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[Intervention Review]

Comparison of different human papillomavirus (HPV) vaccine types and dose schedules for prevention of HPV-related disease in females and males

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ABSTRACT

Background

Uptake of human papillomavirus (HPV) vaccine remains low in many countries, although the bivalent and quadrivalent HPV vaccines given as a three-dose schedule are effective in the prevention of precancerous lesions of the cervix in women. Simpler immunisation schedules, such as those with fewer doses, might reduce barriers to vaccination, as may programmes that include males.

Objectives

To evaluate the efficacy, immunogenicity, and harms of different dose schedules and different types of HPV vaccines in females and males.

Search methods

We conducted electronic searches on 27 September 2018 in Ovid MEDLINE, the Cochrane Central Register of Controlled Trials (CENTRAL) (in the Cochrane Library), and Ovid Embase. We also searched the WHO International Clinical Trials Registry Platform, and ClinicalTrials.gov (both 27 September 2018), vaccine manufacturer websites, and checked reference lists from an index of HPV studies and other relevant systematic reviews.

Selection criteria

We included randomised controlled trials (RCTs) with no language restriction. We considered studies if they enrolled HIV-negative males or females aged 9 to 26 years, or HIV-positive males or females of any age.

Data collection and analysis

We used methods recommended by Cochrane. We use the term 'control' to refer to comparator products containing an adjuvant or active vaccine and 'placebo' to refer to products that contain no adjuvant or active vaccine. Most primary outcomes in this review were clinical outcomes. However, for comparisons comparing dose schedules, the included RCTs were designed to measure antibody responses (i.e. immunogenicity) as the primary outcome, rather than clinical outcomes, since it is unethical to collect cervical samples from girls under 16 years of age. We analysed immunogenicity outcomes (i.e. geometric mean titres) with ratios of means, clinical outcomes (e.g. cancer and intraepithelial neoplasia) with risk ratios or rate ratios and, for serious adverse events and deaths, we calculated odds ratios. We rated the certainty of evidence with GRADE.

Main results

We included 20 RCTs with 31,940 participants. The length of follow-up in the included studies ranged from seven months to five years.

Two doses versus three doses of HPV vaccine in 9- to 15-year-old females

Antibody responses after two-dose and three-dose HPV vaccine schedules were similar after up to five years of follow-up (4 RCTs, moderate- to high-certainty evidence). No RCTs collected clinical outcome data. Evidence about serious adverse events in studies comparing dose schedules was of very low-certainty owing to imprecision and indirectness (three doses 35/1159; two doses 36/1158; 4 RCTs). One death was reported in the three-dose group (1/898) and none in the two-dose group (0/899) (low-certainty evidence).

Interval between doses of HPV vaccine in 9- to 14-year-old females and males

Antibody responses were stronger with a longer interval (6 or 12 months) between the first two doses of HPV vaccine than a shorter interval (2 or 6 months) at up to three years of follow-up (4 RCTs, moderate- to high-certainty evidence). No RCTs collected data about clinical outcomes. Evidence about serious adverse events in studies comparing intervals was of very low-certainty, owing to imprecision and indirectness. No deaths were reported in any of the studies (0/1898, 3 RCTs, low-certainty evidence).

HPV vaccination of 10- to 26-year-old males

In one RCT there was moderate-certainty evidence that quadrivalent HPV vaccine, compared with control, reduced the incidence of external genital lesions (control 36 per 3081 person-years; quadrivalent 6 per 3173 person-years; rate ratio 0.16, 95% CI 0.07 to 0.38; 6254 person-years) and anogenital warts (control 28 per 2814 person-years; quadrivalent 3 per 2831 person-years; rate ratio 0.11, 95% CI 0.03 to 0.38; 5645 person-years). The quadrivalent vaccine resulted in more injection-site adverse events, such as pain or redness, than control (537 versus 601 per 1000; risk ratio (RR) 1.12, 95% CI 1.06 to 1.18, 3895 participants, high-certainty evidence). There was very low-certainty evidence from two RCTs about serious adverse events with quadrivalent vaccine (control 12/2588; quadrivalent 8/2574), and about deaths (control 11/2591; quadrivalent 3/2582), owing to imprecision and indirectness.

Nonavalent versus quadrivalent vaccine in 9- to 26-year-old females and males

Three RCTs were included; one in females aged 9- to 15-years (n = 600), one in females aged 16- to 26-years (n = 14,215), and one in males aged 16- to 26-years (n = 500). The RCT in 16- to 26-year-old females reported clinical outcomes. There was little to no difference in the incidence of the combined outcome of high-grade cervical epithelial neoplasia, adenocarcinoma in situ, or cervical cancer between the HPV vaccines (quadrivalent 325/6882, nonavalent 326/6871; OR 1.00, 95% CI 0.85 to 1.16; 13,753 participants; high-certainty evidence). The other two RCTs did not collect data about clinical outcomes. There were slightly more local adverse events with the nonavalent vaccine (905 per 1000) than the quadrivalent vaccine (846 per 1000) (RR 1.07, 95% CI 1.05 to 1.08; 3 RCTs, 15,863 participants; high-certainty evidence). Comparative evidence about serious adverse events in the three RCTs (nonavalent 243/8234, quadrivalent 192/7629; OR 0.60, 95% CI 0.14 to 2.61) was of low certainty, owing to imprecision and indirectness.

HPV vaccination for people living with HIV

Seven RCTs reported on HPV vaccines in people with HIV, with two small trials that collected data about clinical outcomes. Antibody responses were higher following vaccination with either bivalent or quadrivalent HPV vaccine than with control, and these responses could be demonstrated to have been maintained for up to 24 months in children living with HIV (low-certainty evidence). The evidence about clinical outcomes and harms for HPV vaccines in people with HIV is very uncertain (low- to very low-certainty evidence), owing to imprecision and indirectness.

Authors' conclusions

The immunogenicity of two-dose and three-dose HPV vaccine schedules, measured using antibody responses in young females, is comparable. The quadrivalent vaccine probably reduces external genital lesions and anogenital warts in males compared with control. The nonavalent and quadrivalent vaccines offer similar protection against a combined outcome of cervical, vaginal, and vulval precancer lesions or cancer. In people living with HIV, both the bivalent and quadrivalent HPV vaccines result in high antibody responses. For all comparisons of alternative HPV vaccine schedules, the certainty of the body of evidence about serious adverse events reported during the study periods was low or very low, either because the number of events was low, or the evidence was indirect, or both. Post-marketing surveillance is needed to continue monitoring harms that might be associated with HPV vaccines in the population, and this evidence will

be incorporated in future updates of this review. Long-term observational studies are needed to determine the effectiveness of reduced-dose schedules against HPV-related cancer endpoints, and whether adopting these schedules improves vaccine coverage rates.

PLAIN LANGUAGE SUMMARY

Comparison of different human papillomavirus (HPV) vaccines and the number of doses administered to prevent HPV-related disease in females and males

Human papillomaviruses (HPV) are a group of viruses that infect the skin and mucous membranes. Some types of HPV are sexually transmitted and are common in young people. Most infections will be cleared by the immune system, but some people will experience persistent infection with certain HPV types that go on to cause abnormalities in infected cells. These changes are called 'precancerous' because they can develop into cancers of the cervix, vagina, vulva, anal canal, penis, and head and neck. Infection with other HPV types causes warts in the genital area or around the anus.

Vaccination aims to prevent future HPV infections. Three HPV vaccines are in use – a bivalent one (protects against two HPV types), a quadrivalent one (protects against four HPV types), and a nonavalent one (protects against nine HPV types). In women, three doses of the bivalent or the quadrivalent HPV vaccines protect against precancer of the cervix caused by the HPV types contained in the vaccine. Evidence about the nonavalent vaccine, about the effects of the quadrivalent vaccine in males, and about the effects of HPV vaccines in people with HIV infection, has not yet been reviewed thoroughly. Uptake of HPV vaccines remains low in many countries. Simpler vaccine schedules, or giving the vaccine to both girls and boys, could increase the number of people being vaccinated.

Trials of HPV vaccines are not always designed to collect data about precancer and cancer, for several reasons. Firstly, HPV vaccine is routinely given before girls become sexually active, and it is not ethical to take specimens from the cervix of girls who have not had sex. Secondly, HPV-related precancer and cancer are rare and do not develop until years after HPV infection has occurred. Thirdly, participants in a trial will be offered treatment if precancer develops, so progression to cervical cancer would be even rarer, even without vaccination. An international committee of experts states that, in some circumstances, antibody levels (i.e. showing a strong immune system response), can be used to demonstrate protection against cervical and anal cancer. The antibody levels following vaccination in a trial should not be lower than those found in other studies on adults in whom the vaccine has been shown to protect against severe HPV-related cervical or anal disease.

Review question(s)

How effective or harmful are different HPV vaccine schedules (i.e. number and timing of doses) and different HPV vaccines in females and males?

Main results

These results are based on research evidence to 27 September 2018. We analysed 20 studies involving 31,940 people.

Studies comparing two doses of HPV vaccine to three doses, or comparing the time interval between doses, focus on immune system responses rather than infection or disease outcomes. Two doses of HPV vaccine result in similar immune system responses to three doses, and a longer interval (up to 12 months) between doses gives a stronger immune system response than a shorter interval. There is insufficient evidence to determine whether there was a difference between the vaccine schedules for serious adverse events and death.

In 16- to 26-year-old men, one study showed evidence of moderate certainty that a quadrivalent HPV vaccine provides better protection against external genital lesions and genital warts than a dummy treatment (control). In 16- to 26-year-old women, one study showed that the nonavalent and quadrivalent vaccines provide the same levels of protection against cervical, vaginal, and vulval precancer lesions and cancer (high-certainty evidence).

There was evidence that the quadrivalent vaccine resulted in more local adverse events (such as pain, swelling, and redness at the injection site) than a control treatment in males, and that the nonavalent vaccine resulted in more local adverse events than the quadrivalent vaccine in males and females. Evidence about serious adverse events and deaths from studies comparing different HPV vaccine types or dose schedules was of low or very low-certainty.

In people living with HIV, HPV vaccines result in reasonable levels of immune system response, but evidence about their effects on persistent HPV infection or HPV-related disease outcomes and harms is limited.

Certainty of the evidence

No major issues were identified with the methodological quality of the studies for the measurements of infection and disease outcomes, or for immune system responses. Our certainty in the evidence about serious harms and deaths across all the studies comparing different HPV vaccines and vaccine schedules is low, either because of their low frequency, or because the evidence is indirect, or both. Evidence graded as high certainty means that we were confident that further research is unlikely to change our findings. Moderate-certainty evidence means that there is a possibility that further research may have an important effect on our findings, whilst low-certainty evidence means

that our confidence was limited and further research may have an important impact on our findings. Very low-certainty evidence means that we were uncertain about the result.

Conclusion

A two-dose schedule of HPV vaccines in young females results in immune system responses that are comparable with a three-dose schedule. In males, the quadrivalent HPV vaccine appears to be effective in the prevention of external genital lesions and genital warts. Quadrivalent and nonavalent HPV vaccines in young women result in similar levels of protection against cervical, vaginal, and vulval precancer lesions and cancer. Evidence about the efficacy and harms in people living with HIV is limited. Further long-term population-level studies are needed to continue monitoring safety of these vaccines, to determine for how long two doses of vaccine can provide protection against HPV-related disease, the effect against HPV-related cancer, and whether a two-dose immunisation schedule will increase vaccine coverage.

Summary of findings for the main comparison. Two doses of HPV vaccine compared with three doses of HPV vaccine in 9- to 15-year-old females

Two doses of HPV vaccine compared with three doses of HPV vaccine in 9- to 15-year-old females

Patient or population: 9- to 15-year-old females
Setting: community health centres in Africa, Asia Pacific, Europe, Latin America, North America
Intervention: two doses of HPV vaccine (bivalent, quadrivalent, or nonavalent) administered in months 0 and 2, 0 and 6, or 0 and 12
Comparison: three doses of HPV vaccine (bivalent, quadrivalent, or nonavalent) administered in months 0, 2, and 6, or 0, 1, and 6

Clinical and harms outcomes*	Anticipated absolute effects** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with three doses of HPV vaccine	Risk with two doses of HPV vaccine				
Antibody response (immunogenicity)	Two doses were non-inferior to, or had higher GMTs than, three doses for all HPV vaccine genotypes (bivalent, quadrivalent, and nonavalent vaccines), except HPV 45 (where non-inferiority was inconclusive), at short-term follow-up (4 studies, number of participants ranged from 132 to 1833 depending on HPV type and vaccine; see Appendix 5).				MODERATE/ HIGH*	Short-term results (follow-up 1 month after final dose)
	Two doses of bivalent vaccine had inconclusive non-inferiority for GMTs of HPV 16 and HPV 18 compared with three doses at 60-month follow-up (1 study, 93 participants; see Appendix 5).				LOW*	Long-term results (follow-up 36 to 60 months)
	Two doses of quadrivalent vaccine resulted in non-inferior GMTs for HPV 6, HPV 11 and HPV 16 compared with three doses, while results were inconclusive for HPV 18 at 60-month follow-up (1 study, 101 participants; see Appendix 5).				LOW*	
	Two doses of nonavalent vaccine resulted in non-inferior GMTs for all HPV genotypes measured except HPV 45 and HPV 52 where non-inferiority was inconclusive, compared with three doses, at 36-month follow-up (1 study, 476 to 511 participants depending on HPV type; see Appendix 5).				HIGH*	
High-grade cervical intraepithelial neoplasia, adenocarcinoma in situ, and cervical cancer	No studies were identified that reported on this outcome.					
High-grade cervical, vulval, and vaginal disease	No studies were identified that reported on this outcome.					
Overall local/injection site adverse events	No studies were identified that reported on this outcome. Data for specific local adverse events (pain/swelling/redness at injection site) are presented in the analysis section.					

Overall systemic events and general symptoms	No studies were identified that reported on this outcome.					
Serious adverse events at up to 5-year follow-up	30 per 1000	31 per 1000 (20 to 49)	OR 1.03 (0.64 to 1.66)	2317 (4 RCTs)	⊕⊖⊖⊖ VERY LOW [1,2]	Please see Table 1 for a list of events in each RCT.
Mortality at up to 5-year follow-up	1 per 1000	0 per 1000 (0 to 9)	OR 0.33 (0.01 to 8.19)	1797 (3 RCTs)	⊕⊕⊖⊖ LOW [1]	One death was reported in the three-dose group (nonavalent vaccine).

*Certainty of the evidence (GRADE) for immunogenicity outcomes are presented in detail in Appendix 5.

__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect of the intervention (and its 95% CI).

CI: confidence interval; **GMT**: geometric mean titre; **HPV:** human papillomavirus; **OR**: odds ratio; **RCT:** randomised controlled trial

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

[1]Downgraded two levels for serious imprecision: few events and a wide 95% confidence interval that incorporated a potential large beneficial effect and a potential large harmful effect.
[2]Downgraded one level for indirectness: this outcome is a composite measure of events which may or may not be clinically relevant, may or may not be related to the vaccine and may occur outside a biologically plausible time frame relative to vaccine exposure. This outcome is considered to provide indirect evidence about vaccine safety.

Summary of findings 2. Two doses of HPV vaccine with longer interval compared with two doses of HPV vaccine with shorter interval in 9- to 14-year-old females and males

Two doses of HPV vaccine with longer interval compared with two doses of HPV vaccine with shorter interval in 9- to 14-year-old females and males

Patient or population: 9- to 14-year-old females and males
Setting: community health centres in Africa, Asia Pacific, Europe, Latin America, North America
Intervention: two doses of bivalent or nonavalent HPV vaccine with longer interval (months 0 and 6 or 12)
Comparison: two doses of bivalent or nonavalent HPV vaccine with shorter interval (months 0 and 2 or 6)

Clinical and harms outcomes*	Anticipated absolute effects** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with two doses of HPV vaccine with shorter interval	Risk with two doses of HPV vaccine with longer interval				
Antibody response (geometric mean titre)	Longer intervals between the first two doses of bivalent vaccine resulted in higher and non-inferior GMTs for HPV 16 (n = 971) and HPV 18 (n = 986) compared with shorter intervals in 9- to 14-year-old females at short-term follow-up (2 studies; moderate- to high-certainty evidence, see Appendix 6).				MODERATE/ HIGH*	Short-term results (follow-up one month after final dose)
	A longer interval between the first two doses of nonavalent vaccine resulted in higher and non-inferior GMTs than a shorter interval for all HPV vaccine genotypes in girls and boys at short-term follow-up (1 study, number of participants ranged from 778 to 815 depending on HPV type; high-certainty evidence, see Appendix 6).				HIGH*	
	Longer intervals between the first two doses of bivalent vaccine resulted in higher and non-inferior GMTs for HPV 16 (n=817) and HPV 18 (n=794) compared with shorter intervals in 9- to 14-year-old females at 36 months follow-up (1 study; high-certainty evidence, see Appendix 6).				HIGH*	Long-term results (follow-up 36 months)
	A longer interval between the first two doses of nonavalent vaccine resulted in higher and non-inferior GMTs than a shorter interval for all HPV vaccine genotypes in girls and boys at seven and 36 months follow-up (1 study, number of participants ranged from 236 to 263 depending on HPV type; high-certainty evidence, see Appendix 6).				HIGH*	
Invasive cervical, vaginal, vulval, anal, or penile cancer	No studies were identified that reported on this outcome.					
High-grade cervical, vulval, vaginal, penile, or anal intraepithelial neoplasia	No studies were identified that reported on this outcome.					
Overall local/injection site adverse events	No studies were identified that reported on this outcome. Data for specific local adverse events (pain/swelling/redness at injection site) are presented in the analysis section.					
Overall systemic events and general symptoms	No studies were identified that reported on this outcome.					
Serious adverse events	Bivalent vaccine (0 and 2 months)	Bivalent vaccine (0 and 6 months)	OR 1.15 (0.55 to 2.41)	481 (1 RCT)	⊕⊖⊖⊖ VERY LOW [1,2]	Please see Table 1 for list of events in each RCT.

at up to 5-year follow-up	58 per 1000	67 per 1000 (33 to 130)				Data for nonavalent vaccine include males and females; fully disaggregated data were not available.
	Bivalent vaccine (0 and 6 months) 36 per 1000	Bivalent vaccine (0 and 12 months) 58 per 1000 (32 to 101)	OR 1.63 (0.89 to 2.99)	965 (1 RCT)	⊕⊖⊖⊖ VERY LOW [1,2]	
	Nonavalent vaccine (0 and 6 months) 25 per 1000	Nonavalent vaccine (0 and 12 months) 20 per 1000 (8 to 52)	OR 0.80 (0.31 to 2.07)	903 (1 RCT)	⊕⊖⊖⊖ VERY LOW [1,2]	
Mortality at up to 5-year follow-up	Bivalent vaccine (0 and 2 months) 0 per 1000	Bivalent vaccine (0 and 6 months) 0 per 1000 (0 to 0)	Not estimable	481 (1 RCT)	⊕⊕⊖⊖ LOW [3]	No deaths were reported in the trial.
	Bivalent vaccine (0 and 6 months) 0 per 1000	Bivalent vaccine (0 and 12 months) 0 per 1000 (0 to 0)	Not estimable	965 (1 RCT)	⊕⊕⊖⊖ LOW [3]	No deaths were reported in the trial.
	Nonavalent vaccine (0 and 6 months) 0 per 1000	Nonavalent vaccine (0 and 12 months) 0 per 1000 (0 to 0)	Not estimable	452 (1 RCT)	⊕⊕⊖⊖ LOW [3]	No deaths were reported in the trial.

*Certainty of the evidence (GRADE) for immunogenicity outcomes are presented in detail in Appendix 6.

__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect of the intervention (and its 95% CI).

CI: confidence interval; **GMT**: geometric mean titre; **HPV:** human papillomavirus; **OR**: odds ratio; **RCT:** randomised controlled trial

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

[1]Downgraded two levels for serious imprecision: few events and a wide 95% confidence interval that incorporates a potential large beneficial effect and a potential small harmful effect.
[2]Downgraded one level for indirectness: this outcome is a composite measure of events which may or may not be clinically relevant, may or may not be related to the vaccine and may occur outside a biologically plausible time frame relative to vaccine exposure. This outcome is considered to provide indirect evidence about vaccine safety.
[3]Downgraded two levels for serious imprecision: no events reported, the studies were not powered to detect a difference in mortality.

Summary of findings 3. Three doses HPV vaccine compared with control in 10- to 26-year-old males

Three doses HPV vaccine compared with control in 10- to 26-year-old males

Patient or population: 10- to 26-year-old males
Setting: 18 countries in five regions (Africa, Asia-Pacific, Europe, Latin America, North America)
Intervention: quadrivalent HPV vaccine, 3 doses at months 0, 2, and 6; or bivalent HPV vaccine, 3 doses at months 0, 1, and 6
Comparison: control (vaccine adjuvant-containing placebo), 3 doses at months 0, 2, and 6 or hepatitis B vaccine, 3 doses at months 0, 1, and 6

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk/rate with control	Risk/rate with HPV vaccine				
Invasive anal or penile cancer	No studies were identified that reported on this outcome					
Penile or anal intraepithelial neoplasia at up to 3-year follow-up	3/2824 person-years	0/2833 person-years	Rate ratio 0.17 (0.01 to 3.27)	2805 participants (5657 person-years) (1 RCT)	⊕⊕⊖⊖ LOW [2]	
External genital lesions (any genotype) at up to 3-year follow-up	36/3081 person-years	6/3173 person-years	Rate ratio 0.16 (0.07 to 0.38)	2545 participants (6254 person-years) (1 RCT)	⊕⊕⊕⊖ MODERATE [1]	
Anogenital warts at up to 3-year follow-up	28/2814 person-years	3/2831 person-years	Rate ratio 0.11 (0.03 to 0.38)	2805 participants (5645 person-years) (1 RCT)	⊕⊕⊕⊖ MODERATE [1]	

Overall local/injection site adverse events at 15-day follow-up	537 per 1000	601 per 1000 (569 to 634)	RR 1.12 (1.06 to 1.18)	3895 (1 RCT)	⊕⊕⊕⊕ HIGH[3]	Data for specific local adverse events (pain, swelling, redness at injection site) are presented in the analysis section.
Overall systemic events and general symptoms at 15-day follow-up	248 per 1000	245 per 1000 (223 to 268)	RR 0.99 (0.90 to 1.08)	5008 (2 RCTs)	⊕⊕⊕⊖ MODERATE[4]	
Serious adverse events at up to 3-year follow-up	Control: 11 per 1000	Bivalent vaccine: 17 per 1000 (2 to 141)	OR 1.48 (0.15 to 14.46)	270 (1 RCT)	⊕⊖⊖⊖ VERY LOW [2,4]	In a subgroup from Lehtinen 2018, a cluster-RCT, 58/2436 HPV vaccine recipients (2.4%) and 25/1267 control HBV vaccine recipients (2.0%) experienced serious adverse events. This was also considered very low-certainty evidence[2,4] Please see Table 1 for list of events in each RCT.
	Control: 4 per 1000	Quadrivalent vaccine: 3 per 1000 (1 to 7)	OR 0.69 (0.29 to 1.66)	5162 (2 RCTs)	⊕⊖⊖⊖ VERY LOW [2,4]	Please see Table 1 for list of events in each RCT.
Mortality at up to 3-year follow-up	Control: see comment	Bivalent vaccine: see comment	OR not estimable: see comment	270 (1 RCT)	⊕⊕⊖⊖ LOW [5]	No events were reported
	Control: 4 per 1000	Quadrivalent vaccine: 1 per 1000 (0 to 4)	OR 0.30 (0.09 to 1.01)	5173 (2 RCTs)	⊕⊕⊖⊖ LOW [2]	

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: confidence interval; **HPV:** human papillomavirus; **OR**: odds ratio; **RCT:** randomised controlled trial; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

[1]Downgraded one level for imprecision: few events.
[2]Downgraded two levels for serious imprecision: few events and a wide 95% confidence interval that incorporates a potential large beneficial effect as well as a potential large harmful effect.
[3]Evidence for this outcome was not downgraded: the trial was a large multi-national trial with low risk of bias and precise estimates.
[4]Downgraded one level for indirectness: this outcome is a composite measure of events which may or may not be clinically relevant, may or may not be related to the vaccine and may occur outside a biologically plausible time frame relative to vaccine exposure. This outcome is considered to provide indirect evidence about vaccine safety.
[5]Downgraded two levels for serious imprecision: no events reported.

Summary of findings 4. Nonavalent HPV vaccine compared with quadrivalent HPV vaccine in 9- to 26-year-old females and males

Nonavalent HPV vaccine compared with quadrivalent HPV vaccine in 9- to 26-year-old females and males

Patient or population: 9- to 26-year-old females and males
Setting: community health centres in Asia-Pacific, Europe, Latin America, North America
Intervention: nonavalent HPV vaccine, 3 doses administered at months 0, 2, and 6
Comparison: quadrivalent HPV vaccine, 3 doses administered at months 0, 2, and 6

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with quadrivalent HPV vaccine	Risk with nonavalent HPV vaccine				
High-grade cervical intraepithelial neoplasia, adenocarcinoma in situ, and cervical cancer at up to 4.5-year follow-up	47 per 1000	47 per 1000 (41 to 55)	OR 1.00 (0.85 to 1.16)	13,753 (1 RCT)	⊕⊕⊕⊕ HIGH[1]	No studies were identified which reported on invasive anal or penile cancer in males
High-grade cervical, vulval, and vaginal disease at up to 4.5-year follow-up	49 per 1000	48 per 1000 (42 to 56)	OR 0.99 (0.85 to 1.15)	14,054 (1 RCT)	⊕⊕⊕⊕ HIGH[1]	No studies were identified which reported on penile or anal intraepithelial neoplasia in males
Overall local/injection site adverse events at 15-day follow-up	846 per 1000	905 per 1000 (888 to 914)	RR 1.07 (1.05 to 1.08)	15,863 (3 RCTs)	⊕⊕⊕⊕ HIGH	Data for specific local adverse events (pain, swelling, redness at injection site) are presented in the analysis section.
Overall systemic events and general symptoms at 15-day follow-up	543 per 1000	548 per 1000 (532 to 565)	RR 1.01 (0.98 to 1.04)	15,863 (3 RCTs)	⊕⊕⊕⊖ MODERATE[3]	

Serious adverse events at up to 4.5-year follow-up	25 per 1000	15 per 1000 (4 to 63)	OR 0.60 (0.14 to 2.61)	15,863 (3 RCTs)	⊕⊕⊖⊖ LOW [2,3]	Please see Table 1 for list of events in each RCT. Numbers of events/number of participants (%) were: in 16- to 26-year-old females receiving nonavalent vaccine, 242/7686 (3.1%) vs quadrivalent vaccine, 184/7078 (2.6%) over a period of 4.5 years follow-up; in 16- to 26-year-old males receiving nonavalent vaccine, 0/249 (0%) vs quadrivalent vaccine, 6/251 (2.4%) over 7 months follow-up; in 9- to 15-year-old females receiving nonavalent vaccine, 1/299 (0.3%) vs quadrivalent vaccine, 2/300 (0.7%) over 7 months follow-up.
Mortality at up to 4.5-year follow-up	1 per 1000	1 per 1000 (0 to 3)	OR 1.20 (0.37 to 3.94)	15,248 (3 RCTs)	⊕⊕⊖⊖ LOW [4]	

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: confidence interval; **HPV:** human papillomavirus; **OR**: odds ratio; **RCT:** randomised controlled trial; **RR:** risk ratio; **SAE:** serious adverse event

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

[1]Evidence from this outcome was not downgraded: the included trial was a large multi-national trial with low risk of bias and precise estimates.
[2]Downgraded one level for imprecision: pooled estimate has a wide 95% confidence interval that incorporates a potential large beneficial effect and a potential large harmful effect.
[3]Downgraded one level for indirectness: this outcome is a composite measure of events which may or may not be clinically relevant, may or may not be related to the vaccine and may occur outside a biologically plausible time frame relative to vaccine exposure. This outcome is considered to provide indirect evidence about vaccine safety.
[4]Downgraded two levels for serious imprecision: few events and a wide 95% confidence interval that incorporates a potential large beneficial effect and a potential large harmful effect.

BACKGROUND

Description of the condition

Human papillomavirus (HPV) is the most common viral infection of the reproductive tract in women and men (WHO 2017). Although most HPV infections resolve spontaneously, persistent infections can lead to precancerous lesions and cancer of the cervix, vagina, vulva, anus, penis, and head and neck. HPV-related cancers accounted for an estimated 4.5% of all cancers worldwide in 2012 (de Martel 2017). When stratified by sex, these represent 8.6% of cancers in women and 0.8% of cancers in men, and by development status, 6.7% of all cancers in low- and middle-income countries and 2.8% in high-income countries (de Martel 2017). In 2012, of an estimated 636,000 HPV-related cancers worldwide, 530,000 were cervical cancer, 35,000 anal cancer, 8500 vulval cancer, 13,000 penile cancer, and 37,000 head and neck cancers (de Martel 2017).

Amongst women with normal cytological findings, the worldwide prevalence of infection with any HPV genotype has been estimated in a meta-analysis to be 11.7%, with higher prevalence in sub-Saharan Africa, Latin America, the Caribbean, south-east Asia and eastern Europe (Bruni 2010). Amongst heterosexual men assessed at baseline in a multicentre trial in 18 countries in Africa, Asia-Pacific, Europe, Latin America and North America, penile infection with any HPV genotype was found in 18.7%, scrotal infection in 13.1%, perianal infection in 7.9% and infection at any site in 21.0%. Prevalence was highest in Africa and lowest in the Asia-Pacific region (Vardas 2011). Prevalence of HPV infections in general is higher in men with HIV infection, men who have sex with men (MSM), and highest in MSM with HIV infection (Schim van der Loeff 2014; Smith 2011).

The main types of lesions associated with anogenital HPV infection are anogenital warts (condylomata acuminata) and intraepithelial neoplasia of the cervix (cervical intraepithelial neoplasia, CIN), vulva, vagina, anal canal/perianal area, and penis. Intraepithelial neoplasia is a precursor of some of these cancers, although it can regress at earlier stages and does not progress to invasive cancer in most affected people. A study that followed up women with inadequately treated CIN3 found that 31.3% (95% CI 22.7 to 42.3) developed invasive cancer after 30 years (McCredie 2008). HPV is also associated with squamous cell cancer of the head and neck (HNSCC). Of all head and neck cancers globally in 2012 (534,000), about 7% (37,000) were attributable to HPV, including 29,000 of 96,000 (31%) cases of oropharyngeal cancer (de Martel 2017). The incidence of cancers of the oropharynx has increased over time, more amongst men than women (Gillison 2015). It is likely that HPV is a main contributor to the increase in men, whilst smoking dominates the rise in women (Gillison 2015).

The International Agency for Research on Cancer classifies HPV genotypes according to oncogenic potential, with HPV genotypes 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59 considered as high-risk genotypes (Bouvard 2009). HPV 16 and 18 are the most common genotypes in women worldwide and are associated with most cases of invasive cervical cancer; combined, HPV 16, 18, 31, 33, 45, 52 and 58 cause approximately 90% of all HPV-positive squamous cell carcinomas of the cervix (Alemany 2014; Bruni 2010; de Sanjose 2010). HPV 16 and 18 are also the cause of 90% of all anal cancers (Bosch 2002). HPV 16 is found in around 80% of HPV-related anal squamous cell cancers, in 52% of invasive penile squamous cell carcinoma, and in 90% of penile intraepithelial neoplasia (Krustrup 2009; Schim van der Loeff 2014). In a meta-analysis, HPV was detected in 22% of HNSCC, with 86.7% of those being attributed to HPV 16, although HPV 6 and 11 were also detected in a minority of cases (Syrjänen 2010). HPV 6 and 11 account for up to 90% of anogenital warts (Greer 1995; Sturegard 2013).

Description of the intervention

Three prophylactic HPV vaccines, given by intramuscular injection, are available. All three vaccines are made by genetic technologies and are non-infectious because they do not contain viral DNA. They are made from purified L1 capsid proteins, which form virus-like particles that resemble the structure of specific genotypes of HPV. Each vaccine is directed against two or more high-risk HPV genotypes. All three vaccines contain L1 proteins of HPV genotypes 16 and 18 (WHO 2017), because these cause about 70% of cervical cancer globally. The vaccines are commonly known by the number of different genotypes that they contain (i.e. the valency, Table 2). The bivalent vaccine contains L1 proteins of two HPV genotypes; 16 and 18. The quadrivalent vaccine contains L1 proteins of four HPV genotypes; 16 and 18, plus HPV 6 and 11, which cause genital warts. The nonavalent vaccine is the most recent vaccine and contains L1 proteins of nine HPV genotypes; 16, 18, 31, 33, 45, 52 and 58, plus HPV 6 and 11. All three vaccines contain adjuvants (Table 2). In addition to the licensed vaccines, as of September 2018, there are three vaccines in stage 2 to 3 development, two bivalent vaccines manufactured by Innovax and Walvax in China, and a quadrivalent vaccine manufactured by the Serum Institute of India (LaMontagne 2017).

To prevent HPV infection, all HPV vaccines are intended to be administered, where possible, before the first exposure to HPV, that is, before onset of sexual activity. All national HPV vaccination programmes involve girls, and some countries have extended their programme to boys. According to most modelling studies, HPV vaccination programmes for preadolescent girls will be cost-effective for the prevention of cervical cancer, particularly in settings in which infrastructure for cervical cancer screening is poor (WHO 2017). HPV vaccination of females gives indirect protection to males. These so-called herd effects mean that, at the population level, female-only vaccination programmes have resulted in reductions in HPV infections in both men and women (Drolet 2019). However, herd effects from female-only vaccination do not affect MSM, who experience a high burden of anal cancer and anogenital warts. Modelling studies also indicate that female-only HPV vaccination, even at high levels of coverage, will not prevent all HPV-related cancers in heterosexual men (Bogaards 2015). The cost-effectiveness of vaccinating boys depends on vaccination coverage in girls, the epidemiology of HPV-related disease, and the costs of the vaccine and the programme (WHO 2017).

The uptake of HPV vaccination varies widely between countries that have introduced it as part of their national immunisation programmes. In 2017, across 82 countries coverage rates ranged from 8% to 98% (Brotherton 2018). To date, few countries in Africa and Asia have introduced HPV vaccine. Whilst there is evidence from some low- and middle-income countries (LMICs) that HPV vaccine can be effectively introduced, countries with challenges have also been reported. For example, Uganda reported coverage of more than 80% for the first dose of a two-dose vaccine schedule, but this was not sustained for the second dose (Brotherton 2018). In high-income countries, such as England, Scotland, and Australia, school-based programmes have reached 70% to 80% of girls for

all doses. In other high-income countries, such as France, USA, Japan and Denmark, coverage has either not reached, or has fallen below 50%. The reasons for low coverage differ between countries, but include organisation of programme implementation, resistance from healthcare providers, adverse media coverage, and concerns about safety (Gallagher 2018).

How the intervention might work

HPV vaccines containing virus-like particles of the L1 protein are prophylactic, meaning that they prevent infection and the development of intraepithelial lesions caused by HPV genotypes that are present in the vaccine (Stanley 2006). The virus-like particles in the vaccines produce very high levels of antibodies in serum, but the exact mechanisms by which the vaccines prevent HPV infection are not completely understood. The levels of antibodies needed to provide protection against clinical disease caused by HPV (known as the immunological correlate of protection) have not been established because the number of breakthrough infections after vaccination has been too low. The International Agency for Research on Cancer regards persistent HPV infection with HPV types 16 and 18, measured with standardised and validated tests, as an accurate surrogate marker for the precancerous lesions of the cervix and anus (IARC 2014). Post-licensure data from national immunisation programmes show reductions in high-grade lesions of the cervix and anus with three-dose regimens of the bivalent and quadrivalent vaccines (Markowitz 2018). Since precancer is on the causal pathway to invasive cancer, it is assumed that prevention of precancerous lesions will also be shown to prevent cancer when sufficient follow-up time has accrued in post-licensure studies. Less is known about the prognostic value of persistent HPV infection in the development of vaginal, vulval and oropharyngeal cancers (IARC 2014).

All of the randomised controlled trials (RCTs) that established the efficacy of HPV vaccines in the prevention of high-grade precancerous lesions of the cervix used a three-dose vaccination schedule (Arbyn 2018). Because of low HPV exposure and ethical constraints in conducting research that requires genital examination and specimen collection in adolescent populations (under 15 years of age), randomised efficacy trials of vaccines have typically been first conducted in women aged 15 to 25 or 26 years (Arbyn 2018). Once immunogenicity and harms have been evaluated, non-inferiority of immunological outcomes in 9- to 15-year-olds is assessed in non-randomised bridging studies (e.g. Block 2006; Dobson 2013). The International Agency for Research on Cancer regards bridging studies that demonstrate non-inferiority as a sufficient endpoint for individuals under 16 years of age (IARC 2014).

Vaccine schedules are designed to produce a strong and long-lasting antibody response so that, when challenged by exposure to the real pathogen, the immune system prevents infection. A three-dose vaccine schedule is typical for inactivated protein vaccines for infants; the second dose is given one or two months after the first dose and a third dose six months after the first dose. The first two vaccine doses are called 'prime' doses that generate immune memory via B-lymphocytes produced in the bone marrow (Stanley 2014). The second dose results in higher levels of antibodies than the first and increases the binding affinity of the antibody to the antigen, in a process that lasts several months. As a result of this process (affinity maturation), B cells with very high levels of affinity, differentiate in the bone marrow into memory B cells that respond rapidly to produce antibodies on exposure to antigen and long-lived plasma cells that continuously produce antibody at low levels. A third vaccine dose given at least four months after the prime doses 'boosts' these responses maximally to provide long-lasting protection (Stanley 2014).

Simplified HPV vaccination schedules with fewer doses should allow more people to receive the vaccine. Preadolescents and adolescents (age 9 to 15 years) produce stronger antibody responses to virus-like protein HPV vaccines than older adolescents and adults (Block 2006; Dobson 2013), even after a single dose (Sankaranarayanan 2016). It appears that multiple repeated doses of these vaccines are not required for affinity maturation and that long-lived plasma cells are more important than memory B cells in the immune response (Schiller 2018). It is thought that structural characteristics of the virus-like particles allow efficient production of the long-lived plasma cells, which continuously produce antigen-specific antibodies, resulting in strong long-lasting immune responses with reduced dose schedules (Schiller 2018).

Evidence of the likely efficacy of a two-dose schedule of virus-like particle HPV vaccines in preventing incident vaccine-type HPV infection comes from studies in which data from RCTs were analysed as cohort studies according to the number of doses of HPV vaccine received (Kreimer 2011; Sankaranarayanan 2016). Kreimer and colleagues conducted a secondary analysis of data from an RCT of the bivalent vaccine amongst 18- to 25-year-old women in Costa Rica (Kreimer 2011). In that trial, 20% of women did not receive all three doses of the vaccine. Women were grouped according to the number of HPV vaccine doses that they received. The proportions of women with incident HPV 16/18 infection that persisted for 12 months or more was similar amongst women who received one, two and three doses (Kreimer 2011). An updated analysis combined data from this Costa Rica vaccine trial and a pivotal trial of the bivalent vaccine, Paavonen 2007, according to number of doses received after four years of follow-up (Kreimer 2015). In the modified total vaccinated cohort, vaccine efficacy against HPV 16/18 incident infection that persisted for 12 months or more was 83.7% (95% CI 35.7 to 97.5%) with two doses, and 92.6% (95% CI 89.2 to 95.1%) with three doses. Sankaranarayanan and colleagues analysed an RCT of the quadrivalent vaccine in 10- to 18-year-olds in India (which was stopped before enrolment was completed) according to the number of HPV vaccine doses received (Sankaranarayanan 2016). Incidence of HPV 16/18 was 0.8% (95% CI 0.2 to 1.9%, 4/526) amongst participants who received two doses, and 0.4% (95% CI 0.0 to 1.3%, 2/536) amongst those who received three doses (Sankaranarayanan 2016). Additional data from a systematic review of post-licensure studies in national HPV vaccination programmes, show the receipt of two doses of HPV vaccine was associated with a reduction in the incidence of vaccine-type HPV prevalence, anogenital warts and cervical abnormalities in some, but not all, studies (Markowitz 2018).

Why it is important to do this review

In practice, HPV vaccination rates in many countries remain low.

Simpler HPV immunisation schedules have been identified as a potential strategy to increase the coverage of vaccination (Walling 2016). The World Health Organization (WHO) recommended a two-dose HPV vaccine schedule in 2014, based on a systematic review of studies with immunogenicity as the end-point (D'Addario

2017; WHO 2017). As of 30 December 2017, 80 countries had fully introduced HPV vaccination and four countries had partially introduced HPV vaccination into their national immunisation programmes, with 65 countries having implemented a two-dose schedule in girls 9 to 14 years old (www.who.int/immunization/monitoring_surveillance/data/en).

In 2018, a Cochrane Review concluded that the licensed three-dose schedules of the bivalent and quadrivalent HPV vaccines result in limited adverse events and are effective against precancerous cervical lesions in females (Arbyn 2018). Since the 2014 WHO recommendation and original systematic review of two-dose HPV vaccination schedules (D'Addario 2017; WHO 2017), the evidence base from RCTs about alternative vaccination schedules has expanded to include more data about the nonavalent HPV vaccine (Iversen 2016), about HPV vaccination in males, including MSM (Giuliano 2011), and amongst people living with HIV infection (Toft 2014). This review was initially commissioned in 2016 by the WHO Initiative for Vaccine Research to update the evidence for the two-dose recommendation and is an update of D'Addario 2017. We produced a revised protocol for this update (Bergman 2017).

Cochrane Reviews usually include only RCTs with major clinical disease endpoints because RCTs provide the highest level of certainty about critical outcomes of interventions. However, precancer and cancer do not develop until many years after the acquisition of HPV infection, so it is difficult to determine the efficacy of vaccines against these outcomes. Persistent HPV infection is considered by the International Agency for Research on Cancer to be sufficient as a surrogate marker for cervical and anal cancer and non-inferiority of immunogenicity is sufficient to bridge results to under-16-year-olds. It is therefore important to document all infection and immunological outcomes measured in RCTs of HPV vaccines, even if the intended use of the vaccine is to prevent cancer.

This review aims to extend the evidence base on the efficacy and harms of HPV vaccines by including and evaluating RCTs of different HPV vaccines and different dose schedules in adolescent and adult females and males, as well as women and men living with HIV infection.

While RCTs can identify adverse events that take place during the study period, post-marketing surveillance is needed to continue monitoring harms associated with HPV vaccines in the population, and will be incorporated in future updates of this review.

OBJECTIVES

To evaluate the efficacy, immunogenicity, and harms of different dose schedules and different types of HPV vaccines in females and males.

METHODS

Criteria for considering studies for this review

Types of studies

We included RCTs with no language restrictions. We included unpublished studies, studies in press, and abstracts without a full-text publication, if they met the inclusion criteria.

Types of participants

Females or males aged 9 to 26 years, including MSM. For the comparisons among people living with HIV, we included all age groups.

Types of interventions

Prophylactic administration of licensed bivalent (Cervarix, GlaxoSmithKline), quadrivalent (Gardasil, Merck), or nonavalent (Gardasil 9, Merck) HPV vaccines. We excluded studies if they assessed monovalent or plasmid vaccines, or assessed non-prophylactic uses of bivalent, quadrivalent or nonavalent vaccines. In addition, we considered for inclusion any trials reporting on the efficacy, immunogenicity, or adverse events in vaccines currently in phase 2 or 3 development. Studies comparing bivalent versus quadrivalent vaccines were excluded, as these will be included in an update of a separate Cochrane Review (Arbyn 2018).

For males and people living with HIV, we included comparisons of HPV vaccines to placebo containing no adjuvant or only the adjuvant of the HPV vaccine, or another HPV vaccine.

In this review, we use the term 'control' to refer to comparator products that contain another vaccine or only vaccine adjuvants, regardless of the terminology used in individual study reports. We use the term 'placebo' only to refer to comparator products containing no adjuvant or active vaccine. In Characteristics of included studies we have reported full details of the type of comparison group compound.

The focus of the review was on different dose schedules and comparisons between different types of HPV vaccine. Where possible we stratified data by participant characteristics of age, gender, and HIV status. Specifically, we aimed to investigate the efficacy, immunogenicity, and harms of:

- fewer than three doses of HPV vaccine in females and males;
- different intervals between doses in a two-dose schedule in females and males;
- HPV vaccination compared to control for males (a Cochrane Review for females has been published (Arbyn 2018));
- nonavalent HPV vaccine compared to the other HPV vaccines in females and males;
- HPV vaccination in people living with HIV.

Types of outcome measures

Primary outcomes

Unless otherwise stated, primary outcomes were assessed at the longest follow-up time reported by the included studies.

- Invasive cervical, vaginal, vulval, anal, or penile cancer
- In females, histologically-confirmed high-grade cervical (CIN2, CIN3, and adenocarcinoma in situ), vaginal, vulval, or anal intraepithelial neoplasia, irrespective of HPV genotype, or any lesions associated with the HPV genotypes included in the vaccine
- In males, histologically-confirmed anal, or penile, perianal or perineal intraepithelial neoplasia of any grade, irrespective of HPV genotype, or any lesions associated with the HPV genotypes included in the vaccine
- Anogenital warts

- Adverse events related to the vaccines: local adverse events (overall local/injection site adverse events, redness, swelling, pain at the injection site), assessed at the follow-up times reported in the trials (usually up to seven days); overall systemic events and general symptoms assessed at the follow-up times reported in the trials (usually up to 15 days)
- Serious adverse events and mortality: any events that are fatal, life-threatening, or result in hospitalisation and mortality. We collected information from each trial about whether these events were considered to be vaccine-related and the methods of adverse events data monitoring and collection, including mode of data collection, timing, attribution methods, intensity of ascertainment, harms-related monitoring and stopping rules, and reporting based on event frequency (i.e. frequency-based filter), based on the CONSORT statement extension for reporting harms (Ioannidis 2004; Lineberry 2016).

Secondary outcomes

Unless otherwise stated, secondary outcomes were assessed at the longest follow-up time reported by the included studies.

- Incident infection with vaccine HPV genotypes (HPV 16 and HPV 18 jointly; HPV 6, HPV 11, HPV 16 and HPV 18 jointly; and HPV 31, HPV 33, HPV 45, HPV 52, and HPV 58 jointly)
- Persistent infection (persisting for at least six months or at least 12 months) with vaccine HPV genotypes
- Immunological outcomes (geometric mean titre (GMT) and seropositivity), assessed at one month following the last dose and at the longest-term follow-up

For the comparisons of dose schedules (i.e. number of doses and longer or shorter interval(s) between doses) we considered immunological outcomes as primary outcomes because these trials were designed to show non-inferiority of immunogenicity. While these trials were not designed to evaluate efficacy or safety of the vaccines, we have included clinical outcomes when reported and comparative estimates of harms associated with the different dose schedules.

Search methods for identification of studies

We attempted to identify all relevant studies regardless of language or publication status (published, unpublished, in press and in progress).

Electronic searches

All searches were conducted on 27 September 2018. We searched the following electronic databases:

- the Cochrane Central Register of Controlled Trials (CENTRAL, Issue 9, 2018) (published in the Cochrane Library)
- Ovid MEDLINE (1946 to September week 2 2018);
- Ovid Embase (1980 to 2018 week 39).

The search terms used are detailed in Appendix 1, Appendix 2, and Appendix 3. We also searched ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform (ICTRP) to identify ongoing trials using 'genital warts', 'condyloma', 'anogenital warts', 'venereal warts', 'human papilloma virus vaccine', and 'HPV vaccine' as search terms.

Searching other resources

We searched the reference lists of all included studies, as well as the reference lists of any relevant systematic reviews published within the search dates. We searched vaccine manufacturer web sites for relevant clinical trial reports (GlaxoSmithKline; Merck). In addition, we screened a list of HPV vaccine studies (Jørgensen 2018a), that was constructed through enquiries to HPV vaccine manufacturers and regulators, as well as searches of trial registers and journal publication databases. For each included study, where available, we identified and screened study governance documents (protocols, trial registration listings and results, manufacturers' clinical study reports) for relevant data and outcomes. We also contacted the vaccine manufacturers through the WHO Initiative for Vaccine Research for any additional, potentially relevant studies.

Data collection and analysis

Selection of studies

Two experienced systematic reviewers independently screened citations and abstracts of studies identified from the electronic searches for potential inclusion. A third reviewer resolved any disagreements. We obtained full-text reports for all potentially eligible studies. Two independent reviewers determined the eligibility of studies for inclusion in the review from the full reports according to predefined criteria. A third reviewer resolved any disagreements.

Data extraction and management

For the purpose of the review, we named studies on the basis of the first-named study author and year of publication. Many studies have more than one document associated with them: journal publications (main study reports, reports of long-term follow-up, secondary outcomes and post-hoc analyses), conference abstracts, and study governance documents (protocols, trial registration listings and results, manufacturers' clinical study reports). For each study we grouped these documents together and designated one report as the primary reference for the study; the study name is derived from the name of the first author and year of publication of this particular report.

In cases where study reports emanate from the same parent study, but are planned or reported, or both, as distinct, discrete studies, we have named and handled these separately.

Two reviewers carried out data extraction independently using pretested data extraction forms. We resolved any differences by discussion between the two reviewers and referral to the study reports.

We cross-checked data for the efficacy outcomes and adverse events between the primary trial publications, trial registries, and clinical study reports. We used the data derived from these sources with the longest follow-up time for the primary analysis.

Assessment of risk of bias in included studies

Two reviewers independently carried out 'Risk of bias' assessments using the Cochrane 'Risk of bias' tool for all included studies (Higgins 2011b). We judged the risk of bias for each domain as 'low risk', 'unclear risk' or 'high risk'. We resolved differences by discussion between the two reviewers and if necessary we referred to a third reviewer for arbitration.

Measures of treatment effect

We calculated risk ratios (RR) with 95% confidence intervals (CI) for dichotomous outcomes. We calculated rate ratios with 95% CIs for dichotomous clinical outcomes reported as incidence rates. For outcomes with rare events (i.e. an event rate of < 10%), serious adverse events, and deaths, we calculated Mantel-Haenszel odds ratios (OR) for dichotomous outcomes. We assessed the robustness of the primary analysis for very rare events with alternative statistical methods (see Sensitivity analysis).

For continuous geometric mean titre (GMT) data, we calculated inverse variance (IV) ratios of GMTs with 95% CIs. Initially, we transformed the point estimates as well as the lower and upper bound of the 95% CI of GMT for each group into the logarithmic scale in order to obtain statistically correct standard deviations. Then we calculated the mean difference of the compared group and back-transformed the results (point estimate and 95% CIs) to the original scale through exponentiation. Non-inferiority margins for immunological outcomes were derived from the individual trials (all trials used 0.5 for the GMT ratio). For GMT ratios non-inferiority is demonstrated if the lower 95% CI is greater than 0.5. If the lower confidence interval was below the non-inferiority margin, but the point estimate was within the margin, we considered the result to be inconclusive (Piaggio 2012).

For adverse events and efficacy outcomes we carried out a complete-case analysis (the number analysed) and an intention-to-treat analysis when data were available. For immunogenicity outcomes assessed in non-inferiority trials, we favoured data from per-protocol analyses, in which all participants were HPV-seronegative at baseline. We did not pool studies with participants who were HPV-seropositive at baseline with studies with participants who were HPV-seronegative at baseline.

Unit of analysis issues

If a single trial compared two or more vaccine arms (with or without a control arm), we labelled the arms separately in analyses. We grouped suitable multiple treatment arms (e.g. arms that evaluated different vaccine lots) and excluded irrelevant trial arms. We did not pool data from cluster RCTs with those from individually randomised studies.

