HPV vaccines in females over 25 years

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Key findings

In females aged 25 years and over there was

- Low-certainty evidence of little to no difference in HPV 16 or 18-related CIN2+ for 2- or 4-valent HPV vaccine compared to placebo
- Low-certainty evidence of little to no difference in HPV 6, 11, 16, or 18-related CIN2+ or condyloma for 4-valent HPV vaccine compared to placebo
- Moderate-certainty evidence of reduced HPV 16 or 18-related persistent infection for 2- or 4-valent HPV vaccine compared to placebo
- Moderate-certainty evidence of reduced HPV 6, 11, 16, or 18-related persistent infection for 4-valent HPV vaccine compared to placebo
- High-certainty evidence of significantly higher GMTs and higher rate of seroconversion for HPV 16 and 18 with 2-valent HPV vaccine compared with control (hepatitis B) vaccine at 7 months follow-up
- Low-certainty evidence of significantly higher GMTs for HPV 16 and 18 with 2-valent HPV vaccine compared with 4-valent HPV vaccine at 7 months to 5 years follow-up
- Low-certainty evidence of little to no difference in rate of seropositivity to HPV 16 at 7 months to 5 years follow-up between 2-valent HPV vaccine and with 4-valent vaccine.
- Low-certainty evidence of significantly higher rate of seropositivity for HPV 18 with 2-valent HPV vaccine compared with 4-valent HPV vaccine at 1 to 5 years follow-up.

Abstract

Background

Human papilloma virus (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 Target Update, we review and analyse evidence for the protection afforded by prophylactic HPV vaccines in women over 25 years.

Objectives

To evaluate the efficacy and immunogenicity of HPV vaccines in females over 25 years.

Search methods

We updated a previous review performed by Cochrane Response in 2016, searches were conducted for this update from June 2016 to August 2018, 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 potential relevant study through the WHO Initiative for Vaccines Research Department (IVR).

Selection criteria

Randomised controlled trials (RCTs) were eligible for inclusion. The studies in this document focus on the comparisons of HPV vaccine versus placebo, no vaccine, or control vaccine, and HPV vaccine versus other HPV vaccine in females over 25 years.

Data collection and analysis

Two review authors independently assessed trial eligibility and risk of bias and extracted data. Rate ratios (RR) with 95% confidence intervals (CI) were calculated for binary outcomes reported as rates. For continuous data, where GMTs were reported, we calculated the data as mean differences (95% CI) on the log scale and re-expressed as ratio of GMTs.

Main Results

We included five RCTs (China3, Italy2, Multinational12, Multinational13, and USA8). China3 compared 2-valent vaccine with hepatitis B vaccine (control vaccine) in 1202 females aged 26 to 45 years. Italy2 compared 2-valent HPV vaccine versus no vaccine in 832 females aged 25 years. Multinational12 compared 3 doses 4-valent vaccine to placebo in 3819 females aged 24 to 45 years old, Multinational13 compared 3 doses 4-valent vaccine to placebo in 5752 females aged over 25 years, and USA8 compared 3 doses 2-valent to 3 doses 4-valent HPV vaccine in women aged 18 to 45 years old, we present here the subset of 1106 females aged 27 to 45 years.

No randomised studies were identified that reported data on the efficacy or immunogenicity of the 9-valent HPV vaccine, or that compared different intervals between doses in females aged > 25 years.

The risk of bias was low for China3, Multinational12, and Multinational13. Italy2 and USA8 were considered at unclear risk of selection bias because randomisation and allocation concealment methods were not clearly reported, and Italy2 at high risk of performance bias since the study was not blinded.

2-valent or 4-valent HPV vaccine versus placebo or no vaccine in women over 25 years – clinical outcomes

Italy2, Multinational12, and Multinational13 reported clinical outcomes at 30 months to 7 years follow-up.

For the outcome HPV 16 or 18-related cervical intraepithelial neoplasia, grade 2 and above (CIN2+) there was low-certainty evidence of little to no difference between 2- or 4-valent HPV vaccine versus placebo in women over 24 years old at up to 7 years follow-up in the intention-to-treat (ITT) analysis (RR 0.74, 95% CI 0.52 to 1.05, 9121 participants, 2 RCTs). In the per protocol analysis HPV vaccines (2-valent and 4-valent) showed a significant beneficial effect compared to placebo reducing HPV 16 or 18-related CIN2+ by 84% at up to 7 years follow-up (RR 0.16, 95% CI 0.04 to 0.73, 6836 participants, 2 RCTs).

For the outcomes of HPV 6, 11, 16, or 18-related CIN2+ and HPV 6, 11, 16, or 18-related condyloma, there was low-certainty evidence of little to no difference between 4-valent vaccine and placebo in 24-45-year old women at a mean of 3.8 years follow-up in both the ITT and per protocol analyses.

For the outcome of persistent HPV infection there was moderate-certainty evidence that 2- or 4-valent HPV vaccine reduced persistent infection caused by HPV 16 or 18 in women over 24 years old compared with placebo at up to 7 years follow-up in both the ITT (RR 0.17, 95% CI 0.10 to 0.29, 7327 participants, 2 RCTs) and per protocol analyses. There was moderate-certainty evidence that 4-valent HPV vaccine reduced persistent infection caused by HPV 6, 11, 16 or 18 in 24-45-year old women compared with placebo at a mean of 3.8 years follow-up in both the ITT (RR 0.52, 95% CI 0.42 to 0.65, 3769 participants, 1 RCT) and per protocol analyses.

For the outcome of HPV 16 or 18-related infection there was very low-certainty evidence of little to no difference

between 2-valent vaccine and no vaccine in 25-year old women at 30 months follow-up.

2-valent HPV vaccine versus control vaccine in women over 25 years – immunogenicity outcomes

China3 reported immunogenicity outcomes at 7 months (one month after last vaccine dose) follow-up.

There was high-certainty evidence that 2-valent vaccine increased GMTs for HPV 16 and 18 when compared with placebo (means of 6439.8 EU/mL (HPV 16) and 3563.3 EU/mL (HPV 18) in the vaccine group). Seroconversion for HPV 16 and 18 was 100% and 99% respectively (high-certainty evidence).

2-valent HPV vaccine versus 4-valent HPV vaccine in women over 25 years – immunogenicity outcomes

USA8 reported immunogenicity outcomes at 7 months to 5 years follow-up.

There was low-certainty evidence that 2-valent vaccine increased GMTs for HPV 16 and 18 when compared with 4-valent HPV vaccines in 27 to 45-year old females at 7 months to 5 years follow-up. For HPV 16 seropositivity there was low-certainty evidence of little to no difference between 27 to 45-year old women that received 2-valent or 4-valent HPV vaccine at 7 months to 5 years follow-up. For HPV 18 seropositivity there was low-certainty evidence of little to no difference between 27 to 45-year old women that received 2-valent or 4-valent HPV vaccine at 7 months to 1 year follow-up; for 27-35-year old women there was a higher rate of seropositivity with 2-valent vaccine from 1 to 5 years follow-up, and for 36-45-year old women there was a higher rate of seropositivity with 2-valent vaccine from 1.5 to 5 years follow-up.

