Cochrane Response

Effectiveness and immunogenicity of one dose of HPV vaccine compared with no vaccination, two doses, or three doses

August 2019 – Final report

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Disclaimer: The authors of this report declare no conflicts of interest

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Abbreviations

AIS	Adenocarcinoma in situ
AGW	Anogenital warts
CI	Confidence interval
CIN	Cervical intraepithelial neoplasia
DAG	Directed acyclic graphs
GMT	Geometric mean titre
GW	Genital warts
HAV	Hepatitis A vaccine
HPV	Human papilloma virus
HR	Hazard ratio
HSIL	High-grade squamous intraepithelial lesion
IRD	Incidence rate difference
IRR	Incidence rate ratio
OR	Odds ratio
PAP	Papanicolaou
RCT	Randomised controlled trial
ROBINS-I	Risk of Bias In Non-randomised Studies of Interventions
RR	Risk ratio
SES	Socioeconomic status
SIGN	Scottish Intercollegiate Guidelines Network
SIMD	Scottish Index of Multiple Deprivation
STD	Sexually transmitted disease
STI	Sexually transmitted infection
VE	Vaccine efficacy
WHO IVR	World Health Organisation Initiative for Vaccine Research

Executive summary

This is an update of a systematic review conducted by Cochrane Response for the WHO IVR in December 2018. The data in this report are current to February 29th, 2019, when the most recent literature search was performed.

Details of the review methodology, the included studies, the risk of bias assessments, and the results for clinical and immunological outcomes are provided in the report below and accompanying appendices. Briefly, recommended methods from the Cochrane Handbook were followed to complete the review and the certainty of the evidence was assessed using GRADE methodology.

We did not identify any randomised comparisons from randomised controlled trials (RCTs) which evaluated the efficacy of one dose of licensed HPV vaccine. In this review, we have included 35 studies: thirty-two observational cohort studies, of which three were post-hoc analyses of RCTs, and three case-control studies. All studies reported data on one dose of HPV vaccine for immunogenicity or clinical outcomes. Only two studies were identified which assessed the efficacy of one dose of HPV vaccine in males. The studies were carried out in 21 countries; 10 studies evaluated the bivalent vaccine, 24 studies the quadrivalent vaccine, and one study evaluated both quadrivalent and nonavalent vaccine.

To assess whether included observational studies sufficiently controlled for confounding, important confounders in the relationship between HPV vaccine and the outcomes were first identified from published literature as: age, ethnicity/cultural context, socioeconomic status, peer group, directive sexual education and mass media, contraception, history of sexually transmitted infections and Pap testing, and vaccination delivery setting. The risk of bias was assessed using the ROBINS-I tool for cohort studies and the SIGN-50 checklist for case-control studies. Using the ROBINS-I tool, the overall risk of bias for cohort studies was assessed as moderate (n=3 studies), serious (n=26 studies), or critical (n=1 study). Two conference abstracts were not assessed as they provided no information to judge risk of bias. Three case-control studies were assessed using the SIGN-50 checklist and all were at high risk of bias.

One dose bivalent HPV vaccine compared with no vaccine or control vaccine

One dose of bivalent HPV vaccine resulted in increased HPV 16 and 18 GMTs compared with control vaccine (Hepatitis A vaccine) at 48 months follow-up (moderate certainty evidence).

One dose of bivalent HPV vaccine reduced one-time incident and persistent HPV infections compared with control vaccine (Hepatitis A vaccine) (low to moderate certainty evidence).

Evidence on histological abnormalities (CIN1, CIN2, CIN3, different grades of dyskaryosis) and prevalent HPV infection was of very low-certainty due to serious limitations in study design and imprecision.

One dose quadrivalent HPV vaccine compared with no vaccine

One dose of quadrivalent HPV vaccine resulted in increased HPV 6, 11, 16, and 18 GMTs and seropositivity compared with no vaccine at 72 months follow-up (very low certainty evidence).

Results partially adjusted for confounding from four studies indicated that one dose of quadrivalent HPV vaccine may reduce the incidence of genital warts compared with no vaccine, though two studies found little or no difference between one dose and no vaccine (low certainty evidence).

One dose of quadrivalent HPV vaccine may reduce incident HPV infections compared with no vaccine at up to 7 years follow-up (low certainty evidence).

Evidence on histological abnormalities (CIN1, CIN2, CIN3, high grade abnormalities), cytological abnormalities, and prevalent HPV infection was of very low-certainty due to serious limitations in study design and imprecision.

One dose compared with two doses bivalent HPV vaccine

One dose of bivalent HPV vaccine resulted in reduced GMTs for HPV 16 and 18 compared to two doses at up to 84 months follow-up; non-inferiority between one and two doses was inconclusive (low certainty evidence).

There was little or no difference on HPV 16 and 18 seropositivity with one dose of bivalent HPV vaccine compared to two doses at up to 84 months follow-up (low certainty evidence)

There was little or no difference on 7-year cumulative other carcinogenic (not HPV 16, 18, 31, 33, and 45) HPV infections and noncarcinogenic HPV infections compared to two doses (very low to low certainty evidence).

There was little or no difference on one-time incident HPV infections and persistent HPV infections compared to two doses (very low to low certainty evidence).

Evidence on histological abnormalities (CIN1, CIN2, CIN3), prevalent HPV infection, and 7-year cumulative HPV 16, 18, 31, 33, and 45 infection was of very low-certainty due to serious limitations in study design and imprecision.

One dose compared with two doses quadrivalent HPV vaccine

One dose of quadrivalent HPV vaccine resulted in reduced GMTs for HPV 6, 11, 16, and 18 compared to two doses at up to 72 months follow-up; non-inferiority was inconclusive (low certainty evidence).

Results partially adjusted for confounding from one study with moderate risk of bias indicated little or no difference between one and two doses on incidence of genital warts and one study with serious risk of bias found that one dose may increase incidence of genital warts compared with two doses (low certainty evidence).

There was little or no difference on incident HPV 16 and 18 infections when one dose was compared with two doses (low certainty evidence).

One dose of quadrivalent HPV vaccine may result in more incident HPV 31, 33, and 45 infections compared with two doses (low certainty evidence).

Evidence on HPV 6, 11, 16, and 18 seropositivity, histological abnormalities (CIN1, CIN2, CIN3), cytological abnormalities, and persistent HPV infection was of very low certainty due to serious limitations in study design and imprecision.

A post-hoc sensitivity analysis for this comparison showed that in studies which accounted for pre-existing HPV infections by using a buffer period (excluding participants that did not have sufficient time between vaccination date and outcome measurement date) in the analysis and studies which adjusted for the most confounding (i.e. studies at the least risk of bias) were more likely to report smaller differences in effect between one and two doses.

One dose compared with three doses bivalent HPV vaccine

One dose of bivalent HPV vaccine resulted in reduced GMTs for HPV 16 and 18 compared with three doses at up to 84 months follow-up; one dose was inferior to three doses (moderate certainty evidence).

There was little or no difference on HPV 16 and 18 seropositivity with one dose compared with three doses at up to 84 months follow-up (low certainty evidence).

There was little or no difference on 7-year cumulative other carcinogenic (not HPV 16, 18, 31, 33, and 45) HPV infections and noncarcinogenic HPV infections with one dose compared with three doses (moderate certainty evidence).

There was little or no difference on one-time incident HPV infections and persistent HPV infections with one dose compared with three doses (very low to low certainty evidence).

Evidence on histological abnormalities (CIN1, CIN2, CIN3), prevalent HPV infection, and 7-year cumulative HPV 16, 18, 31, 33, and 45 infection was of very low-certainty due to serious limitations in study design and imprecision.

One dose compared with three doses quadrivalent HPV vaccine

One dose of quadrivalent HPV vaccine resulted in reduced GMTs for HPV 6, 11, 16, and 18 compared with three doses at up to 72 months follow-up; non-inferiority was inconclusive (low certainty evidence).

Results partially adjusted for confounding from three studies (one with moderate risk of bias and two with serious risk of bias) found that one dose may increase the incidence of genital warts compared with three doses (low certainty evidence).

Evidence on HPV 6, 11, 16, and 18 seropositivity, histological abnormalities (CIN1, CIN2, CIN3), cytological abnormalities, and HPV infection was of very low certainty due to serious limitations in study design and imprecision.

These results should be interpreted with caution due to the moderate to serious risk of bias in the included studies. In addition, the estimates of effectiveness between one dose and two or three doses were mostly calculated using raw data reported in the studies as adjusted estimates were not available for many of these comparisons. For many outcomes there was insufficient evidence, due to a small number of participants in the studies receiving only one dose of HPV vaccine, and few events of interest occurring in this group.

As of May 2019, there are at least two (NCT02834637, NCT03180034) ongoing RCTs evaluating the efficacy of one dose of HPV vaccine. These RCTs should help clarify non-inferiority of one dose of HPV vaccine compared to two doses, in terms of immunogenicity and persistent HPV infection. The estimates from RCTs should provide a higher level of certainty than the currently available observational studies.

Introduction

Human papillomavirus (HPV) is the most common viral infection of the reproductive tract and causes a range of conditions in females and males, including precancerous lesions that may progress to cancer. In this report, we summarise the evidence from our systematic review on the protection afforded by one dose of prophylactic HPV vaccines.

Objective

The objective of this systematic review was to evaluate the immunogenicity and effectiveness of one dose of HPV vaccine compared with no vaccination, two doses of HPV vaccine, or with three doses of HPV vaccine.

Methods

Search methods

We updated a systematic review performed by Cochrane Response in 2018. Searches were conducted for this update from August 2018 to 29th February 2019, and all relevant studies regardless of language or publication status were screened.

We searched the following databases: Cochrane Central Register of Controlled Trials (CENTRAL), published in The Cochrane Library; MEDLINE (PubMed); and EMBASE (OVID). We also searched the WHO International Clinical Trials Registry Platform and ClinicalTrials.gov, to identify ongoing trials. Search strategies are available in Appendix 1. Search strategiesWe also searched the reference lists of relevant systematic reviews published within the search dates and a recently published HPV study index (1). HPV vaccine manufacturers' websites were searched for relevant data and experts were contacted via WHO IVR.

Selection criteria

Randomised controlled trials (RCTs) and observational studies capable of providing data on the efficacy, immunogenicity or effectiveness following one dose of HPV vaccine were eligible for inclusion. Studies on female and male participants aged ≥ 9 years, who received at least one dose of HPV vaccine were included.

The HPV vaccines being studied were licensed bivalent (Cervarix, GlaxoSmithKline), quadrivalent (Gardasil, Merck), or nonavalent (Gardasil 9, Merck) HPV vaccines.

We considered studies that provided data on one-dose versus no HPV vaccination/placebo/control vaccine, one-dose versus two doses, or one-dose versus three doses of the licensed HPV vaccines.

The outcomes of interest were:

- Immunological: seroconversion or seropositivity, geometric mean titres (GMT) of HPV antibodies
- Clinical: including, but not limited to cervical intraepithelial neoplasia (CIN) grade 3+, CIN2+, histological and cytological abnormalities, anogenital warts, HPV infection

Study selection and data collection

Two review authors independently assessed eligibility of the newly identified studies from the updated search. One reviewer extracted data and a second reviewer cross-checked the extracted data.

In this report, studies have been given names based upon the country in which they were based. As more than one study may have the same setting, each country-based name also has a number (See Appendix 2. Included studies).

Risk of bias assessment

Two reviewers independently assessed the risk of bias of each included study. Following assessment of all included studies, discussion among the review team ensured reliability and consistency of ratings across the studies. Any further disagreements were resolved through discussion.

For RCTs or quasi-RCTs, the Cochrane Risk of Bias tool for RCTs was used. For case-control studies, a modified version of the Scottish Intercollegiate Guidelines Network checklist (SIGN-50) was used. For observational cohort studies with a comparison, the Cochrane ROBINS-I tool for non-randomised studies of interventions was used. The ROBINS-I tool has assessment checklist questions, which cover domains relating to bias due to confounding, selection bias, information bias, and reporting bias (2).

For the SIGN-50, each domain was judged as unclear, low, or high risk of bias, while each domain of the ROBINS-I was judged as low, moderate, serious, or critical risk of bias. For all assessments, supporting information was provided from the report or reviewer interpretation to rationalise the judgment of bias. Outcome-specific domains were assessed at the outcome level. Judging a result to be at a particular risk of bias for an individual domain implies that the result has an overall risk of bias at least this severe (2).

As part of the risk of bias assessment of observational studies using ROBINS-I and the SIGN-50, a preliminary specification of important confounders and co-interventions was made. These confounders and co-interventions were derived from the adjustment and stratification variables used in analyses of previously included studies, other variables mentioned in the discussion sections of relevant studies, and a recently published systematic review on the effectiveness of fewer than three doses of HPV vaccine (3). Causal directed acyclic graphs (DAGs) were used to determine the minimal set of confounding variables (4) (Appendix 3. Causal DAG model for HPV vaccination in adolescents and young adult study populations). The variables within that minimal set are the ones that studies should be adjusting for, to produce unbiased effect estimates and reduce the potential for over-adjustment or the creation of selection bias by conditioning on colliders (i.e. variables that are common effects of both the exposure and outcome), assuming the causal DAG is correct (5, 6). We used a DAGitty-derived (7) minimal sufficient adjustment set as a guide for assessing confounding-related interval validity and in the decision of meta-analysing studies.

The confounding domains in the minimal adjustment set included:

- **Age (birth year).** The age at which participants receive vaccine will influence their background risk of HPV infection.
- **Ethnicity/cultural context**. To focus on environment as the context for influencing behaviour and not genetics, race was not included in the ethnicity/cultural context variables; however, if race has been accounted or adjusted for in studies, we presumed this to be a reasonable proxy.

- **Socioeconomic status**. Both parental and participant socioeconomic status were included to account for the adolescent and young adult life stages that may be representative of the populations in the studies.
- **Peer group**. This variable refers to the influence and behaviours of the study populations' family and friends.
- **Directive sexual education and mass media**. In addition to sexual education received in the family or schooling environment, study participants may have also been influenced by mass media campaigns on vaccinations. We have denoted 'directive' to focus on messaging that would have included HPV vaccination, specifically.
- **Contraception** refers to oral contraceptive and barrier methods.
- **History of STI & pap testing**. For simplicity, we combined all forms of STI testing, regardless of how initiated (patient, practitioner) or whether part of a population-based screening program.
- **Vaccination delivery setting** was included to acknowledge that delivery and effectiveness of vaccination can be influenced by where and by whom vaccinations are given and how they are stored.

As part of the risk of bias assessment, reviewers extracted information on whether studies measured and controlled for each of these confounding domains, or for factors that could be considered reasonable proxies.

Data analysis

Risk ratios with 95% confidence intervals (CI) were calculated for dichotomous data (incidence of clinical outcomes, seroconversion or seropositivity). Rate ratios were calculated for dichotomous clinical outcomes reported as incidence rates.

For continuous GMT data, ratios of GMTs with 95% CIs were calculated. Initially, the point estimates as well as the lower and upper bound of the 95% CI of GMT for each group were transformed into the logarithmic scale in order to obtain statistically correct standard deviations. Then the mean difference of the compared group was calculated and results (point estimate and 95% CI) were back transformed to the original scale through exponentiation. Non-inferiority for GMTs was considered to be achieved if the lower bound o the 95% CI was greater than 0.5.

When pooling was feasible, a random-effects meta-analysis was employed using the DerSimonian and Laird method (8). Since heterogeneity is inevitable due mainly to confounding in observational studies, a random-effect meta-analysis can naturally incorporate the unexplained heterogeneity in the meta-analysis results (9). Subsequently, we avoided selecting the meta-analysis model based on the results of the chi-squared test.

Where data permitted, we combined adjusted point estimates using ORs and their 95% CIs in the first instance. When data could not be pooled, we reported results narratively. If a mixture of adjusted and unadjusted estimates was reported within a study, we gave preference to the estimate that adjusted for the most important confounders for the review. Raw data were used if available.

A post-hoc sensitivity analysis was also performed to investigate the effect of various sources of bias on effect estimates including the buffer period used (i.e. time between the vaccination and counting of events), the age at vaccination, and confounding.

Summarising and interpreting results

We used the GRADE approach to interpret findings and assess the certainty of the evidence for each outcome following the recommendations in the GRADE handbook. This incorporates details of each included study in the comparison, the magnitude of effect of the interventions examined, and the sum of available data on the relevant outcomes. The certainty of the evidence reflects the extent to which we are confident that an estimate of the effect is correct.

Data from RCTs starts at high certainty, but can be downgraded to moderate, low or very low if there are serious or very serious limitations in the following domains: risk of bias, inconsistency, indirectness or imprecision (Table 1) (10). Each quality element considered to have 'serious' or 'very serious' issues will be rated down by 1 or 2 points respectively.

Data from observational studies starts at low certainty, but may be upgraded to moderate or high certainty if the pooled estimates reveal a large magnitude of effect, negligible concerns about confounders or a strong dose-response gradient (Table 2).

Table 1. Factors that can reduce the certainty of the evidence

Domain	Definition
Risk of bias	Limitations in the study design and execution may bias the estimates of the treatment effect. The more serious the limitations are, the more likely it is that the certainty of evidence will be downgraded. Numerous tools exist to evaluate the risk of bias in randomised trials and observational studies. Our confidence in an estimate of effect decreases if studies suffer from major limitations that are likely to result in a biased assessment of the intervention effect.
Inconsistency	Inconsistency refers to an unexplained heterogeneity of results. True differences in the underlying treatment effect may be likely when there are widely differing estimates of the treatment effect (i.e. heterogeneity or variability in results) across studies. Investigators should explore explanations for heterogeneity, and if they cannot identify a plausible explanation, the quality of evidence should be downgraded. Whether it is downgraded by one or two levels will depend on the magnitude of the inconsistency in the results.
Indirectness	We are more confident in the results when we have direct evidence. Direct evidence consists of research that directly compares the interventions which we are interested in, delivered to the populations in which we are interested, and measures the outcomes important to patients. Authors of systematic reviews and guideline panels making recommendations should consider the extent to which they are uncertain about the applicability of the evidence to their relevant question and downgrade the certainty rating by one or even two levels.
Imprecision	In general, results are imprecise when studies include relatively few patients and few events and thus have a wide confidence interval (CI) around the estimate of the effect. In this case, one may judge the quality of the evidence lower than it otherwise would be considered because of resulting uncertainty about the results. For guideline panels, this refers to the extent to which our confidence in the estimate of an effect is adequate to support a particular decision.
Publication bias	Publication bias is a systematic under-estimation or an over-estimation of the underlying beneficial or harmful effect due to the selective publication of studies. Confidence in the combined estimates of effects from a systematic review can be reduced when publication bias is suspected, even when the included studies themselves have a low risk of bias.

Table 2. Factors that can increase the certainty of the evidence

Domain	Definition
Large magnitude of an effect	When body of evidence from observational studies not downgraded for any of the 5 factors yield large or very large estimates of the magnitude of an intervention effect, then we may be more confident about the results. In those situations, even though observational studies are likely to provide an overestimate of the true effect, the study design that is more prone to bias is unlikely to explain all of the apparent benefit (or harm). Decisions to rate up certainty of evidence because of large or very large effects should consider not only the point estimate but also the precision (width of the CI) around that effect: one should rarely and very cautiously rate up quality of evidence because of apparent large effects, if the CI overlaps substantially with effects smaller than the chosen threshold of clinical importance.
Dose-response gradient	The presence of a dose-response gradient has long been recognized as an important criterion for believing a putative cause-effect relationship. The presence of a dose-response gradient may increase our confidence in the findings of observational studies and thereby increase the certainty of evidence.
Effect of plausible residual confounding	On occasion, all plausible residual confounding from observational studies may be working to reduce the demonstrated effect or increase the effect, if no effect was observed.

The different levels of certainty that resulted from the GRADE assessment were interpreted as follows:

- **High certainty:** further research is very unlikely to change our confidence in the estimate of effect.
- **Moderate certainty:** further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
- **Low certainty:** further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
- **Very low certainty:** we are very uncertain about the estimate.

Results

Results of the search

For this update we screened 2523 records from the update search from August 2018 to February 2019 and included 12 new studies. This review now includes 35 studies. We did not identify any randomised comparisons from RCTs that evaluated the efficacy of one dose of licensed HPV vaccine. There are several ongoing studies evaluating the efficacy of one dose of HPV vaccine, with results expected over the next few years (NCT02834637, NCT03180034, NCT03832049, NCT03747770).

Characteristics of included studies

We included 32 observational cohort studies, of which three were post-hoc analyses of RCTs and two were conference abstracts; and three case-control studies that contained data on clinical or immunogenicity outcomes mainly from females. Only two of the included studies reported on the effectiveness of one dose of HPV vaccine in males (USA11, USA12). USA11 included both males (23%

of cohort) and females but did not report results separately by sex. We have noted in the results text where this study contributed data. USA12 reported on young men attending sexual health clinics and only provided limited data on HPV infections for this report. The three post-hoc analyses of RCTs (Costa Rica1, CVT/PATRICIA, India1) analysed intervention groups according to the number of doses they received, which violated the randomisation – as a result they have been treated as observational cohort studies in this review. The studies were carried out in 21 countries; 10 studies evaluated the bivalent vaccine, 24 studies the quadrivalent vaccine, and one study evaluated both quadrivalent and nonavalent vaccine. The characteristics of individual studies are presented in Appendix 4. Characteristics of included studies.

Potential overlapping populations

Several of the included studies are based on linked data from national or regional registries. In studies from the same country there is potential for "double-counting" of participants, which can lead to misleading estimates from meta-analyses.

Three studies from Australia (Australia1, Australia3, Australia4) used data from the same registries, collected over the same time-period, and reported outcomes for overlapping age groups. Similarly, all six of the included studies from Scotland were sampled from the Scottish Cervical Screening Programme and included overlapping birth cohorts. Two studies (Denmark3, Denmark/Sweden1) also used data from the same time period in Denmark and reported on the same outcome (CIN2).

There was also potential overlap between different studies from the USA. Two studies (USA9, USA13) reported data from the same location and health care system, over the same dates. Three other studies (USA6, USA10, USA11) reported results from administrative databases of health insurance plans with overlapping dates.

As we could not be certain that these studies and the participants within them were independent from each other, we did not perform meta-analyses that combined any of these studies.

Included studies

- **Australia1** (11) was a retrospective cohort study using linked regional data registries (cervical cytology and HPV vaccination registries) from Victoria, Australia, and included vaccine eligible women aged 26 years or younger in 2007. A total of 156,423 women who received at least one dose of quadrivalent HPV vaccine were included in the analysis. Of these, 20,659 women were vaccinated with only one dose. This study reported histological abnormalities (any high grade, CIN3/AIS, CIN2) and cytological abnormalities (high grade, low grade) at up to 4.5 years following vaccination.
- **Australia2** (12) was a case-control study using linked data from registries (pap smear and vaccination registries) in Queensland, Australia. Women eligible for free quadrivalent HPV vaccination (aged 12-26 years in 2007) and attending for their first cervical smear test between April 2007 and March 2011 were included. High grade cases were women with histologically confirmed high grade cervical abnormalities (n=114 who received one dose) and "other cases" were women with any other abnormality at cytology or histology (n=1230 who received one dose). Controls were women with normal cytology (n=9535 who received one dose). The median follow-up time for controls was 654 days following vaccination.
- **Australia3** (13) was a retrospective cohort study using linked data from registries (cervical cytology and HPV vaccination registries) from Victoria, Australia, and included unvaccinated and vaccinated women who were 17 or younger in 2007, attended screening, and who were eligible for quadrivalent HPV vaccination at school. A total of 24,871 women who received at

least one dose of HPV vaccine were included, of whom 1422 received only one dose. This study reported cervical and cytological abnormalities at up to 4.5 years following vaccination.

- **Australia4** (14) was a retrospective cohort study using linked data from national registries (cervical screening and HPV vaccination registries) from Australia and included unvaccinated and vaccinated women who attended screening and were eligible for quadrivalent HPV vaccination at school (aged 15 or younger). A total of 250,648 women were included, of whom 8618 received only one dose. This study reported cervical abnormalities (i.e. CIN2/AIS+ and CIN3/AIS+) at up to 7 years following vaccination.
- **Belgium2** (15) was a retrospective cohort study using sick-fund/insurance data from one of the three largest sick funds in Belgium. A total of 43,499 women aged 16 to 24 years who received at least one dose of quadrivalent HPV vaccine were included in the analysis, of whom 4020 received only one dose of HPV vaccine. The study reported on cases of genital warts at up to 7 years following vaccination.
- **Canada2** (16) was a nested case-control study using linked data from registries (cervical cancer screening and vaccination registries) in Alberta, Canada. Women born between 1994 and 1997 who had at least one Pap test between 2012 and 2015 were included, with those having positive tests (based on the most severe results) being cases (n=47 who received only one dose of quadrivalent HPV vaccine) and those with negative tests as controls (n=280 who received only one dose). The study reported on low and high-grade cytological abnormalities at up to 11 years following vaccination.
- **Canada3** (17) was a retrospective cohort study using linked data from registries (population, vaccination, and prescription claims databases), from Manitoba, Canada. The study included all female participants 9 years and older who received at least 1 dose of quadrivalent HPV vaccine (n=31,464) during the enrolment period and a matched control (unvaccinated) group. Of the participants, 3521 received only one dose of quadrivalent HPV vaccine. The study reported on cases of genital warts at a median of 2.5 years follow-up.
- **Costa Rica1** (18-20) was a post-hoc analysis of a publicly funded, four-year, community-based, randomised phase III trial which randomised 7466 women to receive either the bivalent HPV vaccine or a control hepatitis A vaccine. This post-hoc evaluation included 134 women who received one dose of bivalent HPV vaccine at age 18 to 25, 272 women who received two doses, and 2043 women who received all three doses. For evaluation of immunogenicity outcomes, a smaller subset of women for whom sera was available at all study visits (n=78 who received one dose) was analysed. The study reported on HPV infections at up to 7 years following vaccination and HPV antibody titres at up to 4 years following vaccination.
- **CVT/PATRICIA** (21) In addition to the data reported from the Costa Rica trial (CVT), data from an additional report of a combined analysis with the PATRICIA trial after a mean follow-up of 47.6 months was extracted and presented. PATRICIA was a multisite RCT with 138 study locations in 14 countries including 18,644 females aged 15–25 years, who received either the bivalent HPV vaccine or a control vaccine (hepatitis A vaccine). The combined post-hoc analysis of both trials included 26,110 females, of which 573 received one dose, 977 received two doses and 11,499 received three doses of the bivalent HPV vaccine. The analysis reported on incident and persistent HPV 16/18 and HPV 31/33/45 infections.
- **Denmark2** (22) was a retrospective cohort study using population-based national health registries (population, health insurance, and prescription registries) from Denmark. Girls born between 1985 and 1999, who were vaccinated with the quadrivalent HPV vaccine between October 2006 and December 2012, were included. A total of 361,734 vaccinated girls were included, of whom 55,666 received only one dose. This study reported on the incidence of genital warts at up to 6 years following vaccination. Adjusted incidence rate ratios were

calculated for genital warts, comparing those who received one dose to those who received two doses.

- **Denmark3** (23) was a retrospective cohort study using nationwide demographic and patient registries from Denmark including all women between 17-25 years, living in Denmark between 2006 and 2016. From nationwide registries, individual-level data on vaccination with the quadrivalent HPV vaccine at 16 years or younger were extracted. The cohort comprised 590,083 women, of which 215,309 (36%) women were vaccinated at ≤16 years, and among these, 10,480 received only one dose. This study reported on vaccine efficacy against CIN2+, CIN3+ (cases, person-years, and crude incidence rates), and incidence rate ratios.
- **Denmark /Sweden1** (24) was a population-based prospective cohort study of all women aged 13–30 years, living in Denmark or Sweden during 2006–2013. Participants entered the cohort in October 2006, their 13th birthday or the date of immigration to Denmark/Sweden. The cohort was followed for vaccination status with the quadrivalent HPV vaccine and first occurrence of CIN2+. 2,253,561 women were included, of which 1,800,246 were vaccinated, 712,588 received only one dose. This study reported on vaccine efficacy against CIN2+ (cases, person-years, and crude incidence rates).
- **Fiji1** (25) was a prospective cohort study of 200 Fijian girls 15 to 19 years of age. Girls were recruited who received 1, 2, or 3 doses of quadrivalent HPV vaccine in 2008-2009. Blood samples were collected to determine the immunogenicity before a single dose of bivalent HPV vaccine, and 6 years following the initial vaccination. Seropositivity data was available for 40 girls who received only one dose of quadrivalent HPV vaccine, 60 girls who received two doses, and 66 girls who received three doses.
- **India1** (26, 27) was a post-hoc analysis of a multi-centre cluster randomised trial of two versus three doses of quadrivalent HPV vaccination in India. Suspension of the vaccination due to events unrelated to the study led to per-protocol and partial vaccination of 17,729 unmarried 10 to 18-year-old girls. As a result, a total of 4950 girls received only one dose of HPV vaccine. The study reported immunogenicity and HPV infections at 7 years follow-up.
- **Scotland1** (28) was a cohort study using national cervical screening registry data from Scotland, with additional testing of stored samples from women who received fewer than 3 doses of bivalent HPV vaccine. Samples from women born between 1988 and 1993 were analysed, of which 177 had received only one dose. The study reported prevalence of HPV 16/18 and HPV 31/33/45 in these samples.
- **Scotland2** (29) was a retrospective cohort study using linked national registry data (immunisation and colposcopy registries) from Scotland. Data for 106,052 women born between 1988 and 1992 attending for their first cervical screen at age 20 or above were analysed. Of these, 1315 had received only one dose of bivalent HPV vaccine. The study reported vaccine efficacy estimates (i.e. risk ratios) against CIN1, CIN2, and CIN3.
- **Scotland3** (30) was a retrospective cohort study using linked national registry data (immunisation and colposcopy registries) from Scotland. Data on 137,689 women who had cervical screening at age 20 or 21 were analysed, of which 2258 had received only one dose of bivalent HPV vaccine. The study reported on rates of CIN1, CIN2, and CIN3 stratified by number of doses of HPV vaccine received and socioeconomic status (index of deprivation).
- **Scotland4** (31) was a cohort study using cervical screening registry data and additional testing of 4729 cytology samples from Scotland. Females aged 20-21 attending for cervical screening over the period 2009–2012 were analysed, of which 55 had received only one dose of bivalent HPV vaccine. The study reported on HPV 16/18 prevalence, prevalence of cross-protective HPV types, and other high-risk HPV types.

- **Scotland5** (32) was a cohort study using screening registry data over 7 years, including birth cohorts from 1988 to 1995. 8584 samples were linked to vaccination records, with 223 women having received only one dose of bivalent HPV vaccine. The study reported prevalence of HPV types 16 and 18, HPV types 31, 33, and 45, other high-risk types, and any HPV.
- **Scotland6** (33) was a retrospective cohort study using screening registry data from Scotland, including women born between 1 January 1988 and 5 June 1996, who had a smear test result recorded at age 20. 138 692 women were included of which 74,666 were vaccinated with the bivalent HPV vaccine, 2051 women received only one dose. The study reported on abnormalities at age 20 by age at first dose and immunisation status for borderline changes, low grade dyskaryosis, moderate high grade dyskaryosis, severe dyskaryosis, CIN1, CIN2, CIN3 or worse.
- **Spain2** (34) was a retrospective cohort study using registries (population, vaccination, and medical visit registries) from Valencia, Spain. The study cohort included 279,787 girls and women aged 14 to 19 at the start of the study period, with data on those who received only one dose of quadrivalent vaccine providing 18,142 person-years. The study reported on incidence of genital warts.
- **Sweden1** (35) was a retrospective cohort study using national population-based health registries (vaccination, prescription, and patient registers) from Sweden. The cohort included 115,197 girls and women aged 10 to 24 who received one dose of quadrivalent HPV vaccine. The study reported on incidence of genital warts, stratified by age, with a mean follow-up time of 3.8 years. Adjusted incidence rate ratios were calculated for genital warts, comparing those who received one dose to those who received two doses, and between one dose and three doses.
- **Switzerland1** (36) was a cross-sectional study, including undergraduate female students aged between 18-31 years, attending the Medical School and University of Applied Sciences in Geneva. Included participants were asked to perform a vaginal self-sampling for HPV testing. 409 women were included, of which 284 were vaccinated with the quadrivalent HPV vaccine, 20 with only one dose. The study reported on HPV prevalence.
- **Uganda1** (37) was a prospective cohort study of 376 young girls aged 10 to 11 who participated in an HPV vaccine demonstration project implemented by the government of Uganda in partnership with PATH (2008-2009). Of these girls, 36 received only one dose of bivalent HPV vaccine. The study reported on antibody titres for HPV 16 and 18 after 24 months of follow-up.
- **USA1** (38) was a retrospective cohort study of 4127 adolescent and young adult females aged 11 to 20 on 1st January 2007, attending one of 16 clinics affiliated with a large academic medical centre. The cohort included 695 females who received one dose of quadrivalent HPV vaccine, or who received more than one dose, but either had no cervical cytology screening after the second dose or had an abnormal cervical cytology result between the first and second doses. The study reported on abnormal cervical cytology results at up to 7 years follow-up.
- **USA2** (39) was a retrospective cohort study of female enrolees in three health plans on August 1, 2006, which was the start of HPV vaccine introduction, or who reached age 11 years while enrolled in one of the health plans after this date, and who were aged 15–22 years at any time during the study period. A total of 64,517 eligible female enrolees were identified, 5684 of whom had received only one dose of quadrivalent HPV vaccine. The study reported on incidence of anogenital warts with a mean follow-up of 2.2 years for those receiving one dose.
- **USA6** (40) was a retrospective cohort study using commercial claims database, enrolling 387,906 adolescent females aged 9 to 18. Of these, 30,428 had received one dose of quadrivalent HPV vaccine. The study reported on incidence of genital warts over an average length of follow-up time of 5.64 years. Adjusted incidence rate ratios were calculated for genital

warts, comparing those who received one dose to those who received two doses. Adjusted incidence rate ratios were calculated for genital warts, comparing those who received one dose to those who received three doses.

