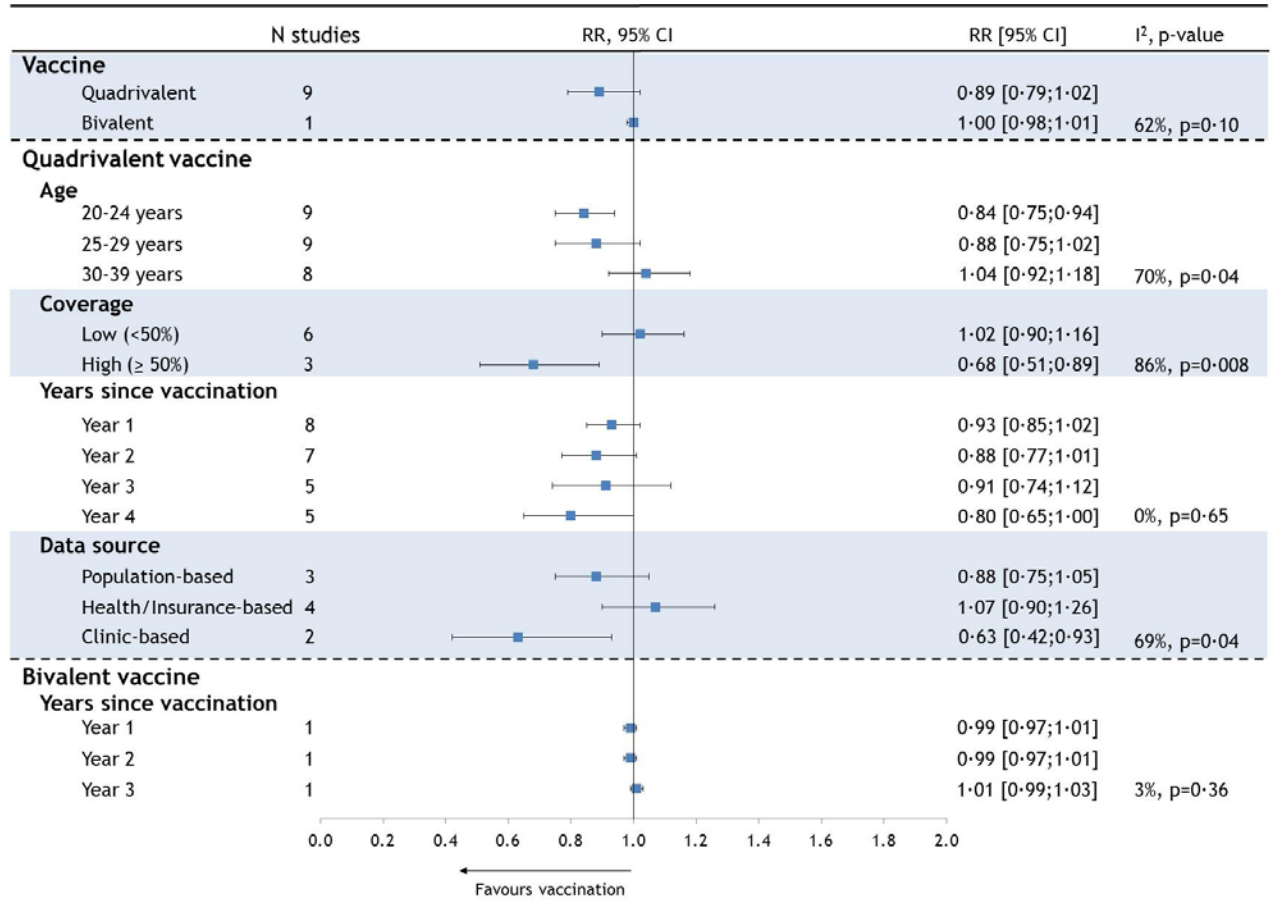
* Before vaccination: Cumulative number of cases and person-years up to three years pre-vaccination, including the year of the introduction of HPV vaccination.
† After vaccination: Cumulative number of cases and person-years from 1 to 4 years after the introduction of vaccination, depending on data available in each study.
‡ Years of post-vaccination follow-up: Number of years after the introduction of HPV vaccination considered in the meta-analysis (see Appendix-Table S5 for more details).
§ Studies were qualitatively ranked by the national/setting-specific vaccination coverage, by considering the number of cohorts vaccinated and vaccination coverage achieved in each cohort. However, it was not possible to estimate the overall vaccination coverage for each study (see Appendix-Table S1 for details about the program description, number of cohorts vaccinated and 3-dose vaccination coverage for each study).

Figure 5. Subgroup analyses of the changes in AGW diagnosis between the pre- and post-vaccination periods among females and males (NOTE: data are for years with female only vaccination programs).