Implications and conclusions

There was no difference between 2-valent or 4-valent HPV vaccine and control on HPV 6, 11, 16, or 18-related CIN2+ or condyloma in women over the age of 25. In a per protocol analysis of women who received all three doses of HPV vaccine, the 2-valent and 4-valent HPV vaccines prevented HPV 16 or 18-related CIN2+ compared to control at up to 7 years follow-up. There was moderate certainty evidence of a benefit with 2-valent or 4-valent HPV vaccines to prevent HPV 6, 11, 16, or 18-related persistent infection compared to control.

There was evidence of higher HPV 16 and 18-related GMTs and seropositivity with the 2-valent compared to the 4-valent vaccine at up to 5 years follow-up.

Summary of Findings: 2-valent or 4-valent HPV vaccine versus placebo or no vaccine in women over 25 years – clinical outcomes

Participants: Females aged 25 years and older (HPV serostatus mixed at baseline)
Setting: Australia, Canada, Colombia, France, Germany, Italy, Mexico, the Netherlands, Peru, Philippines, Portugal, Russia, Singapore, Spain, Thailand, the UK, and the USA
Comparison: 2-valent HPV vaccine (3-doses (Day 0, Month 1, Month 6)) or 4-valent HPV vaccine (3-doses (Day 0, Month 2, Month 6)) versus placebo (vaccine adjuvant) or no vaccine

Outcome	Plain language summary	Absolute effect		Relative effect (95% CI) Nº of participants & studies	Certainty of the evidence (GRADE)
		Placebo or no vaccine	2- or 4-valent HPV vaccine		
CIN2+ associated with HPV 16/18 follow up: up to 7 years	There is low-certainty evidence that females receiving HPV vaccine had little to no difference in incidence of CIN2+ associated with HPV 16 or 18 compared to females receiving placebo	16 per 1,000	12 per 1,000 (8 to 17)	RR 0.74 (0.52 to 1.05) * 9121 participants in 2 RCTs	⊕⊕OO LOW [1]
CIN2+ associated with HPV 6/11/16/18 follow up: 3.8 years (mean)	There is low-certainty evidence that females receiving 4-valent HPV vaccine had little to no difference in incidence of CIN2+ associated with HPV 6, 11, 16, or 18 compared to females receiving placebo	14 per 1,000	11 per 1,000 (6 to 20)	RR 0.77 (0.44 to 1.37) † 3769 participants in 1 RCT	⊕⊕OO LOW [2]
Persistent infection with HPV 16/18 follow up: up to 7 years	There is moderate-certainty evidence that females receiving HPV vaccine had a lower incidence of persistent HPV 16 or 18 infection than females receiving placebo	46 per 1,000	8 per 1,000 (5 to 13)	RR 0.17 (0.10 to 0.29) ‡ 7327 participants in 2 RCTs	⊕⊕⊕O MODERATE [3]
Persistent infection with HPV 6/11/16/18 follow up: 3.8 years (mean)	There is moderate-certainty evidence that females receiving HPV vaccine had a lower incidence of persistent HPV 6, 11, 16, or 18 infection than females receiving placebo	112 per 1,000	58 per 1,000 (47 to 73)	RR 0.52 (0.42 to 0.65) § 3769 participants in 1 RCT	⊕⊕⊕O MODERATE [3]
Infection HPV 16 follow up: 30 months	There is very low-certainty evidence that females receiving 2-valent HPV vaccine had little to no difference in HPV 16 infection compared to females receiving no vaccine	67 per 1,000	32 per 1,000 (13 to 76)	RR 0.47 (0.19 to 1.12) 618 participants in 1 RCT	⊕OOO VERY LOW [1,4]
Infection HPV 18 follow up: 30 months	There is very low-certainty evidence that females receiving 2-valent HPV vaccine had little to no difference in HPV 18 infection compared to females receiving no vaccine	14 per 1,000	16 per 1,000 (4 to 63)	RR 1.14 (0.29 to 4.52) 618 participants in 1 RCT	⊕OOO VERY LOW [2,4]
Condyloma HPV 6/11/16/18 follow up: 3.8 years (mean)	There is low-certainty evidence that females receiving 4-valent HPV vaccine had little to no difference in condyloma associated with HPV 6, 11, 16, or 18 compared to females receiving placebo	6 per 1,000	4 per 1,000 (1 to 9)	RR 0.58 (0.23 to 1.48) ‖ 3769 participants in 1 RCT	⊕⊕OO LOW [2]

CI= confidence interval; CIN2+= cervical intraepithelial neoplasia, grade 2 and above; HPV= human papilloma virus; RR= risk ratio; RCT= randomised controlled trial

*ITT analysis. The per protocol analysis showed a significant beneficial effect with HPV vaccine (RR 0.16 (95% CI 0.04 to 0.73), 6836 participants, 2 RCTs). † ITT analysis. The per protocol analysis also showed no significant beneficial effect with HPV vaccine (RR 0.17 (95% CI 0.02, 1.38), 3222 participants, 1 RCT). ‡ ITT analysis, the per protocol analysis also showed a significant beneficial effect with HPV vaccine (RR 0.11 (0.06 to 0.20), 6651 participants, 2 RCTs) § ITT analysis, the per protocol analysis also showed a significant beneficial effect with HPV vaccine (RR 0.11 (0.05 to 0.21), 3222 participants, 1 RCT) ‖ ITT analysis, the per protocol analysis also showed no significant beneficial effect with HPV vaccine (RR 0.07 (0.00 to 1.17), 3222 participants, 1 RCT)

[1] Downgraded two levels for imprecision: few events and 95% CIs include both no effect and benefit for HPV vaccine

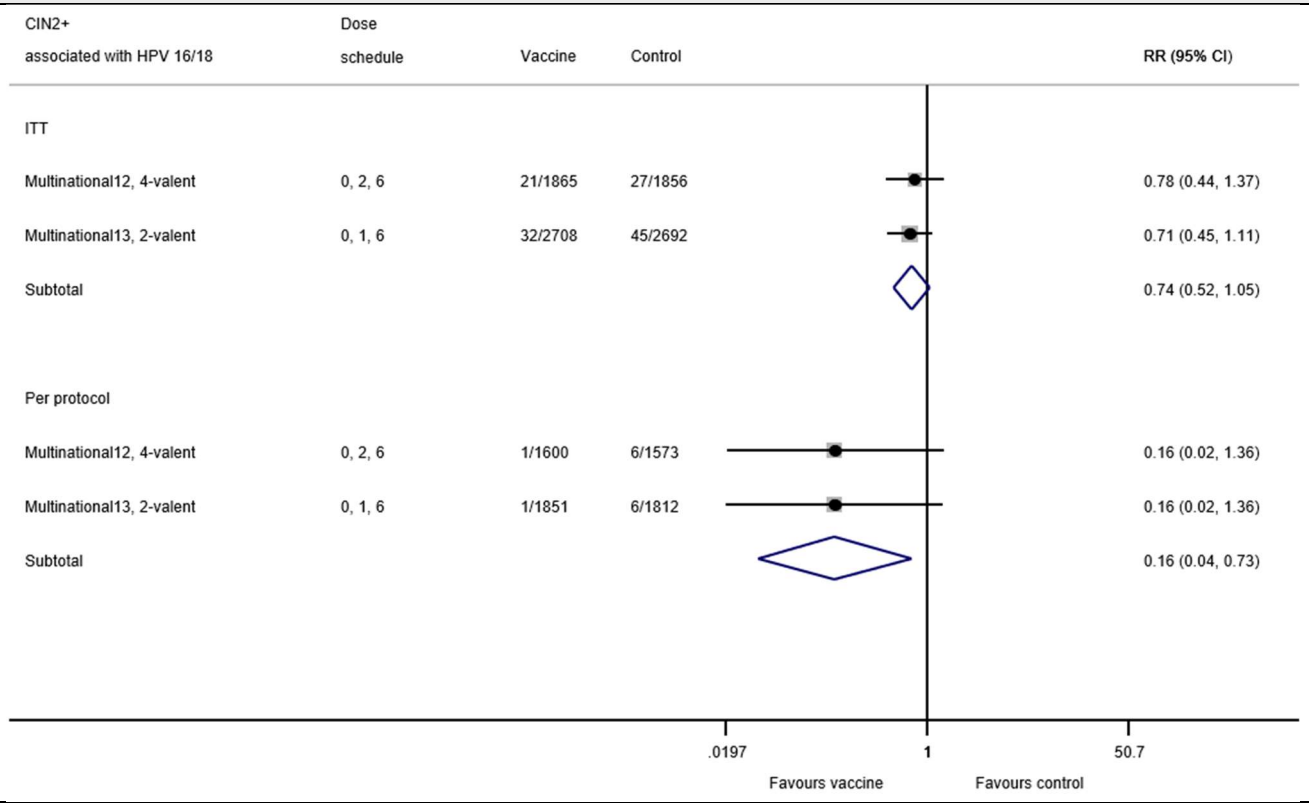
[2] Downgraded two levels for imprecision: few events and 95% CIs include both benefit for both HPV vaccine and placebo as well as no effect

