Longer interval versus shorter interval between two HPV vaccine doses

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Key findings

Longer interval schedule (0, 6 months) versus shorter interval schedule (0, 2 months) of bivalent HPV vaccine in females (9 to 14 years)
In females aged 9 to 14 years receiving the bivalent vaccine, there were higher GMTs for HPV 16 and HPV 18 in those with a longer interval between doses (0, 6 months) than in those with a shorter interval between doses (0, 2 months) at one month after the last dose and 24 months after the first dose (moderate-certainty evidence).

Longer interval schedule (0, 12 months) versus shorter interval schedule (0, 6 months) of bivalent HPV vaccine in females (9 to 14 years)
In females aged 9 to 14 years receiving the bivalent vaccine, there were higher GMTs for HPV 16 and HPV 18 in those with a longer interval between doses (0, 12 months) than in those with a shorter interval between doses (0, 6 months) at one month after the last dose and 36 months after the first dose (high-certainty evidence).

Longer interval schedule (0, 12 months) versus shorter interval schedule (0, 6 months) of nonavalent HPV vaccine in females and males (9 to 14 years)
In females and males aged 9 to 14 years receiving the nonavalent vaccine, there were higher GMTs for all HPV genotypes except for HPV 45, in those with a longer interval between doses (0, 12 months) than in those with a shorter interval between doses (0, 6 months) one month after the last dose (high-certainty evidence).

Longer interval schedules (various intervals) versus shorter interval schedule (various intervals) – data from observational studies
Data from observational studies showed there was either no difference or better outcomes following a longer interval schedule compared to a shorter interval between two doses (low to 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. In this Targeted Update, we review and analyse evidence for the protection afforded by two doses of prophylactic HPV vaccines.

Objectives

This document focuses on comparisons of longer intervals between doses (of any length) versus shorter intervals between doses (of any length) in females and males.

Search methods

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

Selection criteria

Randomised controlled trials (RCTs) and observational studies were eligible for inclusion. The studies in this document focus on the comparison of longer intervals between doses (of any length) versus shorter intervals between doses (of any length).

Data collection and analysis

Two review authors independently assessed trial eligibility and risk of bias and extracted data. Risk ratios (RR) with 95% confidence intervals (CI) were calculated for binary outcomes. For continuous data, where geometric mean titres (GMTs) were reported, we calculated the data as mean differences (95% CI) on the log scale and re-expressed as ratio of GMTs. The non-inferiority threshold for the longer schedule was 0.5 for ratio of GMTs.

Main Results

We included:

a) Two RCTs comparing a longer interval (6 or 12 months) with a shorter interval between doses (2 or 6 months) of bivalent HPV vaccine in 9 to 14-year-old females (Canada/Germany1, Multinational2).

b) One cluster RCT comparing four different interval schedules between doses of bivalent HPV vaccine (Vietnam1). From this study, only data comparing a 6-month interval with a 3-month interval was analysed as the length of follow-up was comparable.

c) One RCT comparing a longer interval (12 months) with a shorter interval between doses (6 months) of nonavalent HPV vaccine in 9 to 14-year-old females and males (Multinational3).

d) Two post-hoc analyses of RCTs, one which compared a 6-month interval with a 1-month interval of bivalent HPV vaccine in 18-26-year-old women (Costa Rica1) and the other which compared a 6-month interval with a 2 month interval of quadrivalent HPV vaccine in 10-18 year old women (India1).

e) One observational cohort study comparing a longer (>90 days) with a shorter interval (<90 days) of bivalent HPV vaccine in 10-11-year-old females (Uganda1).

f) Eleven observational cohort studies which compared longer intervals (from 3 months to 8+ months) with shorter intervals (from 1 month to 6 months) of quadrivalent HPV vaccine (Australia1, Denmark2, Denmark/Sweden1, Fiji1, Sweden2, USA1, USA2, USA6, USA7, USA8, USA11).

The characteristics of all studies and the risk of bias assessments are presented in Appendix 1 and 2. Results for these studies are presented separately in the tables and forest plots below.

There was moderate-certainty evidence of higher GMTs for HPV 16 and HPV 18 at one month follow-up after the last dose and at 24 months in 9 to 14-year old females receiving bivalent HPV vaccine with a 6-month interval between doses (0, 6) compared with a 2-month interval between doses (0, 2).

There was high-certainty evidence of higher GMTs for HPV 16 and HPV 18 at 7 months and 36 months in 9 to 14-year old females receiving bivalent HPV vaccine with a 12-month interval between doses (0, 12) compared with a 6-month interval between doses (0, 6). For seroconversion to HPV 16 and HPV 18, there was high-certainty evidence of no difference between groups at one-month follow-up after the last dose.

There was high-certainty evidence of higher GMTs for all HPV genotypes except for HPV 45, in those receiving 9-valent HPV vaccine with a 12-month interval between doses (0, 12 months) compared to a 6-month interval between doses (0, 6 months). There was also high-certainty evidence of no difference on seroconversion to all HPV types between groups at one-month follow-up after the last dose.

There was moderate-certainty evidence of little to no difference on GMTs to HPV 16 and HPV 18 at 6 months following the second dose in 11 to 13-year old females receiving quadrivalent HPV vaccine with a 6-month interval between doses (0, 6) compared with a 3-month interval between doses (0, 3).

In data from analyses of two post-hoc RCTs (Costa Rica1, India1), there was low certainty evidence of higher GMTs following a longer interval (6 months) than a shorter interval (1 or 2 months) between two doses of bivalent HPV vaccine up to 84 months following the first dose, or quadrivalent HPV vaccine up to 36 months following the first dose.

There was mostly very low certainty evidence on clinical outcomes from these two studies when a longer interval schedule was compared to a shorter interval schedule, due to imprecision and limitations in study design.

Data from observational cohort studies was at serious risk of bias, except for one study (USA2) which had moderate risk of bias. The interval comparisons made by these studies varied and so could not be meta-analysed. There was either no difference or better outcomes following a longer interval schedule compared to a shorter interval between two doses.

Five studies reported on the incidence of genital warts comparing different intervals between two doses of quadrivalent HPV vaccine. From these studies, two reported estimates in favour of longer intervals between doses, two reported no difference, and one reported an estimate in favour of a shorter interval. The study at lowest risk of bias (USA2) reported an estimate in favour of a longer interval.

Implications and conclusions

A longer interval (up to 12 months) between two doses of bivalent, quadrivalent, and nonavalent HPV vaccines appears to result in higher GMTs (also non-inferior) compared to a shorter interval between doses. There was no difference in seroconversion as all participants seroconverted in both groups (moderate to high-certainty evidence). While the certainty of the evidence is lower for clinical outcomes, a longer interval between doses also appears to provide better protection than a shorter interval (very low to low certainty evidence).

DATA FROM RANDOMISED CONTROLLED TRIALS

Summary of Findings: longer interval (6 months) versus shorter interval (2 months) between two doses of bivalent HPV vaccine in females – immunogenicity outcomes at all timepoints

Participants: 9 to 14-year old females (seronegative at baseline).
Setting: Canada, Germany
Comparison: longer interval schedule (0, 6 months) versus shorter interval schedule (0, 2 months) of bivalent HPV vaccine

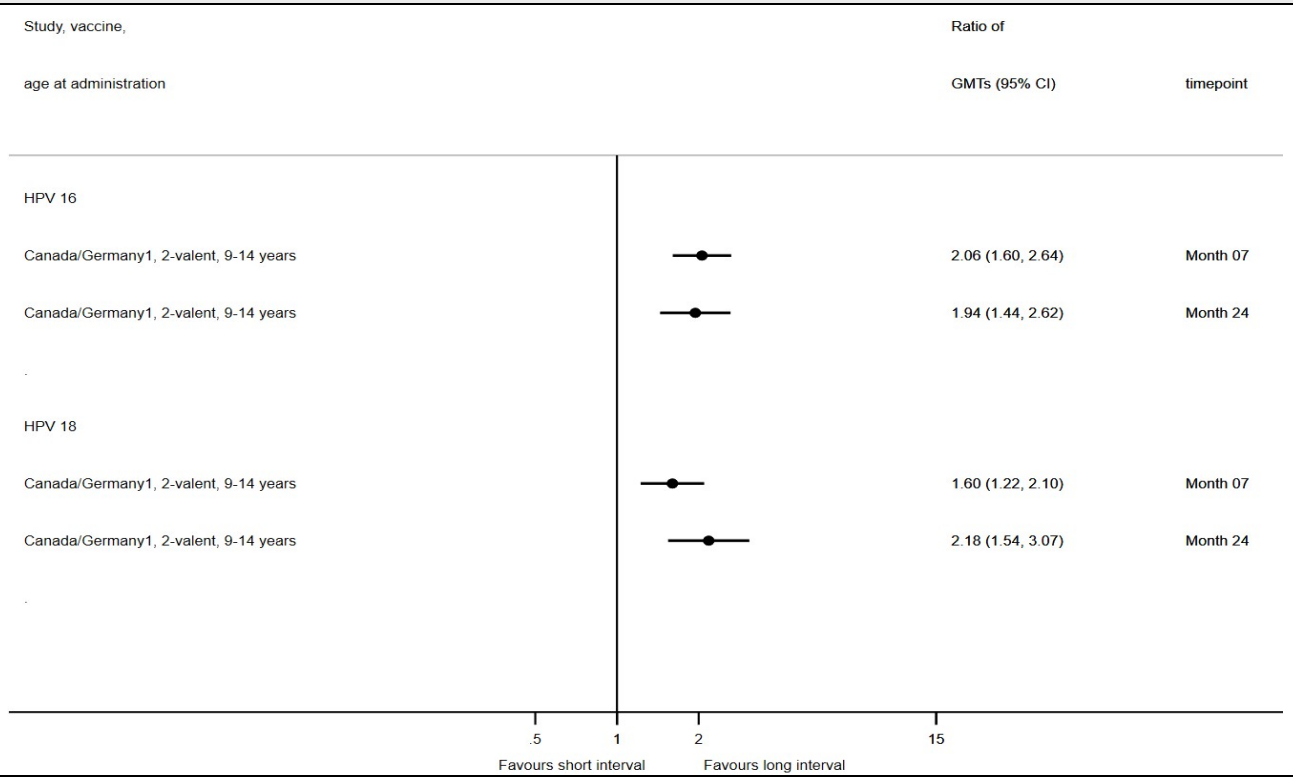
Outcome	Follow up	Plain language summary	Absolute effect		Relative effect (95% CI) Nº of participants & studies	Certainty of the evidence (GRADE)
			0, 2-month schedule	0, 6-month schedule		
GMTs for HPV 16 Follow-up: up to 24 months (Canada/Germany1)	One month after last dose	There was moderate-certainty evidence that females aged 9 to 14 years receiving two doses of the bivalent HPV vaccine with a 6-month interval schedule had higher GMTs for HPV 16 compared to a 2-month interval schedule at one month after the last dose.	Mean: 7442 EU/mL	Mean: 15304 EU/mL	Ratio 2.06 (1.60 to 2.64) 136 participants in 1 study	⊕⊕⊕O MODERATE [1]
	24 months after first dose	There was moderate-certainty evidence that females aged 9 to 14 years receiving two doses of the bivalent HPV vaccine with a 6-month interval schedule had higher GMTs for HPV 16 compared to a 2-month interval schedule at 24 months.	Mean: 1170 EU/mL	Mean: 2274 EU/mL	Ratio 1.94 (1.44 to 2.62) 124 participants in 1 study	⊕⊕⊕O MODERATE [1]
GMTs for HPV 18 Follow-up: up to 24 months (Canada/Germany1)	One month after last dose	There was moderate-certainty evidence that females aged 9 to 14 years receiving two doses of the bivalent HPV vaccine with a 6-month interval schedule had higher GMTs for HPV 18 compared to a 2-month interval schedule at one month after the last dose.	Mean: 5095 EU/mL	Mean: 8155 EU/mL	Ratio 1.60 (1.22 to 2.10) 132 participants in 1 study	⊕⊕⊕O MODERATE [1]
	24 months after first dose	There was moderate-certainty evidence that females aged 9 to 14 years receiving two doses of the bivalent HPV vaccine with a 6-month interval schedule had higher GMTs for HPV 18 compared to a 2-month interval schedule at 24 months.	Mean: 450 EU/mL	Mean: 980 EU/mL	Ratio 2.18 (1.54 to 3.07) 121 participants in 1 study	⊕⊕⊕O MODERATE [1]

