POPULATION-LEVEL IMPACT AND HERD EFFECTS FOLLOWING THE INTRODUCTION OF HUMAN PAPILLOMAVIRUS VACCINATION PROGRAMS: UPDATED SYSTEMATIC REVIEW AND META-ANALYSIS.

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ABSTRACT

Background

More than ten years have elapsed since human papillomavirus (HPV) vaccination was implemented. We performed a systematic review and meta-analysis of the population-level impact of female-only HPV vaccination on HPV infections, anogenital wart diagnoses (AGW) and cervical intraepithelial neoplasia grade 2+ (CIN2+) to summarise the most recent evidence about the effectiveness of HPV vaccines in real-world settings and to quantify the impact of multiple age-cohort vaccination.

Methods

We updated our prior review (01/01/2007–28/02/2014), by searching Medline and Embase (01/02/2014–11/10/2018) for studies that examined changes, between pre- and post-vaccination periods, in HPV infections, AGW, or CIN2+. We stratified all analyses by sex, age, and years since HPV vaccination introduction. We used random-effects models to estimate pooled relative risks and performed subgroup analysis to identify the main sources of heterogeneity.

Findings

We identified 65 eligible articles conducted in 14 high-income countries. After 5-8 years of vaccination, HPV-16/18, AGW, and CIN2+ decreased significantly by about 80%, 70%, and 50% among girls aged 15-19 years and by 65%, 55%, and 30% among women aged 20-24 years. Significant cross-protection and herd effects were also observed. HPV-31/33/45 decreased significantly by 50% among girls aged 15-19 years and AGW decreased significantly by 30-50% among boys/men aged 15-24 years. After 5-8 years of vaccination, countries with multi-cohort vaccination and high coverage (≥50%) had greater reductions in AGW, 44 and 85 percentage points among girls and boys aged 15-19 years, respectively, than countries with single-cohort vaccination and/or low vaccination coverage.

Interpretation

Our meta-analysis, including data from >60 million individuals from 14 high-income countries, shows a substantial impact of female-only HPV vaccination programs on AGW among girls/women and boys/men, and HPV infections and CIN2+ among girls/women. In addition, programs with multi-cohort vaccination and high vaccination coverage lead to greater and faster direct impact and herd effects.

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RESEARCH INTO CONTEXT

Evidence before this study

Since 2007, 99 countries and territories have introduced HPV vaccination programs. In 2015, we conducted a systematic review and meta-analysis to examine the real-world population-level impact of HPV vaccination. The meta-analysis showed substantial decreases in HPV-16/18 infections and anogenital wart diagnoses among females targeted for vaccination, and evidence of herd effects among boys and older women, 4 years after the introduction of HPV vaccination. However, at the time of the meta-analysis, the number of years post-vaccination was insufficient to examine the impact of HPV vaccination on cervical intraepithelial neoplasia grade 2+ (CIN2+). Moreover, in 2016, the World Health Organization (WHO) Strategic Advisory Group of Experts on Immunization revised its position to recommend HPV vaccination of multiple age cohorts of girls, rather than vaccinating a single cohort.

We updated our previous systematic review to 1) summarise the most recent evidence about the impact of HPV vaccination on HPV infections and anogenital wart diagnoses, 2) summarise new evidence about the impact of HPV vaccination on CIN2+, and 3) compare the impact between countries having implemented either a single or multiple age cohort vaccination strategy. To do so, we searched Medline and Embase (Feb 1, 2014 and October 11, 2018), without language restriction, with terms including ("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 47 new eligible articles added to our first review for a total of 65 articles. We contacted all corresponding authors of eligible studies to request a re-analysis of their data using the same data stratification to allow comparison between studies and pooling.

Added value of this study

The current updated systematic review and meta-analysis, which includes data from 60 million individuals and up to 8 years of post-vaccination follow-up, shows compelling evidence of the substantial impact of HPV vaccination programs on HPV infections, anogenital wart diagnoses and CIN2+ among women, and herd effects among boys and older women. Our study also shows greater and faster direct impact and herd effects in countries with multiple age cohort vaccination and high vaccination coverage compared to countries with single age-cohort vaccination or low routine vaccination coverage.
Our study is the first: 1) to present pooled estimates of the population-level impact of HPV vaccination on CIN2+, the most proximal outcome to cervical cancer recognized as a valid proxy for vaccine efficacy against cervical cancer, and 2) to show the real-world additional benefit of vaccinating multiple age cohorts of girls with high vaccination coverage.

Implication of all available evidence

Our results are the strongest yet that HPV vaccination is working to prevent cervical cancer in real-world settings, as both the cause (high-risk HPV infection) and proximal disease endpoints are significantly declining. In terms of global policy implications, these results reinforce the recently revised position of the WHO recommending HPV vaccination of multiple age cohorts of girls and are promising early signs that the WHO call for action on cervical cancer elimination may be possible if sufficient population-level vaccination coverage can be reached.

INTRODUCTION

More than ten years after the licensure of the first human papillomavirus (HPV) vaccines, 99 countries and territories have introduced HPV vaccination programs.[1, 2] Observational data showing the population-level impact of HPV vaccination from the early adopting countries can be immensely useful for decision makers examining whether to introduce or modify HPV vaccination programs. This is because such data demonstrate the effectiveness of HPV vaccines in real-world settings and can assist in the identification of the program characteristics that lead to the greatest reductions in HPV-related infections and diseases.

In 2015, we conducted a systematic review and meta-analysis of the population-level impact of HPV vaccination, including data from nine high-income countries up to four years after the introduction of HPV vaccination.[3] Our meta-analysis showed substantial decreases in HPV-16/18 infections and anogenital wart diagnoses among girls and young women targeted for vaccination. Furthermore, in countries with high vaccination coverage (≥ 50%), there was evidence of vaccine cross-protection and herd effects, with statistically significant reductions in HPV-31/33/45 infection among girls targeted for vaccination and anogenital wart diagnoses among unvaccinated boys and older women, respectively. However, in this previous meta-analysis, the number of years post-vaccination was insufficient to examine the impact of HPV vaccination on the occurrence of cervical intraepithelial neoplasia grade 2+ (CIN2+), the most proximal outcome for cervical cancer.[4]

In this paper, we update our systematic review and meta-analysis for three main reasons. Firstly, the number of countries and studies reporting observational data of the population-level impact of HPV vaccination has increased dramatically since our first review, which will improve both the power and generalizability of results. Secondly, the number of years post-vaccination has increased, which allows analysis of changes in CIN2+ since the introduction of HPV vaccination. Thirdly, the World Health Organization's (WHO) Strategic Advisory Group of Experts on Immunization revised its position in 2016 to recommend HPV vaccination of multiple age cohorts of girls when introducing the vaccine in a country, rather than vaccinating a single age cohort.[5] Prior to this recommendation, some high-income countries had implemented multiple age-cohort vaccination, mainly through catch-up campaigns. A better understanding of the population-level impact of multiple age-cohort vaccination will help inform policy-makers' decisions regarding whether to follow the recent WHO recommendation.

Thus, the aims of this systematic review and meta-analysis are to: 1) update and summarise the most recent evidence about the population-level impact of girls-only HPV vaccination on HPV infections and anogenital wart diagnoses among girls, women, boys and men, 2) summarise new evidence about the population-level impact of girls-only HPV vaccination on CIN2+ occurrence among screened girls/women, and 3) compare the population-level impact of HPV vaccination on anogenital wart diagnoses and CIN2+ between countries having implemented either a single or a multiple age-cohort vaccination strategy.

METHODS

Search strategy and selection of articles

In this updated systematic review, we used the same search strategy as our previous paper[3] and report our methods in accordance with the PRISMA guidelines (Appendix Table S1).[6] Briefly, studies were eligible if they compared the frequency (prevalence or incidence) of at least one HPV-related endpoint: 1) genital HPV infections, 2) anogenital wart diagnoses, or 3) histologically confirmed CIN2+, between the pre- and post-vaccination periods, among the general population and using the same population sources and recruitment methods pre- and post-vaccination. For CIN2+, the population was restricted to screened girls/women, to limit the impact of changes in screening recommendations/participation since the introduction of HPV vaccination. Finally, because our aim was to examine the population-level impact of HPV vaccination programs, we excluded studies if HPV vaccination was administered as part of a randomized trial, and/or if there were no data available for the pre-vaccination period.

To update our first systematic review (Jan 1, 2007 to Feb 28, 2014), we searched Medline and Embase between Feb 1, 2014 and October 11, 2018, with the same combination of Medical Subject heading (MeSH) terms, title, or abstract words ("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") (Appendix Table S2). The identification of eligible articles was performed independently by EB or NP and MD on title and abstract first, and then on the full-text. Disagreement between reviewers was solved by discussion between those authors. Finally, we searched the reference lists of selected articles. If more than one publication from the same data sources and/or research team was available, we kept the publication presenting the most recent or exhaustive data.

Data extraction and quality assessment

Our primary outcome was the relative risk (RR) comparing the frequency (prevalence or incidence) of HPV-related endpoints between the pre- and post-vaccination periods. For HPV infection, we focussed on three subgroups of HPV types: 1) HPV-16/18, 2) HPV-31/33/45, 3) all high-risk types except HPV16/18. MD, EB, and NP extracted the study characteristics and outcomes using a standardised form. MD, EB, NP and MB assessed the methodological quality of all studies, independently from the authors of the original studies, using the criteria developed for our first systematic review (Appendix Tables S5-S7). Potential biases and confounding were assessed by examining the procedures to select or identify participants, endpoint definitions, algorithms used to identify cases, and potential confounders (specific to each HPV-related endpoint) considered in the analysis. Then, MD contacted all corresponding authors of eligible studies to request a re-analysis of their data using the same data stratifications (e.g., age groups, HPV type grouping) to allow comparison between studies and pooling and all authors were able to provide these data. In collaboration with authors from the different countries, MD, EB, and NP also collected detailed information about the characteristics of each country/region HPV vaccination programs (routine program and catch-up campaigns), vaccination coverage, and cervical cancer screening recommendations/participation (Appendix Tables S3-S4). Finally, all authors of eligible studies validated that the information and data from their study, which were included in the manuscript, were accurate.