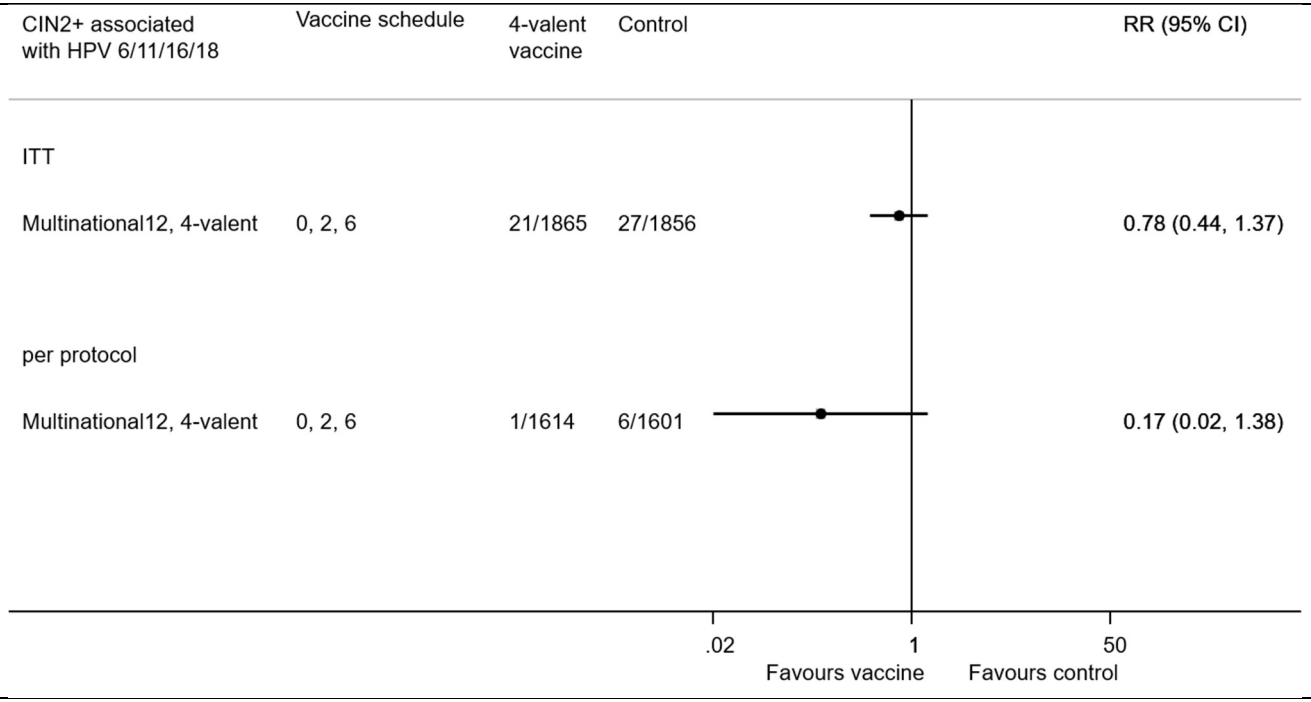
[3] Downgraded one level for imprecision: few events

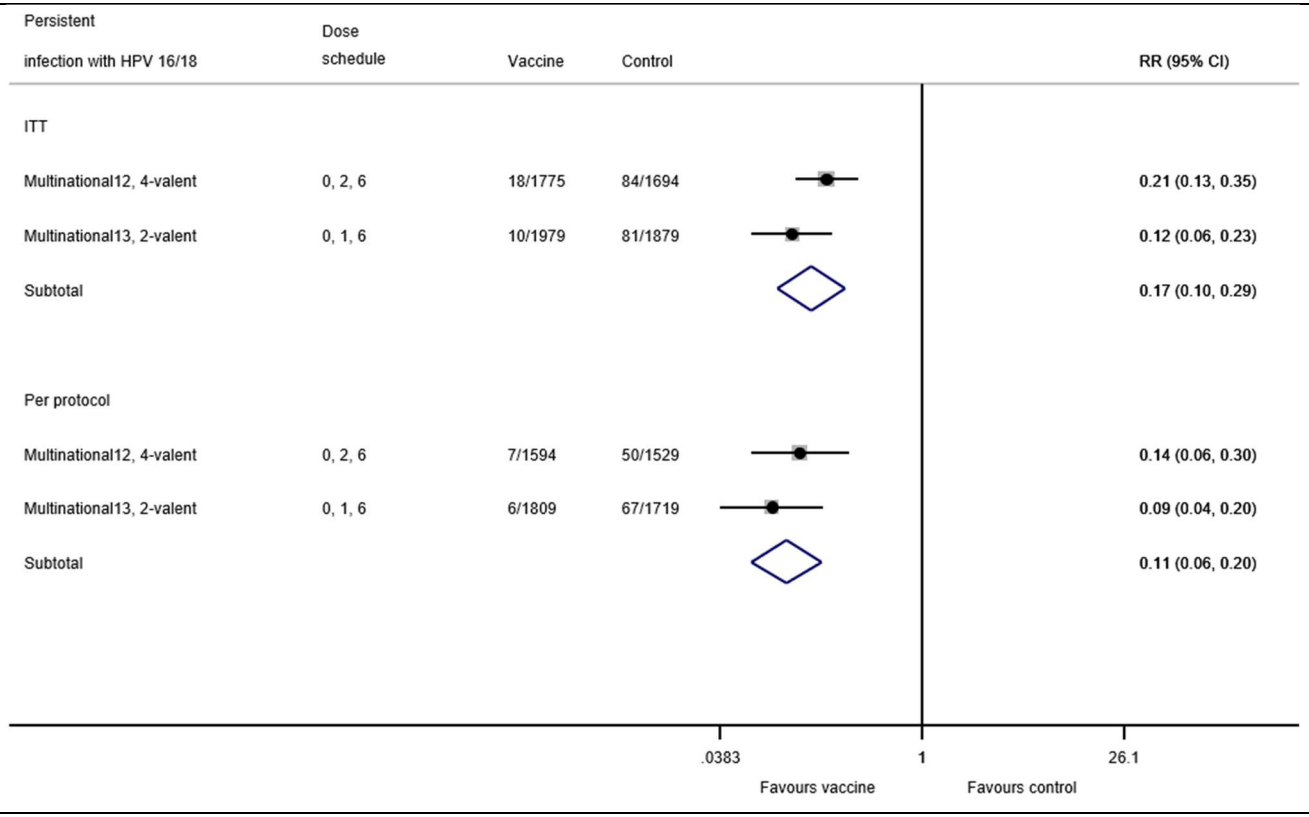
[4] Downgraded one level for risk of bias: randomization and allocation concealment methods were not clearly reported; the study was not blinded to participants and study personnel

