Randomized controlled trials of human papillomavirus vaccines: Systematic reviews prepared by Cochrane Response, London, UK

Evidence summaries:

Two doses of HPV vaccine in younger females (9 to 15 years) versus three doses of HPV vaccine in older females (15 to 26 years)

Contents

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Key findings

Two doses HPV vaccine in younger females versus three doses HPV vaccine in older females – all vaccines at 7 months

GMTs for HPV 6, 11, 16 and 18, were non-inferior or higher for younger females (two doses) when compared with older females (three doses) at 7 months (very low-quality evidence). GMTs for HPV 31, 33, 45, 52, and 58 were higher in younger females (2 doses) compared with older females (3 doses) (moderate-quality evidence). There was of no significant difference between younger (two doses) and older (three doses) in seropositivity for all 9 HPV subtypes measured at 7 months (moderate-quality evidence).

Two doses of 2-valent HPV vaccine in younger females versus three doses of 2-valent HPV vaccine in older females – multiple time points

There was low-quality (7 months) and very low-quality evidence (60 months) of non-inferiority for GMTs for HPV 16 and 18 in younger females (2 doses) when compared to older females (3 doses) of 2-valent vaccine. There was moderate-quality evidence of no significant difference in seropositivity for HPV 16 and 18 in younger versus older females at 7 and 12 months with 2-valent vaccine.

Two doses of 4-valent HPV vaccine in younger females versus three doses of 4-valent HPV vaccine in older females – multiple time points

There was low to moderate-quality evidence of non-inferior or higher GMTs for HPV 6, 11, 16 and 18 in younger females (2 doses) when compared with older females (3 doses) of 4-valent vaccine at 7 months, and very-low quality evidence at 36 months. There was no significant difference in seropositivity for the same HPV subtypes in two-dose vaccinated younger versus three-dose vaccinated older females at 7 and 12 months (moderate-quality evidence).

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 Targeted Update, we review and analyse evidence for the protection afforded by two doses of prophylactic HPV vaccines in younger females (9 to 15 years) compared with three doses in older females (16 to 26 years).

Objectives

To evaluate the effect of HPV vaccination in females, comparing younger versus older females, updating the systematic review by D'Addario et al.

Search methods

Searches were conducted from July 2013 to June 2016, and all relevant studies regardless of language or publication status were searched. 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

Experimental studies with a non-randomised comparison of two doses of HPV vaccine in younger females (9 to 15 years) versus three doses in older females (15 to 26 years) were eligible for inclusion.

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 reported as ratios. For continuous data, where GMTs were reported, we presented the data as mean differences (95% CI) on the log scale and re-expressed as ratio of GMTs. The non-inferiority threshold for younger females (two doses) was 0.5 for the ratio of GMTs.

Main Results

We included six studies (Canada1; Canada/Germany1; Mexico1; Mexico2; Multinational2; Multinational3) comparing 2 doses in girls with 3 doses in women. This update includes two additional trials to the previous review (Mexico2; Multinational3). Canada/Germany1, Mexico1, and Multinational2 assessed 2-valent vaccine, Canada1 and Mexico2 assessed 4-valent vaccine, and Multinational3 assessed 9-valent vaccine. Multinational3 provided no long-term follow up data past 7 months. All outcomes were downgraded for lack of randomised comparison. For some longer-term time points the quality of the evidence was downgraded for risk of bias for low sample size and loss to follow-up.

Two doses HPV vaccine in younger females versus three doses HPV vaccine in older females – all vaccines at 7 months

As in the D'Addario review, we analysed studies comparing two doses of HPV vaccine in younger females versus three doses in older females, reporting immunogenicity outcomes at 7 months, regardless of vaccine type. We added data from Mexico2 and Multinational3 to this comparison. For GMTs for HPV 6, 11, 16 and 18, there was very low-quality evidence of non-inferiority or higher GMTs for younger females (two doses) when compared with older females (three doses) at 7 months. There was high heterogeneity. One possible source of heterogeneity was Mexico2, which included both seronegative and seropositive participants at baseline. For GMTs for HPV 16 and HPV 18, additional possible sources of heterogeneity include the different types of vaccine used, different dose schedules in three dose arms (0,1,6 or 0,2,6), and different assays used to measure GMTs (luminex or ELISA).

For GMTs for HPV 31, 33, 45, 52, and 58, there was moderate-quality evidence of higher GMTs in younger females (2 doses) compared with older females (3 doses). For seropositivity to all HPV subtypes measured, there was moderate-quality evidence of no significant difference between younger (two doses) and older (three doses) at 7 months.

Two doses of 2-valent HPV vaccine in younger females versus three doses of 2-valent HPV vaccine in older females – multiple time points

There was low-quality (7 months) and very low-quality evidence (60 months) of non-inferiority for GMTs for HPV 16 and 18 in younger females (2 doses) when compared to older females (3 doses) of 2-valent vaccine. There was moderate-quality evidence of no significant difference in seropositivity for HPV 16 and 18 in younger versus older females at 7 and 12 months.

Two doses of 4-valent HPV vaccine in younger females versus three doses of 4-valent HPV vaccine in older females – multiple time points

There was low to moderate-quality evidence of non-inferior or higher GMTs for HPV 6, 11, 16 and 18 in younger females (2 doses) when compared to older females (3 doses) at 7 months, and very-low quality evidence at 36 months, with 4-valent vaccine. There was moderate-quality evidence of no significant difference in seropositivity for the same HPV subtypes in two-dose vaccinated younger females versus three-dose vaccinated older females at 7 and 12 months.

Implications and conclusions

The evidence indicates that younger females (two doses) have non-inferior or higher GMT responses than older females (3 doses) at 7 months, which appears to be sustained in longer-term follow-up (60 months with 2-valent and 36 months with 4-valent vaccines). No significant differences were detected in seropositivity between younger and older females at 7 months or with longer follow-up.

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Summary of Findings: Two doses of HPV vaccine in younger (9 to 15-year old) females versus three doses of HPV vaccine in older[3] (15 to 26-year old) females – immunogenicity outcomes at 7 months

Population: **9 to 26-year old females (seronegative at baseline, except in Mexico where participants were both seropositive and negative)**
Setting: **Canada, Chile, Colombia, Czech Republic, Denmark, Germany, Israel, Italy, Korea, Malaysia, Mexico, Norway, South Africa, Spain, Taiwan, Thailand, Turkey, and the US.**
Comparison: **2-, 4-, and 9-valent HPV vaccines in 2 doses (Day 1, Month 6) in 9 to 15-year-old females versus 2-, 4-, and 9-valent HPV vaccines in 3 doses (Day 1, Month 1 or 2, Month 6) in 15 to 26-year-old females**

Outcome	Plain language summary	Absolute effect*		Relative effect (95% CI) Nº of participants & studies	Certainty of the evidence (GRADE)
		Older females	Younger females		
GMTs for HPV 6 follow up: 7 months	There is very low-quality evidence of non-inferiority for GMTs for HPV 6 in younger females (2 doses) when compared to older females (3 doses).	Mean: 387 to 938 mMU/mL	Mean: 306 to 2186 mMU/mL	Ratio 1.63 (0.98 to 2.70); 1271 participants in 3 studies	⊕OOO VERY LOW[1,2]
GMTs for HPV 11 follow up: 7 months	There is very low-quality evidence of higher GMTs for HPV 11 in younger females (2 doses) compared with older females (3 doses).	Mean: 630 to 1277 mMU/mL	Mean: 968 to 2348 mMU/mL	Ratio 1.91 (1.50 to 2.44); 1293 participants in 3 studies	⊕OOO VERY LOW[1,2]
GMTs for HPV 16 follow up: 7 months	There is very low-quality evidence of higher GMTs for HPV 16 in younger females (2 doses) compared with older females (3 doses).	Mean: 2409 to 12858 units**	Mean: 5137 to 11067 units**	Ratio 1.54 (1.08 to 2.21); 3594 participants in 6 studies	⊕OOO VERY LOW[1,2]
GMTs for HPV 18 follow up: 7 months	There is very low-quality evidence of higher GMTs for HPV 18 in younger females (2 doses) compared with older females (3 doses).	Mean: 344 to 5003 units**	Mean: 605 to 5909 units**	Ratio 1.63 (1.29 to 2.05); 3665 participants in 6 studies	⊕OOO VERY LOW[1,2]
GMTs for HPV 31 follow up: 7 months	There is moderate-quality evidence of higher GMTs for HPV 31 in younger females (2 doses) versus older females (3 doses).	Mean: 572 mMU/mL	Mean: 1436 mMU/mL	Ratio 2.51 (2.11 to 2.98); 536 participants in 1 study	⊕⊕⊕O MODERATE[1]
GMTs for HPV 33 follow up: 7 months	There is moderate-quality evidence of higher GMTs for HPV 33 in younger females (2 doses) versus older females (3 doses).	Mean: 348 mMU/mL	Mean: 1030 mMU/mL	Ratio 2.96 (2.53 to 3.47); 552 participants in 1 study	⊕⊕⊕O MODERATE[1]
GMTs for HPV 45 follow up: 7 months	There is moderate-quality evidence of higher GMTs for HPV 45 in younger females (2 doses) versus older females (3 doses).	Mean: 214 mMU/mL	Mean: 358 mMU/mL	Ratio 1.67 (1.39 to 2.01); 554 participants in 1 study	⊕⊕⊕O MODERATE[1]
GMTs for HPV 52 follow up: 7 months	There is moderate-quality evidence of higher GMTs for HPV 52 in younger females (2 doses) versus older females (3 doses).	Mean: 364 mMU/mL	Mean: 581 mMU/mL	Ratio 1.60 (1.37 to 1.86); 543 participants in 1 study	⊕⊕⊕O MODERATE[1]
GMTs for HPV 58 follow up: 7 months	There is moderate-quality evidence of higher GMTs for HPV 58 in younger females (2 doses) versus older females (3 doses).	Mean: 491 mMU/mL	Mean: 1251 mMU/mL	Ratio 2.55 (2.17 to 2.99); 531 participants in 1 study	⊕⊕⊕O MODERATE[1]
Seropositivity for HPV 6 follow up: 7 months	There is moderate-quality evidence of no significant difference in seropositivity for HPV 6 in 2-dose vaccinated younger females versus 3-dose vaccinated older females.	237/238 (99.6%)	257/258 (99.6%)	RR 1.00 (0.99 to 1.01); 993 participants in 1 study	⊕⊕⊕O MODERATE[1]
Seropositivity for HPV 11 follow up: 7 months	There is moderate-quality evidence of no significant difference in seropositivity for HPV 11 in 2-dose vaccinated younger females versus 3-dose vaccinated older females.	237/238 (99.6%)	258/258 (100%)	RR 1.00 (0.99 to 1.02); 1008 participants in 1 study	⊕⊕⊕O MODERATE[1]
Seropositivity for HPV 16	There is moderate-quality evidence of no significant difference in seropositivity for HPV 16 in 2-dose vaccinated younger females	248/249 (99.6%)	272/272 (100%)	RR 1.00 (0.99 to 1.02); 3183 participants in 1	⊕⊕⊕O MODERATE[1]

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follow up: 7 months	versus 3-dose vaccinated older females.			study	
Seropositivity for HPV 18 follow up: 7 months	There is moderate-quality evidence of no significant difference in seropositivity for HPV 18 in 2-dose vaccinated younger females versus 3-dose vaccinated older females.	263/267 (98.5%)	272/272 (100%)	RR 1.02 (1.00 to 1.03); 3254 participants in 1 study	⊕⊕⊕O MODERATE [1]
Seropositivity for HPV 31 follow up: 7 months	There is moderate-quality evidence of no significant difference in seropositivity for HPV 31 in 2-dose vaccinated younger females versus 3-dose vaccinated older females.	263/264 (99.6%)	271/272 (99.6%)	RR 1.00 (0.99 to 1.01); 536 participants in 1 study	⊕⊕⊕O MODERATE [1]
Seropositivity for HPV 33 follow up: 7 months	There is moderate-quality evidence of no significant difference in seropositivity for HPV 33 in 2-dose vaccinated younger females versus 3-dose vaccinated older females.	278/279 (99.6%)	272/273 (99.6%)	RR 1.00 (0.99 to 1.01); 552 participants in 1 study	⊕⊕⊕O MODERATE [1]
Seropositivity for HPV 45 follow up: 7 months	There is moderate-quality evidence of no significant difference in seropositivity for HPV 45 in 2-dose vaccinated younger females versus 3-dose vaccinated older females.	274/280 (97.9)	272/274 (99.3%)	RR 1.00 (0.99 to 1.04) 554 participants in 1 study	⊕⊕⊕O MODERATE [1]
Seropositivity for HPV 52 follow up: 7 months	There is moderate-quality evidence of no significant difference in seropositivity for HPV 52 in 2-dose vaccinated younger females versus 3-dose vaccinated older females.	270/271 (99.6%)	271/272 (99.6%)	RR 1.00 (0.99 to 1.01) 543 participants in 1 study	⊕⊕⊕O MODERATE [1]
Seropositivity for HPV 58 follow up: 7 months	There is moderate-quality evidence of no significant difference in seropositivity for HPV 58 in 2-dose vaccinated younger females versus 3-dose vaccinated older females.	260/261 (99.6%)	270/270 (100%)	RR 1.00 (0.99 to 1.01) 531 participants in 1 study	⊕⊕⊕O MODERATE [1]

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

*Where multiple RCTs have been included the range of means is presented **GMTs measured as both mMU/mL (luminex assay) and EU/mL (ELISA) in different studies

[1]Downgraded one level for risk of bias: non-randomised comparison (younger versus older females). [2] Downgraded two levels for inconsistency: very high heterogeneity (I^2>75%)

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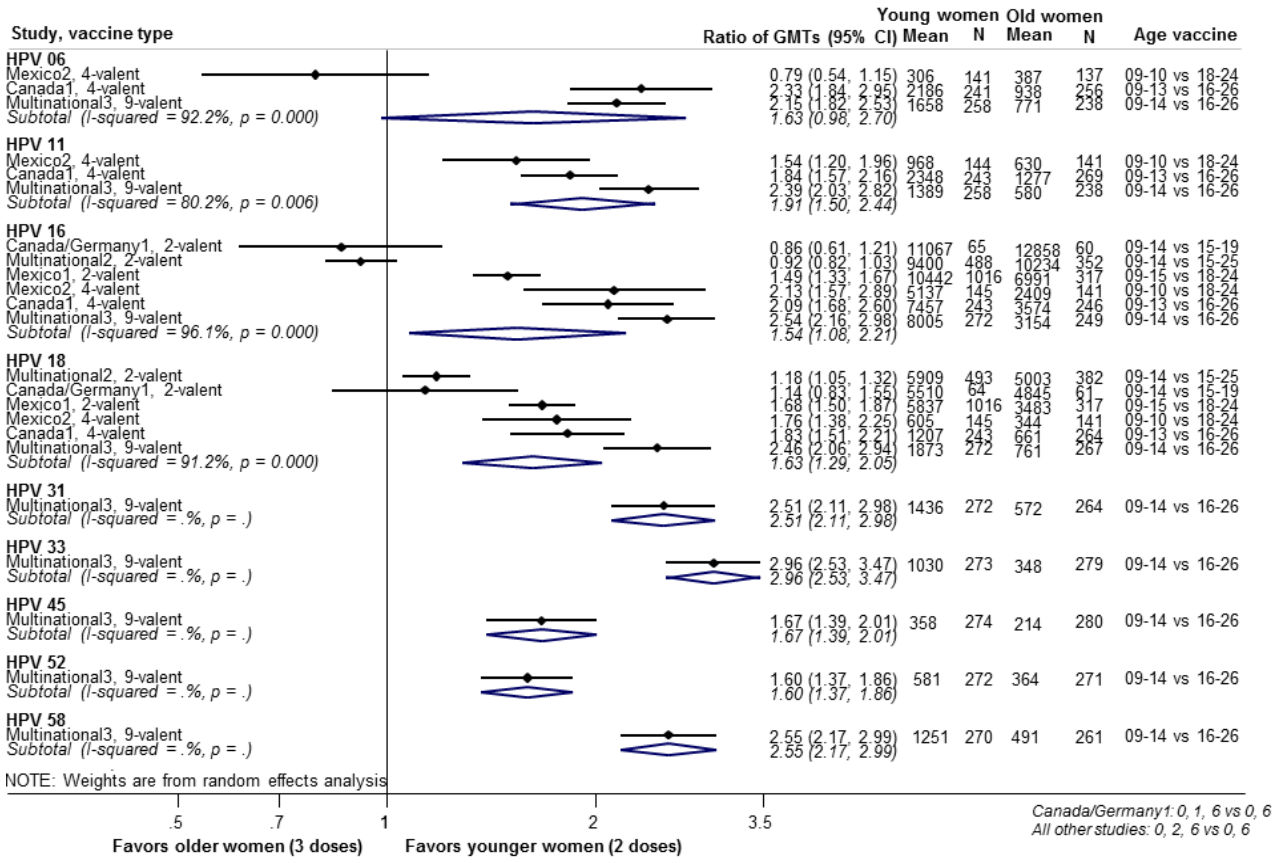
Forest plots: Two doses of HPV vaccine in younger (9 to 15-year old) females versus three doses of HPV vaccine in older (15 to 26[5]-year old) females – immunogenicity outcomes at 7 months

Population: 9 to 26-year old females (seronegative at baseline, except in Mexico where participants were both seropositive and negative)
Setting: Canada, Chile, Colombia, Czech Republic, Denmark, Germany, Israel, Italy, Korea, Malaysia, Mexico, Norway, South Africa, Spain, Taiwan, Thailand, Turkey, and the US.
Comparison: 2-, 4-, and 9-valent HPV vaccines in 2 doses (Day 1, Month 6) in 9 to 15-year-old females versus 2-, 4-, and 9-valent HPV vaccines in 3 doses (Day 1, Month 1 or 2, Month 6) in 15 to 26-year-old females

Outcome	Forest plot	Certainty of the evidence (GRADE)
Ratio of GMTs follow up: 7 months		⊕OOO VERY LOW ⊕OOO VERY LOW ⊕OOO VERY LOW ⊕OOO VERY LOW ⊕⊕⊕O MODERATE ⊕⊕⊕O MODERATE ⊕⊕⊕O MODERATE ⊕⊕⊕O MODERATE ⊕⊕⊕O MODERATE

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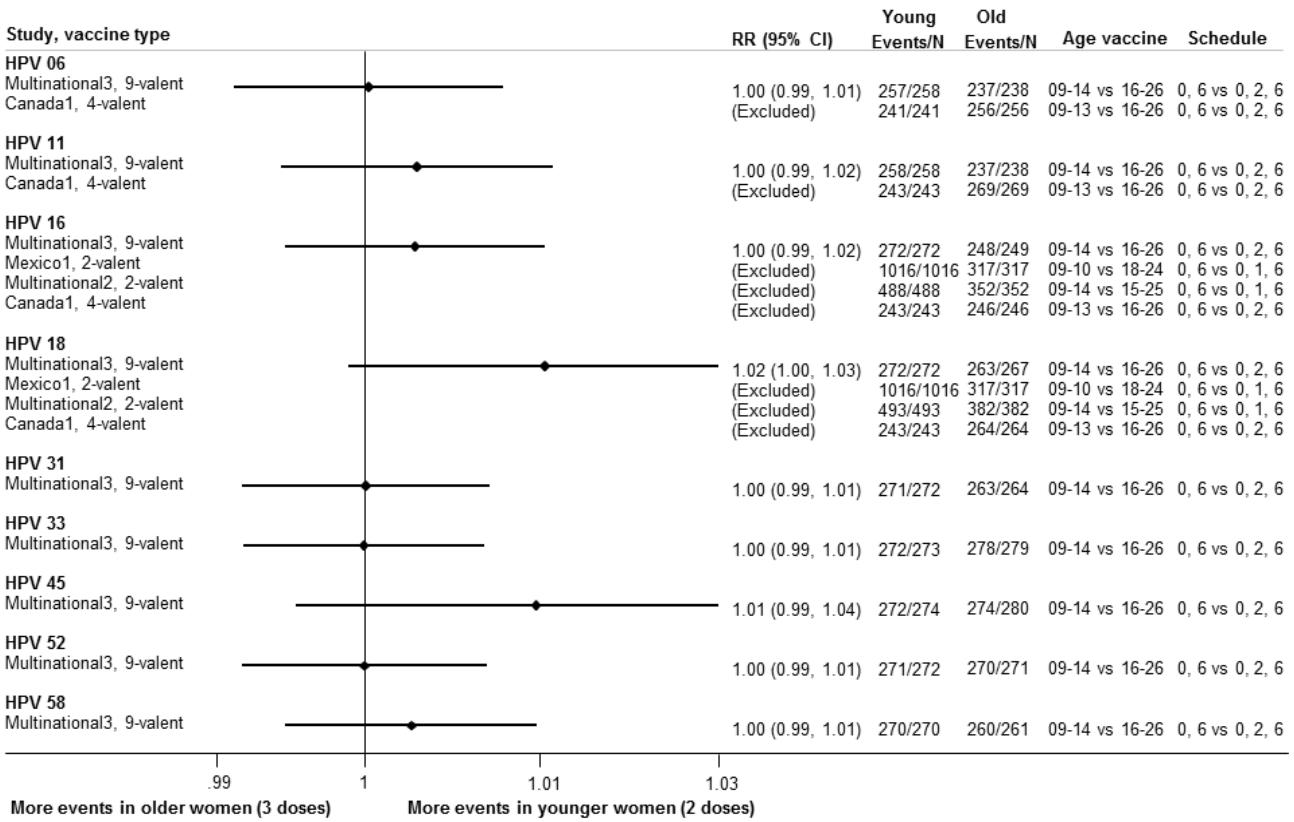
Outcome	Forest plot	Certainty of the evidence (GRADE)
Seropositivity follow up: 7 months		⊕⊕⊕O MODERATE

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Summary of Findings: Two doses of 2-valent HPV vaccine in younger (9 to 15-year old) females versus three doses of 2-valent HPV vaccine in older (15 to 25-year old) females – immunogenicity outcomes at multiple time points

Population: **9 to 25-year old females (seronegative at baseline, except in Mexico where participants were both seropositive and negative)**
Setting: **Canada, Germany, Italy, Mexico, Taiwan, and Thailand**
Comparison: **2-valent HPV vaccine in 2 doses (Day 1, Month 6) in 9 to 15-year-old females versus 2-valent HPV vaccine in 3 doses (Day 1, Month 1, Month 6) in 16 to 25-year-old females**

Outcome			Plain language summary	Absolute effect		Relative effect (95% CI) Nº of participants & studies	Certainty of the evidence (GRADE)
				Older females	Younger females		
GMTs for HPV 16	7mths	Multinational2	There is low-quality evidence of non-inferiority for GMTs for HPV 16 in younger females (2 doses) when compared to older females (3 doses) of 2-valent vaccine at 7 months	Mean: 10234 EU/mL	Mean: 9400 EU/mL	Ratio 0.92 (0.82 to 1.03); 840 participants in 1 study	⊕⊕OO LOW[1,2]
		Mexico1		Mean: 6991 EU/mL	Mean: 10442 EU/mL	Ratio 1.49 (1.33 to 1.67); 1333 participants in 1 study	
	60mths	Canada/Germany1	There is very low-quality evidence of non-inferiority for GMTs for HPV 16 in younger females (2 doses) when compared to older females (3 doses) of 2-valent vaccine at 60 months	Mean: 1454 EU/mL	Mean: 1369 EU/mL	Ratio 0.94 (0.70 to 1.27); 124 participants in 1 study	⊕OOO VERY LOW[1,3,4]
GMTs for HPV 18	7mths	Multinational2	There is low-quality evidence of non-inferiority for GMTs for HPV 18 in younger females (2 doses) when compared to older females (3 doses) of 2-valent vaccine at 7 months	Mean: 5003 EU/mL	Mean: 5909 EU/mL	Ratio 1.18 (1.05 to 1.32); 875 participants in 1 study	⊕⊕OO LOW[1,2]
		Mexico1		Mean: 3483 EU/mL	Mean: 5837 EU/mL	Ratio 1.68 (1.50 to 1.87); 1333 participants in 1 study	
	60mths	Canada/Germany1	There is very low-quality evidence of non-inferiority for GMTs for HPV 18 in younger females (2 doses) when compared to older females (3 doses) of 2-valent vaccine at 60 months	Mean: 635 EU/mL	Mean: 627 EU/mL	Ratio 0.99 (0.68 to 1.43); 119 participants in 1 study	⊕OOO VERY LOW[1,3,4]
Seropositivity for HPV 16	7mths	Multinational2	There is moderate-quality evidence of no significant difference in seropositivity for HPV 16 in 2-dose vaccinated younger females versus 3-dose vaccinated older females at 7 and 12 months.	352/352 (100%)	448/448 (100%)	Not estimable; 800 participants in 1 study	⊕⊕⊕O MODERATE[1]
		Mexico1		317/317 (100%)	1016/1016 (100%)	Not estimable; 1333 participants in 1 study	
	12mths	Multinational2		347/347 (100%)	480/480 (100%)	Not estimable; 827 participants in 1 study	
Seropositivity for HPV 18	7mths	Multinational2	There is moderate-quality evidence of no significant difference in seropositivity for HPV 18 in 2-dose vaccinated younger females versus 3-dose vaccinated older females at 7 and 12 months.	382/382 (100%)	493/493 (100%)	Not estimable; 875 participants in 1 study	⊕⊕⊕O MODERATE[1]
		Mexico1		317/317 (100%)	1016/1016 (100%)	Not estimable; 1333 participants in 1 study	
	12mths	Multinational2		376/376 (100%)	485/485 (100%)	Not estimable; 861 participants in 1 study	

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

*Data available at 12, 24, 36 and 48 months in forest plot below

[1]Downgraded one level for risk of bias: non-randomised comparison (younger versus older females). [2]Downgraded one level for inconsistency: heterogeneity between studies [3]Downgraded one further level for risk of bias: high loss to follow-up [4]Downgraded one level for imprecision: low sample size

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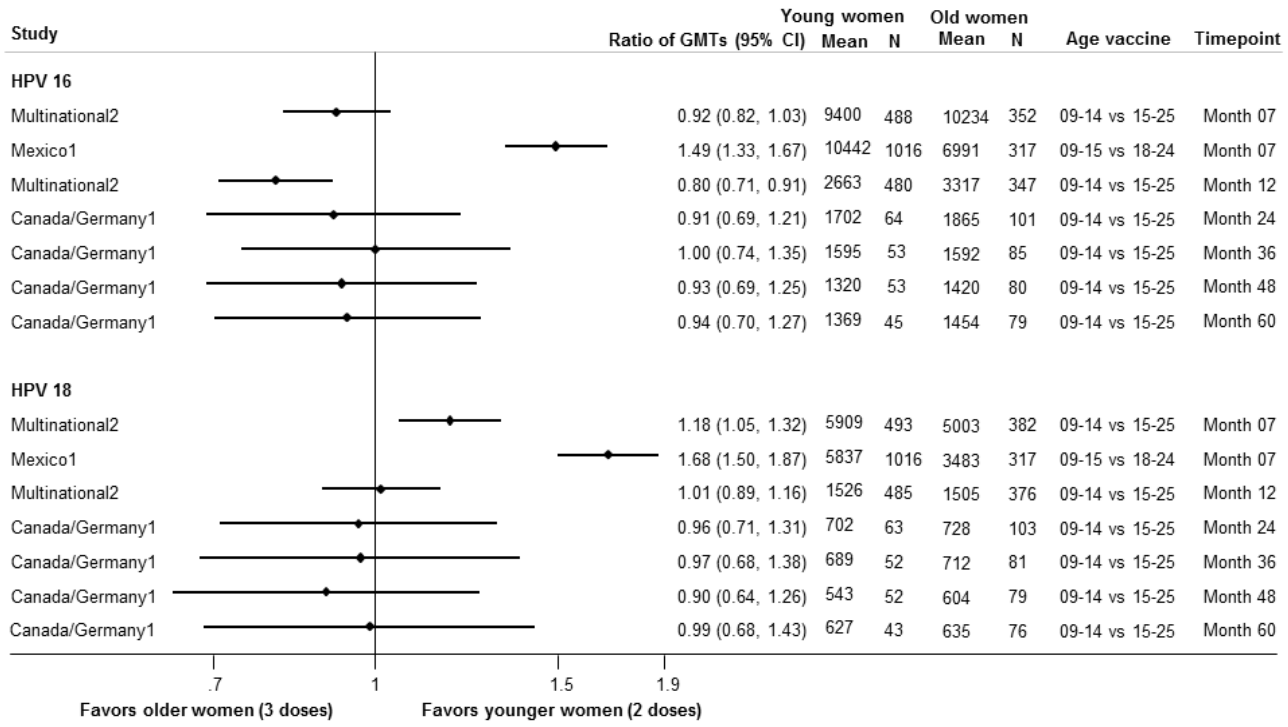
Forest plot: Two doses of 2-valent HPV vaccine in younger (9 to 15-year old) females versus three doses of 2-valent HPV vaccine in older (15 to 25-year old) females – immunogenicity outcomes at multiple time points

Population: **9 to 25-year old females (seronegative at baseline, except in Mexico where participants were both seropositive and negative)**
Setting: **Canada, Germany, Italy, Mexico, Taiwan, and Thailand**
Comparison: **2-valent HPV vaccine in 2 doses (Day 1, Month 6) in 9 to 15-year-old females versus 2-valent HPV vaccines in 3 doses (Day 1, Month 1, Month 6) in 16 to 26-year-old females**

Outcome	Forest plot	Certainty of the evidence (GRADE)
Ratio of GMTs follow up: 7 to 60 months		⊕⊕OO LOW ⊕⊕OO VERY LOW ⊕⊕OO LOW ⊕OOO VERY LOW

* Forest plots for seropositivity are not presented; all participants seroconverted.

Summary of Findings: Two doses of 4-valent HPV vaccine in younger (9 to 13-year old) females versus three doses of 4-valent HPV vaccine in older (16 to 26-year old) females – immunogenicity outcomes at multiple timepoints

Population: **9 to 26-year old females (seronegative at baseline in Canada, mixed at baseline in Mexico)**
Setting: **Canada, Mexico (only GMTs)**
Comparison: **4-valent HPV vaccine in 2 doses (Day 1, Month 6) in 9 to 13-year-old females versus 4-valent HPV vaccines in 3 doses (Day 1, Month 2, Month 6) in 16 to 26-year-old females**

Outcome			Plain language summary	Absolute effect		Relative effect (95% CI) Nº of participants & studies	Certainty of the evidence (GRADE)
				Older females	Younger females		
GMTs for HPV 6	7 mths	Mexico2	There is low-quality evidence of non-inferiority for GMTs for HPV 6 in younger females (2 doses) when compared with older females (3 doses) of 4-valent vaccine at 7 months	Mean: 387.3 mMU/mL	Mean: 306.2 mMU/mL	Ratio 0.79 (0.54 to 1.15); 278 participants in 1 study	⊕⊕OO LOW [1,2]
	7 mths	Canada 1		Mean: 938 mMU/mL	Mean: 2186 mMU/mL	Ratio 2.33 (1.84 to 2.95); 497 participants in 1 study	
	36 mths	Canada 1	There is very low-quality evidence of higher GMTs for HPV 6 in younger females (2 doses) when compared with older females (3 doses) of 4-valent vaccine at 36 months	Mean: 176 mMU/mL	Mean: 239 mMU/mL	Ratio 1.36 (1.03 to 1.79); 176 participants in 1 study	⊕OOO VERY LOW [1,3,4]
GMTs for HPV 11	7 mths	Mexico2	There is moderate-quality evidence of higher GMTs for HPV 11 in younger females (2 doses) when compared with older females (3 doses) of 4-valent vaccine 7 months	Mean: 629.9 mMU/mL	Mean: 968.3 mMU/mL	Ratio 1.54 (1.20 to 1.96); 285 participants in 1 study	⊕⊕⊕O MODERATE [1]
	7 mths	Canada 1		Mean: 1277 mMU/mL	Mean: 2348 mMU/mL	Ratio 1.84 (1.57 to 2.16); 512 participants in 1 study	
	36 mths	Canada 1	There is very low-quality evidence of higher GMTs for HPV 11 in younger females (2 doses) when compared with older females (3 doses) of 4-valent vaccine at 36 months	Mean: 208 mMU/mL	Mean: 298 mMU/mL	Ratio 1.43 (1.09 to 1.89); 183 participants in 1 study	⊕OOO VERY LOW [1,3,4]
GMTs for HPV 16	7 mths	Mexico2	There is moderate-quality evidence of higher GMTs for HPV 16 in younger females (2 doses) when compared with older females (3 doses) of 4-valent vaccine 7 months	Mean: 2408.8 mMU/mL	Mean: 5136.7 mMU/mL	Ratio 2.13 (1.57 to 2.89); 286 participants in 1 study	⊕⊕⊕O MODERATE [1]
	7 mths	Canada 1		Mean: 3574 mMU/mL	Mean: 7457 mMU/mL	Ratio 2.09 (1.68 to 2.60); 489 participants in 1 study	
	36 mths	Canada 1	There is very low-quality evidence of higher GMTs for HPV 16 in younger females (2 doses) when compared with older females (3 doses) of 4-valent vaccine at 36 months	Mean: 678 mMU/mL	Mean: 1151 mMU/mL	Ratio 1.70 (1.23 to 2.34); 172 participants in 1 study	⊕OOO VERY LOW [1,3,4]
GMTs for HPV 18	7 mths	Mexico2	There is moderate-quality evidence of higher GMTs for HPV 18 in younger females (2 doses) when compared with older females (3 doses) of 4-valent vaccine 7 months	Mean: 343.7 mMU/mL	Mean: 605 mMU/mL	Ratio 1.76 (1.38 to 2.25); 286 participants in 1 study	⊕⊕⊕O MODERATE [1]
	7 mths	Canada 1		Mean: 661 mMU/mL	Mean: 1207 mMU/mL	Ratio 1.83 (1.51 to 2.21); 507 participants in 1 study	
	36 mths	Canada 1	There is very low-quality evidence of non-inferiority for GMTs for HPV 18 in younger females (2 doses) when compared with older females (3 doses) of 4-valent vaccine at 36 months	Mean: 71 mMU/mL	Mean: 104 mMU/mL	Ratio 1.46 (0.96 to 2.23); 182 participants in 1 study	⊕OOO VERY LOW [1,3,4]

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Outcome			Plain language summary	Absolute effect		Relative effect (95% CI) Nº of participants & studies	Certainty of the evidence (GRADE)
				Older females	Younger females		
Seropositivity for HPV 6	7 mths	Canada1	There is moderate-quality evidence of no significant difference in seropositivity for HPV 6 in 2-dose vaccinated younger females versus 3-dose vaccinated older females at 7 and 24 months.	256/256 (100%)	241/241 (100%)	Not estimable; 497 participants in 1 study	⊕⊕⊕O MODERATE [1]
	24 mths			195/195 (100%)	193/193 (100%)	Not estimable; 388 participants in 1 study	
	36 mths		There is very low-quality evidence of no significant difference in seropositivity for HPV 6 in 2-dose vaccinated younger females versus 3-dose vaccinated older females at 36 months.	92/92 (100%)	84/84 (100%)	Not estimable; 176 participants in 1 study	⊕OOO VERY LOW [1 3 4]
Seropositivity for HPV 11	7 mths	Canada1	There is moderate-quality evidence of no significant difference in seropositivity for HPV 11 in 2-dose vaccinated younger females versus 3-dose vaccinated older females at 7 to 24 months.	269/269 (100%)	243/243 (100%)	Not estimable; 512 participants in 1 study	⊕⊕⊕O MODERATE [1]
	24 mths			206/206 (100%)	195/195 (100%)	Not estimable; 401 participants in 1 study	
	36 mths		There is very low-quality evidence of no significant difference in seropositivity for HPV 11 in 2-dose vaccinated younger females versus 3-dose vaccinated older females at 36 months.	97/97 (100%)	86/86 (100%)	Not estimable; 183 participants in 1 study	⊕OOO VERY LOW [1 3 4]
Seropositivity for HPV 16	7 mths	Canada1	There is moderate-quality evidence of no significant difference in seropositivity for HPV 16 in 2-dose vaccinated younger females versus 3-dose vaccinated older females at 7 to 36 months.	246/246 (100%)	243/243 (100%)	Not estimable; 489 participants in 1 study	⊕⊕⊕O MODERATE [1]
	24 mths			189/189 (100%)	195/195 (100%)	Not estimable; 384 participants in 1 study	
	36 mths		There is very low-quality evidence of no significant difference in seropositivity for HPV 16 in 2-dose vaccinated younger females versus 3-dose vaccinated older females at 36 months.	86/86 (100%)	86/86 (100%)	Not estimable; 172 participants in 1 study	⊕OOO VERY LOW [1 3 4]
Seropositivity for HPV 18	7 mths	Canada1	There is moderate-quality evidence of no significant difference in seropositivity for HPV 18 in 2-dose vaccinated younger females versus 3-dose vaccinated older females at 7 to 36 months.	264/264 (100%)	243/243 (100%)	Not estimable; 507 participants in 1 study	⊕⊕⊕O MODERATE [1]
	24 mths			167/202 (83%)	174/195 (89%)	RR 1.08 (1.00 to 1.17); 397 participants in 1 study	
	36 mths		There is very low-quality evidence of no significant difference in seropositivity for HPV 18 in 2-dose vaccinated younger females versus 3-dose vaccinated older females at 36 months.	76/96 (79%)	74/86 (86%)	RR 1.09 (0.95 to 1.24); 182 participants in 1 study	⊕OOO VERY LOW [1 3 4]

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

[1]Downgraded one level for study design: non-randomised comparison (younger versus older females) [2]Downgraded one level for inconsistency: heterogeneity between studies [3]Downgraded one further level for risk of bias: high loss to follow-up [4]Downgraded one level for imprecision: low sample size

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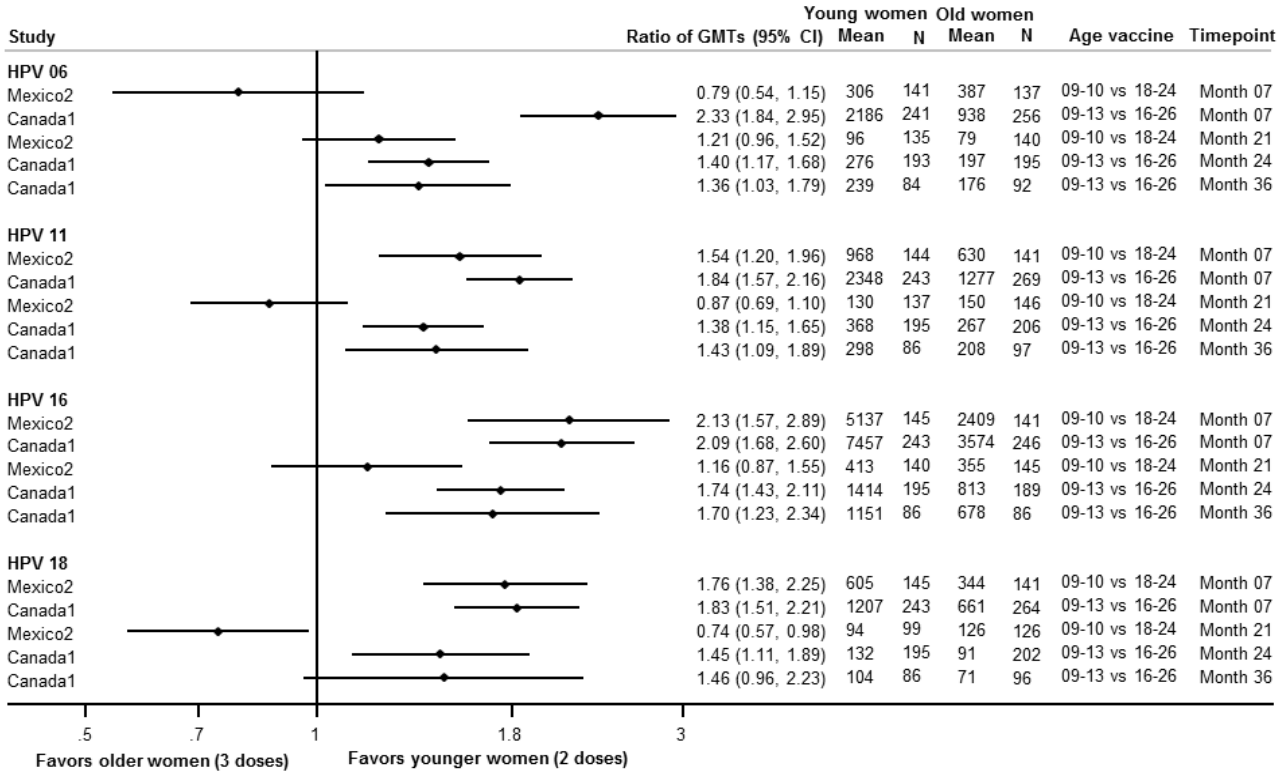
Forest plots: Two doses of 4-valent HPV vaccine in younger (9 to 13-year old) females versus three doses of 4-valent HPV vaccine in older (16 to 26-year old) females – immunogenicity outcomes at multiple timepoints

Population: **9 to 26-year old females (seronegative at baseline in Canada, mixed at baseline in Mexico)**
Setting: **Canada, Mexico (only GMTs)**
Comparison: **4-valent HPV vaccine in 2 doses (Day 1, Month 6) in 9 to 13-year-old females versus 4-valent HPV vaccines in 3 doses (Day 1, Month 2, Month 6) in 16 to 26-year-old females**

Outcome	Forest plot	Certainty of the evidence (GRADE)
Ratio of GMTs follow up: 7 to 36 months		⊕⊕OO LOW ⊕OOO VERY LOW ⊕⊕⊕O MODERATE ⊕OOO VERY LOW ⊕⊕⊕O MODERATE ⊕OOO VERY LOW ⊕⊕⊕O MODERATE ⊕OOO VERY LOW

*Forest plots for seropositivity are not presented; nearly all participants seroconverted.

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Canada1

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Canada/Germany1

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Mexico1

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Multinational2

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Multinational3

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Two doses of HPV vaccine versus three doses of HPV vaccine in younger females (9 to 15 years)

Contents

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Key findings

Two versus three doses of HPV vaccines at 7 months - all vaccines

Two doses were non-inferior to, or had higher GMTs than, three doses, for all nine HPV subtypes measured except HPV 45 (high-quality evidence, except for HPV 16 (low-quality evidence) and 18 (moderate-quality evidence)).

For seroconversion at 7 months, there was high-quality evidence from RCTs of no significant difference between groups for all nine HPV subtypes measured.

Two versus three doses of 2-valent HPV vaccine

GMTs for HPV 16 at 7 months (moderate-quality evidence) and 60 months (low-quality evidence) were inconclusive with regard to non-inferiority with two doses compared with three doses of 2-valent vaccine. GMTs for HPV 18 were non-inferior at 7 months (moderate-quality evidence) but inconclusive at 60 months (low-quality evidence) with two doses compared with three doses of 2-valent vaccine.

There was no significant difference in seropositivity in HPV 16 or 18 at 7 and 60 months; all participants seroconverted (moderate-quality evidence).

Two versus three doses of 4-valent HPV vaccine

GMTs for HPV 6, 11, 16 and 18 were non-inferior with two doses of 4-valent vaccine at 7 months compared with three doses (high-quality evidence). However, with time GMTs tended towards favouring 3 doses, and at 36 months two doses were inconclusive with regard to non-inferiority compared with three doses for GMTs for HPV 6 and 18 (low and moderate-quality evidence, respectively). Two doses were non-inferior for GMTs for HPV 11 and 16 at 36 months (low and moderate-quality evidence, respectively).

Seropositivity for HPV 6, 11, 16 and 18 was not significantly different between two and three doses of 4-valent vaccine at 7 months (high-quality evidence). Seropositivity for HPV 6, 11, and 16 was not significantly different between two and three doses at 36 months (moderate or low-quality

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 Targeted Update, we assess the protection afforded by two doses of prophylactic HPV vaccines compared with three doses in young females.

Objectives

To evaluate the effect of HPV vaccination in females, updating the systematic review by D'Addario et al. This Targeted Update focusses on the comparison of two doses compared with three doses of HPV vaccine in females aged ≤15 years.

Search methods

Searches were conducted from July 2013 to June 2016, and all relevant studies regardless of language or publication status were searched. 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) and non-randomised experimental studies were eligible for inclusion.

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 reported as ratios. 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. The non-inferiority threshold for two doses was 0.5 for ratio of GMTs.

Main Results

We included four RCTs (Canada1; Canada/Germany1; Multinational3; Multinational4) and two non-randomized studies (Mexico1; Mexico2). We also identified one non-randomised study that compared two versus three doses of 4-valent vaccine; however, the age group for inclusion (10 to 18 years) was broader than for this Targeted Update, and was therefore omitted (India1). Multinational4 and Multinational3 were new studies added in this update. The risk of bias was generally low in the four RCTs; however, loss to follow-up at longer time points was high in some studies. All participants in analyses of RCTs were seronegative at baseline.

Two versus three doses of HPV vaccines at 7 months - all vaccines

As in the D'Addario review, we analysed studies comparing two versus three doses of HPV vaccine, reporting immunogenicity outcomes at 7 months, for all vaccine types.