Data analysis

For all endpoints, we stratified all analyses by sex, age and years since the introduction of HPV vaccination. A priori, we chose to present the RRs stratified into two time categories to reflect the post-vaccination follow-up period used in our first meta-analysis (1-4 years), and the additional years available for the current update (5-8 years for HPV infections and anogenital warts / 5-9 years for CIN2+). In addition, we stratified analyses for anogenital warts by the type of vaccine (since only the quadrivalent vaccine includes HPV-6/11, which are associated with 85-95% of anogenital warts[7]). We used prevalence or incidence rate ratios as the measure of effect for all HPV-related endpoints (according to the data available from each study). For HPV infections, most studies directly presented crude and/or adjusted relative risk (RR) with 95% confidence intervals (CI). We preferably included RR adjusted for indicators of sexual activity and/or socio-economic status in the meta-analysis, but we used crude RR if adjusted estimates were not available. For anogenital warts and CIN2+, studies presented the annual frequency (prevalence or incidence) of the endpoint over time for the pre- and post-vaccination periods. Hence, for these endpoints, we estimated pre-vaccination frequency by aggregating the data for up to 3 years before vaccination and calculated crude RR by dividing each post-vaccination year by the pre-vaccination estimate (Appendix Table S8). We used random-effects models on a log scale to obtain pooled estimates of the effect of HPV vaccination for each HPV-related endpoint,[8, 9] using Review Manager version 5.3.5. We used I^2 and χ^2 statistics to assess heterogeneity across studies, and the p value associated with the χ^2 statistic represents the statistical significance of heterogeneity.[10]

The number of studies available for each HPV-related endpoint was too small to perform multivariate meta-regression.[10] Therefore, we performed subgroup analyses to identify the main sources of heterogeneity between studies. Firstly, we examined the impact of vaccination coverage and number of vaccinated cohorts, given that vaccination of a single or multiple cohorts is a key policy question. Because HPV endpoints were estimated from different types of studies, the available information about vaccination coverage and number of cohorts vaccinated varied across type of endpoints. For HPV infections, the vaccination status was directly available for all study participants (except for Dillner et al.[11]). Hence, we used the age-specific proportion of individuals vaccinated with at least one dose in each study and dichotomized the studies' vaccination coverage into < 50% and ≥ 50%. For anogenital warts, most studies were based on population or insurance registries of a country/region. Hence, we used the overall proportion of people vaccinated in the country/region and dichotomized the studies' country/region into: 1) Medium/high proportion of people vaccinated: country/region vaccinating multiple cohorts of girls with a vaccination coverage ≥ 50% for at least 2 doses among the routine cohort, and 2) Low proportion of people vaccinated: country/region vaccinating a single cohort of girls and/or having a coverage for at least 2 doses < 50% among the routine cohort. For CIN2+, studies were based on screened girls/women from screening registries. However, because the vaccination coverage was not available for screened girls/women for all studies, we used the overall country/regional level data and used the same categories as for anogenital warts (see Appendix Table S3). Secondly, we examined the impact of the vaccine used (bivalent, quadrivalent) and the data source (population-based, health provider/insurance-based, clinic-based) for all endpoints. Thirdly, we examined relevant endpoint-specific sources of heterogeneity. Because studies on HPV infection reported either adjusted or crude RR, we examined the impact of RR adjustment (yes, no). Finally, because CIN2+ detection can be influenced by screening recommendations/participation, we examined the potential impact of using HPV testing (yes, no) during the study period and the potential impact of changes that occurred during the study period: introduction of HPV testing (yes, no), older age at screening start (yes, no), and changes in the screening interval during the study period (yes, no).

Role of the funding source

The funders 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 1702 potentially eligible new articles (published between Feb 1, 2014 and Oct 11, 2018), of which 47 eligible articles were added to our first review for an overall total of 65 articles included in this systematic review (23 articles for HPV infection,[11-33] 29 articles for anogenital warts,[34-62] and 13 articles for CIN2+[63-75]) (Figure 1). These studies were conducted in fourteen high-income countries and cumulated data from more than 60 million individuals over 8 years (2007-2015) (Table 1). The vaccination programs, vaccination coverage (Appendix Table S3), and cervical screening recommendations/participation (Appendix Table S4) varied substantially between countries. As of 2015 (year of the most recent available data), 12/14 countries included in the review were vaccinating females-only with 3 doses of the bivalent or quadrivalent vaccine (Appendix Table S3). The only exceptions were Australia and the USA. Australia switched to a gender-neutral program in 2013 (i.e., year 6 after the implementation of HPV vaccination) and the USA recommended gender-neutral vaccination in 2011 (2-dose vaccination coverage among males remained below 20% until 2013, year 7 after the implementation of HPV vaccination). The age of girls/women targeted for vaccination also varied between countries (Appendix Table S3). The age of routine vaccination varied slightly between countries, from 10 to 13 years old. Most countries with multi-cohort vaccination targeted girls up to 18 years of age through routine and catch-up programs. However, Australia, the USA, and Denmark targeted women up to 26 years of age (with decreasing coverage as age increased). All studies were of sufficiently high methodological quality to be included in the meta-analysis (Appendix Tables S5-S7).

HPV Infection

In the first four years following the introduction of HPV vaccination, HPV-16/18 prevalence decreased significantly among girls aged 13-19 years and women aged 20-24 years compared to the pre-vaccination period (Figure 2, Appendix Figure S1). After 5-8 years of vaccination, HPV-16/18 prevalence decreased significantly by 83% (RR 0·17 [95% CI 0·11–0·25]) and 66% (RR 0·34 [95% CI 0·23–0·49]) among girls aged 13-19 years and women aged 20-24 years, respectively, compared to the pre-vaccination period. No significant changes in HPV-16/18 prevalence were observed among women aged 25-29 years (mostly unvaccinated) during the first four years of vaccination whereas a significant decrease was observed during the 5-8 year follow-up period (RR 0·63 [95% CI 0·41-0·97].

For HPV-31/33/45 (cross-protective types), there were substantial but non-significant decreases in prevalence during the first 4 years of vaccination among girls aged 13-19 years. However, after 5-8 years of vaccination, HPV-31/33/45 prevalence decreased significantly by 54% (RR 0·46 [95% CI 0·33–0·66]) among girls aged 13-19 years and non-significantly by 28% (RR 0·72 [95% CI 0·47–1·10]) among women aged 20-24 years. No significant changes in HPV-31/33/45 prevalence were observed among women aged 25-29 years during the 0-4 and 5-8 year follow-up periods. Finally, although non-significant, slight increases in the prevalence of high-risk types not included in the vaccine were observed for all age groups.

In subgroup analyses, studies where participants had a high vaccination coverage (≥ 50%) generally had greater decreases in HPV-16/18 and HPV-31/33/45 prevalence compared to studies with a low vaccination coverage (<50%), but the differences were not always statistically significant (Appendix Table S9). Studies using clinic-based data also showed greater decreases in HPV-16/18 prevalence compared to studies using population-based data. Studies with a high vaccination coverage and/or using clinic-based data showed greater increases in high-risk HPV types other than 16/18 among girls aged 13-19 years and during the first 4 years of vaccination. However, these differences were not maintained with a longer post-vaccination follow-up and were not consistent across the different age groups.

Only two studies were available for genital HPV infections among males (Appendix Figure S1 D,E).[13, 31] Non-significant decreases in HPV-16/18 (RR 0·35 [95% CI 0·09–1·40]) and HPV 31/33/45 (RR 0·31 [95% CI 0·06–1·58]) prevalence were observed among boys aged 16-19 years during the first 4 years of girls-only vaccination. The decreases were very similar after 5-8 years of vaccination in the study by Chow et al.[13] No significant changes were observed among men aged 20-24 years.

Anogenital Wart Diagnoses

In the first four years following the implementation of quadrivalent HPV vaccination, anogenital wart diagnoses decreased significantly among girls/women aged 15-19, 20-24 years, and 25-29 years. In addition, non-significant but substantial decreases were observed among unvaccinated boys aged 15-19 years (Figure 3, Appendix Figure S2). After 5-8 years of HPV vaccination, declines in anogenital wart diagnoses were significant for girls/women aged 15-29 years and for

boys/young men (Figure 3). Anogenital wart diagnoses decreased significantly by 67% (RR 0·33 [95% CI 0·24–0·46]) and 31% (RR 0·69 [95% CI 0·53–0·89]) among girls aged 15-19 years and women aged 25-29 years, respectively, and by 48% (RR 0·52 [95% CI 0·37–0·75]) and 32% (RR 0·68 [95% CI 0·47–0·98]) among boys aged 15-19 years and young men aged 20-24 years, respectively. Three studies examined changes in anogenital wart diagnoses following the implementation of bivalent vaccination and results suggest a slight decrease among girls/women aged 15-19 and 20-24 years, and boys aged 15-19 years (Appendix, Figure S2 A,B, E, F).

In subgroups analyses, studies conducted in countries with multi-cohort vaccination and a population-level vaccination coverage ≥ 50% consistently showed greater decreases in anogenital wart diagnoses among females and males and among different age groups (Appendix, Table S10). Studies using clinic-based data also showed greater decreases of anogenital wart diagnoses compared to studies using population-based data.

Figure 4 shows changes over time in anogenital wart diagnoses among females and males, taking into consideration the main sources of heterogeneity. This figure clearly illustrates the rapid and significant decline in anogenital wart diagnoses over time among girls/women and boys/men aged 15-19, 20-24 and 25-29 years, in countries vaccinating multiple cohorts of girls/women with high routine vaccination coverage. On the other hand, the decline was slower in countries vaccinating a single cohort of girls or having low routine vaccination coverage, with significant decreases observed among girls/women aged 15-19 and 20-24 years, only in the third years of vaccination. In addition, in these countries, increases in anogenital wart diagnoses were observed among the oldest cohorts of men (Figure 4B). A sensitivity analysis restricted to countries with high vaccination coverage (≥50%), showed that multi-cohort vaccination provided substantial additional reductions in anogenital wart diagnoses than single-cohort vaccination (Appendix Figure S4).

CIN2+

In the first four years following the introduction of HPV vaccination, significant CIN2+ decreases were only observed among screened girls aged 15-19 years (Figure 5, Appendix Figure S3). After 5-9 years of HPV vaccination, CIN2+ decreased significantly by 51% (RR 0·49 [95% CI 0·42–0·58]) and 31% (RR 0·69 [95% CI 0·57–0·84]) among screened girls aged 15-19 years and women aged 20-24 years, respectively. However, during the same follow-up period, CIN2+ increased significantly by 19% RR 1·19 [95% CI 1·06–1·32]) and 23% (RR 1·23 [95% CI 1·13–1·34]) among screened and mostly unvaccinated women aged 25-29 and 30-39 years, respectively.