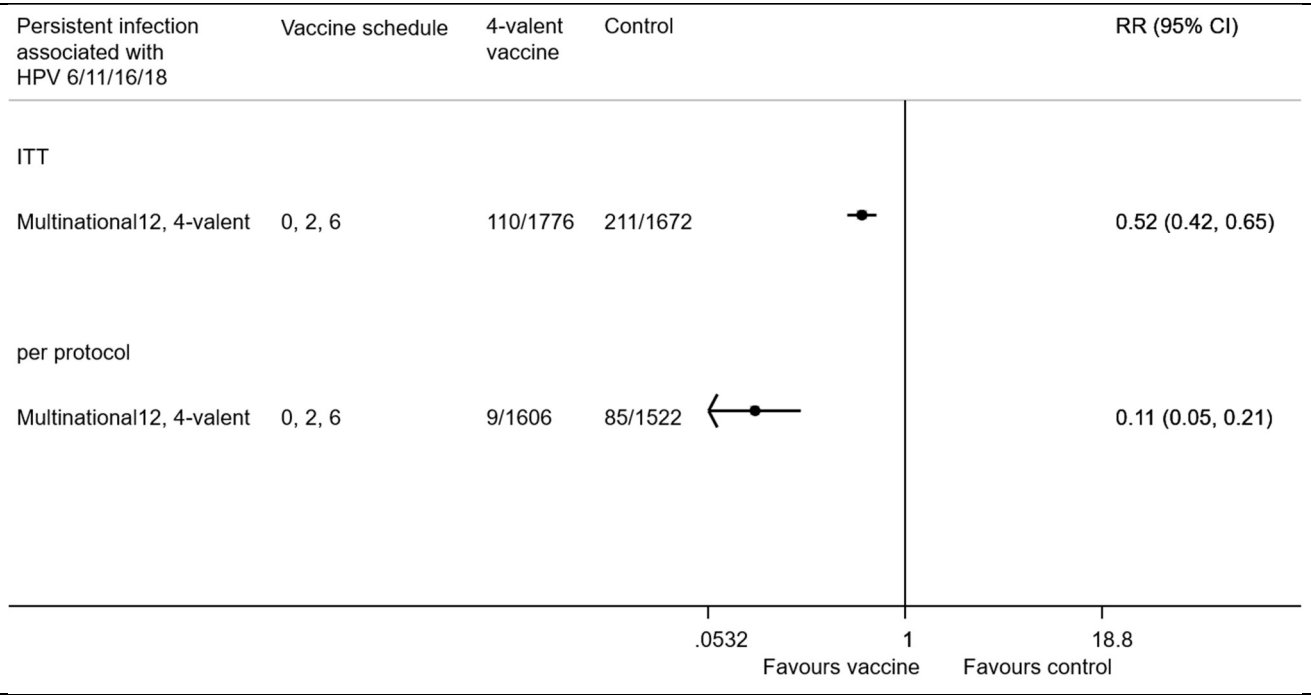
Forest plot: 2-valent or 4-valent HPV vaccine versus placebo or no vaccine in women over 25 years – clinical outcomes

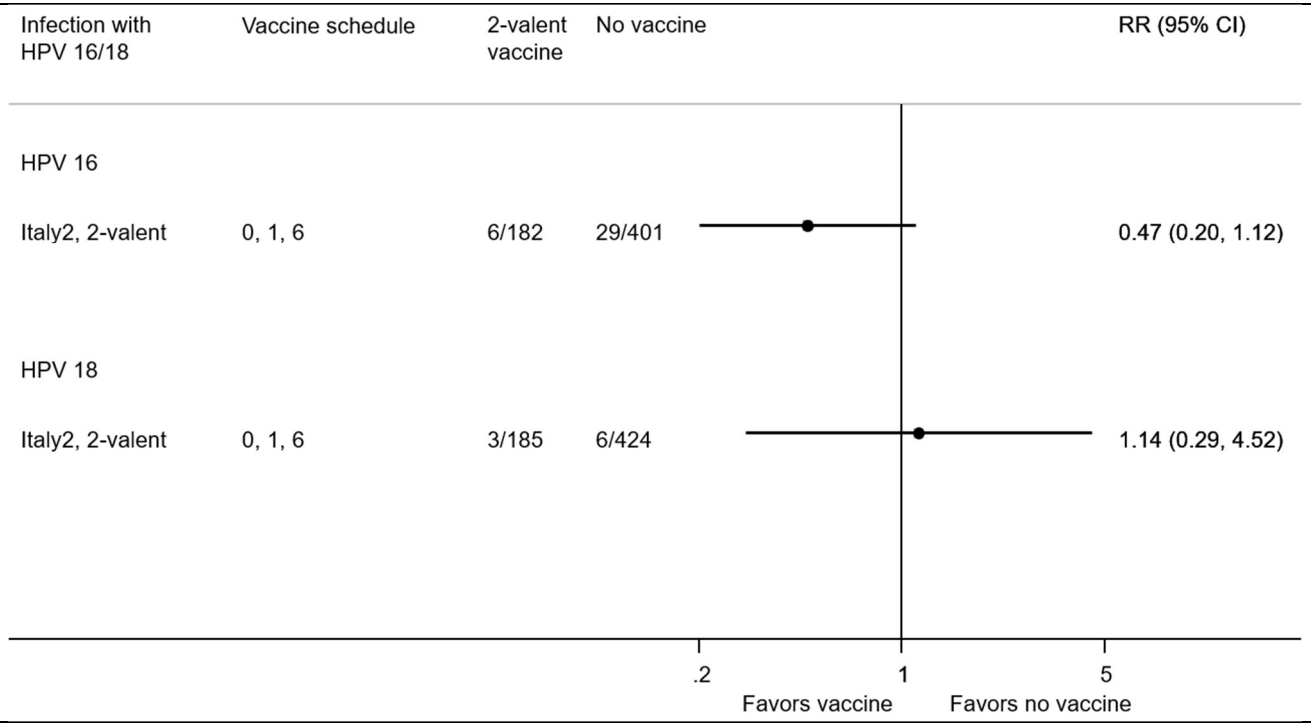
Participants: Females aged 25 years and older (HPV serostatus mixed at baseline)
Setting: Australia, Canada, Colombia, France, Germany, Italy, Mexico, the Netherlands, Peru, Philippines, Portugal, Russia, Singapore, Spain, Thailand, the UK, and the USA
Comparison: 2-valent HPV vaccine (3-doses (Day 0, Month 1, Month 6)) or 4-valent HPV vaccine (3-doses (Day 0, Month 2, Month 6)) versus placebo (vaccine adjuvant) or no vaccine