Dealing with missing data

If data on specific outcomes or population groups were missing, we attempted to contact study authors or data owners to request this data. We did not impute missing outcome data. Where data were missing or losses to follow-up were substantial, we downgraded the certainty of study evidence due to risk of bias according to GRADE criteria (Guyatt 2011a).

Assessment of heterogeneity

We described potential sources of clinical heterogeneity, and downgraded the certainty of the evidence according to GRADE criteria due to inconsistency where appropriate (Guyatt 2011b). When pooling of studies was feasible (i.e. at least two studies included), we inspected forest plots visually for potential outlying studies and variability in the estimated effects across studies. We assessed statistical heterogeneity using the I^2 statistic. This statistic quantifies the percentage of inconsistency in the treatment effects across studies beyond simple chance. We regarded heterogeneity as potentially unimportant if the I^2 was 0% to 40%; that values of 30% to 60% might represent moderate heterogeneity; values between 50% to 90% might represent substantial heterogeneity; and that values between 75% to 100% would represent considerable heterogeneity (Higgins 2011a). Where considerable heterogeneity existed (>75%), we did not pool study data.

Assessment of reporting biases

We had planned to use funnel plots to investigate the possible presence of small-study effects for each outcome. However, we did not produce funnel plots, due to the limited number of studies per outcome (i.e. fewer than 10) (Guyatt 2011c).

Data synthesis

When pooling was considered feasible, we employed a random-effects meta-analysis using the DerSimonian and Laird method (DerSimonian 1986), as it was assumed that effect size might vary across studies and settings. We used data from the last available follow-up for clinical and adverse event outcomes, with the number of participants (rather than the number of events) used in the analysis. For immunological outcomes, we extracted data from one month after the last HPV dose and at the longest-term follow-up.

To assess the harms associated with the HPV vaccine comparisons in this review, we recorded the methods used in each included study to collect adverse event data, and extracted data on common events that we determined a priori as: pain, swelling, redness at the injection site and overall systemic adverse events. For all serious adverse events reported in the included studies, we extracted the number of participants, participants with events and a description of the events. We also extracted information on whether the serious adverse events were considered to be related to the vaccines. We did not conduct statistical hypothesis testing because our protocol did not prespecify hypotheses about differences in the occurrence of any specific serious adverse event.

We prepared 'Summary of findings' tables for each comparison for which data were available for the following outcomes that were assessed as critical or important according to GRADE guidelines (Guyatt 2011d):

- for females: high-grade cervical intraepithelial neoplasia, adenocarcinoma in situ, or cervical cancer; high-grade vulval and vaginal disease;
- for males: invasive anal or penile cancer, external genital lesions;
- for all populations: anogenital warts, overall local/injection site adverse events, overall systemic events and general symptoms, serious adverse events, deaths;
- for comparisons of dose schedules (i.e. number of doses and longer or shorter interval between doses): immunological outcomes.

We assessed the certainty of evidence in the review through discussion between review authors using the GRADE approach using GRADEpro online software (GRADEpro GDT). We assessed only the primary outcomes reported in the 'Summary of findings' tables and appendices using GRADE. We considered the following factors for downgrading: limitations in the study design (risk of bias); inconsistency of results (heterogeneity); indirectness of evidence (applicability); imprecision (few events and wide

confidence intervals); and publication bias (Guyatt 2011a). When evidence was downgraded, we detailed the reasons in footnotes of the 'Summary of findings' tables and summarised these in the Quality of the evidence section. Depending on whether evidence was downgraded or not, we rated the certainty of the evidence for each outcome as follows:

- high-certainty evidence indicates that we are very confident that the true effect lies close to that of the estimate of the effect (evidence was not downgraded);
- moderate-certainty evidence indicates that we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different (evidence was downgraded one step for any of the factors described above);
- low-certainty evidence indicates that our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect (evidence was downgraded two steps for any of the factors described above);
- very low-certainty evidence indicates that we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect (evidence was downgraded three steps for any of the factors described above).

We reported relative risks (ORs or RRs) in the Effects of interventions section for all relevant outcomes, but where the evidence was of very low-certainty we reported the number of events in each group only.

Subgroup analysis and investigation of heterogeneity

We performed subgroup meta-analyses where possible, using vaccine type, gender, and age group (9 to 15 years; 16 to 26 years) as stratifying variables.

Sensitivity analysis

We carried out one post-hoc sensitivity analysis for outcomes using a Mantel-Haenszel odds ratio where events were very rare (i.e. an event rate of < 1% across both trial arms). We compared the results of the primary analysis calculated with Mantel-Haenzsel methods against those with Peto methods (Bradburn 2007). We also planned to conduct sensitivity analyses for the primary outcomes according to allocation concealment (high risk of bias, low risk of bias, and unclear risk of bias) for outcomes for which data could not be pooled because of considerable heterogeneity (I^2 > 75%).

RESULTS

Description of studies

Overall, 20 RCTs were included for analysis in this review (Figure 1). The characteristics of individual studies and assessment of risk of bias are presented in the Characteristics of included studies section and Figure 2.

Figure 1. Study flow diagram.

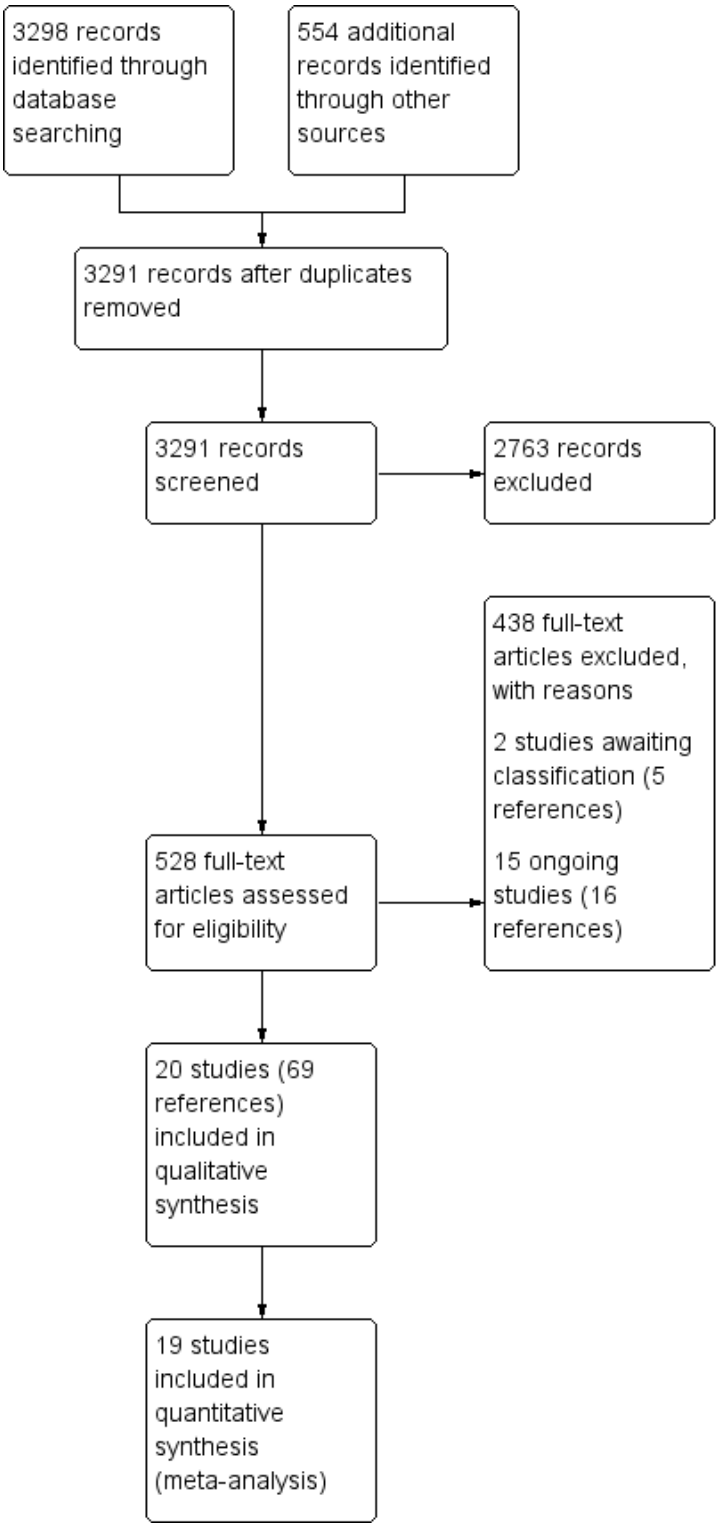


Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

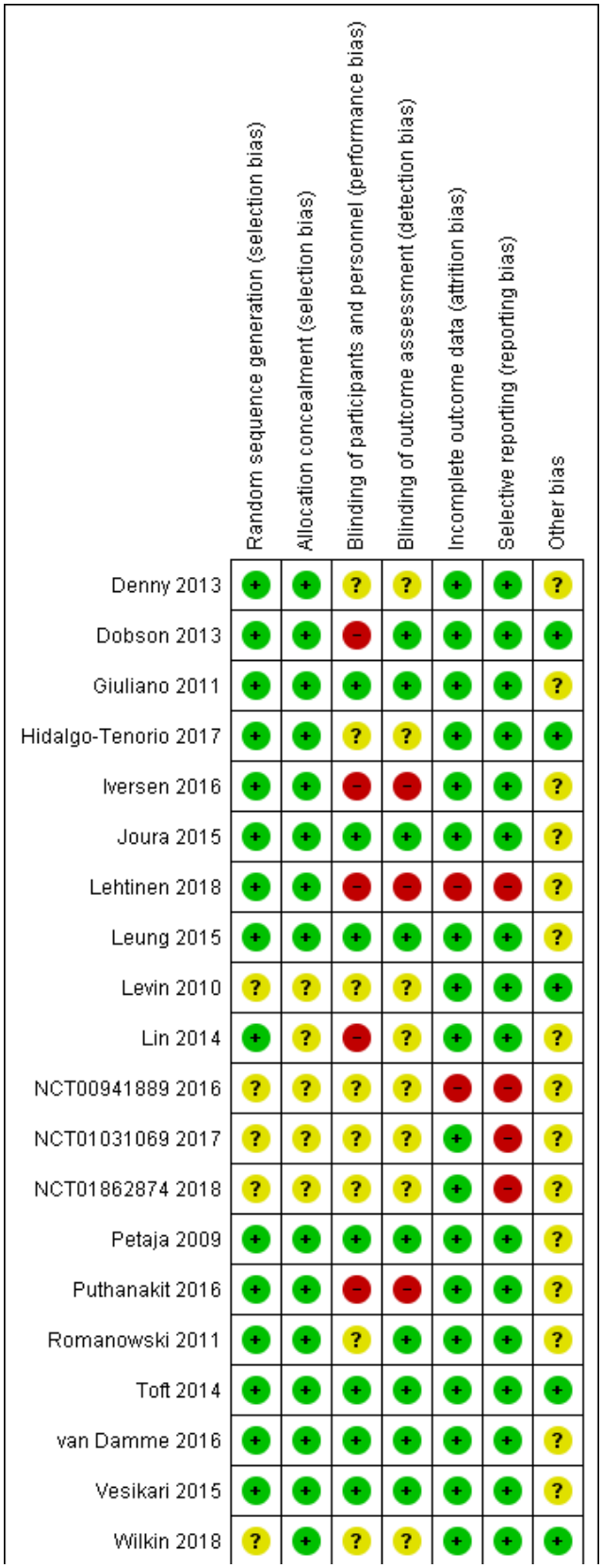
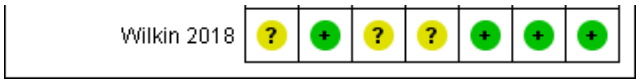


Figure 2. (Continued)



Results of the search

The search identified a total of 3852 records; 3298 from electronic databases and 554 from other sources (systematic reviews, vaccine manufacturers, online trial registrations, WHO IVR department, HPV study index (Jørgensen 2018a)). After de-duplication, 3291 records remained. After excluding irrelevant abstracts, we assessed 528 full texts. We excluded 438 full texts and included 20 RCTs (reported in 69 published and unpublished reports) in this review for analysis (Denny 2013; Dobson 2013; Giuliano 2011; Hidalgo-Tenorio 2017; Iversen 2016; Joura 2015; Lehtinen 2018; Leung 2015; Levin 2010; Lin 2014; NCT00941889 2016; NCT01031069 2017; NCT01862874 2018; Petaja 2009; Puthanakit 2016; Romanowski 2011; Toft 2014; van Damme 2016; Vesikari 2015; Wilkin 2018). We identified 15 ongoing studies (reported in 16 records) and two studies (reported in five references) are awaiting classification.

Included studies

We found 20 RCTs that contained data on vaccine efficacy or harms, or both, and enrolled a total of 31,940 men, women, and children. Ten studies were multi-national and were carried out in two to 18 countries in Africa, Asia, Asia-Pacific, Europe, Latin America, North America, and South America. The other 10 studies were carried out in one country only (USA, including Puerto Rico (3 studies), Finland (2), Canada (1), Denmark (1), Japan (1), Spain (1), South Africa (1)). Owing to differences in the protocols of the included trials, the maximum age for inclusion was either 25 or 26 years.

Description of studies

Four RCTs evaluated the effects of reduced dose schedules (Dobson 2013; Iversen 2016; Leung 2015; Romanowski 2011). All these trials were designed as non-inferiority trials of antibody responses. They reported on immunogenicity as the primary outcome and on adverse events. None of these trials collected data on clinical events. These four RCTs evaluated the effects of two doses of HPV vaccine versus three doses of HPV vaccine in adolescent girls (9 to 15 years). We did not identify any RCTs that evaluated the efficacy or harms of one dose of HPV vaccine.

Four RCTs compared different intervals between doses. Two RCTs compared a longer interval two-dose schedule with a shorter schedule (0 and 6 months versus 0 and 2 months; or 0 and 12 months versus 0 and 6 months) of bivalent HPV vaccine in 9- to 14-year-old females (Puthanakit 2016; Romanowski 2011). One RCT of nonavalent HPV vaccine compared a two-dose schedule with a longer interval (0 and 12 months) and a shorter interval (0 and 6 months) in 9- to 14-year-old females and males (Iversen 2016). One RCT compared a longer interval three-dose schedule (administered at 0, 2 and 12 months) with a shorter schedule (administered at 0, 2 and 6 months) of quadrivalent HPV vaccine in 18- to 25-year-old males (Lin 2014).

Two RCTs compared quadrivalent HPV vaccine versus control in 5189 males aged 16 to 26 years (Giuliano 2011; NCT01862874 2018). A subgroup analysis of Giuliano 2011 also reported on the efficacy and harms of the quadrivalent HPV vaccine compared with control vaccine in MSM. Giuliano 2011 reported on clinical, adverse event, and immunogenicity outcomes, and NCT01862874 2018 reported on clinical outcomes and adverse events. One RCT compared bivalent HPV vaccine versus control hepatitis B virus (HBV) vaccine in 270 boys aged 10 to 18 years and reported on immunogenicity and harms (Petaja 2009). In addition, a cluster-RCT investigating both direct and indirect effects of HPV vaccination of girls and boys (gender-neutral) and girls-only vaccination reported on adverse events in a subgroup of 3703 12- to 15-year-old males vaccinated with the bivalent vaccine or control HBV vaccine (Lehtinen 2018). We identified no studies investigating the clinical efficacy of the nonavalent vaccine in males.

Three RCTs compared three doses of nonavalent vaccine with three doses of quadrivalent vaccine: one in 9- to 15-year-old females (Vesikari 2015), one in 16- to 26-year-old females (Joura 2015), and one in males aged 16 to 26 years (van Damme 2016). Joura 2015 reported clinical outcomes for the 16- to 26-year-old population. All three studies reported on adverse event and immunogenicity outcomes.

Studies including participants living with HIV

We identified seven RCTs that examined HPV vaccines in 1723 people living with HIV (Denny 2013; Hidalgo-Tenorio 2017; Levin 2010; NCT00941889 2016; NCT01031069 2017; Toft 2014; Wilkin 2018):

- Toft 2014 compared bivalent with quadrivalent vaccine in females and males ≥ 18-years old;
- NCT01031069 2017 compared bivalent with quadrivalent vaccine in 15- to 25-year-old females;
- Denny 2013 compared bivalent vaccine with control in women aged 18 to 25 years;
- Hidalgo-Tenorio 2017 compared quadrivalent vaccine with control in MSM ≥ 18-years old;
- Wilkin 2018 compared quadrivalent vaccine with control in females and males ≥ 27-years old;
- NCT00941889 2016 compared quadrivalent vaccine with control in females and males ≥ 18-years old that had been treated for anogenital warts;
- Levin 2010 compared three doses of quadrivalent vaccine with control in 126 children aged 7 to 12 years, and four versus three doses of quadrivalent vaccine in the same participants.

The studies were carried out in Brazil, Denmark, Estonia, India, South Africa, Spain, Thailand, and the USA, including Puerto Rico. Of these, only two reported on clinical outcomes (NCT00941889 2016; Wilkin 2018), as most were designed as non-inferiority trials of antibody responses.

Adverse events

Appendix 4 lists the methods used to collect adverse event data. The mode of data collection was reported in 16 of the 20 studies and was passive in two studies (e.g. patients recording symptoms on diary cards); proactive in three (e.g. investigators observing

participants after vaccine administration, or field workers visiting or calling participants in their homes); both passive and proactive in nine studies; and in two studies, the details were insufficient for us to categorise as passive or proactive. Time frame (duration of follow-up) was reported for all but three studies; for two studies it was unclear, and one study did not report on adverse events (NCT00941889 2016). Methods to determine the relationship between vaccination and adverse events were reported by 10 studies: attribution was done by study investigators in nine studies and by a study co-ordinator in one study. Where the attribution method was not reported, we assumed this role was performed by study investigators. Fourteen studies (74%) provided definitions for the adverse events outcomes. Withdrawals due to adverse events were reported in 14 (70%) studies, but most studies (95%) did not report on how withdrawals would be handled in the analysis. Only one study reported harms-related monitoring and stopping rules (Hidalgo-Tenorio 2017). Seventeen studies reported on all adverse events regardless of frequency (i.e. they did not use a frequency-based filter); NCT01862874 2018 used a 5% threshold for other adverse events; it was unclear whether Dobson 2013 used a filter, and one study did not report on adverse events (NCT00941889 2016).

The length of follow-up for serious adverse events in the included studies ranged from seven months to five years. Table 1 lists the serious adverse events reported in each study. In all studies, the individual serious events were listed for each study arm. In five of the 20 RCTs, 50 or more serious adverse events were reported (Joura 2015, Lehtinen 2018; Puthanakit 2016; Romanowski 2011; Wilkin 2018). Information on whether serious adverse events were considered to be related to the vaccine is reported in the section Effects of interventions.

Studies awaiting classification

We identified two studies that included both males and females randomised to HPV vaccine and control (Li 2012; Reisinger 2007). The male population in these studies would qualify for inclusion in our review, but at the time of preparing this review we were not able to access data for males only. We have requested this information from the study investigators and, should these data become available, they will be included in a future update of this review.

Li 2012 and Reisinger 2007 both compared quadrivalent HPV vaccine to vaccine adjuvant-containing control in 9- to 15-year-old males. The studies reported on the comparison of males with females for immunogenicity outcomes and adverse events for males and females as one group. Li 2012 was carried out in China, and Reisinger 2007 was carried out in 10 countries in North America, Latin America, Europe and Asia. See Characteristics of studies awaiting classification for further details.

Ongoing studies

We identified 15 potentially relevant ongoing studies that have not been completed, but might be relevant for inclusion in future updates of this review. All studies are RCTs and studies may appear in more than one category of the list below:

- eight include healthy females (NCT01735006; NCT02009800; NCT02405520; NCT02562508; NCT02733068; NCT02740777; NCT02834637; NCT03180034);
- four include healthy males and females (NCT01824537; NCT02567955; NCT02710851; NCT02888418);
- one includes HIV-positive MSM (NCT02087384);
- one includes males and females cured of genital warts (NCT03296397);
- one includes females with genital warts (NCT02750202);
- seven are evaluating new vaccines in development in China (NCT01735006; NCT02405520; NCT02562508; NCT02710851; NCT02733068; NCT02740777; NCT02888418);
- four are evaluating the quadrivalent vaccine (NCT02009800; NCT02087384; NCT02750202; NCT03296397);
- one is evaluating the nonavalent vaccine (NCT01824537); and
- three are comparing the bivalent to the nonavalent vaccine (NCT02567955; NCT02834637; NCT03180034).

In addition to the seven studies ongoing in China, three of these studies are ongoing in Canada, and one study each in Costa Rica, France, the Netherlands, South Africa, and Tanzania. See Characteristics of ongoing studies for further details.

Excluded studies

We excluded 438 full texts. Twenty-two of these were potentially relevant studies, and the reasons for their exclusion are included in the Characteristics of excluded studies table. We excluded six studies because they were not RCTs, and two studies because they included females over 26 years of age. Most of the excluded studies contained no comparison of relevance to the review: seven studies compared HPV-vaccinated to HPV-unvaccinated females, five compared different intervals in three-dose schedules in females, one compared three-dose schedules of the bivalent and quadrivalent vaccine in young females, and one evaluated the effect of a booster dose of HPV vaccine.

Risk of bias in included studies

The risk of bias for each included study is detailed in Characteristics of included studies and an overview is presented in Figure 2. Overall risk of bias for each comparison is discussed in each results section below.

Allocation

We assessed most studies as being at low risk of selection bias, as they reported adequate randomisation sequence generation (15/20 = 75%) and allocation concealment procedures (15/20 = 75%). Five studies did not report their methods to conceal allocation adequately (Levin 2010; Lin 2014; NCT01031069 2017; NCT00941889 2016; NCT01862874 2018), and five did not report the method of sequence generation adequately (Levin 2010; NCT01031069 2017; NCT00941889 2016; NCT01862874 2018; Wilkin 2018); we assessed them as being at unclear risk of bias.

Blinding

Blinding of participants and providers was explicitly reported by less than half of the included studies (7/20 = 35%), we assessed those studies that did as being at low risk of performance bias. We assessed eight studies as being at unclear risk of performance bias as they did not report blinding status of participants and personnel clearly (Denny 2013; Hidalgo-Tenorio 2017; Levin 2010; NCT00941889 2016; NCT01031069 2017; NCT01862874 2018; Romanowski 2011; Wilkin 2018), and five studies as being at

high risk of performance bias due to no, or partial blinding, of participants, personnel, or both (Dobson 2013; Lehtinen 2018; Puthanakit 2016; Iversen 2016; Lin 2014).

Less than half of the studies reported adequate blinding of outcome assessors (9/20 = 45%); we considered those that did to be at low risk of detection bias. Eight studies did not report details regarding blinding of outcome assessment and we assessed them as being at unclear risk of bias (Denny 2013; Hidalgo-Tenorio 2017; Levin 2010; Lin 2014; NCT01031069 2017; NCT00941889 2016; NCT01862874 2018; Wilkin 2018), and three studies did not blind outcome assessment and were assessed as being at high risk of detection bias (Iversen 2016; Lehtinen 2018; Puthanakit 2016).

Incomplete outcome data

We assessed most included studies (18/20 = 90%) as having a low risk of attrition bias, as they reported withdrawals and provided adequate reasons for dropouts. We assessed one study as having a high risk of attrition bias because only a subgroup of included participants were analysed (Lehtinen 2018). We assessed another study as having a high risk of attrition bias because data for 62.5% (20/32) of the participants enrolled were missing due to early withdrawals from the study (NCT00941889 2016).

Selective reporting

For the majority of studies (16/20 = 80%) either a study protocol or clinical trial registry entry was available to determine that selective reporting was unlikely; we assessed these studies as having a low risk of reporting bias. We assessed four studies as having a high risk of selective reporting bias; Lehtinen 2018 because most outcomes were not reported separately for boys and girls, indeed, only adverse events were reported separately in boys, but in a selected subset; NCT00941889 2016 because predetermined outcomes, including serious adverse events, were not reported; NCT01031069 2017 because not all outcomes listed in the online trial record were reported in the trial result summary report; and NCT01862874 2018 because HPV disease was not reported as a separate outcome, but were reported as an outcome combined with persistent HPV infection.

Other potential sources of bias

All included studies provided a statement of the funding source for the trial. Thirteen studies were funded by the vaccine manufacturers (GSK, Merck or Sanofi Pasteur) and we rated them as having an unclear risk of other bias. Industry sponsored studies are associated with favourable efficacy results and conclusions (Lundh 2017) which may be mediated by factors other than those assessed by the Cochrane 'Risk of bias' tool. We also rated a further two studies as having an unclear risk of other bias because no published report was identified for either (NCT00941889 2016; NCT01031069 2017), and we extracted data from the clinical trials records, which provided insufficient information to establish whether there was a risk of other bias. We assessed the remaining five studies as being at low risk of other bias (Dobson 2013; Toft 2014; Hidalgo-Tenorio 2017; Levin 2010; Wilkin 2018).

Effects of interventions

See: **Summary of findings for the main comparison** Two doses of HPV vaccine compared with three doses of HPV vaccine in 9- to 15-year-old females; **Summary of findings 2** Two doses of HPV vaccine with longer interval compared with two doses of HPV vaccine with shorter interval in 9- to 14-year-old females and males; **Summary of findings 3** Three doses HPV vaccine compared with control in 10- to 26-year-old males; **Summary of findings 4** Nonavalent HPV vaccine compared with quadrivalent HPV vaccine in 9- to 26-year-old females and males

1. Two doses of HPV vaccine versus three doses of HPV vaccine in 9- to 15-year-old females or males

The results for this comparison are presented in Summary of findings for the main comparison and Appendix 5. We analysed four studies in females that compared two doses (months 0 and 2, or 0 and 6, or 0 and 12) versus three doses (months 0, 1, and 6; or 0, 2, and 6) of HPV vaccine (Dobson 2013; Iversen 2016; Leung 2015; Romanowski 2011), and reported immunogenicity outcomes (seven months to five years) for all vaccine types and adverse event outcomes throughout the study period (one to five years). No studies included for this comparison collected data about clinical outcomes. No evidence was found from RCTs making this comparison in males.

Immunogenicity results comparing two doses with three doses of HPV vaccine are reported in Appendix 5. Briefly, two doses were non-inferior to or had higher GMTs than three doses for all nine HPV genotypes measured except HPV 45 (where non-inferiority was inconclusive) one month after the last dose (moderate- to high-certainty evidence). For seroconversion one month after the last dose, there was evidence of little to no difference between groups for all nine HPV genotypes measured (high-certainty evidence). At 60-month follow-up after the first dose, non-inferiority of two doses of bivalent vaccine was inconclusive for GMTs of HPV 16 and HPV 18 (low-certainty evidence). Two doses of quadrivalent vaccine resulted in non-inferior GMTs for HPV 6, HPV 11 and HPV 16, while results were inconclusive for HPV 18 (low-certainty evidence). At 36-month follow-up after the first dose, two doses of nonavalent vaccine resulted in non-inferior GMTs for all HPV genotypes measured except HPV 45 and HPV 52 where non-inferiority was inconclusive (high-certainty evidence).

Two studies found that two doses of HPV vaccine resulted in little to no difference in pain at the injection site compared with three doses of HPV vaccine (RR 0.96, 95% CI 0.91 to 1.03; 2 studies; 1189 participants; Analysis 1.1), but reduced swelling (RR 0.76, 95% CI 0.65 to 0.89; 2 studies; 1189 participants; Analysis 1.2) and redness (RR 0.85, 95% CI 0.75 to 0.96; 2 studies; 1189 participants; Analysis 1.3) at the injection site at up to seven days follow-up. The comparative evidence about serious adverse events was considered to be of very low-certainty (risk with two doses 36/1158, risk with three doses 35/1159; 4 studies; 2317 participants; Analysis 1.4). We downgraded certainty for imprecision and indirectness of the composite measure of all serious adverse events, which may or may not be clinically relevant, may or may not be related to the vaccine, and may occur outside a biologically plausible time frame relative to vaccine exposure. Two of the studies reported on withdrawals from the study and reported that no participants had withdrawn because of adverse events. One death was reported in the three-dose group (1/898) and no deaths (0/899) in the two-dose group (OR 0.33, 95% CI 0.01 to 8.19; 3 studies; 1797 participants; low-certainty evidence; Analysis 1.5).

2. Two doses of HPV vaccine with longer interval compared with two doses of HPV vaccine with shorter interval in 9- to 14-year-old females or males

The results for this comparison are presented in Summary of findings 2 and Appendix 6. We included three studies in females that compared two doses with a longer interval between the first and second doses (months 0 and 6 or 12) with a shorter interval between the first and second doses (months 0 and 2 or 6) for immunogenicity outcomes at seven months for all vaccine types and adverse event outcomes throughout the study period (one to five years) (Iversen 2016; Puthanakit 2016; Romanowski 2011). One of these studies compared a longer interval (months 0 and 12) with a shorter interval (months 0 and 6) in males (Iversen 2016). No studies included for this comparison collected data about clinical outcomes. As each study compared different intervals, we did not pool the results in the meta-analysis.

Immunogenicity results are reported in Appendix 6. At one month after the final dose, there was evidence of higher (and non-inferior) GMTs for HPV 16 and HPV 18 with the longer interval schedules compared with the shorter intervals in 9- to 14-year-old females who received bivalent HPV vaccine (moderate- to high-certainty evidence). There was also evidence of higher GMTs for HPV 16 and HPV 18 at 36 months with the longer interval schedules compared with the shorter intervals in 9- to 14-year-old females who received bivalent HPV vaccine (high-certainty evidence). For seroconversion to HPV 16 and HPV 18, there was evidence of no difference between groups one month after the final dose (high-certainty evidence). For the nonavalent vaccine in girls and boys, there was evidence that a longer interval produced higher and non-inferior GMTs than a shorter interval for all HPV genotypes (high-certainty evidence).

In Romanowski 2011 there was little to no difference in pain (RR 1.01, 95% CI 0.96 to 1.06; 1 study; 477 participants; Analysis 2.1), swelling (RR 0.95, 95% CI 0.76 to 1.20; 1 study; 477 participants; Analysis 2.2), or redness at the injection site (RR 1.02, 95% CI 0.84 to 1.24; 1 study; 477 participants; Analysis 2.3) when comparing a two-month interval between doses to a six-month interval. In Puthanakit 2016 there was also little to no difference in pain (RR 1.02, 95% CI 0.98 to 1.06; 1 study; 963 participants; Analysis 2.1), swelling (RR 1.01, 95% CI 0.87 to 1.18; 1 study; 963 participants; Analysis 2.2), or redness at the injection site (RR 1.06, 95% CI 0.93 to 1.22; 1 study; 963 participants; Analysis 2.3) when comparing a six-month interval between doses to a 12-month interval.

The evidence about serious adverse events was considered to be of very low-certainty, due to imprecision and indirectness, for comparisons of a two-month (14/240) versus a six-month (16/241) interval (1 study; 481 participants; Analysis 2.4) (Romanowski 2011), and of a six-month (20/550) versus a 12-month (24/415) interval (1 study; 965 participants; Analysis 2.4) (Puthanakit 2016). The evidence about serious adverse events was also considered to be of very low-certainty for the comparison of an interval of six months (15/602) versus 12 months (6/301) between doses of the nonavalent vaccine (1 study; 903 participants; Analysis 2.4) (Iversen 2016). The Iversen 2016 study reported on serious adverse events in males and females, but disaggregated data were not available by sex (Table 1). One of the reported serious adverse events (one case of systemic lupus erythematosus) in the 12-month interval group (Puthanakit 2016), was considered by the study investigators to be related to the vaccine and was the only withdrawal from the studies because of adverse events. No deaths were reported in any of the included trials (Analysis 2.5).

3. Longer interval versus shorter interval between second and third doses of quadrivalent HPV vaccine in 18- to 25-year-old males

The results for this comparison are presented in Appendix 7. We included one study that compared three doses of quadrivalent HPV vaccine with a longer interval between the second and third doses (doses administered at months 0, 2, and 12) against a shorter interval between the second and third doses (doses administered at months 0, 2, and 6) (Lin 2014). For the immunogenicity outcomes (Appendix 8), there was evidence of higher GMTs for HPV 11 with the longer interval schedule compared with the shorter schedule at one month (2 to 6 weeks test window allowed) after the last dose. For GMTs for HPV 6, 16, and 18, there was evidence of little to no difference between groups. The study did not collect data about clinical outcomes.

This study reported local, general, and serious adverse events. No usable data were available for analysis of local and general adverse events so we summarised the results in Analysis 3.1. Briefly, among all study participants 172 local and general reactions were reported. The authors reported no significant difference between groups (P = 0.26). No serious adverse events were reported (120 participants; Analysis 3.2).

4. HPV vaccines versus control in 10- to 26-year-old males

The results for this comparison are presented in Summary of findings 3. Two studies compared quadrivalent HPV vaccine with control (vaccine adjuvant only) (three doses administered at months 0, 2, and 6) in males (Giuliano 2011, NCT01862874 2018), and two studies compared bivalent vaccine with HBV vaccine (Lehtinen 2018; Petaja 2009). Lehtinen 2018, a cluster-randomised trial, was designed to investigate direct and indirect effects of vaccinating boys and girls (gender-neutral) compared with girls-only HPV vaccination. They reported that gender-neutral vaccination was associated with herd effects and cross-protection against a number of non-vaccine HPV types. Clinical outcomes in girls are presented in another Cochrane Review (Arbyn 2018), which covers comparison of bivalent and quadrivalent HPV vaccine with a control HBV vaccine in females; no clinical outcomes in boys were reported.

One study reported clinical outcomes at a median of 2.9 years (Giuliano 2011). There were fewer outcomes of external genital lesions (any genotype) (rate ratio 0.16, 95% CI 0.07 to 0.38; 1 study; 2545 participants; 6254 person-years; moderate-certainty evidence; Analysis 4.1), external genital lesions (HPV 6, 11, 16, 18) (rate ratio 0.10, 95% CI 0.03 to 0.31; 1 study; 2805 participants; 5643 person-years; Analysis 4.2), and anogenital warts (rate ratio 0.11, 95% CI 0.03 to 0.38; 1 study; 2805 participants; 5645 person-years; moderate-certainty evidence; Analysis 4.3) with the quadrivalent HPV vaccine than the control, in both intention-to-treat and per-protocol analyses (per-protocol analyses not shown). There was evidence in favour of quadrivalent HPV vaccine for the outcomes of all penile, perianal, or perineal intraepithelial neoplasia (PIN) lesions (rate ratio 0.17, 95% CI 0.01 to 3.27; 1 study; 2805 participants; 5657 person-years; Analysis 4.4), PIN grade 1 (rate ratio 0.25, 95% CI 0.01 to 6.22; 1 study; 2805 participants; 5659 person-years; Analysis 4.5), or PIN grade 2 or 3 (rate ratio 0.50, 95% CI 0.02 to 14.80; 1 study; 2805 participants; 5658 person-years;

Analysis 4.6), with confidence intervals that included the possibility of both fewer and more events with the quadrivalent vaccine (low-certainty evidence for all outcomes).

In the quadrivalent vaccine group, there were more overall local/injection site adverse events than with the control (RR 1.12, 95% CI 1.06 to 1.18; 1 study; 3895 participants; high-certainty evidence; Analysis 4.7); the events included pain at injection site (RR 1.13, 95% CI 1.07 to 1.19; 2 studies; 5162 participants; Analysis 4.8), swelling at injection site (RR 1.29, 95% CI 1.04 to 1.60; 2 studies; 5162 participants; Analysis 4.9), and redness at injection site (RR 1.12, 95% CI 0.99 to 1.27; 2 studies; 5162 participants; Analysis 4.10). There was little to no difference in overall systemic events and general symptoms (RR 0.99, 95% CI 0.90 to 1.08; 2 studies; 5008 participants; moderate-certainty evidence; Analysis 4.11) at 15-day follow-up. The bivalent HPV vaccine resulted in more pain (RR 1.99, 95% CI 1.57 to 2.53; 1 study; 268 participants; Analysis 4.8), swelling (RR 2.51, 95% CI 1.17 to 5.42; 1 study; 268 participants; Analysis 4.9), and redness (RR 1.66, 95% CI 0.99 to 2.79; 1 study; 268 participants; Analysis 4.10) at the injection site than the HBV vaccine (Petaja 2009).

Evidence about serious adverse events in the Giuliano 2011 study was of very low-certainty due to imprecision and indirectness (8/2574 participants (0.3%) in the quadrivalent vaccine group and 12/2588 participants (0.5%) in the control group; 2 studies; Analysis 4.12). None of the reported serious adverse events was considered by the study investigators to be vaccine-related. Two participants from the quadrivalent group and seven participants from the control group discontinued participation in the studies because of adverse events. There were fewer deaths in the group that received quadrivalent vaccine (3 deaths in quadrivalent group; 11 deaths in control group), but confidence intervals for the difference were compatible with no effect (OR 0.30, 95% CI 0.09 to 1.01; 2 studies; 5173 participants; low-certainty evidence; Analysis 4.13) at up to three years of follow-up (Giuliano 2011). Lehtinen 2018 reported on serious adverse events for a selected subset of males (data not shown). Fifty-eight of the 2436 subset participants (2.4%) who received the HPV vaccine and 25/1267 subset participants (2.0%) who received the control HBV vaccine experienced serious adverse events (very low-certainty evidence). The investigators reported that four serious adverse events among the males who received the HPV vaccine (abdominal pain, ulcerative colitis, type 1 diabetes mellitus, juvenile idiopathic arthritis) could possibly be vaccine-related and one event among the males who received the control (type 1 diabetes mellitus) could possibly be vaccine-related. In the study on bivalent vaccine (Petaja 2009), three serious adverse events were reported in the bivalent vaccine group (3/181) and one in the control group (1/89) (Analysis 4.12; very low-certainty evidence). The study investigators did not consider these to be related to the vaccine, and no deaths were reported in either group.

For the secondary outcome of persistent HPV infection, there was evidence that quadrivalent HPV vaccine reduced persistent infection caused by HPV 6, 11, 16 or 18 combined, or by each HPV genotype individually, in 16- to 26-year-old males compared with control (Appendix 9).

The Giuliano 2011 study also reported immunogenicity outcomes (data not shown). Briefly, there was evidence that quadrivalent vaccine increased GMTs for HPV 6, 11, 16 and 18 when compared with control at 7, 24 and 36 months. There was a trend towards GMTs levelling off after reaching a peak at month seven. Comparative data between quadrivalent vaccine and control were not available for the seropositivity outcomes (control group data not reported), but seropositivity for HPV 6, 11, 16 and 18 at seven months was above 97%. Petaja 2009 also reported immunogenicity outcomes seven months after the first dose of bivalent vaccine were higher than the HBV vaccine (Appendix 10).

5. Nonavalent HPV vaccine versus quadrivalent HPV vaccine in 9- to 26-year-old females and males

The results of this comparison are presented in Summary of findings 4. We included three RCTs that compared nonavalent with quadrivalent HPV vaccine (three doses administered at months 0, 2, and 6): two in females (Joura 2015; Vesikari 2015), and one in males (van Damme 2016). The Joura 2015 study collected data on clinical outcomes in females at up to 4.5 years follow-up. All three trials reported adverse event outcomes throughout the study period and immunogenicity outcomes at seven months for all vaccine types. We did not identify any studies that collected data about clinical outcomes in males.

In females there was little to no difference between nonavalent and quadrivalent HPV vaccines in the incidence of the combined outcome of high-grade cervical epithelial neoplasia, adenocarcinoma in situ, or cervical cancer (OR 1.00, 95% CI 0.85 to 1.16; 1 study; 13,753 participants; high-certainty evidence; Analysis 5.1), or high-grade cervical, vulval, or vaginal disease (OR 0.99, 95% CI 0.85 to 1.15; 1 study; 14,054 participants; high-certainty evidence; Analysis 5.2) at up to 4.5 years follow-up. For high grade cervical disease related to HPV 31, 33, 45, 52, or 58 (i.e. genotypes covered by the nonavalent vaccine but not the quadrivalent vaccine), the effect was in favour of the nonavalent vaccine (OR 0.03, 95% CI 0.00 to 0.21; 1 study; 11,892 participants; Analysis 5.5), but few cases were reported (1/5949 women in the nonavalent vaccine group and 35/5943 women in the quadrivalent vaccine group).

Nonavalent HPV vaccine resulted in slightly more local/injection site adverse events than the quadrivalent vaccine (RR 1.07, 95% CI 1.05 to 1.08; 3 studies; 15,863 participants; high-certainty evidence; Analysis 5.11). There was little to no difference between the vaccines for overall systemic events and general symptoms at 15-day follow-up (RR 1.01, 95% CI 0.98 to 1.04; 3 studies; 15,863 participants; moderate-certainty evidence, Analysis 5.15). For serious adverse events overall, the evidence was considered to be of low-certainty due to imprecision and indirectness (OR 0.60, 95% CI 0.14 to 2.61; 3 studies; 15,863 participants; I^2 = 51%; Analysis 5.16). One study reported similar numbers of events (1/299 with the nonavalent vaccine, 2/300 with the quadrivalent vaccine) in females aged 9 to 15 years over a period of 7 months follow-up (Vesikari 2015). In males, there were no events in 249 participants receiving the nonavalent vaccine and 6/251 with the quadrivalent vaccine over a period of 7 months follow-up (van Damme 2016). In the largest study, in 16- to 26-year-old females, 3.1% (242/7686) of those who received the nonavalent vaccine and 2.6% (184/7078) of those who received the quadrivalent vaccine experienced any serious adverse event after up to 4.5 years of follow-up (Joura 2015). No serious adverse events, when analysed by system organ class, were more common with the nonavalent than with the quadrivalent vaccine. The study authors examined 2269 pregnancy-related events in 2321 women and found no differences between the nonavalent and quadrivalent vaccine arms. The study investigators considered seven serious adverse events to be related to the vaccines,

four in the nonavalent group (allergic reaction; fever, body pain, and headache; hypersomnia; postural orthostatic tachycardia syndrome) and three in the quadrivalent group (headache; paraesthesia and burning sensation; orthostatic intolerance). Thirteen participants who received nonavalent vaccine and six who received quadrivalent vaccine discontinued participation because of adverse events. There was little to no difference in the number of deaths between nonavalent (6/7370) and quadrivalent (5/7378) HPV vaccine groups (OR 1.20, 95% CI 0.37 to 3.94; 2 studies; 15,248 participants; low-certainty evidence; Analysis 5.17) at up to 4.5 years follow-up. The study investigators considered none of the deaths reported to be related to the vaccine.

Secondary outcomes (persistent infection and immunogenicity) are presented in Appendix 11 and Appendix 12. Briefly, there was evidence of decreased rates of persistent infection with HPV 31, 33, 45, 52, and 58 at six and 12 months with nonavalent vaccine compared with quadrivalent vaccine (Joura 2015). There was little to no difference in immunogenicity between the nonavalent and quadrivalent HPV vaccines and GMTs were non-inferior for HPV 6, 11, 16, and 18 at up to 42 months. The nonavalent HPV vaccine resulted in substantially higher GMTs for HPV 31, 33, 45, 52, and 58 than the quadrivalent HPV vaccine. For seroconversion to HPV 6, 11, 16, and 18 up to 24 months follow-up, 100% of participants seroconverted in both the nonavalent and quadrivalent HPV vaccine groups. The data for GMTs and seroconversion to HPV 31, 33, 45, 52, and 58 were not reported in full (Joura 2015; Vesikari 2015).

6. HPV vaccination in HIV-positive females, males and MSM

Seven RCTs reported on the effects of bivalent and quadrivalent HPV vaccines in females, males, or children living with HIV (Denny 2013; Hidalgo-Tenorio 2017; Levin 2010; NCT00941889 2016; NCT01031069 2017; Toft 2014; Wilkin 2018). Two of the studies collected data about clinical outcomes such as anal intraepithelial neoplasia, anogenital warts or persistent infection (NCT00941889 2016; Wilkin 2018). These results are summarised in Table 3; Table 4; and Table 5.

6.1 Quadrivalent HPV vaccine compared with control

6.1.1 Quadrivalent HPV vaccine compared with control in children living with HIV

Levin 2010 included 7- to 12-year-old girls and boys with HIV. The study reported immunogenicity outcomes at seven months (Appendix 13). GMTs for HPV 6, 11, 16 and 18 were 123.8 to 935.8-fold higher at seven months, and 29.6 to 189.4-fold higher at 24 months, than in the control group (described as 'identical placebo', the study did not specify the contents of the placebo) (low-certainty evidence). Seroconversion for the four HPV genotypes was over 97% at seven months (low-certainty evidence). Injection site adverse events were more common with quadrivalent vaccine (21/96) than control (3/30) (1 study; 126 participants; very low-certainty evidence; Analysis 6.4). Three systemic adverse events were reported, two in the quadrivalent group (2/96) and one in the control group (1/30) (1 study; 126 participants; very low-certainty evidence; Analysis 6.5) at 14-day follow-up (three doses administered at months 0, 2, and 6). The study did not report on serious adverse events, but reported that 5/96 (5.2%) children in the quadrivalent vaccine group and 2/30 (6.7%) children in the control group experienced adverse events of grade 3 or 4 severity (OR 0.77, 95% CI 0.14 to 4.18, analysis not shown).

6.1.2 Quadrivalent HPV vaccine compared with control in MSM living with HIV

Hidalgo-Tenorio 2017 included HIV-positive MSM of 18 years of age and above, and compared quadrivalent HPV vaccine with control (saline placebo) (three doses administered at months 0, 2, and 6). This trial reported that 76% of the HPV vaccinated participants were seropositive for at least one of HPV 6, 11, 16, or 18 genotype at seven months compared with 30.2% in the control group (moderate-certainty evidence; Appendix 13). No serious adverse events (1 study; 129 participants; Analysis 6.6) or deaths (1 study; 129 participants; Analysis 6.7) were reported in either group at seven-month follow-up (Table 3).

6.1.3 Quadrivalent HPV vaccine compared with control in adults living with HIV

Two studies included HIV-positive males and females of 18 years of age and above and compared quadrivalent HPV vaccine with control (saline placebo in NCT00941889 2016 and 'placebo vaccine' in Wilkin 2018 - the contents of the placebo were not specified). There was only very low-certainty evidence on high-grade anal intraepithelial neoplasia (46/288 in the quadrivalent group, 45/286 in the control group; 1 study; Analysis 6.1), recurrence of anogenital warts in participants treated for anogenital warts (1/7 in the quadrivalent group, 1/5 in the control group; 1 study; Analysis 6.2), or abnormal anal cytology (58/130 in the quadrivalent group, 72/132 in the control group; 1 study; Analysis 6.3). There was limited evidence for serious adverse events (quadrivalent 33/288 events; control 46/287 events; Analysis 6.6) or deaths (quadrivalent 3/288 deaths; control 6/287 deaths; Analysis 6.7) between the groups. The study investigators considered no serious adverse events to be related to vaccination, and no withdrawals from the studies due to adverse events were reported (Table 3).

6.2 Bivalent HPV vaccine compared with control in females living with HIV

Denny 2013 included HIV-positive 18- to 25-year-old females and reported that, irrespective of baseline HPV serostatus, all participants who received the bivalent HPV vaccine were seropositive for both HPV 16 and HPV 18 after the second vaccine dose (month two), and remained seropositive at month 12 (moderate-certainty evidence). Pain at injection site (RR 1.86, 95% CI 1.38 to 2.51; 1 study; 120 participants; Analysis 7.1) and swelling at injection site (RR 9.19, 95% CI 2.24 to 37.73; 1 study; 120 participants; Analysis 7.2) were more common in the bivalent group than in the control group (vaccine adjuvant only) at seven-day follow-up. The study reported 3/61 serious adverse events in the bivalent vaccine group and 2/59 events in the control group (OR 1.47, 95% CI 0.24 to 9.15; 1 study; 120 participants; low-certainty evidence; Analysis 7.3). No deaths were reported (Analysis 7.4). The study investigators considered no serious adverse events to be related to vaccination, and no withdrawals from the study due to adverse events were reported (Table 4).

6.3 Bivalent HPV vaccine compared with quadrivalent HPV vaccine

6.3.1 Bivalent HPV vaccine compared with quadrivalent HPV vaccine in adults living with HIV

Toft 2014 included 92 HIV-positive females and males of 18 years of age and above, and compared bivalent with quadrivalent HPV vaccine (3 doses administered at months 0, 1.5, and 6). There was

evidence of no difference, and inconclusive non-inferiority, in GMTs for HPV 16 between the bivalent and quadrivalent HPV vaccines at seven- and 12-month follow-up (moderate- to low-certainty evidence; Appendix 13). There was evidence that the quadrivalent vaccine was inferior to bivalent vaccine for GMTs for HPV 18 at seven months (ratio of GMTs 0.13, 95% CI 0.04 to 0.41; moderate-certainty evidence). Injection site reactions were more common in the bivalent group than in the quadrivalent group (RR 1.31, 95% CI 1.06 to 1.62; 1 study; 92 participants; low-certainty evidence; Analysis 8.1) at four-day follow-up. No serious adverse events at six-month follow-up were reported (Analysis 8.2; Table 5).

6.3.2 Bivalent HPV vaccine compared with quadrivalent HPV vaccine in 15- to 25-year-old females living with HIV

One study reported on serious adverse events in 15- to 25-year-old females with HIV who were randomised to receive bivalent or quadrivalent HPV vaccine (NCT01031069 2017). Data for this study were only available through the clinical trials registry, so full details on the methods and other outcome measures were not available. There were nine serious adverse events in 167 female participants with HIV in the bivalent vaccine group and nine in 165 participants in the quadrivalent group (1 study; 332 participants; very low-certainty evidence; Analysis 8.2; Table 5). One participant in the quadrivalent group withdrew due to an adverse event. One serious adverse event (immune thrombocytopenic purpura) was considered by study investigators to be related to the bivalent HPV vaccine.

Sensitivity analysis

We compared the results from the primary analysis with a sensitivity analysis using Peto odds ratios for outcomes with very low event rates (< 1%; Bradburn 2007). This did not change the size of effect for most of the analyses, with the exception of some clinical outcomes in the comparison of nonavalent HPV vaccine versus quadrivalent HPV vaccine in 9- to 26-year-old females (Appendix 14).

Changes were seen in the effect sizes and 95% CIs for the following outcomes:

- high-grade cervical disease related to HPV 31, 33, 45, 52, or 58 (Analysis 5.5) changed from OR 0.03 (0.00 to 0.21) to Peto OR 0.15 (0.08 to 0.29) (Appendix 14);
- cervical intraepithelial neoplasia 2 (CIN2) related to HPV 6, 11, 16, or 18 (Analysis 5.7) changed from OR 3.00 (0.12 to 73.77) to Peto OR 7.40 (0.15 to 373.90) (Appendix 14);
- CIN2 related to HPV 31, 33, 45, 52, or 58 (Analysis 5.8) changed from OR 0.03 (0.00 to 0.23) to Peto OR 0.15 (0.08 to 0.30) (Appendix 14);
- CIN3, adenocarcinoma in situ, and cervical cancer related to HPV 6, 11, 16, or 18 (Analysis 5.9) changed from OR 0.33 (0.01 to 8.19) to Peto OR 0.14 (0.00 to 6.83) (Appendix 14);
- CIN3, adenocarcinoma in situ, and cervical cancer related to HPV 31, 33, 45, 52, or 58 (Analysis 5.10) changed from OR 0.07 (0.00 to 1.16) to Peto OR 0.14 (0.03 to 0.59) (Appendix 14).