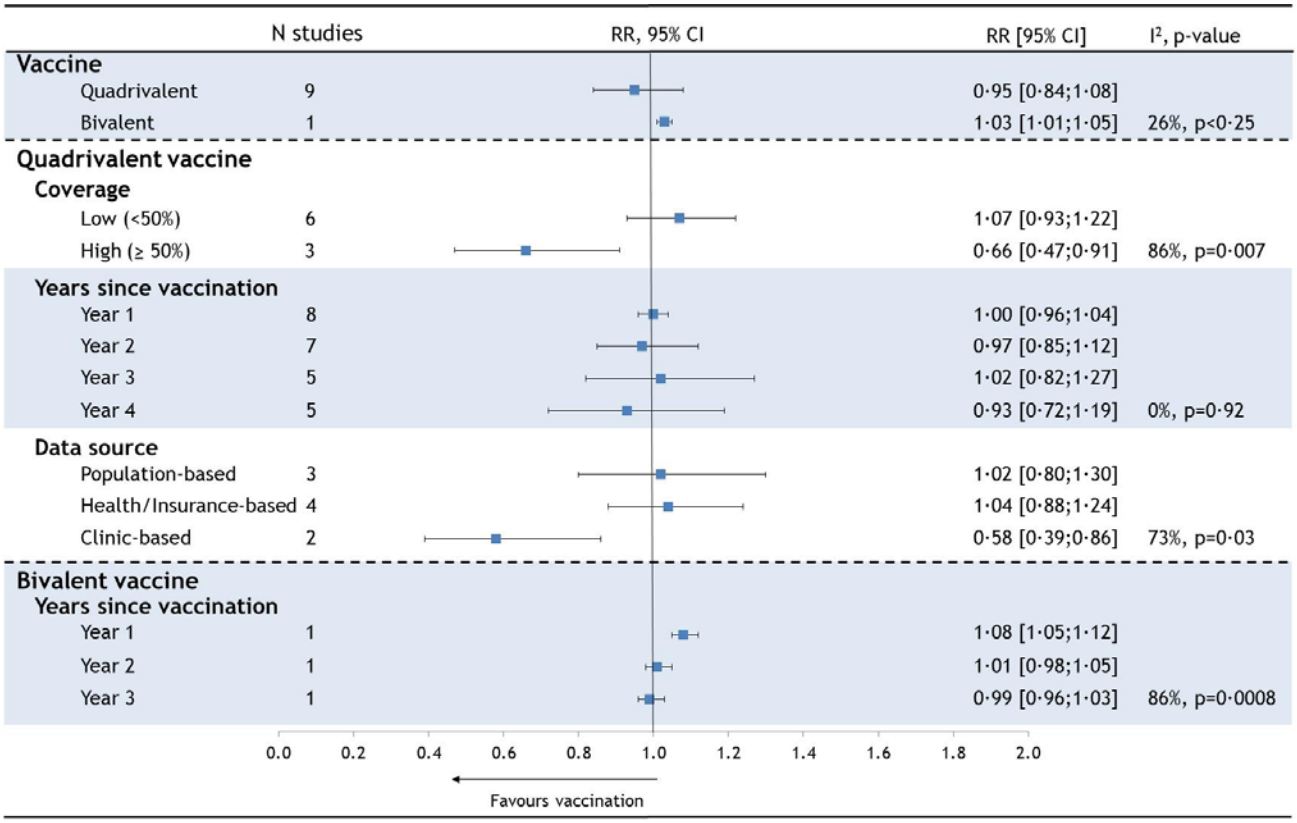
A) Females 15-19 years old



B) Females 20-39 years old



C) Males 14-19 years old



D) Males 20-39 years old

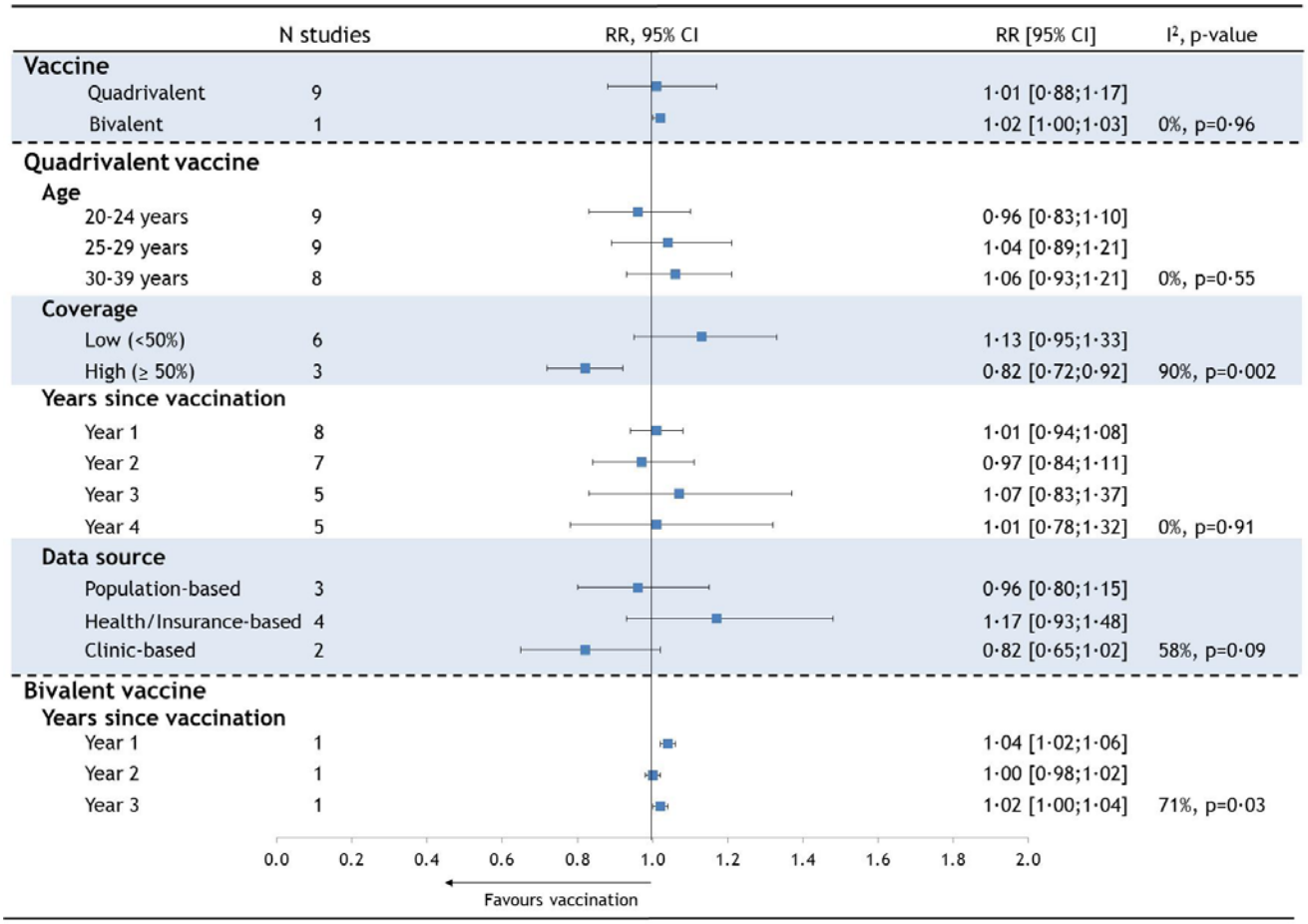
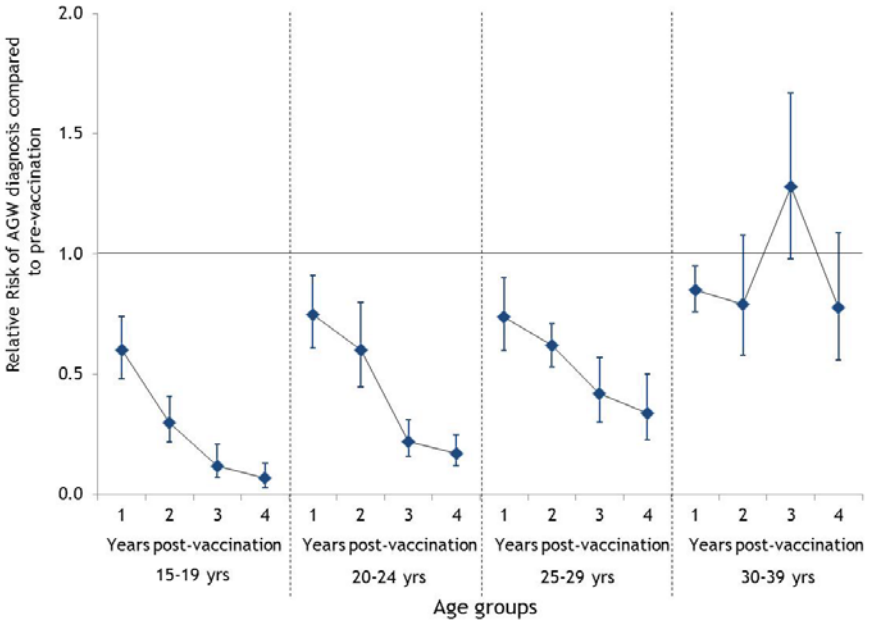
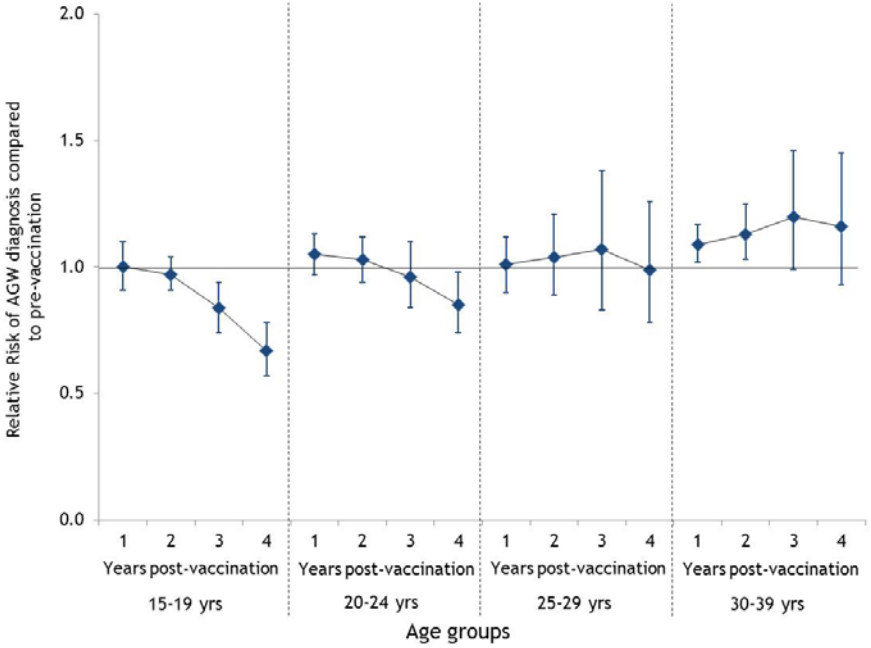


Figure 6. Changes in AGW diagnosis among females and males during the first four years after the introduction of HPV vaccination with the quadrivalent vaccine, stratified for age and females' vaccination coverage.

