Two doses HPV vaccine compared with placebo, no vaccine, or three doses in females and males who received their first dose aged 15 to 18 years

Contents

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Key findings

One RCT conducted in Canada and Germany, one post-hoc analysis of an RCT in India, and four observational studies conducted in Denmark and the USA, reported on the effect of two doses of the quadrivalent HPV vaccine in females and males that received a first dose at age 15 to 18 years. No evidence on the nonavalent vaccine were identified for two doses HPV vaccine in this specific age group.

Two doses quadrivalent HPV vaccine versus no vaccine

In females aged 15 to 18 years when receiving the first dose

- two doses may result in fewer incident HPV infections and anogenital warts than no vaccine (low-certainty evidence)
- the effect on persistent HPV infections or abnormal cervical cytology was inconclusive (very low-certainty evidence).

Two doses versus three doses bivalent HPV vaccine

In females aged 15 to 19 years when receiving the first dose

- two doses were non-inferior to three doses for GMT of HPV 18; non-inferiority was inconclusive for GMT of HPV 16 at one month after the last dose (moderate-certainty evidence).

Two doses versus three doses quadrivalent HPV vaccine

In females aged 15 to 18 years when receiving the first dose

- two doses were non-inferior to three doses for GMTs of HPV 6, 11, 16, and 18 (low-certainty evidence);
- the effects on CIN1, CIN2, CIN3, abnormal cervical cytology, anogenital warts, and HPV infections were inconclusive (very low-certainty evidence)

Abstract

Background

Human papillomavirus (HPV) is the most common viral infection of the reproductive tract and causes a range of conditions in females and males, including precancerous lesions that may progress to cancer. A two-dose schedule is currently recommended for adolescents aged 9-14 years. It is currently unclear whether a two-dose recommendation could be extended to older adolescents (15 to 18 years old), where currently a three-dose schedule is recommended.

Objectives

To assess the evidence on HPV vaccine effectiveness of two doses in females and males receiving their first dose at age 15 to 18 years.

Search methods

A previous review performed by Cochrane Response in 2018 was updated. Searches were conducted for this update from August 2018 to February 2019, and all relevant studies regardless of language or publication status were screened. The following databases were searched: Cochrane Central Register of Controlled Trials (CENTRAL), published in The Cochrane Library; MEDLINE (PubMed); EMBASE (OVID). In addition, the WHO International Clinical Trials Registry Platform and ClinicalTrials.gov were searched to identify ongoing trials and the reference lists of relevant systematic reviews published within the search dates were screened. The vaccine manufacturers were contacted for any potentially relevant studies through the WHO Initiative for Vaccines Research Department (IVR).

Selection criteria

Randomised controlled trials (RCTs) and comparative observational studies were eligible for inclusion. The studies in this document focus on the comparisons of two doses compared with placebo, no vaccine, or three doses in males and females receiving their first dose at age 15 to 18 years.

Data collection and analysis

Two review authors independently assessed trial eligibility and risk of bias and extracted data. For RCTs, the risk of bias was assessed using the Cochrane Risk of Bias tool, and the ROBINS-I tool was used for observational studies. Risk ratios (RR) with 95% confidence intervals (CI) were calculated for dichotomous outcomes. For continuous geometric mean titre (GMT) data, ratios of GMTs with 95% confidence intervals were calculated. For observational studies, where data permitted, adjusted hazard ratios with 95% CIs were expressed on a logarithmic scale with standard errors and combined using generic inverse variance random effects. When data could not be pooled, results are reported narratively. Non-inferiority for GMT ratios was demonstrated if the lower bound of the 95% CI was greater than 0.5.

Main Results

One RCT evaluating the bivalent vaccine in 15-19-year-old females was included (Canada/Germany1). One post-hoc analysis of an RCT (India1) was included and provided both randomised and non-randomised data. Three retrospective cohort studies evaluating the quadrivalent vaccine in females (Denmark2, USA1, USA10), and one in females and males (USA11) were included. Results were not reported separately for females and males in the USA11 study. No studies on the nonavalent HPV vaccine were identified.

The risk of bias was assessed as low in all domains for one of the RCTs except for blinding which was unclear (Canada/Germany1). The risk of bias in the RCT post-hoc analysis (India1) was high for attrition bias, blinding, and potential selection bias. Overall risk of bias was assessed as serious for three observational studies and was not assessed in the fourth due to very limited information (a conference abstract).

There was low-certainty evidence that two doses of quadrivalent HPV vaccine resulted in fewer cases of incident HPV infections than no vaccine in females aged 15 to 18 at the time of the first dose. Evidence for persistent HPV infections was inconclusive and of very low-certainty.

There was very low-certainty evidence that females aged 15 to 18 years who receive two doses of quadrivalent HPV vaccine have reduced abnormal cervical cytology compared with unvaccinated females, although the CIs crossed the line of no effect (adjusted hazard ratio [aHR] 0.71, 95% CI 0.38 to 1.33, 1075 participants, 1 study). Females vaccinated at a younger age (15 to 16 years) showed a larger effect (aHR 0.49, 95% CI 0.28 to 0.86) than females vaccinated at an older age (17 to 18 years; aHR 0.94, 95% CI 0.69 to 1.28), compared with unvaccinated females (USA1).

There was low-certainty evidence that two doses of quadrivalent HPV vaccine compared with no vaccine in females and males aged 15 to 19 at the time of the first dose reduced the incidence of anogenital warts (aHR

0.67, 95% CI 0.51 to 0.89, 256,781 participants). Results from an additional conference abstract (USA10) support this finding (42% vaccine efficacy against anogenital warts in females vaccinated at the age of 15 to 17 years).

There was moderate-certainty evidence that at one month following the last dose, two doses were non-inferior to three doses of the bivalent vaccine in 15 to 19-year-old females for GMTs of HPV 18, and non-inferiority was inconclusive for GMTs of HPV 16 (Canada/Germany1).

There was low-certainty evidence that at one month following the last dose, two doses were non-inferior to three doses of the quadrivalent vaccine in 15 to 18-year-old females for GMTs of HPV 6, 11, 16, and 18 (India1), and that non-inferiority was maintained up to 48 months for these outcomes (India1).

There was inconclusive and very low-certainty evidence from two studies that compared two doses to three doses of quadrivalent HPV vaccine on incidence of CIN1, CIN2, CIN3, persistent and incident HPV infection and abnormal cervical cytology in females aged 15 to 18 at the time of vaccination (India1, USA1).

One study found that the rate of anogenital warts in females aged 16 to 17 at the time of the first quadrivalent HPV vaccine dose was higher after two doses compared with three doses (low certainty evidence, adjusted incidence rate ratio 2.84, 95% CI 1.87 to 4.31, 306,068 participants, 1 study) (Denmark2). Another study found little or no difference between two and three doses on the incidence of anogenital warts in 15 to 19-year-old females and males at 3 months to 5 years follow-up (very low certainty evidence, unadjusted RR 1.00, 95% CI 0.78 to 1.28, 115,119 participants, 1 study) (USA11). Results from these two studies were not pooled due to methodological heterogeneity.

Implications and conclusions

There is moderate-certainty evidence that two doses of bivalent HPV vaccine are non-inferior to three doses for GMTs of HPV 18, but this is inconclusive for GMTs of HPV 16; and low-certainty evidence that two doses of quadrivalent HPV vaccine are non-inferior to three doses for GMTs of HPV 6, 11, 16 and 18.