DISCUSSION

This review reports on evidence about the efficacy, immunogenicity, and adverse events following reduced dose or alternative vaccine schedules in females and males, HPV vaccination compared to control for males, and effects of HPV vaccines in people with HIV infection.

Summary of main results

Immunogenicity, efficacy and adverse events with fewer than three doses of HPV vaccine in females

In adolescent girls (9 to 15 years) a two-dose schedule was non-inferior to a three-dose schedule of any HPV vaccine. There was some evidence that GMTs decrease over time following both two-dose and three-dose schedules, and that a two-dose schedule is non-inferior to a three-dose schedule after five years. There was no difference in seroconversion between two-dose and three-dose schedules at all time points reported; almost all participants seroconverted in both intervention groups. We identified no studies that collected data about efficacy against clinical outcomes. There was very low-certainty evidence of little to no difference in serious adverse events or deaths between dose schedules. No RCTs that evaluated the efficacy or harms of one dose of HPV vaccine were identified.

Immunogenicity, efficacy and adverse events with different intervals between doses of HPV vaccine in females and males

In both females and males, for all HPV vaccines evaluated, a schedule with a longer interval between doses resulted in higher GMTs than a shorter interval. There was very low certainty evidence on the comparative risk of serious adverse events with different intervals between two-doses of HPV vaccine, owing to the very low number of events and indirectness. Results from single studies were consistent with lower or higher rates of serious adverse events with the different intervals tested in the studies.

Efficacy, immunogenicity and adverse events with HPV vaccines in males

Three doses of quadrivalent HPV vaccine reduced the incidence of external genital lesions, anogenital warts, and persistent infection by HPV 6, 11, 16 or 18 compared with control among 16- to 26-year-old males over a median follow-up of 2.9 years (moderate-certainty evidence). The quadrivalent vaccine resulted in more injection-site adverse events, such as pain or redness, than control (high-certainty evidence). There was very low certainty evidence on the comparative risk of serious adverse events and low certainty evidence on the comparative risk of deaths between quadrivalent vaccine and control among 10- to 26-year old males. Limited data were available regarding the efficacy and adverse events with bivalent HPV vaccine in males. We identified no RCTs that evaluated the efficacy of nonavalent vaccine compared with control in males.

Efficacy, immunogenicity and adverse events with the nonavalent HPV vaccine compared with other HPV vaccines in females and males

Among 16- to 26-year-old women, three doses of nonavalent vaccine or of quadrivalent vaccine resulted in a similar incidence of clinical outcomes regardless of HPV genotype at up to 4.5-year follow-up (one RCT, high certainty evidence). The nonavalent vaccine resulted in reduced incidence of persistent HPV infections, CIN1, CIN 2/3, vulval or vaginal intraepithelial neoplasia (grade 1) related to the HPV genotypes unique to the nonavalent vaccine (HPV 31, 33, 45, 52, and 58) compared with the quadrivalent vaccine. Immunogenicity outcomes for nonavalent and quadrivalent HPV vaccines were similar for males and females. There was high-

certainty evidence that the nonavalent vaccine resulted in slightly more local or injection site events but little to no difference in overall systemic events. The evidence comparing serious adverse events was of low-certainty. There was low-certainty evidence of no difference in mortality between these vaccines. There were few vaccine-related serious adverse events reported (seven participants in total) in the included studies.

Efficacy, immunogenicity and adverse events with HPV vaccines in people living with HIV

In children living with HIV, the quadrivalent HPV vaccine results in higher GMTs than control at seven months, but there was only very low-certainty evidence about local or systemic adverse events. In adults living with HIV, the evidence about clinical outcomes and harms of quadrivalent HPV vaccine compared with control or other HPV vaccines, was of very low-certainty. One RCT in adults living with HIV reported that the bivalent vaccine had similar immunogenicity outcomes for HPV 16 to the quadrivalent vaccine, but resulted in higher GMTs and greater rate of seroconversion to HPV 18.

Overall completeness and applicability of evidence

This review collated evidence about the efficacy - in terms of clinical and immunological endpoints - and harms of different HPV vaccines and different dose schedules in females and males. The information sources searched include electronic databases, websites of the vaccine manufacturers, and a published index of HPV studies (Jørgensen 2018a), so the level of completeness is high. The applicability of the evidence to determine clinical efficacy and harms is, however, limited by the nature of HPV-related disease, as well as the design and outcomes of the studies. The evidence from RCTs about efficacy against severe HPV-related disease, including cancer, is limited for three main reasons. First, it is unethical to collect specimens from the cervix of girls who have not had sexual intercourse. Second, few severe clinical outcome events related to HPV infection occur during the study follow-up periods because they take a number of years to develop following HPV infection. Third, trial participants are offered treatment when HPV-related precancer is found, so progression to cervical cancer would be expected to be very low, even without vaccination.

The focus of this review was on clinical outcomes and harms. Immunogenicity is the primary outcome for many trials of alternative HPV vaccine schedules, however, as noted in the Background, randomised efficacy trials of HPV vaccines were first conducted in women aged 15 to 25 or 26 years (Arbyn 2018). Once efficacy, immunogenicity and safety were established in this age group, non-randomised bridging studies assessed non-inferiority of immunogenicity outcomes in 9- to 15-year-old girls (e.g. Block 2006, Dobson 2013). The International Agency for Research on Cancer regards bridging studies that demonstrate non-inferiority as a sufficient endpoint for individuals under 16 years of age (IARC 2014). Bridging studies have also demonstrated non-inferiority of immunogenicity outcomes of a two-dose schedule in boys aged 9- to 14-years compared to three doses in young women aged 15 to 26 years (Iversen 2016). Use of immunogenicity outcomes has limitations because the immunological correlate of protection and the duration of protection remain unknown (Donken 2015). These studies provide lower certainty of evidence, because estimates of clinical outcomes are imprecise and indirect.

The nonavalent HPV vaccine was introduced more recently than the bivalent and quadrivalent HPV vaccines. This review included all studies that compared the nonavalent HPV vaccine with other HPV vaccines; two RCTs were identified in females (Joura 2015; Vesikari 2015), and one in males (van Damme 2016). A separate Cochrane Review of completed RCTs of three-dose schedules with bivalent and quadrivalent HPV vaccines in women aged 16 to 26 years shows protection against lesions of grade CIN3, but not invasive cervical cancer (Arbyn 2018). Further comparisons between the different HPV vaccines in women will be included in an update of the Arbyn 2018 review. Observational studies in countries that have licensed more than one HPV vaccine will also provide important information on the comparative efficacy and harms of the different HPV vaccines.

With regard to serious adverse events, there is a large degree of uncertainty in the evidence comparing different HPV vaccines and different dose schedules. The 'Summary of findings' tables show low numbers of serious adverse events and deaths in most included studies. Even when the total number of events is high (e.g. Joura 2015), specific events of clinical relevance are still too rare for meaningful comparative analyses. In this review, we used a composite outcome, that is, the overall frequency of serious adverse events, for each comparison, however, analyses based on a composite outcome can produce results that are difficult to interpret for several reasons. This outcome can include events that are not clinically relevant or are not biologically related to the vaccine (Lineberry 2016), occur outside a plausible time frame relative to vaccine exposure (Huang 2011), or are not based on standardised definitions (Bonhoeffer 2002). In addition, trials measure serious adverse events at different time points and there is a large variation in duration of follow-up, which could produce misleading summary estimates (Huang 2011). Finally, there is heterogeneity among trials with regard to the age and gender of participants and clinical measurements of serious adverse events (Appendix 4). Meta-analyses of serious adverse events, such as those presented in this review, should be considered exploratory rather than confirmatory as the analyses are not planned in advance (i.e. when the included studies were designed) (Huang 2011). Despite the uncertainty in the evidence about harms when comparing different HPV vaccines and dose schedules, a previous systematic review reported similar rates of serious adverse events when HPV vaccines were compared to control (Arbyn 2018).

Quality of the evidence

The risk of bias of the included studies in this review is generally low. We rated studies that received funding from the vaccine manufacturer as 'unclear' for the 'other risk of bias' domain. This judgement was based on the results of a systematic review which showed more favourable efficacy results and conclusions in studies sponsored by manufacturing companies (Lundh 2017). It has been suggested that industry sponsorship of studies results in overly positive results through a variety of choices in the design and conduct of the trials that leads to bias. Based on the low risk of bias in other methodological domains and adequate reporting in the trials, we did not downgrade the certainty of the evidence using GRADE for this factor. In accordance with Higgins 2017, information on industry sponsorship and other funding sources is captured in the Characteristics of included studies tables.

In studies where participants received a control injection - specifically for the comparisons of HPV vaccines with control in

males and people living with HIV, and different interval schedules - many of the included studies used an adjuvant (either aluminium hydroxide or another aluminium compound) as the control rather than a 'true' placebo (NCT00941889 2016 used a saline placebo; Levin 2010 and Wilkin 2018 did not specify the type of placebo). Aluminium adjuvants have been used in vaccines for many years as they are thought to enhance the immune response (HogenEsch 2018), but their suitability as control vaccines in RCTs has been questioned (Jørgensen 2018b). A previous systematic review found no evidence that aluminium adjuvants in diptheria, tetanus, and pertussis vaccines cause any serious or long-lasting adverse events (Jefferson 2004). The rate of serious adverse events was low for both vaccine and control groups in the studies included in the current review. However, the benefits and harms of aluminium-containing adjuvants are being further assessed in a Cochrane Review (Djurisic 2017), and research is underway to determine how suitable they are as control vaccines for RCTs.

For a number of outcomes presented in the 'Summary of findings' tables, especially serious adverse events and deaths, we downgraded the certainty of the evidence for imprecision. In most cases the sample size of the included RCTs was too small to be able to detect an effect between groups for these outcomes - especially for rare outcomes such as death. This is another limitation of RCTs in determining the harms associated with HPV vaccines, and lends further weight to the future use of large observational studies. We also downgraded the evidence on serious adverse events for indirectness because of the limitations to the use of a composite outcome measure of events, as described in the section on applicability.

Potential biases in the review process

We made great efforts to identify relevant published and unpublished data, through a sensitive electronic database search and screening of vaccine manufacturer websites. By linking clinical trial registry entries with published database searches, and by cross-checking the studies included and excluded from our review against a published index of HPV studies (Jørgensen 2018a), we attempted to minimise the risk of missed studies, though relevant data may remain unregistered or unpublished (Jørgensen 2018a).

We used a priori categories of common adverse events - such as pain or swelling at the injection site - or important outcomes such as serious adverse events and deaths when extracting data from included studies. This method of data extraction could have been limited by the reporting in the included studies, as composite outcomes, such as 'overall injection site/local adverse events', could not be calculated by reports of all events within the study populations. The range of different adverse events reported in the included studies, as well as the range of methods used to assess these in the studies, makes it unfeasible to extract all adverse events for the purpose of meta-analysis.

We analysed and reported on all serious adverse events in the included studies. Serious adverse events are any events that result in hospitalisation and life-threatening illness. This means that any serious injury or illness is included, even if it is unlikely to be related to the vaccine. We also reported on results and attribution methods used to determine whether serious adverse events were related to the vaccine. We did not analyse these results or report them in the ‘Summary of findings’ tables because attribution methods were either not transparent, or not independent of the study investigators (Appendix 4). These results are reported narratively in the Effects of interventions section.

We restricted the sensitivity analysis of very rare events to alternative statistical methods available in Review Manager 5 software. We applied a sensitivity analysis to a number of outcomes where there were studies with zero events in both arms, but they did not contribute information when either method was used. It is possible that other methods could yield different results where there are zero events in both trial arms (Sharma 2017).

Agreements and disagreements with other studies or reviews

The results of this systematic review are in agreement with other published reviews on the efficacy of fewer than three doses of HPV vaccine (D'Addario 2017; Markowitz 2018). The current review aimed to provide further information on clinical outcomes and adverse events. This review provides evidence about other comparisons, such as vaccination of boys and comparisons across types of HPV vaccine, which have not previously been assessed.

AUTHORS' CONCLUSIONS

Implications for practice

In general, the bivalent, quadrivalent and nonavalent human papillomavirus (HPV) vaccines appear to be efficacious in eliciting immunogenic responses in both males and females for the targeted HPV genotypes and, typically, conversion to seropositivity is almost 100% amongst recipients. A two-dose HPV vaccination schedule is simpler to administer than a three-dose schedule. Immunogenicity data show non-inferior results for a two-dose when compared with a three-dose schedule of bivalent, quadrivalent and nonavalent HPV vaccine. The World Health Organization (WHO) strategic advisory group of experts on vaccination recommends a two-dose schedule with at least six months between the first and second dose, irrespective of sex, if the first dose is given before 15 years of age (WHO 2017). In practice, 65 countries worldwide have adopted two-dose HPV vaccination schedules for girls, as of 31 December 2017. Amongst high-income countries that recommend HPV vaccination for boys, Australia, Switzerland and the USA recommend a two-dose schedule. Given the decision of the International Agency for Research on Cancer that immunogenicity is a surrogate endpoint for individuals under 16 years of age, randomised controlled trials (RCTs) with clinical endpoints in this age group are unlikely.

For males, including men who have sex with men (MSM), the quadrivalent HPV vaccine probably reduces the incidence of external genital lesions and anogenital warts (condylomata acuminata) compared with control. There were slightly more injection-site adverse events with the quadrivalent vaccine compared to control, but insufficient evidence to determine the effects of HPV vaccine on serious adverse events or deaths when compared with control.

The nonavalent vaccine and quadrivalent vaccines offer similar protection levels against cervical, vaginal, and vulval precancer lesions and cancer in young women and similar levels of immunogenicity for the four HPV genotypes included in both vaccines in females and males. For high-grade disease related to HPV 31, 33, 45, 52, or 58 (i.e. those genotypes covered by

the nonavalent vaccine and not the quadrivalent vaccine) in women, the effect favours the nonavalent vaccine. No studies that compared nonavalent and quadrivalent HPV vaccines reported on clinical outcomes in males. The nonavalent vaccine was associated with an increase in local adverse events compared to the quadrivalent vaccine. Comparative evidence about serious adverse events was limited by imprecision and indirectness. Most of the evidence for this comparison comes from the 16 to 26 year-old age group in females, and there are far fewer data for younger females and males.

Evidence about the efficacy and harms of HPV vaccines in people living with HIV is limited because very few trials measured clinical outcomes. In children living with HIV, quadrivalent HPV vaccine probably results in higher GMTs than control at seven months. In adults living with HIV the evidence about clinical outcomes and harms of quadrivalent HPV vaccine, compared with control or other HPV vaccines, was of very low-certainty. The duration of protection of HPV vaccines in people with HIV infection and the effect of declining immunity on protection are unknown.

We identified no studies for any new HPV vaccines in phase 2 or 3 development that plan to report on the comparisons of interest in this review.

Implications for research

Further long-term post-licensure studies are needed to determine the duration of protection of one-dose and two-dose schedules, as well as the efficacy against HPV-related cancer endpoints in women, men, MSM, and people with HIV infection. RCTs of the effects of virus-like particle HPV vaccines on cervical and anal cancer are likely to study surrogate endpoints such as immunogenicity and persistent HPV infection. For vulval and vaginal cancer, clinical disease is still recommended as an endpoint because of insufficient knowledge about persistent infection (IARC 2014). The natural history of HPV-associated oropharyngeal cancer is even less well understood. RCTs of the effects of HPV vaccines will be needed, but might rely on persistent HPV infection as an outcome. The elucidation of the immune correlate of protection for HPV vaccines would be extremely valuable.

Further RCTs to compare different vaccine schedules are needed to determine the most cost-effective strategy to reduce the incidence of persistent HPV infection and related cancers. Evidence about the effectiveness of a two-dose HPV vaccine schedule on clinical HPV-related disease still relies on non-randomised comparisons of RCTs (Kreimer 2015; Sankaranarayanan 2016), and on data from national immunisation programmes (Markowitz 2018). These studies provide essential ongoing data, but cannot fully overcome confounding effects of differences between groups that receive a certain number of doses. In immunisation programme data in particular, those receiving two doses as part of a three-dose schedule might only have received the first two doses with a one or two month gap and might be beyond the recommended age for vaccination. In this situation, these studies might actually underestimate the effectiveness of a recommended two-dose schedule with at least six months between doses (Markowitz 2018).

An RCT that commenced in August 2018 will provide information about the non-inferiority of one and two doses of bivalent and nonavalent HPV vaccines against incident HPV genotype 16/18 infections that persist for six months or more in young women (NCT03180034). In addition, long-term surveillance and registry-based studies, such as linking vaccination databases with disease- and population-based registries, are needed to establish vaccine effectiveness and harms over time.

This review included a wide range of comparisons of alternative HPV vaccine schedules. In future, studies of the efficacy of different types of HPV vaccine, studies of alternative dose schedules, and studies of the effectiveness of HPV vaccines in people living with HIV infection could be examined in separate systematic reviews. This review has highlighted the limitations of data about harms collected in RCTs, especially imprecision, owing to the low frequency of serious adverse events. Longer-term follow-up is needed to investigate links with specific adverse events, such as new chronic diseases or adverse pregnancy outcomes. Post-marketing surveillance allows continued monitoring and reports events following HPV vaccination in the population beyond the duration of follow-up in RCTs. Surveillance studies of large registry-based data from real-world vaccination programmes can also provide more precise estimates of the incidence of specific adverse events and investigate prespecified hypotheses. In these studies, attribution of whether serious adverse events and deaths are related to the vaccine can be performed independently of study investigators and potential conflicts of interest. Future updates of this review will include observational long-term post-licensure studies to allow more detailed investigation of specific harms associated with HPV vaccines, long-term data on the effectiveness of HPV vaccines, and the value of different dose schedules in increasing vaccine coverage. Future reviews should also consider the synthesis of evidence from vaccination programmes in the context of gender-neutral HPV vaccination, where consideration of indirect effects of HPV vaccination is needed to provide more relevant estimates of vaccine effectiveness for public health stakeholders.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Denny 2013

Methods	Phase I/II, partially-blind, partially-randomised, placebo-controlled trial
Participants	Participants: 120 HIV-positive women (61 in bivalent vaccine group and 59 in control group) in South Africa Age range: 18–25 years Inclusion criteria: women with an intact cervix who reported no more than 6 lifetime sexual partners and whom the investigator believed would comply with the protocol requirements. Sexually active women had to have a normal colposcopy and normal cervical cytology or no worse than atypical squa-

Denny 2013 *(Continued)*

	mous cells of undetermined significance at the screening visit. All women had to be willing to undergo HIV counselling and testing and to be informed of their HIV status.
Interventions	Vaccine: bivalent HPV vaccine; 3 doses: day 0, month 1, month 6 Control: aluminium adjuvant placebo (aluminium hydroxide ($Al(OH)_3$)); 3 doses: day 0, month 1, month 6
Outcomes	Harms: adverse events Immunogenicity: GMT, seroconversion
Notes	Other groups: 30 HIV-negative women were enrolled as a control group and received bivalent HPV vaccine Last report average follow-up time: 12 months Funding: GlaxoSmithKline Biologicals SA. The study sponsor designed the study in collaboration with the investigators, and co-ordinated collection, analysis, and interpretation of data. Trial ID: NCT00586339.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Centralised, Internet-based randomisation system
Allocation concealment (selection bias)	Low risk	Centralised, Internet-based randomisation system
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Participants were blinded to allocation. No clear statement presented regarding blinding of personnel or outcome assessors.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Participants were blinded to allocation. No clear statement presented regarding blinding of personnel or outcome assessors.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Most analysis per protocol, but baseline data on full cohort provided, data on withdrawals and reasons for withdrawing also provided.
Selective reporting (reporting bias)	Low risk	No reasons to suspect that reporting was selective. Clinical trial record checked.
Other bias	Unclear risk	Trial funded by vaccine manufacturer.

Dobson 2013

Methods	Phase III, open-label, non-inferiority, controlled, randomised, multi-centre trial
Participants	Participants: 520 women and young girls (259 to 2-dose quadrivalent HPV vaccine and 261 to 3-dose quadrivalent HPV vaccine) recruited from 3 Canadian provincial centres Age range: girls aged 9-13 years, young women aged 16-26 years

Dobson 2013 *(Continued)*

	Inclusion criteria: healthy participants 9-13 years of age (girls) or 16-26 years of age (young women), with 4 or fewer lifetime sexual partners
Interventions	Vaccine 1: quadrivalent HPV vaccine; 2 doses: day 1, month 6 Vaccine 2: quadrivalent HPV vaccine; 3 doses: day 1, month 2, month 6
Outcomes	Harms: adverse events Immunogenicity: GMT, seroconversion
Notes	Other groups: in our analyses we did not include the cohort of 16-26-year-old women that were not randomised within the trial Last report average follow-up time: 36 months Funding: Ministries of Health in the provinces of British Columbia, Nova Scotia, and Quebec. Merck Laboratories Inc conducted the antibody assays at no cost to the study. Merck had no role in the design or conduct of the study; collection, management, analysis, or interpretation of the data; or preparation, review, or approval of the manuscript. Trial ID: NCT00501137

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Girls were randomised (1:1) in balanced, stratified blocks of 6 to receive either 2 doses (at 0 and 6 months) or 3 doses (at 0, 2, and 6 months). The co-ordinating centre used SAS, version 9.2 (SAS Institute Inc) to generate randomisation lists for each site.
Allocation concealment (selection bias)	Low risk	Co-ordinating centre generated randomisation sequence and allocated girls.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Impossible to blind girls as to whether they were randomised to 2 or 3 doses; the young women were not randomised, all receiving 3 doses.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Laboratory staff, blinded to group assignment, conducted the HPV antibody assays.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data were reported for both ITT and per protocol populations, with full information on exclusions and withdrawals.
Selective reporting (reporting bias)	Low risk	The primary interest was in the per-protocol population; however, the results presented were the ITT population because these results could be generalised more readily.
Other bias	Low risk	No other bias apparent

Giuliano 2011

Methods	Phase III, double-blind, parallel, placebo-controlled, randomised and multi-site trial
Participants	Participants: 4065 boys and men (2032 to the vaccine group and 2033 to the control group) recruited from 18 countries in five regions (Africa, Asia-Pacific, Europe, Latin America, North America) Age range: 16-26 years Inclusion criteria: heterosexual males 16-23 years old with between 1-5 lifetime female sexual partners, plus males who have sex with male partners 16-26 years old with 1-5 lifetime male or female partners
Interventions	Vaccine: quadrivalent HPV vaccine; 3 doses: day 1, month 2, month 6 Control: aluminium adjuvant placebo (amorphous aluminium hydroxy-phosphate sulphate (AAHS)); 3 doses: day 1, month 2, month 6
Outcomes	Clinical: external genital lesions; penile, perianal, or perineal intraepithelial neoplasia; or penile, perianal, or perineal cancer Harms: adverse events, deaths Immunogenicity: GMT, seroconversion
Notes	Other groups: N/A Last report average follow-up time: 36 months Funding: Merck, in collaboration with external investigators and an external data and safety monitoring board. The sponsor co-designed the trial, collated the data, monitored the conduct of the trial, performed statistical analyses, and co-ordinated the writing of the manuscript with all the authors. Trial ID: NCT00090285

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A computer-generated allocation schedule was produced by the sponsor. Following informed consent and determination that all entry criteria were met, eligible subjects were randomised to a vaccination group. (Hillman 2012, companion paper)
Allocation concealment (selection bias)	Low risk	Following informed consent and determination that all entry criteria were met, eligible subjects were randomised to a vaccination group. All investigators and site personnel, subjects, monitors, and laboratory personnel remained blinded to treatment allocation throughout the study. Staff of the sponsor were blinded from the study onset through the database lock for this analysis. (Hillman 2012, companion paper)
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "visually indistinguishable AAHS-containing placebo"; All investigators and site personnel, subjects, monitors, and laboratory personnel remained blinded to treatment allocation throughout the study. Staff of the sponsor were blinded from the study onset through the database lock for this analysis. (Hillman 2012)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	All biopsy specimens were processed independently to prevent contamination of HPV DNA and were assessed in a blinded fashion, first for the purpose of clinical management by pathologists at the central laboratory (Diagnostic Cytology Laboratories) and then for end-point adjudication by a 4-member panel of pathologists.

Giuliano 2011 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	Data reported adequately.
Selective reporting (reporting bias)	Low risk	No reason to suspect that reporting was selective - clinical trial registry checked.
Other bias	Unclear risk	Trial funded by vaccine manufacturer.

Hidalgo-Tenorio 2017

Methods	Randomised, double blind, placebo-controlled trial
Participants	Participants: 129 HIV-positive men who have sex with men (66 received quadrivalent HPV vaccine and 63 received control) recruited from the Infectious Diseases Service in Spain Age range: ≥18 years of age Inclusion criteria: participants not infected simultaneously by the 4 genotypes of HPV that the quadrivalent vaccine addresses; with a normal high-resolution anoscopy at screening for inclusion, or with only condylomas or low squamous intraepithelial lesion, or both, in anal biopsy.
Interventions	Vaccine: quadrivalent HPV vaccine; 3 doses: day 1, month 2, month 6 Control: saline placebo ("water used in the preparation of injectable with <1 mmol of Na"); 3 doses: day 1, month 2, month 6
Outcomes	Harms: adverse events, deaths
Notes	Other groups: N/A Last report average follow-up time: 7 months Funding: Public Health and Social Progress Foundation of the Government of Andalucia [La Fundación Pública Andaluza Progreso y Salud de la Consejería de Igualdad Salud y Política Social] Trial ID: ISRCTN14732216

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated list of random numbers
Allocation concealment (selection bias)	Low risk	Quote: "The person in charge of generating and keeping the list was not part of the research team and did not participate in evaluation or enrolment of patients, therefore guaranteeing patient blinding."
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Participants were blinded to allocation. No clear statement provided regarding blinding of personnel or outcome assessors.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Participants were blinded to allocation. No clear statement provided regarding blinding of personnel or outcome assessors.

Hidalgo-Tenorio 2017 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	129 of 162 screened subjects were included. Reasons for ineligibility, withdrawal, and protocol violation fully reported.
Selective reporting (reporting bias)	Low risk	No reason to suspect that reporting was selective. Trial registered retrospectively.
Other bias	Low risk	No other bias apparent.

Iversen 2016

Methods	Phasae III, open-label, controlled, randomised and multi-centre trial
Participants	Participants: 1518 girls, boys, and young women (301 girls aged 9–14 years and 301 boys aged 9-14 years received 2 doses 6 months apart; 301 girls and boys aged 9–14 years received 2 doses 12 months apart; 301 girls aged 9-14 years and 314 young women aged 16-26 years received 3 doses at 0, 2, 6 months) recruited from 15 countries (Canada, Chile, Colombia, Czech Republic, Denmark, Israel, Malaysia, Norway, South Korea, South Africa, Spain, Taiwan, Thailand, Turkey, and the USA) Age range: girls and boys aged 9-14 years and girls and young women aged 16-26 years Inclusion criteria: girls and boys 9-14 years had to be generally healthy and not sexually active prior to enrolment. Girls and young women 16-26 years had to be generally healthy with 4 or fewer lifetime sexual partners, without a history of abnormal Papanicolaou test results or other cervical abnormalities, and to agree to use effective contraception through to study month 7.
Interventions	Vaccine 1: nonavalent HPV vaccine; 2 doses: day 1, month 6 Vaccine 2: nonavalent HPV vaccine; 2 doses: day 1, month 12 Vaccine 3: nonavalent HPV vaccine; 3 doses: day 1, month 2, month 6
Outcomes	Harms: adverse events, deaths Immunogenicity: GMT, seroconversion
Notes	Other groups: • boys aged 9-14 years receiving 2 doses nonavalent HPV vaccine; • adolescent girls and young women 16-26 years receiving 3 doses of nonavalent HPV vaccine Last report average follow-up time: 13 months (1 month after the last dose) Funding: Merck & Co, manufacturer of the quadrivalent and nonavalent HPV vaccines. Merck, as the study sponsor, was directly involved in the design and conduct of the study in conjunction with external investigators; collection, management, analysis, and interpretation of the data; and preparation and review of the manuscript. The presentation also underwent formal review by Merck. However, Merck could not prevent submission of the manuscript. Trial ID: NCT01984697

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation occurred centrally using interactive voice response system/integrated web response system (IVRS/IWRS). Subjects were assigned randomly

Iversen 2016 *(Continued)*

		to 1 of the 3 vaccination arms based on their age stratum according to a computer-generated allocation schedule.
Allocation concealment (selection bias)	Low risk	Randomisation occurred centrally using interactive voice response system/integrated web response system (IVRS/IWRS). Subjects were assigned randomly to 1 of the 3 vaccination arms based on their age stratum according to a computer-generated allocation schedule.
Blinding of participants and personnel (performance bias) All outcomes	High risk	This was an open-label trial; therefore, the sponsor, investigator and subject knew the treatment administered.
Blinding of outcome assessment (detection bias) All outcomes	High risk	This was an open-label trial; therefore, the sponsor, investigator and subject knew the treatment administered.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Acceptable dropout rate and reasons for withdrawal provided.
Selective reporting (reporting bias)	Low risk	No reason to suspect that reporting was selective. Trial protocol and clinical trial registry checked.
Other bias	Unclear risk	Trial funded by vaccine manufacturer.

Joura 2015

Methods	Phase II/III, double-blind, randomised, multi-centre trial
Participants	Participants: 14215 women (6792 in the nonavalent HPV vaccine group and 6795 in the quadrivalent HPV vaccine group) recruited from 18 countries (Austria, Brazil, Canada, Chile, Colombia, Denmark, Germany, Hong Kong, Japan, Korea, Mexico, New Zealand, Norway, Peru, Sweden, Taiwan, Thailand, and the USA (including Puerto Rico)) Age range: 16-26 years Inclusion criteria: no history of an abnormal result on a Papanicolaou (Pap) test, no more than 4 lifetime sexual partners, and no previous abnormal finding on cervical biopsy
Interventions	Vaccine 1: nonavalent HPV vaccine; 3 doses: day 1, month 2, month 6 Vaccine 2: quadrivalent HPV vaccine; 3 doses: day 1, month 2, month 6
Outcomes	Clinical: high grade cervical, vulval, and vaginal disease; cervical cancer; persistent HPV infection Harms: adverse events, deaths Immunogenicity: GMT, seroconversion
Notes	Other groups: N/A Last report average follow-up time: 54 months Funding: Merck Trial ID: NCT00543543

Joura 2015 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "An Interactive Voice Response System (IVRS) was used to allocate study subjects and balance randomisation between sites. Subjects were assigned an allocation number from an allocation schedule via the IVRS. Study personnel utilized IVRS at each vaccination visit for assignment of the clinical material from the appropriate vaccination group to be administered to the subject." (From protocol, supplementary material online)
Allocation concealment (selection bias)	Low risk	Quote: "An Interactive Voice Response System (IVRS) was used to allocate study subjects and balance randomisation between sites. Subjects were assigned an allocation number from an allocation schedule via the IVRS. Study personnel utilized IVRS at each vaccination visit for assignment of the clinical material from the appropriate vaccination group to be administered to the subject." (From protocol, supplementary material online)
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "The subjects, investigators (and his/her staff), laboratory staff, members of the Scientific Advisory Committee, and HPV Vaccine Program Pathology Panel will remain blinded to subject vaccination group allocations for the duration of the study." (From protocol, supplementary material online)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "The subjects, investigators (and his/her staff), laboratory staff, members of the Scientific Advisory Committee, and HPV Vaccine Program Pathology Panel will remain blinded to subject vaccination group allocations for the duration of the study. The SPONSOR will remain blinded to subject vaccination allocations until the required number of cases of the primary efficacy endpoint have been observed and the database is unblinded for the primary efficacy analysis, with the exception of unblinded personnel who will provide data summaries for dose selection and DSMB meetings, and those who will determine when the required number of cases of the primary efficacy endpoint have been observed. These unblinded personnel will not be associated with the conduct of the study or the design of any of the statistical analyses for the study (other than those requested by the DSMB)." (From protocol, supplementary material online)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data reported adequately in published report, with extra data published in Supplementary materials online.
Selective reporting (reporting bias)	Low risk	Full protocol published as supplementary material alongside published paper, including analysis plan.
Other bias	Unclear risk	Trial funded by vaccine manufacturer.

Lehtinen 2018

Methods	Partially blind cluster-randomised trial
Participants	Participants: 32,175 early adolescents (20,514 girls and 11,661 boys) living in 33 community clusters in Finland; 3703 male participants were included in narrative results Age range: 12-15 years

Lehtinen 2018 *(Continued)*

	Inclusion criteria: born 1992–1995; parental consent; healthy, as established by medical history. If female, not pregnant and not of child-bearing potential or using adequate contraception for 30 days prior to vaccination and to continue for 2 months after completion of the vaccination series
Interventions	Vaccine 1: 90% of the girls and boys assigned to receive bivalent HPV vaccine (Cervarix) and 10% assigned to receive hepatitis B vaccine (HBV; Engerix) at 0,1 and 6 months (11 clusters) Vaccine 2: 90% of the girls assigned to receive bivalent HPV vaccine, 10% of girls assigned to receive HBV vaccine and all boys received HBV-vaccine (11 clusters) Control: all participants assigned to receive active control HBV vaccine (11 clusters)
Outcomes	Harms: adverse events (active surveillance subgroup 12-month follow-up)
Notes	Other groups: the data provided on harms in the male participants was based on the 2436 in group 1 who received bivalent vaccine and a sub-set of 1267 of those who received HBV vaccine in group 2. Last report average follow-up time: 4 years Funding: GlaxoSmithKline Trial ID: NCT00534638

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Cluster-randomised: "communities were randomly assigned in equal numbers (1:1:1) to the three intervention arms using a random number generator"
Allocation concealment (selection bias)	Low risk	Although the trial used central randomisation: "study participants were to be administered the vaccine dose according to a central randomisation system on Internet"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Although the study was blinded for participants in the first arm (HPV or HBV vaccine), the participants in the third arm were aware of their allocation (all received HBV vaccine).
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "For investigators, the study was open"
Incomplete outcome data (attrition bias) All outcomes	High risk	For active adverse event surveillance, data were collected only for a subset of male participants and it was unclear how these participants were selected. Passive adverse event surveillance was conducted for all participants, but not reported for males separately.
Selective reporting (reporting bias)	High risk	No outcomes were reported completely separately for boys and girls. Adverse events were reported in boys separately, but in a selected subset.
Other bias	Unclear risk	Trial funded by vaccine manufacturer.

Leung 2015

Methods	Phase III, observer-blind, parallel, randomised trial

Leung 2015 *(Continued)*

Participants	Participants:1075 girls (359 to 2 doses of bivalent HPV; 358 to 2 doses of quadrivalent HPV; 358 to 3 doses of quadrivalent HPV; recruited at 21 sites in France, Hong Kong, Singapore and Sweden Age range: 9-14 years Inclusion criteria: healthy girls aged 9–14 years; girls of childbearing potential could be enrolled if they were abstinent or practised adequate contraception for 30 days prior to vaccination, had a negative pregnancy test on the day of each vaccination, and agreed to continue contraception for up to 2 months after completion of the vaccination series.
Interventions	Vaccine 1: quadrivalent HPV vaccine; 2 doses: day 1, month 6 Vaccine 2: quadrivalent HPV vaccine; 3 doses: day 1, month 2, month 6 Girls in the 2-dose group received aluminium adjuvant placebo ($Al(OH)_3$) at month 2 to maintain the observer blinding.
Outcomes	Harms: adverse events, deaths Immunogenicity: GMT, seroconversion
Notes	Other groups: 358 girls aged 9-14 years who received 2 doses of bivalent HPV vaccine. Last report average follow-up time: 36 months Funding: GlaxoSmithKline Biologicals SA funded this study and was involved in all stages of study conduct, including analysis of the data and the development and publication of the manuscript. Trial ID: NCT01462357

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The randomisation code was generated using MATEX, a program developed for use in SAS (Cary, NC, USA), by GSK Vaccines, Belgium.
Allocation concealment (selection bias)	Low risk	Quote: "Treatment allocation at the investigator site was performed using a centralized internet-based randomisation system"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The study was conducted in an observer-blind manner (i.e. vaccines were prepared and administered by qualified medical personnel not otherwise involved in the conduct of this study). Personnel involved in subject evaluation and subjects themselves were blinded to group assignments. Girls in the 2-dose groups received control $Al(OH)_3$ at month 2 to maintain observer blinding.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Personnel involved in subject evaluation, and subjects themselves, were blinded to group assignments.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data appeared to be reported adequately, including reasons for withdrawals.
Selective reporting (reporting bias)	Low risk	No reason to suspect that reporting was selective. Clinical trial registry checked.
Other bias	Unclear risk	Trial funded by vaccine manufacturer.

Levin 2010

Methods	Randomised, double-blind, placebo-controlled trial
Participants	Participants: 126 children with HIV infection (96 received quadrivalent HPV vaccine and 30 received control) from the USA and Puerto Rico Age range: children 7-12 years old Inclusion criteria: CD4% ≥15; at least 3 months of HAART was required for subjects with a CD4% < 25.
Interventions	Vaccine: quadrivalent HPV vaccine; 3 doses: day 1, month 2, month 6 Control: 'identical placebo' (contents of placebo were not specified (e.g. whether it was aluminium adjuvant or saline)); 3 doses: day 1, month 2, month 6
Outcomes	Harms: adverse events Immunological: GMT, seroconversion
Notes	Other groups: N/A Last report average follow-up time: 4-5 years Funding: overall support for the International Maternal Pediatric Adolescent AIDS Clinical Trials Group (IMPAACT) was provided by the National Institute of Allergy and Infectious Diseases (NIAID), the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), and the National Institute of Mental Health (NIMH) Trial ID: NCT01206556

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomly assigned"
Allocation concealment (selection bias)	Unclear risk	No statement provided about allocation concealment.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No detailed statement provided about how blinding was maintained or who was blinded.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No detailed statement provided about how blinding was maintained or who was blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data were provided for the total vaccinated cohort (100% of enrolled participants), together with full information about reasons for exclusions and withdrawals from follow-up.
Selective reporting (reporting bias)	Low risk	No reason to suspect that reporting was selective. Clinical trial record checked.
Other bias	Low risk	No other bias apparent.

Lin 2014

Methods	Open-label, parallel, randomised trial
Participants	Participants: 220 males (111 to the alternate schedule and 109 to the standard schedule) recruited from the USA Age range: 18-25 years old Inclusion criteria: males 18-25 years with 4 or fewer lifetime sexual partners
Interventions	Vaccine 1: standard schedule quadrivalent HPV vaccine; 3 doses at 0, 2, and 6 months Vaccine 2: alternate schedule quadrivalent HPV vaccine; 3 doses at 0, 2 and 12 months
Outcomes	Harms: compliance with third dose, adverse events Immunogenicity: GMT
Notes	Other groups: N/A Last report average follow-up time: month 7 or 13 (depending on group) Funding: the authors and this work were supported in part by a research grant from the Investigator-Initiated Studies Program of Merck & Co, Inc, manufacturer of Gardasil® quadrivalent human papillomavirus vaccine. Trial ID: NCT01184079

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Participants were randomised as they were scheduled for the initial visit using a simple random number sequence to determine the order of assignment into the Standard schedule or the Alternate schedule"
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open label; "Participants were aware of their group assignment"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Out of 220 participants enrolled, 204 completed the study" Reasons for withdrawal and protocol violation fully reported. Results for both ITT and per protocol populations reported.
Selective reporting (reporting bias)	Low risk	No reason to suspect that reporting was selective - clinical trial registry checked
Other bias	Unclear risk	Trial funded by vaccine manufacturer.

NCT00941889 2016

Methods	Double blind, controlled, randomised, single-centre trial
Participants	Participants: 32 HIV-positive males and females with anal warts (15 to the vaccine group and 17 to the control group) recruited from the USA Age range: 18 to 65 years old Inclusion criteria: HIV positive, ≥ 18 years of age, CD4 > 200 and viral RNA < 400 on HAART or CD4 > 350 if not on HARRT, presence of anal warts that required surgical excision or ablation
Interventions	Vaccine: quadrivalent HPV vaccine; 3 doses at 0, 2, and 6 months Control: saline placebo; 3 doses at 0, 2 and 6 months
Outcomes	Clinical: persistence and recurrence of anal warts
Notes	Other groups: N/A Last report average follow-up time: month 18 Funding: Washington University School of Medicine Trial ID: NCT00941889

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The online clinical trials record states "Randomized", but details about how randomisation was achieved were not reported.
Allocation concealment (selection bias)	Unclear risk	Details of allocation concealment were not reported.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	The online clinical trials record states "Masking: Double (Participant, Investigator)", but details about how blinding was achieved were not reported.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	The online clinical trials record states "Masking: Double (Participant, Investigator)", but details about how blinding was achieved were not reported.
Incomplete outcome data (attrition bias) All outcomes	High risk	Data for 62.5% (20/32) of the participants enrolled were missing due to withdrawal from the study, the online trial record states "No outcomes data were collected or analysed due to lack of participant follow-up"
Selective reporting (reporting bias)	High risk	The study did not report on adverse events and the online trial record states "No outcomes data were collected or analysed due to lack of participant follow-up"
Other bias	Unclear risk	No published report was identified for this study, data were extracted from the clinical trials record which had insufficient information to establish whether there was a risk of other bias.

NCT01031069 2017

Methods	Phase IV, observer-blind, randomised, controlled, multi-centric study
Participants	Participants: 649 HIV seropositive and seronegative females aged 15-25 years (331 to the bivalent vaccine group and 330 to the quadrivalent vaccine group) recruited from Brazil, Estonia, India, and Thailand Age range: 15-25 years Inclusion criteria: female 15-25 years old, HIV voluntary counselling and testing
Interventions	Vaccine 1: bivalent HPV vaccine; 3 doses at day 0, week 6, and month 6 Vaccine 2: quadrivalent HPV vaccine; 3 doses at day 0, week 6, and month 6
Outcomes	Harms: adverse events Immunogenicity
Notes	Other groups: N/A Last report average follow-up time: month 7 Funding: GlaxoSmithKline Trial ID: NCT01031069

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The online clinical trials record and clinical trial result summary state "Randomized", but details about how randomisation was achieved were not reported.
Allocation concealment (selection bias)	Unclear risk	Details of allocation concealment were not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	The online clinical trials record states "Triple (Participant, Investigator, Outcomes Assessor)", but details about how blinding was achieved were not reported.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	The online clinical trials record states "Triple (Participant, Investigator, Outcomes Assessor)", but details about how blinding was achieved were not reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data were provided for the total vaccinated cohort (100% of enrolled participants), together with full information about reasons for exclusions and withdrawals from follow-up.
Selective reporting (reporting bias)	High risk	Not all outcomes listed in the online trial registration were reported in the trial result summary report.
Other bias	Unclear risk	No published report was identified for this study; data were extracted from the clinical trials results summary on the manufacturer's web site (https://www.gsk-clinicalstudyregister.com/) which had insufficient information to establish whether there was a risk of other bias.

NCT01862874 2018

Methods	Phase 3, parallel, randomised, controlled trial
Participants	Participants: 1124 boys and men (562 received vaccine, 562 received placebo) recruited from Japan Age range:16-26 years Inclusion criteria: Japanese males with no clinical evidence of sexually transmitted disease and no clinically present external genital warts
Interventions	Vaccine: quadrivalent HPV vaccine; 3 doses at day 1, month 2, month 6 Control: aluminium adjuvant placebo (placebo formulated with aluminium hydroxyphosphate sulfate adjuvant); 3 doses at day 1, month 2, month 6
Outcomes	Incidence of persistent HPV-6/11/16/18 infection or disease Adverse events
Notes	Other groups: N/A Last report average follow-up time: month 36 Funding: Merck Sharp & Dohme Corp Trial ID: NCT01862874

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The online clinical trials record and clinical trial result summary state "Randomized", details about how randomisation was achieved were not reported.
Allocation concealment (selection bias)	Unclear risk	Details of allocation concealment were not reported.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	The clinical trial record states "masking: triple (participant, investigator, outcomes assessor" but no other details were provided.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	The clinical trial record states "masking: triple (participant, investigator, outcomes assessor" but no other details were provided.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Reasons for withdrawals were reported and balanced between groups.
Selective reporting (reporting bias)	High risk	HPV disease (HPV Type 6, 11, 16, or 18-related condyloma acuminate, penile, perianal, or perineal intraepithelial neoplasia or cancer) was not reported separately; persistent HPV infection and HPV disease were reported as a combined outcome.
Other bias	Unclear risk	No published report was identified for this trial. Trial funded by vaccine manufacturer.

Petaja 2009

Methods	Phase I/II, observer-blind, parallel-group, randomised study
Participants	Participants: 270 boys (181 received bivalent HPV vaccine and 89 received hepatitis B vaccine) recruited from 7 study sites in Finland Age range: 10-18 years old Inclusion criteria: boys free of obvious health problems as established by medical history and clinical examination before entering into the study
Interventions	Vaccine: bivalent HPV vaccine; 3 doses: day 1, month 1, month 6 Control: hepatitis B active control vaccine; 3 doses: day 1, month 1, month 6
Outcomes	Harms: adverse events, deaths Immunogenicity: GMT, seroconversion
Notes	Other groups: N/A Last report average follow-up time: 12 months Funding: GlaxoSmithKline Trial ID: NCT00309166

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation list generated at GlaxoSmithKline Biologicals (Rixensart, Belgium) using a standard SAS program (SAS Institute, Cary, NC).
Allocation concealment (selection bias)	Low risk	Participants were assigned a vaccine treatment number; blinding was maintained to the individual treatment allocated.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants were assigned a vaccine treatment number; blinding was maintained to the individual treatment allocated. All study personnel were blinded to the vaccines used, except the study nurse administrating the vaccines.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Participants were assigned a vaccine treatment number; blinding was maintained to the individual treatment allocated. All study personnel were blinded to the vaccines used, except the study nurse administrating the vaccines.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data for all participants enrolled were reported for adverse events. Reasons for exclusion from immunogenicity analysis was provided.
Selective reporting (reporting bias)	Low risk	All relevant outcomes were reported in clinical trials record and clinical study report.
Other bias	Unclear risk	No report of industry funding in publication, though the study report is available on GSK web site.

Puthanakit 2016

Methods	Phase III, open-label, controlled, randomised, multi-centre trial
Participants	Participants: 1447 participants (482 women to the 3-dose schedule (months 0, 1, 6); 550 girls to the 2-dose schedule (months 0 and 6); 415 girls to the 2-dose schedule (0 and 12 months)) recruited from Canada, Germany, Italy, Taiwan, and Thailand Age range: girls 9-14 years old and women 15-25 years old Inclusion criteria: women of childbearing age required to be abstinent or use adequate contraceptive precautions for 30 days before first vaccination and agree to continue such precautions for 2 months after the last vaccine dose
Interventions	Vaccine 1: bivalent HPV vaccine; 2 doses: month 0 and month 6 Vaccine 2: bivalent HPV vaccine; 2 doses: month 0 and month 12
Outcomes	Harms: adverse events, deaths Immunogenicity: GMT, seroconversion
Notes	Other groups: 482 women aged 15-25 years received 3 doses bivalent HPV vaccine, data not extracted Last report average follow-up time: 13 months, study ongoing Funding: GlaxoSmithKline Biologicals SA. GlaxoSmithKline Biologicals designed the study in collaboration with investigators and co-ordinated gathering, analysis, and interpretation of data and writing of the report. Trial ID: NCT01381575

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The randomisation list was generated by GSK Vaccines using a standard SAS program. A randomisation blocking scheme (1:1 ratio) ensured that balance between the two 2-dose schedules was maintained. Treatment allocation at each site used a central randomisation system on the Internet.
Allocation concealment (selection bias)	Low risk	Treatment allocation at each site used a central randomisation system on the Internet.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Investigators and participants were not blinded to group assignment. Girls aged 9–14 years were randomised (1:1) to receive 2-dose schedule (months 0, and 6 or months 0, and 12) and women aged 15–25 years were allocated to receive 3-dose schedule (months 0, 1, and 6).
Blinding of outcome assessment (detection bias) All outcomes	High risk	Investigators and participants were not blinded to group assignment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data reported adequately in published report, with extra data published in Supplementary materials online.
Selective reporting (reporting bias)	Low risk	No reason to suspect that reporting was selective. Clinical trial registry checked.
Other bias	Unclear risk	Trial funded by vaccine manufacturer.

Romanowski 2011

Methods	Phase I/II, partially blind, controlled, age-stratified, randomised and multi-centre trial
Participants	Participants: 960 girls and women (240 in 2-dose schedule 20 µg dose (months 0 and 6); 241 in 2-dose schedule 40 µg dose (months 0 and 6); 240 in 2-dose schedule 40 µg dose (months 0 and 2); 239 in 3-dose schedule 20 µg dose (months 0, 1, and 6)) recruited from Canada and Germany Age range: girls and young women aged 9-25 years at the time of first vaccination Inclusion criteria: participants with childbearing potential had to use adequate contraception for 30 days prior to vaccination, have a negative pregnancy test, and continue contraceptive precautions for 2 months after completion of the vaccination series
Interventions	Vaccine 1: bivalent HPV vaccine; 20 µg dose; 3 doses: day 1, month 1, month 6 Vaccine 2: bivalent HPV vaccine; 20 µg dose; 2 doses: day 1, month 6 Vaccine 3: bivalent HPV vaccine; 40 µg dose; 2 doses: day 1, month 6 Vaccine 4: bivalent HPV vaccine; 40 µg dose; 2 doses: day 1, month 2 In the 2-dose schedule groups, an aluminium adjuvant placebo was administered at month 2 (Groups 20 µg dose (months 0 and 6) and 40 µg dose (months 0 and 6)) or at month 6 (Group 40 µg dose months 0 and 2) to maintain blinding.
Outcomes	Harms: adverse events, deaths Immunogenicity: GMT, seroconversion
Notes	Other groups: N/A Last report average follow-up time: up to month 60 Funding: GlaxoSmithKline Biologicals Trial ID: NCT00541970

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The randomisation list was computer-generated at GlaxoSmithKline Biologicals.
Allocation concealment (selection bias)	Low risk	Treatment allocation at the investigator site was performed using a central randomisation call-in system on the Internet; the randomisation algorithm used a minimisation procedure accounting for centre and age (9–14, 15–19 and 20–25 years).
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	The trial was partially blinded within the 2-dose schedule groups (observers were blinded to group assignment) and open in the 3-dose schedule group. In the 2-dose schedule groups, a placebo was administered at month 2 (Groups 20 µg dose (months 0 and 6) and 40 µg dose (months 0 and 6)) or at month 6 (Group 40 µg dose (months 0 and 2) to maintain blinding.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The trial was partially blinded within the 2-dose schedule groups (observers were blinded to group assignment).

Romanowski 2011 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	Data appeared to be reported adequately, and included reasons for withdrawals.
Selective reporting (reporting bias)	Low risk	No reason to suspect that reporting was selective. Clinical trial registry checked.
Other bias	Unclear risk	Trial funded by vaccine manufacturer.