In subgroup analyses, countries with multi-cohort vaccination and high routine vaccination coverage produced greater decreases in CIN2+ among girls/women aged 15-24 years old than the country with single-cohort vaccination and/or low routine vaccination coverage (Appendix, Table S11). The only study from a country using the bivalent vaccine also showed greater decreases in CIN2+ among women aged 20-24 years, compared to studies from countries using the quadrivalent vaccine (although the country using the bivalent vaccine also had very high vaccination coverage). Subgroup analyses also showed that increases in CIN2+ among women aged 25-29 years during post-vaccination years were significantly greater in the country with single-cohort vaccination and/or low routine vaccination coverage. None of the variables related to changes in screening recommendations/participation since the introduction of HPV vaccination were clearly associated with changes in CIN2+.

Figure 6 shows changes in CIN2+ among screened girls/women, taking into consideration the main sources of heterogeneity (excluding the results from the only country with single-cohort vaccination). Significant declines in CIN2+ were observed among girls aged 15-19 years and women aged 20-24 years after one and three years of vaccination, respectively. On the other hand, significant increases in CIN2+ were observed among mostly unvaccinated women aged 25-29 and 30-39 years.

DISCUSSION

This systematic review and meta-analysis, including data from 14 high-income countries, shows a significant and substantial impact of HPV vaccination on three HPV-related endpoints in the first 9 years after the start of HPV vaccination. Over this time period, HPV-16/18 infections, anogenital wart diagnoses and CIN2+ decreased significantly by about 80%, 70%, and 50%, respectively, among girls aged <20 years, and by 65%, 55%, and 30% among women aged 20-24 years. There was also evidence of vaccine cross-protection and herd effects from girls-only vaccination programs. HPV-31/33/45 decreased significantly by 50% among girls aged <20 years, and anogenital wart diagnoses decreased significantly by 30-50% among boys/men aged 15-24 years and by 30% among women aged 25-29 years. Finally, our meta-analysis illustrates the greater and faster direct impact and herd effects of HPV vaccination in countries with both multi-cohort vaccination and high routine vaccination coverage compared to countries with single-cohort vaccination and/or low routine vaccination coverage. For example, after 5-8 years of HPV vaccination, anogenital wart diagnoses declined by 88% and 86% among

girls and boys aged <20 years, respectively, in countries with multi-cohort vaccination and high routine vaccination coverage compared to 44% and 1% in countries with single-cohort vaccination and/or low routine vaccination coverage.

Our study is the first to show the real-world additional benefit of multi-cohort HPV vaccination and high routine vaccination coverage. After 5-8 years of vaccination, reductions in anogenital wart diagnoses and CIN2+ among girls aged 15-19 years were 44 and >100 percentage points greater, respectively, compared to countries with single-cohort vaccination and/or low routine vaccination coverage. Fast and substantial herd effects were also observed in countries with multi-cohort vaccination and high routine vaccination coverage. After 5-8 years of girls-only vaccination, reductions in anogenital wart diagnoses were 85 percentage points greater among boys aged 15-19 years old compared to single-cohort vaccination and/or low routine vaccination coverage. These results were similar when restricting the analysis to countries with high routine vaccination coverage. Our results are also in line with a recent mathematical modeling study, which estimated that five years after the introduction of HPV vaccination in Australia, half of the observed declines in anogenital wart diagnoses were attributable to multi-cohort vaccination (catch-up of 14-26-year-old females) (Appendix Table S3).[76] In terms of policy implications, these results reinforce the recently revised position of the WHO, recommending HPV vaccination of multiple age cohorts of girls (9-14 years old) when introducing the vaccine in a country, rather than vaccination of a single cohort,[5] to obtain faster and greater population-level impact. However, the optimal number of age cohorts to vaccinate remains an open question and may be country specific. Increasing the number of cohorts will increase the population-level impact, but with diminishing returns on investment for each additional older cohort included. Number needed to vaccinate (NNV) and cost-effectiveness analyses in high income countries suggest that vaccinating multiple cohorts up to 18 years old is highly efficient and cost-effective.[76, 77] However, efficiency (effectiveness per vaccine dose) decreases after 18 years of age, as a high proportion of individuals will already have been infected by HPV vaccine types at the time of vaccination, and 3 doses are required (vs the recent recommendations of 2 doses for persons vaccinated before age 15 years [78, 79]). Hence, decisions/recommendations about the number of age cohorts to be vaccinated is a trade-off between goals of maximising population-level impact (e.g., to reach HPV or cervical cancer elimination goals within a specific time frame) or optimising vaccination efficiency and return on investment (e.g., NNV and incremental cost-effectiveness ratios). In addition, several key factors such as competing priorities, and vaccine affordability and availability can also influence decisions about multi-cohort vaccination. Finally, our results also have implications for the interpretation of surveillance studies. The number of cohorts vaccinated should be considered in addition to the vaccination coverage when comparing surveillance data between countries, as the main driver of HPV vaccination impact is the total percent of the population vaccinated.

Importantly, we also present the first pooled estimates of the population-level impact of HPV vaccination on CIN2+, which is the most proximal outcome to cervical cancer and is recognised as a valid proxy for vaccine efficacy against cervical cancer by regulatory agencies worldwide.[80-83] The results are the strongest yet that HPV vaccination is working to prevent cervical cancer in real-world settings, as both the cause (high-risk HPV infection) and proximal disease endpoint are significantly declining. These results can also inform potential changes to cervical screening programs. Substantial declines in high-risk HPV types and CIN2+ may allow for older age of start of screening and longer screening intervals. However, when examining changes in screening in the era of vaccination, careful attention will have to be focussed on unvaccinated cohorts of women. The decreasing HPV prevalence observed in several settings also support arguments in favour of switching from cytology alone to primary HPV testing followed by cytology triage to benefit from the higher sensitivity of HPV testing to detect pre-cancer lesions and higher specificity of cytology, without substantially increasing false positive results.[84]. However, CIN2+ surveillance data among screened girls/women should be interpreted with caution. First, the greatest and fastest reductions in CIN2+ are among an age group (15-19 years old) not always recommended for screening, and in which the proportion of those screened has been declining both before and since the introduction of HPV vaccination due to efforts in the countries to improve adherence to guidelines (Appendix Table S4). Therefore, although we restricted our analysis to screened girls/women, changes towards a lower risk profile among those that are still screened in this age group could partly contribute to decreases in CIN2+. However, to our knowledge, there is currently no data supporting changes in the risk profiles of screened women in the younger age groups since the introduction of HPV vaccination. Second, several studies have shown that participation in cervical screening and vaccination uptake are associated with the same socio-demographic factors (e.g., ethnicity, socioeconomic level, education),[85-90] and therefore vaccination coverage among screened girls/women may be different [91], and potentially higher, than country/regional level vaccination coverage in some settings. Thirdly, major recent changes in screening recommendations, clinical management recommendations, and/or participation have been documented in several countries in the years surrounding the introduction of HPV vaccination. For example, the use of HPV testing (mainly as triage of low-grade lesions, which led to increased colposcopy referrals) and/or longer routine screening intervals, which are likely to increase the CIN2+ detection rate,[65] have been reported in the USA, Denmark, and Norway (Appendix, Table S4). As done in the Scottish study,[75] future surveillance studies should include, if possible, the vaccination coverage of screened girls/women to more accurately quantify the impact of HPV vaccination on CIN2+.

By examining three main HPV-related endpoints concurrently, we can better understand trends in post-vaccination surveillance data, and draw stronger conclusions about the population-level effectiveness and herd effects of HPV vaccination. Of particular interest are the results suggesting increases in HPV-related endpoints among population subgroups not targeted by vaccination: 1) high-risk non-vaccine HPV types, 2) anogenital wart diagnoses among men aged 25-39 years (particularly in countries with single-cohort vaccination and/or low vaccination coverage of girls), and 3) CIN2+ among screened women aged 25-39 years. Data from several countries suggest that increases in anogenital warts diagnoses [34, 38, 43, 47, 50, 54] and CIN2+ [63, 92] began before the introduction of HPV vaccination. Together, these results suggest that the population-level impact of HPV vaccination could currently be measured within an underlying context of increasing HPV-related endpoints in some countries. Although the reasons for these trends are likely multi-factorial and endpoint-specific, several hypotheses can be made. First, increases in the three HPV-related endpoints could reflect increases in sexual activity. Several data sources indicate that, over the past 10 to 20 years, the number of sexual partners has increased and/or the age at sexual initiation has decreased in several high-income countries.[24, 93-101] Second, endpoint-specific hypotheses could also explain observed increases. Increases in high-risk non vaccine HPV types could partly be explained by HPV-16/18 unmasking (i.e., apparent increased detection of non-vaccine HPV types in a post-vaccination population with fewer HPV-16/18 infections, which could have masked detection of other HPV types prior to vaccination) [102] or less likely by type-replacement (i.e., increased prevalence of non-vaccine HPV types occupying the ecological niche created by preventing HPV-16/18 infections).[103] Increases in anogenital wart diagnoses could be partly explained by increased knowledge, awareness, and health seeking behaviour of the general population about anogenital warts and/or better diagnosis/reporting by health professionals. Finally, as previously discussed, increases in CIN2+ could be attributable to changes in screening recommendations, tests, and/or participation documented in several countries. More research is needed to better understand the factors influencing the increases in trends in non HPV vaccine types and HPV-related diseases in older females and males. If they are due to changes in sexual behaviour or increased health seeking behaviour/diagnoses, population-level effectiveness may be underestimated when comparing the annual frequency of HPV-endpoints between pre- and post-vaccination periods.

In addition to the epidemiological and public health insights discussed above, our study has important additional strengths. All corresponding authors were contacted in order to have standardized age groups and HPV-endpoints permitting pooling of results. Furthermore, the large pooled sample size of person-time at risk and 8-year follow-up since the introduction of HPV vaccination gave sufficient statistical power to demonstrate declines in all three HPV-related endpoints among girls/women targeted for vaccination in both high and low coverage settings, and cross-protection and herd effects in countries with high vaccination coverage and multi-cohort vaccination. Our results should however be interpreted considering the following three limitations. First, because this meta-analysis is based on ecological studies, causality between HPV vaccination and the observed changes in HPV-related endpoints cannot be concluded definitively. However, the: 1) larger and faster decreases in HPV-related endpoints among cohorts targeted for vaccination and in countries with multi-cohort vaccination and high routine vaccination coverage, 2) larger decreases in HPV-related endpoints with longer follow-up since the introduction of HPV vaccination (as the number of cohorts vaccinated increases), and 3) consistency between the results from the different studies and between the three HPV-related endpoints, strongly suggest that the decreases can be largely attributed to HPV vaccination. Second, the number of post-vaccination studies is not yet sufficient to perform multivariate meta-regression in order to simultaneously consider the influence of different program characteristics or study designs. In addition, the number of studies within categories is sometimes limited. For example, greater decreases in CIN2+ were observed in the only study using the bivalent vaccine (from Scotland) compared to the studies using the quadrivalent vaccine. However, it was not possible to tease out the effect of the vaccine type given that Scotland has very high HPV vaccination coverage, had catch-up vaccination, and had no major change in screening recommendation/behaviour since the introduction of HPV vaccination. Third, our results should be extrapolated to low- and middle-income countries with caution, as all studies identified in the systemic review are from high-income countries. The population-level impact of HPV vaccination, including the impact of multi-cohort vaccination strategies, may be different in countries that have substantially different sexual behaviour (e.g., age at start of sexual activity, age-difference between partners, concurrency in partnerships, percent of men that are clients of female sex workers), HPV epidemiology, and/or prevalence of HPV infection/disease cofactors (e.g., HIV).