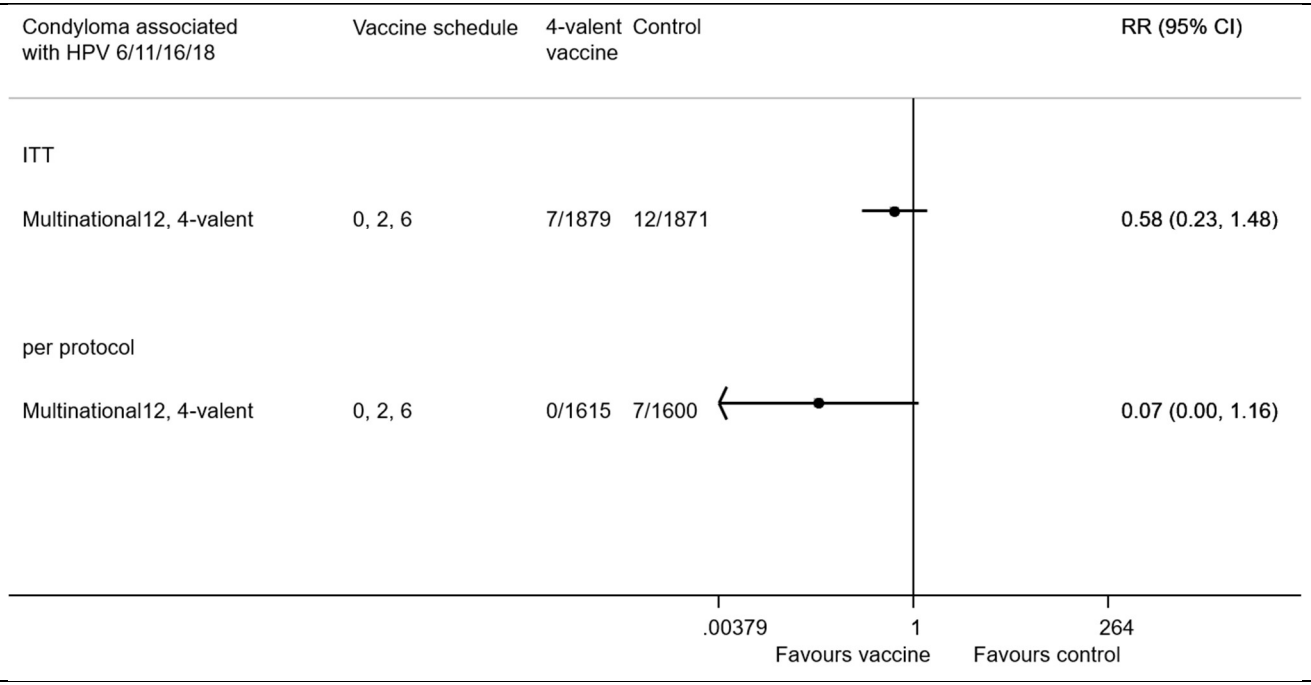
Outcome	Forest plot	Certainty of the evidence (GRADE)
CIN2+ associated with HPV 16/18 follow up: up to 7 years		⨁⨁◯◯ LOW

CIN2+ associated with HPV 6/11/16/18 follow up: 3.8 years (mean)		⊕⊕OO LOW

Persistent infection with HPV 16/18 follow up: up to 7 years		⊕⊕⊕O MODERATE

Persistent infection with HPV 6/11/16/18 follow up: 3.8 years (mean)		⊕⊕⊕O MODERATE

Infection HPV 16/18 follow up: 30 months		⊕OOO VERY LOW

Condyloma HPV 6/11/16/18 follow up: 3.8 years (mean)		⊕⊕OO LOW

CI= confidence interval; CIN2+= cervical intraepithelial neoplasia, grade 2 and above; HPV= human papilloma virus; RR= risk ratio

Summary of Findings: 2-valent HPV vaccine versus control vaccine in women over 25 years – immunogenicity outcomes

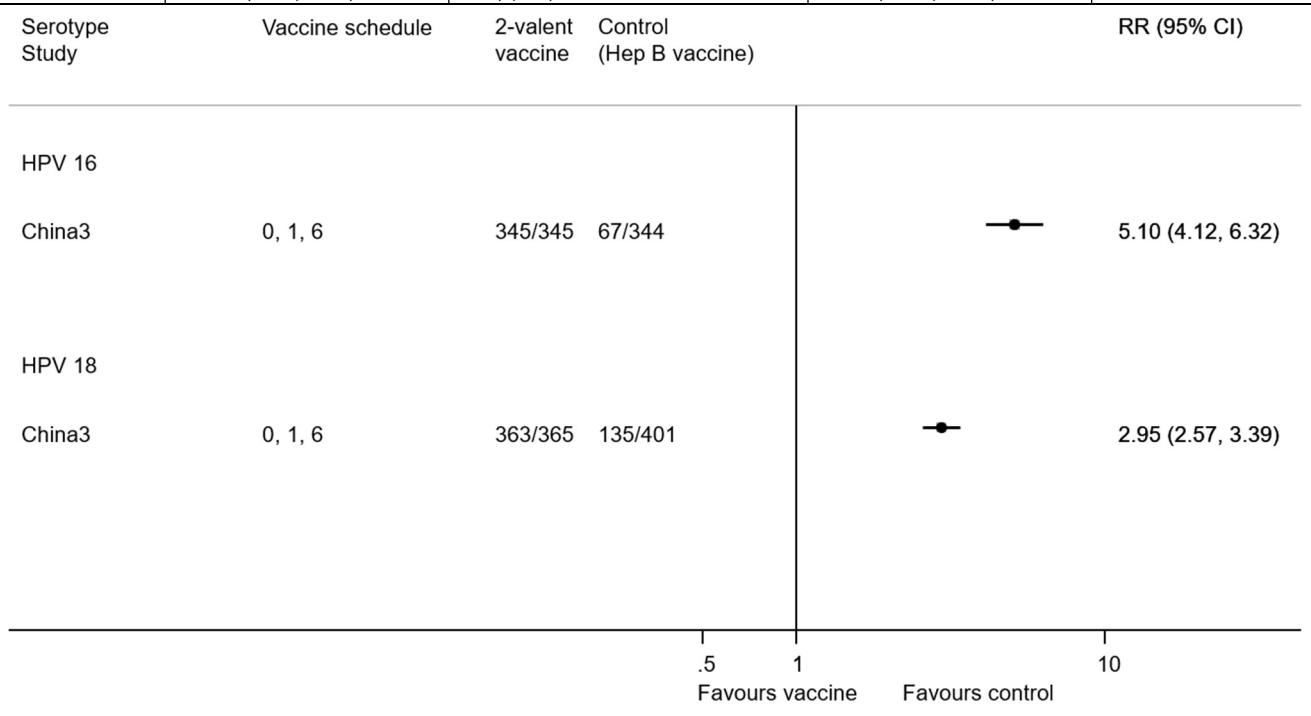
Participants: 26 to 45-year old females (HPV seronegative at baseline)
Setting: China
Comparison: 2-valent HPV vaccine (3-doses (Day 0, Month 1, Month 6)) versus control vaccine (Hepatitis B vaccine)