Toft 2014

Methods	Randomised, double-blind, head-to-head trial
Participants	Participants: 92 male and female HIV-positive participants (46 to 3-dose bivalent vaccine and 46 to 3-dose quadrivalent vaccine) recruited from outpatient clinic in Denmark. Age range: at least 18 years old Inclusion criteria: consenting HIV-seropositive volunteers at least 18 years old
Interventions	Vaccine 1: bivalent HPV vaccine; 3 doses: day 1, month 1.5, month 6 Vaccine 2: quadrivalent HPV vaccine; 3 doses: day 1, month 1.5, month 6
Outcomes	Harms: adverse events Immunogenicity: GMT, seroconversion
Notes	Other groups: N/A Last report average follow-up time: 6 months Funding: Aarhus University, Henrik Henriksen's Foundation, The Hede Nielsen Family Foundation, Aase and Ejnar Danielsen's Foundation, Jørgen Holm and Wife's Foundation, Lykfeldt andWife's Foundation, and the Danish Medical Association Trial ID: NCT01386164

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random allocation sequences were computer generated by the hospital pharmacy. Participants were assigned their study identification number according to the chronological order in which they were enrolled. Participants and investigators were masked to the assigned vaccine throughout the study.
Allocation concealment (selection bias)	Low risk	Random allocation sequences were computer generated by the hospital pharmacy. Participants were assigned their study identification number according to the chronological order in which they were enrolled. Participants and investigators were masked to the assigned vaccine throughout the study.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants and investigators were masked to the assigned vaccine throughout the study.

Toft 2014 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded analysis at the joint Chemical Biology Core Facility of the German Cancer Research Center and the European Molecular Biology Laboratory, Heidelberg, Germany
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data appeared to be reported adequately, and included reasons for withdrawals.
Selective reporting (reporting bias)	Low risk	No reason to suspect that reporting was selective. Clinical trials registry checked.
Other bias	Low risk	No other bias apparent.

van Damme 2016

Methods	Phase III, double-blind, controlled, randomised and multicenter trial
Participants	Participants: 500 males (249 to the nonavalent HPV vaccine arm, 251 to the quadrivalent HPV vaccine arm) recruited from Belgium, Germany, and the Netherlands Age range: 16-26 years Inclusion criteria: good physical health, no more than 5 lifetime female and no male sexual partners
Interventions	Vaccine 1: nonavalent HPV vaccine; 3 doses: day 1, month 2, and month 6 Vaccine 2: quadrivalent HPV vaccine; 3 doses: day 1, month 2, and month 6
Outcomes	Harms: adverse events, deaths Immunogenicity: GMT, seroconversion
Notes	Other groups: N/A Last report average follow-up time: 7 months Funding: Sanofi Pasteur MSD provided financial support for the conduct of the research and preparation of the article and were involved in the study design, in the collection, analysis and interpretation of data and in the writing of the trial report. Trial ID: NCT02114385

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "An interactive Web Response System (IWRS) was used to allocate participants to 9vHPV or qHPV vaccine in a blinded manner. The system assigned an allocation number from a randomised, age-stratified (16-17 years and 18-26 years) allocation schedule."
Allocation concealment (selection bias)	Low risk	Quote: "An interactive Web Response System (IWRS) was used to allocate participants to 9vHPV or qHPV vaccine in a blinded manner. The system assigned an allocation number from a randomised, age-stratified (16-17 years and 18-26 years) allocation schedule."

van Damme 2016 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants and personnel were blinded: "Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)" "We conducted a double-blind, randomised controlled with qHPV vaccine, immunogenicity and safety of the 9vHPV vaccine in young men aged 16-26 years of age."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors were blinded: "Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Fig 1 shows 97.8% completed.
Selective reporting (reporting bias)	Low risk	No reason to suspect that reporting was selective - clinical trial record checked and all immunogenicity outcomes reported.
Other bias	Unclear risk	Trial funded by vaccine manufacturer.

Vesikari 2015

Methods	Phase III, double-blind, controlled, randomised and multi-centre trial
Participants	Participants: 600 girls (300 in the nonavalent HPV vaccine arm, 300 in the quadrivalent HPV vaccine arm), recruited from Belgium, Denmark, Finland, Italy, Spain, and Sweden) Age range: 9-15 years old Inclusion criteria: girls aged ≥ 9 to < 16 years at enrolment, in good physical health, who were virgins and who were not planning to become sexually active before month 7 of the study.
Interventions	Vaccine 1: nonavalent HPV vaccine; 3 doses: day 1, month 2, month 6 Vaccine 2: quadrivalent HPV vaccine; 3 doses: day 1, month 2, month 6
Outcomes	Harms: adverse events, deaths Immunogenicity: GMT, seroconversion
Notes	Other groups: N/A Last report average follow-up time: 7 months Funding: Sanofi Pasteur MSD Trial ID: NCT01304498

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	A central randomisation system, which used an interactive web response system, assigned participants to a vaccine group (blinded) and an allocation number according to the randomised allocation schedules.

Vesikari 2015 *(Continued)*

Allocation concealment (selection bias)	Low risk	A central randomisation system, which used an interactive web response system, assigned participants to a vaccine group (blinded) and an allocation number according to the randomised allocation schedules.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Study reported to be double-blind. Not explicitly stated, however both groups received vaccines at the same time points.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Described as double blind; however, not explicit that outcome assessment was blinded. Given that the outcomes were objective (serology), assessed as low risk of bias.
Incomplete outcome data (attrition bias) All outcomes	Low risk	98.2% completed study (Figure 1), with full information on exclusions and withdrawals.
Selective reporting (reporting bias)	Low risk	No reason to suspect that reporting was selective, clinical trial registry checked
Other bias	Unclear risk	Trial funded by vaccine manufacturer.

Wilkin 2018

Methods	Phase III, double blind, placebo-controlled, randomised, multi-centre trial
Participants	Participants: 575 HIV-positive males and females (288 to the vaccine group and 287 to the control group) recruited from the USA, Brazil, and Puerto Rico Age range: at least 27 years old Inclusion criteria: HIV-1 infection, laboratory values and anal cytology result obtained within 45 days prior to entry
Interventions	Vaccine: quadrivalent HPV vaccine; 3 doses at 0, 8, and 24 weeks Control: 'placebo vaccine' (contents of placebo vaccine were not specified (e.g. whether it was aluminium adjuvant-containing or saline)); 3 doses at 0, 8, and 24 weeks
Outcomes	Clinical: anal intraepithelial neoplasia, persistent infection Harms: adverse events
Notes	Other groups: N/A Last report average follow-up time: 4 years Funding: National Institute of Allergy and Infectious Diseases Trial ID: NCT01461096

Risk of bias

Bias	Authors' judgement	Support for judgement

Wilkin 2018 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Quote: "Permuted-block randomisation was balanced by site and stratified by sex and presence of bHSIL at study screening.", details on how randomisation sequence was generated was not fully reported
Allocation concealment (selection bias)	Low risk	Central allocation: "The treatment assignment was provided electronically to local study pharmacists who prepared identical prefilled vaccine syringes."
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: ""Investigators, participants, and study staff were masked to treatment allocation.", details about how blinding was achieved were not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: ""Investigators, participants, and study staff were masked to treatment allocation.", details about how blinding was achieved were not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data were provided for 99% (569/575) participants; full information about reasons for exclusions and withdrawals were provided.
Selective reporting (reporting bias)	Low risk	All outcomes listed in online trial registration were reported.
Other bias	Low risk	No other bias apparent.

Abbreviations
AAHS: amorphous aluminium hydroxy-phosphate sulphate
CD4%: percentage of white blood cells that are CD4 cells
GMT: geometric mean titre
HAART: highly active antiretroviral therapy
HPV: human papillomavirus
ITT: intention-to-treat
qHPV: quadrivalent human papillomavirus vaccine
9vHPV: nonavalent human papillomavirus vaccine

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Beachler 2016	No relevant comparison, does not meet protocol: bivalent HPV vs hepatitis A vaccine (control) in women (NCT00128661)
Bhatia 2016	No relevant comparison, does not meet protocol: observational study of vaccinated vs unvaccinated females
Bianchi 2016	No relevant comparison, does not meet protocol: observational study of vaccinated vs unvaccinated females
Brown 2012	No relevant comparison, does not meet protocol: 3 doses vs 3 doses comparing intervals in females (NCT00925288)
Canfell 2017	Not a relevant population: women 25-64 years (ACTRN12613001207707)
Carozzi 2016	No relevant comparison, does not meet protocol: vaccinated vs unvaccinated females (NCT02296255)

Study	Reason for exclusion
Choudhury 2016	No relevant comparison, does not meet protocol: observational study of vaccinated vs unvaccinated in HIV+ females, none of the HIV+ population was vaccinated
Esposito 2011	No relevant comparison, does not meet protocol: 3 doses vs 3 doses comparing intervals in females (NCT00552279)
Flagg 2018	No relevant comparison, does not meet protocol: observational study of anogenital warts prevalence before and after national HPV vaccination introduction for females, males were not vaccinated
Garland 2016	No relevant comparison, does not meet protocol: vaccinated versus unvaccinated females (NCT00122681 PATRICIA)
Gilca 2015	No relevant comparison, does not meet protocol: booster dose given to girls who had already received 2 doses of vaccine (NCT01456715)
Hamsikova 2017	No relevant comparison, does not meet protocol: observational study of bivalent versus quadrivalent HPV vaccines
Harari 2016	No relevant comparison, does not meet protocol: HPV vaccine vs hepatitis A vaccine (control) in females (NCT00128661)
Haskins-Coulter 2017	No relevant comparison, does not meet protocol: 3-dose bivalent vaccine vs 3-dose quadrivalent vaccine in young females (NCT00956553)
Lamontagne 2013	No relevant comparison, does not meet protocol: 3 doses vs 3 doses comparing intervals in females (NCT00524745)
Lehtinen 2017	No relevant comparison, does not meet protocol: long-term follow-up of vaccinated versus unvaccinated females combining arms from 3 RCTs (NCT01393470 (unvaccinated arm); NCT00122681 (PATRICIA vaccinated arm); NCT00169494 (HPV-012 vaccinated arm))
Luxembourg 2017	No relevant comparison, does not meet protocol: vaccinated versus unvaccinated females (protocol) (V503-021, NCT02653118)
Money 2016	No relevant comparison, does not meet protocol: single arm HIV+ cohort (ISRCTN33674451)
Neuzil 2011	No relevant comparison, does not meet protocol: 3 doses vs 3 doses comparing intervals in adolescent girls (NCT00524745)
Wheeler 2016	Not a relevant population: women 26 years and older, 7-year follow-up of VIVIANE study (NCT00294047)
Zhu 2017	No relevant comparison, does not meet protocol: HPV vaccine versus aluminium hydroxide control in females (NCT00779766)
Zimmerman 2010	No relevant comparison, does not meet protocol: 3 doses vs 3 doses comparing intervals in females (NCT00572832)

Abbreviations
HIV+: HIV positive
HPV: human papillomavirus
RCT: randomised controlled trial

Characteristics of studies awaiting assessment *[ordered by study ID]*

Li 2012

Methods	Randomised, double-blind, placebo-controlled trial
Participants	Participants: 100 healthy Chinese males and 500 healthy Chinese females (302 received the quadrivalent vaccine and 298 received the control vaccine) from Wuzhou, Guangxi, China Age range: males aged 9–15 years and females aged 9–45 years Inclusion criteria: no history of severe allergic reaction or allergic reaction to any vaccine component and a lifetime number of no more than 4 sex partners. Exclusion criteria: pregnant post-pubertal females; history of an abnormal Papanicolaou test or biopsy showing cervical intraepithelial neoplasia (CIN) or worse
Interventions	Vaccine: quadrivalent HPV vaccine (Gardasil/Silgard, Merck, Whitehouse Station, NJ) (3 doses: day 1, month 2, month 6) Control: adjuvant-containing placebo (3 doses: day 1, month 2, month 6)
Outcomes	Immunogenicity: GMTs, seroconversion Safety: adverse events, serious adverse events, death
Notes	Other groups: N/A Last report average follow-up time: 7 months Funding: Merck Sharp & Dohme Corp Trial ID: NCT01427777

Reisinger 2007

Methods	Randomised, double-blind, placebo-controlled, multicenter study
Participants	Participants: 1781 boys and girls (1181 received the quadrivalent vaccine and 597 received the non-aluminium placebo) from 47 study sites located in 10 countries in North America, Latin America, Europe and Asia Age: 9-15 years old Inclusion criteria: healthy, sexually naive boys and girls
Interventions	Vaccine: quadrivalent HPV-6/11/16/18 L1 VLP vaccine (GARDASIL/SILGARD, Merck and Co, Inc, Whitehouse Station, NJ) Control: placebo vaccine (identical components to those in the vaccine, with the exception of HPV L1 VLPs and aluminium adjuvant)
Outcomes	Immunogenicity: GMT, seroconversion Safety: adverse events, serious adverse events, death
Notes	Other groups: N/A Last report average follow-up time: 18 months Funding: Merck and Co, Inc

Reisinger 2007 *(Continued)*	
	Trial ID: NCT00092547

Abbreviations
GMT: geometric mean titre
HPV: human papillomavirus

Characteristics of ongoing studies *[ordered by study ID]*

NCT01735006

Trial name or title	Efficacy and immunogenicity study of recombinant human papillomavirus bivalent (genotype 16/18) vaccine
Methods	RCT
Participants	Females 18-45 years Country: China
Interventions	• HPV vaccine containing 40 µg HPV 16 virus-like particle antigen and 20 µg HPV 18 virus-like particle antigen adsorbed in alum-adjuvant • Hepatitis E virus (HEV) vaccine contains 30 µg HEV antigen adsorbed in alum-adjuvant
Outcomes	Clinical outcomes, adverse events, immunogenicity
Starting date	November 2012
Contact information	Jun Zhang, Xiamen University; Youlin Qiao, Cancer Institute and Hospital, Chinese Academy of Medical Sciences; Ting Wu, Xiamen University
Notes	Sponsors: Xiamen University; Xiamen Innovax Biotech Co, Ltd; Beijing Wantai Biological Pharmacy Enterprise Co, Ltd; Ministry of Science and Technology of the People's Republic of China Trial status in August 2018: active, not recruiting

NCT01824537

Trial name or title	Transmission reduction and prevention with HPV vaccination (TRAP-HPV) study (TRAP-HPV)
Methods	RCT
Participants	18-45 year-old couples, males and females Country: Canada
Interventions	• Nonavalent HPV vaccine (Gardasil 9, Merck) • Hepatitis A virus vaccine (Havrix, Merck)
Outcomes	HPV DNA positivity
Starting date	September 2013
Contact information	Allita Rodrigues (allita.rodrigues@mcgill.ca); Anna Tzagourni (canepiadm.med@mcgill.ca)
Notes	Sponsors: McGill University

NCT01824537 *(Continued)*

	Trial status in August 2018: recruiting

NCT02009800

Trial name or title	ICI-VPH: Impact of HPV immunisation schedules against HPV (ICI-VPH)
Methods	RCT
Participants	Females 14-16 years old Country: Canada
Interventions	• 2 doses quadrivalent HPV vaccine (Gardasil, Merck) • 3 doses quadrivalent HPV vaccine (Gardasil, Merck)
Outcomes	Incidence of persistent HPV-16/18 infections; GMT of antibodies and seropositivity for HPV genotypes 6, 11, 16 and 18
Starting date	November 2013
Contact information	Chantal Sauvageau, CHU de Quebec-Universite Laval
Notes	Sponsors: CHU de Quebec-Universite Laval; Centre hospitalier de l'Université de Montréal; Quebec Public Health National Institute; Quebec Ministry of Health and Social Services Trial status in August 2018: active, not recruiting

NCT02087384

Trial name or title	HPV (human papilloma virus) vaccination after treatment of anal intraepithelial neoplasia (AIN) (VACCAIN-P)
Methods	RCT
Participants	HIV positive MSM ≥ 18 years old Country: the Netherlands
Interventions	• Quadrivalent HPV vaccine: intramuscular Gardasil vaccination at 0, 2 and 6 months • Control: intramuscular saline 0.9% vaccination at 0, 2 and 6 months
Outcomes	Recurrence of intra-anal or peri-anal high-grade AIN; toxicity/safety; Intra-anal or peri-anal low-grade AIN; anogenital warts; causative HPV genotype in recurrent AIN lesions; HPV genotype-specific antibody response
Starting date	March 2014
Contact information	Jan M Prins, Academisch Medisch Centrum, Universiteit van Amsterdam; Henry JC de Vries, Academisch Medisch Centrum, Universiteit van Amsterdam
Notes	Sponsors: Prof Jan Prins Trial status in August 2018: active, not recruiting

NCT02405520

Trial name or title	Safety and immunogenicity study of the recombinant human papillomavirus virus type 6/11 bivalent vaccine
Methods	RCT
Participants	Males and females 18-55 years Country: China
Interventions	• Low dosage HPV 6/11 bivalent vaccine at 0, 1, 6 month for 3 doses • Medium dosage HPV 6/11 bivalent vaccine at 0, 1, 6 month for 3 doses • High dosage HPV 6/11 bivalent vaccine at 0, 1, 6 month for 3 doses • Aluminium adjuvant at 0, 1, 6 month for 3 doses
Outcomes	Adverse events; anti-HPV 6/11 antibody
Starting date	March 2015
Contact information	Jun Zhang, Xiamen University; Zhao-Jun Mo, Guangxi Center for Disease Prevention and Control; Ting Wu, Xiamen University
Notes	Sponsors: Jun Zhang; Xiamen Innovax Biotech Co, Ltd; Beijing Wantai Biological Pharmacy Enterprise Co, Ltd Trial status in August 2018: active, not recruiting

NCT02562508

Trial name or title	Immunogenicity and safety study of a bivalent human papillomavirus (type 16, 18) recombinant vaccine (E.coli) in healthy female subjects aged 9-17 years
Methods	RCT
Participants	Females 9-26 years Country: China
Interventions	• 3 doses of HPV 16/18 bivalent vaccine • 2 doses of HPV 16/18 bivalent vaccine
Outcomes	Adverse events and immunogenicity
Starting date	5 December 2015
Contact information	Ting Wu, Xiamen University; Yuemei Hu, Jiangsu Provincial Centre for Disease Control and Prevention
Notes	Sponsors: Jun Zhang; Xiamen Innovax Biotech Co, Ltd; Beijing Wantai Biological Pharmacy Enterprise Co, Ltd Trial status in August 2018: completed in August 2016, we contacted study investigators but they had provided no data at the time of submitting this review for publication

NCT02567955

Trial name or title	Immunogenicity and safety of Gardasil-9 and Cervarix
Methods	RCT
Participants	Boys and girls 9-10 years old Country: Canada
Interventions	• Nonavalent HPV vaccine (Gardasil-9) (0.5 mL), 2 doses according to 0-6 month schedule • 1 dose bivalent HPV vaccine (Cervarix) (0.5 mlL) and 1 dose nonavalent HPV vaccine (Gardasil-9) (0.5 mL) according to 0-6 month schedule
Outcomes	Antibodies to 9 HPV genotypes included in the Gardasil-9 vaccine; tolerability profile
Starting date	September 2015
Contact information	Vladimir Gilca (vladimir.gilca@inspq.qc.ca); Chantal Sauvageau (chantal.sauvageau@inspq.qc.ca)
Notes	Sponsors: Laval University Trial status in August 2018: recruiting

NCT02710851

Trial name or title	Immunogenicity study of the recombinant human papillomavirus virus type 6/11 bivalent vaccine
Methods	RCT
Participants	Males and females 18-55 years old Country: China
Interventions	• Low dosage (1:1) bivalent HPV vaccine: virus-like particles genotype 6 and 11 at 1:1 ratio • Low dosage (1:2) bivalent HPV vaccine: virus-like particles genotype 6 and 11 at 1:2 ratio • High dosage (1:1) bivalent HPV vaccine: virus-like particles genotype 6 and 11 at 1:1 ratio • Control: hepatitis E vaccine (Hecolin)
Outcomes	Anti-HPV 6 and anti-HPV 11 seroconversion rates; serious adverse events
Starting date	March 2016
Contact information	Jun Zhang, Xiamen University; Yuemei Hu, Jiangsu Center for Disease Prevention and Control
Notes	Sponsors: Jun Zhang; Xiamen Innovax Biotech Co., Ltd; Beijing Wantai Biological Pharmacy Enterprise Co, Ltd Trial status in August 2018: active, not recruiting

NCT02733068

Trial name or title	A phase III double blinded, randomized controlled study to evaluate efficacy of protection against HPV-16 and 18 related diseases, immunogenicity and safety of HPV-16/18 vaccine in healthy females aged 18-30 years
Methods	RCT
Participants	Females aged 18-30 years Country: China
Interventions	• HPV-16/18 vaccine • placebo
Outcomes	Clinical outcomes, adverse events, immunogenicity
Starting date	November 2014
Contact information	Zhaojun Mo, Guangxi Center for Disease Prevention and Control
Notes	Sponsors: Shanghai Zerun Biotechnology Co, Ltd; Guangxi Center for Disease Control and Prevention Trial status in August 2018: active, not recruiting

NCT02740777

Trial name or title	Immunogenicity study of a 2-dose immunization schedule of recombinant human papillomavirus virus-like particle vaccine (type 16 and 18 l1 proteins, yeast) in adolescent females aged 9 to 14 years
Methods	RCT
Participants	Females aged 9-14 years Country: China
Interventions	HPV-16/18 vaccine (2 doses) HPV-16/18 vaccine (3 doses)
Outcomes	Adverse events and immunogenicity
Starting date	February 2016
Contact information	Zhaojun Mo, Guangxi Center for Disease Prevention and Control
Notes	Sponsors: Shanghai Zerun Biotechnology Co, Ltd; Guangxi Center for Disease Control and Prevention Trial status in August 2018: recruiting

NCT02750202

Trial name or title	Effectiveness study of human papilloma virus (HPV) vaccines to prevent recurrence of genital warts (TheraVACCS)
Methods	RCT
Participants	Females ≦ 16 years with vulval vaginal genital warts Country: South Africa
Interventions	• Quadrivalent HPV vaccine (Gardasil) doses administered intramuscular as 3 separate 0.5 mL doses at month 0, month 2 and month 6 • Control: hepatitis B vaccine doses administered intramuscular as 3 separate 0.5 mL doses at month 0, month 2 and month 6
Outcomes	Change in size of genital wart lesion; surgical treatment of warts; surgical treatment of cervical disease; immunogenicity; HIV status
Starting date	July 2016
Contact information	Greta G Dreyer (Greta.Dreyer@up.ac.za); Cathy Visser (visser.cathy@gmail.com)
Notes	Sponsors: University of Pretoria; University of Stellenbosch Trial status in August 2018: not yet recruiting

NCT02834637

Trial name or title	A dose reduction immunobridging and safety study of two HPV vaccines in Tanzanian girls
Methods	RCT
Participants	Females 9 -14 years Country: Tanzania
Interventions	• Bivalent HPV vaccine • Nonavalent HPV vaccine
Outcomes	Adverse events and immunogenicity
Starting date	23 February 2017
Contact information	Deborah Watson-Jones, London School of Hygiene and Tropical Medicine
Notes	Sponsors: London School of Hygiene and Tropical Medicine; University of York; Catalan Institute of Oncology; National Cancer Institute (NCI); Karolinska Institutet; Technische Universität Berlin; Tanzanian National Institute for Medical Research; University of Glasgow Trial status in August 2018: active, not recruiting

NCT02888418

Trial name or title	Random, double blind, placebo controlled phase I clinical trials to estimate the safety and preliminary immunogenicity of tetravalent recombinant human papilloma virus vaccine (6,11,16,18 type) (Hansenula polymorpha) in women of 9-30 years old and men of 9-17 years old
Methods	RCT
Participants	Males 9-17 years old, females 9-30 years old Country China
Interventions	• Tetravalent recombinant human papillomavirus vaccine (6,11,16,18 type) (Hansenula polymorpha) • Control vaccine
Outcomes	Adverse events and immunogenicity
Starting date	October 2016
Contact information	Beijing Chaoyang District Centre for Disease Control and Prevention
Notes	Sponsors: Beijing Chaoyang District Centre for Disease Control and Prevention Trial status in August 2018: unknown, in August 2016 it was 'Not yet recruiting'

NCT03180034

Trial name or title	A scientific evaluation of one or two doses of vaccine against human papillomavirus: the ESCUDDO study
Methods	RCT
Participants	Females 12-16 years old Country: Costa Rica
Interventions	• Cervarix, 1 dose • Gardasil 9, 1 dose • Cervarix, 2 doses • Gardasil 9, 2 doses
Outcomes	Clinical outcomes, adverse events, immunogenicity
Starting date	26 June 2018
Contact information	Aimee R Kreimer (kreimera@mail.nih.gov), National Cancer Institute
Notes	Sponsors: National Cancer Institute; Bill and Melinda Gates Foundation Trial status in August 2018: recruiting

NCT03296397	
Trial name or title	Efficacy of quadrivalent HPV vaccine to prevent relapses of genital warts after initial therapeutic response (CONDYVAC)
Methods	RCT
Participants	Males and females ≥ 18 years old, cured of genital warts Country: France
Interventions	• Quadrivalent HPV vaccine (Gardasil) • Saline placebo
Outcomes	Relapse free survival; Improvement of quality of life; adverse events
Starting date	November 2017
Contact information	Sebastien Fouere (sebastien.fouere@aphp.fr); Olivier Chosidow (olivier.chosidow@aphp.fr)
Notes	Sponsors: Assistance Publique - Hôpitaux de Paris Trial status in August 2018: recruiting

Abbreviations
AIN: anal intraepithelial neoplasia
HPV: human papillomavirus
MSM: men who have sex with men
RCT: randomised controlled trial

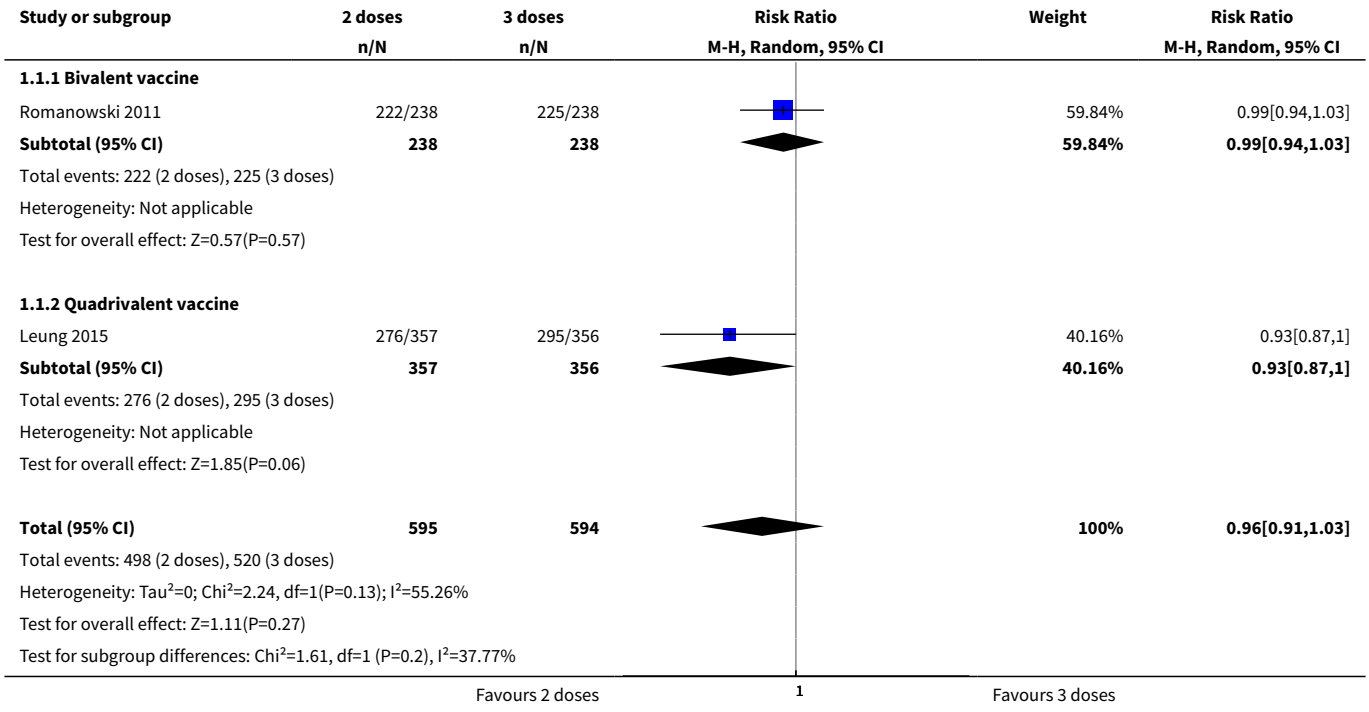
DATA AND ANALYSES

Comparison 1. Two versus three doses of HPV vaccines in 9- to 15-year-old females

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain at injection site	2	1189	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.91, 1.03]
1.1 Bivalent vaccine	1	476	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.94, 1.03]
1.2 Quadrivalent vaccine	1	713	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.87, 1.00]
2 Swelling at injection site	2	1189	Risk Ratio (M-H, Random, 95% CI)	0.76 [0.65, 0.89]
2.1 Bivalent vaccine	1	476	Risk Ratio (M-H, Random, 95% CI)	0.70 [0.57, 0.87]
2.2 Quadrivalent vaccine	1	713	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.66, 1.04]
3 Redness at injection site	2	1189	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.75, 0.96]
3.1 Bivalent vaccine	1	476	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.72, 0.99]
3.2 Quadrivalent vaccine	1	713	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.71, 1.02]

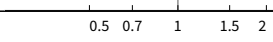
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4 Serious adverse events (overall)	4	2317	Odds Ratio (M-H, Random, 95% CI)	1.03 [0.64, 1.66]
4.1 Bivalent vaccine	1	479	Odds Ratio (M-H, Random, 95% CI)	1.28 [0.64, 2.59]
4.2 Quadrivalent vaccine	2	1236	Odds Ratio (M-H, Random, 95% CI)	0.78 [0.35, 1.74]
4.3 Nonavalent vaccine	1	602	Odds Ratio (M-H, Random, 95% CI)	1.0 [0.32, 3.14]
5 Deaths	3	1797	Odds Ratio (M-H, Random, 95% CI)	0.33 [0.01, 8.19]
5.1 Bivalent vaccine	1	479	Odds Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
5.2 Quadrivalent vaccine	1	716	Odds Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
5.3 Nonavalent vaccine	1	602	Odds Ratio (M-H, Random, 95% CI)	0.33 [0.01, 8.19]

Analysis 1.1. Comparison 1 Two versus three doses of HPV vaccines in 9- to 15-year-old females, Outcome 1 Pain at injection site.



Analysis 1.2. Comparison 1 Two versus three doses of HPV vaccines in 9- to 15-year-old females, Outcome 2 Swelling at injection site.

Study or subgroup	2 doses n/N	3 doses n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.2.1 Bivalent vaccine					
Romanowski 2011	83/238	118/238		51.77%	0.7[0.57,0.87]
Subtotal (95% CI)	**238**	**238**		**51.77%**	**0.7[0.57,0.87]**
Total events: 83 (2 doses), 118 (3 doses)					
Heterogeneity: Not applicable					
Test for overall effect: Z=3.2(P=0)					
1.2.2 Quadrivalent vaccine					
Leung 2015	98/357	118/356		48.23%	0.83[0.66,1.04]
Subtotal (95% CI)	**357**	**356**		**48.23%**	**0.83[0.66,1.04]**
Total events: 98 (2 doses), 118 (3 doses)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.65(P=0.1)					
Total (95% CI)	**595**	**594**		**100%**	**0.76[0.65,0.89]**
Total events: 181 (2 doses), 236 (3 doses)					
Heterogeneity: Tau^2=0; Chi^2=1.07, df=1(P=0.3); I^2=6.16%					
Test for overall effect: Z=3.34(P=0)					
Test for subgroup differences: Chi^2=1.06, df=1 (P=0.3), I^2=5.57%					



Favours 2 doses — Favours 3 doses

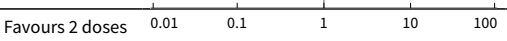
Analysis 1.3. Comparison 1 Two versus three doses of HPV vaccines in 9- to 15-year-old females, Outcome 3 Redness at injection site.

Study or subgroup	2 doses n/N	3 doses n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.3.1 Bivalent vaccine					
Romanowski 2011	123/238	145/238		55.38%	0.85[0.72,0.99]
Subtotal (95% CI)	**238**	**238**		**55.38%**	**0.85[0.72,0.99]**
Total events: 123 (2 doses), 145 (3 doses)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.02(P=0.04)					
1.3.2 Quadrivalent vaccine					
Leung 2015	134/357	157/356		44.62%	0.85[0.71,1.02]
Subtotal (95% CI)	**357**	**356**		**44.62%**	**0.85[0.71,1.02]**
Total events: 134 (2 doses), 157 (3 doses)					
Heterogeneity: Tau^2=0; Chi^2=0, df=0(P<0.0001); I^2=100%					
Test for overall effect: Z=1.78(P=0.08)					
Total (95% CI)	**595**	**594**		**100%**	**0.85[0.75,0.96]**
Total events: 257 (2 doses), 302 (3 doses)					
Heterogeneity: Tau^2=0; Chi^2=0, df=1(P=0.98); I^2=0%					
Test for overall effect: Z=2.69(P=0.01)					
Test for subgroup differences: Chi^2=0, df=1 (P=0.98), I^2=0%					

Favours 2 doses — Favours 3 doses

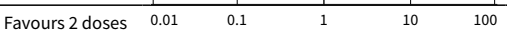
Analysis 1.4. Comparison 1 Two versus three doses of HPV vaccines in 9- to 15-year-old females, Outcome 4 Serious adverse events (overall).

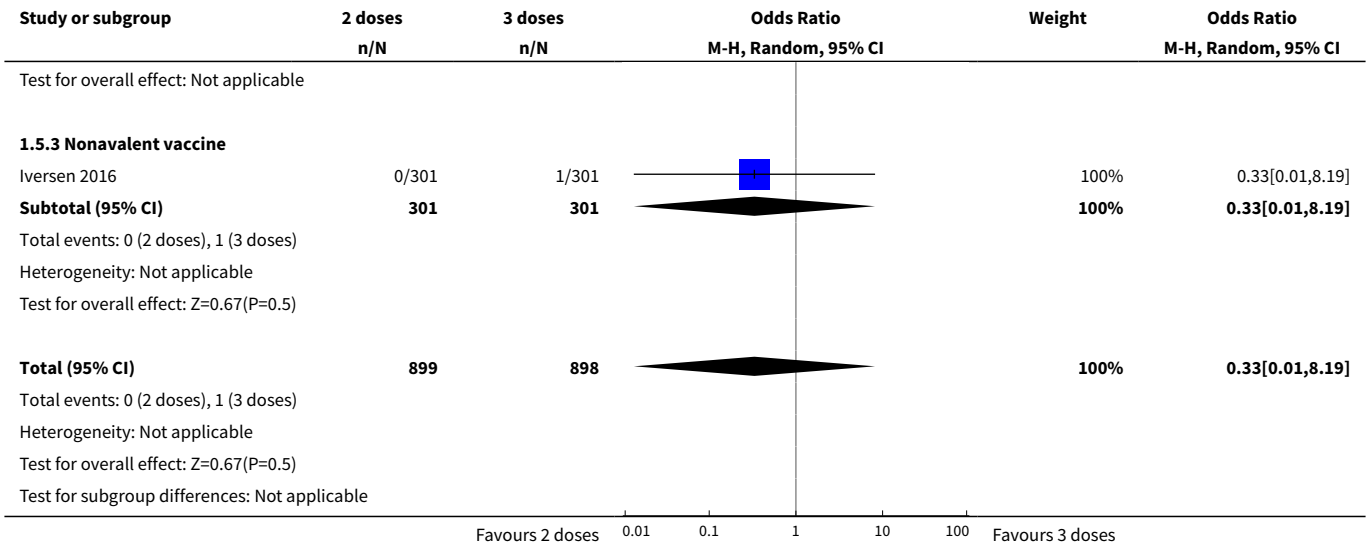
Study or subgroup	2 doses n/N	3 doses n/N	Odds Ratio M-H, Random, 95% CI	Weight	Odds Ratio M-H, Random, 95% CI
1.4.1 Bivalent vaccine					
Romanowski 2011	19/240	15/239		46.72%	1.28[0.64,2.59]
Subtotal (95% CI)	**240**	**239**		**46.72%**	**1.28[0.64,2.59]**
Total events: 19 (2 doses), 15 (3 doses)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.7(P=0.49)					
1.4.2 Quadrivalent vaccine					
Dobson 2013	0/259	0/261			Not estimable
Leung 2015	11/358	14/358		35.65%	0.78[0.35,1.74]
Subtotal (95% CI)	**617**	**619**		**35.65%**	**0.78[0.35,1.74]**
Total events: 11 (2 doses), 14 (3 doses)					
Heterogeneity: Tau^2=0; Chi^2=0, df=0(P<0.0001); I^2=100%					
Test for overall effect: Z=0.61(P=0.54)					
1.4.3 Nonavalent vaccine					
Iversen 2016	6/301	6/301		17.62%	1[0.32,3.14]
Subtotal (95% CI)	**301**	**301**		**17.62%**	**1[0.32,3.14]**
Total events: 6 (2 doses), 6 (3 doses)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
Total (95% CI)	**1158**	**1159**		**100%**	**1.03[0.64,1.66]**
Total events: 36 (2 doses), 35 (3 doses)					
Heterogeneity: Tau^2=0; Chi^2=0.85, df=2(P=0.66); I^2=0%					
Test for overall effect: Z=0.11(P=0.91)					
Test for subgroup differences: Chi^2=0.85, df=1 (P=0.66), I^2=0%					



Analysis 1.5. Comparison 1 Two versus three doses of HPV vaccines in 9- to 15-year-old females, Outcome 5 Deaths.

Study or subgroup	2 doses n/N	3 doses n/N	Odds Ratio M-H, Random, 95% CI	Weight	Odds Ratio M-H, Random, 95% CI
1.5.1 Bivalent vaccine					
Romanowski 2011	0/240	0/239			Not estimable
Subtotal (95% CI)	**240**	**239**			**Not estimable**
Total events: 0 (2 doses), 0 (3 doses)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
1.5.2 Quadrivalent vaccine					
Leung 2015	0/358	0/358			Not estimable
Subtotal (95% CI)	**358**	**358**			**Not estimable**
Total events: 0 (2 doses), 0 (3 doses)					
Heterogeneity: Not applicable					





Comparison 2. Two doses of HPV vaccine with longer interval versus two doses of HPV vaccine with shorter interval in 9- to 14-year-olds

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Pain at injection site	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Bivalent vaccine (0 and 2 months vs 0 and 6 months)	1	477	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.96, 1.06]
1.2 Bivalent vaccine (0 and 6 months vs 0 and 12 months)	1	963	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.98, 1.06]
2 Swelling at injection site	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Bivalent vaccine (0 and 2 months vs 0 and 6 months)	1	477	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.76, 1.20]
2.2 Bivalent vaccine (0 and 6 months vs 0 and 12 months)	1	963	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.87, 1.18]
3 Redness at injection site	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 Bivalent vaccine (0 and 2 months vs 0 and 6 months)	1	477	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.84, 1.24]
3.2 Bivalent vaccine (0 and 6 months vs 0 and 12 months)	1	963	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.93, 1.22]
4 Serious adverse events (overall)	3		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
4.1 Bivalent vaccine (0, 2 months vs 0, 6 months)	1	481	Odds Ratio (M-H, Random, 95% CI)	1.15 [0.55, 2.41]

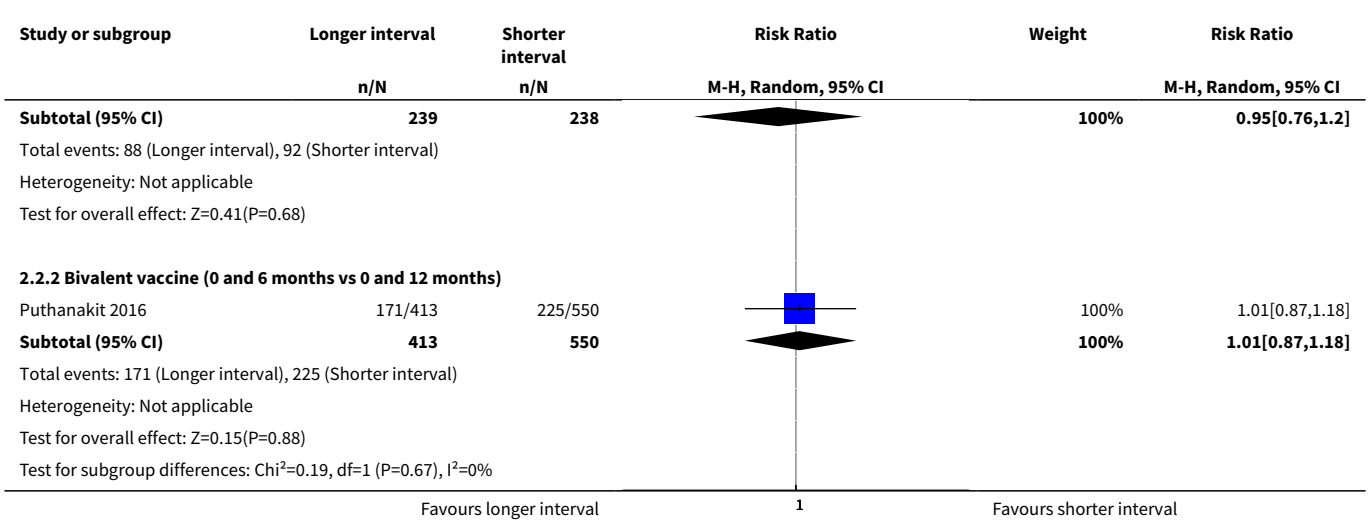
Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
4.2 Bivalent vaccine (0 and 6 months vs 0 and 12 months)	1	965	Odds Ratio (M-H, Random, 95% CI)	1.63 [0.89, 2.99]
4.3 Nonavalent vaccine (0 and 6 months vs 0 and 12 months) - females and males	1	903	Odds Ratio (M-H, Random, 95% CI)	0.80 [0.31, 2.07]
5 Deaths	3		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
5.1 Bivalent vaccine (0 and 2 months vs 0 and 6 months)	1	481	Odds Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
5.2 Bivalent vaccine (0 and 6 months vs 0 and 12 months)	1	965	Odds Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
5.3 Nonavalent vaccine (0 and 6 months vs 0 and 12 months)	1	452	Odds Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Analysis 2.1. Comparison 2 Two doses of HPV vaccine with longer interval versus two doses of HPV vaccine with shorter interval in 9- to 14-year-olds, Outcome 1 Pain at injection site.

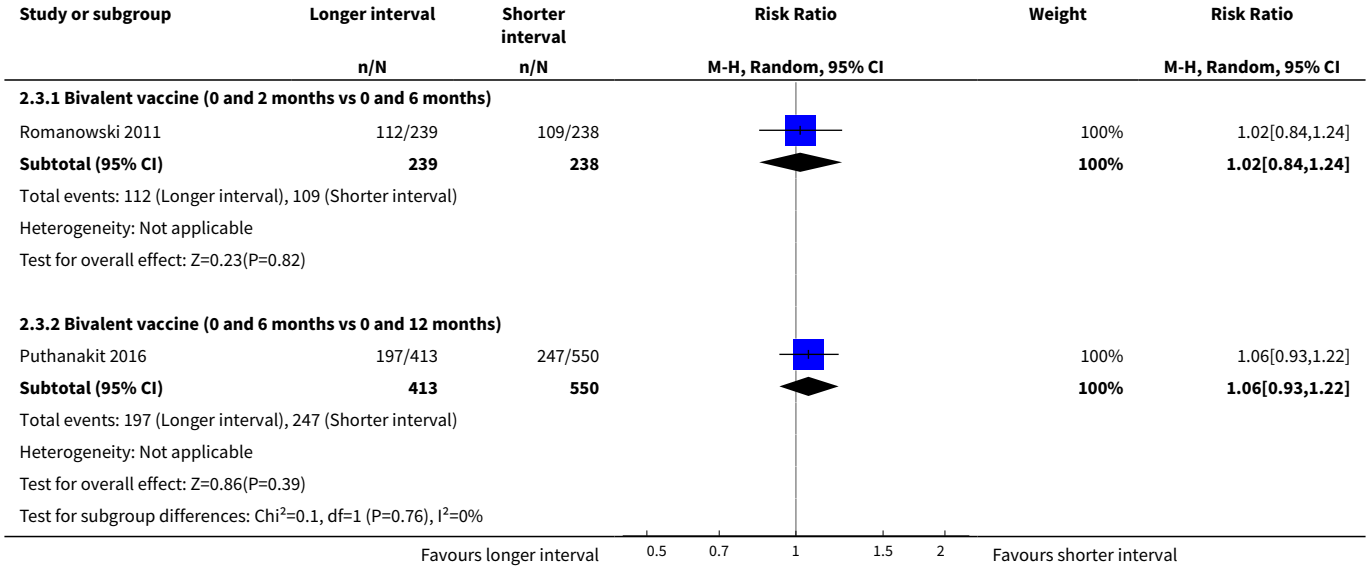
Study or subgroup	Longer interval n/N	Shorter interval n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
2.1.1 Bivalent vaccine (0 and 2 months vs 0 and 6 months)					
Romanowski 2011	225/239	222/238		100%	1.01[0.96,1.06]
Subtotal (95% CI)	**239**	**238**		**100%**	**1.01[0.96,1.06]**
Total events: 225 (Longer interval), 222 (Shorter interval)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.39(P=0.7)					
2.1.2 Bivalent vaccine (0 and 6 months vs 0 and 12 months)					
Puthanakit 2016	381/413	499/550		100%	1.02[0.98,1.06]
Subtotal (95% CI)	**413**	**550**		**100%**	**1.02[0.98,1.06]**
Total events: 381 (Longer interval), 499 (Shorter interval)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.84(P=0.4)					
			Favours longer interval 1 Favours shorter interval		

Analysis 2.2. Comparison 2 Two doses of HPV vaccine with longer interval versus two doses of HPV vaccine with shorter interval in 9- to 14-year-olds, Outcome 2 Swelling at injection site.

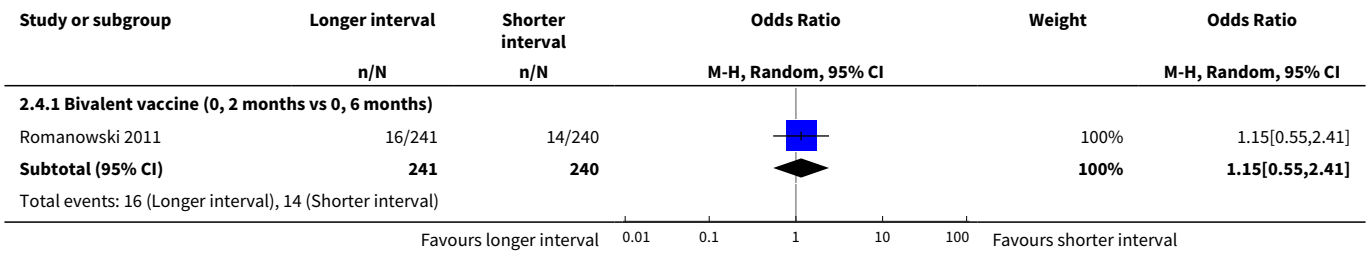
Study or subgroup	Longer interval n/N	Shorter interval n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
2.2.1 Bivalent vaccine (0 and 2 months vs 0 and 6 months)					
Romanowski 2011	88/239	92/238		100%	0.95[0.76,1.2]
			Favours longer interval 1 Favours shorter interval		

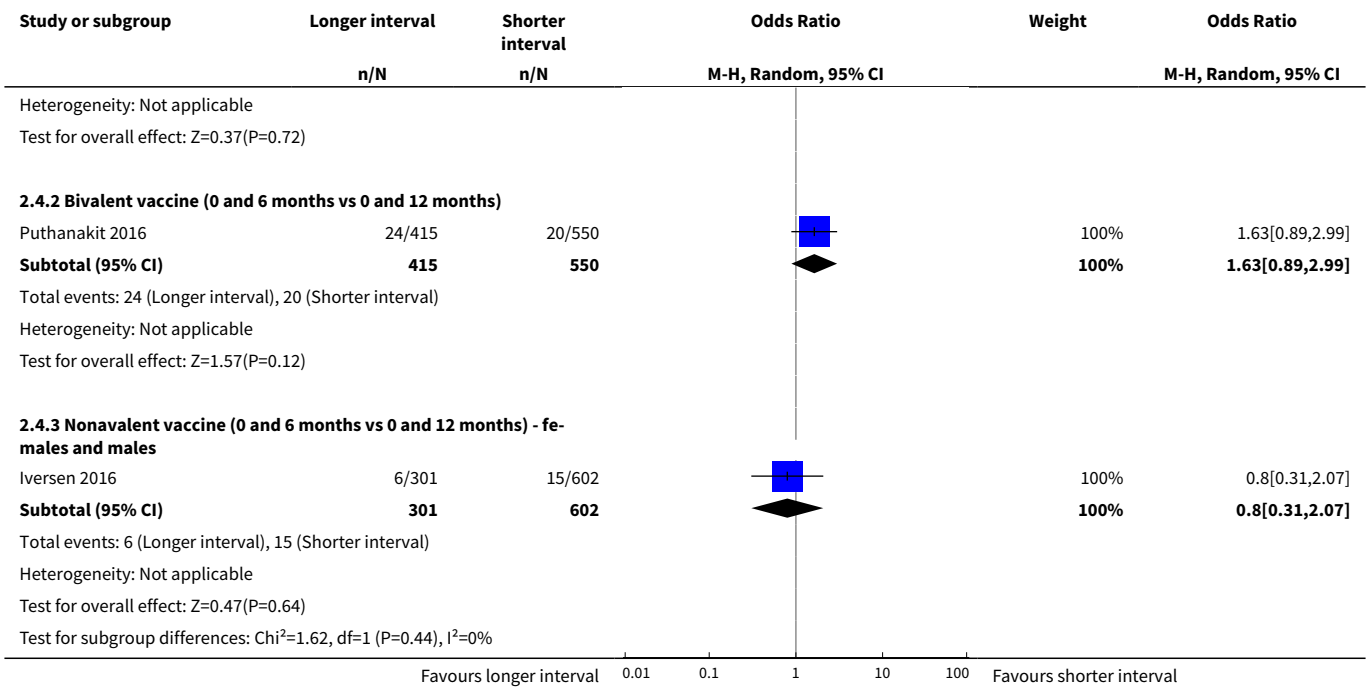


Analysis 2.3. Comparison 2 Two doses of HPV vaccine with longer interval versus two doses of HPV vaccine with shorter interval in 9- to 14-year-olds, Outcome 3 Redness at injection site.

