Additional file 2

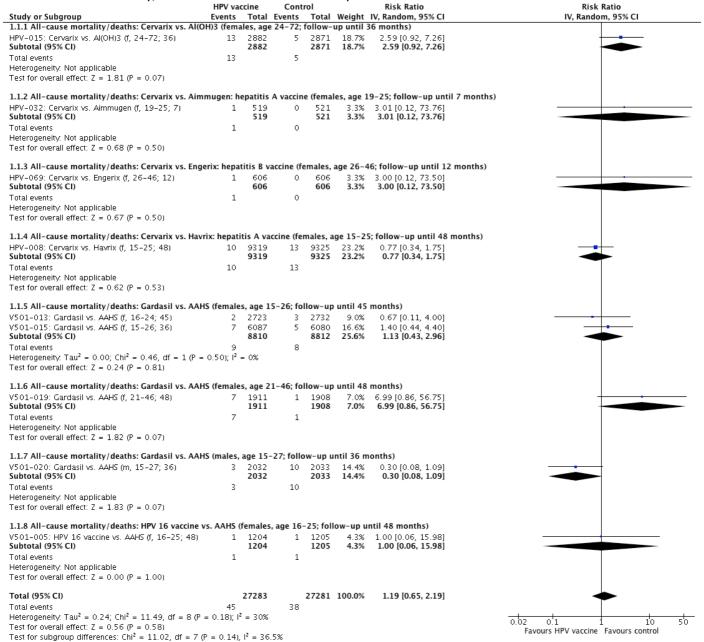
Comparison of HPV vaccine study documents: meta-analyses

Table of contents

<u>1.</u>	Clinical study reports	2
2.	Trial register entries	22
<u>3.</u>	Journal publications	42

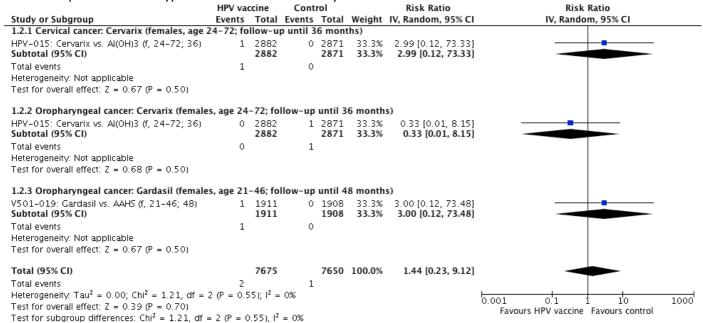
1. Clinical study reports

1.1. All-cause mortality/deaths*: intention to treat analysis



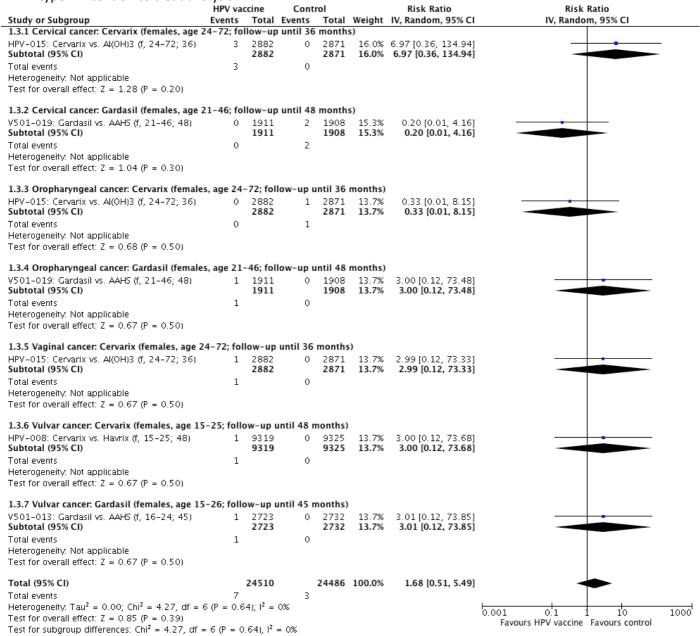
^{*1.1.} Risk ratio for GlaxoSmithKline studies (i.e., HPV-0xx): 1.43 [0.65, 3.15]; risk ratio for Merck Sharp & Dohme studies (i.e., V50x-xxx): 1.08 [0.40, 2.96].

1.2. Mortality/deaths from HPV-related cancers (anal, cervical, oropharyngeal, penile, vaginal and vulvar) irrespective of HPV type*: intention to treat analysis



^{*1.2.} Risk ratio for GlaxoSmithKline studies (i.e., HPV-0xx): 1.00 [0.10, 9.57]; risk ratio for Merck Sharp & Dohme studies (i.e., V50x-xxx): 3.00 [0.12, 73.48].

1.3. Incidence of HPV-related cancers (anal, cervical, oropharyngeal, penile, vaginal and vulvar) irrespective of HPV type*: intention to treat analysis



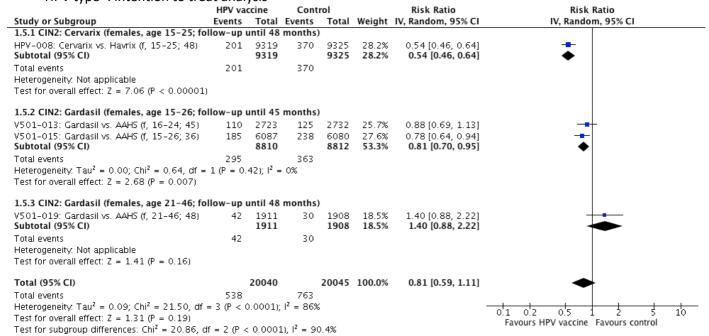
^{*1.3.} Risk ratio for GlaxoSmithKline studies (i.e., HPV-0xx): 2.24 [0.47, 10.74]; risk ratio for Merck Sharp & Dohme studies (i.e., V50x-xxx): 1.14 [0.19, 6.99]. There were no reported cases of anal or penile cancer.

1.4. Incidence of HPV-related carcinoma in situ (anal intraepithelial neoplasia grade 3 [AIN3], cervical adenocarcinoma in situ [AIS], cervical intraepithelial neoplasia grade 3 [CIN3], penile intraepithelial neoplasia grade 3 [PIN3], vaginal intraepithelial neoplasia grade 3 [VIN3] and vulvar intraepithelial neoplasia grade 3 [VaIN3]) irrespective of HPV type*: intention to treat analysis

	HPV va	ccine	Cont	rol		Risk Ratio	Risk Ratio
Study or Subgroup	Events		Events	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
1.4.1 AIS: Cervarix (females, age 15-25; foll	-						
HPV-008: Cervarix vs. Havrix (f, 15-25; 48)	3	9319	13	9325	5.2%	0.23 [0.07, 0.81]	
Gubtotal (95% CI) Fotal events	3	9319	13	9325	5.2%	0.23 [0.07, 0.81]	•
otal events leterogeneity. Not applicable	3		13				
est for overall effect: Z = 2.29 (P = 0.02)							
.4.2 AIS: Gardasil (females, age 15-26; foll							
501-013: Gardasil vs. AAHS (f, 16-24; 45)	1		6	2732	2.1%	0.17 [0.02, 1.39]	
/501-015: Gardasil vs. AAHS (f, 15-26; 36) i ubtotal (95% CI)	5	6087 8810	10	6080 8812	6.6% 8.7%	0.50 [0.17, 1.46] 0.40 [0.15, 1.04]	
otal events	6	0010	16	0012	0.770	0.40 [0.13, 1.04]	
Heterogeneity: Tau² = 0.00; Chi² = 0.82, df =		371: 12 =					
est for overall effect: Z = 1.88 (P = 0.06)	10 - 0.	57,,1	070				
4.2 AIS: Cardacil (females, age 21–46; fell	0W-11B 11	s+il 40 m	aonthe)				
. .4.3 AIS: Gardasil (females, age 21–46; foll '501–019: Gardasil vs. AAHS (f, 21–46; 48)		1911	2	1908	1.1%	0.20 [0.01, 4.16]	
Subtotal (95% CI)		1911	2	1908	1.1%	0.20 [0.01, 4.16]	
Total events	0		2				
leterogeneity. Not applicable							
est for overall effect: Z = 1.04 (P = 0.30)							
.4.4 CIN3: Cervarix (females, age 15-25; fo	llow-up	until 48	months)			
HPV-008: Cervarix vs. Havrix (f, 15-25; 48)	83	9319	145	9325	22.6%	0.57 [0.44, 0.75]	•
ubtotal (95% CI)		9319		9325	22.6%	0.57 [0.44, 0.75]	•
otal events	83		145				
Heterogeneity. Not applicable							
Test for overall effect: $Z = 4.07 (P < 0.0001)$							
.4.5 CIN3: Gardasil (females, age 15-26; fo	llow-up	until 45	months)			
7501-013: Gardasil vs. AAHS (f, 16-24; 45)	84	2723	76	2732	21.5%	1.11 [0.82, 1.51]	+
/501-015: Gardasil vs. AAHS (f, 15-26; 36)	153	6087	208	6080	24.1%	0.73 [0.60, 0.90]	•
ubtotal (95% CI)		8810		8812	45.7%	0.89 [0.59, 1.33]	*
otal events	237		284				
leterogeneity: Tau² = 0.07; Chi² = 4.79, df =	1 (P = 0.	03); 12 =	79%				
est for overall effect: Z = 0.58 (P = 0.56)							
.4.6 CIN3: Gardasil (females, age 21-46; fo	llow-up	until 48	months)			
/501-019: Gardasil vs. AAHS (f, 21-46; 48)	38	1911	30	1908	16.8%	1.26 [0.79, 2.03]	 -
ubtotal (95% CI)		1911		1908	16.8%	1.26 [0.79, 2.03]	*
otal events	38		30				
leterogeneity. Not applicable							
est for overall effect: Z = 0.97 (P = 0.33)							
Total (95% CI)		40080		40090	100.0%	0.73 [0.53, 1.00]	•
Fotal events	367		490				
Heterogeneity: Tau² = 0.10; Chi² = 21.43, df	= 7 (P = 0)	0.003); I	² = 67%				0.001 0.1 1 10 10
est for overall effect: Z = 1.94 (P = 0.05)							Favours HPV vaccine Favours control
est for subgroup differences: Chi² = 14.44, o							no ctudios (i.o. V50v xxx): 0.97 [0.62, 1.22]. Th

^{*1.4.} Risk ratio for GlaxoSmithKline studies (i.e., HPV-0xx): **0.45** [**0.21**, **0.99**]; risk ratio for Merck Sharp & Dohme studies (i.e., V50x-xxx): **0.87** [**0.62**, **1.22**]. There were no reports of AIN3, PIN3, VIN3 or VaIN3 irrespective of HPV type.

1.5. Incidence of HPV-related moderate intraepithelial neoplasia (anal intraepithelial neoplasia grade 2 [AIN2], cervical intraepithelial neoplasia grade 2 [CIN2], penile intraepithelial neoplasia grade 2 [PIN2], vaginal intraepithelial neoplasia grade 2 [VIN2] and vulvar intraepithelial neoplasia grade 2 [VaIN2]) irrespective of HPV type*: intention to treat analysis



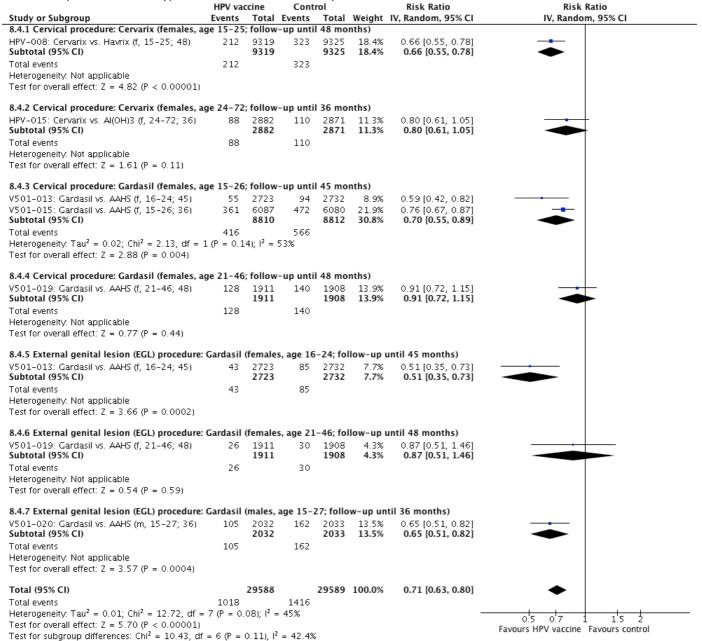
^{*1.5.} Risk ratio for GlaxoSmithKline studies (i.e., HPV-0xx): **0.54 [0.46, 0.64]**; risk ratio for Merck Sharp & Dohme studies (i.e., V50x-xxx): 0.92 [0.70, 1.19]. There were no reports of AIN2, PIN2, VIN2 or VaIN2 irrespective of HPV type.