In conclusion, the results of this meta-analysis, including data from >60 million individuals from 14 high-income countries, show compelling evidence of the substantial impact of three-dose girls-only HPV vaccination programs with the quadrivalent or bivalent vaccines on infections by HPV-16/18 and 31/33/45 as a group, anogenital wart diagnoses and CIN2+ among women, and herd effects among boys and older women. In addition, programs with multi-cohort vaccination and high vaccination coverage lead to a greater and faster direct impact and herd effects. These results should be considered within the rapidly changing landscape of HPV vaccination, with several countries recently switching to 2-dose schedules, gender-neutral vaccination, and/or the nonavalent vaccine, and research examining 1-dose HPV vaccination, 2-doses in older populations, and cervical cancer elimination strategies. Although challenging, it will be crucial to continue monitoring

the population-level impact of HPV vaccination to examine the full impact of these changes in vaccination strategies and to quantify the impact of vaccination in low- and middle-income countries.

CONTRIBUTIONS

MD, MB, and MCB conceived the study. MD, EB and NP did the literature search and performed the analysis. MB and MCB participated in the analysis. MD and MB co-drafted the first version of the article. All other authors (HA, VB, PB, JMLB, DC, MC, EPFC, SC, TD, SLD, CD, BD, CKF, EWF, JWG, SG, NG, BTH, CH, EH, TMI, AMJ, JAK, KK, SKK, EVK, BL, DAM, LM, DM, CM, LN, MN, GO, JO, KGP,MJPH, MSm, MSt, ASS, PSo, PSp, CT,CMW, PJW, BNY) 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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Table 1. Characteristics of the studies included in the systematic review and meta-analysis

Author (Country)	Vaccine	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									
Chow 2015a Chow 2017 (Australia) [12, 13]	Quadrivalent	Clinic-based: STI clinics	Females and males 15-25 yrs attending the Melbourne Sexual Health Centre diagnosed with chlamydia	Females and males 15-24 yrs[Ω]	Prevaccine:2005-2007 Postvaccine:2008-2014	Females N prevaccine:128 N postvaccine:260 Males N prevaccine:115 N postvaccine:411	HPV+ PapType HR HPV genotyping kit (Genera Biosystem) Females: cervical & vaginal swabs Males: urine and urethal swabs	Crude HPV prevalence over time	RR of HPV prevalence (crude)
Cummings 2012 (U.S.)[14]	Quadrivalent	Clinic-based: Primary care clinics	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)
Dillner 2018 [11]	Quadrivalent	Clinic-based: Nationwide cervical screening program of Denmark, Sweden, Norway	Females 18-50 attending routine cervical cancer	Females 18-29 yrs from Denmark and Sweden[**]	Prevaccine: 2006-2008 Postvaccine: 2012-2013	Denmark/ Sweden N prevaccine: 1,188/1,112 N postvaccine: 1,163/1,164	HPV+ Luminex system (Bio-Rad, 35 types)	Difference of HPV prevalence (crude)	RR of HPV prevalence (crude)
Dunne 2015 (USA)[15]	Quadrivalent	Clinic-based: Kaiser Permanente NorthWest	Females 20-29 yrs attending routine cervical cancer screening (cytology)	Females 20-29 yrs	Prevaccine:2007 Postvaccine:2012-2013	N prevaccine:4,138 N postvaccine:4,171	HPV+ Roche Linear Array & HPV-52 quantitative PCR	RR of HPV prevalence (crude)	RR of HPV prevalence (crude)
Grün 2016 (Sweden)[16]	Quadrivalent	Clinic-based: Youth clinic in Stockholm	Females and males (oral infections for males) 15-23 yrs attending a Stockholm youth clinic	Females 15-23 yrs[Ω]	Prevaccine: 2008-2011 Postvaccine: 2013-2015	N prevaccine: 544 [γ] N postvaccine: 332	HPV+ Luminex-based genotyping assay (27 types)	Crude HPV prevalence over time	RR of HPV prevalence (crude)
Kavanagh 2014/ Cameron 2016/Kavanagh 2017(Scotland)[17-19]	Bivalent	Clinic-based: Scottish Cervical screening Call & Recall System	Females 20-21 yrs participating in cervical cancer screening in Scotland	Females 20-21 yrs	Prevaccine:2009-2010 Postvaccine1:2011-2012 Postvaccine2:2013-2015	N prevaccine:2,705 N postvaccine1:1,994 N postvaccine2:3,702	HPV+ Multimetrix HPV assay (18 types)	Crude HPV prevalence over time	RR of HPV prevalence (crude)
Kahn 2012/ Kahn 2016 (USA)[20, 21]	Quadrivalent	Clinic-based: Hospital and health department	Females 13-26 yrs attending 1 hospital-based teen clinic and 2 health department sites in Cincinnati	Females 13-26 yrs, Had had sexual contact	Prevaccine:2006-2007 Postvaccine1:2009-2010 Postvaccine2:2013-2014	N prevaccine:355 N postvaccine1:408 N postvaccine2:400	HPV+ Roche Linear Array (Roche, 37 types)	HPV prevalence difference (adjusted)	RR of HPV prevalence (adjusted)
Machalek 2018 [Ŧ] (Australia) [22]	Quadrivalent	Clinic-based: Family planning clinics	Females 18-35 yrs attending family planning clinics in Victoria and New South Wales	Females 25-29 yrs	Prevaccine:2005-2007 Postvaccine:2015	N prevaccine:102 N postvaccine:114	2005-2007: HPV+ Roche Linear Array (13 types), 2015: Cobas HPV test (Roche Diagnosis) and Roche Linear Array genotyping test (37 types)	RR of HPV prevalence (adjusted)	RR of HPV prevalence (adjusted)
Markowitz 2013/ Markowitz 2016 / Oliver 2017 (USA)[23-25]	Quadrivalent	Population-based: NHANES participants	Nationally representative sample of USA females aged 14-59 yrs	Females 14-29 yrs	Prevaccine:2003-2006 Postvaccine1:2007-2010 Postvaccine2:2011-2014	N prevaccine:2,198 N postvaccine1:1,599 N postvaccine2:1,634	HPV+ Roche Linear Array (Roche, 37 types)	RR of HPV prevalence (adjusted)	RR of HPV prevalence (adjusted)

Author (Country)	Vaccine	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
Mesher 2013/ Mesher 2016/ Mesher 2018 (England)[26-28]	Bivalent	Clinic-based: Community sexual health clinics, GP	Females 16-24 yrs undergoing chlamydia screening in community sexual health / GP /Youth clinics in 7 regions around England	Females 16-24 yrs	Prevaccine:2008 Postvaccine1:2010-2012 Postvaccine2:2013-2016	N prevaccine:2,354 N postvaccine1:7,924 N postvaccine2:7,535	2008: Hybrid Capture 2 and Roche Linear Array ≥2010: HPV+ In-house multiplex PCR and Luminex-based genotyping (18 types)[ł]	OR of HPV prevalence (adjusted)	RR of HPV prevalence (adjusted)
Purriños-Hermida 2018 (Spain) [29]	Bivalent	Clinic-based: Primary care center, gynecology department, family counseling center	Females 18-26 yrs attending health areas of the Galician Public Health Services	Females 18-26 yrs	Prevaccine:2008-2010 Postvaccine:2014-2017	N prevaccine:523 N postvaccine:745	HPV+ Cobas 4800 HPV test with Linear Array HPV genotyping (Roche Diagnostic) (12 types)	RR of HPV prevalence (crude and adjusted)	RR of HPV prevalence (adjusted)
Söderlund-Strand 2014 (Sweden)[30]	Quadrivalent	Clinic-based: Chlamydia screening	Females all ages attending to Chlamydia screening	Females 15-29 yrs	Prevaccine:2008 Postvaccine:2012-2013	N prevaccine:15,767 N postvaccine:5216	HPV + In-house multiplex PCR with genotyping by MALDI-TOF mass spectrometry (16 types)	Crude HPV prevalence over time	RR of HPV prevalence (crude)
Sonnenberg 2013 (England, Scotland, Wales) [31]	Bivalent	Population-based: Natsal participants	Nationally representative sample of males and females aged 16-44 yrs Natsal-2, 16-74 yrs Natsal-3 in Britain	Females and males 18-29 yrs	Prevaccine:1999-2001 Postvaccine:2010-2012	Females N prevaccine:684 N postvaccine:1,426 Males N prevaccine:462 N postvaccine:1061	HPV+ In-house Luminex-based genotyping assay (18 types)[ł] in urine samples	OR of HPV prevalence (age-adjusted)	RR of HPV prevalence (age-adjusted)
Tabrizi 2012/2014 (Australia)[32, 33]	Quadrivalent	Clinic-based: Family planning clinics	Females 18-24 yrs attending 1 of 6 family planning clinics in Sydney, Melbourne, Perth	Females 18-24 yrs	Prevaccine:2005-2007 Postvaccine1:2010-2011 Postvaccine2:2010-2012	N prevaccine:202 N postvaccine1:404 N postvaccine2:1,058	HPV+ Roche Linear Array (13 types),	RR of HPV prevalence (adjusted)	RR of HPV prevalence (adjusted)
Anogenital warts									
Ali 2013/ Chow 2015b, Ali 2017, Callander 2016 (Australia) [34-37]	Quadrivalent	Clinic-based: STI clinics	New clients of 40 sexual health centers across Australia aged ≥ 12 yrs (Australian born)	Australian born females and heterosexual males 15-39 yrs	2004-2015 Prevaccine: 2005-2007 Postvaccine:2008-2015	P-yr prevaccine: 51,010 P-yr postvaccine: 134,614	Clinical diagnosis	Annual proportion of new clients with AGW	RR of AGW proportion (crude)
Baandrup 2013/ Bollerup 2016 (Denmark)[38, 39]	Quadrivalent	Population-based: Statistics Denmark, National Patient Registry	Entire population of Denmark ≥ 12 yrs	Females and males 15-39 yrs	2006-2013 Prevaccine: 2007-2009 Postvaccine:2010-2013	P-yr prevaccine: 5,144,888 P-yr postvaccine: 6,945,980	ICD-10 code A63.0 OR prescription of Podophyllotoxin	Annual incidence rate of diagnosed AGW in the population	RR of AGW incidence (crude)
Bauer 2012 (USA)[40]	Quadrivalent	Health provider /insurance-based: Clinical encounters claims data of a health program	Clients of the California Family Planning access care & treatment (PACT) program aged ≥ 10 yrs (87% 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)
Cocchio 2017 (Italy)[41]	Quadrivalent	Population-based: Hospital records of all Veneto residents (public & private)	Entire population from Veneto, Italy	Females and males 15-39 yrs	2004-2015 Prevaccine:2006-2008 Postvaccine:2009-2015	P-yr prevaccine: 4,567,864 P-yr postvaccine: 9,913,192	ICD-9 code 078.11 and 1 ICD-9 surgical code (70-71, 58, 64, 58.3, 49)	Annual rate of hospitalization for AGW in the population	RR of AGW hospitalizatio (crude)