Outcome	Plain language summary	Absolute effect		Relative effect (95% CI) Nº of participants & studies	Certainty of the evidence (GRADE)
		Control (Hep B) vaccine	2-valent HPV vaccine		
GMTs for HPV 16 follow up: 7 months	There is high-certainty evidence that 26-45-year old women receiving 2-valent HPV vaccine had higher GMTs for HPV 16 and HPV 18 than those receiving Hepatitis B control vaccine	Mean: 12.1 EU/mL	Mean: 6439.8 EU/mL	Ratio of GMTs 532.2 (473.1 to 598.7) 1197 participants in 1 RCT	⊕⊕⊕⊕ HIGH
GMTs for HPV 18 follow up: 7 months		Mean: 8.7 EU/mL	Mean: 3563.3 EU/mL	Ratio of GMTs 409.6 (365.7 to 458.7) 1197 participants in 1 RCT	⊕⊕⊕⊕ HIGH
Seroconversion for HPV 16 follow up: 7 months	There is high-certainty evidence that 26-45-year old women receiving 2-valent HPV vaccine had a higher rate of seroconversion to HPV 16 and HPV 18 than those receiving Hepatitis B control vaccine	19% (67/344)	100% (345/345)	RR 5.10 (4.12 to 6.32) 689 participants in 1 RCT	⊕⊕⊕⊕ HIGH
Seroconversion for HPV 18 follow up: 7 months		34% (135/401)	99% (363/365)	RR 2.95 (2.57 to 3.39) 766 participants in 1 RCT	⊕⊕⊕⊕ HIGH

CI= confidence interval; GMT= Geometric mean titre; HPV= human papilloma virus; EU= ELISA units; RCT= randomised controlled trial; RR= risk ratio

Forest plot: 2-valent HPV vaccine versus control vaccine in women over 25 years – immunogenicity outcomes

Participants: 26 to 45-year old females (HPV seronegative at baseline)
Setting: China
Comparison: 2-valent HPV vaccine (3-doses (Day 0, Month 1, Month 6)) versus control vaccine (Hepatitis B vaccine)

<table>
<tr><th>Outcome</th><th>Forest plot</th><th>Certainty of the evidence (GRADE)</th></tr>
<tr><td rowspan="5">GMTs for HPV 16 and 18
follow up: 7 months</td><td>HPV 16</td><td>2-valent, mean (95% CI)</td><td>Control (HepB), mean (95% CI)</td><td>Ratio of GMTs (95% CI)</td><td>Timepoint</td><td rowspan="5">⊕⊕⊕⊕
HIGH</td></tr>
<tr><td>China3</td><td>6439.8 (6039.8, 6866.3)</td><td>12.1 (11, 13.4)</td><td>532.2 (473.1, 598.7)</td><td>Month 7</td></tr>
<tr><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>HPV 18</td><td>2-valent</td><td>Control (HepB)</td><td>Ratio of GMTs (95% CI)</td><td>Timepoint</td></tr>
<tr><td>China3</td><td>3563.3 (3310, 3836)</td><td>8.7 (8, 9.5)</td><td>409.6 (365.7, 458.7)</td><td>Month 7</td></tr>
<tr><td>Seroconversion for HPV 16 and 18
follow up: 7 months</td><td colspan="4"> 
</td><td>⊕⊕⊕⊕
HIGH</td></tr>
</table>

CI= confidence interval; GMT= Geometric mean titre; HPV= human papilloma virus; RR= risk ratio

Summary of Findings: 2-valent HPV vaccine versus 4-valent HPV vaccine in women over 25 years – immunogenicity outcomes

Participants: 27 to 45-year old females (HPV sero-status mixed at baseline)
Setting: USA
Comparison: 2-valent HPV vaccine (3-doses (Day 0, Month 1, Month 6)) versus 4-valent HPV vaccine (3-doses (Day 0, Month 2, Month 6))

Outcome		Plain language summary	Absolute effect		Relative effect (95% CI) Nº of participants & studies	Certainty of the evidence (GRADE)
			4-valent HPV vaccine	2-valent HPV vaccine		
GMTs for HPV 16 in 27-35-year olds	follow up: 7 months	There is low-certainty evidence that 27-35-year old women receiving 2-valent HPV vaccine had higher GMTs for HPV 16 than those receiving 4-valent vaccine at 7 months to 5 years follow-up*	Mean: 4958.4 EU/mL	Mean: 23907.9 EU/mL	Ratio of GMTs 4.82 (3.44 to 6.75) 175 participants in 1 RCT	⊕⊕OO LOW [1,2]
	follow up: 60 months		Mean: 346.4 EU/mL	Mean: 1925.3 EU/mL	Ratio of GMTs 5.56 (3.07 to 10.07) 72 participants in 1 RCT	
GMTs for HPV 16 in 36-45-year olds	follow up: 7 months	There is low-certainty evidence that 36-45-year old women receiving 2-valent HPV vaccine had higher GMTs for HPV 16 than those receiving 4-valent vaccine at 7 months to 5 years follow-up*	Mean: 7634.4 EU/mL	Mean: 17301.5 EU/mL	Ratio of GMTs 2.27 (1.60 to 3.22) 179 participants in 1 RCT	⊕⊕OO LOW [1,2]
	follow up: 60 months		Mean: 764.9 EU/mL	Mean: 1784.5 EU/mL	Ratio of GMTs 2.33 (1.28 to 4.24) 93 participants in 1 RCT	
GMTs for HPV 18 in 27-35-year olds	follow up: 7 months	There is low-certainty evidence that 27-35-year old women receiving 2-valent HPV vaccine had higher GMTs for HPV 18 than those receiving 4-valent vaccine at 7 months to 5 years follow-up*	Mean: 1043.0 EU/mL	Mean: 9501.6 EU/mL	Ratio of GMTs 9.11 (6.33 to 13.11) 212 participants in 1 RCT	⊕⊕OO LOW [1,2]
	follow up: 60 months		Mean: 74.4 EU/mL	Mean: 967.2 EU/mL	Ratio of GMTs 13.00 (7.53 to 22.46) 90 participants in 1 RCT	
GMTs for HPV 18 in 36-45-year olds	follow up: 7 months	There is low-certainty evidence that 36-45-year old women receiving 2-valent HPV vaccine had higher GMTs for HPV 18 than those receiving 4-valent vaccine at 7 months to 5 years follow-up*	Mean: 1438.8 EU/mL	Mean: 9845.5 EU/mL	Ratio of GMTs 6.84 (4.83 to 9.70) 201 participants in 1 RCT	⊕⊕OO LOW [1,2]
	follow up: 60 months		Mean: 105.3 EU/mL	Mean: 816.6 EU/mL	Ratio of GMTs 7.75 (4.56 to 13.19) 106 participants in 1 RCT	
Seropositivity for HPV 16 in 27-35-year olds	follow up: 7 months	There is low-certainty evidence that 27-35-year old females receiving 2-valent HPV vaccine had little to no difference in ratio of seropositivity for HPV 16 compared to those receiving 4-valent HPV vaccine at 7 months to 5 years follow-up*	100% (85/85)	100% (90/90)	RR 1.00 (not estimable) 175 participants in 1 RCT	⊕⊕OO LOW [1,2]
	follow up: 60 months		97% (28/29)	100% (43/43)	RR 1.04 (0.95 to 1.14) 72 participants in 1 RCT	
	follow up: 7 months	There is moderate-certainty evidence that 36-45-year old females receiving 2-valent HPV vaccine had little	100% (83/83)	100% (96/96)	RR 1.00 (not estimable) 179 participants in 1 RCT	