For most clinical outcomes, the evidence was of very low-certainty, often due to low numbers of events and risk of bias due to confounding in observational studies.

DATA FROM OBSERVATIONAL STUDIES

Summary of Findings: Two doses quadrivalent HPV vaccine versus no vaccine in 15-18-year-old females – clinical outcomes

Participants: 15 to 18-year old females (seronegative at baseline)
Setting: India
Comparison: Two doses quadrivalent HPV vaccine (month 0, 2) versus no vaccine

Outcome	Plain language summary	Absolute effect		Relative effect (95% CI) Nº of participants & studies	Certainty of the evidence (GRADE)
		No vaccine	Two doses		
Incident HPV 16/18 infections Follow up: longer than 7 years (India1*)	There was low certainty evidence that two doses of quadrivalent HPV vaccine resulted in fewer incident HPV 16/18 infections compared with no vaccine in females aged 15 to 18 years at the time of the first dose.	81 per 1000	19 per 1000 (12 to 31)	RR 0.24 (0.15 to 0.38) 2476 participants in 1 study	⨁⨁◯◯ LOW[1,2]
Incident HPV 6/11/16/18 infections Follow up: longer than 7 years (India1*)	There was low certainty evidence that two doses of quadrivalent HPV vaccine resulted in fewer incident HPV 6/11/16/18 infections compared with no vaccine in females aged 15 to 18 years at the time of the first dose.	112 per 1000	29 per 1000 (20 to 43)	RR 0.26 (0.18 to 0.38) 2476 participants in 1 study	⨁⨁◯◯ LOW[1,2]
Incident HPV 31/33/45 infections Follow up: longer than 7 years (India1*)	There was low certainty evidence that two doses of quadrivalent HPV vaccine resulted in fewer incident HPV 31/33/45 infections compared with no vaccine in females aged 15 to 18 years at the time of the first dose.	89 per 1000	38 per 1000 (27 to 54)	RR 0.43 (0.30 to 0.61) 2476 participants in 1 study	⨁⨁◯◯ LOW[1,2]
Incident HPV (any) infections Follow up: longer than 7 years (India1*)	There was low certainty evidence that two doses of quadrivalent HPV vaccine resulted in fewer incident HPV (any) infections compared with no vaccine in females aged 15 to 18 years at the time of the first dose.	323 per 1000	191 per 1000 (165 to 220)	RR 0.59 (0.51 to 0.68) 2476 participants in 1 study	⨁⨁◯◯ LOW[1,2]
Persistent HPV 16/18 infections Follow up: longer than 7 years	The effect of two doses of quadrivalent HPV vaccine on persistent HPV 16/18 infections compared with no vaccine in females aged 15 to 18 years at the time of the first dose was inconclusive and is of very low certainty.	23 per 1000	1 per 1000 (0 to 9)	RR 0.06 (0.01 to 0.42) 2015 participants in 1 study	⨁⨁◯◯ VERY LOW[1,3]

(India1*)					
Persistent HPV 6/11/16/18 infections Follow up: longer than 7 years (India1*)	The effect of two doses of quadrivalent HPV vaccine on persistent HPV 6/11/16/18 infections compared with no vaccine in females aged 15 to 18 years at the time of the first dose was inconclusive and is of very low certainty.	24 per 1000	4 per 1000 (1 to 13)	RR 0.16 (0.05 to 0.52) 2015 participants in 1 study	⊕⊕OO VERY LOW[1,3]
Persistent HPV 31/33/45 infections Follow up: longer than 7 years (India1*)	The effect of two doses of quadrivalent HPV vaccine on persistent HPV 31/33/45 infections compared with no vaccine in females aged 15 to 18 years at the time of the first dose was inconclusive and is of very low certainty.	10 per 1000	1 per 1000 (0 to 10)	RR 0.13 (0.02 to 1.03) 2015 participants in 1 study	⊕⊕OO VERY LOW[1,3]
Persistent HPV (any) infections Follow up: longer than 7 years (India1*)	There was low certainty evidence that two doses of quadrivalent HPV vaccine resulted in fewer persistent HPV (any) infections compared with no vaccine in females aged 15 to 18 years at the time of the first dose.	68 per 1000	31 per 1000 (20 to 49)	RR 0.45 (0.29 to 0.71) 2015 participants in 1 study	⊕⊕OO LOW[1,2]

CI= confidence interval; HPV= human papilloma virus; GMT= geometric mean titre

*Evidence for this comparison (two doses versus no vaccine) comes from the non-randomised part of the India1 study

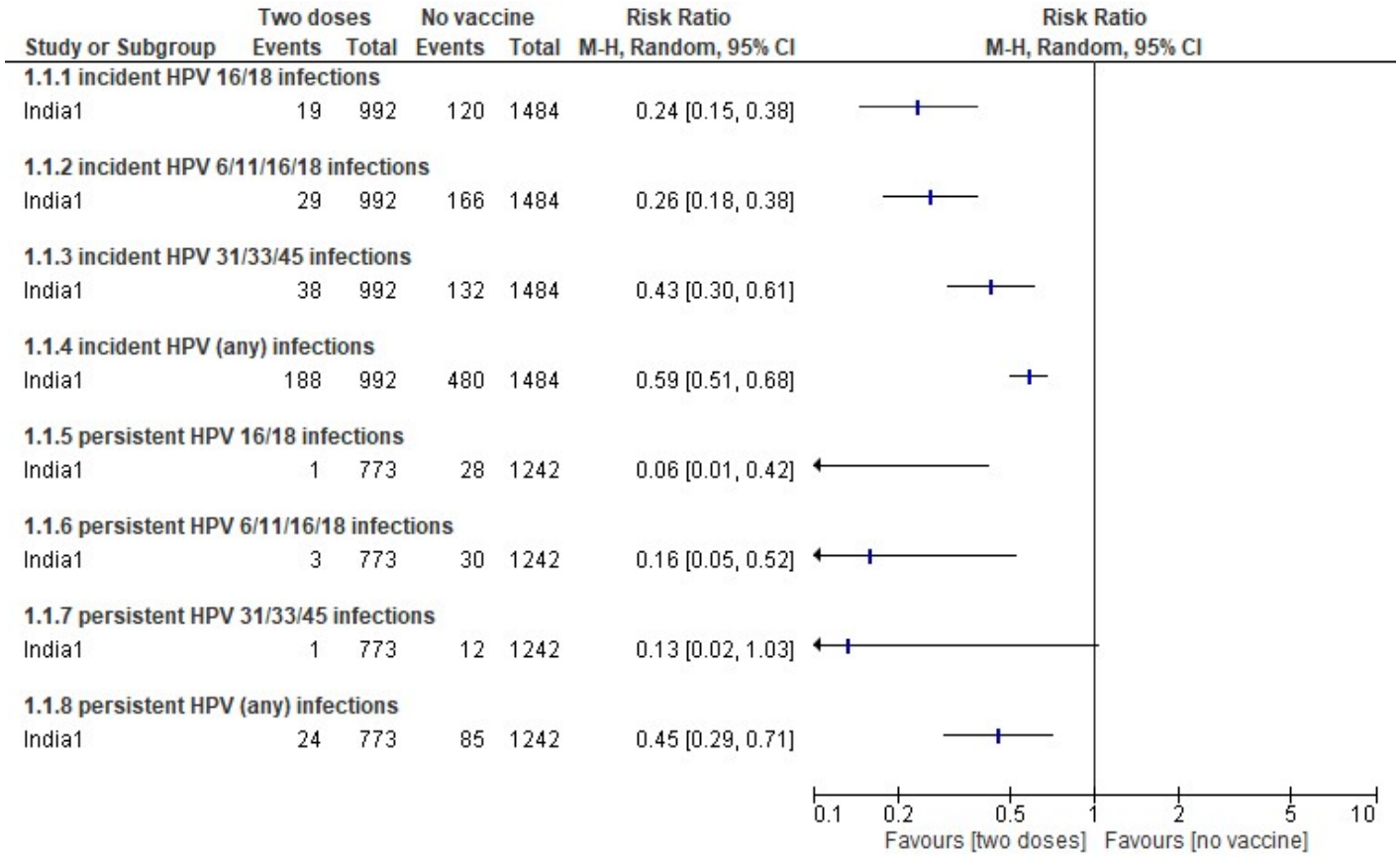
[1]Evidence from non-randomised (observational) studies is initially downgraded to low certainty evidence because of lack of appropriate protection against uncontrolled bias and confounding.