With respect to GMTs, two doses were non-inferior to, or had higher GMTs than, three doses, for all nine HPV subtypes measured except HPV 45 (non-inferiority inconclusive). The quality of the evidence was high, except for HPV 16 and 18, for which there was heterogeneity in the results (low and moderate respectively). Possible sources of heterogeneity were the different types of vaccine used, different dose schedules in the three dose arm (0,1,6 or 0,2,6), and different assays used to measure GMTs (luminex or ELISA). We also analysed separately GMTs for the two non-randomised studies (Mexcio1; Mexico2) (Appendix 1). GMTs were non-inferior with two doses for HPV 11 and 18, but inconclusive for HPV 6 and HPV 16. For seroconversion at 7 months, there was high-quality evidence from RCTs of no significant difference between groups for all nine HPV subtypes measured. Seroconversion was not reported in the non-randomised studies.

Two versus three doses of 2-valent HPV vaccine

There were lower GMTs for HPV 16 at 7 months (moderate-quality evidence) and 60 months (low-quality evidence) with two doses compared with three doses of 2-valent vaccine (inconclusive whether non-inferior). GMTs for HPV 18 were non-inferior at 7 months (moderate-quality evidence) but inconclusive at 60 months (low-quality evidence) with two doses compared with three doses of 2-valent vaccine. There was no significant difference in seropositivity in HPV 16 or 18 at 7 and 60 months; all participants seroconverted (moderate-quality evidence).

Two versus three doses of 4-valent HPV vaccine

There was high-quality evidence of non-inferior GMTs for HPV 6, 11, 16 and 18 with two doses of 4-valent vaccine at 7 months compared with three doses. However, with time GMTs tended towards favouring 3 doses. At 36 months two doses were inconclusive with regard to non-inferiority for GMTs for HPV 6 and 18 (low and moderate-quality evidence, respectively), whereas two doses were non-inferior for GMTs for HPV 11 and 16 at 36 months (low and moderate-quality evidence, respectively). There was high-quality evidence of no significant difference in seropositivity for HPV 6, 11, 16 and 18 between two and three doses of 4-valent vaccine at 7 months, and moderate or low-quality evidence of no significant difference in seropositivity for HPV 6, 11, and 16 between two and three doses of 4-valent vaccine at 36 months; however, two doses had lower seropositivity to HPV 18 at 36 months (moderate-quality evidence).

Implications and conclusions

At 7 months, two doses were generally non-inferior to three doses of HPV vaccine with regard to GMTs, and there was no significant difference in seropositivity for the HPV subtypes measured. With time, GMTs tended towards favouring three doses; however, in general there was no significant difference in seropositivity at longer time points.

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Summary of Findings: Two versus three doses of HPV vaccines in 9 to 15-year old females – all vaccines – immunogenicity outcomes at 7 months

Patients: **9 to 15-year old females (seronegative at baseline)**
Setting**: Canada, Germany, Italy, Taiwan, and Thailand**
Comparison: **2/4/9-valent HPV vaccine (2-doses (Month 0, 6)) versus 2/4/9-valent HPV vaccine (3-doses (Month 0, 2, 6))**

Outcome	Plain language summary	Absolute effect*		Relative effect (95% CI) Nº of participants & studies	Certainty of the evidence (GRADE)
		3 doses	2 doses		
GMTs for HPV 6 follow up: 7 months	There is high-quality evidence of no significant difference (non-inferior) in GMTs for HPV 6 between 2 and 3 doses of HPV vaccine	Mean: 1658-2186 mMU/mL	Mean: 1496-1856 mMU/mL	Ratio 1.13 (0.99 to 1.29) 1001 participants from 2 RCTs	⊕⊕⊕⊕ HIGH
GMTs for HPV 11 follow up: 7 months	There is high-quality evidence of no significant difference (non-inferior) in GMTs for HPV 11 between 2 and 3 doses of HPV vaccine	Mean: 1389-2348 mMU/mL	Mean: 1306-2096 mMU/mL	Ratio 1.09 (0.97 to 1.22) 1006 participants from 2 RCTs	⊕⊕⊕⊕ HIGH
GMTs for HPV 16 follow up: 7 months	There is low-quality evidence that there is no significant difference (non-inferior) in GMTs for HPV 16 between 2 and 3 doses of HPV vaccine	Mean: 5056-11067 units**	Mean: 4807-7640 units**	Ratio 0.89 (0.68 to 1.18) 1816 participants in 4 RCTs	⊕⊕OO LOW[1]
GMTs for HPV 18 follow up: 7 months	There is moderate-quality evidence that there are significantly higher GMTs for HPV 18 after 3 doses of HPV vaccine compared to 2 doses, but 2 doses are non-inferior	Mean: 1207-5510 units**	Mean: 1653-7399 units**	Ratio 0.77 (0.69 to 0.87) 1833 participants in 4 RCTs	⊕⊕⊕O MODERATE[2]
GMTs for HPV 31 follow up: 7 months	There is high-quality evidence that GMTs for HPV 31 are significantly higher with 3 doses compared with 2 doses, although 2 doses are non-inferior	Mean: 1436 mMU/mL	Mean: 1748 mMU/mL	Ratio 0.82 (0.69 to 0.98) 543 participants in 1 RCT	⊕⊕⊕⊕ HIGH
GMTs for HPV 33 follow up: 7 months	There is high-quality evidence that GMTs for HPV 33 are significantly higher with 2 doses compared with 3 doses	Mean: 1030 mMU/mL	Mean: 796 mMU/mL	Ratio 1.29 (1.10 to 1.52) 548 participants in 1 RCT	⊕⊕⊕⊕ HIGH
GMTs for HPV 45 follow up: 7 months	There is high-quality evidence that GMTs for HPV 45 are significantly higher with 3 doses compared with 2 doses, and it is inconclusive if 2 doses are inferior	Mean: 357 mMU/mL	Mean: 662 mMU/mL	Ratio 0.54 (0.45 to 0.65) 549 participants in 1 RCT	⊕⊕⊕⊕ HIGH
GMTs for HPV 52 follow up: 7 months	There is high-quality evidence that GMTs for HPV 52 are significantly higher with 3 doses compared with 2 doses, although 2 doses are non-inferior	Mean: 581 mMU/mL	Mean: 910 mMU/mL	Ratio 0.64 (0.55 to 0.74) 547 participants in 1 RCT	⊕⊕⊕⊕ HIGH
GMTs for HPV 58 follow up: 7 months	There is high-quality evidence of no significant difference (non-inferior) in GMTs for HPV 58 between 2 and 3 doses of HPV vaccine	Mean: 1251 mMU/mL	Mean: 1229 mMU/mL	Ratio 1.02 (0.87 to 1.19) 543 participants in 1 RCT	⊕⊕⊕⊕ HIGH
Seroconversion for HPV 6 follow up: 7 months	There is high-quality evidence of no significant difference in the ratio of seroconversion for HPV 6 between 2 doses and 3 doses of HPV vaccine	500/502 (99.6%)	498/499 (99.8%)	RR 1.00 (0.99 to 1.02) 1001 participants in 2 RCTs	⊕⊕⊕⊕ HIGH

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Seroconversion for HPV 11 follow up: 7 months	There is high-quality evidence of no significant difference in the ratio of seroconversion for HPV 11 between 2 doses and 3 doses of HPV vaccine	504/505 (99.8%)	501/501 (100%)	RR 1.00 (0.99 to 1.01) 1006 participants in 2 RCTs	⊕⊕⊕⊕ HIGH
Seroconversion for HPV 16 follow up: 7 months	There is high-quality evidence of no significant difference in the ratio of seroconversion for HPV 16 between 2 doses and 3 doses of HPV vaccine	909/909 (100%)	907/907 (100%)	RR 1.00 (not estimable) 1816 participants in 4 RCTs	⊕⊕⊕⊕ HIGH
Seroconversion for HPV 18 follow up: 7 months	There is high-quality evidence of no significant difference in the ratio of seroconversion for HPV 18 between 2 doses and 3 doses of HPV vaccine	922/923 (99.9%)	910/910 (100%)	RR 1.00 (0.99 to 1.01) 1833 participants in 4 RCTs	⊕⊕⊕⊕ HIGH
Seroconversion for HPV 31 follow up: 7 months	There is high-quality evidence of no significant difference in the ratio of seroconversion for HPV 31 between 2 doses and 3 doses of 9-valent HPV vaccine	271/271 (100%)	271/272 (99.6%)	RR 1.00 (0.99 to 1.01) 543 participants in 1 RCT	⊕⊕⊕⊕ HIGH
Seroconversion for HPV 33 follow up: 7 months	There is high-quality evidence of no significant difference in the ratio of seroconversion for HPV 33 between 2 doses and 3 doses of 9-valent HPV vaccine	275/275 (100%)	272/273 (99.6%)	RR 1.00 (0.99 to 1.01) 548 participants in 1 RCT	⊕⊕⊕⊕ HIGH
Seroconversion for HPV 45 follow up: 7 months	There is high-quality evidence of no significant difference in the ratio of seroconversion for HPV 45 between 2 doses and 3 doses of 9-valent HPV vaccine	273/275 (99.3%)	272/274 (99.3%)	RR 1.00 (0.99 to 1.01) 549 participants in 1 RCT	⊕⊕⊕⊕ HIGH
Seroconversion for HPV 52 follow up: 7 months	There is high-quality evidence of no significant difference in the ratio of seroconversion for HPV 52 between 2 doses and 3 doses of 9-valent HPV vaccine	274/275 (100%)	271/272 (99.6%)	RR 1.00 (0.99 to 1.01) 547 participants in 1 RCT	⊕⊕⊕⊕ HIGH
Seroconversion for HPV 58 follow up: 7 months	There is high-quality evidence of no significant difference in the ratio of seroconversion for HPV 58 between 2 doses and 3 doses of 9-valent HPV vaccine	273/273 (100%)	270/270 (100%)	RR 1.00 (0.99 to 1.01) 543 participants in 1 RCT	⊕⊕⊕⊕ HIGH

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

* Where multiple RCTs have been included the range of means is presented; **GMTs measured as both mMU/mL (luminex assay) and EU/mL (ELISA) in different studies

[1]Downgraded two levels for serious inconsistency: considerable heterogeneity (I^2 > 75%); [2]Downgraded one level for inconsistency: moderate heterogeneity (I^2 > 30%)

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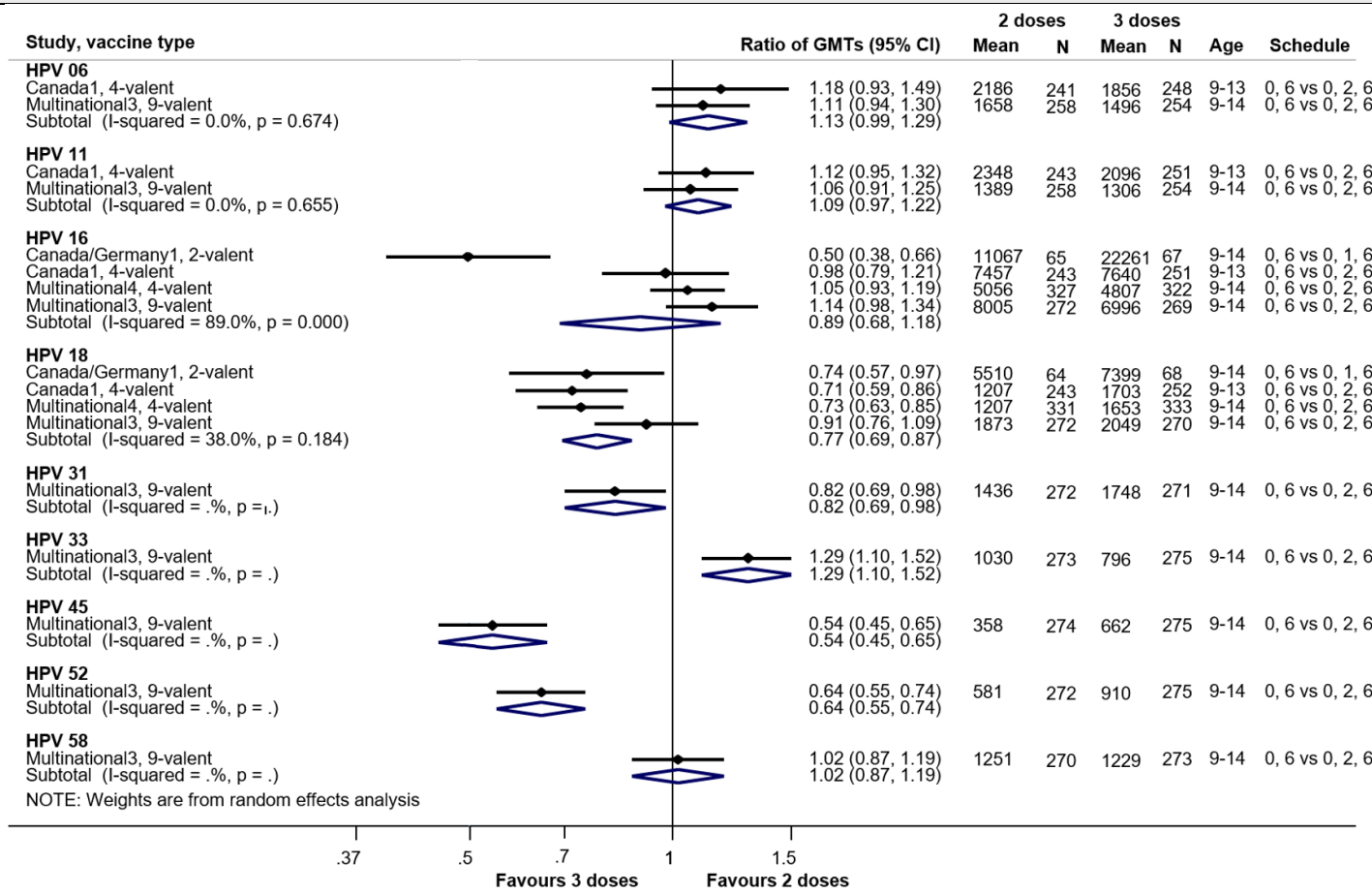
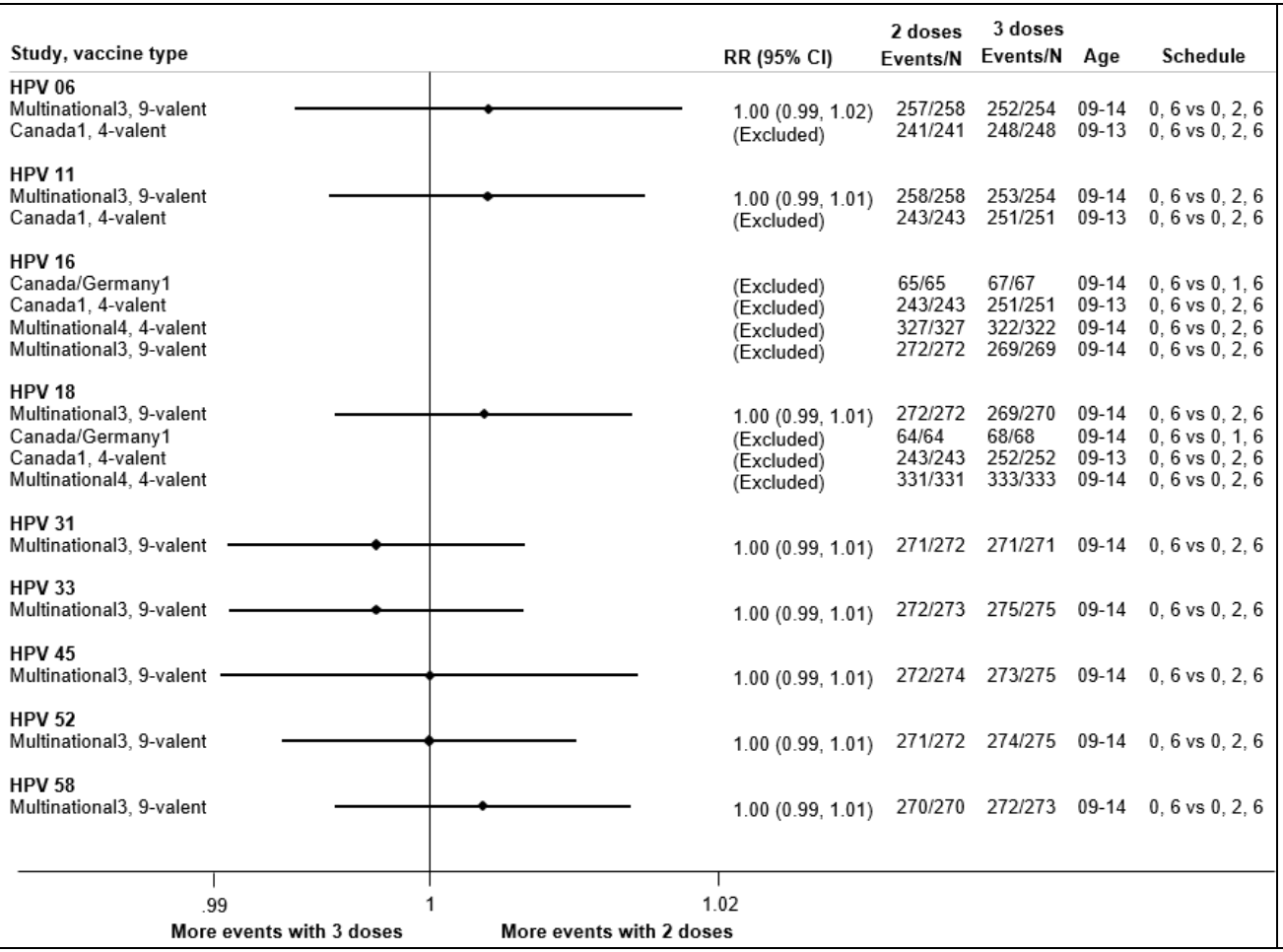
Forest plots: Two versus three doses of HPV vaccines in 9 to 15-year old females – all vaccines – immunogenicity outcomes at 7 months [5]

Patients: 9 to 15-year old females (seronegative at baseline)
Setting: Canada, Germany, Italy, Taiwan, and Thailand
Comparison: 2/4/9-valent HPV vaccine (2-doses (Month 0, 6)) versus 2/4/9-valent HPV vaccine (3-doses (Month 0, 2, 6))

Outcome	Forest plots	Certainty of the evidence (GRADE)
Ratio of GMTs follow up: 7 months		⊕⊕⊕⊕ HIGH ⊕⊕⊕⊕ HIGH ⊕⊕OO LOW ⊕⊕⊕O MODERATE ⊕⊕⊕⊕ HIGH ⊕⊕⊕⊕ HIGH ⊕⊕⊕⊕ HIGH ⊕⊕⊕⊕ HIGH ⊕⊕⊕⊕ HIGH

Seroconversion
follow up: 7 months



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

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Summary of Findings: Two versus three doses of 2-valent HPV vaccine in 9 to 15-year old females – immunogenicity outcomes at multiple timepoints [7]

Patients: **9 to 15-year old females (seronegative at baseline)**
Setting**: Canada, Germany**
Comparison: **2-valent HPV vaccine (2-doses (Month 0, 6)) versus 2-valent HPV vaccine (3-doses (Month 0, 2, 6))**

Outcome		Plain language summary	Absolute effect		Relative effect (95% CI) Nº of participants & studies	Certainty of the evidence (GRADE)
			3 doses	2 doses		
GMTs for HPV 16	7 months	There is moderate-quality evidence of lower GMTs for HPV 16 with two doses compared with three doses; it is inconclusive if the effect of two doses was non-inferior	22261 EU/mL	11067 EUm/L	Ratio 0.50 (0.38 to 0.66) 132 participants 1 RCT	⊕⊕⊕O MODERATE [1]
	60 months*	There is low-quality evidence of lower GMTs for HPV 16 with two doses compared with three doses; it is inconclusive if the effect of two doses was non-inferior	2670.8 EU/mL	1369 EU/mL	Ratio 0.51 (0.36 to 0.73) 93 participants 1 RCT	⊕⊕OO LOW [1 2]
GMTs for HPV 18	7 months	There is moderate-quality evidence of lower but non-inferior GMTs for HPV 18 with two doses compared with three doses	7399 EU/mL	5510 EU/mL	Ratio 0.74 (0.57 to 0.97) 132 participants 1 RCT	⊕⊕⊕O MODERATE [1]
	60 months*	There is low-quality evidence of lower GMTs for HPV 18 with two doses compared with three doses; it is inconclusive if the effect of two doses was non-inferior	908.9 EU/mL	627.2 EU/mL	Ration 0.69 (0.46 to 1.03) 92 participants 1 RCT	⊕⊕OO LOW [1 2]
Seropositivity for HPV 16	7 months	There is moderate-quality evidence of no significant difference in seropositivity for HPV 16 between two doses and three doses	65/65 (100%)	67/67 (100%)	RR 1.00 (not estimable) 132 participants 1 RCT	⊕⊕⊕O MODERATE [1]
	24 months	There is moderate-quality evidence of no significant difference in seropositivity for HPV 16 between two doses and three doses	61/61 (100%)	64/64 (100%)	RR 1.00 (not estimable) 125 participants 1 RCT	⊕⊕⊕O MODERATE [1]
Seropositivity for HPV 18	7 months	There is moderate-quality evidence of no significant difference in seropositivity for HPV 18 between two doses and three doses	64/64 (100%)	68/68 (100%)	RR 1.00 (not estimable) 132 participants 1 RCT	⊕⊕⊕O MODERATE [1]
	24 months	There is moderate-quality evidence of no significant difference in seropositivity for HPV 18 between two doses and three doses	64/64 (100%	63/63 (100%)	RR 1.00 (not estimable) 127 participants 1 RCT	⊕⊕⊕O MODERATE [1]

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

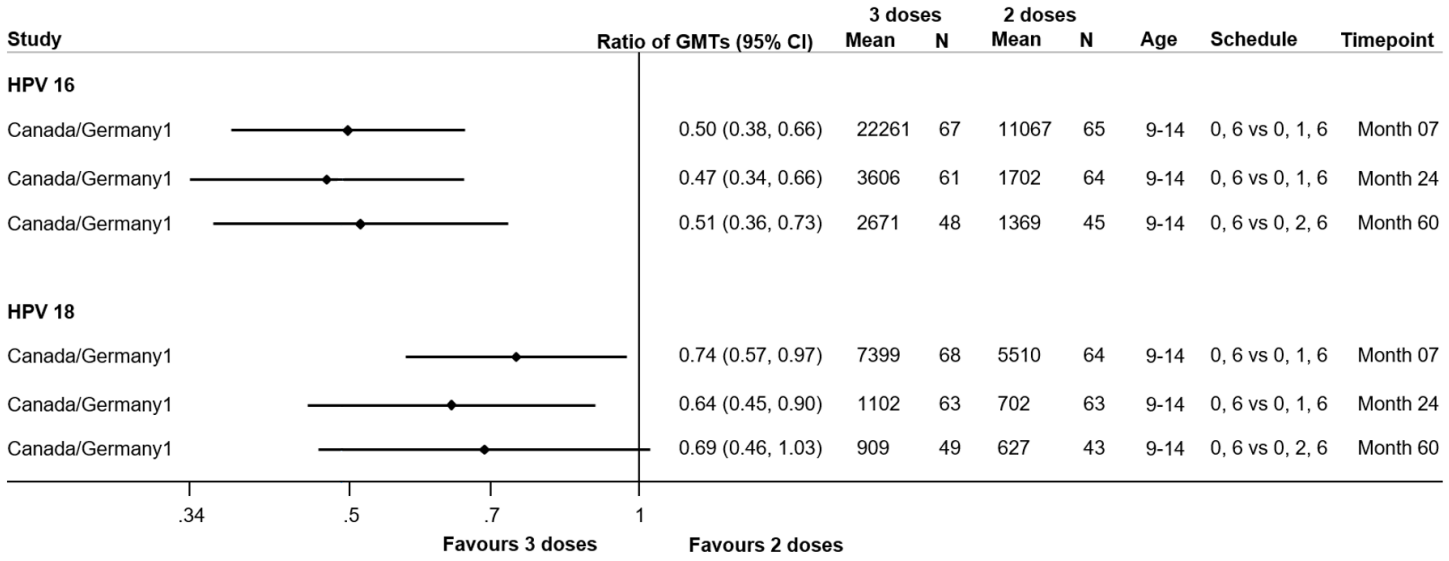
* Data available for additional time points; see forest plot below

[1]Downgraded one level for imprecision: low number of participants

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

Forest plot: Two versus three doses of 2-valent HPV vaccine in 9 to 15-year old females – immunogenicity outcomes at multiple timepoints

Patients: **9 to 15-year old females (seronegative at baseline)**
***Setting*: Canada, Germany, and Mexico**
Comparison: **2-valent HPV vaccine (2-doses (Month 0, 6)) versus 2-valent HPV vaccine (3-doses (Month 0, 2, 6))**

Outcome	Forest plots	Certainty of the evidence (GRADE)
Ratio of GMTs follow up: 7-60 months		⊕⊕⊕O MODERATE ⊕⊕OO LOW ⊕⊕⊕O MODERATE ⊕⊕OO LOW

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

Forest plot not shown for seropositivity as all participants were seropositive

Summary of Findings: Two versus three doses of 4-valent HPV vaccine in 9 to 15-year old females – immunogenicity outcomes at multiple time points [9]

Patients: **9 to 15-year old females (seronegative at baseline)**
***Setting*: Canada, Mexico, France, Hong Kong, Singapore, and Sweden**
Comparison: **4-valent HPV vaccine (2-doses (Month 0, 6)) versus 4-valent HPV vaccine (3 doses (Month 0, 2, 6))**

Outcome		Plain language summary	Absolute effect		Relative effect (95% CI) Nº of participants & studies	Certainty of the evidence (GRADE)
			3 doses	2 doses		
GMTs for HPV 6	7 months	There is high-quality evidence of no significant difference (non-inferior) in GMTs for HPV 6 between 2 and 3 doses of HPV vaccine	1856 mMU/mL	2186 mMU/mL	Ratio 1.18 (0.93 to 1.49) 1 RCT 489 participants	⊕⊕⊕⊕ HIGH
	36 months*	There is low-quality evidence of lower GMTs for HPV 6 with two doses compared with three doses; it is inconclusive if the effect of two was non-inferior	372 mMU/mL	239 mMU/mL	0.64 (0.48 to 0.86) 1 RCT 167 participants	⊕⊕OO LOW [1 2]
GMTs for HPV 11	7 months	There is high-quality evidence of no significant difference (non-inferior) in GMTs for HPV 11 between 2 and 3 doses of HPV vaccine	2096 mMU/mL	2348mMU/mL	1.12 (0.95 to 1.32) 1 RCT 494 participants	⊕⊕⊕⊕ HIGH
	36 months*	There is low-quality evidence of lower, but non-inferior, GMTs for HPV 11 with two doses compared with three doses	410 mMU/mL	298 mMU/mL	0.73 (0.55 to 0.97) 1 RCT 168 participants	⊕⊕OO LOW [1 2]
GMTs for HPV 16	7 months	There is high-quality evidence of no significant difference (non-inferior) in GMTs for HPV 16 between 2 and 3 doses of HPV vaccine	Not estimable (not pooled)	Not estimable (not pooled)	Not estimable (not pooled) 2 RCTs 1143 participants	⊕⊕⊕⊕ HIGH
	36 months*	There is moderate-quality evidence of no significant difference (non-inferior) in GMTs for HPV 16 between 2 and 3 doses of HPV vaccine	Not estimable (not pooled)	Not estimable (not pooled)	Not estimable (not pooled) 2 RCTs 784 participants	⊕⊕⊕O MODERATE [1]
GMTs for HPV 18	7 months	There is high-quality evidence of lower, but non-inferior, GMTs for HPV 18 with two doses compared with three doses	Not estimable (not pooled)	Not estimable (not pooled)	Not estimable (not pooled) 2 RCTs 1159 participants	⊕⊕⊕⊕ HIGH
	36 months*	There is moderate-quality evidence of lower GMTs for HPV 18 with two doses compared with three doses; it is inconclusive if the effect of two is non-inferior	Not estimable (not pooled)	Not estimable (not pooled)	Not estimable (not pooled) 2 RCTs 799 participants	⊕⊕⊕O MODERATE [1]
Seropositivity for HPV 6	7 months	There is high-quality evidence of no significant difference in seropositivity for HPV 6 between two doses and three doses	248/248 (100%)	241/241 (100%)	RR 1.00 (not estimable) 489 participants in 1 RCT	⊕⊕⊕⊕ HIGH

	36 months*	There is low-quality evidence of no significant difference in seropositivity for HPV 6 between two doses and three doses	83/83 (100%)	84/84 (100%)	RR 1.00 (not estimable) 167 participants in 1 RCT	⊕⊕OO LOW [1 2]
Seropositivity for HPV 11	7 months	There is high-quality evidence of no significant difference in seropositivity for HPV 11 between two doses and three doses	251/251 (100%)	243/243 (100%)	RR 1.00 (not estimable) 494 participants in 1 RCT	⊕⊕⊕⊕ HIGH
	36 months*	There is low-quality evidence of no significant difference in seropositivity for HPV 11 between two doses and three doses	82/82 (100%)	86/86 (100%)	RR 1.00 (not estimable) 168 participants in 1 RCT	⊕⊕OO LOW [1 2]
Seropositivity for HPV 16	7 months	There is high-quality evidence of no significant difference in seropositivity for HPV 16 between two doses and three doses	573/573 (100%)	570/570 (100%)	RR 1.00 (not estimable) 1143 participants in 2 RCTs	⊕⊕⊕⊕ HIGH
	36 months*	There is moderate-quality evidence of no significant difference in seropositivity for HPV 16 between two doses and three doses	391/392 (99.7%)	390/392 (99.5%)	Not estimable (not pooled) 784 participants in 2 RCTs	⊕⊕⊕O MODERATE [1]
Seropositivity for HPV 18	7 months	There is high-quality evidence of no significant difference in seropositivity for HPV 18 between two doses and three doses	585/585 (100%)	574/574 (100%)	RR 1.00 (not estimable) 1159 participants in 2 RCTs	⊕⊕⊕⊕ HIGH
	36 months*	There is moderate-quality evidence of lower seropositivity for HPV 18 with two doses than three doses	376/403 (93%)	341/396 (86%)	Not estimable (not pooled) 799 participants in 2 RCTs	⊕⊕⊕O MODERATE [1]

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

*Data also available for other time points, see forest plot below

[1]Downgraded one level for risk of bias: high loss to follow up in one study

[2]Downgraded one level for imprecision: low sample size

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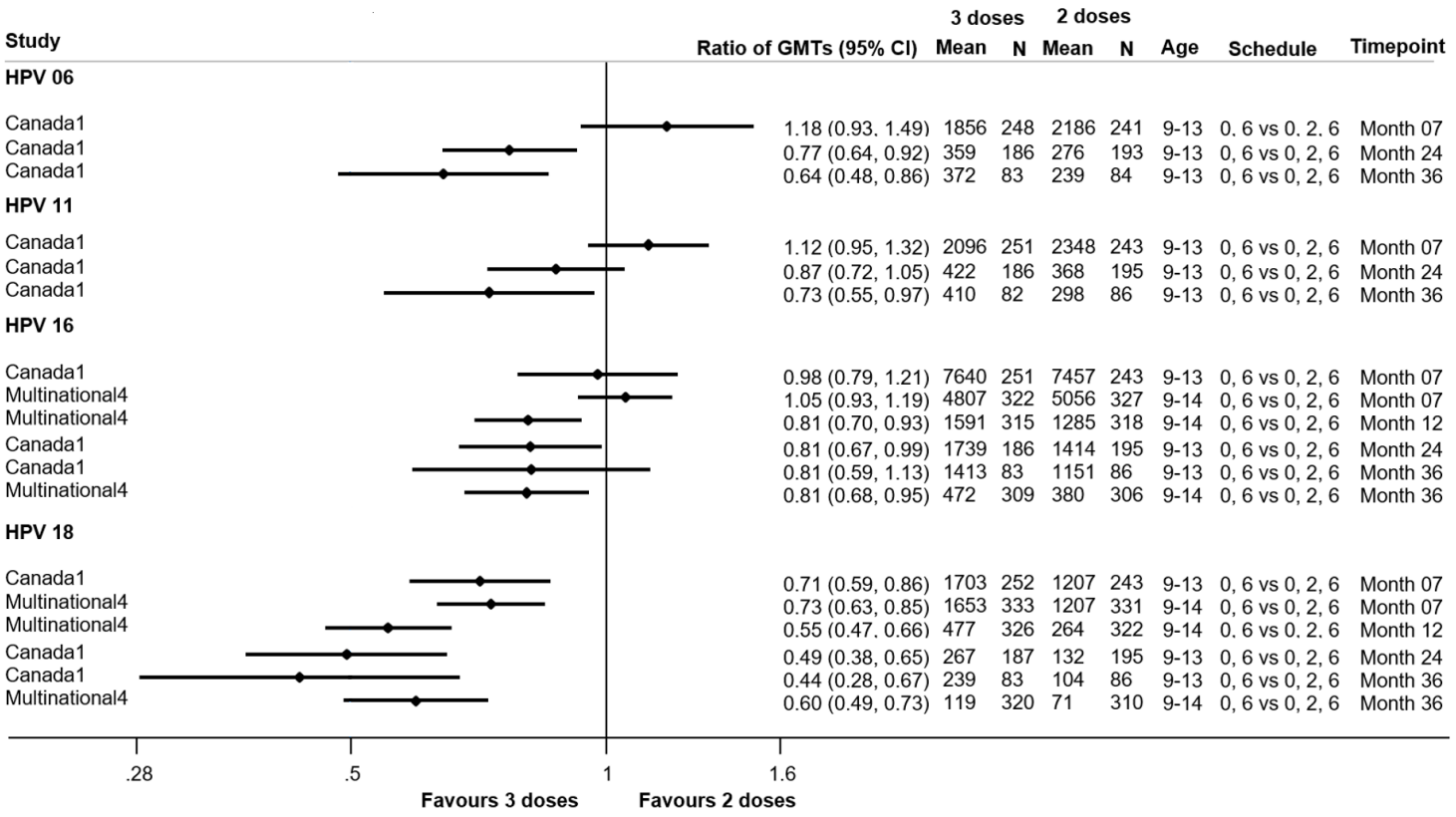
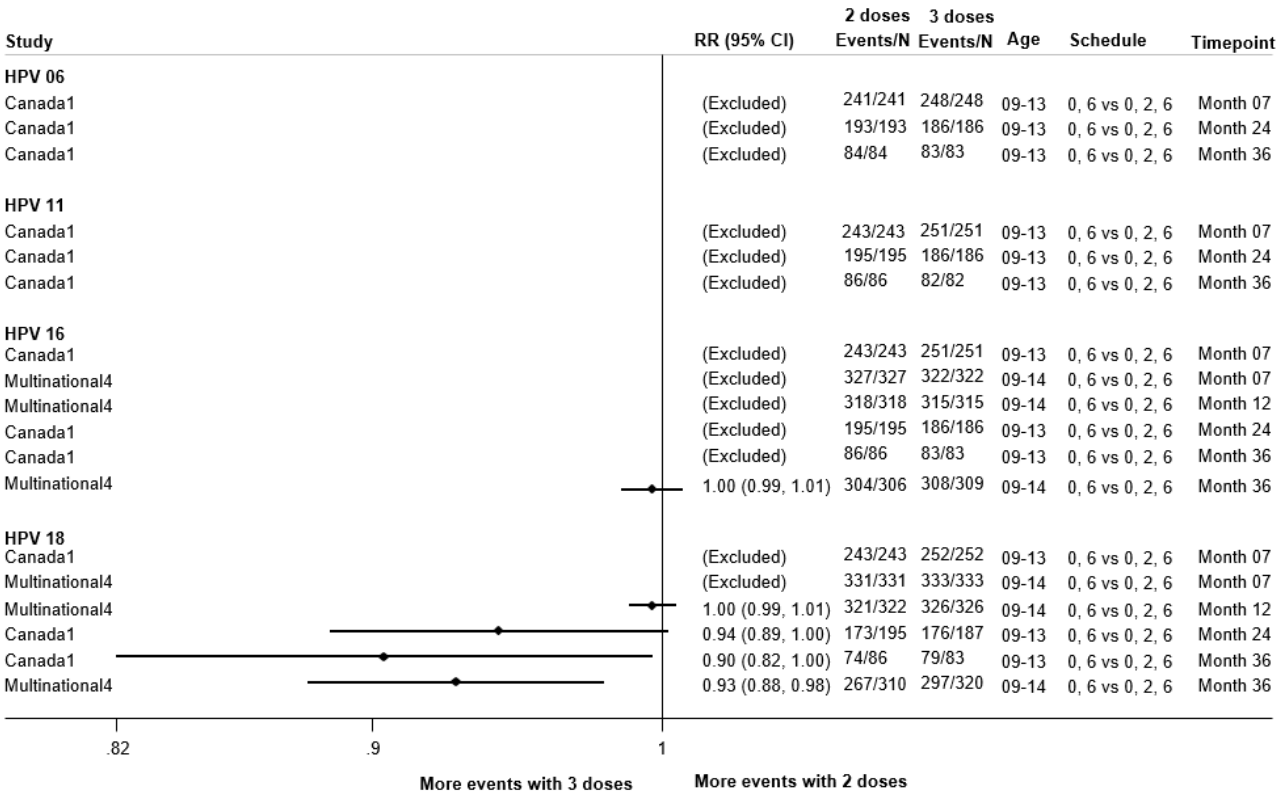
Forest plot: Two versus three doses of 4-valent HPV vaccine in 9 to 15-year old females – immunogenicity outcomes at multiple timepoints

Patients: 9 to 15-year old females (seronegative at baseline)
Setting: Canada, Mexico, France, Hong Kong, Singapore, and Sweden
Comparison: 4-valent HPV vaccine (2-doses (Month 0, 6)) versus 4-valent HPV vaccine (3 doses (Month 0, 2, 6))

Outcome	Forest plot	Certainty of the evidence (GRADE)
Ratio of GMTs follow up: 7-36 months		⊕⊕⊕⊕ HIGH ⊕⊕OO LOW ⊕⊕⊕⊕ HIGH ⊕⊕OO LOW ⊕⊕⊕⊕ HIGH ⊕⊕⊕O MODERATE ⊕⊕⊕⊕ HIGH ⊕⊕⊕O MODERATE

Seropositivity
follow up: 7-36 months



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

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D'Addario systematic review

D'Addario M, Scott P, Redmond S, Low N. Evidence Based Recommendations on Human Papilloma Virus (HPV) Schedules: Background Paper for SAGE Discussions. Annex 1. Geneva: World Health Organization; 2014. [Last accessed on 21 September 2016]. HPV Vaccines: Systematic Review of Literature on Alternative Vaccination Schedules. Report to WHO. Institute of Social and Preventive Medicine (ISPM), University of Bern, Bern, Switzerland (3 March, 2014) Available from: http://www.who.int/immunization/sage/meetings/2014/april/1_HPV_Evidence_based_recommendationsWHO_with_Appendices2_3.pdf?ua=1

Canada1

Dobson SRM, McNeil S, Dionne M et al. Immunogenicity of 2 doses of HPV vaccine in younger adolescents vs 3 doses in young women: a randomized clinical trial. JAMA 2013;309(17):1793-1802

Canada/Germany1

Romanowski B, Schwarz T, Ferguson LM et al. Immunogenicity and safety of the HPV-16/18 AS04-adjuvanted vaccine administered as a 2-dose schedule compared with the licensed 3-dose schedule: results from a randomized study. Human Vaccines 2011;7(12):1-13

Romanowski B, Schwarz T, Ferguson LM et al. Immune response to the HPV-16/18 AS04-adjuvanted vaccine administered as a 2-dose or 3-dose schedule up to 4 years after vaccination: results from a randomized study. Human Vaccines & Immunotherapeutics 2014;10(5):1155-1165

Mexico1

Lazcano-Ponce E, Stanley M, Munoz N et al. Overcoming barriers to HPV vaccination: non-inferiority of antibody response to human papillomavirus 16/18 vaccine in adolescents vaccinated with a two-dose versus a three-dose schedule at 21 months. Vaccine 2014;32:725-732

Mexico2

Hernandez-Avila M, Torres-Ibarra L, Stanley M et al. Evaluation of the immunogenicity of the quadrivalent HPV vaccine using two versus three doses at month 21: an epidemiological surveillance mechanism for alternate vaccination schemes. Human Vaccines & Immunotherapeutics 2016;12(1)30-38

Multinational3

A phase III study of a 2-dose regimen of a multivalent human papillomavirus (HPV) vaccine (V503), administered to 9 to 14 year-olds and compared to young women, 16 to 26 years old (V503-010). Available: https://clinicaltrials.gov/ct2/show/NCT01984697 [accessed 21-09-2016]

Multinational4

Leung TF, Liu APY, Lim FS et al. Comparative immunogenicity and safety of human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine and HPV-6/11/16/18 vaccine administered according to 2- and 3-dose schedules in girls aged 9-14 years: results to month 12 from a randomized trial. Human Vaccines & Immunotherapeutics 2015;11(7):1689-1702

India1

Sankaranarayanan R, Prabhu PR, Pawlita M et al. Immunogenicity and HPV infection after one, two, and three doses of quadrivalent HPV vaccine in girls in India: a multicentre prospective cohort study. Lancet Oncol 2016;17:67-77

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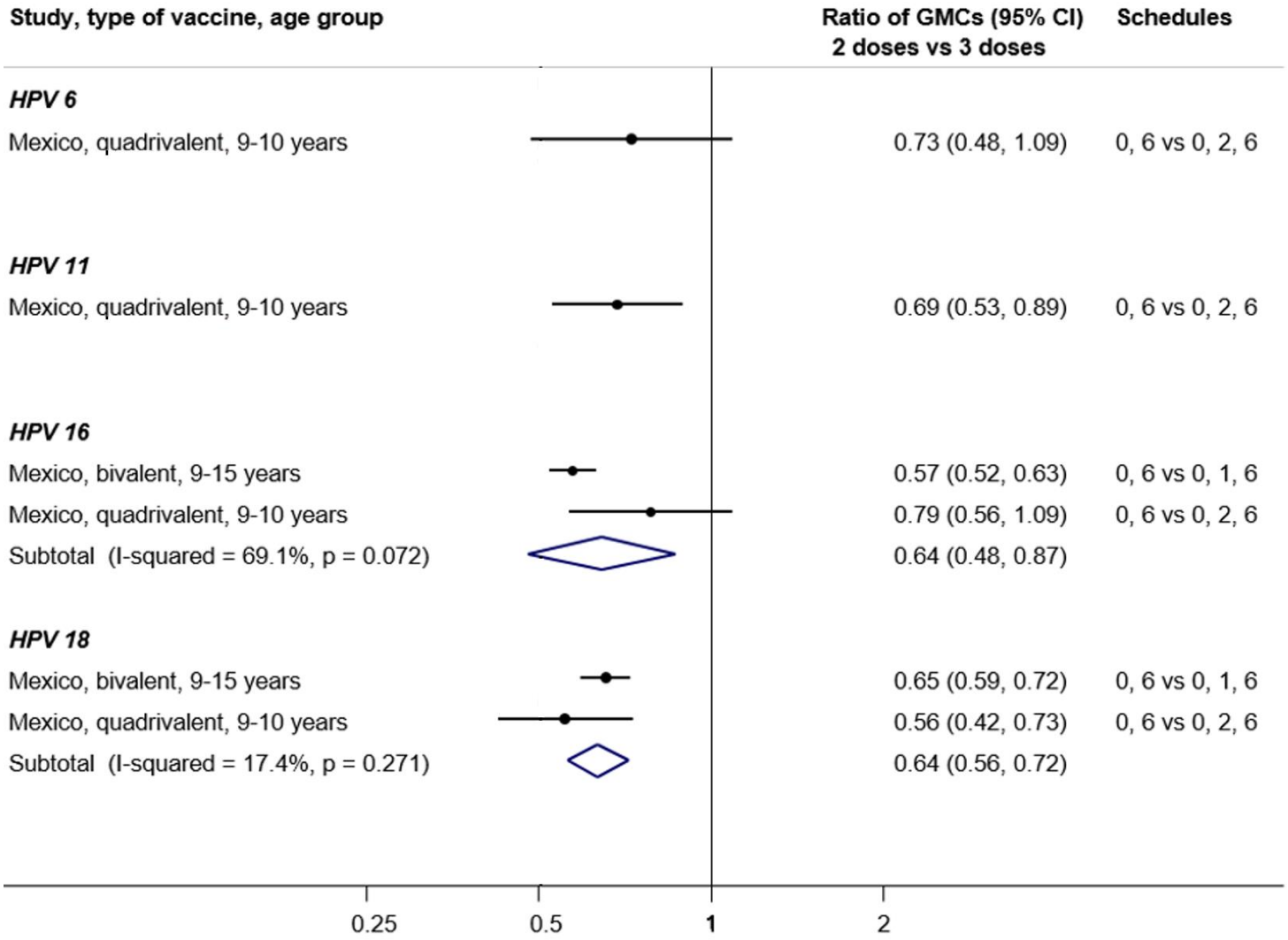
Appendix 1

Non-random comparison of two versus three doses in females aged 9-15 years, GMTs at 7 months



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Longer interval (0, 12) versus shorter interval (0, 6) of 2-valent HPV vaccine in females

Contents

Key findings

Longer interval schedule (0, 12 months) versus shorter interval schedule (0, 6 months) of 2-valent HPV vaccine in females (9 to 14)

- In females aged 9 to 14 years receiving the 2-valent vaccine, there were higher GMTs for HPV 16 and HPV 18 in those receiving a longer interval schedule (0, 12 months) than in those receiving the shorter interval schedule (0, 6 months) at 7 months (moderate-quality evidence).
- There was no significant difference between groups at 7 months for HPV 16 and HPV 18 seroconversion (moderate-quality evidence).