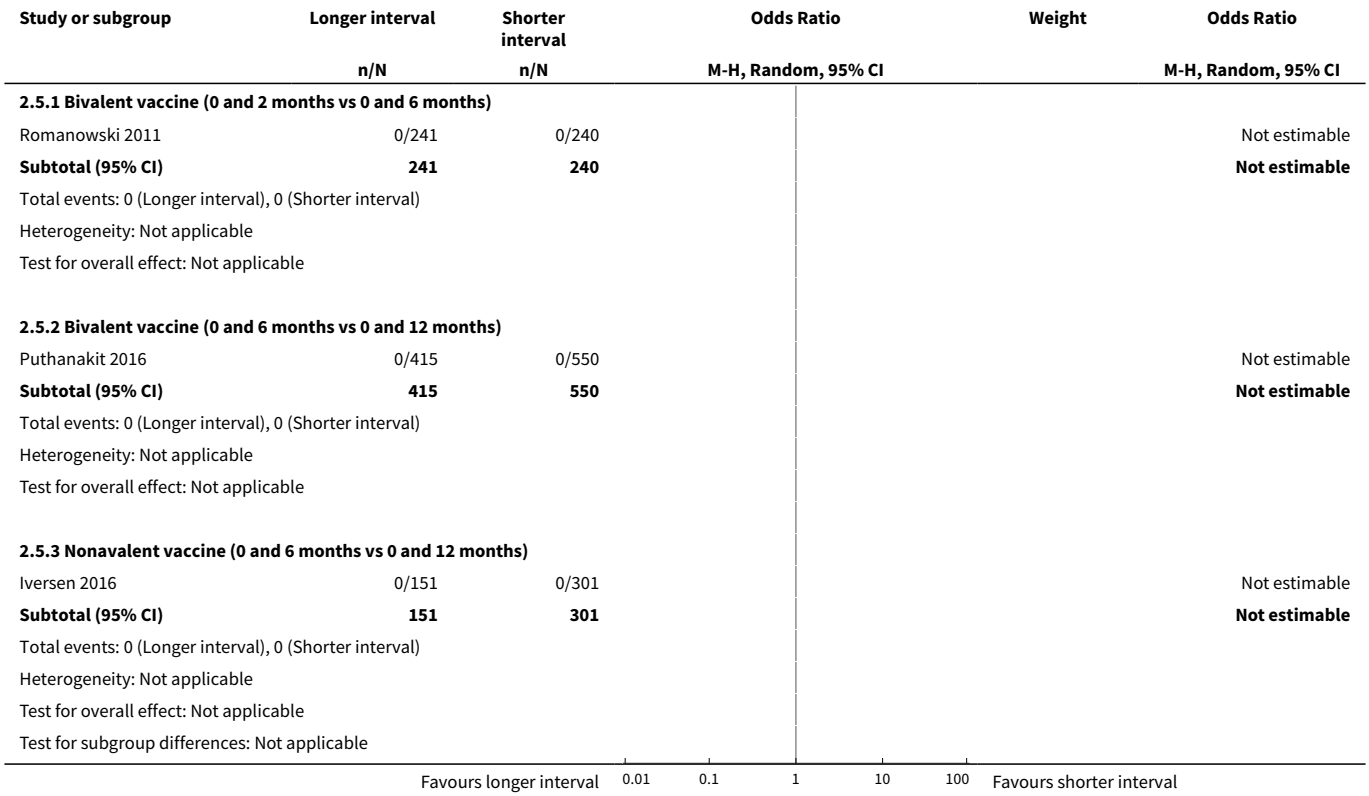


Analysis 2.4. Comparison 2 Two doses of HPV vaccine with longer interval versus two doses of HPV vaccine with shorter interval in 9- to 14-year-olds, Outcome 4 Serious adverse events (overall).





Analysis 2.5. Comparison 2 Two doses of HPV vaccine with longer interval versus two doses of HPV vaccine with shorter interval in 9- to 14-year-olds, Outcome 5 Deaths.



Comparison 3. Three doses of HPV vaccine with longer interval versus three doses of HPV vaccine with shorter interval in 18- to 25-year-old males

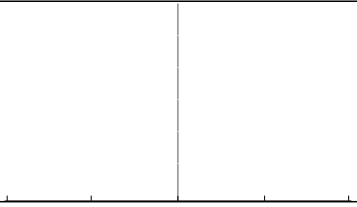
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Adverse events			Other data	No numeric data
2 Serious adverse events (overall)	1	220	Odds Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Analysis 3.1. Comparison 3 Three doses of HPV vaccine with longer interval versus three doses of HPV vaccine with shorter interval in 18- to 25-year-old males, Outcome 1 Adverse events.

Study	Adverse events
Lin 2014	Adverse events data not reported separately for each arm. "Participants reported side effects following 646 separate vaccinations; 172 local and general reactions were reported, with no difference in proportion of side effects reported between Standard (24.4%) and Alternate (28.9%) schedule groups (P = 0.26). The majority of side effects were pain and redness at the injection site (86%; n = 148), with the remainder composed of fever (3.5%; n = 6), and miscellaneous symptoms (10.5%; n = 18). There were no reports of any serious side effects."

Analysis 3.2. Comparison 3 Three doses of HPV vaccine with longer interval versus three doses of HPV vaccine with shorter interval in 18- to 25-year-old males, Outcome 2 Serious adverse events (overall).

Study or subgroup	Longer interval n/N	Shorter interval n/N	Odds Ratio M-H, Random, 95% CI	Weight	Odds Ratio M-H, Random, 95% CI
Lin 2014	0/111	0/109			Not estimable
Total (95% CI)	**111**	**109**			**Not estimable**
Total events: 0 (Longer interval), 0 (Shorter interval)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					



Comparison 4. HPV vaccine versus control in males

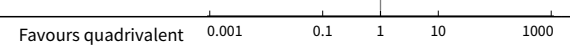
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 External genital lesions (any type)	1		Rate Ratio (Random, 95% CI)	Subtotals only
1.1 Quadrivalent vaccine (16- to 26-year olds)	1		Rate Ratio (Random, 95% CI)	0.16 [0.07, 0.38]
2 External genital lesions (HPV 6, 11, 16, or 18)	1		Rate Ratio (Random, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Quadrivalent vaccine (16- to 26-year olds)	1		Rate Ratio (Random, 95% CI)	0.10 [0.03, 0.31]
3 Anogenital warts	1		Rate Ratio (Random, 95% CI)	Subtotals only
3.1 Quadrivalent vaccine (16- to 26-year olds)	1		Rate Ratio (Random, 95% CI)	0.11 [0.03, 0.38]
4 All penile, perianal, or perineal intraepithelial neoplasia lesions	1		Rate Ratio (Random, 95% CI)	Subtotals only
4.1 Quadrivalent vaccine (16- to 26-year olds)	1		Rate Ratio (Random, 95% CI)	0.17 [0.01, 3.27]
5 Penile, perianal, or perineal intraepithelial neoplasia grade 1	1		Rate Ratio (Random, 95% CI)	Subtotals only
5.1 Quadrivalent vaccine (16- to 26-year olds)	1		Rate Ratio (Random, 95% CI)	0.25 [0.01, 6.22]
6 Penile, perianal, or perineal intraepithelial neoplasia grade 2 or 3	1		Rate Ratio (Random, 95% CI)	Subtotals only
6.1 Quadrivalent vaccine (16- to 26-year olds)	1		Rate Ratio (Random, 95% CI)	0.50 [0.02, 14.80]
7 Overall local/injection site adverse events	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
7.1 Quadrivalent vaccine (16- to 26-year olds)	1	3895	Risk Ratio (M-H, Random, 95% CI)	1.12 [1.06, 1.18]
8 Pain at injection site	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
8.1 Bivalent vaccine (10- to 18-year-olds)	1	268	Risk Ratio (M-H, Random, 95% CI)	1.99 [1.57, 2.53]
8.2 Quadrivalent vaccine (16- to 26-year olds)	2	5162	Risk Ratio (M-H, Random, 95% CI)	1.13 [1.07, 1.19]
9 Swelling at injection site	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
9.1 Bivalent vaccine (10- to 18-year-olds)	1	268	Risk Ratio (M-H, Random, 95% CI)	2.51 [1.17, 5.42]
9.2 Quadrivalent vaccine (16- to 26-year olds)	2	5162	Risk Ratio (M-H, Random, 95% CI)	1.29 [1.04, 1.60]
10 Redness at injection site	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
10.1 Bivalent vaccine (10- to 18-year-olds)	1	268	Risk Ratio (M-H, Random, 95% CI)	1.66 [0.99, 2.79]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
10.2 Quadrivalent vaccine (16- to 26-year olds)	2	5162	Risk Ratio (M-H, Random, 95% CI)	1.12 [0.99, 1.27]
11 Overall systemic events and general symptoms	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
11.1 Quadrivalent vaccine (16- to 26-year olds)	2	5008	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.90, 1.08]
12 Serious adverse events (overall)	3		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
12.1 Bivalent vaccine (10- to 18-year-olds)	1	270	Odds Ratio (M-H, Random, 95% CI)	1.48 [0.15, 14.46]
12.2 Quadrivalent vaccine (16- to 26-year olds)	2	5162	Odds Ratio (M-H, Random, 95% CI)	0.69 [0.29, 1.66]
13 Deaths	3		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
13.1 Bivalent vaccine (10- to 18-year-olds)	1	270	Odds Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
13.2 Quadrivalent vaccine (16- to 26-year olds)	2	5173	Odds Ratio (M-H, Random, 95% CI)	0.30 [0.09, 1.01]

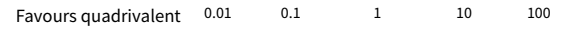
Analysis 4.1. Comparison 4 HPV vaccine versus control in males, Outcome 1 External genital lesions (any type).

Study or subgroup	Quadrivalent vaccine N	Control N	log[Rate Ratio] (SE)	Rate Ratio IV, Random, 95% CI	Weight	Rate Ratio IV, Random, 95% CI
4.1.1 Quadrivalent vaccine (16- to 26-year olds)						
Giuliano 2011	0	0	-1.8 (0.441)		100%	0.16[0.07,0.38]
Subtotal (95% CI)					**100%**	**0.16[0.07,0.38]**
Heterogeneity: Tau²=0; Chi²=0, df=0(P<0.0001); I²=100%						
Test for overall effect: Z=4.13(P<0.0001)						

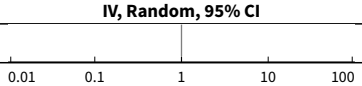


Analysis 4.2. Comparison 4 HPV vaccine versus control in males, Outcome 2 External genital lesions (HPV 6, 11, 16, or 18).

Study or subgroup	Quadrivalent vaccine N	Control N	log[Rate Ratio] (SE)	Rate Ratio IV, Random, 95% CI	Weight	Rate Ratio IV, Random, 95% CI
4.2.1 Quadrivalent vaccine (16- to 26-year olds)						
Giuliano 2011	0	0	-2.3 (0.594)		100%	0.1[0.03,0.31]
Subtotal (95% CI)					**100%**	**0.1[0.03,0.31]**
Heterogeneity: Not applicable						



Study or subgroup	Quadrivalent vaccine N	Control N	log[Rate Ratio] (SE)	Rate Ratio IV, Random, 95% CI	Weight	Rate Ratio IV, Random, 95% CI
Test for overall effect: Z=3.94(P<0.0001)						



Analysis 4.3. Comparison 4 HPV vaccine versus control in males, Outcome 3 Anogenital warts.

Study or subgroup	Quadrivalent vaccine N	Control N	log[Rate Ratio] (SE)	Rate Ratio IV, Random, 95% CI	Weight	Rate Ratio IV, Random, 95% CI
4.3.1 Quadrivalent vaccine (16- to 26-year olds)						
Giuliano 2011	0	0	-2.2 (0.646)		100%	0.11[0.03,0.38]
Subtotal (95% CI)					**100%**	**0.11[0.03,0.38]**
Heterogeneity: Not applicable						
Test for overall effect: Z=3.46(P=0)						

Analysis 4.4. Comparison 4 HPV vaccine versus control in males, Outcome 4 All penile, perianal, or perineal intraepithelial neoplasia lesions.

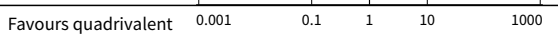
Study or subgroup	Quadrivalent vaccine N	Control N	log[Rate Ratio] (SE)	Rate Ratio IV, Random, 95% CI	Weight	Rate Ratio IV, Random, 95% CI
4.4.1 Quadrivalent vaccine (16- to 26-year olds)						
Giuliano 2011	0	0	-1.8 (1.52)		100%	0.17[0.01,3.27]
Subtotal (95% CI)					**100%**	**0.17[0.01,3.27]**
Heterogeneity: Not applicable						
Test for overall effect: Z=1.18(P=0.24)						

Analysis 4.5. Comparison 4 HPV vaccine versus control in males, Outcome 5 Penile, perianal, or perineal intraepithelial neoplasia grade 1.

Study or subgroup	Quadrivalent vaccine N	Control N	log[Rate Ratio] (SE)	Rate Ratio IV, Random, 95% CI	Weight	Rate Ratio IV, Random, 95% CI
4.5.1 Quadrivalent vaccine (16- to 26-year olds)						
Giuliano 2011	0	0	-1.4 (1.641)		100%	0.25[0.01,6.22]
Subtotal (95% CI)					**100%**	**0.25[0.01,6.22]**
Heterogeneity: Not applicable						
Test for overall effect: Z=0.85(P=0.4)						

Analysis 4.6. Comparison 4 HPV vaccine versus control in males, Outcome 6 Penile, perianal, or perineal intraepithelial neoplasia grade 2 or 3.

Study or subgroup	Quadrivalent vaccine N	Control N	log[Rate Ratio] (SE)	Rate Ratio IV, Random, 95% CI	Weight	Rate Ratio IV, Random, 95% CI
4.6.1 Quadrivalent vaccine (16- to 26-year olds)						
Giuliano 2011	0	0	-0.7 (1.73)		100%	0.5[0.02,14.8]
Subtotal (95% CI)					**100%**	**0.5[0.02,14.8]**
Heterogeneity: Not applicable						
Test for overall effect: Z=0.4(P=0.69)						

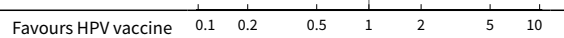


Analysis 4.7. Comparison 4 HPV vaccine versus control in males, Outcome 7 Overall local/injection site adverse events.

Study or subgroup	Quadrivalent vaccine n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
4.7.1 Quadrivalent vaccine (16- to 26-year olds)					
Giuliano 2011	1169/1945	1047/1950		100%	1.12[1.06,1.18]
Subtotal (95% CI)	**1945**	**1950**		**100%**	**1.12[1.06,1.18]**
Total events: 1169 (Quadrivalent vaccine), 1047 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=4.03(P<0.0001)					

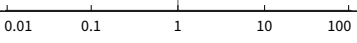
Analysis 4.8. Comparison 4 HPV vaccine versus control in males, Outcome 8 Pain at injection site.

Study or subgroup	HPV vaccine n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
4.8.1 Bivalent vaccine (10- to 18-year-olds)					
Petaja 2009	159/180	39/88		100%	1.99[1.57,2.53]
Subtotal (95% CI)	**180**	**88**		**100%**	**1.99[1.57,2.53]**
Total events: 159 (HPV vaccine), 39 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0, df=0(P<0.0001); I^2=100%					
Test for overall effect: Z=5.63(P<0.0001)					
4.8.2 Quadrivalent vaccine (16- to 26-year olds)					
Giuliano 2011	1116/2020	992/2029		78.7%	1.13[1.06,1.2]
NCT01862874 2018	304/554	271/559		21.3%	1.13[1.01,1.27]
Subtotal (95% CI)	**2574**	**2588**		**100%**	**1.13[1.07,1.19]**
Total events: 1420 (HPV vaccine), 1263 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0, df=1(P=0.98); I^2=0%					
Test for overall effect: Z=4.56(P<0.0001)					
Test for subgroup differences: Chi^2=20.45, df=1 (P<0.0001), I^2=95.11%					



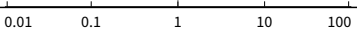
Analysis 4.9. Comparison 4 HPV vaccine versus control in males, Outcome 9 Swelling at injection site.

Study or subgroup	HPV vaccine n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
4.9.1 Bivalent vaccine (10- to 18-year-olds)					
Petaja 2009	36/180	7/88		100%	2.51[1.17,5.42]
Subtotal (95% CI)	**180**	**88**		**100%**	**2.51[1.17,5.42]**
Total events: 36 (HPV vaccine), 7 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.35(P=0.02)					
4.9.2 Quadrivalent vaccine (16- to 26-year olds)					
Giuliano 2011	219/2020	187/2029		58.35%	1.18[0.98,1.42]
NCT01862874 2018	118/554	81/559		41.65%	1.47[1.14,1.9]
Subtotal (95% CI)	**2574**	**2588**		**100%**	**1.29[1.04,1.6]**
Total events: 337 (HPV vaccine), 268 (Control)					
Heterogeneity: Tau^2=0.01; Chi^2=1.9, df=1(P=0.17); I^2=47.38%					
Test for overall effect: Z=2.32(P=0.02)					
Test for subgroup differences: Chi^2=2.68, df=1 (P=0.1), I^2=62.71%					



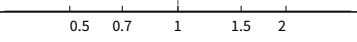
Analysis 4.10. Comparison 4 HPV vaccine versus control in males, Outcome 10 Redness at injection site.

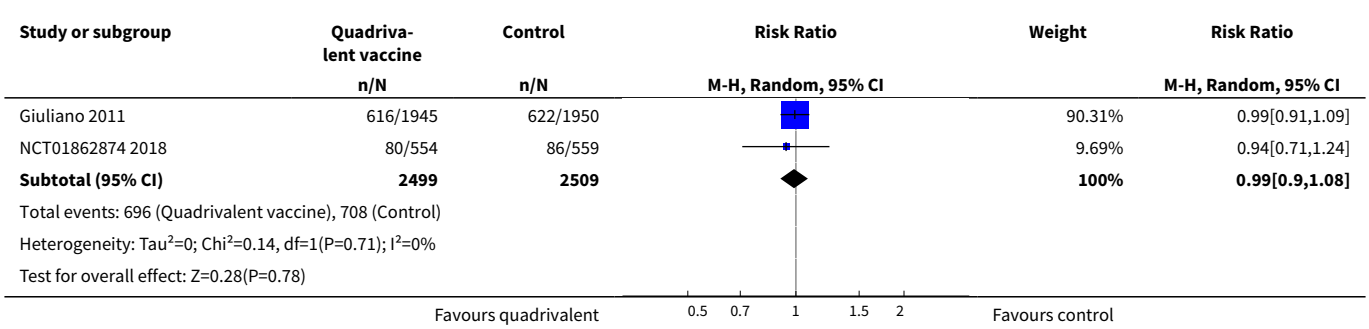
Study or subgroup	HPV vaccine n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
4.10.1 Bivalent vaccine (10- to 18-year-olds)					
Petaja 2009	51/180	15/88		100%	1.66[0.99,2.79]
Subtotal (95% CI)	**180**	**88**		**100%**	**1.66[0.99,2.79]**
Total events: 51 (HPV vaccine), 15 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.93(P=0.05)					
4.10.2 Quadrivalent vaccine (16- to 26-year olds)					
Giuliano 2011	304/2020	275/2029		66.94%	1.11[0.95,1.29]
NCT01862874 2018	136/554	121/559		33.06%	1.13[0.91,1.41]
Subtotal (95% CI)	**2574**	**2588**		**100%**	**1.12[0.99,1.27]**
Total events: 440 (HPV vaccine), 396 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.02, df=1(P=0.87); I^2=0%					
Test for overall effect: Z=1.77(P=0.08)					
Test for subgroup differences: Chi^2=2.14, df=1 (P=0.14), I^2=53.35%					



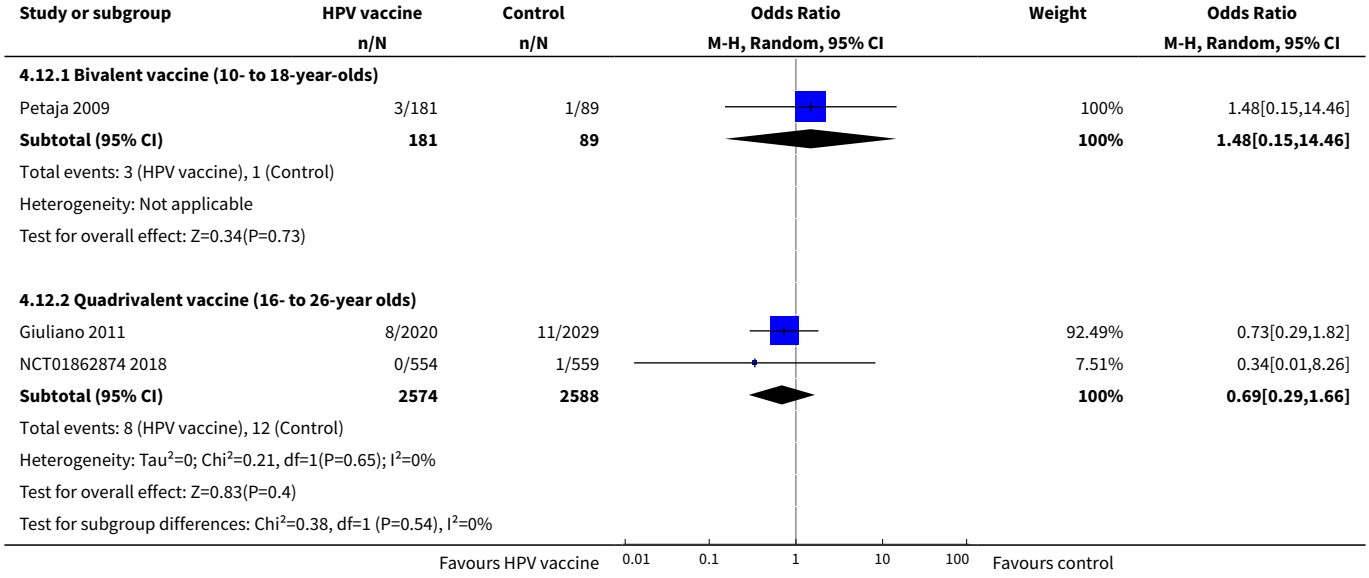
Analysis 4.11. Comparison 4 HPV vaccine versus control in males, Outcome 11 Overall systemic events and general symptoms.

Study or subgroup	Quadrivalent vaccine n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
4.11.1 Quadrivalent vaccine (16- to 26-year olds)					

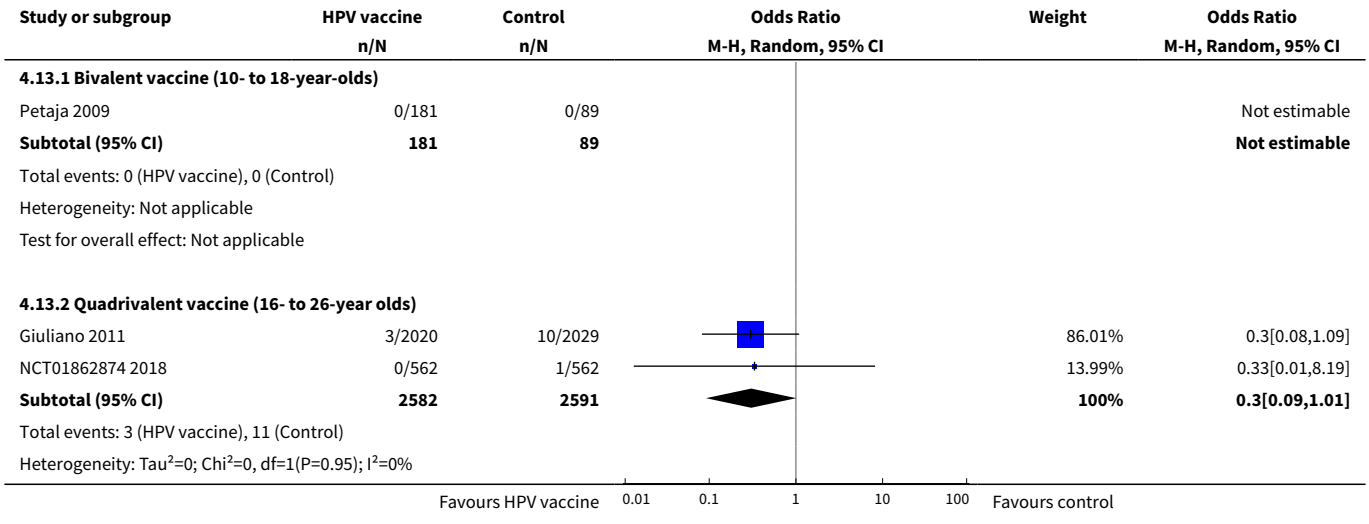


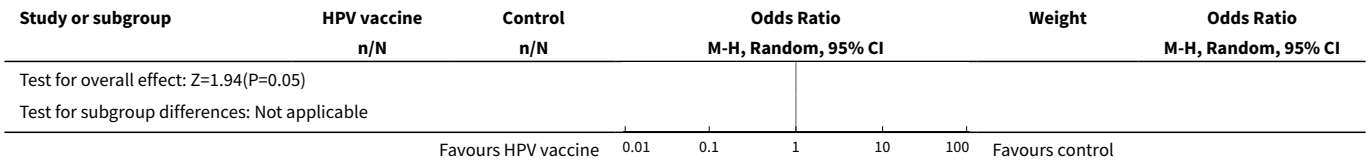


Analysis 4.12. Comparison 4 HPV vaccine versus control in males, Outcome 12 Serious adverse events (overall).



Analysis 4.13. Comparison 4 HPV vaccine versus control in males, Outcome 13 Deaths.



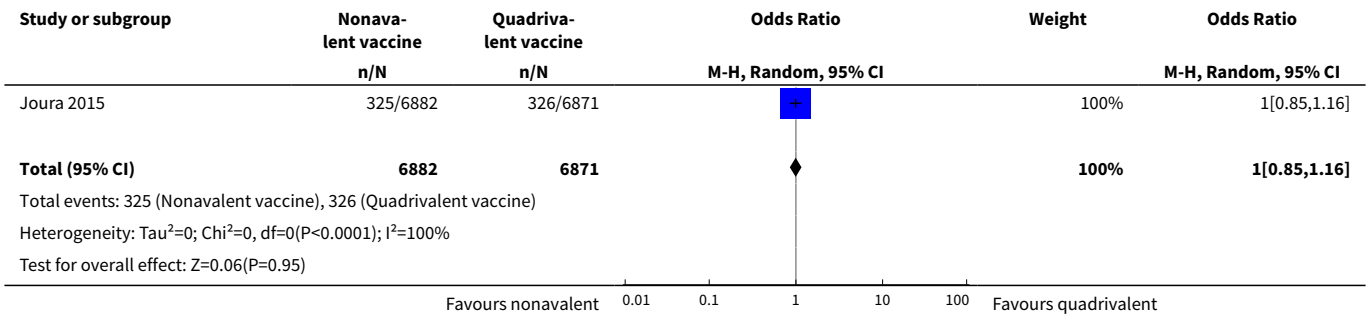


Comparison 5. Nonavalent HPV vaccine versus quadrivalent HPV vaccine in 9- to 26-year-olds

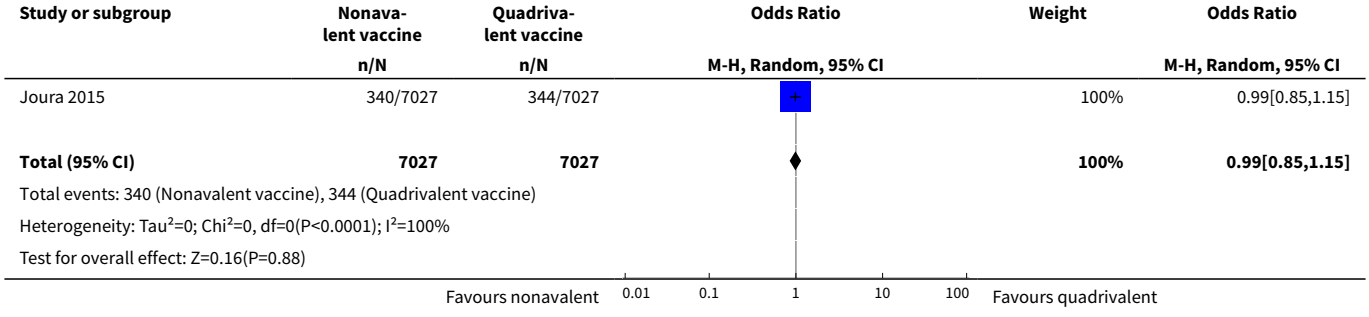
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 High-grade cervical epithelial neoplasia, adenocarcinoma in situ, and cervical cancer	1	13753	Odds Ratio (M-H, Random, 95% CI)	1.00 [0.85, 1.16]
2 High-grade cervical, vulval, and vaginal disease	1	14054	Odds Ratio (M-H, Random, 95% CI)	0.99 [0.85, 1.15]
3 High-grade cervical disease related to HPV 6, 11, 16, or 18	1	11656	Odds Ratio (M-H, Random, 95% CI)	1.00 [0.06, 16.01]
4 High-grade vulval and vaginal disease related to HPV 6, 11, 16, or 18	1	11769	Odds Ratio (M-H, Random, 95% CI)	0.14 [0.01, 2.77]
5 High-grade cervical disease related to HPV 31, 33, 45, 52, or 58	1	11892	Odds Ratio (M-H, Random, 95% CI)	0.03 [0.00, 0.21]
6 High-grade vulval and vaginal disease related to HPV 31, 33, 45, 52, or 58	1	12021	Odds Ratio (M-H, Random, 95% CI)	0.14 [0.01, 2.77]
7 Cervical intraepithelial neoplasia 2 related to HPV 6, 11, 16, or 18	1	11656	Odds Ratio (M-H, Random, 95% CI)	3.00 [0.12, 73.77]
8 Cervical intraepithelial neoplasia 2 related to HPV 31, 33, 45, 52, or 58	1	11892	Odds Ratio (M-H, Random, 95% CI)	0.03 [0.00, 0.23]
9 Cervical intraepithelial neoplasia 3, adenocarcinoma in situ, and cervical cancer related to HPV 6, 11, 16, or 18	1	11656	Odds Ratio (M-H, Random, 95% CI)	0.33 [0.01, 8.19]
10 Cervical intraepithelial neoplasia 3, adenocarcinoma in situ, and cervical cancer related to HPV 31, 33, 45, 52, or 58	1	11892	Odds Ratio (M-H, Random, 95% CI)	0.07 [0.00, 1.16]
11 Overall local/injection site adverse events	3	15863	Risk Ratio (M-H, Random, 95% CI)	1.07 [1.05, 1.08]
11.1 9- to 15-year-old females	1	599	Risk Ratio (M-H, Random, 95% CI)	1.04 [0.98, 1.09]
11.2 16- to 26-year-old females	1	14764	Risk Ratio (M-H, Random, 95% CI)	1.07 [1.05, 1.08]
11.3 16- to 26-year-old males	1	500	Risk Ratio (M-H, Random, 95% CI)	1.10 [1.00, 1.22]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
12 Pain at injection site	3	15863	Risk Ratio (M-H, Random, 95% CI)	1.06 [1.02, 1.11]
12.1 9- to 15-year-old females	1	599	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.96, 1.07]
12.2 16- to 26-year-old females	1	14764	Risk Ratio (M-H, Random, 95% CI)	1.07 [1.06, 1.09]
12.3 16- to 26-year-old males	1	500	Risk Ratio (M-H, Random, 95% CI)	1.12 [1.01, 1.24]
13 Swelling at injection site	3	15863	Risk Ratio (M-H, Random, 95% CI)	1.37 [1.31, 1.44]
13.1 9- to 15-year-old females	1	599	Risk Ratio (M-H, Random, 95% CI)	1.33 [1.10, 1.60]
13.2 16- to 26-year-old females	1	14764	Risk Ratio (M-H, Random, 95% CI)	1.38 [1.31, 1.44]
13.3 16- to 26-year-old males	1	500	Risk Ratio (M-H, Random, 95% CI)	1.58 [0.96, 2.58]
14 Redness at injection site	3	15863	Risk Ratio (M-H, Random, 95% CI)	1.20 [1.00, 1.44]
14.1 9- to 15-year-old females	1	599	Risk Ratio (M-H, Random, 95% CI)	1.16 [0.92, 1.47]
14.2 16- to 26-year-old females	1	14764	Risk Ratio (M-H, Random, 95% CI)	1.32 [1.26, 1.39]
14.3 16- to 26-year-old males	1	500	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.60, 1.33]
15 Overall systemic events and general symptoms	3	15863	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.98, 1.04]
15.1 9- to 15-year-old females	1	599	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.78, 1.07]
15.2 16- to 26-year-old females	1	14764	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.98, 1.04]
15.3 16- to 26-year-old males	1	500	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.82, 1.26]
16 Serious adverse events (overall)	3	15863	Odds Ratio (M-H, Random, 95% CI)	0.60 [0.14, 2.61]
16.1 9- to 15-year-old females	1	599	Odds Ratio (M-H, Random, 95% CI)	0.5 [0.05, 5.54]
16.2 16- to 26-year-old females	1	14764	Odds Ratio (M-H, Random, 95% CI)	1.22 [1.00, 1.48]
16.3 16- to 26-year-old males	1	500	Odds Ratio (M-H, Random, 95% CI)	0.08 [0.00, 1.35]
17 Deaths	3	15248	Odds Ratio (M-H, Random, 95% CI)	1.20 [0.37, 3.94]
17.1 9- to 15-year old females	1	599	Odds Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
17.2 16- to 26-year-old females	1	14149	Odds Ratio (M-H, Random, 95% CI)	1.20 [0.37, 3.94]
17.3 16- to 26-year-old males	1	500	Odds Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

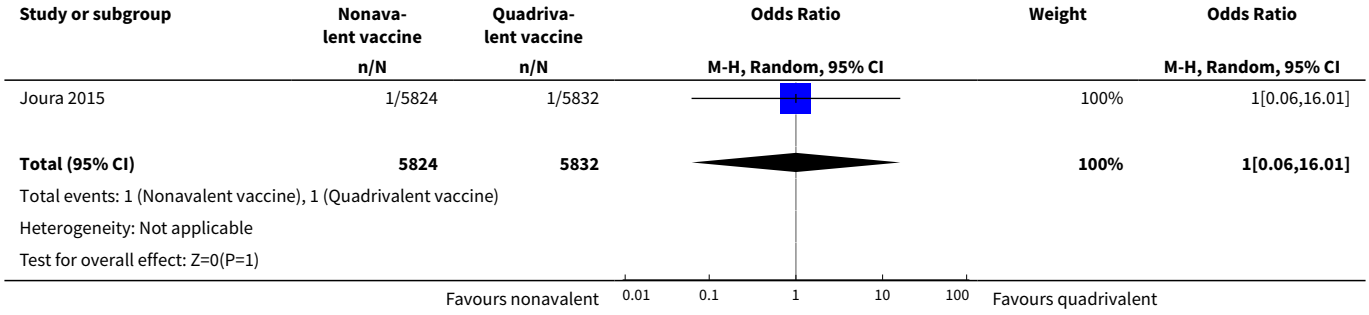
Analysis 5.1. Comparison 5 Nonavalent HPV vaccine versus quadrivalent HPV vaccine in 9- to 26-year-olds, Outcome 1 High-grade cervical epithelial neoplasia, adenocarcinoma in situ, and cervical cancer.



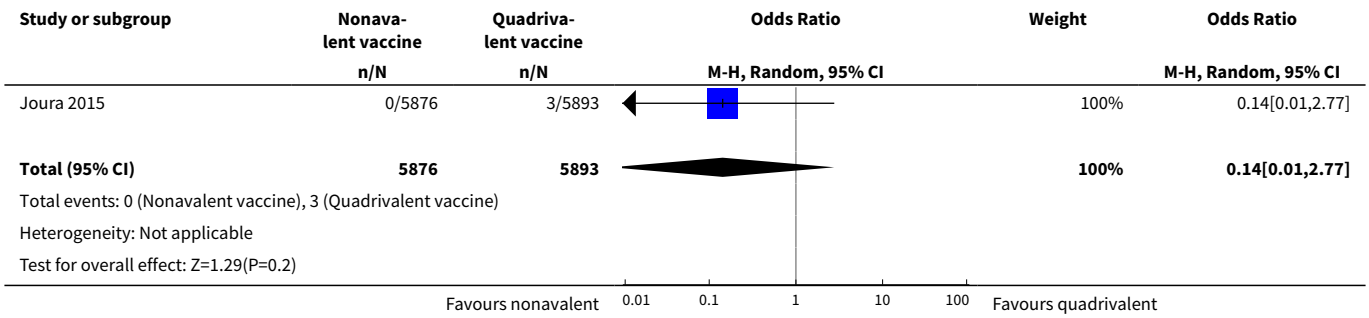
Analysis 5.2. Comparison 5 Nonavalent HPV vaccine versus quadrivalent HPV vaccine in 9- to 26-year-olds, Outcome 2 High-grade cervical, vulval, and vaginal disease.



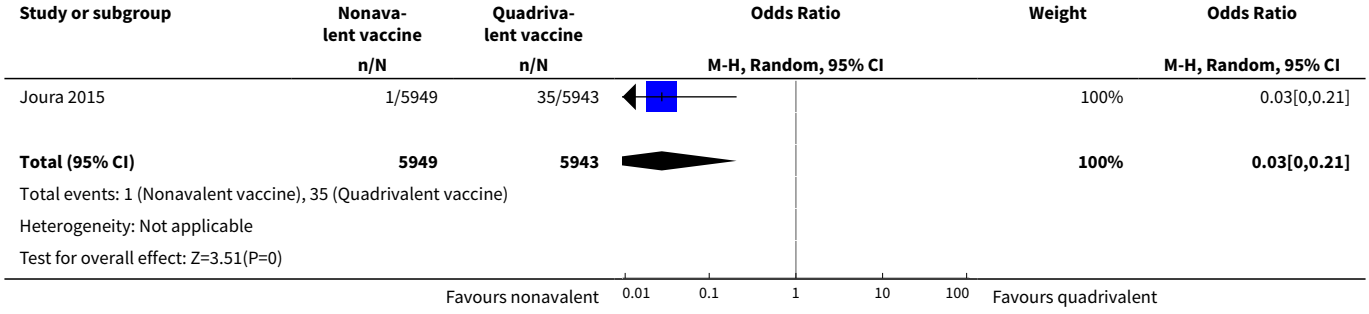
Analysis 5.3. Comparison 5 Nonavalent HPV vaccine versus quadrivalent HPV vaccine in 9- to 26-year-olds, Outcome 3 High-grade cervical disease related to HPV 6, 11, 16, or 18.



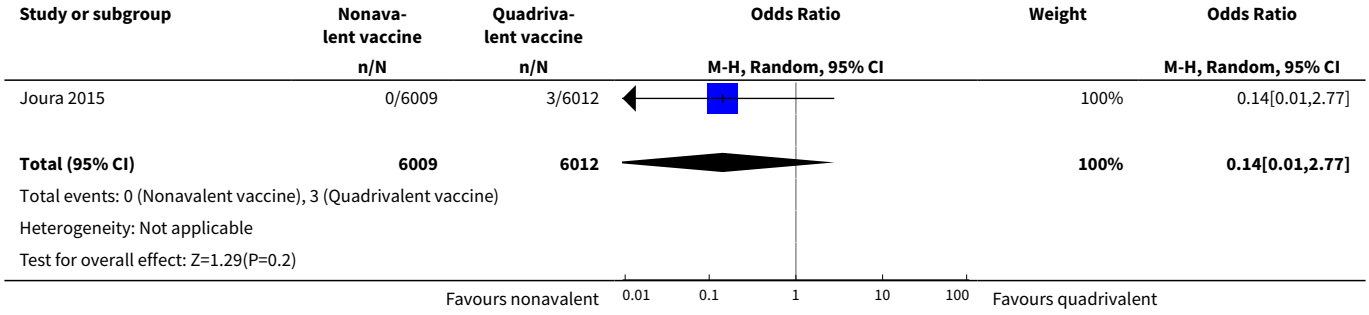
Analysis 5.4. Comparison 5 Nonavalent HPV vaccine versus quadrivalent HPV vaccine in 9- to 26-year-olds, Outcome 4 High-grade vulval and vaginal disease related to HPV 6, 11, 16, or 18.



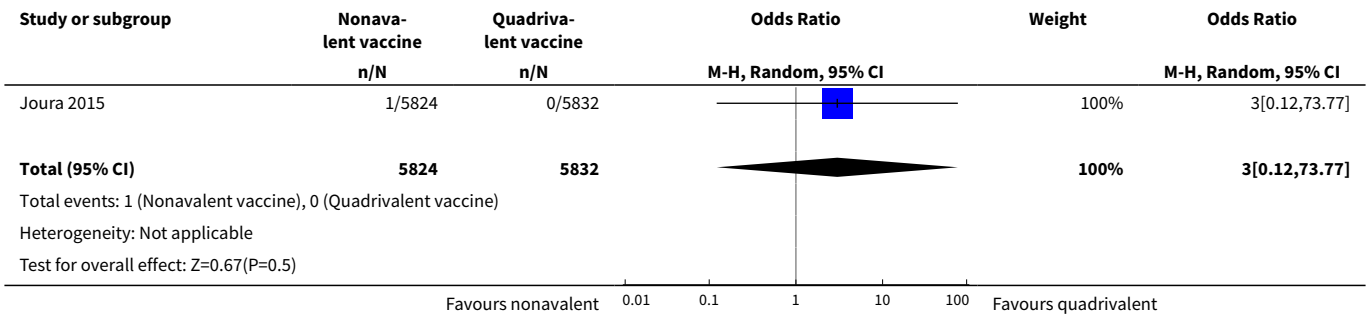
Analysis 5.5. Comparison 5 Nonavalent HPV vaccine versus quadrivalent HPV vaccine in 9- to 26-year-olds, Outcome 5 High-grade cervical disease related to HPV 31, 33, 45, 52, or 58.



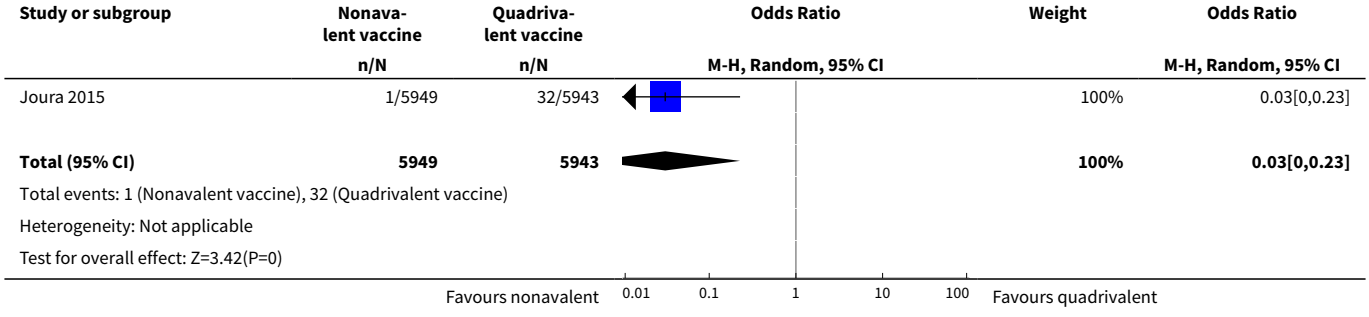
Analysis 5.6. Comparison 5 Nonavalent HPV vaccine versus quadrivalent HPV vaccine in 9- to 26-year-olds, Outcome 6 High-grade vulval and vaginal disease related to HPV 31, 33, 45, 52, or 58.



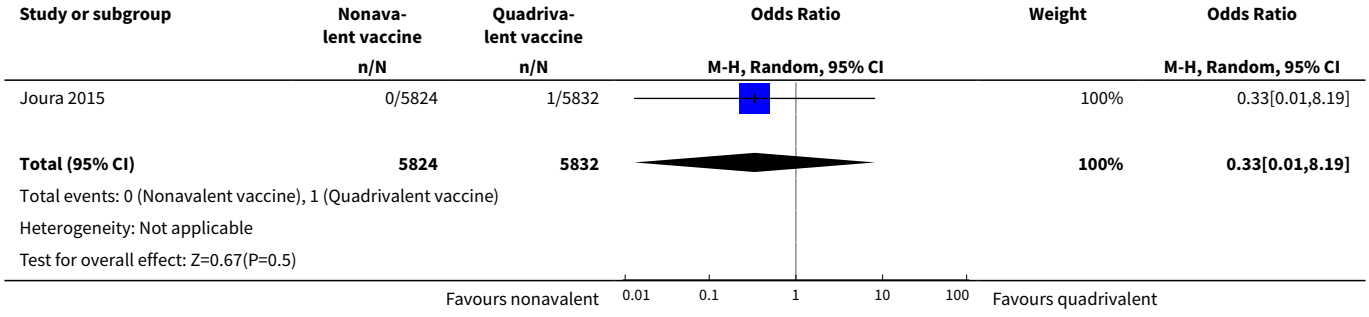
Analysis 5.7. Comparison 5 Nonavalent HPV vaccine versus quadrivalent HPV vaccine in 9- to 26-year-olds, Outcome 7 Cervical intraepithelial neoplasia 2 related to HPV 6, 11, 16, or 18.



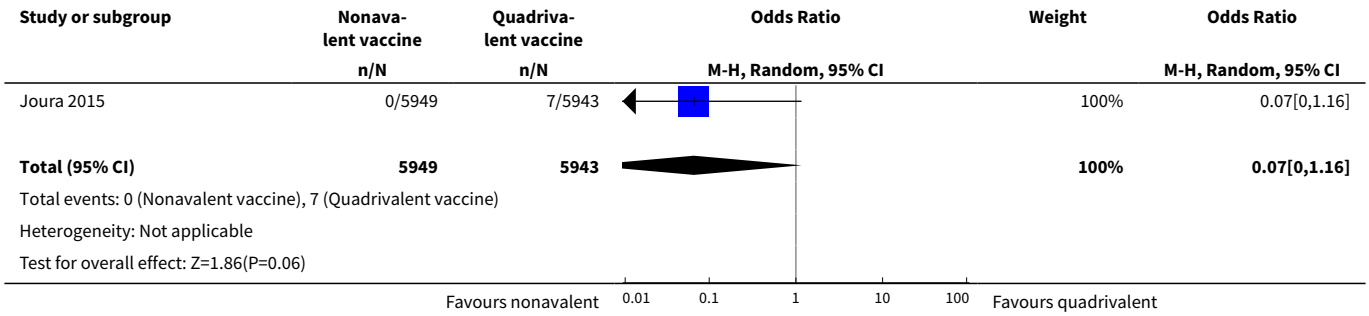
Analysis 5.8. Comparison 5 Nonavalent HPV vaccine versus quadrivalent HPV vaccine in 9- to 26-year-olds, Outcome 8 Cervical intraepithelial neoplasia 2 related to HPV 31, 33, 45, 52, or 58.



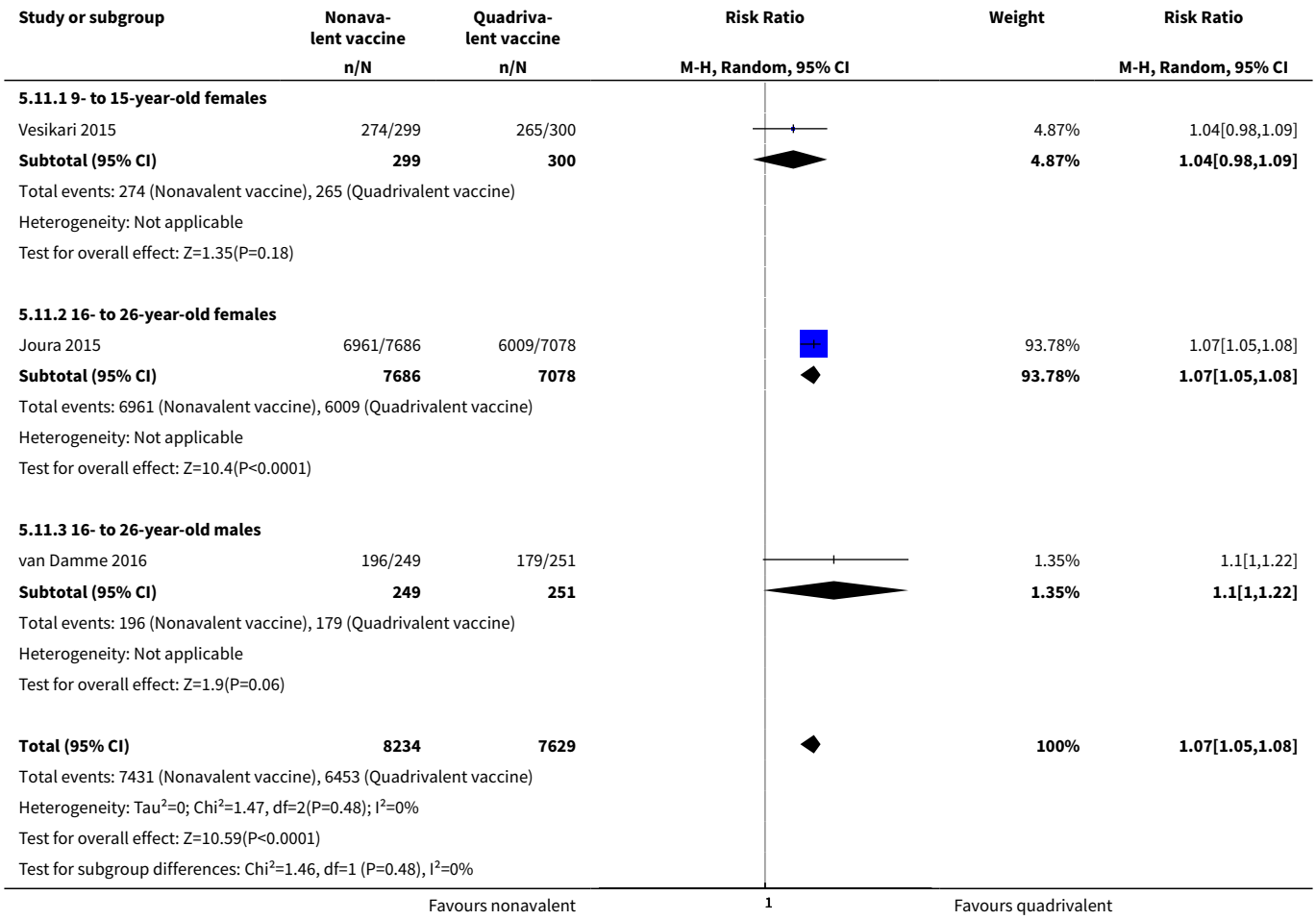
Analysis 5.9. Comparison 5 Nonavalent HPV vaccine versus quadrivalent HPV vaccine in 9- to 26-year-olds, Outcome 9 Cervical intraepithelial neoplasia 3, adenocarcinoma in situ, and cervical cancer related to HPV 6, 11, 16, or 18.



Analysis 5.10. Comparison 5 Nonavalent HPV vaccine versus quadrivalent HPV vaccine in 9- to 26-year-olds, Outcome 10 Cervical intraepithelial neoplasia 3, adenocarcinoma in situ, and cervical cancer related to HPV 31, 33, 45, 52, or 58.



Analysis 5.11. Comparison 5 Nonavalent HPV vaccine versus quadrivalent HPV vaccine in 9- to 26-year-olds, Outcome 11 Overall local/injection site adverse events.