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

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

Forest plot: longer interval (6 months) versus shorter interval (2 months) between two doses of 2-valent HPV vaccine in females – immunogenicity outcomes at all timepoints

Participants: 9 to 14-year old females (seronegative at baseline)
Setting: Canada, Germany
Comparison: longer interval schedule (0, 6 months) versus shorter interval schedule (0, 2 months) of 2-valent HPV vaccine

Outcome	Forest plot	Certainty of the evidence (GRADE)
Ratio of GMTs Follow up: one month after last dose and 24 months after first dose (Canada/Germany1)		⊕⊕⊕O MODERATE

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

Summary of Findings: longer interval (12 months) versus shorter interval (6 months) between two doses of bivalent HPV vaccine in females – immunogenicity outcomes at all timepoints

Participants: 9 to 14-year old females (seronegative at baseline)
Setting: 33 sites in Canada, Germany, Italy, Taiwan, and Thailand
Comparison: longer interval schedule (0, 12 months) versus shorter interval schedule (0, 6 months) of bivalent HPV vaccine

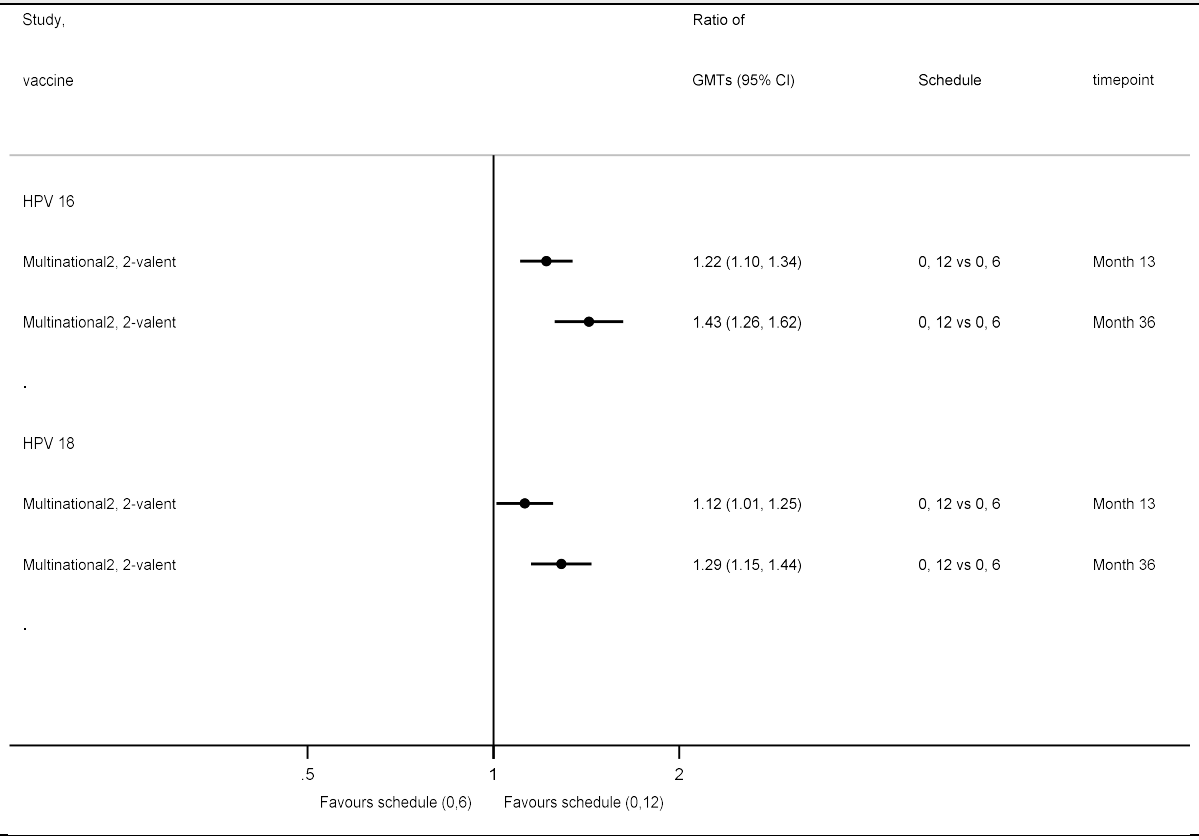
Outcome		Plain language summary	Absolute effect		Relative effect (95% CI) Nº of participants & studies	Certainty of the evidence (GRADE)
			0, 6-month schedule	0, 12-month schedule		
GMTs for HPV 16 Follow-up: up to 36 months (Multinational2)	One month after last dose	There was high-certainty evidence that females aged 9 to 14 years receiving two doses of the bivalent HPV vaccine with a 12-month interval schedule had higher GMTs for HPV 16 compared to a 6-month interval schedule at one month after last dose.	Mean: 9396 EU/mL	Mean: 11,450 EU/mL	Ratio 1.22 (1.10 to 1.34) 835 participants in 1 study	⨁⨁⨁⨁ HIGH
	36 months after first dose	There was high-certainty evidence that females aged 9 to 14 years receiving two doses of the bivalent HPV vaccine with a 12-month interval schedule had higher GMTs for HPV 16 compared to a 6-month interval schedule at 36 months.	Mean: 563 EU/mL	Mean: 804 EU/mL	Ratio 1.43 (1.26 to 1.62) 817 participants in 1 study	⨁⨁⨁⨁ HIGH
GMTs for HPV 18 Follow-up: up to 36 months (Multinational2)	One month after last dose	There was high-certainty evidence that females aged 9 to 14 years receiving two doses of the bivalent HPV vaccine with a 12-month interval schedule had higher GMTs for HPV 18 compared to a 6-month interval schedule at one month after last dose.	Mean: 5921 EU/mL	Mean: 6656 EU/mL	Ratio 1.12 (1.01 to 1.25) 854 participants in 1 study	⨁⨁⨁⨁ HIGH
	36 months after first dose	There was high-certainty evidence that females aged 9 to 14 years receiving two doses of the bivalent HPV vaccine with a 12-month interval schedule had higher GMTs for HPV 18 compared to a 6-month interval schedule at 36 months.	Mean: 1210 EU/mL	Mean: 1559 EU/mL	Ratio 1.29 (1.15 to 1.44) 794 participants in 1 study	⨁⨁⨁⨁ HIGH
Seroconversion to HPV 16 Follow-up: up to 36 months (Multinational2)	One month after last dose	There was high-certainty evidence of no difference in rates of seroconversion to HPV 16 between receiving two doses of the bivalent HPV vaccine with a 12-month interval schedule and a 6-month interval schedule in females aged 9 to 14 years at one month after last dose.	480/480 (100%)	355/355 (100%)	RR 1.00 (not estimable) 835 participants in 1 study	⨁⨁⨁⨁ HIGH
	36 months after first dose	There was high-certainty evidence of no difference in rates of seroconversion to HPV 16 between receiving two doses of the bivalent HPV vaccine with a 12-month interval schedule and a 6-month interval schedule in females aged 9 to 14 years at 36 months.	455/455 (100%)	339/399 (100%)	RR 1.00 (not estimable) 854 participants in 1 study	⨁⨁⨁⨁ HIGH

Seroconversion to HPV 18 Follow-up: up to 36 months (Multinational2)	One month after last dose	There was high-certainty evidence of no difference in rates of seroconversion to HPV 18 between receiving two doses of the bivalent HPV vaccine with a 12-month interval schedule and a 6-month interval schedule in females aged 9 to 14 years at one month after last dose.	485/485 (100%)	369/369 (100%)	RR 1.00 (not estimable) 854 participants in 1 study	⊕⊕⊕⊕ HIGH
	36 months after first dose	There was high-certainty evidence of no difference in rates of seroconversion to HPV 18 between receiving two doses of the bivalent HPV vaccine with a 12-month interval schedule and a 6-month interval schedule in females aged 9 to 14 years at 36 months.	461/462 (99.8%)	355/355 (100%)	RR 0.99 (0.99 to 1.00) 817 participants in 1 study	⊕⊕⊕⊕ HIGH

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

Forest plots: longer interval (12 months) versus shorter interval (6 months) between two doses of bivalent HPV vaccine in females – immunogenicity outcomes at all timepoints

Participants: 9 to 14-year old females (seronegative at baseline)
Setting: 33 sites in Canada, Germany, Italy, Taiwan, and Thailand
Comparison: longer interval schedule (0, 12 months) versus shorter interval schedule (0, 6 months) of bivalent HPV vaccine

Outcome	Forest plot	Certainty of the evidence (GRADE)
Ratio of GMTs Follow up: one month after last dose and 36 months after first dose (Multinational2)		⊕⊕⊕⊕ HIGH

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

Forest plot for seroconversion not included as all participants seroconverted at 7 months.

Summary of Findings: longer interval (12 months) versus shorter interval (6 months) between two doses of nonavalent HPV vaccine in females and males – immunogenicity outcomes one month after last dose

Participants: 9 to 14-year old females and males (seronegative at baseline)
Setting: 66 sites in Africa, Asia, Europe, Latin America, North America
Comparison: longer interval schedule (0, 12 months) versus shorter interval schedule (0, 6 months) of nonavalent HPV vaccine

Outcome		Plain language summary	Absolute effect		Relative effect (95% CI) Nº of participants & studies	Certainty of the evidence (GRADE)
			0, 6-month schedule	0, 12-month schedule		
GMTs for HPV 6 Follow-up: one month after last dose (Multinational3)	Females	There was high-certainty evidence that females aged 9 to 14 years receiving two doses of the nonavalent HPV vaccine with a 12-month interval schedule had higher GMTs for HPV 6 compared to a 6-month interval schedule at one month after the last dose.	Mean: 1657.9 mMU/mL	Mean: 2685.7 mMU/mL	Ratio 1.62 (1.32 to 1.98) 381 participants in 1 study	⊕⊕⊕⊕ HIGH
	Males	There was high-certainty evidence that males aged 9 to 14 years receiving two doses of the nonavalent HPV vaccine with a 12-month interval schedule had higher GMTs for HPV 6 compared to a 6-month interval schedule at one month after the last dose.	Mean: 1557.4 mMU/mL	Mean: 2672.4 mMU/mL	Ratio 1.72 (1.41 to 2.09) 397 participants in 1 study	⊕⊕⊕⊕ HIGH
GMTs for HPV 11 Follow-up: one month after last dose (Multinational3)	Females	There was high-certainty evidence that females aged 9 to 14 years receiving two doses of the nonavalent HPV vaccine with a 12-month interval schedule had higher GMTs for HPV 11 compared to a 6-month interval schedule at one month after the last dose.	Mean: 1388.9 mMU/mL	Mean: 2915.9 mMU/mL	Ratio 2.10 (1.72 to 2.56) 381 participants in 1 study	⊕⊕⊕⊕ HIGH
	Males	There was high-certainty evidence that males aged 9 to 14 years receiving two doses of the nonavalent HPV vaccine with a 12-month interval schedule had higher GMTs for HPV 11 compared to a 6-month interval schedule at one month after the last dose.	Mean: 1423.9 mMU/mL	Mean: 2965.9 mMU/mL	Ratio 2.08 (1.72 to 2.53) 398 participants in 1 study	⊕⊕⊕⊕ HIGH
GMTs for HPV 16 Follow-up: one month after last dose (Multinational3)	Females	There was high-certainty evidence that females aged 9 to 14 years receiving two doses of the nonavalent HPV vaccine with a 12-month interval schedule had higher GMTs for HPV 16 compared to a 6-month interval schedule at one month after the last dose.	Mean: 8004.9 mMU/mL	Mean: 13828.1 mMU/mL	Ratio 1.73 (1.42 to 2.10) 401 participants in 1 study	⊕⊕⊕⊕ HIGH
	Males	There was high-certainty evidence that males aged 9 to 14 years receiving two doses of the nonavalent HPV vaccine with a 12-month interval schedule had higher GMTs for HPV 16 compared to a 6-month interval schedule.	Mean: 8474.8 mMU/mL	Mean: 14825.2 mMU/mL	Ratio 1.75 (1.44 to 2.12) 408 participants in 1 study	⊕⊕⊕⊕ HIGH
GMTs for HPV 18	Females	There was high-certainty evidence that females aged 9 to 14 years receiving two doses of the nonavalent HPV vaccine with a 12-month interval schedule had higher GMTs for HPV 18	Mean: 1872.8 mMU/mL	Mean: 2696 mMU/mL	Ratio 1.44 (1.16 to 1.79) 401 participants in 1 study	⊕⊕⊕⊕ HIGH