1.6. Incidence of HPV-related moderate intraepithelial neoplasia or worse (AIN2+, CIN2+, PIN2+, VIN2+, VaIN2+) irrespective of HPV type*: intention to treat analysis

Study or Subgroup		Total			Weight	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI
.6.1 CIN2+: Cervarix (females, age 15-25; fo							
PV-008: Cervarix vs. Havrix (f, 15-25; 48) ubtotal (95% Cl)	287	9319 9319	428	9325 9325	18.0% 18.0%	0.67 [0.58, 0.78]	‡
otal events	287	9319	428	9323	18.0%	0.67 [0.58, 0.78]	▼
eterogeneity: Not applicable	207		720				
est for overall effect: Z = 5.33 (P < 0.00001)							
6.2. CIN2 Comparin (formalise and 22, 20, fol		12					
.6.2 CIN2+: Cervarix (females, age 22-29; fol	-			463	C 40/	0.46 (0.37.0.70)	_
IPV-063: Cervarix vs. Aimmugen (f, 22-29; 12) ubtotal (95% CI)	19	464 464	41	463 463	6.4% 6.4%	0.46 [0.27, 0.78] 0.46 [0.27, 0.78]	_
otal events	19		41		011,1		
Heterogeneity: Not applicable							
est for overall effect: Z = 2.86 (P = 0.004)							
6.2 CIN2++ Converie (females, age 24-72+fel	llow-up up	til 26 m	onths)				
l. 6.3 CIN2+: Cervarix (females, age 24-72; fo l IPV-015: Cervarix vs. Al(OH)3 (f, 24-72; 36)	10 3	2882	108	2871	13.4%	0.95 [0.73, 1.24]	
Subtotal (95% CI)	103	2882	100	2871		0.95 [0.73, 1.24]	•
otal events	103		108				
Heterogeneity. Not applicable							
est for overall effect: Z = 0.38 (P = 0.70)							
.6.4 CIN2+: Gardasil (females, age 15-26; fol	low-up un	til 45 m	onths)				
/501-013: Gardasil vs. AAHS (f, 16-24; 45)	152	2723	166	2732	15.4%	0.92 [0.74, 1.14]	- -
/501-015: Gardasil vs. AAHS (f, 15-26; 36)	269	6087	350		17.7%	0.77 [0.66, 0.90]	*
ubtotal (95% CI)		8810		8812	33.1%	0.83 [0.70, 0.98]	◆
Fotal events	421	12 4 4 4	516				
Heterogeneity: Tau² = 0.01; Chi² = 1.78, df = 1 Fest for overall effect: Z = 2.15 (P = 0.03)	(P = 0.18);	1" = 449	6				
esciol overali eliett. Z = 2.13 (F = 0.03)							
l.6.5 CIN2+: Gardasil (females, age 21-46; fol	llow-up un	til 48 m	onths)				
/501-019: Gardasil vs. AAHS (f, 21-46; 48)	62	1911	51	1908	10.1%	1.21 [0.84, 1.75]	
Subtotal (95% CI)		1911		1908	10.1%	1.21 [0.84, 1.75]	•
otal events	62		51				
Heterogeneity: Not applicable Test for overall effect: Z = 1.04 (P = 0.30)							
(2.5 () () () () () () () () () (
1.6.6 PIN2+: Gardasil (males, age 15-27; follo	w-up until	36 mon	ths)				
/501-020: Gardasil vs. AAHS (m, 15-27; 36)	3	2032	3	2033	1.0%	1.00 [0.20, 4.95]	
Subtotal (95% CI)	_	2032	_	2033	1.0%	1.00 [0.20, 4.95]	
Fotal events Heterogeneity: Not applicable	3		3				
Fest for overall effect: Z = 0.00 (P = 1.00)							
1.6.7 VIN2+: Gardasil (females, age 15-26; fol	-						
/501-013: Gardasil vs. AAHS (f, 16-24; 45)	12	2723	15	2732	3.7%	0.80 [0.38, 1.71]	
/501-015: Gardasil vs. AAHS (f, 15-26; 36) Subtotal (95% CI)	6	6087 8810	21	6080 8812	2.7% 6.4%	0.29 [0.12, 0.71] 0.49 [0.18, 1.36]	
Total events	18	0010	36		0.170	0.45 [0.10, 1.50]	
Heterogeneity: Tau² = 0.35; Chi² = 2.94, df = 1		l ² = 669					
Test for overall effect: $Z = 1.37$ (P = 0.17)							
6 9 VolN2 to Conducit (formulas ago 15, 26, fo							
l. 6.8 ValN2+: Gardasil (females, age 15-26; fo /501-013: Gardasil vs. AAHS (f, 16-24; 45)					2 19/	0.47 (0.30, 1.00)	
/501-015: Gardasii vs. AAHS (f, 16-24, 43)	8 6	2723 6087	17 9	2732 6080	3.1% 2.1%	0.47 [0.20, 1.09] 0.67 [0.24, 1.87]	
Subtotal (95% CI)	•	8810	_	8812	5.2%	0.54 [0.28, 1.04]	•
otal events	14		26				
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.26$, $df = 1$	(P = 0.61)	$1^2 = 0\%$					
est for overall effect: Z = 1.85 (P = 0.06)							
6.9 VaIN2+: Gardasil (females, age 21-46; fo	ollow-up u	ntil 48 n	nonths)				
7501-019: Gardasil vs. AAHS (f, 21-46; 48)	3	1911	1		0.5%	3.00 [0.31, 28.77]	
Subtotal (95% CI)		1911	-	1908	0.5%	3.00 [0.31, 28.77]	
otal events	3		1				
Heterogeneity. Not applicable							
est for overall effect: Z = 0.95 (P = 0.34)							
.6.10 VIN2+ or VaIN2+: Cervarix (females, ag	e 15-25; fo	ollow-ur	until 4	8 month	hs)		
HPV-008: Cervarix vs. Havrix (f, 15-25; 48)	22	9319	29		6.0%	0.76 [0.44, 1.32]	+
ubtotal (95% CI)		9319		9325	6.0%	0.76 [0.44, 1.32]	◆
Total events	22		29				
Heterogeneity. Not applicable							
est for overall effect: Z = 0.98 (P = 0.33)							
Total (95% CI)		54268		54269	100.0%	0.78 [0.66, 0.91]	◆
otal events	952		1239				-
	40.00	130 12 = 0	: >9/				
Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 25.46$, $df = 0.001$ Test for overall effect: $Z = 3.11$ ($P = 0.002$)	12 (P = 0.0	1), 1 = :	13/0				0.05 0.2 1 5 2

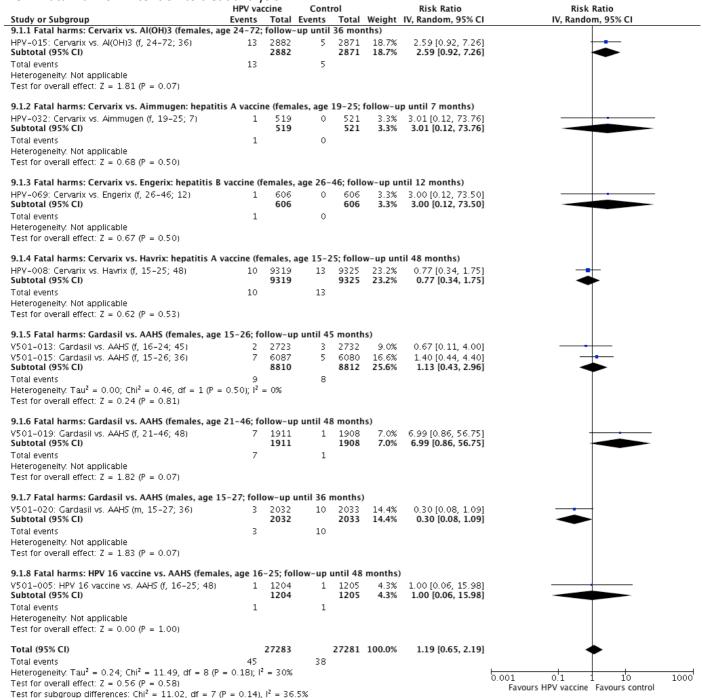
^{*1.6.} Risk ratio for GlaxoSmithKline studies (i.e., HPV-0xx): **0.72** [**0.55, 0.93**]; risk ratio for Merck Sharp & Dohme studies (i.e., V50x-xxx): 0.82 [0.66, 1.02]. There were no reports of AIN2+ irrespective of HPV type.

1.7. Number of treatment procedures (both surgical and non-surgical treatment) due to HPV-related diseases irrespective of HPV type*: intention to treat analysis



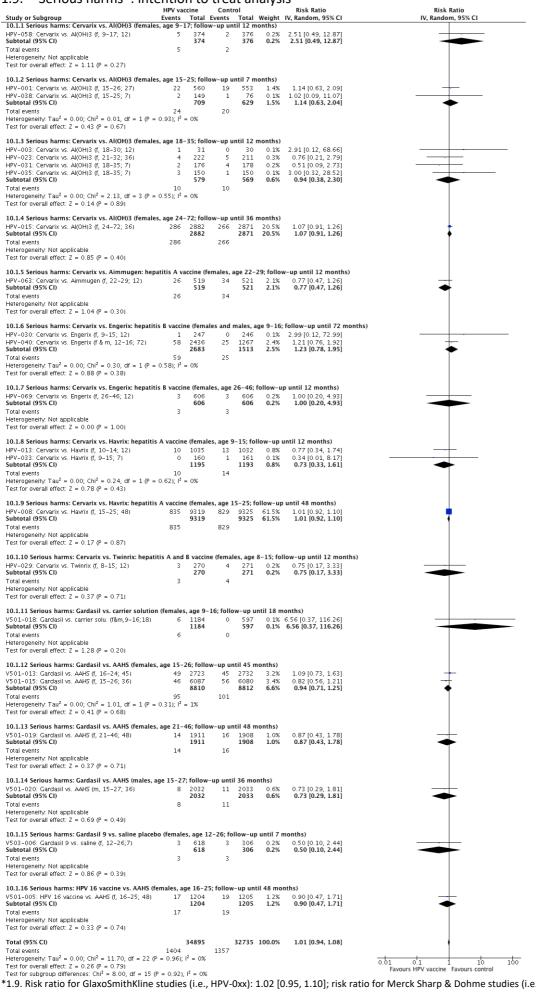
^{*1.7.} Risk ratio for GlaxoSmithKline studies (i.e., HPV-0xx): **0.70 [0.59, 0.84]**; risk ratio for Merck Sharp & Dohme studies (i.e., V50x-xxx): **0.71 [0.60, 0.83]**. Only cervical procedure: 844 in the HPV vaccine group vs. 1,139 in the control group, risk ratio **0.74 [0.65, 0.84]**; only EGL procedure: 174 vs. 277, risk ratio **0.63 [0.50, 0.80]**.

1.8. Fatal harms*: intention to treat analysis



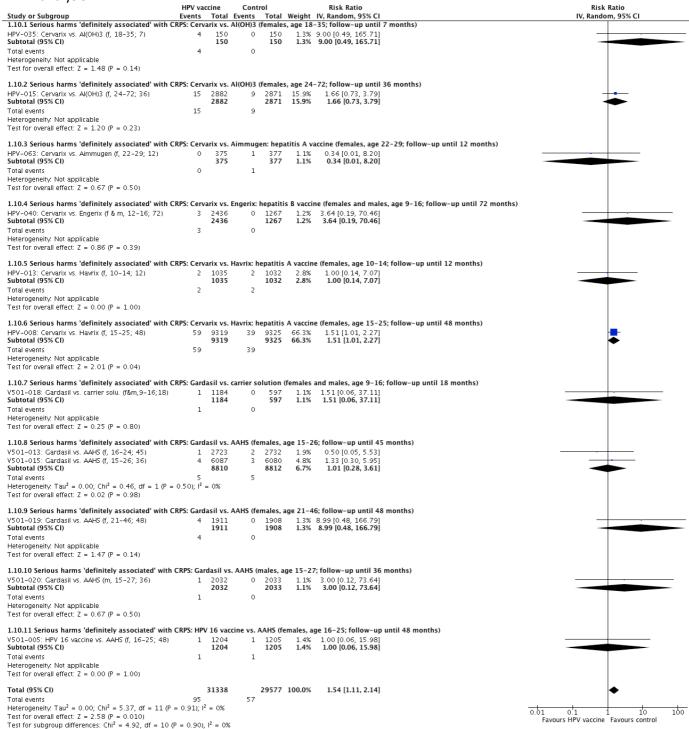
*1.8. Risk ratio for GlaxoSmithKline studies (i.e., HPV-0xx): 1.43 [0.65, 3.15]; risk ratio for Merck Sharp & Dohme studies (i.e., V50x-xxx): 1.08 [0.40, 2.96]. The most common fatal serious harms were: 'road traffic accident' (five in the HPV vaccine group and seven in the control group, risk ratio 0.77 [0.24, 2.46]); 'completed suicide' (four and eight, risk ratio 0.58 [0.15, 2.19]); 'cardiorespiratory arrest' (three and two, risk ratio 0.99 [0.13, 7.65]); 'gunshot wound' (two and three, risk ratio 0.74 [0.09, 5.85]); and 'homicide' (two and two, risk ratio 0.95 [0.14, 6.50]). The fatal serious harms most increased by the HPV vaccines were: 'cardiac arrest' (two in the HPV vaccine group and none in the control group, risk ratio 3.00 [0.31, 28.82]); 'raumatic intracranial haemorrhage' (two and none, risk ratio 3.00 [0.31, 28.82]); 'systemic lupus erythematosus' (two and none, risk ratio 3.00 [0.31, 28.82]); 'metastases to lung' (two and none, risk ratio 3.00 [0.31, 28.82]); and 'renal failure acute' (two and none, risk ratio 3.00 [0.31, 28.82]). The fatal serious harms most decreased by the HPV vaccines were: 'completed suicide' (four in the HPV vaccine group and eight in the control group, risk ratio 0.58 [0.15, 2.19]); and 'road traffic accident' (five and seven, risk ratio 0.77 [0.24, 2.46]).

