Cochrane Response

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

Unpublished data has been redacted from this version of the report

March 2022

Review contributors: Nicholas Henschke, Hanna Bergman, Brian Buckley, Elise Cogo, Jennifer Petkovic, Katrin Probyn, Yanina Sguassero, Ingrid Arevalo Rodriguez, Meghan Sebastianski, Tie Yamato, Gemma Villanueva (Cochrane Response)

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

Address: St Albans House, 57-59 Haymarket, London SW1Y 4QX, UK

E-mail: nhenschke@cochrane.org

Web: www.cochraneresponse.com

Trusted evidence.
Informed decisions.
Better health.

Table of contents

Abbreviations

AIS	Adenocarcinoma in situ
AGW	Anogenital warts
CI	Confidence interval
CIN	Cervical intraepithelial neoplasia
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

Executive summary

This is an update of a systematic review conducted by Cochrane Response for the WHO in December 2019. The data in this report are current to January 2022, 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. Recommended methods from the Cochrane Handbook were followed to complete the review and the certainty of the evidence for selected outcomes was assessed using GRADE methodology.

We included 24 new studies for a total of 59 included studies. This latest update of the review now includes data from two published and two unpublished randomised controlled trials (RCTs) which evaluated the efficacy of one dose of licensed HPV vaccine. In addition, there are four post-hoc follow-up studies of RCTs, one single arm trial, and 50 observational studies. All studies reported data on one dose of bivalent (Cervarix), quadrivalent (Gardasil), nonavalent (Gardasil9) or bivalent (Cecolin) HPV vaccine for immunogenicity or clinical outcomes. Only two studies were identified which assessed the efficacy of one dose of HPV vaccine in males. One study evaluating one dose of HPV vaccine in people living with HIV was also summarised, along with three studies evaluating the interchangeability of HPV vaccines in a two-dose schedule.

The risk of bias in all included studies was assessed using either the Cochrane Risk of Bias 2.0 tool for RCTs, the ROBINS-I tool for observational studies, or the SIGN-50 checklist for case-control studies. The risk of bias was considered lowest for the RCTs, for post-hoc analyses of RCTs it was considered moderate, and most observational studies were at serious risk of bias.

The main findings of the review are summarised below:

One dose HPV vaccine compared with no vaccine

Immunogenicity

- There was high certainty evidence that one dose of HPV vaccine resulted in higher GMTs for HPV 16 and 18 than no vaccine and this was sustained for up to 5 years.
- There was high certainty evidence that one dose of HPV vaccine resulted in higher seropositivity to HPV 16 and 18 than no vaccine and this was sustained for up to 11 years.

HPV infections

- There was high certainty evidence that one dose HPV vaccine resulted in a large reduction in persistent HPV 16/18 infections compared with no vaccine over the short term (up to 18 months follow-up).
- There was moderate certainty evidence that one dose HPV vaccine resulted in a reduction in persistent HPV 16/18 infections compared with no vaccine over the long term (up to 10 years).
- The evidence suggested that one dose of HPV vaccine may reduce prevalence of HPV as well as incident HPV infections compared with no vaccine.

Other clinical outcomes

- Evidence suggests that one dose of HPV vaccine may reduce the incidence of genital warts compared with no vaccine, but this is based on observational studies at serious risk of bias.
- Evidence on one dose of HPV vaccine on the incidence of abnormal cytology or CIN is limited and based on observational studies at serious risk of bias.
- Estimates of effect on clinical outcomes from observational studies were affected by the age of participants and the length of the buffer period used.

One dose compared with two or three doses HPV vaccine

Immunogenicity

- There was high certainty evidence that one dose of HPV vaccine resulted in lower GMTs for HPV 16 and 18 than two or three doses and this was sustained for up to 5 years.
- There was high certainty evidence that one, two or three doses of HPV vaccine resulted in similarly high rates of seropositivity to HPV 16 and 18 and this was sustained for up to 11 years.

HPV infections

- There was low certainty evidence that one dose of HPV vaccine resulted in little to no difference in persistent HPV 16/18 infections compared with two or three doses.

Other clinical outcomes

- There was limited evidence to show a difference between one dose of HPV vaccine and two or three doses of HPV vaccine on genital warts, abnormal cytology, or CIN.
- The estimates of effect between one, two, and three doses of HPV vaccine come mostly from observational studies that are at serious risk of bias due to confounding.

There is high certainty evidence in favour of one dose HPV vaccine compared with no vaccine in terms of immunogenicity and persistent infections in this systematic review update, due to the addition of RCT data. The results from observational studies should continue to be interpreted with caution due to the moderate to serious risk of bias in the included studies.

Introduction

This is an update of a part of a systematic review and meta-analysis performed by Cochrane Response in 2019. This update focusses on single-dose and mixed dose administration of licensed HPV vaccines in females and males. This update was requested by the WHO Immunization, Vaccines, and Biologicals Department (IVB) to incorporate evidence from an updated search strategy (from March 2019 to January 2022) to inform future updates of the WHO HPV vaccines position paper.

Objectives

The objectives of this review update are to:

- Synthesise and critically assess the evidence on the immunogenicity, efficacy, effectiveness, and impact of a single dose of HPV vaccine compared with (1) no vaccine, placebo, or control vaccine; (2) compared with two doses HPV vaccine; or (3) compared with three doses of HPV vaccine.
- Identify and summarise evidence on the immunogenicity, efficacy, effectiveness, and impact of a single dose of HPV vaccine on people living with HIV
- Identify and summarise evidence on the interchangeability of different HPV vaccines (i.e. a two-dose schedule of two different types of HPV vaccine).

Methods

Search methods

We updated a systematic review performed by Cochrane Response in 2019. Searches were conducted for this update from March 2019 to January 2022, 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. We also searched the reference lists of relevant systematic reviews published within the search dates. Trialists of known ongoing studies were contacted for any relevant unpublished data.

Selection criteria

Randomised controlled trials (RCTs) and observational studies capable of providing data on the immunogenicity, efficacy, or effectiveness of 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), nonavalent (Gardasil 9, Merck), and another bivalent HPV vaccine (Cecolin, Innovax).

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. Studies of mixed schedules, where more than one vaccine type is used (i.e., interchangeability), were also included and summarised.

The outcomes of interest were:

- Immunological: seroconversion or seropositivity; geometric mean titres (GMT) of HPV antibodies
- Clinical: including, but not limited to invasive cervical, vaginal, vulval, anal, penile, or head and neck cancer; cervical intraepithelial neoplasia (CIN) grade 3+; CIN2+; histological and cytological abnormalities; anogenital warts; high risk HPV infection (genotype-specific prevalence, incidence and/or persistence)

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).

Risk of bias assessment

One reviewer independently assessed the risk of bias of each included study, and a second reviewer cross-checked assessment. If consensus could not be reached between the two reviewers, referral to a senior reviewer for a final decision was made.

For RCTs we used the revised Cochrane Risk of Bias tool for RCTs. We assessed the effect of assignment to intervention at baseline (the 'intention-to-treat effect'), regardless of whether the interventions were received as intended. We assessed the risk of bias per outcome and comparison in the following domains: 1) risk of bias arising from the randomization process; 2) risk of bias due to deviations from intended interventions; 3) risk of bias due to missing outcome data; 4) risk of bias in measurement of the outcome; 5) risk of bias in selection of the reported result; 6) overall risk of bias based on the assessments in the five domains (Sterne 2019).

In the Cochrane risk of bias tool there are a series of signalling questions within each domain that elicit information relevant to the assessment. The response options to the signalling questions are 'yes,' 'probably yes,' 'probably no,' 'no,' and 'no information'. A risk of bias judgement arising from each domain is generated by an algorithm, based on answers to the signalling questions.

Judgements can be 'low risk of bias,' 'some concerns' or 'high risk of bias'. We considered the overall risk of bias to be low if all domains are at low risk; some concerns if at least one domain is of some concern and no domain is at high risk; and high risk of bias if there is at least one domain considered to be at high risk, or several domains with some concerns (Sterne 2019).

For observational studies, we used the Cochrane ROBINS-I tool for non-randomised studies of interventions (ROBINS-I) to assess the risk of bias. The ROBINS-I tool covers domains relating to confounding, selection bias, information bias, and reporting bias (Sterne 2016).

We have determined the most important confounding domains for the comparisons of interest using directed acyclic graphs (DAG) (Suttorp 2015). In the DAG we used variables derived from the adjustment and stratification variables in analyses of previously included studies, other variables mentioned in the discussion sections, and variables mentioned or arrived at in recently published systematic reviews on HPV vaccines (Drolet 2019, Markowitz 2018, Single Dose Consortium 2020), a follow-up observational study of participants in an RCT receiving fewer than three doses (Basu 2021), and a living systematic review assessing risk of bias in observational studies on COVID vaccines (COVID NMA 2021).

We consider the most important confounding domains to be age, sex, socioeconomic status, ethnicity, geographic location, preventive health seeking behaviour, sexual behaviour, and calendar time (to reflect changing incidence of virus, time since vaccine introduction).

As part of the ROBINS-I tool, we assessed whether included studies adjusted for these confounders to produce unbiased estimates of effect when comparing groups.

Using signalling questions, each domain within the ROBINS-I tool was judged as low, moderate, serious, or critical, with supporting information provided from the report or reviewer interpretation to rationalize the judgment of bias (Sterne 2016). Assessments were made by outcome and comparison. Judging a result to be at a particular level of risk of bias for an individual domain implies that the result has an overall risk of bias at least this severe.

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.

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 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.

Feasibility for pooling data in a meta-analysis was assessed based on the outcomes reported, study characteristics, and age groups at vaccination and at outcome assessment. For all outcomes evaluated, there was sufficient heterogeneity in study characteristics that did not allow for sensible pooling of data, so meta-analysis was not performed. In addition, most 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 or outcome events, which can lead to misleading estimates from meta-analyses.

Sensitivity analysis

From the previous systematic review in 2019, several sources of bias were identified in the included observational studies that reduced the certainty of the findings. To address this, a post-hoc sensitivity analysis was 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. In this review, we have reported the buffer period used for all observational studies and present estimates of effect across different buffer periods when available. A sensitivity analysis considering studies that present effect estimates both adjusted for confounding and with a minimum of 12 months buffer period is reported.

In some cohort studies evaluating the effects of one dose of HPV vaccine, a buffer period has been included in the analysis to correct for prevalent HPV infections at the time of immunisation. For studies which consider vaccination dose status as a time-varying exposure (i.e., participants can contribute follow-up time to more than one dose group), a buffer period can also be used to account for misattribution of events to the wrong dose status.

A buffer period is important to consider in observational studies that begin counting of outcome events directly following vaccination. This can be incorporated into the analysis by excluding outcome events and follow-up time for a certain amount of time. A buffer period can, however, also be present in observational studies by design. In some studies it has been observed that there is a time-lag between HPV vaccination and measurement of outcomes, which occur years later (e.g. school-based vaccination at age 12-13 and first cervical screening occurring at age 20-21 in some countries). Application of a buffer period to the analysis was not considered necessary in the included randomised controlled trials (or post-hoc analyses of randomised trials) as all participants have a known dose status, randomisation should balance prevalent infections across groups (if this is not an exclusion criterion at baseline), and follow-up for all groups begins at the same time.

Due to the lack of data available (i.e. events and denominators for different buffer periods were often not reported) we were unable to perform a more detailed analysis or reanalyse the data from the included studies. Some of the included studies also used a range of different buffer periods, highlighting that it is often unclear how long the buffer period should be for different outcomes. While it is important to exclude prevalent HPV infections when estimating the effectiveness of HPV vaccination from observational data, omitting data from the analysis can also potentially introduce

selection bias by excluding follow-up time (Sterne 2016). The results from these sensitivity analyses should be interpreted with caution.

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 and observational studies starts at high certainty, but can be downgraded to moderate, low or very low certainty if there are serious or very serious limitations in the following domains: risk of bias, inconsistency, indirectness, or imprecision.

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 4984 records from the update search from February 2019 to 7 January 2022, the search strategy is reported in Appendix 1 and the search and screening process in Figure 1. We included 24 new studies. This review now includes 59 studies, see Appendix 2 for full list of references. There are several ongoing studies evaluating the efficacy of one dose of HPV vaccine, with results expected over the next few years, see Appendix 2.

Characteristics of included studies

We included four randomised trials, four post-hoc follow-up studies of RCTs, one single arm trial, and 50 observational studies that contained data on clinical or immunogenicity outcomes.

The studies were carried out in 20 different countries. Eleven studies evaluated the bivalent Cervarix vaccine, 36 studies the quadrivalent Gardasil vaccine, 12 studies evaluated more than one type of vaccine, and one study evaluated the bivalent Cecolin vaccine. The characteristics of individual studies are presented in Appendix 3.

Most studies included females only, four studies included both females and males (Canada4, Canada6, USA11, USA17), and two studies included only males (USA12, USA18).

Only one study assessing single dose HPV vaccination included HIV infected and HIV exposed but uninfected females and males (USA17). This was a prospective cohort study that reported on immunogenicity, and abnormal cytology.

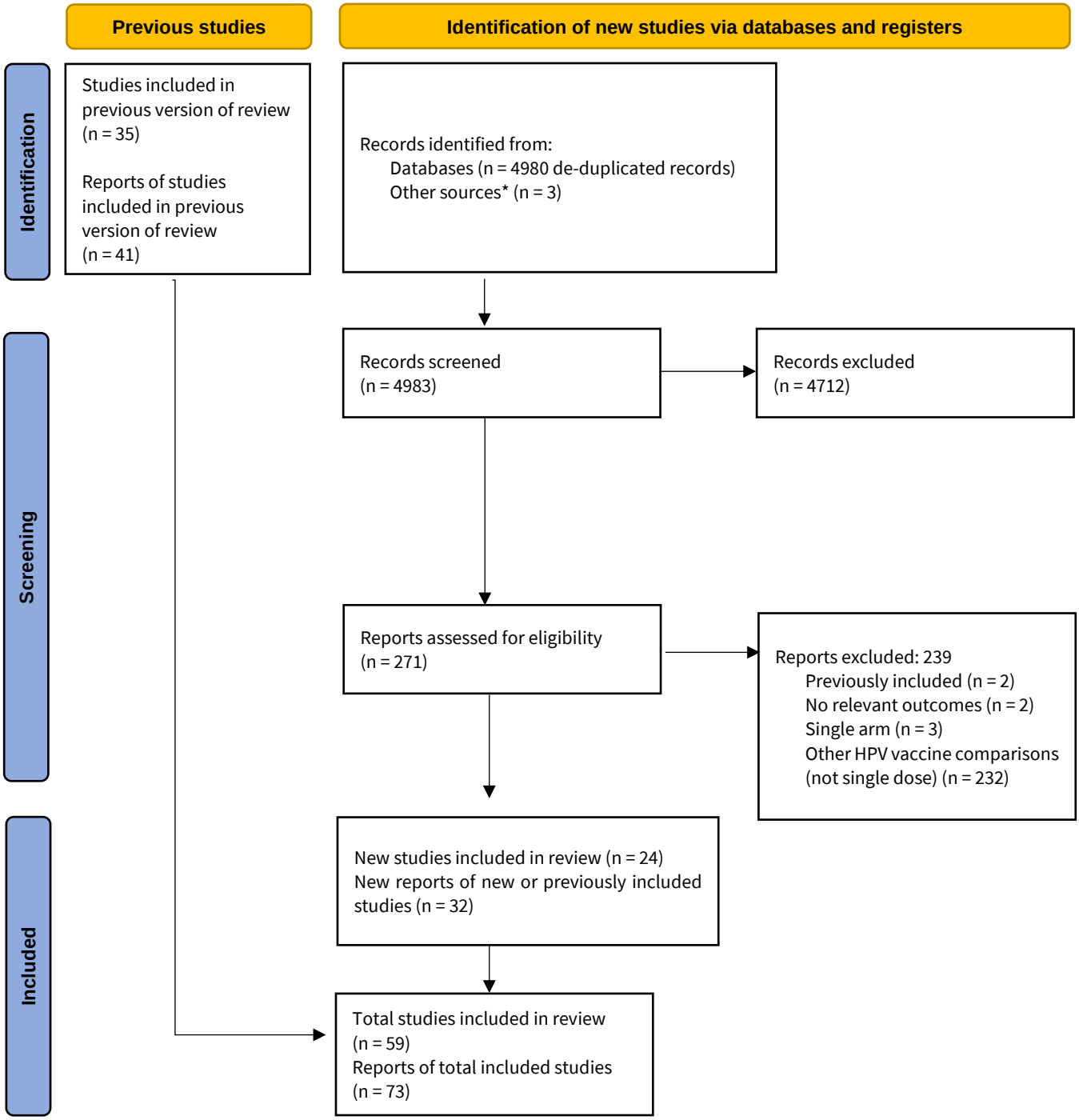
Three studies reported on the efficacy or immunogenicity of a two-dose HPV vaccine schedule with more than one type of vaccine (interchangeability) (Canada4, Canada7, Fiji1). In addition, two post-hoc studies pooled results from Canada4 and Canada7.

Overall risk of bias ranged from low to some concerns for RCTs, mostly moderate for post-hoc RCT follow-up studies, and mostly serious to critical for observational, although there were some observational studies at moderate risk of bias because they measured and controlled for the most important confounders. An overview of risk of bias assessments are presented in Appendix 4-6.

Effectiveness of single dose HPV vaccine

The following results of the systematic review include the most important outcomes from the included studies. Not all the included studies are represented in the forest plots that follow. Some studies did not report single dose data in a way that allowed inclusion in a forest plot. Data for additional outcomes that were considered less important for decision making are not included in this review report. The study names in the forest plots include the study design and the range of ages at vaccination.

Figure 1. Search and screening process – PRISMA flow chart



*Other sources include data obtained by contacting authors of ongoing and completed but unpublished studies.

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

Immunogenicity outcomes

Four studies (Costa Rica1, Netherlands1, Fiji1, Mongolia1) reported on immunogenicity outcomes in women receiving one dose of HPV vaccine compared with HPV unvaccinated women. Following one dose of bivalent (Cervarix) vaccine, the ratio of GMTs for both HPV 16 and HPV 18 were in favour of the vaccine group and sustained over 72 months (Figure 1.1). Following one dose of quadrivalent (Gardasil) vaccine, the ratio of GMTs for HPV 6, 11, 16, and 18 were in favour of the vaccine group over 72 months (Figure 1.2).

Seropositivity following one dose of HPV vaccine was consistently high (approaching 100%) for the vaccine types and sustained up to 11 years (see comparison 2 for data).

There was high certainty evidence that one dose of HPV vaccine resulted in higher GMTs for HPV 16 and 18, as well as higher seropositivity, and this was sustained for up to 5 years (see Evidence profile table 1.4).

Figure 1.1 Immunogenicity – ratio of GMTs following bivalent (Cervarix) vaccine

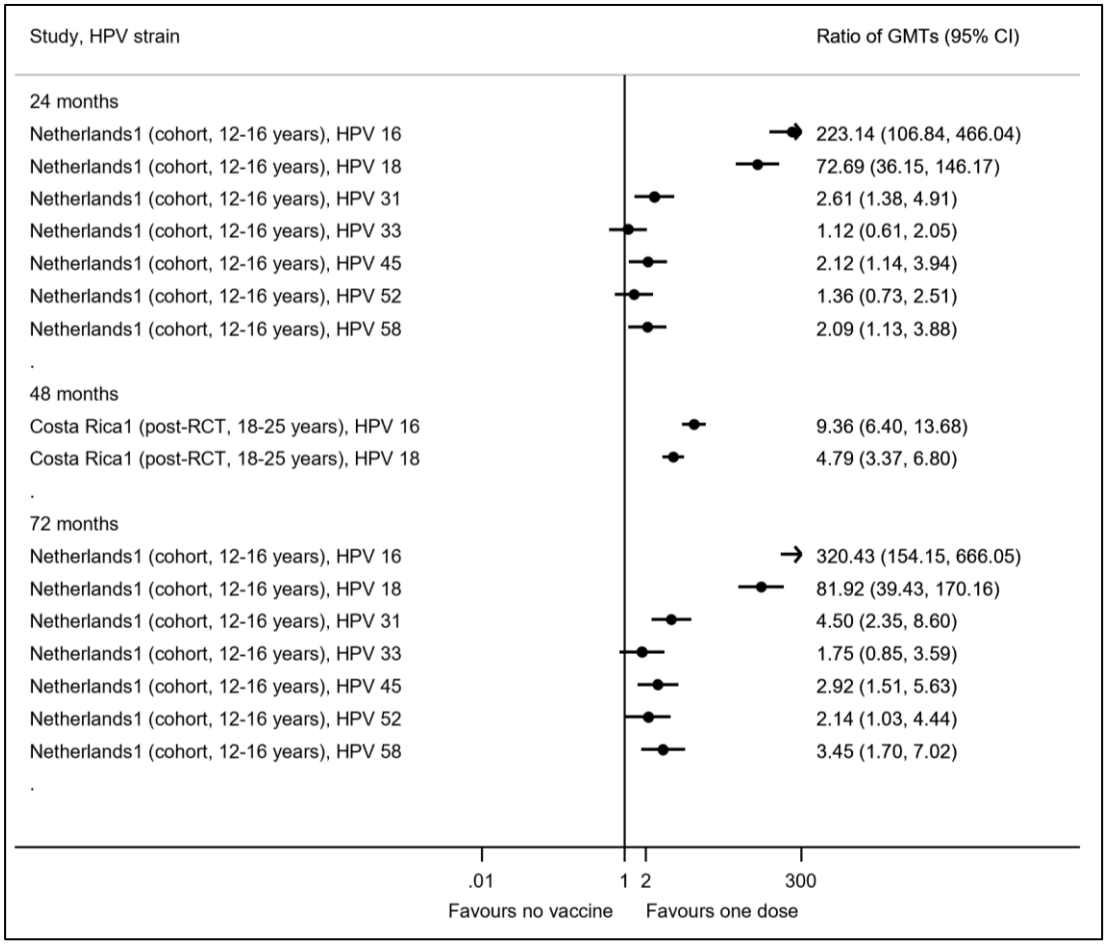
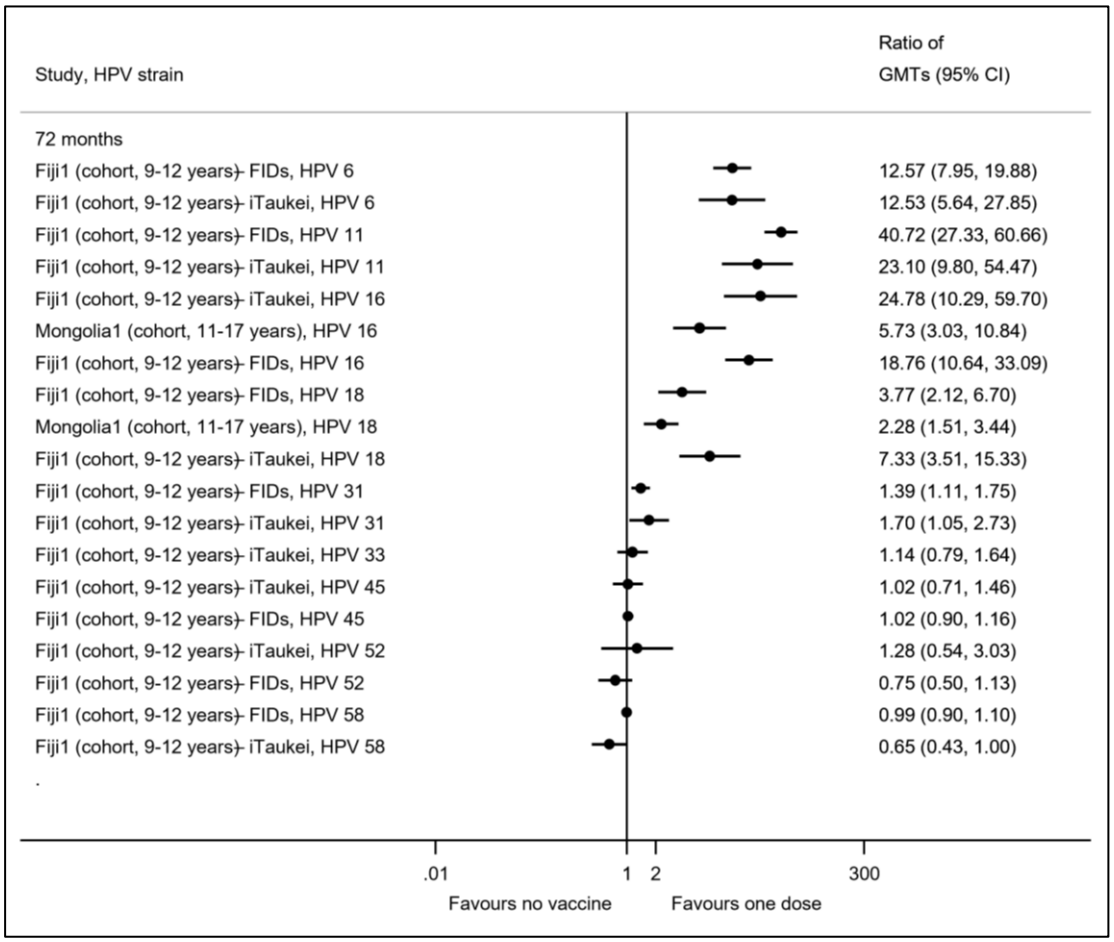


Figure 1.2 Immunogenicity – ratio of GMTs following quadrivalent (Gardasil) vaccine



Clinical outcomes – persistent HPV infection

One randomised controlled trial (Kenya1) and two post-hoc analyses of RCTs (CVT/PATRICIA, India1) reported on prevalent HPV infections in women receiving one dose of HPV vaccine compared with HPV unvaccinated women.

In the RCT (Kenya1), there was a large reduction in persistent HPV infections following one dose of bivalent (Cervarix) vaccine (Figure 1.3) with a vaccine efficacy (VE) of 97.5% (95% confidence interval 81.6% to 99.7%) over 18 months of follow-up. In absolute terms this was a reduction of 74 fewer persistent HPV16/18 infections per 1000 women (95%CI from 76 fewer to 61 fewer).

The same RCT (Kenya1) also showed a large reduction in persistent HPV infections following one dose of nonavalent (Gardasil9) vaccine (Figure 1.4). For HPV 16/18 infections the VE was 97.5% (95%CI 81.7% to 99.7%) and for HPV 16/18/31/33/45/52/58 infections VE was 88.9% (95%CI 68.5% to 96.1%) over 18 months. In absolute terms this was a reduction of 74 fewer persistent HPV 16/18 infections per 1000 (95%CI from 76 fewer to 62 fewer) and 88 fewer persistent HPV 16/18/31/33/45/52/58 infections per 1000 (95%CI from 96 fewer to 65 fewer).

Figure 1.3 Persistent HPV infections following bivalent vaccine (Cervarix) – RCT

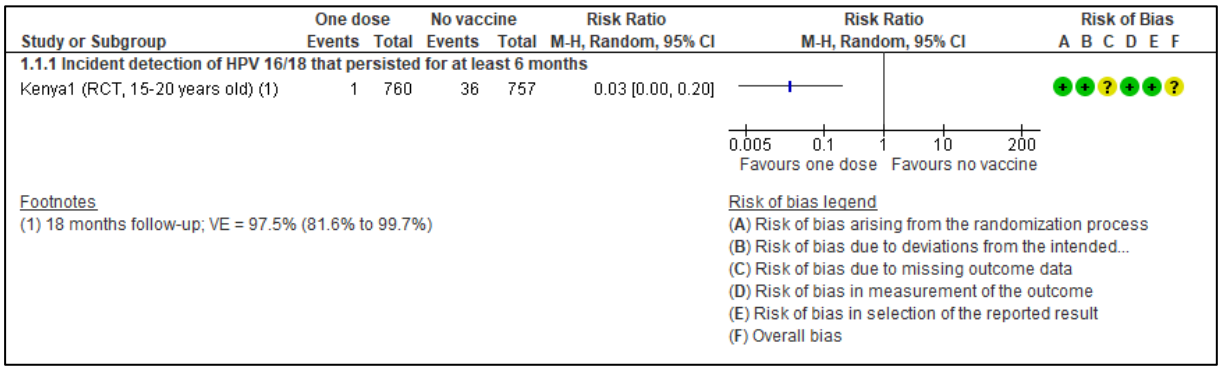
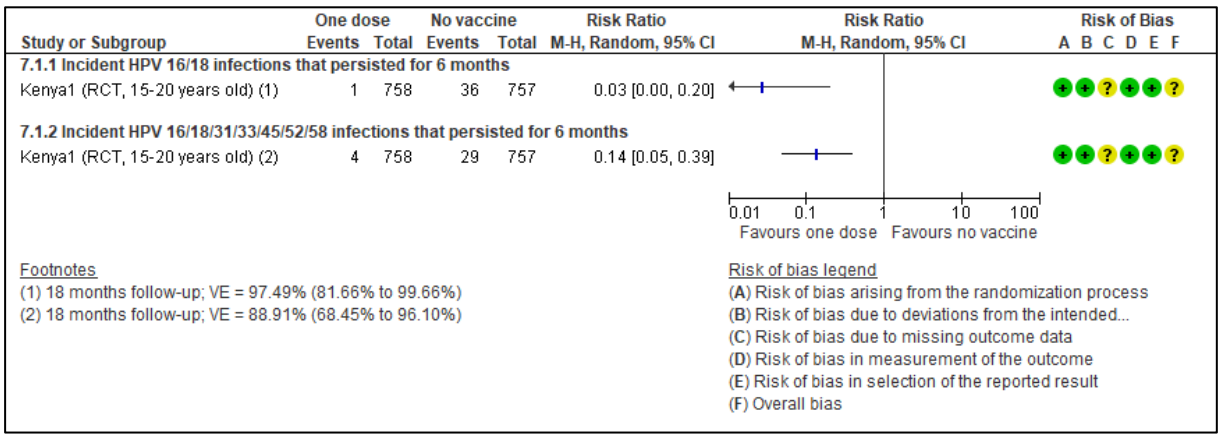


Figure 1.4 Persistent HPV infections following nonavalent vaccine (Gardasil9) – RCT



The post-hoc RCT analyses (CVT/PATRICIA) showed similar results, a very large reduction in 6- and 12-month persistent HPV 16/18 infections following one dose of bivalent (Cervarix) vaccine after 4 years follow-up (Figure 1.5). The effects for persistent HPV 31/33/45 infections (cross-protective types) were in favour of one dose but the CI crossed the line of no effect.

One dose of quadrivalent (Gardasil) vaccine also resulted in a large reduction of persistent HPV 16/18 infections and persistent HPV 6/11/16/18 infections after a 10-year follow-up (Figure 1.6). The effects for persistent HPV 6/11 and HPV 31/33/45 infections were in favour of one dose but the CI crossed the line of no effect.