Follow-up: one month after last dose (Multinational3)		compared to a 6-month interval schedule at one month after the last dose.				
	Males	There was high-certainty evidence that males aged 9 to 14 years receiving two doses of the nonavalent HPV vaccine with a 12-month interval schedule had higher GMTs for HPV 18 compared to a 6-month interval schedule at one month after the last dose.	Mean: 1860.9 mMU/mL	Mean: 2922.5 mMU/mL	Ratio 1.57 (1.27 to 1.95) 409 participants in 1 study	⊕⊕⊕⊕ HIGH
GMTs for HPV 31 Follow-up: one month after last dose (Multinational3)	Females	There was high-certainty evidence that females aged 9 to 14 years receiving two doses of the nonavalent HPV vaccine with a 12-month interval schedule had higher GMTs for HPV 31 compared to a 6-month interval schedule at one month after the last dose.	Mean: 1436.3 mMU/mL	Mean: 2086.4 mMU/mL	Ratio 1.45 (1.18 to 1.79) 404 participants in 1 study	⊕⊕⊕⊕ HIGH
	Males	There was high-certainty evidence that males aged 9 to 14 years receiving two doses of the nonavalent HPV vaccine with a 12-month interval schedule had higher GMTs for HPV 31 compared to a 6-month interval schedule at one month after the last dose.	Mean: 1498.2 mMU/mL	Mean: 2148.1 mMU/mL	Ratio 1.43 (1.17 to 1.76) 407 participants in 1 study	⊕⊕⊕⊕ HIGH
GMTs for HPV 33 Follow-up: one month after last dose (Multinational3)	Females	There was high-certainty evidence that females aged 9 to 14 years receiving two doses of the nonavalent HPV vaccine with a 12-month interval schedule had higher GMTs for HPV 33 compared to a 6-month interval schedule at one month after the last dose.	Mean: 1030 mMU/mL	Mean: 2037.4 mMU/mL	Ratio 1.98 (1.63 to 2.40) 405 participants in 1 study	⊕⊕⊕⊕ HIGH
	Males	There was high-certainty evidence that males aged 9 to 14 years receiving two doses of the nonavalent HPV vaccine with a 12-month interval schedule had higher GMTs for HPV 33 compared to a 6-month interval schedule at one month after the last dose.	Mean: 1040.0 mMU/mL	Mean: 2363.6 mMU/mL	Ratio 2.27 (1.87 to 2.76) 408 participants in 1 study	⊕⊕⊕⊕ HIGH
GMTs for HPV 45 Follow-up: one month after last dose (Multinational3)	Females	There was high-certainty evidence of little to no difference in GMTs for HPV 45 between receiving two doses of the nonavalent HPV vaccine with a 12-month interval schedule and a 6-month interval schedule in females aged 9 to 14 years at one month after the last dose.	Mean: 357.6 mMU/mL	Mean: 439.6 mMU/mL	Ratio 1.23 (0.98 to 1.54) 406 participants in 1 study	⊕⊕⊕⊕ HIGH
	Males	There was high-certainty evidence of little to no difference in GMTs for HPV 45 between receiving two doses of the nonavalent HPV vaccine with a 12-month interval schedule and a 6-month interval schedule in males aged 9 to 14 years at one month after the last dose.	Mean: 352.3 mMU/mL	Mean: 397.6 mMU/mL	Ratio 1.13 (0.90 to 1.41) 409 participants in 1 study	⊕⊕⊕⊕ HIGH
GMTs for HPV 52 Follow-up: one month after last dose	Females	There was high-certainty evidence that females aged 9 to 14 years receiving two doses of the nonavalent HPV vaccine with a 12-month interval schedule had higher GMTs for HPV 52 compared to a 6-month interval schedule at one month after the last dose.	Mean: 581.1 mMU/mL	Mean: 1028.2 mMU/mL	Ratio 1.77 (1.47 to 2.13) 403 participants in 1 study	⊕⊕⊕⊕ HIGH

(Multinational3)	Males	There was high-certainty evidence that males aged 9 to 14 years receiving two doses of the nonavalent HPV vaccine with a 12-month interval schedule had higher GMTs for HPV 52 compared to a 6-month interval schedule at one month after the last dose.	Mean: 640.4 mMU/mL	Mean: 1222.7 mMU/mL	Ratio 1.91 (1.59 to 2.29) 410 participants in 1 study	⊕⊕⊕⊕ HIGH
GMTs for HPV 58 Follow-up: one month after last dose (Multinational3)	Females	There was high-certainty evidence that females aged 9 to 14 years receiving two doses of the nonavalent HPV vaccine with a 12-month interval schedule had higher GMTs for HPV 58 compared to a 6-month interval schedule at one month after the last dose.	Mean: 1251.2 mMU/mL	Mean: 2244.7 mMU/mL	Ratio 1.79 (1.48 to 2.17) 399 participants in 1 study	⊕⊕⊕⊕ HIGH
	Males	There was high-certainty evidence that males aged 9 to 14 years receiving two doses of the nonavalent HPV vaccine with a 12-month interval schedule had higher GMTs for HPV 58 compared to a 6-month interval schedule at one month after the last dose.	Mean: 1325.7 mMU/mL	Mean: 2650.7 mMU/mL	Ratio 2.00 (1.66 to 2.41) 406 participants in 1 study	⊕⊕⊕⊕ HIGH
Seroconversion to HPV 6 Follow-up: one month after last dose (Multinational3)	Females	There was high-certainty evidence of little to no difference in seroconversion to HPV 6 between receiving two doses of the nonavalent HPV vaccine with a 12-month interval schedule and a 6-month interval schedule in females aged 9 to 14 years at one month after the last dose.	257/258 (99.6%)	123/123 (100%)	RR 1.00 (0.99 to 1.02) 381 participants in 1 study	⊕⊕⊕⊕ HIGH
	Males	There was high-certainty evidence of little to no difference in seroconversion to HPV 6 between receiving two doses of the nonavalent HPV vaccine with a 12-month interval schedule and a 6-month interval schedule in males aged 9 to 14 years at one month after the last dose.	263/263 (100%)	134/134 (100%)	RR 1.00 (0.99 to 1.01) 397 participants in 1 study	⊕⊕⊕⊕ HIGH
Seroconversion to HPV 11 Follow-up: one month after last dose (Multinational3)	Females	There was high-certainty evidence of little to no difference in seroconversion to HPV 11 between receiving two doses of the nonavalent HPV vaccine with a 12-month interval schedule and a 6-month interval schedule in females aged 9 to 14 years at one month after the last dose.	258/258 (100%)	123/123 (100%)	RR 1.00 (0.99 to 1.01) 381 participants in 1 study	⊕⊕⊕⊕ HIGH
	Males	There was high-certainty evidence of little to no difference in seroconversion to HPV 11 between receiving two doses of the nonavalent HPV vaccine with a 12-month interval schedule and a 6-month interval schedule in males aged 9 to 14 years at one month after the last dose.	264/264 (100%)	134/134 (100%)	RR 1.00 (0.99 to 1.01) 398 participants in 1 study	⊕⊕⊕⊕ HIGH
Seroconversion to HPV 16 Follow-up: one month after last dose	Females	There was high-certainty evidence of little to no difference in seroconversion to HPV 16 between receiving two doses of the nonavalent HPV vaccine with a 12-month interval schedule and a 6-month interval schedule in females aged 9 to 14 years at one month after the last dose.	272/272 (100%)	129/129 (100%)	RR 1.00 (0.99 to 1.01) 401 participants in 1 study	⊕⊕⊕⊕ HIGH

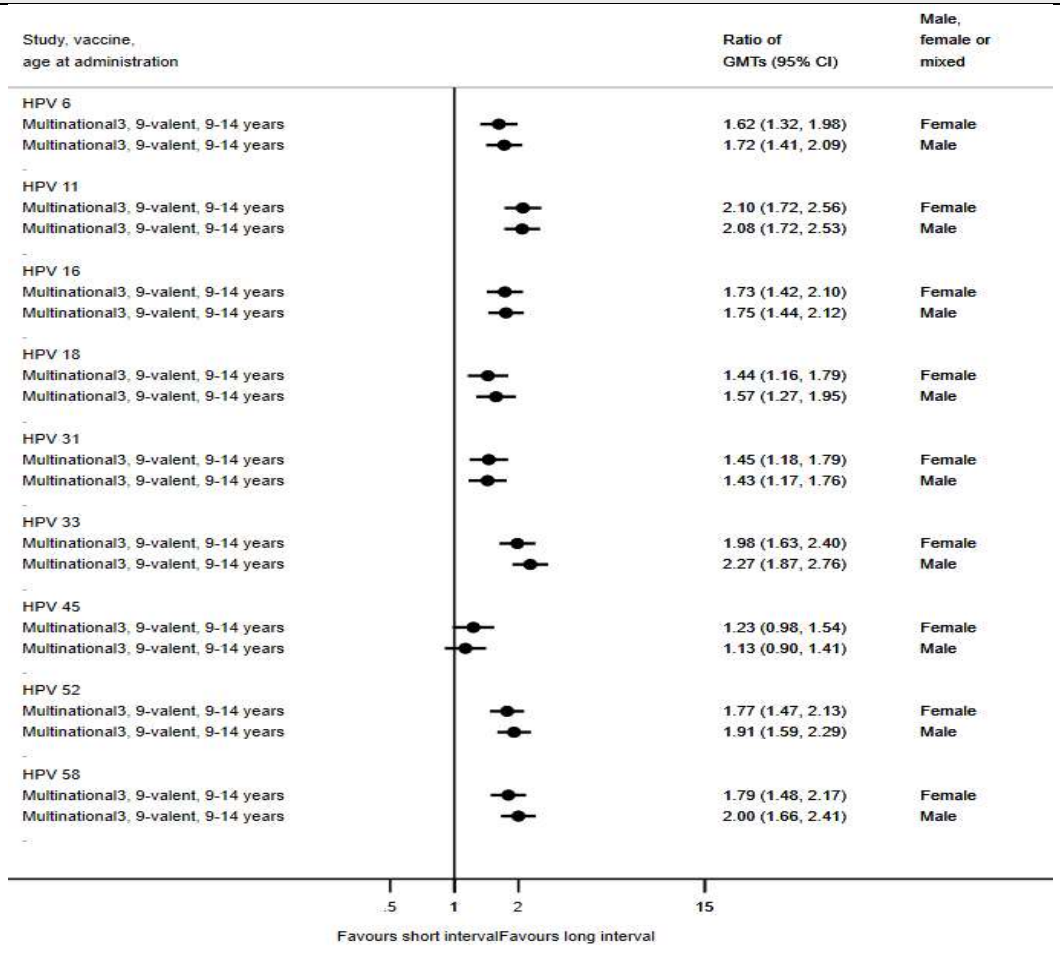
(Multinational3)	Males	There was high-certainty evidence of little to no difference in seroconversion to HPV 16 between receiving two doses of the nonavalent HPV vaccine with a 12-month interval schedule and a 6-month interval schedule in males aged 9 to 14 years at one month after the last dose.	273/273 (100%)	135/135 (100%)	RR 1.00 (0.99 to 1.01) 408 participants in 1 study	⊕⊕⊕⊕ HIGH
Seroconversion to HPV 18 Follow-up: one month after last dose (Multinational3)	Females	There was high-certainty evidence of little to no difference in seroconversion to HPV 18 between receiving two doses of the nonavalent HPV vaccine with a 12-month interval schedule and a 6-month interval schedule in females aged 9 to 14 years at one month after the last dose.	272/272 (100%)	129/129 (100%)	RR 1.00 (0.99 to 1.01) 401 participants in 1 study	⊕⊕⊕⊕ HIGH
	Males	There was high-certainty evidence of little to no difference in seroconversion to HPV 18 between receiving two doses of the nonavalent HPV vaccine with a 12-month interval schedule and a 6-month interval schedule in males aged 9 to 14 years at one month after the last dose.	272/272 (100%)	137/137 (100%)	RR 1.00 (0.99 to 1.01) 409 participants in 1 study	⊕⊕⊕⊕ HIGH
Seroconversion to HPV 31 Follow-up: one month after last dose	Females	There was high-certainty evidence of little to no difference in seroconversion to HPV 31 between receiving two doses of the nonavalent HPV vaccine with a 12-month interval schedule and a 6-month interval schedule in females aged 9 to 14 years at one month after the last dose.	271/272 (99.6%)	132/132 (100%)	RR 1.00 (0.99 to 1.02) 404 participants in 1 study	⊕⊕⊕⊕ HIGH
	Males	There was high-certainty evidence of little to no difference in seroconversion to HPV 31 between receiving two doses of the nonavalent HPV vaccine with a 12-month interval schedule and a 6-month interval schedule in males aged 9 to 14 years at one month after the last dose.	271/271 (100%)	136/136 (100%)	RR 1.00 (0.99 to 1.01) 407 participants in 1 study	⊕⊕⊕⊕ HIGH
Seroconversion to HPV 33 Follow-up: one month after last dose (Multinational3)	Females	There was high-certainty evidence of little to no difference in seroconversion to HPV 33 between receiving two doses of the nonavalent HPV vaccine with a 12-month interval schedule and a 6-month interval schedule in females aged 9 to 14 years at one month after the last dose.	272/273 (99.6%)	132/132 (100%)	RR 1.00 (0.99 to 1.02) 405 participants in 1 study	⊕⊕⊕⊕ HIGH
	Males	There was high-certainty evidence of little to no difference in seroconversion to HPV 33 between receiving two doses of the nonavalent HPV vaccine with a 12-month interval schedule and a 6-month interval schedule in males aged 9 to 14 years at one month after the last dose.	271/271 (100%)	137/137 (100%)	RR 1.00 (0.99 to 1.01) 408 participants in 1 study	⊕⊕⊕⊕ HIGH
Seroconversion to HPV 45	Females	There was high-certainty evidence of little to no difference in seroconversion to HPV 45 between receiving two doses of the nonavalent HPV vaccine with a 12-month interval schedule and	272/274 (99.3%)	132/132 (100%)	RR 1.00 (0.99 to 1.02) 406 participants in 1 study	⊕⊕⊕⊕ HIGH