1.9. Serious harms*: intention to treat analysis



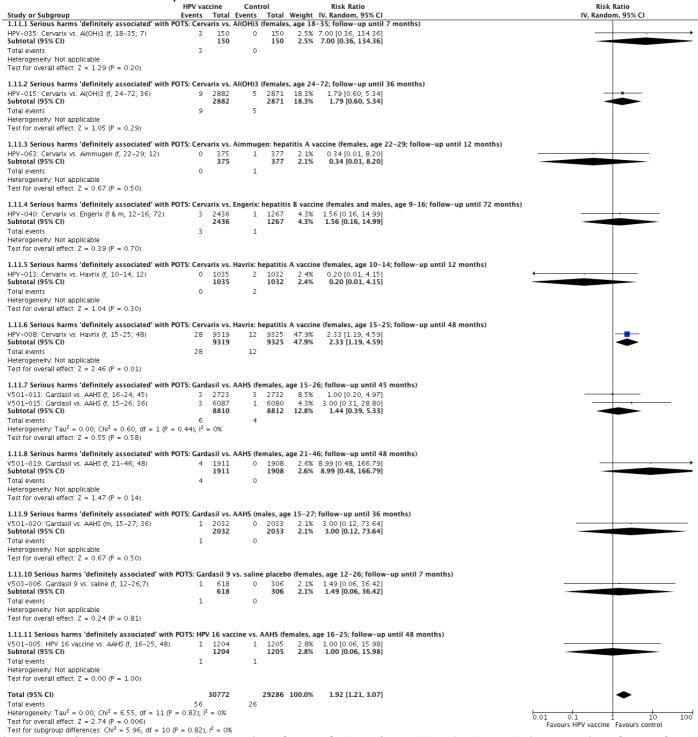
^{*1.9.} Risk ratio for GlaxoSmithKline studies (i.e., HPV-0xx): 1.02 [0.95, 1.10]; risk ratio for Merck Sharp & Dohme studies (i.e., V50x-xxx): 0.91 [0.73, 1.15].

1.10. Serious harms judged as 'definitely associated'* with chronic regional pain syndrome (CRPS): intention to treat analysis



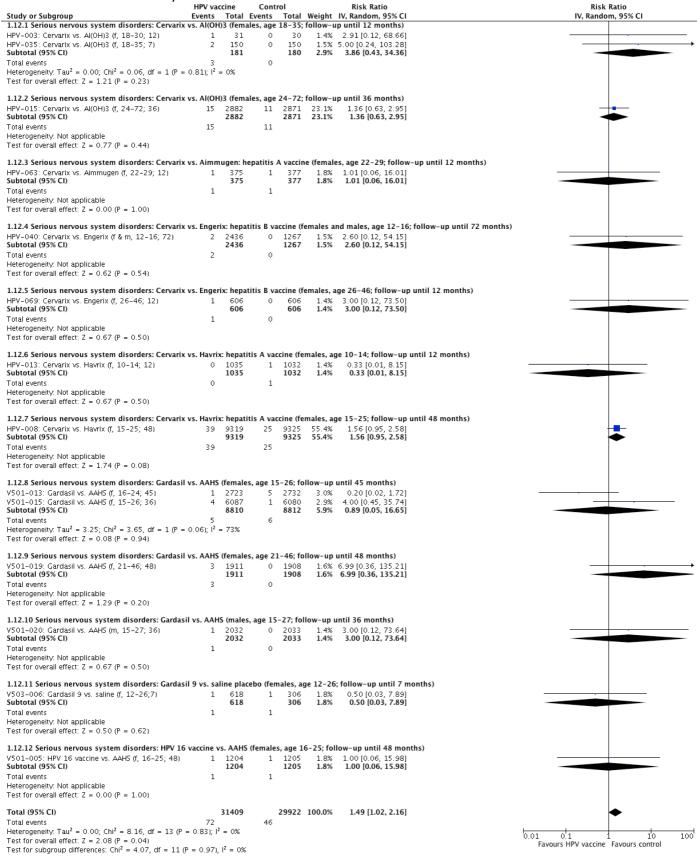
*1.10. Risk ratio for GlaxoSmithKline studies (i.e., HPV-0xx): 1.55 [1.09, 2.20]; risk ratio for Merck Sharp & Dohme studies (i.e., V50x-xxx): 1.47 [0.56, 3.89]. We asked a physician with clinical expertise in CRPS to assess the reported MedDRA preferred terms as 'definitely,' 'probably,' 'probably not' or 'definitely not' associated with CRPS. We sent an Excel sheet to the physician with all the reported MedDRA terms. The physician was blinded, as the Excel sheet contained no outcome data. When the physician had assessed all the MedDRA terms, we synthesized the data for those MedDRA terms that the physician judged 'definitely' associated with CRPS and compared it to the reported serious harms.

1.11. Serious harms judged as 'definitely associated'* with postural orthostatic tachycardia syndrome (POTS): intention to treat analysis



*1.11. Risk ratio for GlaxoSmithKline studies (i.e., HPV-0xx): 1.95 [1.15, 3.32]; risk ratio for Merck Sharp & Dohme studies (i.e., V50x-xxx): 1.82 [0.68, 4.89]. We asked a physician with clinical expertise in POTS to assess the reported MedDRA preferred terms as 'definitely,' 'probably,' 'probably not' or 'definitely not' associated with POTS. We sent an Excel sheet to the physician with all the reported MedDRA terms. The physician was blinded, as the Excel sheet contained no outcome data. When the physician had assessed all the MedDRA terms, we synthesized the data for those MedDRA terms that the physician judged 'definitely' associated with POTS and compared it to the reported serious harms.

1.12. Serious harms reported within the MedDRA system organ class 'nervous system disorders (10029205)'*: intention to treat analysis



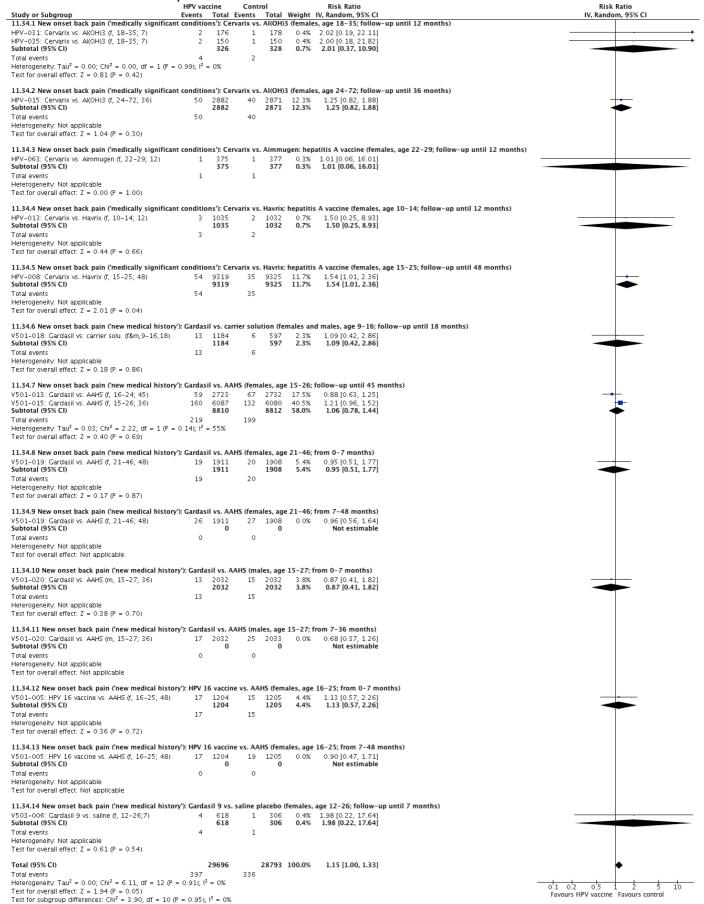
^{*1.12.} Risk ratio for GlaxoSmithKline studies (i.e., HPV-0xx): 1.53 [1.03, 2.28]; risk ratio for Merck Sharp & Dohme studies (i.e., V50x-xxx): 1.25 [0.39, 3.97].