Author (Country)	Vaccine	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
Dominiak-Felden 2015 (Belgium)[42]	Quadrivalent	Health provider /insurance-based: Medical claims, National Union of Independent Sick Funds (MLOZ)	Enrollees in MLOZ, one of the 3 biggest sick fund in Belgium (18% of the Belgium population; 2 million individuals)	Females and males 15-39 yrs	2006-2013 Prevaccine:2006-2007 Postvaccine:2008-2013	P-yr prevaccine: 960,777 P-yr postvaccine: 3,858,172	First prescription of Imiquimod with a level of reimbursement specific for AGW onset	RR of AGW incidence (crude)	RR of AGW incidence (crude)
Flagg 2013/Flagg 2018 (USA)[43, 44]	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	2003-2014 Prevaccine: 2004-2006 Postvaccine:2007-2014	P-yr prevaccine: 11,864,207 P-yr postvaccine: 85,043,491	1) ICD-9 codes 078.11 OR 2) ICD-9 code 078.1, 078.10, or 078.19 and therapeutic procedure diagnosis of benig AG neoplasm OR 3) ≥1 prescription for AGW treatment and therapeutic procedure r diagnosis of benign AG neoplasm	Annual proportion of insured individuals with diagnosed AGW	RR of AGW proportion (crude)
Guerra 2016 (Canada-Ontario)[45]	Quadrivalent	Population-based: Health care encounter database (covers all Ontario residents)	All Ontario residents aged ≥ 15 yrs with a valid health card number	Females and males 15-26 yrs	2004-2013 Prevaccine:2005-2007 Postvaccine:2008-2013	P-yr prevaccine: 6,242,786 P-yr postvaccine: 13,069,534	First physician office visit (12-month wash-out period) with one of 10 possible combination codes: 099 + Z117, 079 + Z117, 629 + Z117, Z549, Z758, Females: Z733, Z736, or Z769; males Z767, Z701	Annual incidence rate of diagnosed AGW in the population	RR of AGW incidence (crude)
Harrison 2014 Ψ (Australia)[46]	Quadrivalent	Clinic-based (BEACH program: randomly selected GP-encounters in Australia)	Patients of 1,000 randomly selected GP across Australia (each year)	Females and males 15-39 yrs	2002-2015 Prevaccine:2005-2007 Postvaccine:2008-2015	P-yr prevaccine: 77,258 P-yr postvaccine: 190,268	ICPC 2 code Y76 (males), X91 (females)	Annual proportion of patients with AGW management	RR of AGW management proportion (crude)
Howell-Jones 2013/ Canvin 2017 (England) [47, 48]	Bivalent Quadrivalent for some girls 15-16 yrs in 2014-2015 α	Population-based: Office for National Statistics, Genitourinary medicine (GUM) clinics	Entire population of England aged 15-24 yrs;	Females and males 15-24 yrs	2002-2015 Prevaccine: 2006-2008 Postvaccine:2009-2015	P-yr prevaccine: 20,370,695 P-yr postvaccine: 48,041,371	Clinical diagnosis	Annual incidence rate of diagnosed AGW in the population	RR of AGW incidence (crude)
Kliewer 2012/ Thompson 2016 (Canada-Manitoba)[49, 50]	Quadrivalent	Population-based: Medical claims and hospital discharge database of all Manitoba residents	Entire population of Manitoba	Females and males 15-39 yrs	2006-2011 Prevaccine: 2006-2008 Postvaccine:2009-2011	P-yr prevaccine: 1,194,786 P-yr postvaccine: 1,245,073	Treatments (1 of 14 tariff codes) OR (hospitalization for AGW + 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)

Author (Country)	Vaccine	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
Leval 2012/ Herweijer 2018 (Sweden)[51, 52]	Quadrivalent	Population-based: Statistics Sweden, National Patient Register, Prescribed Drug Register	Entire population of Sweden aged ≥ 10 yrs	Females and males 15-39 yrs	2006-2012 Prevaccine: 2006 Postvaccine:2007-2012	P-yr prevaccine: 2,930,263 P-yr postvaccine: 18,089,134	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)
Liu 2014 (Australia)[53]	Quadrivalent	Population-based: Australia-wide survey	All Australian women aged 18-39 yrs	Females 18-39 yrs	2001 and 2011 Prevaccine:2001 Postvaccine:2011	P-yr prevaccine: 4,874 P-yr postvaccine: 2,394	Self-reported AGW diagnosis (ever had AGW)	Proportion of women reporting AGW among all respondents	RR of AGW proportion (crude)
Mikolajczyk 2013/ Thönes 2017 (Germany)[54, 55]	Quadrivalent	Health provider /insurance-based: German Pharmaco-epidemiological Research Database	Enrollees in 1 large health insurance company across Germany aged 10-79 yrs	Females and males 15-39 yrs	2005-2010 Prevaccine: 2005-2007 Postvaccine:2008-2010	P-yr prevaccine: 4,974,000 P-yr postvaccine: 5,372,000	ICD-10 code A63.0	Annual incidence rate of diagnosed AGW among insured individuals	RR of AGW incidence (crude)
Oliphant 2011/2017 (New Zealand)[56, 57]	Quadrivalent	Clinic-based: STI clinic	New clients of 4 sexual health service in Auckland aged ≥ 10 yrs	Females and males 15-39 yrs	2007-2013 Prevaccine:2007-2008 Postvaccine:2009-2013	P-yr prevaccine: 9,559 P-yr postvaccine: 26,258	Clinical diagnosis	Annual proportion of new clients diagnosed with AGW	RR of AGW proportion (crude)
Smith 2015/2016 (Australia)[58, 59]	Quadrivalent	Population-based: National Hospital Morbidity Database, Australian Bureau of Statistics	Entire population of Australia aged 12-69 yrs	Females and males 12-69 yrs¥	2005-2011 Prevaccine:2005-2007 Postvaccine:2008-2011	P-yr prevaccine: 45,887,699 P-yr postvaccine: 65,192,250	Hospitalization including ICD-10 code A63.0 as main or contributory diagnosis	Annual rate of hospitalization with AGW diagnosis in the population	RR of AGW hospitalizatio (crude)
Sonnenberg 2017 [60]	Bivalent	Population-based: Natsal participants	Nationally representative sample of males and females aged 16-44 yrs Natsal-2, 16-74 yrs Natsal-3 in Britain	Females and males 16-39 yrs	Prevaccine:1999-2001 Postvaccine:2010-2012	N prevaccine:8,204 N postvaccine:5,849	Ever having a diagnosis of AGW (self-reported)	Proportion of the population who reported ever having a diagnosis of AGW	RR of AGW proportion (crude)
Steben 2018 [61]	Quadrivalent	Health provider /insurance-based : Quebec physician claim and public drug insurance databases	Individuals covered by the Quebec public drug insurance	Females and males 15- ≥30 yrs	2004-2012 Prevaccine:2004-2007 Postvaccine:2009-2012	P-yr prevaccine: 13,159,362 P-yr postvaccine: 13,241,313	ICD-9 code 078.1OR medical procedure specific to condyloma (05314, 06169) OR dispensation of podofilox, imiquimod, or fluorouracil	Annual incidence rate of diagnosed AGW among insured individuals	RR of AGW incidence (crude)
Woestenberg 2017 (Netherlands)[62]	Bivalent	Clinic-based PASSYON study in STI clinics	Patients of STI clinics aged 16-24 yrs old across the Netherlands	Females and males 16-24 yrs	2009, 2011, 2013 Prevaccine: 2009 Postvaccine: 2011, 2013	P-yr prevaccine: 1,662 P-yr postvaccine: 3,859	Clinical diagnosis	Proportion of STI patients diagnosed with AGW	RR of AGW proportion (adjusted)