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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 analyze evidence for the protection afforded by prophylactic HPV vaccines in females.

Objectives

To evaluate the effect of HPV vaccination in females, updating the systematic review by D'Addario et al. This document focuses on the comparison of longer schedule (0 months, 12 months) versus shorter schedule (0 months, 6 months) in females. The systematic review by D'Addario et al. included data on the comparison of 0, 6-month schedule versus 0, 2-month schedule; we found no new data on this comparison and do not present the previous results here.

Search methods

Searches were conducted from July 2013 to June 2016, and all relevant studies regardless of language or publication status were searched. 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 comparison of longer schedule (0, 12 months) versus shorter schedule (0, 6 months).

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 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 found one RCT assessing a longer interval schedule (administered at 0, 12 months) compared with a shorter schedule (administered at 0, 6 months) of 2-valent HPV vaccine in 9 to 14-year old females (Multinational2). The study results were published in 2016 and the study was conducted in 33 sites in Canada, Germany, Italy, Taiwan, and Thailand. The quality of evidence for all outcomes was downgraded by one level for risk of bias; allocation was randomised but not concealed or blinded. All participants were seronegative at baseline.

There was moderate-quality evidence of higher GMTs for HPV 16 and HPV 18 with the longer interval schedule compared with the standard schedule in 9 to 14-year old females at 7 months. For seroconversion for HPV 16 and HPV 18, there was moderate-quality evidence of no significant difference between groups at 7 months.

Implications and conclusions

The longer interval schedule increased GMTs compared with the shorter schedule, but there was no difference in seroconversion as all participants seroconverted in both groups (moderate-quality evidence).

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Summary of Findings: longer interval schedule (0, 12 months) 2-valent HPV vaccine versus shorter interval schedule (0, 6 months) 2-valent HPV vaccine in females (9 to 14 years old)– immunogenicity outcomes at 7 months

Population: **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) 2-valent HPV vaccine versus shorter interval schedule (0, 6 months) 2-valent 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: 7 months	There is moderate-quality evidence of higher GMTs for HPV 16 for longer interval schedule versus standard interval schedule of 2-valent HPV vaccine in 9 to 14-year old females	Mean: 9396 EU/mL	Mean: 11,450 EU/mL	Ratio 1.22 (1.10 to 1.34); 835 participants in 1 study	⊕⊕⊕O MODERATE [1]
GMTs for HPV 18 follow up: 7 months	There is moderate-quality evidence of higher GMTs for HPV 18 for longer interval schedule versus standard interval schedule of 2-valent HPV vaccine in 9 to 14-year old females	Mean: 5921 EU/mL	Mean: 6656 EU/mL	Ratio 1.12 (1.01 to 1.25); 854 participants in 1 study	⊕⊕⊕O MODERATE [1]
Seroconversion for HPV 16 follow up: 7 months	There is moderate-quality evidence of no significant difference in seroconversion for HPV 16 between longer and standard interval schedules of 2-valent HPV vaccine in 9 to 14-year old females	480/480 (100%)	355/355 (100%)	Not estimable*; 835 participants in 1 study	⊕⊕⊕O MODERATE [1]
Seroconversion for HPV 18 follow up: 7 months	There is moderate-quality evidence of no significant difference in seroconversion for HPV 16 between longer and standard interval schedules of 2-valent HPV vaccine in 9 to 14-year old females	485/485 (100%)	469/469 (100%)	Not estimable*; 854 participants in 1 study	⊕⊕⊕O MODERATE [1]

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

* Excluded from analysis due to no non-events; all participants seroconverted.

[1]Downgraded one level for risk of bias: 9 to 14-year old girls were randomised to different schedules but allocation was not concealed or blinded.

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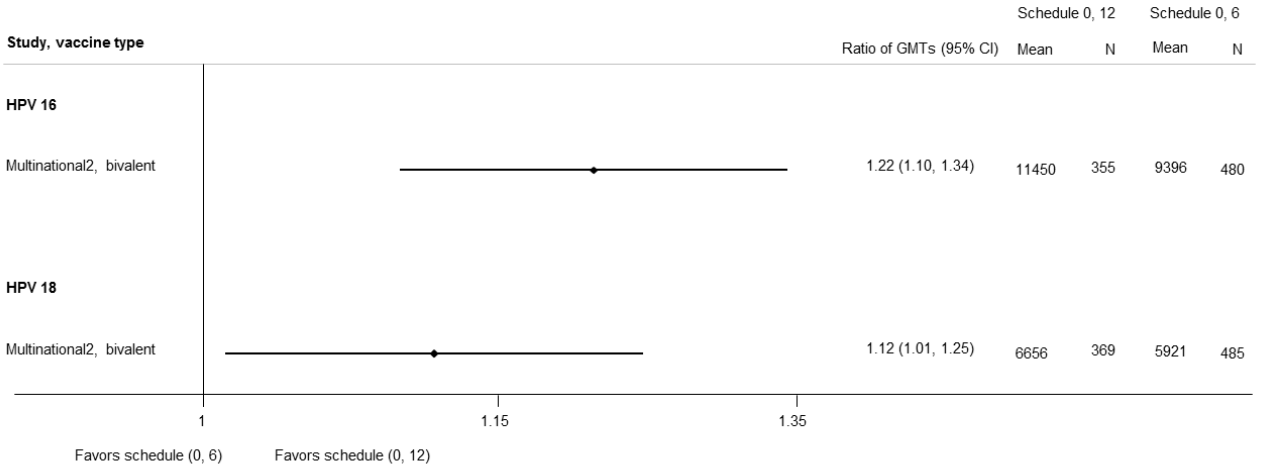
Forest plots: longer interval schedule (0, 12 months) 2-valent HPV vaccine versus shorter interval schedule (0, 6 months) 2-valent HPV vaccine in females (9 to 14 years old)– immunogenicity outcomes at 7 months

Population: 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) 2-valent HPV vaccine versus shorter interval schedule (0, 6 months) 2-valent HPV vaccine

Outcome	Forest plot	Certainty of the evidence (GRADE)
Ratio of GMTs follow up: 7 months		⊕⊕⊕O MODERATE

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

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

References

D'Addario systematic review

D'Addario M, Scott P, Redmond S, Low N. Evidence Based Recommendations on Human Papilloma Virus (HPV) Schedules: Background Paper for SAGE Discussions. Annex 1. Geneva: World Health Organization; 2014. [Last accessed on 21 September 2016]. HPV Vaccines: Systematic Review of Literature on Alternative Vaccination Schedules. Report to WHO. Institute of Social and Preventive Medicine (ISPM), University of Bern, Bern, Switzerland (3 March, 2014) Available from: http://www.who.int/immunization/sage/meetings/2014/april/1_HPV_Evidence_based_recommendationsWHO_with_Appendices2_3.pdf?ua=1

Multinational2

Puthanakit T, Huang LM, Chiu CH, Tang RB, Schwarz TF, Esposito S, et al. Randomized Open Trial Comparing 2-Dose Regimens of the Human Papillomavirus 16/18 AS04-Adjuvanted Vaccine in Girls Aged 9-14 Years Versus a 3-Dose Regimen in Women Aged 15-25 Years. J Infect Dis. 2016 Aug 15;214(4):525-36.

9-valent HPV vaccine versus 4-valent HPV vaccine in females

Contents

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Key findings

In 9 to 15-year old females, 9-valent vaccine was non-inferior to 4-valent vaccine for GMTs for HPV 6, 11, 16, and 18 at 7 months. The 9-valent HPV vaccine resulted in substantially higher GMTs for HPV 31, 33, 45, 52, and 58 than the 4-valent HPV vaccine (moderate-quality evidence).

In 9 to 15-year old females, the ratios of seroconversion to HPV 6, 11, 16, and 18 at 7 months were the same in both the 9-valent and 4-valent HPV vaccine groups (100% seroconversion) (moderate-quality evidence). (Data were not reported in full for seroconversion for HPV 31, 33, 45, 52, and 58.)

In 16 to 26-year old females, there was low to moderate-quality evidence of no significant difference in clinical outcomes between 9-valent and 4-valent HPV vaccines related to HPV 6, 11, 16, and 18. However, with regard to clinical outcomes related to HPV 31, 33, 45, 52, and 58, there was moderate-quality evidence of decreased rates of persistent infection at 6 and 12 months, CIN1, and CIN 2/3 or worse, and low-quality evidence of VIN 1 or VaIN1, with 9-valent vaccine compared with 4-valent vaccine.

In 16 to 26-year old females, 9-valent vaccine was non-inferior to 4-valent vaccine for GMTs for HPV 6, 11, 16, and 18 at 7 months (high-quality evidence) and at 24 months (low-quality evidence). The 9-valent HPV vaccine resulted in substantially higher GMTs for HPV 31, 33, 45, 52, and 58 than the 4-valent HPV vaccine at 7 months (high-quality evidence) and 24 months (moderate-quality evidence).

In 16 to 26-year old females, the ratios of seroconversion were not significantly different between vaccines for HPV 6, 11, 16 and 18 at 7 months (high-quality evidence) and 24 months (moderate-quality evidence), except HPV 18 at 24 months, which favoured 9-valent vaccine. The 9-valent vaccine resulted in higher seropositivity to HPV 31, 33, 45, 52, and 58 at 7 months (high-quality evidence) and 24 months (moderate-quality evidence).

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 Targeted Update, we review and analyse evidence for the protection afforded by 9-valent HPV vaccine compared with 4-valent HPV vaccine in females.

Objectives

To evaluate the efficacy and immunogenicity of the 9-valent HPV vaccine compared with 4-valent HPV vaccine in females.

Search methods

Searches were conducted from July 2013 to June 2016, and all relevant studies regardless of language or publication status were searched. 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.

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 reported as ratios. 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. The non-inferiority threshold for 9-valent vaccine was 0.5 for ratio of GMTs.

Main Results

We included two RCTs (Europe2; Multinational1). Europe2 compared 3 doses of 9-valent vaccine versus 3 doses of 4-valent vaccine in 9 to 15-year old females. The risk of bias was generally low in the RCT, except for the domains of allocation concealment and blinding which were unclear. Multinational1 compared 3 doses of 9-valent vaccine with 3 doses of 4-valent vaccine in 16 to 26-year old females. The risk of bias was low across all domains in this RCT; however, the number of people analysed at 24 months was considerably lower than at 7 months, and therefore we downgraded the quality of the evidence at this time point.

In 9 to 15-year old females, there was moderate-quality evidence of no significant difference and non-inferiority in GMTs for HPV 6, 11, 16, and 18 at 7 months between the 9-valent HPV vaccine and 4-valent HPV vaccine. The 9-valent HPV vaccine resulted in substantially higher GMTs for HPV 31, 33, 45, 52, and 58 than the 4-valent HPV vaccine. The ratios of seroconversion to HPV 6, 11, 16, and 18 at 7 months were the same in both the 9-valent and 4-valent HPV vaccine groups (100% seroconversion). The data were not reported in full for seroconversion for HPV 31, 33, 45, 52, and 58 (Europe2).

In 16 to 26-year old females, there was low to moderate-quality evidence of no significant difference in clinical outcomes between 9-valent and 4-valent HPV vaccines related to HPV 6, 11, 16, and 18. However, with regard to clinical outcomes related to HPV 31, 33, 45, 52, and 58, there was moderate-quality evidence of decreased rates of persistent infection at 6 and 12 months, CIN1, and CIN 2/3 or worse, and low-quality evidence of VIN 1 or VaIN1, with 9-valent vaccine compared with 4-valent vaccine.

In 16 to 26-year old females, there was no significant difference and non-inferiority in GMTs for HPV 6 and 16 at 7 (high-quality evidence) and 24 months (moderate-quality evidence) between the 9-valent HPV vaccine and 4-valent HPV vaccine. The 4-valent vaccine resulted in higher GMTs for HPV 11 but 9-valent was non-inferior, while the 9-valent vaccine resulted in higher GMTs for HPV 18. The 9-valent HPV vaccine also resulted in substantially higher GMTs for HPV 31, 33, 45, 52, and 58 than the 4-valent HPV vaccine at 7 (high-quality evidence) and 24 months (moderate-quality evidence).

In 16 to 26-year old females, the ratios of seroconversion were not significantly different between vaccines for HPV 6, 11, 16 and 18 at 7 months (high-quality evidence) and 24 months (moderate-quality evidence), except HPV 18 at 24 months, which favoured 9-valent vaccine. The 9-valent vaccine resulted in higher seropositivity to HPV 31, 33, 45, 52, and 58 at 7 months (high-quality evidence) and 24 months (moderate-quality evidence).

Implications and conclusions

The evidence shows that 9-valent vaccine is non-inferior to 4-valent HPV vaccine for GMTs for HPV 6, 11, 16 and 18 at 7 months in 9 to 26-year olds, and in 16 to 26-year olds at 24 months. GMTs for HPV 31, 33, 45, 52, and 58 were substantially higher with 9-valent vaccine for all time points. For seropositivity there were no significant differences between 9-valent and 4-valent vaccines for HPV 6, 11, 16 and 18 in both age cohorts at 7 months, and in 16 to 26-year olds at 24 months. The 9-valent vaccine had substantially higher rates for seropositivity for HPV 31, 33, 45, 52, and 58 at 7 months in 9 to 26-year olds, and in 16 to 26-year olds at 24 months. There was no significant difference in clinical outcomes related to HPV 6, 11, 16 and 18 between 9-valent and 4-valent HPV vaccines; however, 9-valent vaccine appeared to decrease many of the clinical outcomes related to HPV types 31, 33, 45, 52, and 58 compared with 4-valent vaccine.

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Summary of Findings: 9-valent HPV vaccine versus 4-valent HPV vaccine in 9 to 15-year old females – immunogenicity outcomes

Patients: **9 to 15-year old females (seronegative at baseline)**
***Setting*: Belgium, Denmark, Finland, Italy, Spain and Sweden**
Comparison: **9-valent HPV vaccine (3-doses (Month 0, 2, 6)) versus 4-valent HPV vaccine (3-doses (Month 0, 2, 6))**

Outcome	Plain language summary	Absolute effect		Relative effect (95% CI) Nº of participants & studies	Certainty of the evidence (GRADE)
		4-valent	9-valent		
GMTs for HPV 6 follow up: 7 months	There is moderate-quality evidence of no significant difference in GMTs for HPV 6 between 9-valent and 4-valent HPV vaccines at 7 months.	Mean: 1565.9 mMU/mL	Mean: 1679.4 mMU/mL	Ratio 1.07 (0.93 to 1.24) 534 participants in 1 RCT	⊕⊕⊕O MODERATE[1]
GMTs for HPV 11 follow up: 7 months	There is moderate-quality evidence of no significant difference in GMTs for HPV 11 between 9-valent and 4-valent HPV vaccines at 7 months.	Mean: 1417.3 mMU/mL	Mean: 1315.6 mMU/mL	Ratio 0.93 (0.80 to 1.08) 534 participants in 1 RCT	⊕⊕⊕O MODERATE[1]
GMTs for HPV 16 follow up: 7 months	There is moderate-quality evidence of no significant difference in GMTs for HPV 16 between 9-valent and 4-valent HPV vaccines at 7 months.	Mean: 6887.4 mMU/mL	Mean: 6739.5 mMU/mL	Ratio 0.98 (0.85 to 1.12) 546 participants in 1 RCT	⊕⊕⊕O MODERATE[1]
GMTs for HPV 18 follow up: 7 months	There is moderate-quality evidence of no significant difference in GMTs for HPV 18 between 9-valent and 4-valent HPV vaccines at 7 months.	Mean: 1795.6 mMU/mL	Mean: 1956.6 mMU/mL	Ratio 1.09 (0.91 to 1.31) 545 participants in 1 RCT	⊕⊕⊕O MODERATE[1]
GMTs for HPV 31 follow up: 7 months	There is moderate-quality evidence that 9-valent HPV vaccine results in a significantly higher GMTs for HPV 31 than 4-valent HPV vaccine at 7 months.	Mean: 22.2 mMU/mL	Mean: 1770.4 mMU/mL	Ratio 79.7 (65.6 to 97) 544 participants in 1 RCT	⊕⊕⊕O MODERATE[1]
GMTs for HPV 33 follow up: 7 months	There is moderate-quality evidence that 9-valent HPV vaccine results in a significantly higher GMTs for HPV 33 than 4-valent HPV vaccine at 7 months.	Mean: 4 mMU/mL	Mean: 937.1 mMU/mL	Ratio 243.3 (201.3 to 272.7) 544 participants in 1 RCT	⊕⊕⊕O MODERATE[1]
GMTs for HPV 45 follow up: 7 months	There is moderate-quality evidence that 9-valent HPV vaccine results in a significantly higher GMTs for HPV 45 than 4-valent HPV vaccine at 7 months.	Mean: 3.2 mMU/mL	Mean: 622.4 mMU/mL	Ratio 194.5 (162.1 to 233.4) 546 participants in 1 RCT	⊕⊕⊕O MODERATE[1]
GMTs for HPV 52 follow up: 7 months	There is moderate-quality evidence that 9-valent HPV vaccine results in a significantly higher GMTs for HPV 52 than 4-valent HPV vaccine at 7 months.	Mean: 1.9 mMU/mL	Mean: 927.3 mMU/mL	Ratio 488 (429.5 to 554.6) 545 participants in 1 RCT	⊕⊕⊕O MODERATE[1]
GMTs for HPV 58 follow up: 7 months	There is moderate-quality evidence that 9-valent HPV vaccine results in a significantly higher GMTs for HPV 58 than 4-valent HPV vaccine at 7 months.	Mean: 9.4 mMU/mL	Mean: 1348.8 mMU/mL	Ratio 143.5 (119.8 to 171.8) 528 participants in 1 RCT	⊕⊕⊕O MODERATE[1]
Seroconversion for HPV 6 follow up: 7 months	There is moderate-quality evidence that there is no significant difference in the ratio of seroconversion for HPV 6 between 9-valent and 4-valent HPV vaccines at 7 months.	261/261 (100%)	273/273 (100%)	RR 1.00 (not estimable) 534 participants in 1 RCT	⊕⊕⊕O MODERATE[1]
Seroconversion for HPV 11	There is moderate-quality evidence that there is	261/261 (100%)	273/273 (100%)	RR 1.00 (not estimable)	⊕⊕⊕O

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follow up: 7 months	no significant difference in the ratio of seroconversion for HPV 11 between 9-valent and 4-valent HPV vaccines at 7 months.			534 participants in 1 RCT	⊕⊕⊕O MODERATE[1]
Seroconversion for HPV 16 follow up: 7 months	There is moderate-quality evidence that there is no significant difference in the ratio of seroconversion for HPV 16 between 9-valent and 4-valent HPV vaccines at 7 months.	270/270 (100%)	276/276 (100%)	RR 1.00 (not estimable) 546 participants in 1 RCT	⊕⊕⊕O MODERATE[1]
Seroconversion for HPV 18 follow up: 7 months	There is moderate-quality evidence that there is no significant difference in the ratio of seroconversion for HPV 18 between 9-valent and 4-valent HPV vaccines at 7 months.	269/269 (100%)	276/276 (100%)	RR 1.00 (not estimable) 545 participants in 1 RCT	⊕⊕⊕O MODERATE[1]
Seroconversion for HPV 31/33/45/52/58 follow up: 7 months	The paper did not report in full seroconversion data for the 4-valent vaccine: "All participants seroconverted for HPV 31/33/45/52/58 after receiving 3 doses of the 9vHPV vaccine, except 1 participant who did not seroconvert for HPV 45" "The qHPV vaccine also induced some level of postdose 3 immune responses to the HPV types not included in the vaccine… including a seroconversion rate as high as 73.5% for HPV31 and 54.8% for HPV 58."				⊕⊕OO LOW[1 2]

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

[1]Downgraded 1 level for risk of bias: unclear allocation concealment

[2]Downgraded 1 further level for risk of bias: incomplete reporting

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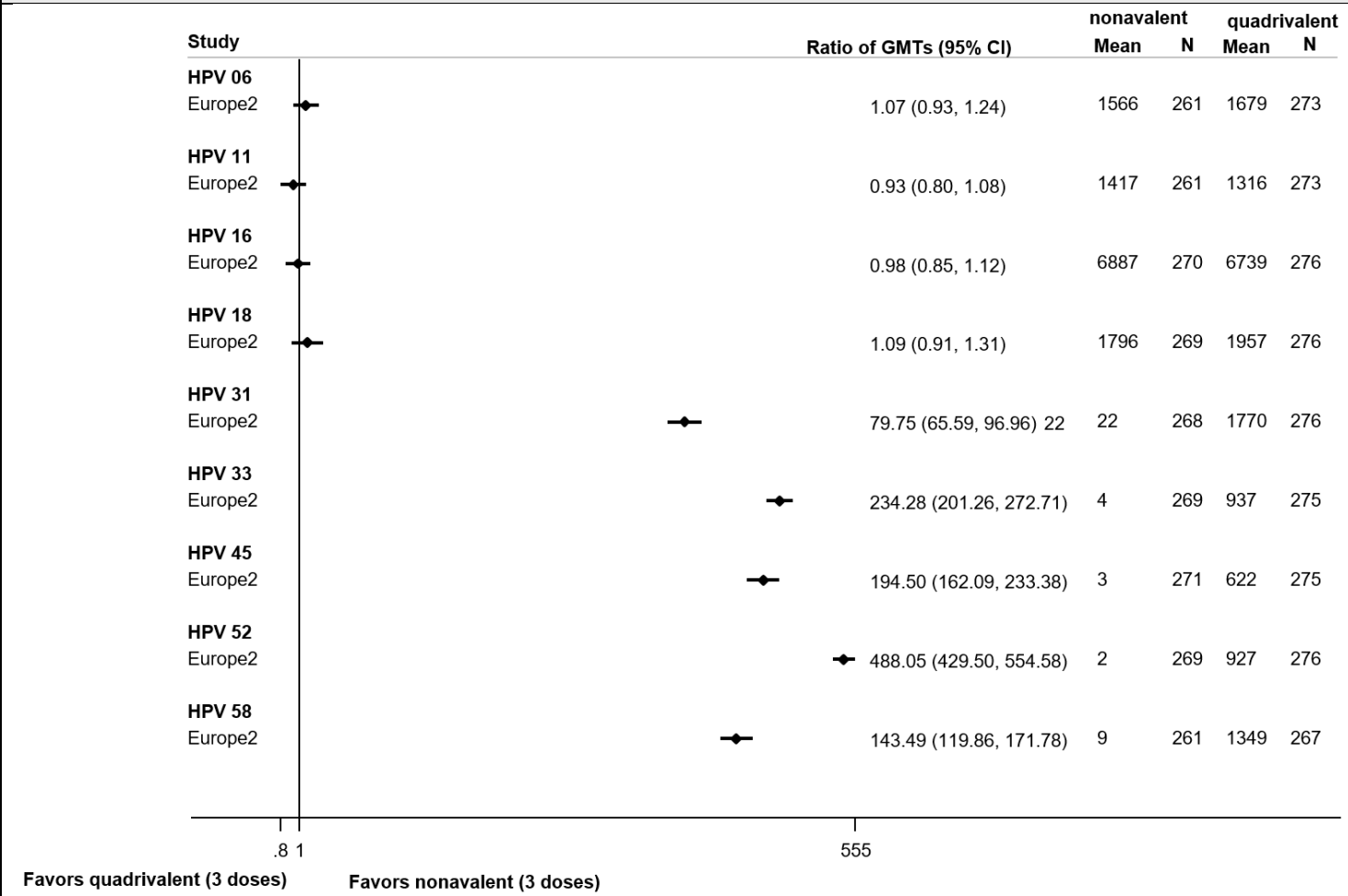
Forest plot: 9-valent HPV vaccine versus 4-valent HPV vaccine in 9 to 15-year old females – immunogenicity outcomes

Patients: **9 to 15-year old females (seronegative at baseline)**
***Setting*: Belgium, Denmark, Finland, Italy, Spain and Sweden**
Comparison: **9-valent HPV vaccine (3-doses (Month 0, 2, 6)) versus 4-valent HPV vaccine (3-doses (Month 0, 2, 6))**

Outcome	Forest plot	Certainty of the evidence (GRADE)
Ratio of GMTs for HPV follow up: 7 months		⨁⨁⨁◯ MODERATE

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

Forest plot for seroconversion not presented, as all 100% seroconversion for all HPV subtypes with full data available

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Summary of Findings: 9-valent HPV vaccine versus 4-valent HPV vaccine in 16 to 26-year old females – clinical outcomes for HPV 6/11/16/18

Patients: **16 to 26-year old females (seronegative at baseline)**
***Setting*: Austria, Brazil, Canada, Chile, Colombia, Denmark, Germany, Hong Kong, Japan, Korea, Mexico, New Zealand, Norway, Peru, Sweden, Taiwan, Thailand, and United States (including Puerto Rico)**
Comparison: **9-valent HPV vaccine (3-doses (Month 0, 2, 6)) versus 4-valent HPV vaccine (3-doses (Month 0, 2, 6))**

Outcome	Plain language summary	Absolute effect		Relative effect (95% CI) Nº of participants & studies	Certainty of the evidence (GRADE)
		4-valent	9-valent		
Persistent HPV infection >6 months	There is moderate-quality evidence of no significant difference on incidence of persistent HPV infection (>6 months) between 9-valent and 4-valent HPV vaccines	5 per 1000 person-yrs	3.6 per 1000 person-yrs	RR 0.72 (0.51 to 1.01) 11642 participants in 1 RCT	⊕⊕⊕O MODERATE [1]
Persistent HPV infection >12 months	There is moderate-quality evidence of no significant difference on incidence of persistent HPV infection (>12 months) between 9-valent and 4-valent HPV vaccines	2 per 1000 person-yrs	1.4 per 1000 person-yrs	RR 0.70 (0.41 to 1.20) 11642 participants in 1 RCT	⊕⊕⊕O MODERATE [1]
CIN1	There is moderate-quality evidence of no significant difference on incidence of CIN1 between 9-valent and 4-valent HPV vaccines	0.1 per 1000 person-yrs	No events	RR (not estimable) 11655 participants in 1 RCT	⊕⊕⊕O MODERATE [1]
CIN 2/3 or worse	There is low-quality evidence of no significant difference on incidence of CIN 2/3 or worse between 9-valent and 4-valent HPV vaccines	0.1 per 1000 person-yrs	0.1 per 1000 person-yrs	RR 1.00 (0.06 to 15.99) 11655 participants in 1 RCT	⊕⊕OO LOW [1 2]
Condyloma	There is low-quality evidence of no significant difference on incidence of condyloma between 9-valent and 4-valent HPV vaccines	0.1 per 1000 person-yrs	0.3 per 1000 person-yrs	RR 3.00 (0.35 to 25.68) 11769 participants in 1 RCT	⊕⊕OO LOW [1 2]
VIN1 or VaIN1	There is moderate-quality evidence of no significant difference on incidence of VIN1 or VaIN1 between 9-valent and 4-valent HPV vaccines	0.1 per 1000 person-yrs	No events	RR (not estimable) 11769 participants in 1 RCT	⊕⊕⊕O MODERATE [1]
VIN 2/3 or VaIN 2/3 or worse	There is moderate-quality evidence of no significant difference on incidence of VIN 2/3 or VaIN 2/3 or worse between 9-valent and 4-valent HPV vaccines	0.1 per 1000 person-yrs	No events	RR (not estimable) 11769 participants in 1 RCT	⊕⊕⊕O MODERATE [1]

CI= confidence interval; HPV= human papilloma virus; CIN=cervical intraepithelial neoplasia; RR= rate ratio; VIN= vulvar intraepithelial neoplasia; VaIN= vaginal intraepithelial neoplasia

[1]Downgraded one level for imprecision: low event rate

[2]Downgraded one further level for imprecision: very wide confidence intervals

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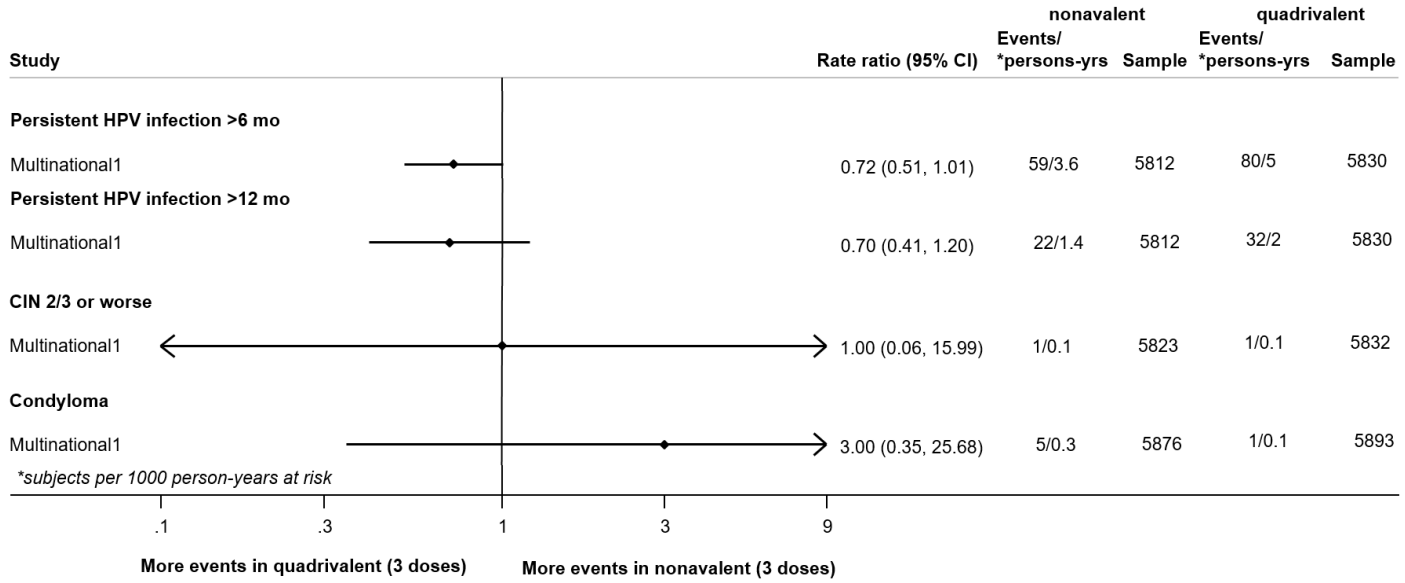
Forest plot: 9-valent HPV vaccine versus 4-valent HPV vaccine in 16 to 26-year old females – clinical outcomes for HPV 6/11/16/18

Patients: **16 to 26-year old females (seronegative at baseline)**
***Setting*: Austria, Brazil, Canada, Chile, Colombia, Denmark, Germany, Hong Kong, Japan, Korea, Mexico, New Zealand, Norway, Peru, Sweden, Taiwan, Thailand, and United States (including Puerto Rico)**
Comparison: **9-valent HPV vaccine (3-doses (Month 0, 2, 6)) versus 4-valent HPV vaccine (3-doses (Month 0, 2, 6))**

Outcome	Forest plot	Certainty of the evidence (GRADE)
Clinical outcomes for HPV 6, 11, 16, 18		⊕⊕⊕O MODERATE ⊕⊕⊕O MODERATE ⊕⊕OO LOW ⊕⊕OO LOW

CI= confidence interval; HPV= human papilloma virus; CIN=cervical intraepithelial neoplasia; RR= rate ratio

Only outcomes with an event in both arms are presented in this forest plot

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Summary of Findings: 9-valent HPV vaccine versus 4-valent HPV vaccine in 16 to 26-year old females – clinical outcomes for HPV 31/33/45/52/58

Patients: **16 to 26-year old females (seronegative at baseline)**
Setting**: Austria, Brazil, Canada, Chile, Colombia, Denmark, Germany, Hong Kong, Japan, Korea, Mexico, New Zealand, Norway, Peru, Sweden, Taiwan, Thailand, and United States (including Puerto Rico)**
Comparison: **9-valent HPV vaccine (3-doses (Month 0, 2, 6)) versus 4-valent HPV vaccine (3-doses (Month 0, 2, 6))**

Outcome	Plain language summary	Absolute effect		Relative effect (95% CI) Nº of participants & studies	Certainty of the evidence (GRADE)
		4-valent	9-valent		
Persistent HPV infection >6 months	There is moderate-quality evidence of increased persistent HPV infection (>6 months) with 4-valent vaccine compared with 9-valent vaccine	52.4 per 1000 person-yrs	2.1 per 1000 person-yrs	RR 0.04 (0.03 to 0.06) 11656 participants in 1 RCT	⊕⊕⊕O MODERATE [1]
Persistent HPV infection >12 months	There is moderate-quality evidence of increased persistent HPV infection (>12 months) with 4-valent vaccine compared with 9-valent vaccine	34.5 per 1000 person-yrs	1.3 per 1000 person-yrs	0.04 (0.02 to 0.06) 11656 participants in 1 RCT	⊕⊕⊕O MODERATE [1]
CIN1	There is moderate-quality evidence of increased CIN1 with 4-valent vaccine compared with 9-valent vaccine	4 per 1000 person-yrs	0.1 per 1000 person-yrs	RR 0.02 (0.00 to 0.18) 11891 participants in 1 RCT	⊕⊕⊕O MODERATE [1]
CIN 2/3 or worse	There is moderate-quality evidence of increased CIN2/3 or worse with 4-valent vaccine compared with 9-valent vaccine	1.5 per 1000 person-yrs	0.1 per 1000 person-yrs	RR 0.07 (0.01 to 0.49) 11655 participants in 1 RCT	⊕⊕⊕O MODERATE [1]
Condyloma	There is moderate-quality evidence of no significant difference on incidence of condyloma between 9-valent and 4-valent HPV vaccines	0.2 per 1000 person-yrs	0.2 per 1000 person-yrs	RR (not estimable) 12024 participants in 1 RCT	⊕⊕⊕O MODERATE [1]
VIN1 or VaIN1	There is low-quality evidence of no significant difference on incidence of VIN1 or VaIN1 between 9-valent and 4-valent HPV vaccines	0.6 per 1000 person-yrs	0.1 per 1000 person-yrs	RR 0.17 (0.02 to 1.28) 11769 participants in 1 RCT	⊕⊕OO LOW [1 2]
VIN 2/3 or VaIN 2/3 or worse	There is moderate-quality evidence of no significant difference on incidence of VIN 2/3 or VaIN 2/3 or worse between 9-valent and 4-valent HPV vaccines	0.2 per 1000 person-yrs	0.2 per 1000 person-yrs	RR (not estimable) 12024 participants in 1 RCT	⊕⊕⊕O MODERATE [1]

CI= confidence interval; HPV= human papilloma virus; CIN=cervical intraepithelial neoplasia; RR= rate ratio; VIN= vulvar intraepithelial neoplasia; VaIN= vaginal intraepithelial neoplasia

[1]Downgraded one level for imprecision: low event rate

[2]Downgraded one further level for imprecision: crosses line of no effect

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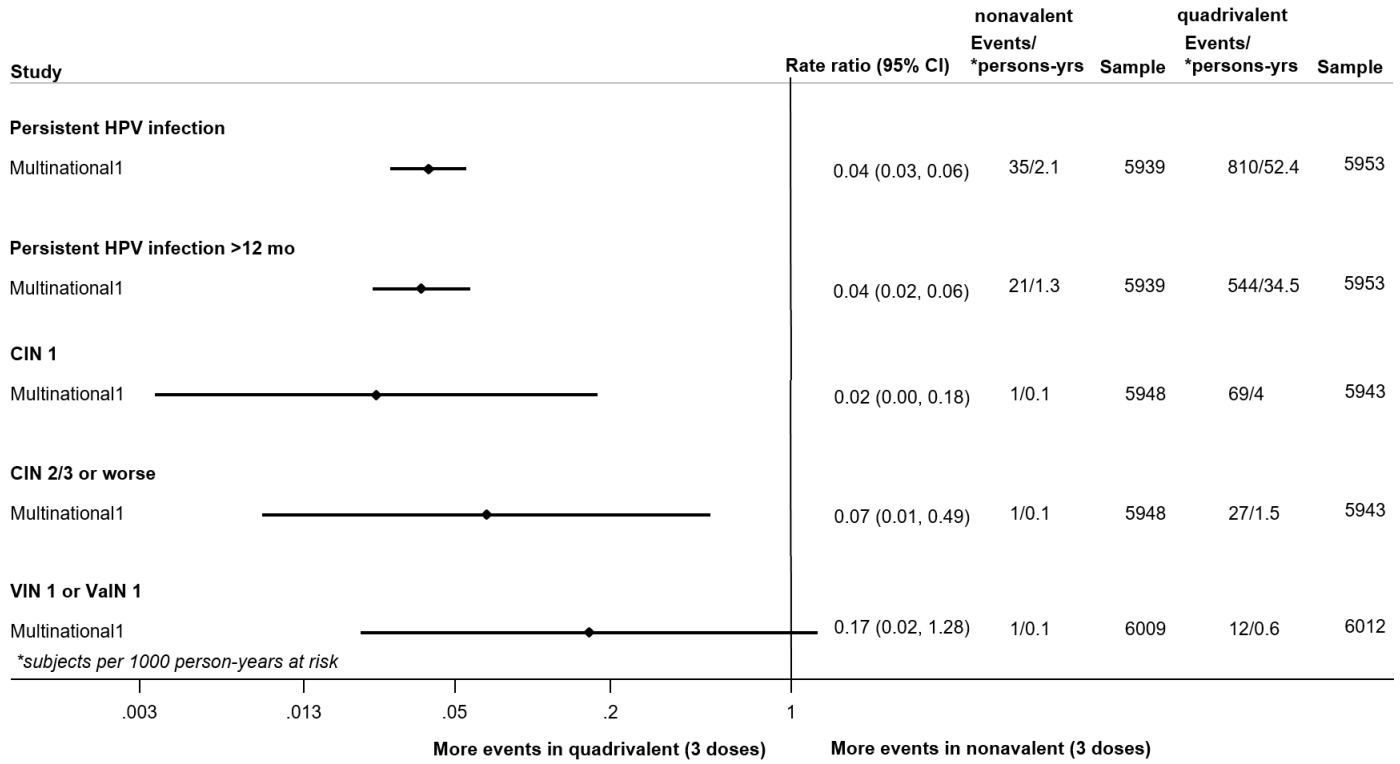
Forest plot: 9-valent HPV vaccine versus 4-valent HPV vaccine in 16 to 26-year old females – clinical outcomes for HPV 31/33/45/52/58

Patients: **16 to 26-year old females (seronegative at baseline)**
***Setting*: Austria, Brazil, Canada, Chile, Colombia, Denmark, Germany, Hong Kong, Japan, Korea, Mexico, New Zealand, Norway, Peru, Sweden, Taiwan, Thailand, and United States (including Puerto Rico)**
Comparison: **9-valent HPV vaccine (3-doses (Month 0, 2, 6)) versus 4-valent HPV vaccine (3-doses (Month 0, 2, 6))**

Outcome	Forest plot	Certainty of the evidence (GRADE)
Clinical outcomes for HPV 31, 33, 45, 52, 58		⊕⊕⊕O MODERATE ⊕⊕⊕O MODERATE ⊕⊕⊕O MODERATE ⊕⊕⊕O MODERATE ⊕⊕OO LOW

CI= confidence interval; HPV= human papilloma virus; CIN=cervical intraepithelial neoplasia; RR= rate ratio; VIN= vulvar intraepithelial neoplasia; VaIN= vaginal intraepithelial neoplasia
Only outcomes with an event in both arms are presented in this forest plot

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Summary of Findings: 9-valent HPV vaccine versus 4-valent HPV vaccine in 16 to 26-year old females – immunogenicity outcomes at 7 months

Patients: **16 to 26-year old females (seronegative at baseline)**
***Setting*: Austria, Brazil, Canada, Chile, Colombia, Denmark, Germany, Hong Kong, Japan, Korea, Mexico, New Zealand, Norway, Peru, Sweden, Taiwan, Thailand, and United States (including Puerto Rico)**
Comparison: **9-valent HPV vaccine (3-doses (Month 0, 2, 6)) versus 4-valent HPV vaccine (3-doses (Month 0, 2, 6))**

Outcome	Plain language summary	Absolute effect		Relative effect (95% CI) Nº of participants & studies	Certainty of the evidence (GRADE)
		4-valent	9-valent		
GMTs for HPV 6 follow up: 7 months	There is-high-quality evidence of no significant difference in GMTs for HPV 6 between 9-valent and 4-valent HPV vaccines at 7 months.	Mean: 875 mMU/mL	Mean: 893 mMU/mL	Ratio 1.02 (0.99 to 1.06) 7968 participants in 1 RCT	⊕⊕⊕⊕ HIGH
GMTs for HPV 11 follow up: 7 months	There is high-quality evidence that 4-valent HPV vaccine results in a significantly higher GMTs for HPV 11 than 9-valent HPV vaccine at 7 months, although results are non-inferior for 9-valent vaccine.	Mean: 830 mMU/mL	Mean: 666 mMU/mL	Ratio 0.80 (0.77 to 0.83) 7977 participants in 1 RCT	⊕⊕⊕⊕ HIGH
GMTs for HPV 16 follow up: 7 months	There is high-quality evidence of no significant difference in GMTs for HPV 16 between 9-valent and 4-valent HPV vaccines at 7 months.	Mean: 3157 mMU/mL	Mean: 3131 mMU/mL	Ratio 0.99 (0.96 to 1.03) 8094 participants in 1 RCT	⊕⊕⊕⊕ HIGH
GMTs for HPV 18 follow up: 7 months	There is high-quality evidence that 9-valent HPV vaccine results in a significantly higher GMTs for HPV 18 than 4-valent HPV vaccine at 7 months.	Mean: 679 mMU/mL	Mean: 805 mMU/mL	Ratio 1.19 (1.14 to 1.23) 9080 participants in 1 RCT	⊕⊕⊕⊕ HIGH
GMTs for HPV 31 follow up: 7 months	There is high-quality evidence that 9-valent HPV vaccine results in a significantly higher GMTs for HPV 31 than 4-valent HPV vaccine at 7 months.	Mean: 9.7 mMU/mL	Mean: 658.4 mMU/mL	Ratio 64.9 (64.6 to 71.3) 8843 participants in 1 RCT	⊕⊕⊕⊕ HIGH
GMTs for HPV 33 follow up: 7 months	There is high-quality evidence that 9-valent HPV vaccine results in a significantly higher GMTs for HPV 33 than 4-valent HPV vaccine at 7 months.	Mean: < 4 mMU/mL	Mean: 415.9 mMU/mL	Ratio (not estimable) 9393 participants in 1 RCT	⊕⊕⊕⊕ HIGH
GMTs for HPV 45 follow up: 7 months	There is high-quality evidence that 9-valent HPV vaccine results in a significantly higher GMTs for HPV 45 than 4-valent HPV vaccine at 7 months.	Mean: < 3 mMU/mL	Mean: 252.8 mMU/mL	Ratio (not estimable) 9542 participants in 1 RCT	⊕⊕⊕⊕ HIGH
GMTs for HPV 52 follow up: 7 months	There is high-quality evidence that 9-valent HPV vaccine results in a significantly higher GMTs for HPV 52 than 4-valent HPV vaccine at 7 months.	Mean: < 3 mMU/mL	Mean: 379.7 mMU/mL	Ratio (not estimable) 8790 participants in 1 RCT	⊕⊕⊕⊕ HIGH
GMTs for HPV 58 follow up: 7 months	There is high-quality evidence that 9-valent HPV vaccine results in a significantly higher GMTs for HPV 58 than 4-valent HPV vaccine at 7 months.	Mean: < 4 mMU/mL	Mean: 482.5 mMU/mL	Ratio (not estimable) 8932 participants in 1 RCT	⊕⊕⊕⊕ HIGH
Seroconversion for HPV 6	There is high-quality evidence of no significant	3967/3975 (99.8%)	3985/3993 (99.8%)	RR 1.00 (0.99 to 1.00)	⊕⊕⊕⊕