- **USA9** (41) was a nested case-control study of females aged 14-26 enrolled in an integrated health-care delivery system in California, USA including 26,130 women. Cases were women with a new diagnosis of CIN2+ or CIN3+ (n=118 received only one dose of the quadrivalent HPV vaccine) and incidence density-selected controls were women without CIN2+ or CIN3+ (n= 638 received only one dose) at the time each case occurred. The study reported in risk of CIN2+ and CIN3+ by HPV vaccination status/dose versus no vaccination.
- **USA10** (42) was a retrospective cohort using healthcare claims data for 2003-2014. 270,481 females aged 9-17 years old in 2006, who were continuously enrolled were included. AGW diagnoses, and age at receipt of first and second dose of quadrivalent HPV vaccine were ascertained. Only 75,735 (28%) received more than one dose. The study reported on vaccine effectiveness against anogenital warts split by age group in a conference abstract only.
- **USA11** (43) was a retrospective cohort study using health-insurance claims database. The study reported on incidence of anogenital warts starting 3 months after the last dose of the quadrivalent HPV vaccine. 440,532 females and 133,394 males aged between 9-26 years were included of which 54,280 received only one dose of the quadrivalent HPV vaccine. The study reported on incidence of anogenital warts starting 3 months after the last dose of the quadrivalent HPV vaccine.
- **USA12** (44) was a prospective cohort study of young men aged 13-26 years old recruited from hospital-based teen health centre and a health department sexually transmitted disease (STD) clinic in Cincinnati, Ohio, USA, who completed a survey and were tested for 36 anogenital HPV types. 236 participants were included, of which 26% had received at least one HPV vaccine dose. The study reported on the association between number of doses and vaccine type HPV.
- **USA13** (45) was a prospective cohort study of women aged 21–24 years who underwent cervical screening at Kaiser Permanente Northern California. 75,008 women were included. Women were categorised in age groups (vaccinated at ages <18, 18–20, and 21–24 years) and compared to those who were unvaccinated. 14,590 were vaccinated of which 3542 received only one dose. The study reported on low-grade cytology (HPV-positive atypical squamous cells of undetermined significance or low-grade squamous intraepithelial lesion cytology) and high-grade cytology (cancer, adenocarcinoma in situ, high-grade squamous intraepithelial lesion (HSIL), atypical squamous cells, or atypical glandular cells cytology), stratified by age at vaccination.
- **USA14** (46) was a cross-sectional study in four waves of women 13 to 26 years of age, who were recruited from hospital-based and community health clinics for four surveillance studies from 2006 to 2017. 1580 women were included, of which, 0% received at least one dose of the quadrivalent HPV vaccinations in wave 1, 59.2% in wave 2, 71.5% in wave 3, and 84.3% wave 4. The study reported on vaccine type HPV infection (1 versus 3 doses).
- **USA15** (47) was a cross-sectional study of young women 13–26 years of age who were recruited between 2013 and 2017 from two primary care clinics. Included participants completed a survey and provided a cervicovaginal swab that was tested for 36 HPV genotypes. A total of 735 participants were included, of which 559 received at least one dose of the HPV vaccine (91% quadrivalent, 9% nonavalent). The study reported on prevalence of vaccine and non-vaccine type HPV in a conference abstract only.
- **USA16** (48) was a retrospective cohort study of female military service members aged 17-26 years who received one to three doses of quadrivalent HPV vaccine and had pre- and post-immunisation serum specimens in the Department of Defense Serum Repository (DoDSR). Post-

immunisation specimens were drawn 4 to 6 years after the last dose of vaccine. A total of 2091 participants were randomly sampled, of which 411 subjects had received one dose, 420 subjects had received two doses, and 1260 subjects had completed the three-dose series. This study reported on seropositivity to HPV 6, 11, 16 and 18.

Risk of bias in included studies

Below we summarise the risk of bias in the included studies. Appendix 5. ROBINS-I Summary and Appendix 6. SIGN-50 Summary have summary tables of the assessments and detailed assessments for each study can be seen at this link. Thirty observational cohort studies were assessed with the ROBINS-I risk of bias tool and three case-control studies (Australia2, Canada2, USA9) were assessed using the SIGN-50 checklist. Two of the included studies (USA10, USA15) were conference abstracts and were not assessed for risk of bias due to a lack of reporting of study methods.

Bias due to confounding

There was potential for confounding of the effect of intervention in all studies through the variables identified in the minimal adjustment set (Appendix 3). As per ROBINS-I guidance, all studies were first checked to see if evidence existed that controlling for confounders in the minimal adjustment set was not necessary. This can be achieved through statistical comparison of baseline characteristics between intervention groups, observing the (lack of) association between the potential confounder and the outcome, and consideration of the study setting and inclusion criteria. None of the included studies accounted for baseline differences in all variables in the minimal adjustment set. Two studies (Costa Rica1 and CVT/PATRICIA) showed that the intervention and control groups were similar on many baseline characteristics and reasons for missing doses of vaccine were similar across groups and not related to the intervention.

Eight studies (Australia3, Belgium2, Denmark/Sweden1, Denmark2, Denmark3, Spain2, Sweden1, USA2) split participant's follow-up time according to the time spent in different intervention groups. For these studies, the risk of bias due to time-varying confounding was considered. However, no post-baseline variables were identified which predict a switch of intervention (i.e. from one dose to two doses) and change with time. As a result, adjusting for time-varying confounding was considered unnecessary and for all included studies it was considered enough to adjust for baseline confounding only.

For the specific outcomes and data extracted for this review, no study used an appropriate analysis method to control for all important confounding domains in the minimal adjustment set. This was to be expected in most cases as many retrospective studies are limited by the data already recorded. Several studies adjusted results for age and socioeconomic status but remained at risk of residual confounding, for example, through health and sexual behaviours. These adjusted results are presented alongside the unadjusted estimates in this report.

Six studies (Scotland1, Scotland2, Scotland3, Scotland4, Scotland5, Scotland6) reported adjusted estimates for the comparison of one dose with unvaccinated participants with the bivalent HPV vaccine. Fourteen studies (Australia1, Australia3, Australia4, Belgium2, Canada3, Denmark2, Denmark3, Denmark/Sweden1, Spain2, Sweden1, USA1, USA2, USA9, USA11) reported adjusted estimates for the comparison of one dose of quadrivalent HPV vaccine with unvaccinated participants.

Eight studies (Australia4, Denmark1, Denmark3, Denmark2, Sweden1, Switzerland1, USA2, USA6) reported adjusted estimates for the comparisons of one dose compared with two doses or with three doses. These estimates were extracted and are presented in the results.

Of the included cohort studies assessed, 27/30 (90%) were considered at serious risk of bias due to confounding. All three case-control studies were considered to be at high risk of bias due to confounding as this was not controlled by the design (i.e. matching) or analysis. The remaining three cohort studies (Costa Rica1, CVT/PATRICIA, USA2) were considered at moderate risk of bias for confounding. As noted above, Costa Rica1 and CVT/PATRICIA showed that the intervention groups were similar on baseline characteristics, while USA2 adjusted for numerous confounders in a propensity-weighted analysis which accounted for all domains in the minimal adjustment set. These three studies, however, were judged at moderate risk of bias as they remain at risk of residual or unmeasured confounding and cannot be considered comparable to randomised controlled trials.

Selection bias

Selection bias occurs when some eligible participants, or the initial follow-up time of some participants, or some outcome events, are excluded in a way that leads to the association between intervention and outcome differing from the association that would have been observed in a target trial (2). The term “selection bias” is intended to refer only to biases that are internal to the study, and not to issues of indirectness (generalisability, applicability or transferability to people who were excluded from the study).

For 17/30 (57%) of the assessed cohort studies (i.e. Australia1, Australia3, Australia4, Fiji1, Scotland1, Scotland2, Scotland3, Scotland4, Scotland5, Scotland6, Switzerland1, USA1, USA6, USA12, USA13, USA14, USA16), participants were selected into the study based on presence of outcome data (e.g. cytology testing, cervical screening registry entries). These studies risk omitting participants who receive the intervention but do not have an outcome, which can result in selection bias.

Four studies were considered at low risk of selection bias (Costa Rica1, CVT/PATRICIA, India1, Uganda1) as participants were selected and analysed based on receiving the intervention or the comparison intervention.

The remaining 9 studies were considered at moderate risk of selection bias as they included participants based on receiving the intervention but did so in a retrospective manner, which introduces a potential bias related to completeness of the databases used.

One study (USA12) was considered at critical risk of selection bias as participants were enrolled from a sexual health clinic and not the general population.

The use of a buffer period (i.e. delaying case counting) in the analysis can potentially reduce the impact of pre-existing HPV infection or anogenital warts and thus control for one potential source of selection bias. For all studies, we report in the characteristics of included studies table (Appendix 2) when a buffer period was considered in the analysis, or where it was not necessary (given enough time between vaccination and outcome measure, or where baseline HPV status is measured). Further detail on the effect of the buffer period was explored in a sensitivity analysis (Figures 38 to 40).

All three case-control studies were assessed as having a low risk of bias in the selection of participants.

Bias in classification of interventions

For all included studies, intervention groups were clearly defined as the number of HPV vaccine doses received. For studies using vaccination registers or medical records, information to define the intervention groups was recorded at the start of the intervention and considered to be at low risk of bias.

Where classification of the number of doses received came from sources known to be at risk of incomplete information or from self-report (i.e. Switzerland1, USA12), studies were considered to be at serious risk of bias due to classification of interventions.

Two of the case-control studies (Australia2, USA9) had unclear risk of bias in assessment of the exposure, while the other (Canada2) was at low risk of bias.

Bias due to deviations from intended interventions

The intended intervention in the context of this review was a single dose of HPV vaccine (or no vaccine, two doses, or three doses as comparators). As the intervention groups were defined by the number of doses that the participants received, deviations from the interventions were considered unlikely for all studies.

For the purpose of this review it was assumed that the interventions were successfully implemented and adhered to (as the intended intervention in the context of this review was a single dose of HPV vaccine, or no vaccine, two doses, or three doses as comparators).

However, there exists the possibility that participants who receive the vaccine may also receive co-interventions such as sexual health education – and these may affect the outcome. Co-interventions were most often not reported, or no information on them was provided, so it could not be determined whether these were balanced between groups.

The judgement of the risk of bias for this domain takes into account that in the majority of studies there is no information on co-interventions, no information on how the interventions were delivered, and no information was presented on any adverse events that may lead to discontinuing the intervention. The exceptions to this are three studies (Costa Rica1, CVT/PATRICIA, India1), which set out as RCTs, and it was assumed co-interventions were monitored and controlled.

All studies were carried out in a setting of national three-dose recommendation, which may have affected the likelihood that participants return for the second or third dose. Only one study (Costa Rica1, by extension also CVT/PATRICIA) explored reasons for not receiving all doses in HPV versus control (Hepatitis A vaccine), showing the reasons were similar in both arms.

Bias due to missing data

For most of the included studies, outcome data were available for all (or nearly all) participants as these were retrospective studies where the outcome measure (e.g. cervical screening result) was an inclusion criterion (e.g. national cervical screening register). However, the flow of participants through the studies was seldom reported.

Most studies (28/30=93%) did not exclude participants due to missing data on intervention status (i.e. number of doses) and it was assumed that participants in these cases would be included in the unvaccinated group. Again, most studies (19/30=63%) did not exclude participants from the analyses when data was missing on other variables needed for the analysis.

However, studies generally did not provide details on the proportions of missing data across intervention groups, reasons for missing data, and how missing data was handled. Therefore, no assumptions were made regarding the robustness of study results in the presence of missing data.

Fourteen studies (47%) were considered at low risk of bias due to missing data and sixteen studies (53%) were considered at moderate risk of bias.

Bias in measurement of outcomes

It was assumed that the outcome measures (of which all are objective) were unlikely to be influenced by knowledge of the intervention received (i.e. number of doses) by either participants or by outcome assessors. In the context of this review, the outcome assessments were often tests carried out by the participants' routine health care providers but interpreted in an external laboratory setting.

However, most studies (22/30=73%) were assessed to be at moderate risk of bias in this domain, which reflects the uncertainty (i.e. lack of reporting) in the methods used to measure the outcomes. For studies reporting on genital warts as the outcome, it is possible that doctors and patients were more aware of potential for genital warts based on knowledge of exposure to vaccinations. This may lead to detection bias as doctors may screen more often for genital warts in participants with fewer doses.

In all studies it was assumed that methods of outcome assessment were comparable across intervention groups. Despite limited information reported on the methods of outcome assessment - especially around the registry data - no study reported different methods across the intervention groups.

Eight studies (28%) were considered at low risk of bias in measurement of outcomes as the methods were explicitly reported.

Bias in selection of the reported result

Selective outcome reporting occurs when the effect estimate for an outcome measurement was selected from among analyses of multiple outcome measurements for the outcome domain. This was considered unlikely in all studies as the outcome measures were objective and determined through standard procedures in most cases.

The risk of bias for this domain was considered moderate for almost all studies as no pre-registered protocols or statistical analysis plans were identified. Only one study (CVT/PATRICIA) reported that a pre-existing statistical analysis plan was used and was rated at low risk of bias.

Overall risk of bias

Overall, risk of bias was judged as serious for all outcomes in 26/30 (87%) studies. The Costa Rica1, CVT/PATRICIA, and USA2 studies were judged at moderate risk of bias. As per the ROBINS-I guidance, moderate risk of bias indicates that the study appears to provide sound evidence for a non-randomised study but cannot be considered comparable to a well-performed randomised trial. Serious risk of bias indicates that the study has some important problems.

One study (USA12) was considered at critical risk of bias, indicating the study is too problematic to provide any useful evidence and should not be included in any synthesis. Two conference abstracts (USA10, USA15) provided no information on which to base a judgement about risk of bias. All three case-control studies were also considered to be at high risk of bias due to confounding.

A lack of appropriate adjustment for confounding was considered to introduce serious risk of bias across almost all included studies and the assessment of other bias domains varied according to outcome and study design.

Comparison 1. Effectiveness and immunogenicity of one dose of HPV vaccine compared with no HPV vaccination

This section summarises the findings from the included studies comparing one dose HPV vaccine versus no HPV vaccination. Analyses are stratified by type of HPV vaccine (bivalent or quadrivalent). It is noted where concerns exist regarding risk of bias, imprecision of the estimates (due to small sample sizes, few events, or wide confidence intervals) and heterogeneity across studies being pooled. Certainty of the evidence is reported below and detailed reasons for downgrading or upgrading the certainty, according to guidance summarised in Table 1 and Table 2, are provided in Appendix 7. GRADE tables.

Bivalent HPV vaccine

There were nine included studies (Costa Rica1, CVT/PATRICIA, Scotland1, Scotland2, Scotland3, Scotland4, Scotland5, Scotland6, Uganda1) that reported on immunogenicity or clinical outcomes for women receiving one dose of the bivalent HPV vaccine compared with HPV unvaccinated women.

1. Immunogenicity

One study (Costa Rica1) reported on antibody titres for HPV 16 and 18 following one dose of bivalent HPV vaccine or control (hepatitis A virus (HAV) vaccine) at 48 months follow-up.

Antibody titres were in favour of one dose compared with control for both HPV 16 (ratio of GMTs 9.36, 95% CI 6.40 to 13.68, 191 participants, 1 study) and HPV 18 (ratio of GMTs 4.79, 95% CI 3.37 to 6.80, 191 participants, 1 study) (Figure 1). Evidence was of moderate certainty.

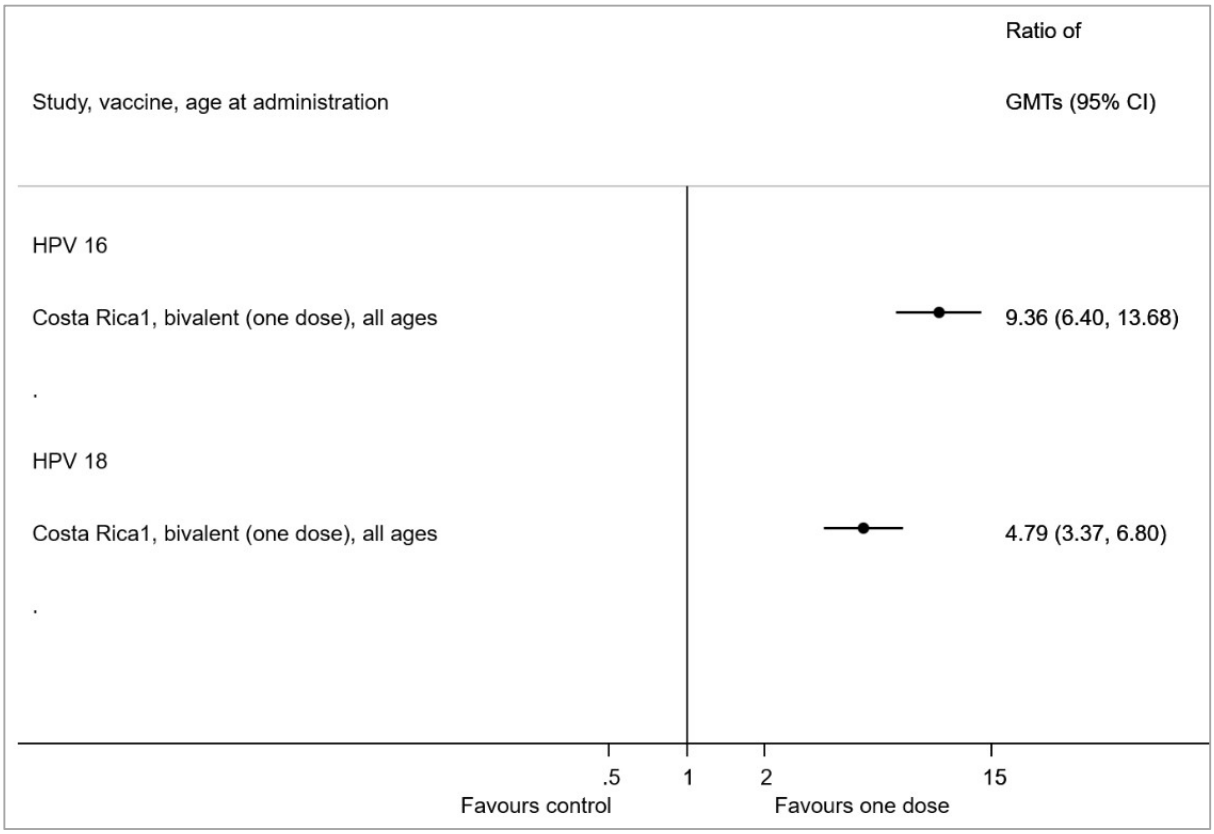


Figure 1. Ratio of HPV 16 and 18 GMTs for one dose bivalent HPV vaccine versus control (HAV vaccine) at 48 months follow-up, unadjusted results

2. Histological abnormalities

Three studies (Scotland2, Scotland3, Scotland6) reported adjusted estimates on cases of CIN1, CIN2, or CIN3+ and different grades of dyskaryosis (low-grade, moderate-high-grade, severe-high-grade, and borderline changes) after one dose of bivalent HPV vaccine compared with no vaccine (Figure 2). Due to the high likelihood of overlapping cohorts and cases between the Scotland studies, we did not pool estimates.

Studies found little or no difference between one dose and no vaccine, except for low-grade dyskaryosis where one study found a small effect in favour of no vaccine (OR 1.27, 95% CI 1.05 to 1.54, 50,399 participants). All outcomes were of very-low certainty due to a serious risk of bias due to confounding, selection bias, and imprecision due to wide 95% CIs.

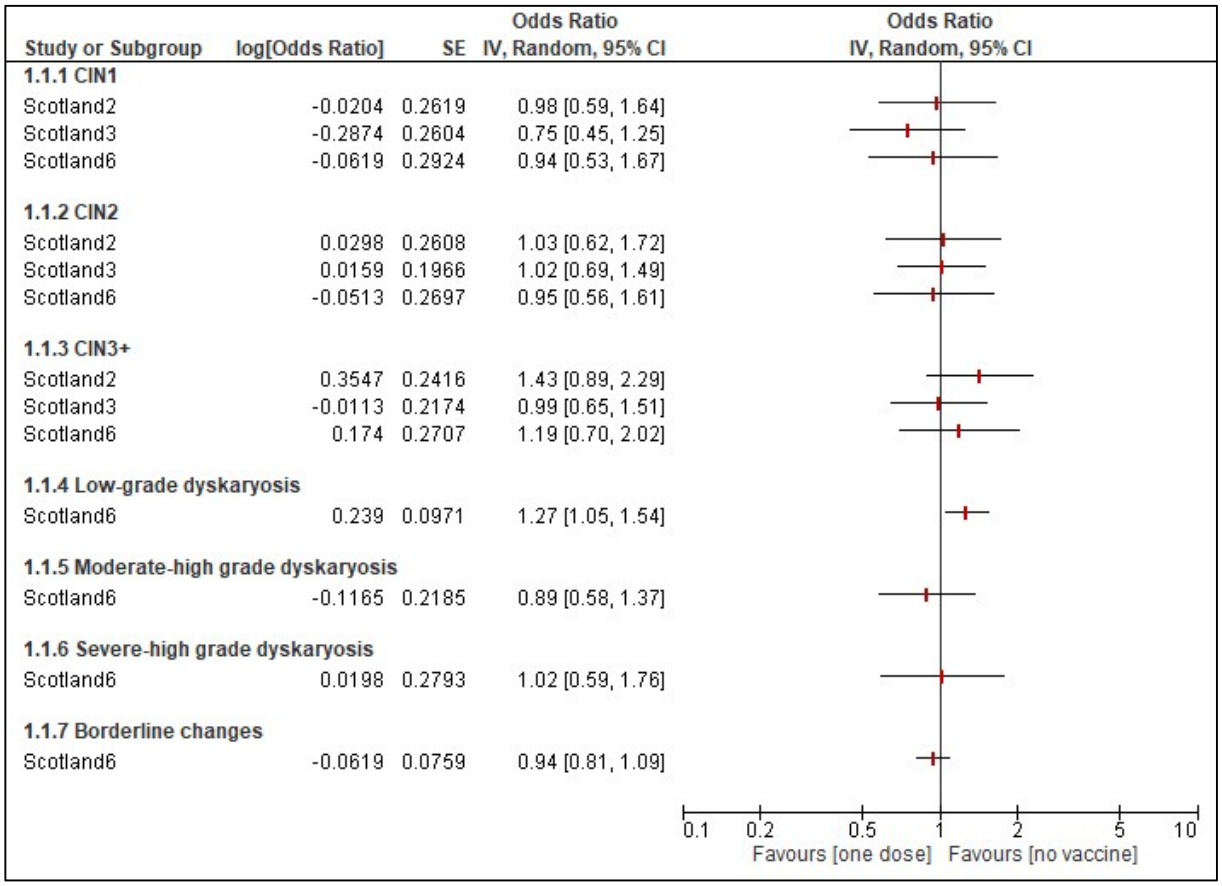


Figure 2. Histological abnormalities for one dose bivalent HPV vaccine versus no vaccine, adjusted results.

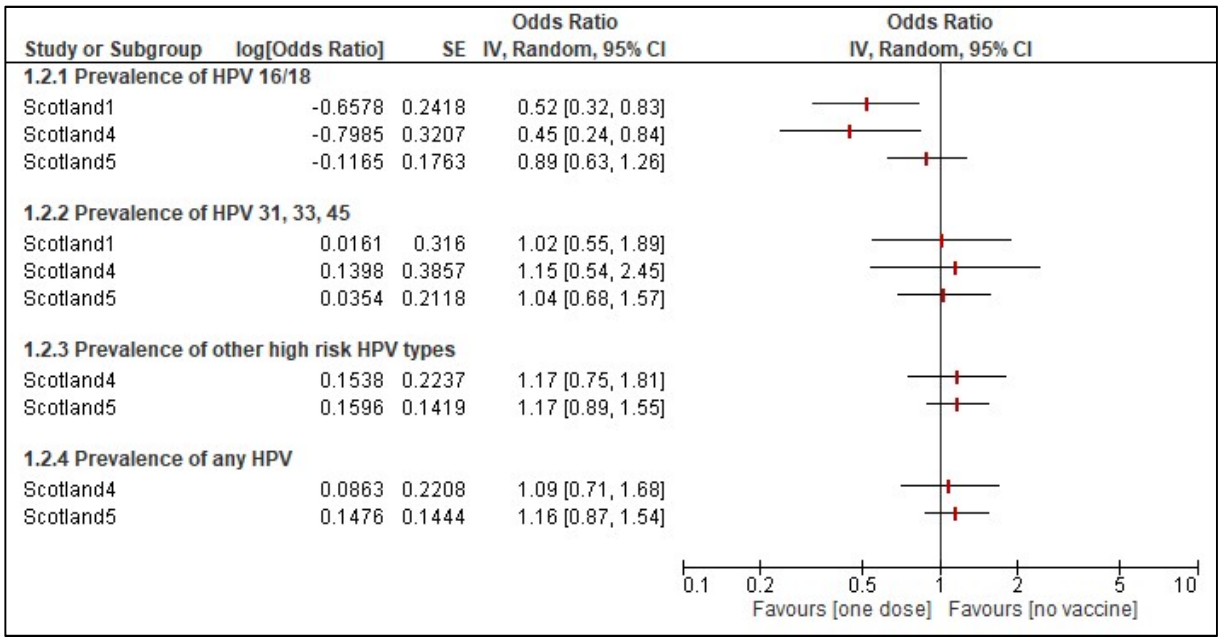
3. HPV infection

Three studies from Scotland (Scotland1, Scotland4, Scotland5) reported adjusted estimates on HPV infections after one dose of bivalent HPV vaccine or no vaccine. A post-hoc analysis of two RCTs (CVT/PATRICIA) reported outcomes of incident HPV infection after one dose of bivalent HPV vaccine compared with control (HAV vaccine), as well as 6-month and 12-month persistent HPV infections.

Prevalent HPV infection

Three studies (Scotland1, Scotland4, Scotland5) reported adjusted estimates on prevalence of HPV. Due to the high likelihood of overlapping cohorts and cases between the Scotland studies, we did not pool estimates (Figure 3).

Studies found little or no difference between one dose and no vaccine, except for prevalence of HPV16/18 where two studies found an effect in favour of one dose whereas one study found little or no difference. All outcomes were of very-low certainty due to serious risk of bias due to confounding, selection bias, and imprecision due to wide 95% CIs.



Scotland1 and Scotland4 were adjusted for age at first vaccination, birth cohort and Scottish Index of Multiple Deprivation (SIMD) quintile; Scotland5 adjusted for birth cohort and SIMD quintile.

Figure 3. Prevalence of HPV infection for one dose bivalent HPV vaccine versus no vaccine, adjusted results

One-time incident and persistent HPV infection

One study (CVT/PATRICIA), which was a post-hoc analysis of two RCTs, reported outcomes of incident, 6-month and 12-month persistent HPV infections. For one-time incident HPV 16/18 infection there was a large effect in favour of one dose compared to control (Hepatitis A vaccine) (RR 0.14, 95% CI 0.07 to 0.30, 2202 participants, moderate certainty evidence). For one-time incident HPV 31/33/35 infections there was an effect in favour of one dose compared to no vaccine, but the 95% CI crossed the line of no effect (Figure 4). There was a large effect in favour of one dose for persistent HPV 16 or 18 infections and an effect in favour of one dose for persistent HPV 31, 33 or 45 infections, but the 95% CI crossed the line of no effect (Figure 5). Evidence for these outcomes was of low-certainty due to imprecision and risk of bias due to confounding.

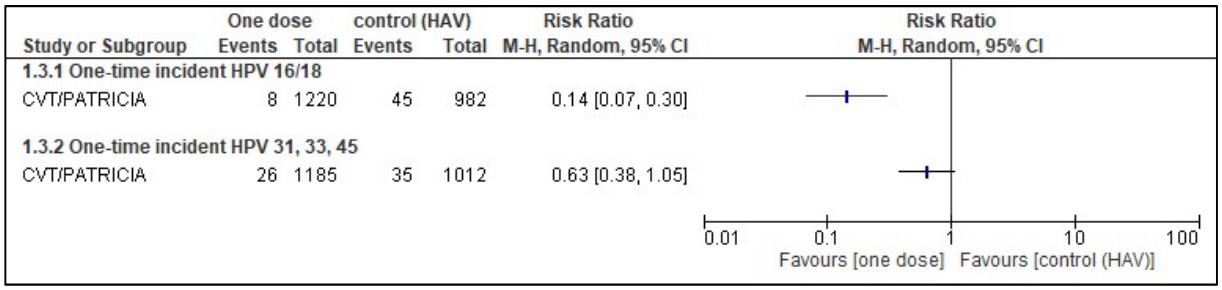


Figure 4. One-time incident HPV infection for one dose bivalent HPV vaccine versus control (HAV), unadjusted results

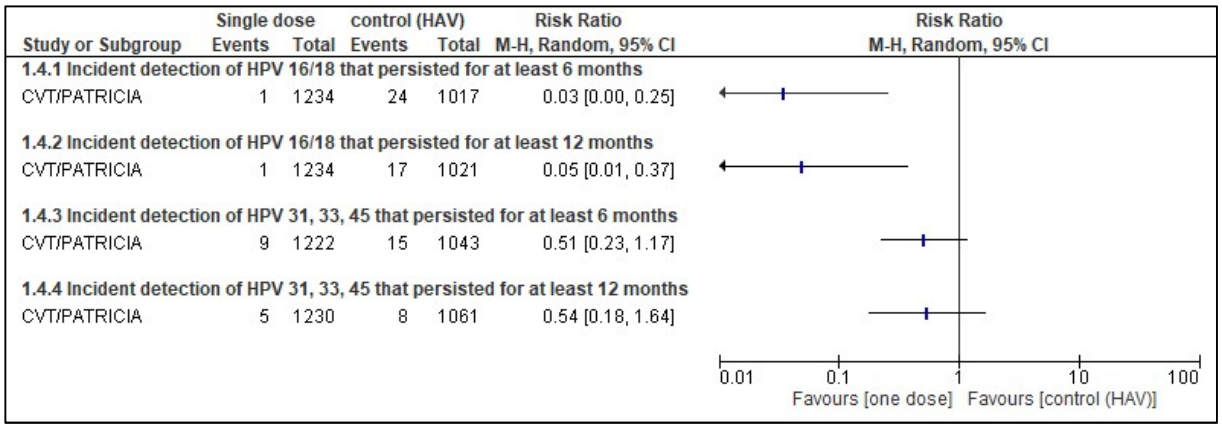


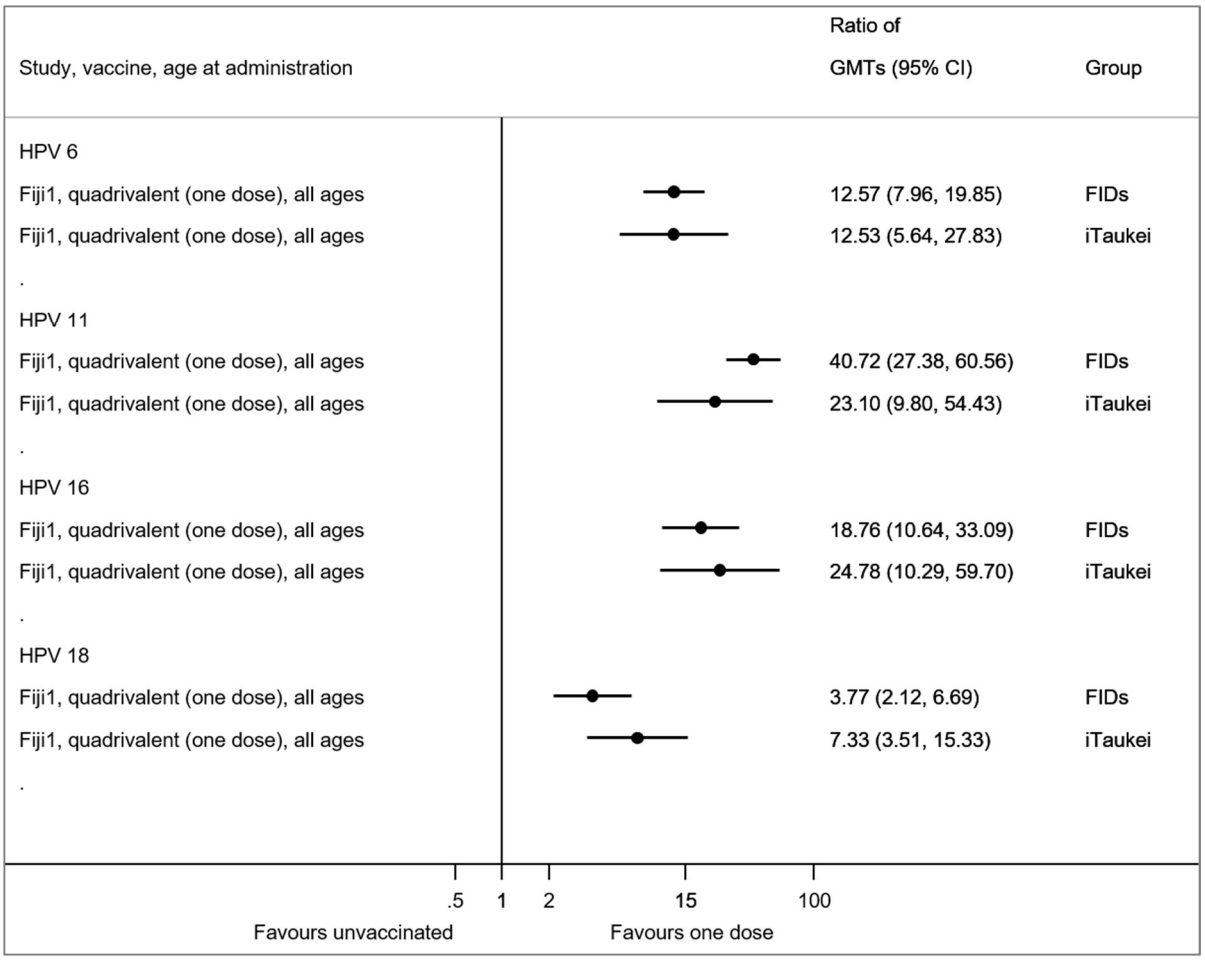
Figure 5. Persistent HPV infection for one dose bivalent HPV vaccine versus control (HAV), unadjusted results

Quadrivalent HPV vaccine

There were 19 included studies (Australia1, Australia2, Australia3, Australia4, Belgium2, Canada2, Canada3, Denmark2, Denmark3, Denmark/Sweden1, Fiji1, India1, Spain2, Sweden1, USA1, USA2, USA6, USA9, USA11) that reported on immunogenicity or clinical outcomes for women and men (USA12) receiving one dose of the quadrivalent HPV vaccine compared to no vaccine. Due to the high likelihood of overlapping cohorts and cases between Australia1, Australia3, and Australia4 (all containing data from Victoria, Australia), we focus here on the results of Australia4 (using national rather than state databases) along with the other studies.