Follow-up: one month after last dose (Multinational3)		a 6-month interval schedule in females aged 9 to 14 years at one month after the last dose.				
	Males	There was high-certainty evidence of little to no difference in seroconversion to HPV 45 between receiving two doses of the nonavalent HPV vaccine with a 12-month interval schedule and a 6-month interval schedule in males aged 9 to 14 years at one month after the last dose.	271/273 (99.3%)	136/136 (100%)	RR 1.00 (0.99 to 1.02) 409 participants in 1 study	⊕⊕⊕⊕ HIGH
Seroconversion to HPV 52 Follow-up: one month after last dose (Multinational3)	Females	There was high-certainty evidence of little to no difference in seroconversion to HPV 52 between receiving two doses of the nonavalent HPV vaccine with a 12-month interval schedule and a 6-month interval schedule in females aged 9 to 14 years at one month after the last dose.	272/274 (99.3%)	132/132 (100%)	RR 1.00 (0.99 to 1.02) 406 participants in 1 study	⊕⊕⊕⊕ HIGH
	Males	There was high-certainty evidence of little to no difference in seroconversion to HPV 52 between receiving two doses of the nonavalent HPV vaccine with a 12-month interval schedule and a 6-month interval schedule in males aged 9 to 14 years at one month after the last dose.	271/273 (99.3%)	136/136 (100%)	RR 1.00 (0.99 to 1.02) 409 participants in 1 study	⊕⊕⊕⊕ HIGH
Seroconversion to HPV 58 Follow-up: one month after last dose (Multinational3)	Females	There was high-certainty evidence of little to no difference in seroconversion to HPV 58 between receiving two doses of the nonavalent HPV vaccine with a 12-month interval schedule and a 6-month interval schedule in females aged 9 to 14 years at one month after the last dose.	270/270 (100%)	129/129 (100%)	RR 1.00 (0.99 to 1.01) 399 participants in 1 study	⊕⊕⊕⊕ HIGH
	Males	There was high-certainty evidence of little to no difference in seroconversion to HPV 58 between receiving two doses of the nonavalent HPV vaccine with a 12-month interval schedule and a 6-month interval schedule in males aged 9 to 14 years at one month after the last dose.	270/270 (100%)	136/136 (100%)	RR 1.00 (0.99 to 1.01) 406 participants in 1 study	⊕⊕⊕⊕ HIGH

CI= confidence interval; GMT= geometric mean titre; HPV= human papilloma virus; mMU= milli-Merck units

Forest plots: longer interval (12 months) versus shorter interval (6 months) between two doses of nonavalent HPV vaccine in females and males – immunogenicity outcomes one month after last dose

Participants: 9 to 14-year old females and males (seronegative at baseline)
Setting: 66 sites in Africa, Asia, Europe, Latin America, North America
Comparison: longer interval schedule (0, 12 months) versus shorter interval schedule (0, 6 months) of nonavalent HPV vaccine

Outcome	Forest plot	Certainty of the evidence (GRADE)
Ratio of GMTs Follow up: one month after last dose (Multinational3)		⊕⊕⊕⊕ HIGH

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

Summary of Findings: longer interval (6 months) versus shorter interval (3 months) between two doses of quadrivalent HPV vaccine in females – immunogenicity outcomes 6 months after the second dose

Participants: 11 to 13-year old females (seronegative at baseline).
Setting: Vietnam
Comparison: longer interval schedule (0, 6 months) versus shorter interval schedule (0, 3 months) of 4-valent HPV vaccine

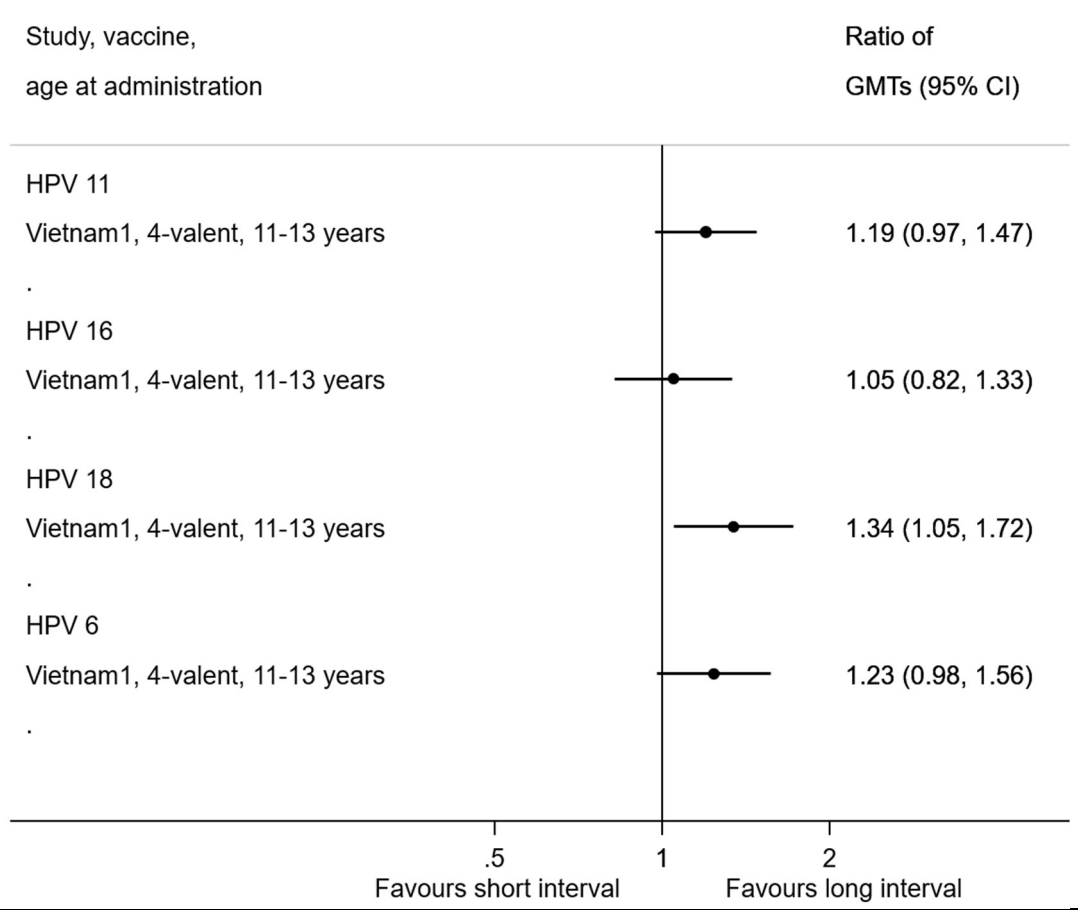
Outcome	Plain language summary	Absolute effect		Relative effect (95% CI) Nº of participants & studies	Certainty of the evidence (GRADE)
		0, 3-month schedule	0, 6-month schedule		
GMTs for HPV 6 Follow-up: 6 months after the second dose (Vietnam1)	There was moderate-certainty evidence of little to no difference in GMTs for HPV 6 between receiving two doses of the quadrivalent HPV vaccine with a 6-month interval schedule and a 3-month interval schedule in females aged 11 to 13 years at six months after the second dose.	Mean: 132.0 AU/mL	Mean: 163.0 AU/mL	Ratio 1.23 (0.98 to 1.56) 447 participants in 1 study	⨁⨁⨁◯ MODERATE [1]
GMTs for HPV 11 Follow-up: 6 months after the second dose (Vietnam1)	There was moderate-certainty evidence of little to no difference in GMTs for HPV 11 between receiving two doses of the quadrivalent HPV vaccine with a 6-month interval schedule and a 3-month interval schedule in females aged 11 to 13 years at six months after the second dose.	Mean: 219.5 AU/mL	Mean: 262.1 AU/mL	Ratio 1.19 (0.97 to 1.47) 447 participants in 1 study	⨁⨁⨁◯ MODERATE [1]
GMTs for HPV 16 Follow-up: 6 months after the second dose (Vietnam1)	There was moderate-certainty evidence of little to no difference in GMTs for HPV 16 between receiving two doses of the quadrivalent HPV vaccine with a 6-month interval schedule and a 3-month interval schedule in females aged 11 to 13 years at six months after the second dose.	Mean: 880.6 AU/mL	Mean: 920.6 AU/mL	Ratio 1.05 (0.82 to 1.33) 447 participants in 1 study	⨁⨁⨁◯ MODERATE [1]
GMTs for HPV 18 Follow-up: 6 months after the second dose (Vietnam1)	There was moderate-certainty evidence that females aged 11 to 13 years receiving two doses of the quadrivalent HPV vaccine with a 6-month interval schedule had higher GMTs for HPV 18 compared to a 3-month interval schedule at six months after the second dose.	Mean: 100.8 AU/mL	Mean: 135.0 AU/mL	Ratio 1.34 (1.05 to 1.72) 447 participants in 1 study	⨁⨁⨁◯ MODERATE [1]

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

[1]Downgraded one level due to limitations in study design: this was a cluster RCT and correlation between the clusters were not taken into account in this analysis.