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follow up: 7 months	difference in seroconversion for HPV 6 between 9-valent and 4-valent HPV vaccines at 7 months.			7968 participants in 1 RCT	HIGH
Seroconversion for HPV 11 follow up: 7 months	There is high-quality evidence of no significant difference in the ratio of seroconversion for HPV 11 between 9-valent and 4-valent HPV vaccines at 7 months.	3978/3982 (99.9%)	3995/3995 (100%)	RR 1.00 (1.00 to 1.00) 7977 participants in 1 RCT	⊕⊕⊕⊕ HIGH
Seroconversion for HPV 16 follow up: 7 months	There is high-quality evidence of no significant difference in seroconversion for HPV 16 between 9-valent and 4-valent HPV vaccines at 7 months.	4062/4062 (100%)	4032/4032 (100%)	RR 1.00 (not estimable) 8094 participants in 1 RCT	⊕⊕⊕⊕ HIGH
Seroconversion for HPV 18 follow up: 7 months	There is high-quality evidence of no significant difference in seroconversion for HPV 18 between 9-valent and 4-valent HPV vaccines at 7 months.	4527/4541 (99.7%)	4530/4539 (99.8%)	RR 1.00 (0.99 to 1.00) 9080 participants in 1 RCT	⊕⊕⊕⊕ HIGH
Seroconversion for HPV 31 follow up: 7 months	There is high-quality evidence that 9-valent HPV vaccine results in a significantly higher ratio of seroconversion for HPV 31 than 4-valent HPV vaccine.	2193/4377 (50.1%)	4457/4466 (99.8%)	RR 1.99 (1.93 to 2.05) 8843 participants in 1 RCT	⊕⊕⊕⊕ HIGH
Seroconversion for HPV 33 follow up: 7 months	There is high-quality evidence that 9-valent HPV vaccine results in a significantly higher ratio of seroconversion for HPV 33 than 4-valent HPV vaccine.	596/4691 (12.7%)	4688/4702 (99.7%)	RR 7.85 (7.28 to 8.46) 9393 participants in 1 RCT	⊕⊕⊕⊕ HIGH
Seroconversion for HPV 45 follow up: 7 months	There is high-quality evidence that 9-valent HPV vaccine results in a significantly higher ratio of seroconversion for HPV 45 than 4-valent HPV vaccine.	437/4750 (9.2%)	4773/4792 (99.6%)	RR 10.83 (9.90 to 11.84) 9542 participants in 1 RCT	⊕⊕⊕⊕ HIGH
Seroconversion for HPV 52 follow up: 7 months	There is high-quality evidence that 9-valent HPV vaccine results in a significantly higher ratio of seroconversion for HPV 52 than 4-valent HPV vaccine.	113/4335 (2.6%)	4446/4455 (99.8%)	RR 38.26 (31.86 to 45.9) 8790 participants in 1 RCT	⊕⊕⊕⊕ HIGH
Seroconversion for HPV 58 follow up: 7 months	There is high-quality evidence that 9-valent HPV vaccine results in a significantly higher ratio of seroconversion for HPV 58 than 4-valent HPV vaccine.	907/4446 (20.4%)	4477/4486 (99.8%)	RR 4.89 (4.6 to 5.18) 8932 participants in 1 RCT	⊕⊕⊕⊕ HIGH

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

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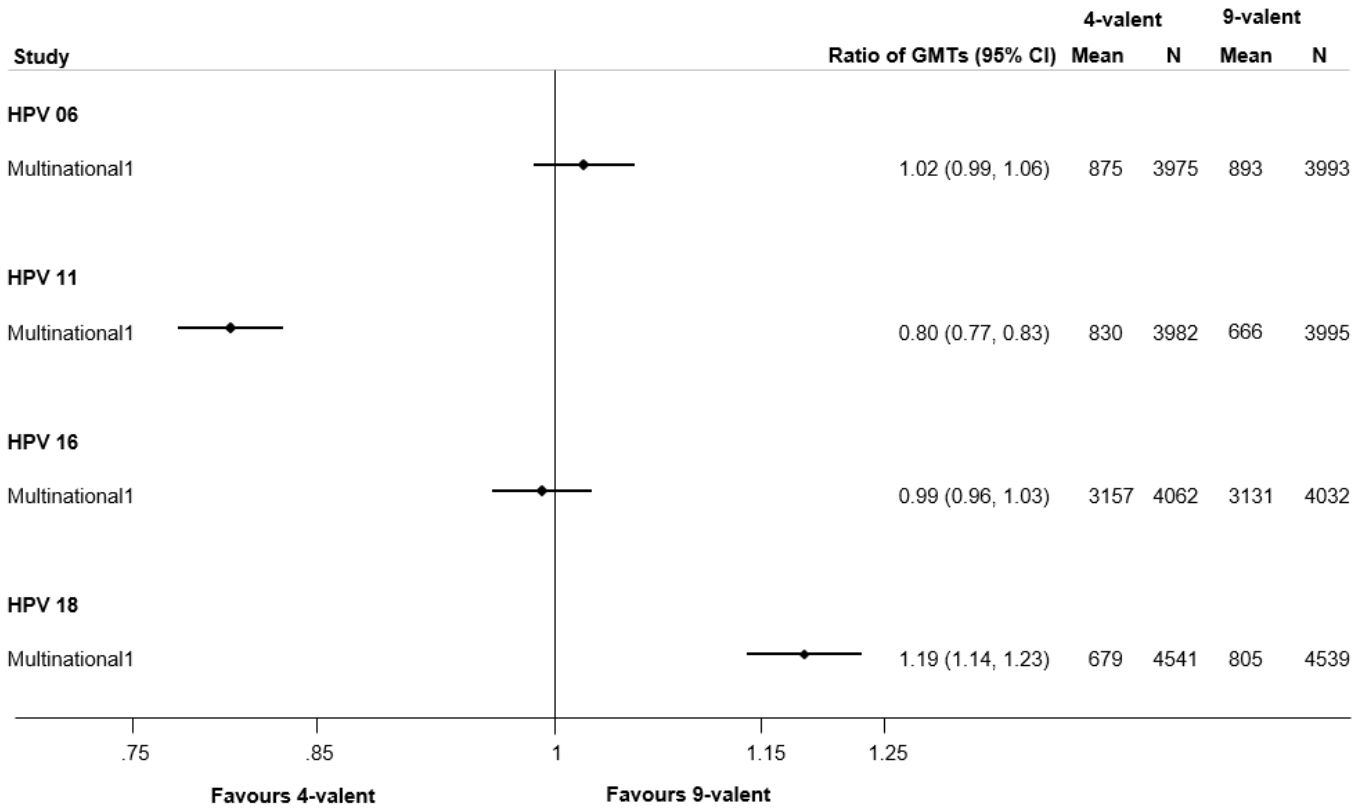
Forest plots: 9-valent HPV vaccine versus 4-valent HPV vaccine in 16 to 26-year old females – immunogenicity outcomes

Patients: **16 to 26-year old females (seronegative at baseline)**
***Setting*: Austria, Brazil, Canada, Chile, Colombia, Denmark, Germany, Hong Kong, Japan, Korea, Mexico, New Zealand, Norway, Peru, Sweden, Taiwan, Thailand, and United States (including Puerto Rico)**
Comparison: **9-valent HPV vaccine (3-doses (Month 0, 2, 6)) versus 4-valent HPV vaccine (3-doses (Month 0, 2, 6))**

Outcome	Forest plots	Certainty of the evidence (GRADE)
GMTs for HPV 6, 11, 16, 18 follow up: 7 months		⊕⊕⊕⊕ HIGH ⊕⊕⊕⊕ HIGH ⊕⊕⊕⊕ HIGH ⊕⊕⊕⊕ HIGH

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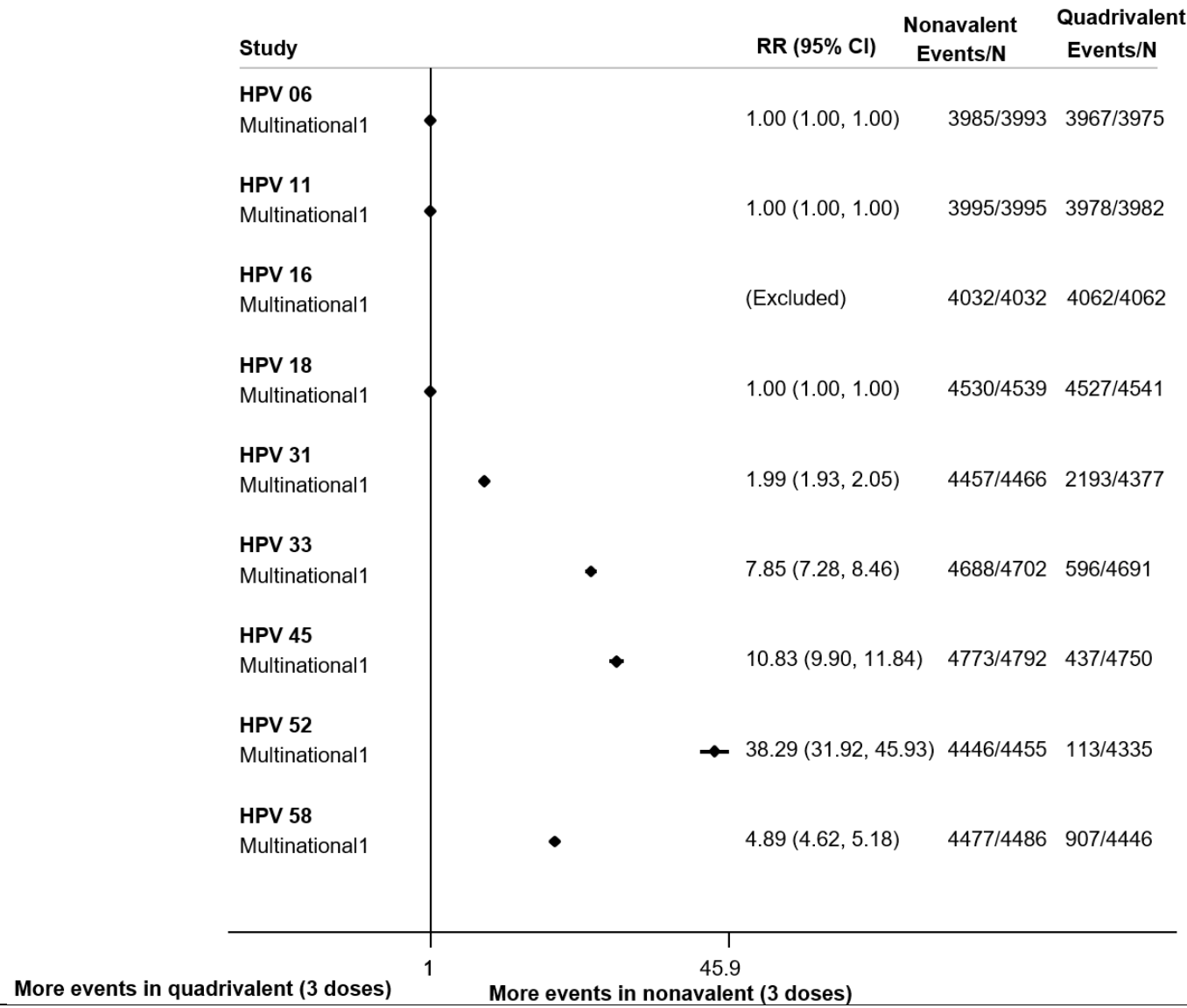
Seroconversion

follow up: 7 months



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

GMTs for HPV 31/33/45/52/58 not shown in forest plot; no exact numbers reported GMTs for HPV 33/45/52/58 with 4-valent vaccine

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Summary of Findings: 9-valent HPV vaccine versus 4-valent HPV vaccine in 16 to 26-year old females – immunogenicity outcomes at 24 months

Patients: **16 to 26-year old females (seronegative at baseline)**
***Setting*: Austria, Brazil, Canada, Chile, Colombia, Denmark, Germany, Hong Kong, Japan, Korea, Mexico, New Zealand, Norway, Peru, Sweden, Taiwan, Thailand, and United States (including Puerto Rico)**
Comparison: **9-valent HPV vaccine (3-doses (Month 0, 2, 6)) versus 4-valent HPV vaccine (3-doses (Month 0, 2, 6))**

Outcome	Plain language summary	Absolute effect		Relative effect (95% CI) Nº of participants & studies	Certainty of the evidence (GRADE)
		4-valent	9-valent		
GMTs for HPV 6 follow up: 24 months	There is moderate-quality evidence of no significant difference in GMTs for HPV 6 between 9-valent and 4-valent HPV vaccines at 24 months.	Mean: 205 mMU/mL	Mean: 209 mMU/mL	Ratio 1.02 (0.93 to 1.12) 1404 participants in 1 RCT	⊕⊕⊕O MODERATE [1]
GMTs for HPV 11 follow up: 24 months	There is moderate-quality evidence that 4-valent HPV vaccine results in significantly higher GMTs for HPV 11 than 9-valent HPV vaccine at 24 months, although results are non-inferior for 9-valent vaccine.	Mean: 148 mMU/mL	Mean: 123 mMU/mL	Ratio 0.83 (0.76 to 0.91) 1497 participants in 1 RCT	⊕⊕⊕O MODERATE [1]
GMTs for HPV 16 follow up: 24 months	There is moderate-quality evidence of no significant difference in GMTs for HPV 16 between 9-valent and 4-valent HPV vaccines at 24 months.	Mean: 507 mMU/mL	Mean: 521 mMU/mL	Ratio 1.03 (0.93 to 1.14) 1536 participants in 1 RCT	⊕⊕⊕O MODERATE [1]
GMTs for HPV 18 follow up: 24 months	There is moderate-quality evidence that 9-valent HPV vaccine results in significantly higher GMTs for HPV 18 than 4-valent HPV vaccine at 24 months.	Mean: 68 mMU/mL	Mean: 86 mMU/mL	Ratio 1.26 (1.12 to 1.43) 1732 participants in 1 RCT	⊕⊕⊕O MODERATE [1]
GMTs for HPV 31 follow up: 24 months	There is moderate-quality evidence that 9-valent HPV vaccine results in a significantly higher GMTs for HPV 31 than 4-valent HPV vaccine at 24 months.	Mean: < 4 mMU/mL	Mean: 101.9 mMU/mL	Ratio (not estimable) 1667 participants in 1 RCT	⊕⊕⊕O MODERATE [1]
GMTs for HPV 33 follow up: 24 months	There is moderate-quality evidence that 9-valent HPV vaccine results in a significantly higher GMTs for HPV 33 than 4-valent HPV vaccine at 24 months.	Mean: < 4 mMU/mL	Mean: 65.3 mMU/mL	Ratio (not estimable) 1776 participants in 1 RCT	⊕⊕⊕O MODERATE [1]
GMTs for HPV 45 follow up: 24 months	There is moderate-quality evidence that 9-valent HPV vaccine results in a significantly higher GMTs for HPV 45 than 4-valent HPV vaccine at 24 months.	Mean: < 3 mMU/mL	Mean: 33 mMU/mL	Ratio (not estimable) 1809 participants in 1 RCT	⊕⊕⊕O MODERATE [1]
GMTs for HPV 52 follow up: 24 months	There is moderate-quality evidence that 9-valent HPV vaccine results in a significantly higher GMTs for HPV 52 than 4-valent HPV vaccine at 24 months.	Mean: < 3 mMU/mL	Mean: 57.9 mMU/mL	Ratio (not estimable) 1675 participants in 1 RCT	⊕⊕⊕O MODERATE [1]
GMTs for HPV 58 follow up: 24 months	There is moderate-quality evidence that 9-valent HPV vaccine results in a significantly higher GMTs for HPV 58 than 4-valent HPV vaccine at 24 months.	Mean: < 4 mMU/mL	Mean: 80.3 mMU/mL	Ratio (not estimable) 1686 participants in 1 RCT	⊕⊕⊕O MODERATE [1]

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Seropositivity for HPV 6 follow up: 24 months	There is moderate-quality evidence of no significant difference in the ratio seropositive for HPV 6 between 9-valent and 4-valent HPV vaccines at 24 months.	671/689 (97.4%)	701/715 (98%)	RR 1.01 (0.99 to 1.02) 1404 participants in 1 RCT	⊕⊕⊕O MODERATE [1]
Seropositivity for HPV 11 follow up: 24 months	There is moderate-quality evidence of no significant difference in the ratio seropositive for HPV 11 between 9-valent and 4-valent HPV vaccines at 24 months.	724/734 (98.6%)	753/763 (98.7%)	RR 1.00 (0.99 to 1.01) 1497 participants in 1 RCT	⊕⊕⊕O MODERATE [1]
Seropositivity for HPV 16 follow up: 24 months	There is moderate-quality evidence of no significant difference in the ratio seropositive for HPV 16 between 9-valent and 4-valent HPV vaccines at 24 months.	752/758 (99.2%)	777/778 (99.9%)	RR 1.01 (1.00 to 1.01) 1536 participants in 1 RCT	⊕⊕⊕O MODERATE [1]
Seropositivity for HPV 18 follow up: 24 months	There is moderate-quality evidence that 9-valent HPV vaccine results in a significantly higher ratio of seropositivity for HPV 18 than 4-valent HPV vaccine.	685/846 (81.0%)	766/886 (86.5%)	RR 1.07 (1.02 to 1.11) 1732 participants in 1 RCT	⊕⊕⊕O MODERATE [1]
Seropositivity for HPV 31 follow up: 24 months	There is moderate-quality evidence that 9-valent HPV vaccine results in a significantly higher ratio of seropositivity for HPV 31 than 4-valent HPV vaccine.	116/804 (14.4%)	839/863 (97.2%)	RR 6.74 (5.69 to 7.98) 1667 participants in 1 RCT	⊕⊕⊕O MODERATE [1]
Seropositivity for HPV 33 follow up: 24 months	There is moderate-quality evidence that 9-valent HPV vaccine results in a significantly higher ratio of seropositivity for HPV 33 than 4-valent HPV vaccine.	65/867 (7.5%)	896/909 (98.6%)	RR 13.15 (10.40 to 16.61) 1776 participants in 1 RCT	⊕⊕⊕O MODERATE [1]
Seropositivity for HPV 45 follow up: 24 months	There is moderate-quality evidence that 9-valent HPV vaccine results in a significantly higher ratio of seropositivity for HPV 45 than 4-valent HPV vaccine.	17/881 (1.9%)	811/928 (87.4%)	RR 45.29 (28.27 to 72.56) 1809 participants in 1 RCT	⊕⊕⊕O MODERATE [1]
Seropositivity for HPV 52 follow up: 24 months	There is moderate-quality evidence that 9-valent HPV vaccine results in a significantly higher ratio of seropositivity for HPV 52 than 4-valent HPV vaccine.	31/808 (3.8%)	852/867 (98.3%)	RR 25.61 (18.13 to 36.18) 1675 participants in 1 RCT	⊕⊕⊕O MODERATE [1]
Seropositivity for HPV 58 follow up: 24 months	There is moderate-quality evidence that 9-valent HPV vaccine results in a significantly higher ratio of seropositivity for HPV 58 than 4-valent HPV vaccine.	71/834 (8.5%)	836/852 (98.1%)	RR 11.53 (9.22 to 14.40) 1686 participants in 1 RCT	⊕⊕⊕O MODERATE [1]

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

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

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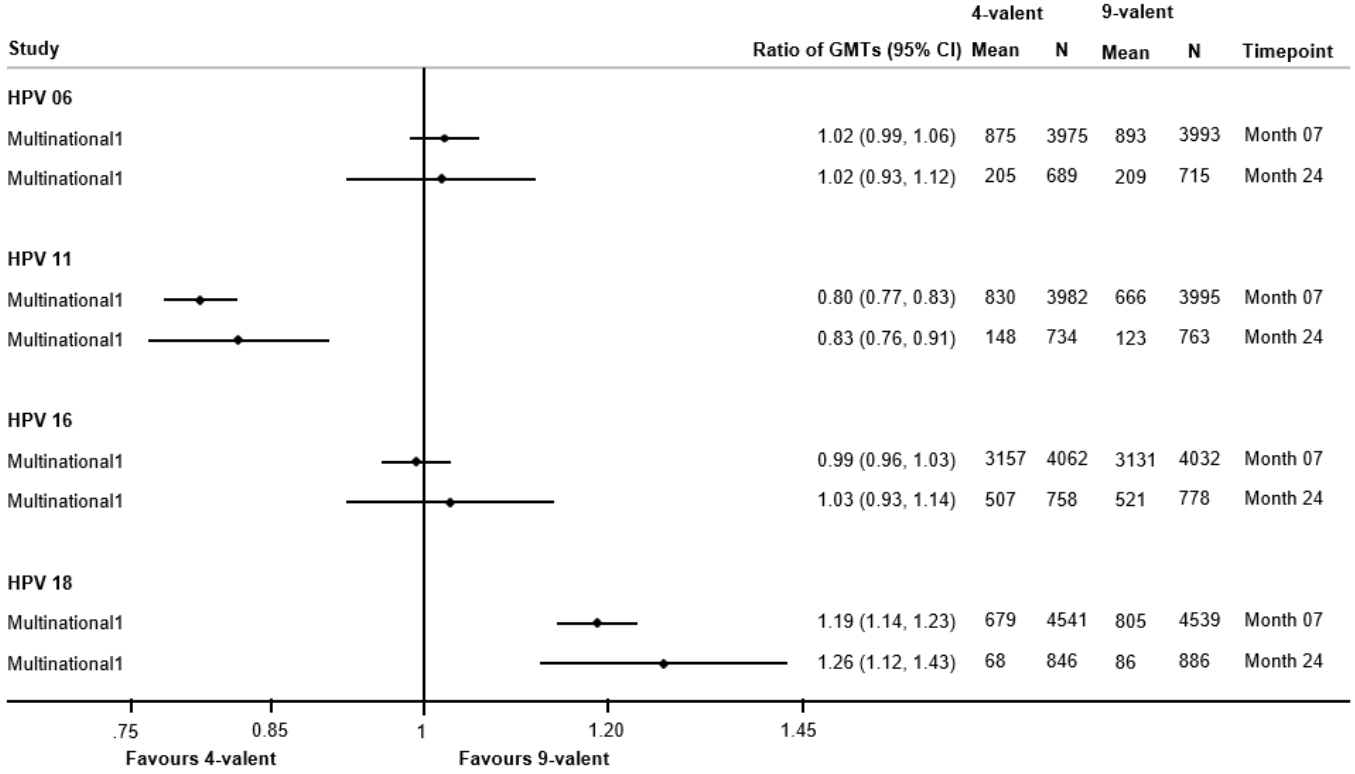
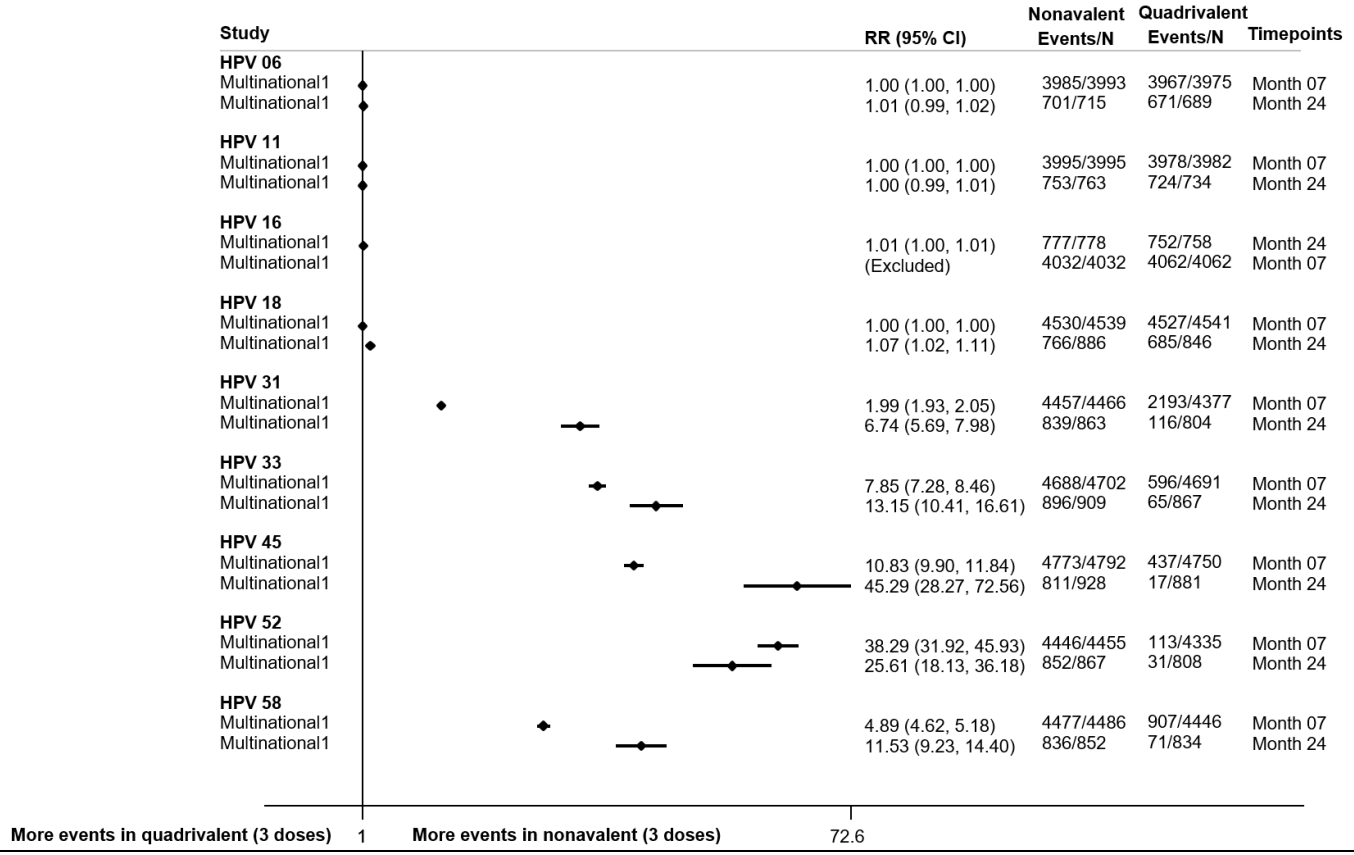
Forest plots: 9-valent HPV vaccine versus 4-valent HPV vaccine in 16 to 26-year old females – immunogenicity outcomes

Patients: **16 to 26-year old females (seronegative at baseline)**
***Setting*: Austria, Brazil, Canada, Chile, Colombia, Denmark, Germany, Hong Kong, Japan, Korea, Mexico, New Zealand, Norway, Peru, Sweden, Taiwan, Thailand, and United States (including Puerto Rico)**
Comparison: **9-valent HPV vaccine (3-doses (Month 0, 2, 6)) versus 4-valent HPV vaccine (3-doses (Month 0, 2, 6))**

Outcome	Forest plots	Certainty of the evidence (GRADE)
GMTs for HPV 6, 11, 16, 18 follow up: 7-24 months		⊕⊕⊕⊕ HIGH ⊕⊕⊕O MODERATE ⊕⊕⊕⊕ HIGH ⊕⊕⊕O MODERATE ⊕⊕⊕⊕ HIGH ⊕⊕⊕O MODERATE ⊕⊕⊕⊕ HIGH ⊕⊕⊕O MODERATE

Seropositivity

follow up: 7-24 months



⊕⊕⊕⊕ HIGH
⊕⊕⊕O MODERATE

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

GMTs for HPV 31/33/45/52/58 not shown in forest plot; no exact numbers reported GMTs for HPV 31/33/45/52/58 with 4-valent vaccine

References

Europe2

Vesikari T, Brodszki N, van Damme P et al. A randomized, double-blind, phase III study of the immunogenicity and safety of a 9-valent human papillomavirus L1 virus-like particle vaccine (V503) versus Gardasil® in 9–15-year-old girls. Pediatr Infect Dis J 2015;34:992-998.

Multinational1

Joura EA, Giuliano AR, Iverson OE et al. A 9-valent HPV vaccine against infection and intraepithelial neoplasia in women. NEJM 2015;372(8):711-723.

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HPV vaccines versus placebo (or control vaccine) in males

Contents

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Key findings

In males aged 10-14 years, comparative data between 2-valent vaccine and control vaccine were not available; however, at 7 months, GMTs for HPV 16 and 18 were 27891.6 EU/mL and 10593.7 EU/mL, respectively, and seroconversion for HPV 16 and 18 were both 100% (very low-quality evidence).

In males aged 16 to 26 years, at a median follow-up of 2.9 years, 4-valent HPV vaccine reduced the proportion of males with external genital lesions (any type), external genital lesions (HPV6, 11, 16, 18), and condyloma acuminatum, compared with placebo, in both intention-to-treat and per-protocol analyses (ITT-analyses not shown; moderate-quality evidence). There was no significant difference between 4-valent HPV vaccine and placebo in the proportion of men with all PIN lesions, PIN grade 1, or PIN grade 2 or 3, in both intention-to-treat and per-protocol analyses (ITT analyses not shown); however, the vaccine was more effective in the per-protocol analyses (low-quality evidence).

In males aged 16 to 26 years, at a mean follow-up of 2.9 years, 4-valent HPV vaccine reduced persistent infection caused by HPV 6, 11, 16 or 18 combined, or by each HPV subtype individually, compared with placebo (moderate-quality evidence).

In males aged 16 to 26 years, 4-valent vaccine increased GMTs for HPV 6, 11, 16 and 18 when compared with placebo at 7, 24 and 36 months (moderate-quality evidence). There was a trend towards GMTs levelling off after reaching a peak at month 7. Comparative data between 4-valent vaccine and placebo were not available for seropositivity outcomes; however, seropositivity for HPV 6, 11, 16 and 18 at 7 months was >97%, and at 36 months was >88% for HPV 6, 11 and 16, but 57% for HPV 18 (low-quality evidence).

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 analyze evidence for the protection afforded by prophylactic HPV vaccines in men.

Objectives

To evaluate the efficacy and immunogenicity of HPV vaccines in males. This document focuses on the comparison of vaccine versus placebo (or control vaccine) in males, for those results that were reported regardless of sexual orientation.

Search methods

Searches were conducted from January 2006 to June 2016, and all relevant studies regardless of language or publication status were searched. 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 comparison of vaccine versus placebo (or control vaccine) in males. Data for men who have sex with men are reported in a separate Target Update.

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 two RCTs (Finland1; Multinational8). Finland1 compared 2-valent vaccine with hepatitis B vaccine (control vaccine) in 270 males aged 10 to 18 years; we present here the subset of males aged 10 to 14 years (the target vaccination population). Multinational8 compared 4-valent HPV vaccine versus placebo in 4,065 males aged 16 to 26 years. The risk of bias was low for all categories for both studies, except for selective reporting which was judged as high: full data for the control group were not reported for some immunogenicity outcomes.

2-valent HPV vaccine versus control vaccine in 10 to 14-year old males

The Finland1 study reported immunogenicity outcomes at 7 months (1 month after last dose). Comparative data between 2-valent vaccine and control vaccine were not available (control group data not reported); however, GMTs for HPV 16 and 18 were 27891.6 EU/mL and 10593.7 EU/mL, respectively, and seroconversion for HPV 16 and 18 were both 100%. The evidence was judged of very low quality.

4-valent HPV vaccine versus placebo in 16 to 26-year old males

The Multinational8 study reported clinical outcomes at a median of 2.9 years. For the outcomes of external genital lesions (any type), external genital lesions (HPV6, 11, 16, 18), and condyloma acuminatum, there was moderate-quality evidence that 4-valent HPV vaccine reduced the proportion of males with these outcomes compared with placebo, in both intention-to-treat and per-protocol analyses (ITT analyses not shown). For the outcomes of all penile, perianal, or perineal intraepithelial neoplasia (PIN) lesions, PIN grade 1, or PIN grade 2 or 3, there was low-quality evidence of no significant difference between 4-valent HPV vaccine and placebo in both intention-to-treat and per-protocol analyses; however, in the per-protocol analyses the effect estimate for each outcome favoured vaccine, whereas in the intention-to-treat analyses the effect estimate for all PIN lesions and PIN grade 2 or 3 favoured placebo (ITT analyses not shown).

For the outcome of persistent infection, there was moderate-quality evidence that 4-valent HPV vaccine reduced persistent infection caused by HPV 6, 11, 16 or 18 combined, or by each HPV subtype individually, in 16 to 26-year old males compared with placebo.

The multinational8 study also reported immunogenicity outcomes. There was moderate quality evidence that 4-valent vaccine increased GMTs for HPV 6, 11, 16 and 18 when compared with placebo at 7, 24 and 36 months. There was a trend towards GMTs levelling off after reaching a peak at month 7. Comparative data between 4-valent vaccine and placebo were not available for the seropositivity outcomes (placebo group data not reported); however, seropositivity for HPV 6, 11, 16 and 18 at 7 months was >97%. At 36 months seropositivity was >88% for HPV 6, 11 and 16, but 57% for HPV 18.

Implications and conclusions

Evidence for the effect of the 2-valent vaccine is of very low quality, but shows beneficial effects on immunogenicity outcomes at 7 months. The 4-valent vaccine appears to be effective at preventing external genital lesions and condyloma acuminatum at 3 years, but there is no significant difference compared with placebo for PIN lesions at 3 years. The 4-valent vaccine is also effective at preventing persistent infections. Beneficial effects up to 3 years on immunogenicity outcomes were shown with 4-valent vaccine.

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Summary of Findings: 2-valent HPV vaccine versus control vaccine in 10 to 14-year old males – immunogenicity outcomes

Patients: **10 to 14-year old males (seronegative at baseline)**
Setting**: Finland**
Comparison: **2-valent HPV vaccine (3-doses (Month 0, 1, 6)) versus hepatitis B vaccine control vaccine (3-doses)**

Outcome	Plain language summary	Absolute effect		Relative effect (95% CI) Nº of participants & studies	Certainty of the evidence (GRADE)
		Control vaccine	4-valent HPV vaccine		
GMTs for HPV 16 follow up: 7 months	We do not have data about the effect of 2-valent vaccine on GMTs for HPV 16 in males when compared with placebo, as no placebo data were reported for this outcome. However, the mean GMT in the vaccine group was 27891.6 EU/mL	Not reported	Mean: 27891.6 EU/mL	Not estimable Based on data from 79 participants in one RCT	⨁⨁⨁◯ VERY LOW [1,2]
GMTs for HPV 18 follow up: 7 months	We do not have data about the effect of 2-valent vaccine on GMTs for HPV 18 in males when compared with placebo, as no placebo data were reported for this outcome. However, the mean GMT in the vaccine group was 10593.7 EU/mL	Not reported	Mean: 10593.7 EU/mL	Not estimable Based on data from 72 participants in one RCT	⨁⨁⨁◯ VERY LOW [1,2]
Seroconversion for HPV 16 follow up: 7 months	We do not have data about the effect of 2-valent vaccine on seroconversion for HPV 16 in males when compared with placebo, as no placebo data were reported for this outcome. However, the seroconversion rate in the vaccine group was 100%.	Not reported	79/79 (100%)	Not estimable Based on data from 79 participants in one RCT	⨁⨁⨁◯ VERY LOW [1,2]
Seroconversion for HPV 18 follow up: 7 months	We do not have data about the effect of 2-valent vaccine on seroconversion for HPV 18 in males when compared with placebo, as no placebo data were reported for this outcome. However, the seroconversion rate in the vaccine group was 100%.	Not reported	72/72 (100%)	Not estimable Based on data from 72 participants in one RCT	⨁⨁⨁◯ VERY LOW [1,2]

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

[1] Downgraded two levels for risk of bias: no placebo data reported in the paper for immunogenicity outcomes.

[2] Downgraded one level for imprecision: low number of participants.

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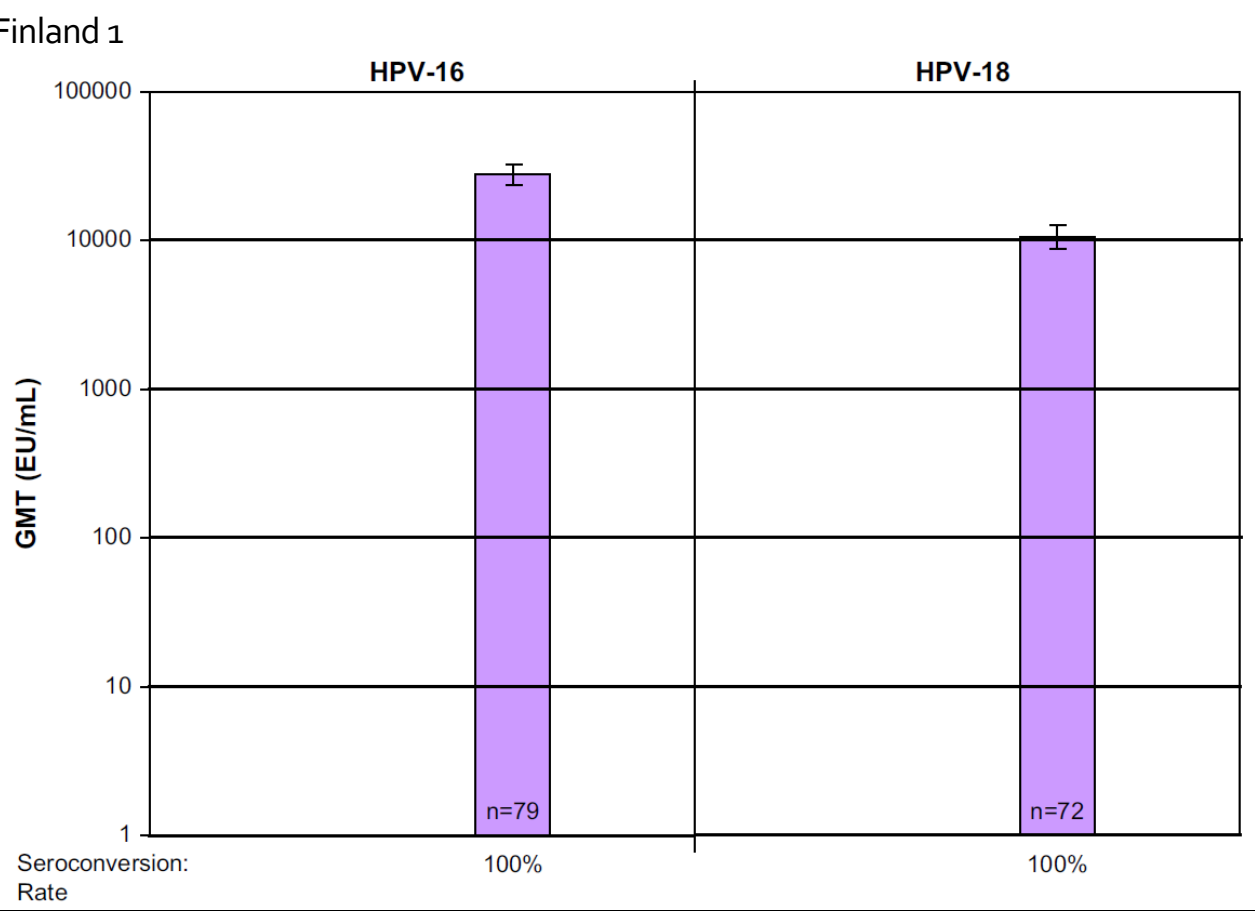
Graph: 2-valent HPV vaccine versus control vaccine in 10 to 14-year old males – immunogenicity outcomes

Patients: **10 to 14-year old males (seronegative at baseline)**
***Setting*: Finland**
Comparison: **2-valent HPV vaccine (3-doses (Month 0, 1, 6)) versus hepatitis B vaccine control vaccine (3-doses)**

Outcome	Graph	Certainty of the evidence (GRADE)
GMTs and seroconversion for HPV 16 and 18 follow up: 7 months		⊕⊕⊕O VERY LOW

Analyses not performed as no placebo group data available for these outcomes.

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Summary of Findings: 4-valent HPV vaccine versus placebo in 16 to 26-year old males – clinical outcomes, lesions – per-protocol analyses [5]

Patients: **16 to 26-year old males (seronegative at baseline)**
Setting**: 71 sites in 18 countries from Africa, Australia, Europe, Latin America and North America.**
Comparison: **4-valent HPV vaccine (3-doses (Day 1, Month 2, Month 6)) versus placebo (3-doses (Day 1, Month 2, Month 6))**

Outcome	Plain language summary	Absolute effect		Relative effect (95% CI) Nº of participants & studies	Certainty of the evidence (GRADE)
		Placebo	4-valent HPV vaccine		
Clinical: External genital lesions (Any type) follow up: median 2.9 years	There is moderate-quality evidence that 4-valent HPV vaccine reduces the number of males with external genital lesions of any type compared with placebo	36/3081 person-years	6/3173 person-years	RR 0.16 (0.07 to 0.38) Based on data from 2545 participants (6254 person-years) in 1 RCT	⊕⊕⊕O MODERATE [1]
Clinical: External genital lesions (HPV6, 11, 16, 18) follow up: median 2.9 years	There is moderate quality evidence that 4-valent HPV vaccine reduces the number of males with external genital lesions of HPV6, 11, 16, or 18 type compared with placebo	31/2812 person-years	3/2831 person-years	RR 0.10 (0.03 to 0.31) Based on data from 2805 participants (5643 person-years) in 1 RCT	⊕⊕⊕O MODERATE [1]
Clinical: condyloma acuminatum follow up: median 2.9 years	There is moderate-quality evidence that 4-valent HPV vaccine reduces the number of males with condyloma acuminatum compared with placebo	28/2814 person-years	3/2831 person-years	RR 0.11 (0.03 to 0.35) Based on data from 2805 participants (5645 person-years) in 1 RCT	⊕⊕⊕O MODERATE [1]
Clinical: All PIN lesions follow up: median 2.9 years	There is low-quality evidence of no significant difference between 4-valent HPV vaccine and placebo on the number of males with PIN lesions (all grades).	3/2824 person-years	0/2833 person-years	RR 0.14 (0.01 to 2.76) Based on data from 2805 participants (5657 person-years) in 1 RCT	⊕⊕OO LOW [2]
Clinical: PIN grade 1 follow up: median 2.9 years	There is low-quality evidence of no significant difference between 4-valent HPV vaccine and placebo on the number of males with grade 1 PIN lesions.	2/2826 person-years	0/2833 person-years	RR 0.20 (0.01 to 4.16) Based on data from 2805 participants (5659 person-years) in 1 RCT	⊕⊕OO LOW [2]
Clinical: PIN grade 2 or 3 follow up: median 2.9 years	There is low-quality evidence of no significant difference between 4-valent HPV vaccine and placebo on the number of males with grade 2 or 3 PIN lesions	1/2825 person-years	0/2833 person-years	RR 0.33 (0.01 to 8.16) Based on data from 2805 participants (5658 person-years) in 1 RCT	⊕⊕OO LOW [2]

CI= confidence interval; GL= genital lesion; HPV= human papilloma virus; PIN= penile, perianal, or perineal intraepithelial neoplasia; RR= rate ratio

[1] Downgraded one level for imprecision: Very low event rate.

[2] Downgraded two levels for imprecision: 95% CI around the pooled estimate of effect includes appreciable benefit for both the intervention and control groups, as well as no effect.