The evidence for one dose HPV vaccine compared with no vaccine on persistent HPV 16/18 infections was considered of moderate to high certainty (see Evidence profile table 1.4).

Figure 1.5 Persistent HPV infections following bivalent vaccine (Cervarix) – post-hoc RCT analyses

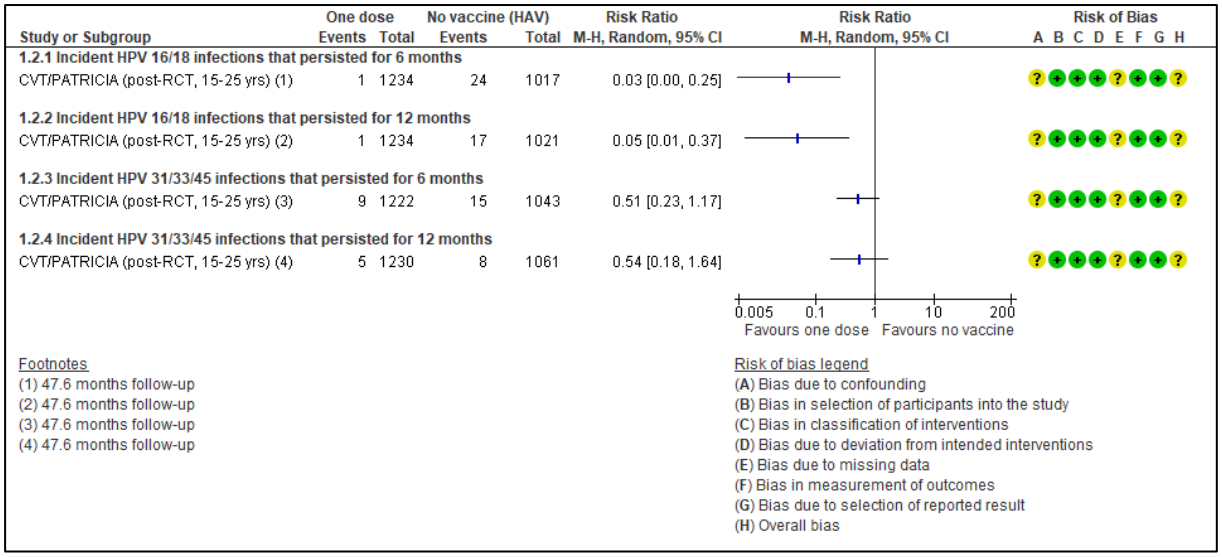
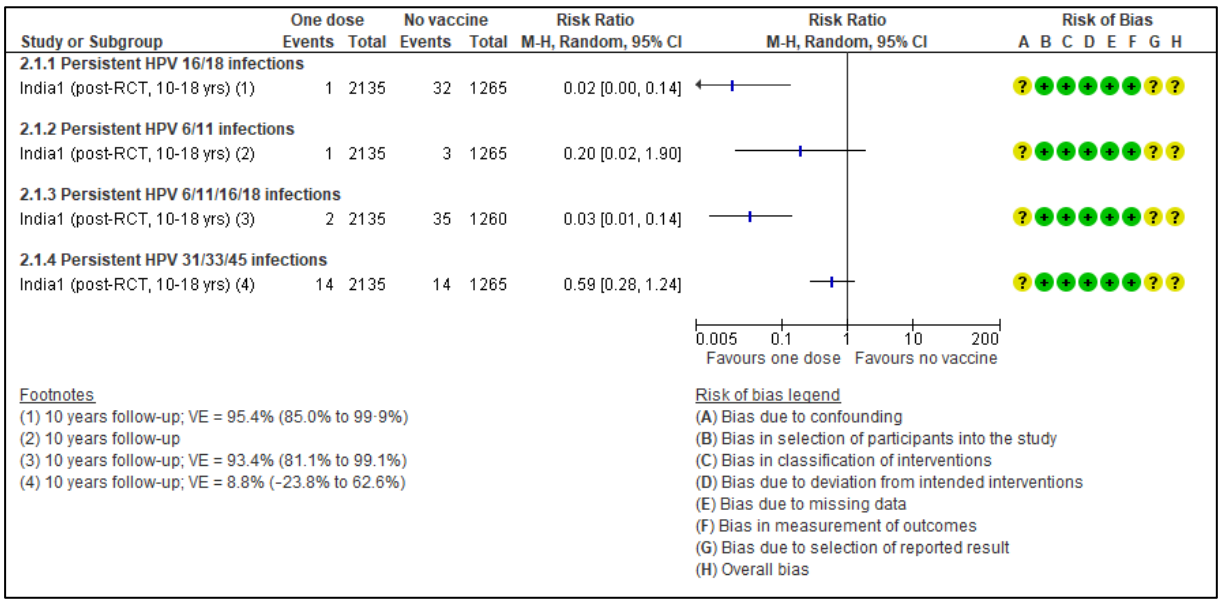


Figure 1.6 Persistent HPV infections following quadrivalent vaccine (Gardasil) - post-hoc RCT analyses



Clinical outcomes – prevalent and incident HPV infection

A community RCT (Thailand1) evaluating the effectiveness of one dose of bivalent (Cervarix) vaccine on HPV 16/18 prevalence reported [redacted]

Additional data on prevalent and incident HPV infections following one dose of vaccine come from post-hoc analyses of RCTs (Costa Rica1, India1) and observational studies (Scotland 1, Scotland4, Scotland5, Mongolia1, USA18, USA25).

For prevalent HPV 16/18 infections following bivalent (Cervarix) vaccine, one study (Costa Rica1) reported a VE of 82.1% (40.2% to 97%) after 11 years follow-up (Figure 1.7). Adjusted estimates from the Scotland studies (Figure 1.8) resulted in VE that ranged from 27.6% to 55%.

For incident HPV 16/18 infections the effect was non-significant following one dose bivalent (Cervarix) vaccine (Figure 1.9) but a VE of 63.5% (51.2% to 73.1%) after 10 years follow-up following one dose of quadrivalent (Gardasil) vaccine (Figure 1.10).

Figure 1.7 Prevalent HPV infections following bivalent vaccine (Cervarix) – post-hoc RCT analyses

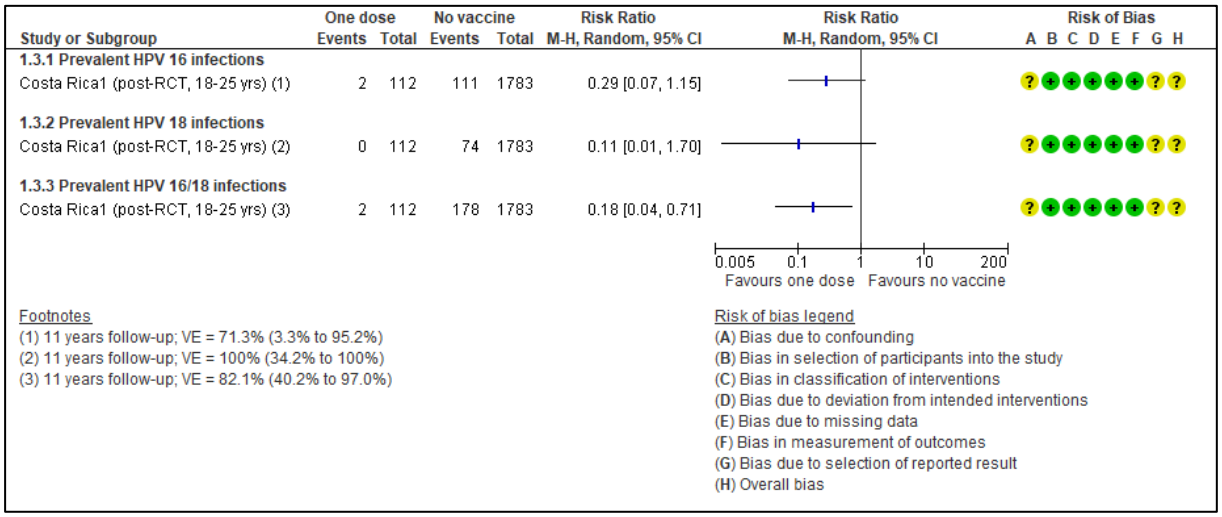


Figure 1.8 Prevalent HPV infections following bivalent vaccine (Cervarix) – observational studies, adjusted data

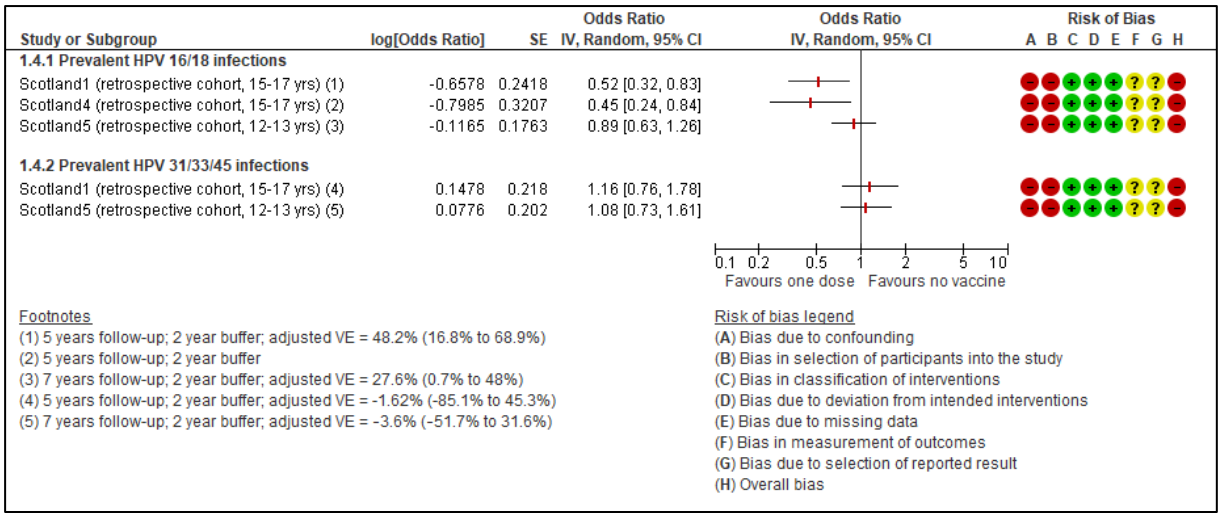


Figure 1.9 Incident HPV infections following bivalent vaccine (Cervarix) – post-hoc RCT analyses

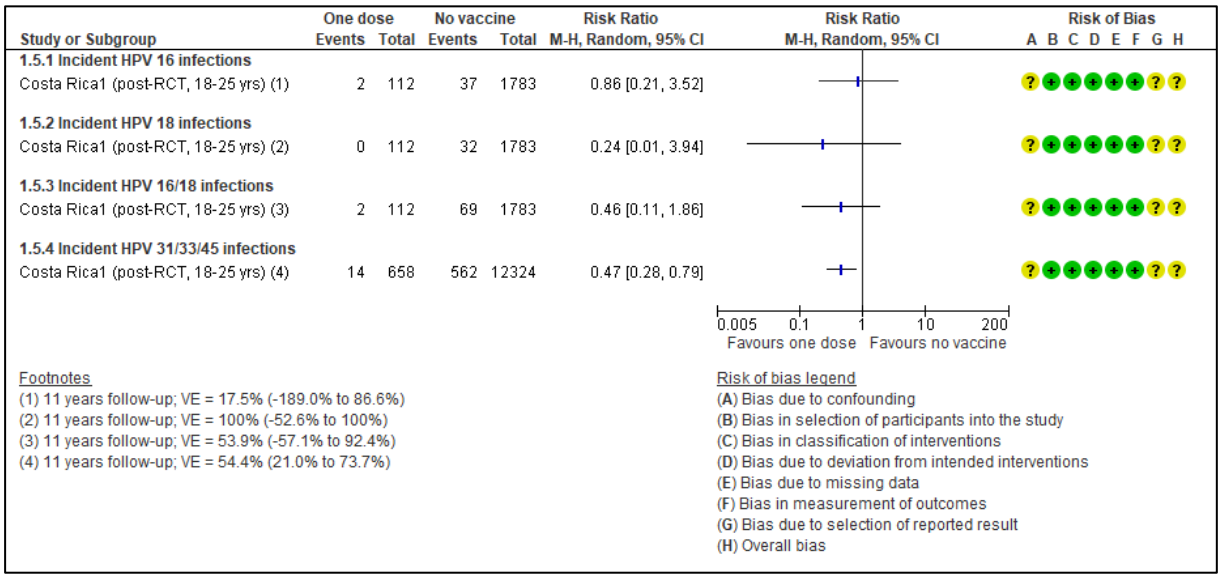


Figure 1.10 Incident HPV infections following quadrivalent vaccine (Gardasil) - post-hoc RCT analyses

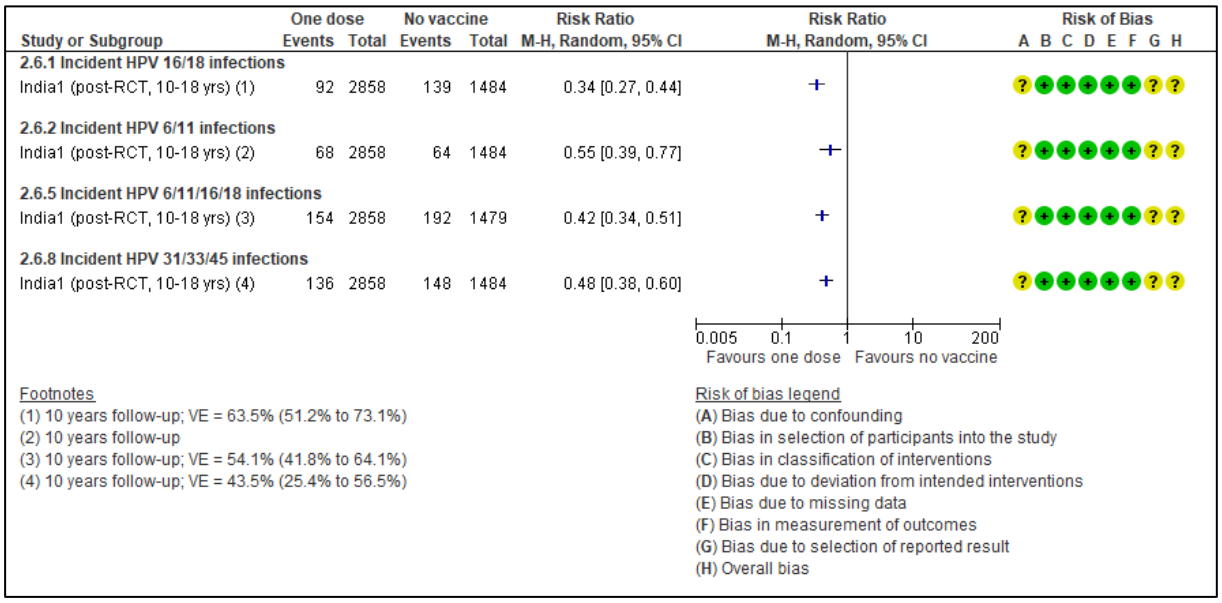
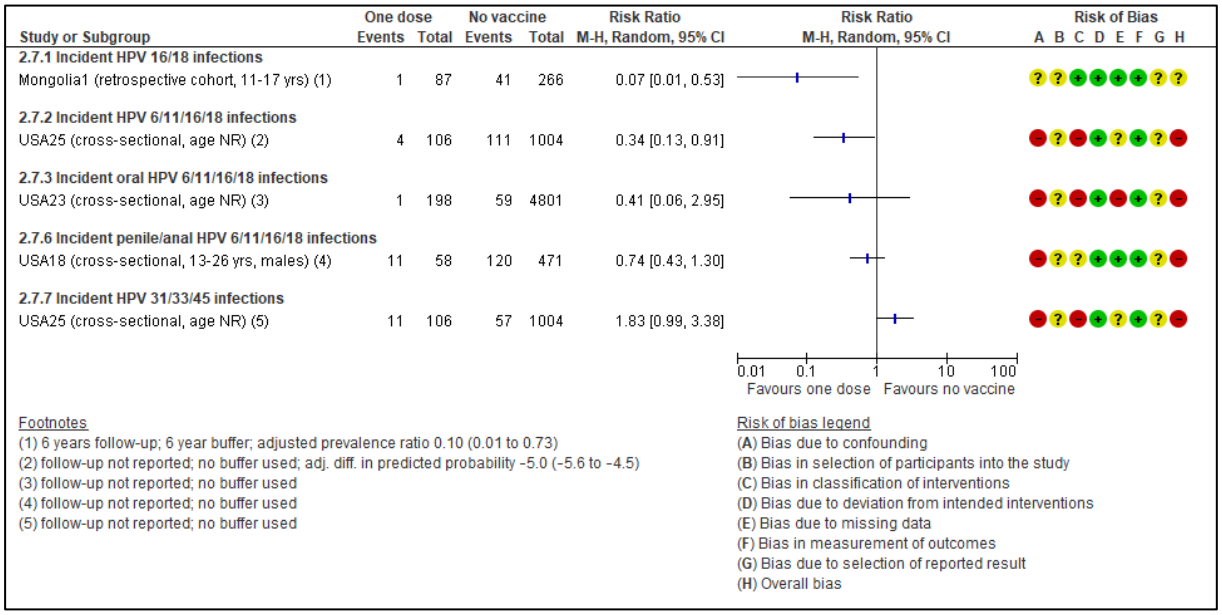


Figure 1.11 Incident HPV infections following quadrivalent vaccine (Gardasil) – observational studies, unadjusted data



Clinical outcomes – genital warts

There were 11 observational studies that reported the effect of one dose quadrivalent (Gardasil) vaccine on genital warts (Figure 1.12). The studies were not pooled due to reporting different types of estimates (i.e. VE, HR, RR, IRR, IRD) and potential overlapping populations between the Denmark, Spain, and USA studies. Most studies were at serious risk of bias due to residual confounding and the unadjusted results were inconsistent regarding the effect of one dose. USA2 was considered at moderate risk of bias due to the use of propensity score weighted hazard ratios to control for confounding.

Nine studies reported effect estimates adjusted for confounding across different age groups (Table 1.1). When a sensitivity analysis was applied, including only studies with adjusted estimates calculated after a 12-month buffer period, three studies remained (Canada3, Sweden1, USA2). The Canada3 study reported an adjusted hazard ratio (HR) for those vaccinated between 9-18 years of 0.6 (95%CI 0.2 to 1.8) and for those vaccinated over 19 years of 3.7 (95%CI 2.1 to 6.8). The Sweden1 study reported adjusted incidence rate ratios (IRR) of 0.33 (95%CI 0.24 to 0.44) for those vaccinated between 10-19 years (10-16 years IRR 0.24 (95%CI 0.15 to 0.39); 17-19 years IRR 0.42 (95%CI 0.29 to 0.62). The USA2 study reported a propensity score weighted HR of 0.32 (95%CI 0.20 to 0.52) following a 12-month buffer. All these estimates were in favour of one dose compared with no vaccine.

Figure 1.12 Genital warts following quadrivalent vaccine (Gardasil) – observational studies, unadjusted data

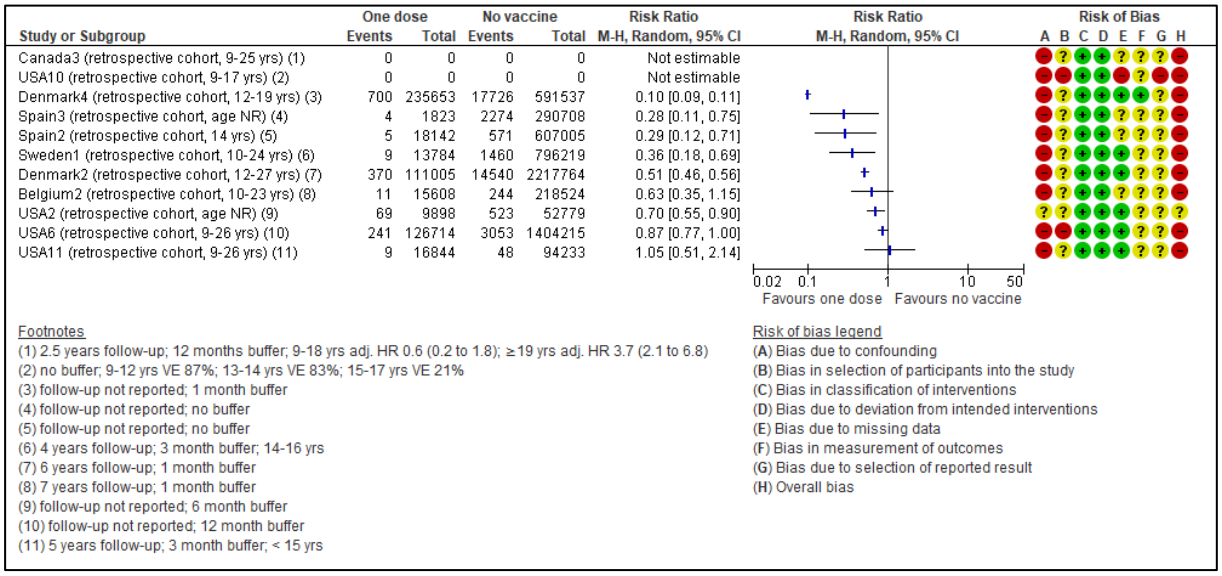


Table 1.1 Adjusted estimates of effect for genital warts following one dose quadrivalent (Gardasil) vaccine

Study	Age at vaccination	Buffer period	Adjusted estimate (95% CI) *
Spain2	14-19 years	no buffer	**RR 0.39 (0.13 to 0.8)**
Spain3	All ages	no buffer	**RR 0.25 (0.08 to 0.56)**
Denmark4	12-14 years	1 month	**IRR 0.29 (0.22 to 0.38)**
Denmark4	15-16 years	1 month	**IRR 0.38 (0.29 to 0.49)**
Denmark4	17-18 years	1 month	**IRR 0.56 (0.42 to 0.73)**
Denmark4	> 19 years	1 month	IRR 1.36 (1.24 to 1.49) **
Denmark2	All ages	1 month	**IRR 0.51 (0.46 to 0.56)**
Belgium2	All ages	1 month	VE 36.6% (-16.1% to 65.4%)
USA11	< 15 years	3 months	HR 0.80 (0.34 to 1.90)
USA11	15-19 years	3 months	**HR 0.65 (0.49 to 0.85)**
USA11	> 19 years	3 months	HR 0.96 (0.72 to 1.28)
Sweden1	14-16 years	3 months	**IRR 0.33 (0.21 to 0.52)**
Sweden1	17-19 years	3 months	**IRR 0.71 (0.55 to 0.92)**
USA2	All ages	6 months	HR 0.81 (0.60 to 1.08)
USA2	All ages	12 months	**HR 0.32 (0.20 to 0.52)**
Canada3	9-18 years	12 months	HR 0.6 (0.2 to 1.8)
Canada3	> 18 years	12 months	HR 3.7 (2.1 to 6.8) **
Sweden1	10-19 years	12 months	**IRR 0.33 (0.24 to 0.44)**
Sweden1	10-16 years	12 months	**IRR 0.24 (0.15 to 0.39)**
Sweden1	17-19 years	12 months	**IRR 0.42 (0.29 to 0.62)**

* Estimates in bold indicate reduced risk of genital warts after one dose. ** estimates indicate increased risk of genital warts after one dose. HR = hazard ratio; IRR = incidence rate ratio; RR = relative risk; VE = vaccine efficacy

Clinical outcomes – cytological outcomes

There were 7 observational studies that reported the effect of one dose quadrivalent (Gardasil) vaccine on abnormal cervical cytology (Figure 1.13). All studies were at serious risk of bias due to residual confounding and the results were inconsistent regarding the effect of one dose.

Six studies reported effect estimates adjusted for confounding across different age groups (Table 1.2). When a sensitivity analysis was applied, including only studies with adjusted estimates calculated after a 12-month buffer period, two studies remained (Italy1, USA22). The Italy1 study reported an adjusted odds ratio (OR) of 0.57 (95%CI 0.32 to 1.00) for any abnormal cytology after applying a 12-month buffer. The USA22 study reported adjusted HRs of 1.09 (95%CI 0.48 to 2.45) for high grade cases in those vaccinated before 15 years of age, for those vaccinated between 15-19 years HR 0.87 (95%CI 0.69 to 1.08), and those vaccinated over 20 years of age HR 1.07 (0.84 to 1.35), following a 12-month buffer. All estimates had confidence intervals that included no effect between one dose and no vaccine.

Figure 1.13 Abnormal cytology following quadrivalent vaccine (Gardasil) – observational studies, unadjusted data

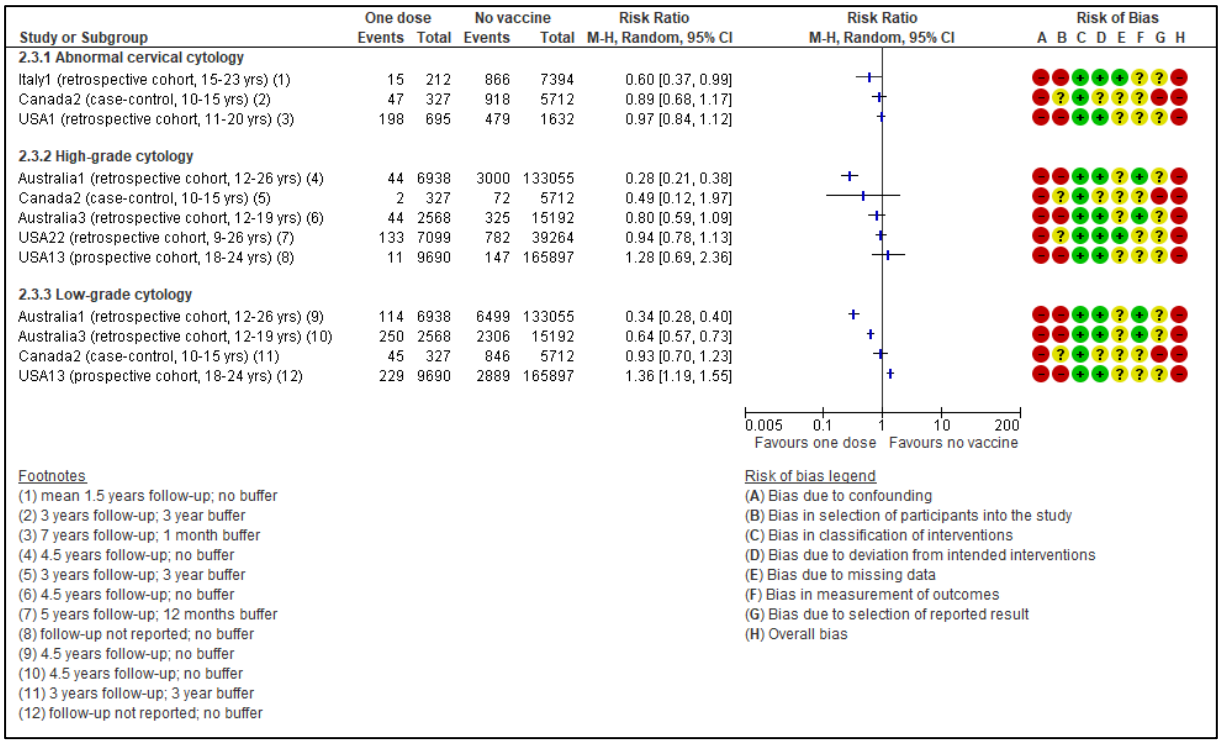


Table 1.2. Adjusted estimates of effect for abnormal cytology following one dose quadrivalent (Gardasil) vaccine

Outcome	Study	Age at vaccination	Buffer period	Adjusted estimate (95% CI) *
Abnormal cytology	Italy1	15-23 years	No buffer	**OR 0.52 (0.30 to 0.91)**
	USA1	All ages	1 month	HR 1.05 (0.88 to 1.26)
	USA1	11-14 years	1 month	HR 0.41 (0.10 to 1.63)
	USA1	15-16 years	1 month	HR 1.45 (0.88 to 2.37)

	USA1	17-18 years	1 month	HR 1.03 (0.77 to 1.39)
	USA1	19-20 years	1 month	HR 1.07 (0.81 to 1.42)
	Italy1	15-23 years	6 months	**OR 0.53 (0.30 to 0.93)**
	Italy1	15-23 years	12 months	OR 0.57 (0.32 to 1.00)
High grade cytology	Australia1	All ages	No buffer	**HR 0.44 (0.32 to 0.59)**
	Australia1	< 16 years	No buffer	HR 0.97(0.35 to 2.70)
	Australia1	17-19 years	No buffer	**HR 0.48 (0.28 to 0.82)**
	Australia1	20-23 years	No buffer	**HR 0.45 (0.29 to 0.70)**
	Australia3	All ages	No buffer	HR 0.85 (0.62 to 1.17)
	USA13	21-24 years	No buffer	RR 1.24 (0.73 to 2.11)
	USA22	< 15 years	12 months	HR 1.09 (0.48 to 2.45)
	USA22	15-19 years	12 months	HR 0.87 (0.69 to 1.08)
	USA22	> 20 years	12 months	HR 1.07 (0.84 to 1.35)
Low grade cytology	Australia1	All ages	No buffer	**HR 0.48 (0.40 to 0.58)**
	Australia1	< 16 years	No buffer	HR 0.82 (0.43 to 1.55)
	Australia1	17-19 years	No buffer	**HR 0.61 (0.46 to 0.82)**
	Australia1	20-23 years	No buffer	**HR 0.43 (0.32 to 0.58)**
	Australia3	All ages	No buffer	**HR 0.67 (0.59 to 0.76)**
	USA13	<18	No buffer	RR 0.48 (0.16 to 1.44)
	USA13	18-20	No buffer	RR 0.72 (0.27 to 1.93)
	USA13	21-24	No buffer	**RR 2.20 (1.44 to 3.36) ****

* Estimates in bold indicate reduced risk of abnormal cytology after one dose. ** estimates indicate increased risk of abnormal cytology after one dose. HR = hazard ratio; OR = odds ratio; RR = relative risk.

Clinical outcomes – histological outcomes

One post-hoc analysis of an RCT (Figure 1.14) and twelve observational studies (Figure 1.15, Figure 1.16) reported on histological outcomes such as cervical intraepithelial neoplasia (CIN), or invasive cancer.

The post-hoc RCT analysis (India1) reported little to no difference between one dose and no vaccine on these outcomes after 10-year follow-up. There were very few events reported in either group.

Three studies from Scotland (Scotland1, Scotland2, Scotland6) reported adjusted OR for cases of CIN1, CIN2, or CIN3+ that showed little to no difference following one dose bivalent (Cervarix) vaccine. These studies included a minimum of two-year buffer from vaccination to outcome by design, but effects were imprecise, possibly related to the short follow-up and young age of women attending for cervical screening.