1.13. New onset diseases ('medically significant conditions' and 'new medical history'*): intention to treat analysis

Study or Subgroup 11.1.1 New onset diseases (medically significant	conditions	'): Cerva	rix vs. A	I(OH)3 (females, a		until 12 months)	IV, Random, 95% CI
HPV-058: Cervarix vs. Al(OH)3 (f, 9-17; 12) Subtotal (95% CI)	10	374 374	10	376 376	0.1% 0.1%	1.01 [0.42, 2.39] 1.01 [0.42, 2.39]		-
Heterogeneity. Not applicable Test for overall effect: Z = 0.01 (P = 0.99)								
11.1.2 New onset diseases ('medically significant							p until 7 months)	
HPV-038: Cervarix vs. AI(0H)3 (f, 15-25; 7) Subtotal (95% CI) Total events	34	149 149	10	76 76	0.2% 0.2%	1.73 [0.91, 3.32] 1.73 [0.91, 3.32]		•
Heterogeneity: Not applicable Test for overall effect: Z = 1.66 (P = 0.10)	34		10					
11.1.3 New onset diseases ('medically significant							p until 7 months)	
HPV-031: Cervarix vs. AI(OH)3 (f, 18-35; 7) HPV-035: Cervarix vs. AI(OH)3 (f, 18-35; 7) Subtotal (95% CI)	13 42	176 150 326	24 24	178 150 328	0.2% 0.4% 0.6%	0.55 [0.29, 1.04] 1.75 [1.12, 2.74] 1.00 [0.32, 3.13]		
Total events Heterogeneity: Tau ² = 0.59; Chi ² = 8.46, df = 1 (P	55 = 0.0041: I ²		48	320	0.070	1.00 [0.52, 5.15]		
Test for overall effect: Z = 0.00 (P = 1.00)								
11.1.4 New onset diseases ('medically significant HPV-015: Cervarix vs. Al(OH)3 (f, 24-72; 36) Subtotal (95% CI)				2871	10.4% 10.4%	1.02 [0.96, 1.09] 1.02 [0.96, 1.09]	p until 36 months)	·
Total events Heterogeneity, Not applicable	1170	2002	1140	2071	10.4%	1.02 [0.30, 1.03]		
Test for overall effect: Z = 0.69 (P = 0.49)								
11.1.5 New onset diseases ('medically significant HPV-032: Cervarix vs. Aimmugen (f, 19-25; 7) Subtotal (95% CI)	conditions 98	519 519 519	115		en: hepati 1.3% 1.3%	0.86 [0.67, 1.09] 0.86 [0.67, 1.09]	ss, age 22–29; follow-up until 12 months)	_
Total events Heterogeneity, Not applicable	98	319	115	321	1.5%	0.86 [0.67, 1.05]		7
Test for overall effect: Z = 1.27 (P = 0.20)								
11.1.6 New onset diseases ('medically significant HPV-030: Cervarix vs. Engerix (f, 9-15; 12)	28	247	22	246	0.3%	1.27 [0.75, 2.15]	nd males, age 9-15; follow-up until 12 months)	
HPV-040: Cervarix vs. Engerix (f & m, 12-16; 72) Subtotal (95% CI) Total events	47 75	643 890	76 98	1047 1293	0.6% 0.9%	1.01 [0.71, 1.43] 1.08 [0.81, 1.45]		+
Heterogeneity: Tau ² = 0.00; Chi ² = 0.50, df = 1 (P - Test for overall effect: Z = 0.52 (P = 0.61)		- 0%	30					
11.1.7 New onset diseases ('medically significant							ge 26-46; follow-up until 12 months)	
HPV-069: Cervarix vs. Engerix (f, 26-46; 12) Subtotal (95% CI)	5	606 606	7	606 606	0.1% 0.1%	0.71 [0.23, 2.24] 0.71 [0.23, 2.24]		
Total events Heterogeneity: Not applicable Test for overall effect: Z = 0.58 (P = 0.56)	5		7					
11.1.8 New onset diseases ('medically significant	conditions	'): Cerva	rix vs. H	łavrix: h	epatitis A	vaccine (females, aç	e 9-15; follow-up until 12 months)	
HPV-013: Cervarix vs. Havrix (f, 10-14; 12) HPV-033: Cervarix vs. Havrix (f, 9-15; 7)	130 11	1035 160	160 10	1032 161	1.6% 0.1%	0.81 [0.65, 1.00] 1.11 [0.48, 2.53]		
Subtotal (95% CI) Total events Heterogeneity: Tau ² = 0.00; Chi ² = 0.51, df = 1 (P =	141	1195	170	1193	1.7%	0.83 [0.67, 1.02]		•
Test for overall effect: Z = 1.80 (P = 0.07)	= 0.47), 111	= 0%						
11.1.9 New onset diseases ('medically significant HPV-008: Cervarix vs. Havrix (f, 15-25; 48)	conditions 3298	9319	rix vs. H 3378	9325	15.6%	0.98 [0.94, 1.02]	e 15-25; follow-up until 48 months)	ļ
Subtotal (95% CI) Total events	3298	9319	3378	9325	15.6%	0.98 [0.94, 1.02]		
Heterogeneity: Not applicable Test for overall effect: Z = 1.19 (P = 0.23)								
11.1.10 New onset diseases ('medically significan HPV-029: Cervarix vs. Twinrix (f, 8-15; 12)	it condition 23	270	arix vs. 31	271	0.3%	0.74 [0.45, 1.24]	males, age 8-15; follow-up until 12 months)	
Subtotal (95% CI) Total events	23	270	31	271	0.3%	0.74 [0.45, 1.24]		•
Heterogeneity: Not applicable Test for overall effect: Z = 1.13 (P = 0.26)								
11.1.11 New onset diseases ('new medical history V501-018: Gardasil vs. carrier solu. (f&m,9-16;18)		vs. carri 1184	ier solut 280	tion (fen 597	nales and 5.3%	males, age 9-16; fo 0.94 [0.84, 1.04]	llow-up until 18 months)	4
Subtotal (95% CI) Total events	520	1184	280	597	5.3%	0.94 [0.84, 1.04]		•
Heterogeneity: Not applicable Test for overall effect: Z = 1.20 (P = 0.23)								
11.1.12 New onset diseases ('new medical history V501-013: Gardasil vs. AAHS (f, 16-24; 45)					15-26; fo	llow-up until 45 m 1.01 [0.99, 1.03]	onths)	
V501-015: Gardasil vs. AAHS (f, 15-26; 36) Subtotal (95% CI)	4357	6087 8810	4399	6080 8812	19.4% 38.8%	0.99 [0.97, 1.01] 1.00 [0.98, 1.02]		1
Total events Heterogeneity. Tau ² = 0.00; Chi ² = 1.78, df = 1 (P = Test for overall effect: Z = 0.01 (P = 0.99)	6685 = 0.18); l ² =	= 44%	6710					
11.1.13 New onset diseases ('new medical history	/'): Gardasil	vs. AAH	IS (fema	les, age	21-46; fr	om 0-7 months)		
V501-019: Gardasil vs. AAH5 (f, 21-46; 48) Subtotal (95% CI)	756	1911 1911	702	1908 1908	7.8% 7.8 %	1.08 [0.99, 1.17] 1.08 [0.99, 1.17]		•
Total events Heterogeneity: Not applicable Test for overall effect: Z = 1.76 (P = 0.08)	756		702					
11.1.14 New onset diseases ('new medical history	/ˈ): Gardasil	vs. AAH	IS (fema	les. age	21-46: fr	om 7-48 months)		
V501-019: Gardasil vs. AAH5 (f, 21-46; 48) Subtotal (95% CI)	958	1911 0	985	1908 0		Not estimable Not estimable		
Total events Heterogeneity: Not applicable	0		0					
Test for overall effect: Not applicable 11.1.15 New onset diseases ('new medical history	/'): Gardasil	vs. AAH	IS (male	s. age 1	5-27: fror	n 0-7 months)		
V501-020: Gardasii vs. AAHS (m, 15-27; 36) Subtotal (95% CI)		2032 2032	463		5.0% 5.0 %	1.08 [0.96, 1.20] 1.08 [0.96, 1.20]		
Total events Heterogeneity: Not applicable	498		463					
Test for overall effect: Z = 1.29 (P = 0.20) 11.1.16 New onset diseases ('new medical history	/): Gardasil	vs. AAH	IS (male	s. age 1	5-27: from	n 7-36 months)		
V501-020: Gardasii vs. AAHS (m, 15-27; 36) Subtotal (95% CI)		2032		2033	21,110	Not estimable Not estimable		
Total events Heterogeneity. Not applicable	0		0					
Test for overall effect: Not applicable 11.1.17 New onset diseases ('new medical history	ان Cardaeil)	9 vc. ca	line nla	caba (fa	males an	a 12-26: fallow-un	until 7 months)	
V503-006: Gardasil 9 vs. saline (f, 12-26;7) Subtotal (95% CI)	175	618 618	99	306 306	1.7% 1.7%	0.88 [0.71, 1.07] 0.88 [0.71, 1.07]	until / months	•
Total events Heterogeneity. Not applicable	175		99					-
Test for overall effect: Z = 1.27 (P = 0.20)	A- HDV 1C :	vaccino :	(c AA!"	(fam.)	ae aeo 10	-25: from 0 - 7 w	the)	
11.1.18 New onset diseases ('new medical history V501-005: HPV 16 vaccine vs. AAHS (f, 16-25; 48) Subtotal (95% CI)		1204 1 204	753		es, age 16 10.3% 10.3%	-25; from 0-7 mon 0.95 [0.89, 1.01] 0.95 [0.89, 1.01]	ura <i>j</i>	1
Total events Heterogeneity: Not applicable	715		753			()]
Test for overall effect: Z = 1.56 (P = 0.12)	D. LUNCO	,						
11.1.19 New onset diseases ('new medical history V501-005: HPV 16 vaccine vs. AAHS (f, 16-25; 48) Subtotal (95% CI)		vaccine v 1204 0	834	5 (female 1205 0	es, age 16	-25; from 7-48 mo Not estimable Not estimable	nuns)	
Total events Heterogeneity: Not applicable	0	Ū	0	v		camable		
Test for overall effect: Not applicable								
Total (95% CI) Total events Heterogeneity: Tau ² = 0.00; Chi ² = 33.56, df = 19	14258		14014	31720	100.0%	0.99 [0.97, 1.02]		
	r = 0.021	= 43%					0.02	0.1 1 10 50

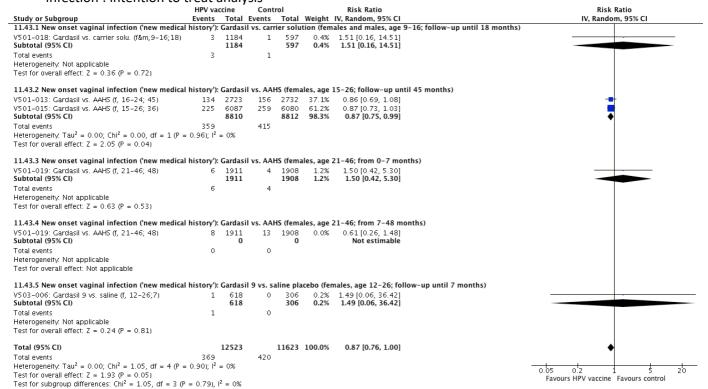
*1.13. Risk ratio for 'medically significant conditions' (GlaxoSmithKline): 0.98 [0.90, 1.06]; risk ratio for 'new medical history' (Merck Sharp & Dohme): 1.00 [0.97, 1.03]; risk ratio for the follow-up periods for the trials V501-005, V501-019 and V501-020 (Merck Sharp & Dohme): 0.98 [0.94, 1.01] (2,296 participants with new medical history in the HPV vaccine group vs. 2,365 participants with new medical history in the control group. The trials V501-005, V501-019 and V501-020 split the reporting of new onset diseases into the vaccination period and the follow-up period. To avoid double counting of participants in the total risk ratio estimate, we only included the new onset diseases reported in the vaccination period for the trials V501-005, V501-019 and V501-020).

1.14. New onset diseases most associated with the HPV vaccines ('medically significant conditions'*) - 'back pain': intention to treat analysis



^{*1.14.} Risk ratio for 'medically significant conditions' (GlaxoSmithKline): **1.40 [1.05, 1.86]**; risk ratio for 'new medical history' (Merck Sharp & Dohme): 1.08 [0.91, 1.28]; risk ratio for the follow-up periods for the trials V501-005, V501-019 and V501-020: 0.85 [0.60, 1.19]. The trials V501-005, V501-019 and V501-020 split the reporting of new onset diseases into the vaccination period and the follow-up period. To avoid double counting of participants in the total risk ratio estimate, we only included the new onset diseases reported in the vaccination period for the trials V501-005, V501-019 and V501-020.

1.15. New onset diseases most inversely associated with the HPV vaccines ('new medical history'*) - 'vaginal infection': intention to treat analysis



^{*1.15.} Risk ratio for 'medically significant conditions' (GlaxoSmithKline): not applicable; risk ratio for 'new medical history' (Merck Sharp & Dohme): **0.87 [0.76, 1.00]**; risk ratio for the follow-up period for the trial V501-019: 0.61 [0.26, 1.48]. The trial V501-019 split the reporting of new onset diseases into the vaccination period and the follow-up period. To avoid double counting of participants in the total risk ratio estimate, we only included the new onset diseases reported in the vaccination period for the trial V501-019.

1.16. New onset diseases ('medically significant conditions' and 'new medical history'*) reported within the MedDRA system organ class 'vascular disorders (10047065)': intention to treat analysis