[2]Not downgraded for imprecision: there are few events, however, estimates and 95% CI are clearly in favour of intervention group.

[3]Downgraded one level for imprecision: few events

Forest plot: Two doses quadrivalent HPV vaccine versus no vaccine in 15-18-year-old females – clinical outcomes

Participants: 15 to 18-year old females (seronegative at baseline)
Setting: India
Comparison: Two doses quadrivalent HPV vaccine (month 0, 2) versus no vaccine

Outcome	Forest plot	Certainty of the evidence (GRADE)
Incident and persistent HPV infections Follow up: longer than 7 years (India1)		⊕⊕OO LOW ⊕⊕OO VERY LOW

CI= confidence interval; HPV= human papilloma virus; GMT= geometric mean titre

Summary of Findings: Two doses quadrivalent HPV vaccine versus no vaccine in 15-18-year-old females and males – clinical outcomes

Participants: 15 to 19-year old females and males (seronegative and -positive at baseline)
Setting: retrospective cohort studies of health care insurance claims and health care clinic data in the USA
Comparison: Two doses quadrivalent HPV vaccine (dose schedule was not reported) versus no vaccine

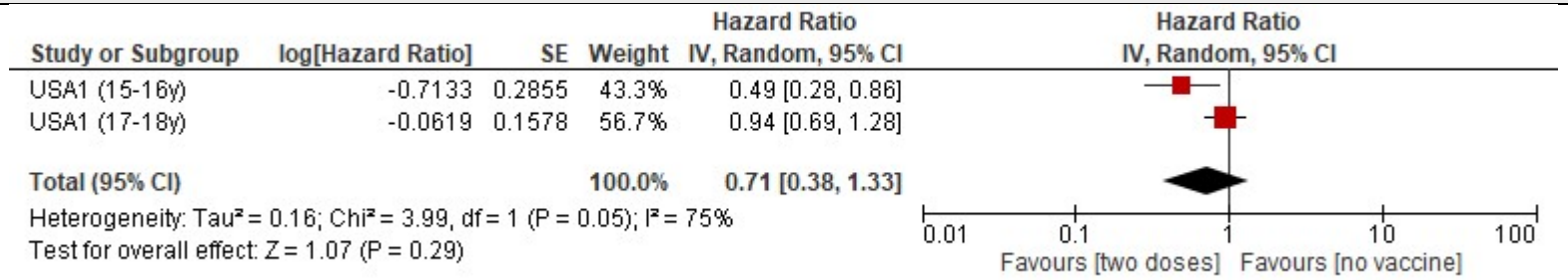
Outcome	Gender Two-dose interval (months)	Plain language summary	Absolute effect		Relative effect (95% CI) Nº of participants & studies	Certainty of the evidence (GRADE)
			No vaccine	Two doses		
Abnormal cervical cytology Follow up: up to 12 years (USA1)	Females No information	There was very low-certainty evidence that two doses of quadrivalent HPV vaccine in females aged 15 to 18 years reduces the incidence of abnormal cervical cytology compared with no vaccine, although the 95% CI crosses the line of no effect. Females vaccinated at a younger age (15 to 16 years) showed a larger effect (aHR* 0.49, 95% CI 0.28 to 0.86) than females vaccinated at an older age (17 to 18 years; aHR* 0.94, 95% CI 0.69 to 1.28), compared with unvaccinated females.	No information adjusted HRs	No information adjusted HRs	aHR*: 0.71 (0.38 to 1.33) 1075 participants in 1 study	⊕OOO VERY LOW[1,2,3]
Anogenital warts Follow up: 3 months to 5 years (USA11)	Females and males <6 months or ≥6 months	There was low-certainty evidence that two doses of quadrivalent HPV vaccine in females and males aged 15 to 19 years reduces the incidence of anogenital warts compared with no vaccine.	No information adjusted HRs	No information adjusted HRs	aHR§: 0.67 (0.51 to 0.89)‡ 256,781 participants in 1 study†	⊕⊕OO LOW[1]

CI= confidence interval; HPV= human papilloma virus; aHR= adjusted hazard ratio; VE= vaccine efficacy.
*HR adjusted for number of doses; age; language; insurance; clinic type; abnormal baseline cervical cytology result; and baseline Chlamydia screening.
§HR adjusted for sex, region, and history of sexually transmitted diseases.
†Results from a conference abstract (USA10) found 42% (p<0.001) vaccine efficacy against anogenital warts in 15-17-year-old females (data not reported).
‡Two doses with less than 6-month interval vs no vaccine: aHR 0.65 (0.45 to 0.94); n=156,259. Two doses with greater than 6-month interval vs no vaccine: 0.69 (0.44 to 1.07); n=154,949.

[1]Evidence from non-randomized (observational) studies is initially downgraded to low certainty evidence because of lack of appropriate protection against uncontrollable bias and confounding.
[2]Downgraded one level for limitations in study design: serious risk of selection bias as only those attending cervical cytology screening were included.
[3]The pooled estimate had moderate heterogeneity (I^2=75%) with wide CIs but we did not downgrade for inconsistency or imprecision because age at vaccination could explain both the inconsistency and the imprecision.