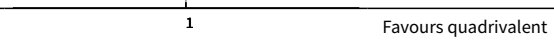


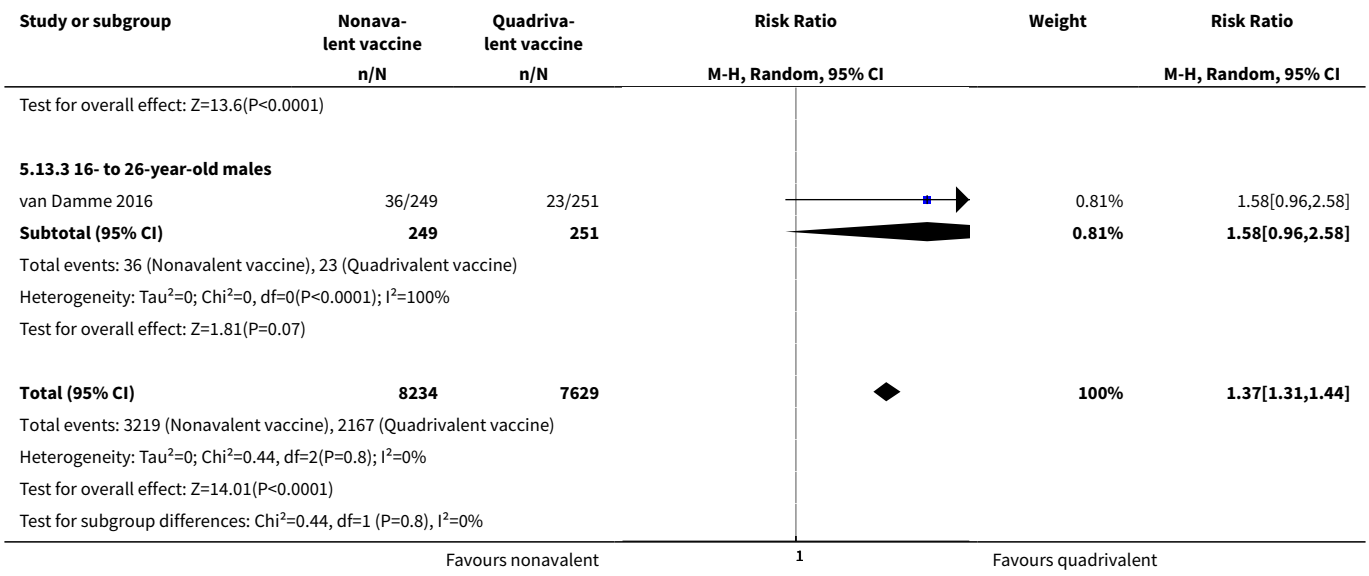
Analysis 5.12. Comparison 5 Nonavalent HPV vaccine versus quadrivalent HPV vaccine in 9- to 26-year-olds, Outcome 12 Pain at injection site.

Study or subgroup	Nonavalent vaccine n/N	Quadrivalent vaccine n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
5.12.1 9- to 15-year-old females					
Vesikari 2015	269/299	266/300		30.53%	1.01[0.96,1.07]
Subtotal (95% CI)	**299**	**300**		**30.53%**	**1.01[0.96,1.07]**
Total events: 269 (Nonavalent vaccine), 266 (Quadrivalent vaccine)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.51(P=0.61)					
5.12.2 16- to 26-year-old females					
Joura 2015	6900/7686	5911/7078		56.1%	1.07[1.06,1.09]
Subtotal (95% CI)	**7686**	**7078**		**56.1%**	**1.07[1.06,1.09]**
Total events: 6900 (Nonavalent vaccine), 5911 (Quadrivalent vaccine)					
Heterogeneity: Not applicable					
Test for overall effect: Z=11.06(P<0.0001)					
5.12.3 16- to 26-year-old males					
van Damme 2016	193/249	174/251		13.37%	1.12[1.01,1.24]
Subtotal (95% CI)	**249**	**251**		**13.37%**	**1.12[1.01,1.24]**
Total events: 193 (Nonavalent vaccine), 174 (Quadrivalent vaccine)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.06(P=0.04)					
Total (95% CI)	**8234**	**7629**		**100%**	**1.06[1.02,1.11]**
Total events: 7362 (Nonavalent vaccine), 6351 (Quadrivalent vaccine)					
Heterogeneity: Tau^2=0; Chi^2=4.6, df=2(P=0.1); I^2=56.48%					
Test for overall effect: Z=2.66(P=0.01)					
Test for subgroup differences: Chi^2=4.56, df=1 (P=0.1), I^2=56.17%					

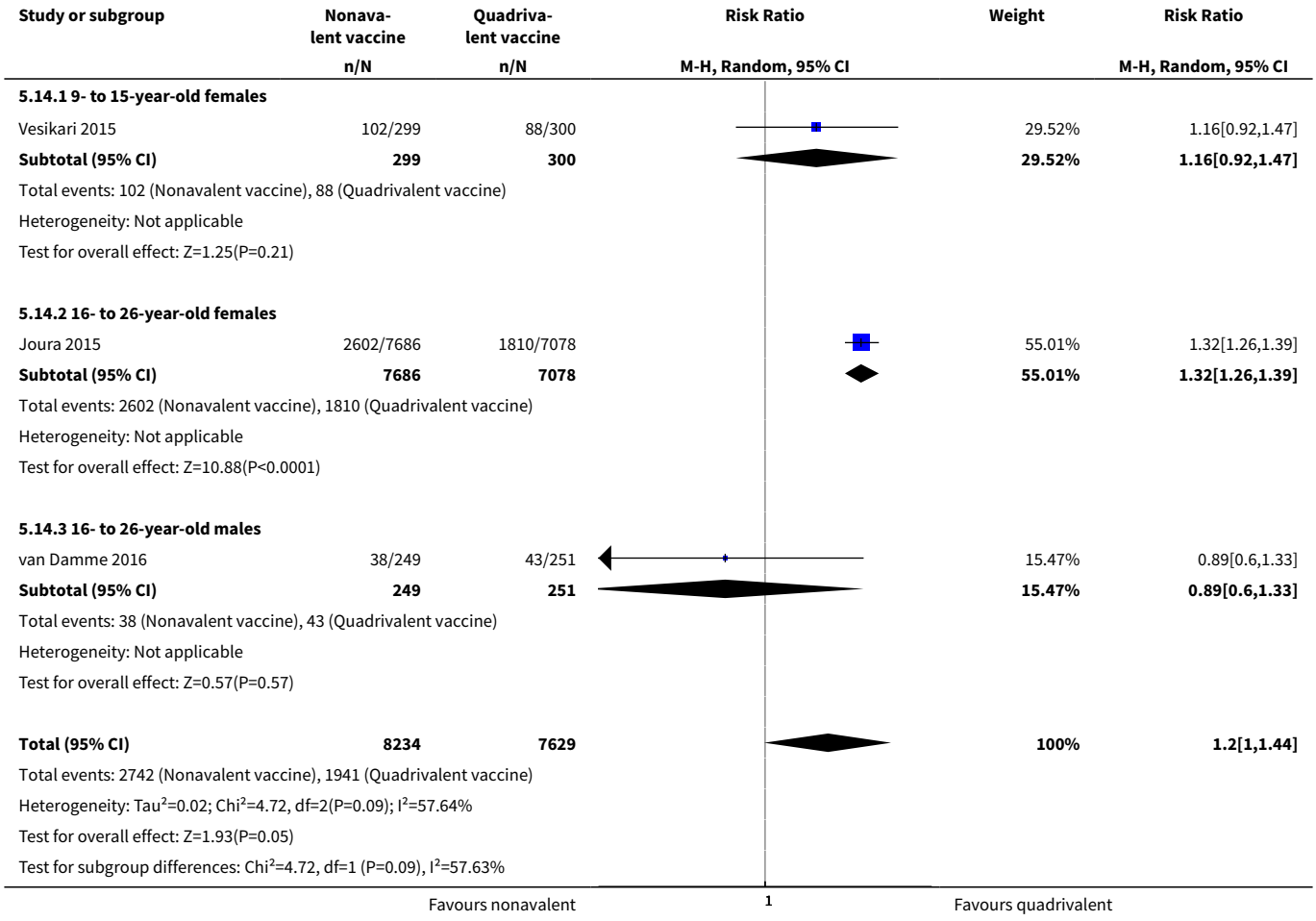
Analysis 5.13. Comparison 5 Nonavalent HPV vaccine versus quadrivalent HPV vaccine in 9- to 26-year-olds, Outcome 13 Swelling at injection site.

Study or subgroup	Nonavalent vaccine n/N	Quadrivalent vaccine n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
5.13.1 9- to 15-year-old females					
Vesikari 2015	144/299	109/300		5.45%	1.33[1.1,1.6]
Subtotal (95% CI)	**299**	**300**		**5.45%**	**1.33[1.1,1.6]**
Total events: 144 (Nonavalent vaccine), 109 (Quadrivalent vaccine)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.9(P=0)					
5.13.2 16- to 26-year-old females					
Joura 2015	3039/7686	2035/7078		93.73%	1.38[1.31,1.44]
Subtotal (95% CI)	**7686**	**7078**		**93.73%**	**1.38[1.31,1.44]**
Total events: 3039 (Nonavalent vaccine), 2035 (Quadrivalent vaccine)					
Heterogeneity: Not applicable					

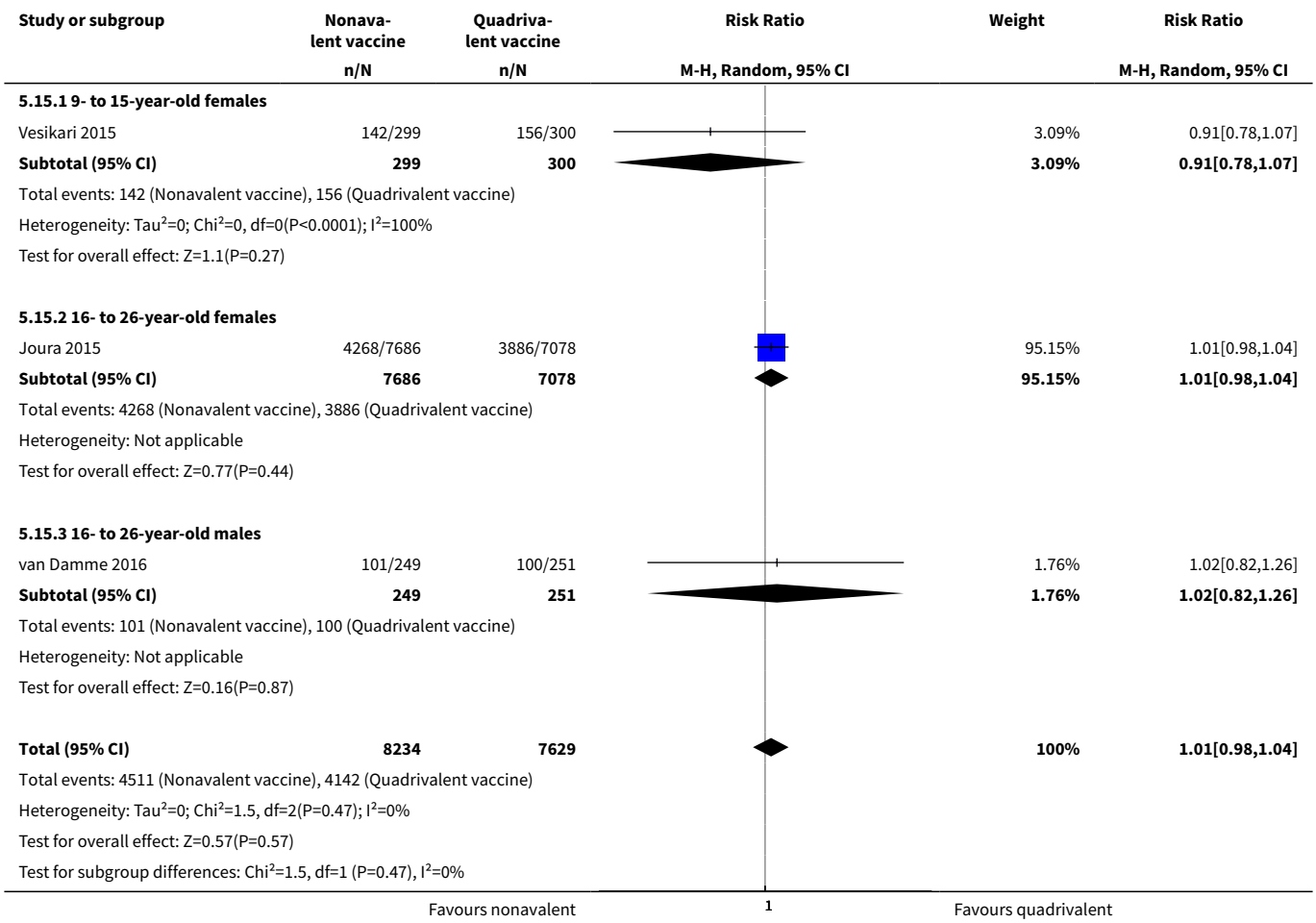




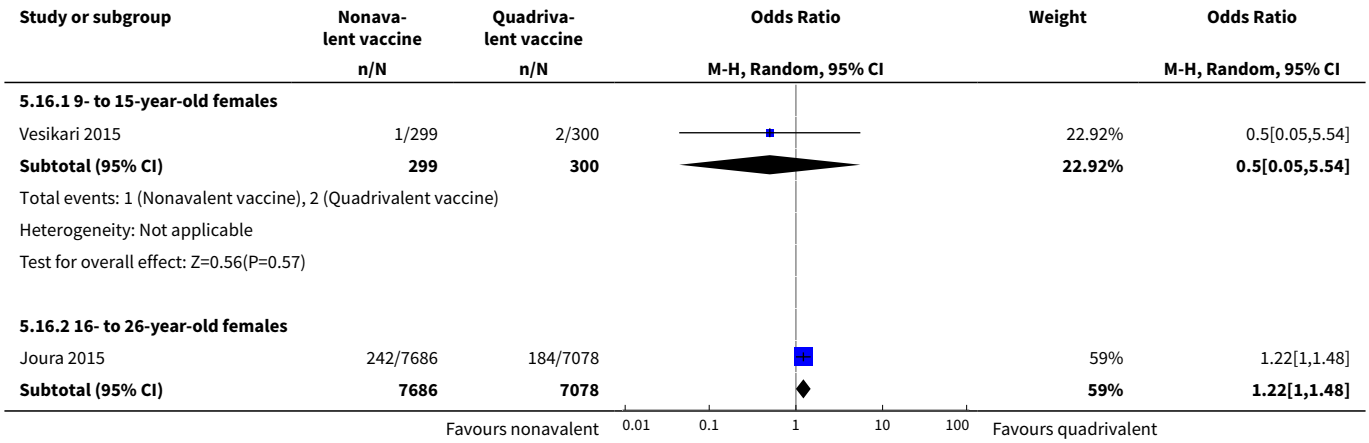
Analysis 5.14. Comparison 5 Nonavalent HPV vaccine versus quadrivalent HPV vaccine in 9- to 26-year-olds, Outcome 14 Redness at injection site.

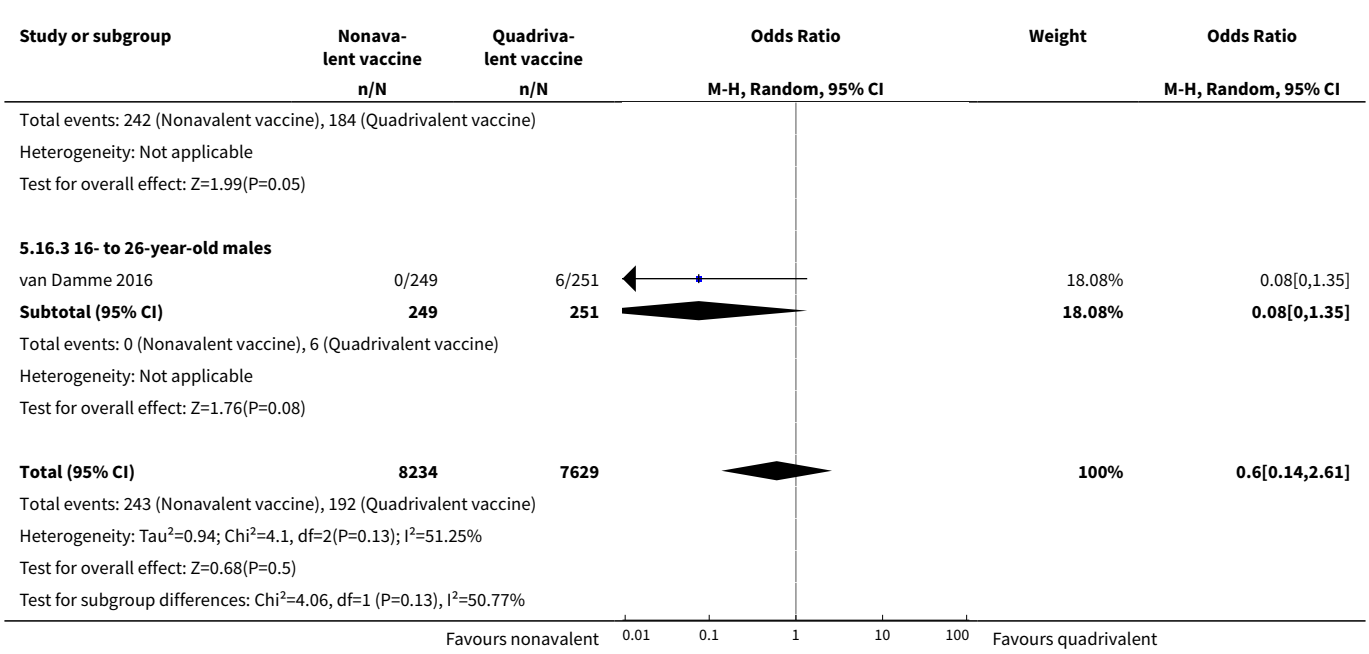


Analysis 5.15. Comparison 5 Nonavalent HPV vaccine versus quadrivalent HPV vaccine in 9- to 26-year-olds, Outcome 15 Overall systemic events and general symptoms.

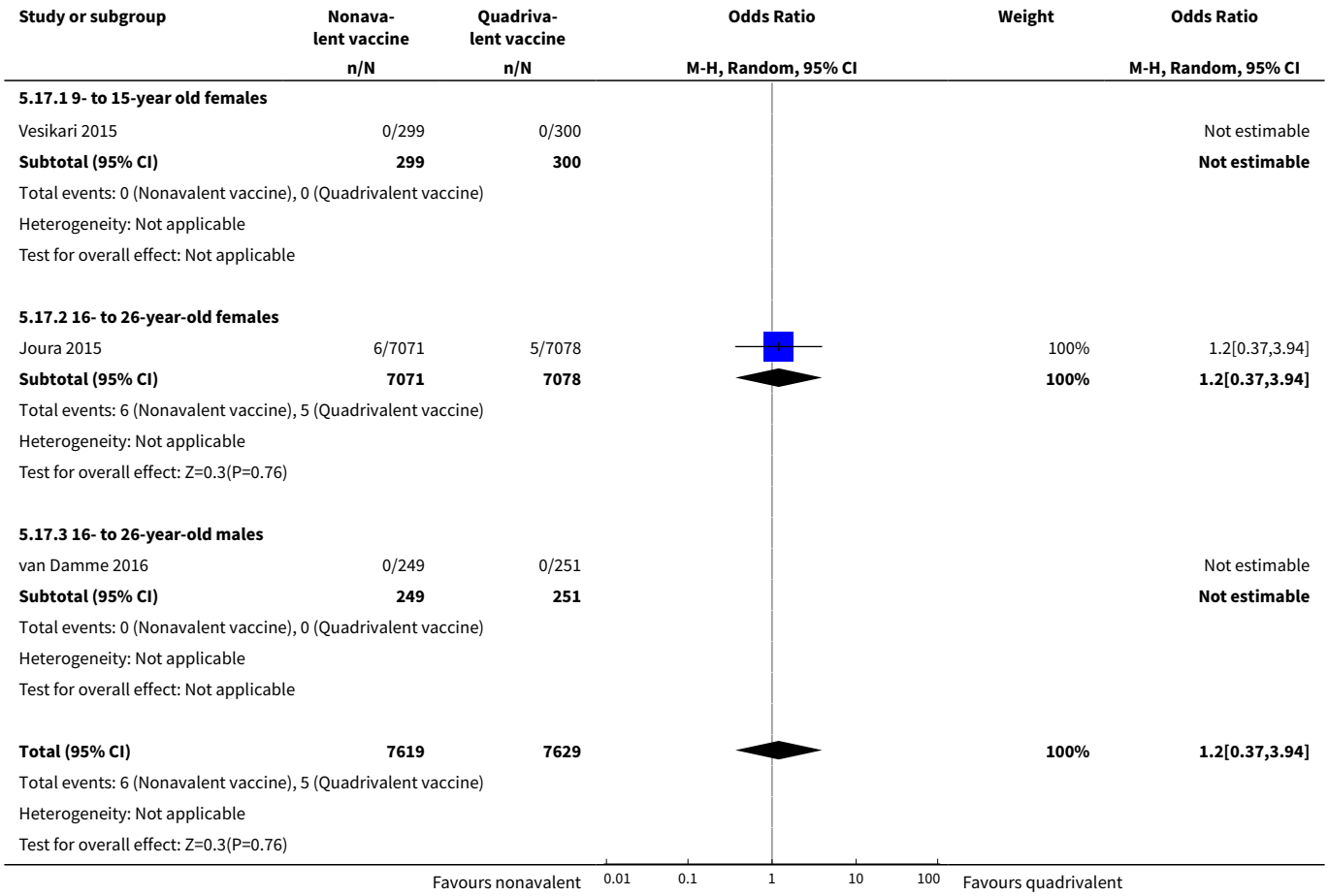


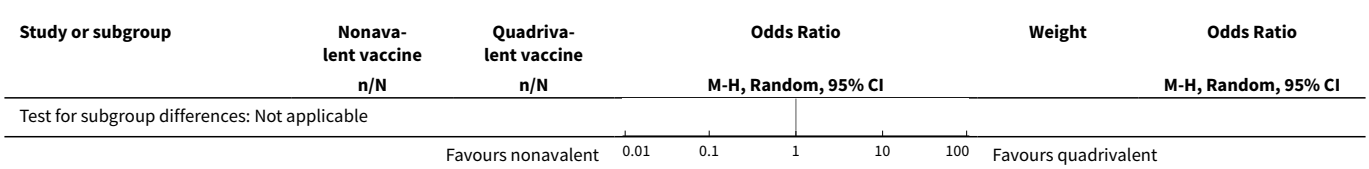
Analysis 5.16. Comparison 5 Nonavalent HPV vaccine versus quadrivalent HPV vaccine in 9- to 26-year-olds, Outcome 16 Serious adverse events (overall).





Analysis 5.17. Comparison 5 Nonavalent HPV vaccine versus quadrivalent HPV vaccine in 9- to 26-year-olds, Outcome 17 Deaths.





Comparison 6. Quadrivalent HPV vaccine versus control in people living with HIV

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 High-grade anal intraepithelial neoplasia	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 ≥ 27-year-old females and males with HIV	1	574	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.70, 1.48]
2 Recurrence of anogenital warts	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 18- to 65-year-old females and males with HIV treated for anogenital warts	1	12	Risk Ratio (M-H, Random, 95% CI)	0.71 [0.06, 8.90]
3 Abnormal anal cytology	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 ≥ 27-year-old females and males with HIV	1	262	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.64, 1.05]
4 Overall local/injection site adverse events	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4.1 7- to 12-year-old children with HIV	1	126	Risk Ratio (M-H, Random, 95% CI)	2.19 [0.70, 6.83]
5 Overall systemic event and general symptoms	1		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
5.1 7- to 12-year-old children with HIV	1	126	Odds Ratio (M-H, Random, 95% CI)	0.62 [0.05, 7.05]
6 Serious adverse events (overall)	2		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
6.1 ≥ 27 year old females and males with HIV	1	575	Odds Ratio (M-H, Random, 95% CI)	0.68 [0.42, 1.10]
6.2 ≥ 18-year-old MSM with HIV	1	129	Odds Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
7 Deaths	2		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
7.1 ≥ 27-year-old females and males with HIV	1	575	Odds Ratio (M-H, Random, 95% CI)	0.49 [0.12, 1.99]
7.2 ≥ 18-year-old MSM with HIV	1	129	Odds Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Analysis 6.1. Comparison 6 Quadrivalent HPV vaccine versus control in people living with HIV, Outcome 1 High-grade anal intraepithelial neoplasia.

Study or subgroup	Quadrivalent vaccine n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
6.1.1 ≥ 27-year-old females and males with HIV					
Wilkin 2018	46/288	45/286		100%	1.02[0.7,1.48]
Subtotal (95% CI)	**288**	**286**		**100%**	**1.02[0.7,1.48]**
Total events: 46 (Quadrivalent vaccine), 45 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.08(P=0.94)					

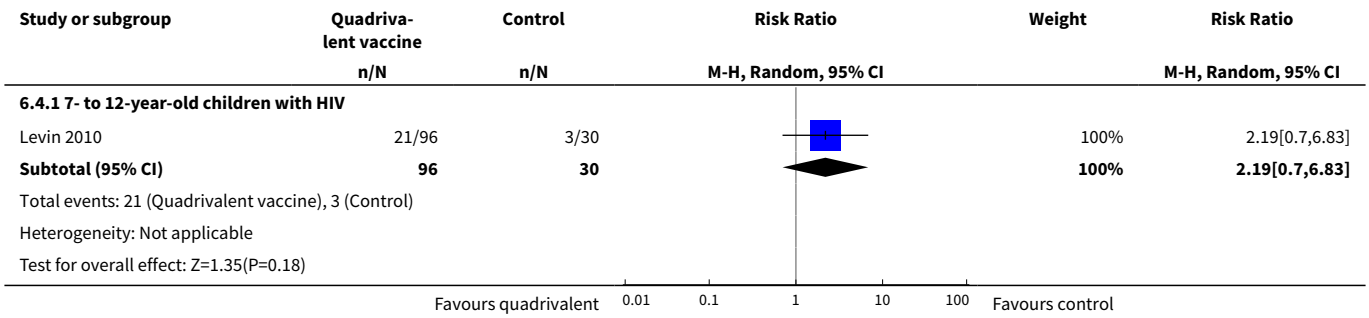
Analysis 6.2. Comparison 6 Quadrivalent HPV vaccine versus control in people living with HIV, Outcome 2 Recurrence of anogenital warts.

Study or subgroup	Quadrivalent vaccine n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
6.2.1 18- to 65-year-old females and males with HIV treated for anogenital warts					
NCT00941889 2016	1/7	1/5		100%	0.71[0.06,8.9]
Subtotal (95% CI)	**7**	**5**		**100%**	**0.71[0.06,8.9]**
Total events: 1 (Quadrivalent vaccine), 1 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.26(P=0.79)					

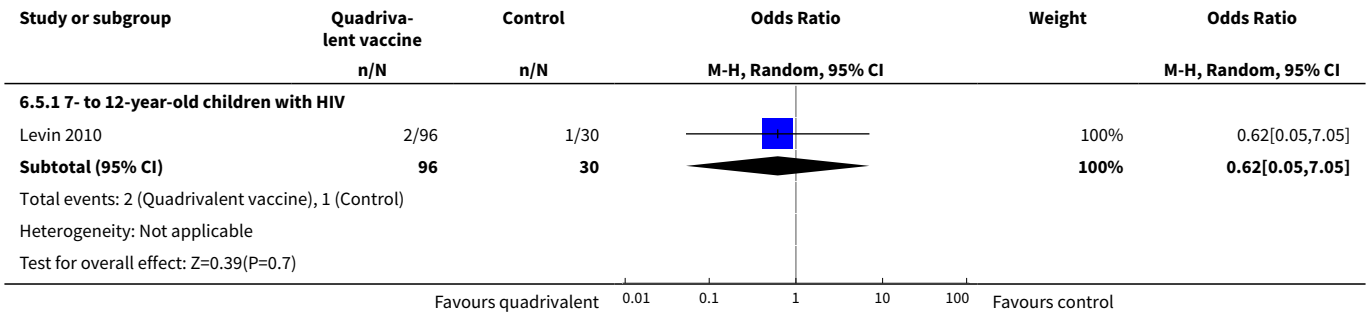
Analysis 6.3. Comparison 6 Quadrivalent HPV vaccine versus control in people living with HIV, Outcome 3 Abnormal anal cytology.

Study or subgroup	Quadrivalent vaccine n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
6.3.1 ≥ 27-year-old females and males with HIV					
Wilkin 2018	58/130	72/132		100%	0.82[0.64,1.05]
Subtotal (95% CI)	**130**	**132**		**100%**	**0.82[0.64,1.05]**
Total events: 58 (Quadrivalent vaccine), 72 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.6(P=0.11)					

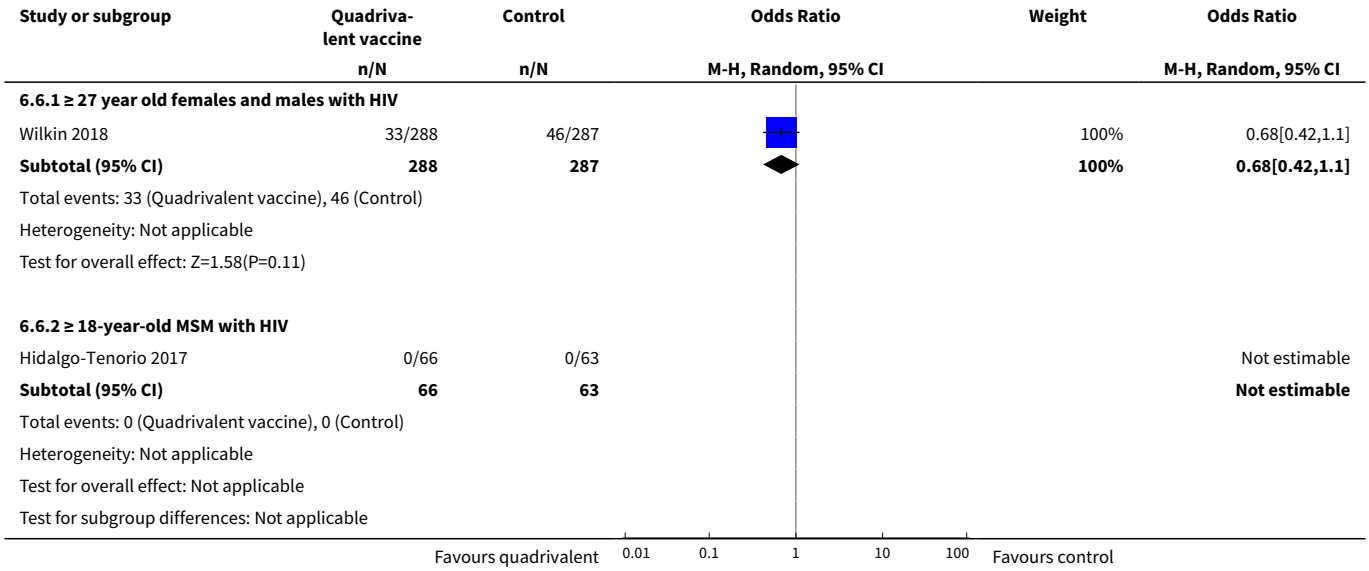
Analysis 6.4. Comparison 6 Quadrivalent HPV vaccine versus control in people living with HIV, Outcome 4 Overall local/injection site adverse events.



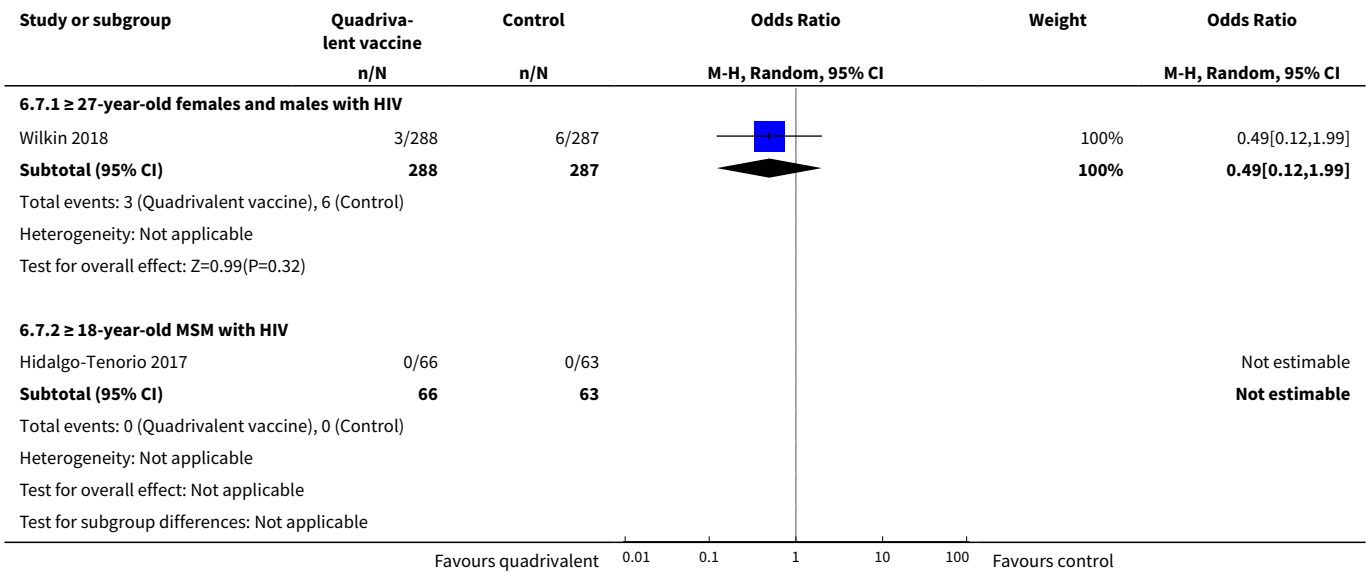
Analysis 6.5. Comparison 6 Quadrivalent HPV vaccine versus control in people living with HIV, Outcome 5 Overall systemic event and general symptoms.



Analysis 6.6. Comparison 6 Quadrivalent HPV vaccine versus control in people living with HIV, Outcome 6 Serious adverse events (overall).



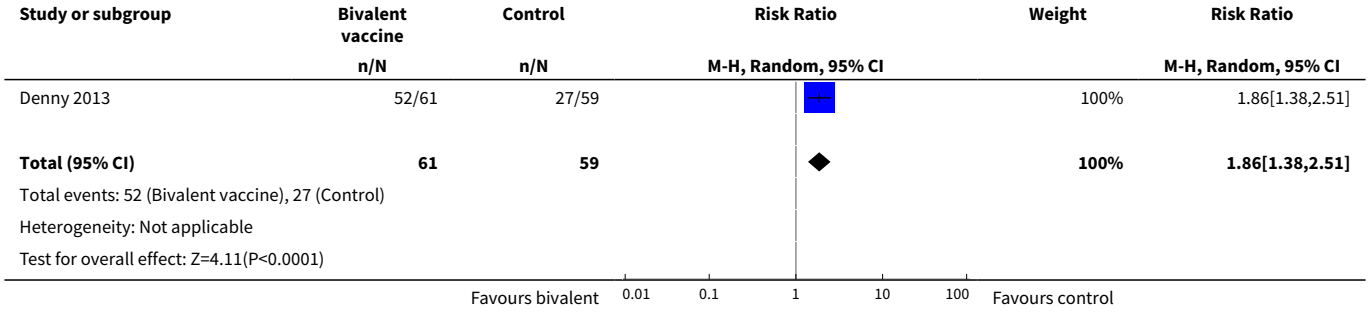
Analysis 6.7. Comparison 6 Quadrivalent HPV vaccine versus control in people living with HIV, Outcome 7 Deaths.



Comparison 7. Bivalent HPV vaccine versus control in 18- to 25-year-old females with HIV

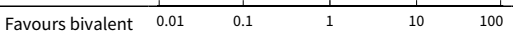
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain at injection site	1	120	Risk Ratio (M-H, Random, 95% CI)	1.86 [1.38, 2.51]
2 Swelling at injection site	1	120	Risk Ratio (M-H, Random, 95% CI)	9.19 [2.24, 37.73]
3 Serious adverse events (overall)	1	120	Odds Ratio (M-H, Random, 95% CI)	1.47 [0.24, 9.15]
4 Deaths	1	120	Odds Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Analysis 7.1. Comparison 7 Bivalent HPV vaccine versus control in 18- to 25-year-old females with HIV, Outcome 1 Pain at injection site.



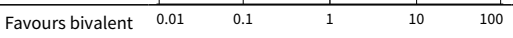
Analysis 7.2. Comparison 7 Bivalent HPV vaccine versus control in 18- to 25-year-old females with HIV, Outcome 2 Swelling at injection site.

Study or subgroup	Bivalent vaccine n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Denny 2013	19/61	2/59		100%	9.19[2.24,37.73]
Total (95% CI)	**61**	**59**		**100%**	**9.19[2.24,37.73]**
Total events: 19 (Bivalent vaccine), 2 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=3.08(P=0)					



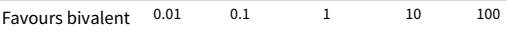
Analysis 7.3. Comparison 7 Bivalent HPV vaccine versus control in 18- to 25-year-old females with HIV, Outcome 3 Serious adverse events (overall).

Study or subgroup	Bivalent vaccine n/N	Control n/N	Odds Ratio M-H, Random, 95% CI	Weight	Odds Ratio M-H, Random, 95% CI
Denny 2013	3/61	2/59		100%	1.47[0.24,9.15]
Total (95% CI)	**61**	**59**		**100%**	**1.47[0.24,9.15]**
Total events: 3 (Bivalent vaccine), 2 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.42(P=0.68)					



Analysis 7.4. Comparison 7 Bivalent HPV vaccine versus control in 18- to 25-year-old females with HIV, Outcome 4 Deaths.

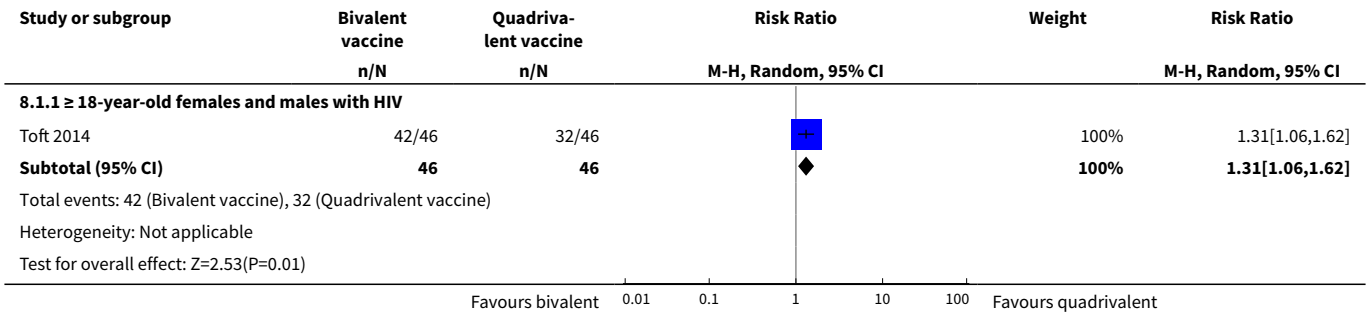
Study or subgroup	Bivalent vaccine n/N	Control n/N	Odds Ratio M-H, Random, 95% CI	Weight	Odds Ratio M-H, Random, 95% CI
Denny 2013	0/61	0/59			Not estimable
Total (95% CI)	**61**	**59**			**Not estimable**
Total events: 0 (Bivalent vaccine), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					



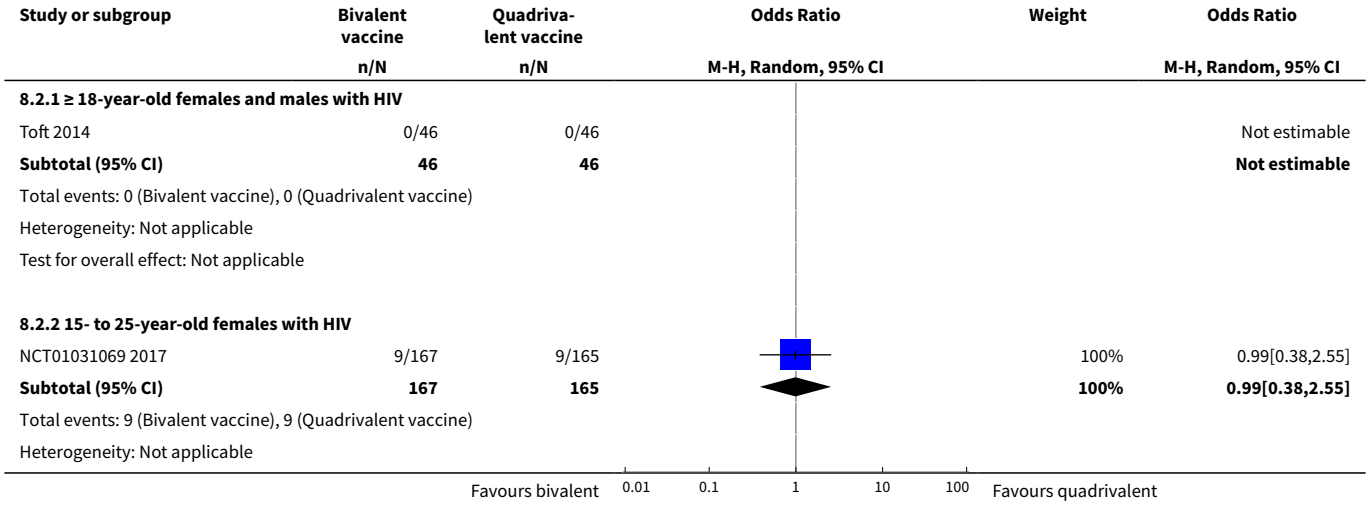
Comparison 8. Bivalent HPV vaccine versus quadrivalent HPV vaccine in people living with HIV

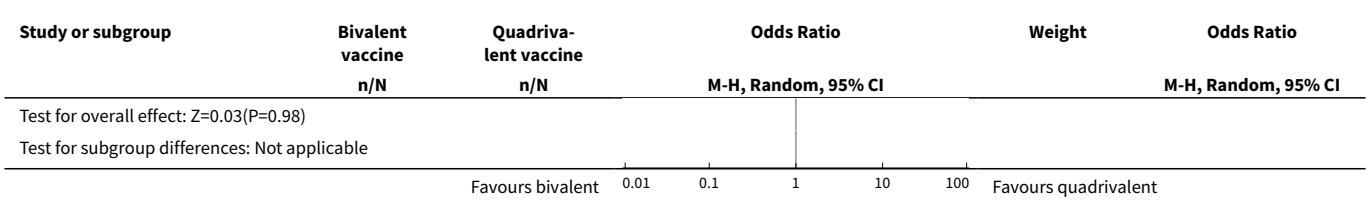
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Overall local/injection site adverse events	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 ≥ 18-year-old females and males with HIV	1	92	Risk Ratio (M-H, Random, 95% CI)	1.31 [1.06, 1.62]
2 Serious adverse events (overall)	2		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 ≥ 18-year-old females and males with HIV	1	92	Odds Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.2 15- to 25-year-old females with HIV	1	332	Odds Ratio (M-H, Random, 95% CI)	0.99 [0.38, 2.55]

Analysis 8.1. Comparison 8 Bivalent HPV vaccine versus quadrivalent HPV vaccine in people living with HIV, Outcome 1 Overall local/injection site adverse events.



Analysis 8.2. Comparison 8 Bivalent HPV vaccine versus quadrivalent HPV vaccine in people living with HIV, Outcome 2 Serious adverse events (overall).





ADDITIONAL TABLES

Table 1. Serious adverse events

Study	Group	Number of participants with serious adverse events	Details of serious adverse events*
Denny 2013	Vaccine (bivalent)	3/61	Gastroenteritis, bacterial pneumonia, migraine
	Control	2/59	Lobar pneumonia, skull fracture
Dobson 2013	Vaccine (quadrivalent; 2-dose)	0/259	
	Vaccine (quadrivalent; 3-dose)	0/261	
Giuliano 2011	Vaccine (quadrivalent)	8/2020	8 participants with 12 events: cardiac arrest, non-cardiac chest pain, hypersensitivity, appendicitis, cellulitis, varicella infection, cervical vertebral fracture, gunshot wound, road traffic accident, traumatic brain injury, traumatic intracranial haemorrhage, convulsion
	Control	11/2033	11 participants with 13 events: myocardial ischaemia, pericardial haemorrhage, accidental overdose, chemical poisoning, contusion, gunshot wound (3), head injury, multiple drug overdose, road traffic accident, completed suicide (2)
NCT01031069 2017	Vaccine (bivalent)	9/167	9 participants with 10 events: immune thrombocytopenic purpura, gastritis, meningitis tuberculous, pneumonia, pneumonia mycoplasmal, tonsillitis, viral infection, road traffic accident, miscarriage, renal failure
	Vaccine (quadrivalent)	9/165	9 participants with 10 events: appendicitis (2), pneumonia bacterial, pulmonary tuberculosis, tonsillitis, urinary tract infection, monoarthritis, abortion spontaneous complete, pre-eclampsia, suicide attempt
NCT01862874 2018	Vaccine (quadrivalent)	0/554	
	Control	1/559	Completed suicide

Table 1. Serious adverse events *(Continued)*

Hidalgo-Tenorio 2017	Vaccine (quadrivalent)	0/66	
	Control	0/63	
Iversen 2016	Vaccine (nonavalent; 2-dose, 6-month interval in females)	6/301	6 participants with 7 events: abdominal pain (2), appendicitis, dengue fever, pharyngitis, foreign body injury, ovarian cyst
	Vaccine (nonavalent; 2-dose, 6-month interval in males)	9/301	9 participants with 10 events: Wolff-Parkinson-White syndrome, diarrhoea, animal bite, appendicitis, rotavirus gastroenteritis, Chikungunya virus infection, bacterial meningitis, pneumonia, concussion, epilepsy
	Vaccine (nonavalent; 2-dose, 12-month interval in males and females)	3(6)/301	1 female participant with atopic dermatitis 2 male participants with appendicitis, forearm fracture At 37 month follow-up there were 3 additional serious adverse events: gastritis, oral herpes, radiculopathy (disaggregated data by sex were not available)
	Vaccine (nonavalent; 3-dose in females)	6/301	6 participants with 8 events: cardiac arrest, appendicitis, subcutaneous abscess, papillary thyroid cancer, encephalitis autoimmune, status epilepticus, depression, ovarian cyst
Joura 2015	Vaccine (nonavalent)	242/7686	242 participants with 269 events: Anaemia, aortic valve incompetence, postural orthostatic tachycardia syndrome, vertigo positional, anal fistula, coeliac disease, Crohn's disease, diarrhoea, gastritis, haemorrhoids, inguinal hernia, irritable bowel syndrome, pyrexia, sudden death, cholangitis, cholecystitis, cholelithiasis, allergy to vaccine, anaphylactic reaction, hypersensitivity, sarcoidosis, jaw abscess, appendicitis (10), cholecystitis infective, chronic tonsillitis, dengue fever, infectious enteritis (2), gastroenteritis, viral gastroenteritis, haemorrhagic fever, infectious mononucleosis, influenza, pharyngitis, pyelonephritis (2), pyelonephritis acute, septic shock, tonsillitis, tonsillitis streptococcal, urinary tract infection (3), urosepsis, wound infection, bladder injury, burns second degree, craniocerebral injury, femur fracture, humerus fracture (2), ligament rupture, lower limb fracture, multiple injuries (2), pubis fracture, road traffic accident, spinal compression fracture, hyperglycaemia, myalgia, osteoarthritis, acute lymphocytic leukaemia, acute promyelocytic leukaemia, adenocarcinoma of the cervix, brain neoplasm, ependymoma, leukaemic infiltration brain, malignant melanoma (2), malignant melanoma in situ, nasal cavity cancer, ovarian neoplasm, diabetic coma, epilepsy, hypersomnia, Intracranial venous sinus thrombosis, migraine, multiple sclerosis (2), presyncope, sciatica, sensory disturbance, syncope (2), tension headache, abortion spontaneous (40), abortion spontaneous incomplete, blighted ovum, cephalo-pelvic disproportion (4), cervix dystocia, false labour, foetal death (2), foetal distress syndrome (5), labour complication, pre-eclampsia (2), premature labour, premature rupture of membranes (4), prolonged labour (2), uterine contractions during pregnancy, anorexia and bulimia syndrome, bipolar disorder (3), completed suicide, major depression, calculus ureteric, calculus urinary, nephrolithiasis, renal failure (2), bartholinitis, cervical dysplasia (5), cervix haemorrhage uterine, endometriosis (2), ovarian cyst, pelvic pain, asthmatic crisis, pneumonia aspiration, pneumothorax, respiratory failure, vocal cord polyp, abortion induced (79), deep vein thrombosis, hypovolaemic shock (2)

Table 1. Serious adverse events *(Continued)*

	Vaccine (quadrivalent)	184/7078	184 participants with 197 events: Anaemia, cleft lip and palate, Meckel's diverticulum, abdominal pain (2), abdominal pain lower, colitis ulcerative, enterocolitis, gastritis, inguinal hernia, omental infarction, cholecystitis , cholelithiasis (2), appendicitis (16), bronchitis (2), cellulitis, conjunctivitis, gastroenteritis (2), influenza, pelvic inflammatory disease, post abortion infection, pyelonephritis, pyelonephritis acute (2), urinary tract infection (2), viral pharyngitis, foreign body in eye, fracture displacement, hand fracture, head injury, joint dislocation (2), neck injury, poisoning, post procedural haemorrhage (2), spinal cord injury, spinal cord injury cervical, fibromyalgia (2), adenocarcinoma gastric, malignant palate neoplasm, pituitary tumour benign, respiratory papilloma, thyroid cancer, benign intracranial hypertension, cerebral haemorrhage, epilepsy, facial paresis, headache, hydrocephalus, hypoesthesia, multiple sclerosis, neuritis, orthostatic intolerance, spondylitic myelopathy, tension headache, abortion spontaneous (28), abortion spontaneous complete (2), blighted ovum, cephalo-pelvic disproportion (6), cervix dystocia, ectopic pregnancy, foetal distress syndrome, foetal malposition, foetal malpresentation, gestational diabetes, oligohydramnios, pre-eclampsia, premature labour, premature rupture of membranes (2), prolonged labour, anorexia nervosa, bipolar disorder, depression, cystitis haemorrhagic, renal failure acute, cervical dysplasia (3), dysmenorrhoea, endometriosis, fallopian tube cyst, ovarian cyst (2), dyspnoea, nasal polyps, abortion induced (53), axillary vein thrombosis
Lehtinen 2018	Vaccine (quadrivalent)	58/2436	58 participants with 62 events: Splenomegaly, vitello-intestinal duct remnant, abdominal pain (2), colitis ulcerative, constipation, food poisoning, chest pain, pyrexia, cholesystitis, appendicitis (5), appendicitis perforated, infectious mononucleosis (4), peritonsillar abscess, pneumonia (2), pneumonia bacterial, salmonellosis, tonsillitis (4), alcohol poisoning (3), cervical vertebral fracture, concussion (4), contusion (2), forearm fracture, hand fracture (2), limb injury, lower limb fracture, muscle rupture, neck injury, radius fracture (2), upper limb fracture (2), type 1 diabetes mellitus, exostosis, juvenile idiopathic arthritis, syncope (2), anxiety, disturbance in social behaviour, emotional disorder of childhood, psychotic disorder, testicular torsion, acne, dermatitis
	Vaccine (control, HBV)	25/1267	25 participants with 25 events: Appendicitis (3), appendicitis perforated, bronchitis, gastroenteritis bacterial, infectious mononucleosis, peritonsillar abscess, sinusitis, sinusitis bacterial, alcohol poisoning, foot fracture (2), forearm fracture, hand fracture, joint dislocation, splenic rupture, tibia fracture, traumatic renal injury, type 1 diabetes mellitus, astrocytoma low grade, depression, panic disorder, suicide attempt, dyspnoea
Leung 2015	Vaccine (bivalent; 2-dose)	11/358	11 participants with 13 events: Abdominal pain lower, mouth cyst, appendicitis, gastroenteritis viral, lung abscess, peritonitis, viral infection, joint dislocation, teratoma, epilepsy, seizure, asthma, eczema
	Vaccine (bivalent; 3-dose)	14/358	14 participants with 16 events: Lymphadenitis, vertigo positional, abdominal pain, anaphylactic shock, upper respiratory tract infection, pneumonia, influenza, vulval ulceration, ankle fracture, overdose, tendon injury, presyncope, tension headache, abortion spontaneous incomplete, completed suicide, depression, menorrhagia
Levin 2010	Vaccine (quadrivalent)	0/96	
	Control	0/30	
Lin 2014	Vaccine (quadrivalent; 10-month interval)	0/111	