Ten observational studies reported on CIN following one dose of quadrivalent (Gardasil) vaccine and reported estimates of effect adjusted for confounding (Table 1.3). When a sensitivity analysis was applied, including only studies with adjusted estimates calculated after a 12-month buffer period, four studies remained (Australia1, Australia4, USA21, USA22). Australia4 reported an adjusted HR of 0.54 (0.38 to 0.76) for CIN2 after a 12-month buffer and 0.59 (0.39 to 0.89) after a 24-month buffer. USA21 reported an adjusted OR 0.53 (0.37 to 0.76) for CIN2+ after a 24-month buffer and USA22 an adjusted HR 0.64 (0.47 to 0.88) for CIN2+ following a 12-month buffer. Australia1 reported an adjusted HR of 0.56 (0.33 to 0.93) for CIN3 after applying a 12-month buffer and 0.39 (0.16 to 0.95) after a 24-month buffer.

Figure 1.14 CIN (and invasive cancer) following quadrivalent vaccine (Gardasil) – post-hoc RCT analyses

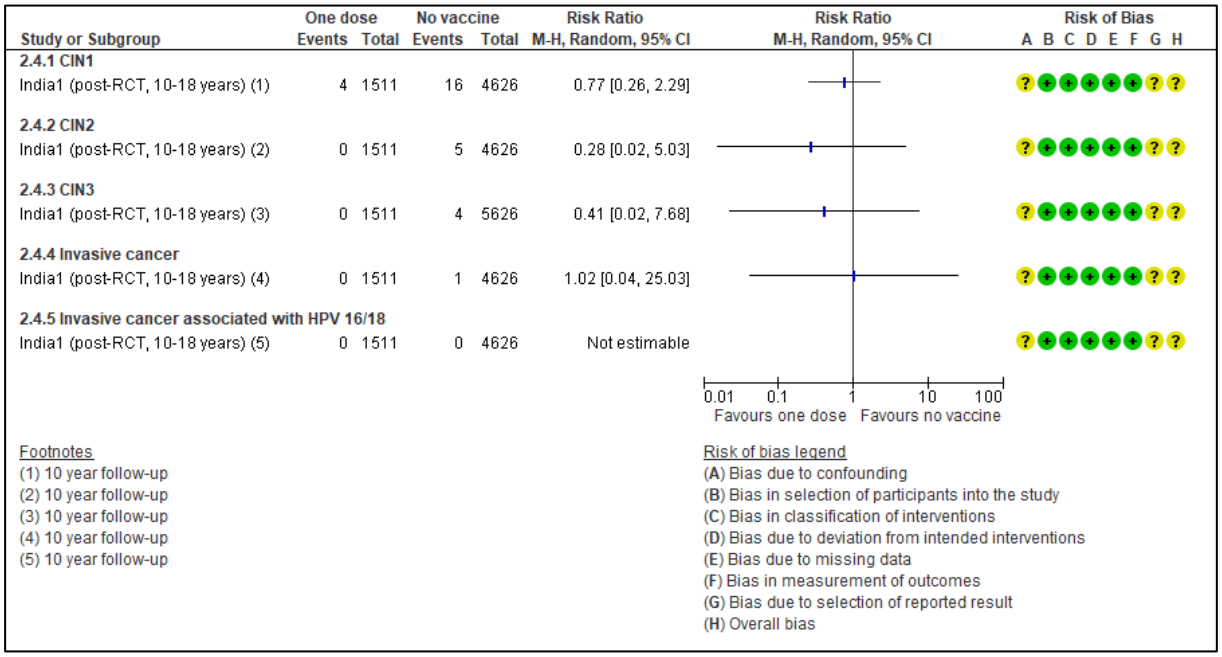


Figure 1.15 CIN following bivalent vaccine (Cervarix) – observational studies, adjusted data

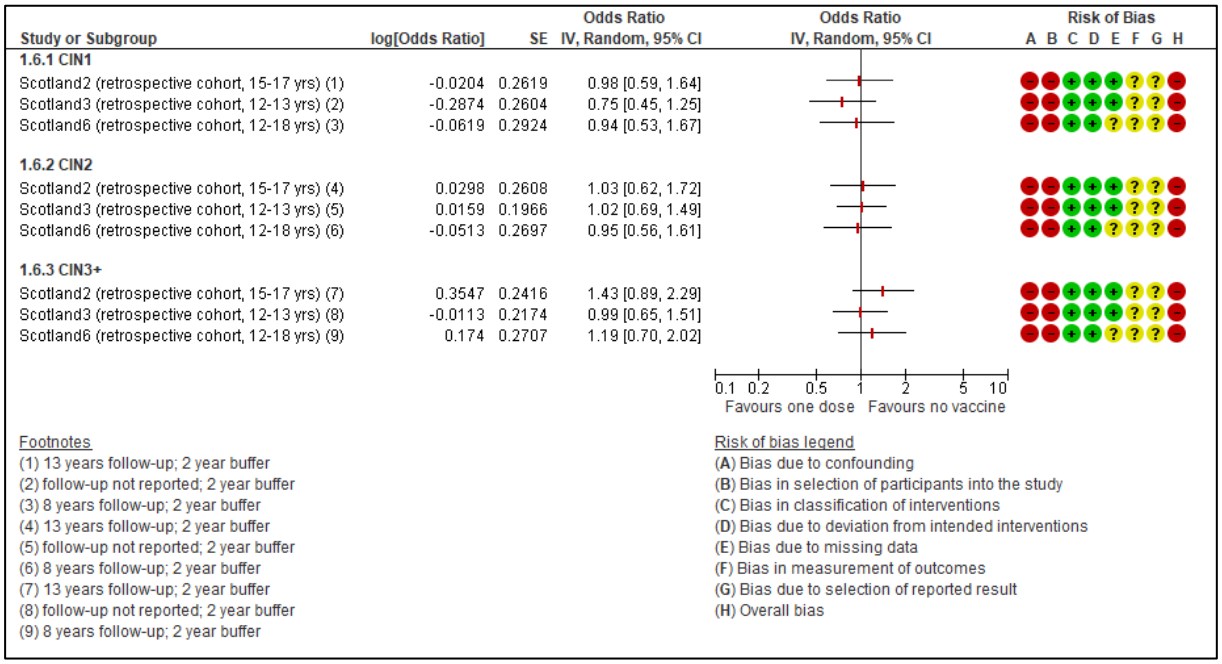


Figure 1.16 CIN following quadrivalent vaccine (Gardasil) – observational studies, unadjusted data

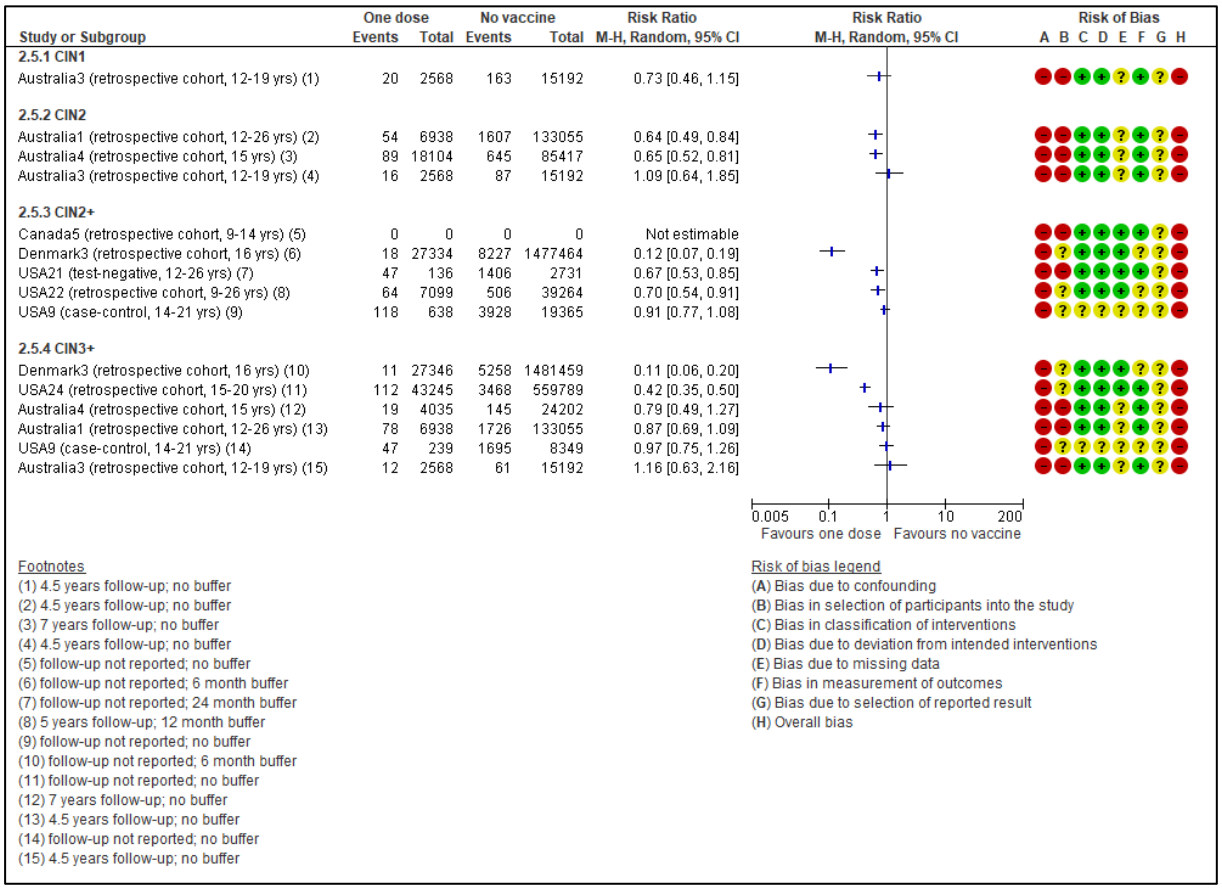


Table 1.3. Adjusted estimates of effect for histological outcomes following one dose quadrivalent (Gardasil) vaccine

Outcome	Study	Age at vaccination	Buffer period	Adjusted estimate (95% CI)
CIN1	Australia3	All ages	No buffer	HR 0.89 (0.56 to 1.41)
CIN2	Australia1	All ages	No buffer	HR 0.98 (0.75 to 1.29)
	Australia1	<16 years	No buffer	HR 0.55 (0.13 to 2.27)
	Australia1	17-19	No buffer	HR 0.66 (0.38 to 1.15)
	Australia1	20-23	No buffer	HR 1.03 (0.69 to 1.54)
	Australia3	All ages	No buffer	HR 1.29 (0.76 to 2.20)
	Australia4	< 15 years	No buffer	**HR 0.65 (0.52 to 0.81)**
	Australia4	< 15 years	12 months	**HR 0.54 (0.38 to 0.76)**
	Australia4	< 15 years	24 months	**HR 0.59 (0.39 to 0.89)**
CIN2+	Canada5	9-14 years	No buffer	RR 1.21 (0.43 to 2.86)
	USA9	14-21 years	No buffer	rate ratio 0.84 (0.68 to 1.03)
	Denmark/Sweden1	≤16 y	6 months	IRR 0.23 (0.01 to 5.24)
	Denmark/Sweden1	17-19 y	6 months	IRR 0.58 (0.15 to 2.19)
	Denmark/Sweden1	20-29 y	6 months	**IRR 1.56 (1.13 to 2.15) ****
	Denmark3	all ages	6 months	**IRR 0.34 (0.13 to 0.87)**
	USA22	< 15 years	12 months	HR 0.87 (0.28 to 2.68)
	USA22	15-19 years	12 months	**HR 0.64 (0.47 to 0.88)**

	USA22	>=20 years	12 months	HR 1.16 (0.89 to 1.52)
	USA21	12-26 years	24 months	**OR 0.53 (0.37 to 0.76)**
CIN3+	USA9	14-29 years	No buffer	rate ratio 0.90 (0.65 to 1.24)
	Australia3	All ages	No buffer	HR 1.40 (0.75 to 2.61)
	USA24	All ages	No buffer	**RR 0.60 (0.50 to 0.73)**
	Australia4	< 15 years	No buffer	RR 0.66 (0.41 to 1.06)
	Australia1	All ages	No buffer	**HR 1.41 (1.12 to 1.77) ****
	Australia1	<16 years	No buffer	HR 1.20 (0.37 to 3.92)
	Australia1	17-19	No buffer	HR 1.38 (0.89 to 2.15)
	Australia1	20-23	No buffer	HR 1.30 (0.91 to 1.85)
	Denmark3	All ages	6 months	**IRR 0.38 (0.14 to 0.98)**
	Australia1	All ages	12 months	**HR 0.56 (0.33 to 0.93)**
	Australia1	All ages	24 months	**HR 0.39 (0.16 to 0.95)**

* Estimates in bold indicate reduced risk of CIN after one dose. ** estimates indicate increased risk of CIN after one dose. HR = hazard ratio; OR = odds ratio; RR = relative risk.

Evidence profile 1: Effectiveness and immunogenicity of one dose of HPV vaccine compared with no HPV vaccination

Table 1.4. GRADE evidence profile for single dose HPV vaccine compared with no vaccine for HPV infection, seroconversion, and antibody titres

Certainty assessment						№ of patients		Effect		Certainty	Comments
№ of studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Single dose bivalent HPV infection	no vaccine	Relative (95% CI)	Absolute (95% CI)		
Persistent HPV 16/18 infections: short term follow-up, 18 months											
1 RCT	not serious[1]	not serious	not serious	not serious[2]	none	2/985 (0.2%)	36/473 (7.6%)	**RR 0.03** (0.01 to 0.11)	74 fewer per 1000 (from 75 fewer to 68 fewer)	⊕⊕⊕⊕ High	Kenya1 (KEN-SHE), bivalent (Cervarix) and nonavalent (Gardasil 9), 15-20 years old at vaccination
Persistent HPV 16/18 infections: long term follow-up, 4-10 years											
2 post-hoc analyses of RCTs	serious[3]	not serious	not serious	not serious[2]	none	2/3369 (0.1%)	56/2282 (2.5%)	**RR 0.03** (0.01 to 0.10)	24 fewer per 1000 (from 24 fewer to 22 fewer)	⊕⊕⊕◯ Moderate	CVT/PATRICIA, bivalent (Cervarix), 15-25 years old at vaccination India1, quadrivalent (Gardasil), 10-18 years old at vaccination
Seroconversion to HPV 16: follow-up 6 months to 11 years											
2 RCTs, 1 post-hoc analysis of RCT, 3 observational studies	not serious	not serious	not serious	not serious	none	Seroconversion following one dose ranged from 89.8% to 100% at up to 11 years follow-up.				⊕⊕⊕⊕ High	Kenya1, China1, Costa Rica1, Fiji1, Mongolia1, USA16
Seroconversion to HPV 18: follow-up 6 months to 11 years											

2 RCTs, 1 post-hoc analysis of RCT, 3 observational studies	not serious	not serious	not serious	not serious	none	Seroconversion following one dose ranged from 56.7% to 100% at up to 11 years follow-up.	⊕⊕⊕⊕ High	Kenya1, China1, Costa Rica1, Fiji1, Mongolia1, USA16
Geometric mean titres (GMT) for HPV 16: follow-up 4-6 years								
1 post-hoc analysis of RCT, 3 observational studies	not serious	not serious	not serious	not serious	none	Ratio of GMTs following one dose ranged from 5.73 to 320.43.	⊕⊕⊕⊕ High	Costa Rica1, Netherlands1 Fiji1, Mongolia1
Geometric mean titres (GMT) for HPV 18: follow-up 4-6 years								
1 post-hoc analysis of RCT, 3 observational studies	not serious	not serious	not serious	not serious	none	Ratio of GMT following one dose ranged from 4.79 to 81.92.	⊕⊕⊕⊕ High	Costa Rica1, Netherlands1 Fiji1, Mongolia1

CI: confidence interval; **HPV**: human papillomavirus; **RCT**: randomized controlled trial; **RR:** risk ratio

1. Not downgraded despite some concerns with missing outcome data, estimates from unpublished data of modified intention-to-treat analysis of participants HPV naïve at baseline.
2. Not downgraded for imprecision due to large effect estimates, despite few events.
3. Downgraded one level due to some concerns with bias due to confounding and selection of the reported result.

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

Immunogenicity outcomes

Two RCTs (China1, Tanzania1), two post hoc analyses of RCTs (Costa Rica1, India1), and five observational studies (Netherlands1, Fiji1, Mongolia1, Uganda1, USA16) reported on immunogenicity outcomes in women receiving one dose of HPV vaccine compared with two doses. Following one dose of bivalent (Cervarix) vaccine, the ratio of GMTs for HPV 16 and 18 were in favour of two doses and sustained over 132 months (Figure 2.1). Following one or two doses of quadrivalent (Gardasil) vaccine, the ratio of GMTs for HPV 6, 11, 16, and 18 were in favour of two doses over 48 months, but no difference was detected for indigenous populations in Fiji1 (Figure 2.2). For nonavalent (Gardasil9) vaccine, [redacted]. For bivalent Cecolin vaccine, the ratio of GMTs for HPV 16 and 18 were in also favour of two doses at 6 months (Figure 2.4).

Seropositivity following one dose of bivalent (Cervarix) vaccine was very high, sustained over 11 years, and comparable to two or three doses (Table 2.1). Similarly, following one dose of quadrivalent (Gardasil) vaccine, seropositivity was very high for the vaccine HPV types and sustained up to 4-6 years (Table 2.2). Seropositivity to HPV 16 or 18 was very high and comparable to two or three doses following nonavalent (Gardasil9) vaccine (Table 2.3). Seropositivity to HPV 16 and 18 following one dose of bivalent Cecolin vaccine was very high and comparable to two doses (Table 2.4).

There was high certainty evidence of higher GMTs for HPV 16 and 18 following two doses of HPV vaccine compared with one dose. There was also high certainty evidence of little to no difference in seropositivity to HPV 16 or 18 following one or two doses of HPV vaccine.

Figure 2.1 Immunogenicity – ratio of GMTs following bivalent (Cervarix) vaccine

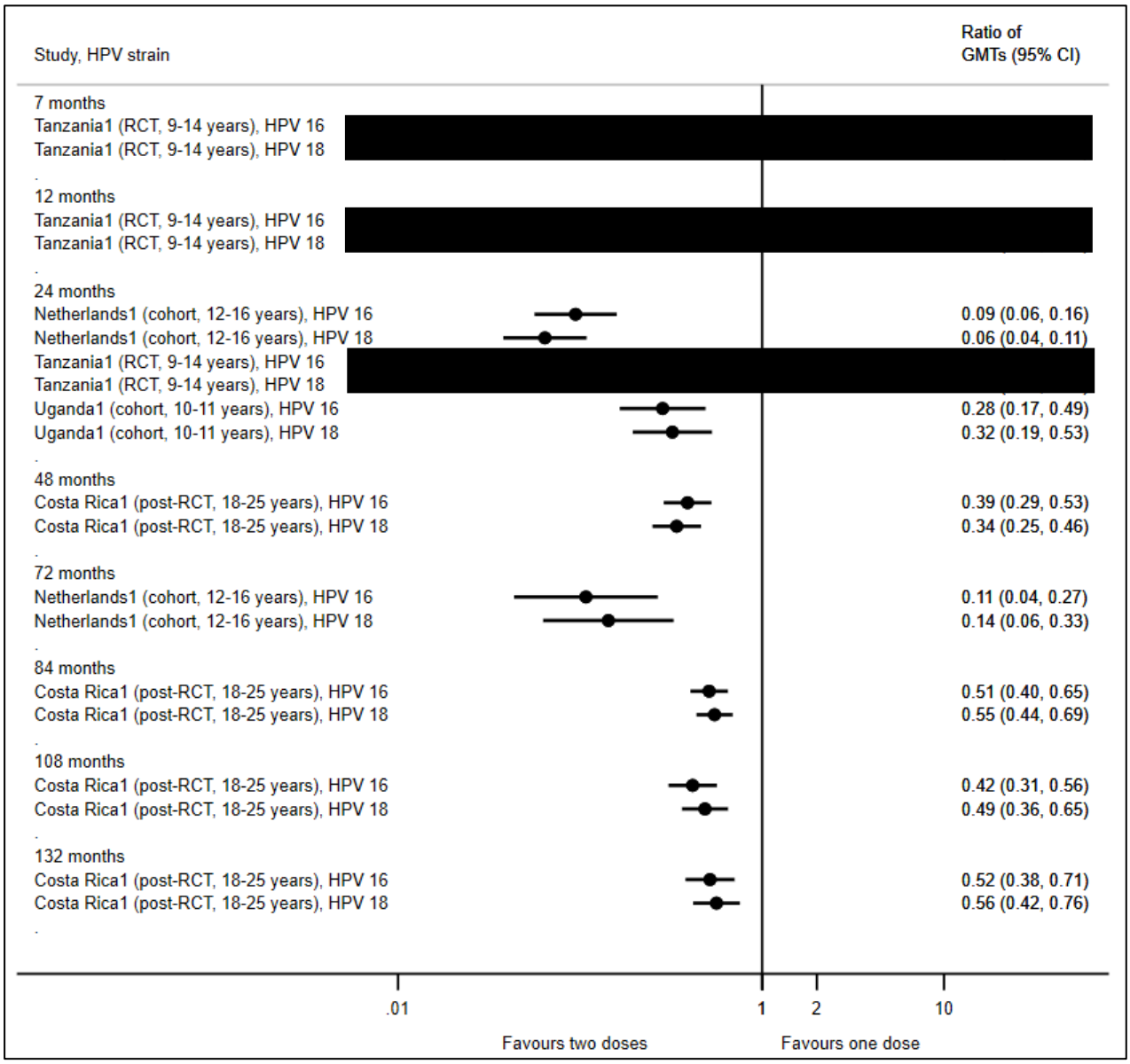


Figure 2.2 Immunogenicity – ratio of GMTs following quadrivalent (Gardasil) vaccine

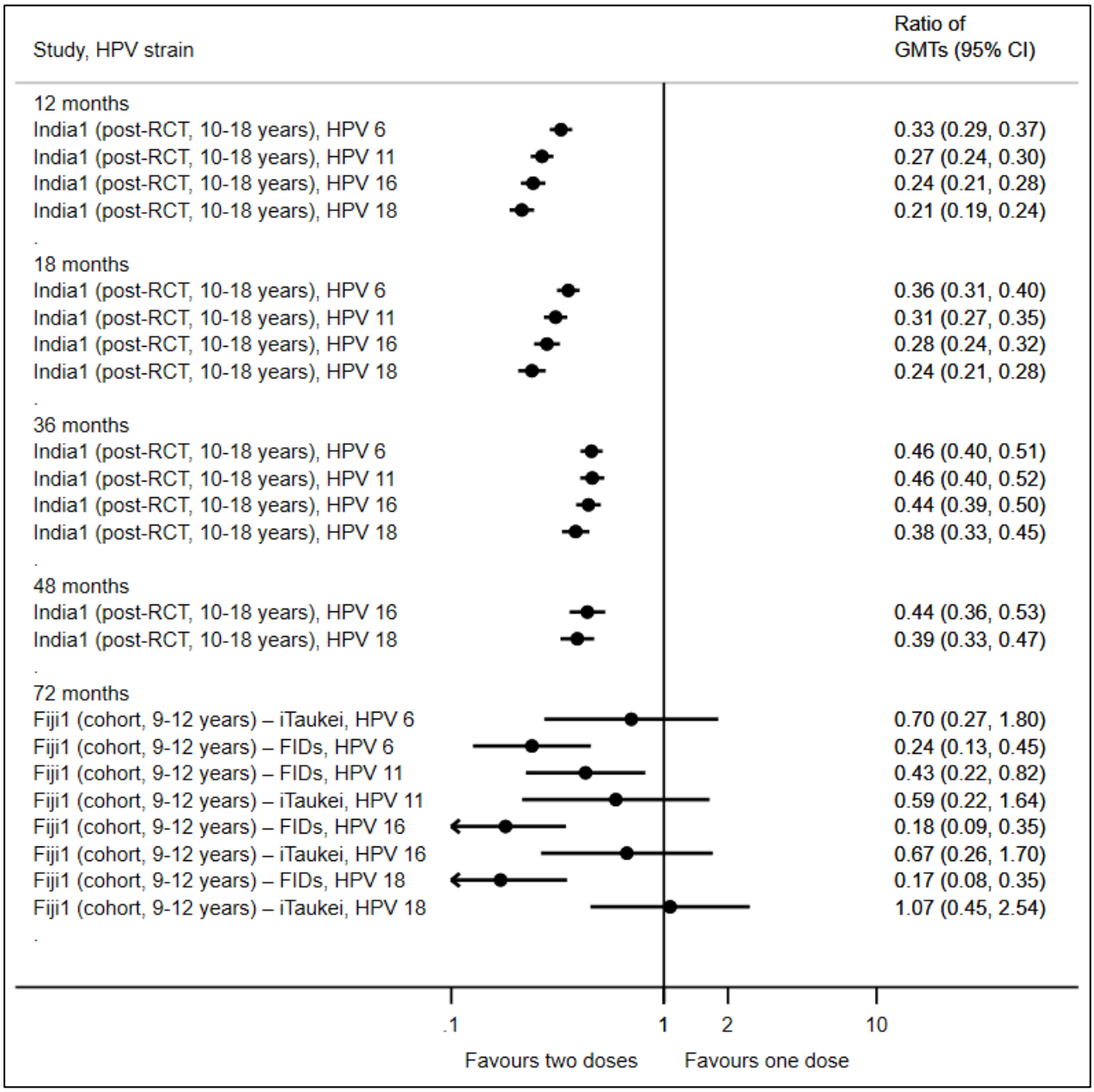


Figure 2.3 Immunogenicity – ratio of GMTs following nonavalent (Gardasil9) vaccine

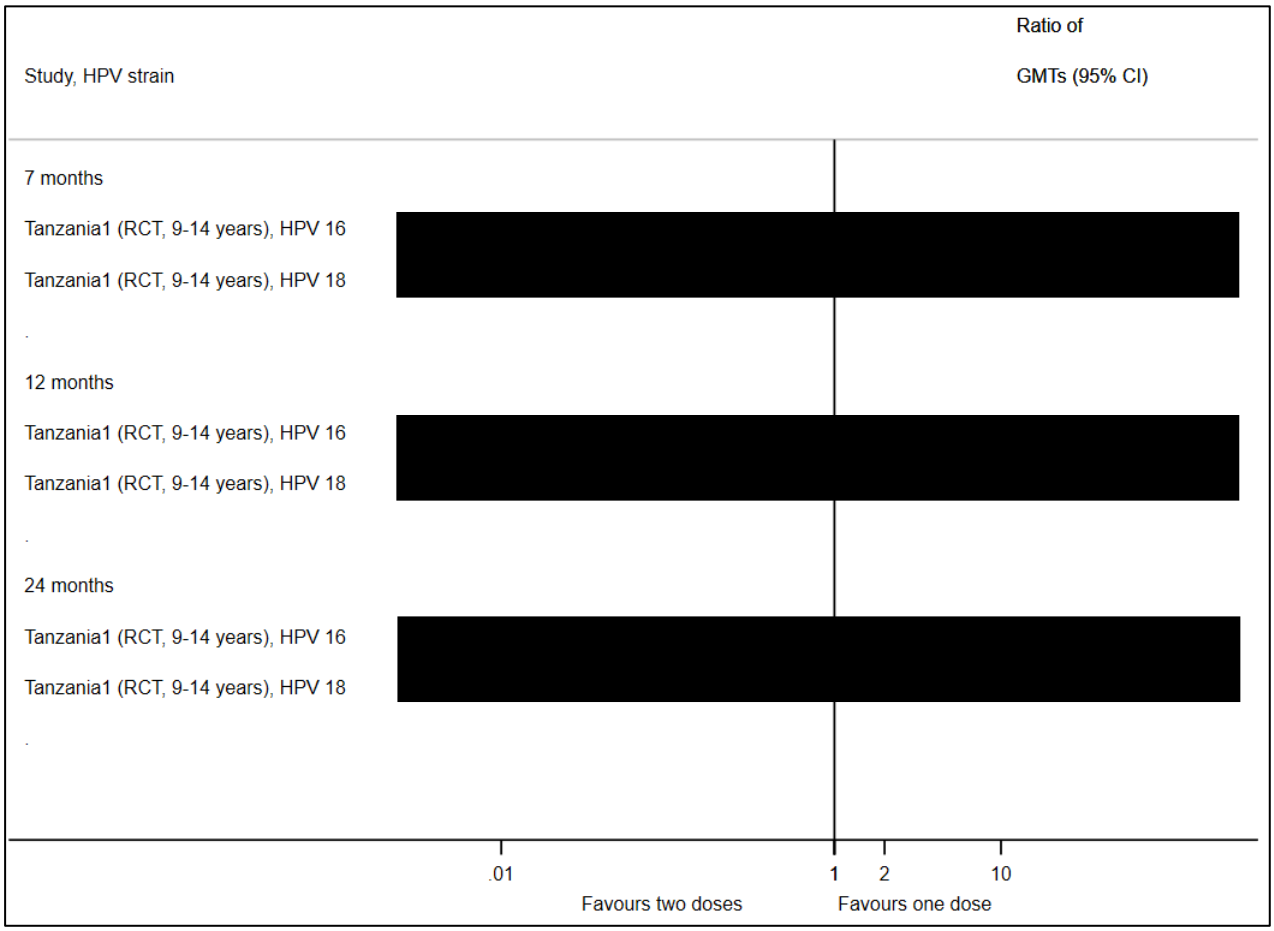


Figure 2.4 Immunogenicity – ratio of GMTs following bivalent (Cecolin) vaccine

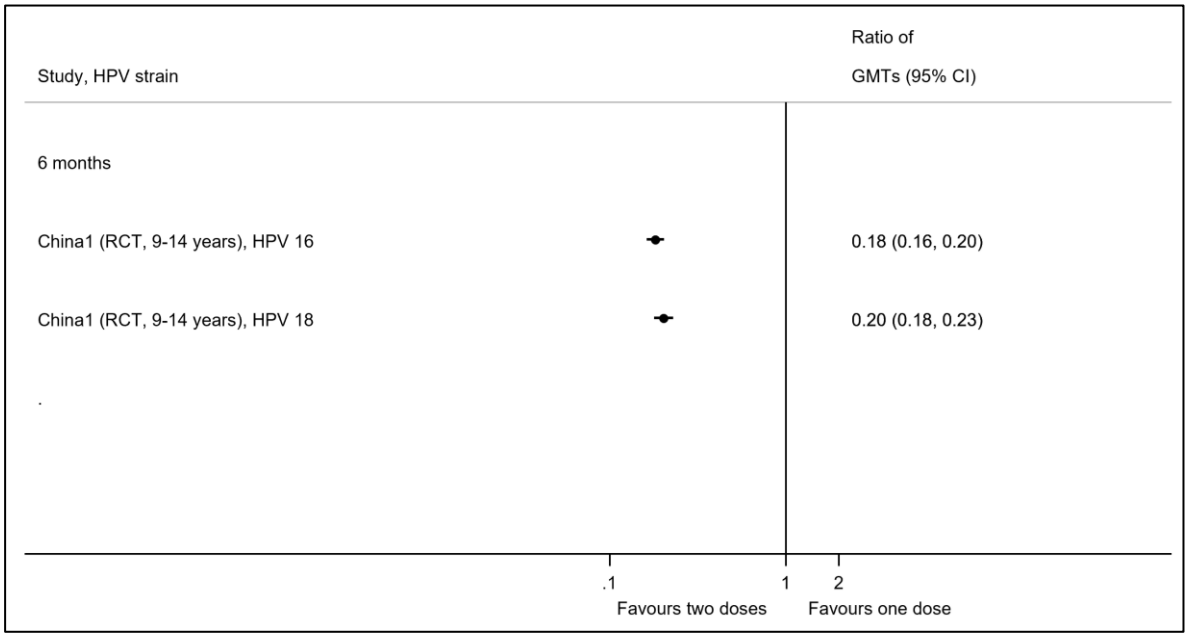


Table 2.1 Immunogenicity – seropositivity following bivalent (Cervarix) vaccine

Study	HPV type	Timepoint	One dose		Two doses		Three doses	
			N	% seropositive	N	% seropositive	N	% seropositive
Tanzania1	HPV 16	7 months						
Tanzania1	HPV 18	7 months						
Tanzania1	HPV 16	12 months						
Tanzania1	HPV 18	12 months						
Tanzania1	HPV 16	24 months						
Tanzania1	HPV 18	24 months						
Uganda1	HPV 16	24 months	36	100	145	98.6	195	99.5
Uganda1	HPV 18	24 months	36	97.2	145	98.6	195	99.5
Netherlands1	HPV 16	24 months	48	97.9	51	100	51	100
Netherlands1	HPV 18	24 months	48	89.6	51	100	51	100
Costa Rica1	HPV 16	48 months	78	100	140	100	120	100
Costa Rica1	HPV 16	108 months	118	100	66	100	1365	100
Costa Rica1	HPV 18	108 months	118	100	66	100	1365	100
Costa Rica1	HPV 16	132 months	118	100	66	100	1365	100
Costa Rica1	HPV 18	132 months	118	100	66	100	1365	100

Table 2.2 Immunogenicity – seropositivity following quadrivalent (Gardasil) vaccine

Study	HPV type	Timepoint	One dose		Two doses		Three doses	
			N	% seropositive	N	% seropositive	N	% seropositive
Fiji1	HPV 6	72 months	40	90	60	93.3	66	100
Fiji1	HPV 11	72 months	40	92.5	60	93.3	66	100
Fiji1	HPV 16	72 months	40	95	60	100	66	100
Fiji1	HPV 18	72 months	40	67.5	60	90	66	87.9
Mongolia1	HPV 16	72 months	30	90				
Mongolia1	HPV 18	72 months	30	56.7				
USA16	HPV 6	4-6 years	213	92	253	96.8	747	98.1
USA16	HPV 11	4-6 years	246	97.6	287	99.7	845	99.4
USA16	HPV 16	4-6 years	264	89.8	303	97.0	928	98.8
USA16	HPV 18	4-6 years	352	82.7	354	81.1	1054	79.6

Table 2.3 Immunogenicity – seropositivity following nonavalent (Gardasil9) vaccine

Study	HPV type	Timepoint	One dose		Two doses		Three doses	
			N	% seropositive	N	% seropositive	N	% seropositive
Tanzania1	HPV 16	7 months						
Tanzania1	HPV 18	7 months						
Tanzania1	HPV 16	12 months						
Tanzania1	HPV 18	12 months						
Tanzania1	HPV 16	24 months						
Tanzania1	HPV 18	24 months						

Table 2.4 Immunogenicity – seropositivity following bivalent (Cecolin) vaccine

Study	HPV type	Timepoint	One dose		Two doses	
			N	% seropositive	N	% seropositive
China1	HPV 16	6 months	267	100	246	100
China1	HPV 18	6 months	275	98.5	262	100

Clinical outcomes – persistent HPV infection

Two post-hoc analyses of RCTs (CVT/PATRICIA, India1) reported on prevalent HPV infections in women receiving one dose of HPV vaccine compared with two doses.