Forest plot: Two doses quadrivalent HPV vaccine versus no vaccine in 15-18-year-old females – clinical outcomes

Participants: 15 to 18-year old females (seronegative and -positive at baseline)
Setting: retrospective cohort studies of health care insurance claims and health care clinic data in the USA
Comparison: Two doses quadrivalent HPV vaccine (dose schedule was not reported) versus no vaccine

Outcome	Forest plot	Certainty of the evidence (GRADE)
Abnormal cervical cytology Follow up: up to 12 years (USA1)	 HRs were adjusted for number of doses; age; language; insurance; clinic type; abnormal baseline cervical cytology result; and baseline Chlamydia screening	⊕OOO VERY LOW

CI= confidence interval; HPV= human papilloma virus; HR= hazard ratio

DATA FROM RANDOMISED CONTROLLED TRIALS

Summary of Findings: Two doses versus three doses bivalent HPV vaccine in 15-19-year-old females – immunogenicity outcomes

Participants: 15 to 19-year old females (seronegative at baseline)
Setting: Canada and Germany
Comparison: Two doses bivalent HPV vaccine (month 0, 6) versus three doses (month 0, 1, 6) bivalent HPV vaccine

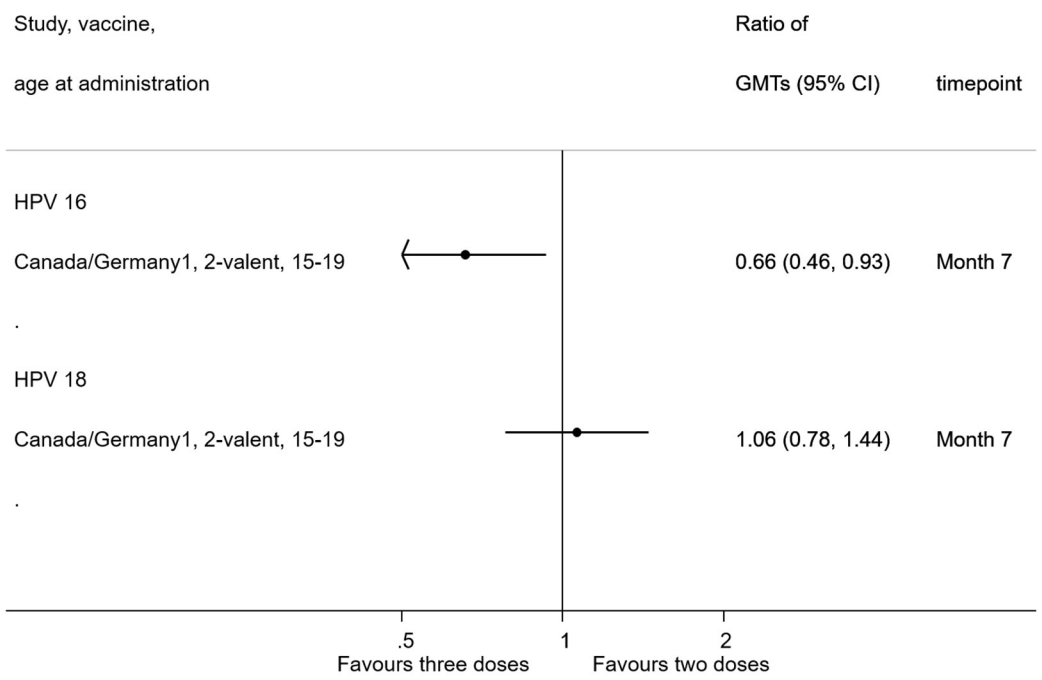
Outcome	Plain language summary	Absolute effect		Relative effect (95% CI) Nº of participants & studies	Certainty of the evidence (GRADE)
		Three doses	Two doses		
GMT of HPV 16 Follow-up: one month after the last dose (Canada/Germany1)	There was moderate certainty evidence that non-inferiority was inconclusive when comparing two doses to three doses of bivalent HPV vaccine on GMT of HPV 16 in 15-19-year-old females	Mean: 12858 EU/mL	Mean: 8442 EU/mL	Ratio 0.66 (0.46 to 0.93) 122 participants in 1 study	⨁⨁⨁◯ MODERATE[1]
GMT of HPV 18 Follow-up: one month after the last dose (Canada/Germany1)	There was moderate certainty evidence of non-inferiority of two doses compared to three doses of bivalent HPV vaccine on GMTs of HPV 18 in 15-19-year-old females	Mean: 4845 EU/mL	Mean: 5142 EU/mL	Ratio 1.06 (0.78 to 1.44) 124 participants in 1 study	⨁⨁⨁◯ MODERATE[1]

CI= confidence interval; HPV= human papilloma virus; GMT= geometric mean titre

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

Forest plot: Two doses versus three doses bivalent HPV vaccine in 15-19-year-old females – immunogenicity outcomes

Participants: 15 to 19-year old females (seronegative at baseline)
Setting: Canada and Germany
Comparison: Two doses bivalent HPV vaccine (month 0, 6) versus three doses (month 0, 1, 6) bivalent HPV vaccine

Outcome	Forest plot	Certainty of the evidence (GRADE)
Ratio of GMTs for HPV 16 and 18 Follow up: one month after the last dose (Canada/Germany1)		⊕⊕⊕O MODERATE

CI= confidence interval; HPV= human papilloma virus; GMT= geometric mean titre

Summary of Findings: Two doses versus three doses quadrivalent HPV vaccine in 15-18-year-old females – immunogenicity outcomes

Participants: 15 to 18-year old females (seronegative at baseline)
Setting: India
Comparison: Two doses quadrivalent HPV vaccine (month 0, 6) versus three doses (month 0, 2, 6) quadrivalent HPV vaccine

Outcome	Follow up	Plain language summary	Absolute effect		Relative effect (95% CI) Nº of participants & studies	Certainty of the evidence (GRADE)
			Three doses	Two doses		
GMT of HPV 6 Follow-up: up to 48 months (India1*)	7 months	There was low certainty evidence that two doses of quadrivalent HPV vaccine had non-inferior GMTs to HPV 6 compared to three doses of quadrivalent HPV vaccine in 15-18-year-old females at 7 months	Mean: 4509 MFI	Mean: 4461 MFI	Ratio 0.99 (0.89 to 1.11) 297 participants in 1 study	⊕⊕OO LOW[1]
	48 months	There was low certainty evidence that two doses of quadrivalent HPV vaccine had non-inferior GMTs to HPV 6 compared to three doses of quadrivalent HPV vaccine in 15-18-year-old females at 48 months	Mean: 367 MFI	Mean: 380 MFI	Ratio 1.04 (0.78 to 1.37) 224 participants in 1 study	⊕⊕OO LOW[1]
GMT of HPV 11 Follow-up: up to 48 months (India1*)	7 months	There was low certainty evidence that two doses of quadrivalent HPV vaccine had non-inferior GMTs to HPV 11 compared to three doses of quadrivalent HPV vaccine in 15-18-year-old females at 7 months	Mean: 5899 MFI	Mean: 6506 MFI	Ratio 1.10 (1.01 to 1.21) 297 participants in 1 study	⊕⊕OO LOW[1]
	48 months	There was low certainty evidence that two doses of quadrivalent HPV vaccine had non-inferior GMTs to HPV 11 compared to three doses of quadrivalent HPV vaccine in 15-18-year-old females at 48 months	Mean: 395 MFI	Mean: 576 MFI	Ratio 1.46 (1.11 to 1.92) 224 participants in 1 study	⊕⊕OO LOW[1]
GMT of HPV 16 Follow-up: up to 48 months (India1*)	7 months	There was low certainty evidence that two doses of quadrivalent HPV vaccine had non-inferior GMTs to HPV 16 compared to three doses of quadrivalent HPV vaccine in 15-18-year-old females at 7 months	Mean: 5150 MFI	Mean: 5384 MFI	Ratio 1.05 (0.92 to 1.19) 297 participants in 1 study	⊕⊕OO LOW[1]
	48 months	There was low certainty evidence that two doses of quadrivalent HPV vaccine had non-inferior GMTs to HPV 16 compared to three doses of quadrivalent HPV vaccine in 15-18-year-old females at 48 months	Mean: 156 MFI	Mean: 164 MFI	Ratio 1.05 (0.80 to 1.38) 224 participants in 1 study	⊕⊕OO LOW[1]
GMT of HPV 18 Follow-up: up to 48 months	7 months	There was low certainty evidence that two doses of quadrivalent HPV vaccine had non-inferior GMTs to HPV 18 compared to three doses of quadrivalent HPV vaccine in 15-18-year-old females at 7 months	Mean: 2636 MFI	Mean: 2423 MFI	Ratio 0.92 (0.76 to 1.11) 297 participants in 1 study	⊕⊕OO LOW[1]