Table 1. Serious adverse events *(Continued)*

	Vaccine (quadrivalent; 4-month interval)	0/109	
NCT00941889 2016	Vaccine (quadrivalent)	Not reported	Not reported
	Control	Not reported	Not reported
Wilkin 2018	Vaccine (quadrivalent)	33/288	33 participants with 40 events: Pericardial effusion, abdominal mass, abdominal pain, anal fistula, colitis, chest pain (2), death, appendicitis, cellulitis, chlamydial infection, gastroenteritis viral, influenza (2), meningitis viral, peritonsillar abscess, pneumonia, pneumonia pneumococcal, pseudomembranous colitis, sepsis, lower limb fracture, multiple injuries, stab wound, anal cancer, basal cell carcinoma, Hodgkin's disease, prostate cancer, transitional cell carcinoma, cerebrovascular accident, seizure, acute psychosis, alcohol withdrawal syndrome, depression, suicide attempt, acute respiratory failure, alveolitis allergic, asthma, pleural effusion, intervertebral disc operation
	Control	46/287	46 participants with 79 events: Acute myocardial infarction (2), coronary artery disease, myocardial infarction, abdominal pain, gastrointestinal haemorrhage, large intestine perforation, pancreatitis, pancreatitis acute (2), pancreatitis chronic, small intestinal obstruction (3), chest pain (5), pyrexia, cholelithiasis, bronchitis (2), diverticulitis (2), gastroenteritis (2), gastroenteritis viral, influenza (2), orchitis, perirectal abscess, pneumonia (3), pneumonia streptococcal, primary syphilis, pyelonephritis, scrotal abscess, sepsis (3), viral infection, fall, foot fracture, overdose, radius fracture, road traffic accident, weight decreased, dehydration, osteoarthritis, anal cancer, anal squamous cell carcinoma, B-cell lymphoma, basal cell carcinoma, follicle centre lymphoma diffuse small cell lymphoma, oesophageal adenocarcinoma, pancreatic carcinoma metastatic, prostate cancer, renal cell carcinoma, squamous cell carcinoma of head and neck, haemorrhagic stroke, syncope (2), alcohol withdrawal syndrome, completed suicide, mental status changes, psychotic disorder, substance abuse, suicide attempt, genital ulceration, chronic obstructive pulmonary disease (4), dyspnoea, pleural effusion, pulmonary hypertension, hypotension
Petaja 2009	Vaccine (bivalent)	3/181	Crohn’s disease, appendicitis, epilepsy
	Control (HBV)	1/89	Osteochondrosis
Puthanakit 2016	Vaccine (bivalent; 2-dose, 6-month interval)	20/550	20 participants with 34 events: Lymphadenitis, autoimmune thyroiditis, strabismus, abdominal strangulated hernia, abdominal pain, anal haemorrhage, gastritis, nausea, chronic gastritis, anaphylactic reaction, cholelithiasis, infections and infestations (13), injury, poisoning and procedural complications (4), type 1 diabetes mellitus, cholesteatoma, convulsion, seizure, IgA nephropathy, respiratory disorder
	Vaccine (bivalent; 2-dose, 12-month interval)	24/415	24 participants with 38 events: Lymphadenitis, supraventricular tachycardia, abdominal pain lower, constipation, dyspepsia, faecaloma, drug hypersensitivity, infections and infestations (25), injury, poisoning and procedural complications, hypovolaemia, systemic lupus erythematosus, VIIth nerve paralysis, tonsillar hypertrophy, circulatory collapse
	Vaccine (bivalent; 3-dose)	28/482	28 participants with 53 events: Infections and infestations (32), injury, poisoning and procedural complications (3), hypovolaemia (2), synovial cyst, medulloblastoma, synovial sarcoma, uterine leiomyoma, hyperemesis gravidarum, premature

Table 1. Serious adverse events *(Continued)*

			baby, abortion threatened, postpartum haemorrhage, stillbirth, schizoaffective disorder (3), psychotic disorder, ovarian cyst ruptured, transient tachypnoea of the newborn, ectopic pregnancy termination
Romanowski 2011	Vaccine (bivalent; 3-dose)	15/239	15 participants with 20 events: Basedow's disease, abdominal pain, appendix disorder, gastroenteritis, appendicitis, pharyngitis streptococcal, tonsillitis (2), urinary tract infection, ligament rupture, multiple injuries, ligament laxity, polyarthritis, migraine with aura, abortion spontaneous incomplete, abnormal behaviour, depression, renal colic, renal disorder, erythema multiforme
	Vaccine (bivalent; 2-dose)	16/241	16 participants with 26 events: Abdominal pain, umbilical hernia (2), obstructive vomiting, gastroenteritis viral, cholecystitis acute, acute tonsillitis, appendicitis (2), endometritis decidual, vestibular neuronitis, tibia fracture, contusion, fall, fibroma, fibrosarcoma, pre-eclampsia, premature baby, abortion missed, depression, major depression, psychotic disorder, suicide attempt, cystitis haemorrhagic, hyperventilation, circulatory collapse
	Vaccine (bivalent; 2-dose, 6-month interval)	19/240	19 participants with 23 events: Atrial septal defect, spina bifida, bile duct stone, appendicitis (4), tonsillitis bacterial, humerus fracture, road traffic accident, tibia fracture, upper limb fracture, malignant melanoma stage IV, basilar artery thrombosis, cerebrovascular accident, abortion spontaneous, abortion spontaneous incomplete (2), foetal distress syndrome, anorexia nervosa, bulimia nervosa, depression, circulatory collapse
	Vaccine (bivalent; 2-dose, 2-month interval)	14/240	14 participants with 16 events: Abdominal pain (3), hepatomegaly, pilonidal cyst, urinary tract infection, vestibular neuronitis, concussion, stab wound, coccydynia, uterine leiomyoma, benign hydatidiform mole, abortion spontaneous, ectopic pregnancy, adenomyosis, ovarian cyst
Toft 2014	Vaccine (bivalent)	0/46	
	Vaccine (quadrivalent)	0/46	
van Damme 2016	Vaccine (nonavalent)	0/249	
	Vaccine (quadrivalent)	6/251	Joint dislocation, ligament injury, ligament rupture, foot fracture, concussion, cytomegalovirus infection
Vesikari 2015	Vaccine (nonavalent)	1/299	One participant with two events: Anaemia and pulmonary vasculitis
	Vaccine (quadrivalent)	2/300	Complex partial seizures, Henoch-Schonlein purpura

Abbreviations
*For each event, n = 1 unless otherwise stated.
HBV: hepatitis B vaccine

Table 2. Characteristic of licensed prophylactic HPV vaccines

	Bivalent vaccine	Quadrivalent vaccine	Nonavalent vaccine
Manufacturer	GlaxoSmithKline (GSK, Rixensart, Belgium)	Merck, Sharp & Dome (Merck & Co, Whitehouse Station, NJ, USA)	Merck, Sharp & Dome (Merck & Co, Whitehouse Station, NJ, USA)
Antigens	L1 VLPs of HPV16 (20 µg) and HPV18 (20 µg)	L1 VLPs of HPV6 (20 µg), HPV11 (40 µg), HPV16 (40 µg) and HPV18 (20 mg)	L1 VLPs of HPV6 (30 µg), HPV11 (40 µg), HPV16 (60 µg), HPV18 (40 mg),HPV31 (20 µg), HPV33 (20 µg), HPV45 (20 µg), HPV52 (20 µg)and HPV58 (20 µg)
Vaccination schedule	3 doses: at day 1, month 1, and month 6	3 doses: at day 1, month 2, and month 6	3 doses: at day 1, month 2, and month 6
Adjuvant	AS04: 500 µg aluminium hydroxide, 50 µg 3-deacylated monophosphoryl lipid A (MPL)	225 µg amorphous aluminium hydroxyl-phosphate sulphate	500 µg amorphous aluminium hydroxyl-phosphate sulphate
Trade name	Cervarix	Gardasil, Silgard	Gardasil-9
Produced by recombinant technology using	Baculovirus in *Trichoplusia* in insect cells	*Saccharomyces cerevisae* (Baker's yeast)	*Saccharomyces cerevisae* (Baker's yeast)

Abbreviations
HPV: human papillomavirus
MPL: monophosphoryl lipid
VLP: virus-like particle

Table 3. Summary of findings: Quadrivalent HPV vaccine compared with control in children, adults, and MSM with HIV

Quadrivalent HPV vaccine compared with control in children, adults, and MSM with HIV

Patient or population: children (7 to 12 years old) with HIV, adults (≥ 18 years old) with HIV, and MSM (≥ 18 years old) with HIV

Settings: Brazil, Puerto Rico, Spain, the USA

Intervention: quadrivalent HPV vaccine (3 doses at 0, 2, and 6 months)

Comparison: control (3 doses at 0, 2 and 6 months; not specified whether placebo contained vaccine adjuvant)

Outcomes	Population	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
		Risk with control	Risk with quadrivalent HPV vaccine			
High-grade anal intraepithelial neoplasia at 4-year follow-up	Females and males with HIV (≥ 27 years)	157 per 1000	160 per 1000 (110 to 233)	RR 1.02 (0.70 to 1.48)	574 (1 study)	⊕⊖⊖⊖ VERY LOW[1,2]
Recurrence of anogenital warts at 18-month follow-up	Females and males with HIV treated for	200 per 1000	143 per 1000 (7 to 778)	RR 0.71 (0.06 to 8.90)	12 (1 study)	⊕⊖⊖⊖ VERY LOW[2,3]

Table 3. Summary of findings: Quadrivalent HPV vaccine compared with control in children, adults, and MSM with HIV *(Continued)*

	anogenital warts (18-65 years)					
Abnormal anal cytology at 4-year follow-up	Females and males with HIV (≥ 27 years)	545 per 1000	447 per 1000 (349 to 573)	RR 0.82 (0.64 to 1.05)	262 (1 study)	⊕⊖⊖⊖ VERY LOW[1,4]
Overall local/injection site adverse events at 15-day follow-up	Children with HIV (7-12 years)	100 per 1000	219 per 1000 (70 to 683)	RR 2.19 (0.70 to 6.83)	126 (1 study)	⊕⊖⊖⊖ VERY LOW[1,2]
Overall systemic events and general symptoms at 15-day follow-up	Children with HIV (7-12 years)	33 per 1000	21 per 1000 (2 to 235)	RR 0.62 (0.05 to 7.05)	126 (1 study)	⊕⊖⊖⊖ VERY LOW[1,2,6]
Serious adverse events at 4-year follow-up (adults) or 7-month follow-up (MSM)	Females and males with HIV (≥ 27 years)	160 per 1000	115 per 1000 (74 to 174)	OR 0.68 (0.42 to 1.10)	575 (1 study)	⊕⊖⊖⊖ VERY LOW[1,4,6,7]
	MSM with HIV (≥ 18 years)	0 per 1000	0 per 1000 (0 to 0)	Not estimable, no events were reported	129 (1 study)	⊕⊖⊖⊖ VERY LOW[5,6,7]
Mortality at 4-year follow-up (adults) or 7-month follow-up (MSM)	Females and males with HIV (≥ 27 years)	21 per 1000	10 per 1000 (3 to 41)	OR 0.49 (0.12 to 1.99)	575 (1 study)	⊕⊖⊖⊖ VERY LOW[1,2]
	MSM with HIV (≥ 18 years)	0 per 1000	0 per 1000 (0 to 0)	Not estimable, no events were reported	129 (1 study)	⊕⊕⊖⊖ LOW[5]

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: confidence interval; **HIV:** human immunodeficiency virus; **HPV:** human papillomavirus; **MSM:** men who have sex with men; **OR:** odds ratio; **RR:** risk ratio

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: 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 quality: We are very uncertain about the estimate.

[1]Downgraded one level for risk of bias: details about how randomisation sequence was generated or how blinding was achieved were not reported.
[2]Downgraded two levels for serious imprecision: few events and a wide 95% confidence interval that incorporated a potentially beneficial effect and a potentially harmful effect.
[3]Downgraded two levels for serious risk of bias: data for 62.5% (20/32) of the participants enrolled were missing due to lack of follow-up. In addition, details about how randomisation, allocation concealment, and blinding were achieved were not reported.
[4]Downgraded two levels for imprecision: few events and wide 95% confidence interval that incorporated a potential beneficial effect and no effect.
[5]Downgraded two levels for serious imprecision: no events reported, the study was not powered to detect a difference in serious adverse events or mortality.

[6]Downgraded one level for indirectness: This outcome is a composite measure of events which may or may not be clinically relevant, may or may not be related to the vaccine and may occur outside a biologically plausible time frame relative to vaccine exposure. This outcome is considered to provide indirect evidence about vaccine safety.
[7]See Table 1 for details of each serious event.

Table 4. Summary of findings: Bivalent HPV vaccine compared with control in 18- to 25-year-old females with HIV

Bivalent HPV vaccine compared with control in 18- to 25-year-old females with HIV

Patient or population: 18- to 25-year-old females with HIV

Settings: South Africa

Intervention: bivalent HPV vaccine (3 doses at 0, 1, and 6 months)

Comparison: control (vaccine adjuvant-containing placebo) (3 doses at 0, 1 and 6 months)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Risk with control	Risk with bivalent HPV vaccine			
High-grade cervical epithelial neoplasia, adenocarcinoma in situ, and cervical cancer	No studies were identified that reported on this outcome.				
High-grade cervical, vulval, and vaginal disease	No studies were identified that reported on this outcome.				
Overall local/injection site adverse events	No studies were identified that reported on this outcome. Data for specific local adverse events (pain and swelling at injection site) are presented in the Data and analyses and Effects of interventions sections.				
Overall systemic events and general symptoms	No studies were identified that reported on this outcome.				
Serious adverse events at 12-month follow-up	34 per 1000	49 per 1000 (8 to 243)	OR 1.47 (0.24 to 9.15)	120 (1 study)	⊕⊖⊖⊖ VERY LOW[1,3,4]
Mortality at 12-month follow-up	0 per 1000	0 per 1000 (0 to 0)	Not estimable, no events were reported	120 (1 study)	⊕⊕⊖⊖ LOW[2]

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **HIV:** human immunodeficiency virus; **HPV:** human papillomavirus; **OR:** odds ratio

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: 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 quality: We are very uncertain about the estimate.

[1]Downgraded two levels for serious imprecision: few events and a wide 95% confidence interval that incorporated a potentially large beneficial effect and a potentially large harmful effect.

[2]Downgraded two levels for serious imprecision: no events reported, the study was not powered to detect a difference in mortality.
[3]Downgraded one level for indirectness: This outcome is a composite measure of events which may or may not be clinically relevant, may or may not be related to the vaccine and may occur outside a biologically plausible time frame relative to vaccine exposure. This outcome is considered to provide indirect evidence about vaccine safety.
[4]See Table 1 for details of each serious event.

Table 5. Summary of findings: Bivalent HPV vaccine compared with quadrivalent HPV vaccine in adults with HIV

Bivalent HPV vaccine compared with quadrivalent HPV vaccine in adults with HIV

Patient or population: adults and adolescents (combined male and female) with HIV, ≥ 15 years old

Settings: Brazil, Denmark, Estonia, India, and Thailand

Intervention: bivalent HPV vaccine (3 doses at 0, 1.5, and 6 months)

Comparison: quadrivalent HPV vaccine (3 doses at 0, 1.5, and 6 months)

Outcomes	Population	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
		Risk with quadrivalent HPV vaccine	Risk with bivalent HPV vaccine			
High-grade neoplasia, cancer		No studies were identified that reported on this outcome.				
Overall local/injection site adverse events at 4-day follow-up	Females and males with HIV (≥ 18 years)	696 per 1000	911 per 1000 (737 to 1000)	RR 1.31 (1.06 to 1.62)	92 (1 study)	⊕⊕⊖⊖ LOW[1]
Overall systemic events and general symptoms		No studies were identified that reported on this outcome.				
Serious adverse events at 6-month follow-up (adults) and 7-month follow-up (females)	Females and males with HIV (≥ 18 years)	0 per 1000	0 per 1000 (0 to 0)	Not estimable, no events were reported	92 (1 study)	⊕⊖⊖⊖ VERY LOW[2,5,6]
	Females with HIV (15-25 years)	55 per 1000	54 per 1000 (21 to 128)	OR 0.99 (0.38 to 2.55)	332 (1 study)	⊕⊖⊖⊖ VERY LOW[3,4,5,6]
Mortality		No studies were identified that reported on this outcome.				

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **HIV:** human immunodeficiency virus; **HPV:** human papillomavirus; **OR:** odds ratio; **RR:** risk ratio

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: 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 quality: We are very uncertain about the estimate.

[1]Downgraded two levels for serious imprecision: few events reported.
[2]Downgraded two levels for serious imprecision: no events reported, the study was not powered to detect a difference in serious adverse events or mortality.
[3]Downgraded one level for risk of bias: details on how randomisation, allocation concealment, and blinding was achieved was not reported.
[4]Downgraded two levels for serious imprecision: few events and a wide 95% confidence interval that incorporate a potentially large beneficial effect and a potentially large harmful effect.
[5]Downgraded one level for indirectness: This outcome is a composite measure of events which may or may not be clinically relevant, may or may not be related to the vaccine and may occur outside a biologically plausible time frame relative to vaccine exposure. This outcome is considered to provide indirect evidence about vaccine safety.
[6]See Table 1 for details of each serious event.

APPENDICES

Appendix 1. Ovid MEDLINE search strategy

1. exp Papillomavirus Infections/

2. exp PAPILLOMAVIRIDAE/

3. (human papilloma virus or human papillomavirus).tw.

4. 1 or 2 or 3

5. exp Immunization/

6. (vaccin* or immuni*).tw.

7. 5 or 6

8. 4 and 7

9. exp Papillomavirus Vaccines/

10. (human papilloma virus adj (vaccin* or immuni*)).tw.

11. (human papillomavirus adj (vaccin* or immuni*)).tw.

12. HPV vaccin*.tw.

13. (cervarix or gardasil).tw.

14. 9 or 10 or 11 or 12 or 13

15. 8 or 14

16. randomised controlled trial.pt.

17. controlled clinical trial.pt.

18. randomized.ab.

19. placebo.ab.

20. clinical trials as topic.sh.

21. randomly.ab.

22. trial.ti.

23. 16 or 17 or 18 or 19 or 20 or 21 or 22

24. (animals not (humans and animals)).sh.

25. 23 not 24

26. 15 and 25

Appendix 2. Ovid Embase search strategy

1. exp papillomavirus infection/

2. exp Papillomaviridae/

3. (human papilloma virus or human papillomavirus).tw.

4. 1 or 2 or 3

5. exp immunization/

6. (vaccin* or immuni*).tw.

7. 5 or 6

8. 4 and 7

9. exp Wart virus vaccine/

10. (human papilloma virus adj (vaccin* or immuni*)).tw.

11. (human papillomavirus adj (vaccin* or immuni*)).tw.

12. HPV vaccin*.tw.

13. (cervarix or gardasil).tw.

14. 9 or 10 or 11 or 12 or 13

15. 8 or 14

16. crossover procedure/

17. double-blind procedure/

18. randomised controlled trial/

19. single-blind procedure/

20. random*.mp.

21. factorial*.mp.

22. (crossover* or cross over* or cross-over*).mp.

23. placebo*.mp.

24. (double* adj blind*).mp.

25. (singl* adj blind*).mp.

26. assign*.mp.

27. allocat*.mp.

28. volunteer*.mp.

29. 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28

30. 15 and 29

Appendix 3. The Cochrane Library search strategy

#1 MeSH descriptor: [Papillomavirus Infections] explode all trees

#2 MeSH descriptor: [Papillomaviridae] explode all trees

#3 ("human papilloma virus" or "human papillomavirus").ti,ab,kw

#4 #1 or #2 or #3

#5 MeSH descriptor: [Immunization] explode all trees

#6 (vaccin* or immuni*):ti,ab,kw

#7 #5 or #6

#8 #4 and #7

#9 MeSH descriptor: [Papillomavirus Vaccines] explode all trees

#10 (human papilloma virus NEAR (vaccin* or immuni*)):ti,ab,kw

#11 (human papillomavirus NEAR (vaccin* or immuni*)):ti,ab,kw

#12 (HPV NEXT vaccin*):ti,ab,kw

#13 (cervarix or gardasil):ti,ab,kw

#14 {or #9-#13}

#15 #8 or #14

Appendix 4. Methods used to collect adverse event data

Study	Mode of data collection	Time frame	Attribution methods	Intensity of ascertainment	Harms-related monitoring and stopping rules	Frequency-based filter
Denny 2013	Proactive: trained field workers to visit subjects or instruct subjects to come back to a field station for the recording of solicited and unsolicited symptoms. Case report forms were used.	Time frame was specified. (Solicited AEs were recorded for 7 days after each vaccination. Unsolicited AEs were recorded for 30 days after each vaccination. SAEs, medically significant AEs, new-onset chronic diseases (NOCDs), pregnancies and their outcome were recorded up to month 12).	Not reported	Information relative to premature discontinuation of the investigational product was documented. The investigator was to document whether the decision to discontinue further vaccination was made by the subject or the investigator and which of the following possible reasons was responsible for withdrawal: SAE, non-serious AE, other (specified). No woman with-	Stopping rules not reported	No filter used ("For the analysis of unsolicited AEs/ SAEs/ Medically significant conditions/ NOCDs/ concomitant medication, all vaccinated subjects will be considered and subjects who did not report an event will be considered

(Continued)

				drew from the study due to AEs, however information on how withdrawals would have been handled in the analysis was not reported.		as subjects without an event").
Dobson 2013	Passive: "information on AEs was collected at the next visit or if the participant called with concerns"	Time frame was specified ("Because this was a post-licensure study, data were only collected on SAEs occurring within 30 days of each vaccination").	Not reported	Not reported	Stopping rules not reported	Unclear. Results were reported narratively only ("Scheduled vaccine doses were received by 98.6% of study participants with no SAEs reported").
Giuliano 2011	Proactive and passive: subjects recorded AEs on vaccination report cards. SAEs were recorded by investigators, including all deaths.	Time frame was specified ("any AEs occurring at the injection site on days 1 through 5 after receiving each dose of vaccine or placebo"). They also recorded systemic AEs and all SAEs that occurred on days 1 to 15 after receiving each dose. All SAEs that investigators believed to be associated with the vaccine or the study procedure and all deaths were recorded during the entire study period)	Attribution made by investigators ("Vaccine-related AEs were those determined by the investigator to be possibly, probably, or definitely related to the vaccine").	Number of withdrawals were reported, but without reasons. No information on how withdrawals were handled presented in the analysis.	Stopping rules not reported	Filter not used. AEs were reported as n/N. Study also reported number of participants with no event, and number with at least 1 event, but did not distinguish between participants with 1 or multiple AEs.

(Continued)

Hidalgo-Tenorio 2017	Proactive for local reactions: "Questionnaire that included the most frequent local reactions" Rare occurrences were also recorded, but mode of data collection is unclear.	Time frame is unclear (possibly at 2 and 6 months).	Attribution and blinding not reported. Definition used was provided ("Frequent local reactions included fever, nausea, vomiting, dizziness, syncope, headache and others such as allergic reaction, pruritus, difficulty breathing and/or wheezing. Rare occurrences included lymphadenopathies, chest and lower-limb pain, confusion, chills, muscle pain", but it is unclear if they were predefined. "The AEs were graded on a scale of 1–4")	Reasons for discontinuation were separated by arm. No information on how withdrawals were handled in the analysis. Attribution was not reported.	Monitoring stopping rules were reported ("In case of AE grade 4, the blind of the vial administered was broken and, if the code identified the vaccine, the reaction was communicated immediately to the relevant drug-vigilance authorities")	No filter used
Iversen 2016	Proactive and passive: immediate reactions were proactively collected: "Participants were observed for 30 mins after each injection for any immediate reaction". Non-serious injection site and systemic events "were not actively solicited".	Time frame was specified ("SAEs were to be reported irrespective of causality from day 1 (month 0) through 6 months after the last vaccination").	Attribution made by investigators ("Investigators were instructed to assign causality to adverse events on the basis of exposure, time course, likely cause, and consistency with the vaccine's known safety profile"). Blinding was not reported. No definition given for non-serious AEs. SAEs were predefined ("those events that resulted in death, were deemed life-threatening, led to a persistent or significant disability, required hospitalization, or were associated with a congenital anomaly, cancer, or other important medical event").	Reasons for discontinuation were separated by arm, and after each dose administration. Attribution was not reported. No information on how withdrawals were handled in the analysis.	Stopping rules not reported	No filter used

(Continued)

Joura 2015	Mode of data collection was not reported.	Time frame was specified ("Deaths and serious vaccine-related AEs were reported throughout the study. Other SAEs were reported from day 1 to 6 months following the last vaccination; events of fetal loss were reported as SAEs for any pregnancy with a last menstrual period before 6 months following the last vaccination").	Attribution was made by the investigator ("were deemed by the investigator"). Blinding was not reported. SAEs were predefined ("any AE that resulted in death, were deemed by the investigator to be life-threatening, resulted in a persistent or significant disability or incapacity, resulted in or prolonged an existing inpatient hospital stay, or were congenital anomalies, cancers, or other so-called important medical events").	Attribution was made by the safety monitoring committee ("The external data and safety monitoring committee whose members were aware of the group assignments assessed safety findings throughout the study"). No information on how withdrawals were handled in the analysis.	Stopping rules not reported	No filter used. AEs were reported as n/N. Study also reported number of participants with at least 1 event, but did not distinguish between participants with 1 or multiple AEs.
Lehtinen 2018	Proactive and passive: for active safety surveillance, a small subset of male adolescents receiving either vaccine were selected to use diary cards. Serious adverse events were actively monitored in the diary card subset and in other male participants in one cluster (90% HPV, 10% HBV) from month 1 to month 12. Passive monitoring of SAEs and new-onset autoimmune diseases continued for all study participants during the whole follow-up period by linkage to inpatient and outpatient health care use recorded in the Care Register for Social Welfare and Health Care.	Active surveillance: • to 30 minutes after vaccination for rash and urticarial (diary card subset); • to 30 days after vaccination for symptoms (diary card subset); • to month 12 for medically significant conditions (diary card subset); • to month 12 for serious adverse events (diary card subset and other male participants in one cluster). Passive SAE and new-onset	Attribution by investigator, blinded to treatment.	Active surveillance of SAEs, non-serious AEs and other events was only conducted for a small subset of male participants. Reasons for discontinuation were separated by arm and reported for withdrawals due to SAEs, non-serious AEs and other reasons.	Stopping rules not reported	No filter used

(Continued)

		autoimmune disease surveillance: • for entire study period (to approximately 4 years).				
Leung 2015	Passive for solicited local and general symptoms: "diary cards"	Time frame was specified ("Solicited local and general symptoms were recorded for 7 days after each vaccination"; "Unsolicited symptoms were recorded for 30 days after each vaccination"; "SAEs, medically significant AEs, pIMDs and pregnancy were reported throughout the study"; "SAEs up to month 36")	Attribution and blinding were not reported. Only Grade 3 symptoms were defined ("redness or swelling > 50 mm in diameter, fever > 39C")	No information on how withdrawals would have been handled in the analysis, however "no subject was withdrawn from the study due to an AE" Attribution was not reported.	Stopping rules not reported	No filter used. Results reported as percentage of participants with symptoms, therefore did not distinguish between participants with 1 or multiple AEs.
Levin 2010	Proactive: "Subjects were observed in clinic for 30 minutes post vaccination. A report card of relevant signs and symptoms was maintained by the caregiver for 15 days after each injection. Body temperature was recorded for 5 days beginning after the injection. Telephone contact with the caregiver was made on the third day after each injection to inquire about reactions. The caregiver was instructed to immediately report unusual injection site reactions"; "Routine hematologic and chemistry screens were performed at the study site's laboratory at entry, 4 weeks after the first dose, and just before and 4 weeks after the next 2 doses. CD4% and CD4 number were determined at entry, 8 weeks after the first dose, 4 weeks after the sec-	Time frame was specified (see methods of data collection).	Attribution was made by the study co-ordinator. Blinding not reported. The severity of AEs was done using the "Division of AIDS Table for Grading the Severity of Adverse Events".	No information on how withdrawals were handled in the analysis.	Unclear. "A clinic visit was required within 24 hours whenever the study coordinator considered that a reaction might be ≥ grade 3". However, clear rules regarding termination of the study were not reported.	No filter used

(Continued)

	ond dose, and just before and 4 weeks after the third dose".					
Lin 2014	Unclear: "Following each vaccination visit, participants were screened for adverse events".	Time frame is unclear.	Not reported	Reasons for discontinuation were separated by arm, and after each dose administration. Attribution was not reported. No information on how withdrawals were handled in the analysis.	Stopping rules not reported	No filter used. However, results were only reported narratively as proportions. P-value only reported for overall occurrence of AEs. Specific AEs were not reported separately by group.
NCT00941889 2016	Not applicable, serious and/or other non-serious adverse events were not collected or assessed.	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable
NCT01031069 2017	Mode of data collection was not reported.	Solicited local and general symptoms within 7 days after each and any vaccination; unsolicited symptoms within 30 days (days 0-29) after any vaccination; SAEs, medically significant conditions, pregnancy outcomes, clinically relevant abnormalities in haematological and biochemical parameters up to 30 days after the last dose of vaccine.	Attribution, blinding or definitions were not reported.	Reasons for discontinuation were separated by arm. All vaccinated subjects for whom data were available were included in the analysis. Attribution was not reported.	Stopping rules not reported	No filter used
NCT01862874 2018	Mode of data collection was not reported, except that a	Serious and other adverse events fol-	Attribution, blinding or definitions were not reported.	Reasons for discontinuation	Stopping rules not reported	Threshold above which

(Continued)

	vaccination report card was used.	lowed up for 36 months; injection-site AEs were reported up to 5 days after any vaccination; systemic AEs were reported up to 15 days after any vaccination.		were separated by arm. All vaccinated subjects for whom data were available were included in the analysis. Attribution was not reported.		other adverse events are reported: 5%
Wilkin 2018	Mode of data collection was not reported.	Grade 3 or 4 AEs that were possibly, probably, or definitely related to the vaccine: to participant's last study visit, for up to 4 years.	Attribution determined by the local investigator, blinding not reported. Grade 3 or 4 adverse events were defined using the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events.	Reasons for discontinuation were separated by arm. All vaccinated subjects for whom data were available were included in the analysis. Attribution was made by the local investigator.	Stopping rules not reported	No filter used
Petaja 2009	Proactive and passive: "Participants used diary cards to report solicited local and general symptoms during a 7-day follow-up period after each vaccine dose"; "Unsolicited signs and symptoms were reported within 30 days after each dose". Data collection forms available from GSK report.	Time frame was specified: 7-day follow-up for local and general symptoms; 30 days for unsolicited signs and symptoms; SAEs, NOCDs and other medically significant conditions (MSCs) were reported throughout the study period (up to month 12).	Attribution method not explicitly described in methods section. However, it seems it was done by the investigator "Neither of the SAEs were fatal, and both events were considered by the investigator to be unrelated to study vaccination"; "the determination of whether a chronic disease is considered to be of new onset will be based on review of the subject's pre-vaccination medical history". Blinding was not reported. Outcome definition: • "Solicited local AEs included pain, redness, and swelling at the injection site"; • "Solicited general AEs included	Reasons for discontinuation were separated by arm. Attribution was not reported. No information on how withdrawals were handled in the analysis.	Stopping rules not fully described, "Your participation in the study may be stopped the study doctor decides it is in the best interest of your health and welfare to discontinue participation in the study"	Filter not used. AEs were reported as n/N. GSK report lists all symptoms individually. Study did not distinguish between participants with 1 or multiple AEs.

(Continued)

fever, headache, fatigue, gastrointestinal symptoms (i.e. nausea, vomiting, diarrhoea, abdominal pain), arthralgia, myalgia, rash, and urticaria"

- "Grade 3 solicited AEs were defined as pain that prevented normal activity, redness or swelling larger than 50 mm, fever higher than 39.0 °C (axillary temperature), urticaria distributed on at least four body areas, or events that prevented normal, everyday activities. Urticaria or rash that appeared within 30 minutes of each vaccine dose was also documented by the investigator"
- "An SAE was defined as any untoward medical occurrence that resulted in death, was life-threatening, required hospitalization, resulted in disability or incapacity, was an important medical event or was a congenital anomaly/birth defect in the offspring of a study subject"
- "MSCs were defined as non-serious AEs prompting either emergency room or physician visits not related to either common diseases or routine visits for physical examination or vaccination, or SAEs not related to common diseases"
- "Common diseases included upper res-

(Continued)

			piratory infections, sinusitis, pharyngitis, gastroenteritis, urinary tract infections, and injury"			
Puthanakit 2016	Proactive and passive: "Solicited local and general symptoms were recorded on diary cards for 7 days after each vaccination. Unsolicited symptoms were recorded for 30 days after each vaccination. Pregnancies and outcomes, serious adverse events, medically significant adverse events, and potential immune-mediated diseases were reported throughout the study".	Time frame was specified (see methods of data collection).	Attribution and blinding not reported. Grade 3 symptoms were defined ("as redness or swelling >50 mm in diameter, fever >39°C, urticaria distributed on ≥4 body areas, and, for other symptoms, as preventing normal activity").	Reasons for discontinuation were separated by arm, and after each dose administration. Attribution was not reported. No information on how withdrawals were handled in the analysis.	Stopping rules not reported	No filter used, however, results were provided as number of participants with at least 1 event, therefore did not distinguish between participants with 1 or multiple AEs.
Romanowski 2011	Proactive and passive: "Solicited local symptoms (pain, redness or swelling at injection site) and general symptoms (fever, headache, fatigue, gastrointestinal symptoms, arthralgia, myalgia, rash or urticaria) occurring within 7 d after each vaccination were recorded by the subject or her parent/legally acceptable representative using a diary card. Investigators documented the presence or absence of urticaria/rash within 30 min after each vaccine. dose. Unsolicited AEs occurring within one month of each vaccine dose were documented by the investigator. "SAEs and other medically significant conditions were reported in all subjects regardless of causal relationship to vaccination and intensity."	Time frame was specified (see methods of data collection).	Attribution and blinding not reported. Outcome definition reported ("Medically significant condition = AE prompting emergency room or physician visits that was not related to common diseases. New onset autoimmune diseases (which excluded allergy-related events or isolated signs and symptoms) were identified by comparing all reported AEs with a pre-defined list of potential chronic autoimmune events derived from the Medical Dictionary for Regulatory Activities").	Attribution was not reported. No information on how withdrawals would have been handled in the analysis, however "no subject was withdrawn from the study due to an AE or a SAE"	Stopping rules not reported	No filter used. However, for many of the AEs, results were provided as number of participants with at least 1 event, therefore did not distinguish between participants with 1 or multiple AEs.
Toft 2014	Proactive and passive: "Participants were observed for 30 minutes after each immunization to evaluate im-	Time frame was specified (see methods of data collection).	Attribution was unclear (see below).	Withdrawals were not reported by group. No infor-	Stopping rules not reported	Filter not used. Solicited AEs re-

(Continued)

	mediate AEs. Solicited AEs occurring during the first 4 days after each immunization (injection site pain, swelling, erythema, fever, headache, nausea, myalgia, arthralgia and rash) and other signs of illness and/or changes in medication occurring within 15 days after immunization were recorded on diary cards".		Blinding was not reported. Outcome definition was reported ("Solicited and unsolicited AEs, as well as laboratory tests, were graded according to the common toxicity criteria version 2.0. All solicited local (injection site) and influenza-like (fever, arthralgia, chills, and fatigue) reactions were considered causally related to vaccination. Other AEs were evaluated by the primary investigator and graded as "unlikely" or "probably" related to the study vaccines").	mation on how withdrawals were handled in the analysis was provided. Attribution was not reported.		ported as n/N. Study also reported number of participants with at least 1 event, but did not distinguish between participants with 1 or multiple AEs.
van Damme 2016	Proactive and passive: "Following each vaccination, participants were observed for 30 min for any untoward effects, including allergic reactions. All participants received a vaccination report card (VRC) at each vaccination visit. They were asked to record their oral temperature on the VRC from day 1 to day 5 after each vaccination (starting on the evening after vaccination), and any injection-site and systemic AEs) for a total of 15 days including the day of vaccination … SAEs were collected for the entire duration of the study irrespective of cause".	Time frame was specified (see methods of data collection).	Attribution was made by investigators based on the information provided by the patients ("The study site personnel reviewed the VRC for completeness and could not alter the original information recorded by the participants on the VRC. The investigator determined the causality of systemic AEs reported on the VRC, and classified each AE reported on the VRC as a serious or non-serious AE"). Blinding was not reported. Outcome definition was reported ("An oral temperature 37.8 C during the follow-up period was considered an elevated temperature (fever). For each AE, participants were asked to rate the symptom as mild (awareness of signor symptom but easily tolerated), moderate	Reasons for discontinuation were separated by arm. Attribution was not reported. No information provided about how withdrawals were handled in the analysis.	Stopping rules not reported	Filter not used. AEs were reported as n/N. Study also reported number of participants with no event, and number with at least 1 event, but did not distinguish between participants with 1 or multiple AEs.

(Continued)

			(discomfort enough to cause interference with usual activities), or severe (incapacitating with inability to work or do usual activity); injection-site AEs of swelling and erythema were rated by size. Investigators were instructed to assign causality to AEs on the basis of exposure, time course, likely cause, and consistency with the vaccine's known profile. Serious AEs (SAEs) were predefined as any AE that resulted in death, deemed by the investigator to be life-threatening, or that resulted in a persistent or significant disability or incapacity, resulted in or prolonged an existing inpatient hospitalization, or was a congenital anomaly, a cancer, or an 'other important medical event").			
Vesikari 2015	Proactive and passive: "Participants were observed for 30 mins after each vaccination for any immediate reaction. All subjects received a vaccination report card at the day 1, month 2 and month 6 study vaccination visits. Oral temperature was reported from day 1 to day 5 after any vaccination, and injection-site reactions and systemic AEs were recorded on the vaccination report card from day 1 to day 15 after any vaccination. SAEs were monitored throughout the study regardless of cause".	Time frame was specified (see methods of data collection).	Attribution was made by the investigator ("Investigators assigned causality to AEs based on exposure, time course, likely cause and consistency with the vaccine's known profile. Vaccine-related AEs were determined by the investigator to be possibly, probably or definitely vaccine-related"). Blinding was not reported. Outcome definition was reported ("An elevated temperature (fever) was defined as maximum temperature ≥37.8°C. For each AE, participants rated the symptom as	Reasons for discontinuation were separated by arm, and after each dose administration. Attribution was not reported. No information provided about how withdrawals were handled in the analysis.	Stopping rules not reported	Filter not used. AEs were reported as n/N. Study also reported number of participants with no event, and number with at least 1 event, but did not distinguish between participants with 1 or multiple AEs.

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					mild (awareness of symptom but easily tolerated), moderate (discomfort enough to cause interference with usual activities) or severe (incapacitating with inability to work or do usual activity); injection-site AEs of swelling and erythema were rated by size. SAEs were predefined as any AE that resulted in death, were deemed by the investigator to be life-threatening, resulted in a persistent or significant disability or incapacity, resulted in or prolonged an existing in-patient hospitalization or was a congenital anomaly, a cancer or an "other important medical event".	

Abbreviations

AE: adverse event
HBV: hepatitis B vaccine
HPV: human papillomavirus
NOCD: new onset chronic disease
pIMD: potentially immune mediated diseases
SAE: serious adverse event
VRC: vaccination report card

Appendix 5. Two versus three doses of HPV vaccine in 9- to 15-year old females - immunogenicity outcomes

Outcome or subgroup*	Follow-up	Studies	Participants	Statistical method	Effect estimate (95% CI)	Certainty of the evidence (GRADE)
1.1 GMT of HPV 6 (mMU/mL)	1 month after last dose	2 (Dobson 2013; Iversen 2016)	1001	Ratio of GMTs (IV, random-effects, 95% CI)	Ratio of GMTs 1.13 (0.99 to 1.29)	⊕⊕⊕⊕ HIGH
1.1.1 Quadrivalent vaccine	1 month after last dose	1 (Dobson 2013)	489	Ratio of GMTs (IV, random-effects, 95% CI)	Ratio of GMTs 1.18 (0.93 to 1.49)	

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1.1.2 Nonavalent vaccine	1 month after last dose	1 (Iversen 2016)	512	Ratio of GMTs (IV, random-effects, 95% CI)	Ratio of GMTs 1.11 (0.94 to 1.30)	
1.2 GMT of HPV 11 (mMU/mL)	1 month after last dose	2 (Dobson 2013; Iversen 2016)	1006	Ratio of GMTs (IV, random-effects, 95% CI)	Ratio of GMTs 1.09 (0.97 to 1.22)	⊕⊕⊕⊕ HIGH
1.2.1 Quadrivalent vaccine	1 month after last dose	1 (Dobson 2013)	494	Ratio of GMTs (IV, random-effects, 95% CI)	Ratio of GMTs 1.12 (0.95 to 1.32)	
1.2.2 Nonavalent vaccine	1 month after last dose	1 (Iversen 2016)	512	Ratio of GMTs (IV, random-effects, 95% CI)	Ratio of GMTs 1.06 (0.91 to 1.25)	
1.3 GMT of HPV 16						Not pooled due to considerable heterogeneity across studies (I^2 = 89%)
1.3.1 Bivalent vaccine	1 month after last dose	1 (Romanowski 2011)	132	Ratio of GMTs (IV, random-effects, 95% CI)	Ratio of GMTs 0.50 (0.38 to 0.66)	⊕⊕⊕⊖ MODERATE[1,4]
1.3.2 Quadrivalent vaccine	1 month after last dose	2 (Dobson 2013; Leung 2015)	1143	Ratio of GMTs (IV, random-effects, 95% CI)	Ratio of GMTs 1.03 (0.92 to 1.15)	⊕⊕⊕⊕ HIGH
1.3.3 Nonavalent vaccine	1 month after last dose	1 (Iversen 2016)	541	Ratio of GMTs (IV, random-effects, 95% CI)	Ratio of GMTs 1.14 (0.98 to 1.34)	⊕⊕⊕⊕ HIGH
1.4 GMT of HPV 18	1 month after last dose	4 (Romanowski 2011; Dobson 2013; Iversen 2016; Leung 2015)	1833	Ratio of GMTs (IV, random-effects, 95% CI)	Ratio of GMTs 0.77 (0.69 to 0.87)	⊕⊕⊕⊖ MODERATE[2]
1.4.1 Bivalent vaccine	1 month after last dose	1 (Romanowski 2011)	132	Ratio of GMTs (IV, random-effects, 95% CI)	Ratio of GMTs 0.74 (0.57 to 0.97)	
1.4.2 Quadrivalent vaccine	1 month after last dose	2 (Dobson 2013; Leung 2015)	1159	Ratio of GMTs (IV, ran-	Ratio of GMTs 0.72 (0.64 to 0.81)	

(Continued)

				dom-effects, 95% CI)		
1.4.3 Nonavalent vaccine	1 month after last dose	1 (Iversen 2016)	542	Ratio of GMTs (IV, random-effects, 95% CI)	Ratio of GMTs 0.91 (0.76 to 1.09)	
1.5 GMT of HPV 31 (mMU/mL)	1 month after last dose	1 (Iversen 2016)	543	Ratio of GMTs (IV, random-effects, 95% CI)	Ratio of GMTs 0.82 (0.69 to 0.98)	⊕⊕⊕⊕ HIGH
1.6 GMT of HPV 33 (mMU/mL)	1 month after last dose	1 (Iversen 2016)	548	Ratio of GMTs (IV, random-effects, 95% CI)	Ratio of GMTs 1.29 (1.10 to 1.52)	⊕⊕⊕⊕ HIGH
1.7 GMT of HPV 45 (mMU/mL)	1 month after last dose	1 (Iversen 2016)	549	Ratio of GMTs (IV, random-effects, 95% CI)	Ratio of GMTs 0.54 (0.45 to 0.65)	⊕⊕⊕⊕ HIGH
1.8 GMT of HPV 52 (mMU/mL)	1 month after last dose	1 (Iversen 2016)	547	Ratio of GMTs (IV, random-effects, 95% CI)	Ratio of GMTs 0.64 (0.55 to 0.74)	⊕⊕⊕⊕ HIGH
1.9 GMT of HPV 58 (mMU/mL)	1 month after last dose	1 (Iversen 2016)	543	Ratio of GMTs (IV, random-effects, 95% CI)	Ratio of GMTs 1.02 (0.87 to 1.19)	⊕⊕⊕⊕ HIGH
1.10 Seroconversion to HPV 6	1 month after last dose	2 (Dobson 2013; Iversen 2016)	1001	RR (M-H, random-effects, 95% CI)	RR 1.00 (0.99 to 1.01)	⊕⊕⊕⊕ HIGH
1.10.1 Quadrivalent vaccine	1 month after last dose	1 (Dobson 2013)	489	RR (M-H, random-effects, 95% CI)	RR 1.00 (0.99 to 1.01)	
1.10.2 Nonavalent vaccine	1 month after last dose	1 (Iversen 2016)	512	RR (M-H, random-effects, 95% CI)	RR 1.00 (0.99 to 1.02)	
1.11 Seroconversion to HPV 11	1 month after last dose	2 (Dobson 2013; Iversen 2016)	1006	RR (M-H, random-effects, 95% CI)	RR 1.00 (0.99 to 1.01)	⊕⊕⊕⊕ HIGH
1.11.1 Quadrivalent vaccine	1 month after last dose	1 (Dobson 2013)	494	RR (M-H, random-effects, 95% CI)	RR 1.00 (0.99 to 1.01)	
1.11.2 Nonavalent vaccine	1 month after last dose	1 (Iversen 2016)	512	RR (M-H, random-effects, 95% CI)	RR 1.00 (0.99 to 1.01)	

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1.12 Seroconversion to HPV 16	1 month after last dose	4 (Romanowski 2011; Dobson 2013; Iversen 2016; Leung 2015)	1816	RR (M-H, random-effects, 95% CI)	RR 1.00 (1.00 to 1.00)	⊕⊕⊕⊕ HIGH
1.12.1 Bivalent vaccine	1 month after last dose	1 (Romanowski 2011)	132	RR (M-H, random-effects, 95% CI)	RR 1.00 (0.97 to 1.03)	
1.12.2 Quadrivalent vaccine	1 month after last dose	2 (Dobson 2013; Leung 2015)	1143	RR (M-H, random-effects, 95% CI)	RR 1.00 (1.00 to 1.00)	
1.12.3 Nonavalent vaccine	1 month after last dose	1 (Iversen 2016)	541	RR (M-H, random-effects, 95% CI)	RR 1.00 (0.99 to 1.01)	
1.13 Seroconversion to HPV 18	1 month after last dose	4 (Romanowski 2011; Dobson 2013; Iversen 2016; Leung 2015)	1833	RR (M-H, random-effects, 95% CI)	RR 1.00 (1.00 to 1.00)	⊕⊕⊕⊕ HIGH
1.13.1 Bivalent vaccine	1 month after last dose	1 (Romanowski 2011)	132	RR (M-H, random-effects, 95% CI)	RR 1.00 (0.97 to 1.03)	
1.13.2 Quadrivalent vaccine	1 month after last dose	2 (Dobson 2013; Leung 2015)	1159	RR (M-H, random-effects, 95% CI)	RR 1.00 (1.00 to 1.00)	
1.13.3 Nonavalent vaccine	1 month after last dose	1 (Iversen 2016)	542	RR (M-H, random-effects, 95% CI)	RR 1.00 (0.99 to 1.01)	
1.14 Seroconversion to HPV 31	1 month after last dose	1 (Iversen 2016)	543	RR (M-H, random-effects, 95% CI)	RR 1.00 (0.99 to 1.01)	⊕⊕⊕⊕ HIGH
1.15 Seroconversion to HPV 33	1 month after last dose	1 (Iversen 2016)	548	RR (M-H, random-effects, 95% CI)	RR 1.00 (0.99 to 1.01)	⊕⊕⊕⊕ HIGH
1.16 Seroconversion to HPV 45	1 month after last dose	1 (Iversen 2016)	549	RR (M-H, random-effects, 95% CI)	RR 1.00 (0.99 to 1.01)	⊕⊕⊕⊕ HIGH
1.17 Seroconversion to HPV 52	1 month after last dose	1 (Iversen 2016)	547	RR (M-H, random-effects, 95% CI)	RR 1.00 (0.99 to 1.01)	⊕⊕⊕⊕ HIGH
1.18 Seroconversion to HPV 58	1 month after last dose	1 (Iversen 2016)	543	RR (M-H, random-effects, 95% CI)	RR 1.00 (0.99 to 1.01)	⊕⊕⊕⊕ HIGH

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1.19 GMT of HPV 6 (mMU/mL)						
1.19.1 Quadrivalent vaccine	60 months after first dose	1 (Dobson 2013)	101	Ratio of GMTs (IV, random-effects, 95% CI)	Ratio of GMTs 0.73 (0.50 to 1.06)	⊕⊕⊖⊖ LOW[3,4]
1.19.2 Nonavalent vaccine	36 months after first dose	1 (Iversen 2016)	476	Ratio of GMTs (IV, random-effects, 95% CI)	Ratio of GMTs 0.90 (0.76 to 1.08)	⊕⊕⊕⊕ HIGH
1.20 GMT of HPV 11 (mMU/mL)						
1.20.1 Quadrivalent vaccine	60 months after first dose	1 (Dobson 2013)	101	Ratio of GMTs (IV, random-effects, 95% CI)	Ratio of GMTs 0.99 (0.68 to 1.44)	⊕⊕⊖⊖ LOW[2,3]
1.20.2 Nonavalent vaccine	36 months after first dose	1 (Iversen 2016)	476	Ratio of GMTs (IV, random-effects, 95% CI)	Ratio of GMTs 0.84 (0.70 to 1.01)	⊕⊕⊕⊕ HIGH
1.21 GMT of HPV 16 (mMU/mL)						
1.21.1 bivalent vaccine	60 months after first dose	1 (Romanowski 2011)	93	Ratio of GMTs (IV, random-effects, 95% CI)	Ratio of GMTs 0.51 (0.36 to 0.72)	⊕⊕⊖⊖ LOW[3,4]
1.21.2 Quadrivalent vaccine	60 months after first dose	1 (Dobson 2013)	101	Ratio of GMTs (IV, random-effects, 95% CI)	Ratio of GMTs 1.14 (0.76 to 1.73)	⊕⊕⊖⊖ LOW[3,4]
1.21.3 Nonavalent vaccine	36 months after first dose	1 (Iversen 2016)	503	Ratio of GMTs (IV, random-effects, 95% CI)	Ratio of GMTs 0.85 (0.69 to 1.04)	⊕⊕⊕⊕ HIGH
1.22 GMT of HPV 18 (mMU/mL)						
1.22 1 Bivalent vaccine	60 months after first dose	1 (Romanowski 2011)	92	Ratio of GMTs (IV, random-effects, 95% CI)	Ratio of GMTs 0.69 (0.47 to 1.02)	⊕⊕⊖⊖ LOW[3,4]
1.22.2 Quadrivalent vaccine	60 months after first dose	1 (Dobson 2013)	101	Ratio of GMTs (IV, random-effects, 95% CI)	Ratio of GMTs 0.57 (0.34 to 0.96)	⊕⊕⊖⊖ LOW[3,4]
1.22.3 Nonavalent vaccine	36 months after first dose	1 (Iversen 2016)	504	Ratio of GMTs (IV, ran-	Ratio of GMTs 0.77 (0.65 to 0.91)	⊕⊕⊕⊕ HIGH

(Continued)

				dom-effects, 95% CI)		
1.23 GMT of HPV 31 (mMU/mL)	36 months after first dose	1 (Iversen 2016)	506	Ratio of GMTs (IV, random-effects, 95% CI)	Ratio of GMTs 0.62 (0.51 to 0.75)	⊕⊕⊕⊕ HIGH
1.24 GMT of HPV 33 (mMU/mL)	36 months after first dose	1 (Iversen 2016)	510	Ratio of GMTs (IV, random-effects, 95% CI)	Ratio of GMTs 1.11 (0.94 to 1.31)	⊕⊕⊕⊕ HIGH
1.25 GMT of HPV 45 (mMU/mL)	36 months after first dose	1 (Iversen 2016)	511	Ratio of GMTs (IV, random-effects, 95% CI)	Ratio of GMTs 0.46 (0.39 to 0.56)	⊕⊕⊕⊕ HIGH
1.26 GMT of HPV 52 (mMU/mL)	36 months after first dose	1 (Iversen 2016)	509	Ratio of GMTs (IV, random-effects, 95% CI)	Ratio of GMTs 0.57 (0.49 to 0.67)	⊕⊕⊕⊕ HIGH
1.27 GMT of HPV 58 (mMU/mL)	36 months after first dose	1 (Iversen 2016)	505	Ratio of GMTs (IV, random-effects, 95% CI)	Ratio of GMTs 0.88 (0.74 to 1.05)	⊕⊕⊕⊕ HIGH
1.28 Seropositivity to HPV 6						
1.28.1 Quadrivalent vaccine	60 months after first dose	1 (Dobson 2013)	101	RR (M-H, random-effects, 95% CI)	RR 0.98 (0.91 to 1.05)	⊕⊕⊖⊖ LOW[3,4]
1.28.2 Nonavalent vaccine	36 months after first dose	1 (Iversen 2016)	476	RR (M-H, random-effects, 95% CI)	RR 0.97 (0.94 to 1.01)	⊕⊕⊕⊕ HIGH
1.29 Seropositivity to HPV 11						
1.29.1 Quadrivalent vaccine	60 months after first dose	1 (Dobson 2013)	101	RR (M-H, random-effects, 95% CI)	RR 1.00 (95% CI not estimable, all participants were seropositive)	⊕⊕⊖⊖ LOW[3,4]
1.29.2 Nonavalent vaccine	36 months after first dose	1 (Iversen 2016)	476	RR (M-H, random-effects, 95% CI)	RR 0.95 (0.92 to 0.99)	⊕⊕⊕⊕ HIGH
1.30 Seropositivity to HPV 16						
1.30.1 Bivalent vaccine	60 months after first dose	1 (Romanowski 2011)	490	RR (M-H, random-effects, 95% CI)	RR 1.00 (95% CI not estimable, all partici-	⊕⊕⊕⊕ HIGH

(Continued)

					pants were seropositive)	
1.30.2 Quadrivalent vaccine	60 months after first dose	1 (Dobson 2013)	101	RR (M-H, random-effects, 95% CI)	RR 1.00 (95% CI not estimable, all participants were seropositive)	⊕⊕⊖⊖ LOW[3,4]
1.30.3 Nonavalent vaccine	36 months after first dose	1 (Iversen 2016)	503	RR (M-H, random-effects, 95% CI)	RR 0.98 (0.96 to 1.00)	⊕⊕⊕⊕ HIGH
1.31 Seropositivity to HPV 18						
1.31.1 Bivalent vaccine	60 months after first dose	1 (Romanowski 2011)	480	RR (M-H, random-effects, 95% CI)	RR 1.00 (0.99 to 1.01)	⊕⊕⊕⊕ HIGH
1.31.2 Quadrivalent vaccine	60 months after first dose	1 (Dobson 2013)	101	RR (M-H, random-effects, 95% CI)	RR 0.89 (0.78 to 1.03)	⊕⊕⊖⊖ LOW[3,4]
1.31.3 Nonavalent vaccine	36 months after first dose	1 (Iversen 2016)	504	RR (M-H, random-effects, 95% CI)	RR 0.98 (0.95 to 1.02)	⊕⊕⊕⊕ HIGH
1.32 Seropositivity to HPV 31	36 months after first dose	1 (Iversen 2016)	506	RR (M-H, random-effects, 95% CI)	RR 0.96 (0.93 to 1.00)	⊕⊕⊕⊕ HIGH
1.33 Seropositivity to HPV 33	36 months after first dose	1 (Iversen 2016)	510	RR (M-H, random-effects, 95% CI)	RR 0.96 (0.92 to 0.99)	⊕⊕⊕⊕ HIGH
1.34 Seropositivity to HPV 45	36 months after first dose	1 (Iversen 2016)	511	RR (M-H, random-effects, 95% CI)	RR 0.92 (0.86 to 0.98)	⊕⊕⊕⊕ HIGH
1.35 Seropositivity to HPV 52	36 months after first dose	1 (Iversen 2016)	509	RR (M-H, random-effects, 95% CI)	RR 0.96 (0.92 to 0.99)	⊕⊕⊕⊕ HIGH
1.36 Seropositivity to HPV 58	36 months after first dose	1 (Iversen 2016)	505	RR (M-H, random-effects, 95% CI)	RR 0.99 (0.97 to 1.01)	⊕⊕⊕⊕ HIGH

*Results were stratified into subgroups by type of HPV vaccine and time point. GMTs and seropositivity to HPV 31, 33, 45, 52, and 58 are only measured in nonavalent vaccine trials (Iversen 2016).