tudy or Subgroup 1.27.1 New onset vascular disorders ('medically sig	Events Total E Inificant condition	ns'): Cervarix ((females, age 24-72; follow-up until 36 months)	
PV-015: Cenvarix vs. Al(OH)3 (f, 24-72; 36) ubtotal (95% Cl)	65 2882 2882	95 2871 2871	30.4% 30.4 %	0.68 [0.50, 0.93] 0.68 [0.50, 0.93]	±
tal events	65	95	30.470	0.00 (0.50, 0.55)	
terogeneity: Not applicable st for overall effect: Z = 2.41 (P = 0.02)					
27.2 New onset vascular disorders ('medically sig	anificant conditio	ns'): Cervarix v	vs. Aimmu	gen: hepatitis A vaccine (females, age 22-29; follow-up until 1	2 months)
/-063: Cervarix vs. Aimmugen (f, 22-29; 12)	1 375 375	1 377 377	0.4%	1.01 [0.06, 16.01] 1.01 [0.06, 16.01]	
al events	1	1	0.4%	1.01 [0.06, 16.01]	
terogeneity. Not applicable st for overall effect: Z = 0.00 (P = 1.00)					
27.3 New onset vascular disorders ('medically sig	nificant conditio	ns'): Cervarix v	vs. Havrix:	hepatitis A vaccine (females, age 10-14; follow-up until 12 mo	onths)
/-013: Cervarix vs. Havrix (f, 10-14; 12)	4 1035 1035	2 1032 1032		1.99 [0.37, 10.86] 1.99 [0.37, 10.86]	
al events	4	2	1.070	1.55 (0.57, 10.00)	
erogeneity. Not applicable t for overall effect: Z = 0.80 (P = 0.42)					
27.4 New onset vascular disorders ('medically sig	gnificant conditio	ns'): Cervarix (vs. Havrix:	hepatitis A vaccine (females, age 15-25; follow-up until 48 mo	onths)
/-008: Cervarix vs. Havrix (f, 15-25; 48) ototal (95% CI)	41 9319 9319		15.4% 15.4%	1.05 [0.68, 1.63] 1.05 [0.68, 1.63]	<u> </u>
al events	41	39	_3.7,0		Ť
erogeneity: Not applicable t for overall effect: Z = 0.23 (P = 0.82)					
	nificant conditio	ns'): Cervarix v	vs. Twinrix	hepatitis A and B vaccine (females, age 8-15; follow-up until	12 months)
V-029: Cervarix vs. Twinrix (f, 8-15; 12)	0 270 270	1 271 271		0.33 [0.01, 8.18] 0.33 [0.01, 8.18]	
al events	0	1	3.5,0		
erogeneity: Not applicable it for overall effect: Z = 0.67 (P = 0.50)					
				nales and males, age 9–16; follow-up until 18 months)	
01-018: Gardasil vs. carrier solu. (f&m,9-16;18) ototal (95% CI)	1 1184 1184	2 597 597		0.25 [0.02, 2.77] 0.25 [0.02, 2.77]	
al events	1	2		,	
erogeneity: Not applicable st for overall effect: Z = 1.13 (P = 0.26)					
27.7 New onset vascular disorders ('new medical	history'): Gardasi	l vs. AAHS (fe	males, age	15-26; follow-up until 45 months)	
01-013: Gardasil vs. AAHS (f, 16-24; 45) 01-015: Gardasil vs. AAHS (f, 15-26; 36)	36 2723 65 6087	34 2732 85 6080	13.6% 28.6%	1.06 [0.67, 1.69] 0.76 [0.55, 1.05]	
btotal (95% CI)	8810	8812	42.2%	0.86 [0.63, 1.18]	→
tal events terogeneity: Tau² = 0.01; Chi² = 1.31, df = 1 (P = 0	101 0.25): I ² = 23%	119			
st for overall effect: Z = 0.94 (P = 0.35)	,				
.27.8 New onset vascular disorders ('new medical 01-019: Gardasil vs. AAHS (f, 21-46; 48)	history'): Gardasi 9 1911	22 1908		21-46; from 0-7 months) 0.41 [0.19, 0.88]	
btotal (95% CI)	1911	1908		0.41 [0.19, 0.88]	•
tal events terogeneity: Not applicable	9	22			
st for overall effect: Z = 2.27 (P = 0.02)					
27.9 New onset vascular disorders ('new medical 01-019: Gardasil vs. AAHS (f, 21-46; 48)	history'): Gardasi 45 1911	I vs. AAHS (fe 39 1908		21-46; from 7-48 months) 1.15 [0.75, 1.76]	
ototal (95% CI)	0	0		Not estimable	
al events erogeneity: Not applicable	0	0			
st for overall effect: Not applicable					
. 27.10 New onset vascular disorders ('new medica 01-020: Gardasil vs. AAHS (m, 15-27; 36)	al history'): Garda 2 2032	sil vs. AAHS (n 3 2032		15-27; from 0-7 months) 0.67 [0.11, 3.99]	
ototal (95% CI)	2032	2032		0.67 [0.11, 3.99]	
al events erogeneity. Not applicable	2	3			
t for overall effect: Z = 0.44 (P = 0.66)					
27.11 New onset vascular disorders ('new medica					
01-020: Gardasil vs. AAHS (m, 15-27; 36) ototal (95% CI)	7 2032 0	12 2033 0		0.58 [0.23, 1.48] Not estimable	
al events erogeneity: Not applicable	0	0			
t for overall effect: Not applicable					
27.12 New onset vascular disorders ('new medica					
01-005: HPV 16 vaccine vs. AAHS (f, 16-25; 48) ototal (95% CI)	10 1204 1204	10 1205 1205		1.00 [0.42, 2.40] 1.00 [0.42, 2.40]	-
al events erogeneity: Not applicable	10	10			
st for overall effect: Z = 0.00 (P = 1.00)					
tal (95% CI)	29022		100.0%	0.80 [0.67, 0.94]	•
tal events terogeneity: $Tau^2 = 0.00$; $Chi^2 = 9.54$, $df = 10$ (P =	234 0.48): I ² = 0%	294			0.02 0.1 1 10
					0.02 0.1 1 10

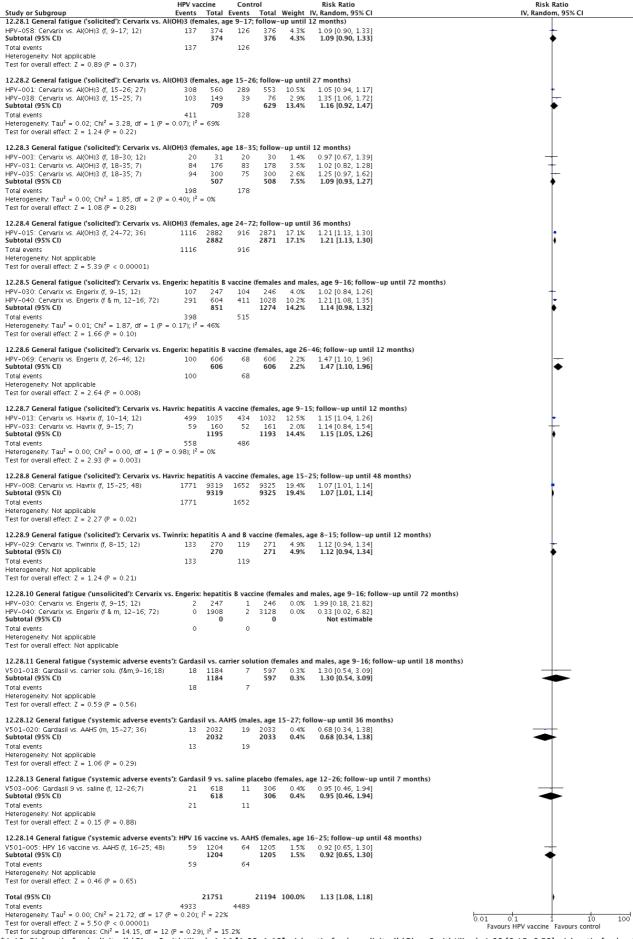
^{*1.16.} Risk ratio for 'medically significant conditions' (GlaxoSmithKline): 0.80 [0.63, 1.03]; risk ratio for 'new medical history' (Merck Sharp & Dohme): 0.78 [0.60, 1.03]; risk ratio for the follow-up periods for the trials V501-019 and V501-020: 0.93 [0.51, 1.73]. The trials V501-019 and V501-020 split the reporting of new onset diseases into the vaccination period and the follow-up period. To avoid double counting of participants in the total risk ratio estimate, we only included the new onset diseases reported in the vaccination period for the trials V501-019 and V501-020.

1.17. General harms ('solicited and unsolicited' and 'systemic adverse events'*): intention to treat analysis

dy or Subgroup 1.1 General harms ('solicited' and 'unsolicited		l(OH)3 (fem	iales, ag	e 9-17; fo		IV, Random, 95% CI
'-058: Cenvarix vs. Al(0H)3 (f, 9-17; 12) total (95% CI)		74 275 74	376 376	5.3% 5.3%	1.07 [0.99, 1.17] 1.07 [0.99, 1.17]	•
al events erogeneity: Not applicable t for overall effect: Z = 1.75 (P = 0.08)	294	275				
1.2 General harms ('solicited' and 'unsolicited	l'): Cervarix vs. A	J(OH)3 (fem	nales, ag	e 15-26;	ollow-up until 27 months)	
'-001: Cervarix vs. Al(OH)3 (f, 15-26; 27) '-038: Cervarix vs. Al(OH)3 (f, 15-25; 7) total (95% CI)	136 1 7	60 462 49 55 09	553 76 629	6.3% 3.2% 9.6%	0.98 [0.93, 1.03] 1.26 [1.09, 1.46] 1.10 [0.86, 1.41]	
il events erogeneity. Tau ² = 0.03; Chi ² = 10.00, df = 1 (for overall effect: $Z = 0.76$ ($P = 0.45$)	594 [P = 0.002); I ² =	517 90%				
L.3 General harms ('solicited' and 'unsolicited' -003: Cervarix vs. Al(OH)3 (f, 18-30; 12)		I (OH)3 (fer 31 29	nales, ag	e 18-35;	ollow-up until 12 months) 0.93 [0.82, 1.07]	
'-031: Cervarix vs. A(OH)3 (f, 18-35; 7) '-031: Cervarix vs. A(OH)3 (f, 18-35; 7) '-035: Cervarix vs. A(OH)3 (f, 18-35; 7)	25 1	76 20 50 114	178 150	0.4% 4.5%	1.26 [0.73, 2.19] 1.19 [1.08, 1.32]	
-053, Cervarix vs. A(0H)5 (f, 16-33, 7) total (95% CI) il events erogeneity. Tau ² = 0.02; Chi ² = 8.35, df = 2 (P	3 189	57 163	358	8.5%	1.08 [0.88, 1.33]	
t for overall effect: Z = 0.74 (P = 0.46)		•				
I.4 General harms ('solicited' and 'unsolicited' -015: Cervarix vs. Al(OH)3 (f, 24-72; 36)	l'): Cervarix vs. A 2111 28			e 24-72 ; 7.0%	1.07 [1.03, 1.10]	+
total (95% CI) al events	28 2111	82 1970	2871	7.0%	1.07 [1.03, 1.10]	•
erogeneity: Not applicable t for overall effect: Z = 3.86 (P = 0.0001)						
					males and males, age 12-16; follow-up until 72 months)	
'-030: Cervarix vs. Engerix (f, 9-15; 12) '-040: Cervarix vs. Engerix (f & m, 12-16; 72)	484 6	47 195 04 676	246 1028	5.1% 6.1%	1.03 [0.95, 1.13] 1.22 [1.15, 1.29]	Ţ
total (95% CI)	686	51 871	1274	11.3%	1.12 [0.96, 1.32]	
erogeneity: $Tau^2 = 0.01$; $Chi^2 = 9.62$, $df = 1$ (P for overall effect: $Z = 1.41$ (P = 0.16)	= 0.002); I ² = 9	0%				
					males, age 26-46; follow-up until 12 months)	
'-069: Cervarix vs. Engerix (f, 26-46; 12) total (95% CI)	6	06 148 06	606 606	2.5% 2.5%	1.36 [1.14, 1.63] 1.36 [1.14, 1.63]	
al events erogeneity: Not applicable	202	148				
t for overall effect: Z = 3.39 (P = 0.0007)	ID: 5 '	tarred .				
L.7 General harms ('solicited' and 'unsolicited' -013: Cervarix vs. Havrix (f, 10-14; 12)	577 10	35 468	1032	5.1%	1.23 [1.13, 1.34]	-
-033: Cervarix vs. Havrix (f, 9-15; 7) total (95% CI)	11		161 1193	2.7% 7.8%	1.08 [0.91, 1.28] 1.18 [1.04, 1.33]	-
all events erogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.76$, $df = 1$ (P	680 = 0.19); I ² = 43	564 %				
for overall effect: Z = 2.68 (P = 0.007)	ID: C '	tarred .			and an area of the African and Afr	
'-008: Cervarix vs. Havrix (f, 15-25; 48)	2626 93	19 2531	9325	6.6%	nales, age 15–25; follow-up until 48 months) 1.04 [0.99, 1.09]	
itotal (95% CI) al events	93 2626	19 2531	9325	6.6%	1.04 [0.99, 1.09]	•
erogeneity: Not applicable t for overall effect: Z = 1.58 (P = 0.11)						
					ine (females, age 8-15; follow-up until 12 months)	
'-029: Cervarix vs. Twinrix (f, 8-15; 12) total (95% CI)	2	70 191 70	271 271	4.8% 4.8 %	1.14 [1.03, 1.26] 1.14 [1.03, 1.26]	•
al events erogeneity. Not applicable	217	191				
t for overall effect: Z = 2.65 (P = 0.008)	ch Cardaeil ···	arries s-l	ion #	aloc and	males and 9–16: follow up until 10 ms t- c	
1.10 General harms ('systemic adverse events 11-018: Gardasil vs. carrier solu. (f&m,9-16;18;	541 11	84 260	597	4.3%	1.05 [0.94, 1.17]	±
al events	541	84 260	597	4.3%	1.05 [0.94, 1.17]	
erogeneity: Not applicable t for overall effect: Z = 0.85 (P = 0.39)						
L.11 General harms ('systemic adverse events						
1-013: Gardasil vs. AAHS (f, 16-24; 45) 1-015: Gardasil vs. AAHS (f, 15-26; 36)	1746 27 448 60	87 453	2732 6080	6.8% 3.8%	1.03 [0.99, 1.07] 0.99 [0.87, 1.12] 1.03 [0.99, 1.07]	_
total (95% CI) al events	2194	2154	8812	10.6%	1.03 [0.99, 1.07]	Ţ
erogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.38$, $df = 1$ (P t for overall effect: $Z = 1.30$ (P = 0.20)	= U.54); I ² = 0%					
1.12 General harms ('systemic adverse events						
1-019: Gardasil vs. AAHS (f, 21-46; 48) total (95% CI)	1121 19 19	11	1908 1908	6.4% 6.4 %	0.99 [0.94, 1.04] 0.99 [0.94, 1.04]	
al events erogeneity: Not applicable t for overall effect: 7 = 0.53 /P = 0.60	1121	1135				
t for overall effect: Z = 0.52 (P = 0.60) L.13 General harms ('systemic adverse events	s'r: Gardasil ve A	AHS (male	s. ana 15	-27: falls	w-up until 36 months)	
:1-020: Gardasil vs. AAHS (m, 15-27; 36) total (95% Cl)	616 20 20	32 613		4.9% 4.9 %	1.01 [0.92, 1.10] 1.01 [0.92, 1.10]	\pm
al events	616	613	2033	7.3/0	202 [0.56, 2.20]	
erogeneity: Not applicable for overall effect: Z = 0.11 (P = 0.91)						
L.14 General harms ('systemic adverse events			cebo (fen			
3-006: Gardasil 9 vs. saline (f, 12-26;7) total (95% CI)	6	18	306 306	4.2% 4.2 %	1.05 [0.93, 1.17] 1.05 [0.93, 1.17]	*
al events erogeneity: Not applicable t for overall effect: 7 = 0.77 (P = 0.44)	374	177				
t for overall effect: Z = 0.77 (P = 0.44)	:'h- HPN 16	10 VE AALIE	(female	s ago 10	.25: follow-up until 48 months)	
1.15 General harms ('systemic adverse events 11-005: HPV 16 vaccine vs. AAHS (f, 16-25; 48 Itotal (95% CI)	803 12	04 825	1205	6.3%	0.97 [0.92, 1.03]	_
	803	0 4 825	1205	6.3%	0.97 [0.92, 1.03]	7
al events						
al events erogeneity: Not applicable	323 . 13248	22 12394	31764	100.0%	1.07 [1.03, 1.11]	•