(India1*)	48 months	There was low certainty evidence that two doses of quadrivalent HPV vaccine had non-inferior GMTs to HPV 18 compared to three doses of quadrivalent HPV vaccine in 15-18-year-old females at 48 months	Mean: 99 MFI	Mean: 92 MFI	Ratio 0.93 (0.76 to 1.11) 224 participants in 1 study	⊕⊕OO LOW[1]

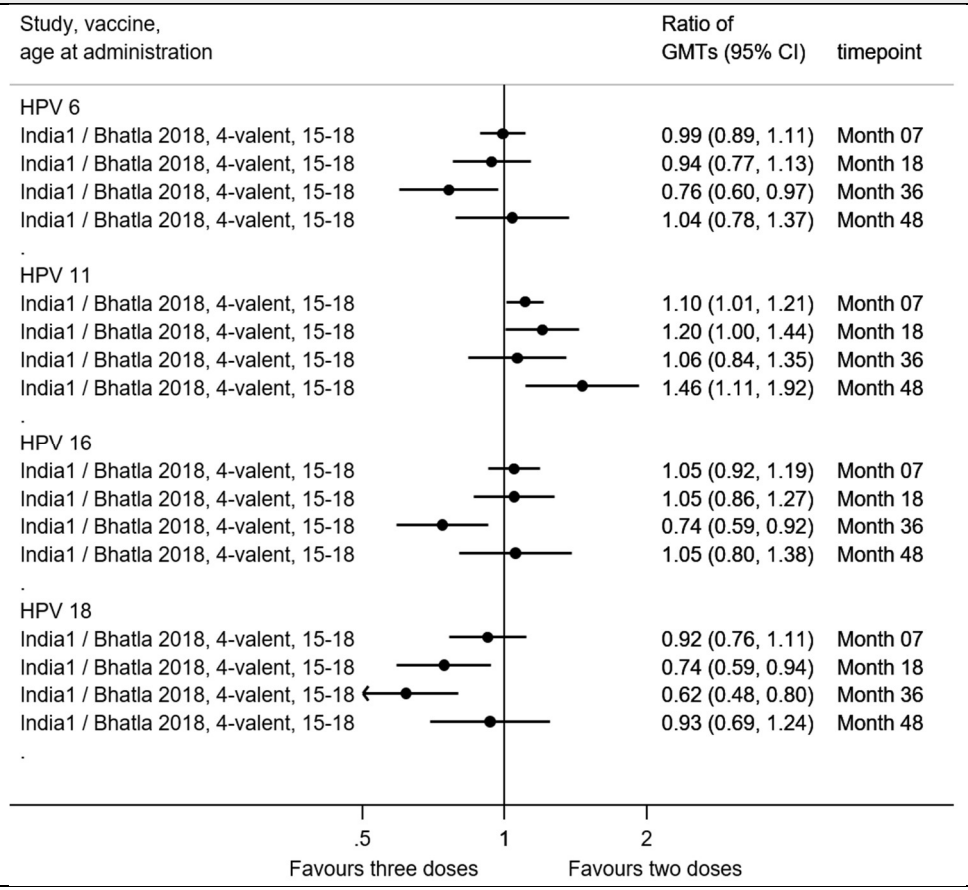
CI= confidence interval; HPV= human papilloma virus; GMT= geometric mean titre; MFI= median fluorescence intensity

*Evidence for this comparison (two doses versus three doses) comes from the randomised part of the India1 study

[1]Downgraded two levels for limitations in study design: post-hoc subgroup analysis of a randomised controlled trial with high risk of attrition bias and potential selection bias.

Forest plot: Two doses versus three doses quadrivalent HPV vaccine in 15-18-year-old females – immunogenicity outcomes

Participants: 15 to 18-year old females (seronegative at baseline)
Setting: India
Comparison: Two doses quadrivalent HPV vaccine (month 0, 6) versus three doses (month 0, 2, 6) quadrivalent HPV vaccine

Outcome	Forest plot	Certainty of the evidence (GRADE)
Ratio of GMTs for HPV 6, 11, 16 and 18 Follow up: up to 48 months (India1)		⊕⊕OO LOW

CI= confidence interval; HPV= human papilloma virus; GMT= geometric mean titre

Summary of Findings: Two doses versus three doses quadrivalent HPV vaccine in 15-18-year-old females – clinical outcomes

Participants: 15 to 18-year old females (seronegative at baseline)
Setting: India
Comparison: Two doses quadrivalent HPV vaccine (month 0, 2) versus three doses (month 0, 2, 6) quadrivalent HPV vaccine

Outcome	Plain language summary	Absolute effect		Relative effect (95% CI) Nº of participants & studies	Certainty of the evidence (GRADE)
		No vaccine	Two doses		
Incident HPV 16/18 infections Follow up: longer than 7 years (India1*)	The effect of two doses of quadrivalent HPV vaccine on incident HPV 16/18 infections compared with three doses in females aged 15 to 18 years at the time of the first dose was inconclusive and is of very low certainty.	13 per 1000	19 per 1000 (9 to 39)	RR 1.46 (0.71 to 2.99) 1905 participants in 1 study	⊕OOO VERY LOW[1,2]
Incident HPV 6/11/16/18 infections Follow up: longer than 7 years (India1*)	The effect of two doses of quadrivalent HPV vaccine on persistent HPV 6/11/16/18 infections compared with three doses in females aged 15 to 18 years at the time of the first dose was inconclusive and is of very low certainty.	22 per 1000	29 per 1000 (17 to 51)	RR 1.33 (0.76 to 2.34) 1905 participants in 1 study	⊕OOO VERY LOW[1,2]
Incident HPV 31/33/45 infections Follow up: longer than 7 years (India1*)	There was low certainty evidence that two doses of quadrivalent HPV vaccine resulted in fewer incident HPV 31/33/45 infections compared with three doses in females aged 15 to 18 years at the time of the first dose.	60 per 1000	39 per 1000 (25 to 57)	RR 0.64 (0.42 to 0.95) 1905 participants in 1 study	⊕⊕OO LOW[1]
Incident HPV (any) infections Follow up: longer than 7 years (India1*)	There was low certainty evidence that two doses of quadrivalent HPV vaccine resulted in little to no difference in incident HPV (any) infections compared with three doses in females aged 15 to 18 years at the time of the first dose.	211 per 1000	190 per 1000 (159 to 226)	RR 0.90 (0.75 to 1.07) 1905 participants in 1 study	⊕⊕OO LOW[1]
Persistent HPV 16/18 infections Follow up: longer than 7 years (India1*)	The effect of two doses of quadrivalent HPV vaccine on persistent HPV 16/18 infections compared with three doses in females aged 15 to 18 years at the time of the first dose was inconclusive and is of very low certainty.	1 per 1000	1 per 1000 (0 to 21)	RR 1.18 (0.07 to 18.85) 1686 participants in 1 study	⊕OOO VERY LOW[1,2]