1. Immunogenicity

One study (Fiji1) reported unadjusted immunogenicity data 72 months following one dose of quadrivalent HPV vaccine compared to no vaccine. The study found a large effect on ratio of GMTs for HPV 6, 11, 16 and 18 (Figure 6) and seropositivity to HPV 6, 11, 16, and 18 (Figure 7) favouring one dose, with some differences among the two ethnic subgroups (Fijians of Indian descent and indigenous Fijians). The evidence was of very low-certainty due to a risk of bias due to confounding and selection bias.



FID= Fijians of Indian Descent; iTaukei= indigenous Fijians

Figure 6. Ratios of HPV GMTs for one dose quadrivalent HPV vaccine versus no vaccine at 72 months follow-up, unadjusted results

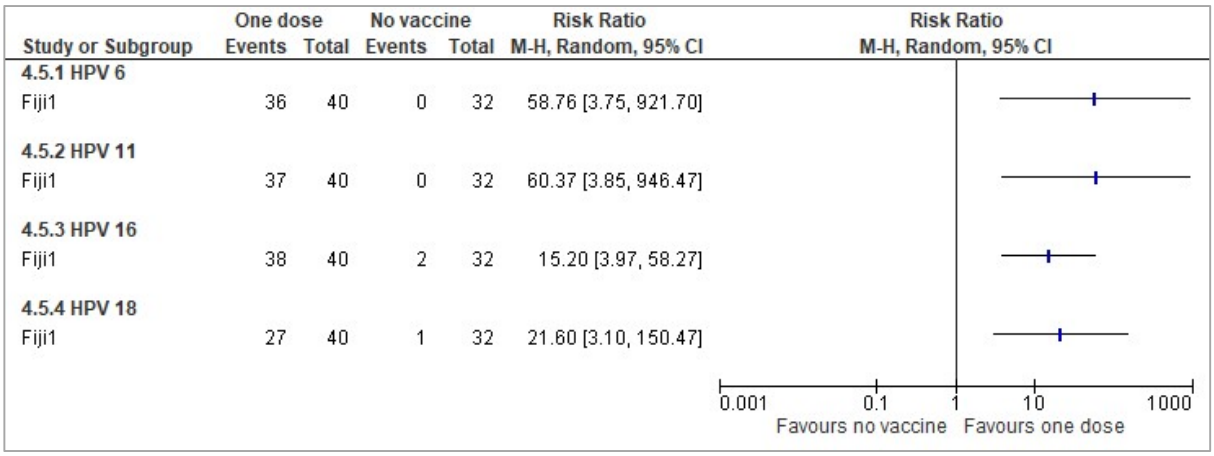


Figure 7. HPV 6, 11, 16, and 18 seropositivity at 72 months follow-up for one dose quadrivalent HPV vaccine versus no vaccine

2. Histological abnormalities

Six studies (Australia1, Australia3, Australia4, Denmark3, Denmark/Sweden1, USA9) reported adjusted estimates on histological abnormalities following one dose of quadrivalent HPV vaccine. The studies could not be pooled due to reporting different types of effect estimates (i.e. RRs, HRs, or

IRRs) and potential overlap between the Australia studies and between the Denmark studies (Table 3).

Five studies measured CIN3/AIS or CIN3+ and results were inconsistent; one study found an effect in favour of no vaccine (Australia1), one study found an effect in favour of one dose (Denmark3), one study found an effect in in favour of no vaccine but the 95% CI crossed the line of no effect (Australia3), one study found an effect in favour of one dose but the 95% CI crossed the line of no effect (Australia4), and one study found little or no difference between one dose and no vaccine (USA9). Evidence for this outcome was of very low-certainty due to risk of bias due to residual confounding, selection bias, and inconsistency.

Four studies measured CIN2+, three studies found an effect in favour of one dose (Australia4, Denmark3, USA9), one study found an effect in favour of one dose in 13-19-year-olds but an effect in favour of no vaccine in 20-29-year-olds (Denmark/Sweden). Evidence for this outcome was of low-certainty due to risk of bias due to residual confounding.

Two studies with overlapping populations reported on CIN2 and found little or no difference between one dose and no vaccine (Australia1) and an effect in favour of no vaccine, but with a 95% CI which crossed the line of no effect (Australia3). The same two studies, with overlapping populations reported on any high-grade histological abnormalities and both found effects in favour of no vaccine, with 95% CIs crossing the line of no effect. One study (Australia1) reported on CIN1 and found little or no difference between one dose and no vaccine. All outcomes were of very low-certainty evidence due to risk of bias due to residual confounding and imprecision and selection bias.

Table 3. Adjusted estimates for histological abnormalities comparing one dose of quadrivalent HPV vaccine with no vaccine

Outcome	Study	Risk of bias	Adjusted estimate (95% CI)	Direction of effect	Number of participants
CIN3/AIS or CIN3+	Australia1*	Serious	HR 1.41 (1.12 to 1.77)	No vaccination	139,993
	Australia3†	Serious	HR 1.40 (0.75 to 2.61)	No vaccination	17,760
	Australia4†	Serious	HR 1.53 (0.94 to 2.46)	One dose	28,237
	Denmark3‡	Serious	IRR 0.38 (0.14 to 0.98)	One dose	384,807 person-years
	USA9§	Serious	RR 0.90 (0.65 to 1.24)	Little or no difference	28,591 participants
CIN2+	Australia4†	Serious	HR 0.65 (0.52 to 0.81)	One dose	57,463
	Denmark3‡	Serious	IRR 0.34 (0.13 to 0.87)	One dose	385,254 person-years
	USA9§	Serious	RR 0.84 (0.68 to 1.03)	One dose	28,591 participants

CIN2+, 13-16 years	Denmark/ Sweden1‖	Serious	IRR 0.23 (0.01 to 5.24)	One dose	804,541 unvaccinated; 1 dose not reported
CIN2+, 17-19 years	Denmark/ Sweden1‖	Serious	IRR 0.58 (0.15 to 2.19)	One dose	701,907 unvaccinated; 1 dose not reported
CIN2+, 20-29 years	Denmark/ Sweden1‖	Serious	IRR 1.56 (1.13 to 2.15)	No vaccination	2,639,725 unvaccinated; 1 dose not reported
CIN2	Australia1*	Serious	HR 0.98 (0.75 to 1.29)	Little or no difference	139,993
	Australia3†	Serious	HR 1.29 (0.76 to 2.20)	No vaccination	17,760
CIN1	Australia3†	Serious	HR 0.89 (0.56 to 1.41)	Little or no difference	17,760
Any high-grade histological abnormalities	Australia1*	Serious	HR 1.19 (0.99 to 1.43)	No vaccination	139,993
	Australia3†	Serious	HR 1.47 (0.97 to 2.23)	No vaccination	17,760

* adjusted for age in 2007, remoteness, SES; † adjusted for remoteness, SES, age at first screen; ‡ adjusted for maternal education, attained age; § adjusted for smoking, hormonal contraceptive use, race and ethnicity, recent STI, livebirths, prior outpatient visits, immunosuppression status; ‖ adjusted for attained age, mother's education, country AIS= adenocarcinoma in situ; CIN= cervical intraepithelial neoplasia; HR= hazard ratio; IRR= incidence rate ratio; RR= risk ratio; SES= socioeconomic status; STI= sexually transmitted infection

Six studies (Australia1, Australia2, Australia3, Australia4, Denmark3, USA9) reported unadjusted data on cases of CIN1, CIN2, or CIN3, or high-grade or "other" histological abnormalities after one dose of quadrivalent HPV vaccine or no vaccine. Studies were not pooled due to overlapping populations for Australia1, Australia3, and Australia4, and due to very high heterogeneity for CIN2+ and CIN3+ (see Figure 8). All outcomes were considered to be at very low-certainty due to serious risk of bias due to confounding and selection bias.

One study (Australia3) reported on CIN1 and found little or no difference between one dose and no vaccine. Two studies (Australia1, Australia3) reported on CIN2 and results were inconsistent; one study found an effect in favour of one dose whereas the other study found little or no difference between the two groups. Five studies (Australia1, Australia3, Australia4, Denmark3, USA9) reported on CIN2+ and results were very inconsistent with one study reporting a large effect in favour of one dose, two studies found a small effect in favour of one dose, and the other two studies found little or no difference between one dose and no vaccine. The same five studies (Australia1, Australia3, Australia4, Denmark3, USA9) also reported on CIN3+ and again results were inconsistent with one study (Denmark3) reporting a large effect in favour of one dose (likely due to the fact that this study restricted analyses to girls < 16 years old at vaccination) and the remaining four studies showing little or no difference between one dose and no vaccine. Three studies (Australia1, Australia2, Australia3) reported on any high-grade histological abnormalities; one study found a small effect in favour of one dose and the other two studies found little or no difference between the two groups.

Finally, one study reported on "other" histological abnormality and found little or no difference between the two groups.

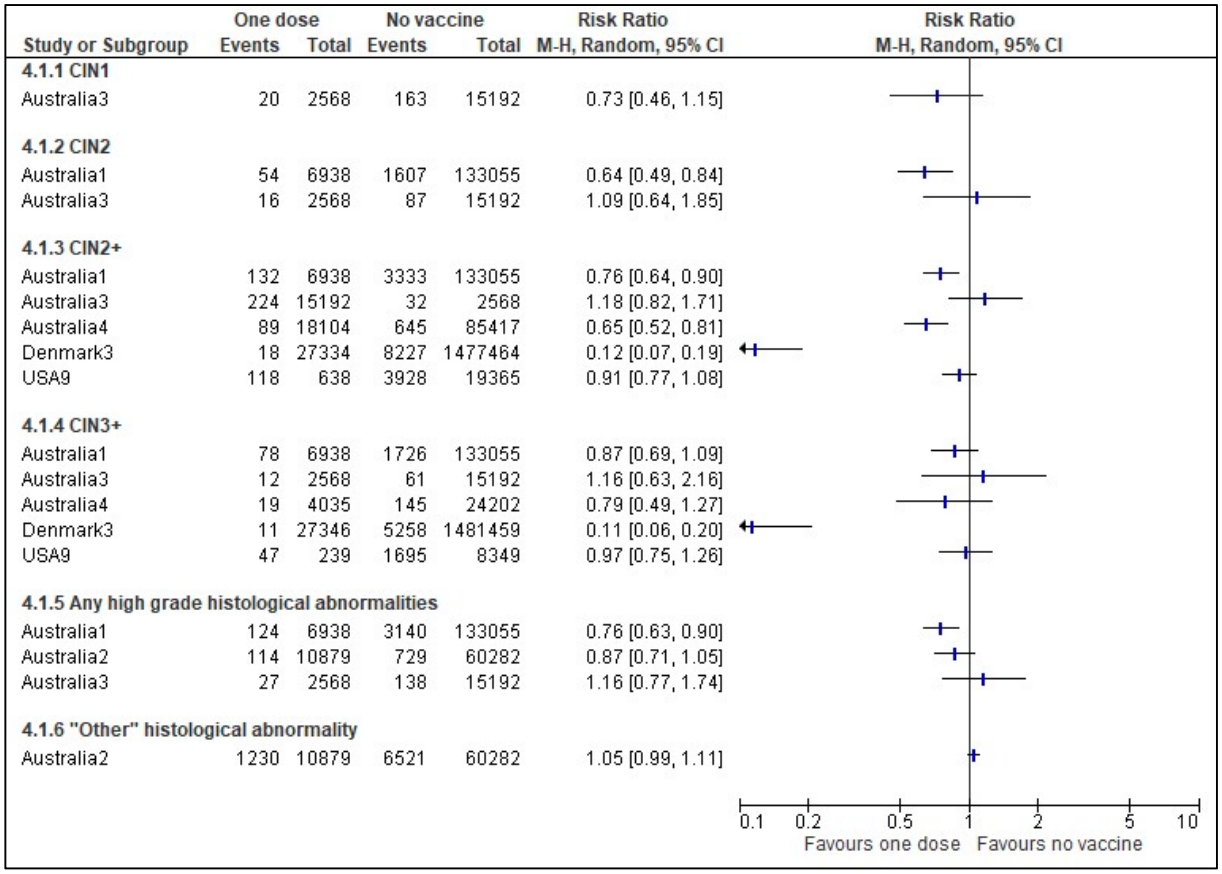


Figure 8. Histological abnormalities for one dose quadrivalent HPV vaccine versus no vaccine, unadjusted results

3. Cytological abnormalities

Three studies (Australia1, Australia3, USA1) reported adjusted estimates on cytological abnormalities. The studies were not pooled due to potential overlap between the Australia studies (Table 4). All outcomes were of very low-certainty due to a risk of bias due to residual confounding and selection bias.

Two studies (Australia1, Australia3) reported on high-grade and low-grade cytology. Results for high-grade cytology were inconsistent, one study found an effect in favour of one dose and the other study found little or no difference between one dose and no vaccine. For low-grade cytology both studies found an effect in favour of one dose compared with no vaccine. One study (USA1) reported on abnormal cervical cytology and found little or no difference between one dose and no vaccine.

Table 4. Adjusted estimates for cytological abnormalities comparing one dose of quadrivalent HPV vaccine with no vaccine

Outcome	Study	Risk of bias	Adjusted estimate (95% CI)	Direction of effect	Number of participants
High-grade cytology	Australia1*	Serious	HR 0.44 (0.32 to 0.59)	One dose	139,993

	Australia3†	Serious	HR 0.85 (0.62 to 1.17)	Little or no difference	17,760
Low-grade cytology	Australia1*	Serious	HR 0.48 (0.40 to 0.58)	One dose	139,993
	Australia3†	Serious	HR 0.67 (0.59 to 0.76)	One dose	17,760
Abnormal cervical cytology	USA1‡	Serious	HR 1.05 (0.88 to 1.26)	Little or no difference	2,327

*adjusted for age in 2007, remoteness, SES; †adjusted for remoteness, SES and age at first screen; ‡ adjusted for number of doses; age as of January 1, 2007; language; insurance; clinic type; abnormal baseline cervical cytology result; baseline Chlamydia screening

Five studies (Australia1, Australia3, Canada2, USA1, USA13) reported unadjusted data on cases of high-grade, low-grade, or any abnormal cytology after one dose of quadrivalent HPV vaccine or no vaccine. Studies were not pooled due to overlapping populations for Australia1 and Australia3, and due to very high heterogeneity ($I^2 > 90\%$) for high-grade and low-grade cytology (see Figure 9).

However, two studies (Canada2, USA1) could be pooled and showed little to no difference on abnormal cervical cytology for one dose compared with no vaccine (RR 0.95, 95% CI 0.84 to 1.08, 8366 participants, very low-certainty evidence due to serious risk of bias due to confounding and selection bias).

Four studies (Australia1, Australia3, Canada2, USA13) reported on high-grade and low-grade cytology, results were inconsistent and of very low certainty due to the inconsistency, serious risk of bias due to confounding, and selection bias (Figure 9).

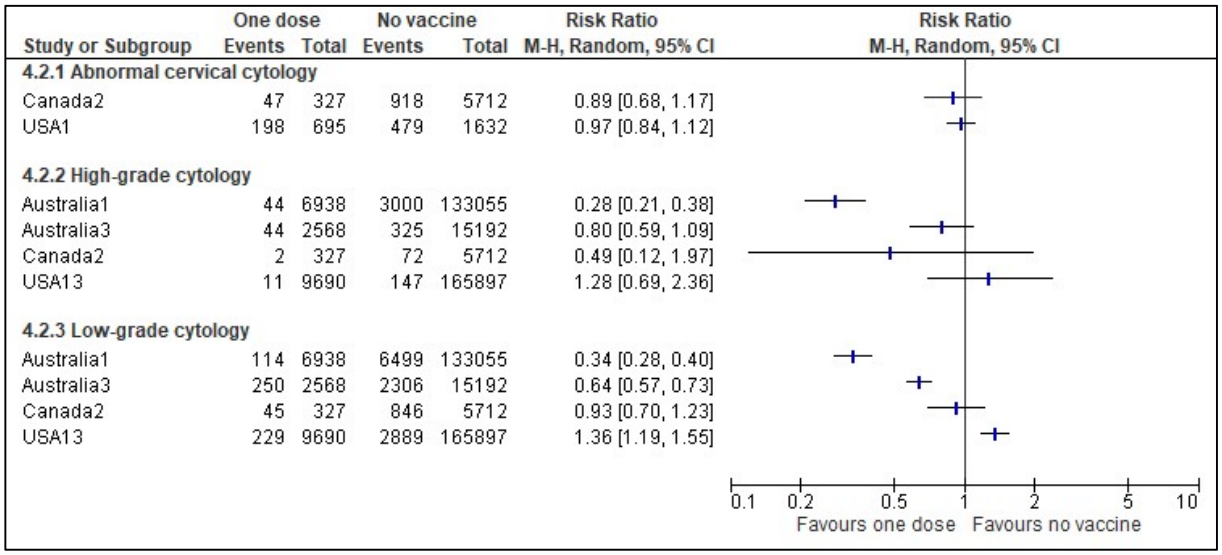


Figure 9. Cytological abnormalities for one dose quadrivalent HPV vaccine versus no vaccine, unadjusted results

4. Genital warts

Six studies (Belgium2, Canada3, Spain2, Sweden1, USA2, USA11) reported adjusted estimates for genital warts following one dose of HPV vaccine (Table 5). The studies were not pooled due to reporting different types of estimates (i.e. VE, HR, RR, IRR, IRD) and potential overlap between the USA studies. Results were at low-certainty due to risk of bias due to residual confounding.

Four studies showed an adjusted effect favouring one dose compared with no vaccine (Spain2, Sweden1, USA2 (12-month buffer period), USA11 (15-19 years), although with a six month buffer period USA2 found little or no difference and in the <15 years and ≥20 years age groups the USA11 study there was also little or no difference. Two studies (Belgium2, Canada3) found little or no difference between one dose and no vaccine, although for the ≥19 years age group in Canada3, results favoured no vaccine. Evidence for this outcome was considered at low certainty due to a risk of bias due to residual confounding.

Table 5. Adjusted estimates for genital warts comparing one dose of quadrivalent HPV vaccine with no vaccine

Study	Subgroup	Risk of bias	Adjusted estimate (95% CI)	Direction of effect	Number of participants
USA2§	6 m buffer	Moderate	HR 0.81 (0.60 to 1.08)	One dose	62,677 person-years
	12 m buffer	Moderate	HR 0.32 (0.20 to 0.52)	One dose	60,256 person-years
Belgium2*		Serious	VE 36.6 (-16.1 to 65.4)	One dose	234,132 person-years
Canada3**	9 to 18 years	Serious	HR 0.6 (0.2 to 1.8)	One dose	193,054 person-years unvaccinated; 1 dose not reported
	≥19 years	Serious	HR 3.7 (2.1 to 6.8)	No vaccination	29,339 person-years unvaccinated, 1,287 person-years 1 dose sexually active; 1 dose not sexually active not reported
Spain2†	14 years	Serious	RR 0.39 (0.13 to 0.8)	One dose	625,147.93 person-years
Sweden1‡	10 to 16 years	Serious	IRR 0.31 (0.20 to 0.49) IRD 384 (305 to 464)	One dose	1,785,870 person-years
	10 to 19 years	Serious	IRR 0.54 (0.43 to 0.68) IRD 257 (189 to 326)	One dose	2,576,943 person-years
	14 to 16 years	Serious	IRR 0.33 (0.21 to 0.52)	One dose	810,003 person-years
	17 to 19 years	Serious	IRR 0.71 (0.55 to 0.92) IRD 162	One dose	791,073 person-years

			(58 to 266)		
USA11‖	<15 years	Serious	HR 0.80 (0.34 to 1.90)	Little or no difference	168,205 participants
	15 to 19 years	Serious	HR 0.65 (0.49 to 0.85)	One dose	61,961 participants
	≥20 years	Serious	HR 0.96 (0.72 to 1.28)	Little or no difference	111,077 participants

§ propensity score weighted for race/ethnicity, health plan (site), age at enrolment in the health plan, age at beginning of study period, age at first evidence of probable sexual activity, age at first dose of HPV vaccine, indicator for whether the person was continuously enrolled from index date to the end of the study period, months enrolled in the health plan, indicator for whether the person had any preventive health visits, Medicaid enrolment, oral contraceptive use, or history of tests for pregnancy, chlamydia, or gonorrhoea; * adjusted for age; ** adjusted for matching variables plus previous hospitalization and previous physician visit; † adjusted for vaccination state, age, healthcare department and year; ‡ adjusted for attained age and parental education level; || adjusted for sex, region, and the history of sexually transmitted diseases. This study includes male participants (23%) as well as females.

Eight studies (Belgium2, Canada3, Denmark2, Spain2, Sweden1, USA2, USA6, USA11) reported unadjusted data on genital warts after one dose of quadrivalent HPV vaccine or no vaccine. Results were at very low-certainty due to risk of bias due to confounding and inconsistency. Five studies (Belgium2, Denmark2, Spain2, Sweden1, USA2) favoured one dose compared with no vaccine and two studies (Canada3, USA6, USA11) reported little or no difference (Figure 10).

In addition, one study (USA10) reported vaccine efficacy (VE) estimates without CIs for one dose compared with no vaccine of 87% in 9 to 12-year olds, 83% in 13 to 14-year olds, and 21% in 15 to 17-year olds (all p<0.001) in a conference abstract.

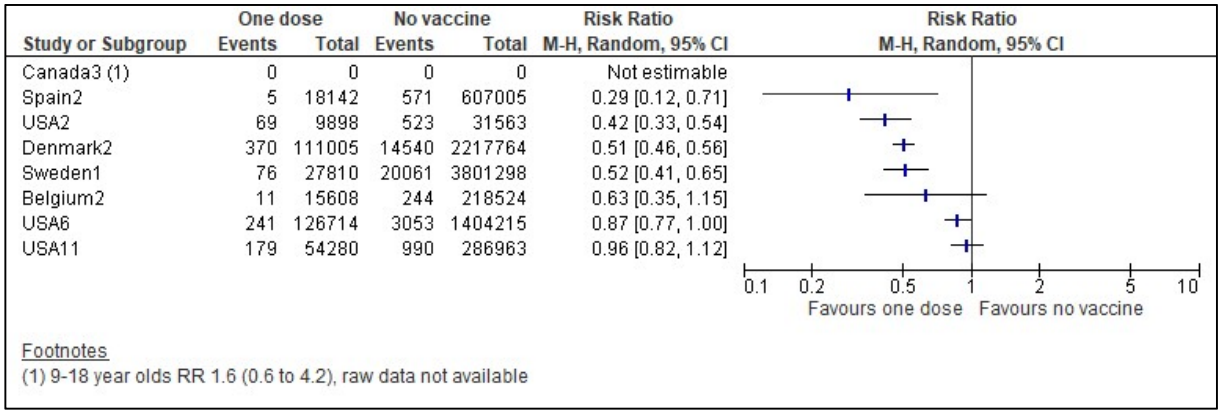


Figure 10. Genital warts for one dose quadrivalent HPV vaccine versus no vaccine, unadjusted results

5. HPV infections

One study (India1) reported unadjusted data on incident HPV 16/18, HPV 31/33/45, and non-vaccine HPV type (excluding 31, 33, 45) infections, as well as persistent HPV 16/18, HPV 31/33/45, and non-vaccine HPV type (excluding 31, 33, 45) infections over a 7-year follow-up period (Figure 11).

With one dose compared with no vaccine, the study found a moderate reduction in incident HPV16/18 and HPV 6/11/16/18 infections and small reduction in incident HPV 31/33/45 and any HPV

infections. The evidence was considered to be at low certainty due to risk of bias due to confounding. Due to few events, data were imprecise and inconclusive for persistent HPV infection outcomes, resulting in very low-certainty evidence due to risk of bias due to confounding and imprecision.

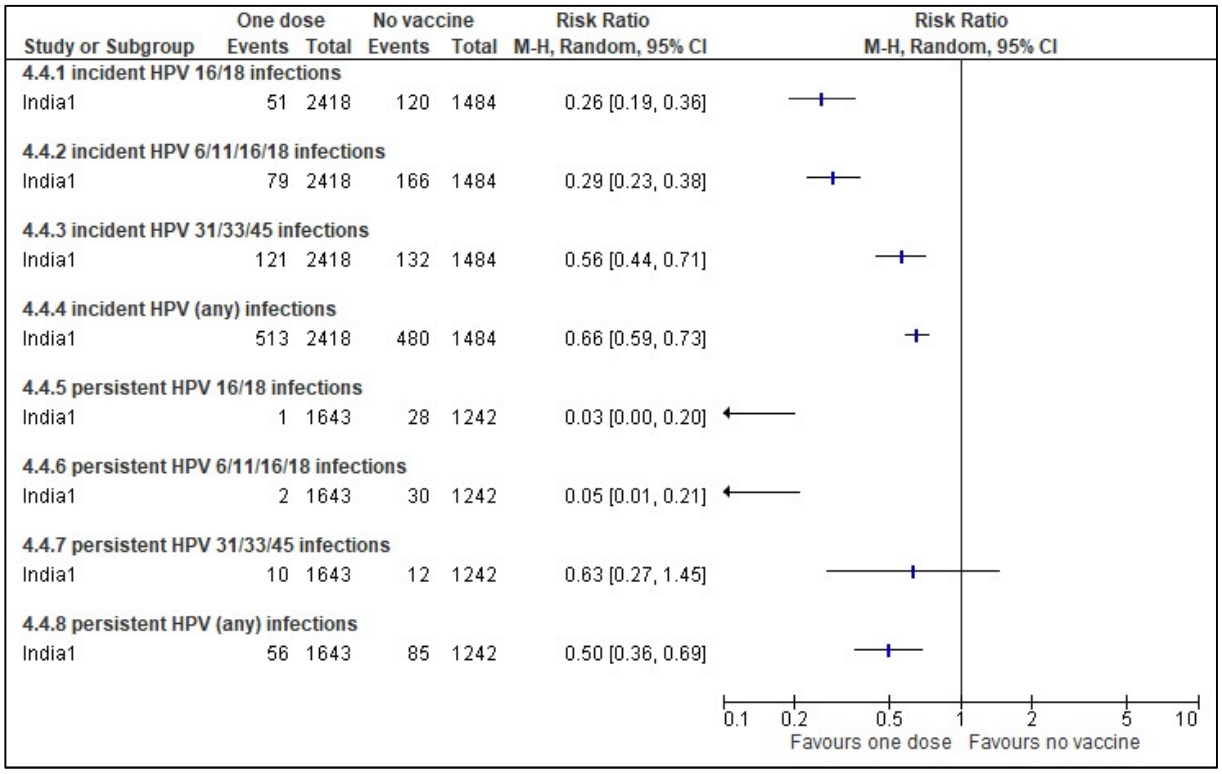


Figure 11. HPV infections for one dose quadrivalent HPV vaccine versus no vaccine over a 7-year follow-up period, unadjusted results

Comparison 2. Effectiveness and immunogenicity of one dose of HPV vaccine compared with two doses

This section summarises the findings from the included studies comparing one dose versus two doses of HPV vaccine. Analyses are stratified by type of HPV vaccine (bivalent or quadrivalent). It is noted where concerns exist regarding risk of bias, imprecision of the estimates (due to small sample sizes, few events, or wide confidence intervals) and heterogeneity across studies being pooled. Certainty of the evidence is reported below and detailed reasons for downgrading or upgrading the certainty, according to guidance summarised in Table 1 and Table 2, are provided in Appendix 7. GRADE tables.

Bivalent HPV vaccine

There were eight included studies (Costa Rica1, Scotland1, Scotland2, Scotland3, Scotland4, Scotland5, Scotland6, Uganda1) that reported on immunogenicity or clinical outcomes for women receiving one dose compared with two doses of the bivalent HPV vaccine.

1. Immunogenicity

Two studies (Costa Rica1, Uganda1) reported unadjusted estimates on antibody titres for HPV 16 and 18 following one or two doses of bivalent HPV vaccine at 24 to 84 months follow-up. These studies were not pooled due to different duration of follow-up (24, 48, and 84 months).

Antibody titres were in favour of two doses compared with one dose for both HPV 16 and 18 at 24, 48 and 84 months; non-inferiority of one dose compared with two doses was inconclusive (Figure 12). Evidence was of low-certainty due to risk of bias due to confounding and imprecision from wide confidence intervals.