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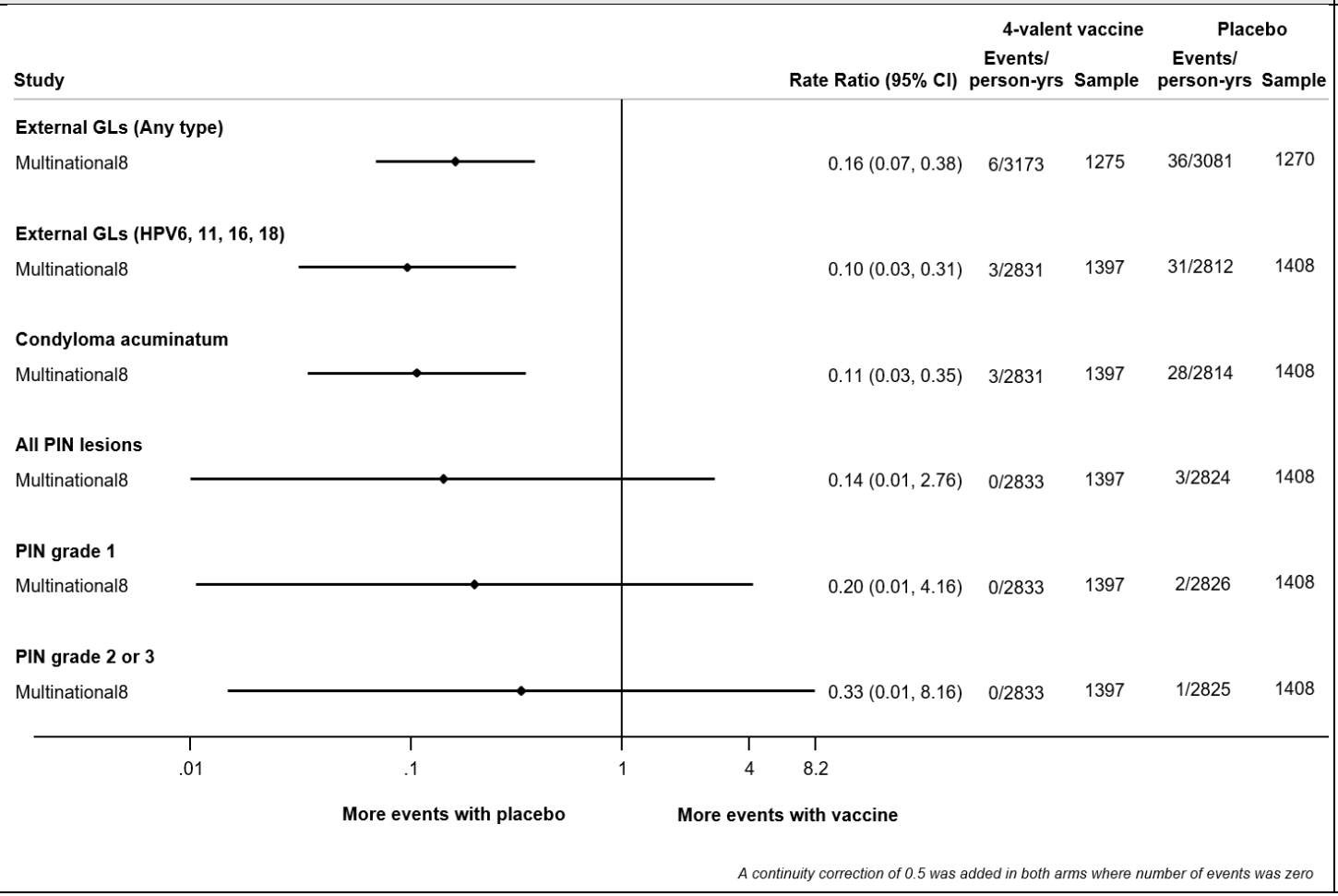
Forest plot: 4-valent HPV vaccine versus placebo in 16 to 26-year old males – clinical outcomes, lesions – per-protocol analyses

Patients: **16 to 26-year old males (seronegative at baseline)**
Setting**: 71 sites in 18 countries from Africa, Australia, Europe, Latin America and North America.**
Comparison: **4-valent HPV vaccine (3-doses (Day 1, Month 2, Month 6)) versus placebo (3-doses (Day 1, Month 2, Month 6))**

Outcome	Forest plot	Certainty of the evidence (GRADE)
Clinical outcomes, lesions – per-protocol analyses follow up: median 2.9 years		⊕⊕⊕O MODERATE ⊕⊕⊕O MODERATE ⊕⊕⊕O MODERATE ⊕⊕OO LOW ⊕⊕OO LOW ⊕⊕OO LOW

GL= genital lesion; HPV= human papilloma virus; PIN= penile, perianal, or perineal intraepithelial neoplasia

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Summary of Findings: 4-valent HPV vaccine versus placebo in 16 to 26-year old males – clinical outcomes, infection – per-protocol analyses

Patients: **16 to 26-year old males (seronegative at baseline)**
Setting**: 71 sites in 18 countries from Africa, Australia, Europe, Latin America and North America.**
Comparison: **4-valent HPV vaccine (3-doses (Day 1, Month 2, Month 6)) versus placebo (3-doses (Day 1, Month 2, Month 6))**

Outcome	Plain language summary	Absolute effect		Relative effect (95% CI) Nº of participants & studies	Certainty of the evidence (GRADE)
		Placebo	4-valent HPV vaccine		
Persistent infection HPV 6, 11, 16 or 18 Follow-up: mean 2.9 years	There is moderate-quality evidence that 4-valent HPV vaccine reduces persistent HPV 6, 11, 16 or 18 infection in 16 to 26-year old males compared with placebo	101/2469 person years at risk	15/2549 person years at risk	Rate ratio 0.14 (0.08 to 0.25); 2790 participants in 1 study	⨁⨁⨁◯ MODERATE [1]
Persistent infection HPV 6 Follow-up: mean 2.9 years	There is moderate-quality evidence that 4-valent HPV vaccine reduces persistent HPV 6 infection in 16 to 26-year old males compared with placebo	33/2297 person years at risk	4/2230 person years at risk	Rate ratio 0.12 (0.04 to 0.34); 2477 participants in 1 study	⨁⨁⨁◯ MODERATE [1]
Persistent infection HPV 11 Follow-up: mean 2.9 years	There is moderate-quality evidence that 4-valent HPV vaccine reduces persistent HPV 11 infection in 16 to 26-year old males compared with placebo	15/2315 person years at risk	1/2323 person years at risk	Rate ratio 0.07 (0.01 to 0.50); 2477 participants in 1 study	⨁⨁⨁◯ MODERATE [1]
Persistent infection HPV 16 Follow-up: mean 2.9 years	There is moderate-quality evidence that 4-valent HPV vaccine reduces persistent HPV 16 infection in 16 to 26-year old males compared with placebo	41/2313 person years at risk	9/2382 person years at risk	Rate ratio 0.21 (0.10 to 0.44); 2554 participants in 1 study	⨁⨁⨁◯ MODERATE [1]
Persistent infection HPV 18 Follow-up: mean 2.9 years	There is moderate-quality evidence that 4-valent HPV vaccine reduces persistent HPV 18 infection in 16 to 26-year old males compared with placebo	25/2453 person years at risk	1/2462 person years at risk	Rate ratio 0.04 (0.01 to 0.29); 2674 participants in 1 study	⨁⨁⨁◯ MODERATE [1]

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

[1] Downgraded one level for imprecision: Very low event rate.

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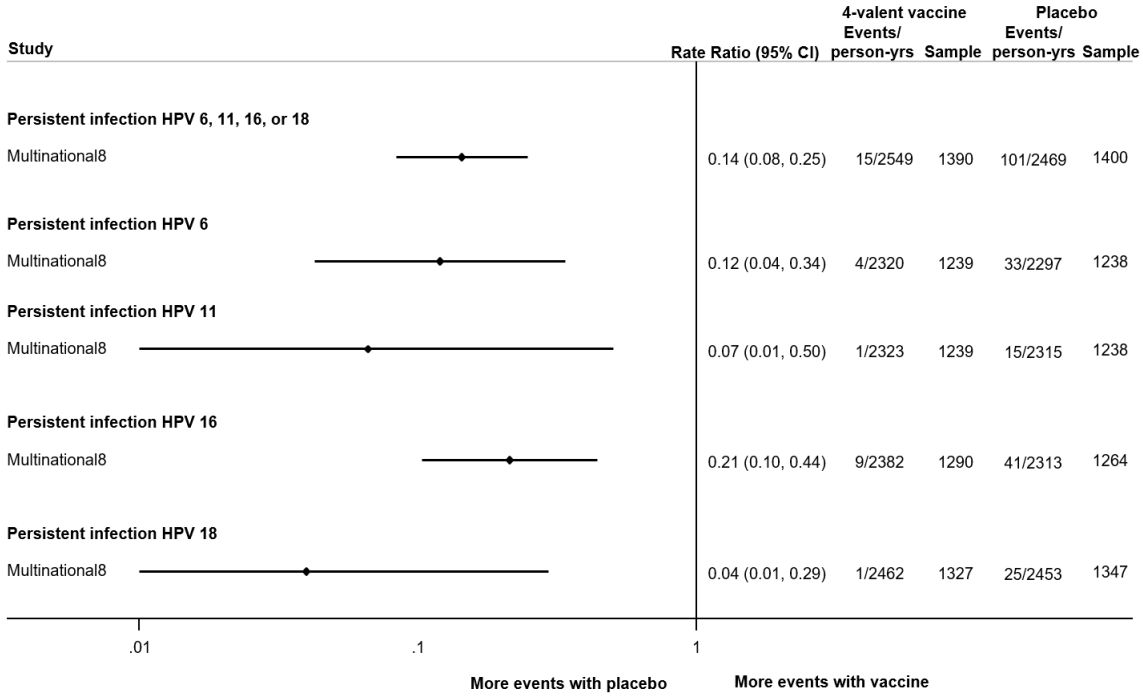
Forest plot: 4-valent HPV vaccine versus placebo in 16 to 26-year old males – clinical outcomes, infection – per-protocol analyses

Patients: **16 to 26-year old males (seronegative at baseline)**
Setting**: 71 sites in 18 countries from Africa, Australia, Europe, Latin America and North America.**
Comparison: **4-valent HPV vaccine (3-doses (Day 1, Month 2, Month 6)) versus placebo (3-doses (Day 1, Month 2, Month 6))**

Outcome	Forest plot	Certainty of the evidence (GRADE)
Clinical outcomes, infection – per-protocol analyses follow up: mean 2.9 years		⊕⊕⊕O MODERATE

CI= confidence interval; HPV= human papilloma virus

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Summary of Findings: 4-valent HPV vaccine versus placebo in 16 to 26-year old males – immunogenicity outcomes

Patients: **16 to 26-year old males (seronegative at baseline)**
Setting**: 71 sites in 18 countries from Africa, Australia, Europe, Latin America and North America.**
Comparison: **4-valent HPV vaccine (3-doses (Day 1, Month 2, Month 6)) versus placebo (3-doses (Day 1, Month 2, Month 6))**

Outcome		Plain language summary	Absolute effect		Relative effect Nº of participants & studies	Certainty of the evidence (GRADE)
			Placebo	4-valent HPV vaccine		
GMTs for HPV 6	7 months	There is moderate quality evidence that 4-valent vaccine increases GMTs for HPV 6 when compared with placebo at 7 and 36 months. There was a trend towards GMTs levelling off after reaching a peak at month 7.	7.0 mMU/mL	447.6 mMU/mL	Relative effect not estimable Data from 1 RCT enrolling 4,065 men	⊕⊕⊕O MODERATE [1]
	36 months		7.0 mMU/mL	71.5 mMU/mL		⊕⊕⊕O MODERATE [1]
GMTs for HPV 11	7 months	There is moderate quality evidence that 4-valent vaccine increases GMTs for HPV 11 when compared with placebo at 7 and 36 months. There was a trend towards GMTs levelling off after reaching a peak at month 7.	8.4 mMU/mL	624 mMU/mL		⊕⊕⊕O MODERATE [1]
	36 months		8.3 mMU/mL	82.6 mMU/mL		⊕⊕⊕O MODERATE [1]
GMTs for HPV 16	7 months	There is moderate quality evidence that 4-valent vaccine increases GMTs for HPV 16 when compared with placebo at 7 and 36 months. There was a trend towards GMTs levelling off after reaching a peak at month 7.	11.0 mMU/mL	2404.3 mMU/mL		⊕⊕⊕O MODERATE [1]
	36 months		10.8 mMU/mL	293.3 mMU/mL		⊕⊕⊕O MODERATE [1]
GMTs for HPV 18	7 months	There is moderate quality evidence that 4-valent vaccine increases GMTs for HPV 18 when compared with placebo at 7 and 36 months. There was a trend towards GMTs levelling off after reaching a peak at month 7.	9.7 mMU/mL	402.3 mMU/mL		⊕⊕⊕O MODERATE [1]
	36 months		9.6 mMU/mL	33.1 mMU/mL		⊕⊕⊕O MODERATE [1]
Seropositiity for HPV 6	7 months	We do not have data about the effect of 4-valent vaccine on seroconversion/seropositivity for HPV 6 in males when compared with placebo, as no placebo data were reported for this outcome. However, the seropositivity in the vaccine group was 98.9% and 88.9% at 7 and 36 months, respectively	Not reported	98.9%	Relative effect not estimable Data from 1 RCT enrolling 4,065 men	⊕⊕⊕O LOW [2]
	36 months		Not reported	88.9%		⊕⊕⊕O LOW [2]
Seropositivity for HPV 11	7 months	We do not have data about the effect of 4-valent vaccine on seroconversion/seropositivity for HPV 11 in males when compared with placebo, as no placebo data were reported for this outcome. However, the seropositivity in the vaccine group was 99.2% and 94.0% at 7 and 36 months, respectively	Not reported	99.2%		⊕⊕⊕O LOW [2]
	36 months		Not reported	94.0%		⊕⊕⊕O LOW [2]
Seropositivity for HPV 16	7 months	We do not have data about the effect of 4-valent vaccine on seroconversion/seropositivity for HPV 16 in males when compared with placebo, as no placebo data were reported for this outcome. However, the seropositivity in the vaccine group was 98.8% and 97.9% at 7 and 36 months, respectively	Not reported	98.8%		⊕⊕⊕O LOW [2]
	36 months		Not reported	97.9%		⊕⊕⊕O LOW [2]
Serocopositivity for HPV 18	7 months	We do not have data about the effect of 4-valent vaccine on seroconversion/seropositivity for HPV 18 in males when compared with placebo, as no placebo data were reported for this outcome. However, the seropositivity in the vaccine group was 97.4% and 57.0% at 7 and 36 months, respectively	Not reported	97.4%		⊕⊕⊕O LOW [2]
	36 months		Not reported	57.0%		⊕⊕⊕O LOW [2]

GMT= Geometric mean titre; HPV= human papilloma virus

[1] Downgraded one level for risk of bias: no 95% CIs reported in the paper for the placebo group [2] Downgraded two levels for risk of bias: no placebo group data reported in the paper for seropositivity

Forest plot: 4-valent HPV vaccine versus placebo in 16 to 26-year old males – immunogenicity outcomes

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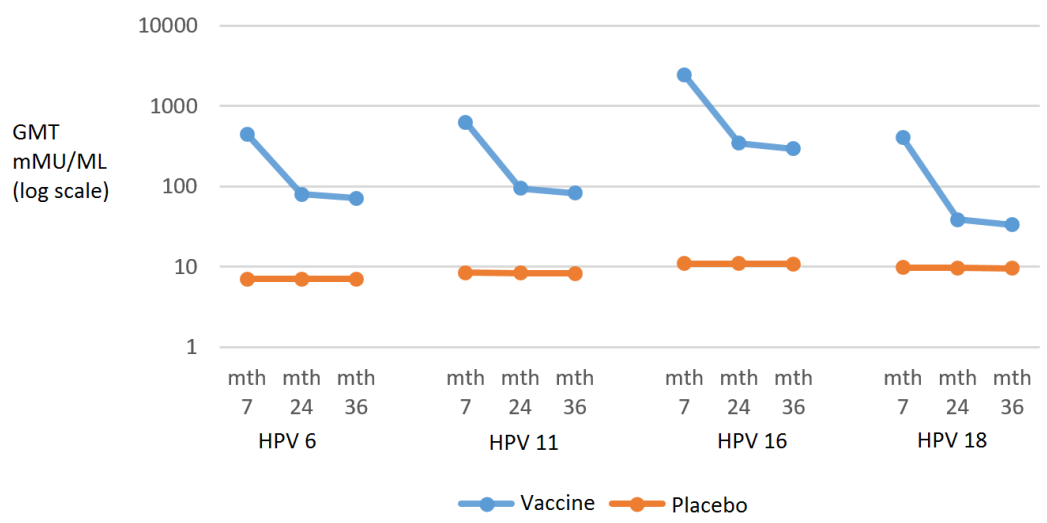
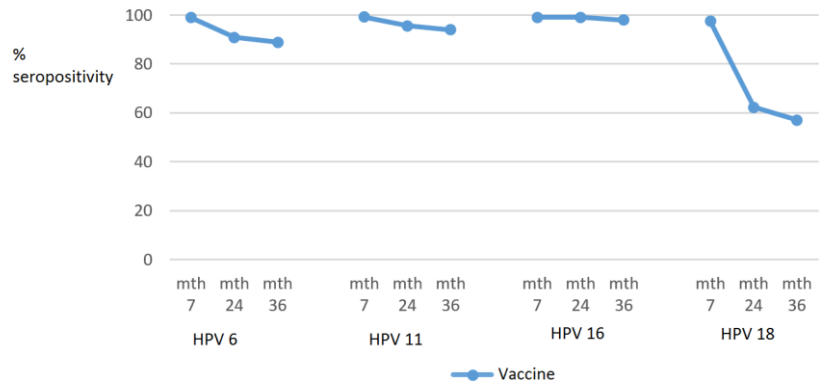
Patients: 16 to 26-year old males (seronegative at baseline)
Setting: 71 sites in 18 countries from Africa, Australia, Europe, Latin America and North America.
Comparison: 4-valent HPV vaccine (3-doses (Day 1, Month 2, Month 6)) versus placebo (3-doses (Day 1, Month 2, Month 6))

Outcome	Graph	Certainty of the evidence (GRADE)
GMT for HPV 6, 11, 16, 18 at 7 months, 24 months and 36 months	 Multinational8	⊕⊕⊕O MODERATE
Seropositivity for HPV 6, 11, 16, 18 at 7 months, 24 months and 36 months	 Multinational8	⊕⊕⊕O LOW

Analyses not performed as no 95% CIs were reported for the placebo group for these GMTs, and no placebo group data reported for seropositivity.

References

Multinational8

Giuliano AR, Palefsky JM, Goldstone S et al. Efficacy of quadrivalent HPV vaccine against HPV Infection and disease in males. N Engl J Med. 2011 Feb 3;364(5):401-11. doi: 10.1056/NEJMoa0909537.

Hillman RJ, Giuliano AR, Palefsky JM et al. Immunogenicity of the quadrivalent human papillomavirus (type 6/11/16/18) vaccine in males 16 to 26 years old. Clinical and vaccine immunology. 2012;CVI-05208.

Finland1

Petaja T, Keranen H, Karppa T et al. Immunogenicity and safety of human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine in healthy boys aged 10-18 years. J Adolesc Health. 2009;44(1):33-40.

HPV vaccines in males versus HPV vaccines in females

Contents

Trusted evidence.
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Key findings

2-valent HPV vaccine in males versus in females (12 to 15)

- In males and females aged 12 to 15 years receiving the 2-valent vaccine, there were higher GMTs for HPV 16 in males than in females at 7 months, although at 42 months the effect was not significant but non-inferior. GMTs for HPV 18 were non-inferior in males at 7 and 42 months. For the outcome of seropositivity for HPV 16 and 18, there was no significant difference between groups at 7 and 42 months (low-quality evidence).

4-valent HPV vaccine in males versus in females (9 to 15)

- In males and females aged 9 to 15 years receiving the 4-valent vaccine, there was no significant difference in persistent infection and disease, related to HPV 6, 11, 16 or 18 at 96 months between males and females (very low-quality evidence).
- There was no significant difference in GMTs for HPV 6 and HPV 11 between males and females at 7 months (non-inferior), and with time, this effect gradually moved towards slightly higher GMTs in females at 96 months. For HPV 16 and 18 the GMTs were higher in males in one study but again the effect gradually moved towards females at 96 months (moderate and low quality evidence).
- There was no significant difference between males and females for seropositivity HPV 6, 11, 16 and 18 (moderate quality evidence).

9-valent HPV vaccine in males versus in females (9 to 15)

Three doses

- In males and females aged 9 to 15 years receiving three doses of the 9-valent vaccine, at 7 months, GMTs for all 9 HPV subtypes covered by the 9-valent vaccine were higher in males than in females (moderate-quality evidence), and at 36 months males also had higher GMTs than females, (not all significant results but all non-inferior) except for HPV 52 (low-quality evidence).
- There was no significant difference between males and females for seropositivity to all 9 HPV subtypes covered by the 9-valent vaccine at 7 months (moderate-quality evidence) and 36 months (low-quality evidence).

Two doses

- In males and females aged 9 to 15 years receiving two doses of the 9-valent vaccine, there was no significant difference between males and females for seropositivity for all 9 HPV subtypes covered by the 9-valent vaccine at 7 months (moderate-quality evidence).

9-valent HPV vaccine in males versus in females (16 to 26)

- In males and females aged 9 to 15 years receiving the three doses of the 9-valent vaccine, there was no significant difference between males and females for GMTs (non-inferior) and seropositivity for all 9 HPV subtypes covered by the 9-valent vaccine at 7 months (moderate-quality evidence).

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 analyze evidence for the protection afforded by prophylactic HPV vaccines in males compared with females.

Objectives

To evaluate the efficacy and immunogenicity of HPV vaccines in males compared with females.

Search methods

Searches were conducted from January 2006 to June 2016, and all relevant studies regardless of language or publication status were searched. 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) with a non-random comparison of HPV vaccine in males versus HPV vaccine in females, or non-randomised studies for the same comparison, were eligible for inclusion. Data for men who have sex with men are reported in a separate Target Update.

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, and risk ratios were calculated for other binary outcomes. 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. The non-inferiority threshold for males was 0.5 for the ratio of GMTs.

Main Results

We found one cluster randomised RCT (non-randomised comparison for males versus females) assessing 2-valent HPV vaccine in 12 to 15-year old males versus in females (Finland2); two RCTs (non-randomised comparisons for males versus females) assessing 4-valent vaccine in 9 to 15-year old males versus in females (Multinational7; China1); two non-randomised studies assessing 9-valent HPV vaccine in 9 to 15-year old males versus in females, one assessing three doses (Multinational5) and one assessing two doses (Multinational3); and one non-randomised study assessing 9-valent vaccine in 16 to 26-year old males versus in females (Multinational6). The quality of evidence for all outcomes was downgraded by one level for non-random comparisons between males and females. The loss to follow-up at longer time points was high in some studies. Some studies did not blind outcome assessment or blinding was unclear; however, we did not downgrade the quality of evidence as most outcomes are objectively assessed (immunogenicity). Most outcomes were reported in per protocol analyses, where all participants were seronegative at baseline.

2-valent HPV vaccine in males versus in females (12 to 15)

There was low-quality evidence of higher GMTs for HPV 16 in vaccinated males than in females at 7 months; at 42 months the effect was not significant but non-inferior. GMTs for HPV 18 were non-inferior in males at 7 and 42 months. For the outcome of seropositivity for HPV 16 and 18, there was low-quality evidence of no significant difference between groups at 7 and 42 months (Finland2).

4-valent HPV vaccine in males versus in females (9 to 15)

There was very low-quality evidence of no significant difference in persistent infection and disease, related to HPV 6, 11, 16 or 18, with 4-valent HPV vaccine, between males and females at 96 months. However, the number of events were low and confidence intervals are wide, and results are uncertain (Multinational7). There was low-quality evidence of no significant difference in GMTs for HPV 6 and HPV 11 between vaccinated males and females at 7 months (non-inferior in all but one study at 7 months), and with time, this effect gradually moved towards slightly higher GMTs in females at 96 months (Multinational7; China1). For HPV 16 and 18 there was low and moderate-quality evidence of higher GMTs in males in one study (Multinational7), but again the effect gradually moved towards females at 96 months.

With regard to seropositivity, there was moderate-quality evidence of no significant difference between males and females for HPV 6, 11, 16 and 18.

9-valent HPV vaccine in males versus in females (9 to 15)

Three doses

For the outcome of GMTs for all 9 HPV subtypes covered by the 9-valent vaccine, the evidence was moderate quality at 7 months and low quality at 36 months. At 7 months GMTs were higher in the males than females, and at 36 months males also had higher GMTs (not all significant results but all non-inferior) except for HPV 52 (also non-inferior). There was moderate-quality evidence at 7 months and low-quality evidence at 36 months of no significant difference between males and females for seropositivity to all 9 HPV subtypes covered by the 9-valent vaccine.

Two doses

There was moderate-quality evidence at 7 months of no significant difference between males and females for seropositivity for all 9 HPV subtypes covered by the 9-valent vaccine.

9-valent HPV vaccine in males versus in females (16 to 26)

There was moderate-quality evidence at 7 months of higher GMTs in males than in females, and of no significant difference between males and females for seropositivity for all 9 HPV subtypes covered by the 9-valent vaccine.

Implications and conclusions

There were limited clinical data reported for this comparison, which is as expected for these immune-bridging studies. For all vaccine types males tended to have higher GMTs at 7 months (all non-inferior), and there was a trend towards favouring females with time; however, this trend may plateau. For all vaccines there appeared to be no significant difference in seropositivity between males and females at 7 months, which persisted with time. For the 9-valent vaccine, these results were consistent when assessed in different age groups, and whether 2 or 3 doses were given.

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Summary of Findings: 2-valent HPV vaccine in 12 to 15-year old males versus 2-valent HPV vaccine in 12 to 15-year old females – immunogenicity outcomes [3]

Population: **12 to 15-year old males and females (seronegative at baseline)**
Setting: **Finland**
Comparison: **2-valent HPV vaccine 3-doses (Day 1, Month 1, Month 6) in males versus 2-valent HPV vaccine 3-doses (Day 1, Month 1, Month 6) in females**

Outcome		Plain language summary	Absolute effect		Relative effect (95% CI) Nº of participants & studies	Certainty of the evidence (GRADE)
			Females	Males		
GMTs for HPV 16	follow up: 7 months	There is low-quality evidence of higher GMTs for HPV 16 in vaccinated males than in females at 7 months. At 42 months, this effect was not significant but non-inferior.	Mean: 21327.2 EL.U/mL	Mean: 23959.1 EL.U/mL	Ratio 1.12 (1.03 to 1.22) 957 participants in 1 RCT	⊕⊕OO LOW [1]
	follow up: 42 months		Mean: 2609.6 EL.U/mL	Mean: 2759.5 EL.U/mL	Ratio 1.06 (0.92 to 1.22 436 participants in 1 RCT	
GMTs for HPV 18	follow up: 7 months	There is low-quality evidence of no significant difference (non-inferiority) in GMTs for HPV 18 between vaccinated males and females.	Mean: 8227.3 EL.U/mL	Mean: 8583.9 EL.U/mL	Ratio 1.04 (0.96 to 1.14) 961 participants in 1 RCT	⊕⊕OO LOW [1]
	follow up: 42 months		Mean: 890 EL.U/mL	Mean: 837.7 EL.U/mL	Ratio 0.94 (0.80 to 1.10) 440 participants in 1 RCT	
Seropositivity for HPV 16	follow up: 7 months	There is low-quality evidence of no significant difference in seropositivity for HPV 16 with 2-valent HPV vaccine between males and females.	1163/1163 (100%)	536/536 (100%)	Not estimable* 1699 participants in 1 RCT	⊕⊕OO LOW [1]
	follow up: 42 months		688/688 (100%)	217/217 (100%)	Not estimable* 905 participants in 1 RCT	
Seropositivity for HPV 18	follow up: 7 months	There is low-quality evidence of no significant difference in seropositivity for HPV 18 with 2-valent HPV vaccine between males and females.	1160/1160 (100%)	535/535 (100%)	Not estimable* 1695 participants in 1 RCT	⊕⊕OO LOW [1]
	follow up: 42 months		685/686 (99.9%)	217/217 (100%)	RR 1.00 (0.99 to 1.01) 903 participants in 1 RCT	

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

*Excluded from analysis due to no non-events; all seropositive participants.

[1]Downgraded two levels for risk of bias: non-randomised comparison (males versus females), high loss to follow up.

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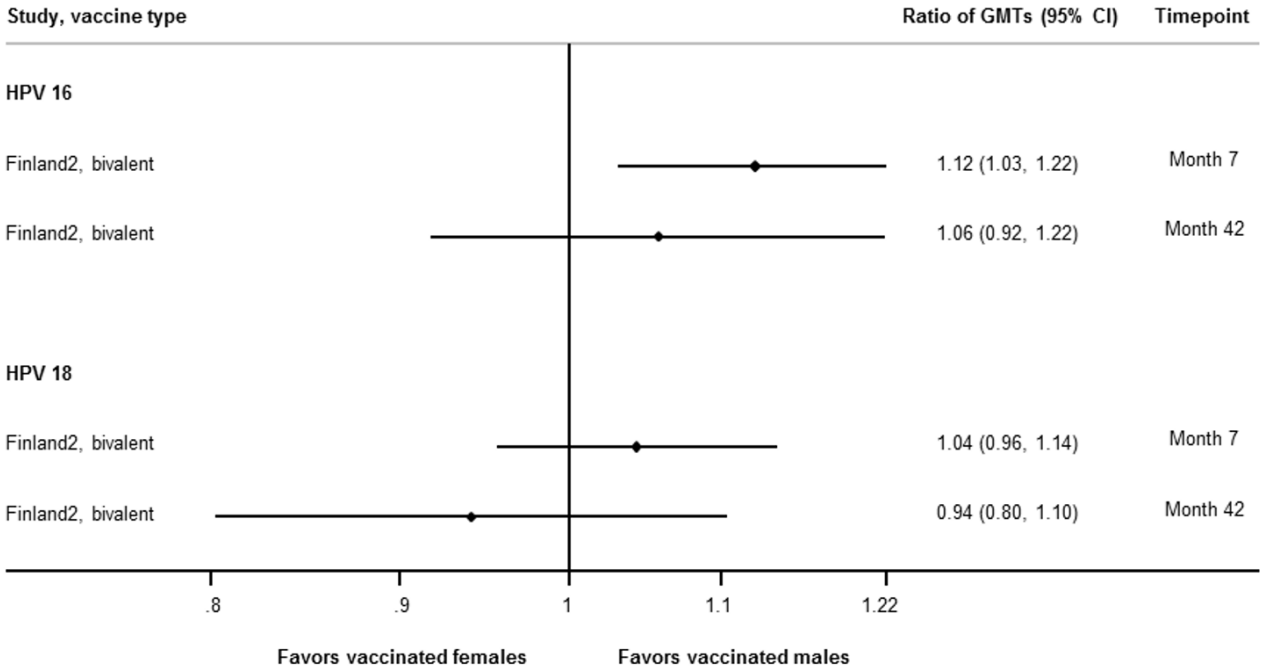
Forest plot: 2-valent HPV vaccine in 12 to 15-year old males versus 2-valent HPV vaccine in 12 to 15-year old females – immunogenicity outcomes [4]

Population: **12 to 15-year old males and females (seronegative at baseline)**
Setting: **Finland**
Comparison: **2-valent HPV vaccine (3-doses (Day 1, Month 1, Month 6)) in males versus 2-valent HPV vaccine (3-doses (Day 1, Month 1, Month 6)) in females**

Outcome	Forest plot	Certainty of the evidence (GRADE)
Ratio of GMTs follow up: 7-42 months		⊕⊕OO LOW [1]

No forest plot for seropositivity outcomes: 100% seropositivity in all but one group, as indicated in the Summary of Findings table above

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Summary of Findings: 4-valent HPV vaccine in 9 to 15-year old males versus 4-valent HPV vaccine in 9 to 15-year old females – clinical outcomes [5]

Population: **9 to 15-year old males and females* (seronegative at baseline)**
Setting: **10 countries in North America, Latin America, Europe and Asia.**
Comparison: **4-valent HPV vaccine (3-doses (Day 1, Month 2, Month 6)) in males versus 4-valent HPV vaccine (3-doses (Day 1, Month 2, Month 6)) in females**

Outcome	Plain language summary	Absolute effect		Relative effect (95% CI) Nº of participants & studies	Certainty of the evidence (GRADE)
		Females	Males		
Persistent infection (HPV 6, 11, 16 or 18 related) follow up: 96 months Setting: Multinational	There is very low-quality evidence of no significant difference in persistent infection with 4-valent HPV vaccine between males and females.	3 per 1000 person/years	4 per 1000 person/years	Rate ratio 1.33 (0.19 to 9.47) 1167 participants in 1 RCT	⨁⨁⨁◯ VERY LOW [1,2]
Persistent infection (HPV 6, 11, 16 or 18 related) or disease follow up: 96 months Setting: Multinational	There is very low-quality evidence of no significant difference in persistent infection or disease with 4-valent HPV vaccine between males and females.	3 per 1000 person/years	4 per 1000 person/years	Rate ratio 1.33 (0.19 to 9.47) 1167 participants in 1 RCT	⨁⨁⨁◯ VERY LOW [1,2]

CI= confidence interval; HPV= human papilloma virus

*Sometimes reported as 9 to 16-year olds in references.

[1]Downgraded two levels for risk of bias: non-random comparison and high loss to follow up.

[2]Downgraded two levels for imprecision: Very low event rate.

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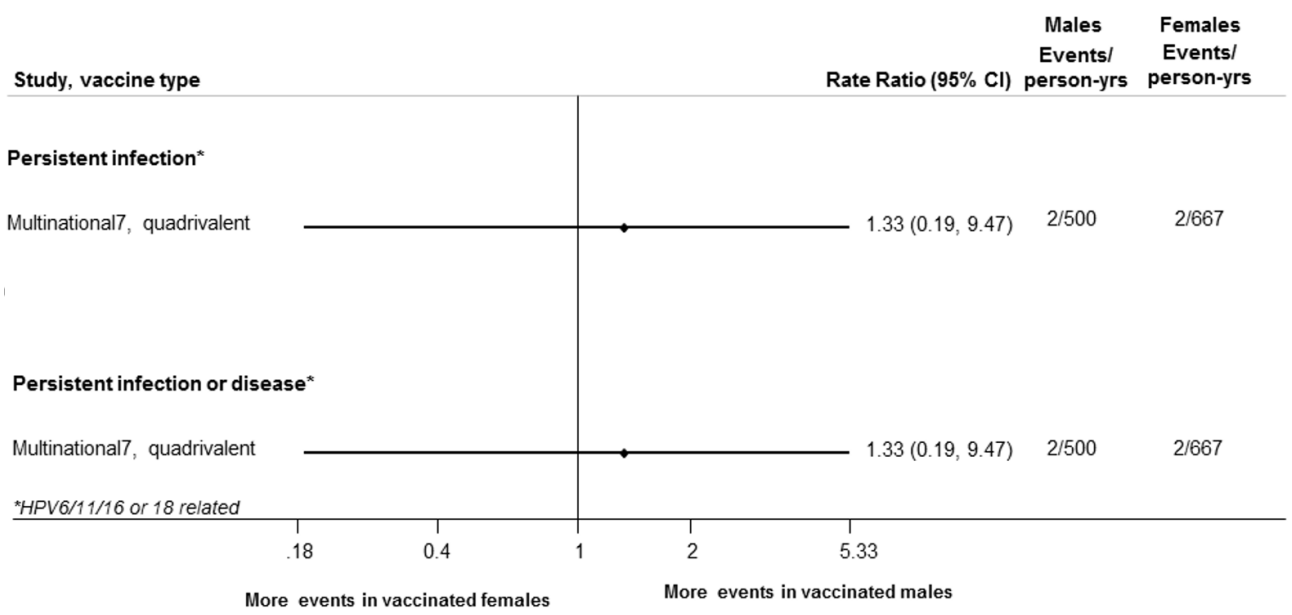
Forest plot: 4-valent HPV vaccine in 9 to 15-year old males versus 4-valent HPV vaccine in 9 to 15-year old females – clinical outcomes

Population: **9 to 15-year old males and females* (mixed at baseline; intention-to-treat population)**
Setting: **10 countries in North America, Latin America, Europe and Asia.**
Comparison: **4-valent HPV vaccine 3-doses (Day 1, Month 2, Month 6) in males versus 4-valent HPV vaccine 3-doses (Day 1, Month 2, Month 6) in females**

Outcome	Forest plot	Certainty of the evidence (GRADE)
Persistent infection and disease follow up: 96 months		⊕⊕⊕O VERY LOW ⊕⊕⊕O VERY LOW

*Sometimes reported as 9 to 16-year olds in references.

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Summary of Findings: 4-valent HPV vaccine in 9 to 15-year old males versus 4-valent HPV vaccine in 9 to 15-year old females – immunogenicity outcomes [7]

Population: **9 to 15-year old males and females***
Setting: **China, and 10 countries in North America, Latin America, Europe and Asia.**
Comparison: **4-valent HPV vaccine 3-doses (Day 1, Month 1 or 2, Month 6) in males versus 4-valent HPV vaccine 3-doses (Day 1, Month 1 or 2, Month 6) in females**

Outcome			Plain language summary	Absolute effect		Relative effect (95% CI) Nº of participants & studies	Certainty of the evidence (GRADE)
				Females	Males		
GMTs for HPV 6	7 months	Setting: China	There is low-quality evidence of no significant difference in GMTs for HPV 6 between vaccinated males and females at 7 months (non-inferior in one study; inconclusive in the other). With time, this effect gradually moved towards slightly higher GMTs in females at 96 months.	744 mMU/mL	580 mMU/mL	Ratio 0.78 (0.46 to 1.33) 94 participants in 1 RCT	⊕⊕OO LOW [1,2]
		Setting: Multinational		893.9 mMU/mL	962.7 mMU/mL	Ratio 1.08 (0.95 to 1.23) 957 participants in 1 RCT	
	96 months**	Setting: Multinational		77.7 mMU/mL	63.2 mMU/mL	Ratio 0.81 (0.66 to 1.00) 439 participants in 1 RCT	⊕⊕OO LOW [1,3]
GMTs for HPV 11	7 months	Setting: China	There is low-quality evidence of no significant difference (non-inferior) in GMTs for HPV 11 between vaccinated males and females at 7 months. With time, this effect gradually moved towards slightly higher GMTs in females at 96 months.	1225 mMU/mL	1040 mMU/mL	Ratio 0.85 (0.58 to 1.25) 94 participants in 1 RCT	⊕⊕OO LOW [1,2]
		Setting: Multinational		1356.8 mMU/mL	1370.8 mMU/mL	Ratio 1.01 (0.89 to 1.15) 958 participants in 1 RCT	
	96 months**	Setting: Multinational		72.7 mMU/mL	61.7 mMU/mL	Ratio 0.85 (0.67 to 1.08) 439 participants in 1 RCT	⊕⊕OO LOW [1,3]
GMTs for HPV 16	7 months	Setting: China	There is low-quality evidence of slightly higher GMTs for HPV 16 in vaccinated males than in females at 7 months, and with time this effect gradually started moving towards slightly higher GMTs in females until 96 months.	4410 mMU/mL	4032 mMU/mL	Ratio 0.91 (0.55 to 1.52) 96 participants in 1 RCT	⊕⊕OO LOW [1,2]
		Setting: Multinational		4992.2 mMU/mL	6091 mMU/mL	Ratio 1.22 (1.05 to 1.42) 957 participants in 1 RCT	
	96 months**	Setting: Multinational		353 mMU/mL	293.6 mMU/mL	Ratio 0.83 (0.65 to 1.07) 436 participants in 1 RCT	⊕⊕OO LOW [1,3]
GMTs for HPV 18	7 months	Setting: China	There is moderate-quality evidence of slightly higher GMTs for HPV 18 in vaccinated males than females at 7 months, and with time this effect gradually diminished until 96 months (low-quality evidence).	1263 mMU/mL	1365 mMU/mL	Ratio 1.08 (0.71 to 1.64) 96 participants in 1 RCT	⊕⊕⊕O MODERATE [1]
		Setting: Multinational		1130.8 mMU/mL	1470.7 mMU/mL	Ratio 1.30 (1.11 to 1.52) 961 participants in 1 RCT	
	96 months**	Setting: Multinational		41.8 mMU/mL	42.8 mMU/mL	Ratio 1.02 (0.77 to 1.35) 440 participants in 1 RCT	⊕⊕OO LOW [1,3]

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Outcome	Plain language summary	Absolute effect		Relative effect (95% CI) Nº of participants & studies	Certainty of the evidence (GRADE)
		Females	Males		
Seropositivity for HPV 6 follow up: 18 months Setting: Multinational	There is moderate-quality evidence of no significant difference in seropositivity for HPV 6 with 4-valent HPV vaccine between males and females.	471/481 (97.9%)	439/449 (97.8%)	RR 1.00 (0.98 to 1.02) 930 participants in 1 RCT	⊕⊕⊕O MODERATE [1]
Seropositivity for HPV 11 follow up: 18 months Setting: Multinational	There is moderate-quality evidence of no significant difference in seropositivity for HPV 11 with 4-valent HPV vaccine between males and females.	477/481 (99.2%)	447/450 (99.3%)	RR 1.00 (0.99 to 1.01) 931 participants in 1 RCT	⊕⊕⊕O MODERATE [1]
Seropositivity for HPV 16 follow up: 18 months Setting: Multinational	There is moderate-quality evidence of no significant difference in seropositivity for HPV 16 with 4-valent HPV vaccine between males and females.	477/478 (93.5%)	445/448 (99.3%)	RR 1.00 (0.99 to 1.00) 926 participants in 1 RCT	⊕⊕⊕O MODERATE [1]
Seropositivity for HPV 18 follow up: 18 months Setting: Multinational	There is moderate-quality evidence of no significant difference in seropositivity for HPV 18 with 4-valent HPV vaccine between males and females.	442/483 (91.5%)	417/451 (92.5%)	RR 1.00 (0.91 to 1.09) 934 participants in 1 RCT	⊕⊕⊕O MODERATE [1]

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

*Sometimes reported as 9 to 16-year olds in references.

**Data also available for 18, 42 and 60 months, see forest plot below.

[1] Downgraded one level for risk of bias: non-random comparison.

[2] Downgraded one level for inconsistency: heterogeneity between the two studies at 7 months.