Persistent HPV 6/11/16/18 infections Follow up: longer than 7 years (India1*)	The effect of two doses of quadrivalent HPV vaccine on persistent HPV 6/11/16/18 infections compared with three doses in females aged 15 to 18 years at the time of the first dose was inconclusive and is of very low certainty.	2 per 1000	4 per 1000 (1 to 23)	RR 1.77 (0.30 to 10.58) 1686 participants in 1 study	⊕OOO VERY LOW[1,2]
Persistent HPV 31/33/45 infections Follow up: longer than 7 years (India1*)	The effect of two doses of quadrivalent HPV vaccine on persistent HPV 31/33/45 infections compared with three doses in females aged 15 to 18 years at the time of the first dose was inconclusive and is of very low certainty.	3 per 1000	1 per 1000 (0 to 12)	RR 0.39 (0.04 to 3.78) 1686 participants in 1 study	⊕OOO VERY LOW[1,2]
Persistent HPV (any) infections Follow up: longer than 7 years (India1*)	The effect of two doses of quadrivalent HPV vaccine on persistent HPV (any) infections compared with three doses in females aged 15 to 18 years at the time of the first dose was inconclusive and is of very low certainty.	26 per 1000	31 per 1000 (18 to 54)	RR 1.18 (0.68 to 2.06) 1686 participants in 1 study	⊕OOO VERY LOW[1,2]
CIN1, 2, 3 (HPV 16/18 and any HPV type) Follow up: 7.1 years (median) (India1*)	The effect of two doses compared with three doses on CIN1, 2, and 3 in females aged 15 to 18 years at the time of the first quadrivalent HPV vaccine dose was inconclusive and is of very low certainty.	Not estimable**	Not estimable**	Not estimable** 841 participants in 1 study	⊕OOO VERY LOW[1,2]

CI= confidence interval; HPV= human papilloma virus; GMT= geometric mean titre; CIN= cervical intraepithelial neoplasia; RR= relative risk

*Evidence for this comparison (two doses versus three doses) comes from the randomised part of the India1 study. Comparison between the longer interval (0, 6 months) two-dose group and the three-dose group is presented in Appendix 3.

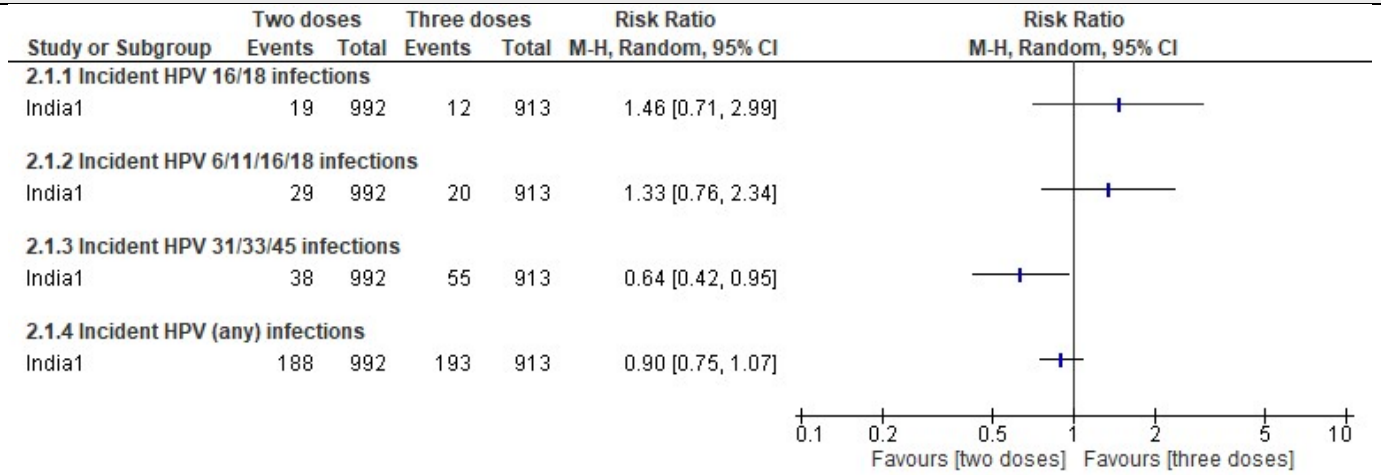
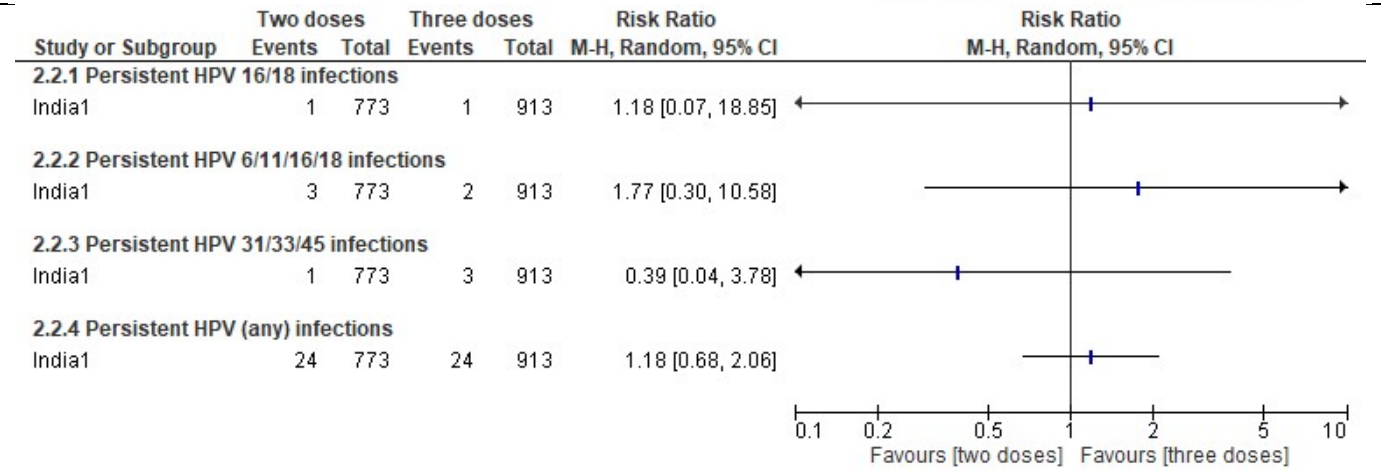
**No events were reported for any outcomes (HPV 16/18 and any HPV type CIN1, CIN2, CIN3) except any HPV type CIN1 where only one event was reported in the three-dose group.

[1]Downgraded two levels for limitations in study design: post-hoc subgroup analysis of a randomised controlled trial with high risk of attrition bias and potential selection bias.