Author (Country)	Vaccine	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
Cervical intraepithelial neoplasia grade 2+									
Baldur-Felskov 2014/2015 (Denmark) [63, 64]	Quadrivalent	Population-based: Nationwide Danish Pathology Data Bank	Females aged ≥ 12 yrs living in Denmark and screened for cervical cancer	Screened females 15-39 yrs	2007-2013 Prevaccine:2007-2009 Postvaccine:2010-2013	P-yr prevaccine: 1,810,881 P-yr postvaccine: 1,840,066	Histopathologically confirmed CIN2+	Annual incidence of CIN2+ among screened females	RR of CIN2- incidence (crude)
Benard 2017 (USA)[65]	Quadrivalent	Population-based: New Mexico HPV pap registry	Females aged 15-29 yrs living in New Mexico and screened for cervical cancer	Screened females 15-29 yrs	2007-2014 Prevaccine:2007 Postvaccine:2008-2014	P-yr prevaccine: 74,115 P-yr postvaccine: 386,146	Histopathologically confirmed CIN2+	Annual incidence of CIN2+ among screened females	RR of CIN2- incidence (crude)
Brotherton 2011/ AIHW 2016/2018 (Australia) §[66-68]	Quadrivalent	Population-based: Cervical cancer screening program registry	Females aged <69 yrs living in Australia and screened for cervical cancer	Screened females 15-39 yrs	2005-2016 Prevaccine:2005-2007 Postvaccine:2008-2016	P-yr prevaccine: 3,213,016 P-yr postvaccine: 9,200,381	Histopathologically confirmed CIN2+	Annual incidence of CIN2+ among screened females	RR of CIN2- incidence (crude)
Flagg 2016 (USA)[69]	Quadrivalent	Health provider /insurance-based: Truven Health Analytics Market Scan Commercial Claims and Encounters Database	Females aged 15-39 yrs, enrolled in 100-170 employers and health private insurance plans across USA and screened for cervical cancer	Screened females 15-39 yrs	2007-2014 Prevaccine:2007 Postvaccine:2008-2014	P-yr prevaccine: 1,542,598 P-yr postvaccine: 15,643,924	Histopathologically confirmed CIN2+ (ICD-9 code 622.12, 233.1)	Annual prevalence of CIN2+ among screened females	RR of CIN2- proportion (crude)
Gargano 2018 (USA- California, Connecticut, New York, Oregon, Tennessee) [70]	Quadrivalent	Population-based: HPV-IMPACT surveillance system. Number of screened women estimated from different sources	Females aged 18-39 yrs with a high-grade lesion in HPV-IMPACT (a laboratory-based surveillance system including areas from California, Connecticut, New York, Oregon, and Tennessee)	Screened females 18-39 yrs£	2008-2015 Prevaccine:2008 Postvaccine:2009-2015	P-yr prevaccine: 268,186 P-yr postvaccine: 1,470,273	Histopathologically confirmed CIN2+	Annual incidence of CIN2+ among screened females	RR of CIN2- incidence (crude)
Niccolai 2013/2017 (USA- Connecticut)€ [71, 72]	Quadrivalent	Population-based: Connecticut surveillance system (all 34 pathology laboratories). Number of screened women estimated from BRFSS	Females aged 21-39 yrs living in Connecticut with a high-grade lesion in the surveillance system	Screened females 20-39 yrs£	2008-2014 Prevaccine:2008 Postvaccine:2009-2014	P-yr prevaccine: 211,134 P-yr postvaccine: 643,071	Histopathologically confirmed CIN2+	Annual incidence of CIN2+ among screened females	RR of CIN2- incidence (crude)
Nygård 2017 (via Liaw 2014) (Norway) [73 Φ]	Quadrivalent	Population-based: Norwegian cervical cancer screening program registry	All females living in Norway and screened for cervical cancer	Screened females 15-39 yrs	2007-2014 Prevaccine:2007-2009 Postvaccine:2010-2014	P-yr prevaccine: 1,262,014 P-yr postvaccine: 1,948,739	Histopathologically confirmed CIN2+	Annual incidence of CIN2+ among screened females	RR of CIN2- incidence (crude)

Author (Country)	Vaccine	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
Ogilvie 2015 (Canada-British Columbia) [74]	Quadrivalent	Population-based: BC Cervical cancer screening program registry	Females aged 15-22 yrs living in British-Columbia (Canada) and screened for cervical cancer	Screened females 15-17 yrs ¶	2006-2012 Prevaccine:2006-2008 Postvaccine:2009-2012	P-yr prevaccine: 27,523 P-yr postvaccine: 27,054	Histopathologically confirmed CIN2+	Annual incidence of CIN2+ among screened females	RR of CIN2+ incidence (crude)
Pollock 2014 (Scotland) [75]	Bivalent	Population-based: Scottish Cervical cancer screening program registry	Females aged 20-21 yrs living in Scotland and screened for cervical cancer	Screened females 20-21 yrs	2008-2014 Prevaccine:2008 Postvaccine:2008-2014	P-yr prevaccine: 20,891 P-yr postvaccine: 111,230	Histopathologically confirmed CIN2+	Annual incidence of CIN2+ among screened females	RR of CIN2+ incidence (crude)

AGW: Anogenital warts; AIHW: Australian Institute of Health and Welfare; BRFSS: Behavioral Risk Factor Surveillance System; NHANES: National Health and Nutrition Examination Survey; NATSAL: National Survey of Sexual Attitudes and Lifestyles; OR: Odds ratio; RR: Relative risk (Post-vaccination prevalence or incidence / Pre-vaccination prevalence or incidence); STI: Sexually transmitted infection: GP: General practitioner

* Data sources are considered as: 1) Population-based when the study population includes the total population of a given country/region or a registry, 2) Health provider/insurance-based when the study population is constituted of a subgroup of the total population enrolled in a specific insurance plan, 3) Clinic-based when the study population is constituted of individuals who received health services (e.g., medical consultation).

† For studies on HPV infection, the pre- and post-vaccination periods were already determined in most 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 purposes of this systematic review as described in the Appendix-Table S8.

‡ 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. The post-vaccination sample size corresponds to the cumulative number of person-years from 1 to 8 years after the introduction of vaccination, depending on data available in each study.

ß For HPV infection, the investigators recalculated the RR (adjusted or crude) 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.

** The study by Dillner et al. included data from Denmark, Sweden and Norway among women aged ≥ 18 years in 2012-2013. However , since the vaccination program of 12 year-old girls began in 2009 in Norway, women included in the study (≥ 18 years old) were too old to be covered by the vaccination program (vaccination coverage < 2%). For this reason, we did not include data from Norway in the meta-analysis.

Ω Since only oral infections were available for males, we did not include data for males from this study in our meta-analysis.

γ The pre-vaccine sample excludes 65 women who were vaccinated (10.6% of the sample). The prevalence of all HPV types, HPV 16/18, and other common HPV types did not statistically differ between the vaccinated and unvaccinated women of the pre-vaccination sample (unpublished data).

Ŧ The study by Machalek includes a subset of women included in the studies by Tabrizi and a group of women aged 25-35 years (not previously included in Tabrizi). To avoid double counting the same women, we only kept the results from the older group of women not previously included in Tabrizi.

Ɨ 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

Ψ Published data were available until 2012, but the author provided data up to 2015.

α In 2014: 14% and 72% of 15 yr old girls received the quadrivalent and bivalent vaccine, respectively. In 2015, 57% and 29% of 15 yr old girls received the quadrivalent and bivalent vaccine, respectively; 14% and 57% of 16 yr old girls received the quadrivalent and bivalent vaccine, respectively.

¥ Permission could not be obtained from the data custodian to release data in the age strata requested for this meta-analysis, therefore results for age groups 15-19, 20-24, 25-29 and 30-39 years in this meta-analysis used published data from the age groups 12-17, 18-26, 27-30 and 31-69 years, respectively, as reported in Smith 2015. [58]

§ Data from Brotherton et al. 2011 [66] are restricted to the Victorian registry data. Supplementary data from the Australian Institute of Health and Welfare 2016 report were provided by Dr. Brotherton. Since the report covers all regions of Australia, it was used as our main data source for the review.

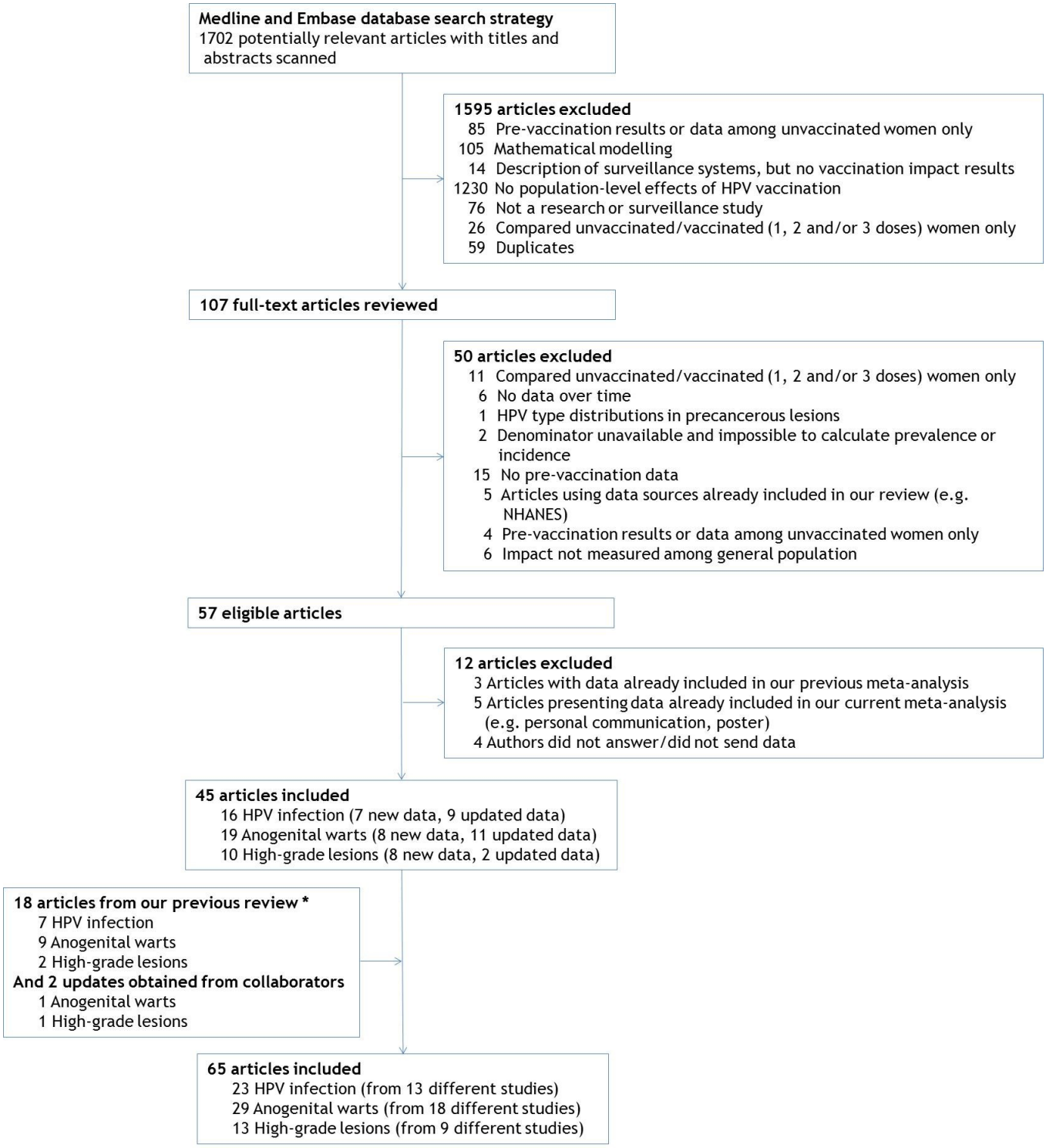
£ The number of screened women is not directly available in these studies. Different data sources (individual or aggregate-level) have been used to estimate the denominator (i.e., the number of screened women of the different catchment areas).