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

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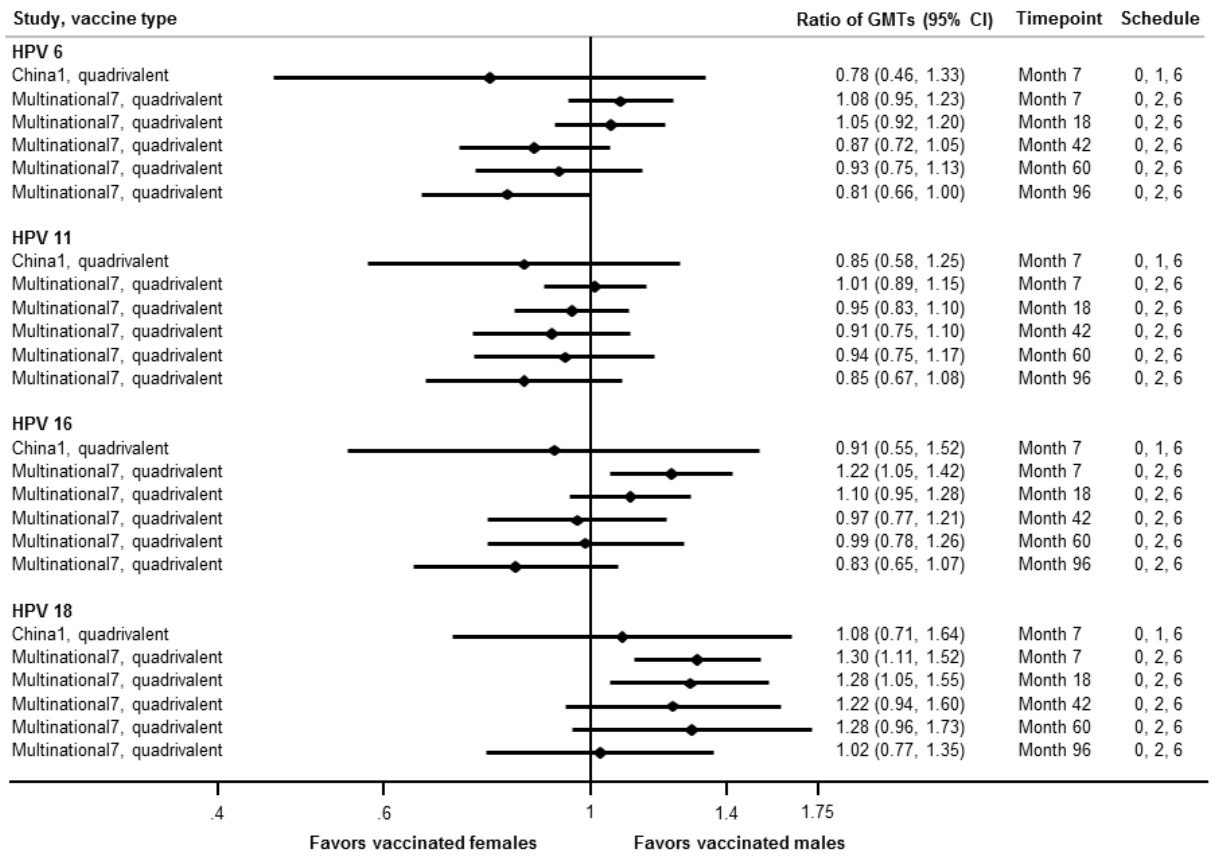
Forest plots: 4-valent HPV vaccine in 9 to 15-year old males versus 4-valent HPV vaccine in 9 to 15-year old females – immunogenicity outcomes

Population: 9 to 15-year old males and females*
***Setting*:** China, Multinational.
Comparison: 4-valent HPV vaccine 3-doses (Day 1, Month 1 or 2, Month 6) in males versus 4-valent HPV vaccine 3-doses (Day 1, Month 1 or 2, Month 6) in females

Outcome	Forest plot	Certainty of the evidence (GRADE)
GMTs follow up: 7-96 months		⊕⊕OO LOW ⊕⊕OO LOW ⊕⊕OO LOW ⊕⊕OO LOW ⊕⊕OO LOW ⊕⊕⊕O MODERATE ⊕⊕OO LOW

Plots continued overleaf

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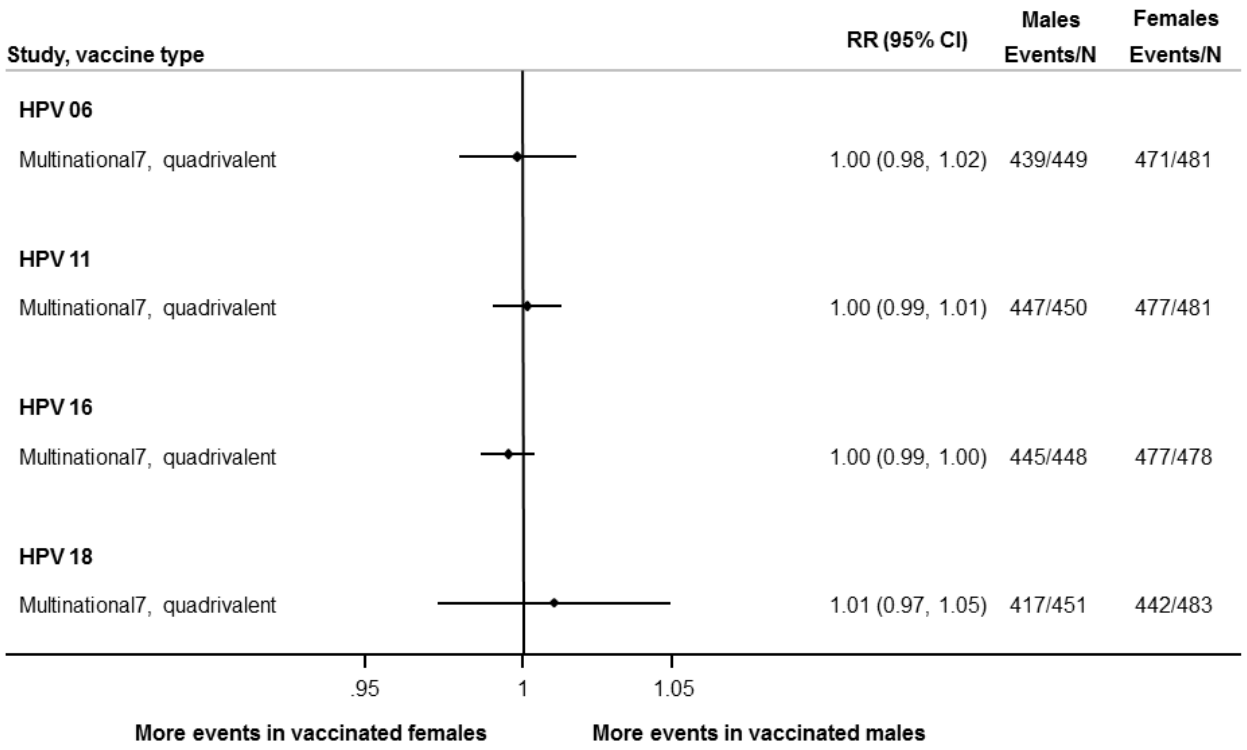
Outcome	Forest plot	Certainty of the evidence (GRADE)
Seropositivity follow up: 18 months		⊕⊕⊕O MODERATE ⊕⊕⊕O MODERATE ⊕⊕⊕O MODERATE ⊕⊕⊕O MODERATE

*Sometimes reported as 9 to 16-year olds in references

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Summary of Findings: 9-valent HPV vaccine in 9 to 15-year old males versus 9-valent HPV vaccine in 9 to 15-year old females – immunogenicity outcomes (3 doses)

Population: **9 to 15-year old males and females (seronegative at baseline)**
***Setting*: Austria, Belgium, Brazil, Canada, Chile, Colombia, Costa Rica, Czech Republic, Denmark, Finland, India, Israel, Malaysia, Norway, Peru, Poland, South Africa, South Korea, Spain, Sweden, Taiwan, Thailand, Turkey and the United States**
Comparison: **9-valent HPV vaccine (3-doses (Day 1, Month 2, Month 6)) in males versus 9-valent HPV vaccine (3-doses (Day 1, Month 2, Month 6)) in females**

Outcome		Plain language summary	Absolute effect		Relative effect (95% CI) Nº of participants & studies	Certainty of the evidence (GRADE)
			Females	Males		
GMTs for HPV 6	7 mths	There is moderate-quality evidence of higher GMTs for HPV 6 in males compared with females at 7 months. At 36 months the effect was not significant but non-inferior (low-quality)	1712.0 mMU/mL	2084.7 mMU/mL	Ratio 1.22 (1.12 to 1.32); 2156 participants in 1 study	⊕⊕⊕O MODERATE [1] ⊕⊕OO LOW [1,2]
	36 mths*		252.8 mMU/mL	262.7 mMU/mL	Ratio 1.04 (0.92 to 1.17); 864 participants in 1 study	
GMTs for HPV 11	7 mths	There is moderate-quality evidence of higher GMTs for HPV 11 in males compared with females at 7 months. At 36 months the effect was not significant but non-inferior (low-quality)	1278.7 mMU/mL	1487.1 mMU/mL	Ratio 1.16 (1.07 to 1.26); 2156 participants in 1 study	⊕⊕⊕O MODERATE [1] ⊕⊕OO LOW [1,2]
	36 mths*		145.8 mMU/mL	156.6 mMU/mL	Ratio 1.07 (0.94 to 1.23); 874 participants in 1 study	
GMTs for HPV 16	7 mths	There is moderate-quality evidence of higher GMTs for HPV 16 in males compared with females at 7 months. At 36 months the effect was not significant but non-inferior (low-quality)	7071.6 mMU/mL	8628.9 mMU/mL	Ratio 1.22 (1.13 to 1.32); 2196 participants in 1 study	⊕⊕⊕O MODERATE [1] ⊕⊕OO LOW [1,2]
	36 mths*		857.4 mMU/mL	944.1 mMU/mL	Ratio 1.10 (0.96 to 1.26); 888 participants in 1 study	
GMTs for HPV 18	7 mths	There is moderate-quality (7 months) and low-quality (36 months) evidence of higher GMTs for HPV 18 in males compared with females	2081.2 mMU/mL	2822.8 mMU/mL	Ratio 1.36 (1.24 to 1.49); 2208 participants in 1 study	⊕⊕⊕O MODERATE [1] ⊕⊕OO LOW [1,2]
	36 mths*		167.8 mMU/mL	244.2 mMU/mL	Ratio 1.46 (1.24 to 1.71); 888 participants in 1 study	
GMTs for HPV 31	7 mths	There is moderate-quality evidence of higher GMTs for HPV 31 in males compared with females at 7 months. At 36 months the effect was not significant but non-inferior (low-quality)	1879.3 mMU/mL	2221.2 mMU/mL	Ratio 1.18 (1.08 to 1.29); 2181 participants in 1 study	⊕⊕⊕O MODERATE [1] ⊕⊕OO LOW [1,2]
	36 mths*		216.6 mMU/mL	246.3 mMU/mL	Ratio 1.14 (0.98 to 1.33); 881 participants in 1 study	
GMTs for HPV 33	7 mths	There is moderate-quality (7 months) and low-quality (36 months) evidence of higher GMTs for HPV 33 in males compared with females	944.1 mMU/mL	1198.7 mMU/mL	Ratio 1.27 (1.17 to 1.38); 2204 participants in 1 study	⊕⊕⊕O MODERATE [1] ⊕⊕OO LOW [1,2]
	36 mths*		94.1 mMU/mL	120.8 mMU/mL	Ratio 1.28 (1.11 to 1.48); 883 participants in 1 study	
GMTs for HPV 45	7 mths	There is moderate-quality (7 months) and low-quality (36 months) evidence of higher GMTs for HPV 45 in males compared with females	737.1 mMU/mL	907.0 mMU/mL	Ratio 1.23 (1.11 to 1.37); 2217 participants in 1 study	⊕⊕⊕O MODERATE [1] ⊕⊕OO LOW [1,2]
	36 mths*		64.7 mMU/mL	76.7 mMU/mL	Ratio 1.19 (0.99 to 1.42); 892 participants in 1 study	
GMTs for HPV 52	7 mths	There is moderate-quality evidence of higher GMTs for HPV 52 in males compared with females at 7 months. At 36 months the difference was not significant but non-inferior (low-quality)	970.5 mMU/mL	1037.8 mMU/mL	Ratio 1.07 (0.98 to 1.17); 2210 participants in 1 study	⊕⊕⊕O MODERATE [1] ⊕⊕OO LOW [1,2]
	36 mths*		109.6 mMU/mL	104.9 mMU/mL	Ratio 0.96 (0.83 to 1.10); 891 participants in 1 study	
GMTs for HPV 58	7 mths	There is moderate-quality (7 months) and low-quality (36 months) evidence of higher GMTs for HPV 58 in males compared with females	1277.7 mMU/mL	1567.7 mMU/mL	Ratio 1.23 (1.13 to 1.33); 2196 participants in 1 study	⊕⊕⊕O MODERATE [1] ⊕⊕OO LOW [1,2]
	36 mths*		147.4 mMU/mL	170.9 mMU/mL	Ratio 1.16 (1.00 to 1.34); 887 participants in 1 study	

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Outcome		Plain language summary	Absolute effect		Relative effect (95% CI) Nº of participants & studies	Certainty of the evidence (GRADE)
			Females	Males		
Seropositivity for HPV 6	7mths	There is moderate-quality (7mths) and low-quality (36mths) evidence of no significant difference in seropositivity for HPV 6 in males compared with females	1591/1597 (99.6%)	558/559 (99.8%)	RR 1.00 (0.99 to 1.01); 2156 participants in 1 study	⊕⊕⊕O MODERATE[1]
	36 mths*		401/407 (98.5%)	451/457 (98.7%)	RR 1.00 (1.00 to 1.01); 864 participants in 1 study	⊕⊕OO LOW[1,2]
Seropositivity for HPV 11	7 mths	There is moderate-quality (7mths) and low-quality (36mths) evidence of no significant difference in seropositivity for HPV 11 in males compared with females	1595/1597 (99.9%)	559/559 (100%)	RR 1.00 (1.00 to 1.00); 2156 participants in 1 study	⊕⊕⊕O MODERATE[1]
	36 mths*		408/411 (99.3%)	455/463 (98.3%)	RR 0.99 (0.98 to 1.00); 874 participants in 1 study	⊕⊕OO LOW[1,2]
Seropositivity for HPV 16	7 mths	There is moderate-quality (7mths) and low-quality (36mths) evidence of no significant difference in seropositivity for HPV 16 in males compared with females	1625/1627 (99.9%)	569/569 (100%)	RR 1.00 (1.00 to 1.00); 2196 participants in 1 study	⊕⊕⊕O MODERATE[1]
	36 mths*		415/416 (99.8%)	470/472 (99.6%)	RR 1.00 (0.99 to 1.01); 888 participants in 1 study	⊕⊕OO LOW[1,2]
Seropositivity for HPV 18	7 mths	There is moderate-quality (7mths) and low-quality (36mths) evidence of no significant difference in seropositivity for HPV 18 in males compared with females	1638/1641 (99.8%)	567/567 (100%)	RR 1.00 (1.00 to 1.00); 2208 participants in 1 study	⊕⊕⊕O MODERATE[1]
	36 mths*		395/418 (94.5%)	454/470 (96.6%)	RR 1.02 (0.99 to 1.05); 888 participants in 1 study	⊕⊕OO LOW[1,2]
Seropositivity for HPV 31	7 mths	There is moderate-quality (7mths) and low-quality (36mths) evidence of no significant difference in seropositivity for HPV 31 in males compared with females	1615/1617 (99.9%)	564/564 (100%)	RR 1.00 (1.00, 1.00); 2181 participants in 1 study	⊕⊕⊕O MODERATE[1]
	36 mths*		411/414 (99.3%)	460/467 (98.5%)	RR 0.99 (0.98, 1.01); 881 participants in 1 study	⊕⊕OO LOW[1,2]
Seropositivity for HPV 33	7 mths	There is moderate-quality (7mths) and low-quality (36mths) evidence of no significant difference in seropositivity for HPV 33 in males compared with females	1635/1637 (99.9%)	567/567 (100%)	RR 1.00 (1.00, 1.00); 2204 participants in 1 study	⊕⊕⊕O MODERATE[1]
	36 mths*		406/412 (98.5%)	465/471 (98.7%)	RR 1.00 (0.99, 1.02); 883 participants in 1 study	⊕⊕OO LOW[1,2]
Seropositivity for HPV 45	7 mths	There is moderate-quality (7mths) and low-quality (36mths) evidence of no significant difference in seropositivity for HPV 45 in males compared with females	1644/1647 (99.8%)	570/570 (100%)	RR 1.00 (1.00, 1.00); 2217 participants in 1 study	⊕⊕⊕O MODERATE[1]
	36 mths*		393/419 (93.8%)	440/473 (93.0%)	RR 0.99 (0.96, 1.03); 892 participants in 1 study	⊕⊕OO LOW[1,2]
Seropositivity for HPV 52	7 mths	There is moderate-quality (7mths) and low-quality (36mths) evidence of no significant difference in seropositivity for HPV 52 in males compared with females	1640/1642 (99.9%)	568/568 (100%)	RR 1.00 (1.00, 1.00); 2210 participants in 1 study	⊕⊕⊕O MODERATE[1]
	36 mths*		415/419 (99.0%)	462/472 (97.9%)	RR 0.99 (0.97, 1.00); 891 participants in 1 study	⊕⊕OO LOW[1,2]
Seropositivity for HPV 58	7 mths	There is moderate-quality (7mths) and low-quality (36mths) evidence of no significant difference in seropositivity for HPV 58 in males compared with females	1628/1630 (99.9%)	566/566 (100%)	RR 1.00 (1.00, 1.00); 2196 participants in 1 study	⊕⊕⊕O MODERATE[1]
	36 mths*		413/417 (99.0%)	466/470 (99.1%)	RR 1.00 (0.99, 1.01); 887 participants in 1 study	⊕⊕OO LOW[1,2]

CI= confidence interval; GMT= geometric mean titre; HPV= human papilloma virus; *Data for 12 and 24 months also available, see forest plot below.

[1]Downgraded one level for risk of bias: non-random comparison [2]Downgraded one level for risk of bias: high loss to follow-up.

Forest plots: 9-valent HPV vaccine in 9 to 15-year old males versus 9-valent HPV vaccine in 9 to 15-year old females – immunogenicity outcomes (3 doses)

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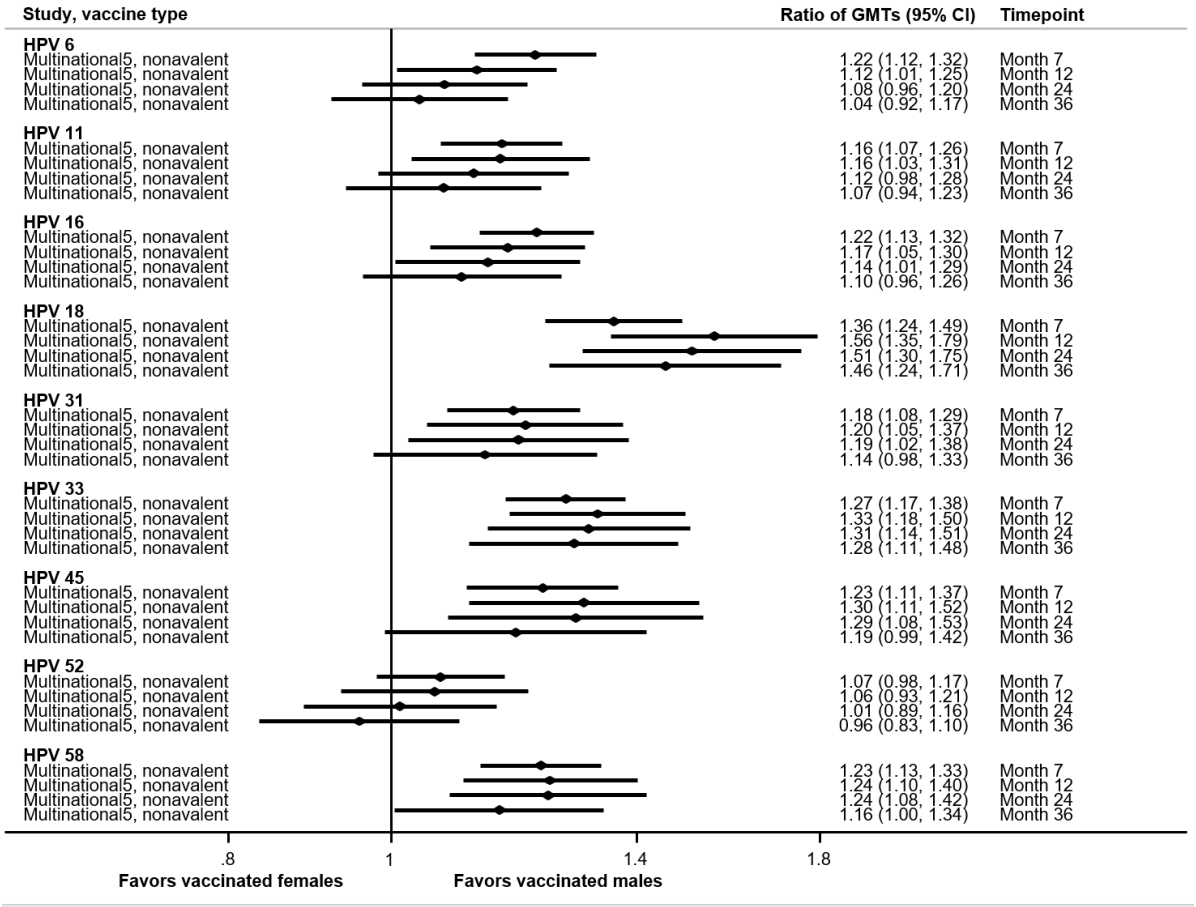
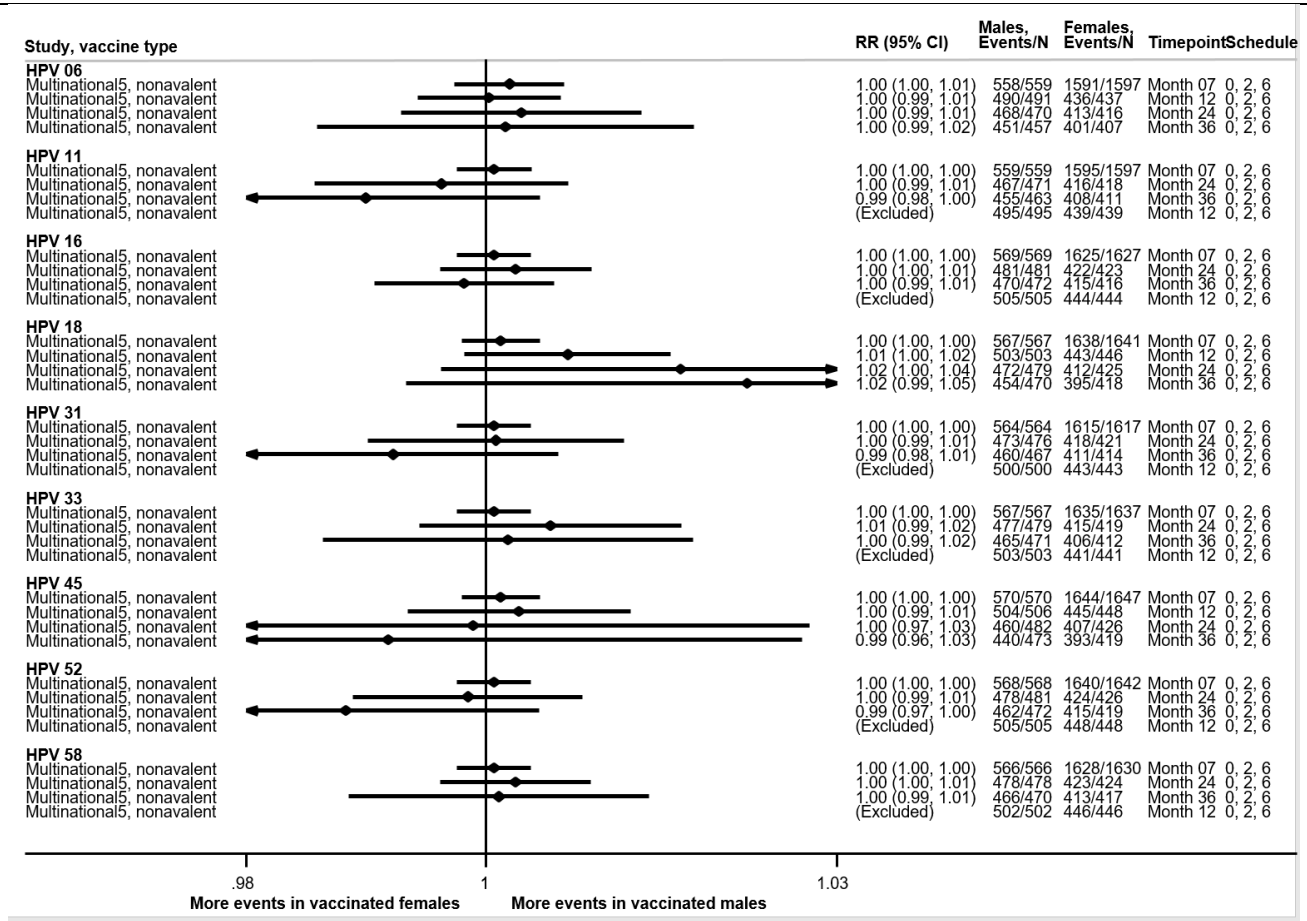
Population: 9 to 15-year old males and females (seronegative at baseline)
***Setting*:** Austria, Belgium, Brazil, Canada, Chile, Colombia, Costa Rica, Czech Republic, Denmark, Finland, India, Israel, Malaysia, Norway, Peru, Poland, South Africa, South Korea, Spain, Sweden, Taiwan, Thailand, Turkey and the United States
Comparison: 9-valent HPV vaccine (3-doses (Day 1, Month 2, Month 6)) in males versus 9-valent HPV vaccine (3-doses (Day 1, Month 2, Month 6)) in females

Outcome	Forest plot	Certainty of the evidence (GRADE)
GMTs follow up: 7-36 months		⊕⊕⊕O MODERATE ⊕⊕OO LOW ⊕⊕⊕O MODERATE ⊕⊕OO LOW ⊕⊕⊕O MODERATE ⊕⊕OO LOW ⊕⊕⊕O MODERATE ⊕⊕OO LOW ⊕⊕⊕O MODERATE ⊕⊕OO LOW ⊕⊕⊕O MODERATE ⊕⊕OO LOW ⊕⊕⊕O MODERATE ⊕⊕OO LOW ⊕⊕⊕O MODERATE ⊕⊕OO LOW

Outcome	Forest plot	Certainty of the evidence (GRADE)
Seropositivity follow up: 7-36 months		⊕⊕⊕O MODERATE ⊕⊕OO LOW ⊕⊕⊕O MODERATE ⊕⊕OO LOW ⊕⊕⊕O MODERATE ⊕⊕OO LOW ⊕⊕⊕O MODERATE ⊕⊕OO LOW ⊕⊕⊕O MODERATE ⊕⊕OO LOW ⊕⊕⊕O MODERATE ⊕⊕OO LOW ⊕⊕⊕O MODERATE ⊕⊕OO LOW ⊕⊕⊕O MODERATE ⊕⊕OO LOW ⊕⊕⊕O MODERATE ⊕⊕OO LOW

Summary of findings: 9-valent HPV vaccine in 9 to 15-year old males versus 9-valent HPV vaccine in 9 to 15-year old females – immunogenicity outcomes (2 doses) [15]

Population: **9 to 15-year old males and females (seronegative at baseline)**
***Setting*: Multinational (countries not reported)**
Comparison: **9-valent HPV vaccine (2-doses (Day 0, Month 6)) in males versus 9-valent HPV vaccine (2-doses (Day 0, Month 6)) in females**

Outcome	Plain language summary	Absolute effect		Relative effect (95% CI) Nº of participants & studies	Certainty of the evidence (GRADE)
		Females	Males		
Seropositivity for HPV 6 7 months	There was moderate-quality evidence of no significant difference in seropositivity for HPV 6 between males and females	257/258 (99.6%)	263/263 (100%)	RR 1.00 (0.99 to 1.01); 521 participants in 1 study	⊕⊕⊕O MODERATE[1]
Seropositivity for HPV 11 7 months	There was moderate-quality evidence of no significant difference in seropositivity for HPV 11 between males and females	258/258 (100%)	264/264 (100%	Not estimable*; 522 participants in 1 study	⊕⊕⊕O MODERATE[1]
Seropositivity for HPV 16 7 months	There was moderate-quality evidence of no significant difference in seropositivity for HPV 16 between males and females	272/272 (100%	273/273 (100%)	Not estimable*; 545 participants in 1 study	⊕⊕⊕O MODERATE[1]
Seropositivity for HPV 18 7 months	There was moderate-quality evidence of no significant difference in seropositivity for HPV 18 between males and females	272/272 (100%)	272/272 (100%)	Not estimable*; 544 participants in 1 study	⊕⊕⊕O MODERATE[1]
Seropositivity for HPV 31 7 months	There was moderate-quality evidence of no significant difference in seropositivity for HPV 31 between males and females	271/272 (99.6%)	271/271 (100%)	RR 1.00 (0.99 to 1.01); 543 participants in 1 study	⊕⊕⊕O MODERATE[1]
Seropositivity for HPV 33 7 months	There was moderate-quality evidence of no significant difference in seropositivity for HPV 33 between males and females	272/273 (99.6%)	271/271 (100%)	RR 1.00 (0.99 to 1.01); 544 participants in 1 study	⊕⊕⊕O MODERATE[1]
Seropositivity for HPV 45 7 months	There was moderate-quality evidence of no significant difference in seropositivity for HPV 45 between males and females	272/274 (99.3%)	271/273 (99.3%)	RR 1.00 (0.99 to 1.01); 547 participants in 1 study	⊕⊕⊕O MODERATE[1]
Seropositivity for HPV 52 7 months	There was moderate-quality evidence of no significant difference in seropositivity for HPV 52 between males and females	271/272 (99.6%)	273/273 (100%)	RR 1.00 (0.99 to 1.01); 545 participants in 1 study	⊕⊕⊕O MODERATE[1]
Seropositivity for HPV 58 7 months	There was moderate-quality evidence of no significant difference in seropositivity for HPV 58 between males and females	270/270 (100%)	270/270 (100%)	RR 1.00 (0.99 to 1.01); 540 participants in 1 study	⊕⊕⊕O MODERATE[1]

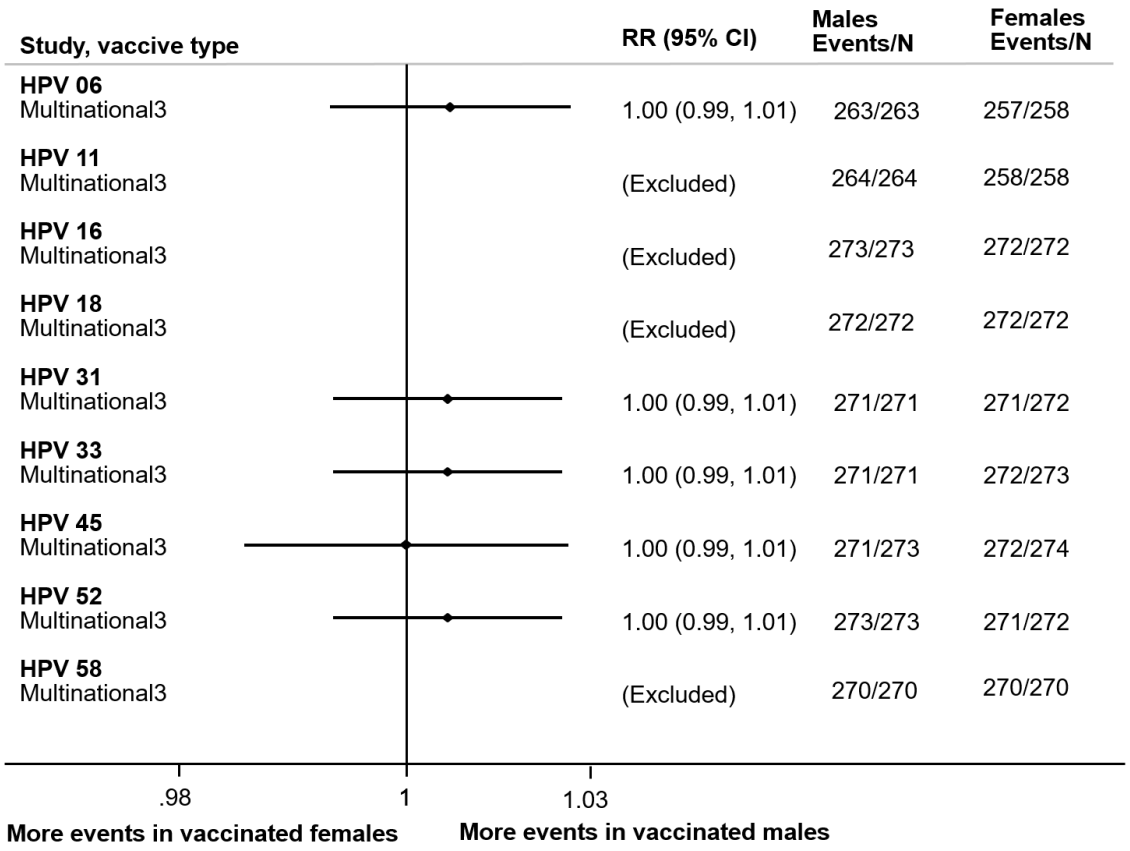
CI= confidence interval; HPV= human papilloma virus

*Excluded from analysis due to no non-events; all participants seropositive.

[1]Downgraded one level for risk of bias: non-random comparison.

Forest plot: 9-valent HPV vaccine in 9 to 15-year old males versus 9-valent HPV vaccine in 9 to 15-year old females – immunogenicity outcomes (2 doses)

Population: 9 to 15-year old males and females (seronegative at baseline)
***Setting*:** Multinational (countries not reported)
Comparison: 9-valent HPV vaccine (2-doses (Day 0, Month 6)) in males versus 9-valent HPV vaccine (2-doses (Day 0, Month 6)) in females

Outcome	Forest plot	Certainty of the evidence (GRADE)
Seroconversion follow up: 7 months		⊕⊕⊕O MODERATE

Summary of Findings: 9-valent HPV vaccine in 16 to 26-year old males versus 9-valent HPV vaccine in 16 to 26-year old females – immunogenicity outcomes

Patients: **16 to 26-year old heterosexual males and females (seronegative at baseline)**

Setting**: Canada, Colombia, Denmark, Germany, Israel, Malaysia, Mexico, Norway, Peru, the Philippines, Poland, South Africa, Spain, Sweden, Thailand, Turkey and the United States**

Comparison: **9-valent HPV vaccine (3-doses (Day 1, Month 2, Month 6)) in males versus 9-valent HPV vaccine (3-doses (Day 1, Month 2, Month 6)) in females**

Outcome	Plain language summary	Absolute effect		Relative effect (95% CI) Nº of participants & studies	**Certainty of the evidence (GRADE)**
		Females	Males		
GMTs for HPV 6 7 mths	There is moderate-quality evidence of higher GMTs for HPV 6 in males compared with females	703.9 mMU/mL	782 mMU/mL	Ratio 1.11 (1.02 to 1.21); 1555 participants in 1 study	⊕⊕⊕O MODERATE[1]
GMTs for HPV 11 7 mths	There is moderate-quality evidence of higher GMTs for HPV 11 in males compared with females	564.9 mMU/mL	616.7 mMU/mL	Ratio 1.09 (1.00 to 1.19); 1563 participants in 1 study	⊕⊕⊕O MODERATE[1]
GMTs for HPV 16 7 mths	There is moderate-quality evidence of higher GMTs for HPV 16 in males compared with females	2788.3 mMU/mL	3346 mMU/mL	Ratio 1.20 (1.10 to 1.31); 1680 participants in 1 study	⊕⊕⊕O MODERATE[1]
GMTs for HPV 18 7 mths	There is moderate-quality evidence of higher GMTs for HPV 18 in males compared with females	679.8 mMU/mL	808.2 mMU/mL	Ratio 1.19 (1.08 to 1.31); 1737 participants in 1 study	⊕⊕⊕O MODERATE[1]
GMTs for HPV 31 7 mths	There is moderate-quality evidence of higher GMTs for HPV 31 in males compared with females	570.1 mMU/mL	708.5 mMU/mL	Ratio 1.24 (1.13 to 1.37); 1734 participants in 1 study	⊕⊕⊕O MODERATE[1]
GMTs for HPV 33 7 mths	There is moderate-quality evidence of higher GMTs for HPV 33 in males compared with females	322 mMU/mL	384.8 mMU/mL	Ratio 1.20 (1.10 to 1.30); 1754 participants in 1 study	⊕⊕⊕O MODERATE[1]
GMTs for HPV 45 7 mths	There is moderate-quality evidence of higher GMTs for HPV 45 in males compared with females	185.7 mMU/mL	235.6 mMU/mL	Ratio 1.27 (1.14 to 1.41); 1780 participants in 1 study	⊕⊕⊕O MODERATE[1]
GMTs for HPV 52 7 mths	There is moderate-quality evidence of higher GMTs for HPV 52 in males compared with females	335.2 mMU/mL	386.8 mMU/mL	Ratio 1.15 (1.05 to 1.26); 1756 participants in 1 study	⊕⊕⊕O MODERATE[1]
GMTs for HPV 58 7 mths	There is moderate-quality evidence of higher GMTs for HPV 58 in males compared with females	409.3 mMU/mL	509.8 mMU/mL	Ratio 1.25 (1.14 to 1.36); 1736 participants in 1 study	⊕⊕⊕O MODERATE[1]

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Summary of findings continued

Outcome	Plain language summary	Absolute effect		Relative effect (95% CI) Nº of participants & studies	**Certainty of the evidence (GRADE)**
		Females	Males		
Seropositivity for HPV 6 7 months	There was moderate-quality evidence of no significant difference in seropositivity for HPV 6 between males and females	705/708 (99.6%)	844/847 (99.6%)	RR 1.00 (0.99 to 1.01); 1555 participants in 1 study	⊕⊕⊕O MODERATE[1]
Seropositivity for HPV 11 7 months	There was moderate-quality evidence of no significant difference in seropositivity for HPV 11 between males and females	711/712 (99.9%)	851/851 (100%)	RR 1.00 (1.00 to 1.01); 1563 participants in 1 study	⊕⊕⊕O MODERATE[1]
Seropositivity for HPV 16 7 months	There was moderate-quality evidence of no significant difference in seropositivity for HPV 16 between males and females	780/781 (99.9%)	899/899 (100%)	RR 1.00 (1.00 to 1.00); 1680 participants in 1 study	⊕⊕⊕O MODERATE[1]
Seropositivity for HPV 18 7 months	There was moderate-quality evidence of no significant difference in seropositivity for HPV 18 between males and females	829/831 (99.8%)	905/906 (99.9%)	RR 1.00 (1.00 to 1.01); 1737 participants in 1 study	⊕⊕⊕O MODERATE[1]
Seropositivity for HPV 31 7 months	There was moderate-quality evidence of no significant difference in seropositivity for HPV 31 between males and females	826/826 (100%)	908/908 (100%)	*Not estimable; 1734 participants in 1 study	⊕⊕⊕O MODERATE[1]
Seropositivity for HPV 33 7 months	There was moderate-quality evidence of no significant difference in seropositivity for HPV 33 between males and females	852/853 (99.9%)	901/901 (100%)	RR 1.00 (1.00 to 1.00); 1754 participants in 1 study	⊕⊕⊕O MODERATE[1]
Seropositivity for HPV 45 7 months	There was moderate-quality evidence of no significant difference in seropositivity for HPV 45 between males and females	867/871 (99.5%)	907/909 (99.8%)	RR 1.00 (1.00 to 1.01); 1780 participants in 1 study	⊕⊕⊕O MODERATE[1]
Seropositivity for HPV 52 7 months	There was moderate-quality evidence of no significant difference in seropositivity for HPV 52 between males and females	847/849 (99.8%)	907/907 (100%)	RR 1.00 (1.00 to 1.01); 1756 participants in 1 study	⊕⊕⊕O MODERATE[1]
Seropositivity for HPV 58 7 months	There was moderate-quality evidence of no significant difference in seropositivity for HPV 58 between males and females	837/839 (99.8%)	897/897 (100%)	RR 1.00 (1.00 to 1.01); 1736 participants in 1 study	⊕⊕⊕O MODERATE[1]

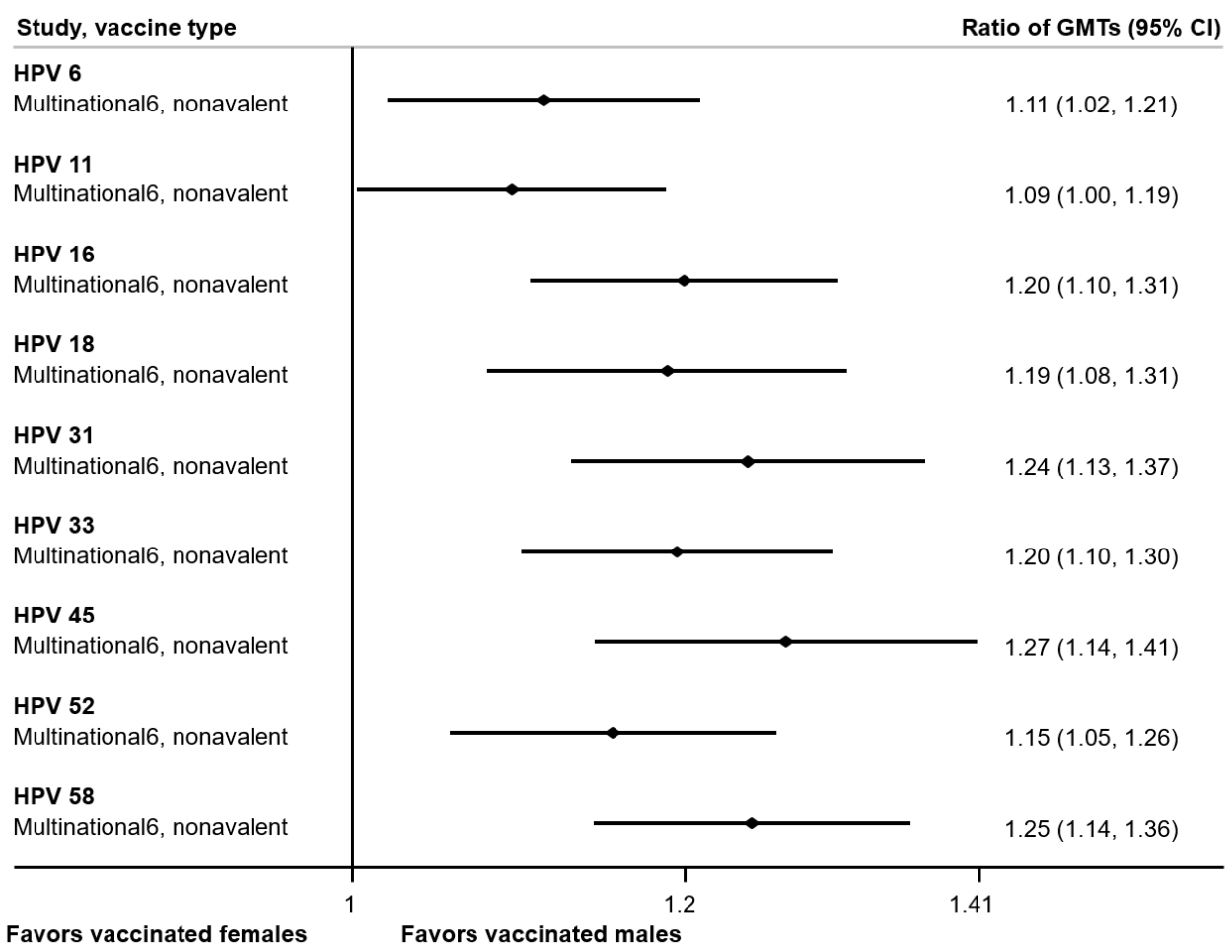
CI= confidence interval; HPV= human papilloma virus

*Excluded from analysis due to no non-events; all participants seropositive.

[1]Downgraded one level for risk of bias: non-random comparison.

Forest plots: 9-valent HPV vaccine in 16 to 26-year old males versus 9-valent HPV vaccine in 16 to 26-year old females – immunogenicity outcomes

Patients: **16 to 26-year old heterosexual males and females (seronegative at baseline)**
***Setting*: Canada, Colombia, Denmark, Germany, Israel, Malaysia, Mexico, Norway, Peru, the Philippines, Poland, South Africa, Spain, Sweden, Thailand, Turkey and the United States)**
Comparison: **9-valent HPV vaccine (3-doses (Day 1, Month 2, Month 6)) in males versus 9-valent HPV vaccine (3-doses (Day 1, Month 2, Month 6)) in females**

Outcome	Forest plot	Certainty of the evidence (GRADE)
GMTs follow up: 7 months		

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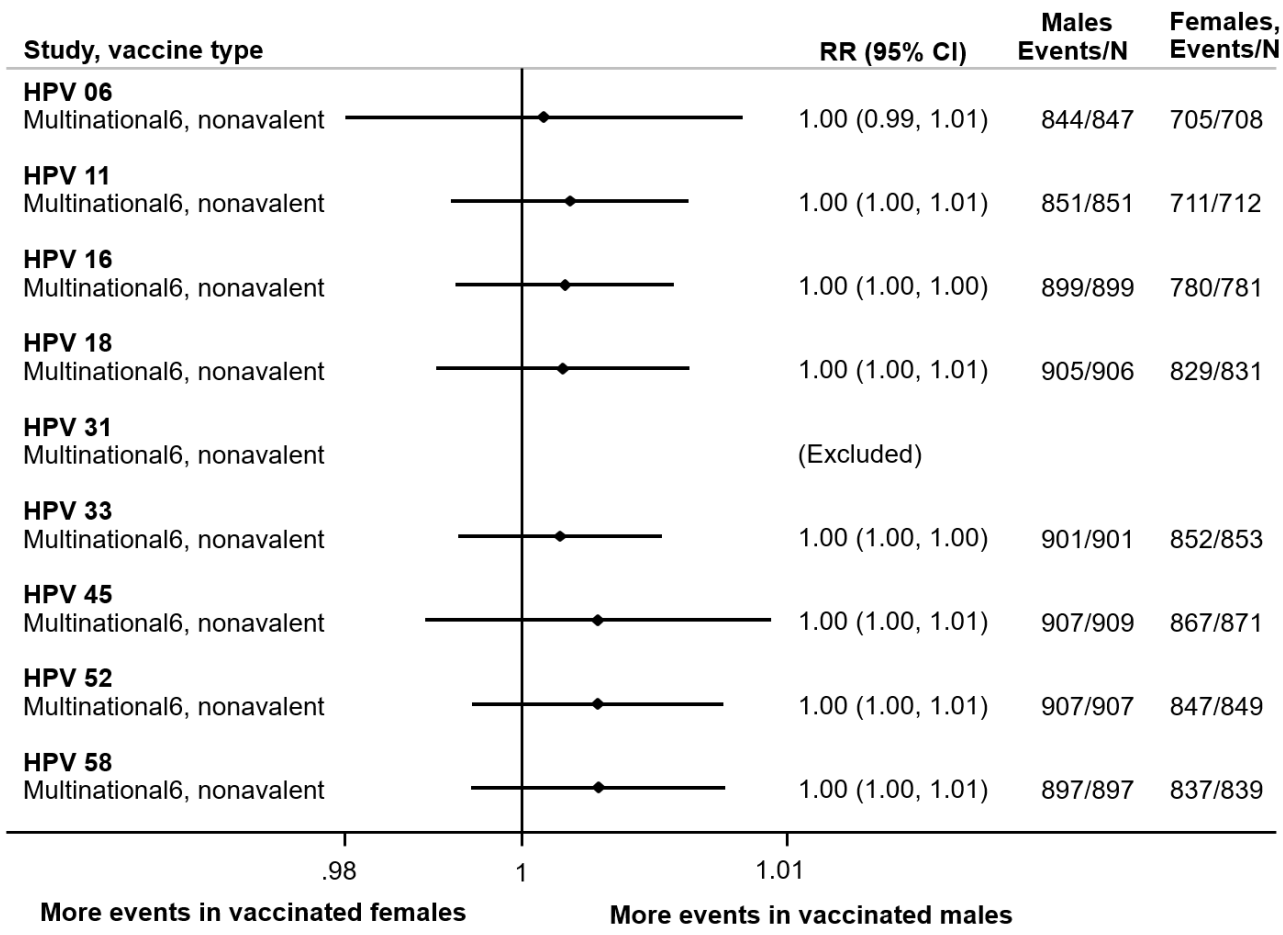
Outcome	Forest plot	Certainty of the evidence (GRADE)
Seropositivity follow up: 7 months		

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9-valent HPV vaccine versus 4-valent HPV vaccine in males

Contents

Key findings

In males aged 16-26 years, the 9-valent vaccine resulted in higher GMTs than the 4-valent vaccine for HPV 6 and similar (non-inferior) GMTs for HPV 11, 16 and 18, 7 months after first vaccination (high-quality evidence). The GMTs for HPV 31, 33, 45, 52 and 58 are substantially higher following immunisation with the 9-valent vaccine 7 months after first vaccination versus the 4-valent vaccine, which does not include these HPV types (high-quality evidence).

In males aged 16-26, there was no significant difference between the 9-valent and 4-valent vaccines in the rate of seroconversion for HPV 6, 11, 16 and 18. Seroconversion was considerably higher for HPV 31, 33, 45, 52 and 58 following vaccination with the 9-valent vaccine versus the 4-valent vaccine (high-quality evidence).

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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 Targeted Update, we assess the protection afforded by 9-valent HPV vaccine compared with 4-valent HPV vaccine in males.

Objectives

To compare the effectiveness of 9-valent and 4-valent HPV vaccination in males.

Search methods

Searches were conducted from January 2006 to June 2016, and all relevant studies regardless of language or publication status were searched. 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) and non-randomised experimental studies were eligible for inclusion.