Forest plots: longer interval (6 months) versus shorter interval (3 months) between two doses of quadrivalent HPV vaccine in females – immunogenicity outcomes 6 months after the second dose

Participants: 11 to 13-year old females (seronegative at baseline).
Setting: Vietnam
Comparison: longer interval schedule (0, 6 months) versus shorter interval schedule (0, 3 months) of quadrivalent HPV vaccine

Outcome	Forest plot	Certainty of the evidence (GRADE)
Ratio of GMTs Follow up: 6 months after the second dose (Vietnam1)		⊕⊕⊕O MODERATE

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

DATA FROM POST-HOC ANALYSES OF RCTS

Summary of Findings: longer interval (6 months) versus shorter interval (1 month) between two doses of bivalent HPV vaccine in females – clinical outcomes at 84 months

Participants: 18 to 25-year old females (seronegative at baseline).
Setting: Costa Rica
Comparison: longer interval schedule (0, 6 months) versus shorter interval schedule (0, 1 months) of bivalent HPV vaccine

Outcome	Plain language summary	Absolute effect		Relative effect (95% CI) Nº of participants & studies	Certainty of the evidence (GRADE)
		0, 1-month schedule	0, 6-month schedule		
Cumulative incident HPV 16 infections Follow-up: 84 months (Costa Rica1)	In females aged 18 to 25 years receiving two doses of the bivalent HPV vaccine with a 6-month interval schedule or a 1-month interval schedule, there was very low-certainty evidence of an effect on cumulative incidence of HPV 16 infections in favour of a 6-month interval at 84 months follow-up. However, the confidence intervals were very wide and crossed the line of no effect.	28 per 1000	14 per 1000 (2 to 115)	RR 0.49 (0.06 to 4.15) 253 participants in 1 study	⊕OOO VERY LOW[1,2,3]
Cumulative incident HPV 18 infections Follow-up: 84 months (Costa Rica1)	In females aged 18 to 25 years receiving two doses of the bivalent HPV vaccine with a 6-month interval schedule or a 1-month interval schedule, there was very low-certainty evidence of an effect on cumulative incidence of HPV 18 infections in favour of a 1-month interval at 84 months follow-up. However, the confidence intervals were very wide and crossed the line of no effect.	11 per 1000	26 per 1000 (4 to 179)	RR 2.40 (0.34 to 16.72) 265 participants in 1 study	⊕OOO VERY LOW[1,2,3]
Cumulative incident HPV 16/18 infections Follow-up: 84 months (Costa Rica1)	There was very low-certainty evidence of little to no difference in cumulative incidence of HPV 16/18 infections between receiving two doses of the bivalent HPV vaccine with a 6-month interval schedule and a 1-month interval schedule in females aged 18 to 25 years at 84 months follow-up.	36 per 1000	38 per 1000 (10 to 145)	RR 1.05 (0.28 to 3.98) 270 participants in 1 study	⊕OOO VERY LOW[1,2,3]
Cumulative incident HPV 31/33/45 infections Follow-up: 84 months (Costa Rica1)	In females aged 18 to 25 years receiving two doses of the bivalent HPV vaccine with a 6-month interval schedule or a 1-month interval schedule, there was very low-certainty evidence of an effect on cumulative incidence of HPV 31/33/45 infections in favour of a 6-month interval at 84 months follow-up. However, the confidence intervals were very wide and crossed the line of no effect.	150 per 1000	89 per 1000 (41 to 194)	RR 0.59 (0.27 to 1.29) 272 participants in 1 study	⊕OOO VERY LOW[1,2,3]
Cumulative incident HPV infections (other carcinogenic) Follow-up: 84 months	There was low-certainty evidence of little to no difference in cumulative incidence of HPV infections (other carcinogenic) between receiving two doses of the bivalent HPV vaccine with a 6-month interval schedule and a 1-month interval schedule in females aged 18 to 25 years at 84 months follow-up.	461 per 1000	443 per 1000 (332 to 590)	RR 0.96 (0.72 to 1.28) 272 participants in 1 study	⊕⊕OO LOW[1,2,4]

(Costa Rica1)					
Cumulative incident HPV infections (non-carcinogenic) Follow-up: 84 months (Costa Rica1)	There was low-certainty evidence of little to no difference in cumulative incidence of HPV infections (non-carcinogenic) in females aged 18 to 25 years receiving two doses of the bivalent HPV vaccine with a 6-month interval schedule compared to a 1-month interval schedule at 84 months follow-up.	575 per 1000	529 per 1000 (420 to 673)	RR 0.92 (0.73 to 1.17) 272 participants in 1 study	⊕⊕OO LOW[1,2,4]

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

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

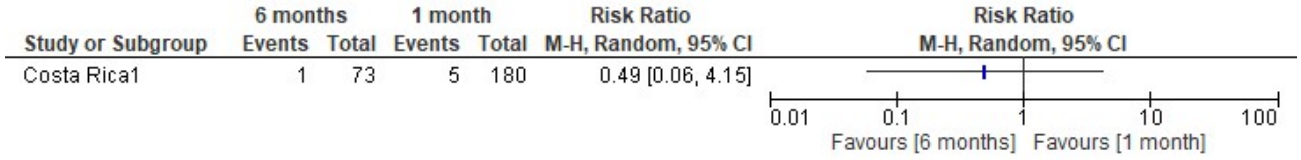
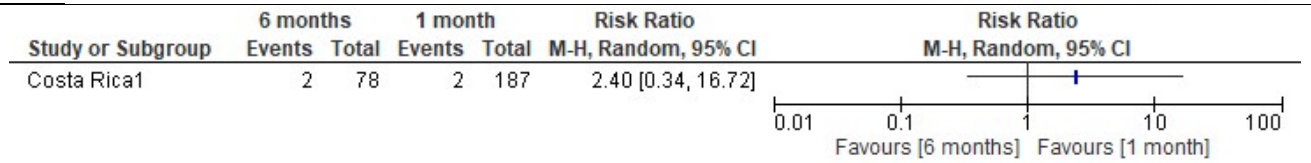
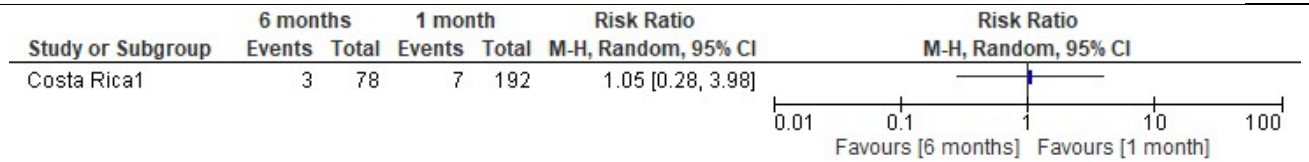
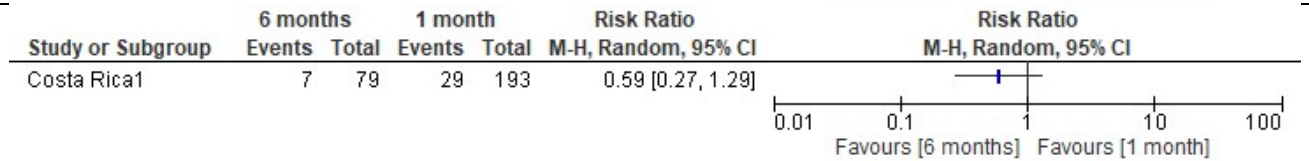
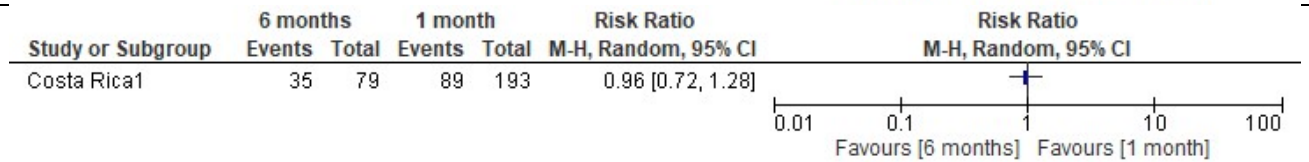
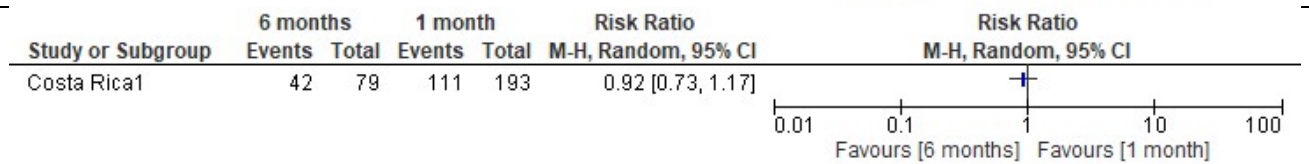
[2]Upgraded one level: observational study that demonstrates moderate control of confounding factors

[3]Downgraded two levels for imprecision: few events and a 95% CI that encompasses a potential large harm and potential large benefit

[4]Downgraded one level for imprecision: few events

Forest plots: longer interval (6 months) versus shorter interval (1 month) between two doses of 2-valent HPV vaccine in females – clinical outcomes at 84 months

Participants: 18 to 25-year old females (seronegative at baseline).
Setting: Costa Rica
Comparison: longer interval schedule (0, 6 months) versus shorter interval schedule (0, 1 months) of 2-valent HPV vaccine

Outcome	Forest plot	Certainty of the evidence (GRADE)
Cumulative incident HPV 16 infections Follow up: 84 months (Costa Rica1)		⊕OOO VERY LOW
Cumulative incident HPV 18 infections Follow up: 84 months (Costa Rica1)		⊕OOO VERY LOW
Cumulative incident HPV 16/18 infections Follow up: 84 months (Costa Rica1)		⊕OOO VERY LOW
Cumulative incident HPV 31/33/45 infections Follow up: 84 months (Costa Rica1)		⊕OOO VERY LOW
Cumulative incident HPV infections (other carcinogenic) Follow up: 84 months (Costa Rica1)		⊕⊕OO LOW
Cumulative incident HPV infections (non- carcinogenic) Follow up: 84 months (Costa Rica1)		⊕⊕OO LOW

Summary of Findings: longer interval (6 months) versus shorter interval (1 month) between two doses of bivalent HPV vaccine in females – immunogenicity outcomes at 48 and 84 months

Participants: 18 to 25-year old females (seronegative at baseline).
Setting: Costa Rica
Comparison: longer interval schedule (0, 6 months) versus shorter interval schedule (0, 1 months) of bivalent HPV vaccine

Outcome		Plain language summary	Absolute effect		Relative effect (95% CI) Nº of participants & studies	Certainty of the evidence (GRADE)
			0, 1-month schedule	0, 6-month schedule		
GMT of HPV 16 Follow-up: up to 84 months (Costa Rica1)	48 months	There was low-certainty evidence that females aged 18 to 25 years receiving two doses of the bivalent HPV vaccine with a 6-month interval schedule had higher GMTs for HPV 16 compared to a 1-month interval schedule at 48 months follow-up.	Mean: 407 EU/mL	Mean: 555 EU/mL	Ratio 1.36 (1.06 to 1.76) 272 participants in 1 study	⨁⨁◯◯ LOW[1,2,3]
	84 months	There was low-certainty evidence of little to no difference in GMTs of HPV 16 between receiving two doses of the bivalent HPV vaccine with a 6-month interval schedule and a 1-month interval schedule in females aged 18 to 25 years at 84 months follow-up.	Mean: 379 EU/mL	Mean: 460 EU/mL	Ratio 1.21 (0.94 to 1.57) 272 participants in 1 study	⨁⨁◯◯ LOW[1,2,3]
GMT of HPV 18 Follow-up: up to 84 months (Costa Rica1)	48 months	There was low-certainty evidence that females aged 18 to 25 years receiving two doses of the bivalent HPV vaccine with a 6-month interval schedule had higher GMTs for HPV 18 compared to a 1-month interval schedule at 48 months follow-up. However, the confidence intervals crossed the line of no effect.	Mean: 232 EU/mL	Mean: 296 EU/mL	Ratio 1.28 (0.99 to 1.65) 272 participants in 1 study	⨁⨁◯◯ LOW[1,2,3]
	84 months	There was low-certainty evidence of little to no difference in GMTs of HPV 18 between receiving two doses of the bivalent HPV vaccine with a 6-month interval schedule and a 1-month interval schedule in females aged 18 to 25 years at 84 months follow-up.	Mean: 228 EU/mL	Mean: 270 EU/mL	Ratio 1.18 (0.93 to 1.52) 272 participants in 1 study	⨁⨁◯◯ LOW[1,2,3]