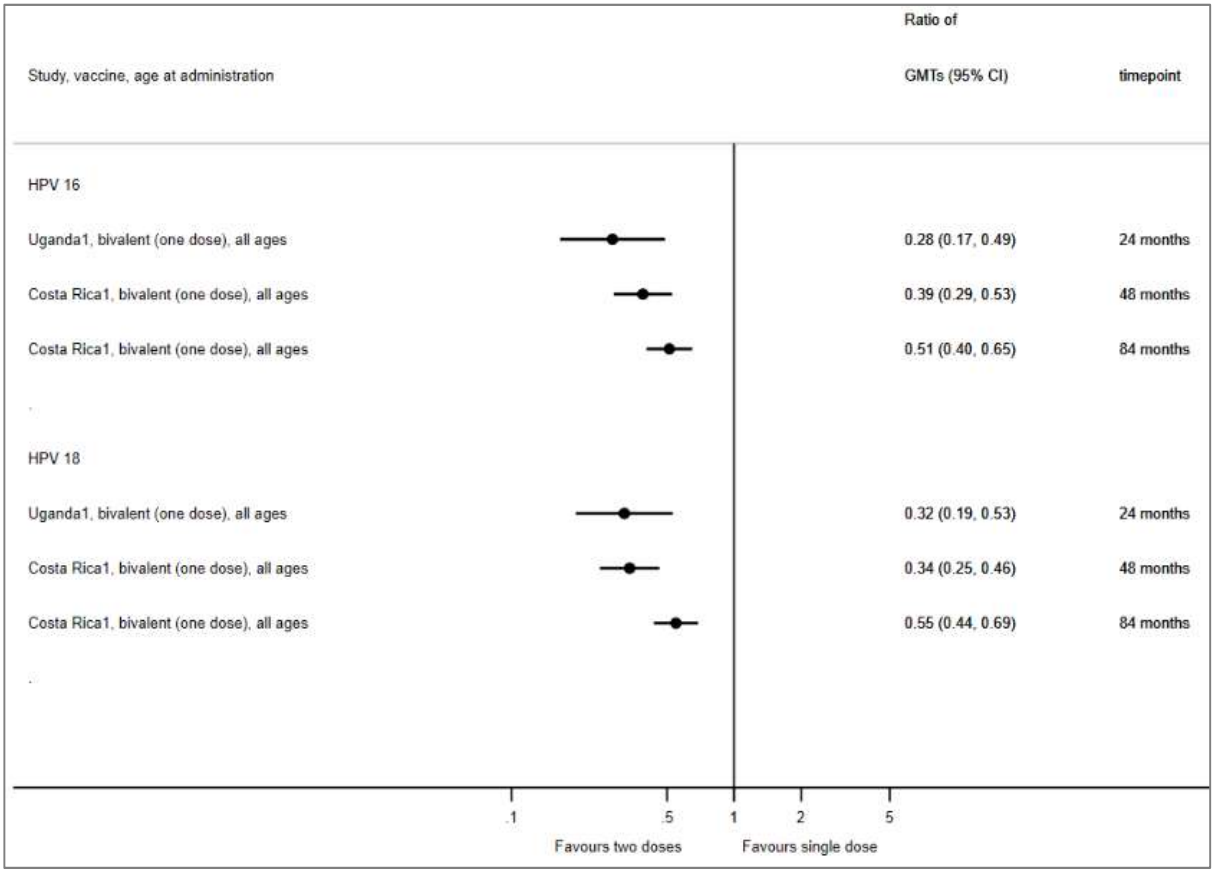


Figure 12. HPV 16 and 18 antibody titres for one dose versus two doses bivalent HPV vaccine at 24 to 84 months follow-up, unadjusted results

Two studies (Costa Rica1, Uganda1) reported unadjusted estimates on seropositivity for HPV 16 and 18 following one or two doses of bivalent HPV vaccine at 24- and 48-months follow-up. These studies were not pooled due to different duration of follow-up (24 and 48 months).

There was no difference between one and two doses on seropositivity to HPV 16 at 24 months (RR 1.00, 95% CI 0.96 to 1.05, 181 participants) or at 48 months (RR 1.00, 95% CI 0.98 to 1.02, 218 participants), or HPV 18 at 24 months (RR 0.99, 95% CI 0.93 to 1.05, 181 participants) (Figure 13). Evidence was of low-certainty due to risk of bias due to confounding and imprecision from few events.

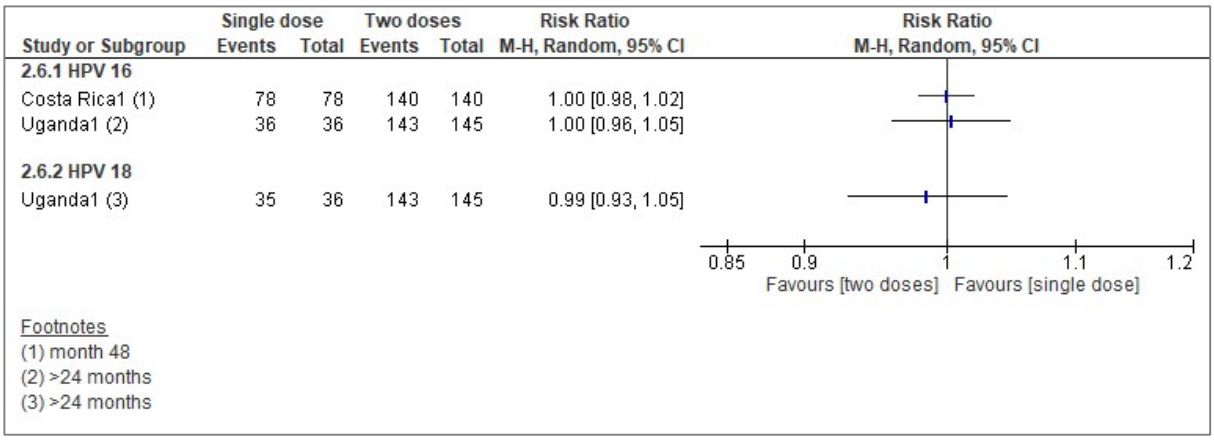


Figure 13. HPV 16 and 18 seropositivity for one dose versus two doses bivalent HPV vaccine at 24- and 48-months follow-up, unadjusted results

2. Histological abnormalities

Two studies (Scotland2, Scotland3) reported unadjusted estimates on cases of CIN1, CIN2, or CIN3 after one or two doses of bivalent HPV vaccine. These studies were not pooled due to the potential for overlapping populations.

Due to few events, data were too imprecise to determine if a difference exists between one dose and two doses of bivalent HPV vaccine on these outcomes (Figure 14). All outcomes were of very low-certainty due to risk of bias due to confounding, selection bias, and imprecision from few events.

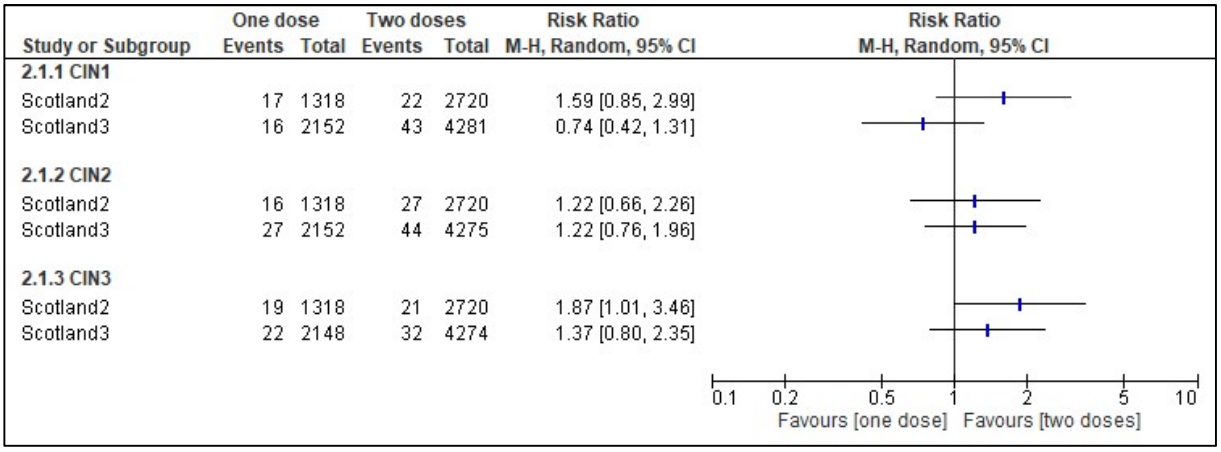


Figure 14. CIN1, CIN2, CIN3 for one versus two doses bivalent HPV vaccine, unadjusted results

3. HPV infections

Prevalent HPV infection

Three studies from Scotland (Scotland1, Scotland4, Scotland5) reported unadjusted estimates on HPV infections after one or two doses of bivalent HPV vaccine. These studies were not pooled due to the potential for overlapping populations.

Studies found little or no difference between one and two doses on prevalence of HPV 16 or 18, prevalence of other HPV types (not 16, 18, 31, 33, 45), and prevalence of any HPV type. The studies showed results favouring two doses compared with one dose on prevalence of HPV 31, 33, or 45 (Figure 15). All outcomes were of very low-certainty due to a risk of bias due to confounding, selection bias, and imprecision from few events.

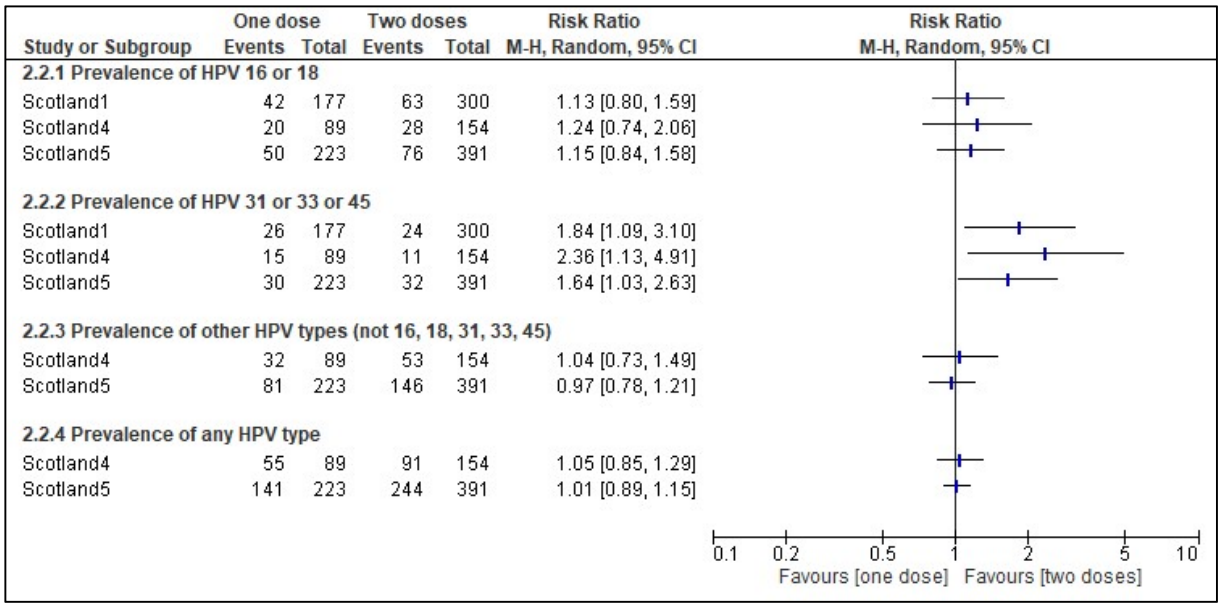


Figure 15. Prevalence of HPV infection for one versus two doses bivalent HPV vaccine, unadjusted results

7-year cumulative incidence of HPV infection

One study (Costa Rica1) reported unadjusted estimates of cumulative HPV infections over 7 years after one or two doses (with a two-month interval between doses) of bivalent HPV vaccine (Figure 16).

There were very few reported events to determine if there is any difference on cumulative HPV 16, HPV 18, HPV 16/18, or HPV 31/33/45 infections between one dose and two doses of HPV vaccine over 7 years. Evidence for these outcomes were of very low certainty due to a risk of bias due to confounding and serious imprecision from few events.

There appears to be little to no difference between one dose and two doses of bivalent HPV vaccine on cumulative other carcinogenic HPV infections (RR 0.86, 95% CI 0.66 to 1.11, 327 participants, 1 study) and one dose appeared to result in slightly fewer cases of noncarcinogenic HPV infections than two doses (RR 0.77, 95% CI 0.61 to 0.96, 327 participants, 1 study). Evidence for these outcomes were of low certainty due to imprecision from few events.

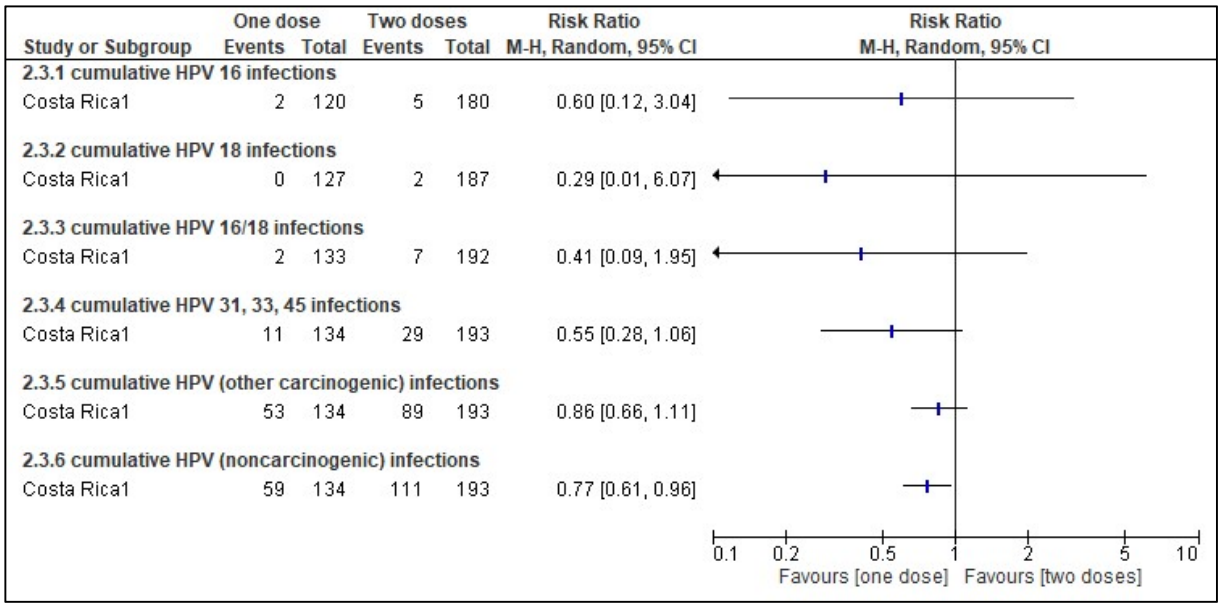


Figure 16. 7-year cumulative HPV infection for one versus two doses bivalent HPV vaccine, unadjusted results

One-time incident and persistent HPV infection

One study (CVT/PATRICIA), which was a post-hoc analysis of two RCTs, reported unadjusted estimates for incident and persistent HPV infections. There was little to no difference on incident HPV 16/18 and HPV 31/33/45 infections (Figure 17) between one and two doses. There was an effect in favour of one dose for 6- and 12-month persistent HPV infections, but the confidence intervals were very wide and crossed the line of no effect (Figure 18). All outcomes were of very low-certainty due to a risk of bias due to confounding and imprecision from few events.

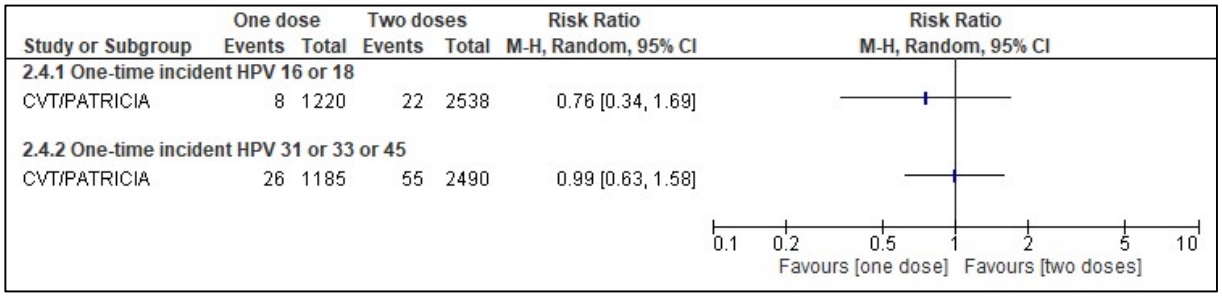


Figure 17. One-time incidence of HPV infection for one versus two doses bivalent HPV vaccine, unadjusted results

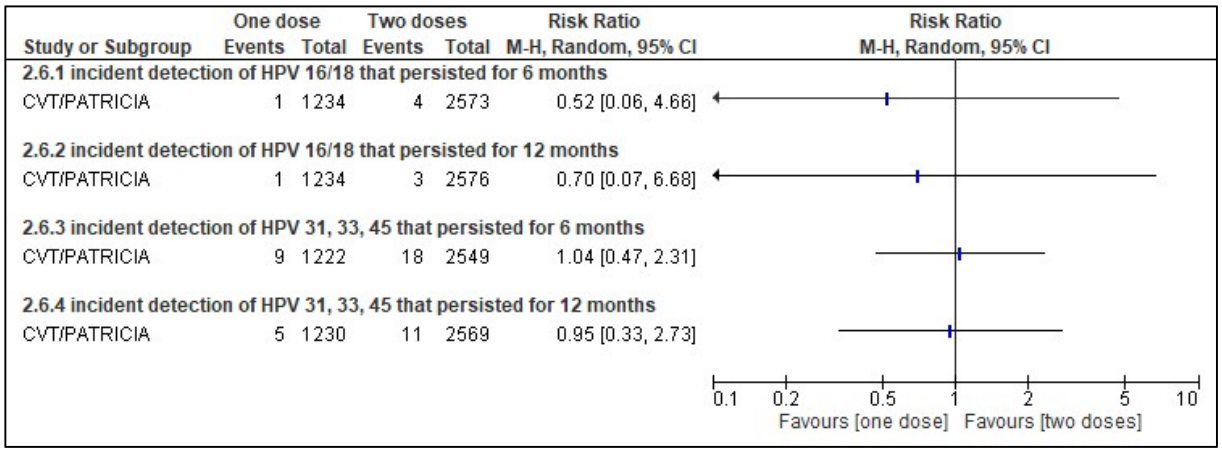


Figure 18. Persistent HPV infection for one versus two doses bivalent HPV vaccine, unadjusted results

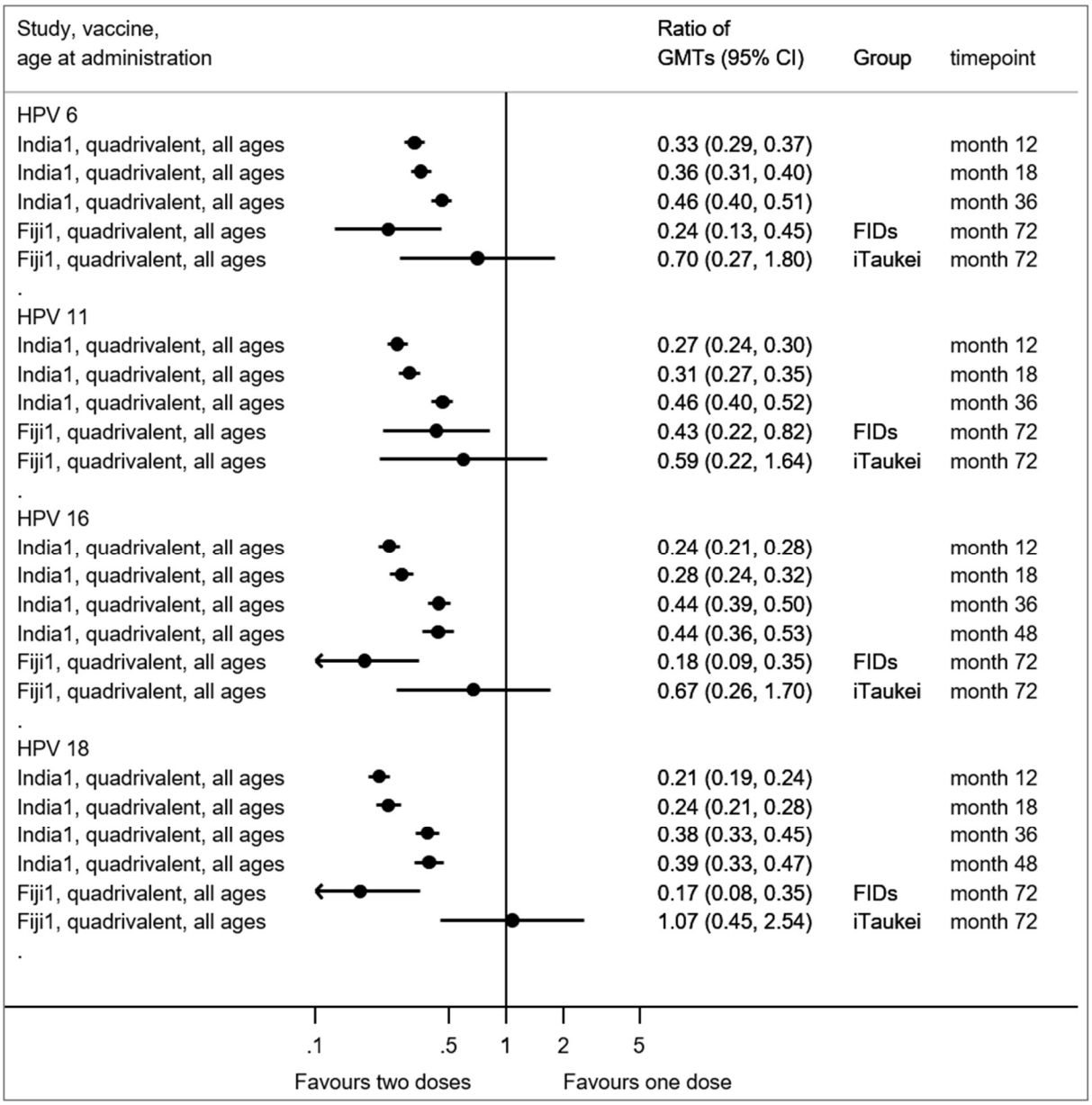
Quadrivalent HPV vaccine

There were 19 included studies (Australia1, Australia2, Australia3, Australia4, Belgium2, Canada2, Canada3, Denmark2, Denmark3, Fiji1, India1, Spain2, Sweden1, USA1, USA2, USA6, USA9, USA11, USA16) that reported on immunogenicity or clinical outcomes for women receiving one dose compared with two doses of the quadrivalent HPV vaccine. Due to the high likelihood of overlapping cohorts and cases between Australia1, Australia3, and Australia4 (all carried out with data from the state of Victoria) and USA6 and USA11 (same data source and dates), we focus here on the results of Australia4 (included national databases) and USA6 (included a larger sample size).

1. Immunogenicity

Two studies (Fiji1, India1) reported on antibody titres for HPV 6, 11, 16 and 18 following one or two doses of quadrivalent HPV vaccine up to 72 months follow-up.

Over all timepoints, and for all HPV types, two doses of HPV vaccine resulted in higher antibody titres than one dose, except for indigenous Fijian girls (iTaukei) where effects were smaller and not statistically significant at 72 months follow-up (Figure 19). GMTs following one dose were inferior to those following two doses at all timepoints, except for 36-month HPV 6, 11 and 16, 48-month HPV 16 (India1), and for all HPV types in indigenous Fijian girls at 72 months, where the confidence intervals crossed the line of non-inferiority (0.5). Evidence was of low-certainty due to a risk of bias due to confounding.



FID= Fijians of Indian Descent; iTaukei= indigenous Fijians

Figure 19. Ratio of GMTs for one dose versus two doses quadrivalent HPV vaccine at 12 to 72 months follow-up.

Two studies (Fiji1, USA16) reported on seropositivity to HPV 6, 11, 16, and 18 for one dose compared with two doses of quadrivalent HPV vaccine after 6 years follow-up (Figure 20).

There was little to no difference in rate of seropositivity for HPV 6, HPV 11, or HPV 16, though estimates from USA16 were slightly in favour of two doses. For HPV 18 seropositivity was lower in the study from Fiji (RR 0.75, 95% CI 0.60 to 0.94) and there was little to no difference in the study from the USA (RR 1.02, 95% CI 0.95 to 1.09). Evidence was of very low certainty due to a risk of bias due to confounding and selection bias.

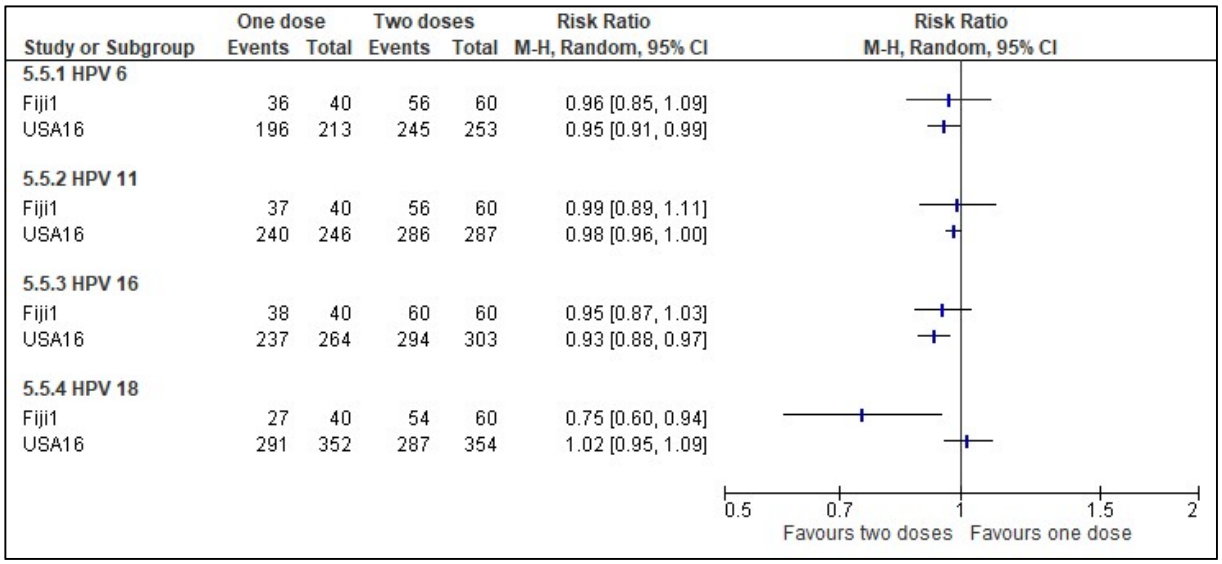


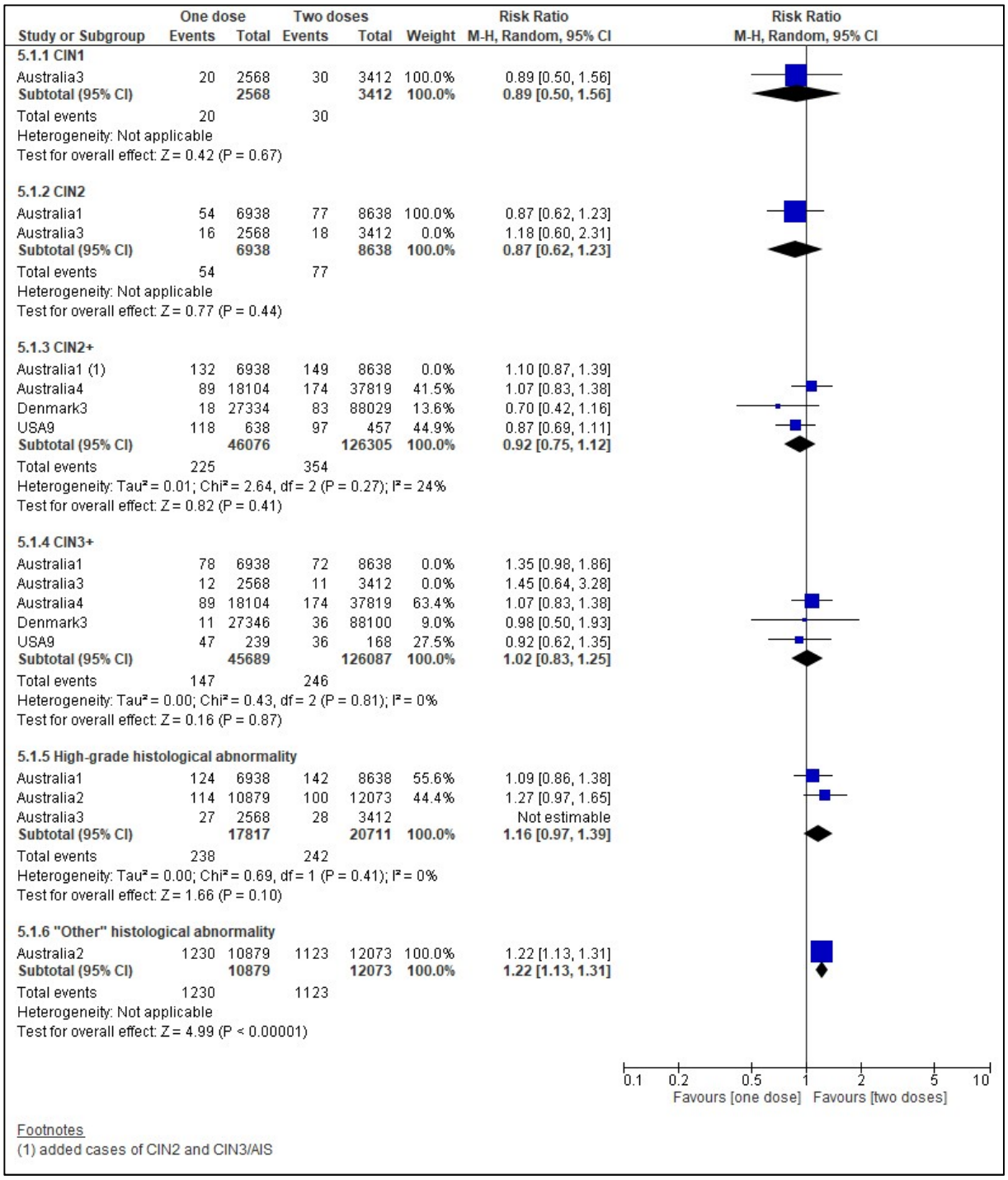
Figure 20. HPV 6, 11, 16, and 18 seropositivity for one dose versus two doses quadrivalent HPV vaccine after 6 years follow-up

2. Histological abnormalities

One study (Denmark3) reported adjusted incidence rate ratios (adjusted for maternal education and attained age) on CIN2+ (IRR 1.00, 95% CI 0.61 to 1.64) and CIN3+ (IRR 0.89, 95% CI 0.53 to 1.52), showing little or no difference between one and two doses of quadrivalent vaccine for these outcomes. Another study (Australia4) reported adjusted hazard ratios (adjusted for age, area of residence, and socioeconomic status) on CIN2+ (HR 0.94, 95% CI 0.73 to 1.21) and CIN3+ (HR 0.64, 95% CI 0.35 to 1.16) also showing little or no difference between one and two doses of quadrivalent vaccine for these outcomes. This was considered very low-certainty evidence due to a risk of bias due to residual confounding and imprecision from wide confidence intervals.

Six studies (Australia1, Australia2, Australia3, Australia4, Denmark3, USA9) reported unadjusted data on cases of CIN1, CIN2, or CIN3, or high-grade or "other" histological abnormalities after one or two doses of quadrivalent HPV vaccine. Evidence for these outcomes was of low to very low certainty due to a risk of bias due to confounding, selection bias, and imprecision from few events.

There was insufficient evidence to determine if a difference exists between one dose and two doses of quadrivalent HPV vaccine on CIN1 and CIN2, due to the limited number of cases reported (Figure 21). There was little or no difference on CIN2+ (RR 0.92, 95% CI 0.75 to 1.12, 172,381 person-years, 4 studies), CIN3+ (RR 1.02, 95% CI 0.83 to 1.25, 171,776 person-years, 4 studies), or high-grade histological abnormalities (RR 1.12, 95% CI 0.86 to 1.46, 38,528 person-years, 2 studies) between one and two doses (Figure 21). For any other histological abnormalities, there were slightly more cases in the one dose group compared with the two-dose group (RR 1.30, 95% CI 0.99 to 1.69, 22,952 participants, 1 study).



In analyses including both Australia1 and Australia3, due to participant overlap, Australia3 (with the narrower range of birth cohorts of the two) was excluded from the meta-analysis. In analyses including Australia1, Australia3, and Australia4, due to the high likelihood of overlapping cohorts and cases, Australia1 and Australia3 (data from the state of Victoria) were excluded and we focus here on the results of Australia4 (national databases).