A difference was not detected for 6- and 12-month persistent HPV 16/18 infections between one and two doses of bivalent (Cervarix) vaccine after 4 years follow-up (Figure 2.5) or for HPV 6/11/16/18 following quadrivalent (Gardasil) vaccine after 10 years follow-up (Figure 2.6), although estimates were imprecise due to few events. For persistent HPV 31/33/45 infections (cross-protective types), a difference between one and two doses was not detected for bivalent vaccine (Cervarix); for quadrivalent vaccine (Gardasil) a difference in favour of two doses was detected.

There was low certainty evidence of little to no difference in persistent HPV infections following one or two doses HPV vaccine.

Figure 2.5 Persistent HPV infections following bivalent vaccine (Cervarix) – post-hoc RCT analyses

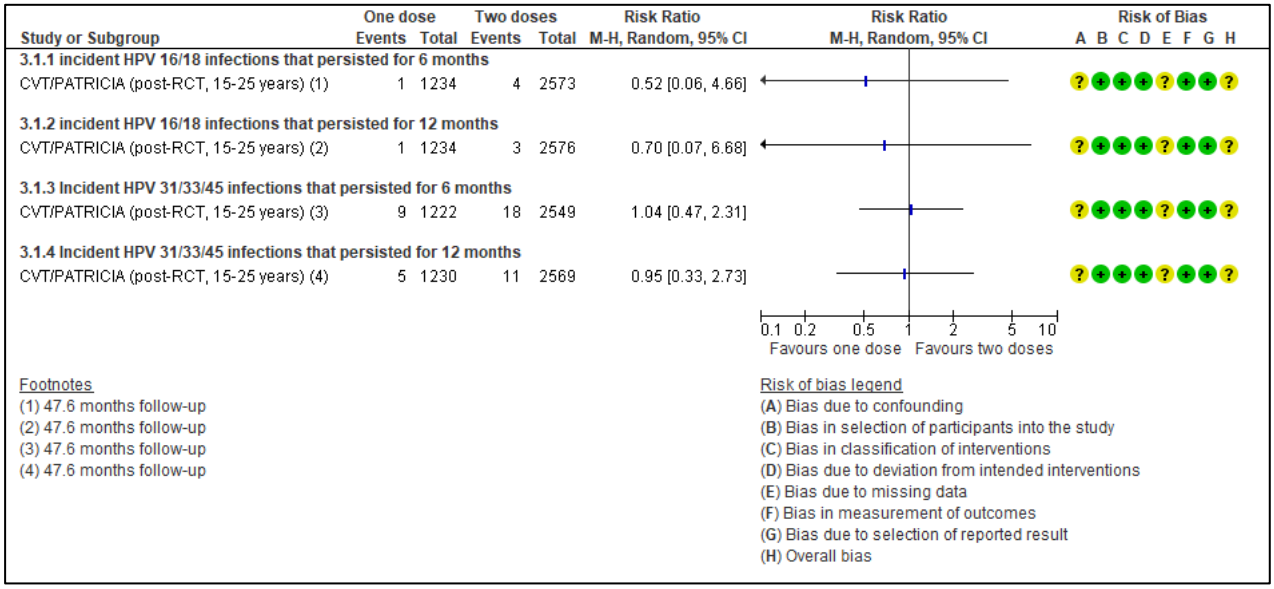
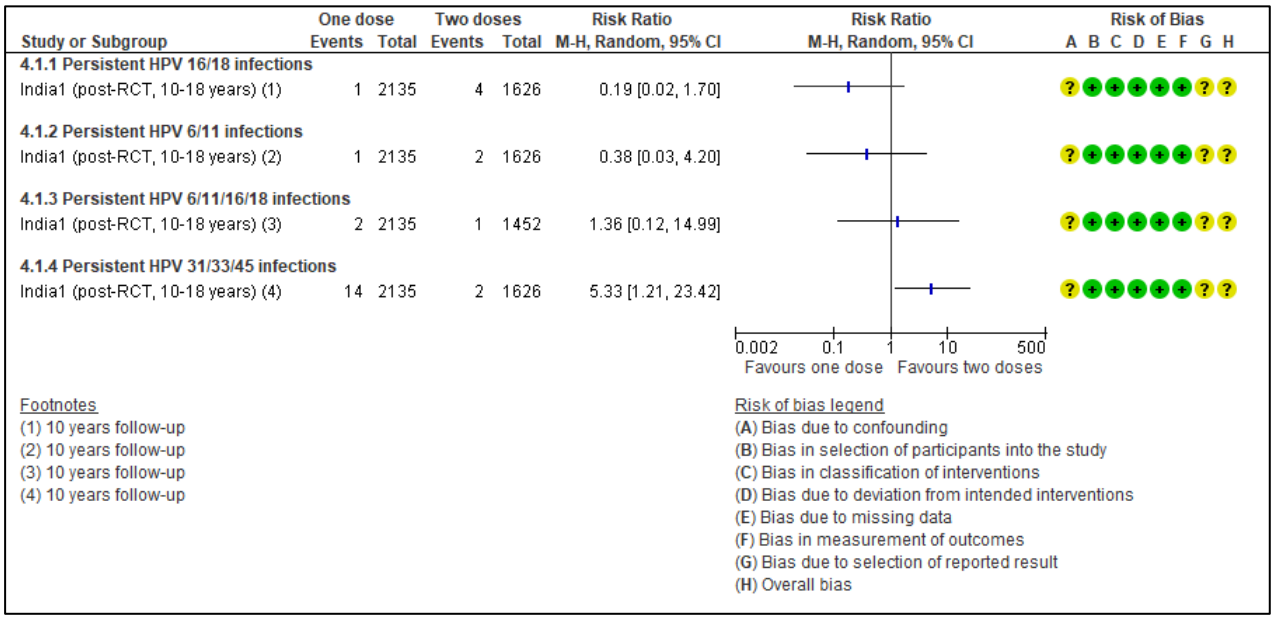


Figure 2.6 Persistent HPV infections following quadrivalent vaccine (Gardasil) - post-hoc RCT analyses



Clinical outcomes – prevalent and incident HPV infection

One community randomised trial (Thailand1), two post-hoc analyses of RCTs (CVT/PATRICIA, India1), and six observational studies (Scotland1, Scotland4, Scotland5, USA18, USA23, USA25) reported on prevalent and incident HPV infection.

A community RCT (Thailand1) evaluating the effectiveness of one or two doses of bivalent (Cervarix) vaccine on HPV 16/18 prevalence [redacted]

A difference was not detected between one and two doses bivalent vaccine (Cervarix) for prevalent HPV 16/18 infection at up to 11 years follow-up (Figure 2.7 and 2.8) or for incident HPV 16/18 infection at 11 years (Figure 2.9). Similarly, a difference was not detected for incident HPV 6/11/16/18 infection between one and two doses of quadrivalent vaccine (Gardasil) at up to 10 years follow-up (Figure 2.10), including oral infection and penile/anal infection in males (Figure 2.11). Regarding cross-protective HPV types 31/33/45, effects favouring two doses were shown for both bivalent (Cervarix) and quadrivalent (Gardasil) vaccine.

Figure 2.7 Prevalent HPV infections following bivalent vaccine (Cervarix) – post-hoc RCT analyses

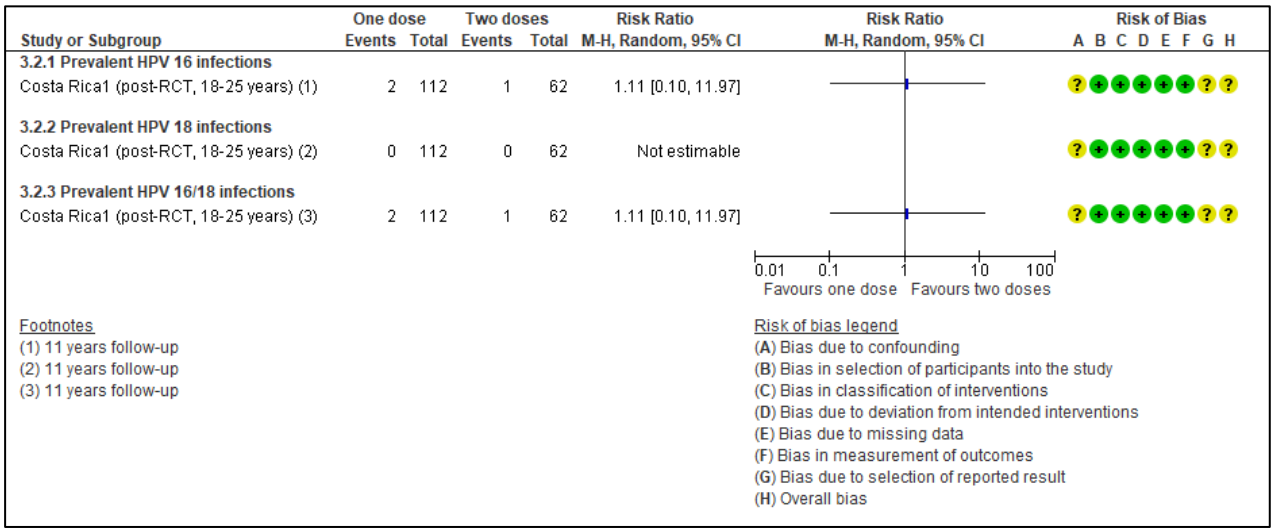


Figure 2.8 Prevalent HPV infections following bivalent vaccine (Cervarix) – observational studies, unadjusted data

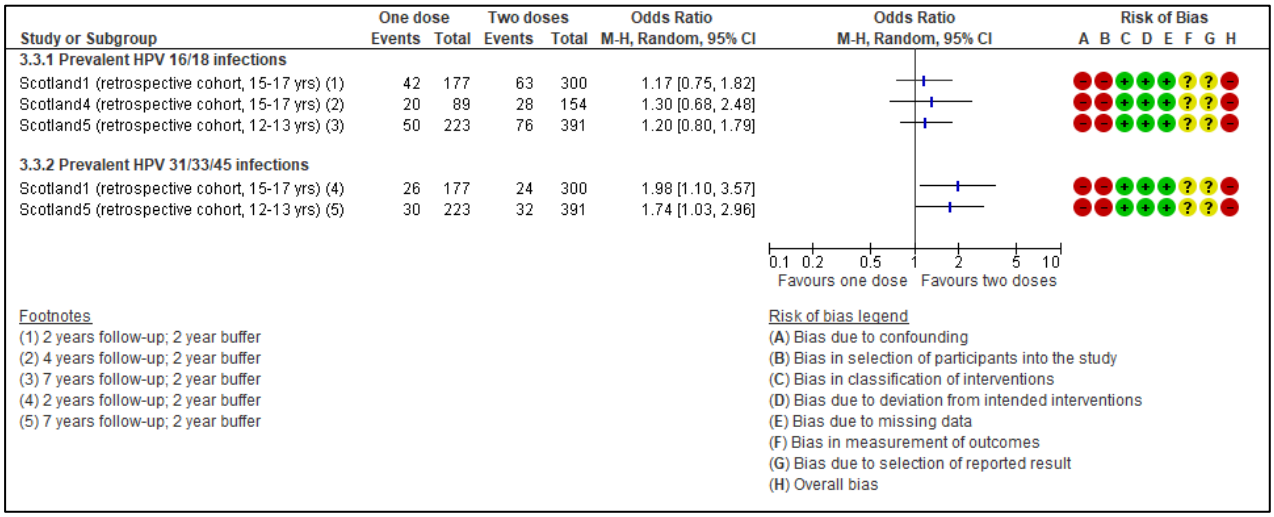


Figure 2.9 Incident HPV infections following bivalent vaccine (Cervarix) – post-hoc RCT analyses

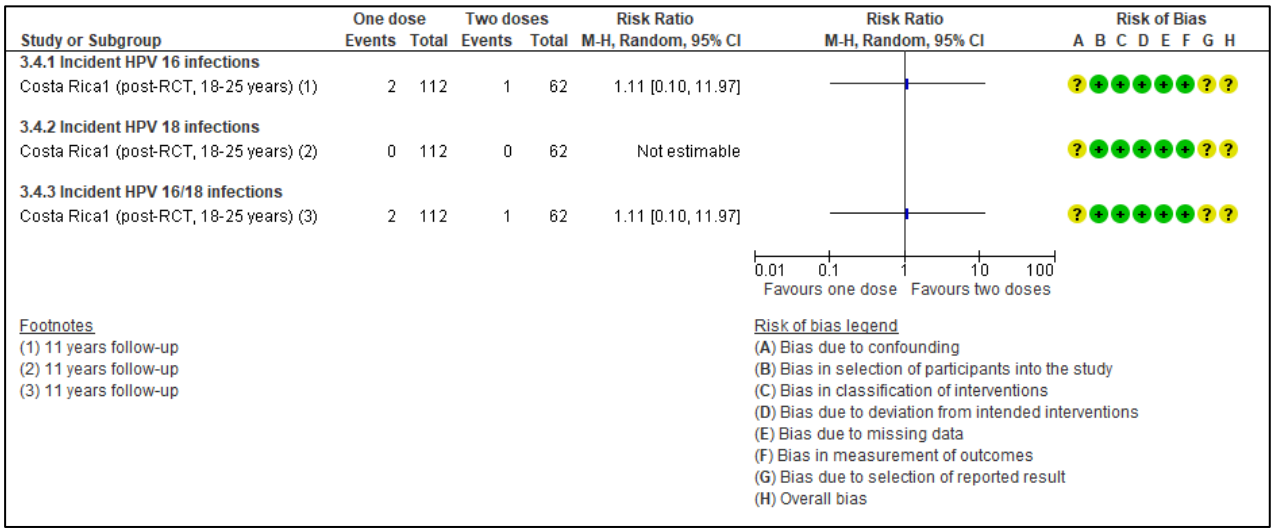


Figure 2.10 Incident HPV infections following quadrivalent vaccine (Gardasil) - post-hoc RCT analyses

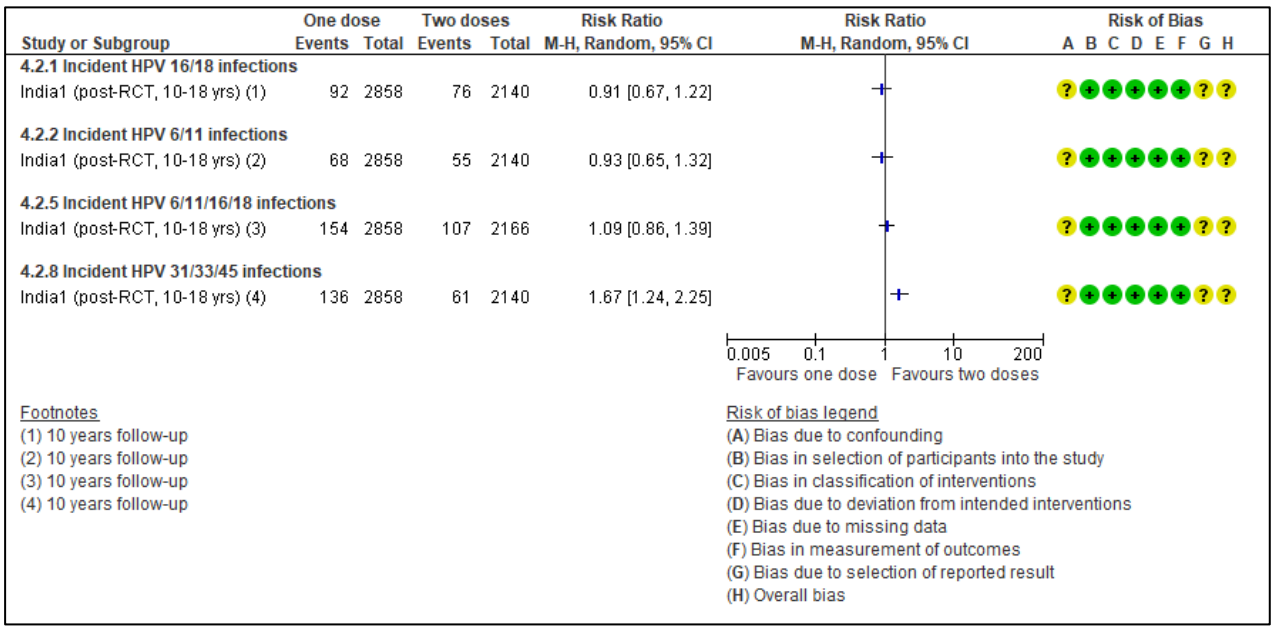
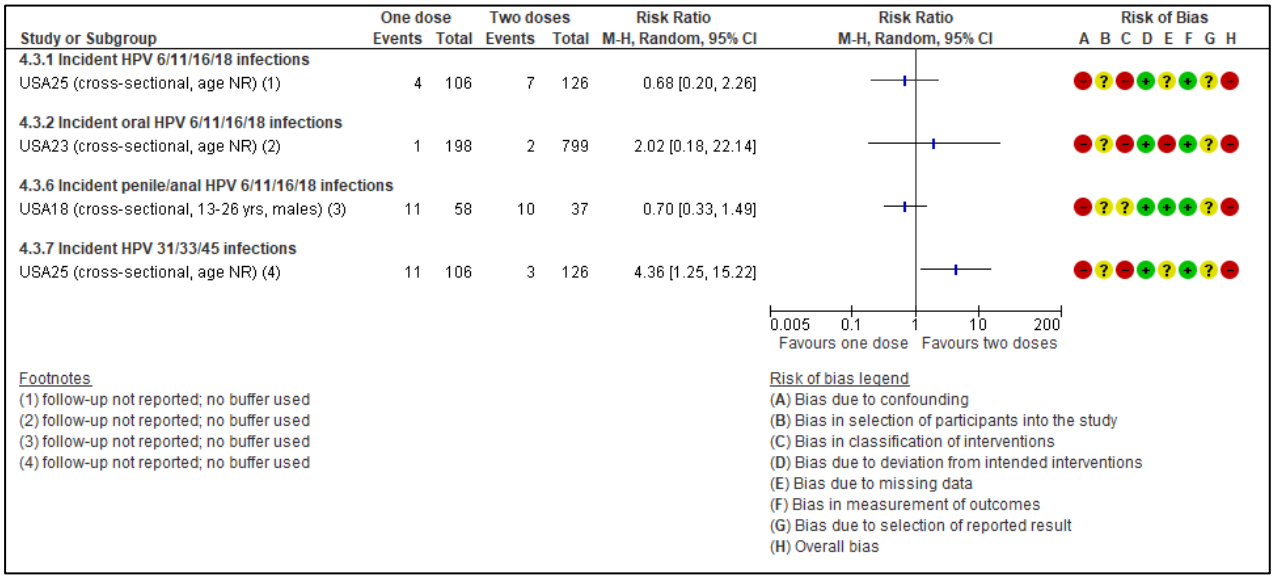


Figure 2.11 Incident HPV infections following quadrivalent vaccine (Gardasil) – observational studies, unadjusted data



Clinical outcomes – genital warts

There were 9 observational studies that reported unadjusted data for one dose compared with two doses quadrivalent (Gardasil) vaccine on genital warts (Figure 2.12). The studies were not pooled due to reporting different types of estimates (i.e. VE, HR, RR, IRR, IRD) and potential overlapping populations between the Denmark, Spain, and USA studies. Most studies were at serious risk of bias due to confounding and the results were inconsistent regarding the effect of one dose at up to 7 years follow-up. Buffer periods ranged from no buffer to 12 months.

Four studies reported effect estimates adjusted for confounding across different age groups (Table 2.5). When a sensitivity analysis was applied, including only studies with adjusted estimates calculated after a 12-month buffer period, two studies remained (Sweden1, USA2). The Sweden1 study reported adjusted incidence rate ratios (IRR) of 0.59 (95%CI 0.38 to 0.91) for those vaccinated between 10-19 years (10-16 years IRR 0.81 (95%CI 0.43 to 1.53); 17-19 years IRR 0.45 (95%CI 0.25 to 0.83). The USA2 study reported a propensity score weighted HR of 0.74 (95%CI 0.35 to 1.60) following a 12-month buffer.

Figure 2.12 Genital warts following quadrivalent vaccine (Gardasil) – observational studies, unadjusted data

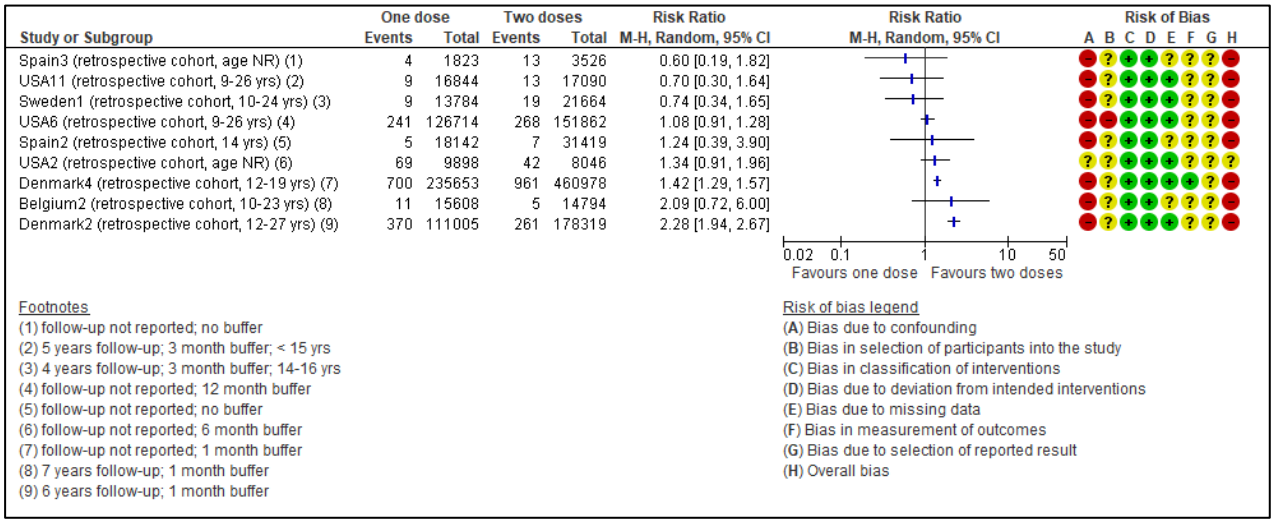


Table 2.5. Adjusted estimates of effect for genital warts comparing one dose quadrivalent (Gardasil) vaccine with two doses

Study	Age at vaccination	Buffer period	Adjusted estimate (95% CI) *
Denmark4	12-14 years	1 month	IRR 0.76 (0.56 to 1.03)
Denmark4	15-16 years	1 month	IRR 0.84 (0.62 to 1.14)
Denmark4	17-18 years	1 month	IRR 0.88 (0.61 to 1.26)
Denmark4	> 19 years	1 month	**IRR 0.76 (0.67 to 0.85)**
Denmark2	All ages	1 month	**IRR 0.44 (0.37 to 0.51)**
Sweden1	10-19 years	3 months	**IRR 0.59 (0.43 to 0.81)**
Sweden1	10-16 years	3 months	IRR 0.91 (0.52 to 1.59)
Sweden1	17-19 years	3 months	**IRR 0.49 (0.33 to 0.73)**
USA2	All ages	6 months	**HR 0.39 (0.20 to 0.76)**
USA2	All ages	12 months	HR 0.74 (0.35 to 1.60)
Sweden1	10-19 years	12 months	**IRR 0.59 (0.38 to 0.91)**
Sweden1	10-16 years	12 months	IRR 0.81 (0.43 to 1.53)
Sweden1	17-19 years	12 months	**IRR 0.45 (0.25 to 0.83)**

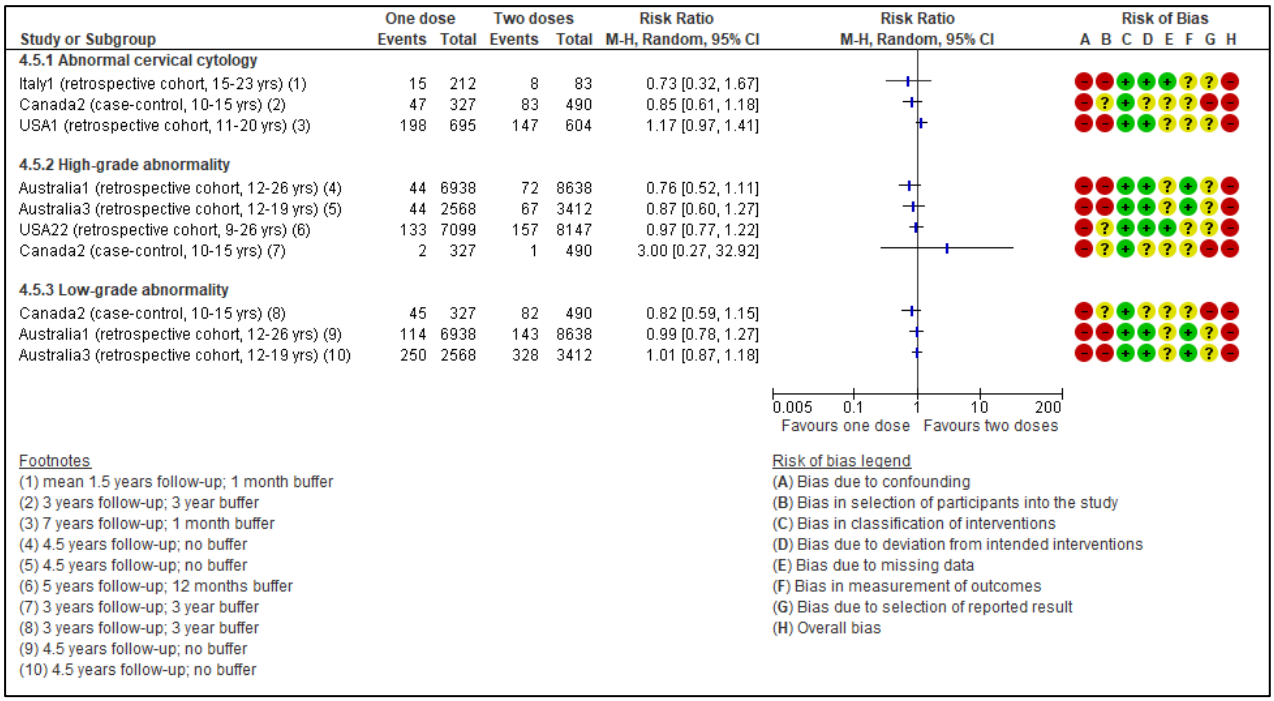
* Estimates in bold indicate reduced risk of genital warts after two doses compared with one dose. HR = hazard ratio; IRR = incidence rate ratio.