[2]Downgraded one level for imprecision: few events and wide 95% CI that encompass a potential benefit and a potential harm from the intervention

Forest plot: Two doses versus three doses quadrivalent HPV vaccine in 15-18-year-old females – clinical outcomes

Participants: 15 to 18-year old females (seronegative at baseline)
Setting: India
Comparison: Two doses quadrivalent HPV vaccine (month 0, 2) versus three doses (month 0, 2, 6) quadrivalent HPV vaccine

Outcome	Forest plot	Certainty of the evidence (GRADE)
Incident HPV infections Follow up: longer than 7 years (India1)		⊕OOO VERY LOW ⊕⊕OO LOW
Persistent HPV infections Follow up: longer than 7 years (India1)		⊕OOO VERY LOW

CI= confidence interval; HPV= human papilloma virus; GMT= geometric mean titre

DATA FROM OBSERVATIONAL STUDIES

Summary of Findings: Two doses versus three doses quadrivalent HPV vaccine in 15-18-year-old females and males – clinical outcomes

Participants: 15 to 19-year old females and males (seronegative and -positive at baseline)
Setting: retrospective cohort studies in Denmark and the USA
Comparison: Two doses quadrivalent HPV vaccine (Denmark: month 0, 2; USA1 and USA11: dose schedule not reported) versus three doses (Denmark: month 0, 2, 6: USA1 and USA11: dose schedule not reported) quadrivalent HPV vaccine

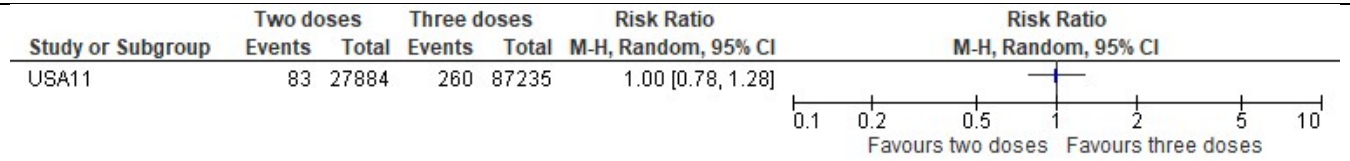
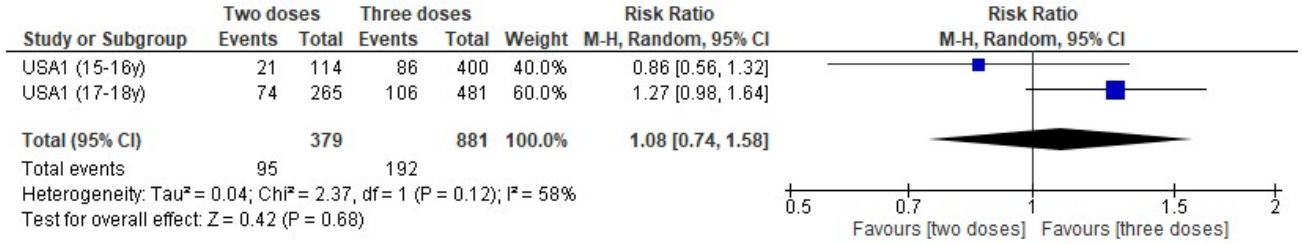
Outcome	Gender Two-dose interval (months)	Plain language summary	Absolute effect		Relative effect (95% CI) Nº of participants & studies	Certainty of the evidence (GRADE)
			Three doses	Two doses		
Anogenital warts Follow up: up to 6 years (Denmark2)	Female Two months	There was low certainty evidence that the rate of anogenital warts in females aged 16 to 17 years at the time of the first quadrivalent HPV vaccine dose was higher after two doses compared with three doses.	IR: 30.9 (per 100,000 P-Y)	IR: 137.4 (per 100,000 P-Y)	IRR* 2.84 (1.87 to 4.31) 306,068 participants in 1 study	⊕⊕OO LOW[1]
Anogenital warts Follow up: 3 months to 5 years (USA11)	Female and male <6 months to ≥6 months	The effect on anogenital warts with two doses compared with three doses in females aged 15 to 19 years at the time of the first quadrivalent HPV vaccine dose was inconclusive and is of very low certainty.	3 per 1000	3 per 1000 (2 to 4)	RR 1.00 (0.78 to 1.28) 115,119 participants in 1 study	⊕OOO VERY LOW[1,4]
Abnormal cervical cytology Follow up: up to 12 years (USA1)	Female No information	The effect on abnormal cervical cytology with two doses compared with three doses in females aged 15 to 18 years at the time of the first quadrivalent HPV vaccine dose was inconclusive and is of very low certainty.	218 per 1000	235 per 1000 (161 to 344)	RR 1.08 (0.74 to 1.58) 1260 participants in 1 study	⊕OOO VERY LOW[1,2,3]

CI= confidence interval; HPV= human papillomavirus; IR= incidence rate; IRR= incidence rate ratio; RR= relative risk; P-Y= person-years.
*adjusted for age at vaccination, maternal educational level, disposable income, and calendar time.

[1]Evidence from non-randomised (observational) studies is initially downgraded to low certainty evidence because of lack of appropriate protection against uncontrolled bias and confounding.
[2]Downgraded one level for limitations in study design: serious risk of selection bias as only those attending cervical cytology screening were included.
[3]Downgraded one level due to imprecision: wide 95% confidence intervals in both pooled and age-stratified results.
[4]Downgraded one level due to imprecision: wide 95% confidence intervals that encompass no effect, a potential benefit, and a potential harm from two doses compared with three doses

Forest plots: Two doses versus three doses quadrivalent HPV vaccine in 15-18-year-old females - clinical outcomes

Participants: 15 to 18-year old females (seronegative and -positive at baseline)
Setting: retrospective cohort studies in Denmark and the USA
Comparison: Two doses quadrivalent HPV vaccine (Denmark: month 0, 2; USA1 and USA11: dose schedule not reported) versus three doses (Denmark: month 0, 2, 6; USA1 and USA11: dose schedule not reported) quadrivalent HPV vaccine

Outcome	Forest plot	Certainty of the evidence (GRADE)
Anogenital warts Follow up: up to 6 years (Denmark2)	Adjusted IRR 2.84, 95% CI 1.87 to 4.31, 306,068 participants, 1 study	⊕⊕OO LOW
Anogenital warts Follow up: 3 months to 5 years (USA11)		⊕OOO VERY LOW
Abnormal cervical cytology Follow up: up to 12 years (USA1)		⊕OOO VERY LOW

CI= confidence interval; HPV= human papilloma virus; IRR= incidence rate ratio

References

Canada/Germany1
Romanowski B, Schwarz TF, Ferguson LM, Peters K, Dionne M, Schulze K, et al. Immunogenicity and safety of the HPV-16/18 AS04-adjuvanted vaccine administered as a 2-dose schedule compared to the licensed 3-dose schedule: Results from a randomized study. Human vaccines. 2011;7(12):1374-86.

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Romanowski B, Schwarz TF, Ferguson L, Peters K, Dionne M, Behre U, et al. Sustained immunogenicity of the HPV-16/18 AS04-adjuvanted vaccine administered as a two-dose schedule in adolescent girls: five-year clinical data and modeling predictions from a randomized study. Human vaccines & immunotherapeutics. 2016;12(1):20-9.

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Bhatla N, Nene BM, Joshi S, Esmy PO, Poli URR, Joshi G, et al. Are two doses of human papillomavirus vaccine sufficient for girls aged 15-18 years? Results from a cohort study in India. Papillomavirus Res. 2018;5:163-71.

USA1
Hofstetter AM, Ompad DC, Stockwell MS, Rosenthal SL, Soren K. Human papillomavirus vaccination and cervical cytology outcomes among urban low-income minority females. JAMA pediatrics. 2016;170(5):445-52.