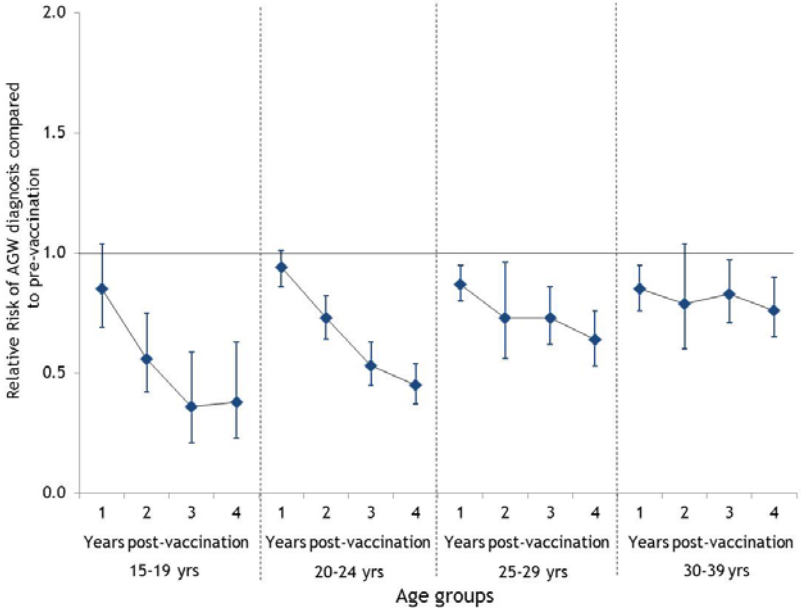
A) Females – High female coverage (≥50%) *



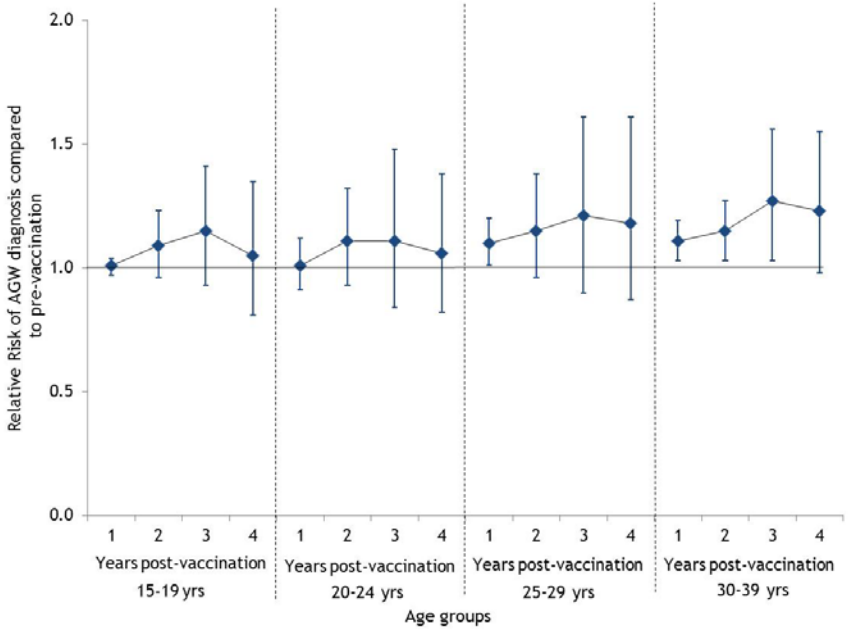
B) Females – Low female coverage (<50%) †



B) **C) Males - High female coverage (≥50%) ***



D) Males – Low female coverage (< 50%) †



* High coverage: the results from the following studies were combined depending on the years of follow-up available: Year 1 and 2: Oliphant 2011, Baandrup 2013, Ali 2013; Year 3 and 4: Ali 2013 (see Appendix-Table S1 for information about each study vaccination coverage).

† Low coverage: the results from the following studies were combined depending on the years of follow-up available: Year 1 : Leval 2013, Kliewer 2012, Flagg 2013, Nsouli-Maktabi 2013, Mikolajczyk 2013; Year 2, 3, 4 : Leval 2013, Flagg 2013, Nsouli-Maktabi 2013; Bauer 2013 (see Appendix-Table S1 for information about each study vaccination coverage).

Supplementary appendix

Table S1. Description of HPV vaccination programs and vaccination coverage for each study country/region

Country	Vaccine used	Financing	Availability of vaccine / Program start	Program description*	3 doses Vaccination coverage (year)†
Australia	Quadrivalent	Public	April 2007	School-based program: • Girls 12-13 yrs • Boys 12-13 yrs since February 2013 School-based catch-up: • Girls 14-17 yrs (2007-2009) • Boys 14-15 yrs (2013-2014)	School-based program: • Girls 12-13 yrs: 71% (2012) • Boys 12-13: NA School-based catch-up: • Girls 14-17 yrs:70% (2012) • Boys 14-15 yrs: NA
			July 2007	GP/Community catch-up: • Women 18-26 yrs (2007-2009)	GP/Community catch-up: • Women 18-19 yrs: 69% (2012) • Women 20-26 yrs: 44% (2012)‡
Canada (Manitoba)	Quadrivalent	Private	August 2006 (vaccine available privately)	Private vaccination: • Girls/women 9-26 yrs	Private vaccination: • Girls/women 9-26 yrs: 3% at least one dose (2009)
		Public	September 2008	School-based program: • Girls Grade 6 (≈ 11-12 yrs)	School-based program: Girls 11-12 yrs : about 50% (2009)
Denmark	Quadrivalent	Private	October 2006	Private vaccination: • Girls and boys ≥ 9 yrs	Private vaccination: • No information for total group of females. About 15% for those born in 1985-1992
		Public	January 2009	GP Childhood vaccination program: • Girls 12 yrs	Children vaccination program by GPs: • Girls 12 yrs: 79% (2012)
			October 2008	GP Catch-up girls: • Girls 13-15 yrs (2008-2010)	Catch-up: • Girls 13-15 yrs: 81% (2012)
			August 2012	GP Catch-up women: • Women 20-27 yrs (2012-2013)	GP Catch-up women: Women 20-27 yrs: 2% (2012)§
Germany	Quadrivalent and Bivalent (Quadrivalent: 90% of doses)	Public	March 2007	GP/community program • Routine vaccination of girls 12-17 yrs	Girls 16-18: about 40% (2009)
New Zealand	Quadrivalent	Public	September 2008	School-based/GP/community program: • Girls 11-12 yrs; School-based/GP/community catch-up: • Girls 13-20 yrs (2008-2010)	School-based/GP/community program: • Girls 11-12 yrs: around 55% (2012) (57% in Auckland) School-based/GP/community catch-up: Girls 13-20 yrs (2008-2010): 50% (2012)

Country	Vaccine used	Financing	Availability of vaccine / Program start	Program description*	3 doses Vaccination coverage (year)†
Sweden	Quadrivalent	Partially subsidized	October 2006 (Opportunistic vaccination)	Opportunistic vaccination: • Girls 13-20	25% at least one dose (2011) Leval 2013
		Public	2012	School-based program: • Girls 11-12 yrs; School-based catch-up: Girls 13-18 yrs	NA NA
UK - England	Bivalent, switch to Quadrivalent in September 2012	Public	September 2008	School-based program: • Girls 12-13 yrs School-based/GP catch-up: • Girls 14-17 yrs	School-based program: • Girls 12-13 yrs: 84% (2011) Catch-up: • Girls 14-17 yrs: 56% (range from 39 to 76%) (2011)
UK- Scotland	Bivalent, switch to Quadrivalent in September 2012	Public	September 2008	School-based program: • Girls 12-13 yrs School-based/GP catch-up: • Girls 14-17 yrs	School-based program: • Girls 12-13 yrs: 90% (2011) Catch-up (in and out of school): • Girls 13-17 yrs: 88% (33% among school leavers) (2011)
US	Quadrivalent and Bivalent (mostly Quadrivalent)	Mix of public and private	June 2006	Primary care providers vaccination: • Girls/women 11-12 yrs routine and 13-26 yrs, if not previously vaccinated • Boys/men 11-12 yrs routine and 13-21 yrs if not previously vaccinated since October 2011 • MSM 22-26 yrs or immunocompromised since October 2011	Routine and catch-up vaccination: • Girls 13-17 yrs: 33% (2012) • Women 19-26 yrs: 21% at least one dose (2010)

* The predominant delivery method is stated where mixed methods were allowed
† 3-dose coverage reported, but if unavailable, coverage for at least one dose is indicated
‡ Possible underreporting of HPV vaccination coverage for women 20-26 years old as reported in Brotherton et al. Vaccine 2014
§ Few women have received 3 doses of the vaccine at this time since the catch-up program was not initiated before 2012 (37-50% had received the first HPV vaccine, and 28-39% had received the second)

Data sources for vaccination coverage and program descriptions:

Australia

1. Ali H, Donovan B, Wand H, et al. Genital warts in young Australians five years into national human papillomavirus vaccination programme: national surveillance data. *BMJ* 2013; **346**: f2032.
2. Australian Government Department of Health. Information about the national Human papillomavirus (HPV) Vaccination Program funded under the Immunise Australia Program. http://www.health.gov.au/internet/immunise/publishing.nsf/content/immunise-hpv/ (accessed April 2014).
3. Personal communication with Julia Brotherton
4. National HPV Vaccination Program Register. HPV vaccination coverage by dose number (Australia) for females by age group in mid 2012. http://www.hpvregister.org.au/research/coverage-data/coverage-by-dose-2012 (accessed April 2014).