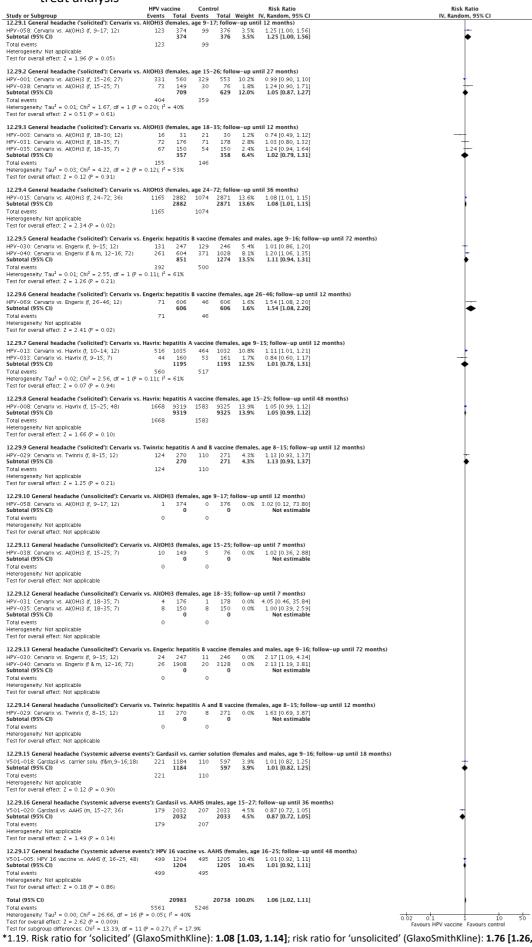
^{*1.17.} Risk ratio for 'solicited and solicited' (GlaxoSmithKline): 1.11 [1.06, 1.16]; risk ratio for 'systemic adverse events' (Merck Sharp & Dohme): 1.01 [0.98, 1.03]. The total numbers of participants with general harms in GlaxoSmithKline studies were reported as 'solicited [SGAE] and unsolicited [UGAE]' combined.

1.18. General harms most associated with the HPV vaccines ('solicited' and 'unsolicited') - 'fatigue': intention to treat analysis



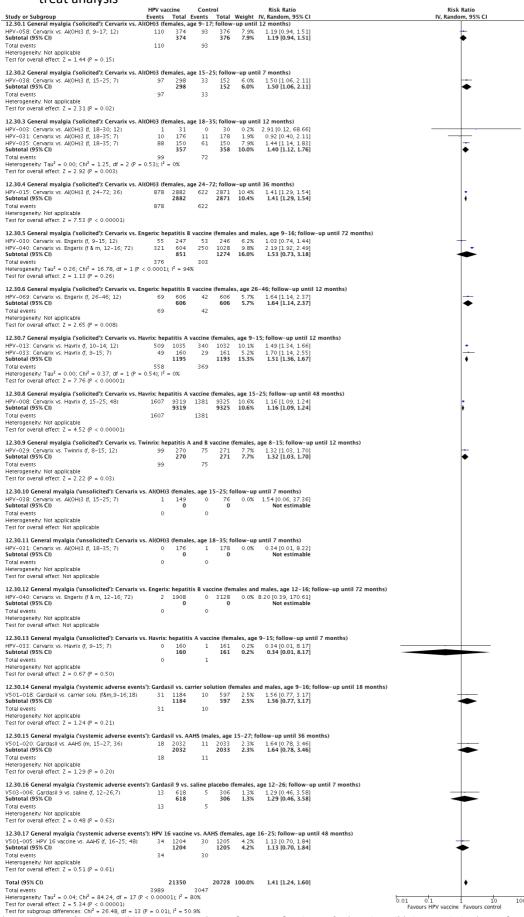
^{*1.18.} Risk ratio for 'solicited' (GlaxoSmithKline): **1.14 [1.09, 1.19]**; risk ratio for 'unsolicited' (GlaxoSmithKline): **1.00 [0.15, 6.53]**; risk ratio for 'systemic adverse events' (Merck Sharp & Dohme): 0.92 [0.70, 1.20]. To avoid double counting of participants in the total risk ratio estimate, we excluded the 'unsolicited' adverse events from total risk ratio estimate for studies that reported 'solicited' adverse events.

1.19. General harms most associated with the HPV vaccines ('solicited' and 'unsolicited') - 'headache': intention to treat analysis



^{*1.19.} Risk ratio for 'solicited' (GlaxoSmithKline): 1.08 [1.03, 1.14]; risk ratio for 'unsolicited' (GlaxoSmithKline): 1.76 [1.26, 2.47]; risk ratio for 'systemic adverse events' (Merck Sharp & Dohme): 0.98 [0.90, 1.07]. To avoid double counting of participants in the total risk ratio estimate, we excluded the 'unsolicited' adverse events from total risk ratio estimate for studies that reported 'solicited' adverse events.

1.20. General harms most associated with the HPV vaccines ('solicited' and 'unsolicited') - 'myalgia': intention to treat analysis



^{*1.20.} Risk ratio for 'solicited' (GlaxoSmithKline): 1.42 [1.24, 1.63]; risk ratio for 'unsolicited' (GlaxoSmithKline): 1.15 [0.24, 5.57]; risk ratio for 'systemic adverse events' (Merck Sharp & Dohme): 1.33 [0.95, 1.85]. To avoid double counting of participants in the total risk ratio estimate, we excluded the 'unsolicited' adverse events from total risk ratio estimate for studies that reported 'solicited' adverse events.

2. <u>Trial register entries</u>

2.1. All-cause mortality/deaths*: intention to treat analysis HPV vaccine Control Risk Ratio

	HPV vac		Cont			Risk Ratio	Risk Ratio
Study or Subgroup 2.1.1 All-cause mortality/deaths: Cervarix vs. Al(0	Events					IV, Random, 95% CI	IV, Random, 95% CI
HPV-015: Cervarix vs. Al(OH)3 (f, 24-72; 36)	13 (Ieilia	2882	5 24-72 ,		•	2.59 [0.92, 7.26]	
Subtotal (95% CI)		2882	-	2871		2.59 [0.92, 7.26]	
Total events	13		5				
Heterogeneity. Not applicable							
Test for overall effect: Z = 1.81 (P = 0.07)							
2.1.2 All-cause mortality/deaths: Cervarix vs. Aim	ımugen: he	epatitis	A vaccir	ne (fema	les, age 1	9-25; follow-up until 7 mon	nths)
HPV-032: Cervarix vs. Aimmugen (f, 19-25; 7)	1	519	0			3.01 [0.12, 73.76]	-
Subtotal (95% CI)		519		521	3.1%	3.01 [0.12, 73.76]	
Total events Heterogeneity: Not applicable	1		0				
Test for overall effect: Z = 0.68 (P = 0.50)							
3.1.3.All		isia D.				0 . 16. falla	72
2.1.3 All-cause mortality/deaths: Cervarix vs. Eng HPV-040: Cervarix vs. Engerix (f & m, 12-16; 72)		14837		17338		1.17 [0.34, 4.04]	/2 months)
Subtotal (95% CI)		14837	,	17338		1.17 [0.34, 4.04]	
Total events	5		5				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.25 (P = 0.81)							
2.1.4 All-cause mortality/deaths: Cervarix vs. Eng	erix: hepat	titis B v	accine (f	emales,	age 26-4	6; follow-up until 12 month	s)
HPV-069: Cervarix vs. Engerix (f, 26-46; 12)	0	606	0			Not estimable	
Subtotal (95% CI)		606		606		Not estimable	
Total events	0		0				
Heterogeneity: Not applicable Test for overall effect: Not applicable							
rest for overall effect. Not applicable							
2.1.5 All-cause mortality/deaths: Cervarix vs. Hav					age 15-25		(1)
HPV-008: Cervarix vs. Havrix (f, 15-25; 48)	0	9319	0			Not estimable	
Subtotal (95% CI) Fotal events	0	9319	0	9325		Not estimable	
Heterogeneity. Not applicable	v						
Test for overall effect: Not applicable							
2.1.6 All-cause mortality/deaths: Gardasil vs. AAI	JC (famala)	1	E 26, fo	llaw m	s until 4F	months)	
V501–013: Gardasii vs. AAHS (f, 16–24; 45)	15 (Terriale: 2	2723		2732	7.7%	1.00 [0.14, 7.12]	
V501-015: Gardasii vs. AAHS (f, 15-26; 36)	7	6087	5			1.40 [0.44, 4.40]	
Subtotal (95% CI)		8810		8812	26.1%	1.28 [0.48, 3.46]	-
Total events	9		7				
Heterogeneity: Tau² = 0.00; Chi² = 0.08, df = 1 (P = Test for overall effect: Z = 0.50 (P = 0.62)	= 0.77); 14 =	= 0%					
rest for overall effect. Z = 0.30 (F = 0.02)							
2.1.7 All-cause mortality/deaths: Gardasil vs. AAI							
V501-019: Gardasil vs. AAHS (f, 21-46; 48)	8	1911	4			2.00 [0.60, 6.62]	
Subtotal (95% CI) Fotal events	8	1911	4	1908	17.3%	2.00 [0.60, 6.62]	
Heterogeneity. Not applicable			7				
Test for overall effect: Z = 1.13 (P = 0.26)							
2.1.8 All-cause mortality/deaths: Gardasil vs. AAl	JS (males	200 15.	- 27: foll	0W-UD I	ıntil 26 m	onths)	
2.1.8 All-cause mortality/deaths: Gardasii vs. AAr /501–020: Gardasil vs. AAHS (m, 15–27; 36)	ns (maies,	2032	-27; 10 11 10	-	15.5%	0.30 [0.08, 1.09]	
Subtotal (95% CI)	٠	2032	10	2033		0.30 [0.08, 1.09]	
Total events	3		10			-	
Heterogeneity. Not applicable							
Fest for overall effect: Z = 1.83 (P = 0.07)							
2.1.9 All-cause mortality/deaths: HPV 16 vaccine	vs. AAHS (1	females	s, age 16	-25; fol	low-up ui	ntil 48 months)	
/501-005: HPV 16 vaccine vs. AAHS (f, 16-25; 48)	0	1204	0	1205	-	Not estimable	
Subtotal (95% CI)	_	1204		1205		Not estimable	
Total events	0		0				
Heterogeneity: Not applicable Test for overall effect: Not applicable							
							_
Total (95% CI)		42120		44619	100.0%	1.30 [0.73, 2.30]	◆
Fotal events	39	7.10/	31				
Heterogeneity: Tau² = 0.12; Chi² = 7.55, df = 6 (P = Test for overall effect: Z = 0.89 (P = 0.37)	= U.Z/J; F =	= 21%					0.02 0.1 1 10 5
est for subgroup differences: Chi² = 0.37) Test for subgroup differences: Chi² = 7.47, df = 5 (P	0.100.18	2 _ 22 1	19/				Favours HPV vaccine Favours control

^{*2.1.} Risk ratio for GlaxoSmithKline studies (i.e., HPV-0xx): 1.92 [0.89, 4.15]; risk ratio for Merck Sharp & Dohme studies (i.e., V50x-xxx): 0.98 [0.41, 2.33].