Seropositivity for HPV 16 in 36-45-year olds	follow up: 60 months	to no difference in ratio of seropositivity for HPV 16 compared to those receiving 4-valent HPV vaccine at 7 months to 5 years follow-up*	96% (45/47)	100% (46/46)	RR 1.04 (0.97 to 1.12) 93 participants in 1 RCT	⊕⊕OO LOW [1,2]
Seropositivity for HPV 18 in 27-35-year olds	follow up: 7 months	There is low-certainty evidence that 27-35-year old females receiving 2-valent HPV vaccine had little to no difference in ratio of seropositivity for HPV 18 compared to those receiving 4-valent HPV vaccine at 7 months, but a higher rate of seropositivity with 2-valent vaccine from 1 to 5 years follow-up*	98% (99/101)	100% (102/102)	RR 1.02 (0.99 to 1.05) 203 participants in 1 RCT	⊕⊕OO LOW [1,2]
	follow up: 60 months		61% (22/36)	98% (53/54)	RR 1.61 (1.23 to 2.09) 90 participants in 1 RCT	⊕⊕OO LOW [1,2]
Seropositivity for HPV 18 in 36-45-year olds	follow up: 7 months	There is low-certainty evidence that 36-45-year old females receiving 2-valent HPV vaccine had little to no difference in ratio of seropositivity for HPV 18 compared to those receiving 4-valent HPV vaccine at 7 to 12 months, but a higher rate of seropositivity with 2-valent vaccine from 1.5 to 5 years follow-up*	100% (91/91)	100% (110/110)	RR 1.00 (not estimable) 201 participants in 1 RCT	⊕⊕OO LOW [1,2]
	follow up: 60 months		75% (38/51)	100% (55/55)	RR 1.34 (1.14 to 1.58) 106 participants in 1 RCT	⊕⊕OO LOW [1,2]

CI= confidence interval; GMT= Geometric mean titre; HPV= human papilloma virus; EU= ELISA units; RCT= randomised controlled trial; RR= risk ratio

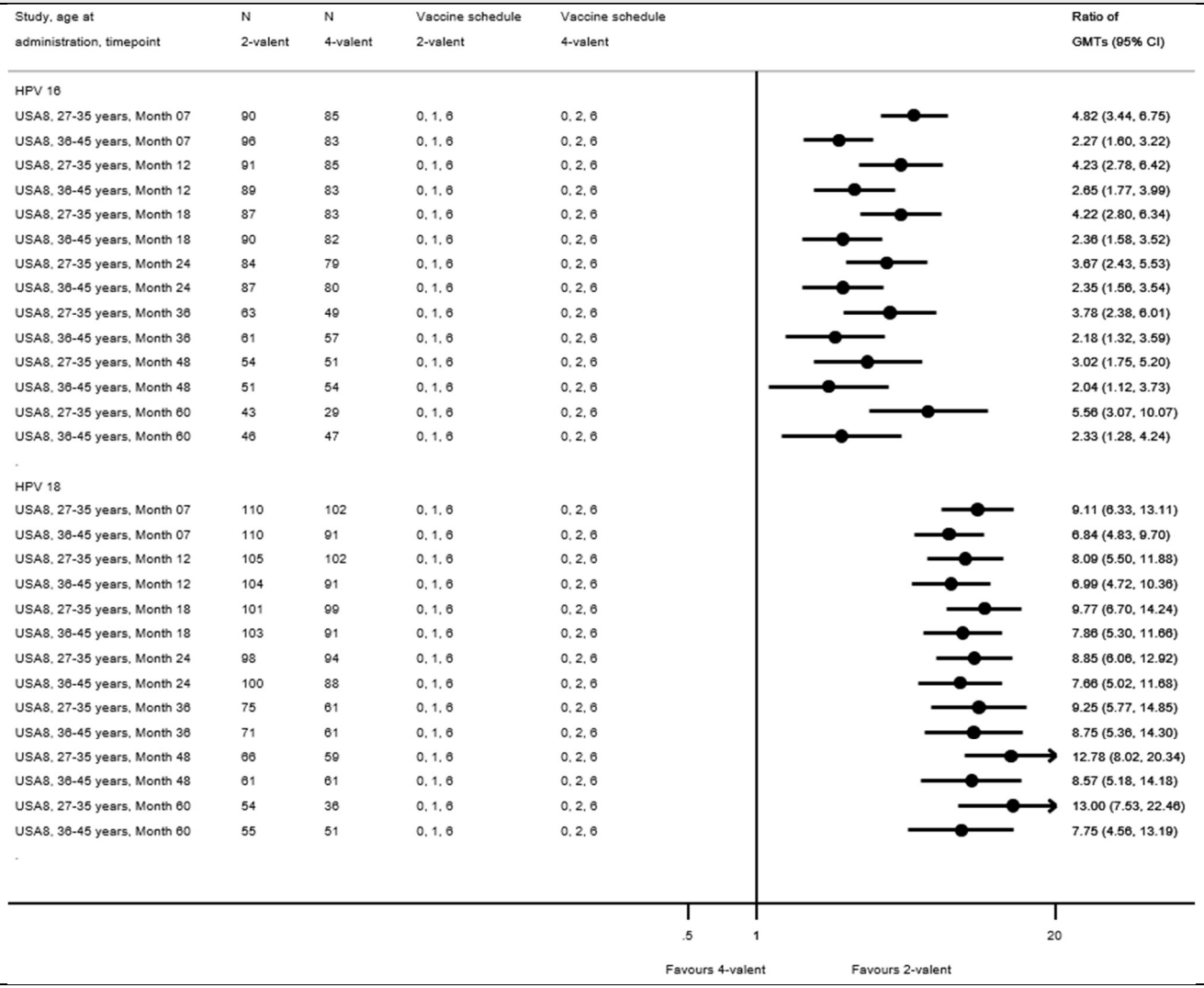
*** See forest plot for all timepoints, including 7 months, 1 year, 1.5 years, 2 years, 3 years, 4 years, and 5 years**

[1] Downgraded one level for risk of bias: randomization and allocation concealment methods were not clearly reported

[2] Downgraded one level for imprecision: few participants

Forest plot: 2-valent HPV vaccine versus 4-valent HPV vaccine in women over 25 years – immunogenicity outcomes

Participants: 27 to 45-year old females (HPV serostatus mixed at baseline)
Setting: USA
Comparison: 2-valent HPV vaccine (3-doses (Day 0, Month 1, Month 6)) versus 4-valent HPV vaccine (3-doses (Day 0, Month 2, Month 6))