5. Brotherton JM, Liu B, Donovan B, Kaldor JM, Saville M. Human papillomavirus (HPV) vaccination coverage in young Australian women is higher than previously estimated: independent estimates from a nationally representative mobile phone survey. *Vaccine* 2014; **32**(5): 592-7.

Canada

1. Kliewer E, Mahmud S, Demers A, Lambert P, Musto G. Human papillomavirus vaccination and anogenital warts in Manitoba. Winnipeg: CancerCare Manitoba, 20pp, 2012.
2. Kliewer E, Demers A, Lambert P. Uptake of the human papillomavirus vaccine in Manitoba August 2006-December 2009. Winnipeg: CancerCare Manitoba, 43pp, 2012.

Denmark

1. Widgren K, Simonsen J, Valentier-Branth P, Molbak K. Uptake of the human papillomavirus-vaccination within the free-of-charge childhood vaccination programme in Denmark. *Vaccine* 2011; **29**: 9663-7.
2. Baandrup L, Blomberg M, Dehlendorff C, Sand C, Andersen KK, Kjaer SK. Significant decrease in the incidence of genital warts in young Danish women after implementation of a national human papillomavirus vaccination program. *Sex Transm Dis* 2013; **40**(2): 130-5.
3. Blomberg M, Dehlendorff C, Munk C, Kjaer SK. Strongly decreased risk of genital warts after vaccination against human papillomavirus: nationwide follow-up of vaccinated and unvaccinated girls in Denmark. *Clin Infect Dis* 2013; **57**(7): 929-34.
4. Statens Serum Institut. HPV vaccination-Coverage 2012. http://www.ssi.dk/English/News/EPI-NEWS/2013/No%2020%20-%202013.aspx (accessed April 2014).
5. Personnal communication with Louise Baandrup

Germany

1. Mikolajczyk RT, Kraut AA, Horn J, Schulze-Rath R, Garbe E. Changes in incidence of anogenital warts diagnoses after the introduction of human papillomavirus vaccination in Germany-an ecologic study. *Sex Transm Dis* 2013; **40**(1): 28-31.

New Zealand

1. Ministry of Health. History of the HPV immunisation programme. http://www.health.govt.nz/our-work/preventative-health-wellness/immunisation/hpv-immunisation-programme/history-hpv-immunisation-programme (accessed April 2014).
2. Oliphant J, Perkins N. Impact of the human papillomavirus (HPV) vaccine on genital wart diagnoses at Auckland Sexual Health Services. *The New Zealand medical journal* 2011; **124**(1339): 51-8.

Sweden

1. Leval A, Herweijer E, Arnheim-Dahlstrom L, et al. Incidence of genital warts in sweden before and after quadrivalent human papillomavirus vaccine availability. *J Infect Dis* 2012; **206**(6): 860-6.

UK (England)

1. Mesher D, Soldan K, Howell-Jones R, et al. Reduction in HPV 16/18 prevalence in sexually active young women following the introduction of HPV immunisation in England. *Vaccine* 2013; **32**(1): 26-32.
2. Department of Health. Annual HPV vaccine coverage in England201/2011. http://media.dh.gov.uk/network/211/files/2012/03/120319_HPV_UptakeReport2010-11-revised_acc.pdf (accessed April 2014).

UK (Scotland)

1. Kavanagh K, Pollock KG, Potts A, et al. Introduction and sustained high coverage of the HPV bivalent vaccine leads to a reduction in prevalence of HPV 16/18 and closely related HPV types. *Br J Cancer* 2014; **110**(11): 2804-11.
2. Information Services Division. HPV immunisation uptake rates by mid-August 2012, for girls in the catch-up cohort. https://isdscotland.scot.nhs.uk/Health-Topics/Child-Health/Publications/2012-09-25/HPV_Catch-up_Programme.xls (accessed June 2014).

US

1. Centers for Disease Control and Prevention. Adult Vaccination Coverage — United States, 2010. MMWR 2012;61:66- 72;
2. Centers for Disease Control and Prevention. Human Papillomavirus Vaccination Coverage Among Adolescent Girls, 2007–2012, and Postlicensure Vaccine Safety Monitoring, 2006–2013 — United States. MMWR 2013;62:591-595.

Table S2. Methodological quality and risk of bias in studies examining changes in HPV infection between the pre- and post-vaccination periods.

Authors	Cummings 2012	Kahn 2012	Tabrizi 2012	Markowitz 2013	Mesher 2013	Sonnenberg 2013	Kavanagh 2014
Study design	Time-trend analysis	Time-trend analysis	Time-trend analysis	Time-trend analysis	Time-trend analysis	Time-trend analysis	Time-trend analysis
Country	United States	United States	Australia	United States	England	Britain	Scotland
Funding	National Institutes of Health	National Institutes of Health	Australian National Health and Medical Research Council, and Anti-Cancer Council for Victoria	Centers for Disease Control and Prevention	Public Health England	UK Medical Research Council, Wellcome Trust, Economic and Social Research Council and the Department of Health	Scottish government, Chief Scientist Office
Risk of selection bias							
Subjects included in the study	Clinic-based: Women attending 1 of 3 urban primary care clinics in Indianapolis	Clinic-based: Young women attending 2 primary care clinics in Cincinnati who had had sexual contact. Great proportion of minority and low-income women	Clinic-based: Women recruited from participating family planning clinics for Pap screening in Sydney, Melbourne, and Perth	Population-based: Participants in NHANES which is designed to be nationally representative of the civilian, non-institutionalized US population	Clinic-based: Women undergoing chlamydia screening at community sexual health services, general practice and youth clinics in 7 regions around England	Population-based: Participants in NATSAL which is designed to be nationally representative of the British population	Population based: Women attending their cervical screening appointment across Scotland
Potential for selection bias: Changes in the study population characteristics between the pre- and post-vaccination periods	Low Unlikely changes in the clientele of primary care clinics between the pre- and post-vaccination periods	Low Unlikely changes in the clientele of primary care clinics between the pre- and post-vaccination periods	Low Unlikely changes in the clientele of family planning clinics between the pre- and post-vaccination periods	Low Unlikely changes in the NHANES participants between the pre- and post-vaccination periods	Medium Documented changes in the clientele receiving chlamydia testing between the pre- and post-vaccination periods	Medium Possible changes in the NATSAL participants between the pre- and post-vaccination periods (> 10 yrs between the 2 periods). Both surveys are weighted to Census data from the time.	Low No documented changes in screening rates of women aged 20-24 years old between the pre- and post-vaccination periods
Risk of information bias							
HPV testing	PCR Roche Linear Array test which detects 37 different HPV types	PCR Roche Linear Array test which detects 37 different HPV types	Amplicor HPV test kit (Roche Molecular system) (13 HPV types) and PGMY09-PGMY11 PCR-ELISA Roche Linear Array HPV Genotyping test	PCR Roche Linear Array test which detects 37 different HPV types	2008: Hybrid Capture 2 and Roche Linear Array 2010-2012: HPV+ In-house multiplex PCR and Luminex-based genotyping test (13 HPV types)	In-house Luminex-based genotyping assay (20 HPV types) in urine samples	Multimetrix HPV Assay which detects 18 high-risk types
Performance of the HPV test used	Unreported	Unreported	Unreported	Unreported	Unreported	Unreported	Unreported
Outcome used in publication	Odds ratios of HPV prevalence (crude)	HPV prevalence difference (adjusted)	Odds ratios of HPV prevalence (adjusted)	HPV prevalence ratio (crude)	Odds ratios of HPV prevalence (adjusted)	Odds ratios of HPV prevalence (adjusted)	HPV prevalence over time
Potential for information bias: Errors in the identification of HPV+ during the pre and post-vaccination period	Medium Potential for masking by HPV16/18, particularly in the pre-vaccine period	Medium Potential for masking by HPV16/18, particularly in the pre-vaccine period	Medium Potential for masking by HPV16/18, particularly in the pre-vaccine period	Medium Potential for masking by HPV16/18, particularly in the pre-vaccine period	Medium/High Potential for masking by HPV16/18, particularly in the pre-vaccine period; different tests used in the pre- and post-vaccination periods Which may have contributed to higher prevalence of non-vaccine types in the post-vaccination period	High Potential for masking by HPV16/18, particularly in the pre-vaccine period; Urine is a suboptimum specimen for the detection of HPV; Differences in methods of sample collection, preparation and storage between the pre- and post-vaccination periods	Medium Potential for masking by HPV16/18, particularly in the pre-vaccine period
Risk of confounding							
Potential confounders considered	Analysis matched on age at enrollment, clinic site and reported sexual activity (yes, never) at time of enrollment	Analysis adjusted for demographic characteristics (race, health insurance plan…), gynecologic history (number of times pregnant, history of Chlamydia, AGW), behaviors (age at first sexual intercourse, number male sexual partners, condom use, smoking…) using propensity scores	Analysis adjusted for age, contraceptive use, region, socioeconomic group and smoking status (these variables differed significantly between the 3 groups of women)	Analysis adjusted for race/ethnicity, lifetime number of sex partners for girls aged 14-19 years old. No adjustment for the other age groups, but all analysis weighted to represent the U.S population	Analysis adjusted for sexual history, age, venue type, ethnicity and chlamydia positivity	No adjustment in the comparison of HPV prevalence between the pre- and post-vaccination periods, but all analysis weighted to represent the British population	No adjustment in the analysis of changes of HPV prevalence over time
Potential for confounding: Changes in HPV infection between the pre and post-vaccination periods could be diluted/exacerbated by other variables	Medium Few risk factors considered and residual confounding by other factors associated with HPV vaccination and infection is possible (e.g., changes in sexual activity)	Low/Medium Several risk factors were considered. However, residual confounding by other factors associated with HPV vaccination and infection may still be present	Medium Few sexual behavior factors considered and residual confounding by other factors associated with HPV vaccination and infection is possible (e.g., changes in sexual activity)	Low/Medium Few factors considered for girls aged 14-19 years old, but weighted analysis	Medium Several risk factors were considered. However, residual confounding by other factors associated with HPV vaccination and infection can still be present (e.g., changes in sexual activity)	Medium/High No adjusted analysis of changes in HPV prevalence over time and likely changes over a 10-year period in factors associated with HPV vaccination and infection (e.g., changes in sexual activity documented when comparing NATSAL-2 and -3 [1])	Medium No adjusted analysis of changes in HPV prevalence over time. Confounding by factors associated with HPV vaccination and infection may be present (e.g., changes in sexual activity)