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

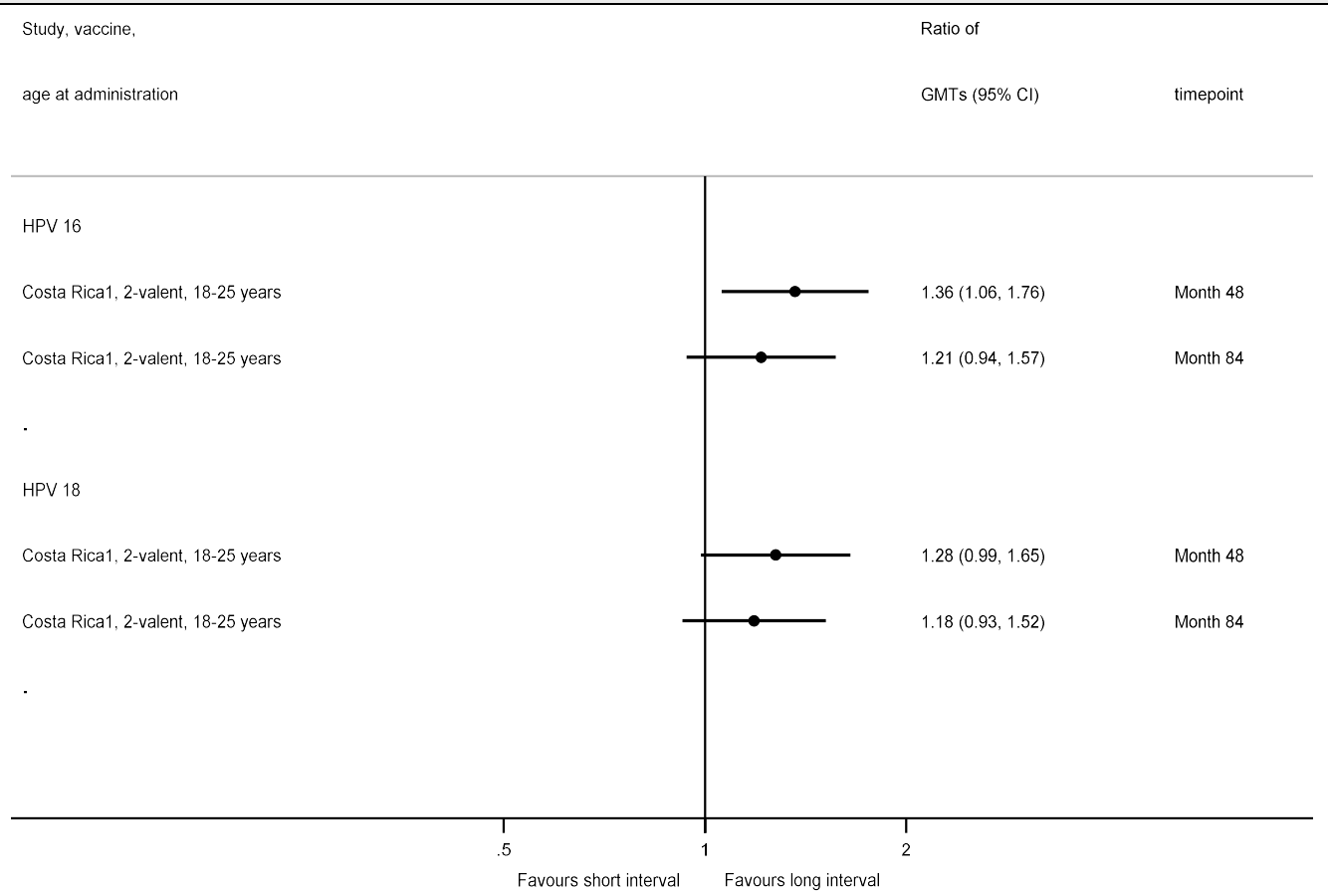
[1]Evidence from non-randomized (observational) studies is initially downgraded to low certainty evidence because of lack of appropriate protection against uncontrolled bias and confounding.

[2]Upgraded one level: observational study that demonstrates moderate control of confounding factors

[3]Downgraded one level for imprecision: wide 95% confidence intervals

Forest plots: longer interval (6 months) versus shorter interval (1 month) between two doses of bivalent HPV vaccine in females – immunogenicity outcomes at 48 and 84 months

Participants: 18 to 25-year old females (seronegative at baseline).
Setting: Costa Rica
Comparison: longer interval schedule (0, 6 months) versus shorter interval schedule (0, 1 months) of bivalent HPV vaccine

Outcome	Forest plot	Certainty of the evidence (GRADE)
Ratio of GMTs Follow up: up to 84 months (Costa Rica1)		⊕⊕OO LOW

Summary of Findings: longer interval (6 months) versus shorter interval (2 months) between two doses of quadrivalent HPV vaccine in females – clinical outcomes over a 7 year period

Participants: 10 to 18-year old females (seronegative at baseline).
Setting: India
Comparison: longer interval schedule (0, 6 months) versus shorter interval schedule (0, 2 months) of quadrivalent HPV vaccine

Outcome	Plain language summary	Absolute effect		Relative effect (95% CI) Nº of participants & studies	Certainty of the evidence (GRADE)
		0, 2-month schedule	0, 6-month schedule		
Incident HPV 16/18 infections Follow-up: 7-year period (India1)	There was very low certainty evidence that females aged 10 to 18 years receiving two doses of the quadrivalent HPV vaccine with a 6-month interval schedule had fewer incident HPV 16/18 infections compared to a 2-month interval schedule. However, the confidence intervals were wide and crossed the line of no effect.	23 per 1000	16 per 1000 (10 to 26)	RR 0.70 (0.43 to 1.12) 3461 participants in 1 study	⊕OOO VERY LOW[1,2]
Incident HPV 6/11/16/18 infections Follow-up: 7-year period (India1)	There was very low certainty evidence that females aged 10 to 18 years receiving two doses of the quadrivalent HPV vaccine with a 6-month interval schedule had fewer incident HPV 6/11/16/18 infections compared to a 2-month interval schedule.	37 per 1000	23 per 1000 (15 to 34)	RR 0.62 (0.42 to 0.92) 3461 participants in 1 study	⊕OOO VERY LOW[1,2]
Incident HPV 31/33/45 infections Follow-up: 7-year period (India1)	There was very low certainty evidence that females aged 10 to 18 years receiving two doses of the quadrivalent HPV vaccine with a 6-month interval schedule had more incident HPV 31/33/45 infections compared to a 2-month interval schedule.	32 per 1000	45 per 1000 (32 to 62)	RR 1.41 (1.00 to 1.97) 3461 participants in 1 study	⊕OOO VERY LOW[1,2]
Persistent HPV 16/18 infection Follow-up: 7-year period (India1)	There was very low certainty evidence that females aged 10 to 18 years receiving two doses of the quadrivalent HPV vaccine with a 6-month interval schedule had fewer persistent HPV 16/18 infections compared to a 2-month interval schedule. However, the confidence intervals were wide and crossed the line of no effect.	2 per 1000	1 per 1000 (0 to 9)	RR 0.40 (0.04 to 3.83) 2318 participants in 1 study	⊕OOO VERY LOW[1,3]
Persistent HPV 6/11/16/18 infection Follow-up: 7-year period (India1)	There was very low certainty evidence that females aged 10 to 18 years receiving two doses of the quadrivalent HPV vaccine with a 6-month interval schedule had fewer persistent HPV 6/11/16/18 infections compared to a 2-month interval schedule. However, the confidence intervals were wide and crossed the line of no effect.	4 per 1000	1 per 1000 (0 to 8)	RR 0.24 (0.03 to 2.05) 2318 participants in 1 study	⊕OOO VERY LOW[1,3]

Persistent HPV 31/33/45 infection Follow-up: 7-year period (India1)	There was very low certainty evidence that females aged 10 to 18 years receiving two doses of the quadrivalent HPV vaccine with a 6-month interval schedule had more persistent HPV 31/33/45 infections compared to a 2-month interval schedule.	2 per 1000	8 per 1000 (2 to 36)	RR 4.79 (1.02 to 22.50) 2318 participants in 1 study	⊕OOO VERY LOW[1,3]

CI= confidence interval; HPV= human papilloma virus; RR= risk ratio

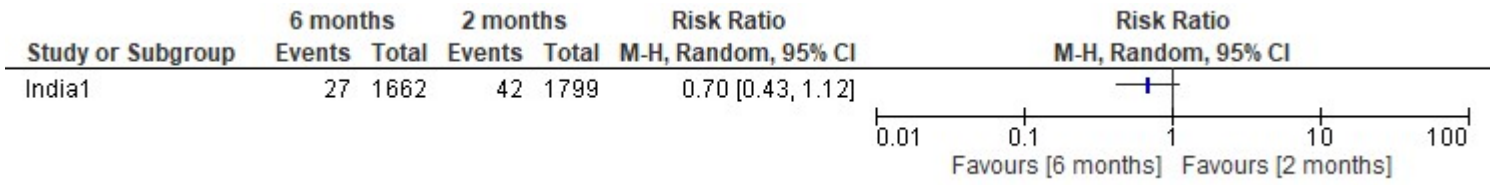
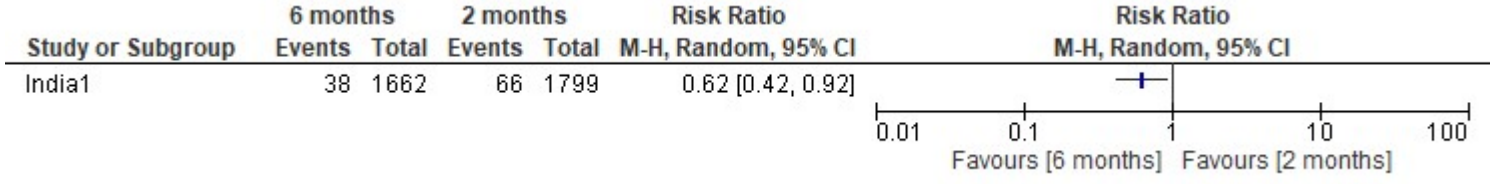
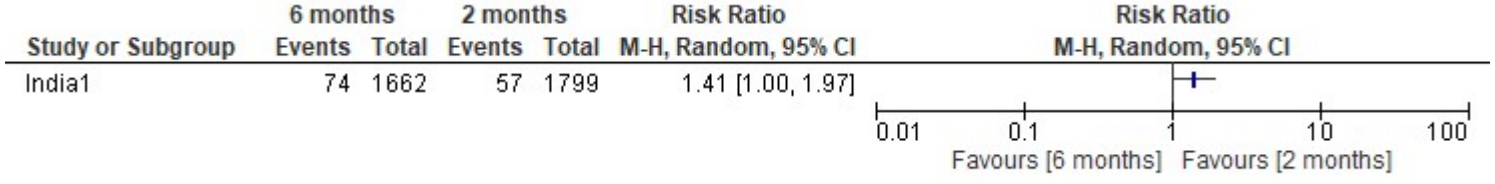
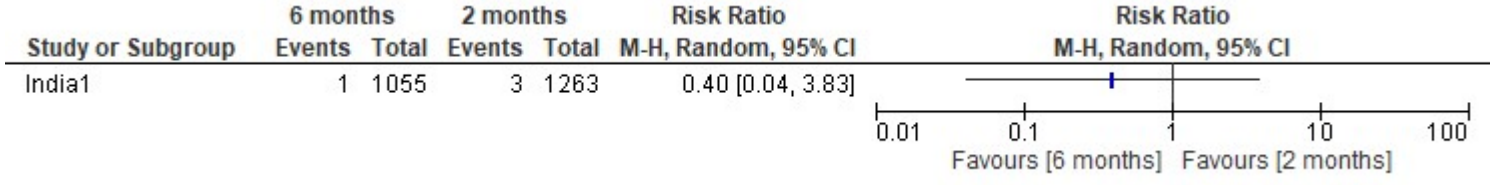
[1]Evidence from non-randomized (observational) studies is initially downgraded to low certainty evidence because of lack of appropriate protection against uncontrolled bias and confounding.