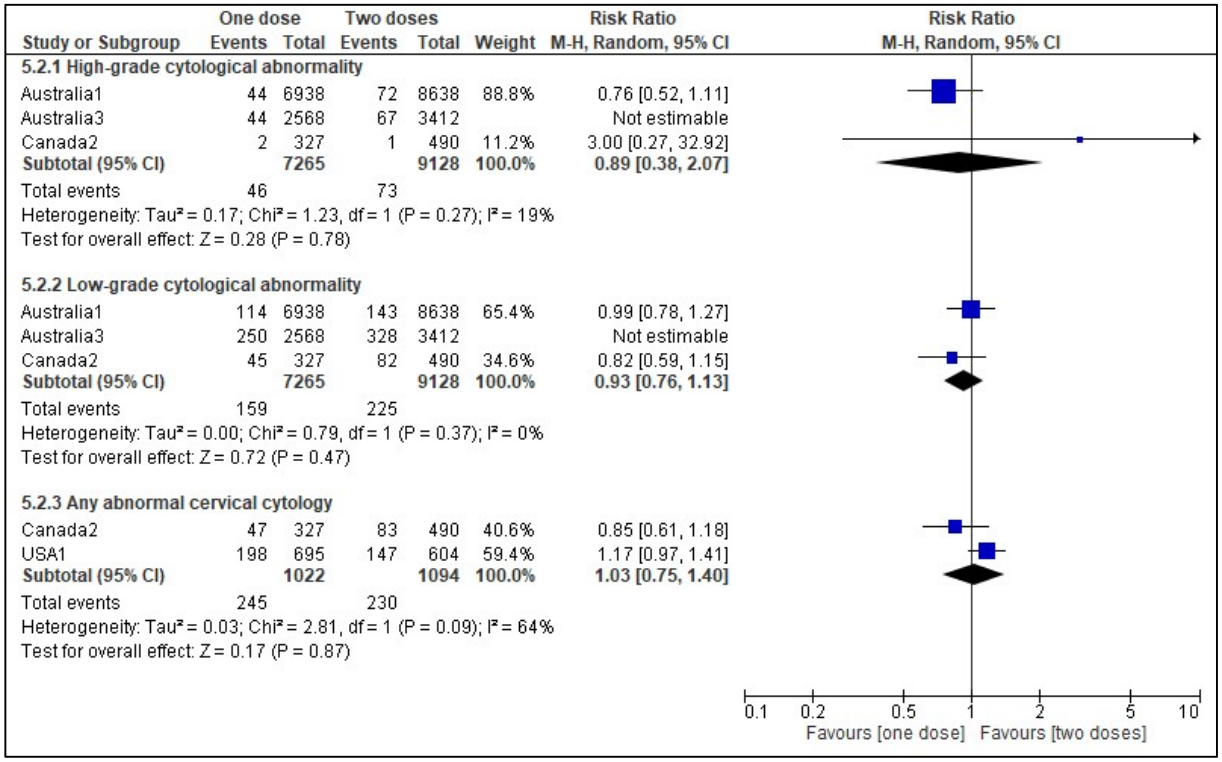
Figure 21. Histological abnormalities one dose versus two doses quadrivalent HPV vaccine, unadjusted results.

3. Cytological abnormalities

Four studies (Australia1, Australia3, Canada2, USA1) reported unadjusted data on cases of high-grade, low-grade, or any abnormal cytology after one or two doses of quadrivalent HPV vaccine.

There was little to no difference between one and two doses of quadrivalent HPV vaccine on high-grade cytology (RR 0.89, 95% CI 0.38 to 2.07, 16,393 person-years, 2 studies) (Figure 22) or low-grade

abnormal cytology (RR 0.93, 95% CI 0.76 to 1.13, 16,393 person-years, 2 studies). For any abnormal cytology little to no difference was found between one dose and two doses of quadrivalent vaccine (RR 1.03, 95% CI 0.75 to 1.40, 2116 participants, 2 studies, I^2 =64%). Evidence was of very low-certainty due to a risk of bias due to confounding, selection bias, imprecision (high grade cytological abnormality) and inconsistency (any abnormal cytology).



Due to participant overlap between Australa1 and Australia3, Australia3 (with the narrower range of birth cohorts of the two) was excluded from the meta-analyses where they both appear.

Figure 22. Cytological abnormalities one dose versus two doses quadrivalent HPV vaccine, unadjusted results.

4. Genital warts

Two studies (Sweden1, USA2) reported adjusted estimates for genital warts after one or two doses of quadrivalent HPV vaccine (Table 6). One study was at moderate risk of bias (USA2) and one was at serious risk of bias (Sweden1). With a 6 month buffer period from the last vaccine dose, USA2 reported propensity score-weighted HR 1.13 (95% CI 0.68 to 1.87) with <6 month interval between the two doses, and propensity score-weighted HR 0.39 (95% CI 0.20 to 0.76) with >6 month interval between the two doses, indicating that a two-dose schedule with a longer interval is slightly more protective against genital warts than one dose, whereas a two-dose schedule with a shorter interval is not. With a 12-month buffer there was little to no difference when one dose was compared to two doses with a >6-month interval, however the effect was in favour of one dose when compared to two doses with <6-month interval. Sweden1 reported adjusted incidence rate ratios with buffer periods up to 12 months, all indicating a reduced incidence of genital warts with two doses of quadrivalent vaccine compared with one dose. Evidence for this outcome was of low certainty due to a risk of bias due to residual confounding.

Table 6. Adjusted estimates for genital warts comparing two doses with one dose of quadrivalent HPV vaccine

Study	Risk of bias	Subgroup	Adjusted estimate (95% CI)	Direction of effect	Number of participants
USA2‡	Moderate	<6m interval; 6m buffer	HR 1.13 (0.68 to 1.87)	Little or no difference	13,803 person-years
	Moderate	<6m interval; 12m buffer	HR 2.23 (1.09 to 4.56)	One dose	10,782 person-years
	Moderate	>6m interval; 6m buffer	HR 0.39 (0.20 to 0.76)	Two doses	14,039 person-years
	Moderate	>6m interval; 12m buffer	HR 0.74 (0.35 to 1.60)	Two doses	14,224 person-years
Sweden1†	Serious	3m buffer	IRR 0.59 (95% CI 0.43 to 0.81)	Two doses	70,329 person-years for 10-19-year olds receiving 1 or 2 doses
	Serious	6m buffer	IRR 0.54 (0.38 to 0.76)	Two doses	70,329 person-years for 10-19-year olds receiving 1 or 2 doses
	Serious	12m buffer	IRR 0.59 (0.38 to 0.91)	Two doses	70,329 person-years for 10-19-year olds receiving 1 or 2 doses

† adjusted for attained age and parental education level; ‡ propensity-score weighted for race/ethnicity, health plan (site), age at enrolment in the health plan, age at beginning of study period, age at first evidence of probable sexual activity, age at first dose of HPV vaccine, indicator for whether the person was continuously enrolled from index date to the end of the study period, months enrolled in the health plan, indicator for whether the person had any preventive health visits, Medicaid enrolment, oral contraceptive use, or history of tests for pregnancy, chlamydia, or gonorrhoea.

Eight studies (Belgium2, Canada3, Denmark2, Spain2, Sweden1, USA2, USA6, USA11) reported unadjusted data on genital warts after one or two doses of quadrivalent HPV vaccine. Due to serious inconsistency in the results (I^2 = 88%) and the overlap between the USA studies, we did not pool the estimates.

Four studies found little to no difference between one and two doses and four studies found moderate to large effects in favour of two doses (Canada3, Denmark2, Sweden1, USA2) (Figure 23). Evidence was of very low-certainty due to a risk of bias due to confounding and inconsistency.

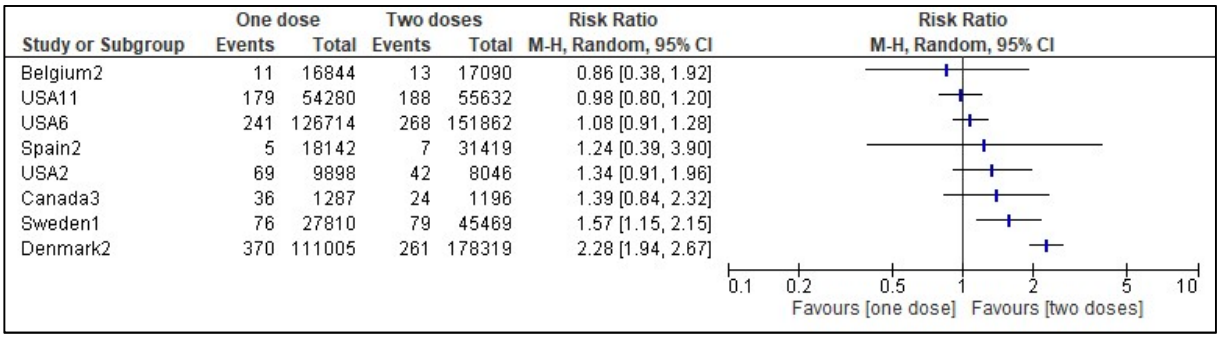


Figure 23. Genital warts for one dose versus two doses quadrivalent HPV vaccine, unadjusted results.

5. HPV infections

One study (India1) reported unadjusted estimates of incident HPV 16/18, HPV 6/11/16/18, HPV 31/33/45, and any HPV type infections, as well as persistent HPV 16/18, HPV 6/11/16/18, HPV 31/33/45, and any HPV type infections after one or two doses of quadrivalent HPV vaccine, over a 7-year follow-up period (Figure 24).

There was insufficient evidence to determine if a difference exists between one dose and two doses of quadrivalent HPV vaccine on most of these outcomes, due to the limited number of cases reported. There was little to no difference in incident HPV 16/18 infections between one dose and two doses (RR 0.90, 95% CI 0.60 to 1.35, 4217 participants, 1 study, low-certainty evidence due to a risk of bias due to confounding). For incident HPV 31/33/45 infections, there was an effect in favour of two doses over one dose (RR 1.58, 95% CI 1.16 to 2.15, 4217 participants, low-certainty evidence due to a risk of bias due to confounding). For any HPV type infections, there was also a small effect in favour of two doses over one dose (RR 1.20, 95% CI 1.06 to 1.36, 4217 participants, low-certainty evidence due to a risk of bias due to confounding).

Evidence for persistent HPV type infections was of very low certainty due to a risk of bias due to confounding and imprecision from few events.

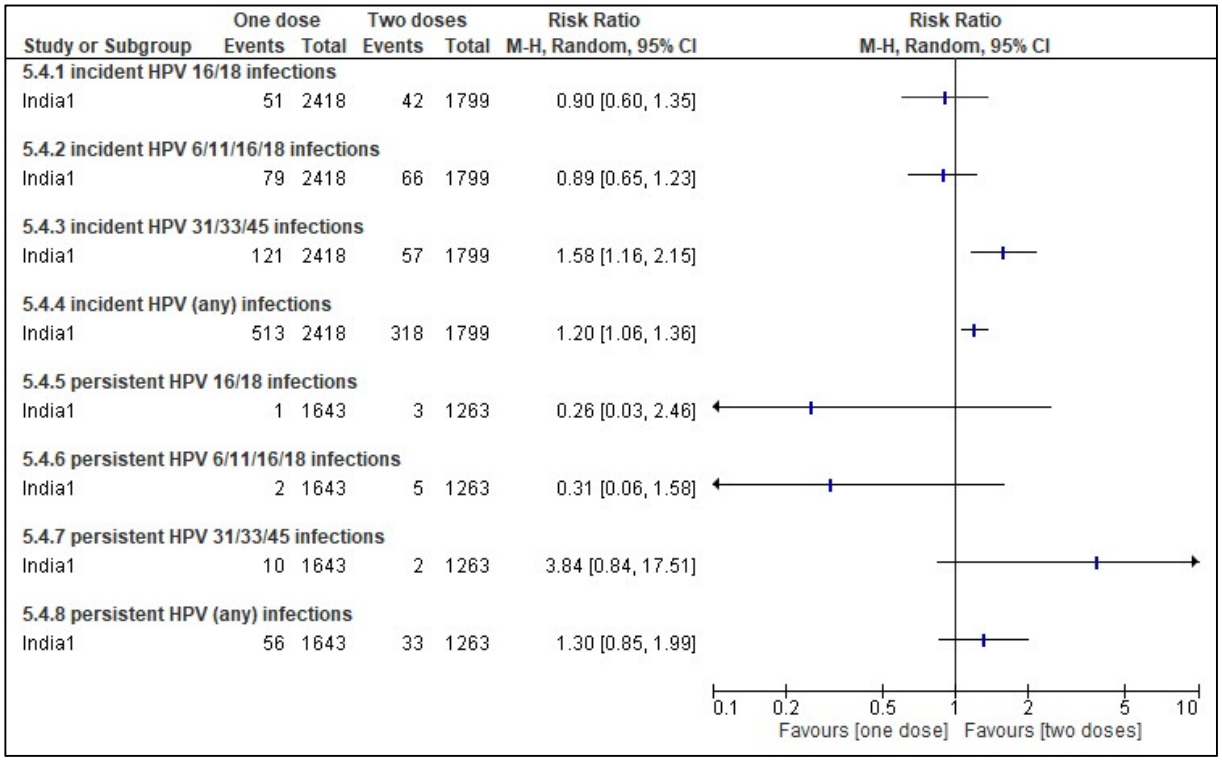


Figure 24. HPV incident and persistent infection for one dose versus two doses quadrivalent HPV vaccine at 7 years follow-up, unadjusted results.

Comparison 3. Effectiveness and immunogenicity of one dose of HPV vaccine compared with three doses

This section summarises the findings from the included studies comparing one dose versus three doses. Analyses are stratified by type of HPV vaccine (bivalent or quadrivalent). It is noted where concerns exist regarding risk of bias, imprecision of the estimates (due to small sample sizes, few events, or wide confidence intervals) and heterogeneity across studies being pooled. Certainty of

the evidence is reported below and detailed reasons for downgrading or upgrading the certainty, according to guidance summarised in Table 1 and Table 2, are provided in Appendix 7. GRADE tables.

Bivalent HPV vaccine

There were seven included studies (Costa Rica1, Scotland1, Scotland2, Scotland3, Scotland4, Scotland5, Uganda1) that reported on immunogenicity or clinical outcomes for women receiving one dose compared with three doses of the bivalent HPV vaccine.

1. Immunogenicity

Two studies (Costa Rica1, Uganda1) reported on antibody titres for HPV 16 and 18 following one or three doses of bivalent HPV vaccine up to 84 months follow-up. The studies were not pooled due to different duration of follow-up (24, 48, and 84 months).

For antibody titres, there was an effect in favour of three doses compared with one dose for both HPV 16 and 18 (Figure 25). Evidence was of moderate certainty which was upgraded due to large effects. For seropositivity, there was little or no difference between one and three doses for HPV 16 at 24 months or at 48 months, or for HPV 18 at 24 months (Figure 26). Evidence for this outcome was of low certainty due to imprecision.

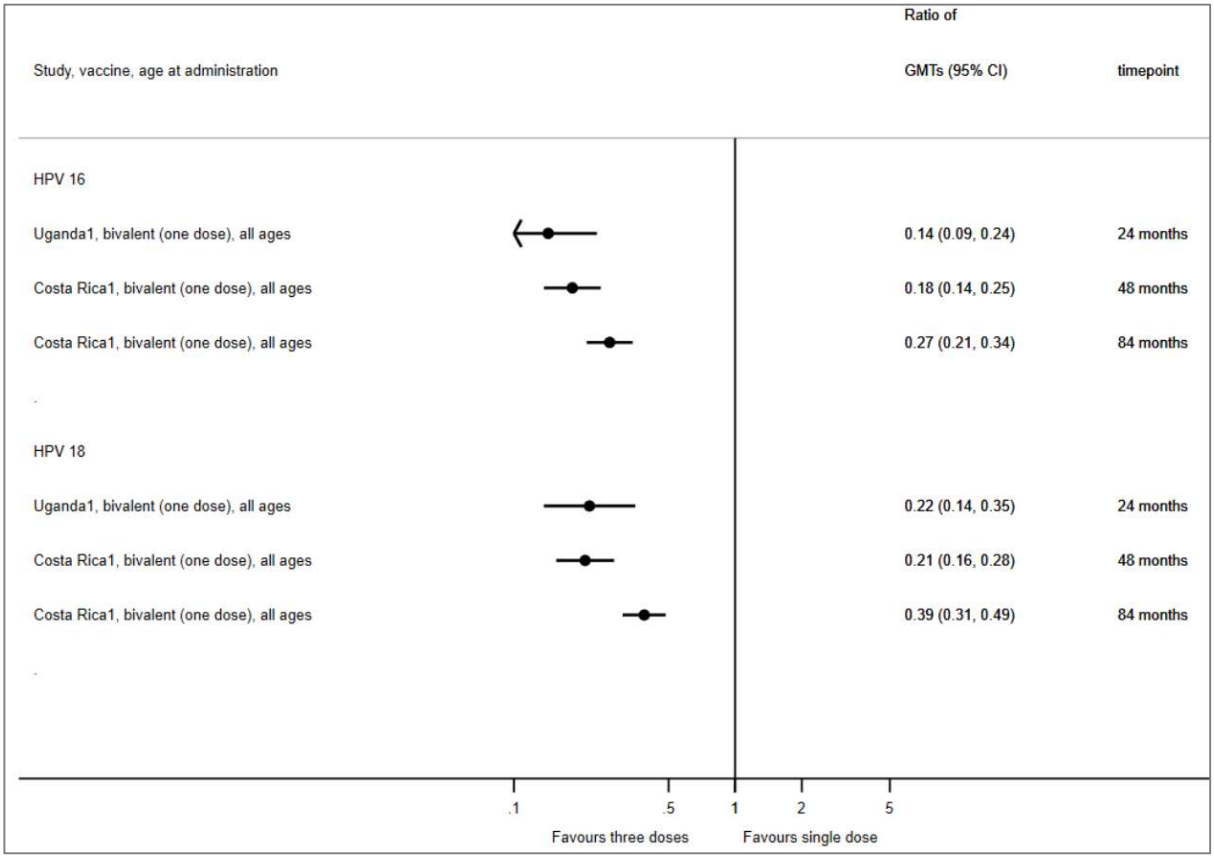


Figure 25. HPV 16 and 18 antibody titres for one dose versus three doses of bivalent HPV vaccine at 24 to 84 months follow-up

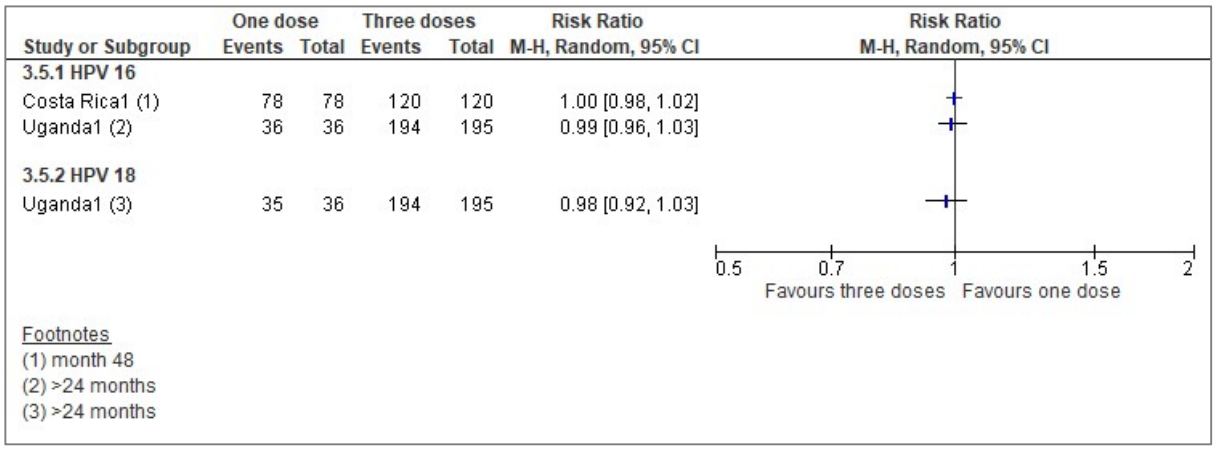


Figure 26. HPV 16 and 18 seropositivity for one dose versus three doses of bivalent HPV vaccine at 24 to 48 months follow-up

2. Histological abnormalities

Two studies (Scotland2, Scotland3) reported data on cases of CIN1, CIN2, or CIN3 after one or three doses of bivalent HPV vaccine. The studies were not pooled due to the likelihood of overlapping study populations.

The estimates of effect were inconsistent for CIN1: Scotland2 reported an effect in favour of three doses while Scotland3 reported little or no difference. For CIN2 and CIN3 both studies reported an effect in favour of three doses (Figure 27). Evidence for these outcomes was of very low certainty due to risk of bias due to confounding, selection bias, and imprecision from few events.

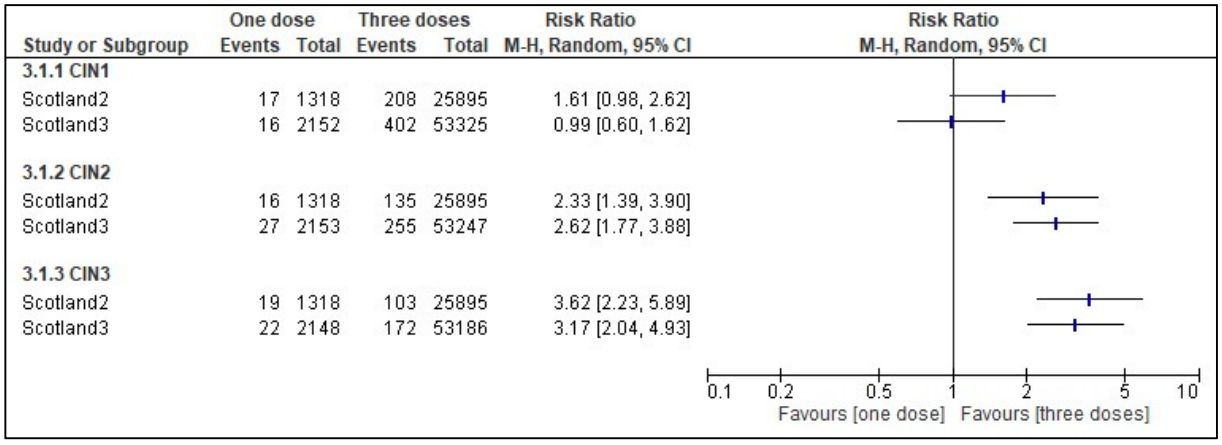


Figure 27. CIN1, CIN2, and CIN3 for one dose versus three doses quadrivalent HPV vaccine, unadjusted results.

3. HPV infections

Prevalent HPV infection

Three studies from Scotland (Scotland1, Scotland4, Scotland5) reported on HPV infections after one or three doses of bivalent HPV vaccine. The studies were not pooled due to the likelihood of overlapping study populations.

For prevalence of HPV 16/18 and HPV 31/33/45, there was an effect in favour of three doses compared with one dose. For other high-risk HPV types (not 16, 18, 31, 33, or 45), there was little or no difference between three doses and one dose. For any HPV type, Scotland4 reported little or no difference between three doses and one dose while Scotland5 reported a small effect in favour of

three doses (Figure 28). Evidence was of very low-certainty due to risk of bias due to confounding and risk of selection bias.

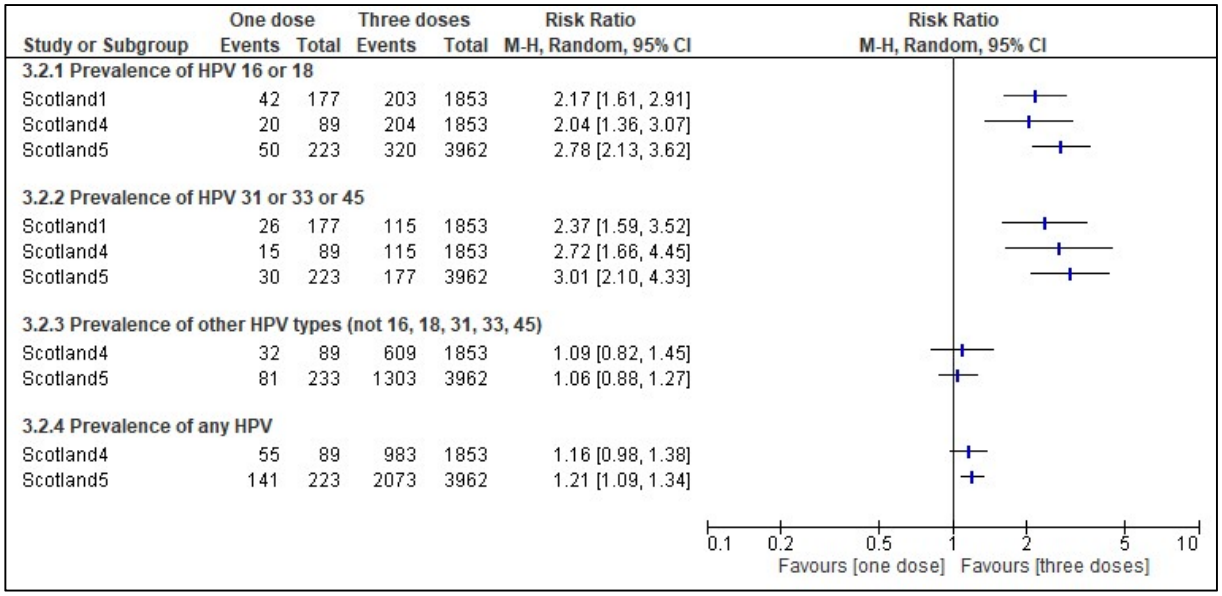


Figure 28. Prevalence of HPV infection for one dose versus three doses quadrivalent HPV vaccine, unadjusted results.

7-year cumulative incidence of HPV infection

One study (Costa Rica1) reported on cumulative HPV infections over 7 years.

For cumulative HPV 16, HPV 18, or HPV 16/18 infections over 7 years, there was an effect in favour of one dose compared to three doses, but the 95% CI crossed the line of no effect (Figure 29). For cumulative HPV 31/33/45 infections, other carcinogenic HPV infections and noncarcinogenic HPV infections over 7 years there was little or no difference between one and three doses (Figure 29). The certainty of the evidence varied depending on the outcome. For HPV 16, HPV 18, and HPV 16/18 infections there was only very low certainty evidence (due to risk of bias due to confounding and serious imprecision due to few events), for cumulative HPV 31/33/45 infections there was low certainty evidence (due to imprecision), and for cumulative other carcinogenic or non-carcinogenic infections there was moderate certainty evidence.

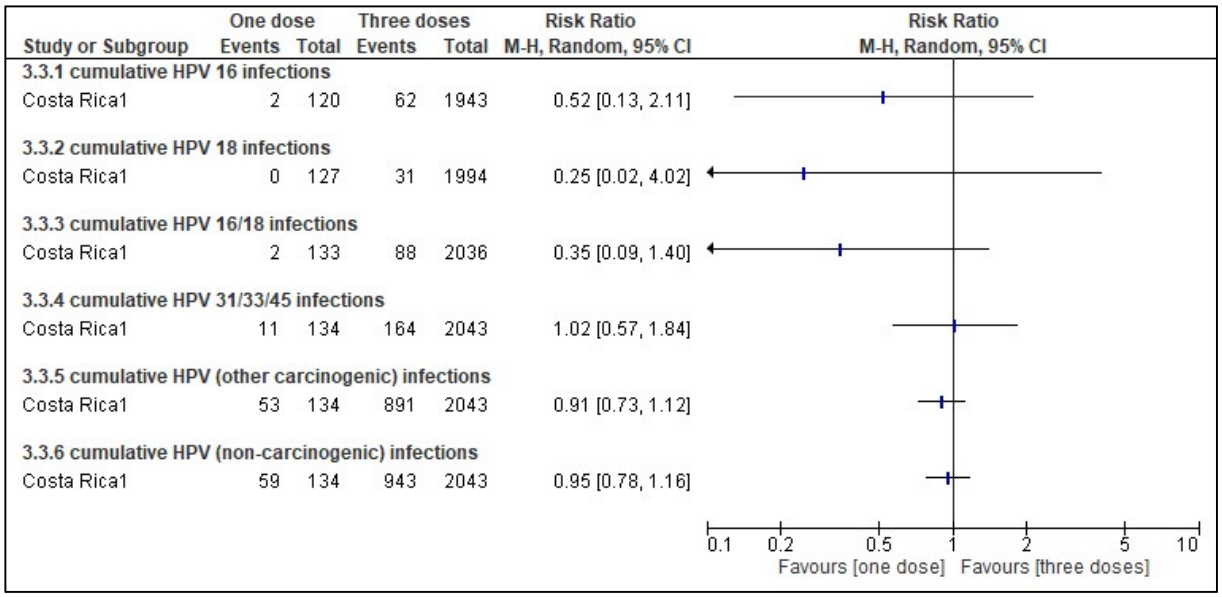


Figure 29. 7-year cumulative incidence of HPV infection for one dose versus three doses quadrivalent HPV vaccine, unadjusted results.

One-time incident and persistent HPV infection

One study (CVT/PATRICIA), reported outcomes of incident and persistent HPV infections. For one-time incident HPV 16 or 18 infection there was an effect in favour of one dose compared to three doses, but the 95% CI crossed the line of no effect (Figure 30). For one-time incident HPV 31, 33 or 45 infection, there was an effect in favour of three doses compared to one dose, but the 95% CI crossed the line of no effect. Evidence was of low-certainty due to imprecision and risk of bias due to confounding.

For persistent HPV 16/18 infection lasting 6 or 12 months, there was an effect in favour of one dose compared to three doses, but the 95% CI crossed the line of no effect (Figure 31). Evidence was of very low certainty due to serious imprecision. For persistent HPV 31, 33 or 45 infection lasting 6 or 12 months, there was little or no difference between one and three doses (Figure 31). Evidence was of low-certainty due to imprecision and risk of bias due to confounding.

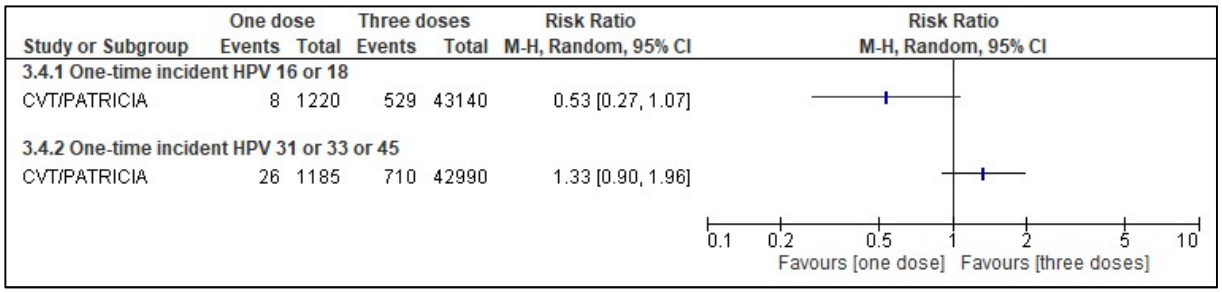


Figure 30. One-time incident HPV infection for one dose versus three doses quadrivalent HPV vaccine, unadjusted results.

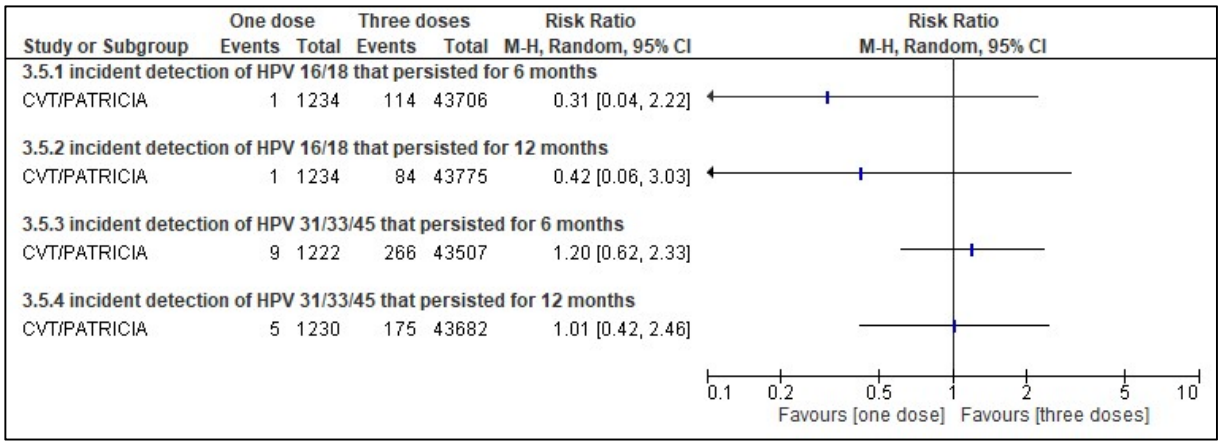


Figure 31. One-time persistent HPV infection for one dose versus three doses quadrivalent HPV vaccine, unadjusted results.