2.2. Mortality/deaths from HPV-related cancers (anal, cervical, oropharyngeal, penile, vaginal and vulvar) irrespective of HPV type: intention to treat analysis

	HPV va	ccine	Cont	rol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
2.2.1 Cervical cancer: Cervarix (females, age	24-72; fo	llow-u	p until 3	6 mon	ths)		
HPV-015: Cervarix vs. Al(OH)3 (f, 24-72; 36) Subtotal (95% CI)	0	2882 2882	0	2871 2871		Not estimable Not estimable	
Total events Heterogeneity: Not applicable	0		0				
Test for overall effect: Not applicable							
2.2.2 Oropharyngeal cancer: Cervarix (female	es, age 24	-72; fo	llow-up	until 3	6 month	ıs)	
HPV-015: Cervarix vs. Al(OH)3 (f, 24-72; 36) Subtotal (95% CI)	0	2882 2882	0	2871 2871		Not estimable Not estimable	
Total events	0		0				
Heterogeneity. Not applicable							
Test for overall effect: Not applicable							
2.2.3 Oropharyngeal cancer: Gardasil (female	es, age 21	-46; fo	llow-up	until 4	8 month	ns)	
V501-019: Gardasil vs. AAHS (f, 21-46; 48) Subtotal (95% CI)	0	1911 1911	0	1908 1908		Not estimable Not estimable	
Total events	0		0				
Heterogeneity. Not applicable							
Test for overall effect: Not applicable							
Total (95% CI)		7675		7650		Not estimable	
Total events	0		0				
Heterogeneity: Not applicable							0.001 0.1 1 10 1000
Test for overall effect: Not applicable							Favours HPV vaccine Favours control
Test for subgroup differences: Not applicable							

^{*2.2.} Risk ratio for 'medically significant conditions' (GlaxoSmithKline): not applicable; risk ratio for 'new medical history' (Merck Sharp & Dohme): not applicable.

2.3. Incidence of HPV-related cancers (anal, cervical, oropharyngeal, penile, vaginal and vulvar) irrespective of HPV type: intention to treat analysis

type. Intention to treat and	•			
	HPV vaccine	Control	Risk Ratio	Risk Ratio
Study or Subgroup			ight IV, Random, 95% CI	IV, Random, 95% CI
2.3.1 Cervical cancer: Cervarix (females, age				
HPV-015: Cervarix vs. Al(OH)3 (f, 24-72; 36) Subtotal (95% CI)	0 2882 288 2		Not estimable Not estimable	
	0	. 20/1	Not estimable	
Total events Heterogeneity. Not applicable	U	U		
Test for overall effect: Not applicable				
reservor overain erreet. Not applicable				
2.3.2 Cervical cancer: Gardasil (females, age	21-46; follow-u	p until 48 months)		
V501-019: Gardasil vs. AAHS (f, 21-46; 48)	0 1911	0 1908	Not estimable	
Subtotal (95% CI)	191	1908	Not estimable	
Total events	0	0		
Heterogeneity: Not applicable				
Test for overall effect: Not applicable				
2.2.2 Oranhamingaal cancer Convariy (famale	s 200 24 72: fo	llow-up uptil 26 mo	nths)	
2.3.3 Oropharyngeal cancer: Cervarix (female HPV-015: Cervarix vs. Al(OH)3 (f, 24-72; 36)	o 2882		Not estimable	
Subtotal (95% CI)	2887		Not estimable	
Total events	0	0		
Heterogeneity: Not applicable	•	•		
Test for overall effect: Not applicable				
2.3.4 Oropharyngeal cancer: Gardasil (female				
V501-019: Gardasil vs. AAHS (f, 21-46; 48)	0 1911		Not estimable	
Subtotal (95% CI)	1911		Not estimable	
Total events	0	0		
Heterogeneity. Not applicable Test for overall effect: Not applicable				
rest for overall effect. Not applicable				
2.3.5 Vaginal cancer: Cervarix (females, age 2	24-72; follow-u	p until 36 months)		
HPV-015: Cervarix vs. Al(OH)3 (f, 24-72; 36)	0 2882	0 2871	Not estimable	
Subtotal (95% CI)	2882	2871	Not estimable	
Total events	0	0		
Heterogeneity: Not applicable				
Test for overall effect: Not applicable				
2.3.6 Vulvar cancer: Cervarix (females, age 1	5-25: follow-up	until 48 months)		
HPV-008: Cervarix vs. Havrix (f. 15-25; 48)	0 9315		Not estimable	
Subtotal (95% CI)	9319		Not estimable	
Total events	0	0		
Heterogeneity: Not applicable	•	-		
Test for overall effect: Not applicable				
2.3.7 Vulvar cancer: Gardasil (females, age 1				
V501-013: Gardasil vs. AAHS (f, 16-24; 45)	0 2723		Not estimable	
Subtotal (95% CI)	2723		Not estimable	
Total events	0	0		
Heterogeneity: Not applicable Test for overall effect: Not applicable				
restroi overan enect. Not applicable				
Total (95% CI)	24510	24486	Not estimable	
Total events	0	0		
Heterogeneity. Not applicable			ļ,	0.001 0.1 1 10 1000
Test for overall effect: Not applicable			,	Favours HPV vaccine Favours control
Test for subgroup differences: Not applicable				

Test for subgroup differences: Not applicable

*2.3. Risk ratio for 'medically significant conditions' (GlaxoSmithKline): not applicable; risk ratio for 'new medical history' (Merck Sharp & Dohme): not applicable.

2.4. Incidence of HPV-related carcinoma in situ (anal intraepithelial neoplasia grade 3 [AIN3], cervical adenocarcinoma in situ [AIS], cervical intraepithelial neoplasia grade 3 [CIN3], penile intraepithelial neoplasia grade 3 [PIN3], vaginal intraepithelial neoplasia grade 3 [VIN3] and vulvar intraepithelial neoplasia grade 3 [VaIN3]) irrespective of HPV type: intention to treat analysis

[valita], in superstitution in	HPV va	ccine	Cont	rol	Risk Ratio	Risk Ratio
Study or Subgroup			Events		Weight IV, Random, 95% CI	IV, Random, 95% CI
2.4.1 AIS: Cervarix (females, age 15-25; fol	low-up ur	ntil 48 n	nonths)			
HPV-008: Cervarix vs. Havrix (f, 15-25; 48)	0	9319	0	9325	Not estimable	
Subtotal (95% CI)		9319		9325	Not estimable	
Total events	0		0			
Heterogeneity. Not applicable Test for overall effect: Not applicable						
2.4.2 AIS: Gardasil (females, age 15-26; fol	low-up ur	ntil 45 n	nonths)			
V501-013: Gardasil vs. AAHS (f, 16-24; 45)	0	2723	0	2732	Not estimable	
V501-015: Gardasil vs. AAHS (f, 15-26; 36) Subtotal (95% CI)	0	6087 8810	0	6080 8812	Not estimable Not estimable	
Total events	0		0			
Heterogeneity: Not applicable Test for overall effect: Not applicable						
2.4.3 AIS: Gardasil (females, age 21-46; fol	low-up ur	ntil 48 n	nonths)			
V501-019: Gardasil vs. AAHS (f, 21-46; 48) Subtotal (95% CI)	0	1911 1911	0	1908 1908	Not estimable Not estimable	
Total events	0		0			
Heterogeneity. Not applicable Test for overall effect: Not applicable						
2.4.4 CIN3: Cervarix (females, age 15-25; fo	ollow-up	until 48	months))		
HPV-008: Cervarix vs. Havrix (f, 15-25; 48)	0	9319	0	9325	Not estimable	
Subtotal (95% CI)		9319		9325	Not estimable	
Total events	0		0			
Heterogeneity. Not applicable						
Test for overall effect: Not applicable						
2.4.5 CIN3: Gardasil (females, age 15-26; fo	ollow-up	until 45	months))		
V501-013: Gardasil vs. AAHS (f, 16-24; 45)	0	2723	0		Not estimable	
V501-015: Gardasil vs. AAHS (f, 15-26; 36)	0	6087	0	6080	Not estimable	
Subtotal (95% CI)	0	8810	0	8812	Not estimable	
Total events Heterogeneity: Not applicable	U		U			
Test for overall effect: Not applicable						
2.4.6 CIN3: Gardasil (females, age 21-46; fo	ollow-up	until 48	months))		
V501-019: Gardasil vs. AAHS (f, 21-46; 48)	0	1911	0	1908	Not estimable	
Subtotal (95% CI)		1911		1908	Not estimable	
Total events	0		0			
Heterogeneity. Not applicable Test for overall effect: Not applicable						
Total (95% CI)		40080		40090	Not estimable	
Total events	0		0			
Heterogeneity. Not applicable						0.001 0.1 1 10 1000
Test for overall effect: Not applicable						Favours HPV vaccine Favours control
Tost for subgroup differences: Not applicable						. a. ours in a raceine Turours control

Test for subgroup differences: Not applicable

*2.4. Risk ratio for 'medically significant conditions' (GlaxoSmithKline): not applicable; risk ratio for 'new medical history' (Merck Sharp & Dohme): not applicable.

2.5. Incidence of HPV-related moderate intraepithelial neoplasia (anal intraepithelial neoplasia grade 2 [AIN2], cervical intraepithelial neoplasia grade 2 [CIN2], penile intraepithelial neoplasia grade 2 [PIN2], vaginal intraepithelial neoplasia grade 2 [VIN2] and vulvar intraepithelial neoplasia grade 2 [VaIN2]) irrespective of HPV type: intention to treat analysis

, po	HPV va		Cont	rol	Risk Ratio	Risk Ratio
Study or Subgroup	Events		Events		Weight IV, Random, 95% CI	IV, Random, 95% CI
2.5.1 CIN2: Cervarix (females, age 15-25; fo	llow-up	until 48	months)			
HPV-008: Cervarix vs. Havrix (f, 15-25; 48) Subtotal (95% CI)	0	9319 9319	0	9325 9325	Not estimable Not estimable	
Total events	0		0			
Heterogeneity. Not applicable						
Test for overall effect: Not applicable						
2.5.2 CIN2: Gardasil (females, age 15-26; fo	ollow-up i	until 45	months)			
V501-013: Gardasil vs. AAHS (f, 16-24; 45)	0	2723	0	2732	Not estimable	
V501-015: Gardasil vs. AAHS (f, 15-26; 36)	0	6087	0	6080	Not estimable	
Subtotal (95% CI)		8810		8812	Not estimable	
Total events	0		0			
Heterogeneity. Not applicable						
Test for overall effect: Not applicable						
2.5.3 CIN2: Gardasil (females, age 21-46; fo	ollow-up	until 48	months)			
V501-019: Gardasil vs. AAHS (f, 21-46; 48)	0	1911	0	1908	Not estimable	
Subtotal (95% CI)		1911		1908	Not estimable	
Total events	0		0			
Heterogeneity. Not applicable						
Test for overall effect: Not applicable						
Total (95% CI)		20040		20045	Not estimable	
Total events	0		0			
Heterogeneity: Not applicable						0'1 0'2 0'5 1 2 5 10
Test for overall effect: Not applicable						Favours HPV vaccine Favours control
Total Commission of the commis						ravours nev vaccine Pavours control

Test for subgroup differences: Not applicable

*2.5. Risk ratio for 'medically significant conditions' (GlaxoSmithKline): not applicable; risk ratio for 'new medical history' (Merck Sharp & Dohme): not applicable.