Clinical outcomes – cytological outcomes

Six observational studies (Australia1, Australia3, Canada2, Italy1, USA1, USA22) reported the effect of one dose compared with two doses quadrivalent (Gardasil) vaccine on abnormal cervical cytology at up to 7 years follow-up (Figure 2.13). All studies were at serious risk of bias due to confounding and none of the studies detected a difference between one and two doses in unadjusted analyses. Buffer periods ranged from no buffer to 3 years.

No studies reported estimates adjusted for confounding between the one dose and two dose groups.

Figure 2.13 Abnormal cytology following quadrivalent vaccine (Gardasil) – observational studies, unadjusted data



Clinical outcomes – histological outcomes

One post-hoc analysis of an RCT and ten observational studies (Figure 2.14, Figure 2.15) reported on histological outcomes, such as cervical intraepithelial neoplasia (CIN) or invasive cancer.

The post-hoc RCT analysis (India1) reported no cases of CIN grade 2 or higher and very few cases of CIN grade 1 in both one-dose and two-dose groups after 10-year follow-up (Figure 2.14). Unadjusted observational data showed little or no difference in CIN 1, 2, 3, and 3+ between one and two doses of bivalent (Cervarix) and quadrivalent (Gardasil) vaccines; all studies were at serious risk of bias (Figures 2.15 and 2.16).

There were three studies that reported on CIN following one dose of quadrivalent (Gardasil) vaccine compared with two doses and reported estimates of effect adjusted for confounding (Table 2.6). When a sensitivity analysis was applied, the only study with adjusted estimates calculated after a 12-month buffer period was USA21 for CIN2+. The adjusted odds ratio was 0.96 (95%CI 0.55 to 1.68), indicating no difference between one and two doses.

Table 2.6. Adjusted estimates of effect for CIN comparing one dose quadrivalent (Gardasil) vaccine with two doses

Outcome	Study	Age at vaccination	Buffer period	Adjusted estimate (95% CI)
CIN2	Australia4	< 15 years	No buffer	HR 0.94 (0.73 to 1.21)
CIN2+	Denmark3	all ages	6 months	IRR 1.00 (0.61 to 1.64)
	USA21	12-26 years	24 months	OR 0.96 (0.55 to 1.68)
CIN3+	Denmark3	All ages	6 months	IRR 0.89 (0.53 to 1.52)
	Australia4	< 15 years	No buffer	RR 0.64 (0.35 to 1.16)

HR = hazard ratio; OR = odds ratio; IRR = incidence rate ratio; RR = risk ratio.

Figure 2.14 CIN (and invasive cancer) following quadrivalent vaccine (Gardasil) – post-hoc RCT analyses

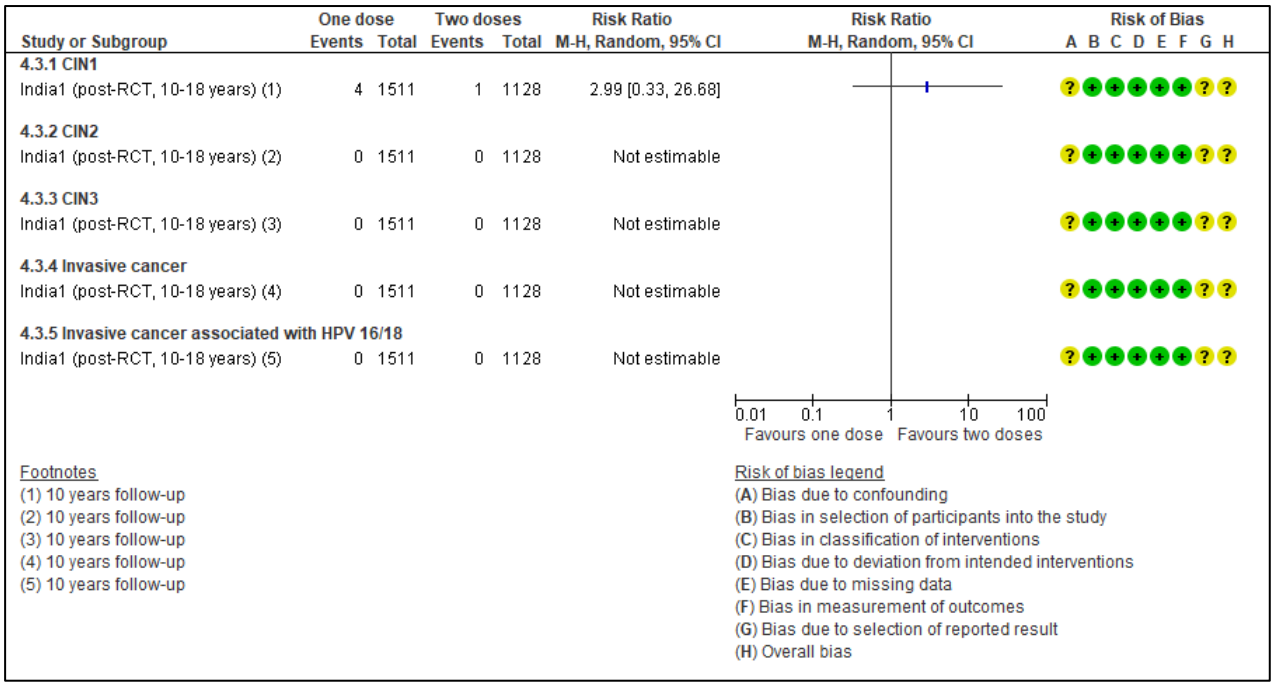


Figure 2.15 CIN following bivalent vaccine (Cervarix) – observational studies, unadjusted data

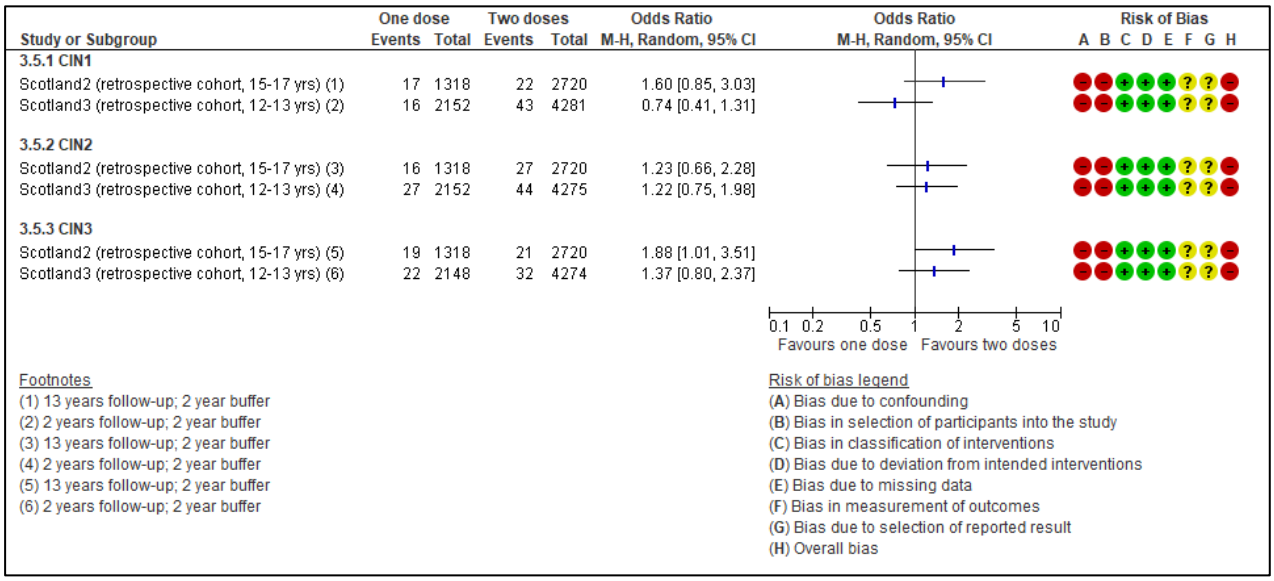
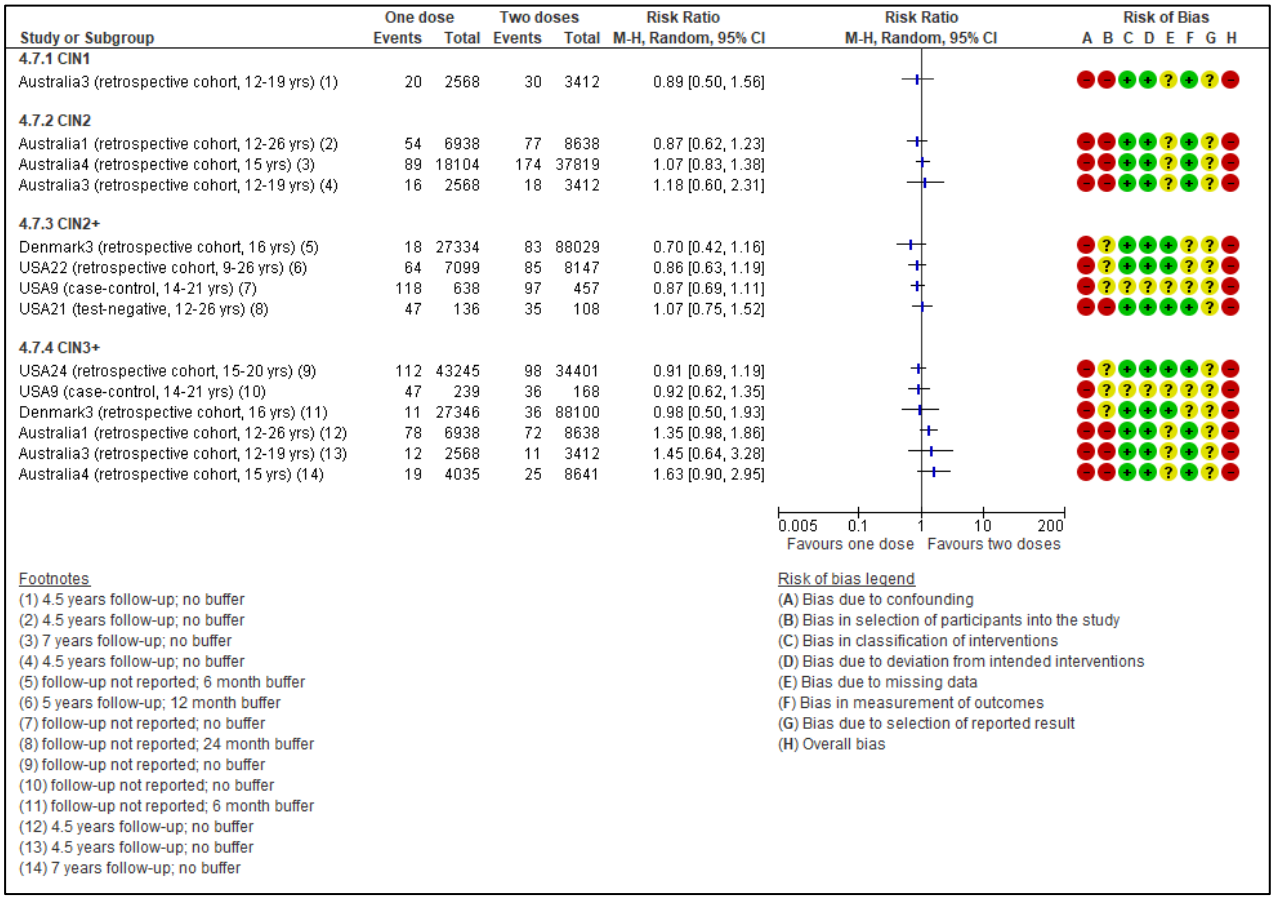


Figure 2.16 CIN following quadrivalent vaccine (Gardasil) – observational studies, unadjusted data



Evidence profile 2: Effectiveness and immunogenicity of one dose of HPV vaccine compared with two doses

Table 2.7. GRADE evidence profile for single dose HPV vaccine compared with two doses for HPV infection, seroconversion, and antibody titres

Certainty assessment						№ of patients		Effect		Certainty	Comments
№ of studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Single dose bivalent HPV infection	no vaccine	Relative (95% CI)	Absolute (95% CI)		
Persistent HPV 16/18 infections: long term follow-up, 4-10 years											
2 post-hoc analyses of RCTs	serious[1]	not serious	not serious	serious[4]	none	2/3369 (0.06%)	8/4199 (0.19%)	**RR 0.32** (0.07 to 1.48)	1 fewer per 1000 (from 2 fewer to 1 more)	⨁⨁◯◯ Low	CVT/PATRICIA, bivalent (Cervarix), 15-25 years old at vaccination India1, quadrivalent (Gardasil), 10-18 years old at vaccination
Seroconversion to HPV 16: follow-up 6 months to 11 years											
2 RCTs, 1 post-hoc analysis of RCT, 2 observational studies	not serious	not serious	not serious	not serious	none	Seroconversion following one dose ranged from 89.8% to 100% and following two doses 97% to 100% at up to 11 years follow-up.				⨁⨁⨁⨁ High	Tanzania1, China1, Costa Rica1, Fiji1, USA16
Seroconversion to HPV 18: follow-up 6 months to 11 years											
2 RCTs, 1 post-hoc analysis of RCT, 2 observational studies	not serious	not serious	not serious	not serious	none	Seroconversion following one dose ranged from 56.7% to 100% and following two doses 81.1% to 100% at up to 11 years follow-up.				⨁⨁⨁⨁ High	Tanzania1, China1, Costa Rica1, Fiji1, USA16
Geometric mean titres (GMT) for HPV 16: follow-up 6 months to 11 years											

2 RCTs, 1 post-hoc analysis of RCT, 1 observational study	not serious	not serious	not serious	not serious	none	Ratio of GMTs comparing one with two doses ranged from 0.11 to 0.67 at up to 11 years follow-up.	⊕⊕⊕⊕ High	Tanzania1, China1, Costa Rica1, Fiji1
Geometric mean titres (GMT) for HPV 18: follow-up 6 to 11 years								
2 RCTs, 1 post-hoc analysis of RCT, 1 observational study	not serious	not serious	not serious	not serious	none	Ratio of GMTs comparing one with two doses ranged from 0.17 to 1.07 at up to 11 years follow-up.	⊕⊕⊕⊕ High	Tanzania1, China1, Costa Rica1, Fiji1

CI: confidence interval; **HPV**: human papillomavirus; **RCT**: randomized controlled trial; **RR:** risk ratio

1. Downgraded one level due to some concerns with bias due to confounding and selection of the reported result.
2. Downgraded one level due to imprecision, few events and a 95% confidence interval that encompasses a benefit, no effect, and a harm.

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

Immunogenicity outcomes

Two post hoc analyses of RCTs (Costa Rica1, India1), and five observational studies (Netherlands1, Fiji1, Uganda1) reported on immunogenicity outcomes in women receiving one dose of HPV vaccine compared with three doses. Following one dose of bivalent (Cervarix) vaccine, the ratio of GMTs for HPV 16 and 18 were in favour of three doses and sustained over 132 months (Figure 3.1). Following one or three doses of quadrivalent (Gardasil) vaccine, the ratio of GMTs for HPV 6, 11, 16, 18 were in favour of three doses over 48 months, but smaller or no difference was detected for indigenous population in Fiji1 (Figure 3.2). Following one dose of nonavalent (Gardasil9) vaccine [redacted]

Figure 3.1 Immunogenicity – ratio of GMTs following bivalent (Cervarix) vaccine

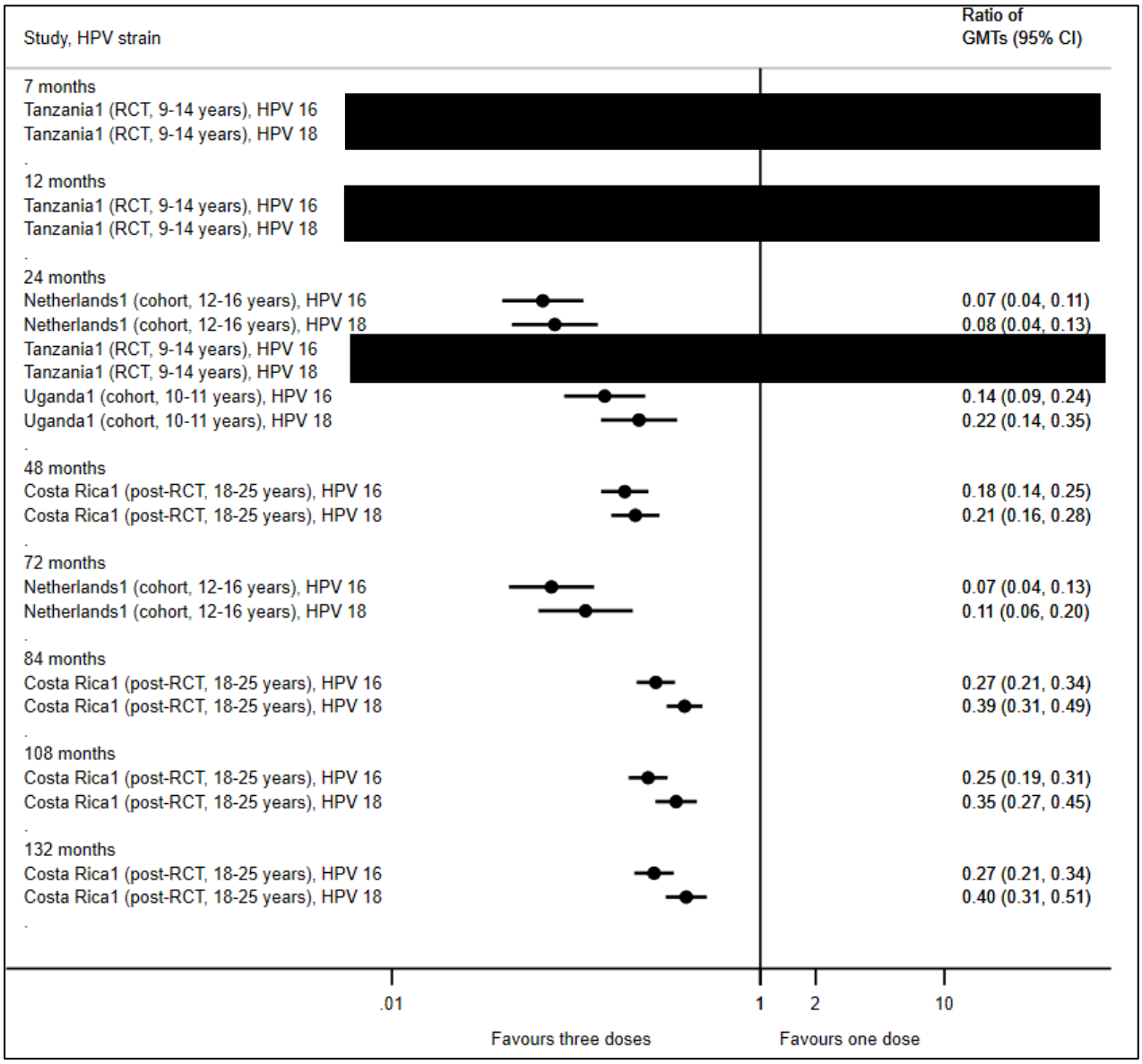


Figure 3.2 Immunogenicity – ratio of GMTs following quadrivalent (Gardasil) vaccine

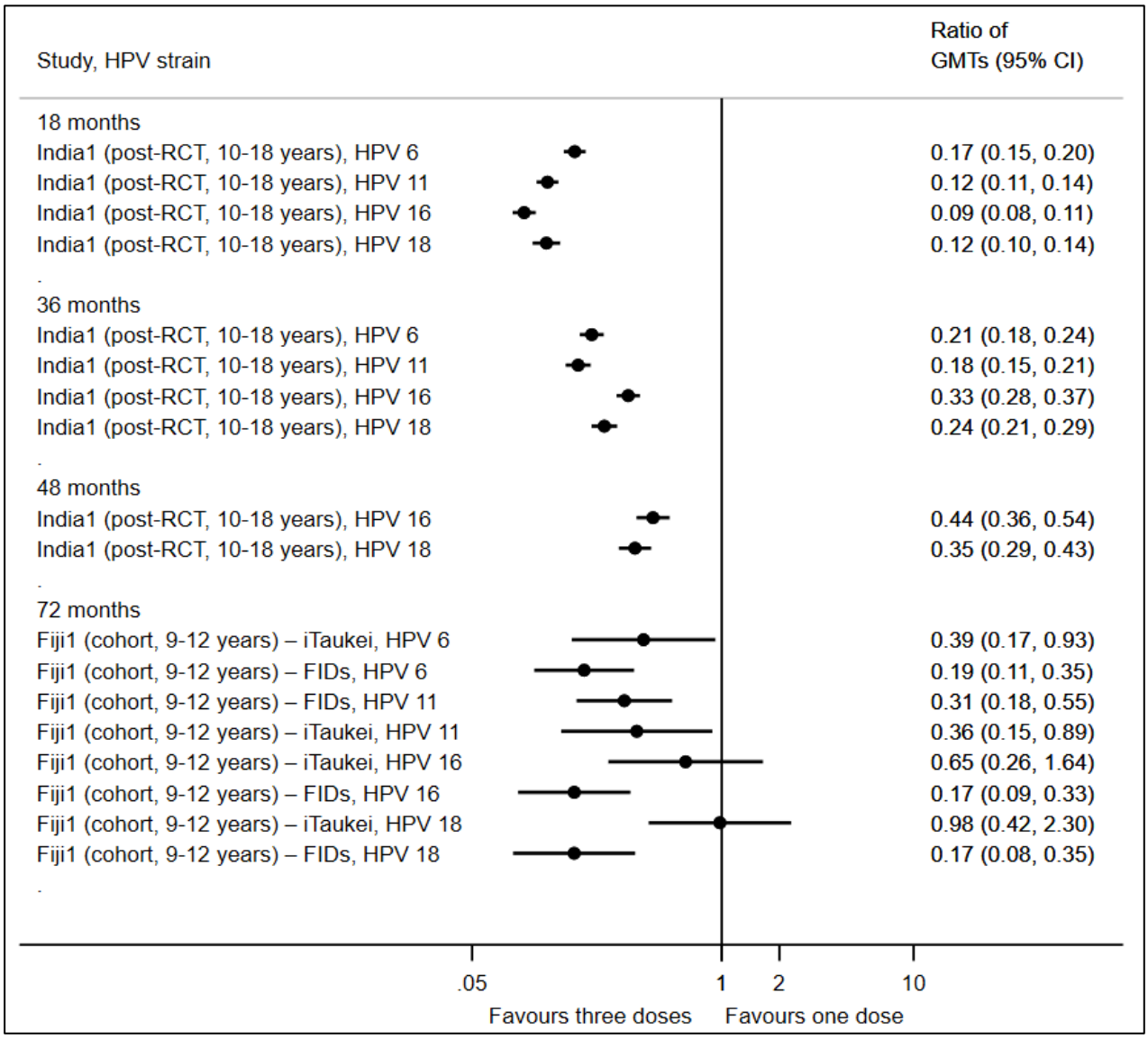
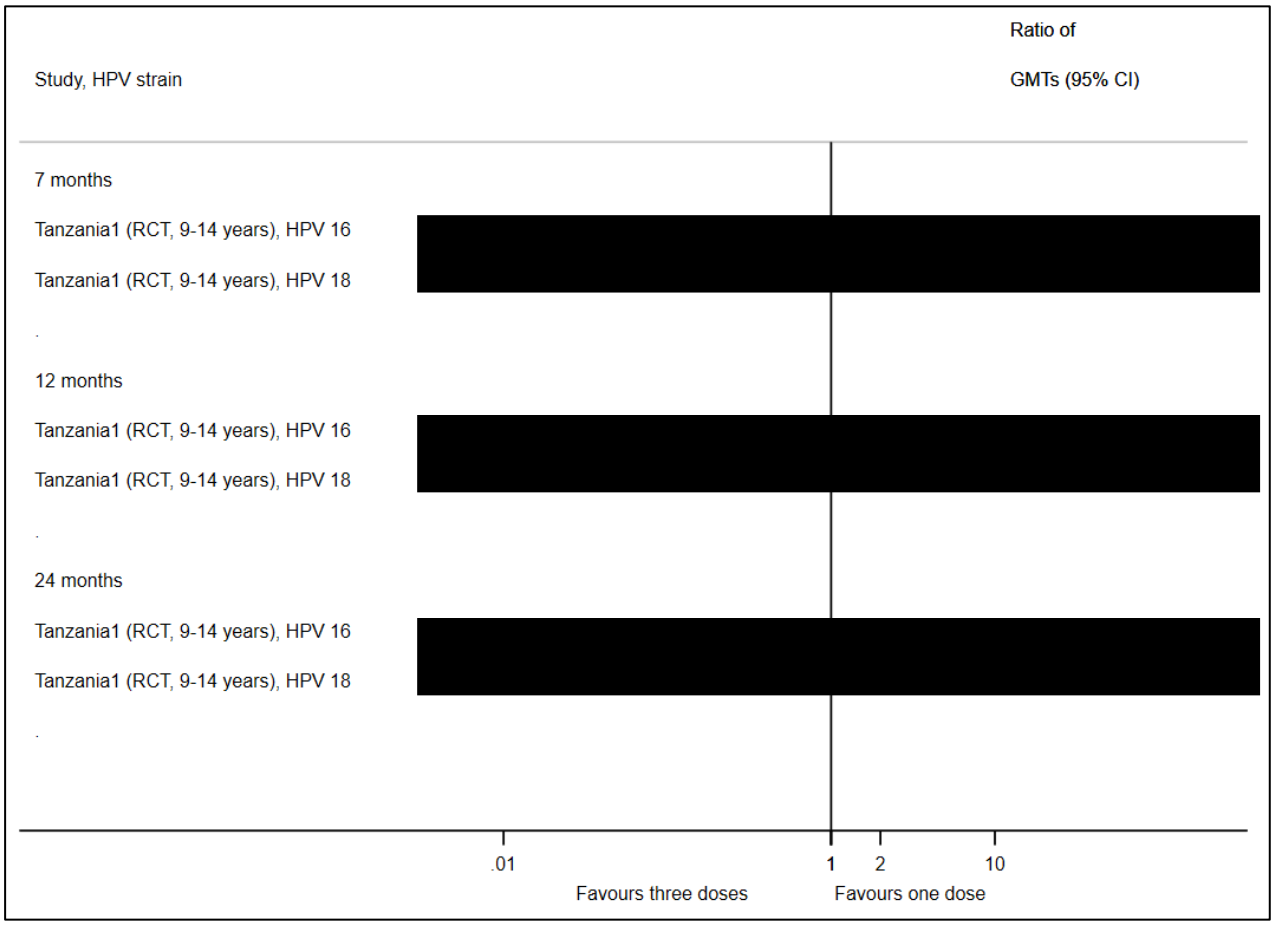


Figure 3.3 Immunogenicity – ratio of GMTs following nonavalent (Gardasil9) vaccine



Clinical outcomes – persistent HPV infection

Two post-hoc analyses of RCTs (CVT/PATRICIA, India1) reported on prevalent HPV infections in women receiving one dose of HPV vaccine compared with three doses.

A difference was not detected for 6- and 12-month persistent HPV 16/18 infections between one and three doses of bivalent (Cervarix) vaccine after 4 years follow-up (Figure 3.4) or for HPV 6/11/16/18 following quadrivalent (Gardasil) vaccine after 10 years follow-up (Figure 3.5), although estimates were imprecise due to few events. For persistent HPV 31/33/45 infections (cross-protective types), a difference between one and three doses was not detected for either vaccine.

Figure 3.4 Persistent HPV infections following bivalent vaccine (Cervarix) – post-hoc RCT analyses

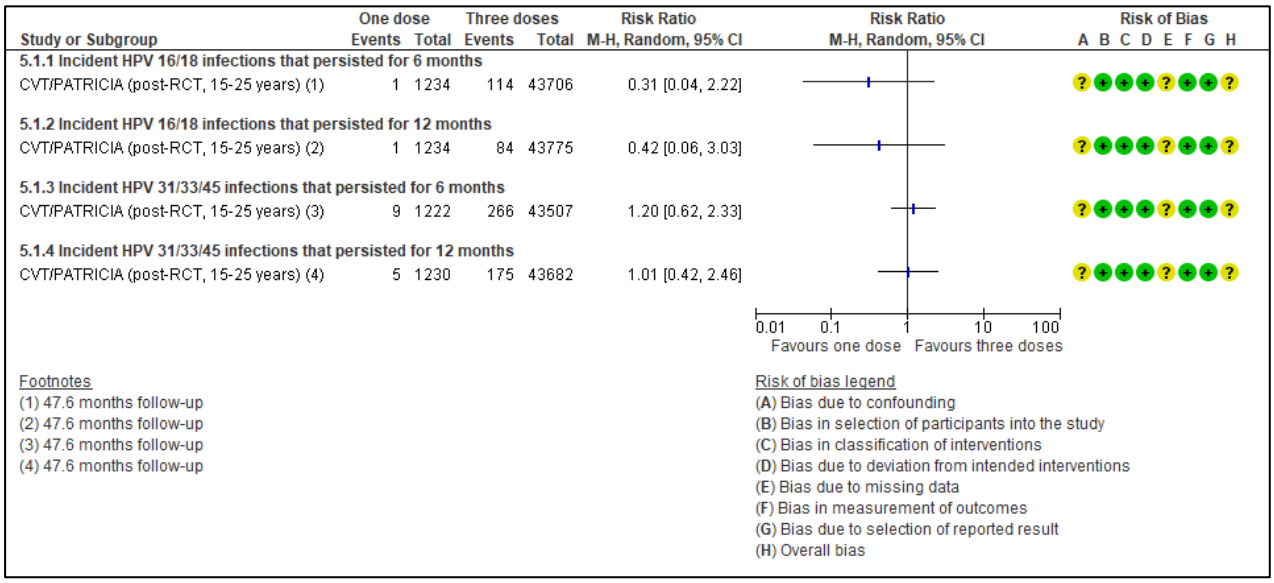
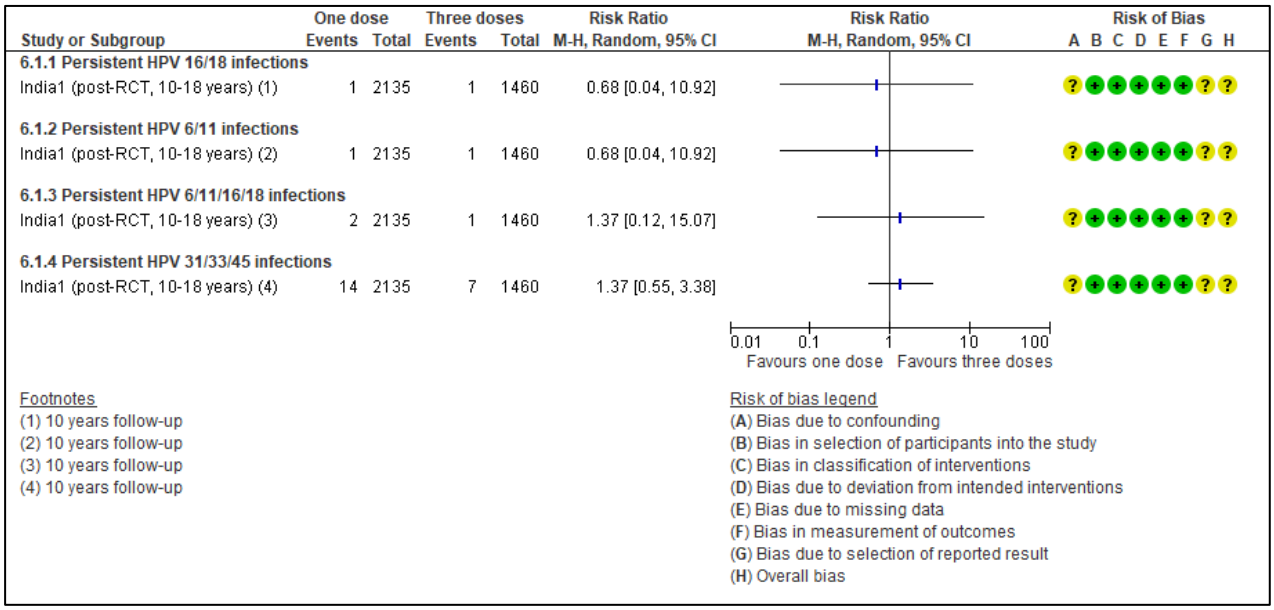


Figure 3.5 Persistent HPV infections following quadrivalent vaccine (Gardasil) – post-hoc RCT analyses



Clinical outcomes – prevalent and incident HPV infection

Two post-hoc analyses of RCTs (CVT/PATRICIA, India1), and six observational studies (Scotland1, Scotland4, Scotland5, USA18, USA25) reported on prevalent and incident HPV infection.