Authors	Cummings 2012	Kahn 2012	Tabrizi 2012	Markowitz 2013	Mesher 2013	Sonnenberg 2013	Kavanagh 2014
Study design	Time-trend analysis	Time-trend analysis	Time-trend analysis	Time-trend analysis	Time-trend analysis	Time-trend analysis	Time-trend analysis
Country	United States	United States	Australia	United States	England	Britain	Scotland
External validity							
External validity: Results can be generalized to the population at the country/region level	Medium Young women attending to urban primary care clinics may not represent the overall population (e.g., different vaccination coverage)	Low/Medium Women attending to the 2 primary care clinics may not be representative of the overall population (e.g., different vaccination coverage). Minorities and women from low socio-economic status are overrepresented	Medium Young women attending family planning clinics may not represent the overall population (e.g., different vaccination coverage)	Medium/High The survey was designed to be representative of the general population but non-participants could still be different than participants with respect to variables not considered in the sampling design.	Medium Chlamydia screening recommended for all sexually-active young women and uptake was 40% in 2011. However, women undergoing chlamydia screening may not be representative of the overall population (e.g., different vaccination coverage)	Medium/High The survey was designed to be representative of the general population. However, participants and those providing urine samples might not be fully representative of the general population, despite efforts to adjust for known biases and the use of additional weights for urine selection and urine non-response.	Medium Women participating in screening may not represent to overall population (e.g., different vaccination coverage)

References:

1. Mercer CH, Tanton C, Prah P, Erens B, Sonnenberg P, Clifton S, Macdowall W, Lewis R, Field N, Datta J, Copas AJ, Phelps A, Wellings K, Johnson AM. Changes in sexual attitudes and lifestyles in Britain through the life course and over time: findings from the National Surveys of Sexual Attitudes and Lifestyles (Natsal). L*ancet* 2013; **382**:1781-94

Table S3. Methodological quality and risk of bias in studies examining changes in anogenital warts between the pre- and post-vaccination periods.

Authors	Oliphant 2011	Bauer 2012	Kliewer 2012	Leval 2012	Ali 2013	Baandrup 2013	Howell-Jones 2013	Flagg 2013	Mikolajczyk 2013	Nsouli-Maktabi 2013	Sandø 2013
Study design	Time-trends	Time-trends	Time-trends	Time-trends	Time-trends	Time-trends	Time-trends	Time-trends	Time-trends	Time-trends	Time-trends
Country	New Zealand	United States	Canada	Sweden	Australia	Denmark	England	United States	Germany	United States	Denmark
Funding	No funding required	CDC, California Department of Public Health	Department of Health of Manitoba	National Research School in Health Care Sciences, Strategic Research Program (Karolinska Institutet), Erasmus Programme	CSL Biotherapies	Aragon Foundation, Aase and Ejnar Danielsen Foundation, Mermaid II Project	Public Health England	Centers for Disease Control and Prevention	Sanofi-Pasteur MSD	Not mentioned	Not mentioned
Risk of selection bias											
Subjects included in the study	Clinic-based: New clients of 1 sexual health service in Auckland	Health provider/insurance-based: Clients of the California Family Planning access care & treatment (FPACT) program	Population-based: Manitoba population from the population registry	Population-based: Sweden population from Statistics Sweden	Clinic-based: New clients of 8 sexual health services across Australia (Australian born)	Population-based: Denmark population from Statistics Denmark	Health provider/ based : Women diagnosed at Genitourinary medicines (GUM) and England population from national statistics as denominator;	Health provider/insurance-based : Enrollees in approximately 100 private health insurance plans across US	Health provider/insurance-based : Enrollees in 1 large health insurance company across Germany	Health provider/insurance-based : All individuals who served in the US Armed Forces	Population-based: Denmark population from Statistics Denmark
Potential for of selection bias: Changes in the study population characteristics between the pre- and post-vaccination periods	Medium/High Possible changes in the clientele of the sexual health service as reflected by an increasing annual number of clients in the post-vaccination period	Low Unlikely change in the FPACT (family planning program for low-income individuals) clientele between the pre- and post-vaccination periods	Low Entire population of Manitoba	Low Entire population of Sweden	Medium/High Possible changes in the clientele of the sexual health services in the pre- and post-vaccination periods as reflected by increasing annual number of clients and % of clients with chlamydia after 2006	Low Entire population of Denmark	Low/Medium Possible changes in GUM services clientele in the pre- and post-vaccination periods	Low Unlikely change in enrollees of insurance plans between the pre and post-vaccination periods. No decrease in Pap test or pelvic examination (opportunities to diagnose AGW) over time	Low Unlikely change in enrollees of insurance plans between the pre- and post-vaccination periods	Low Unlikely change in the Armed Forces population between the pre- and post-vaccination periods	Low Entire population of Denmark
Risk of information bias											
Data source	Medical records (available in the sexual health clinic database)	FPACT database (clinical encounter claims data)	Manitoba medical claims and hospital discharges	National patient register, Prescribed drug register	Medical records	National patient register	Genitourinary Medicine Clinic Activity Dataset (GUMCAD) (diagnoses at GUM clinics nationally	Truven Health Analytics MarketScan Commercial Claims and Encounters Database	German Pharmaco-epidemiological research database	Defense Medical Surveillance System	National patient register, Medical Products Statistics Register
Anogenital wart case definition	Clinical diagnosis	ICD-9 codes 078.10, 078.11 OR prescription of Imiquimod or Podophyllotoxin	Treatments (1 of 14 tariff codes for AGW treatments) OR hospitalization for AGW with ICD-9 code 078.11 OR 078.1, 078.10, 078.19 and related procedure OR ICD-10 A630 OR B07 and related procedure)	ICD-10 code A63 OR prescription of Imiquimod or Podophyllotoxin	Clinical diagnosis	ICD-10 code A63.0	Clinical diagnosis	1) ICD-9 codes 078.11 OR 2) ICD-9 code 078.1, 078.10, 078.19 and therapeutic procedure or diagnosis of benign anogenital neoplasm OR 3) ≥ 1 prescription for AGW treatment and therapeutic procedure or diagnosis of benign anogenital neoplasm	ICD-10 code A63.0	ICD-9 code 078.1	ICD-10 code A63.0, OR prescription of Podophyllotoxin
Outcome used	Annual proportion of new clients diagnosed with AGW	Annual proportion of FPACT clients diagnosed with AGW	Annual incidence rate of diagnosed AGW in the population	Annual incidence rate of diagnosed AGW in the population	Annual proportion of new clients with diagnosed AGW	Annual incidence rate of diagnosed AGW in the population	Annual incidence rate of GUM-diagnosed AGW in the population	Annual proportion of insured individuals with diagnosed AGW	Annual incidence rate of diagnosed AGW among insured individuals	Annual incidence rate of diagnosed AGW among US Forces members	Annual proportion of the population with diagnosed AGW
Numerator	Number of newly diagnosed AGW cases between Jan 2007 – June 2010	Number of first ever cases diagnosed after 2007 (cases prior to 2007 excluded) per year	Number of newly diagnosed AGW case each year (washout period of 12 months)	Number of newly diagnosed AGW cases each year, (washout period of 6 months)	Number of newly diagnosed AGW cases per year	Number of newly diagnosed AGW cases each year (washout period of 12 months)	Number of first diagnosed AGW cases since 2006, each year	Number of patients with AGW diagnosis each year	Number of newly diagnosed case each year, (washout period of 12 months)	Number of first ever diagnosed AGW case	Number of AGW cases each year