USA10
Flagg EW, Torrone EA. O17.2 Population effectiveness of human papillomavirus vaccination against anogenital warts among female enrollees in private health plans in the united states, 2006–2014. Sexually Transmitted Infections. 2017;93(Suppl 2):A39-A.

USA11
Zeybek B, Lin Y-L, Kuo Y-F, Rodriguez AM. The Impact of Varying Numbers of Quadrivalent Human Papillomavirus Vaccine Doses on Anogenital Warts in the United States: A Database Study. J Low Genit Tract Dis. 2018;22(3):189-94.

Appendix 1. Study characteristics

Study name	Publication year & funding	Study design	Date range	HPV vaccine comparison	Participants (number, sex)	Age at vaccination (V) and outcome (O) in years	Outcomes reported
Canada/ Germany1	2011 GlaxoSmithKline	Randomised controlled trial	October 2007 to May 2010	2-valent HPV vaccine: 2 doses versus 3 doses	158 females	V: 15-19 O: 15-19	Immunogenicity: geometric mean titre
Denmark2	2015 Aragon Foundation; the Aase and Ejnar Danielsens Foundation; and the Mermaid II project	Retrospective cohort study using population-based national health registries	October 2006 to December 2012	4-valent HPV vaccine: 2 doses versus 3 doses	306,068 females (aged 12-27) received 2 or 3 doses. Number aged 16-17 not reported	V: 16-17 O: NR (up to 6 years follow up)	Anogenital warts (adjusted result provided comparing two doses to three doses)
India1	2016 Bill & Melinda Gates Foundation	Post-hoc analysis of RCT	September 2009 to April 2010	4-valent HPV vaccine: 2 doses versus 3 doses	1,761 females (clinical outcomes); 3,310 females (immunogenicity outcome)	V: 15-18 O: 19-22	CIN1, 2, and 3, HPV infection: incidence and persistent infection (unadjusted). Immunogenicity: geometric mean titre
USA1	2016 Merck Investigator-Initiated Studies Program	Retrospective cohort study using medical centre databases	2007 to 2014	4-valent HPV vaccine: 2 doses versus 3 doses; 2 doses versus no vaccine	2,390 females	V: 15-18 O: NR (up to 12 years follow up)	Abnormal cervical cytology (adjusted result provided comparing two doses to no vaccine)
USA10	2017 Funding not reported	Retrospective cohort using healthcare claims data	2003 to 2014	4-valent HPV vaccine: 2 doses versus no vaccine	270,481 females aged 9-17 in 2006. Number aged 15-17 not reported.	V: 15-17 O: NR (up to 8 years follow up)	Anogenital warts (vaccine effectiveness from conference abstract)

Study name	Publication year & funding	Study design	Date range	HPV vaccine comparison	Participants (number, sex)	Age at vaccination (V) and outcome (O) in years	Outcomes reported
USA11	2018 William & Mary McGanity Research Fund Award from the Department of Obstetrics & Gynecology at The University of Texas Medical Branch at Galveston	Retrospective cohort using health insurance claims database	2006 to 2015	4-valent HPV vaccine: 2 doses versus 3 doses; 2 doses versus no vaccine	256,781 females and males aged 15-19 years	V: 15-19 O: 15-24	Anogenital warts

V= age at vaccination; O= age at outcome

Appendix 2. Risk of bias assessments

Risk of bias: Randomised controlled trials (Cochrane Risk of Bias Tool)							
	Random sequence generation (selection bias)	**Allocation concealment (selection bias)**	**Blinding of participants and personnel (performance bias)**	**Blinding of outcome assessment (detection bias)**	**Incomplete outcome data (attrition bias)**	**Selective reporting (reporting bias)**	**Other bias**
Canada/Germany1	Low	Low	Unclear	Low	Low	Low	Unclear
India1	Low	Low	High	Low	High	Unclear	High

Risk of bias: observational studies (Cochrane Risk of bias in non-randomized studies of interventions (ROBINS-I) tool								
	Bias due to confounding	**Bias in selection of participants into the study**	**Bias in classification of interventions**	**Bias due to deviations from intended interventions**	**Bias due to missing data**	**Bias in measurement of outcomes**	**Bias in selection of the reported result**	**Overall**
Denmark2	Serious	Moderate	Low	Moderate	Low	Moderate	Moderate	Serious
India1	Serious	Low	Low	Low	Moderate	Low	Moderate	Serious
USA1	Serious	Serious	Low	Moderate	Moderate	Moderate	Moderate	Serious
USA10	Unable to assess risk of bias for this study as only a conference abstract was available.							
USA11	Serious	Moderate	Low	Moderate	Low	Moderate	Moderate	Serious

ROBINS-I interpretation

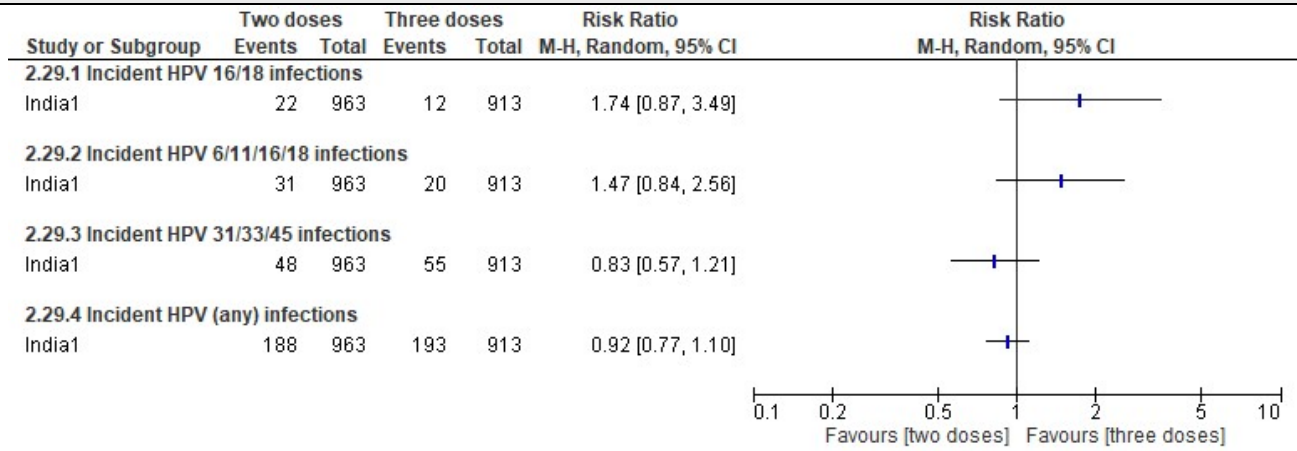
Low risk	the study is comparable to a well-performed randomized trial
Moderate risk	the study provides sound evidence for a non-randomized study but cannot be considered comparable to a well-performed randomized trial
Serious risk	the study has some important problems
Critical risk	the study is too problematic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

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

Appendix 3. Additional analysis

Forest plot: Two doses versus three doses quadrivalent HPV vaccine in 15-18-year-old females – clinical outcomes

Participants: 15 to 18-year old females (seronegative at baseline)
Setting: India
Comparison: Two doses quadrivalent HPV vaccine (month 0, 6) versus three doses (month 0, 2, 6) quadrivalent HPV vaccine

Outcome	Forest plot
Incident HPV infections Follow up: longer than 7 years (India1)	
Persistent HPV infections Follow up: longer than 7 years (India1)