€ One county from Connecticut (New Haven) is included in the HPV-IMPACT surveillance system. To avoid double counting women from this county in estimates from HPV-IMPACT (Gargano 2018) and Connecticut (Niccolai 2017), we decided with the authors, to excluded New Haven from the Connecticut data to keep them in HPV-IMPACT.

Φ CIN2+ data from Norway were identified in the article by Liaw et al [73] and were provided by Mari Nygård (personal communication)

¶ Data directly available in the article to estimate RR of CIN2+ incidence among screened females available only for females ages 15-17 years old.

Figure 1. Flowchart of study selection



* 2 articles on anogenital warts from our previous review were not included in this update: 1) Sando et al:[104] in our previous review, we identified two studies from Denmark analysing the entire Danish population for the same time period,[38, 104] We included the Baandrup et al. study in our main analysis and verified that results were unchanged when using the Sando et al. study. Given that Baandrup et al. updated their data in a new publication, we kept this study with a longer follow-up for the current meta-analysis; 2) Nsouli-Maktabi:[105] we excluded this study conducted among USA armed force members since we revised our eligibility criteria to exclude studies not conducted in the general population.

Figure 2. Changes in the prevalence of HPV infections between the pre-vaccination and post-vaccination periods (1-4, 5-8 years)

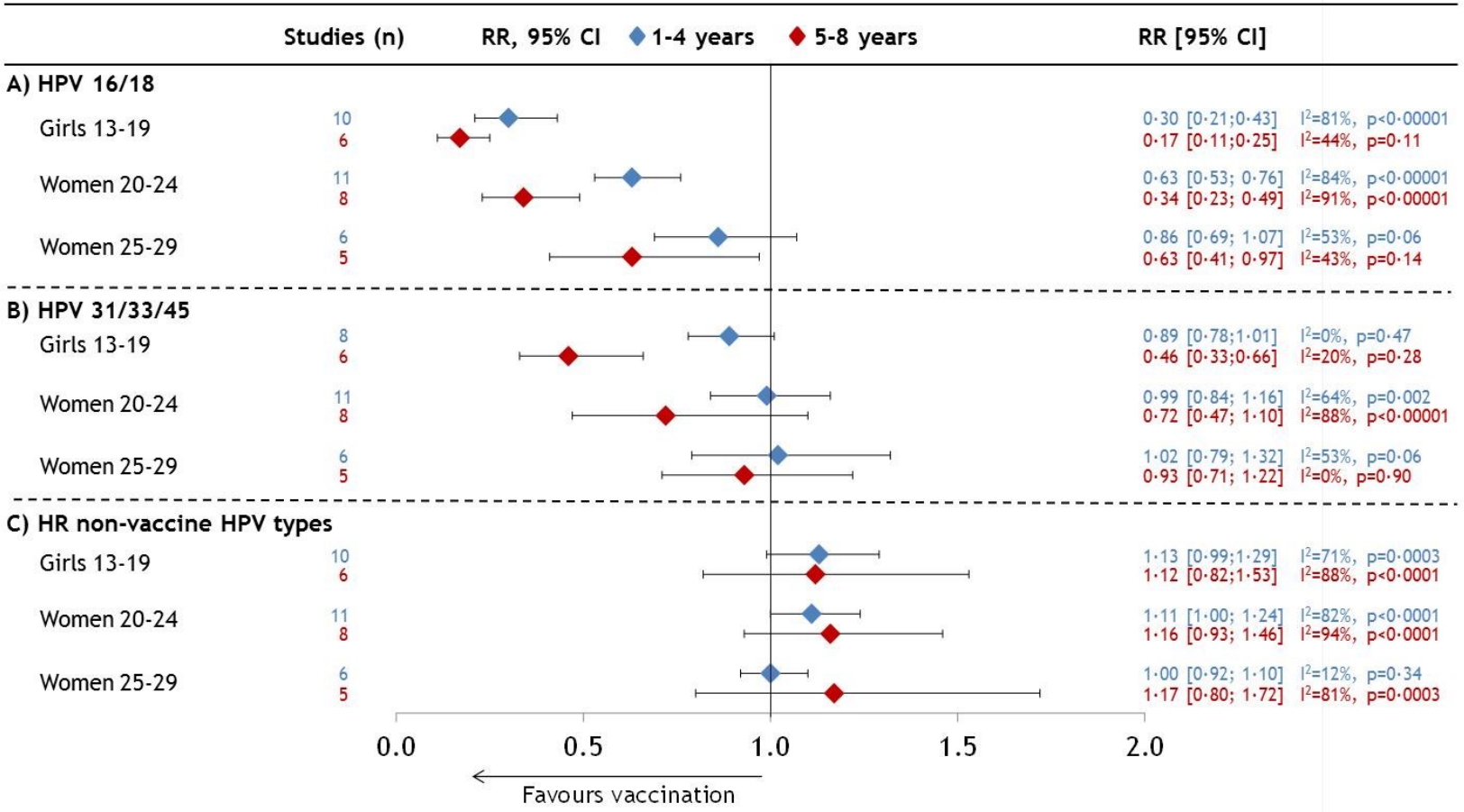


Figure 3. Changes in anogenital wart diagnoses between the pre-vaccination and post-vaccination periods (1-4, 5-8 years) in countries using the quadrivalent vaccine

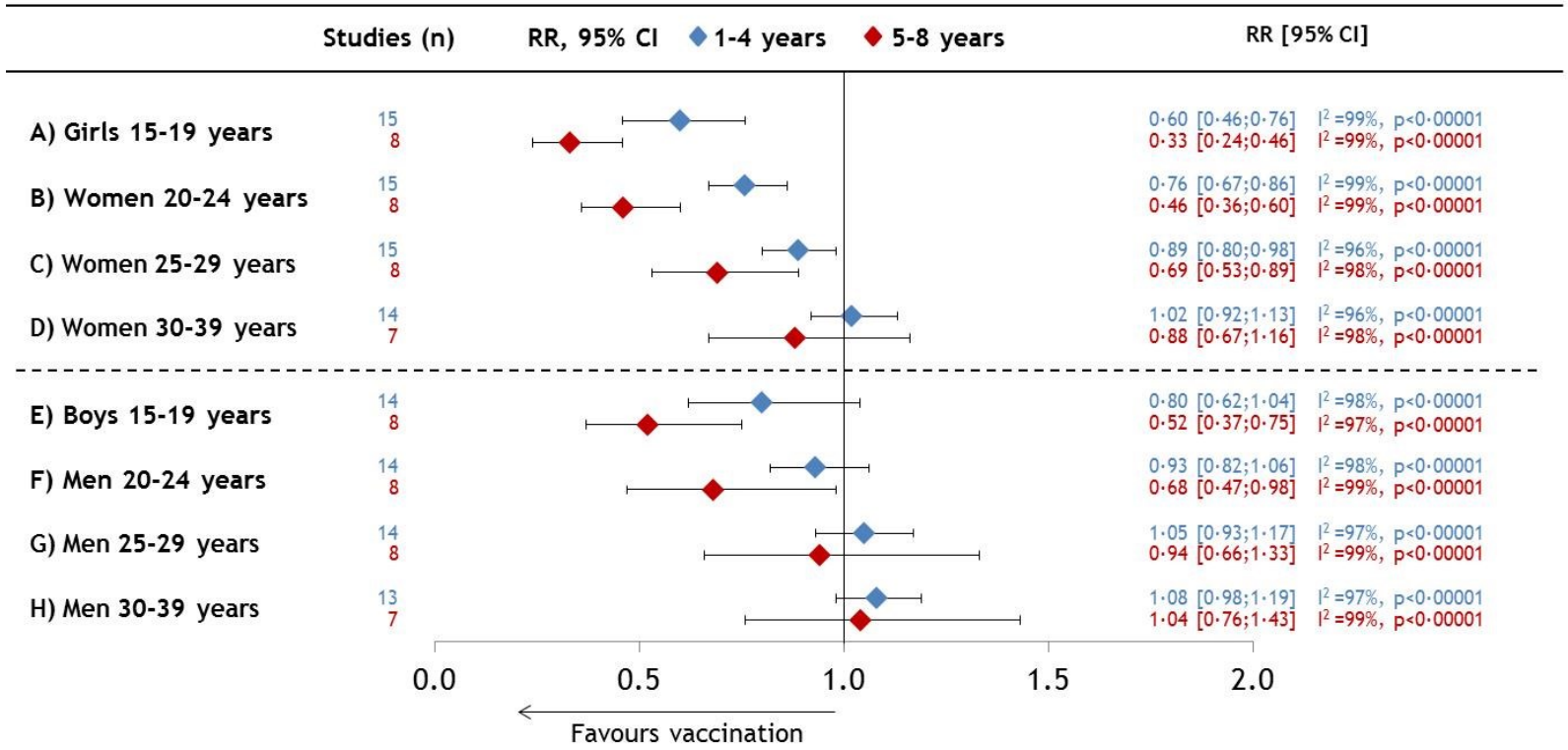
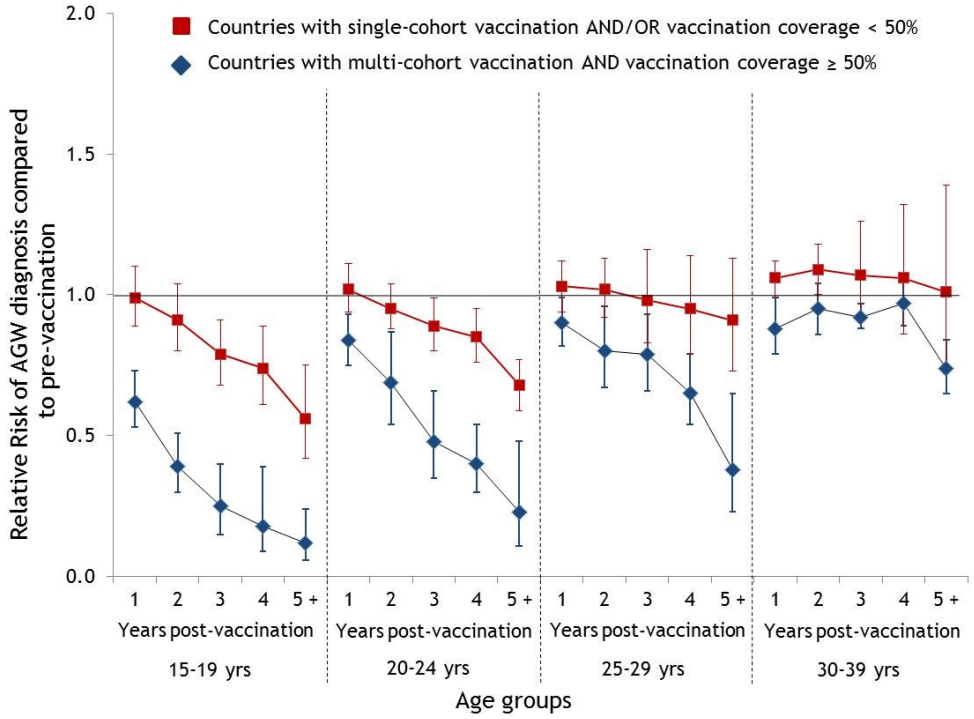
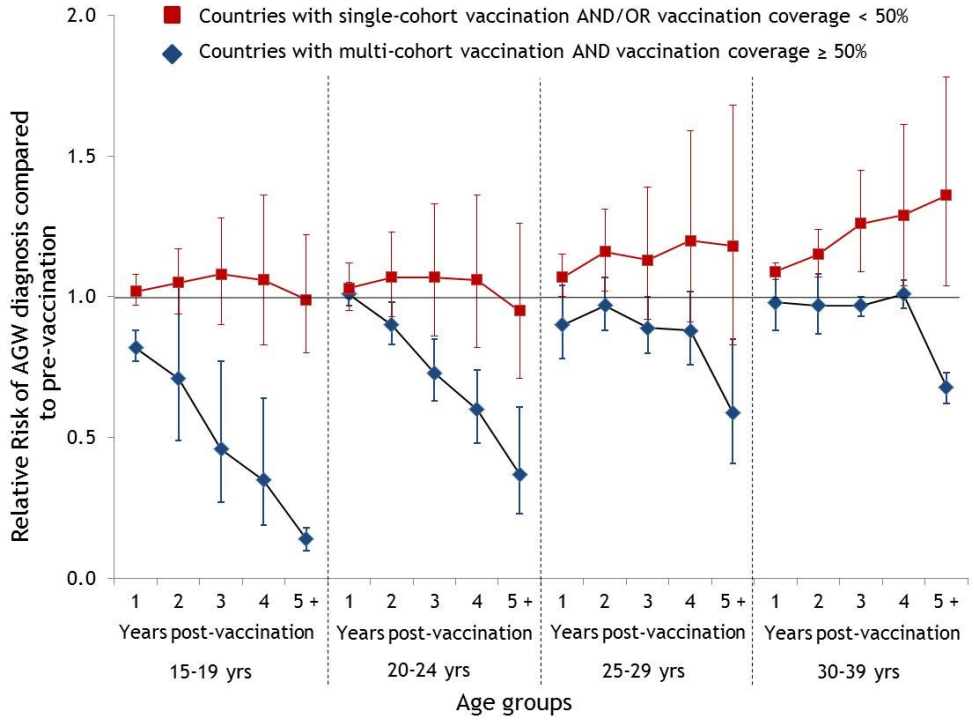