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 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 9-valent vaccine was 0.5 for the ratio of GMTs.

Main Results

We included one RCT (Belgium1), comparing 9-valent vaccine with 4-valent vaccine in males aged 16 to 26 years (3 doses in each arm). The risk of bias was low for all domains.

The study reported immunogenicity outcomes at 7 months. With regard to GMTs, there was high-quality evidence of higher GMTs with 9-valent than with 4-valent vaccine for HPV 6, 31, 33, 45, 52 and 58 (substantially higher for HPV 31, 33, 45, 52 and 58, HPV types not included in the 4-valent vaccine). There was high-quality evidence of no significant difference between 9-valent vaccine and 4-valent vaccine for HPV 11, 16 and 18. The 9-valent vaccine was non inferior to 4-valent vaccine for GMTs for all HPV subtypes measured.

There was high-quality evidence of no significant difference in seroconversion between 9-valent vaccine and 4-valent vaccine for HPV 6, 11, 16 and 18. There was high-quality evidence of substantially higher rates of seroconversion for HPV 31, 33, 45, 52 and 58 with 9-valent vaccine compared with 4-valent vaccine.

Implications and conclusions

The 9-valent vaccine was non-inferior to 4-valent vaccine in males aged 16-26 years at follow-up of 7 months for GMTS for HPV 6, 11, 16 and 18, and had substantially higher GMTs for HPV types not included in the 4-valent vaccine: 31, 33, 24, 52 and 58. Similar results were reported for seroconversion.

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Summary of Findings: 9-valent HPV vaccine versus 4-valent HPV vaccine in 16 to 26-year old males – immunogenicity outcomes [3]

Patients: **16 to 26-year old males (seronegative at baseline)**
Setting**: Belgium**
Comparison: **9-valent HPV vaccine (3-doses (Day 1, Month 2, Month 6)) versus 4-valent vaccine (3-doses (Day 1, 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 vaccine	9-valent vaccine		
GMTs for HPV 6 follow up: 7 months	There is high-quality evidence of higher GMTs for HPV 6 with 9-valent vs 4-valent HPV vaccines in 16 to 26-year old males 7 months after first vaccination	Mean: 618.4 mMU/mL	Mean: 758.3 mMU/mL	Ratio 1.23 (1.03 to 1.45) 454 participants in 1 study	⊕⊕⊕⊕ HIGH
GMTs for HPV 11 follow up: 7 months	There is high-quality evidence of no significant difference in the ratios of GMTs for HPV 11 with 9-valent vs 4-valent HPV vaccines in 16 to 26-year old males 7 months after first vaccination	Mean: 769.1 mMU/mL	Mean: 681.7 mMU/mL	Ratio 0.89 (0.75 to 1.04) 454 participants in 1 study	⊕⊕⊕⊕ HIGH
GMTs for HPV 16 follow up: 7 months	There is high-quality evidence of no significant difference in the ratios of GMTs for HPV 16 with 9-valent vs 4-valent HPV vaccines in 16 to 26-year old males 7 months after first vaccination	Mean: 3787.9 mMU/mL	Mean: 3924.1 mMU/mL	Ratio 1.04 (0.88 to 1.21) 471 participants in 1 study	⊕⊕⊕⊕ HIGH
GMTs for HPV18 follow up: 7 months	There is high-quality evidence of no significant difference in the ratios of GMTs for HPV 18 with 9-valent vs 4-valent HPV vaccines in 16 to 26-year old males 7 months after first vaccination	Mean: 790.9 mMU/mL	Mean: 884.3 mMU/mL	Ratio 1.12 (0.91 to 1.37) 470 participants in 1 study	⊕⊕⊕⊕ HIGH
GMTs for HPV 31 follow up: 7 months	There is high-quality evidence of higher GMTs for HPV 31 with 9-valent vs 4-valent HPV vaccines in 16 to 26-year old males 7 months after first vaccination	Mean: 14.8 mMU/mL	Mean: 794.4 mMU/mL	Ratio 52.96 (42.69 to 65.71) 471 participants in 1 study	⊕⊕⊕⊕ HIGH
GMTs for HPV 33 follow up: 7 months	There is high-quality evidence of higher GMTs for HPV 33 with 9-valent vs 4-valent HPV vaccines in 16 to 26-year old males 7 months after first vaccination	Mean: 3.4 mMU/mL	Mean: 460.5 mMU/mL	Ratio 135.44 (117.18 to 156.54) 472 participants in 1 study	⊕⊕⊕⊕ HIGH
GMTs for HPV 45 follow up: 7 months	There is high-quality evidence of higher GMTs for HPV 45 with 9-valent vs 4-valent HPV vaccines in 16 to 26-year old males 7 months after first vaccination	Mean: 2.5 mMU/mL	Mean: 262.9 mMU/mL	Ratio 105.16 (87.87 to 125.85) 468 participants in 1 study	⊕⊕⊕⊕ HIGH
GMTs for HPV 52 follow up: 7 months	There is high-quality evidence of higher GMTs for HPV 52 with 9-valent vs 4-valent HPV vaccines in 16 to 26-year old males 7 months after first vaccination	Mean: 1.9 mMU/mL	Mean: 430.7 mMU/mL	Ratio 226.68 (194.71 to 263.90) 471 participants in 1 study	⊕⊕⊕⊕ HIGH
GMTs for HPV 58 follow up: 7 months	There is high-quality evidence of higher GMTs for HPV 58 with 9-valent vs 4-valent HPV vaccines in 16 to 26-year old males 7 months after first vaccination	Mean: 5.7 mMU/mL	Mean: 691 mMU/mL	Ratio 121.23 (101.71 to 144.49) 465 participants in 1 study	⊕⊕⊕⊕ HIGH

Continued overleaf

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Summary of Findings continued

Seroconversion for HPV 6 follow up: 7 months	There is high quality evidence of no difference in seroconversion for HPV 6 with 9-valent vs 4-valent HPV vaccines in 16 to 26-year old males 7 months after first vaccination.	223/226 (98.7%)	224/228 (98.2%)	RR 1.00 (0.97 to 1.02) 454 participants in 1 study	⊕⊕⊕⊕ HIGH
Seroconversion for HPV 11 follow up: 7 months	There is high quality evidence of no difference in seroconversion for HPV 11 with 9-valent vs 4-valent HPV vaccines in 16 to 26-year old males 7 months after first vaccination.	226/226 (100%)	228/228 (100%)	Not estimable* 454 participants in 1 study	⊕⊕⊕⊕ HIGH
Seroconversion for HPV 16 follow up: 7 months	There is high quality evidence of no difference in seroconversion for HPV 16 with 9-valent vs 4-valent HPV vaccines in 16 to 26-year old males 7 months after first vaccination.	237/237 (100%)	234/234 (100%)	Not estimable* 471 participants in 1 study	⊕⊕⊕⊕ HIGH
Seroconversion for HPV 18 follow up: 7 months	There is high quality evidence of no difference in seroconversion for HPV 18 with 9-valent vs 4-valent HPV vaccines in 16 to 26-year old males 7 months after first vaccination.	235/236 (99.6%)	233/234 (99.6%)	RR 1.00 (0.99 to 1.01) 470 participants in 1 study	⊕⊕⊕⊕ HIGH
Seroconversion for HPV 31 follow up: 7 months	There is high quality evidence of higher rates of seroconversion for HPV 31 with 9-valent vs 4-valent HPV vaccines in 16 to 26-year old males 7 months after first vaccination.	146/237 (61.6%)	234/234 (100%)	RR 1.62 (1.47 to 1.79) 471 participants in 1 study	⊕⊕⊕⊕ HIGH
Seroconversion for HPV 33 follow up: 7 months	There is high quality evidence of higher rates of seroconversion for HPV 33 with 9-valent vs 4-valent HPV vaccines in 16 to 26-year old males 7 months after first vaccination.	40/236 (16.9%)	236/236 (100%)	RR 5.84 (4.41 to 7.73) 472 participants in 1 study	⊕⊕⊕⊕ HIGH
Seroconversion for HPV 45 follow up: 7 months	There is high quality evidence of higher rates of seroconversion for HPV 45 with 9-valent vs 4-valent HPV vaccines in 16 to 26-year old males 7 months after first vaccination.	22/236 (9.3%)	232/232 (100%)	RR 10.51 (7.09 to 15.57) 468 participants in 1 study	⊕⊕⊕⊕ HIGH
Seroconversion for HPV 52 follow up: 7 months	There is high quality evidence of higher rates of seroconversion for HPV 52 with 9-valent vs 4-valent HPV vaccines in 16 to 26-year old males 7 months after first vaccination.	6/236 (2.5%)	235/235 (100%)	RR 36.38 (17.05 to 77.66) 471 participants in 1 study	⊕⊕⊕⊕ HIGH
Seroconversion for HPV 58 follow up: 7 months	There is high quality evidence of higher rates of seroconversion for HPV 58 with 9-valent vs 4-valent HPV vaccines in 16 to 26-year old males 7 months after first vaccination.	84/233 (36.1%)	232/232 (100%)	RR 2.76 (2.33 to 3.28) 465 participants in 1 study	⊕⊕⊕⊕ HIGH

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

* Excluded from analysis due to no non-events; all participants seropositive.

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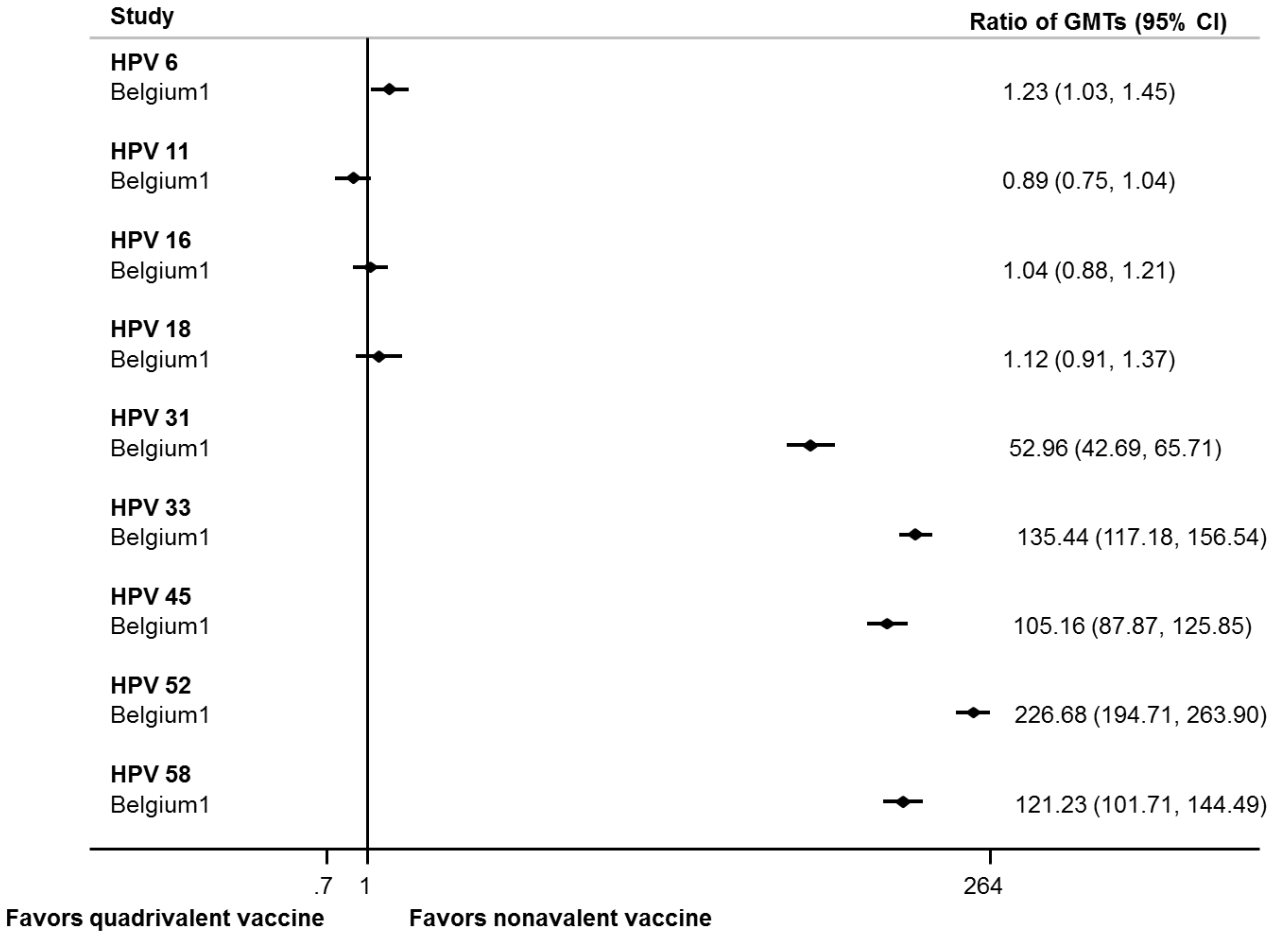
Forest plots: 9-valent HPV vaccine versus 4-valent HPV vaccine in 16 to 26-year old males – immunogenicity outcomes

Patients: **16 to 26-year old males (seronegative at baseline)**
***Setting*: Belgium**
Comparison: **9-valent HPV vaccine (3-doses (Day 1, Month 2, Month 6)) versus 4-valent vaccine (3-doses (Day 1, Month 2, Month 6))**

Outcome	Forest plot	Certainty of the evidence (GRADE)
GMTs follow up: 7 months		⊕⊕⊕⊕ HIGH

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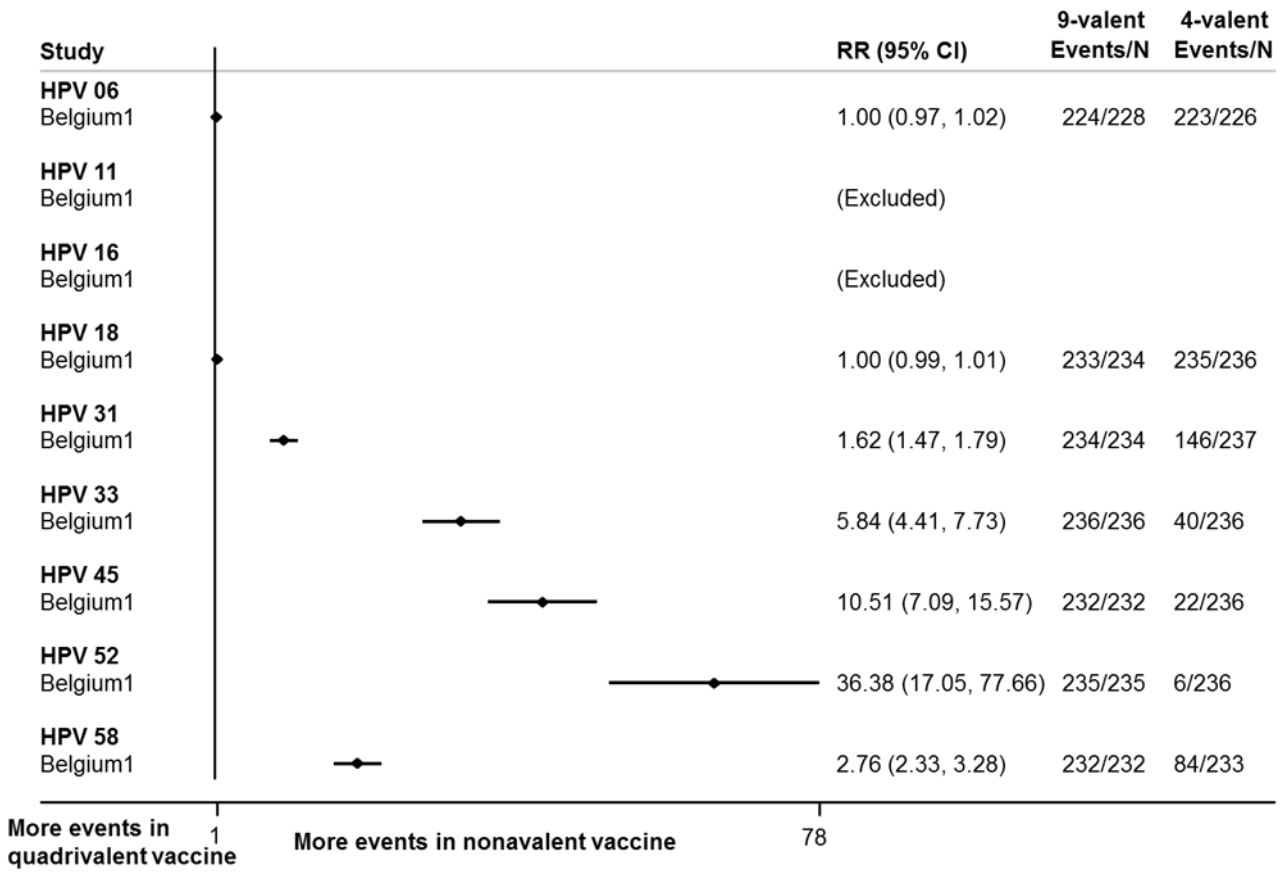
Outcome	Forest plot	Certainty of the evidence (GRADE)
Seroconversion follow up: 7 months		⊕⊕⊕⊕ HIGH

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Belgium1

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HPV vaccines in men who have sex with men (MSM)

Contents

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Key findings

4-valent HPV vaccine versus placebo in MSM (16 to 26)

- In MSM aged 16 to 26 years, 4-valent HPV vaccine reduced anal intraepithelial neoplasia (AIN; any HPV type), AIN (HPV 6, 11, 16 18), AIN grade 1, and AIN grade 2 or 3, in 16 to 26-year old MSM at mean follow up of 2.9 years compared with placebo (moderate-quality evidence).
- There was no significant difference in condyloma acuminatum (low-quality evidence).
- There were no events for anal cancer in either the 4-valent vaccine or placebo group.
- In MSM aged 16 to 26 years, 4-valent vaccine reduced persistent infection by HPV 6, 11, 16 or 18 (combined outcome), and persistent infection by HPV 6, 16 and 18 individually (moderate-quality evidence).
- There was no significant difference between 4-valent vaccine and placebo on persistent infection by HPV 11 (low-quality evidence).

9-valent HPV vaccine in MSM versus in females (16 to 26)

- GMTs were lower but non-inferior for the 9 HPV subtypes covered by the 9-valent vaccine in vaccinated MSM than in vaccinated females at 7 months (moderate-quality evidence).
- There was no significant difference in seropositivity for all HPV subtypes covered by the 9-valent vaccine between vaccinated MSM and vaccinated females at 7 months (moderate-quality evidence).

9-valent HPV vaccine in MSM versus in heterosexual males (16 to 26)

- GMTs were lower but non-inferior for all 9 HPV subtypes covered by the 9-valent vaccine in vaccinated MSM compared with heterosexual at 7 months (moderate-quality evidence).
- There was no significant difference in seropositivity for all HPV subtypes covered by the 9-valent vaccine between vaccinated MSM and vaccinated heterosexual men at 7 months (moderate-quality evidence).

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 analyze evidence for the protection afforded by prophylactic HPV vaccines in men who have sex with men (MSM).

Objectives

To evaluate the efficacy and immunogenicity of HPV vaccines in MSM.

Search methods

Searches were conducted from January 2006 to June 2016, and all relevant studies regardless of language or publication status were searched. 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) of HPV vaccine versus placebo in MSM, and RCTs with a non-random comparison of HPV vaccine in MSM versus HPV vaccine in females and heterosexual males, or non-randomised studies for the same comparisons, were eligible for inclusion.

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, and risk ratios were calculated for other binary outcomes. 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. For the comparisons of MSM versus females, and MSM versus heterosexual men, the non-inferiority threshold for MSM was 0.5 for the ratio of GMTs.

Main Results

We found one RCT assessing clinical outcomes of 4-valent HPV vaccine in 16 to 26-year old MSM (Multinational9); and one non-randomised comparative study assessing 9-valent HPV vaccines in MSM versus females, and MSM versus heterosexual males (Multinational6). The risk of bias for all domains for the RCT was low. For the non-random study, the quality of evidence for immunogenicity outcomes was downgraded by one level. We did not downgrade the quality of evidence for lack of blinding in the non-randomised study because outcomes were objectively assessed (immunogenicity). Some outcomes were downgraded for imprecision. All outcomes were reported in per protocol analyses, where all participants were seronegative at baseline.

4-valent HPV vaccine versus placebo in MSM (16 to 26)

There was moderate-quality evidence that 4-valent HPV vaccine reduces anal intraepithelial neoplasia (AIN; any HPV type), AIN (HPV 6, 11, 16 18), AIN grade 1, and AIN grade 2 or 3, in 16 to 26-year old MSM compared with placebo. There was low-quality evidence of no significant difference in condyloma acuminatum. There were no events for anal cancer in either group. Mean follow-up for all was 2.9 years (Multinational9).

With regard to persistent infection, there was moderate-quality evidence that 4-valent vaccine reduced persistent infection by HPV 6, 11, 16 or 18 (combined outcome), and reduced persistent infection by HPV 6, 16 and 18 individually. There was low-quality evidence of no significant difference between 4-valent vaccine and placebo on persistent infection by HPV 11 (Multinational9).

9-valent HPV vaccine in MSM versus in females (16 to 26)

There was moderate-quality evidence of lower GMTs for all 9 HPV subtypes covered by the 9-valent vaccine in vaccinated MSM than in females at 7 months, although for HPV 18 the effect was not significant; however, results were non-inferior for GMTs for all HPV subtypes in MSM compared with females. For the outcome of seropositivity, there was moderate-quality evidence of no significant difference for all HPV subtypes covered by the 9-valent vaccine between vaccinated MSM and vaccinated females at 7 months (Multinational6).

9-valent HPV vaccine in MSM versus in heterosexual males (16 to 26)

There was moderate-quality evidence of lower but non-inferior GMTs for all 9 HPV subtypes covered by the 9-valent vaccine in MSM compared with heterosexual males at 7 months. For the outcome of seropositivity, there was moderate-quality evidence of no significant difference for all 9 HPV genotypes between vaccinated MSM and vaccinated heterosexual males at 7 months (Multinational6).

Implications and conclusions

The 4-valent HPV vaccine was effective in reducing clinical outcomes of AIN and persistent infection compared with placebo at a mean follow up for 2.9 years, with the exception of condyloma acuminatum (no significant difference) and persistent infection caused by HPV 11 (no significant difference). For 9-valent HPV vaccine, MSM tended to have lower but non-inferior GMTs at 7 months compared with females and heterosexual males. There was no significant difference in seropositivity for 9-valent HPV vaccine between MSM and females and between MSM and heterosexual males at 7 months.

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Summary of findings: 4-valent HPV vaccine versus placebo in 16 to 26 year old MSM – clinical outcomes, AIN and anal cancer – per protocol analyses

Patients: **16 to 26 year-old MSM (seronegative at baseline)**
***Setting*: Australia, Brazil, Canada, Croatia, Germany, Spain, and the United States**
Intervention: **4-valent HPV vaccine (3-doses (Day 1, Month 2, Month 6)) versus placebo (3-doses (Day 1, Month 2, Month 6))**

Outcome	Plain language summary	Absolute effect		Relative effect (95% CI) Nº of participants & studies	Certainty of the evidence (GRADE)
		Placebo	4-valent HPV vaccine		
AIN (Any HPV type) follow up: mean 2.9 years	There is moderate-quality evidence that 4-valent HPV vaccine reduces AIN (Any HPV type) in 16 to 26-year old MSM compared with placebo.	28/315 person years at risk	12/299 person years at risk	Rate ratio 0.45 (0.23 to 0.89); 255 participants in 1 study	⊕⊕⊕O MODERATE [1]
AIN (HPV 6, 11, 16 18) follow up: mean 2.9 years	There is moderate-quality evidence that 4-valent HPV vaccine reduces AIN (HPV 6, 11, 16 18) in 16 to 26-year old MSM compared with placebo.	24/412 person years at risk	5/381 person years at risk	Rate ratio 0.23 (0.09 to 0.59); 402 participants in 1 study	⊕⊕⊕O MODERATE [1]
AIN grade 1 follow up: mean 2.9 years	There is moderate-quality evidence that 4-valent HPV vaccine reduces AIN grade 1 in 16 to 26-year old MSM compared with placebo.	16/414 person years at risk	4/383 person years at risk	Rate ratio 0.27 (0.09 to 0.81); 402 participants in 1 study	⊕⊕⊕O MODERATE [1]
Condyloma acuminatum follow up: mean 2.9 years	There is low-quality evidence of no significant difference on condyloma acuminatum between 4-valent HPV vaccine compared with placebo in 16 to 26-year old MSM.	6/418 person years at risk	0/387 person years at risk	Rate ratio 0.09 (0.01 to 1.61); 402 participants in 1 study	⊕⊕OO LOW [1 2]
AIN grade 2 or 3 follow up: mean 2.9 years	There is moderate-quality evidence that 4-valent HPV vaccine reduces AIN grade 2 or 3 in 16 to 26-year old MSM compared with placebo.	13/417 person years at risk	3/384 person years at risk	Rate ratio 0.25 (0.07 to 0.88); 402 participants in 1 study	⊕⊕⊕O MODERATE [1]
Anal cancer follow up: mean 2.9 years	We cannot estimate the effect of 4-valent HPV vaccine in MSM on anal cancer; no events were reported.	0/421 person years at risk	0/386 person years at risk	Not estimable*	⊕⊕⊕O MODERATE [1]

AIN= anal intraepithelial neoplasia; CI= confidence interval; HPV= human papilloma virus; MSM= men who have sex with men; RR= rate ratio * No events were reported.

[1] Downgraded one level for imprecision: Very low event rate. [2] Downgraded one further level for imprecision: 95% CI around the pooled estimate of effect includes appreciable benefit for both the intervention and control groups, as well as no effect.

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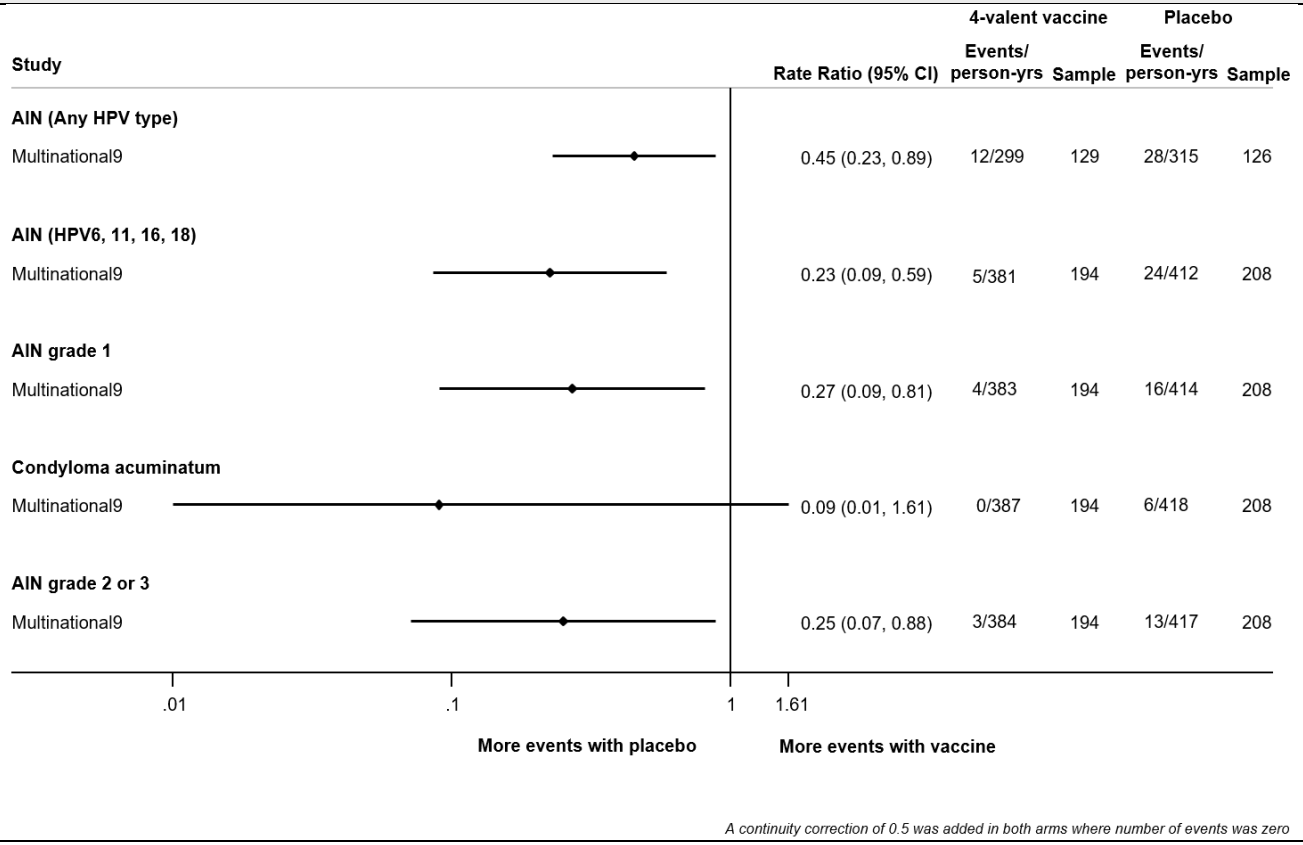
Forest plots: 4-valent HPV vaccine versus placebo in 16 to 26 year old MSM – clinical outcomes, AIN and anal cancer – per protocol analyses

Patients: **16 to 26 year-old MSM (seronegative at baseline)**
***Setting*: Australia, Brazil, Canada, Croatia, Germany, Spain, and the United States**
Intervention: **4-valent HPV vaccine (3-doses (Day 1, Month 2, Month 6)) versus placebo (3-doses (Day 1, Month 2, Month 6))**

Outcome	Forest plot	Certainty of the evidence (GRADE)
Anal Intraepithelial Neoplasia (AIN), Condyloma acuminatum and Anal Cancer* Follow up: mean 2.9 years		⊕⊕⊕O MODERATE ⊕⊕⊕O MODERATE ⊕⊕⊕O MODERATE ⊕⊕OO LOW ⊕⊕⊕O MODERATE

AIN= anal intraepithelial neoplasia
*No events for anal cancer in both groups, therefore excluded from forest plot

Summary of findings: 4-valent HPV vaccine versus placebo in 16 to 26 year old MSM – clinical outcomes, persistent infection – per protocol analyses

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Patients: **16 to 26 year-old MSM (seronegative at baseline)**
Setting**: Australia, Brazil, Canada, Croatia, Germany, Spain, and the United States**
Intervention: **4-valent HPV vaccine (3-doses (Day 1, Month 2, Month 6)) versus placebo (3-doses (Day 1, Month 2, Month 6))**

Outcome	Plain language summary	Absolute effect		Relative effect (95% CI) Nº of participants & studies	Certainty of the evidence (GRADE)
		Placebo	4-valent HPV vaccine		
Persistent infection HPV 6, 11, 16 or 18 Follow-up: mean 2.9 years	There is moderate-quality evidence that 4-valent HPV vaccine reduces persistent HPV 6, 11, 16 or 18 infection in 16 to 26-year old MSM compared with placebo.	39/381 person years at risk	2/386 person years at risk	Rate ratio 0.05 (0.01 to 0.21); 401 participants in 1 study	⨁⨁⨁◯ MODERATE [1]
Persistent infection HPV 6 Follow-up: mean 2.9 years	There is moderate-quality evidence that 4-valent HPV vaccine reduces persistent HPV 6 infection in 16 to 26-year old MSM compared with placebo.	13/287 person years at risk	1/278 person years at risk	Rate ratio 0.08 (0.01 to 0.61); 284 participants in 1 study	⨁⨁⨁◯ MODERATE [1]
Persistent infection HPV 11 Follow-up: mean 2.9 years	There is low-quality evidence of no significant difference on persistent HPV 11 infection between 4-valent HPV vaccine compared with placebo in 16 to 26-year old MSM.	5/296 person years at risk	0/279 person years at risk	Rate ratio 0.10 (0.01 to 1.74); 284 participants in 1 study	⨁⨁◯◯ LOW [1 2]
Persistent infection HPV 16 Follow-up: mean 2.9 years	There is moderate-quality evidence that 4-valent HPV vaccine reduces persistent HPV 16 infection in 16 to 26-year old MSM compared with placebo.	16/330 person years at risk	1/331 person years at risk	Rate ratio 0.06 (0.01 to 0.47); 336 participants in 1 study	⨁⨁⨁◯ MODERATE [1]
Persistent infection HPV 18 Follow-up: mean 2.9 years	There is moderate-quality evidence that 4-valent HPV vaccine reduces persistent HPV 18 infection in 16 to 26-year old MSM compared with placebo.	10/376 person years at risk	0/346 person years at risk	Rate ratio 0.05 (0.00 to 0.88); 365 participants in 1 study	⨁⨁⨁◯ MODERATE [1]

CI= confidence interval; HPV= human papilloma virus; MSM= men who have sex with men; RR= rate ratio

[1] Downgraded one level for imprecision: Very low event rate. [2] Downgraded one further level for imprecision: 95% CI around the pooled estimate of effect includes appreciable benefit for both the intervention and control groups, as well as no effect.

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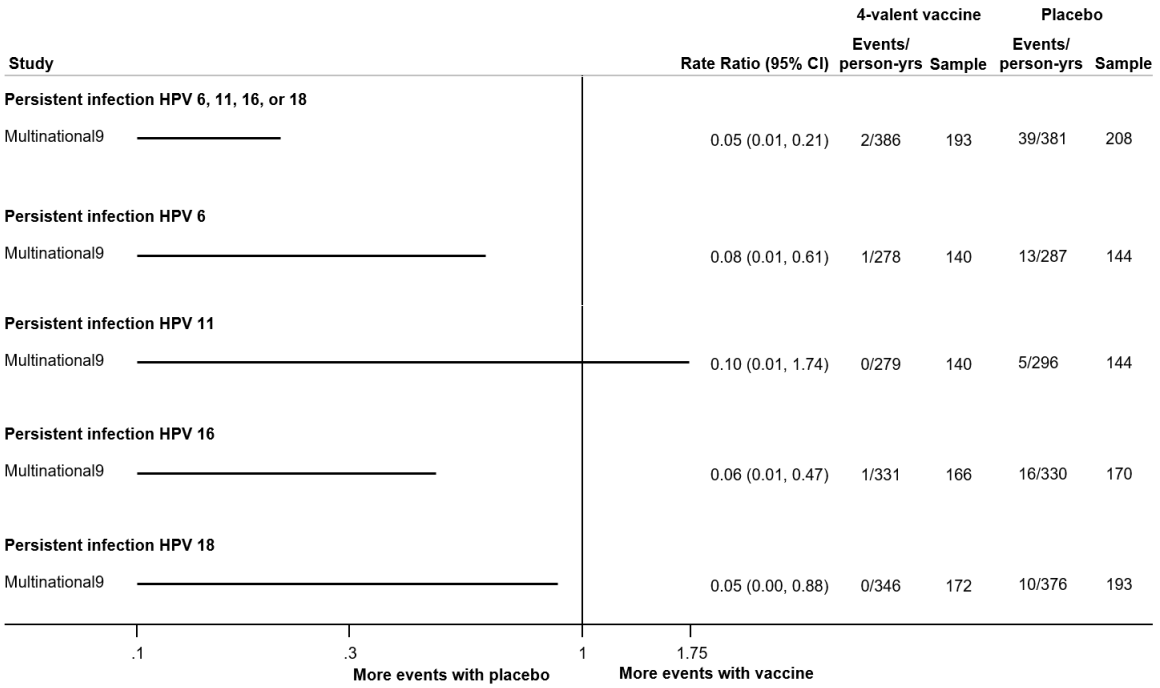
Forest plots: 4-valent HPV vaccine versus placebo in 16 to 26 year old MSM – clinical outcomes, persistent infection – per protocol analyses

Patients: **16 to 26 year-old MSM (seronegative at baseline)**
***Setting*: Australia, Brazil, Canada, Croatia, Germany, Spain, and the United States**
Intervention: **4-valent HPV vaccine (3-doses (Day 1, Month 2, Month 6)) versus placebo (3-doses (Day 1, Month 2, Month 6))**

Outcome	Forest plot	Certainty of the evidence (GRADE)
Persistent infection Follow-up: mean 2.9 years		⊕⊕⊕O MODERATE ⊕⊕⊕O MODERATE ⊕⊕OO LOW ⊕⊕⊕O MODERATE ⊕⊕⊕O MODERATE

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Summary of Findings: 9-valent HPV vaccine in 16-26 year old MSM versus 9-valent HPV vaccine in 16-26 year old females – immunogenicity outcomes

Patients: **16 to 26-year old MSM and females (seronegative at baseline)**
Setting**: Canada, Colombia, Denmark, Germany, Israel, Malaysia, Mexico, Norway, Peru, the Philippines, Poland, South Africa, Spain, Sweden, Thailand, Turkey and the United States**
Intervention: **9-valent HPV vaccine (3-doses (Day 1, Month 2, Month 6))**

Outcome	Plain language summary	Absolute effect		Relative effect (95% CI) Nº of participants & studies	Certainty of the evidence (GRADE)
		Females	MSM		
GMTs for HPV 6 follow up: 7 months	There is moderate-quality evidence of lower but non-inferior GMTs for HPV 6 in MSM compared with females	703.9 mMU/mL	568.9 mMU/mL	Ratio 0.81 (0.70 to 0.94); 872 participants in 1 study	⊕⊕⊕O MODERATE[1]
GMTs for HPV 11 follow up: 7 months	There is moderate-quality evidence of lower but non-inferior GMTs for HPV 11 in MSM compared with females	564.9 mMU/mL	437.7 mMU/mL	Ratio 0.77 (0.67 to 0.90); 877 participants in 1 study	⊕⊕⊕O MODERATE[1]
GMTs for HPV 16 follow up: 7 months	There is moderate-quality evidence of lower but non-inferior GMTs for HPV 16 in MSM compared with females	2788.3 mMU/mL	2294 mMU/mL	Ratio 0.82 (0.72 to 0.94); 993 participants in 1 study	⊕⊕⊕O MODERATE[1]
GMTs for HPV 18 follow up: 7 months	There is moderate-quality evidence of no significant difference in GMTs for HPV 18 between MSM and females; MSM were non-inferior	679.8 mMU/mL	608.1 mMU/mL	Ratio 0.89 (0.77 to 1.05); 1051 participants in 1 study	⊕⊕⊕O MODERATE[1]
GMTs for HPV 31 follow up: 7 months	There is moderate-quality evidence of lower but non-inferior GMTs for HPV 31 in MSM compared with females	570.1 mMU/mL	420.7 mMU/mL	Ratio 0.74 (0.63 to 0.86); 1053 participants in 1 study	⊕⊕⊕O MODERATE[1]
GMTs for HPV 33 follow up: 7 months	There is moderate-quality evidence of lower but non-inferior GMTs for HPV 33 in MSM compared with females	322 mMU/mL	252.3 mMU/mL	Ratio 0.78 (0.69 to 0.89); 1083 participants in 1 study	⊕⊕⊕O MODERATE[1]
GMTs for HPV 45 follow up: 7 months	There is moderate-quality evidence of lower but non-inferior GMTs for HPV 45 in MSM compared with females	185.7 mMU/mL	157.5 mMU/mL	Ratio 0.85 (0.72 to 1.00); 1103 participants in 1 study	⊕⊕⊕O MODERATE[1]
GMTs for HPV 52 follow up: 7 months	There is moderate-quality evidence of lower but non-inferior GMTs for HPV 52 in MSM compared with females	335.2 mMU/mL	233.1 mMU/mL	Ratio 0.70 (0.60 to 0.80); 1081 participants in 1 study	⊕⊕⊕O MODERATE[1]
GMTs for HPV 58 follow up: 7 months	There is moderate-quality evidence of lower but non-inferior GMTs for HPV 58 in MSM compared with females	409.3 mMU/mL	319.8 mMU/mL	Ratio 0.78 (0.68 to 0.90); 1062 participants in 1 study	⊕⊕⊕O MODERATE[1]

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Outcome	Plain language summary	Absolute effect		Relative effect (95% CI) Nº of participants & studies	Certainty of the evidence (GRADE)
		Females	MSM		
Seropositivity for HPV 6 follow up: 7 months	There is moderate-quality evidence of no significant difference in seropositivity for HPV 6 between MSM and females	705/708 (99.6%)	163/164 (99.4%)	RR 1.00 (0.99 to 1.01) 872 participants in 1 study	⊕⊕⊕O MODERATE[1]
Seropositivity for HPV 11 follow up: 7 months	There is moderate-quality evidence of no significant difference in seropositivity for HPV 11 between MSM and females	711/712 (99.9%)	165/165 (100%)	RR 1.00 (0.99 to 1.01) 877 participants in 1 study	⊕⊕⊕O MODERATE[1]
Seropositivity for HPV 16 follow up: 7 months	There is moderate-quality evidence of no significant difference in seropositivity for HPV 16 between MSM and females	780/781 (99.9%	212/212 (100%)	RR 1.00 (0.99 to 1.01) 993 participants in 1 study	⊕⊕⊕O MODERATE[1]
Seropositivity for HPV 18 follow up: 7 months	There is moderate-quality evidence of no significant difference in seropositivity for HPV 18 between MSM and females	829/831 (99.8%)	219/220 (99.5%)	RR 1.00 (0.99 to 1.01) 1051 participants in 1 study	⊕⊕⊕O MODERATE[1]
Seropositivity for HPV 31 follow up: 7 months	There is moderate-quality evidence of no significant difference in seropositivity for HPV 31 between MSM and females	826/826 (100%)	227/227 (100%)	Not estimable*; 1053 participants in 1 study	⊕⊕⊕O MODERATE[1]
Seropositivity for HPV 33 follow up: 7 months	There is moderate-quality evidence of no significant difference in seropositivity for HPV 33 between MSM and females	852/853 (99.9%)	230/230 (100%)	RR 1.00 (0.99 to 1.01) 1083 participants in 1 study	⊕⊕⊕O MODERATE[1]
Seropositivity for HPV 45 follow up: 7 months	There is moderate-quality evidence of no significant difference in seropositivity for HPV 45 between MSM and females	867/871 (99.5%)	232/232 (100%)	RR 1.00 (1.00 to 1.01) 1103 participants in 1 study	⊕⊕⊕O MODERATE[1]
Seropositivity for HPV 52 follow up: 7 months	There is moderate-quality evidence of no significant difference in seropositivity for HPV 52 between MSM and females	847/849 (99.8%)	232/232 (100%)	RR 1.00 (0.99 to 1.01) 1081 participants in 1 study	⊕⊕⊕O MODERATE[1]
Seropositivity for HPV 58 follow up: 7 months	There is moderate-quality evidence of no significant difference in seropositivity for HPV 58 between MSM and females	837/839 (99.8%)	223/223 (100%)	RR 1.00 (0.99 to 1.01) 1062 participants in 1 study	⊕⊕⊕O MODERATE[1]

CI= confidence interval; GMT= geometric mean titre; HPV= human papilloma virus; MSM= men who have sex with men; RR=risk ratio

*Excluded from analysis due to no non-events; all participants seropositive.

[1]Downgraded one level for risk of bias: non-random comparison.