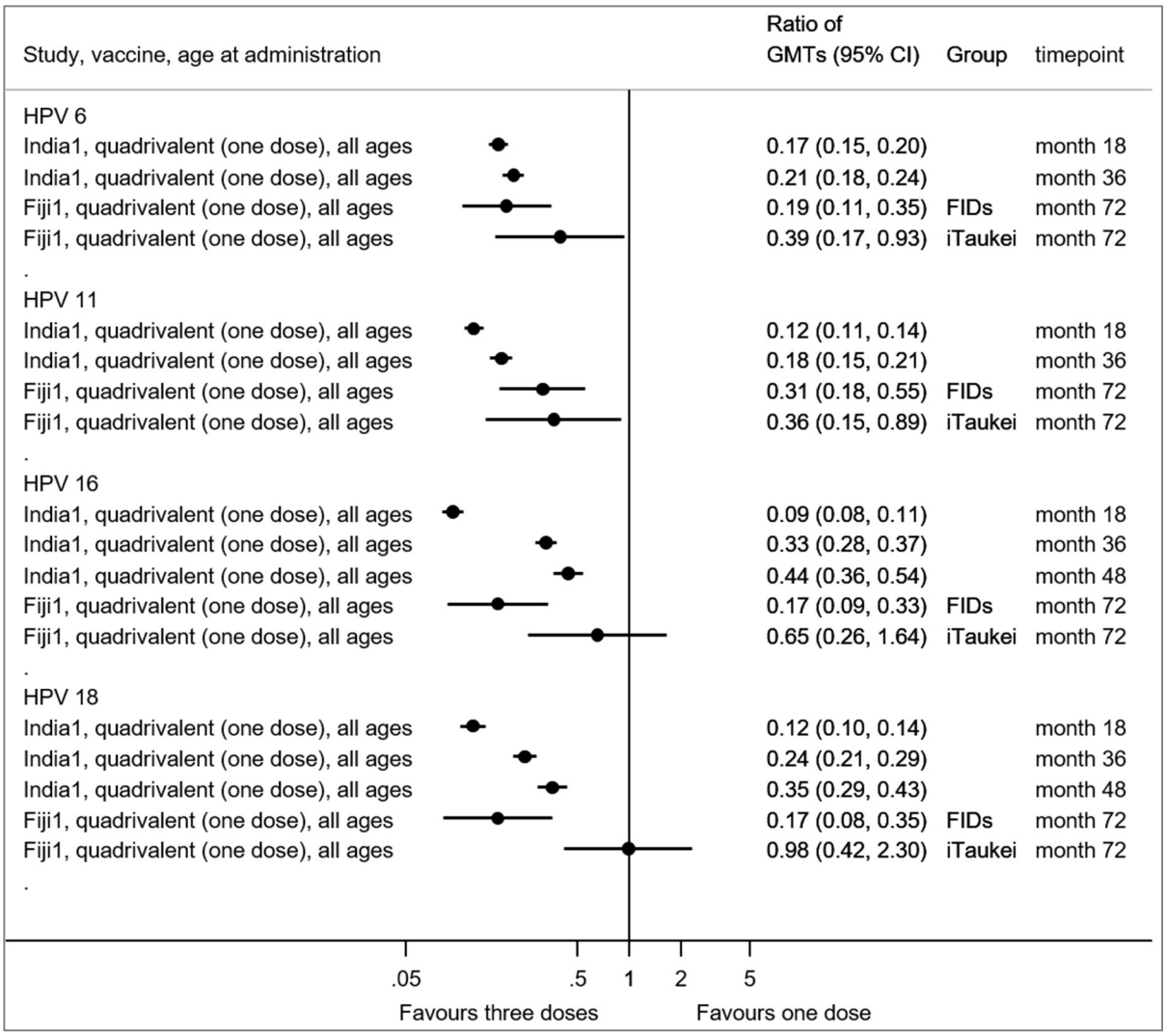
Quadrivalent HPV vaccine

There were 21 included studies (Australia1, Australia2, Australia3, Belgium2, Canada2, Canada3, Denmark2, Denmark3, Fiji1, India1, Spain2, Sweden1, USA1, USA2, USA6, USA9, USA11, USA12, USA14, USA15, USA16) that reported on immunogenicity or clinical outcomes for women and men receiving one dose compared to three doses of the quadrivalent HPV vaccine. Due to the high likelihood of overlapping cohorts and cases between Australia1 and Australia3 (both carried out in the state of Victoria) and USA6 and USA11 (overlapping data sources and dates), we focus here on the results of Australia1 (included the widest range of birth cohorts among the two studies) and USA6 (largest sample size).

1. Immunogenicity

Two studies (Fiji1, India1) reported on antibody titres for HPV 6, 11, 16 and 18 following one or three doses of quadrivalent HPV vaccine up to 72 months follow-up.

For antibody titres, there was an effect in favour of three doses compared with one dose for all HPV types and all timepoints in Indians and in Fijians of Indian descent. In indigenous Fijian girls (iTaukei) there was an effect in favour of three doses compared with one dose for HPV 6 and 11, while for HPV 16 the 95% CI crossed the line of no effect, and for HPV 18 there was little or no effect (Figure 32). Evidence was of low certainty due to risk of bias due to confounding.



FID= Fijians of Indian Descent; iTaukei= indigenous Fijians

Figure 32. Ratio of GMTs for one dose versus three doses quadrivalent HPV vaccine at 18 to 72 months follow-up.

Two studies (Fiji1, USA16) reported on seropositivity to HPV 6, 11, 16, and 18 for one dose compared to three doses of quadrivalent HPV vaccine after 6 years follow-up. For HPV 6, 11 and 16, there were small effects in favour of three doses. For HPV 18 there was inconsistent results from the two studies (Figure 33). The evidence was of very low certainty due to risk of bias due to confounding and selection bias.

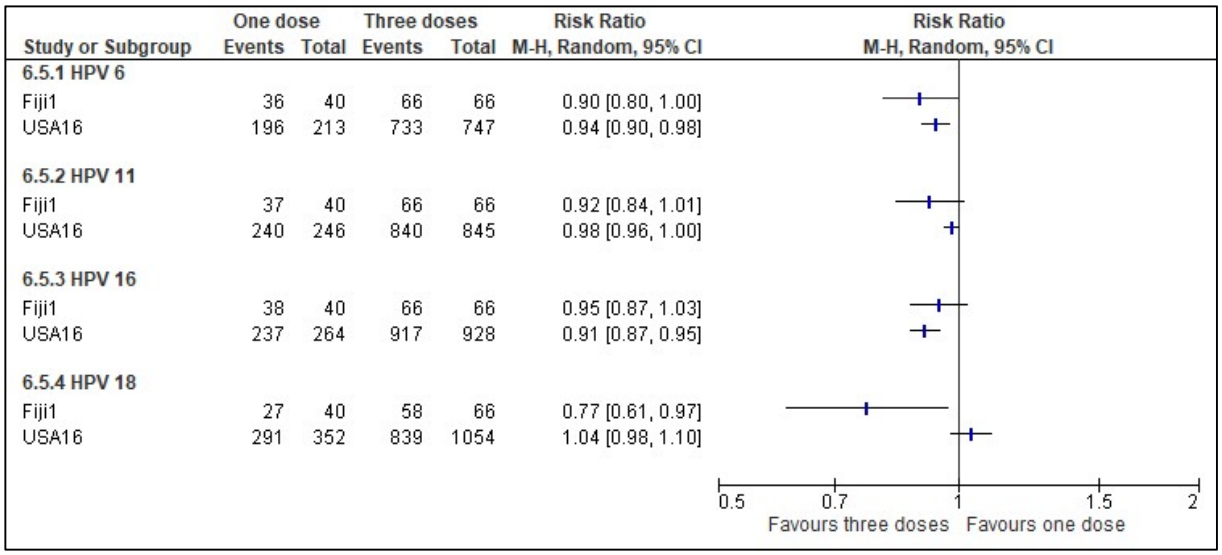


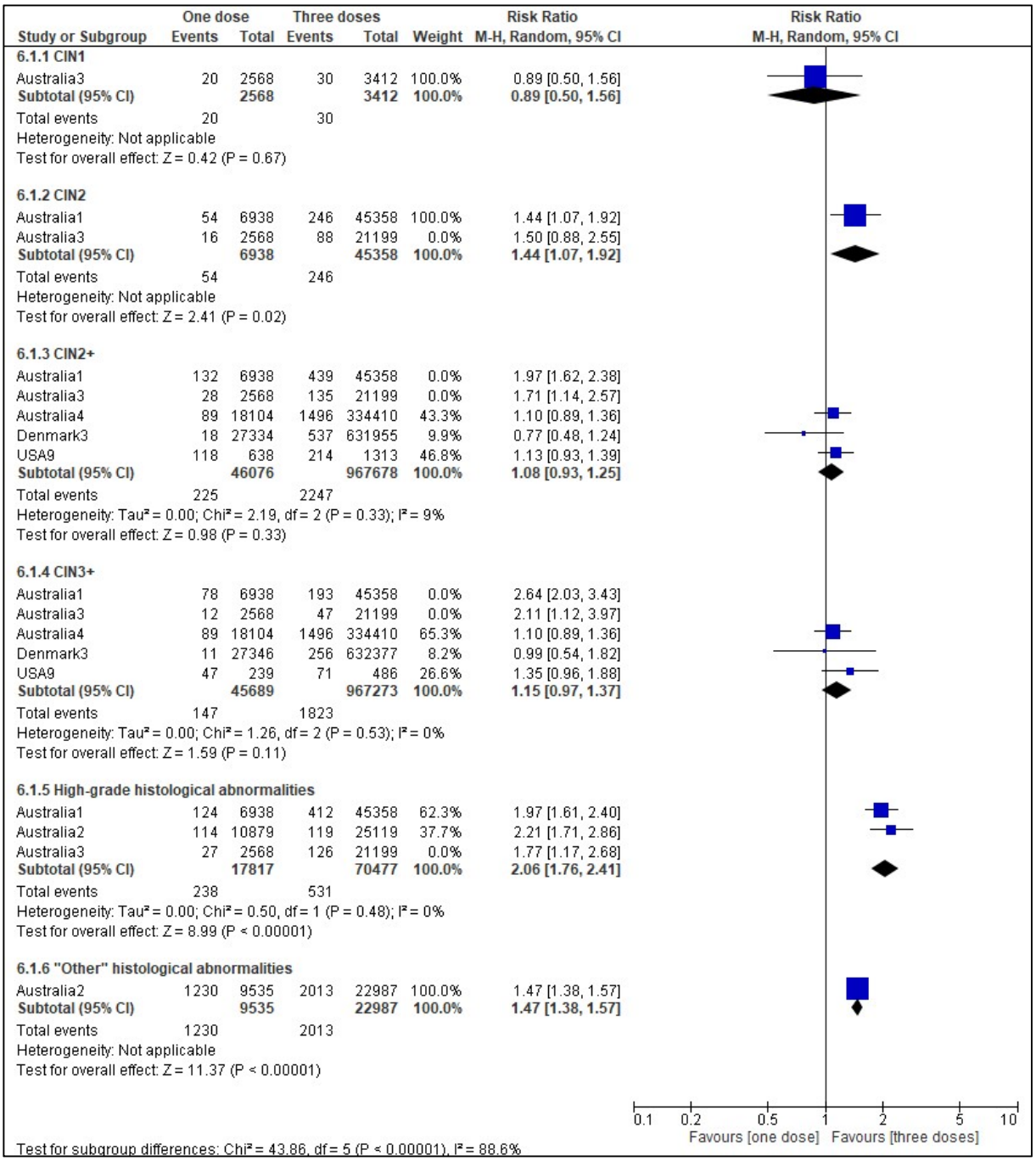
Figure 33. HPV seropositivity for one dose versus three doses quadrivalent HPV vaccine at 72 months follow-up.

2. Histological abnormalities

One study (Denmark3) reported adjusted incidence rate ratios (adjusted for maternal education and attained age) on CIN2+ (IRR 0.99, 95% CI 0.64 to 1.53) and CIN3+ (IRR 0.95, 95% CI 0.60 to 1.51), showing little or no difference between one and three doses of quadrivalent vaccine for these outcomes. Another study (Australia4) reported adjusted hazard ratios (adjusted for age, area of residence, and socioeconomic status) on CIN2+ (HR 0.91, 95% CI 0.74 to 1.13) and CIN3+ (HR 0.66, 95%CI 0.41 to 1.05). This was considered very low-certainty evidence due to imprecision and risk of bias due to residual confounding.

Six studies (Australia1, Australia2, Australia3, Australia4, Denmark3, USA9) reported unadjusted data on cases of CIN1, CIN2, or CIN3, or high-grade or "other" histological abnormalities after one or three doses of quadrivalent HPV vaccine.

For CIN1, there was little or no difference between one dose and three doses. For CIN2, there was an effect in favour of three doses compared with one dose. For CIN2+, there was little or no difference between one dose and three doses (RR 1.08, 95% CI 0.93 to 1.25). For CIN3+, there was an effect in favour of three doses compared with one dose, but the 95% CI crossed the line of no effect. For high-grade and "other" histological abnormalities, there was an effect in favour of three doses compared with one dose (Figure 34). Evidence was of very low certainty for all outcomes due to risk of bias due to confounding, selection bias, and imprecision.



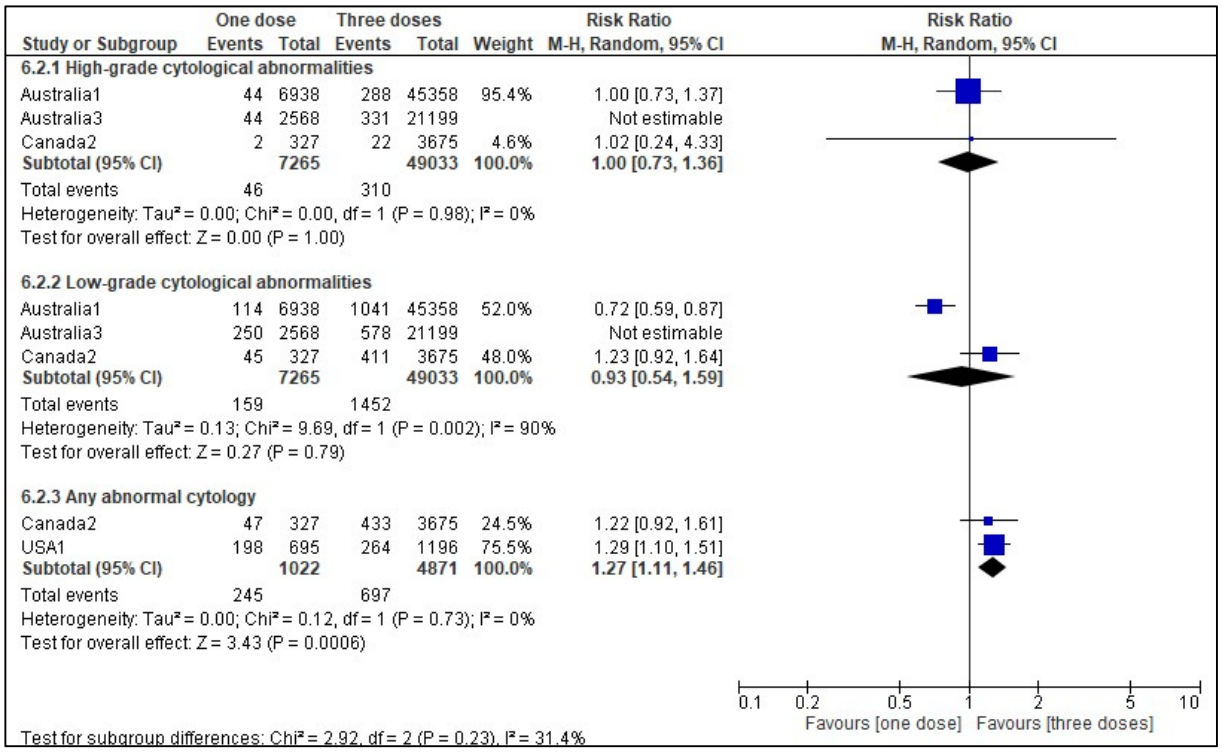
In analyses including bothAustrala1 and Australia3, due to participant overlap, Australia3 (with the narrower range of birth cohorts of the two) was excluded from the meta-analyses where they both appear. In analyses including Australia1, Australia3, and Australia4, due to the high likelihood of overlapping cohorts and cases, Australia1 and Australia3 (data from the state of Victoria) were excluded and we focus here on the results of Australia4 (national databases).

Figure 34. Histological abnormalities for one dose versus three doses of quadrivalent HPV vaccine, unadjusted results.

3. Cytological abnormalities

Four studies (Australia1, Australia3, Canada2, USA1) reported unadjusted data on cases of high-grade, low-grade, or any abnormal cytology after one or three doses of quadrivalent HPV vaccine.

For high-grade and low-grade cytological abnormalities, there was little or no difference between one dose and three doses. For any abnormal cytology, there was an effect in favour of three doses compared with one dose (Figure 35). Evidence was of very low-certainty due to risk of bias due to confounding and selection bias.



Due to participant overlap between Australa1 and Australia3, Australia3 (with the narrower range of birth cohorts of the two) was excluded from the meta-analyses where they both appear.

Figure 35. Abnormal cytology for one dose versus three doses of quadrivalent HPV vaccine, unadjusted results.

4. Genital warts

Three studies (Sweden1, USA2, USA6) reported adjusted estimates of effect on incidence of genital warts comparing three doses with one dose of quadrivalent HPV vaccine (Table 7). Sweden1 reported adjusted incidence rate ratios with buffer periods of 3, 9 and 12 months, all indicating an effect in favour of three doses compared with one dose in terms of reduced incidence of genital warts. USA6 reported an adjusted incidence rate ratio that indicated a small effect in favour of three doses compared with one dose. These estimates were assessed to be at serious risk of bias. USA2 reported a propensity score-weighted hazard ratio with buffer periods of 6 and 12 months that indicated an effect in favour of three doses compared with one dose, assessed to be at moderate risk of bias. Evidence was of low certainty due to risk of bias due to residual confounding.

Table 7. Adjusted estimates for genital warts comparing one dose with three doses of quadrivalent HPV vaccine

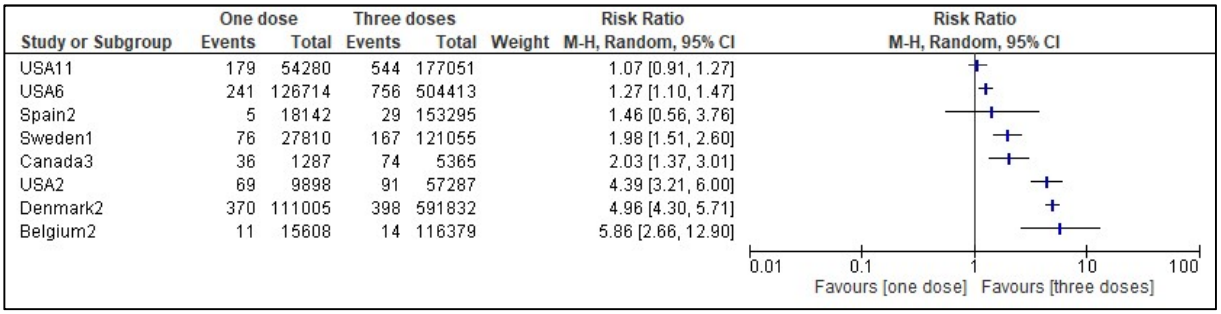
Study	Risk of bias	Subgroup	Adjusted estimate (95% CI)	Direction of effect	Number of participants
USA2†	Moderate	6m buffer	HR 0.29 (0.20 to 0.42)	Three doses	64,517
	Moderate	12m buffer	HR 0.63 (0.37 to 1.09)	Three doses	64,517
Sweden1*	Serious	3m buffer	IRR 0.37 (0.28 to 0.48)	Three doses	137,647 person-years
	Serious	6m buffer	IRR 0.41 (0.31 to 0.56)	Three doses	137,647 person-years
	Serious	12m buffer	IRR 0.60 (0.41 to 0.86)	Three doses	137,647 person-years

USA6‡	Serious		IRR 1.22 (1.05 to 1.41)	Three doses	631,127 person-years

* adjusted for attained age and parental education level; † propensity-score weighted for race/ethnicity, health plan (site), age at enrolment in the health plan, age at beginning of study period, age at first evidence of probable sexual activity, age at first dose of HPV vaccine, indicator for whether the person was continuously enrolled from index date to the end of the study period, months enrolled in the health plan, indicator for whether the person had any preventive health visits, Medicaid enrolment, oral contraceptive use, or history of tests for pregnancy, chlamydia, or gonorrhoea; ‡ adjusted for age, geographic region, income, proportion of minorities in county of residence, and calendar year.

Eight studies (Belgium2, Canada3, Denmark2, Spain2, Sweden1, USA2, USA6, USA11) reported unadjusted data on genital warts after one or three doses of quadrivalent HPV vaccine. The pooled effect of these studies was very inconsistent (I^2 = 98%), so is not presented.

Six studies reported effects in favour of three doses compared with one dose (Belgium2, Canada3, Denmark2, Sweden1, USA2, USA6), one study reported an effect in favour of three dose, but the 95% CI crossed the line of no effect (Spain2), and one study reported little or no difference between one or three doses (USA11) (Figure 36). The evidence was of very low certainty due to risk of bias due to confounding and inconsistency.



Results were not pooled due to very high heterogeneity (I^2 = 98%).

Figure 36. Genital warts for one dose versus three doses quadrivalent HPV vaccine, unadjusted results.

5. HPV infections

Two studies reported adjusted estimates on HPV infections following one or three doses of quadrivalent HPV vaccine (Table 8). Switzerland1 reported an effect in favour of three doses compared with one dose, but the 95% CI crossed the line of no effect, while USA14 found an effect favouring three doses compared with one dose 3.2 times the adjusted odds. The risk of bias was assessed to be serious for Switzerland1 and could not be assessed for USA14. Evidence for these outcomes was of very low certainty due to limitations in study design.

Table 8. Estimates for HPV infections comparing one dose with three doses of quadrivalent HPV vaccine

Study	Risk of bias	Subgroup	Adjusted estimate (95% CI)	Direction of effect	Number of participants
Switzerland1	Serious	HPV infection	adjusted OR 1.5 (0.7-2.1)	3 doses	224 participants
USA14	Not assessed, conference abstract	4-valent vaccine type HPV (6, 11, 16, 18) infection	3.2 times the adjusted odds (p=0.04)	3 doses	Unclear. ≥1 dose 865 participants.

One study (India1) reported on incident and persistent HPV 16/18, HPV 6/11/16/18, HPV 31/33/45, and any HPV type infections over a 7-year follow-up period.

For incident HPV infections there was little to no difference between one dose and three doses. For persistent HPV 16/18 and HPV 6/11/16/18 infections, there were effects in favour of one dose compared with three, but the 95% CI crossed the line of no effect and the analyses included very few events (Figure 37). For persistent HPV 31/33/45 infection, there was an effect in favour of three doses compared with one, but the 95% CI crossed the line of no effect. For persistent any HPV infections, there was little to no difference between one dose compared with three. The evidence was of very low certainty for most outcomes due to risk of bias due to confounding and imprecision due to few events. For the outcomes of incident any HPV infections the evidence was of low certainty.

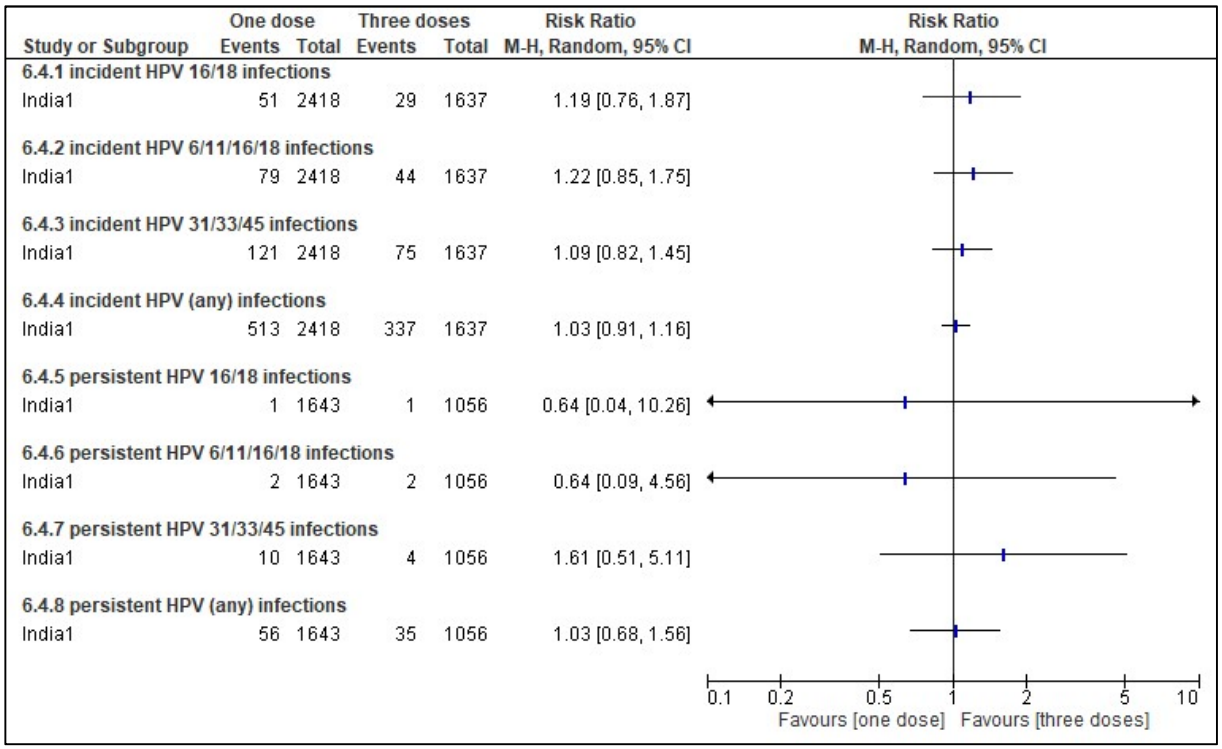


Figure 37. HPV infections for one dose versus three doses quadrivalent HPV vaccine over a 7-year follow-up period, unadjusted results.

In addition, USA12 and USA15 reported unadjusted estimates of effect relating to HPV infections. USA12 reported little or no difference between one dose and three doses (OR 0.99; 95% CI 0.33 to 2.96) in males attending a sexual health clinic and USA15 reported an effect favouring three doses compared with one (OR 3.23; 95% CI 1.22 to 8.33). The evidence was of very low certainty due to limitations in study design.

Sensitivity analysis by risk of bias

A post-hoc sensitivity analysis was performed on the included studies comparing one dose to two doses of HPV vaccine, to determine the effect of different sources of bias on the effect estimates. For this analysis, the following sources of bias were investigated:

- The buffer period used in the analysis – the buffer period is the time-lag between the first dose of vaccine and counting of outcome events. For studies which consider vaccination dose status as a time-varying exposure, a buffer period is used to account for pre-existing HPV infections and misattribution of events to the wrong dose status.

- The age at vaccination – the efficacy of HPV vaccine is affected by age at first vaccine dose. We extracted results stratified by age at first vaccine dose and investigated whether the effect of the buffer period differs by age at vaccination.
- Control of confounding – adequate control of confounding is needed to ensure groups are as comparable as possible. We extracted effect estimates from studies that included both a buffer period in the analysis and displayed adequate control for confounding.

There were eight studies that compared one dose to two doses of bivalent HPV vaccine. None of these studies reported the use of a buffer period in the analysis so a sensitivity analysis on studies of bivalent HPV vaccine was not carried out.

There were 19 studies that compared one dose to two doses of quadrivalent HPV vaccine. Two outcomes – genital warts and histological abnormalities – included eight studies each and are the focus of this analysis.

Of the eight studies reporting on genital warts after fewer than three doses of quadrivalent HPV vaccine, two studies (USA2, Sweden1) reported on the effect of using different buffer periods in the analysis. Three studies (Sweden1, Canada3, USA11) reported age stratified data. The age strata in these studies were not comparable and could not be analysed together (Sweden1: 10-16, 17-19; Canada3: 9-18, 19-25; USA11: <15, 15-19, >20). Two studies (USA2, Sweden1) reported adjusted effect estimates comparing two doses to one dose.

As the buffer period increased, from no buffer to 12 months, the effect estimates for one and two doses (compared to no vaccine) also increase (Figure 38). As the length of the buffer period increases, the effect estimates of one dose approaches that of two doses. This appears to be more apparent in the younger age groups (i.e. 10-16 years) than the older age group (i.e. 17-19 years).

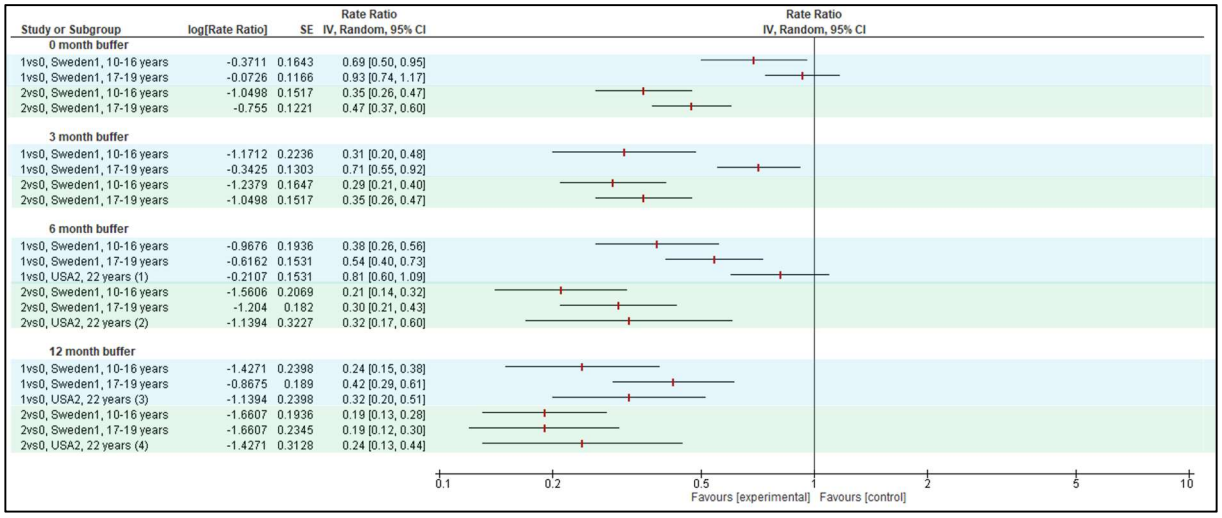


Figure 38. Sensitivity analysis by length of buffer period and age at first vaccine on genital warts for one dose and two doses versus no vaccine, adjusted estimates.

A similar analysis was performed using adjusted estimates of effect comparing one dose with two doses in the Sweden1 and USA2 studies. With no buffer the estimates are in favour of two doses over one dose (Figure 39). However, with a 12-month buffer period there appears to be little or no difference between one dose and two doses for two of the estimates. For the older age group in the Sweden study (17-19 years), two doses appear to result in fewer cases of genital warts than one dose even after applying the 12-month buffer. The adjusted estimates are imprecise, with wide confidence intervals which are likely due to few events in both groups and small sample sizes.

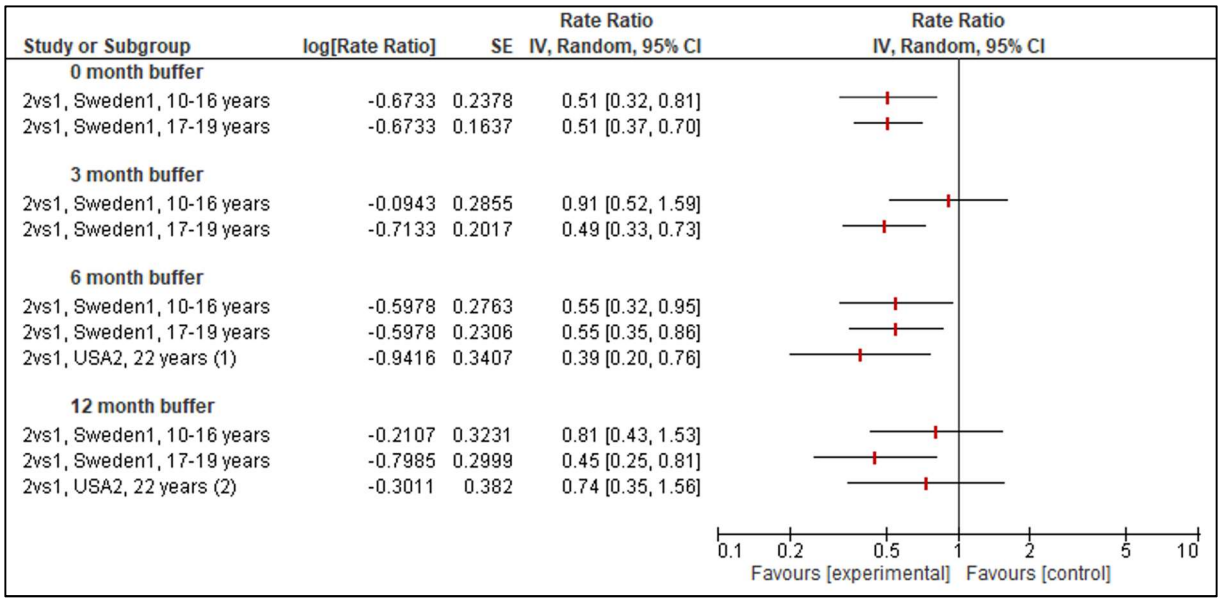


Figure 39. Sensitivity analysis by length of buffer period and age at first vaccine on genital warts for two doses versus one dose quadrivalent HPV vaccine, adjusted estimates.