Authors	Oliphant 2011	Bauer 2012	Kliewer 2012	Leval 2012	Ali 2013	Baandrup 2013	Howell-Jones 2013	Flagg 2013	Mikolajczyk 2013	Nsouli-Maktabi 2013	Sandø 2013
Study design	Time-trends	Time-trends	Time-trends	Time-trends	Time-trends	Time-trends	Time-trends	Time-trends	Time-trends	Time-trends	Time-trends
Country	New Zealand	United States	Canada	Sweden	Australia	Denmark	England	United States	Germany	United States	Denmark
Denominator	Total number of new patients per year	All clients registered in the FPACT each year	Annual population estimates	Annual population estimates	Total number of new patients per year	Annual population estimates	Annual population estimates	Total number of clients enrolled in in health insurance plans each year	Total number of clients of 1 large insurance company each year	Total number of individuals who served in the US Forces each year	Annual population estimates
Potential for information bias: Errors in the identification of diagnosed AGW cases during the pre and post-vaccination period	Low AGW are directly diagnosed by physicians	Medium Sensitivity/specif-icity of algorithm to correctly identify diagnosed AGW not specified, unlikely to change over time unless awareness is associated with likelihood of including code	Medium Sensitivity/speci-ficity of algorithm to correctly identify diagnosed AGW not specified, unlikely to change over time unless awareness is associated with likelihood of including code	Medium Sensitivity/specifi-city of algorithm to correctly identify diagnosed AGW not specified, unlikely to change over time unless awareness is associated with likelihood of including code	Low AGW are directly diagnosed by physicians	Medium Sensitivity/speci-ficity of algorithm to correctly identify diagnosed AGW not specified and AGW treated by GP not included, unlikely to change over time unless awareness is associated with likelihood of including code	Low AGW are directly diagnosed by physicians in GUM clinics,	Medium Sensitivity/speci-ficity of algorithm to correctly identify diagnosed AGW not specified, unlikely to change over time unless awareness is associated with likelihood of including code	Medium Sensitivity/speci-ficity of algorithm to correctly identify diagnosed AGW not specified, unlikely to change over time unless awareness is associated with likelihood of including code	Medium Sensitivity/speci-ficity of algorithm to correctly identify diagnosed AGW not specified, unlikely to change over time unless awareness is associated with likelihood of including code	Medium Sensitivity/specificity of algorithm to correctly identify diagnosed AGW not specified, unlikely to change over time unless awareness is associated with likelihood of including code
Risk of confounding											
Potential confounders considered	Analysis stratified by age and gender	Analysis stratified by age and gender	Analysis stratified by age and gender	Analysis stratified by age and gender	Analysis stratified by age, gender, sexual orientation and residential status	Analysis stratified by age and gender	Analysis stratified by age and gender, and adjusted for chlamydia diagnoses and area	Analysis stratified by age, gender, region, and insurance plan type	Analysis stratified by age and gender	Analysis stratified by age and gender	Analysis stratified by age and gender
Potential for confounding: Changes in diagnosed AGW between pre and post-vaccination periods could be diluted/exacerba-ted by other variables	Medium Other factors could potentially cause changes in AGW frequency over time (e.g., changes in sexual activity)	Medium Other factors could potentially cause changes in AGW frequency over time (e.g., changes in sexual activity)	Medium Other factors could potentially cause changes in AGW frequency over time (e.g., changes in sexual activity, health seeking behaviour)	Medium Other factors could potentially cause changes in AGW frequency over time (e.g., changes in sexual activity); data suggesting increasing sexual activity over time in Sweden	High Other factors could potentially cause changes in AGW frequency over time (e.g., changes in sexual activity, health seeking behaviour); data suggest increasing proportion of clients with chlamydia after 2007	Medium Other factors could potentially cause changes in AGW frequency over time (e.g., changes in sexual activity, health seeking behaviour)	Medium Other factors could potentially cause changes in AGW frequency over time (e.g., changes in sexual activity, health seeking behaviour)	Medium Other factors could potentially cause changes in AGW frequency over time (e.g., changes in sexual activity, health seeking behaviour)	Medium Other factors could potentially cause changes in AGW frequency over time (e.g., changes in sexual activity, health seeking behaviour)	Medium Other factors could potentially cause changes in AGW frequency over time (e.g., changes in sexual activity, health seeking behaviour); data suggesting increases in diagnosis of all STIs	Medium Other factors could potentially cause changes in AGW frequency over time (e.g., changes in sexual activity, health seeking behaviour)
External validity											
External validity: Results can be generalized to the population at the country/region level	Medium Clients of 1 sexual health clinic may not represent the overall population (e.g., different vaccination coverage)	Medium FPACT is a program for low-income individuals and 87% of participants are females. Results could be different for medium/high-income individuals (e.g., different vaccination coverage)	High Entire population	High Entire population	Medium Clients of 8 sexual health clinics possibly representative of sexual health clinic clients in Australia, may not represent the overall population (e.g., different vaccination coverage)	Medium/High Entire population Contains all cases of AGW admitted to hospital or in outpatient clinics	Medium/High About 95% of AGW diagnoses are made in GUM clinics (~85% sample of national data used)	Medium/High The Truven Health Analytics contains data from 100 health insurance plan throughout the US (n=13 million in 2010). Results could be different for uninsured individuals	Medium/High The insurance plan includes > 6million individuals, 8% of the German population and is demographically representative. Results could be different in uninsured individuals	Medium/High All members of the Armed Forces are included, but results could be different for individuals not in the Armed Forces	High Entire population

CDC: Centers for Disease Control and Prevention

Table S4. Methodological quality and risk of bias in studies examining changes in high-grade lesions between the pre- and post-vaccination periods.

Authors	Brotherton 2011/AIHW 2013	Niccolai 2013
Study design	Time-trend analysis	Time-trend analysis
Country	Australia	United States
Funding	none	Centers for Disease Control and Prevention
Risk of selection bias		
Subjects included in analysis	Population-based: Women included in the Victorian Cervical Cytology Registry	Population-based: Statewide surveillance registry in Connecticut
Potential for selection bias: Changes in the study population characteristics between the pre- and post-vaccination periods	Medium Possible changes in participants to cervical cancer screening between the pre- and post-vaccination periods	Medium Possible changes in participants to cervical cancer screening between the pre- and post-vaccination periods
Risk of information bias		
Diagnosis of cervical lesions	The registry receives data from almost all cytology and cervical histopathology taken in Australia	The surveillance system receives data from all 34 pathology laboratories in Connecticut
Outcome used	Annual incidence of high grade lesions	Annual incidence of high grade lesions
Potential for information bias: Errors in the identification of pre-cancerous cervical lesions during the pre and post-vaccination period	Medium Sensitivity/specificity may change after vaccination, but unlikely to change during the first years of the vaccination program.	Medium Sensitivity/specificity may change after vaccination, but unlikely to change during the first years of the vaccination program.
Risk of confounding		
Potential confounders considered	Analysis stratified by age	Analysis stratified by age, area-based measures of ethnicity and race, and county type (urban-rural)
Potential for confounding: Changes in precancerous between pre and post-vaccination periods could be diluted/exacerbated by other variables	Medium/High Other factors could potentially cause changes in the incidence of precancerous cervical lesions (e.g., changes in screening guidelines, sexual activity). Changes in screening guidelines documented in 2006[1].	Medium/High Other factors could potentially cause changes in the incidence of precancerous cervical lesions (e.g., changes in screening guidelines, sexual activity). Changes in screening guidelines and in screening among women documented in the US[2].
External validity		
Results can be generalized to the population at the country/region level	Medium/High Women participating in screening may not be representative of the overall population (e.g., different vaccination coverage)	Medium/High Women participating in screening may not be representative of the overall population (e.g., different vaccination coverage)

AIHW: Australian Institute of Health and Welfare

References:

1. NHMRC. Screening to prevent cervical cancer: guidelines for the management of asymptomatic women with screen detected abnormalities, 2005. http://www.nhmrc.gov.au/publications/synopses/wh39syn.htm (accessed Dec 2010).
2. MMWR Jan 2013. Cervical cancer screening among women aged 18-30 years – United States, 2000-2010

Table S5. Pre and post-vaccination years considered in the meta-analysis.