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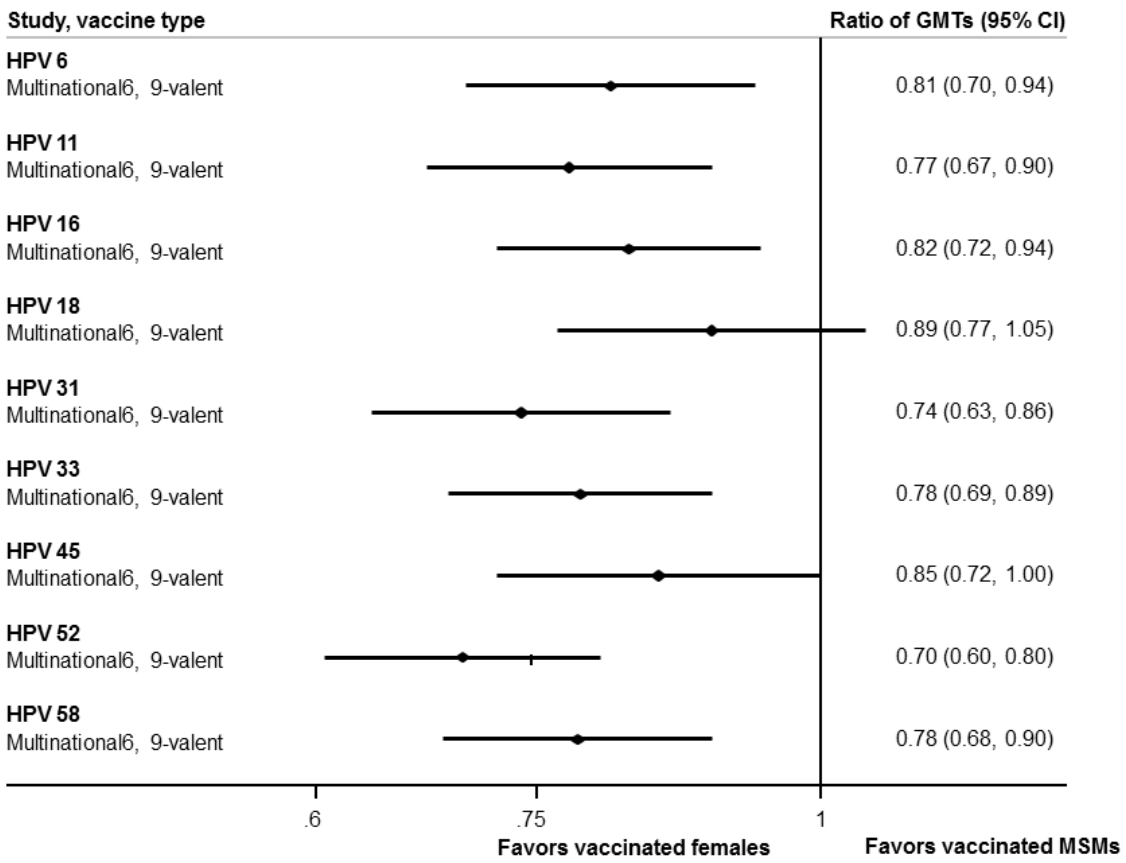
Forest plots: 9-valent HPV vaccine in 16-26 year old MSM versus 9-valent HPV vaccine in 16-26 year old females – immunogenicity outcomes [9]

Patients: **16 to 26-year old MSM and females (seronegative at baseline)**
***Setting*: Canada, Colombia, Denmark, Germany, Israel, Malaysia, Mexico, Norway, Peru, the Philippines, Poland, South Africa, Spain, Sweden, Thailand, Turkey and the United States**
Intervention: **9-valent HPV vaccine (3-doses (Day 1, Month 2, Month 6))**

Outcome	Forest plot	Certainty of the evidence (GRADE)
Ratio of GMTs follow up: 7 months		⊕⊕⊕O MODERATE

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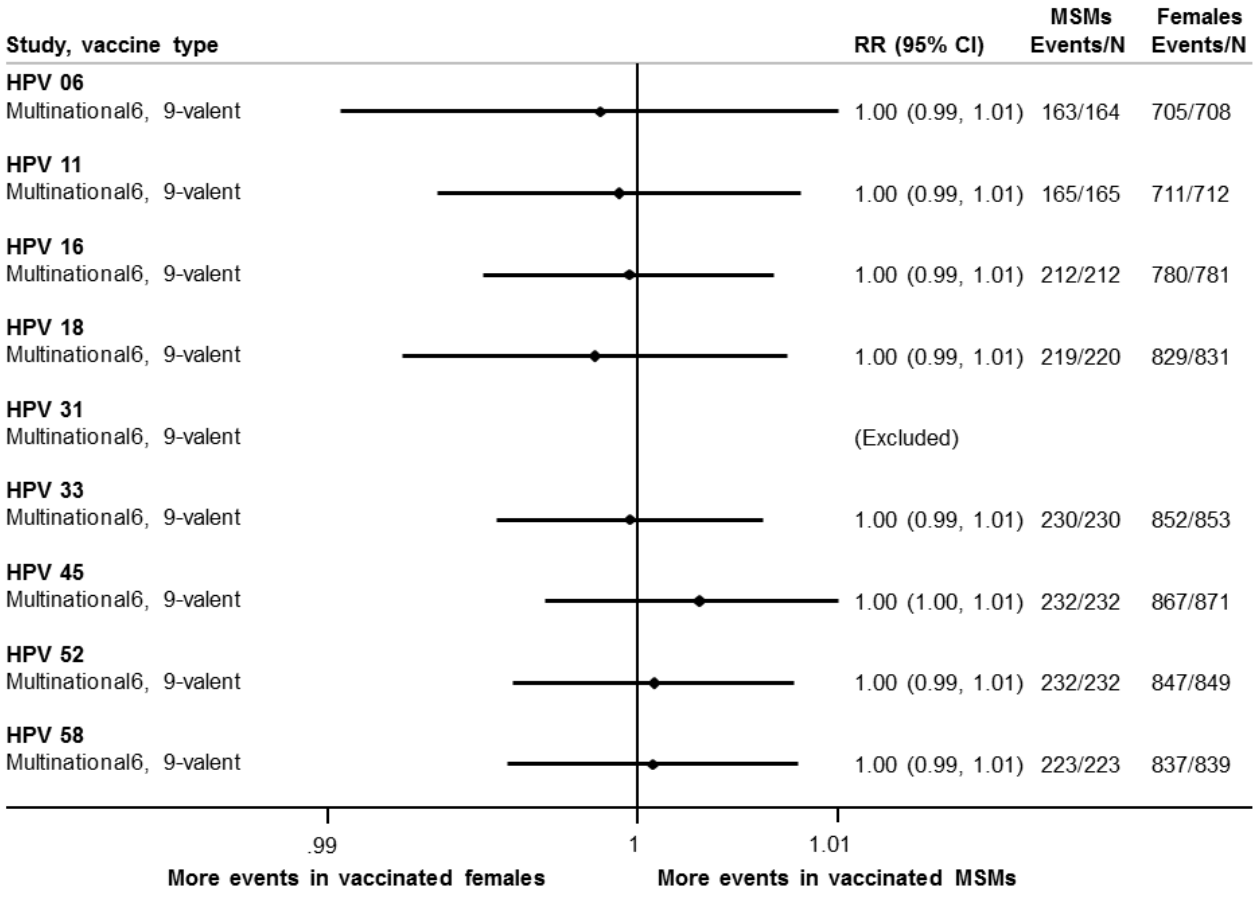
Outcome	Forest plot	Certainty of the evidence (GRADE)
Seropositivity follow up: 7 months		⊕⊕⊕O MODERATE

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Summary of Findings: 9-valent HPV vaccine in 16-26 year old MSM versus 9-valent HPV vaccine in 16-26 year old heterosexual males – immunogenicity outcomes [11]

Patients: **16 to 26-year old MSM and heterosexual males (seronegative at baseline)**

Setting**: Canada, Colombia, Denmark, Germany, Israel, Malaysia, Mexico, Norway, Peru, the Philippines, Poland, South Africa, Spain, Sweden, Thailand, Turkey and the United States**

Comparison: **9-valent HPV vaccine (3-doses (Day 1, Month 2, Month 6))**

Outcome	Plain language summary	Absolute effect		Relative effect (95% CI) Nº of participants & studies	Certainty of the evidence (GRADE)
		Heterosexual males	MSM		
GMTs for HPV 6 follow up: 7 months	There is moderate-quality evidence of lower but non-inferior GMTs for HPV 6 in MSM compared with heterosexual males	782 mMU/mL	568.9 mMU/mL	Ratio 0.73 (0.63 to 0.84) 1011 participants in 1 study	⊕⊕⊕O MODERATE[1]
GMTs for HPV 11 follow up: 7 months	There is moderate-quality evidence of lower but non-inferior GMTs for HPV 11 in MSM compared with heterosexual males	616.7 mMU/mL	437.7 mMU/mL	Ratio 0.71 (0.62 to 0.82) 1016 participants in 1 study	⊕⊕⊕O MODERATE[1]
GMTs for HPV 16 follow up: 7 months	There is moderate-quality evidence of lower but non-inferior GMTs for HPV 16 in MSM compared with heterosexual males	3346 mMU/mL	2294 mMU/mL	Ratio 0.69 (0.60 to 0.78) 1111 participants in 1 study	⊕⊕⊕O MODERATE[1]
GMTs for HPV18 follow up: 7 months	There is moderate-quality evidence of lower but non-inferior GMTs for HPV 18 in MSM compared with heterosexual males	808.2 mMU/mL	608.1 mMU/mL	Ratio 0.75 (0.64 to 0.88) 1126 participants in 1 study	⊕⊕⊕O MODERATE[1]
GMTs for HPV 31 follow up: 7 months	There is moderate-quality evidence of lower but non-inferior GMTs for HPV 31 in MSM compared with heterosexual males	708.5 mMU/mL	420.7 mMU/mL	Ratio 0.59 (0.51 to 0.69) 1135 participants in 1 study	⊕⊕⊕O MODERATE[1]
GMTs for HPV 33 follow up: 7 months	There is moderate-quality evidence of lower but non-inferior GMTs for HPV 33 in MSM compared with heterosexual males	384.8 mMU/mL	252.3 mMU/mL	Ratio 0.66 (0.57 to 0.75) 1131 participants in 1 study	⊕⊕⊕O MODERATE[1]
GMTs for HPV 45 follow up: 7 months	There is moderate-quality evidence of lower but non-inferior GMTs for HPV 45 in MSM compared with heterosexual males	235.6 mMU/mL	157.5 mMU/mL	Ratio 0.67 (0.57 to 0.79) 1141 participants in 1 study	⊕⊕⊕O MODERATE[1]
GMTs for HPV 52 follow up: 7 months	There is moderate-quality evidence of lower but non-inferior GMTs for HPV 52 in MSM compared with heterosexual males	386.8 mMU/mL	233.1 mMU/mL	Ratio 0.60 (0.52 to 0.69) 1139 participants in 1 study	⊕⊕⊕O MODERATE[1]
GMTs for HPV 58 follow up: 7 months	There is moderate-quality evidence of lower but non-inferior GMTs for HPV 58 in MSM compared with heterosexual males	509.8 mMU/mL	319.8 mMU/mL	Ratio 0.63 (0.55 to 0.72) 1120 participants in 1 study	⊕⊕⊕O MODERATE[1]

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Outcome	Plain language summary	Absolute effect		Relative effect (95% CI) Nº of participants & studies	Certainty of the evidence (GRADE)
		Heterosexual males	MSM		
Seropositivity for HPV 6 follow up: 7 months	There is moderate-quality evidence of no significant difference in seropositivity for HPV 6 between MSM and heterosexual males	844/847 (99.6%)	163/164 (99.4%)	RR 1.00 (0.98 to 1.01) 1011 participants in 1 study	⊕⊕⊕O MODERATE[1]
Seropositivity for HPV 11 follow up: 7 months	There is moderate-quality evidence of no significant difference in seropositivity for HPV 11 between MSM and heterosexual males	851/851 (100%)	165/165 (100%)	Not estimable*; 1016 participants in 1 study	⊕⊕⊕O MODERATE[1]
Seropositivity for HPV 16 follow up: 7 months	There is moderate-quality evidence of no significant difference in seropositivity for HPV 16 between MSM and heterosexual males	899/899 (100%)	212/212 (100%)	Not estimable*; 1111 participants in 1 study	⊕⊕⊕O MODERATE[1]
Seropositivity for HPV 18 follow up: 7 months	There is moderate-quality evidence of no significant difference in seropositivity for HPV 18 between MSM and heterosexual males	905/906 (99.9%)	219/220 (99.5%)	RR 1.00 (0.99 to 1.01) 1126 participants in 1 study	⊕⊕⊕O MODERATE[1]
Seropositivity for HPV 31 follow up: 7 months	There is moderate-quality evidence of no significant difference in seropositivity for HPV 31 between MSM and heterosexual males	908/908 (100%)	227/227 (100%)	Not estimable*; 1135 participants in 1 study	⊕⊕⊕O MODERATE[1]
Seropositivity for HPV 33 follow up: 7 months	There is moderate-quality evidence of no significant difference in seropositivity for HPV 33 between MSM and heterosexual males	901/901 (100%)	230/230 (100%)	Not estimable*; 1131 participants in 1 study	⊕⊕⊕O MODERATE[1]
Seropositivity for HPV 45 follow up: 7 months	There is moderate-quality evidence of no significant difference in seropositivity for HPV 45 between MSM and heterosexual males	907/909 (99.8%)	232/232 (100%)	RR 1.00 (0.99 to 1.01) 1141 participants in 1 study	⊕⊕⊕O MODERATE[1]
Seropositivity for HPV 52 follow up: 7 months	There is moderate-quality evidence of no significant difference in seropositivity for HPV 52 between MSM and heterosexual males	907/907 (100%)	232/232 (100%)	Not estimable*; 1139 participants in 1 study	⊕⊕⊕O MODERATE[1]
Seropositivity for HPV 58 follow up: 7 months	There is moderate-quality evidence of no significant difference in seropositivity for HPV 58 between MSM and heterosexual males	897/897 (100%)	223/223 (100%)	Not estimable*; 1120 participants in 1 study	⊕⊕⊕O MODERATE[1]

CI= confidence interval; GMT= geometric mean titre; HPV= human papilloma virus; HS= heterosexual; MSM= men who have sex with men; RR=risk ratio

*Excluded from analysis due to no non-events; all participants seropositive.

[1]Downgraded one level for risk of bias: non-random comparison.

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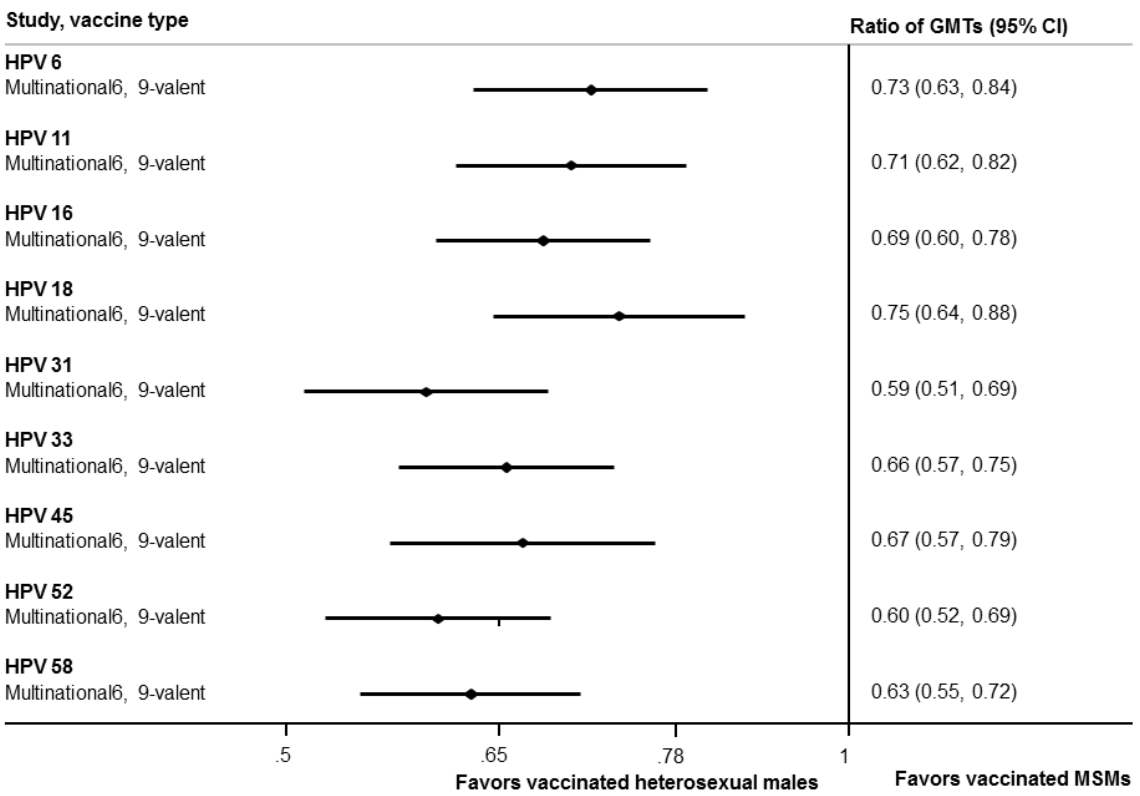
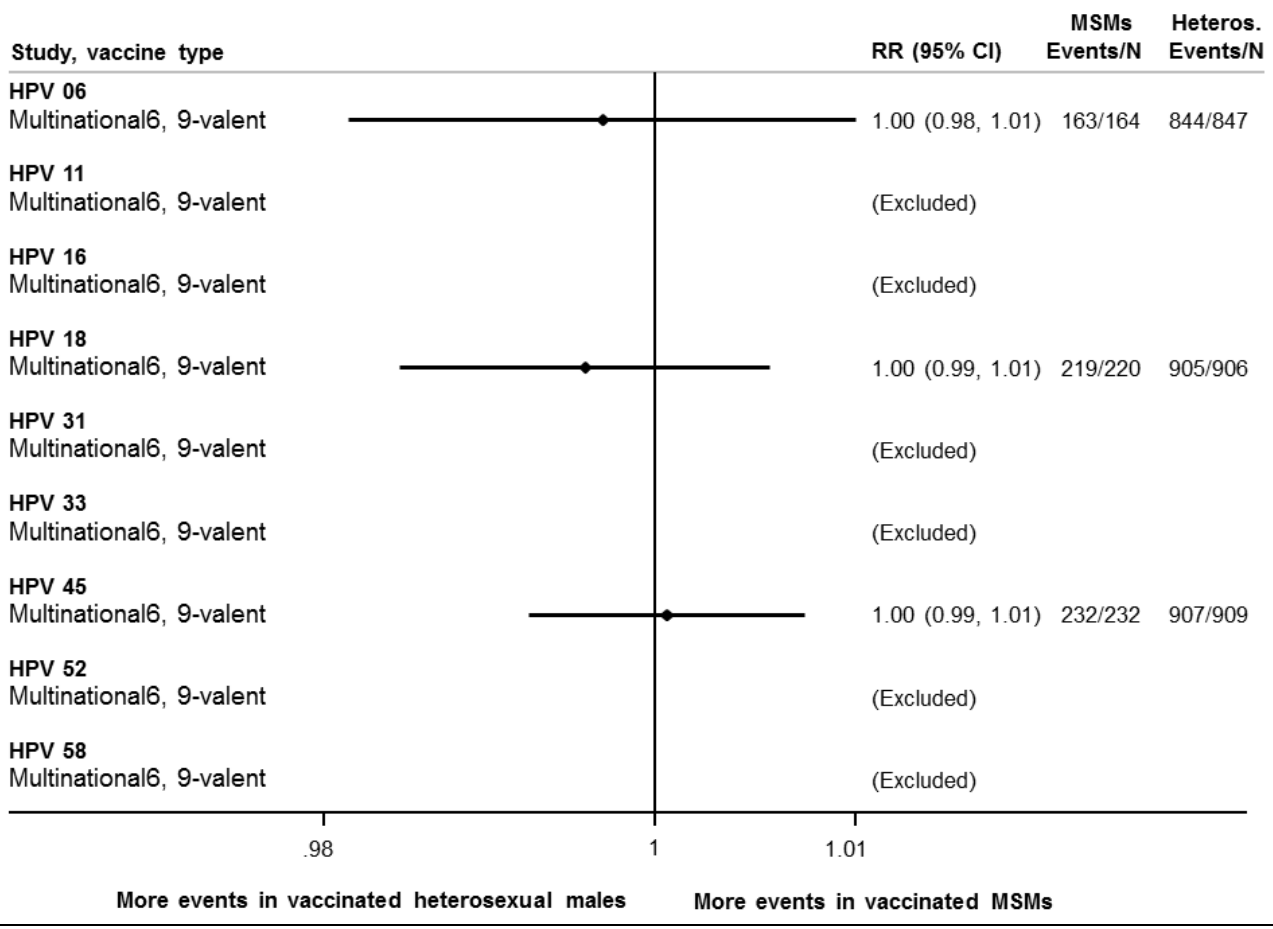
Forest plots: 9-valent HPV vaccine in 16-26 year old MSM versus 9-valent HPV vaccine in 16-26 year old heterosexual males – immunogenicity outcomes

Patients: **16 to 26-year old MSM and heterosexual males (seronegative at baseline)**
***Setting*: Canada, Colombia, Denmark, Germany, Israel, Malaysia, Mexico, Norway, Peru, the Philippines, Poland, South Africa, Spain, Sweden, Thailand, Turkey and the United States**
Comparison: **9-valent HPV vaccine (3-doses (Day 1, Month 2, Month 6))**

Outcome	Forest plot	Certainty of the evidence (GRADE)
Ratio of GMTs follow up: 7 months		⊕⊕⊕O MODERATE

Plots continued overleaf

Outcome	Forest plot	Certainty of the evidence (GRADE)
Seropositivity follow up: 7 months		⊕⊕⊕O MODERATE

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Multinational6

Castellsagué X, Giuliano AR, Goldstone S, et al. Immunogenicity and safety of the 9-valent HPV vaccine in men. Vaccine. 2015 Nov 27;33(48):6892-901. doi: 10.1016/j.vaccine.2015.06.088. Epub 2015 Jul 2.

Multinational9

PalefskyJ M, Giuliano AR, Goldstone S, Moreira ED, Aranda C, Jessen H, et al. HPV vaccine against anal HPV infection and anal intraepithelial neoplasia. N Engl J Med. 2011 Oct 27;365(17):1576-85. doi: 10.1056/NEJMoa1010971.

HPV vaccines in HIV-infected males and females

Contents

Trusted evidence.
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Key findings

In 7 to 12-year old HIV-infected children, GMTs for HPV 6, 11, 16 and 18 were higher after 4-valent HPV vaccine than placebo at 7 to 24 months, and seroconversion for the four HPV types was >97% at 7 months. The evidence was judged to be of moderate quality.

In 18 to 25-year old females given the 2-valent HPV vaccine, there was low-quality evidence that GMTs for HPV 16 and 18 were significantly lower in women with HIV than women without HIV, although non-inferiority was inconclusive. With regard to seropositivity, 100% of HIV-infected and HIV-uninfected women were seropositive at 12 months.

In adults over 18 years, there was low-quality evidence of no significant difference, and inconclusive non-inferiority, in GMTs for HPV 16 between the 2-valent and 4-valent HPV vaccines at 7 and 12 months. There was low-quality evidence that the 4-valent vaccine is inferior to 2-valent vaccine for GMTs for HPV 18 at 7 months; at 12 months non-inferiority was inconclusive. There was low-quality evidence of no significant difference in ratios seropositive to HPV 16 between the 2-valent and 4-valent vaccines at 12 months, however the 2-valent vaccine had a significantly higher ratio of seropositivity to HPV 18 at 12 months.

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. Patients living with human immunodeficiency virus (HIV) have a higher risk of developing HPV-related cancer. In this Targeted Update, we review and analyse evidence for the protection afforded by prophylactic HPV vaccines in people living with HIV.

Objectives

To evaluate the efficacy and immunogenicity of HPV vaccines in people living with HIV.

Search methods

Searches were conducted from January 2006 to June 2016, and all relevant studies regardless of language or publication status were searched. 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 industries for any potential relevant study through the WHO Initiative for Vaccines Research Department (IVR).

Selection criteria

Randomised controlled trials (RCTs) and non-randomised experimental studies were eligible for inclusion. We included studies with comparisons against placebo, comparisons among different types of HPV vaccine, and comparisons to people living without HIV.

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 reported as ratios. 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. For the comparisons of HIV-infected females versus non-HIV-infected females, and 4-valent versus 2-valent HPV vaccine in HIV-infected adults, the non-inferiority threshold for HIV-infected females and 4-valent vaccine, respectively, was 0.5 for the ratio of GMTs.

Main Results

We identified four RCTs (USA/Puerto Rico1; South Africa1; Denmark1; Italy1). USA/Puerto Rico1 compared 4-valent vaccine versus placebo vaccine in 126 HIV-infected children aged 7 to 12 years. South Africa1 compared 2-valent HPV vaccine in 150 women aged 18 to 25 living with and without HIV. Denmark1 compared 2-valent with 4-valent vaccine in 92 adults living with HIV. Italy1 compared 4-valent vaccine in 92 adolescents living with and without HIV; however, it did not report immunogenicity data for the separate HPV subtypes and was therefore omitted from this Targeted Update.

The risk of bias was unclear for some domains in USA/Puerto Rico and South Africa1, but were all low for Denmark1. We downgraded the quality of the evidence for the non-randomised comparison of females with and without HIV, but we did not downgrade for lack of clarity around blinding as outcomes were assessed objectively (immunological outcomes).

4-valent HPV vaccine versus placebo vaccine in 7 to 12-year old HIV-infected children

The USA/Puerto Rico1 study reported immunogenicity outcomes at 7 and 24 months. GMTs for HPV 6, 11, 16 and 18 were 123.8 to 935.8-fold higher at 7 months, and 29.6 to 189.4-fold higher at 24 months, than in the placebo group. Seroconversion for the four HPV types was >97% at 7 months. The evidence was judged to be of moderate quality.

2-valent HPV vaccine in 18 to 25-year old females with and without HIV

The South Africa1 study reported immunogenicity outcomes at 7 months. There was low-quality evidence that the GMTs for HPV 16 and 18 were significantly lower in women with HIV than women without HIV, although non-inferiority was inconclusive. With regard to seropositivity, 100% of HIV-infected and HIV-uninfected women were seropositive at 12 months.

4-valent HPV vaccine versus 2-valent HPV vaccine in HIV-infected adults

The Denmark1 study reported immunogenicity outcomes at 7 and 12 months. There was low-quality evidence of no significant difference, and inconclusive non-inferiority, in GMTs for HPV 16 between the 2-valent and 4-valent HPV vaccines at 7 and 12 months. There was low-quality evidence that the 4-valent vaccine is inferior to 2-valent vaccine for GMTs for HPV 18 at 7 months; at 12 months non-inferiority was inconclusive. There was no significant difference in ratios seropositive to HPV 16 between the 2-valent and 4-valent vaccines at 12 months, however the 2-valent vaccine had a significantly higher ratio of seroconversion to HPV 18 at 12 months.

Implications and conclusions

Evidence for the immunogenicity of HPV vaccines in children living with HIV shows beneficial effects compared with placebo at 7 months. In HIV-infected women the 2-valent vaccine produced lower GMTs than in HIV-uninfected women; however, the rate of seroconversion is the same between groups (low-quality evidence). The 2-valent vaccine has similar immunogenicity to HPV 16 as the 4-valent vaccine, but results in higher GMTs and greater rate of seroconversion to HPV 18 in adults living with HIV.

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Summary of Findings: 4-valent HPV vaccine versus placebo in 7 to 12-year old HIV-infected children – immunogenicity outcomes [3]

Patients: **7 to 12-year old males and females (seronegative at baseline)**
Setting**: United States and Puerto Rico**
Comparison: **4-valent HPV vaccine (3-doses (Month 0, 2, 6)) versus placebo vaccine (3-doses)**

Outcome		Plain language summary	Absolute effect		Relative effect (95% CI) Nº of participants & studies	Certainty of the evidence (GRADE)
			Placebo vaccine	4-valent HPV vaccine		
GMTs for HPV 6	7 months	There is moderate-quality evidence that 4-valent HPV vaccine results in significantly higher GMTs for HPV 6 than placebo in HIV-infected children until 24 months.	Mean: 4.46 mMU/mL	Mean: 552 mMU/mL	Ratio 123.8 (89.0 to 172.1) 126 participants in 1 RCT	⊕⊕⊕O MODERATE [1]
	24 months		Mean: 4.54 mMU/mL	Mean: 229 mMU/mL	Ratio 50.4 (34.2 to 74.4) 116 participants in 1 RCT	
GMTs for HPV 11	7 months	There is moderate-quality evidence that 4-valent HPV vaccine results in significantly higher GMTs for HPV 11 than placebo in HIV-infected children until 24 months.	Mean: 4.15 mMU/mL	Mean: 1371 mMU/mL	Ratio 330.4 (261.6 to 417.2) 126 participants in 1 RCT	⊕⊕⊕O MODERATE [1]
	24 months		Mean: 4 mMU/mL	Mean: 275 mMU/mL	Ratio 68.8 (49.3 to 95.8) 116 participants in 1 RCT	
GMTs for HPV 16	7 months	There is moderate-quality evidence that 4-valent HPV vaccine results in significantly higher GMTs for HPV 16 than placebo in HIV-infected children until 24 months.	Mean: 5.59 mMU/mL	Mean: 5231 mMU/mL	Ratio 935.8 (724.5 to 1208.7) 126 participants in 1 RCT	⊕⊕⊕O MODERATE [1]
	24 months		Mean: 5.4 mMU/mL	Mean: 1023 mMU/mL	Ratio 189.4 (129.3 to 277.6) 116 participants in 1 RCT	
GMTs for HPV 18	7 months	There is moderate-quality evidence that 4-valent HPV vaccine results in significantly higher GMTs for HPV 18 than placebo in HIV-infected children until 24 months.	Mean: 4.92 mMU/mL	Mean: 931 mMU/mL	Ratio 189.2 (132.8 to 269.7) 126 participants in 1 RCT	⊕⊕⊕O MODERATE [1]
	24 months		Mean: 4.87 mMU/mL	Mean: 144 mMU/mL	Ratio 29.6 (18.1 to 48.4) 116 participants in 1 RCT	
Seroconversion for HPV 6 follow up: 7 months		There is moderate-quality evidence that 4-valent HPV vaccine results in a significantly higher ratio of seroconversion for HPV 6 than placebo.	0/27 (0%)	87/87 (100%)	RR 55.7 (3.6 to 868.4) 114 participants in 1 RCT	⊕⊕⊕O MODERATE [1]
Seroconversion for HPV 11 follow up: 7 months		There is moderate-quality evidence that 4-valent HPV vaccine results in a significantly higher ratio of seroconversion for HPV 11 than placebo.	0/27 (0%)	90/90 (100%)	RR 55.7 (3.6 to 868.6) 117 participants in 1 RCT	⊕⊕⊕O MODERATE [1]
Seroconversion for HPV 16 follow up: 7 months		There is moderate-quality evidence that 4-valent HPV vaccine results in a significantly higher ratio of seroconversion for HPV 16 than placebo.	1/27 (4%)	90/90 (100%)	RR 18.6 (3.9 to 88.1) 117 participants in 1 RCT	⊕⊕⊕O MODERATE [1]
Seroconversion for HPV 18 follow up: 7 months		There is moderate-quality evidence that 4-valent HPV vaccine results in a significantly higher ratio of seroconversion for HPV 18 than placebo.	0/27 (0%)	87/90 (97%)	RR 53.9 (3.5 to 840.0) 117 participants in 1 RCT	⊕⊕⊕O MODERATE [1]

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

[1] Downgraded one level for imprecision: low number of participants.

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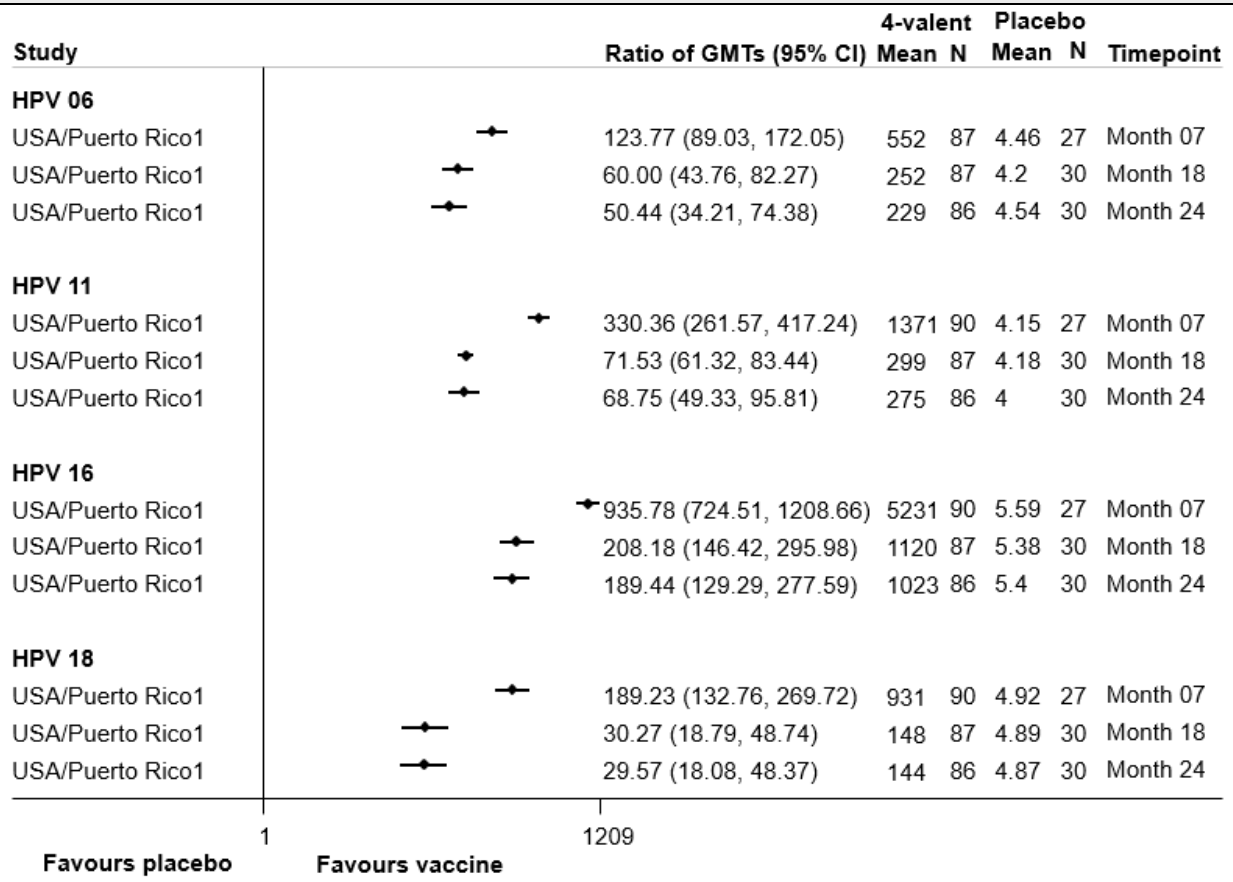
Graph: 4-valent HPV vaccine versus placebo vaccine in 7 to 12-year old HIV-infected children – immunogenicity outcomes

Patients: **7 to 12-year old males and females (seronegative at baseline)**
***Setting*: United States and Puerto Rico**
Comparison: **4-valent HPV vaccine (3-doses (Month 0, 2, 6)) versus placebo vaccine (3-doses)**

Outcome	Graph	Certainty of the evidence (GRADE)
GMTs for HPV 6, 11, 16 and 18 follow up: 7-24 months		⊕⊕⊕O MODERATE ⊕⊕⊕O MODERATE ⊕⊕⊕O MODERATE ⊕⊕⊕O MODERATE ⊕⊕⊕O MODERATE ⊕⊕⊕O MODERATE ⊕⊕⊕O MODERATE ⊕⊕⊕O MODERATE ⊕⊕⊕O MODERATE ⊕⊕⊕O MODERATE ⊕⊕⊕O MODERATE ⊕⊕⊕O MODERATE

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

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Summary of Findings: 2-valent HPV vaccine in 18 to 25-year old HIV-infected females versus non-HIV-infected females – immunogenicity outcomes

Patients: **18 to 25-year old females (mixed sero-status at baseline)**
Setting**: South Africa**
Comparison: **2-valent HPV vaccine (3-doses (Day 1, Month 1, Month 6)) in HIV-infected females versus 2-valent HPV vaccine (3-doses (Day 1, Month 1, Month 6)) in non-HIV-infected females**

Outcome	Plain language summary	Absolute effect		Relative effect (95% CI) Nº of participants & studies	Certainty of the evidence (GRADE)
		Non-HIV-infected females	HIV-infected females		
GMTs for HPV 16 follow up: 7 months	There is low-quality evidence that 2-valent HPV vaccine results in significantly lower GMTs for HPV 16 at 7 months in HIV-infected females than non-HIV-infected females; non-inferiority is inconclusive.	Mean: 8168.8 EU/mL	Mean: 3558.2 EU/mL	Ratio 0.44 (0.30 to 0.63) 150 participants in 1 RCT	⊕⊕OO LOW[1,2]
GMTs for HPV 18 follow up: 7 months	There is low-quality evidence that the 2-valent HPV vaccine results in significantly lower GMTs for HPV 18 at 7 months in HIV-infected females than in non-HIV-infected females; non-inferiority is inconclusive.	Mean: 3703 EU/mL	Mean: 1945.8 EU/mL	Ratio 0.53 (0.32 to 0.86) 150 participants in 1 RCT	⊕⊕OO LOW[1,2]
Seropositivity for HPV 16 follow up: 12 months	There is low-quality evidence of no significant difference in ratios of seropositivity for HPV 16 with 2-valent HPV vaccine between HIV-infected and non-HIV-infected females.	22/22 (100%)	42/42 (100%)	RR 1.00 (not estimable) 64 participants in 1 RCT	⊕⊕OO LOW[1,2]
Seropositivity for HPV 18 follow up: 12 months	There is low-quality evidence of no significant difference in ratios of seropositivity for HPV 18 with 2-valent HPV vaccine between HIV-infected and non-HIV-infected females.	22/22 (100%)	42/42 (100%)	RR 1.00 (not estimable) 64 participants in 1 RCT	⊕⊕OO LOW[1,2]

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

[1]Downgraded one level for design: non-randomized comparison

[2]Downgraded one level for imprecision: low number of participants.

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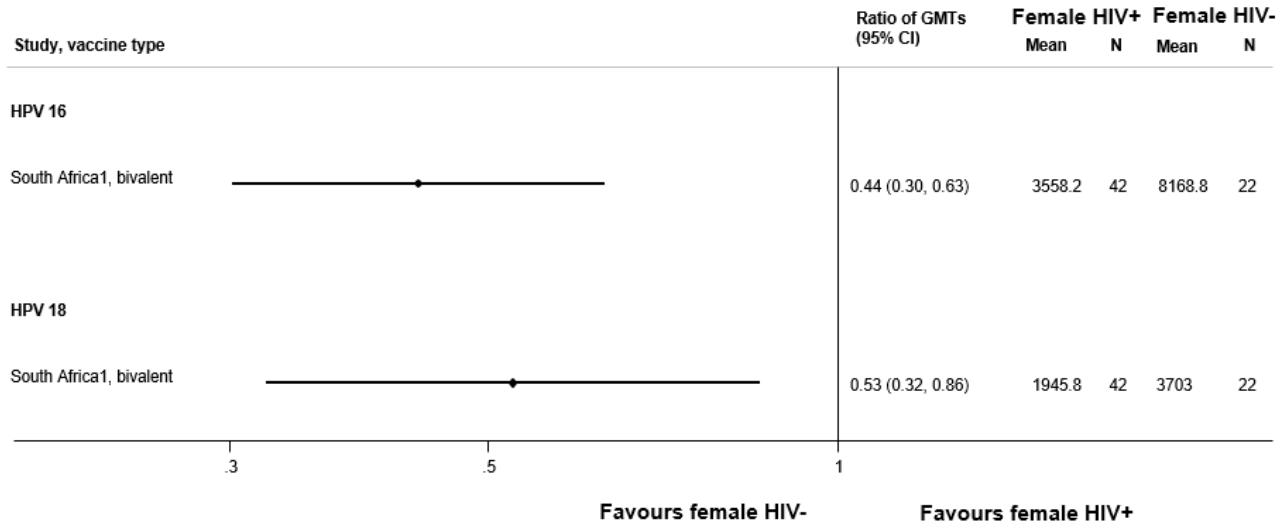
Forest plot: 2-valent HPV vaccine in 18 to 25-year old HIV-infected females versus non-HIV-infected females – immunogenicity outcomes

Patients: **18 to 25-year old females (mixed sero-status at baseline)**
Setting**: South Africa**
Comparison: **2-valent HPV vaccine (3-doses (Day 1, Month 1, Month 6)) in HIV-infected females versus 2-valent HPV vaccine (3-doses (Day 1, Month 1, Month 6)) in non-HIV-infected females**

Outcome	Forest plot	Certainty of the evidence (GRADE)
Ratio of GMTs follow-up: 7 months		⊕⊕OO LOW ⊕⊕OO LOW

CI= confidence interval; GMT= Geometric mean titre; HPV= human papilloma virus; HIV= human immunodeficiency virus

Forest plot for seroconversion not shown, as all participants in both groups seroconverted.

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Summary of Findings: 4-valent HPV vaccine versus 2-valent HPV vaccine in HIV-infected adult males and females – immunogenicity outcomes

Patients: **18+ year old HIV-infected males and females (seronegative at baseline)**
Setting**: Denmark**
Comparison: **4-valent HPV vaccine (3-doses (Day 1, Month 1.5, Month 6)) versus 2-valent HPV vaccine (3-doses (Day 1, Month 1.5, Month 6))**

Outcome		Plain language summary	Absolute effect*		Relative effect (95% CI) Nº of participants & studies	Certainty of the evidence (GRADE)
			2-valent HPV vaccine	4-valent HPV vaccine		
GMTs for HPV 16	Month 7	There is low-quality evidence of no significant difference, and inconclusive non-inferiority, in GMTs for HPV 16 between 2-valent and 4-valent HPV vaccines up to 12 months	Mean: 59112	Mean: 46906	Ratio 0.79 (0.25 to 2.52) 92 participants in 1 RCT	⊕⊕OO LOW [1]
	Month 12		Mean: 14027	Mean: 9363	Ratio 0.67 (0.21 to 2.08) 92 participants in 1 RCT	
GMTs for HPV 18	Month 7	There is low-quality evidence that 4-valent vaccine is inferior to 2-valent vaccine for GMTs for HPV 18 at 7 months; at 12 months non-inferiority is inconclusive	Mean: 24368	Mean: 3208	Ratio 0.13 (0.04 to 0.41) 92 participants in 1 RCT	⊕⊕OO LOW [1]
	Month 12		Mean: 6135	Mean: 3208	Ratio 0.52 (0.16 to 1.76) 92 participants in 1 RCT	
Seropositivity for HPV 16 follow up: 12 months		There is low-quality evidence of no significant difference in ratios of seropositivity for HPV 16 between 2-valent and 4-valent HPV vaccines	45/45 (100%)	44/46 (96%)	RR 0.96 (0.89 to 1.03) 91 participants in 1 RCT	⊕⊕OO LOW [1]
Seropositivity for HPV 18 follow up: 12 months		There is low-quality evidence that 4-valent HPV vaccine results in a significantly lower ratio of seropositivity for HPV 18 compared with 2-valent HPV vaccine	44/45 (98%)	34/46 (74%)	RR 0.76 (0.63 to 0.90) 91 participants in 1 RCT	⊕⊕OO LOW [1]

*GMTs were computed using the log10 transformation of titres

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

[1] Downgraded two levels for imprecision: very low number of participants.

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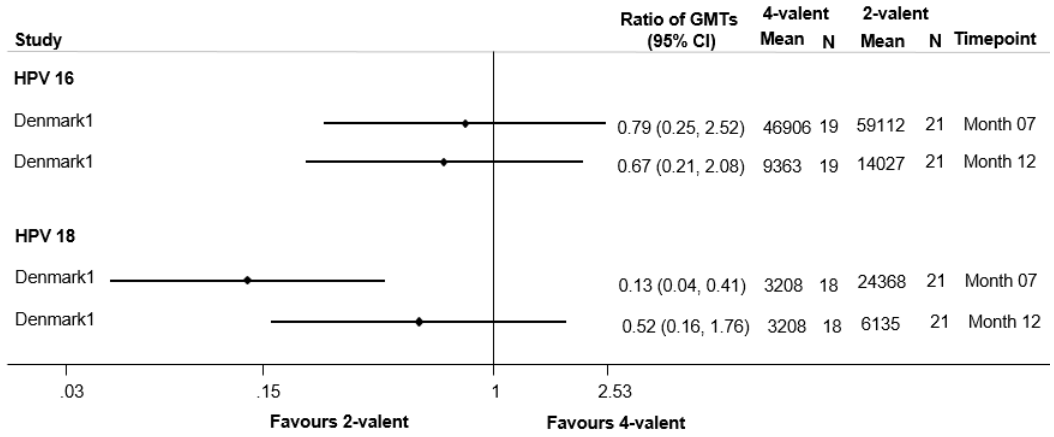
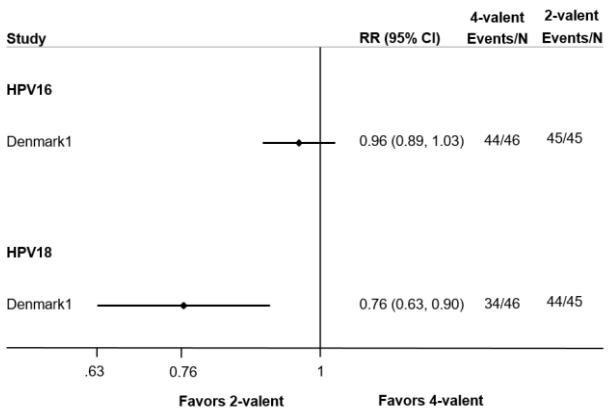
Forest plot: 4-valent HPV vaccine versus 2-valent HPV vaccine in HIV-infected adult males and females – immunogenicity outcomes

Patients: **18+ year old HIV-infected males and females (seronegative at baseline)**
***Setting*: Denmark**
Comparison: **4-valent HPV vaccine (3-doses (Day 1, Month 1.5, Month 6)) versus 2-valent HPV vaccine (3-doses (Day 1, Month 1.5, Month 6))**

Outcome	Forest plot	Certainty of the evidence (GRADE)
Ratio of GMTs* follow up: 7-12 months		⊕⊕OO LOW
Seropositivity Follow up: 12 months		⊕⊕OO LOW

*GMTs were computed using the log10 transformation of titres. CI= confidence interval; GMT= Geometric mean titre; HPV= human papilloma virus; HIV= human immunodeficiency virus; RR= risk ratio

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