Figure 4. Changes in anogenital wart diagnoses during the 8 years after the introduction of girls-only HPV vaccination in countries using the quadrivalent vaccine, stratified by number of cohorts vaccinated and routine vaccination coverage

A) Girls and women



B) Boys and men



■ Single-cohort and high-coverage: Canada (Kliewer 2012/Thompson 2016, Guerra 2016), Italy (Cocchio 2017); Multi-cohort and low coverage: Germany (Mikolajcyk 2013/Thöne 2017), Belgium (Dominiak-Fleden 2015), Sweden (Leval 2012/Herweijer 2018), USA(Bauer 2012, Flagg 2013/2018)

◆ Australia (Ali 2013/Callander 2016, Smith 2015, Harrison 2014, Liu 2014); Denmark (Baandrup 2013/Bollerup 2016); New Zealand (Oliphant 2011/2017), Canada (Steben 2018)

Figure 5. Changes in CIN2+ among screened girls/women between the pre-vaccination and post-vaccination periods (1-4, 5-9 years)

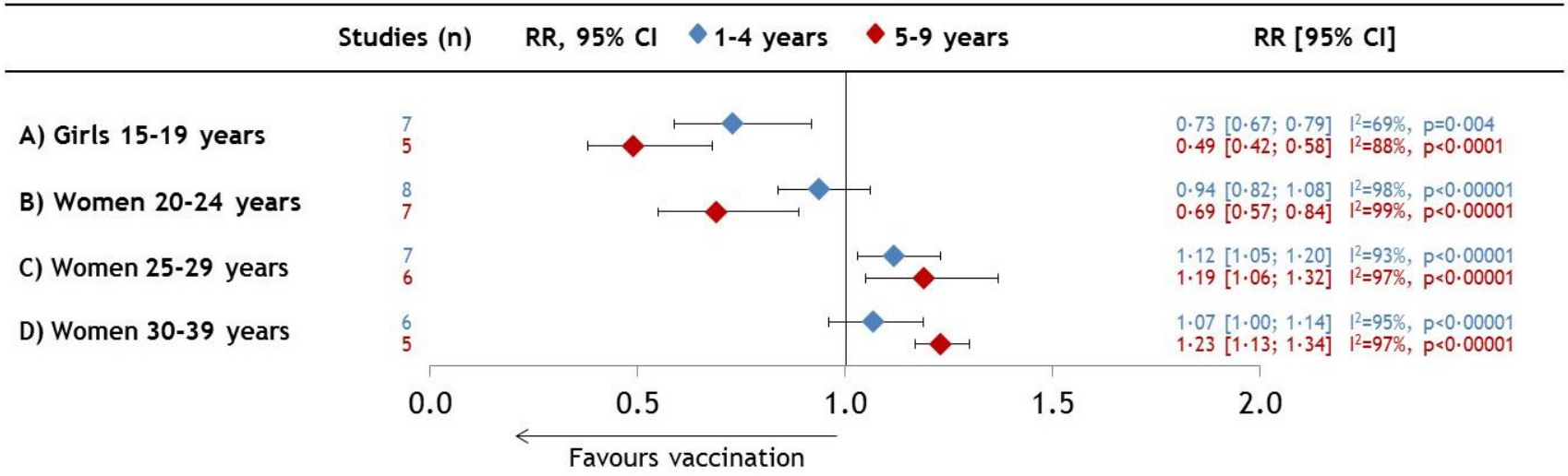
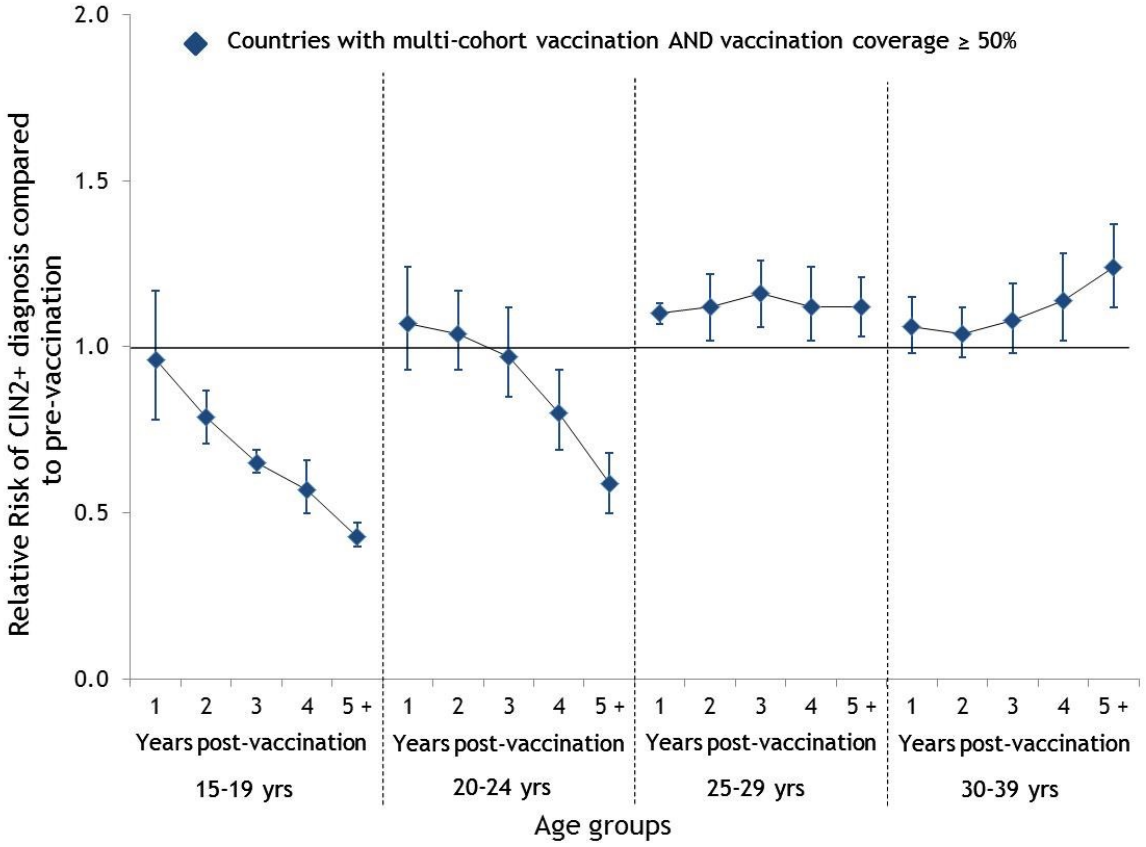


Figure 6. Changes in CIN2+ among screened girls/women during the first 7 years after the introduction of girls-only HPV vaccination in countries vaccinating multiple cohorts of girls and having a coverage ≥50% among the routine cohort.



◆ Australia (Brotherton 2011/AIHW2018), Canada (Ogilvie 2015), Denmark (Baldur-Felskov 2014), Scotland (Pollock 2014), USA* (Flagg 2016, Niccolai 2017, Gargano 2018, Benard 2017)

* For CIN2+ analysis, USA was categorized as a country with multi-cohort vaccination and high routine vaccination coverage because several USA data indicate an association between screening participation and HPV vaccination.[86, 88, 89, 91] The vaccination coverage among screened girls/women is thus likely to be higher than the overall vaccination coverage in the population. We performed a sensitivity analysis excluding the USA from countries with multi-cohort and high vaccination coverage and results were unchanged.