Study	Country	HPV vaccination introduction	Pre-vaccination years considered in the meta-analysis	Post-vaccination years [¶]				
				1	2	3	4	5 [§]
HPV infection [*]								
Cummings 2012	U.S.	2006	1995-2005				2010	
Kahn 2012 [‡]	U.S.	2006	2006-2007			2009	2010	
Tabrizi 2012	Australia	2007	2005-2007			2010	2011	
Markowitz 2013	U.S.	2006	2003-2006	2007	2008	2009	2010	
Mesher 2013	England	2008	2008		2010	2011	2012	
Sonnenberg 2013	Britain	2008	1999-2001		2010	2011	2012	
Kavanagh 2014 [‡]	Scotland	2008	2009-2010			2011	2012	
AGW consultations [†]								
Oliphant 2011	New Zealand	2008	2007-2008	2009	2010			
Bauer 2012 [‡]	U.S.	2006	2007		2008	2009	2010	
Kliewer 2012	Canada	2008	2006-2008	2009				
Leval 2012	Sweden	2006	2006	2007	2008	2009	2010	
Ali 2013	Australia	2007	2005-2007	2008	2009	2010	2011	2012
Baandrup 2013	Denmark	2009	2007-2009	2010	2011			
Howell-Jones 2013	England	2008	2006-2008	2009	2010	2011		
Flagg 2013	U.S.	2006	2004-2006	2007	2008	2009	2010	
Mikolajczyk 2013	Germany	2007	2005-2007	2008				
Nsouli-Maktabi 2013	U.S.	2006	2004-2006	2007	2008	2009	2010	2011
Sandø 2013	Denmark	2009	2007-2009	2010	2011			
High–grade precancerous lesions								
Brotherton 2011/AIHW 2013	Australia	2007	2005-2007	2008	2009	2010	2011	
Niccolai 2013 [‡]	U.S.	2006	2008			2009	2010	2011

AIHW: Australian Institute of Health and Welfare

[*] For HPV infection, pre- and post-vaccination years were determined in original studies. The impact measure presented in original studies compared the combined post-vaccination years to the combined pre-vaccination. The only exception is the study by Kavanagh et al., in which yearly prevalence was presented separately for 2009,

2010, 2011, and 2012. We considered 2009 and 2010 as pre-vaccination years since the vaccination coverage was very low and 2011 and 2012 as post-vaccination years.

† For anogenital warts, pre-vaccination years (up to 3 according to the data available) were determined for the purpose of the meta-analysis. We included the calendar year of HPV vaccination introduction in the pre-vaccination period because year-end vaccination coverage with more than one dose was very low. All subsequent years were considered as post-vaccination years.

‡ Studies where the pre-vaccination years considered in the analysis included 1 or 2 years after the introduction of HPV vaccination, but during which the vaccination coverage was considered low (i.e. < 15%).

§ Since only two studies examined AGW during the fifth year after the introduction of HPV vaccination (1 with a high coverage and 1 with a low coverage), we restricted the analysis to four years. Similarly, for cervical lesions, the analysis was restricted to the first four years.

‖ Blanks in the post-vaccination years indicate that the study did not evaluate the outcome in this year

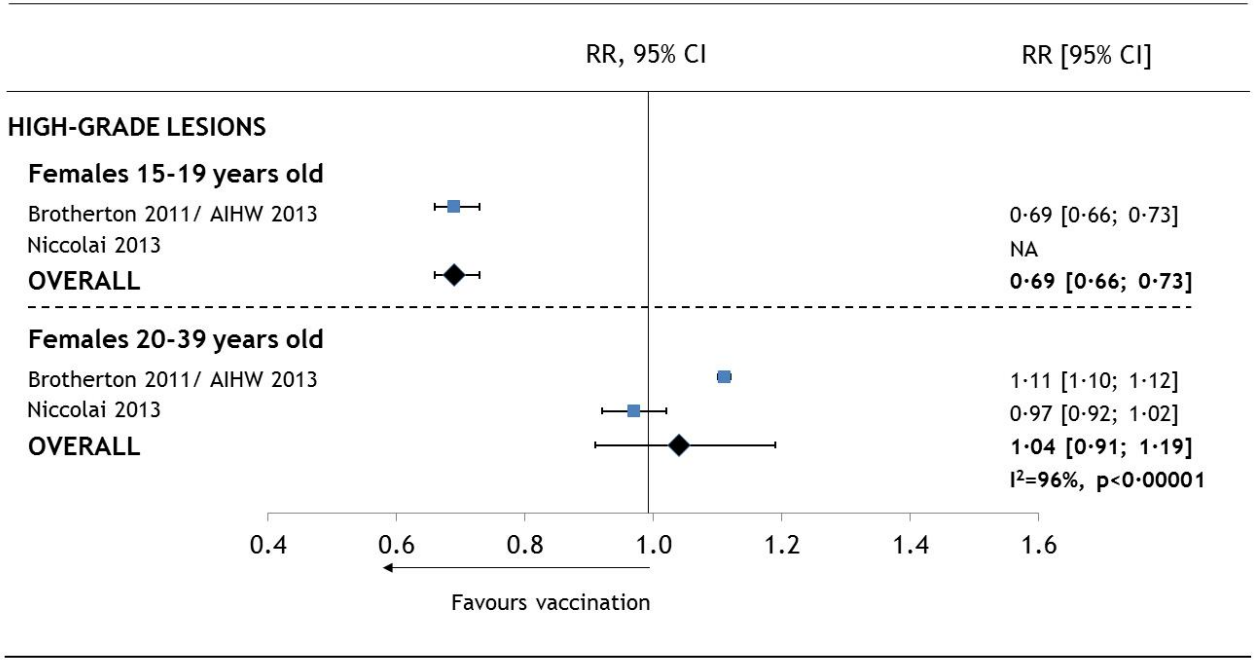
Table S6. Results of the sensitivity analysis using the results of Sandø et al instead of Baandrup et al.