For prevalent (Figure 3.6 and Figure 3.7) and incident (Figure 3.8) HPV 16 or 18 infection comparing one with three doses of bivalent vaccine (Cervarix), a difference was not detected from post hoc analyses of RCTs at 11 years follow-up; estimates are imprecise because there were very few events. A difference in incident HPV 6/11/16/18 or 31/33/45 was not detected between one and three doses quadrivalent vaccine (Gardasil) at 10 years follow-up (Figure 3.9). Unadjusted results at up to 7 years follow-up from

observational studies at serious risk of bias favoured three bivalent vaccine (Cervarix) doses over one dose for HPV 16/18 and for HPV 31/33/45 (Figure 3.7) and did not detect a difference between one and three quadrivalent vaccine (Gardasil) doses for HPV 6/11/16/18 and for HPV 31/33/45 (Figure 3.10).

Figure 3.6 Prevalent HPV infections following bivalent vaccine (Cervarix) – post-hoc RCT analyses

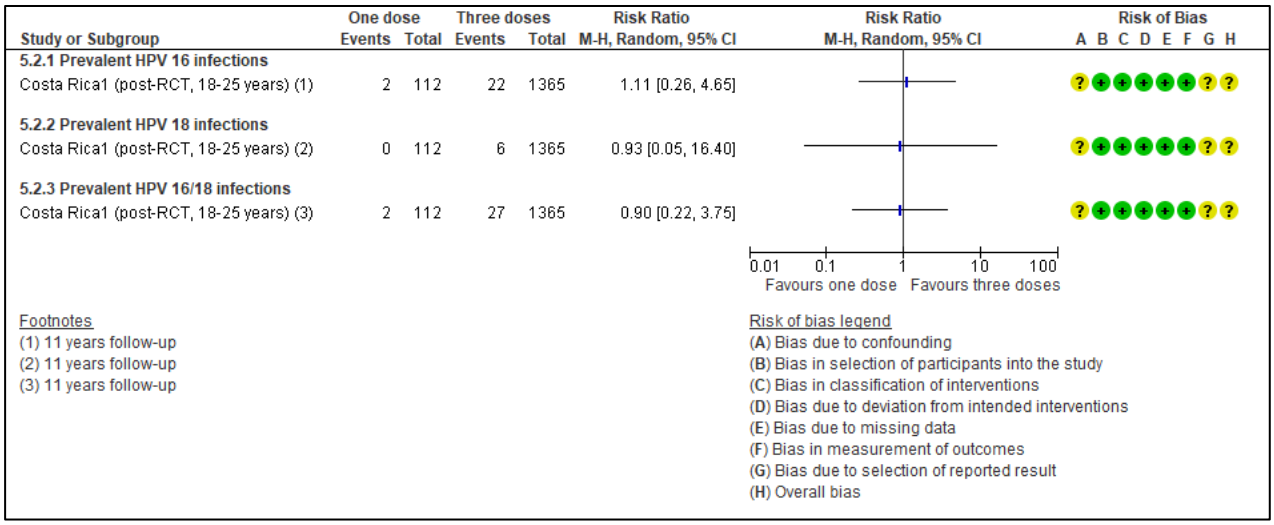


Figure 3.7 Prevalent HPV infections following bivalent vaccine (Cervarix) – observational studies, unadjusted data

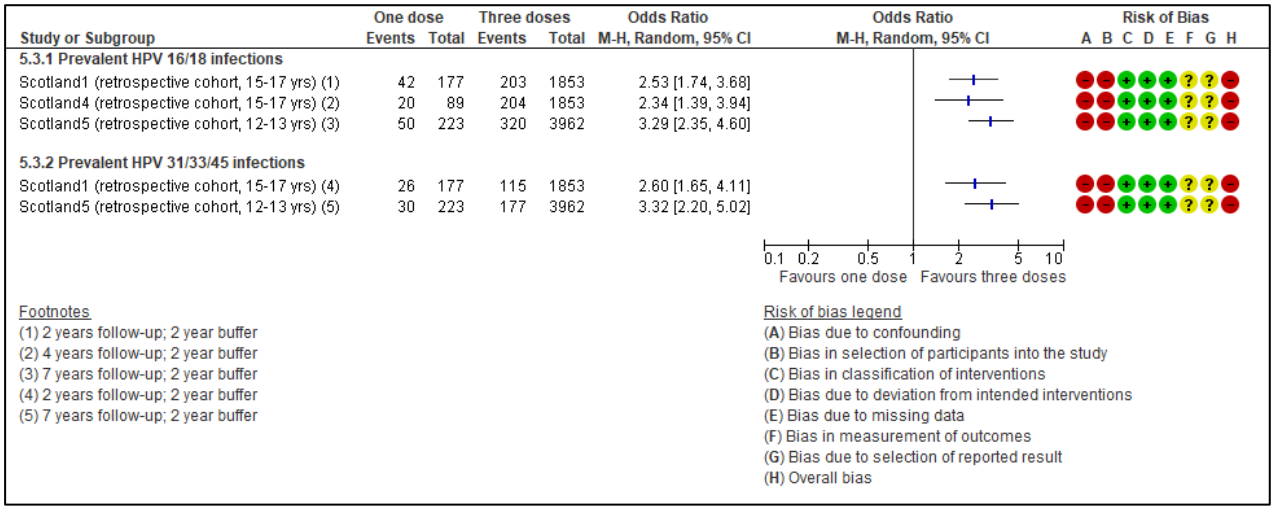


Figure 3.8 Incident HPV infections following bivalent vaccine (Cervarix) - post-hoc RCT analyses

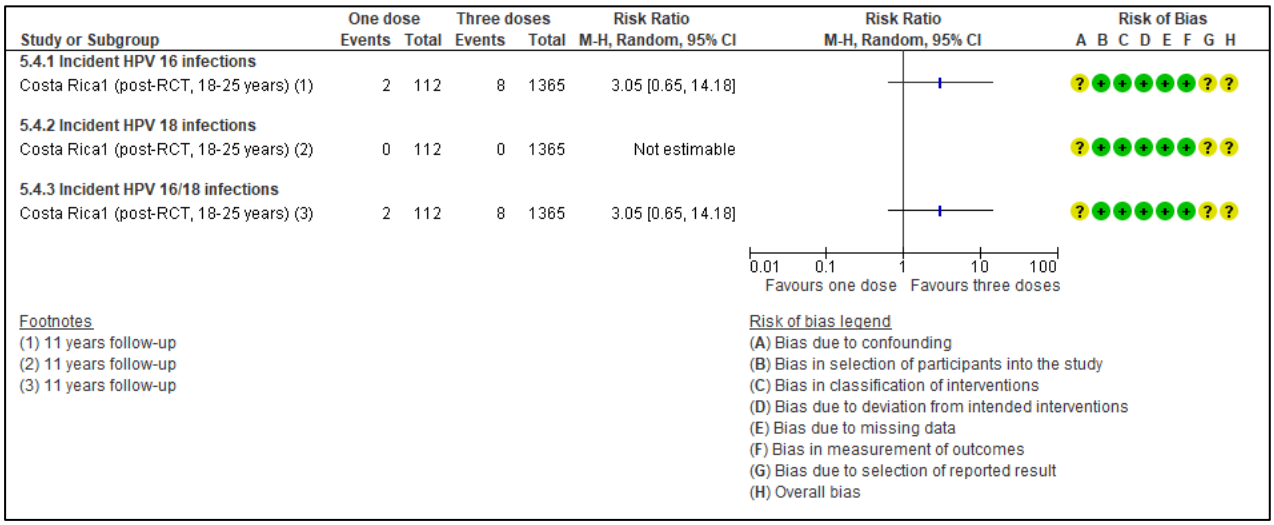


Figure 3.9 Incident HPV infections following quadrivalent vaccine (Gardasil) - post-hoc RCT analyses

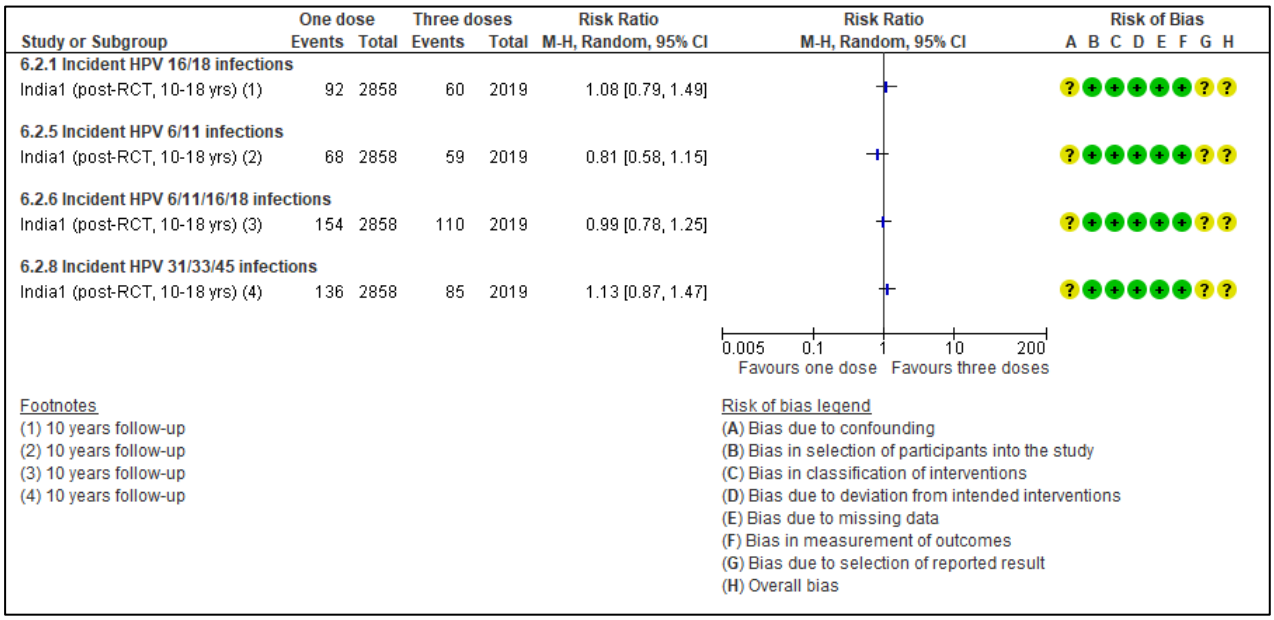
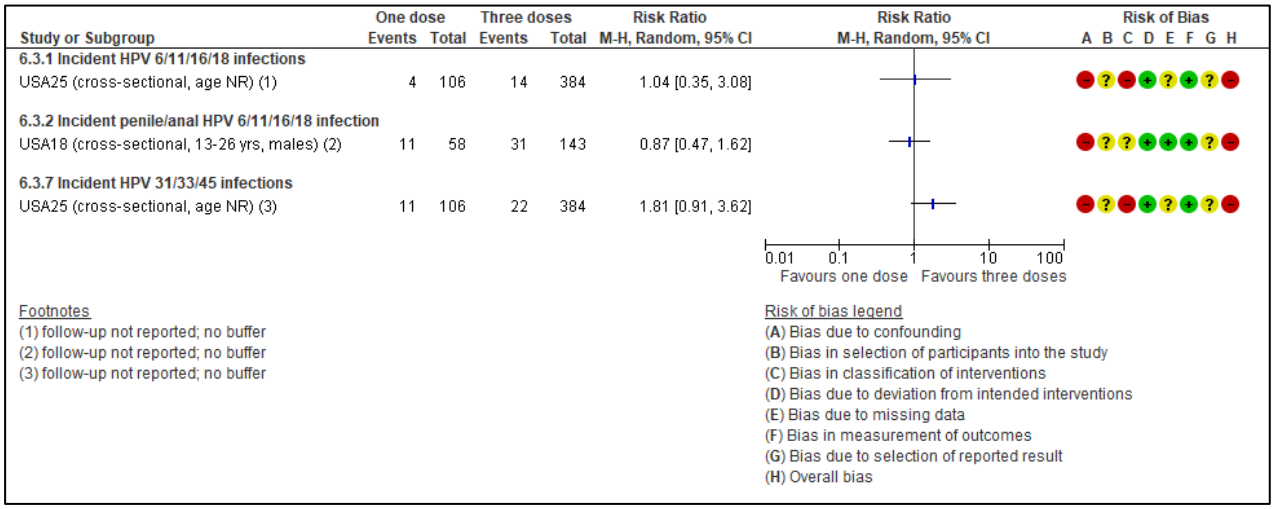


Figure 3.10 Incident HPV infections following quadrivalent vaccine (Gardasil) – observational studies, unadjusted data



Clinical outcomes – genital warts

There were 9 observational studies that reported unadjusted data for one dose compared with three doses quadrivalent (Gardasil) vaccine on genital warts (Figure 3.11). The studies were not pooled due to reporting different types of estimates (i.e. VE, HR, RR, IRR, IRD) and potential overlapping populations between the Denmark, Spain, and USA studies. Most studies were at serious risk of bias due to confounding and the results were inconsistent regarding the effect of one dose, although most favoured three doses at up to 7 years follow-up. Buffer periods ranged from no buffer to 12 months.

Three studies reported effect estimates adjusted for confounding across different age groups (Table 3.1). When a sensitivity analysis was applied, including only studies with adjusted estimates calculated after a 12-month buffer period, two studies remained (Sweden1, USA2). The Sweden1 study reported adjusted incidence rate ratios (IRR) of 0.60 (95%CI 0.41 to 0.86) for those vaccinated between 10-19 years (10-16 years IRR 0.78 (95%CI 0.45 to 1.37); 17-19 years IRR 0.49 (95%CI 0.30 to 0.81). The USA2 study reported a propensity score weighted HR of 0.63 (95%CI 0.37 to 1.09) following a 12-month buffer.

Figure 3.11 Genital warts following quadrivalent vaccine (Gardasil) – observational studies, unadjusted data

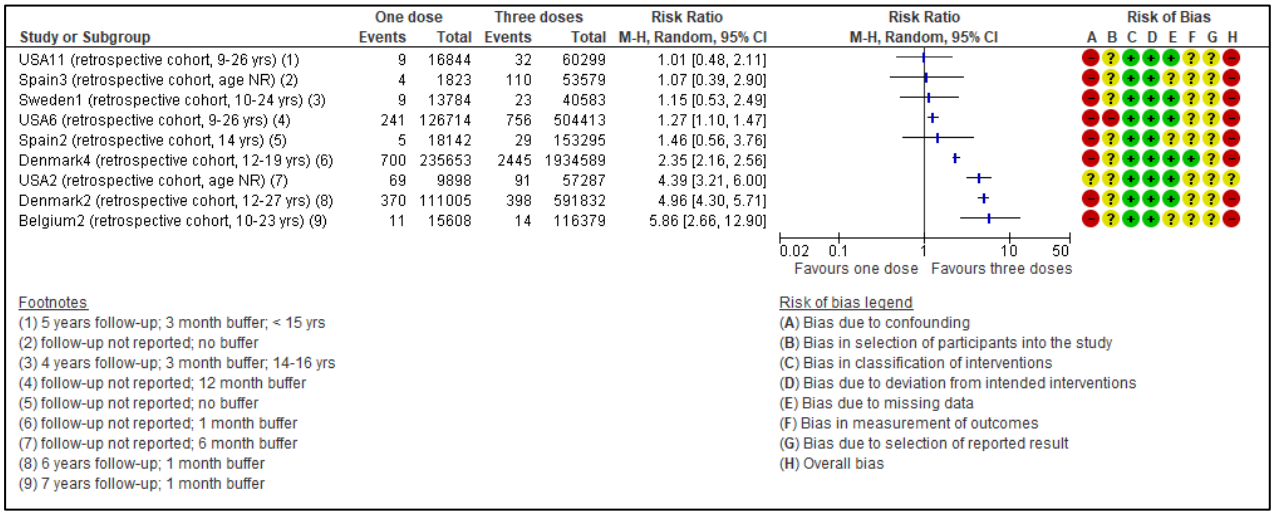


Table 3.1 Adjusted estimates of effect for genital warts comparing one dose quadrivalent (Gardasil) vaccine with three doses

Study	Age at vaccination	Buffer period	Adjusted estimate (95% CI) *
Denmark4	12-14 years	1 month	**IRR 0.56 (0.43 to 0.73)**
Denmark4	15-16 years	1 month	**IRR 0.53 (0.41 to 0.70)**
Denmark4	17-18 years	1 month	**IRR 0.51 (0.41 to 0.70)**
Denmark4	> 19 years	1 month	**IRR 0.56 (0.50 to 0.62)**
Sweden1	10-19 years	3 months	**IRR 0.37 (0.28 to 0.48)**
Sweden1	10-16 years	3 months	**IRR 0.57 (0.35 to 0.94)**
Sweden1	17-19 years	3 months	**IRR 0.32 (0.23 to 0.45)**
USA2	All ages	6 months	**HR 0.29 (0.20 to 0.42)**
USA2	All ages	12 months	HR 0.63 (0.37 to 1.09)
Sweden1	10-19 years	12 months	**IRR 0.60 (0.41 to 0.86)**
Sweden1	10-16 years	12 months	IRR 0.78 (0.45 to 1.37)
Sweden1	17-19 years	12 months	**IRR 0.49 (0.30 to 0.81)**

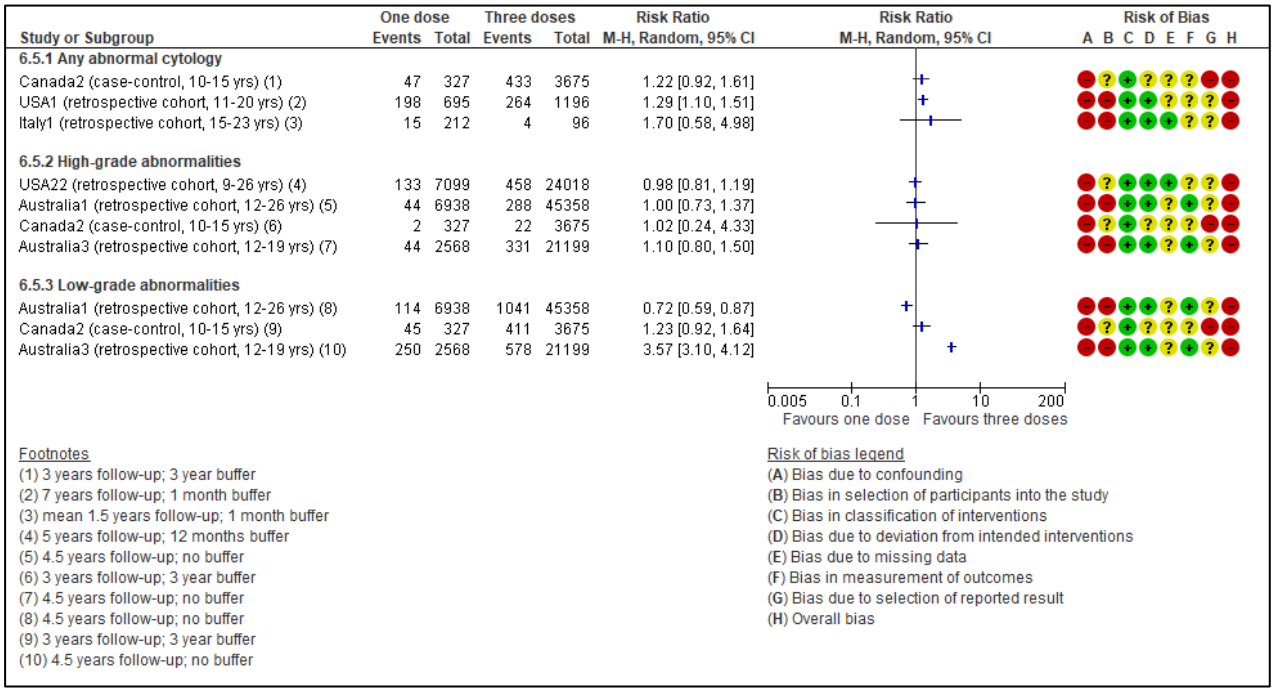
* Estimates in bold indicate reduced risk of genital warts after three doses compared with one dose. HR = hazard ratio; IRR = incidence rate ratio.

Clinical outcomes – cytological outcomes

Six observational studies (Australia1, Australia3, Canada2, Italy1, USA1, USA22) reported the effect of one dose compared with three doses quadrivalent (Gardasil) vaccine on abnormal cervical cytology at up to 7 years follow-up. All studies were at serious risk of bias due to confounding and results from unadjusted analyses were inconsistent (Figure 3.12). Buffer periods ranged from no buffer to 3 years.

No studies reported estimates adjusted for confounding between the one dose and three dose groups.

Figure 3.12 Abnormal cytology following quadrivalent vaccine (Gardasil) – observational studies, unadjusted data



Clinical outcomes – histological outcomes

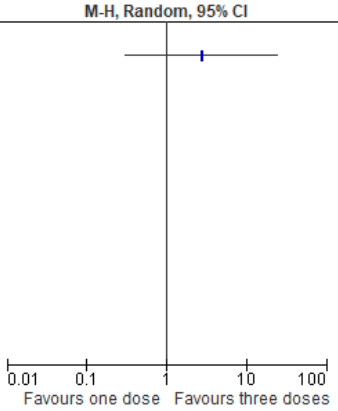
One post-hoc analysis of an RCT and ten observational studies reported on histological outcomes, such as cervical intraepithelial neoplasia (CIN) or invasive cancer.

The post-hoc RCT analysis (India1) reported no cases of CIN grade 2 or higher and very few cases of CIN grade 1 in both one-dose and three-dose groups after 10-year follow-up (Figure 3.13). Unadjusted observational data were inconsistent and showed either little or no difference or an effect favouring three doses for CIN 1, 2, 3, and 3+; all studies were at serious risk of bias (Figures 3.14 and 3.15).

There were three studies that reported on CIN following one dose of quadrivalent (Gardasil) vaccine compared with three doses and reported estimates of effect adjusted for confounding (Table 3.2). When a sensitivity analysis was applied, the only study with adjusted estimates calculated after a 12-month buffer period was USA21 for CIN2+. The adjusted odds ratio was 0.61 (95%CI 0.38 to 0.99), indicating lower odds of CIN2+ with three doses.

Figure 3.13 CIN (and invasive cancer) following quadrivalent vaccine (Gardasil) – post-hoc RCT analyses

Study or Subgroup	One dose Events	Total	Three doses Events	Total	Risk Ratio M-H, Random, 95% CI
6.5.1 CIN1					
India1 (post-RCT, 10-18 years) (1)	4	1511	1	1037	2.75 [0.31, 24.53]
6.5.2 CIN2					
India1 (post-RCT, 10-18 years) (2)	0	1511	0	1037	Not estimable
6.5.3 CIN3					
India1 (post-RCT, 10-18 years) (3)	0	1511	0	1037	Not estimable
6.5.4 Invasive cancer					
India1 (post-RCT, 10-18 years) (4)	0	1511	0	1037	Not estimable
6.5.5 Invasive cancer associated with HPV 16/18					
India1 (post-RCT, 10-18 years) (5)	0	1511	0	1037	Not estimable

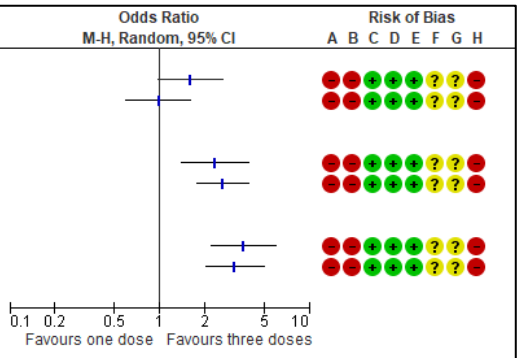


Footnotes
(1) 10 years follow-up
(2) 10 years follow-up
(3) 10 years follow-up
(4) 10 years follow-up
(5) 10 years follow-up

Risk of bias legend
(A) Bias due to confounding
(B) Bias in selection of participants into the study
(C) Bias in classification of interventions
(D) Bias due to deviation from intended interventions
(E) Bias due to missing data
(F) Bias in measurement of outcomes
(G) Bias due to selection of reported result
(H) Overall bias

Figure 3.14 CIN following bivalent vaccine (Cervarix) – observational studies, unadjusted data

Study or Subgroup	One dose Events	Total	Three doses Events	Total	Odds Ratio M-H, Random, 95% CI
5.5.1 CIN1					
Scotland2 (retrospective cohort, 15-17 yrs) (1)	17	1318	208	25895	1.61 [0.98, 2.65]
Scotland3 (retrospective cohort, 12-13 yrs) (2)	16	2152	402	53325	0.99 [0.60, 1.63]
5.5.2 CIN2					
Scotland2 (retrospective cohort, 15-17 yrs) (3)	16	1318	135	25895	2.34 [1.39, 3.95]
Scotland3 (retrospective cohort, 12-13 yrs) (4)	27	2153	255	53247	2.64 [1.77, 3.93]
5.5.3 CIN3					
Scotland2 (retrospective cohort, 15-17 yrs) (5)	19	1318	103	25895	3.66 [2.24, 5.99]
Scotland3 (retrospective cohort, 12-13 yrs) (6)	22	2148	172	53186	3.19 [2.04, 4.98]



Footnotes
(1) 13 years follow-up; 2 year buffer
(2) 2 years follow-up; 2 year buffer
(3) 13 years follow-up; 2 year buffer
(4) 2 years follow-up; 2 year buffer
(5) 13 years follow-up; 2 year buffer
(6) 2 years follow-up; 2 year buffer

Risk of bias legend
(A) Bias due to confounding
(B) Bias in selection of participants into the study
(C) Bias in classification of interventions
(D) Bias due to deviation from intended interventions
(E) Bias due to missing data
(F) Bias in measurement of outcomes
(G) Bias due to selection of reported result
(H) Overall bias

Figure 3.15 CIN following quadrivalent vaccine (Gardasil) – observational studies, unadjusted data

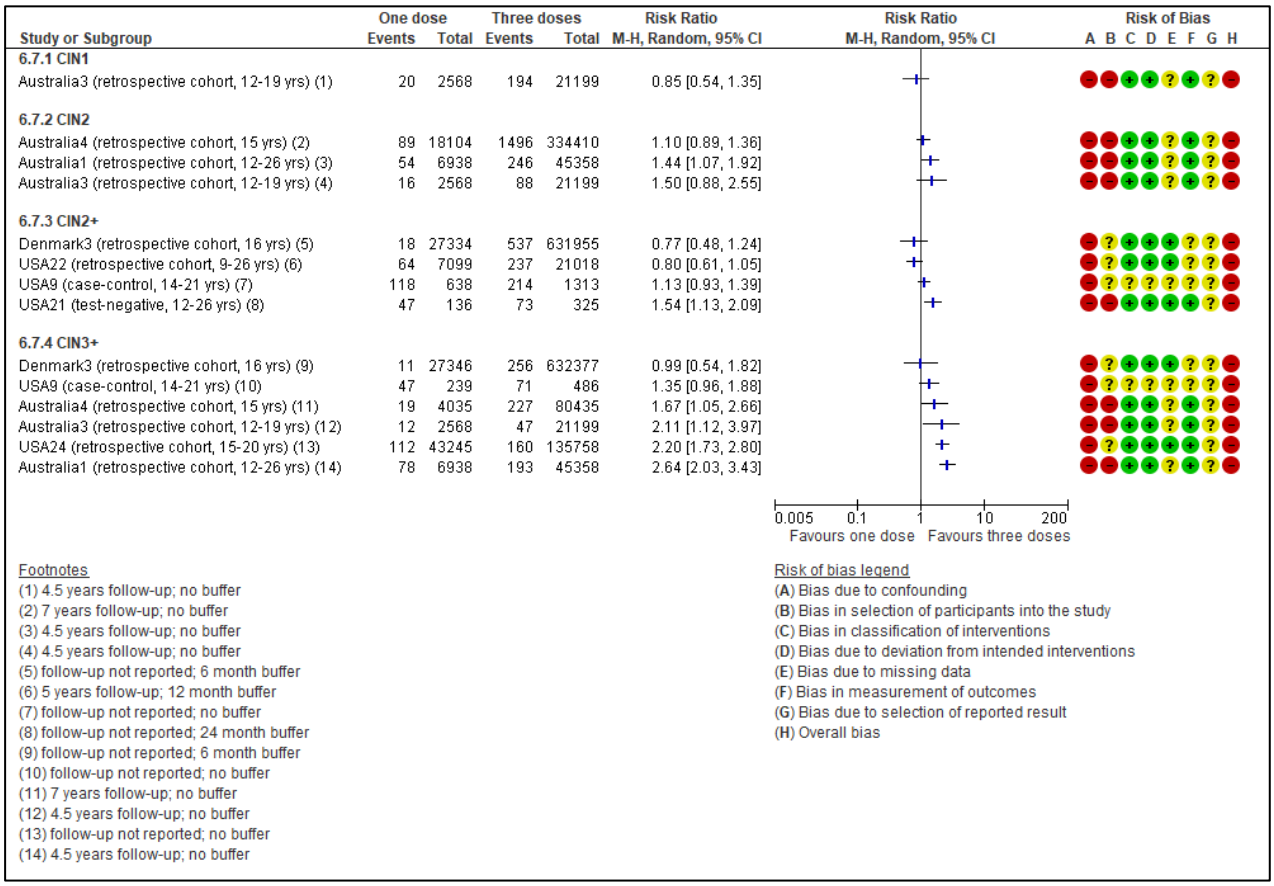


Table 3.2 Adjusted estimates of effect for CIN comparing one dose quadrivalent (Gardasil) vaccine with three doses

Outcome	Study	Age at vaccination	Buffer period	Adjusted estimate (95% CI)
CIN2	Australia4	< 15 years	No buffer	HR 0.91 (0.74 to 1.13)
CIN2+	Denmark3	all ages	6 months	IRR 0.99 (0.64 to 1.53)
	USA21	12-26 years	24 months	**OR 0.61 (0.38 to 0.99)**
CIN3+	Denmark3	All ages	6 months	**IRR 0.95 (0.60 to 1.51)**
	Australia4	< 15 years	No buffer	RR 0.66 (0.41 to 1.05)

* Estimates in bold indicate reduced risk of CIN after one dose. ** estimates indicate increased risk of CIN after one dose. HR = hazard ratio; OR = odds ratio; RR = relative risk.