Of eight studies reporting on CIN2+ following fewer than three doses of HPV vaccine, three studies (Australia1, Australia2, Australia4) reported on the effect of using different buffer periods in the analysis. Three studies (Australia1, Australia2, USA1) reported age stratified data but the age strata in these studies were not comparable and further analysis was not possible (Australia1: <16, 17-19, 20-23, 24-26; Australia2: 11-14, 15-18, 19-22, 23-27; USA1: 11-14, 15-16, 17-18, 19-20). Two studies (Australia4, Denmark3) reported adjusted effect estimates for CIN2+ comparing two doses with one dose.

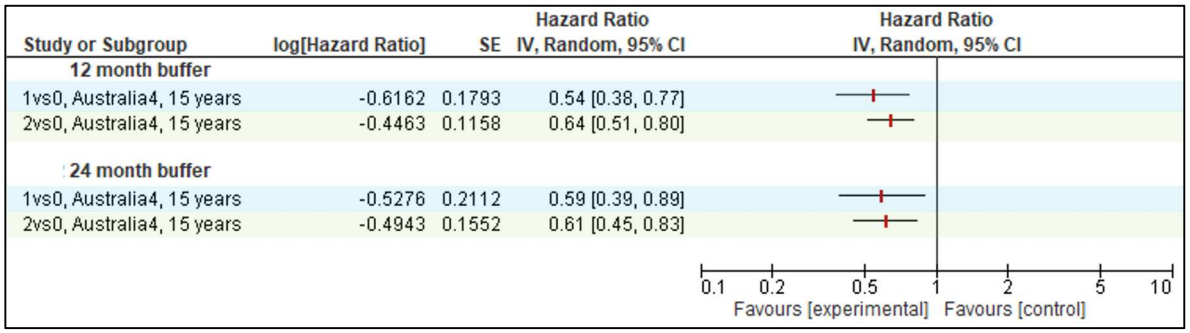


Figure 40. Sensitivity analysis by length of buffer period and age at first vaccine on CIN2+ for one dose and two doses versus no vaccine, adjusted estimates.

Due to potential overlapping populations in the studies from Australia, only the results from Australia4 were considered in this sensitivity analysis. There were large effects, of similar size, in favour of both one dose and two doses compared with no vaccine when the buffer period was 12 months or 24 months (Figure 40).

Two studies (Denmark3, Australia4) reported effect estimates using a buffer period and adjusted for potential confounding when two doses were compared with one dose. Denmark3 reported an IRR of 1.00 (95% CI 0.61 to 1.64) for CIN2+ and 0.89 (95%CI 0.53 to 1.52) for CIN3+. Australia4 reported an adjusted HR of 0.94 (95%CI 0.73 to 1.21) for CIN2+ and 0.64 (0.35 to 1.16) for CIN3+. Both studies reported on younger age groups at first vaccine dose (Denmark3 <16 years, Australia4 <15 years) and

showed little or no difference in effect between two doses and one dose of quadrivalent HPV vaccine.

Conclusions

This review presents the available evidence on the comparative effectiveness and immunogenicity of one dose of HPV vaccine to no vaccine, and to two or three doses of HPV vaccine. There are currently no published randomised trials that directly address these comparisons. Therefore, the evidence is based on 35 observational studies of various designs, reporting on clinical and immunological outcomes.

The risk of bias for all studies and all outcomes was assessed and deemed to be moderate in three studies, serious (or high) in 29 studies, and critical in one study. The risk of bias assessment for each study evaluated domains of bias due to confounding, selection bias, information bias, and reporting bias. To assess whether included observational studies sufficiently controlled for confounding, important confounders were first identified from published literature. None of the included studies were assessed to have controlled for all these confounders (to the point where they were comparable to a randomised trial). For this reason, all studies were considered to have a moderate to serious risk of bias due to residual confounding. Several studies were also at serious risk of selection bias as they were retrospective in nature and included participants based on availability of outcome measures. There was moderate risk of bias in the other domains due to a lack of explicit reporting about methods of exposure and outcome measurement, missing data, and potential for selective reporting.

One main limitation of this report is that many of the included studies did not provide estimates adjusted for confounding which compared effectiveness of one dose to two or three doses. The estimates of effectiveness between one dose and two or three doses in this report were thus calculated using raw data reported in the studies. For many outcomes there was insufficient evidence, due to a small number of participants in the studies receiving only one dose of HPV vaccine, and few events of interest occurring in this group. A post-hoc sensitivity analysis indicated that when sources of bias are controlled for, the efficacy of one dose may approach that of two doses.

At present, for most outcomes there is insufficient evidence to determine whether there is a difference between one dose of HPV vaccine and two or three doses, and what evidence is available is at high risk of bias. As of October 2018, there are at least two (NCT02834637, NCT03180034) ongoing RCTs evaluating the efficacy of one dose of HPV vaccine. These RCTs will help clarify non-inferiority of one dose of HPV vaccine compared to two doses, in terms of immunogenicity and HPV infection. The estimates from RCTs should provide a higher level of certainty than the currently available observational studies.

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Appendix 1. Search strategies

MEDLINE, Ovid

(Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE® Daily and Ovid MEDLINE® 1946-Present)

1. (HPV or (human adj (papilloma virus* or papillomavirus*))).mp.
2. exp Papillomaviridae/
3. exp Papillomavirus Infections/
4. or/1-3
5. (vaccin* or immuni* or inoculat* or innoculat*).mp.
6. 4 and 5
7. (cervarix or gardasil).mp.
8. exp Papillomavirus Vaccines/
9. or/6-8
10. limit 9 to ed=20180801-20190227
11. (201808* or 201809* or 201810* or 201811* or 201812* or 2019*).dt,ez.
12. 9 and 11
13. 10 or 12
14. limit 9 to yr="2018 -Current"
15. 13 or 14

Embase, Ovid

(Embase Classic+Embase 1947 to 2019 February 26)

1. exp papillomaviridae/
2. exp papillomavirus infection/
3. Papilloma virus/
4. (HPV or (human adj (papilloma virus* or papillomavirus*)) or ((papilloma virus* or papillomavirus*) adj infection*)).mp.
5. or/1-4
6. (vaccin* or immuni* or inoculat* or innoculat*).mp.
7. 5 and 6
8. (cervarix or gardasil).mp.
9. Wart virus vaccine/
10. or/7-9
11. limit 10 to yr="2018 -Current"
12. (201808* or 201809* or 201810* or 201811* or 201812* or 2019*).dc,dd,dp,rd.
13. 10 and 12
14. 11 or 13

The Cochrane Library, Wiley

(CENTRAL and CDSR)

#1 MeSH descriptor: [Papillomavirus Infections] explode all trees
#2 MeSH descriptor: [Papillomaviridae] explode all trees
#3 HPV or "human papilloma virus" or "human papillomavirus" or "papilloma virus infection" or "papillomavirus infection".ti,ab,kw (Word variations have been searched)
#4 #1 or #2 or #3
#5 vaccin* or immuni* or inoculat* or innoculat*.ti,ab,kw (Word variations have been searched)
#6 #4 and #5
#7 MeSH descriptor: [Papillomavirus Vaccines] explode all trees
#8 cervarix or gardasil (Word variations have been searched)
#9 #6 or #7 or #8 with Cochrane Library publication date Between Aug 2018 and Feb 2019
#10 #6 or #7 or #8 with Publication Year from 2018 to 2019, in Trials
#11 #9 or #10

Appendix 2. Included studies

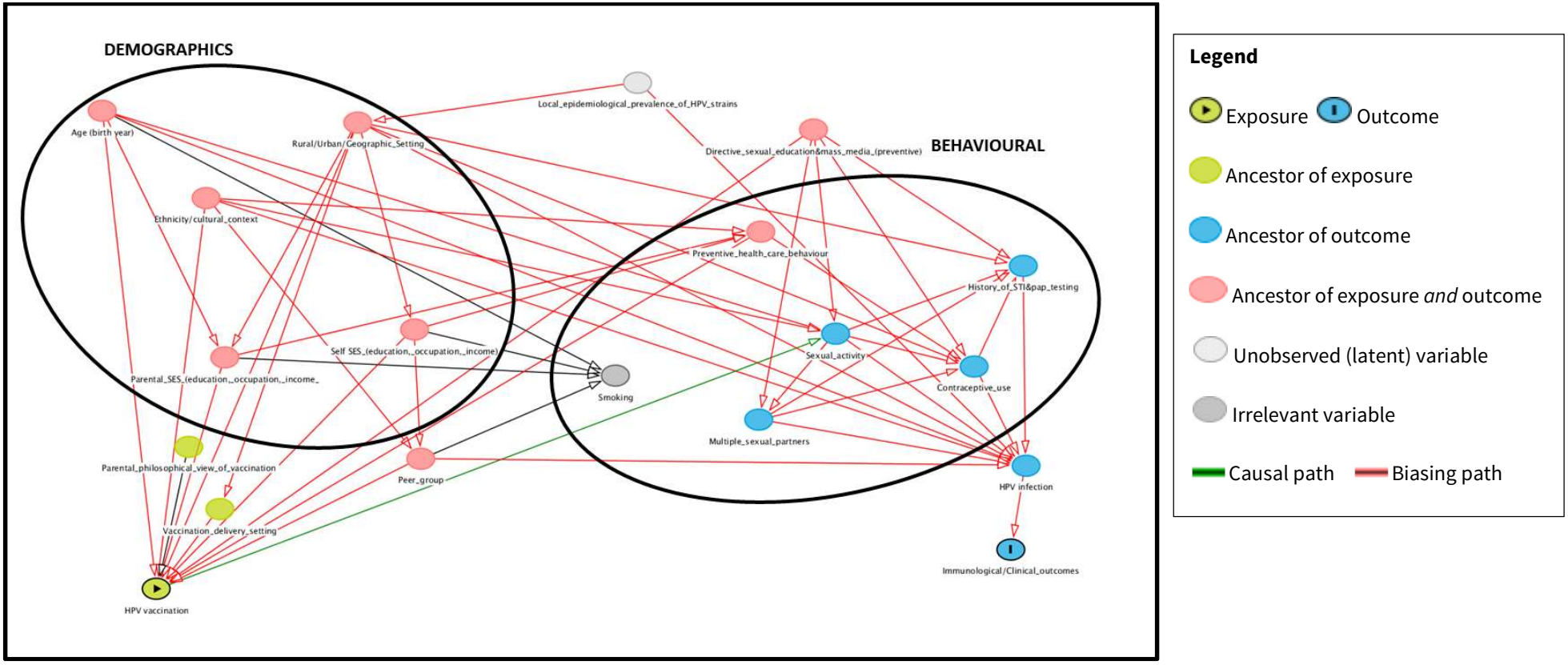
Study ID	Reference(s)
Australia1	Brotherton JML, Malloy M, Budd AC, Saville M, Drennan KT, Gertig DM. Effectiveness of less than three doses of quadrivalent human papillomavirus vaccine against cervical intraepithelial neoplasia when administered using a standard dose spacing schedule: Observational cohort of young women in Australia. Papillomavirus Research. 2015;1:59-73.
Australia2	Crowe E, Pandeya N, Brotherton JM, Dobson AJ, Kisely S, Lambert SB, et al. Effectiveness of quadrivalent human papillomavirus vaccine for the prevention of cervical abnormalities: case-control study nested within a population based screening programme in Australia. BMJ. 2014;348:g1458.
Australia3	Gertig DM, Brotherton JM, Budd AC, Drennan K, Chappell G, Saville AM. Impact of a population-based HPV vaccination program on cervical abnormalities: a data linkage study. BMC medicine. 2013;11(1):227.
Australia4	Brotherton JM, Budd A, Rompotis C, Bartlett N, Malloy MJ, Andersen RL, et al. Is one dose of human papillomavirus vaccine as effective as three?: A national cohort analysis. Papillomavirus Research. 2019:100177.
Belgium2	Dominiak-Felden G, Gobbo C, Simondon F. Evaluating the Early Benefit of Quadrivalent HPV Vaccine on Genital Warts in Belgium: A Cohort Study. PLoS One. 2015;10(7):e0132404.
Canada2	Kim J, Bell C, Sun M, Kliewer G, Xu L, McInerney M, et al. Effect of human papillomavirus vaccination on cervical cancer screening in Alberta. Canadian Medical Association Journal. 2016:cmaj. 151528.
Canada3	Willows K, Bozat-Emre S, Righolt CH, Kliewer EV, Mahmud SM. Early Evidence of the Effectiveness of the Human Papillomavirus Vaccination Program Against Anogenital Warts in Manitoba, Canada: A Registry Cohort Study. Sex Transm Dis. 2018;45(4):254-9.
Costa Rica1	Safaeian M, Porras C, Pan Y, Kreimer A, Schiller JT, Gonzalez P, et al. Durable antibody responses following one dose of the bivalent human papillomavirus L1 virus-like particle vaccine in the Costa Rica Vaccine Trial. Cancer Prev Res (Phila). 2013;6(11):1242-50.
	Safaeian M, Sampson JN, Pan Y, Porras C, Kemp TJ, Herrero R, et al. Durability of Protection Afforded by Fewer Doses of the HPV16/18 Vaccine: The CVT Trial. J Natl Cancer Inst. 2018;110(2).
	Kreimer AR, Rodriguez AC, Hildesheim A, Herrero R, Porras C, Schiffman M, et al. Proof-of-principle evaluation of the efficacy of fewer than three doses of a bivalent HPV16/18 vaccine. J Natl Cancer Inst. 2011;103(19):1444-51.
CVT/PATRICIA	Kreimer A, Struyf F, Del Rosario-Raymundo MR, Hildesheim A, Skinner SR, Wacholder S, et al. Efficacy of fewer than three doses of an HPV-16/18 AS04-adjuvanted vaccine: combined analysis of data from the Costa Rica Vaccine and PATRICIA trials. The Lancet Oncology. 2015;16(7):775-86.
	Kreimer AR, Herrero R, Sampson JN, Porras C, Lowy DR, Schiller JT, et al. Evidence for single-dose protection by the bivalent HPV vaccine-Review of the Costa Rica HPV vaccine trial and future research studies. Vaccine. 2018;36(32 Pt A):4774-82.

Denmark2	Blomberg M, Dehlendorff C, Sand C, Kjaer SK. Dose-Related Differences in Effectiveness of Human Papillomavirus Vaccination Against Genital Warts: A Nationwide Study of 550,000 Young Girls. Clin Infect Dis. 2015;61(5):676-82.
Denmark3	Verdoodt F, Dehlendorff C, Kjaer SK. Dose-related effectiveness of quadrivalent human papillomavirus vaccine against cervical intraepithelial neoplasia: A Danish nationwide cohort study. Clinical Infectious Diseases. 2019.
Denmark/Sweden1	Dehlendorff C, Sparén P, Baldur-Felskov B, Herweijer E, Arnheim-Dahlström L, Ploner A, et al. Effectiveness of varying number of doses and timing between doses of quadrivalent HPV vaccine against severe cervical lesions. Vaccine. 2018;36(43):6373-8.
Fiji1	Toh ZQ, Russell FM, Reyburn R, Fong J, Tuivaga E, Ratu T, et al. Sustained Antibody Responses 6 Years Following 1, 2, or 3 Doses of Quadrivalent Human Papillomavirus (HPV) Vaccine in Adolescent Fijian Girls, and Subsequent Responses to a Single Dose of Bivalent HPV Vaccine: A Prospective Cohort Study. Clin Infect Dis. 2017;64(7):852-9.
	Toh ZQ, Cheow KWB, Russell FM, Hoe E, Reyburn R, Fong J, et al. Cellular Immune Responses 6 Years Following 1, 2, or 3 Doses of Quadrivalent HPV Vaccine in Fijian Girls and Subsequent Responses to a Dose of Bivalent HPV Vaccine. Open Forum Infect Dis. 2018;5(7):ofy147.
India1	Sankaranarayanan R, Prabhu PR, Pawlita M, Gheit T, Bhatla N, Muwonge R, et al. Immunogenicity and HPV infection after one, two, and three doses of quadrivalent HPV vaccine in girls in India: a multicentre prospective cohort study. The Lancet Oncology. 2016;17(1):67-77.
	Sankaranarayanan R, Joshi S, Muwonge R, Esmy PO, Basu P, Prabhu P, et al. Can a single dose of human papillomavirus (HPV) vaccine prevent cervical cancer? Early findings from an Indian study. Vaccine. 2018;36(32 Pt A):4783-91.
Scotland1	Cuschieri K, Kavanagh K, Moore C, Bhatia R, Love J, Pollock KG. Impact of partial bivalent HPV vaccination on vaccine-type infection: a population-based analysis. Br J Cancer. 2016;114(11):1261-4.
Scotland2	Pollock KG, Kavanagh K, Potts A, Love J, Cuschieri K, Cubie H, et al. Reduction of low- and high-grade cervical abnormalities associated with high uptake of the HPV bivalent vaccine in Scotland. Br J Cancer. 2014;111(9):1824-30.
Scotland3	Cameron RL, Kavanagh K, Cameron Watt D, Robertson C, Cuschieri K, Ahmed S, et al. The impact of bivalent HPV vaccine on cervical intraepithelial neoplasia by deprivation in Scotland: reducing the gap. J Epidemiol Community Health. 2017;71(10):954-60.
Scotland4	Kavanagh K, Pollock KG, Potts A, Love J, Cuschieri K, Cubie H, 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.
	Cameron RL, Kavanagh K, Pan J, Love J, Cuschieri K, Robertson C, et al. Human Papillomavirus Prevalence and Herd Immunity after Introduction of Vaccination Program, Scotland, 2009-2013. Emerg Infect Dis. 2016;22(1):56-64.
Scotland5	Kavanagh K, Pollock KG, Cuschieri K, Palmer T, Cameron RL, Watt C, et al. Changes in the prevalence of human papillomavirus following a national bivalent human papillomavirus vaccination programme in Scotland: a 7-year cross-sectional study. The Lancet Infectious Diseases. 2017;17(12):1293-302.
Scotland6	Palmer T, Wallace L, Pollock KG, Cuschieri K, Robertson C, Kavanagh K, et al. Prevalence of cervical disease at age 20 after immunisation with bivalent HPV vaccine at age 12-13 in Scotland: retrospective population study. BMJ. 2019;365:l1161.

Spain2	Navarro-Illana E, Lopez-Lacort M, Navarro-Illana P, Vilata JJ, Diez-Domingo J. Effectiveness of HPV vaccines against genital warts in women from Valencia, Spain. Vaccine. 2017;35(25):3342-6.
Sweden1	Herweijer E, Leval A, Ploner A, Eloranta S, Simard JF, Dillner J, et al. Association of varying number of doses of quadrivalent human papillomavirus vaccine with incidence of condyloma. JAMA. 2014;311(6):597-603.
Switzerland1	Jeannot E, Viviano M, De Pree C, Amadane M, Kabengele E, Vassilakos P, et al. Prevalence of Vaccine Type Infections in Vaccinated and Non-Vaccinated Young Women: HPV-IMPACT, a Self-Sampling Study. International Journal of Environmental Research and Public Health. 2018;15(7):1447.
Uganda1	LaMontagne DS, Mugisha E, Pan Y, Kumakech E, Ssemaganda A, Kemp TJ, et al. Immunogenicity of bivalent HPV vaccine among partially vaccinated young adolescent girls in Uganda. Vaccine. 2014;32(47):6303-11.
USA1	Hofstetter AM, Ompad DC, Stockwell MS, Rosenthal SL, Soren K. Human papillomavirus vaccination and cervical cytology outcomes among urban low-income minority females. JAMA pediatrics. 2016;170(5):445-52.
USA2	Hariri S, Schuler MS, Naleway AL, Daley MF, Weinmann S, Crane B, et al. Human Papillomavirus Vaccine Effectiveness Against Incident Genital Warts Among Female Health-Plan Enrollees, United States. Am J Epidemiol. 2018;187(2):298-305.
USA6	Perkins RB, Lin M, Wallington SF, Hanchate A. Impact of Number of Human Papillomavirus Vaccine Doses on Genital Warts Diagnoses Among a National Cohort of U.S. Adolescents. Sex Transm Dis. 2017;44(6):365-70.
USA9	Silverberg MJ, Leyden WA, Lam JO, Gregorich SE, Huchko MJ, Kulasingam S, et al. Effectiveness of catch-up human papillomavirus vaccination on incident cervical neoplasia in a US health-care setting: a population-based case-control study. The Lancet Child & Adolescent Health. 2018;2(10):707-14.
USA10	Flagg EW, Torrone EA. O17.2 Population effectiveness of human papillomavirus vaccination against anogenital warts among female enrollees in private health plans in the united states, 2006–2014. Sexually Transmitted Infections. 2017;93(Suppl 2):A39-A.
USA11	Zeybek B, Lin Y-L, Kuo Y-F, Rodriguez AM. The Impact of Varying Numbers of Quadrivalent Human Papillomavirus Vaccine Doses on Anogenital Warts in the United States: A Database Study. J Low Genit Tract Dis. 2018;22(3):189-94.
USA12	Chandler E, Ding L, Gorbach P, Franco EL, Brown DA, Widdice LE, et al. Epidemiology of Any and Vaccine-Type Anogenital Human Papillomavirus Among 13–26-Year-Old Young Men After HPV Vaccine Introduction. Journal of Adolescent Health. 2018;63(1):43-9.
USA13	Castle PE, Xie X, Xue X, Poitras NE, Lorey TS, Kinney WK, et al. Impact of human papillomavirus vaccination on the clinical meaning of cervical screening results. Preventive Medicine. 2019;118:44-50.
USA14	Spinner C, Ding L, Bernstein DI, Brown DR, Franco EL, Covert C, et al. Human Papillomavirus Vaccine Effectiveness and Herd Protection in Young Women. Pediatrics. 2019;143(2):e20181902.
USA15	Washington C, Ding L, Gorbach P, Rosen B, Kahn J. Individual and Partner-Level Characteristics Associated with Vaccine-Type and Non-Vaccine-Type Human Papillomavirus Infection in Young Women after Vaccine Introduction. Journal of Adolescent Health. 2018;62(2):S2.

USA16	Hurt L, Nsouli-Maktabi H, Rohrbeck P, & Clark LL (2016). Use of quadrivalent human papillomavirus vaccine and the prevalence of antibodies to vaccine-targeted strains among female service members before and after vaccination. *MSMR*, *23*(2), 6-13.

Appendix 3. Causal DAG model for HPV vaccination in adolescents and young adult study populations



Abbreviations: HPV = human papillomavirus; SES = socioeconomic status.

Minimal sufficient adjustment set for estimating the total effect of HPV vaccination on outcomes: Age (birth year), Directive_sexual_education&mass_media_(preventive), Ethnicity/cultural_context, Peer_group, Preventive_health_care_behaviour, Rural/Urban/Geographic_Setting.

Appendix 4. Characteristics of included studies

Study name	Publication year & funding	Date range	Study design	HPV vaccine	Participants (number, sex)	N by dose	Age at vaccination (V) and outcome (O)	Buffer period used in analysis	Outcomes reported
Australia1	2015 VCS Foundation (health promotion charity)	April 2007 to December 2011	Retrospective cohort study using linked regional data registries	quadrivalent	289,478 females	0: 133,055 1: 20,659 2: 27,500 3: 108,264	V: 12-26 O: 12-30	Yes:1, 6, 12, 24 months	Histological abnormalities (any high grade, CIN3/AIS, CIN2) Cytological abnormalities (high grade, low grade)
Australia2	2014 No specific project funding was received	April 2007 to March 2011	Case control study using linked data from registries	quadrivalent	108,353 females	0: 53,761 1: 9649 2: 10,950 3: 23,106	V: 12-26 O: 11-31	Yes: 1, 6, 12 months	Cervical abnormalities
Australia3	2013 Not reported	1 April 2007 to 31 December 2011	Retrospective cohort study using linked data from registries	quadrivalent	38,956 females	0: 14,085 1: 1422 2: 2268 3: 21,151	V: 12-19 O: 12-21	Yes: time between 1st and 3rd dose	Cervical abnormalities, Cytological abnormalities
Australia4	2019 Australian Department of Health	April 2007 to December 2014	Retrospective cohort study using linked regional data registries	quadrivalent	250,648 females	0: 48,845 1: 8618 2: 18190 3: 174995	V: <15 O: >=12	Yes: 12 and 24 months	Histological abnormalities
Belgium2	2015 Sanofi Pasteur	January 2006 to December 2013	Retrospective cohort study using sick-fund/ insurance data	quadrivalent	106,579 females	0: 63,180 1: 4020 2: 3587 3: 35,792	V: 10-23 O: 16-23	Yes: 1 month	Anogenital warts
Canada2	2016 Not reported	2008 - 2015	Nested case-control study using linked data from registries	quadrivalent	10,204 females	0: 5712 1: 327 2: 490 3: 3675	V: 10-15 O: 18-21	No, 3 years between vaccine and outcome	Cytology outcome (low-grade and high-grade abnormalities)

Study name	Publication year & funding	Date range	Study design	HPV vaccine	Participants (number, sex)	N by dose	Age at vaccination (V) and outcome (O)	Buffer period used in analysis	Outcomes reported
Canada3	2018 Merck Canada	September 2006 and March 2013	Retrospective cohort study using linked data from registries, with matched control (unvaccinated) group	quadrivalent	31,464 females	0: 94,327 1: 3521 2: 6666 3: 21,277	V: 9-25 O: 9-25	Yes: 12 months	Anogenital warts
Costa Rica1	2013 National Institutes of Health, GlaxoSmithKline (vaccine and support for aspects of the trial associated with regulatory submission needs of the company)	2004-2005	Post-hoc analysis of RCT	bivalent	7,466 females	1: 277 2: 488 3: 2965	V: 18-25 O: 25-32	No, post-hoc analysis of RCT	Antibody geometric mean titre, Seropositivity, HPV infection, persistent HPV infection
CVT/PATRICIA	2015 US National Cancer Institute, National Institutes of Health Office of Research on Women's Health, and Ministry of Health of Costa Rica (CVT); GlaxoSmithKline (PATRICIA).	2004-2005	Post-hoc analysis of two RCTs	bivalent	26,110 females	0: 13,361 1: 573 2: 977 3: 11,499	V: 15-25 O: 25-32	No, post-hoc analysis of RCT	HPV infection, persistent HPV infection
Denmark2	2015 Aragon Foundation; the Aase and Ejnar Danielsens Foundation; the Mermaid II project	October 2006 to December 2012	Retrospective cohort study using population-based health national registries	quadrivalent	550,690 females	0: 188,956 1: 55,666 2: 93,519 3: 212,549	V: 12-27 O: 12-27	Yes: 1 month	Anogenital warts

Study name	Publication year & funding	Date range	Study design	HPV vaccine	Participants (number, sex)	N by dose	Age at vaccination (V) and outcome (O)	Buffer period used in analysis	Outcomes reported
Denmark3	2019 the Mermaid Project	2006-2016	Non-randomised, retrospective cohort	quadrivalent	550,690; females	0: 374,327, 1: 10,480, 2: 30,259, 3: 174,532	V: <16 O: 17-25	Yes: 6 months	Anogenital warts
Denmark/Sweden1	2018 the Mermaid Project	2006-2013	Retrospective observational cohort	quadrivalent	2,253,561; females	0: 2,091,579 1: 712,588 2: 557,528 3: 530,130	V: 13-16, 17-19, 20-29 O: 13-29	Yes: 6 months	CIN2+
Fiji1	2017 Department of Foreign Affairs and Trade of the Australian government and the Fiji Health Sector Support Program	February and March 2015	Prospective cohort study	quadrivalent	200 females	0: 32 1: 40 2: 60 3: 66	V: 9-13 O: 15-19	No, 6 years between vaccine and outcome	Antibody geometric mean titre, Seroconversion
India1	2016 Bill & Melinda Gates Foundation	Sept 1, 2009, to April 8, 2010	Post-hoc analysis of RCT	quadrivalent	17,729 females	1: 4950 2: 8431 3: 4348	V: 10-18 O: 12-20	No, post-hoc analysis of RCT	Antibody geometric mean titre, HPV infection
Scotland1	2016 Not reported	from 2009	Cohort study using screening registry data with additional sampling of women with < 3 doses	bivalent	5949 females	0: 3619 1: 177 2: 300 3: 1853	V: 15-17 O: 20-21	No, 3 years between vaccine and outcome	HPV infection
Scotland2	2014 partially funded by Scottish Government Chief Scientists Office	2008–2012	Retrospective cohort study using linked national registry data	bivalent	106,052 females	0: 75,113 1: 1315 2: 2725 3: 25,898	V: 15-17 O: 20-21	No, 3 years between vaccine and outcome	CIN 1, 2, 3

Study name	Publication year & funding	Date range	Study design	HPV vaccine	Participants (number, sex)	N by dose	Age at vaccination (V) and outcome (O)	Buffer period used in analysis	Outcomes reported
Scotland3	2017 Not reported	2008-2015	Retrospective cohort study using linked national registry data	bivalent	137,689 females	0: 75,684 1: 2258 2: 4462 3: 55,303	V: 12-13 O: 20-21	No, 7 years between vaccine and outcome	CIN 1, 2, 3
Scotland4	2014 Scottish Government and Chief Scientists Office	2009-2012	Cohort study using screening registry data	bivalent	4729 females	0: 3418 1: 55 2: 106 3: 1100	V: 15-17 O: 20-21	No, 3 years between vaccine and outcome	HPV infection
Scotland5	2017 Scottish Government and Chief Scientists Office	2009-2015	Cohort study using screening registry data	bivalent	8584 females	0: 4008 1: 223 2: 391 3: 3962	V: 12-13 O: 20-21	No, 7 years between vaccine and outcome	HPV infection
Scotland6	2019 Scottish National Health Service. No funding has been received from industry	2008-2016	Non-randomised, retrospective cohort	bivalent	138,692; females	0: 64,026, 1: 2051, 2: 4135, 3: 68,480	V: 12-18 O: 20	No, 2 years between vaccine and outcome	Cytological and histological abnormalities
Spain2	2017 The Foundation for the Promotion of Health and Biomedical Research of Valencia Region (FISABIO); Sanofi Pasteur sponsored the medical writer	Jan 2009 - Dec 2014	Retrospective cohort study using national registries	quadrivalent	279,787 females	0: NR 1: NR 2: NR 3: NR	V: 14 O: 14-19	No	Anogenital warts

Study name	Publication year & funding	Date range	Study design	HPV vaccine	Participants (number, sex)	N by dose	Age at vaccination (V) and outcome (O)	Buffer period used in analysis	Outcomes reported
Sweden1	2014 Swedish Foundation for Strategic Research, Sanofi Pasteur Merck Sharp Dome and GlaxoSmithKline	January 1, 2006, to December 31, 2010	Retrospective cohort study using population-based health registries	quadrivalent	1,045,165 females	0: 926,119 1: 115,197 2: 107,338 3: 89,836	V: 10-19 O: 10-24	Yes: 0 to 12 months	Anogenital warts
Switzerland1	2018 Received no external funding	January 2016 and October 2017	Non-randomised, cross sectional study	quadrivalent	409 females	0: 125, 1: 20, 2: 60, 3: 204	V: 11-26 O: 18-31	No	HPV positivity
Uganda1	2014 Bill & Melinda Gates Foundation	2008-2009	Prospective cohort study	bivalent	376 females	1: 36 2: 145 3: 195	V: 10-11 O: 12-15	No, 38 months between vaccine and outcome	Antibody geometric mean titre
USA1	2016 Merck Investigator-Initiated Studies Program	2007-2014	Retrospective cohort study using medical centre databases	quadrivalent	4127 females	0: 1632 1: 695 2: 604 3: 1196	V: 11-20 O: 11-27	Yes: 1 month	Abnormal cervical cytology
USA2	2017 Centre for Disease Control and Prevention	2006-2012	Retrospective cohort study	quadrivalent	64,517 females	0: 31,563 1: 5864 2: 5459 3: 21,631	NR	Yes: 6 and 12 months	Anogenital warts
USA6	2017 American Cancer Society	Jan 2007 - Dec 2013	Retrospective cohort study using commercial claims database	quadrivalent	387,906 females	0: 201,933 1: 30,438 2: 36,583 3: 118,962	V: 9-25 O: 9-25	Yes: 12 months	Anogenital warts