[1]GRADE rating applies to specific vaccine type and outcome

[2]Downgraded one level for inconsistency: moderate heterogeneity (I^2 > 30%)

[3]Downgraded one level for risk of bias: high loss to follow up

[4]Downgraded one level for imprecision: small sample size

Abbreviations

CI: confidence interval
GMT: geometric mean titre
HPV: human papillomavirus
IV: inverse variance
M-H: Mantel-Haenszel
RR: risk ratio
SMD: standard mean difference
mMU: milli-Merck unit

Appendix 6. Two doses of HPV vaccine with longer interval versus two doses of HPV vaccine with shorter interval in 9- to 14-year old females and males - immunogenicity outcomes

Outcome or subgroup*	Population	Follow-up	Studies	Participants	Statistical method	Effect estimate (95% CI)	Certainty of the evidence (GRADE)
3.1 GMT of HPV 6 (mMU/mL)							
3.1.1 Nonavalent vaccine (0 and 6 months) vs (0 and 12 months)	9- to 14-year-old females	1 month after last dose	1 (Iversen 2016)	381	Ratio of GMTs (IV, random-effects, 95% CI)	Ratio of GMTs 1.62 (1.32 to 1.98)	⊕⊕⊕⊕ HIGH
3.1.2 Nonavalent vaccine (0 and 6 months) vs (0 and 12 months)	9- to 14-year-old males	1 month after last dose	1 (Iversen 2016)	397	Ratio of GMTs (IV, random-effects, 95% CI)	Ratio of GMTs 1.72 (1.41 to 2.09)	⊕⊕⊕⊕ HIGH
3.2 GMT of HPV 11 (mMU/mL)							
3.2.1 Nonavalent vaccine (0 and 6 months) vs (0 and 12 months)	9- to 14-year-old females	1 month after last dose	1 (Iversen 2016)	381	Ratio of GMTs (IV, random-effects, 95% CI)	Ratio of GMTs 2.10 (1.82 to 2.40)	⊕⊕⊕⊕ HIGH
3.2.2 Nonavalent vaccine (0 and 6 months) vs (0 and 12 months)	9- to 14-year-old males	1 month after last dose	1 (Iversen 2016)	398	Ratio of GMTs (IV, random-effects, 95% CI)	Ratio of GMTs 2.08 (1.71 to 2.53)	⊕⊕⊕⊕ HIGH
3.3 GMT of HPV 16 (EU/mL or mMU/mL)							
3.3.1 Bivalent vaccine (0 and 2 months) vs (0 and 6 months	9- to 14-year-old females	1 month after last dose	1 (Romanowski 2011)	136	Ratio of GMTs (IV, random-effects, 95% CI)	Ratio of GMTs 2.06 (1.60 to 2.64)	⊕⊕⊕⊖ MODERATE[1]
3.3.2 Bivalent vaccine (0 and 6	9- to 14-year-old females	1 month after last dose	1 (Puthanakit 2016)	835	Ratio of GMTs (IV, random-effects, 95% CI)	Ratio of GMTs 1.22 (1.10 to 1.34)	⊕⊕⊕⊕ HIGH

(Continued)

months) vs (0 and 12 months)							
3.3.3 Nonavalent vaccine (0 and 6 months) vs (0 and 12 months)	9- to 14-year-old females	1 month after last dose	1 (Iversen 2016)	401	Ratio of GMTs (IV, random-effects, 95% CI)	Ratio of GMTs 1.73 (1.42 to 2.10)	⊕⊕⊕⊕ HIGH
3.3.4 Nonavalent vaccine (0 and 6 months) vs (0 and 12 months)	9- to 14-year-old males	1 month after last dose	1 (Iversen 2016)	408	Ratio of GMTs (IV, random-effects, 95% CI)	Ratio of GMTs 1.75 (1.44 to 2.12)	⊕⊕⊕⊕ HIGH
3.4 GMT of HPV 18 (EU/mL or mMU/mL)							
3.4.1 Bivalent vaccine (0 and 2 months) vs (0 and 6 months	9- to 14-year-old females	1 month after last dose	1 (Romanowski 2011)	132	Ratio of GMTs (IV, random-effects, 95% CI)	Ratio of GMTs 1.60 (1.22 to 2.10)	⊕⊕⊕⊖ MODERATE[1]
3.4.2 Bivalent vaccine (0 and 6 months) vs (0 and 12 months)	9- to 14-year-old females	1 month after last dose	1 (Puthanakit 2016)	854	Ratio of GMTs (IV, random-effects, 95% CI)	Ratio of GMTs 1.12 (1.01 to 1.25)	⊕⊕⊕⊕ HIGH
3.4.3 Nonavalent vaccine (0 and 6 months) vs (0 and 12 months)	9- to 14-year-old females	1 month after last dose	1 (Iversen 2016)	401	Ratio of GMTs (IV, random-effects, 95% CI)	Ratio of GMTs 1.44 (1.16 to 1.79)	⊕⊕⊕⊕ HIGH
3.4.4 Nonavalent vaccine (0 and 6 months) vs (0 and 12 months)	9- to 14-year-old males	1 month after last dose	1 (Iversen 2016)	409	Ratio of GMTs (IV, random-effects, 95% CI)	Ratio of GMTs 1.57 (1.27 to 1.95)	⊕⊕⊕⊕ HIGH
3.5 GMT of HPV 31 (mMU/mL)							
3.5.1 Nonavalent vaccine (0 and 6 months) vs (0 and 12 months)	9- to 14-year-old females	1 month after last dose	1 (Iversen 2016)	404	Ratio of GMTs (IV, random-effects, 95% CI)	Ratio of GMTs 1.45 (1.18 to 1.79)	⊕⊕⊕⊕ HIGH

(Continued)

3.5.2 Nonavalent vaccine (0 and 6 months) vs (0 and 12 months)	9- to 14-year-old males	1 month after last dose	1 (Iversen 2016)	407	Ratio of GMTs (IV, random-effects, 95% CI)	Ratio of GMTs 1.43 (1.17 to 1.76)	⊕⊕⊕⊕ HIGH
3.6 GMT of HPV 33 (mMU/mL)							
3.6.1 Nonavalent vaccine (0 and 6 months) vs (0 and 12 months)	9- to 14-year-old females	1 month after last dose	1 (Iversen 2016)	405	Ratio of GMTs (IV, random-effects, 95% CI)	Ratio of GMTs 1.98 (1.63 to 2.40)	⊕⊕⊕⊕ HIGH
3.6.2 Nonavalent vaccine (0 and 6 months) vs (0 and 12 months)	9- to 14-year-old males	1 month after last dose	1 (Iversen 2016)	408	Ratio of GMTs (IV, random-effects, 95% CI)	Ratio of GMTs 2.27 (1.87 to 2.76)	⊕⊕⊕⊕ HIGH
3.7 GMT of HPV 45 (mMU/mL)							
3.7.1 Nonavalent vaccine (0 and 6 months) vs (0 and 12 months)	9- to 14-year-old females	1 month after last dose	1 (Iversen 2016)	406	Ratio of GMTs (IV, random-effects, 95% CI)	Ratio of GMTs 1.23 (0.98 to 1.54)	⊕⊕⊕⊕ HIGH
3.7.2 Nonavalent vaccine (0 and 6 months) vs (0 and 12 months)	9- to 14-year-old males	1 month after last dose	1 (Iversen 2016)	409	Ratio of GMTs (IV, random-effects, 95% CI)	Ratio of GMTs 1.13 (0.90 to 1.41)	⊕⊕⊕⊕ HIGH
3.8 GMT of HPV 52 (mMU/mL)							
3.8.1 Nonavalent vaccine (0 and 6 months) vs (0 and 12 months)	9- to 14-year-old females	1 month after last dose	1 (Iversen 2016)	403	Ratio of GMTs (IV, random-effects, 95% CI)	Ratio of GMTs 1.77 (1.47 to 2.13)	⊕⊕⊕⊕ HIGH
3.8.2 Nonavalent vaccine (0 and 6 months) vs (0 and 12 months)	9- to 14-year-old males	1 month after last dose	1 (Iversen 2016)	410	Ratio of GMTs (IV, random-effects, 95% CI)	Ratio of GMTs 1.91 (1.59 to 2.29)	⊕⊕⊕⊕ HIGH

(Continued)

3.9 GMT of HPV 58 (mMU/mL)							
3.9.1 Nonavalent vaccine (0 and 6 months) vs (0 and 12 months)	9- to 14-year-old females	1 month after last dose	1 (Iversen 2016)	399	Ratio of GMTs (IV, random-effects, 95% CI)	Ratio of GMTs 1.79 (1.48 to 2.17)	⊕⊕⊕⊕ HIGH
3.9.2 Nonavalent vaccine (0 and 6 months) vs (0 and 12 months)	9- to 14-year-old males	1 month after last dose	1 (Iversen 2016)	406	Ratio of GMTs (IV, random-effects, 95% CI)	Ratio of GMTs 2.00 (1.66 to 2.41)	⊕⊕⊕⊕ HIGH
3.10 Seroconversion to HPV16	9- to 14-year-old females	1 month after last dose	1 (Puthanakit 2016)	835	RR (M-H, random-effects, 95% CI)	RR 1.00 (1.00 to 1.00)	
3.10.1 Bivalent vaccine (0 and 6 months) vs (0 and 12 months)	9- to 14-year-old females	1 month after last dose	1 (Puthanakit 2016)	835	RR (M-H, random-effects, 95% CI)	RR 1.00 (1.00 to 1.00)	⊕⊕⊕⊕ HIGH
3.11 Seroconversion to HPV 18	9- to 14-year-old females	1 month after last dose	1 (Puthanakit 2016)	854	RR (M-H, random-effects, 95% CI)	RR 1.00 (1.00 to 1.00)	
3.11.1 Bivalent vaccine (0 and 6 months) vs (0 and 12 months)	9- to 14-year-old females	1 month after last dose	1 (Puthanakit 2016)	854	RR (M-H, random-effects, 95% CI)	RR 1.00 (1.00 to 1.00)	⊕⊕⊕⊕ HIGH
3.12 GMT of HPV 6 (mMU/mL)†							
3.12.1 Nonavalent vaccine (0 and 6 months) vs (0 and 12 months)	9- to 14-year-old males and females long interval (0, 12 months)	36 months after first dose	1 (Iversen 2016)	246	Mean GMT (95% CI)	Mean 401.2 (354.8 to 453.7)	
	9- to 14-year-old females short interval (0, 6 months)			236		Mean 209.6 (184.9 to 237.6)	

(Continued)

	9- to 14-year-old males short interval (0, 6 months)			254		Mean 160.1 (141.9 to 180.7)	
3.13 GMT of HPV 11 (mMU/mL)†							
3.13.1 Nonavalent vaccine (0 and 6 months) vs (0 and 12 months)	9- to 14-year-old males and females long interval (0, 12 months)	36 months after first dose	1 (Iversen 2016)	246	Mean GMT (95% CI)	Mean 308.2 (271.8 to 349.6)	
	9- to 14-year-old females short interval (0, 6 months)			236		Mean 133.7 (117.6 to 152.1)	
	9- to 14-year-old males short interval (0, 6 months)			255		Mean 115.2 (101.8 to 130.3)	
3.14 GMT of HPV 16 (mMU/mL)†							
3.14.1 Bivalent vaccine (0 and 6 months) vs (0 and 12 months)	9- to 14-year-old females	36 months after first dose	1 (Puthanakit 2016)	817	Ratio of GMTs (IV, random-effects, 95% CI)	Ratio of GMTs 1.29 (1.15 to 1.44)	⊕⊕⊕⊕ HIGH
3.14.3 Nonavalent vaccine (0 and 6 months) vs (0 and 12 months)	9- to 14-year-old males and females long interval (0, 12 months)	36 months after first dose	1 (Iversen 2016)	253	Mean GMT (95% CI)	Mean 1534.3 (1328.8 to 1771.5)	
	9- to 14-year-old females short interval (0, 6 months)			263		Mean 673.8 (582.8 to 779.1)	
	9- to 14-year-old males short interval (0, 6 months)			248		Mean 592.6 (514.7 to 682.4)	
3.15 GMT of HPV 18 (mMU/mL)†							
3.15.1 Bivalent vaccine (0 and 6 months) vs (0 and 12 months)	9- to 14-year-old females	36 months after first dose	1 (Puthanakit 2016)	794	Ratio of GMTs (IV, random-effects, 95% CI)	Ratio of GMTs 1.43 (1.26 to 1.62)	⊕⊕⊕⊕ HIGH
3.15.3 Nonavalent vaccine (0 and 6 months) vs (0 and 12 months)	9-14 year old males and females long interval (0, 12 months)	36 months after first dose	1 (Iversen 2016)	255	Mean GMT (95% CI)	Mean 276.4 (245.3 to 311.6)	

(Continued)

	9- to 14-year-old females short interval (0, 6 months)			248		Mean 158.9 (140.8 to 179.4)
	9- to 14-year-old males short interval (0, 6 months)			262		Mean 141.7 (125.9 to 159.4)
3.16 GMT of HPV 31 (mMU/mL)†						
3.16.1 Nonavalent vaccine (0 and 6 months) vs (0 and 12 months)	9- to 14-year-old males and females long interval (0, 12 months)	36 months after first dose	1 (Iversen 2016)	257	Mean GMT (95% CI)	Mean 218.0 (190.6 to 249.4)
	9- to 14-year-old females short interval (0, 6 months)			248		Mean 127.8 (111.4 to 146.5)
	9- to 14-year-old males short interval (0, 6 months)			261		Mean 106.9 (93.5 to 122.1)
3.17 GMT of HPV 33 (mMU/mL)†						
3.17.1 Nonavalent vaccine (0 and 6 months) vs (0 and 12 months)	9- to 14-year-old males and females long interval (0, 12 months)	36 months after first dose	1 (Iversen 2016)	258	Mean GMT (95% CI)	Mean 240.4 (213.8 to 270.3)
	9- to 14-year-old females short interval (0, 6 months)			249		Mean 106.0 (94.1 to 119.5)
	9- to 14-year-old males short interval (0, 6 months)			261		Mean 95.7 (85.1 to 107.5)
3.18 GMT of HPV 45 (mMU/mL)†						
3.18.1 Nonavalent vaccine (0 and 6 months) vs (0 and 12 months)	9- to 14-year-old males and females long interval (0, 12 months)	36 months after first dose	1 (Iversen 2016)	257	Mean GMT (95% CI)	Mean 43.6 (38.3 to 49.7)
	9- to 14-year-old females short interval (0, 6 months)			250		Mean 30.6 (26.9 to 35.0)
	9- to 14-year-old males short interval (0, 6 months)			263		Mean 26.8 (23.6 to 30.4)

(Continued)

3.19 GMT of HPV 52 (mMU/mL)†						
3.19.1 Nonavalent vaccine (0 and 6 months) vs (0 and 12 months)	9- to 14-year-old males and females long interval (0, 12 months)	36 months after first dose	1 (Iversen 2016)	257	Mean GMT (95% CI)	Mean 143.2 (128.3 to 159.9)
	9- to 14-year-old females short interval (0, 6 months)			248		Mean 66.2 (59.1 to 74.0)
	9- to 14-year-old males short interval (0, 6 months)			263		Mean 63.4 (56.8 to 70.7)
3.20 GMT of HPV 58 (mMU/mL)†						
3.20.1 Nonavalent vaccine (0 and 6 months) vs (0 and 12 months)	9- to 14-year-old males and females long interval (0, 12 months)	36 months after first dose	1 (Iversen 2016)	255	Mean GMT (95% CI)	Mean 265.3 (234.8 to 299.8)
	9- to 14-year-old females short interval (0, 6 months)			246		Mean 125.8 (111.1 to 142.5)
	9- to 14-year-old males short interval (0, 6 months)			261		Mean 119.2 (105.6 to 134.5)

*Results were stratified into subgroups by type of HPV vaccine, gender, schedule, and time point

†Data for nonavalent vaccine at 36 month follow-up (Iversen 2016) was not disaggregated for gender, therefore only mean values (95% CI) are presented per group.

[1]Downgraded one level for imprecision: small sample size

Abbreviations

CI: confidence interval
EU: enzyme-linked immunosorbent assay (ELISA) unit
GMT: geometric mean titre
HPV: human papillomavirus
IV: inverse variance
M-H: Mantel-Haenszel
RR: risk ratio
mMU: milli-Merck unit

Appendix 7. Summary of findings: Longer interval versus shorter interval between second and third doses of quadrivalent HPV vaccine in 18- to 25-year-old males

Patient or population: 18- to 25-year-old males

Settings: community health centres in the USA

Intervention: quadrivalent HPV vaccine (3 doses at 0, 2 and 6 months)

Comparison: quadrivalent HPV vaccine (3 doses at 0, 2 and 12 months)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)
	Risk with longer interval	Risk with shorter interval			
Invasive anal or penile cancer	No studies were identified that reported on this outcome				
Penile or anal intraepithelial neoplasia	No studies were identified that reported on this outcome				
External genital lesions (any genotype)	No studies were identified that reported on this outcome				
Overall local/injection site adverse events	Adverse events data not reported separately for each arm				
Overall systemic events and general symptoms	Adverse events data not reported separately for each arm				
Serious adverse events at 13-month follow-up	0 per 1000	0 per 1000	Not estimable, no events were reported	220 (1 study)	⊕⊖⊖⊖ VERY LOW[1,2,3]
Mortality	No studies were identified that reported on this outcome				

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

(Continued)

CI: confidence interval; **HPV:** human papillomavirus

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

Footnotes

[1]Downgraded one level for risk of bias: allocation concealment was not reported and the trial was open label.

[2]Downgraded two levels for serious imprecision: no events reported, the study was not powered to detect a difference in serious adverse events.

[3]Downgraded one level for indirectness: This outcome is a composite measure of events which may or may not be clinically relevant, may or may not be related to the vaccine and may occur outside a biologically plausible time frame relative to vaccine exposure. This outcome is considered to provide indirect evidence about vaccine safety.

Appendix 8. Three doses of HPV vaccine with shorter interval versus three doses of HPV vaccine with longer interval in 18- to 25-year-old males - immunogenicity outcomes

Outcome	Follow-up	Studies	Participants	Statistical method	Effect estimate (95% CI)
7.1 GMT of HPV 6	1 month after last dose	1 (Lin 2014)	170	Ratio of GMTs (IV, random-effects, 95% CI)	Ratio of GMTs 1.31 (0.88 to 1.96)
7.2 GMT of HPV 11	1 month after last dose	1 (Lin 2014)	172	Ratio of GMTs (IV, random-effects, 95% CI)	Ratio of GMTs 1.83 (1.18 to 2.84)
7.3 GMT of HPV 16	1 month after last dose	1 (Lin 2014)	173	Ratio of GMTs (IV, random-effects, 95% CI)	Ratio of GMTs 1.32 (0.90 to 1.93)
7.4 GMT of HPV 18	1 month after last dose	1 (Lin 2014)	174	Ratio of GMTs (IV, random-effects, 95% CI)	Ratio of GMTs 1.35 (0.65 to 2.78)

Abbreviations

CI: confidence interval
GMT: geometric mean titre
HPV: human papillomavirus
IV: inverse variance

Appendix 9. Quadrivalent HPV vaccine compared to control in 16- to 26-year old males - secondary outcomes

Outcome	Studies	Participants	Statistical method	Effect estimate (95% CI)

(Continued)

4.1 Persistent infection of HPV 6, 11, 16, or 18	1 (Giuliano 2011)	2790	Rate ratio (IV, random-effects, 95% CI)	Rate ratio 0.14 (0.08 to 0.26)
4.2 Persistent infection of HPV 6, 11, 16, or 18	1 (NCT01862874 2018)	995	Rate ratio (IV, random-effects, 95% CI)	Rate ratio 0.14 (0.04 to 0.47)
4.3 Combined persistent HPV type 6-, 11-, 16-, or 18-related infection or disease (HPV type 6, 11, 16, or 18-related condyloma acuminate, penile, perianal, or perineal intraepithelial neoplasia or cancer)	1 (NCT01862874 2018)	996	Rate ratio (IV, random-effects, 95% CI)	Rate ratio 0.13 (0.04 to 0.45)

Abbreviations

CI: confidence interval
HPV: human papillomavirus
IV: inverse variance

Appendix 10. Bivalent HPV vaccine versus control vaccine in 10- to 18-year-old males - immunogenicity outcomes

Outcome	Follow-up	Studies	Participants	Statistical method	Effect estimate (95% CI)
5.1 Seroconversion to HPV 16	1 month after last dose	1 (Petaja 2009)	10- to 18-year-old males	RR (M-H, random-effects, 95% CI)	RR 55.83 (11.43 to 272.67)
5.2 Seroconversion to HPV 18	1 month after last dose	1 (Petaja 2009)	10- to 18-year-old males	RR (M-H, random-effects, 95% CI)	RR 34.68 (10.22 to 117.68)
5.3 GMT of HPV 16	1 month after last dose	1 (Petaja 2009)	10- to 18-year-old males	SMD (IV, random-effects, 95% CI)	SMD 1.50 (1.21 to 1.79)
5.4 GMT of HPV 18	1 month after last dose	1 (Petaja 2009)	10- to 18-year-old males	SMD (IV, random-effects, 95% CI)	SMD 1.36 (1.07 to 1.64)

Abbreviations

CI: confidence interval
GMT: geometric mean titre
HPV: human papillomavirus
IV: inverse variance
M-H: Mantel-Haenszel
RR: risk ratio
SMD: standard mean difference

Appendix 11. Nonavalent HPV vaccine versus quadrivalent HPV vaccine in females - secondary outcomes

Outcome or subgroup*	Follow-up	Studies	Participants	Statistical method	Effect estimate (95% CI)

(Continued)

2.1 GMT of HPV 6 (mMU/mL)					
2.1.1 9- to 15-year olds	1 month after last dose	1 (Vesikari 2015)	534	Ratio of GMTs (IV, random-effects, 95% CI)	Ratio of GMTs 1.07 (0.93 to 1.24)
2.1.2 16- to 26-year olds	1 month after last dose	1 (Joura 2015)	7968	Ratio of GMTs (IV, random-effects, 95% CI)	Ratio of GMTs 1.02 (0.99 to 1.06)
2.2 GMT of HPV 11 (mMU/mL)					
2.2.1 9- to 15-year olds	1 month after last dose	1 (Vesikari 2015)	534	Ratio of GMTs (IV, random-effects, 95% CI)	Ratio of GMTs 0.93 (0.80 to 1.08)
2.2.2 16- to 26-year olds	1 month after last dose	1 (Joura 2015)	7977	Ratio of GMTs (IV, random-effects, 95% CI)	Ratio of GMTs 0.80 (0.77 to 0.83)
2.3 GMT of HPV 16 (mMU/mL)					
2.3.1 9- to 15-year olds	1 month after last dose	1 (Vesikari 2015)	546	Ratio of GMTs (IV, random-effects, 95% CI)	Ratio of GMTs 0.98 (0.85 to 1.12)
2.3.2 16- to 26-year olds	1 month after last dose	1 (Joura 2015)	8094	Ratio of GMTs (IV, random-effects, 95% CI)	Ratio of GMTs 0.99 (0.96 to 1.03)
2.4 GMT of HPV 18 (mMU/mL)					
2.4.1 9- to 15-year olds	1 month after last dose	1 (Vesikari 2015)	545	Ratio of GMTs (IV, random-effects, 95% CI)	Ratio of GMTs 1.09 (0.91 to 1.31)
2.4.2 16- to 26-year olds	1 month after last dose	1 (Joura 2015)	9080	Ratio of GMTs (IV, random-effects, 95% CI)	Ratio of GMTs 1.19 (1.14 to 1.23)
2.5 Seroconversion to HPV 6	1 month after last dose	2 (Joura 2015; Vesikari 2015)	8502	RR (M-H, random-effects, 95% CI)	RR 1.00 (1.00 to 1.00)
2.5.1 9- to 15-year olds	1 month after last dose	1 (Vesikari 2015)	534	RR (M-H, random-effects, 95% CI)	RR 1.00 (0.99 to 1.01)
2.5.2 16- to 26-year olds	1 month after last dose	1 (Joura 2015)	7968	RR (M-H, random-effects, 95% CI)	RR 1.00 (1.00 to 1.00)
2.6 Seroconversion to HPV 11	1 month after last dose	2 (Joura 2015; Vesikari 2015)	8511	RR (M-H, random-effects, 95% CI)	RR 1.00 (1.00 to 1.00)
2.6.1 9- to 15-year olds	1 month after last dose	1 (Vesikari 2015)	534	RR (M-H, random-effects, 95% CI)	RR 1.00 (0.99 to 1.01)

(Continued)

2.6.2 16- to 26-year olds	1 month after last dose	1 (Joura 2015)	7977	RR (M-H, random-effects, 95% CI)	RR 1.00 (1.00 to 1.00)
2.7 Seroconversion to HPV 16	1 month after last dose	2 (Joura 2015; Vesikari 2015)	8640	RR (M-H, random-effects, 95% CI)	RR 1.00 (1.00 to 1.00)
2.7.1 9- to 15-year olds	1 month after last dose	1 (Vesikari 2015)	546	RR (M-H, random-effects, 95% CI)	RR 1.00 (0.99 to 1.01)
2.7.2 16- to 26-year olds	1 month after last dose	1 (Joura 2015)	8094	RR (M-H, random-effects, 95% CI)	RR 1.00 (1.00 to 1.00)
2.8 Seroconversion to HPV 18	1 month after last dose	2 (Vesikari 2015; Joura 2015)	9625	RR (M-H, random-effects, 95% CI)	RR 1.00 (1.00 to 1.00)
2.8.1 9- to 15-year olds	1 month after last dose	1 (Vesikari 2015)	545	RR (M-H, random-effects, 95% CI)	RR 1.00 (0.99 to 1.01)
2.8.2 16- to 26-year olds	1 month after last dose	1 (Joura 2015)	9080	RR (M-H, random-effects, 95% CI)	RR 1.00 (1.00 to 1.00)
2.9 GMT of HPV 6 (mMU/mL)					
2.9.1 16- to 26-year olds	42 months after first dose	1 (Joura 2015)	1367	Ratio of GMTs (IV, random-effects, 95% CI)	Ratio of GMTs 1.02 (0.92 to 1.13)
2.10 GMT of HPV 11 (mMU/mL)					
2.10.1 16- to 26-year olds	42 months after first dose	1 (Joura 2015)	1367	Ratio of GMTs (IV, random-effects, 95% CI)	Ratio of GMTs 0.82 (0.74 to 0.90)
2.11 GMT of HPV 16 (mMU/mL)					
2.11.1 16- to 26-year olds	42 months after first dose	1 (Joura 2015)	1399	Ratio of GMTs (IV, random-effects, 95% CI)	Ratio of GMTs 0.96 (0.85 to 1.07)
2.12 GMT of HPV 18 (mMU/mL)					
2.12.1 16- to 26-year olds	42 months after first dose	1 (Joura 2015)	1576	Ratio of GMTs (IV, random-effects, 95% CI)	Ratio of GMTs 1.17 (1.03 to 1.33)
2.13 Seropositivity to HPV 6					
2.13.1 16- to 26-year olds	24 months after first dose	1 (Joura 2015)	1404	RR (M-H, random-effects, 95% CI)	RR 1.01 (0.99 to 1.02)

(Continued)

2.14 Seropositivity to HPV 11					
2.14.1 16- to 26-year olds	24 months after first dose	1 (Joura 2015)	1497	RR (M-H, random-effects, 95% CI)	RR 1.00 (0.99 to 1.01)
2.15 Seropositivity to HPV 16					
2.15.1 16- to 26-year olds	24 months after first dose	1 (Joura 2015)	1536	RR (M-H, random-effects, 95% CI)	RR 1.01 (1.00 to 1.01)
2.16 Seropositivity to HPV 18					
2.16.1 16- to 26-year olds	24 months after first dose	1 (Joura 2015)	1732	RR (M-H, random-effects, 95% CI)	RR 1.07 (1.02 to 1.11)
2.17 6 months' persistent infection of HPV 6, 11, 16, or 18	median 4 years	1 (Joura 2015)	11,642	RR (M-H, random-effects, 95% CI)	RR 0.72 (0.53 to 0.98)
2.18 6 months' persistent infection of HPV 31, 33, 45, 52, or 58	median 4 years	1 (Joura 2015)	11,896	RR (M-H, random-effects, 95% CI)	RR 0.04 (0.03 to 0.06)
2.19 12 months' persistent infection of HPV 6, 11, 16, or 18	median 4 years	1 (Joura 2015)	11,642	RR (M-H, random-effects, 95% CI)	RR 0.72 (0.43 to 1.20)
2.20 12 months' persistent infection of HPV 31, 33, 45, 52, or 58	median 4 years	1 (Joura 2015)	11,896	RR (M-H, random-effects, 95% CI)	RR 0.04 (0.02 to 0.05)

*Results were stratified into subgroups by age group

Abbreviations

CI: confidence interval
GMT: geometric mean titre
HPV: human papillomavirus
IV: inverse variance
M-H: Mantel-Haenszel
RR: risk ratio
mMU: milli-Merck unit

Appendix 12. Nonavalent HPV vaccine versus quadrivalent HPV vaccine in males - secondary outcomes

Outcome	Follow-up	Studies	Participants	Statistical method	Effect estimate (95% CI)
6.1 GMT of HPV 6	1 month after last dose	1 (van Damme 2016)	454	Ratio of GMTs (IV, random-effects, 95% CI)	Ratio of GMTs 1.23 (1.03 to 1.45)

(Continued)

6.2 GMT of HPV 11	1 month after last dose	1 (van Damme 2016)	454	Ratio of GMTs (IV, random-effects, 95% CI)	Ratio of GMTs 0.89 (0.75 to 1.04)
6.3 GMT of HPV 16	1 month after last dose	1 (van Damme 2016)	471	Ratio of GMTs (IV, random-effects, 95% CI)	Ratio of GMTs 1.04 (0.88 to 1.21)
6.4 GMT of HPV 18	1 month after last dose	1 (van Damme 2016)	470	Ratio of GMTs (IV, random-effects, 95% CI)	Ratio of GMTs 1.12 (0.91 to 1.37)
6.5 GMT of HPV 31	1 month after last dose	1 (van Damme 2016)	471	Ratio of GMTs (IV, random-effects, 95% CI)	Ratio of GMTs 52.96 (42.69 to 65.71)
6.6 GMT of HPV 33	1 month after last dose	1 (van Damme 2016)	472	Ratio of GMTs (IV, random-effects, 95% CI)	Ratio of GMTs 135.44 (117.18 to 156.54)
6.7 GMT of HPV 45	1 month after last dose	1 (van Damme 2016)	468	Ratio of GMTs (IV, random-effects, 95% CI)	Ratio of GMTs 105.16 (887.87 to 125.85)
6.8 GMT of HPV 52	1 month after last dose	1 (van Damme 2016)	471	Ratio of GMTs (IV, random-effects, 95% CI)	Ratio of GMTs 226.68 (194.71 to 263.90)
6.9 GMT of HPV 58	1 month after last dose	1 (van Damme 2016)	465	Ratio of GMTs (IV, random-effects, 95% CI)	Ratio of GMTs 121.23 (101.71 to 144.49)
6.10 Seroconversion to HPV 6	1 month after last dose	1 (van Damme 2016)	454	RR (M-H, random-effects, 95% CI)	RR 1.00 (0.97 to 1.02)
6.11 Seroconversion to HPV 11	1 month after last dose	1 (van Damme 2016)	454	RR (M-H, random-effects, 95% CI)	RR 1.00 (0.99 to 1.01)
6.12 Seroconversion to HPV 16	1 month after last dose	1 (van Damme 2016)	471	RR (M-H, random-effects, 95% CI)	RR 1.00 (0.99 to 1.01)
6.13 Seroconversion to HPV 18	1 month after last dose	1 (van Damme 2016)	470	RR (M-H, random-effects, 95% CI)	RR 1.00 (0.99 to 1.01)
6.14 Seroconversion to HPV 31	1 month after last dose	1 (van Damme 2016)	471	RR (M-H, random-effects, 95% CI)	RR 1.62 (1.47 to 1.79)
6.15 Seroconversion to HPV 33	1 month after last dose	1 (van Damme 2016)	472	RR (M-H, random-effects, 95% CI)	RR 5.84 (4.41 to 7.73)
6.16 Seroconversion to HPV 45	1 month after last dose	1 (van Damme 2016)	468	RR (M-H, random-effects, 95% CI)	RR 10.51 (7.09 to 15.57)
6.17 Seroconversion to HPV 52	1 month after last dose	1 (van Damme 2016)	471	RR (M-H, random-effects, 95% CI)	RR 36.38 (17.05 to 77.66)
6.18 Seroconversion to HPV 58	1 month after last dose	1 (van Damme 2016)	465	RR (M-H, random-effects, 95% CI)	RR 2.76 (2.33 to 3.28)

Abbreviations

CI: confidence interval

GMT: geometric mean titre
HPV: human papillomavirus
IV: inverse variance
M-H: Mantel-Haenszel
RR: risk ratio

Appendix 13. HPV vaccines for people living with HIV - secondary outcomes

Outcome	Follow-up	Studies	Participants	Statistical method	Effect estimate (95% CI)	Certainty of the evidence (GRADE)
8.1 GMT of HPV 6	1 month after last dose	1 (Levin 2010) quadrivalent	114 children with HIV (7 to 12 years old)	Ratio of GMTs (IV, random-effects, 95% CI)	Ratio of GMTs 123.8 (89.0 to 172.1)	⊕⊕⊖⊖ LOW[1,2]
	24 months after first dose	1 (Levin 2010)	116 children with HIV (7 to 12 years old)	Ratio of GMTs (IV, random-effects, 95% CI)	Ratio of GMTs 50.44 (34.21 to 74.38)	
8.2 GMT of HPV 11	1 month after last dose	1 (Levin 2010)	117 children with HIV (7 to 12 years old)	Ratio of GMTs (IV, random-effects, 95% CI)	Ratio of GMTs 330.4 (261.6 to 417.2)	⊕⊕⊖⊖ LOW[1,2]
	24 months after first dose	1 (Levin 2010)	116 children with HIV (7 to 12 years old)	Ratio of GMTs (IV, random-effects, 95% CI)	Ratio of GMTs 68.75 (49.33 to 95.81)	
8.3 GMT of HPV 16	1 month after last dose	1 (Levin 2010)	117 children with HIV (7 to 12 years old)	Ratio of GMTs (IV, random-effects, 95% CI)	Ratio of GMTs 935.8 (724.5 to 1208.7)	⊕⊕⊖⊖ LOW[1,2]
	24 months after first dose	1 (Levin 2010)	116 children with HIV (7 to 12 years old)	Ratio of GMTs (IV, random-effects, 95% CI)	Ratio of GMTs 189.44 (129.29 to 277.59)	
8.4 GMT of HPV 18	1 month after last dose	1 (Levin 2010)	117 children with HIV (7 to 12 years old)	Ratio of GMTs (IV, random-effects, 95% CI)	Ratio of GMTs 189.2 (132.8 to 269.7)	⊕⊕⊖⊖ LOW[1,2]
	24 months after first dose	1 (Levin 2010)	116 children with HIV (7 to 12 years old)	Ratio of GMTs (IV, random-effects, 95% CI)	Ratio of GMTs 29.57 (18.08 to 48.37)	
8.5 Seroconversion to HPV 6	1 month after last dose	1 (Levin 2010)	114 children with HIV (7 to 12 years old)	RR (M-H, random-effects, 95% CI)	RR 55.7 (3.6 to 868.4)	⊕⊕⊖⊖ LOW[1,2]
8.6 Seroconversion to HPV 11	1 month after last dose	1 (Levin 2010)	117 children with HIV (7 to 12 years old)	RR (M-H, random-effects, 95% CI)	RR 55.7 (3.6 to 868.6)	⊕⊕⊖⊖ LOW[1,2]
8.7 Seroconversion to HPV 16	1 month after last dose	1 (Levin 2010)	117 children with HIV (7 to 12 years old)	RR (M-H, random-effects, 95% CI)	RR 18.6 (3.9 to 88.1)	⊕⊕⊖⊖ LOW[1,2]

(Continued)

8.8 Seroconversion to HPV 18	1 month after last dose	1 (Levin 2010)	117 children with HIV (7 to 12 years old)	RR (M-H, random-effects, 95% CI)	RR 53.9 (3.5 to 840.0)	⊕⊕⊖⊖ LOW[1,2]
8.9 Seropositivity, HPV 6, 11, 16, 18	1 month after last dose	1 (Hidalgo-Tenorio 2017)	128 HIV-infected MSM (≥ 18 years old)	RR (M-H, random-effects, 95% CI)	RR 2.47 (1.66 to 3.68)	⊕⊕⊕⊖ MODERATE[1]
8.10 GMT of HPV 16	1 month after last dose	1 (Toft 2014)	40 HIV-infected males and females	Ratio of GMTs (IV, random-effects, 95% CI)	Ratio of GMTs 0.79 (0.25 to 2.52)	⊕⊕⊖⊖ LOW[3]
	6 months after last dose	1 (Toft 2014)	40 HIV-infected males and females	Ratio of GMTs (IV, random-effects, 95% CI)	Ratio of GMTs 0.67 (0.21 to 2.08)	⊕⊕⊖⊖ LOW[3]
8.11 GMT of HPV 18	1 month after last dose	1 (Toft 2014)	39 HIV-infected males and females	Ratio of GMTs (IV, random-effects, 95% CI)	Ratio of GMTs 0.13 (0.04 to 0.41)	⊕⊕⊕⊖ MODERATE[1]
	six months after last dose	1 (Toft 2014)	39 HIV-infected males and females	Ratio of GMTs (IV, random-effects, 95% CI)	Ratio of GMTs 0.52 (0.16 to 1.76)	⊕⊕⊖⊖ LOW[3]
8.12 Seropositivity at 12 months, HPV 16	6 months after last dose	1 (Toft 2014)	91 HIV-infected males and females	RR (M-H, random-effects, 95% CI)	RR 0.96 (0.89 to 1.03)	⊕⊕⊕⊖ MODERATE[1]
8.13 Seropositivity at 12 months, HPV 18	6 months after last dose	1 (Toft 2014)	91 HIV-infected males and females	RR (M-H, random-effects, 95% CI)	RR 0.76 (0.63 to 0.90)	⊕⊕⊕⊖ MODERATE[1]
8.14 Persistent anal infection (HPV 6, 11, 16, 18)	1 month after last dose	1 (Wilkin 2018)	575 HIV-positive males and females	RR (M-H, random-effects, 95% CI)	RR 0.81 (0.41 to 1.62)	⊕⊕⊕⊖ MODERATE[4]
8.16 GMT of HPV 16	1 month after last dose	1 (Denny 2013)	82 HIV-positive females	Ratio of GMTs (IV, random-effects, 95% CI)	Ratio of GMTs 131.73 (80.57 to 215.39)	⊕⊕⊕⊖ MODERATE[1]
	12 months after first dose	1 (Denny 2013)	78 HIV-positive females	Ratio of GMTs (IV, random-effects, 95% CI)	Ratio of GMTs 36.14 (21.42 to 60.97)	
8.17 GMT of HPV 18	1 month after last dose	1 (Denny 2013)	83 HIV-positive females	Ratio of GMTs (IV, random-effects, 95% CI)	Ratio of GMTs 134.63 (79.88 to 226.89)	⊕⊕⊕⊖ MODERATE[1]
	12 months after first dose	1 (Denny 2013)	79 HIV-positive females	Ratio of GMTs (IV, random-effects, 95% CI)	Ratio of GMTs 26.39 (15.32 to 45.48)	

(Continued)

8.18 Seroconversion to HPV 16	12 months after first dose	1 (Denny 2013)	79 HIV-positive females	RR (M-H, random-effects, 95% CI)	RR 1.29 (1.07 to 1.56)	⊕⊕⊕⊖ MODERATE[1]
8.19 Seroconversion to HPV 18	12 months after first dose	1 (Denny 2013)	79 HIV-positive females	RR (M-H, random-effects, 95% CI)	RR 1.53 (1.21 to 1.95)	⊕⊕⊕⊖ MODERATE[1]

*Results were stratified into subgroups by type of HPV vaccine and gender

[1]Downgraded one level for imprecision: small sample size.

[2]Downgraded one level for risk of bias: details about how randomisation sequence was generated or how blinding was achieved were not reported.

[3]Downgraded two levels for imprecision: small sample size and very wide 95% confidence interval that incorporates a potential large beneficial effect and a potential large harmful effect.

[4]Downgraded one level for imprecision: wide 95% confidence interval that incorporates a potential beneficial effect and a potential harmful effect.

Abbreviations

CI: confidence interval
GMT: geometric mean titre
HPV: human papillomavirus
IV: inverse variance
M-H: Mantel-Haenszel
RR: risk ratio

Appendix 14. Sensitivity analysis using Peto odds ratio for outcomes with very rare events

Analysis number, outcome (subgroup)	Studies	Participants	Odds ratio (M-H, random-effects model, 95% CI)	Peto odds ratio (Peto, fixed-effect model, 95% CI)
1.5.3 Deaths (nonavalent vaccine)	1	602	0.33 (0.01 to 8.19)	0.14 (0.00 to 6.82)
4.12 Serious adverse events (overall)	2	5162	0.69 (0.29 to 1.66)	0.67 (0.28 to 1.62)
4.13 Deaths	2	5173	0.30 (0.09 to 1.01)	0.32 (0.11 to 0.91)
6.2 High-grade cervical disease related to HPV 6 to 11, 16, or 18	1	11,656	1.00 (0.06 to 16.01)	1.00 (0.06 to 16.01)
6.3 High-grade vulval and vaginal disease related to HPV 6, 11, 16, or 18	1	11,769	0.14 (0.01 to 2.77)	0.14 (0.01 to 1.30)
6.4 High-grade cervical disease related to HPV 31, 33, 45, 52, or 58	1	11,892	0.03 (0.00 to 0.21)	0.15 (0.08 to 0.29)
6.5 High-grade vulval and vaginal disease related to HPV 31, 33, 45, 52, or 58	1	12,021	0.14 (0.01 to 2.77)	0.14 (0.01 to 1.30)

(Continued)

6.7 Cervical intraepithelial neoplasia 2 related to HPV 6, 11, 16, or 18	1	11,656	3.00 (0.12 to 73.77)	7.40 (0.15 to 373.90)
6.8 Cervical intraepithelial neoplasia 2 related to HPV 31, 33, 45, 52, or 58	1	11,892	0.03 (0.00 to 0.23)	0.15 (0.08 to 0.30)
6.9 Cervical intraepithelial neoplasia 3, adenocarcinoma in situ, and cervical cancer related to HPV 6, 11, 16, or 18	1	11,656	0.33 (0.01 to 8.19)	0.14 (0.00 to 6.83)
6.10 Cervical intraepithelial neoplasia 3, adenocarcinoma in situ, and cervical cancer related to HPV 31, 33, 45, 52, or 58	1	11,892	0.07 (0.00 to 1.16)	0.14 (0.03 to 0.59)
6.17.2 Deaths (16- to 26- year olds)	1	14,149	1.00 (0.29 to 3.46)	1.00 (0.29 to 3.46)
8.2 Overall systemic events and general symptoms	1	126	0.62 (0.05 to 7.05)	0.59 (0.04 to 8.54)

Abbreviations

CI: confidence interval
HPV: human papillomavirus
M-H: Mantel-Haenszel

CONTRIBUTIONS OF AUTHORS

HB, NH, BSB, GV, JP, CG, and AXRB were involved in the conception and design of the protocol for this review. VL designed and ran the electronic database searches. HB, NH, BSB, GV, and JP were involved in screening abstracts and full-texts, data extraction and analysis. NH and HB drafted the review manuscript with assistance from NL. BSB, GV, JP, CG, AXRB, and NL provided critical input into the interpretation and intellectual content of the review. All authors read and approved the final version of the review.

DECLARATIONS OF INTEREST

None of the authors have a conflict of interest in relation to this review.

Cochrane Response, which is an evidence consultancy operated by The Cochrane Collaboration, was commissioned to perform part of this review for the WHO Initiative for Vaccine Research.

Hanna Bergman: HB works for Cochrane Response, an evidence services unit operated by the Cochrane Collaboration, and was paid by Cochrane Response for contributing to this review.

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Vittoria Lutje: VL works as an independent consultant conducting literature searches for various research groups. None of them has any potential relevance to the submitted work.

Alina Ximena Riveros-Balta: AXRB is an employee of the WHO Initiative for Vaccine Research, which commissioned the review.

Nicola Low: NL was the principal author of the original systematic review of alternative HPV vaccination schedules (D'Addario 2017), which was commissioned by the WHO Initiative for Vaccine Research.

Nicholas Henschke: NH works for Cochrane Response, an evidence services unit operated by Cochrane, and was paid by Cochrane Response for contributing to this review.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The original protocol of this review was developed to match the needs of the WHO Initiative for Vaccine Research, and a number of comparisons investigated were not included in the current review.

The protocol did not include adverse events as outcomes, these were extracted and included in this version of the review. In addition, for this version of the review, immunogenicity outcomes were considered as secondary outcomes and included only as Appendices. The outcome of histologically confirmed high-grade disease was amended for males, to include all clinical outcomes.

We did not plan to assess the impact of statistical method to calculate odds ratios for very rare events in the protocol. We decided to assess the robustness of our analyses for very rare events (rates less than 1%) in view of the alternative statistical methods that can be used in this scenario (Bradburn 2007).

The following comparisons, for non-randomised immuno-bridging studies were included in the original protocol, but were not reported in the current review:

- fewer than three doses in adolescent girls (9 to 14 years) versus three doses in young women (15 to 26 years), using the same vaccine and the same dosage (three-dose arm using the WHO recommended schedule);
- one dose in adolescent girls (9 to 14 years) versus two doses in young women (15 to 26 years), using the same vaccine and the same dosage;
- males versus the same HPV vaccine type in females;
- any HPV vaccine type in men who have sex with men (MSM) versus the same vaccine type in females or heterosexual males;
- any HPV vaccine type in people with HIV infection compared with people without HIV infection.