4. Effectiveness and immunogenicity of one dose of HPV vaccine in males

Six studies on one dose HPV vaccination included males (Canada4, Canada6, USA11, USA12, USA17, USA18). Only two of these studies reported results separately for males only (USA12, USA18).

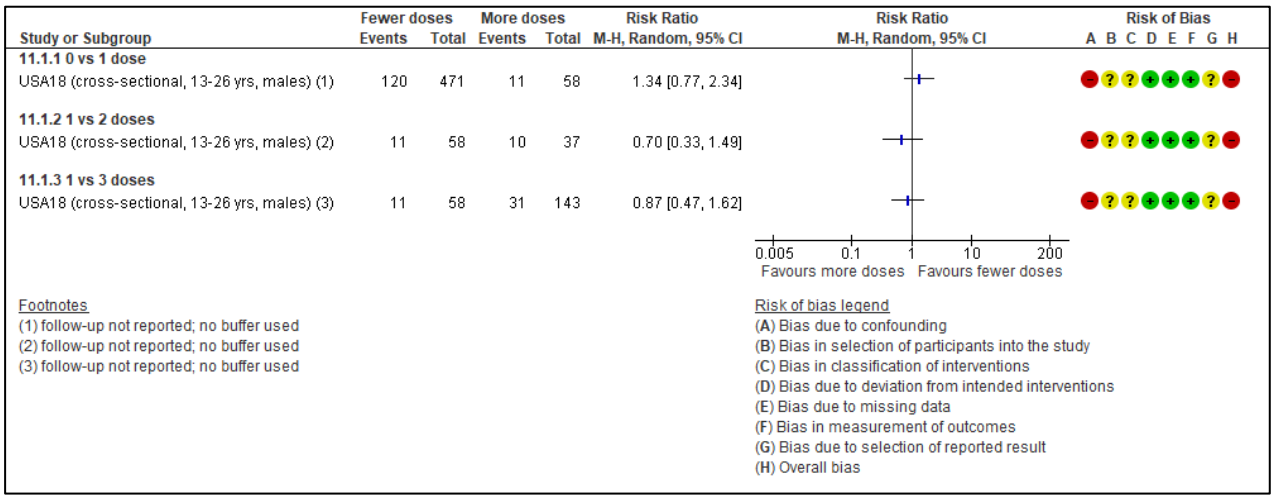
USA12 and USA18 were retrospective observational studies reporting on young men (13 to 26 years of age) attending sexual health clinics and provided unadjusted data on HPV infections for those vaccinated with one dose quadrivalent (Gardasil) or nonavalent (Gardasil9) HPV vaccine. The studies are likely to have some population overlap because recruitment occurred from sites and dates that overlapped.

USA12 did not detect a difference in anogenital (penile, anal, perianal) HPV 6/11/16/18 infections between one dose compared with three doses quadrivalent (Gardasil) vaccine (OR 0.99, 95% CI 0.33 to 2.96). Data were not adjusted for confounding, and it was not reported how many participants received one dose; 49 participants received three doses and 236 males were included in total.

USA18 also reported on HPV 6/11/16/18 anogenital infection (penile or anal). Out of 746 young men, most received quadrivalent (Gardasil) vaccine, 12 (1.6%) received nonavalent (Gardasil9) vaccine, and 23 (3.1%) received a combination of quadrivalent (Gardasil) and nonavalent (Gardasil9) vaccine doses. Data were not adjusted for confounding and no differences between one dose and no vaccination or between one dose and two or three doses were reported (Figure 4.1).

These results should be interpreted with caution due to risk of bias due to confounding, selection bias from a population attending sexual health clinics, self-reported vaccination status, mixed duration of follow-up, and small sample size.

Figure 4.1. Incident penile and anal HPV 6/11/16/18 infections in 13–16-year-old males vaccinated at mean age 15-16 years, unadjusted data from retrospective cohort



5. Effectiveness and immunogenicity of one dose of HPV vaccine in people living with HIV

One observational study (USA17) included 451 perinatally HIV infected (HIV+) and 227 perinatally HIV exposed but uninfected (HEU) young females and males (mean 16.7 years) that had received one, two, or three quadrivalent (Gardasil) vaccine doses at around the age of 13 years. A sexually active unvaccinated cohort was also included.

Immunogenicity outcomes

Geometric mean titres (GMTs) for HPV 6, 11, 16, and 18 were reported separately among HIV infected males and females and HIV exposed uninfected males and females. Within each cohort (HEU or HIV+), GMTs were similar whether they received 1, 2, or 3 doses. Compared with HEU, HIV+ had lower GMTs regardless of dose, see Table 5.1.

Table 5.1. GMTs and titre fold changes in HIV infected and HIV exposed uninfected females and males

Doses		1 dose		2 doses		3 doses	
Population		HIV+	HEU	HIV+	HEU	HIV+	HEU
N		88	80	28	12	82	11
HPV 6	GMT*	123	152	108	227	134	300
	Fold change among HIV+**	2 vs 1: 1.38 (−1.23 to 2.34); 3 or more doses vs 1: −1.06 (−1.72 to 1.52)					
HPV 11	GMT*	144	262	124	399	152	393
	Fold change among HIV+**	2 vs 1: 1.64 (−1.14 to 3.07); 3 or more vs 1: −1.00 (−1.77 to 1.76)					
HPV 16	GMT*	585	1428	401	1888	584	1814
	Fold change among HIV+**	2 vs 1: 1.55 (−1.30 to 3.15); 3 or more vs 1: −1.06 (−2.01 to 1.79)					
HPV 18	GMT*	70	159	63	245	71	170
	Fold change among HIV+**	2 vs 1: 1.52 (−1.21 to 2.80); 3 or more vs 1: −1.24 (−2.16 to 1.41)					

*Participants who received their first vaccine dose before their 15th birthday, adjusted for time since last vaccine dose.
**Multivariable Models for Fold-changes in Antibody Titre (An effect of 1.00 represents no influence of the independent variable on antibody titre in the raw scale, an effect of 2 represents a doubling in titre (i.e., 200 to 400 or 1000 to 2000), and an effect of −2 is a halving of titre (i.e., 100 to 50).
HEU = HIV exposed uninfected

Seropositivity for HPV 6, 11, 16, and 18 were reported separately among HIV infected males and females and HIV exposed uninfected males and females (Table 5.2). A larger proportion of both HIV+ and HEU people seroconverted for all four HPV types after one dose compared with the unvaccinated group. The study did not detect a difference between one and two doses or between one and three doses. A larger proportion of HEU people compared with HIV+ people that had received one dose seroconverted for all four HPV types.

These results should be interpreted with caution due to risk of bias due to confounding, mixed duration of follow-up with varying buffer periods (from 20 days, mean 2.9 (SD 1.5) years), and small sample sizes.

Table 5.2. HPV 6, 11, 16, and 18 seropositivity in HIV infected and HIV exposed uninfected females and males

	Population	Total N	HPV 6 seropositive	HPV 11 seropositive	HPV 16 seropositive	HPV 18 seropositive
Unvaccinated	HIV+	32	4 (12.5%)	3 (9.4%)	9 (28.1%)	4 (12.5%)
	HEU	33	9 (27.3%)	9 (27.3%)	14 (42.4%)	13 (39.4%)
1 dose	HIV+	154	124 (80.5%)	120 (77.9%)	149 (96.8%)	129 (83.8%)
	HEU	91	86 (94.5%)	86 (94.5%)	91 (100%)	87 (95.6%)
2 doses	HIV+	34	30 (88.3%)	30 (88.3%)	33 (97.1%)	27 (79.4%)
	HEU	13	13 (100%)	13 (100%)	13 (100%)	13 (100%)
3 doses	HIV+	90	73 (81.1%)	70 (77.8%)	88 (97.8%)	79 (87.8%)
	HEU	11	11 (100%)	11 (100%)	11 (100%)	11 (100%)

HEU = HIV exposed uninfected

Clinical outcomes - abnormal cytology

Abnormal cytology was defined as atypical squamous cells of undetermined significance (ASCUS) or worse, collected from the annual medical record. For one-dose recipients, this outcome was reported only for HIV infected females. A difference between 1 and 2 or 1 and 3 doses received prior to sexual debut was not detected but the results should be interpreted with caution due to risk of bias due to confounding, a small sample size and wide 95% CIs, see Table 5.3.

Table 5.3. Abnormal cytology in HIV infected females

Doses prior to sexual debut	Cases/PY	IR (95% CI) per 100 PY	IRR (95% CI) 1 dose vs. 3 doses
1 dose	8/41.3	19.4 (10.3-36.5)	1.19 (0.51-2.78)
2 doses	7/35.0	20.0 (8.8-45.6)	
3 doses	8/49.3	16.2 (9.3-28.5)	

CI = confidence interval; IR = incidence rate; IRR = incidence rate ratio; PY = person-years

6. Efficacy and immunogenicity of mixed HPV vaccine doses (interchangeability)

One RCT (Canada4), one single arm trial (Canada7), and one observational cohort (Fiji1) reported on the efficacy or immunogenicity of a two-dose HPV vaccine schedule with more than one type of vaccine (interchangeability). In addition, two post-hoc studies were identified that pooled results from Canada4 and Canada7 (Sauvageau 2020, Gilca 2019).

Only one study reported comparative data; Canada4 randomised 371 9- to 10-year-old girls and boys into three groups: two doses of nonavalent (Gardasil9) vaccine, one dose bivalent (Cervarix) and one dose nonavalent (Gardasil9) vaccine, or one dose nonavalent (Gardasil9) and one dose bivalent (Cervarix) vaccine, all with a 6-month interval between doses. One month after the second dose all participants seroconverted for HPV 6, 11, 16, and 18. The ratio of GMTs was in favour of the homologous schedule (i.e. two doses of nonvalent (Gardasil9) vaccine) for all HPV types, except for HPV 16 and 18, which favoured the heterologous schedules (Figure 6.1).

Canada7 was a single arm trial that enrolled 31 13- to 18-year-old girls that had received one dose quadrivalent (Gardasil) vaccine 3-8 years earlier to receive a dose of nonavalent (Gardasil9) vaccine. One month after the second dose all girls had seroconverted for the nine vaccine HPV types and a GMT fold-increase of 36.1 to 89.1 was reported.

The post-hoc analysis of the Canad4 and Canada7 studies (Canada4/7) included an additional group of girls that received one dose of nonavalent (Gardasil9) vaccine. This group was compared to the groups that had received either bivalent (Cervarix) or quadrivalent (Gardasil) vaccine. One month after nonavalent (Gardasil9) dose administration, all subjects were seropositive to HPV 31/33/45/52 and 58. Subjects who had previously received bivalent (Cervarix) or quadrivalent (Gardasil) vaccine had significantly higher GMTs than naive subjects for HPV31/33/45/52 types but not for HPV58 (Figure 6.2). GMTs to HPV31/33/45/52 and 58 were not significantly different between subjects who received a bivalent (Cervarix) or quadrivalent (Gardasil) vaccine dose prior to nonavalent (Gardasil9) dose administration.

Fiji1 was a prospective cohort study that enrolled 200 15–19-year-old girls that had received 1, 2, or 3 doses quadrivalent (Gardasil) vaccine six years earlier. GMTs for girls that had received one dose were 5- to 30-fold higher than unvaccinated girls, but lower than two- and three-dose recipients. They all received one bivalent (Cervarix) vaccine dose. One month later, GMTs for HPV 16/18 were not statistically different between girls who had received 1, 2, or 3 doses of the quadrivalent (Gardasil) vaccine six years earlier.

Figure 6.1. Ratio of GMTs following heterologous schedule (nonavalent + bivalent or bivalent + nonavalent) one month after the second dose compared with a homologous schedule (nonavalent + nonavalent)

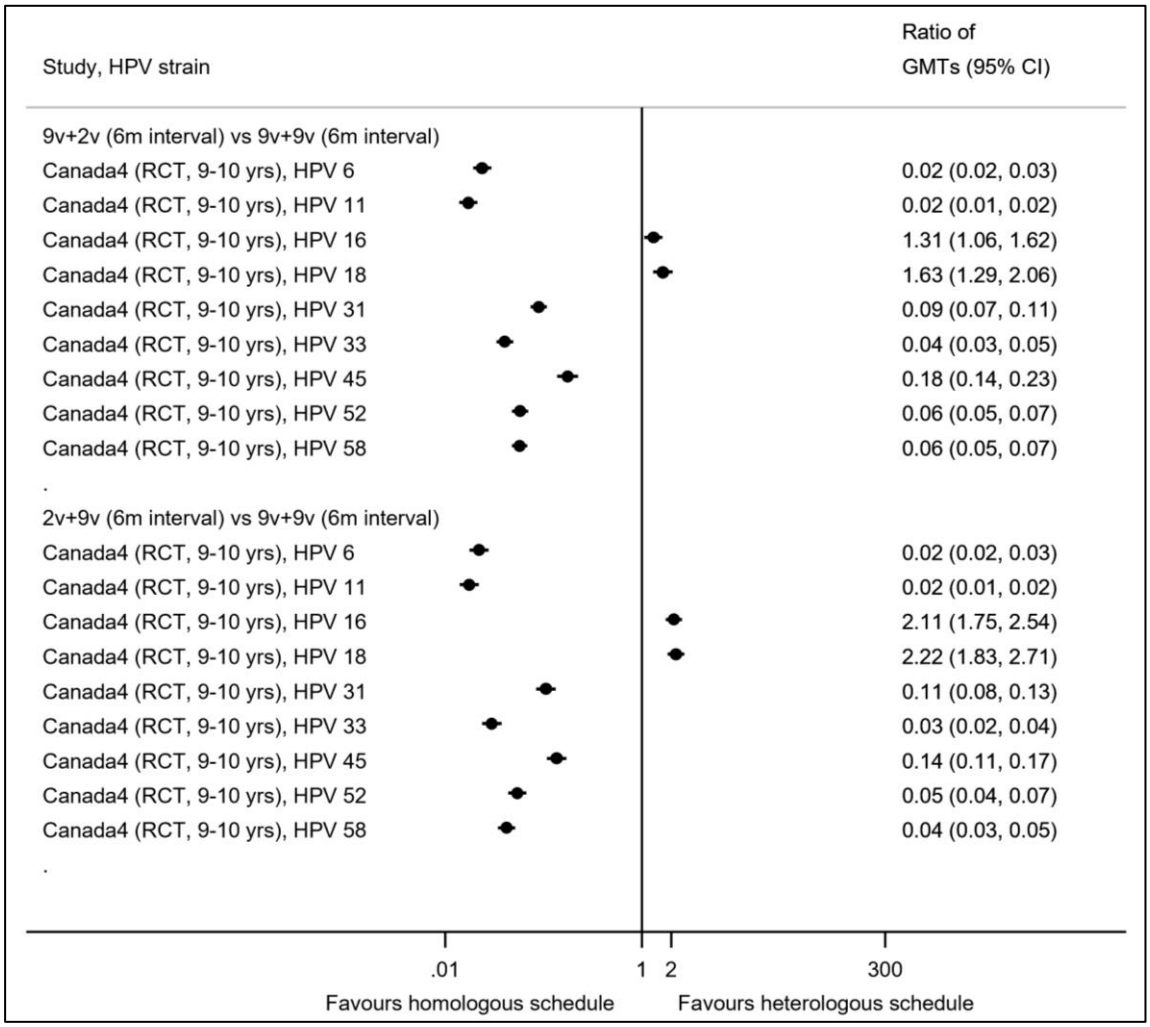
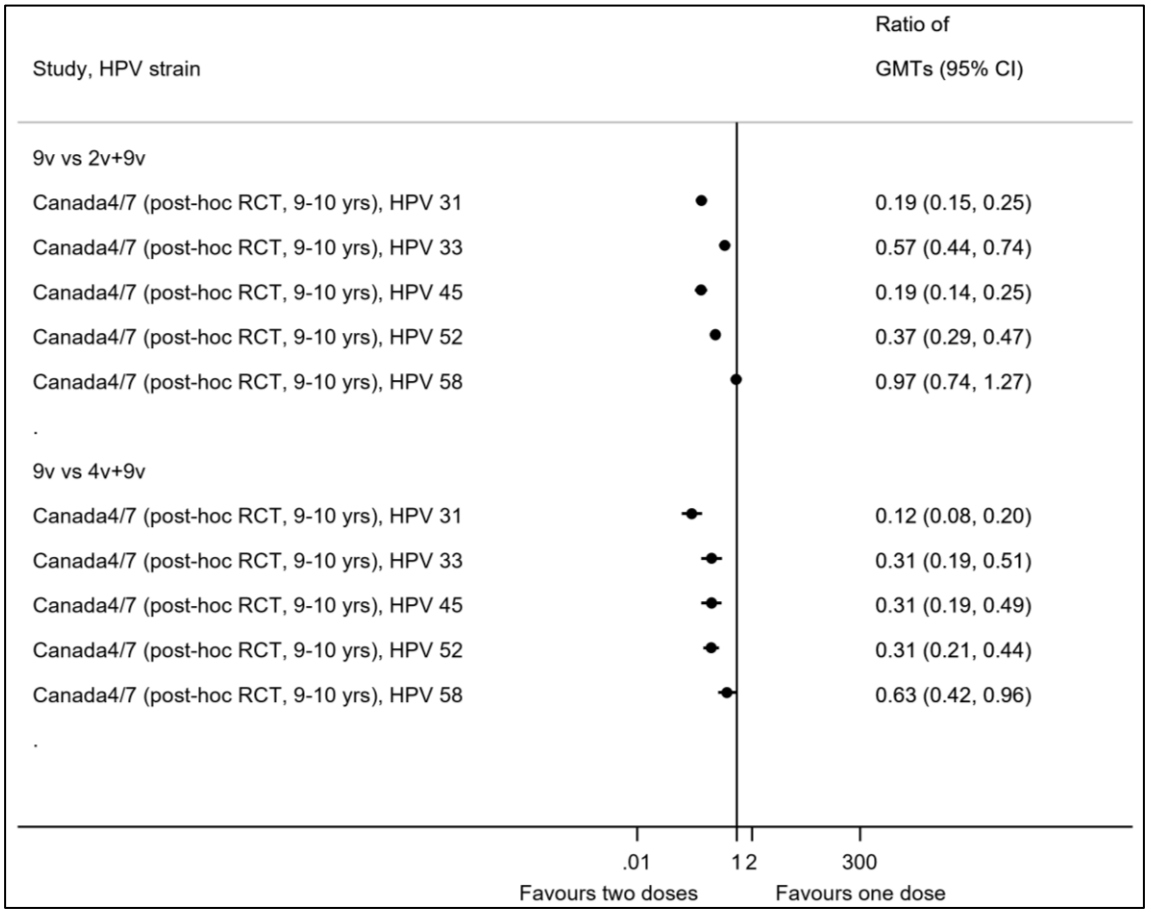


Figure 6.2. Ratio of GMTs following one dose nonavalent (Gardasil9) vaccine or two doses on a heterologous schedule (nonvalent + bivalent or bivalent + nonavalent)



References

Basu P, Malvi SG, Joshi S, Bhatla N, Muwonge R, Lucas E, et al. Vaccine efficacy against persistent human papillomavirus (HPV) 16/18 infection at 10 years after one, two, and three doses of quadrivalent HPV vaccine in girls in India: a multicentre, prospective, cohort study. Lancet Oncol. 2021 Nov;22(11):1518-1529.

COVID NMA. COVID-19 vaccine effectiveness on variants of concern: Observational studies. 2021. Available from: https://covid-nma.com/vaccines/os_vaccines/

Drolet M, Bénard E, Pérez N, Brisson M. Population-level impact and herd effects following the introduction of human papillomavirus vaccination programmes: updated systematic review and meta-analysis. Lancet. 2019;394(10197): 497–509.

Markowitz LE, Drolet M, Perez N, Jit M, Brisson M. Human papillomavirus vaccine effectiveness by number of doses: systematic review of data from national immunization programs. Vaccine 2018;36(32 Pt A):4806-15.

Single-Dose HPV Vaccine Evaluation Consortium. Review of the current published evidence on single-dose HPV vaccination. 3rd Edition, 2020. Availabe from: https://path.azureedge.net/media/documents/SDHPV_Evidence_Review_Edition_3_Final_Fin3p80.pdf

Sterne JAC, Hernán MA, Reeves BC, Savović J, Berkman ND, Viswanathan M, et al. ROBINS-I: a tool for assessing risk of bias in non-randomized studies of interventions. BMJ 2016; 355; i4919.

Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ 2019; 366: l4898.

Suttorp MM, Siegerink B, Jager KJ, Zoccali C, Dekker FW. Graphical presentation of confounding in directed acyclic graphs. Nephrol Dial Transplant. 2015 Sep;30(9):1418-23.

Appendix 1. Search strategies

HPV Vaccines - One Dose SR Update (January 7, 2022):
Multidatabase Search Strategy for MEDLINE, Embase & Cochrane CENTRAL (all via Ovid)

1. (HPV or (human adj (papilloma virus* or papillomavirus*))).tw,kf.
2. exp Papillomaviridae/
3. exp Papillomavirus Infections/
4. or/1-3
5. (vaccin* or immuni* or inoculat* or innoculat*).tw,kf.
6. 4 and 5
7. (cervarix or gardasil).tw,kf.
8. exp Papillomavirus Vaccines/
9. or/6-8
10. limit 9 to yr="2019 -Current"
11. (201903* or 201904* or 201905* or 201906* or 201907* or 201908* or 201909* or 201910* or 201911* or 201912* or 2020* or 2021*).dt,ez.
12. 9 and 11
13. 10 or 12
14. exp animals/ not humans/
15. 13 not 14
16. (comment or editorial).pt.
17. 15 not 16
18. papillomavirus infection/ or papilloma virus infections.mp. or Papilloma virus/
19. "human papillomavirus infection*".mp.
20. 18 or 19
21. (vaccin* or immuni*).ti. or (vaccin* or immuni*).ab.
22. 20 and 21
23. HPV vaccin*.ti. or HPV vaccin*.ab.
24. (Gardasil or cervarix).ti. or (Gardasil or cervarix).ab.
25. 22 or 23 or 24
26. exp animal/ not exp human/
27. 25 not 26
28. limit 27 to yr="2019 -Current"
29. (HPV or (human adj (papilloma virus* or papillomavirus*))).mp.
30. exp Papillomaviridae/
31. exp Papillomavirus Infections/
32. or/29-31
33. (vaccin* or immuni* or inoculat* or innoculat*).mp.
34. 32 and 33
35. (cervarix or gardasil).mp.

36. exp Papillomavirus Vaccines/
37. or/34-36
38. limit 37 to yr="2019 -Current"
39. 17 use medall
40. 28 use emczd
41. 38 use cctr
42. 39 or 40 or 41
43. limit 42 to yr="1946 - 2019"
44. limit 42 to yr="2020 -Current"
45. remove duplicates from 43
46. remove duplicates from 44
47. 45 or 46

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.
Canada4	Gilca V, Sauvageau C, Panicker G, De Serres G, Ouakki M, Unger ER. Immunogenicity and safety of a mixed vaccination schedule with one dose of nonavalent and one dose of bivalent HPV vaccine versus two doses of nonavalent vaccine - A randomized clinical trial. Vaccine. 2018 Oct 9. Hum Vaccin Immunother. 2019;15(2):503–507.
Canada4/7	Gilca V, Sauvageau C, Panicker G, De Serres G, Schiller J, Ouakki M, et al. Long intervals between two doses of HPV vaccines and magnitude of the immune response: a post hoc analysis of two clinical trials. Hum Vaccin Immunother. 2019;15(7-8):1980-1985.
	Sauvageau C, Panicker G, Unger ER, et al. Priming effect of bivalent and quadrivalent vaccine for HPV 31/33/45/52: an exploratory analysis from two clinical trials. Human vaccines & immunotherapeutics. 2020;16(3):590–594.
Canada5	Donken R, Albert A, Racey CS, Smith L, Van Niekerk D, Spinelli J, et al. Effectiveness of the quadrivalent HPV vaccine against HSIL and CIN: A data-linkage study. Sexually Transmitted Infections. 2019. 95(Suppl 1):A349-A350
Canada6	Wissing MD, Burchell AN, El-Zein M, Tellier P-P, Coutlée F, Franco EL. Vaccination of Young Women Decreases Human Papillomavirus Transmission in Heterosexual Couples: Findings from the HITCH Cohort Study. Cancer Epidemiol Biomarkers Prev. 2019 Nov;28(11):1825-1834.
Canada7	Gilca V, Sauvageau C, Panicker G, De Serres G, Ouakki M, Unger ER. Antibody persistence after a single dose of quadrivalent HPV vaccine and the effect of a dose of nonavalent vaccine given 3-8 years later – an exploratory study. Hum Vaccines Immunother. 2018 Sept 25:1–5.
China1	Hu Y-M, Guo M, Li C-G, Chu K, He W-G, Zhang J, et al. Immunogenicity noninferiority study of 2 doses and 3 doses of an Escherichia coli-produced HPV bivalent vaccine in girls vs. 3 doses in young women. Sci China Life Sci. 2020;63(4):582-591.

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.
	Kreimer AR, Sampson JN, Porras C, et al. Evaluation of durability of a single dose of the bivalent HPV vaccine: the CVT trial. Journal of the National Cancer Institute. 2020;112(10):1038–1046. https://doi.org/10.1093/jnci/djaa011.
	Tsang SH, Sampson JN, Schussler J, et al. Durability of cross-protection by different schedules of the bivalent HPV vaccine: the CVT trial. Journal of the National Cancer Institute. 2020;112(10):1030–1037. https://doi.org/10.1093/jnci/djaa010.
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.
Denmark4	Baandrup L, Dehlendorff C, Kjaer SK. One-Dose Human Papillomavirus Vaccination and the Risk of Genital Warts: A Danish Nationwide Population-based Study. Clin Infect Dis. 2021 Nov 2;73(9):e3220-e3226
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.
	Toh ZQ, Kosasih J, Russell FM, Reyburn R, Fong J, Tuivaga E, et al. Selective Persistence of HPV Cross-Neutralising Antibodies following Reduced-Dose HPV Vaccine Schedules. Vaccines (Basel). 2019 Nov 28;7(4):200
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.

	Basu P, Malvi SG, Joshi S, Bhatla N, Muwonge R, Lucas E, et al. Vaccine efficacy against persistent human papillomavirus (HPV) 16/18 infection at 10 years after one, two, and three doses of quadrivalent HPV vaccine in girls in India: a multicentre, prospective, cohort study. Lancet Oncol. 2021 Nov;22(11):1518-1529.
Italy1	Acuti Martellucci C, Nomura S, Yoneoka D, Ueda P, Brotherton J, Canfell K, et al. Human papillomavirus vaccine effectiveness within a cervical cancer screening programme: cohort study. BJOG. 2021;128(3):532-539
Kenya1	Barnabas RV, Brown ER, Onono MA, Bukusi EA, Njoroge B, Winer RL, et al. Efficacy of single-dose HPV vaccination among young African women. ResearchSquare. 2021. doi: 10.21203/rs.3.rs-1090565/v1 [pre-print]
	Barnabas RV, Brown ER, Onono M, Bukusi EA, Njoroge B, Winer RL, et al. Single-dose HPV vaccination efficacy among adolescent girls and young women in Kenya (the KEN SHE Study): study protocol for a randomized controlled trial. Trials. 2021 Sep 27;22(1):661.
Mongolia1	Batmunkh T, Dalmau MT, Munkhsaikhan ME, et al. A single dose of quadrivalent human papillomavirus (HPV) vaccine is immunogenic and reduces HPV detection rates in young women in Mongolia, six years after vaccination. Vaccine. 2020;38(27):4316–4324. https://doi.org/10.1016/j.vaccine.2020.04.041.
Netherlands1	Pasmans H, Schurink-Van't Klooster TM, Bogaard MJM, et al. Long-term HPV-specific immune response after one versus two and three doses of bivalent HPV vaccination in Dutch girls. Vaccine. 2019;37(49):7280–7288. https://doi.org/10.1016/j.vaccine.2019.09.066.
New Zealand1	Innes CR, Williman JA, Simcock BJ, et al. Impact of human papillomavirus vaccination on rates of abnormal cervical cytology and histology in young New Zealand women. New Zealand Medical Journal. 2020;133(1508):72–84. https://pubmed.ncbi.nlm.nih.gov/31945044/.
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.
Spain3	Muñoz-Quiles C, López-Lacort M, Díez-Domingo J, Rodrigo-Casares V, Orrico-Sánchez A. Human papillomavirus vaccines effectiveness to prevent genital warts: A population-based study using health system integrated databases, 2009–2017. Vaccine. 2022;40(2):316-324.