Outcome	Forest plot	Certainty of the evidence (GRADE)
GMTs for HPV 16 and 18 follow up: 7 to 60 months		⊕⊕OO LOW

Seropositivity for HPV 16 and 18 follow up: 7 to 60 months	**HPV 16**	**2-valent**	**4-valent**	**RR (95% CI)**	**Timepoint**	⊕⊕OO LOW
	USA8, 27-35 years	90/90	85/85	RR 1.00 (not estimable)	Month 7	
	USA8, 36-45 years	96/96	83/83	RR 1.00 (not estimable)	Month 7	
	USA8, 27-35 years	91/91	84/85	1.01 (0.98, 1.05)	Month 12	
	USA8, 36-45 years	89/89	83/83	RR 1.00 (not estimable)	Month 12	
	USA8, 27-35 years	87/87	82/83	1.01 (0.98, 1.05)	Month 18	
	USA8, 36-45 years	90/90	82/82	RR 1.00 (not estimable)	Month 18	
	USA8, 27-35 years	84/84	77/79	1.03 (0.98, 1.07)	Month 24	
	USA8, 36-45 years	87/87	80/80	RR 1.00 (not estimable)	Month 24	
	USA8, 27-35 years	63/63	49/49	RR 1.00 (not estimable)	Month 36	
	USA8, 36-45 years	61/61	57/57	RR 1.00 (not estimable)	Month 36	
	USA8, 27-35 years	54/54	49/51	1.04 (0.97, 1.11)	Month 48	
	USA8, 36-45 years	50/51	53/54	1.00 (0.95, 1.05)	Month 48	
	USA8, 27-35 years	43/43	28/29	1.04 (0.95, 1.14)	Month 60	
	USA8, 36-45 years	46/46	45/47	1.04 (0.97, 1.12)	Month 60	
	HPV 18	**2-valent**	**4-valent**	**RR (95% CI)**	**Timepoint**	
	USA8, 27-35 years	102/102	99/101	1.02 (0.99, 1.05)	Month 7	
	USA8, 36-45 years	110/110	91/91	RR 1.00 (not estimable)	Month 7	
	USA8, 27-35 years	104/105	92/102	1.20 (1.03, 1.17) *	Month 12	
	USA8, 36-45 years	104/104	90/91	1.01 (0.98, 1.04)	Month 12	
	USA8, 27-35 years	101/101	74/99	1.34 (1.19, 1.50) *	Month 18	
	USA8, 36-45 years	102/103	79/91	1.14 (1.05, 1.24) *	Month 18	
	USA8, 27-35 years	98/98	68/94	1.38 (1.22, 1.56) *	Month 24	
	USA8, 36-45 years	99/100	68/88	1.28 (1.14, 1.44) *	Month 24	
	USA8, 27-35 years	75/75	43/61	1.42 (1.20, 1.67) *	Month 36	

	USA8, 36-45 years	69/71	45/61	1.32 (1.13, 1.54) *	Month 36	
	USA8, 27-35 years	66/66	34/59	1.73 (1.39, 2.15) *	Month 48	
	USA8, 36-45 years	59/61	44/61	1.34 (1.14, 1.58) *	Month 48	
	USA8, 27-35 years	53/54	22/36	1.61 (1.23, 2.09) *	Month 60	
	* Statistically significant difference between 2-valent and 4-valent HPV vaccine					

CI= confidence interval; GMT= Geometric mean titre; HPV= human papilloma virus; EU= ELISA units; RR= risk ratio

References

China3

Zhu F, Li J, Hu Y, Zhang X, Yang X, Zhao H, et al. Immunogenicity and safety of the HPV-16/18 AS04-adjuvanted vaccine in healthy Chinese girls and women aged 9 to 45 years. Hum Vaccin Immunother. 2014;10(7):1795-806.

GSK HPV-069 [114590]. Immunogenicity and safety study of GSK Biologicals' HPV vaccine (GSK 580299) in healthy adult Chinese female subjects. https://www.gsk-clinicalstudyregister.com/files2/gsk-114590-clinical-study-report-redact.pdf (accessed on 09 Sep 2018)

Italy2

Carozzi FM, Ocello C, Burroni E, Faust H, Zappa M, Paci E, et al. Effectiveness of HPV vaccination in women reaching screening age in Italy. J Clin Virol. 2016 Nov;84:74-81.

Multinational12

Muñoz N, Manalastas R Jr, Pitisuttithum P, Tresukosol D, Monsonego J, Ault K, et al. Safety, immunogenicity, and efficacy of quadrivalent human papillomavirus (types 6, 11, 16, 18) recombinant vaccine in women aged 24–45 years: a randomised, double-blind trial. Lancet. 2009 Jun 6;373(9679):1949-57.

Castellsagué X1, Muñoz N, Pitisuttithum P, Ferris D, Monsonego J, Ault K, et al. End-of-study safety, immunogenicity, and efficacy of quadrivalent HPV (types 6, 11, 16, 18) recombinant vaccine in adult women 24-45 years of age. Br J Cancer. 2011 Jun 28;105(1):28-37.

Multinational13

Skinner SR, Szarewski A, Romanowski B, Garland SM, Lazcano-Ponce E, Salmerón J, et al. Efficacy, safety, and immunogenicity of the human papillomavirus 16/18 AS04-adjuvanted vaccine in women older than 25 years: 4-year interim follow-up of the phase 3, double-blind, randomised controlled VIVIANE study. Lancet. 2014 Dec 20;384(9961):2213-27.

Wheeler CM, Skinner SR, Del Rosario-Raymundo MR, Garland SM, Chatterjee A, Lazcano-Ponce E, et al. Efficacy, safety, and immunogenicity of the human papillomavirus 16/18 AS04-adjuvanted vaccine in women older than 25 years: 7-year follow-up of the phase 3, double-blind, randomised controlled VIVIANE study. Lancet Infect Dis. 2016 Oct;16(10):1154-1168.

GSK HPV-028 [109801]. Complementary testing to further evaluate the immunogenicity of a GSK Biologicals' HPV vaccine (580299) in healthy female subjects aged over 26 years enrolled in study 104820. https://www.gsk-clinicalstudyregister.com/files2/gsk-109801-clinical-study-report-redact.pdf (accessed on 09 Sep 2018)

USA8

Einstein MH, Baron M, Levin MJ, Chatterjee A, Edwards RP, Zepp F, et al. Comparison of the immunogenicity and safety of Cervarix and Gardasil human papillomavirus (HPV) cervical cancer vaccines in healthy women aged 18-45 years. Hum Vaccin. 2009 Oct;5(10):705-19.

Einstein MH, Baron M, Levin MJ, Chatterjee A, Fox B, Scholar S, et al. Comparison of the immunogenicity of the human papillomavirus (HPV)-16/18 vaccine and the HPV-6/11/16/18 vaccine for oncogenic non-vaccine types HPV-31 and HPV-45 in healthy women aged 18-45 years. Hum Vaccin. 2011 Dec;7(12):1359-73.

Einstein MH, Takacs P, Chatterjee A, Sperling RS, Chakhtoura N, Blatter MM, et al. Comparison of long-term immunogenicity and safety of human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine and HPV-6/11/16/18 vaccine in healthy women aged 18-45 years: end-of-study analysis of a Phase III randomized trial. Hum Vaccin Immunother. 2014;10(12):3435-45.