	Baandrup et al.				Sandø et al.			
	Females		Males		Females		Males	
	< 20 yrs	20-39 yrs	< 20 yrs	20-39 yrs	< 20 yrs	20-39 yrs	< 20 yrs	20-39 yrs
Results presented in Figure 3								
Study estimate	0·54 (0·49;0·60)	0·79 (0·74;0·83)	0·80 (0·63;1·01)	0·82 (0·77;0·87)	0·48 (0·46;0·51)	0·97 (0·95;0·99)	0·67 (0·63;0·72)	1·09 (1·07;1·12)
Summary for the quadrivalent vaccine	0·69 (0·60;0·79)	0·89 (0·79;1·02)	0·95 (0·84;1·08)	1·01 (0·88;1·17)	0·67 (0·56;0·80)	0·92 (0·82;1·03)	0·91 (0·78;1·07)	1·05 (0·93;1·18)
Heterogeneity for the quadrivalent summary estimate	I^2 = 97% p<0·00001	I^2 = 99% p<0·00001	I^2 = 93% p<0·00001	I^2 = 99% p<0·00001	I^2 = 99% p<0·00001	I^2 = 99% p<0·00001	I^2 = 96% p<0·00001	I^2 = 99% p<0·00001
Results presented in Figure S2- Appendix								
Vaccine								
Quadrivalent	0·69 (0·60;0·79)	0·89 (0·79;1·02)	0·95 (0·84;1·08)	1·01 (0·88;1·17)	0·67 (0·56;0·80)	0·92 (0·82;1·03)	0·91 (0·78;1·07)	1·05 (0·93;1·18)
Bivalent	0·96 (0·94;0·97)	1·00 (0·98;1·01)	1·03 (1·01;1·05)	1·02 (1·00;1·03)	0·96 (0·94;0·97)	1·00 (0·98;1·01)	1·03 (1·01;1·05)	1·02 (1·00;1·03)
	I^2 = 95% p<0·00001	I^2 = 62% p=0·10	I^2 = 26% P=0·25	I^2 = 0% p=0·96	I^2 = 93% p=0·0001	I^2 = 50% p=0·16	I^2 = 53% p=0·15	I^2 = 0% ·p=0·65
Quadrivalent vaccine								
Coverage								
Low	0·86 (0·79;0·94)	1·02 (0·90;1·16)	1·07 (0·93;1·22)	1·13 (0·95;1·33)	0·86 (0·79;0·94)	1·02 (0·90;1·16)	1·07 (0·93;1·22)	1·13 (0·95;1·33)
High	0·39 (0·22;0·71)	0·68 (0·51;0·89)	0·66 (0·47;0·91)	0·82 (0·72;0·92)	0·38 (0·23;0·63)	0·73 (0·48;1·10)	0·63 (0·51;0·77)	0·90 (0·68;1·20)
	I^2 = 85% p=0·01	I^2 = 86% p=0·008	I^2 = 86% p=0·007	I^2 = 90% p=0·002	I^2 =89% p=0·002	I^2 = 59% p=0·12	I^2 = 94% p<0·0001	I^2 = 42% p=0·19
Age								
15-19 yrs	0·69 (0·60;0·79)		0·95 (0·84;1·08)		0·67 (0·56;0·80)		0·91 (0·78;1·07)	
20-24 yrs		0·84 (0·75;0·94)		0·96 (0·83;1·10)		0·86 (0·77;0·95)		0·97 (0·86;1·10)
25-29 yrs		0·88 (0·75;1·02)		1·04 (0·89;1·21)		0·91 (0·80;1·04)		1·08 (0·95;1·23)
30-39 yrs		1·04 (0·92;1·18)		1·06 (0·93;1·21)		1·08 (0·96;1·20)		1·11 (0·99;1·24)
		I^2 = 70% p=0·04		I^2 = 0% p=0·55		I^2 = 78% p=0·01		I^2 = 20% p=0·29
Years since vaccination								
Year 1	0·84 (0·73;0·97)	0·93 (0·85;1·02)	1·00 (0·96;1·04)	1·01 (0·94;1·08)	0·82 (0·68;0·99)	0·96 (0·88;1·03)	0·96 (0·88;1·05)	1·03 (0·97;1·10)
Year 2	0·67 (0·56;0·80)	0·88 (0·77;1·01)	0·97 (0·85;1·12)	0·97 (0·84;1·11)	0·62 (0·45;0·84)	0·94 (0·85;1·05)	0·86 (0·68;1·09)	1·04 (0·94;1·16)

	Baandrup et al.				Sandø et al.			
	Females		Males		Females		Males	
	< 20 yrs	20-39 yrs	< 20 yrs	20-39 yrs	< 20 yrs	20-39 yrs	< 20 yrs	20-39 yrs
Year 3	0·73 (0·62;0·86)	0·91 (0·74;1·12)	1·02 (0·82;1·27)	1·07 (0·83;1·37)	0·73 (0·62;0·86)	0·91 (0·74;1·12)	1·02 (0·82;1·27)	1·07 (0·83;1·37)
Year 4	0·59 (0·48;0·71)	0·80 (0·65;1·00)	0·93 (0·72;1·19)	1·01 (0·78;1·32)	0·59 (0·48;0·71)	0·80 (0·65;1·00)	0·93 (0·72;1·19)	1·01 (0·78;1·32)
	I^2 = 68% p=0·02	I^2 = 0% p=0·65	I^2 = 0% p=0·92	I^2 = 0% P=0·91	I^2 = 56% P=0·08	I^2 = 0% p=0·53	I^2 = 0% p=0·75	I^2 = 0% ·p=0·99
Data source								
Population-based	0·81 (0·52;1·26)	0·88 (0·74;1·05)	1·02 (0·80;1·30)	0·96 (0·80;1·15)	0·78 (0·44;1·38)	0·97 (0·96;0·99)	0·94 (0·61;1·45)	1·07 (1·04;1·11)
Health/Insurance-based	0·81 (0·76;0·87)	1·07 (0·90;1·26)	1·04 (0·88;1·24)	1·17 (0·93;1·48)	0·81 (0·76;0·87)	1·07 (0·90;1·26)	1·04 (0·88;1·24)	1·17 (0·93;1·48)
Clinic-based	0·33 (0·11;0·99)	0·63 (0·42;0·93)	0·58 (0·39;0·86)	0·82 (0·65;1·02)	0·33 (0·11;0·99)	0·63 (0·42;0·93)	0·58 (0·39;0·86)	0·82 (0·65;1·02)
	I^2 = 23% p=0·27	I^2 = 69% p=0·04	I^2 = 73% p=0·03	I^2 = 58% P=0·09	I^2 = 24% p=0·27	I^2 = 65% p=0·06	I^2 = 72% p=0·03	I^2 = 67% p=0·05
Results presented in Figure 4								
High coverage								
< 20 yrs								
Year 1	0·60 (0·48;0·74)		0·85 (0·69;1·04)		0·59 (0·49;0·71)		0·82 (0·76;0·89)	
Year 2	0·30 (0·22;0·41)		0·56 (0·42;0·75)		0·31 (0·23;0·42)		0·52 (0·47;0·57)	
Year 3	0·12 (0·07;0·21)		0·36 (0·21;0·59)		0·12 (0·07;0·21)		0·36 (0·21;0·59)	
Year 4	0·07 (0·03;0·13)		0·38 (0·23;0·63)		0·07 (0·03;0·13)		0·38 (0·23;0·63)	
20-24 yrs								
Year 1		0·75 (0·61;0·91)		0·94 (0·86;1·01)		0·77 (0·59;1·00)		0·97 (0·82;1·14)
Year 2		0·60 (0·45;0·80)		0·73 (0·64;0·82)		0·69 (0·49;0·96)		0·85 (0·69;1·04)
Year 3		0·22 (0·16;0·31)		0·53 (0·45;0·63)		0·22 (0·16;0·31)		0·53 (0·45;0·63)
Year 4		0·17 (0·12;0·25)		0·45 (0·37;0·54)		0·17 (0·12;0·25)		0·45 (0·37;0·54)
25-29 yrs								
Year 1		0·74 (0·60;0·90)		0·87 (0·80;0·95)		0·78 (0·56;1·10)		0·96 (0·78;1·18)
Year 2		0·62 (0·53;0·71)		0·73 (0·56;0·96)		0·76 (0·52;1·13)		0·94 (0·74;1·20)
Year 3		0·42 (0·30;0·57)		0·73 (0·62;0·86)		0·42 (0·30;0·57)		0·73 (0·62;0·86)
Year 4		0·34 (0·23;0·50)		0·64 (0·53;0·76)		0·34 (0·23;0·50)		0·64 (0·53;0·76)

	Baandrup et al.				Sandø et al.			
	Females		Males		Females		Males	
	< 20 yrs	20-39 yrs	< 20 yrs	20-39 yrs	< 20 yrs	20-39 yrs	< 20 yrs	20-39 yrs
30-39 yrs								
Year 1		0·85 (0·76;0·95)		0·85 (0·76;0·95)		0·91 (0·75;1·11)		0·92 (0·73;1·17)
Year 2		0·79 (0·58;1·08)		0·79 (0·60;1·04)		0·97 (0·86;1·09)		0·99 (0·79;1·24)
Year 3		1·28 (0·98;1·67)		0·83 (0·71;0·97)		1·28 (0·98;1·67)		0·83 (0·71;0·97)
Year 4		0·78 (0·56;1·09)		0·76 (0·65;0·90)		0·78 (0·56;1·09)		0·76 (0·65;0·90)

Figure S1. Changes in the incidence of high-grade cervical lesions between the pre and post-vaccination period among females aged 15-39 years old.



AIHW: Australian Institute of Health and Welfare