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.
Tanzania1 (DoRIS)	Unpublished data received by email from Prof Deborah Watson-Jones to Dr Nicholas Henschke on 7 February, 2022.
	Baisley KJ, Whitworth HS, Changalucha J, Pinto L, Dillner J, Kapiga S, et al. A dose-reduction HPV vaccine immunobridging trial of two HPV vaccines among adolescent girls in Tanzania (the DoRIS trial) - Study protocol for a randomised controlled trial. Contemp Clin Trials. 2021. 101:106266.
Thailand1	Jiamsiri S, Rhee C, Anh HS, Poudyal N, Seo H-W, Klinsupa W, et al. A community intervention effectiveness study of single dose or two doses of bivalent HPV vaccine (CERVARIX) in female school students in Thailand. [unpublished data tables received by email from Dr Hyeon Seon Ahn to Dr Nicholas Henschke on 9 February, 2022]
	Jiamsiri S, Rhee C, Anh HS, Poudyal N, Seo H-W, Klinsupa W, et al. A community intervention effectiveness study of single dose or two doses of bivalent HPV vaccine (CERVARIX) in female school students in Thailand. [unpublished protocol under review received by email from Dr Julia Lynch to Dr Nicholas Henschke on 17 December, 2021]
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.
USA17	Moscicki AB, Karalius B, Tassiopoulos K, et al. Human papillomavirus antibody levels and quadrivalent vaccine clinical effectiveness in perinatally human immunodeficiency virus-infected and exposed, uninfected youth. Clinical Infectious Diseases. 2019;69(7):1183–1191.
USA18	Widdice LE, Bernstein DI, Franco EL, Ding L, Brown DR, Ermel AC, et al. Decline in vaccine-type human papillomavirus prevalence in young men from a Midwest metropolitan area of the United States over the six years after vaccine introduction. Vaccine. 2019;37(45):6832-6841
USA19	Covert C, Kahn J, Ding L, Franco E, Brown D, Ermel A, et al. HPV Vaccine Effectiveness with Different Dosing Schedules in a Community Setting. J Adolesc Health. 2020. 66(2 Supplement):S35-S36.
USA20	Markowitz LE, Naleway AL, Klein NP, et al. Human papillomavirus vaccine effectiveness against HPV infection: evaluation of one, two, and three doses. Journal of Infectious Diseases. 2020;221(6):910–918.
USA21	Johnson Jones ML, Gargano JW, Powell M, et al. Effectiveness of 1, 2, and 3 doses of human papillomavirus vaccine against high-grade cervical lesions positive for human papillomavirus 16 or 18. American Journal of Epidemiology. 2020;189(4):265–276.
USA22	Rodriguez AM, Zeybek B, Vaughn M, et al. Comparison of the long-term impact and clinical outcomes of fewer doses and standard doses of human papillomavirus vaccine in the United States: a database study. Cancer. 2020;126(8):1656–1667.
USA23	Abel MK, Mann AK, Sonawane K, Kapp DS, Deshmukh AA, Chan JK. Prevalence of Oral Human Papillomavirus Infection by Number of Vaccine Doses Among US Adults. JNCI Cancer Spectr. 2021; 5(6): pkab086.
USA24	Gargano JW, You M, Potter R, Alverson G, Swanson R, Saraiya M, et al. An Evaluation of Dose-Related HPV Vaccine Effectiveness Using Central Registries in Michigan. Cancer Epidemiol Biomarkers Prev. 2021 [online ahead of print]
USA25	Sonawane K, Nyitray AG, Nemutlu GS, Swartz MD, Chhatwal J, Deshmukh AA. Prevalence of human papillomavirus infection by number of vaccine doses among US women. JAMA Network Open. 2019;2(12):e1918571.

Ongoing single dose studies

ESCUDDO, Costa Rica	Porras C, Sampson JN, Herrero R, Gail MH, Cortés B, Hildesheim A, et al. Rationale and design of a double-blind randomized non-inferiority clinical trial to evaluate one or two doses of vaccine against human papillomavirus including an epidemiologic survey to estimate vaccine efficacy: The Costa Rica ESCUDDO trial. Vaccine. 2022. 40(1):76-88.
	NCT03180034. Comparing One or Two Doses of the Human Papillomavirus Vaccine for the Prevention of Human Papillomavirus Infection, ESCUDDO Study (ESCUDDO). Available from: https://clinicaltrials.gov/ct2/show/NCT03180034 (accessed 02/02/2022).

HANDS, Gambia	NCT03832049. HPV Vaccination in Africa- New Delivery Schedules Alias The HANDS HPV Vaccine Trial (HPV). Available from: https://clinicaltrials.gov/ct2/show/NCT03832049 (accessed 02/02/2022).
Add-Vac, Tanzania	NCT04953130. Adding Male Single Dose HPV Vaccination to Female HPV Vaccination in Tanzania (Add-Vacc). Available from: https://clinicaltrials.gov/ct2/show/NCT04953130 (accessed 02/02/2022).
NCT02568566, USA	Zeng Y, Moscicki A-B, Sahasrabuddhe VV, Garcia F, Woo H, Hsu C-H, et al. A prospective, single-arm, open-label, non-randomized, phase IIa trial of a nonavalent prophylactic HPV vaccine to assess immunogenicity of a prime and deferred-booster dosing schedule among 9-11 year-old girls and boys - clinical protocol. BMC Cancer. 2019;19(1):290.
	NCT02568566. Recombinant Human Papillomavirus Nonavalent Vaccine in Preventing Human Papilloma Virus in Younger Healthy Participants. Available from: https://clinicaltrials.gov/ct2/show/NCT02568566 (accessed 21/02/2022).
Case-control, USA	Oliveira CR, Ortiz AM, Sheth SS, Shapiro ED, Niccolai LM. Effectiveness of HPV vaccine by age at vaccination and number of doses: protocol for a population-based matched case-control study. BMJ Open. 2021. 11(4):e043093.

Appendix 3. Characteristics of included studies

Study name	Date range	Study design	HPV vaccine	Participants (number, sex)	N by dose	Age at vaccination (V) and outcome (O)	Buffer periods in analysis*	Outcomes reported	Funding
Australia1 Brotherton 2015	April 2007 to December 2011	Retrospective cohort study using linked regional data registries	Quadrivalent (Gardasil)	289,478 females	0: 133,055 1: 20,659 2: 27,500 3: 108,264	V: 12-26 O: 12-30	Not in primary analysis; sensitivity analysis with 1, 6, 12, 24 months	Histological abnormalities (any high grade, CIN3/AIS, CIN2) Cytological abnormalities (high grade, low grade)	VCS Foundation (health promotion charity)
Australia2 Crowe 2014	April 2007 to March 2011	Case-control study using linked data from registries	Quadrivalent (Gardasil)	108,353 females	0: 53,761 1: 9649 2: 10,950 3: 23,106	V: 12-26 O: 11-31	Not in primary analysis; sensitivity analysis with 1, 6, 12 months	Cervical abnormalities	No specific project funding was received
Australia3 Gertig 2013	1 April 2007 to 31 December 2011	Retrospective cohort study using linked data from registries	Quadrivalent (Gardasil)	38,956 females	0: 14,085 1: 1422 2: 2268 3: 21,151	V: 12-19 O: 12-21	Not in primary analysis; sensitivity analysis excluded time during vaccination course	Cervical abnormalities, Cytological abnormalities	Not reported
Australia4 Brotherton 2019	April 2007 to December 2014	Retrospective cohort study using linked regional data registries	Quadrivalent (Gardasil)	250,648 females	0: 48,845 1: 8618 2: 18190 3: 174995	V: <15 O: >=12	Not in primary analysis; sensitivity analysis with 12 and 24 months	Histological abnormalities	Australian Department of Health

Belgium2 Dominiak-Felden 2015	January 2006 to December 2013	Retrospective cohort study using sick fund/ insurance data	Quadrivalent (Gardasil)	106,579 females	0: 63,180 1: 4020 2: 3587 3: 35,792	V: 10-23 O: 16-23	Yes, 1 month	Anogenital warts	Sanofi Pasteur
Canada2 Kim 2016	2008 - 2015	Nested case-control study using linked data from registries	Quadrivalent (Gardasil)	10,204 females	0: 5712 1: 327 2: 490 3: 3675	V: 10-15 O: 18-21	Yes, minimum of 3 years between vaccination and outcome	Cytology outcome (low-grade and high-grade abnormalities)	Not reported
Canada3 Willows 2018	September 2006 and March 2013	Retrospective cohort study using linked data from registries, with matched control (unvaccinated) group	Quadrivalent (Gardasil)	31,464 females	0: 94,327 1: 3521 2: 6666 3: 21,277	V: 9-25 O: 9-25	Yes, 12 months	Anogenital warts	Merck Canada
Canada4 Gilca 2018	Not reported	RCT	Bivalent (Cervarix), nonavalent (Gardasil9)	371 females and males	2 homologous: 184 2 mixed: 187	V: 9-10 O: 9-10	No, RCT	GMTs and seroconversion	Quebec Ministry of Health and Social Services; Bill & Melinda Gates Foundation
Canada5 Donken 2019	Not reported	Retrospective cohort study using linked data from registries	Quadrivalent (Gardasil)	34097 females	0: 19,496; 1: 471; 2/3 (complete schedule): 14,130	V: 9-14 O: not reported	No	HSIL, CIN 2+	Not reported
Canada6 Wissing 2019	2005-2013	Prospective cohort study following young couples	Quadrivalent (Gardasil)	497 females and males (couples)	0: 434; 1: 12; 2: 16; 3: 35	V: 15-24 O: median 21 to 20 years	No	HPV infection and persistent infection	Canadian Institutes of Health Research; the U.S. National Institutes of Health; Merck-Frosst Canada Ltd. and Merck & Co. Ltd.
Canada7 Gilca 2018	2008-2013	Single arm trial	Quadrivalent (Gardasil);	31 females	1d. 4v + 1d. 9v: 200	V: not reported O: 13-18	1 month	GMTs	Quebec Ministry of Health and Social Services

			Nonavalent (Gardasil 9)						
Canada4/7 Gilca 2019 Sauvageau 2019	2015–2017 (recruitment)	Post-hoc follow-up of 2 RCTs	Bivalent (Cervarix), quadrivalent (Gardasil), nonavalent (Gardasil9)	205 females and males	1 (9v): 88; 2: 117 (2v + 9v, 6m interval: 86, 4v + 9v, 36-96m interval: 31)	V: 9-14 O: 9-14	No, two post-hoc analyses of RCTs	GMTs of HPV 6/11/16/18/ 31/33/45/52 and 58	Not reported
China1 Hu 2020	2015	RCT	Bivalent (Cecolin)	605 females	1: 301 (finally received 2 doses) 2: 304 (finally received 3 doses)	V: 9-14 O: 9-14	No, RCT	Seroconversion and antibody geometric mean titre	National Natural Science Foundation of China, the Chinese National Major Scientific and Technological Special Project for "Significant New Drugs Development", the Fujian Provincial Major Scientific and Technological Project, and Xiamen Innovax
Costa Rica1 Safaeian 2013 Kreimer 2011 Safaeian 2018 Kreimer 2020 Tsang 2020	2004-2005	Post-hoc analysis of RCT	Bivalent (Cervarix)	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	National Institutes of Health, GlaxoSmithKline (vaccine and support for aspects of the trial associated with regulatory submission needs of the company)
CVT/PATRICIA Kreimer 2015 Kreimer 2018	2004-2005	Post-hoc analysis of two RCTs	Bivalent (Cervarix)	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	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).
Denmark2 Blomberg 2015	October 2006 to December 2012	Retrospective cohort study using population-based health national registries	Quadrivalent (Gardasil)	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	Aragon Foundation; the Aase and Ejnar Danielsens Foundation; the Mermaid II project
Denmark3 Verdoodt 2019	2006-2016	Retrospective cohort study using national registries	Quadrivalent (Gardasil)	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	the Mermaid Project
Denmark4 Baandrup 2020	2006-2016	Retrospective cohort study using national registries	Quadrivalent (Gardasil), bivalent (Cervarix)	1,076,945 females	0: 485408; 1: NR	V: ≥12 O: not reported	Yes, 1 month	Anogenital warts	the Mermaid Project
Denmark/Sweden1 Dehlendorff 2018	2006-2013	Retrospective cohort study using national registries	Quadrivalent (Gardasil)	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+	the Mermaid Project
Fiji1 Toh 2017 Toh 2018 Toh 2019	February and March 2015	Prospective cohort study	Quadrivalent (Gardasil)	200 females	0: 32 1: 40 2: 60 3: 66	V: 9-13 O: 15-19	Yes, minimum of 6 years between vaccination and outcome	Antibody geometric mean titre, seroconversion	Department of Foreign Affairs and Trade of the Australian government and the Fiji Health Sector Support Program
India1 Sankaranarayanan 2016 Sankaranarayanan 2019 Basu 2021	Sept 1, 2009, to April 8, 2010	Post-hoc analysis of RCT	Quadrivalent (Gardasil)	17,729 females	1: 4950 2: 8431 3: 4348	V: 10-18 O: 12-28	No, post-hoc analysis of RCT	Antibody geometric mean titre, HPV infection	Bill & Melinda Gates Foundation
Italy1 Acuti Martellucci 2021	2011-2018	Retrospective cohort study using	Quadrivalent (Gardasil), bivalent (Cervarix)	7785 females	0: 7394; 1: 212; 2: 83; 3: 96	V: 15-23 O: 25-32	Not in primary analysis; sensitivity	abnormal cervical cytology	No specific project funding was received

		administrative health data					analysis with 1, 6, and 12 months		
Kenya1 Barnabas 2021	2018-2021	RCT	Bivalent (Cervarix), nonavalent (Gardasil9)	2275 females	0 (Meningococcal vaccine): 757; 1 (2v): 760; 1 (9v): 758	V: 15-20 O: 16-22	No, RCT	Persistent (>6 months) infection with high-risk HPV types, antibody titre, B cell markers, cost	Bill & Melinda Gates Foundation and the University of Washington King K. Holmes Endowed Professorship in STDs and AIDS
Mongolia1 Batmunkh 2020	2018-2019	Retrospective cohort study	Quadrivalent (Gardasil)	475 females	0: 357; 1: 118	V: 11-17 O: 16-26	Yes, minimum of 6 years between vaccination and outcome	Incident HPV infection, seropositivity, neutralizing antibody titres	Bill and Melinda Gates Foundation
Netherlands1 Pasmans 2019	2009-2016	Serial cross-sectional study	Bivalent (Cervarix)	890 females	0: 51; 1: 239; 2: 222; 3: 378	V: 12-16 O: 19-23	No	seroconversion, specific IgG antibody concentrations	Dutch Ministry of Health, Welfare and Sports
New Zealand1 Innes 2020	2010-2015	Retrospective cohort study using national registries	Quadrivalent (Gardasil)	104313 females	not reported	V: not reported O: 20-24	No	CIN 2+	None reported
Scotland1 Cuschieri 2016	from 2009	Retrospective cohort study using screening registry data with additional sampling of women with < 3 doses	Bivalent (Cervarix)	5949 females	0: 3619 1: 177 2: 300 3: 1853	V: 15-17 O: 20-21	Yes, minimum of 2 years between vaccination and outcome	HPV infection	Not reported
Scotland2 Pollock 2014	2008–2012	Retrospective cohort study using linked national registry data	Bivalent (Cervarix)	106,052 females	0: 75,113 1: 1315 2: 2725 3: 25,898	V: 15-17 O: 20-21	Yes, minimum of 2 years between vaccination	CIN 1, 2, 3	partially funded by Scottish Government Chief Scientists Office

							and outcome		
Scotland3 Cameron 2017	2008-2015	Retrospective cohort study using linked national registry data	Bivalent (Cervarix)	137,689 females	0: 75,684 1: 2258 2: 4462 3: 55,303	V: 12-17 O: 20-21	Yes, minimum of 2 years between vaccination and outcome	CIN 1, 2, 3	Not reported
Scotland4 Kavanagh 2014 Cameron 2016	2009-2012	Retrospective cohort study using linked national registry data	Bivalent (Cervarix)	4729 females	0: 3418 1: 55 2: 106 3: 1100	V: 15-17 O: 20-21	Yes, minimum of 2 years between vaccination and outcome	HPV infection	Scottish Government and Chief Scientists Office
Scotland5 Kavanagh 2017	2009-2015	Retrospective cohort study using linked national registry data	Bivalent (Cervarix)	8584 females	0: 4008 1: 223 2: 391 3: 3962	V: 12-17 O: 20-21	Yes, minimum of 2 years between vaccination and outcome	HPV infection	Scottish Government and Chief Scientists Office
Scotland6 Palmer 2019	2008-2016	Retrospective cohort study using linked national registry data	Bivalent (Cervarix)	138,692 females	0: 64,026, 1: 2051, 2: 4135, 3: 68,480	V: 12-17 O: 20	Yes, minimum of 2 years between vaccination and outcome	Cytological and histological abnormalities	Scottish National Health Service. No funding has been received from industry
Spain2 Navarro-Illana 2017	Jan 2009 - Dec 2014	Retrospective cohort study using national registries	Quadrivalent (Gardasil)	279,787 females	0: NR 1: NR 2: NR 3: NR	V: 14 O: 14-19	No	Anogenital warts	The Foundation for the Promotion of Health and Biomedical Research of Valencia Region (FISABIO); Sanofi Pasteur sponsored the medical writer

Spain3 Muñoz-Quiles 2022	2009-2017	Retrospective cohort study using regional database	Bivalent (Cervarix), quadrivalent (Gardasil)	555,185 females	0: 290,708; 1 2v: 10,410; 1 4v: 1823; 2 2v: 27,517; 2 4v: 3526; 3 2v: 89,213; 3 4v: 53,579	V: not reported O: 14-23	Not in primary analysis; sensitivity analysis with 6 months	Anogenital warts	Merck Sharp & Dohme
Sweden1 Herweijer 2014	January 1, 2006, to December 31, 2010	Retrospective cohort study using population-based health registries	Quadrivalent (Gardasil)	1,045,165 females	0: 926,119 1: 115,197 2: 107,338 3: 89,836	V: 10-19 O: 10-24	Yes, 3 months; sensitivity analyses with 0 to 12 months	Anogenital warts	Swedish Foundation for Strategic Research, Sanofi Pasteur Merck Sharp Dome and GlaxoSmithKline
Switzerland1 Jeannot 2018	January 2016 and October 2017	Cross-sectional study	Quadrivalent (Gardasil)	409 females	0: 125, 1: 20, 2: 60, 3: 204	V: 11-26 O: 18-31	No	HPV positivity	Received no external funding
Uganda1 LaMontagne 2014	2008-2009	Prospective cohort study	Bivalent (Cervarix)	376 females	1: 36 2: 145 3: 195	V: 10-11 O: 12-15	Yes, minimum 38 months between vaccination and outcome	Antibody geometric mean titre	Bill & Melinda Gates Foundation
Tanzania1 (DoRIS) NCT02834637	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Thailand1 NCT03747770	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
USA1 Hofstetter 2016	2007-2014	Retrospective cohort study using medical	Quadrivalent (Gardasil)	4127 females	0: 1632 1: 695 2: 604 3: 1196	V: 11-20 O: 11-27	Yes, 1 month	Abnormal cervical cytology	Merck Investigator-Initiated Studies Program

		centre databases							
USA2 Hariri 2018	2006-2012	Retrospective cohort study using health insurance database	Quadrivalent (Gardasil)	64,517 females	0: 31,563 1: 5864 2: 5459 3: 21,631	NR	Not in primary analysis, sensitivity analysis with 6 and 12 months	Anogenital warts	Centre for Disease Control and Prevention
USA6 Perkins 2017	Jan 2007 - Dec 2013	Retrospective cohort study using commercial claims database	Quadrivalent (Gardasil)	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	American Cancer Society
USA9 Silverberg 2018	Jan 1, 1995, and June 30, 2014	Case-control study	Quadrivalent (Gardasil)	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+	US National Cancer Institute
USA10 Flagg 2017	2003–2014	Retrospective cohort study	Quadrivalent (Gardasil)	270,481 females	>=1: 75,735	V: Median age 15 years O: NR	No	Anogenital warts	Not reported
USA11 Zeybek 2018	2006 - 2015	Retrospective cohort	Quadrivalent (Gardasil)	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	William & Mary McGanity Research Fund Award from the Department of Obstetrics & Gynecology at The University of Texas Medical Branch at Galveston
USA12 Chandler 2018	2013-2015	Prospective cohort study	Quadrivalent (Gardasil)	236; males	>=1: 104 3: 49	V: NR O: 13-26	No	HPV infection	National Institute of Allergy and Infectious Diseases, National Institute of Health
USA13 Castle 2019	December 12, 2006, to December 13, 2016	Prospective cohort study	Quadrivalent (Gardasil)	75,008; females	0: 59,860 1: 3,542 2 or more: 11,048	V: <18–24 O: 21–24	No	Cytological abnormalities	Not reported

USA14 Spinner 2019	2006-2017	Cross-sectional study (4 waves)	Quadrivalent (Gardasil)	1580 females	NR	V: unclear O: 13-26	No	HPV infection	the National Institutes of Health
USA15 Washington 2018	2013-2017	Cross-sectional study	Quadrivalent (Gardasil), nonavalent (Gardasil9)	735; females	>=1: 559 3: 448	V: NR O: 13-26	No	HPV infection	National Institute of Allergy and Infectious Diseases, National Institute of Health
USA16 Hurt 2016	2006-2012	Retrospective cohort study	Quadrivalent (Gardasil)	2091; females	1: 146; 2: 166; 3: 480	V: NR O: 4-6 years	No	Seroconversion	Not reported
USA17 Moscicki 2019	2007-2017	Prospective cohort study	Quadrivalent (Gardasil)	458 HIV infected or exposed uninfected females and males	0: 66; 1: 245; 2: 47; 3: 101	V: mean 13.3 (SD 2.5) O: mean 16.7 (SD 2.4)	No	antibody titres, seroconversion, genital warts, abnormal cytology	Eunice Kennedy Shriver National Institute of Child Health and Human Development
USA18 Widdice 2019	2013–2014, 2016-2017	Cross-sectional survey study	Quadrivalent (Gardasil), nonavalent (Gardasil9)	746 males	0: 471; 1: 58; 2: 37; 3: 143; unknown: 38	V: mean 15.1 to 16.2 O: 13-26	No	Penile or anal HPV infection	National Institute of Allergy and Infectious Diseases
USA19 Covert 2020	2009-2017	Cross-sectional surveillance study	Quadrivalent (Gardasil)	1209 females	at least 1: 825	V: mean 14.4 O: 13-26	No	HPV prevalence from cervico-vaginal swabs	Not reported
USA20 Markowitz 2020	2012-2017	Retrospective cohort study	Quadrivalent (Gardasil)	4269 females	0: 1052; 1: 303; 2: 304; 3: 2610	V: not reported O: 20-29	Yes, median 5-6 years between vaccination and outcome	Prevalence of HPV types in cytology samples at routine cervical cancer screening	Centers for Disease Control and Prevention
USA21 Johnson Jones 2020	2008-2014	Test-negative design	Quadrivalent (Gardasil)	3300 females	0: 2731; 1: 136; 2: 108; 3: 325	V: 12-26 O: 18-34	Yes, 24 months as primary analysis; sensitivity analysis with 1, 12, 24, 36 months	CIN2+	Centers for Disease Control and Prevention
USA22 Rodriguez 2020	2006-2015	Retrospective matched cohort study using	Quadrivalent (Gardasil)	133082 females	0: 66541; 1: 13630; 2: 14088; 3: 38823	V: 9-26 O: 14-31	Yes, 12 months	CIN2+; HSIL	National Institutes of Health; Cancer Prevention

		administrative databases							Research Institute of Texas
USA23 Abel 2021	2009-2016	Cross-sectional study	Quadrivalent (Gardasil)	5798 females	0: 4801; 1: 198; 2-3: 799	V: not reported O: 18-36	No	Prevalence of oral HPV infections	Denise Cobb Hale and The Fisher Family Fund
USA24 Gargano 2021	2009-2016	Retrospective cohort study using linked regional registries	Bivalent (Cervarix); Quadrivalent (Gardasil); Nonavalent (Gardasil9)	773,193 females	0: 559,789; 1: 43,245; 2-3 doses: 170,159	V: 80% <20 years O: not reported	No	CIN3+	Immunization grant funds under the Public Health Service Act and National Program of Cancer Registries grant awards
USA25 Sonawane 2019	2009-2016	Cross-sectional study	Quadrivalent (Gardasil)	1620 females	0: 1004; 1: 106; 2: 126; 3: 384	V: not reported O: 18-26	No	HPV infection	the National Cancer Institute of the National Institutes of Health and The Cancer Prevention Research Institute of Texas

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. *Buffer period indicates the time lag between vaccination and counting of outcomes.

Appendix 4. ROB 2 assessments for RCTs

Study name	1. Risk of bias arising from the randomization process	2. Risk of bias due to deviations from the intended interventions	3. Missing outcome data	4. Risk of bias in measurement of the outcome	5. Risk of bias in selection of the reported result	6. Overall risk of bias
Canada4 Gilca 2018	Some concerns	Low	Low	Low	Low	Some concerns
	Allocation sequence random. No information on allocation concealment. No significant baseline differences between groups.	"Subjects and their parents were blinded to which group they were allocated" (report) "Masking: Triple (Participant, Care Provider, Outcomes Assessor)" (registry).	345 participants were analysed out of 371 randomized. Nearly all participants were analysed.	Methods of measuring the outcomes were appropriate and unlikely to have differed between groups. Outcomes were measured by objective lab test so is unlikely to have been influenced by knowledge of the intervention received.	Results were reported according to outcome list in online trial record.	
China1 Hu 2020	Some concerns	Low	Some concerns	Low	Low	Some concerns
	Allocation sequence random. No information on allocation concealment. No significant baseline differences between groups.	Only investigators and outcome assessors were blinded to the intervention groups; participants were not blinded. There was no reason to suspect important non-protocol interventions were not balanced or that there were failures in implementing the intervention. Only one participant crossed over, which we consider negligible.	Outcome data were not available for all or nearly all participants (605 randomized; 513 (HPV16) to 537 (HPV 18) analysed). Although reasons for missing data were not reported for all missing participants, it was unlikely that missingness depended on the true value of the outcome since missing proportions were similar between groups.	Methods of measuring the outcomes were appropriate and unlikely to have differed between groups. Outcome assessors were blinded.	Results were reported according to analysis plan in prospectively registered trial record.	
Kenya1	Low	Low	Some concerns	Low	Low	Some concerns

Study name	1. Risk of bias arising from the randomization process	2. Risk of bias due to deviations from the intended interventions	3. Missing outcome data	4. Risk of bias in measurement of the outcome	5. Risk of bias in selection of the reported result	6. Overall risk of bias
Barnabas 2021	Allocation sequence random and concealed. No significant baseline differences between groups.	Participants, carers, and people delivering the interventions were blinded to the intervention groups. Available case analysis was used which is considered appropriate for estimating the effect of assignment to intervention.	Outcome data were not available for all or nearly all participants (2275 randomized; 1457 analysed).	Methods of measuring the outcomes were appropriate and unlikely to have differed between groups. Outcome assessors were blinded.	Results were reported according to analysis plan in protocol and prospectively registered trial record.	
Tanzania1 DoRIS						

Appendix 5. ROBINS-I assessment for non-randomised studies

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	Low	Moderate	Low	Moderate	Serious
Australia3	Serious	Serious	Low	Low	Moderate	Low	Moderate	Serious
Australia4	Serious	Serious	Low	Low	Moderate	Low	Moderate	Serious
Belgium2	Serious	Moderate	Low	Low	Moderate	Moderate	Moderate	Serious
Canada3	Serious	Moderate	Low	Low	Moderate	Moderate	Moderate	Serious
Canada5	Serious	Serious	Low	Low	Low	Low	Moderate	Serious
Canada6	Serious	Serious	Serious	Low	Low	Low	Moderate	Serious
Costa Rica1	Moderate	Low	Low	Low	Low	Low	Moderate	Moderate
CVT/PATRICIA	Moderate	Low	Low	Low	Moderate	Low	Low	Moderate
Denmark2	Serious	Moderate	Low	Low	Low	Moderate	Moderate	Serious
Denmark3	Serious	Moderate	Low	Low	Low	Moderate	Moderate	Serious
Denmark4	Serious	Moderate	Low	Low	Low	Low	Moderate	Serious
Denmark/Sweden1	Serious	Moderate	Low	Low	Low	Moderate	Moderate	Serious
Fiji1	Serious	Serious	Low	Low	Low	Low	Moderate	Serious
India1	Moderate	Low	Low	Low	Low	Low	Moderate	Moderate
Italy1	Serious	Serious	Low	Low	Low	Moderate	Moderate	Serious
Mongolia1	Moderate	Moderate	Low	Low	Low	Low	Moderate	Moderate

Netherlands1	Critical	Serious	Low	Low	Serious	Low	Moderate	Critical
New Zealand1	Critical	Serious	Low	Low	Moderate	Moderate	Moderate	Critical
Scotland1	Serious	Serious	Low	Low	Low	Moderate	Moderate	Serious
Scotland2	Serious	Serious	Low	Low	Low	Moderate	Moderate	Serious
Scotland3	Serious	Serious	Low	Low	Low	Moderate	Moderate	Serious
Scotland4	Serious	Serious	Low	Low	Low	Moderate	Moderate	Serious
Scotland5	Serious	Serious	Low	Low	Low	Moderate	Moderate	Serious
Scotland6	Serious	Serious	Low	Low	Moderate	Moderate	Moderate	Serious
Spain2	Serious	Moderate	Low	Low	Moderate	Moderate	Moderate	Serious
Spain3	Serious	Moderate	Low	Low	Moderate	Moderate	Moderate	Serious
Sweden1	Serious	Moderate	Low	Low	Low	Moderate	Moderate	Serious
Switzerland1	Serious	Serious	Serious	Low	Moderate	Moderate	Moderate	Serious
Thailand1								
Uganda1	Serious	Low	Low	Low	Low	Low	Moderate	Serious
USA1	Serious	Serious	Low	Low	Moderate	Moderate	Moderate	Serious
USA2	Moderate	Moderate	Low	Low	Low	Moderate	Moderate	Moderate
USA6	Serious	Serious	Low	Low	Low	Moderate	Moderate	Serious
USA10	Critical	Critical	Low	Low	Serious	Moderate	Serious	Critical
USA11	Serious	Moderate	Low	Low	Low	Moderate	Moderate	Serious
USA12	Serious	Critical	Serious	Low	Moderate	Low	Moderate	Critical
USA13	Serious	Serious	Low	Low	Moderate	Moderate	Moderate	Serious
USA14	Serious	Serious	Low	Low	Moderate	Low	Moderate	Serious
USA15	Critical	Critical	Serious	Low	Serious	Moderate	Serious	Critical
USA16	Serious	Serious	Low	Low	Moderate	Low	Moderate	Serious
USA17	Critical	Critical	Serious	Low	Moderate	Low	Low	Critical
USA18	Serious	Moderate	Moderate	Low	Low	Low	Moderate	Serious
USA19	Serious	Moderate	Serious	Low	Serious	Moderate	Moderate	Serious
USA20	Serious	Serious	Low	Low	Low	Low	Moderate	Serious
USA21	Serious	Serious	Low	Low	Low	Low	Moderate	Serious

USA22	Serious	Moderate	Low	Low	Low	Moderate	Moderate	Serious
USA23	Serious	Moderate	Serious	Low	Serious	Low	Moderate	Serious
USA24	Serious	Moderate	Low	Low	Low	Low	Moderate	Serious
USA25	Serious	Moderate	Serious	Low	Moderate	Low	Moderate	Serious

Note: to perform the assessment of ROBINS-I shown above we selected one outcome of interest (for this review) that was reported from each study. The specific outcome selected differs per study so this assessment should not be used to compare studies. For other outcomes reported in the studies, the assessment may change.

Appendix 6. SIGN-50 assessment for case-control studies

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