Study name	Publication year & funding	Date range	Study design	HPV vaccine	Participants (number, sex)	N by dose	Age at vaccination (V) and outcome (O)	Buffer period used in analysis	Outcomes reported
USA9	2018 US National Cancer Institute	Jan 1, 1995, and June 30, 2014	Nested case control study	quadrivalent	26,130 females	0: 3928 cases / 19365 controls, 1: 118/638 2: 97/457 3: 214/1313	V: 14-21 O: Up to 34	No	CIN2+, CIN3+
USA10	2017 Not reported	2003–2014	Non-randomised, retrospective cohort	quadrivalent	270,481 females	>=1: 75,735	V: Median age 15 years O: NR	No	Anogenital warts
USA11	2018 William & Mary McGanity Research Fund Award from the Department of Obstetrics & Gynecology at The University of Texas Medical Branch at Galveston	2006 - 2015	Retrospective cohort	quadrivalent	440,532; females; 133,394; males	0: 220,266 1: 54,280 2: 55,632 3:177,051	V: 9-26 O: 9-29	Yes: 3 months	Anogenital warts
USA12	2018 National Institute of Allergy and Infectious Diseases, National Institute of Health	2013-2015	Prospective cohort	quadrivalent	236; males	>=1: 104 3: 49	V: NR O: 13-26	No	HPV infection
USA13	2019 Not reported	December 12, 2006 to December 13, 2016	Prospective cohort study	quadrivalent	75,008; females	0: 59,860 1: 3,542 2 or more: 11,048	V: <18–24 O: 21–24	No	Cytological abnormalities
USA14	2019 the National Institutes of Health	2006-2017	Cross-sectional study (4 waves)	quadrivalent	1580 females	NR	V: unclear O: 13-26	No	HPV infection

Study name	Publication year & funding	Date range	Study design	HPV vaccine	Participants (number, sex)	N by dose	Age at vaccination (V) and outcome (O)	Buffer period used in analysis	Outcomes reported
USA15	2018 National Institute of Allergy and Infectious Diseases, National Institute of Health	2013-2017	Non-randomised cross-sectional study	Mixed: quadrivalent, nonavalent	735; females	>=1: 559 3: 448	V: NR O: 13-26	No	HPV infection
USA16	2016 Not reported	2006-2012	Retrospective cohort study	Quadrivalent	2091; females	1: 146; 2: 166; 3: 480	V: NR O: 4-6 years	No	Seroconversion

AIS= adenocarcinoma in situ; CIN= cervical intraepithelial neoplasia; HPV= human papilloma virus; NR= not reported; O= (age at) outcome; RCT= randomised controlled trial; V= (age at) vaccination

Appendix 5. ROBINS-I Summary

Low risk		the study is comparable to a well-performed randomised trial
Moderate risk		the study provides sound evidence for a non-randomised study but cannot be considered comparable to a well-performed randomised trial
Serious risk		the study has some important problems
Critical risk		the study is too problematic to provide any useful evidence and should not be included in any synthesis

	Bias due to confounding	Bias in selection of participants into the study	Bias in classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result	Overall
Australia1	Serious	Serious	Low	Moderate	Moderate	Moderate	Moderate	Serious
Australia3	Serious	Serious	Low	Moderate	Moderate	Moderate	Moderate	Serious
Australia4	Serious	Serious	Low	Moderate	Moderate	Moderate	Moderate	Serious
Belgium2	Serious	Moderate	Low	Moderate	Moderate	Moderate	Moderate	Serious
Canada3	Serious	Moderate	Low	Moderate	Moderate	Moderate	Moderate	Serious
Costa Rica1	Moderate	Low	Low	Low	Moderate	Low	Moderate	Moderate
CVT/PATRICIA	Moderate	Low	Low	Low	Moderate	Low	Low	Moderate
Denmark2	Serious	Moderate	Low	Moderate	Low	Moderate	Moderate	Serious
Denmark3	Serious	Moderate	Low	Moderate	Low	Moderate	Moderate	Serious
Denmark/Sweden1	Serious	Moderate	Low	Moderate	Low	Moderate	Moderate	Serious
Fiji1	Serious	Serious	Low	Moderate	Low	Low	Moderate	Serious
India1	Serious	Low	Low	Low	Moderate	Low	Moderate	Serious
Scotland1	Serious	Serious	Low	Moderate	Low	Moderate	Moderate	Serious
Scotland2	Serious	Serious	Low	Moderate	Low	Moderate	Moderate	Serious
Scotland3	Serious	Serious	Low	Moderate	Low	Moderate	Moderate	Serious
Scotland4	Serious	Serious	Low	Moderate	Low	Moderate	Moderate	Serious

Scotland5	Serious	Serious	Low	Moderate	Low	Moderate	Moderate	Serious
Scotland6	Serious	Serious	Low	Moderate	Moderate	Moderate	Moderate	Serious
Spain2	Serious	Moderate	Low	Moderate	Moderate	Moderate	Moderate	Serious
Sweden1	Serious	Moderate	Low	Moderate	Low	Moderate	Moderate	Serious
Switzerland1	Serious	Serious	Serious	Moderate	Moderate	Moderate	Moderate	Serious
Uganda1	Serious	Low	Low	Moderate	Low	Low	Moderate	Serious
USA1	Serious	Serious	Low	Moderate	Moderate	Moderate	Moderate	Serious
USA2	Moderate	Moderate	Low	Moderate	Low	Moderate	Moderate	Moderate
USA6	Serious	Serious	Low	Moderate	Low	Moderate	Moderate	Serious
USA11	Serious	Moderate	Low	Moderate	Low	Moderate	Moderate	Serious
USA12	Serious	Critical	Serious	Moderate	Moderate	Low	Moderate	Critical
USA13	Serious	Serious	Low	Moderate	Moderate	Moderate	Moderate	Serious
USA14	Serious	Serious	Low	Moderate	Moderate	Low	Moderate	Serious
USA16	Serious	Serious	Low	Moderate	Moderate	Low	Moderate	Serious

Complete risk of bias assessments for each study can be found through the following link:
https://www.dropbox.com/sh/kqgsxyezpc5inb8/AADbFV29htLRY9SuM3i9IB3ta?dl=0

Appendix 6. SIGN-50 Summary

Low risk	
Unclear risk	
High risk	
Critical questions	

	Clear Q & Protocol	**Selection of subjects**						**Assessment of exposure**		**Confounding**	**Other bias**		**Final**
	1.1	1.2	1.3	1.4	1.5	1.6	1.7	1.8	1.9	1.10	1.11	1.12	
Australia2	High	Low	Low	Low	Unclear	Low	High	Low	Unclear	High	Low	Low	High
Canada2	High	Low	Low	Unclear	Unclear	Low	Low	Low	Low	High	Unclear	Low	High
USA9	High	Low	Low	Low	Unclear	Low	Unclear	Unclear	Unclear	High	Low	Low	High

Complete risk of bias assessments for each study can be found through the following link:
https://www.dropbox.com/sh/kqgsxyezpc5inb8/AADbFV29htLRY9SuM3i9IB3ta?dl=0

Appendix 7. GRADE tables

Effectiveness and immunogenicity of one dose of HPV vaccine compared with no vaccination

Estimate	Outcome	Studies	GRADE	GRADE supporting notes
BIVALENT VACCINE				
Unadjusted Figure 1	HPV antibody titres (GMTs)	Costa Rica1	Moderate	1. Observational studies start at low certainty (lack of appropriate protection against uncontrolled bias and confounding) 2. Moderate risk bias, upgraded one level 3. Imprecision due to few participants not downgraded because of a large effect in favour of intervention – no concerns about precision of estimate
Adjusted Figure 2	CIN1	Scotland2, Scotland3, Scotland6	Very low	1. Observational studies start at low certainty (lack of appropriate protection against uncontrolled bias and confounding) 2. serious risk of selection bias, 3. Imprecision due to wide 95% CIs
Adjusted Figure 2	CIN2	Scotland2, Scotland3, Scotland	Very low	
Adjusted Figure 2	CIN3+	Scotland2, Scotland3, Scotland6	Very low	
Adjusted Figure 2	Low grade dyskaryosis	Scotland6	Very low	1. Observational studies start at low certainty (lack of appropriate protection against uncontrolled bias and confounding) 2. serious risk of selection bias
Adjusted Figure 2	Moderate-high grade dyskaryosis	Scotland6	Very low	1. Observational studies start at low certainty (lack of appropriate protection against uncontrolled bias and confounding) 2. serious risk of selection bias, 3. Imprecision due to wide 95% CIs
Adjusted Figure 2	Severe-high grade dyskaryosis	Scotland6	Very low	
Adjusted Figure 2	Borderline changes (histology)	Scotland6	Very low	1. Observational studies start at low certainty (lack of appropriate protection against uncontrolled bias and confounding)

				2. serious risk of selection bias,
Adjusted Figure 3	Prevalent HPV 16/18 infection	Scotland1, Scotland4, Scotland5	Very low	1. Observational studies start at low certainty (lack of appropriate protection against uncontrolled bias and confounding) 2. serious risk of selection bias, 3. Imprecision due to wide 95% CIs
Adjusted Figure 3	Prevalent HPV 31/33/45 infection	Scotland1, Scotland4, Scotland5	Very low	
Adjusted Figure 3	Prevalent HPV infection – other high-risk HPV types	Scotland4, Scotland5	Very low	
Adjusted Figure 3	Prevalent HPV infection – any HPV types	Scotland4, Scotland5	Very low	
Unadjusted Figure 4	One-time incident HPV 16/18 infection	CVT/PATRICIA	Moderate	1. Observational studies start at low certainty (risk of bias due to confounding) 2. Moderate risk of bias, upgraded one level
Unadjusted Figure 4	One-time incident HPV 31/33/45 infection	CVT/PATRICIA	Low	1. Observational studies start at low certainty (risk of bias due to confounding) 2. Moderate risk of bias, upgraded one level 3. Imprecision, few events
Unadjusted Figure 5	6 to 12 months persistent HPV 16/18 infection	CVT/PATRICIA	Low	1. Observational studies start at low certainty (lack of appropriate protection against uncontrolled bias and confounding) 2. Moderate risk of bias, upgraded one level 3. Imprecision, few events
Unadjusted Figure 5	6 to 12 months persistent HPV 31/33/45 infection	CVT/PATRICIA	Low	
QUADRIVALENT VACCINE				
Unadjusted Figure 6	HPV antibody titres (GMTs)	Fiji1	Very low	1. Observational studies start at low certainty (lack of appropriate protection against uncontrolled bias and confounding) 2. serious risk of selection bias 3. Imprecision not downgraded because of a large effect in favour of intervention – no concerns about precision of estimate
Unadjusted Figure 7	Seropositivity	Fiji1	Very low	

Adjusted Table 3	CIN3/AIS or CIN3+	Australia1, Australia3, Australia4, Denmark3, USA9	Very low	1. Observational studies start at low certainty (lack of appropriate protection against uncontrolled bias and confounding) 2. serious risk of selection bias for 3 of the 5 studies, 3. Inconsistency across studies
Adjusted Table 3	CIN2+	Australia4, Denmark3, USA9, Denmark/Sweden1	Low	1. Observational studies start at low certainty (lack of appropriate protection against uncontrolled bias and confounding) 2. Inconsistent results across studies not downgraded as this is explained by age at vaccination
Adjusted Table 3	CIN2	Australia1, Australia3	Very low	1. Observational studies start at low certainty (lack of appropriate protection against uncontrolled bias and confounding) 2. serious risk of selection bias 3. Imprecision, wide CIs
Adjusted Table 3	CIN1	Australia3	Very low	
Adjusted Table 3	any high-grade histological abnormalities	Australia1, Australia3	Very low	
Unadjusted Figure 8	CIN1	Australia3	Very low	1. Observational studies start at low certainty (lack of appropriate protection against uncontrolled bias and confounding) 2. serious risk of selection bias
Unadjusted Figure 8	CIN2	Australia1, Australia3	Very low	
Unadjusted Figure 8	CIN2+	Australia1, Australia3, Australia4, Denmark3, USA9	Very low	1. Observational studies start at low certainty (lack of appropriate protection against uncontrolled bias and confounding) 2. serious risk of selection bias for 3 of 5 studies 3. inconsistency that could be explained by the age at vaccination
Unadjusted Figure 8	CIN3+	Australia1, Australia3, Australia4, Denmark3, USA9	Very low	
Unadjusted Figure 8	Any high-grade histological abnormalities	Australia1, Australia2, Australia3	Very low	1. Observational studies start at low certainty (lack of appropriate protection against uncontrolled bias and confounding) 2. serious risk of selection bias for 2 of 4 studies
Unadjusted Figure 8	“other” histological abnormalities	Australia2	Very low	
Adjusted Table 4	High-grade cytology	Australia1, Australia3	Very low	1. Observational studies start at low certainty (lack of

Adjusted Table 4	Low-grade cytology	Australia1, Australia3	Very low	appropriate protection against uncontrolled bias and confounding) 2. serious risk of selection bias
Adjusted Table 4	abnormal cervical cytology	USA1	Very low	
Unadjusted Figure 9	abnormal cervical cytology	Canada2, USA1	Very low	1. Observational studies start at low certainty (lack of appropriate protection against uncontrolled bias and confounding) 2. serious risk of selection bias (USA1)
Unadjusted Figure 10	Genital warts	Belgium2, Canada3, Denmark2, Spain2, Sweden1, USA2, USA6, USA11	Very low	1. Observational studies start at low certainty (lack of appropriate protection against uncontrolled bias and confounding) 2. downgrade due to inconsistency. We didn't pool but if we had done then I=sq 90%
Unadjusted Figure 11	Incident HPV 16/18 infections	India1	Low	1. Observational studies start at low certainty (lack of appropriate protection against uncontrolled bias and confounding) 2. borderline few events, did not downgrade for imprecision
Unadjusted Figure 11	Incident HPV 6/11/16/18 infections	India1	Low	
Unadjusted Figure 11	Incident HPV 31/33/45 infections	India1	Low	
Unadjusted Figure 11	Incident HPV (any) infections	India1	Low	1. Observational studies start at low certainty (lack of appropriate protection against uncontrolled bias and confounding)
Unadjusted Figure 11	Persistent HPV 16/18 infections	India1	Very low	1. Observational studies start at low certainty (lack of appropriate protection against uncontrolled bias and confounding) 2. Imprecision, few events
Unadjusted Figure 11	Persistent HPV 6/11/16/18 infections	India1	Very low	
Unadjusted Figure 11	Persistent HPV 31/33/45 infections	India1	Very low	
Unadjusted Figure 11	Persistent HPV (any) infections	India1	Very low	

Effectiveness and immunogenicity of one dose of HPV vaccine compared with two doses

Estimate	Outcome	Studies	GRADE	GRADE supporting notes
BIVALENT VACCINE				
Unadjusted Figure 12	HPV antibodies (GMTs)	Costa Rica1, Uganda1	Low	1. Observational studies start at low certainty (lack of appropriate protection against uncontrolled bias and confounding) 2. Moderate risk of bias, upgraded one level (Costa Rica1) 3. Imprecision (CI crosses non-inferiority threshold)
Unadjusted Figure 13	Seroconversion	Costa Rica1, Uganda1	Low	1. Observational studies start at low certainty (lack of appropriate protection against uncontrolled bias and confounding) 2. Moderate risk of bias, upgraded one level (Costa Rica1) 3. Imprecision: few events
Unadjusted Figure 14	CIN1	Scotland2, Scotland3	Very low	1. Observational studies start at low certainty (lack of appropriate protection against uncontrolled bias and confounding) 2. serious risk of selection bias, 3. Imprecision, few events
Unadjusted Figure 14	CIN2	Scotland2, Scotland3	Very low	
Unadjusted Figure 14	CIN3	Scotland2, Scotland3	Very low	
Unadjusted Figure 15	Prevalent HPV 16/18 infection	Scotland1, Scotland4, Scotland5	Very low	1. Observational studies start at low certainty (lack of appropriate protection against uncontrolled bias and confounding) 2. serious risk of selection bias, 3. Imprecision, few events
Unadjusted Figure 15	Prevalent HPV 31/33/45 infection	Scotland1, Scotland4, Scotland5	Very low	
Unadjusted Figure 15	Prevalent HPV infection other types (not 16,18,31,33,45)	Scotland4, Scotland5	Very low	1. Observational studies start at low certainty (lack of appropriate protection against

Unadjusted Figure 15	Prevalent infection any HPV type	Scotland4, Scotland5	Very low	uncontrolled bias and confounding) 2. serious risk of selection bias
Unadjusted Figure 16	cumulative HPV 16 infections	Costa Rica1	Very Low	1. Observational studies start at low certainty (lack of appropriate protection against uncontrolled bias and confounding) 2. Moderate risk of bias, upgraded one level 3. very serious Imprecision, few events and very wide CIs
Unadjusted Figure 16	cumulative HPV 18 infections	Costa Rica1	Very Low	
Unadjusted Figure 16	cumulative HPV 16/18 infections	Costa Rica1	Very Low	
Unadjusted Figure 16	cumulative HPV 31/33/45 infections	Costa Rica1	Very Low	
Unadjusted Figure 16	cumulative other carcinogenic HPV types infections	Costa Rica1	Low	1. Observational studies start at low certainty (lack of appropriate protection against uncontrolled bias and confounding) 2. Moderate risk of bias, upgraded one level 3. Imprecision, few events
Unadjusted Figure 16	cumulative non-carcinogenic HPV types infections	Costa Rica1	Low	
Unadjusted Figure 17	One-time incident HPV 16 / 18 infection	CVT/PATRICIA	Low	1. Observational studies start at low certainty (lack of appropriate protection against uncontrolled bias and confounding) 2. Moderate risk of bias, upgraded one level 3. Imprecision, few events and wide CIs
Unadjusted Figure 17	One-time incident HPV 31 / 33 / 45 infection	CVT/PATRICIA	Low	
Unadjusted Figure 18	6 to 12-month persistent HPV 16/18 infection	CVT/PATRICIA	Very low	1. Observational studies start at low certainty (lack of appropriate protection against uncontrolled bias and confounding) 2. Moderate risk of bias, upgraded one level 3. very serious imprecision, very few events and very wide CIs

Unadjusted Figure 18	6 to 12-month persistent HPV 31/33/45 infection	CVT/PATRICIA	Low	1. Observational studies start at low certainty (lack of appropriate protection against uncontrolled bias and confounding) 2. Moderate risk of bias, upgraded one level 3. imprecision, few events and wide CIs
QUADRIVALENT VACCINE				
Unadjusted Figure 19	HPV antibody titres (GMTs)	Fiji1, India1	Low	1. Observational studies start at low certainty (lack of appropriate protection against uncontrolled bias and confounding) 2. smaller study Fiji risk of selection bias, we did not downgrade
Unadjusted Figure 20	Seropositivity	Fiji1, USA16	Very low	1. Observational studies start at low certainty (lack of appropriate protection against uncontrolled bias and confounding) 2. risk of selection bias (both studies) 3. HPV 18 inconsistent
Adjusted Page 41	CIN2+, CIN3+	Denmark3, Australia4	Very low	1. Observational studies start at low certainty (lack of appropriate protection against uncontrolled bias and confounding) 2. Imprecision, wide CIs
Unadjusted Figure 21	CIN1	Australia3	Very low	1. Observational studies start at low certainty (lack of appropriate protection against uncontrolled bias and confounding) 2. serious risk of selection bias, 3. Imprecision, few events
Unadjusted Figure 21	CIN2	Australia1, Australia3	Very low	
Unadjusted Figure 21	CIN2+	Australia1, Australia4, Denmark3, USA9	Very low	1. Observational studies start at low certainty (lack of appropriate protection against uncontrolled bias and confounding) 2. Largest study (Australia4) at serious risk of selection bias

Unadjusted Figure 21	CIN3+	Australia1, Australia3, Australia4, Denmark3, USA9	Very low	1. Observational studies start at low certainty (lack of appropriate protection against uncontrolled bias and confounding) 2. Largest study (Australia4) at serious risk of selection bias 3. Imprecision: wide CIs
Unadjusted Figure 21	high-grade histological abnormality	Australia1, Australia2, Australia3	Very low	1. Observational studies start at low certainty (lack of appropriate protection against uncontrolled bias and confounding) 2. selection bias
Unadjusted Figure 21	Other histological abnormality	Australia2	Very low	
Unadjusted Figure 22	high-grade abnormal cytology	Australia1, Australia3, Canada2	Very low	1. Observational studies start at low certainty (lack of appropriate protection against uncontrolled bias and confounding) 2. risk of selection bias, 3. imprecision: few events with wide CIs
Unadjusted Figure 22	low-grade abnormal cytology	Australia1, Australia3, Canada2	Very low	1. Observational studies start at low certainty (lack of appropriate protection against uncontrolled bias and confounding) 2. risk of selection bias,
Unadjusted Figure 22	any abnormal cytology	Canada2, USA1	Very low	1. Observational studies start at low certainty (lack of appropriate protection against uncontrolled bias and confounding) 2. risk of selection bias (larger study, USA1) 3. inconsistency, I-sq=64%
Adjusted Table 6	Genital warts	Sweden1, USA2	Low	1. Observational studies start at low certainty (lack of appropriate protection against uncontrolled bias and confounding) 2. adequate control of confounding in one study 3. Inconsistency in results can be explained by interval duration

Unadjusted Figure 23	Genital warts	Belgium2, Canada3, Denmark2, Spain2, Sweden1, USA2, USA6, USA11	Very low	1. Observational studies start at low certainty (lack of appropriate protection against uncontrolled bias and confounding) 2. inconsistency
Unadjusted Figure 24	Incident HPV 16/18 infections	India1	Low	1. Observational studies start at low certainty (lack of appropriate protection against uncontrolled bias and confounding)
Unadjusted Figure 24	Incident HPV 31/33/45 infections	India1	Low	
Unadjusted Figure 24	Persistent HPV 16/18 infections	India1	Very low	1. Observational studies start at low certainty (lack of appropriate protection against uncontrolled bias and confounding) 2. Imprecision, few events and wide CIs
Unadjusted Figure 24	Persistent HPV 31/33/45 infections	India1	Very low	

Effectiveness and immunogenicity of one dose of HPV vaccine compared with three doses

Vaccine	Outcome	Studies	GRADE	GRADE notes
BIVALENT VACCINE				
Unadjusted Figure 25	HPV antibody titres (GMTs) >24, 48, 84 months	Costa Rica1, Uganda1	Moderate	1. Observational studies start at low certainty (lack of appropriate protection against uncontrolled bias and confounding) 2. Moderate risk of bias, upgrade one level (Costa Rica1) 3. large effects, precision is not a concern as one dose is inferior to three doses
Unadjusted Figure 26	Seroconversion >24, 48 months	Costa Rica1, Uganda1	Low	1. Observational studies start at low certainty (lack of appropriate protection against uncontrolled bias and confounding) 2. Moderate risk of bias, upgrade one level (Costa Rica1) 3. Imprecision, few events
Unadjusted Figure 27	CIN1 up to 13 years	Scotland2, Scotland3	Very low	1. Observational studies start at low certainty (lack of appropriate protection against uncontrolled bias and confounding) 2. serious risk of selection bias
Unadjusted Figure 27	CIN2 up to 13 years	Scotland2, Scotland3	Very low	
Unadjusted Figure 27	CIN3 / CIN3+ up to 13 years	Scotland2, Scotland3	Very low	
Unadjusted Figure 28	Prevalent infection HPV 16, 18 up to 7 years	Scotland1, Scotland4, Scotland5	Very low	1. Observational studies start at low certainty (lack of appropriate protection against uncontrolled bias and confounding) 2. serious risk of selection bias
Unadjusted Figure 28	Prevalent infection HPV 31, 33, 45 up to 7 years	Scotland1, Scotland4, Scotland5	Very low	
	Prevalent infection other HPV types (not 16, 18, 31, 33, 45) up to 7 years	Scotland4, Scotland5	Very low	1. Observational studies start at low certainty (lack of appropriate protection against uncontrolled bias and confounding) 2. serious risk of selection bias 3. Imprecision: 95% CI includes benefit with three doses and no effect

Vaccine	Outcome	Studies	GRADE	GRADE notes
Unadjusted Figure 28	Prevalent infection any HPV type up to 7 years	Scotland4, Scotland5	Very low	1. Observational studies start at low certainty (lack of appropriate protection against uncontrolled bias and confounding) 2. serious risk of selection bias
Unadjusted Figure 29	cumulative HPV infections • HPV16 • HPV18 • HPV16/18 7 years	Costa Rica1	Very low	1. Observational studies start at low certainty (lack of appropriate protection against uncontrolled bias and confounding) 2. Moderate risk of bias, upgrade one level (Costa Rica1) 3. very serious imprecision – very few events and wide CI, downgrade 2 steps
Unadjusted Figure 29	cumulative HPV infections • HPV31, 33, 45 7 years	Costa Rica1	Low	1. Observational studies start at low certainty (lack of appropriate protection against uncontrolled bias and confounding) 2. Moderate risk of bias, upgrade one level (Costa Rica1) 3. Imprecision – few events, downgrade one step
Unadjusted Figure 29	cumulative HPV infections • other carcinogenic HPV infections • non-carcinogenic HPV infections 7 years	Costa Rica1	Moderate	1. Observational studies start at low certainty (lack of appropriate protection against uncontrolled bias and confounding) 2. Moderate risk of bias, upgrade one level (Costa Rica1)
Unadjusted Figure 30	One-time incident HPV infection	CVT/PATRICIA	Low	1. Observational studies start at low certainty (lack of appropriate protection against uncontrolled bias and confounding) 2. Moderate risk of bias, upgrade one level (CVT/PATRICIA) 3. imprecision, downgrade one step: 95% CIs include no effect and benefit (HPV16,18) or harm (HPV31,33,45) with one dose

Vaccine	Outcome	Studies	GRADE	GRADE notes
Unadjusted Figure 31	6 month and 12-month persistent HPV 16, 18 infection	CVT/PATRICIA	Very low	1. Observational studies start at low certainty (lack of appropriate protection against uncontrolled bias and confounding) 2. Moderate risk of bias, upgrade one level (CVT/PATRICIA) 3. very serious imprecision, downgrade two steps: few events and 95% CIs include no effect, large harm, and large benefit with one dose
Unadjusted Figure 31	6 month and 12-month persistent HPV 31, 33, 45 infection	CVT/PATRICIA	Low	1. Observational studies start at low certainty (lack of appropriate protection against uncontrolled bias and confounding) 2. Moderate risk of bias, upgrade one level (CVT/PATRICIA) 3. imprecision, downgrade one step: 95% CIs include no effect, harm, and benefit with one dose
QUADRIVALENT VACCINE				
Unadjusted Figure 32	HPV antibody titres (GMTs) Up to 6 years	Fiji1, India1	Low	1. Observational studies start at low certainty (lack of appropriate protection against uncontrolled bias and confounding) 2. smaller study Fiji risk of selection bias, we did not downgrade
Unadjusted Figure 33	Seropositivity Up to 6 years	Fiji1, USA16	Very low	1. Observational studies start at low certainty (lack of appropriate protection against uncontrolled bias and confounding) 2. serious risk of selection bias (both studies)
Adjusted Page 52	CIN2+ CIN3+	Denmark3, Australia4	Very low	1. Observational studies start at low certainty (lack of appropriate protection against uncontrolled bias and confounding) 2. Imprecision, wide CIs

Vaccine	Outcome	Studies	GRADE	GRADE notes
Unadjusted Figure 34	CIN1	Australia3	Very low	1. Observational studies start at low certainty (lack of appropriate protection against uncontrolled bias and confounding) 2. serious risk of selection bias, 3. Imprecision, wide CIs
Unadjusted Figure 34	CIN2	Australia1, Australia3	Very low	1. Observational studies start at low certainty (lack of appropriate protection against uncontrolled bias and confounding) 2. serious risk of selection bias,
Unadjusted Figure 34	CIN2+	Australia1, Australia3, Australia4, Denmark3, USA9	Very low	1. Observational studies start at low certainty (lack of appropriate protection against uncontrolled bias and confounding) 2. serious risk of selection bias, 3. Imprecision, wide CIs
Unadjusted Figure 34	CIN3+	Australia1, Australia3, Australia4, Denmark3, USA9	Very low	
Unadjusted Figure 34	high-grade histological abnormalities	Australia1, Australia2, Australia3	Very low	1. Observational studies start at low certainty (lack of appropriate protection against uncontrolled bias and confounding) 2. serious risk of selection bias,
Unadjusted Figure 34	Other histological abnormalities	Australia2	Very low	
Unadjusted Figure 35	High-grade cytological abnormalities	Australia1, Australia3, Canada2	Very low	1. Observational studies start at low certainty (lack of appropriate protection against uncontrolled bias and confounding) 2. serious risk of selection bias 3. Imprecision – wide CIs
Unadjusted Figure 35	Low-grade cytological abnormalities	Australia1, Australia3, Canada2	Very low	1. Observational studies start at low certainty (lack of appropriate protection against uncontrolled bias and confounding) 2. serious risk of selection bias 3. Inconsistency (I-sq 90%)
Unadjusted Figure 35	Any abnormal cytology	Canada2, USA1	Very low	1. Observational studies start at low certainty (lack of appropriate protection against uncontrolled bias and confounding) 2. serious risk of selection bias

Vaccine	Outcome	Studies	GRADE	GRADE notes
Adjusted Table 7	Genital warts	Sweden1, USA2, USA6	Low	1. Observational studies start at low certainty (lack of appropriate protection against uncontrolled bias and confounding) 2. consistent direction of results
Unadjusted Figure 36	Genital warts	Belgium2, Canada3, Denmark2, Spain2, Sweden1, USA2, USA6, USA11	Very low	1. Observational studies start at low certainty (lack of appropriate protection against uncontrolled bias and confounding) 2. inconsistent, I-sq 98%, not pooled
Adjusted Table 8	HPV infection	Switzerland1	Very low	1. Observational studies start at low certainty (lack of appropriate protection against uncontrolled bias and confounding) 2. serious risk of selection bias 3. wide 95% CIs
Adjusted Table 8	HPV infections: Vaccine-type (6, 11, 16, 18) HPV infection	USA14	Very low	1. Observational studies start at low certainty (lack of appropriate protection against uncontrolled bias and confounding) 2. conference abstract
Unadjusted Figure 37	HPV infection: incident HPV16/18	India1	Low	1. Observational studies start at low certainty (lack of appropriate protection against uncontrolled bias and confounding)
Unadjusted Figure 37	HPV infection: incident HPV6/11/16/18	India1	Very low	Observational studies start at low certainty (lack of appropriate protection against uncontrolled bias and confounding) 2. Imprecision: wide CIs
Unadjusted Figure 37	HPV infection: incident HPV31/33/45	India1	Very low	Observational studies start at low certainty (lack of appropriate protection against uncontrolled bias and confounding) 2. Imprecision: wide CIs

Vaccine	Outcome	Studies	GRADE	GRADE notes
Unadjusted Figure 37	HPV infection: incident HPV any infection	India1	Low	1. Observational studies start at low certainty (lack of appropriate protection against uncontrolled bias and confounding)
Unadjusted Figure 37	HPV infection: persistent HPV16/18	India1	Very low	1. Observational studies start at low certainty (lack of appropriate protection against uncontrolled bias and confounding) 2. very serious imprecision: few events and very wide CIs
Unadjusted Figure 37	HPV infection: persistent HPV6/11/16/18	India1	Very low	1. Observational studies start at low certainty (lack of appropriate protection against uncontrolled bias and confounding) 2. very serious imprecision: few events and very wide CIs
Unadjusted Figure 37	HPV infection: persistent HPV31/33/45	India1	Very low	1. Observational studies start at low certainty (lack of appropriate protection against uncontrolled bias and confounding) 2. very serious imprecision: few events and very wide CIs
Unadjusted Figure 37	HPV infection: persistent HPV any infection	India1	Very low	1. Observational studies start at low certainty (lack of appropriate protection against uncontrolled bias and confounding) 2. serious imprecision: few events and wide CIs
Unadjusted Page 55	HPV infection	USA12 and USA15	Very low	1. Observational studies start at low certainty (lack of appropriate protection against uncontrolled bias and confounding) 2. very serious risk of bias: one study conference abstract (no information to assess fully) and one study critical selection bias