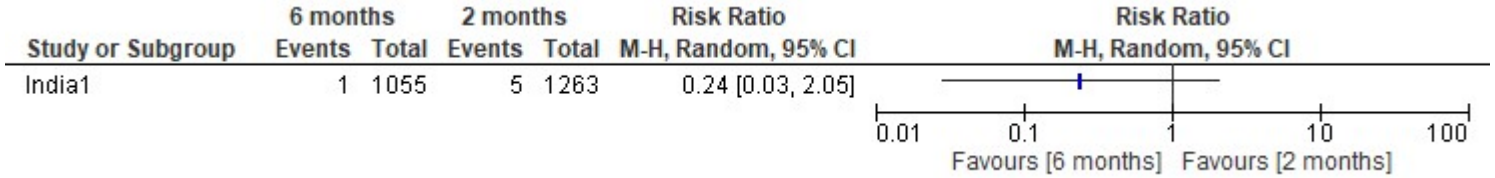
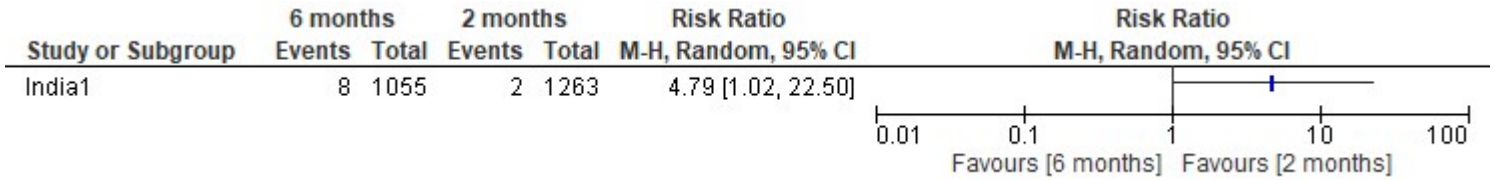
[2]Downgraded one level for imprecision: few events

[3]Downgraded two levels for serious imprecision: few events and a 95% CI that encompasses a potential large beneficial effect and a potential large harmful effect

Forest plots: longer interval (6 months) versus shorter interval (2 months) between two doses of quadrivalent HPV vaccine in females – clinical outcomes over a 7 year period

Participants: 10 to 18-year old females (seronegative at baseline).
Setting: India
Comparison: longer interval schedule (0, 6 months) versus shorter interval schedule (0, 2 months) of quadrivalent HPV vaccine

Outcome	Forest plot	Certainty of the evidence (GRADE)
Incident HPV 16/18 infections Follow-up: 7-year period (India1)		⊕OOO VERY LOW
Incident HPV 6/11/16/18 infections Follow-up: 7-year period (India1)		⊕OOO VERY LOW
Incident HPV 31/33/45 infections Follow-up: 7-year period (India1)		⊕⊕OO LOW
Persistent HPV 16/18 infection Follow-up: 7-year period (India1)		⊕OOO VERY LOW

Persistent HPV 6/11/16/18 infection Follow-up: 7-year period (India1)		⊕OOO VERY LOW
Persistent HPV 31/33/45 infection Follow-up: 7-year period (India1)		⊕OOO VERY LOW

CI= confidence interval; HPV= human papilloma virus

Summary of Findings: longer interval (6 months) versus shorter interval (2 months) between two doses of quadrivalent HPV vaccine in females – immunogenicity outcomes at 18 and 36 months

Participants: 10 to 18-year old females (seronegative at baseline).
Setting: India
Comparison: longer interval schedule (0, 6 months) versus shorter interval schedule (0, 2 months) of quadrivalent HPV vaccine

Outcome		Plain language summary	Absolute effect		Relative effect (95% CI) Nº of participants & studies	Certainty of the evidence (GRADE)
			0, 2-month schedule	0, 6-month schedule		
GMT of HPV 6 Follow-up: up to 36 months (India1)	18 months	There was low-certainty evidence that females aged 10 to 18 years receiving quadrivalent HPV vaccine with a 6-month interval schedule had higher GMTs for HPV 6 compared to a 2-month interval schedule at 18 months follow-up.	Mean: 476 MFI	Mean: 830 MFI	Ratio 1.74 (1.54 to 1.97) 763 participants in 1 study	⊕⊕OO LOW[1]
	36 months	There was low-certainty evidence that females aged 10 to 18 years receiving quadrivalent HPV vaccine with a 6-month interval schedule had higher GMTs for HPV 6 compared to a 2-month interval schedule at 36 months follow-up.	Mean: 287 MFI	Mean: 472 MFI	Ratio 1.64 (1.43 to 1.90) 791 participants in 1 study	⊕⊕OO LOW[1]
GMT of HPV 11 Follow-up: up to 36 months (India1)	18 months	There was low-certainty evidence that females aged 10 to 18 years receiving quadrivalent HPV vaccine with a 6-month interval schedule had higher GMTs for HPV 11 compared to a 2-month interval schedule at 18 months follow-up.	Mean: 530 MFI	Mean: 1328 MFI	Ratio 2.51 (2.23 to 2.81) 763 participants in 1 study	⊕⊕OO LOW[1]
	36 months	There was low-certainty evidence that females aged 10 to 18 years receiving quadrivalent HPV vaccine with a 6-month interval schedule had higher GMTs for HPV 11 compared to a 2-month interval schedule at 36 months follow-up.	Mean: 265 MFI	Mean: 653 MFI	Ratio 2.46 (2.14 to 2.83) 791 participants in 1 study	⊕⊕OO LOW[1]
GMT of HPV 16 Follow-up: up to 36 months (India1)	18 months	There was low-certainty evidence that females aged 10 to 18 years receiving quadrivalent HPV vaccine with a 6-month interval schedule had higher GMTs for HPV 16 compared to a 2-month interval schedule at 18 months follow-up.	Mean: 401 MFI	Mean: 1222 MFI	Ratio 3.05 (2.68 to 3.47) 763 participants in 1 study	⊕⊕OO LOW[1]
	36 months	There was low-certainty evidence that females aged 10 to 18 years receiving quadrivalent HPV vaccine with a 6-month interval schedule had higher GMTs for HPV 16	Mean: 136 MFI	Mean: 163 MFI	Ratio 1.20 (1.05 to 1.36) 791 participants in 1 study	⊕⊕OO LOW[1]

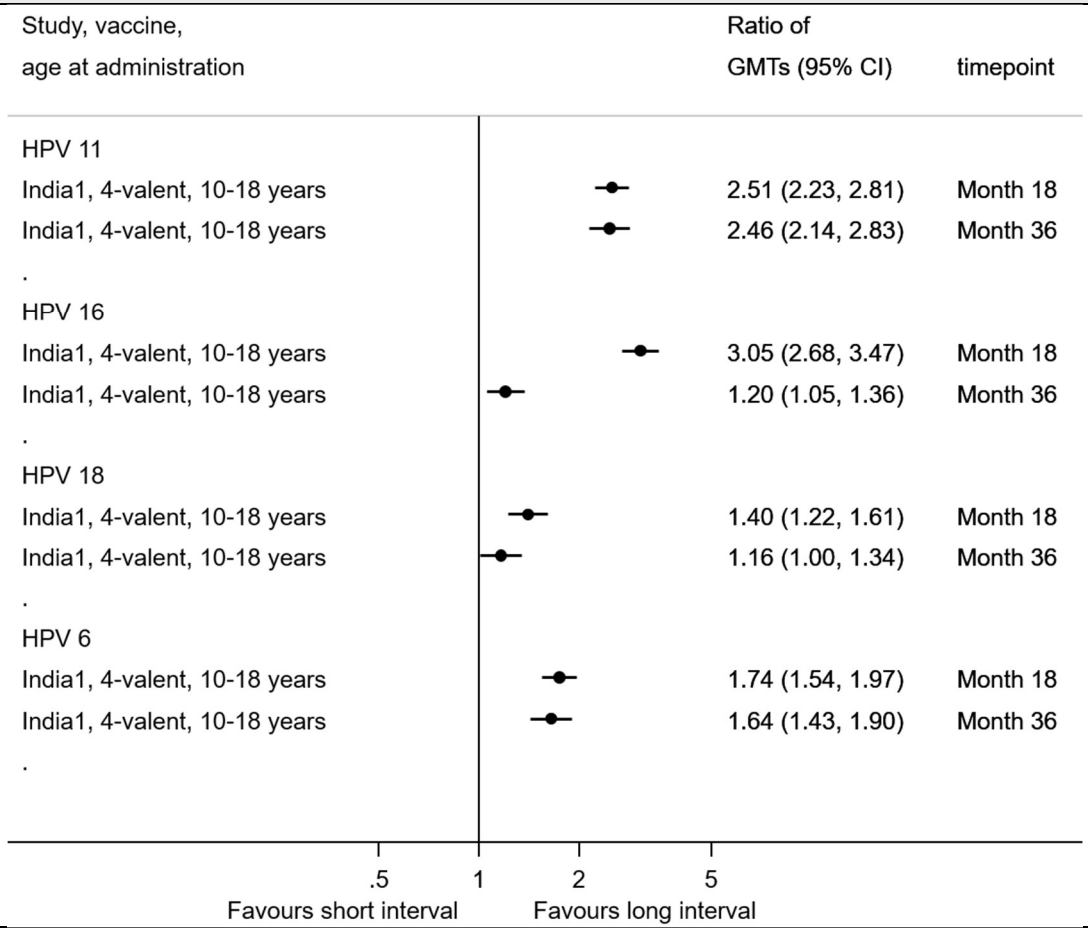
		compared to a 2-month interval schedule at 36 months follow-up.				
GMT of HPV 18 Follow-up: up to 36 months (India1)	18 months	There was low-certainty evidence that females aged 10 to 18 years receiving quadrivalent HPV vaccine with a 6-month interval schedule had higher GMTs for HPV 18 compared to a 2-month interval schedule at 18 months follow-up.	Mean: 192 MFI	Mean: 269 MFI	Ratio 1.40 (1.22 to 1.61) 763 participants in 1 study	⊕⊕OO LOW[1]
	36 months	There was low certainty evidence that females aged 10 to 18 years receiving quadrivalent HPV vaccine with a 6-month interval schedule had a higher GMT for HPV 18 compared to a 2-month interval schedule at 36 months follow-up.	Mean: 101 MFI	Mean: 117 MFI	Ratio 1.16 (1.00 to 1.34) 791 participants in 1 study	⊕⊕OO LOW[1]

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

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

Forest plot: longer interval (6 months) versus shorter interval (2 months) between two doses of quadrivalent HPV vaccine in females – immunogenicity outcomes at 18 and 36 months

Participants: 10 to 18-year old females (seronegative at baseline).
Setting: India
Comparison: longer interval schedule (0, 6 months) versus shorter interval schedule (0, 2 months) of quadrivalent HPV vaccine

Outcome	Forest plot	Certainty of the evidence (GRADE)
Ratio of GMTs Follow up: up to 36 months (India1)		⊕⊕OO LOW

DATA FROM OBSERVATIONAL STUDIES

In addition to the above studies, twelve observational cohort studies were also included which compared a longer and a shorter interval between two doses of the bivalent HPV vaccine (Uganda1) or quadrivalent HPV vaccine (Australia1, Denmark2, Denmark/Sweden1, Fiji1, Sweden2, USA1, USA2, USA6, USA7, USA8, USA11). These studies were all rated at serious risk of bias apart from USA2, which had moderate risk of bias (Appendix 2).

One observational cohort study comparing a longer (>90 days) with a shorter interval (<90 days) of bivalent HPV vaccine in 10-11-year-old females (Uganda1). No statistical differences in antibody levels for HPV 16 and HPV 18 were found between these groups in post-hoc analysis.

Eleven observational cohort studies compared longer intervals (from 3 months to 8+ months) with shorter intervals (from 1 month to 6 months) of quadrivalent HPV vaccine (Australia1, Denmark2, Denmark/Sweden1, Fiji1, Sweden2, USA1, USA2, USA6, USA7, USA8, USA11).

- Three studies reported on immunogenicity outcomes (Fiji1, USA7, USA8). Fiji1 reported no significant differences in titres were seen for all 4 HPV types in females who received their second dose <6 months or ≥6 months apart. USA7 and USA8 both reported significantly higher GMTs for all 4 HPV types in the groups with a longer interval between doses compared to a shorter interval.
- One study reported on high grade histology outcomes (Australia1) and found no reduction of effect (i.e. compared to unvaccinated women) when women who received two doses were stratified into those with ≥6 months between doses and <6 months. Another study (USA1) reported that in participants with at least 6 months between their first and second doses, the risk of an abnormal cervical cytology result was similar to those who received two doses irrespective of second dose timing.
- One study (Denmark/Sweden1) reported on CIN2+ incidence and showed that for women who received their first dose at age <16 years, there was a decrease in risk of CIN2+ if the time between the first and second dose was extended to 5 months or more, compared to 0–4 months, but with confidence interval including unity (IRR 0.34, 95%CI 0.10 to 1.13). For women aged 17–19 years at first vaccination the incidence rate was similar for 0–4 months compared to 5 or more months (IRR 1.01, 95% CI 0.45 to 2.25), while for women 20+ years at first vaccination the risk was statistically significantly higher for 5 or more months between doses (IRR 1.33, 95% 1.04 to 1.70).
- Five studies reported on anogenital warts (Denmark2, Sweden2, USA2, USA6, USA11) (Table 1). The intervals compared in the different studies were too heterogenous to allow meta-analyses. Denmark2 reported that the incidence of genital warts was statistically significantly reduced when a two-month interval was compared to dosing intervals of 3, 4, 5, and 6 months by 27% (95% CI, 4% to 45%), 45% (20% to 62%), 55% (35% to 69%), and 63% (44% to75%) respectively. Sweden2 reported that in participants receiving vaccine before age 16, the incidence rate was higher in those with an 8+ month interval between doses (IR 351, 95% CI 168 to 737) than a 4-7 month interval (IR 95 95% CI 48 to 190) or a 0-3 month interval (IR 84 95% CI 66 to 108). USA2 reported a rate ratio of 0.38 (0.19 to 0.74) when an interval of ≥6 months was compared to an interval of <6 months, in favour of the longer interval. The propensity score-weighted HR was 0.35 (0.17 to 0.72). USA6 reported an IR of 1.84 (1.54 to 2.20) when two doses were separated by 5 or more months, and an IR of 1.71 (1.46 to 2.01) with <5 months between doses. USA11 reported in males and females receiving vaccination at age 15-19, adjusted hazard ratios compared to unvaccinated participants were 0.69 (95% CI, 0.44 to 1.07) with ≥6-month interval and 0.65 (0.45 to 0.94) with < 6-month interval. In those receiving vaccine at age >20, the hazard ratios were 1.23 (0.76 to 1.98) for ≥6-month interval and 1.11 (0.79 to 1.55) for < 6 months interval.

Table 1. Results from observational cohort studies comparing interval between two doses and reporting on genital warts

Study ID	Reported estimate	Favours (i.e. direction of effect)	Number of participants (2 doses)	Risk of bias
Denmark2	Reduction in incidence of genital warts: • 2 vs 3 months: 27% (95% CI 4% to 45%) • 2 vs 4 months: 45% (95% CI 20% to 62%) • 2 vs 5 months: 55% (95% CI 35% to 69%) • 2 vs 6 months: 63% (95% CI 44% to 75%)	In favour of longer interval	2 doses: 93,519 Interval n values: not reported	Serious
Sweden2	Incidence rate (IR) of genital warts (receiving vaccine before age 16): • 0-3-month interval: IR 84 (95% CI 66 to 108) • 4-7-month interval: IR 95 (95% CI 48 to 190) • 8-month interval: IR 351 (95% CI 168 to 737)	In favour of shorter interval	0-3 months: 204,103 4-7 months: 8,095 ≥8 months: 1,894	Serious
USA2	≥ 6-months compared with < 6-months: • Rate ratio 0.38 (95% CI 0.19 to 0.74) • Propensity score-weighted HR 0.35 (95% CI 0.17 to 0.72)	In favour of longer interval	< 6months: 2,730 ≥6 months: 2,729	Moderate
USA6	• <5-month interval: IR 1.71 (95% CI 1.46 to 2.01) • >5-month interval: IR 1.84 (95% CI 1.54 to 2.20)	No difference	<5 months: 18,757 ≥5 months: 17,826	Serious
USA11	Adjusted hazard ratios compared to unvaccinated (age 15-19): • ≥ 6-month interval: 0.69 (95% CI 0.44 to 1.07) • 6-month interval: 0.65 (95% CI 0.45 to 0.94) Age >20: • ≥ 6-month interval: 1.23 (95% CI 0.76 to 1.98) • < 6-month interval: 1.11 (95% CI 0.79 to 1.55)	No difference	6 months: 21,552 ≥6 months: 16,990	Serious

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Canada/Germany1
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Appendix 1 – Included study characteristics

Study name	Publication year	Study design	Date range	HPV vaccine	Interval between doses	N by second dose timepoint	Outcomes reported
Canada/Germany1	2011	RCT	17 October 2007 to 18 March 2013	Bivalent	0,2 months 0,6 months	2 months:240 6 months:241	Immunogenicity: geometric mean titre, seroconversion
Multinational2	2016	RCT	June 2011 to November 2014	Bivalent	0,6 months 0,12 months	6 months: 550 12 months: 415	Immunogenicity: geometric mean titre, seroconversion
Multinational3	2016	RCT	12 December 2013 to 24 July 2017	Nonavalent	0,6 months 0,12 months	6 months: 602 12 months: 301	Immunogenicity: geometric mean titre, seroconversion
Vietnam1	2011	Cluster randomised RCT	October 2007 and January 2010	Quadrivalent	0, 2 months 0,3 months 0,6 months 0,12 months	2 months: 206 3 months: 197 6 months: 193 12 months: 213	Immunogenicity
Costa Rica1	2013	Post-hoc analysis of RCT	2004-2005	Bivalent	0, 1 months 0,6 months	1 month: 140 6 months: 52	Antibody geometric mean titre HPV incidence and prevalence Antibody avidity
India1	2016	Post-hoc analysis of RCT	Sept 1, 2009, to April 8, 2010	Quadrivalent	0, 2 months 0,6 months	2 months: 3,452 6 months: 4,979	Antibody geometric mean titre HPV incidence

Australia1	2015	Retrospective cohort study using linked regional data registries	April 2007 to December 2011	Quadrivalent	O, <6 months 0, ≥6 months	<6months: 20,297 ≥6 months: 7,204	Histological abnormalities (any high grade, CIN3/AIS, CIN2) CIN3/AIS
Denmark/ Sweden1	2018	observational cohort	2006–2013	Quadrivalent	0, 4 months 0, ≥5 months	4 months: 513,507 ≥5 months: 44,021	CIN2+
Denmark2	2015	Retrospective cohort study using population-based health national registries	October 2006 to December 2012	Quadrivalent	0,2 months 0,3 months 0,4 months 0,5 months 0,6 months	2 dose: 93,519 Interval n values: NR	Anogenital warts (IRR)
Fiji1	2017	Prospective cohort study	February and March 2015 (previous vaccinations 2008-9)	Quadrivalent	0, <6 months 0, ≥6 months	2 dose: 60 Interval n values: not reported	GMT
Sweden2	2017	Retrospective cohort study	1 January 2006 and 31 December 2012	Quadrivalent	0,3 months 4-7 months ≥8 months	0-3 months: 204,103 4-7 months: 8,095 ≥8 months: 1,894	Condyloma
Uganda1	2014	Prospective cohort study	2008-2009	Bivalent	0, <=90 days 0, >90 days	<=90 days: 113 >90 days 28	Antibody geometric mean titre
USA1	2016	Retrospective cohort study using medical centre databases	Jan 2007 - Jan 2014	Quadrivalent	0, < 6 months 0, ≥6 months	<6 months: 376 ≥6 months: 228	Abnormal cervical cytology
USA2	2017	Retrospective cohort study	2006-2012	Quadrivalent	0, < 6months 0, ≥6 months	< 6months: 2,730 ≥6 months: 2,729	Anogenital warts
USA6	2017	Retrospective cohort study using	Jan 2007 - Dec 2013	Quadrivalent	0, <5 months 0, ≥5 months	<5 months: 18,757 ≥5 months: 17,826	Anogenital warts

		commercial claims database					
USA7	2015	Prospective cohort study	June 2009 and March 2012	Quadrivalent	0, ≥30 to ≤90 days 0, >90 days	≥30 to ≤90: 39 >90 days: 126	Immunogenicity
USA8	2018	Retrospective cohort	June 2010 and August 2013	Quadrivalent	0, 51-70 days 0, ≥240 days	51-70 days: 192 ≥240 days: 198	Immunogenicity
USA11	2018	Retrospective cohort	2006 and 2015	Quadrivalent	0, <6 months 0, ≥6 months	<6 months: 21,552 ≥6 months: 16,990	Anogenital warts

Appendix 2 – Risk of bias assessments

Risk of bias: Randomised controlled trials (including cluster randomised 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
Multinational2	Low	Low	High	High	Low	Low	Unclear
Multinational3	Low	Low	High	High	Low	Low	Unclear
Vietnam1	Low	Low	High	Low	Low	Low	Unclear

Risk of bias: observational studies (including post-hoc analyses) (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
Australia1	Serious	Serious	Low	Moderate	Moderate	Moderate	Moderate	Serious
Costa Rica1	Moderate	Moderate	Low	Low	Moderate	Moderate	Moderate	Moderate
Denmark2	Serious	Moderate	Low	Moderate	Low	Moderate	Moderate	Serious
Denmark/Sweden 1	Serious	Moderate	Low	Moderate	Low	Moderate	Moderate	Serious
Fiji1	Serious	Moderate	Low	Moderate	Low	Low	Moderate	Serious
India1	Serious	Low	Low	Low	Moderate	Low	Moderate	Serious
Sweden2	Serious	Moderate	Low	Moderate	Moderate	Serious	Moderate	Serious
Uganda1	Serious	Moderate	Low	Moderate	Low	Low	Moderate	Serious
USA1	Serious	Serious	Low	Moderate	Moderate	Moderate	Moderate	Serious
USA2	Moderate	Moderate	Low	Moderate	Low	Moderate	Moderate	Moderate
USA6	Serious	Serious	Low	Moderate	Low	Moderate	Moderate	Serious
USA7	Serious	Moderate	Low	Moderate	Serious	Low	Moderate	Serious
USA8	Serious	Moderate	Low	Moderate	Moderate	Low	Moderate	Serious
USA11	Serious	Moderate	Low	Moderate	Low	Moderate	Moderate	Serious

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