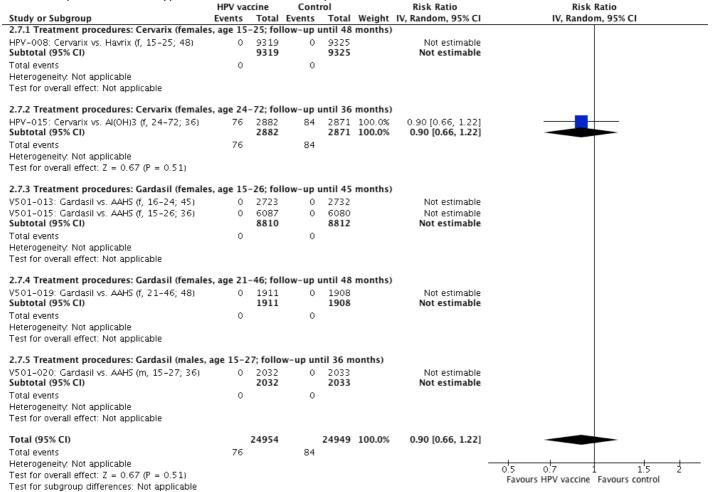
2.6. Incidence of HPV-related moderate intraepithelial neoplasia or worse (AIN2+, CIN2+, PIN2+, VIN2+, VaIN2+) irrespective of HPV type: intention to treat analysis

Study or Subgroup	HPV va Events	Total E			Risk Ratio Weight IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI
2.6.1 CIN2+: Cervarix (females, age 15-25; fol						
HPV-008: Cervarix vs. Havrix (f, 15-25; 48)	0	9319	0	9325	Not estimable	
ubtotal (95% CI)		9319		9325	Not estimable	
otal events	0		0			
Heterogeneity: Not applicable Fest for overall effect: Not applicable						
est for overall effect. Not applicable						
2.6.2 CIN2+: Cervarix (females, age 22-29; fol	low-up un	til 12 mo	nths)			
HPV-063: Cervarix vs. Aimmugen (f, 22-29; 12)	0	464	0	463	Not estimable	
Subtotal (95% CI)		464		463	Not estimable	
Total events	0		0			
Heterogeneity: Not applicable Fest for overall effect: Not applicable						
est for overall effect. Not applicable						
2.6.3 CIN2+: Cervarix (females, age 24-72; fol	low-up un	til 36 mo	nths)			
HPV-015: Cervarix vs. Al(OH)3 (f, 24-72; 36)	0	2882	0	2871	Not estimable	
ubtotal (95% CI)		2882		2871	Not estimable	
Total events	0		0			
Heterogeneity. Not applicable						
est for overall effect: Not applicable						
2.6.4 CIN2+: Gardasil (females, age 15-26; fol	low-up un	til 45 moi	nths)			
/501-013: Gardasil vs. AAHS (f, 16-24; 45)	0	2723	0	2732	Not estimable	
/501-015: Gardasil vs. AAHS (f, 15-26; 36)	Ö	6087	Ŏ	6080	Not estimable	
Subtotal (95% CI)		8810		8812	Not estimable	
Fotal events	0		0			
Heterogeneity. Not applicable						
est for overall effect: Not applicable						
2.6.5 CIN2+: Gardasil (females, age 21-46; fol	low-un un	til 48 mo	nths)			
/501-019: Gardasil vs. AAHS (f, 21-46; 48)	0	1911	0	1908	Not estimable	
Subtotal (95% CI)	~	1911		1908	Not estimable	
otal events	0		0			
Heterogeneity. Not applicable						
Fest for overall effect: Not applicable						
2.6.6 RING Condocil (moles are 15, 27, falle		36	\			
2.6.6 PIN2+: Gardasil (males, age 15-27; follo	-			2022	Not a stine alala	
/501–020: Gardasil vs. AAHS (m, 15–27; 36) Subtotal (95% CI)	0	2032 2032	0	2033 2033	Not estimable Not estimable	
Fotal events	0	2032	0	2033	Not estimable	
Heterogeneity. Not applicable	~		~			
Test for overall effect: Not applicable						
2.6.7 VIN2+: Gardasil (females, age 15-26; fol						
/501-013: Gardasil vs. AAHS (f, 16-24; 45)	0	2723	0	2732	Not estimable	
/501-015: Gardasil vs. AAHS (f, 15-26; 36) Subtotal (95% CI)	0	6087 8810	0	6080 8812	Not estimable Not estimable	
Total events	0	0010	0	0012	Not estimable	
Heterogeneity: Not applicable	v		V			
Fest for overall effect: Not applicable						
2.6.8 VaIN2+: Gardasil (females, age 15-26; fo						
/501-013: Gardasil vs. AAHS (f, 16-24; 45)	0	2723	0	2732	Not estimable	
/501-015: Gardasil vs. AAHS (f, 15-26; 36)	0	6087	0	6080	Not estimable Not estimable	
Subtotal (95% CI)	^	8810	^	8812	NOT ESTIMABLE	
Fotal events Heterogeneity: Not applicable	0		0			
est for overall effect: Not applicable						
2.6.9 VaIN2+: Gardasil (females, age 21-46; fo	llow-up u	ntil 48 mo	nths)			
/501-019: Gardasil vs. AAHS (f, 21-46; 48)	0	1911	0	1908	Not estimable	
Subtotal (95% CI)		1911		1908	Not estimable	
otal events	0		0			
Heterogeneity. Not applicable						
est for overall effect: Not applicable						
.6.10 VIN2+ or VaIN2+: Cervarix (females, ag	e 15-25; fo	ollow-up	until 4	8 months	s)	
HPV-008: Cervarix vs. Havrix (f, 15-25; 48)	0	9319	0	9325	Not estimable	
ubtotal (95% CI)		9319		9325	Not estimable	
Total events	0		0			
Heterogeneity. Not applicable						
est for overall effect: Not applicable						
Fotal (95% CI)		54268		54269	Not estimable	
otal (95% CI) otal events	0	37208	0	34209	Not estimable	
otal events Heterogeneity: Not applicable	U		U		_	
Fest for overall effect: Not applicable						0.05 0.2 1 5 2
est for subgroup differences: Not applicable						Favours HPV vaccine Favours control

Test for subgroup differences: Not applicable

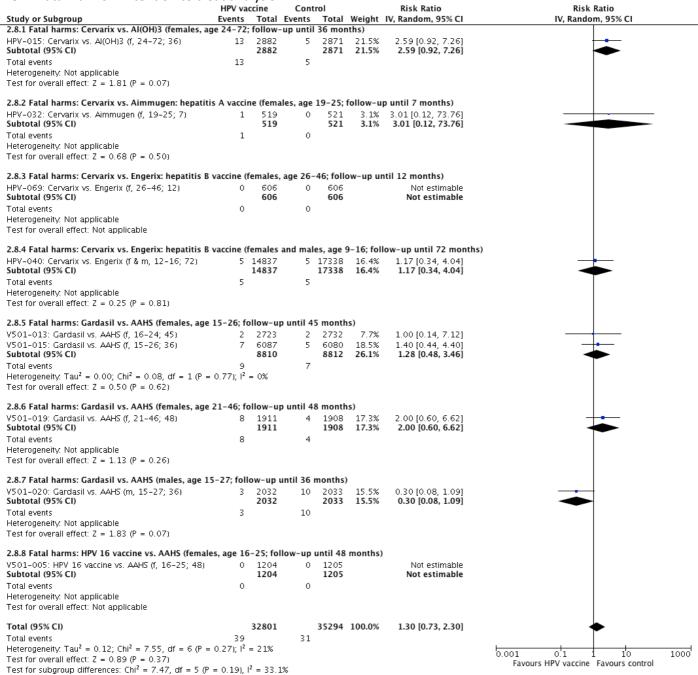
*2.6. Risk ratio for 'medically significant conditions' (GlaxoSmithKline): not applicable; risk ratio for 'new medical history' (Merck Sharp & Dohme): not applicable.

2.7. Number of treatment procedures (both surgical and non-surgical treatment) due to HPV-related diseases irrespective of HPV type: intention to treat analysis



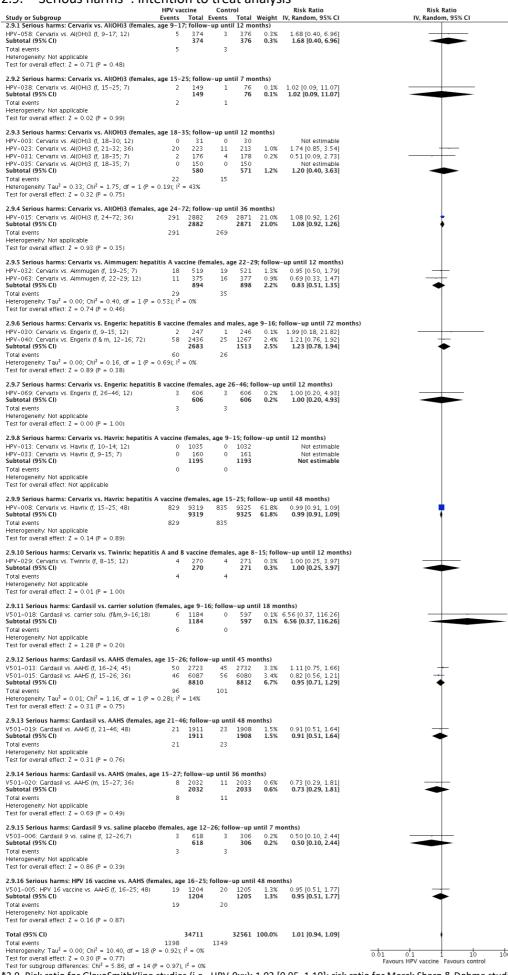
^{*2.7.} Risk ratio for GlaxoSmithKline studies (i.e., HPV-0xx): 0.90 [0.66, 1.22]; risk ratio for Merck Sharp & Dohme studies (i.e., V50x-xxx): not applicable.

2.8. Fatal harms*: intention to treat analysis



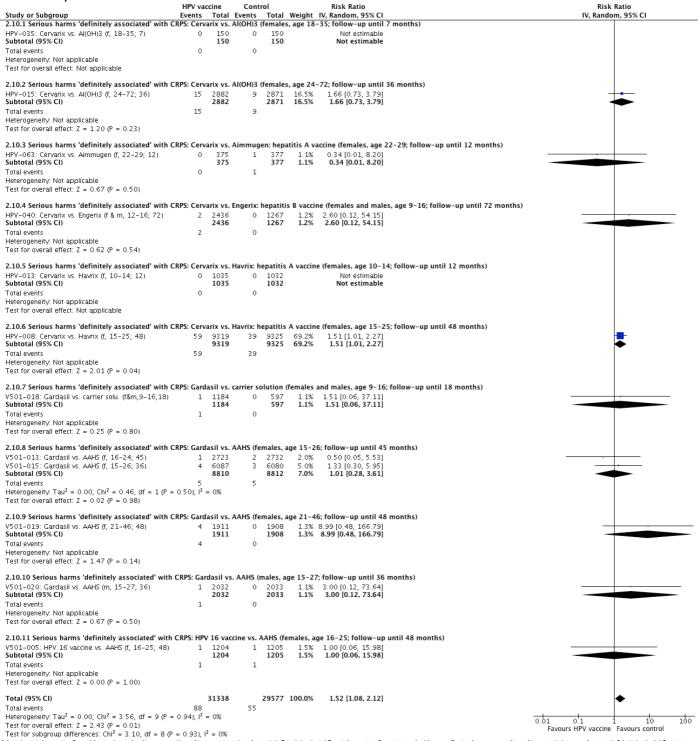
^{*2.8.} Risk ratio for GlaxoSmithKline studies (i.e., HPV-0xx): 1.92 [0.89, 4.15]; risk ratio for Merck Sharp & Dohme studies (i.e., V50x-xxx): 0.98 [0.41, 2.33].

2.9. Serious harms*: intention to treat analysis



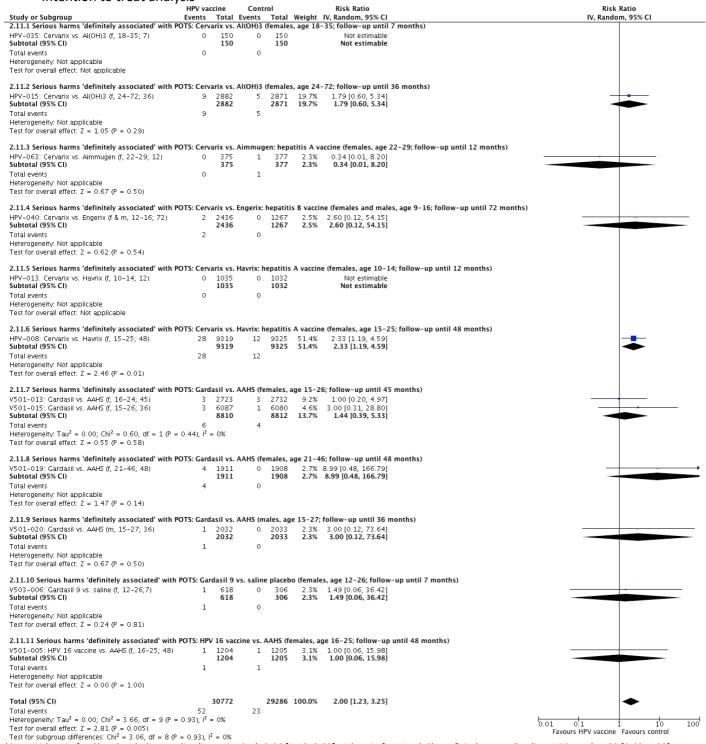
^{*2.9.} Risk ratio for GlaxoSmithKline studies (i.e., HPV-0xx): 1.02 [0.95, 1.10]; risk ratio for Merck Sharp & Dohme studies (i.e., V50x-xxx): 0.93 [0.74, 1.16].

2.10. Serious harms judged as 'definitely associated'* with chronic regional pain syndrome (CRPS): intention to treat analysis



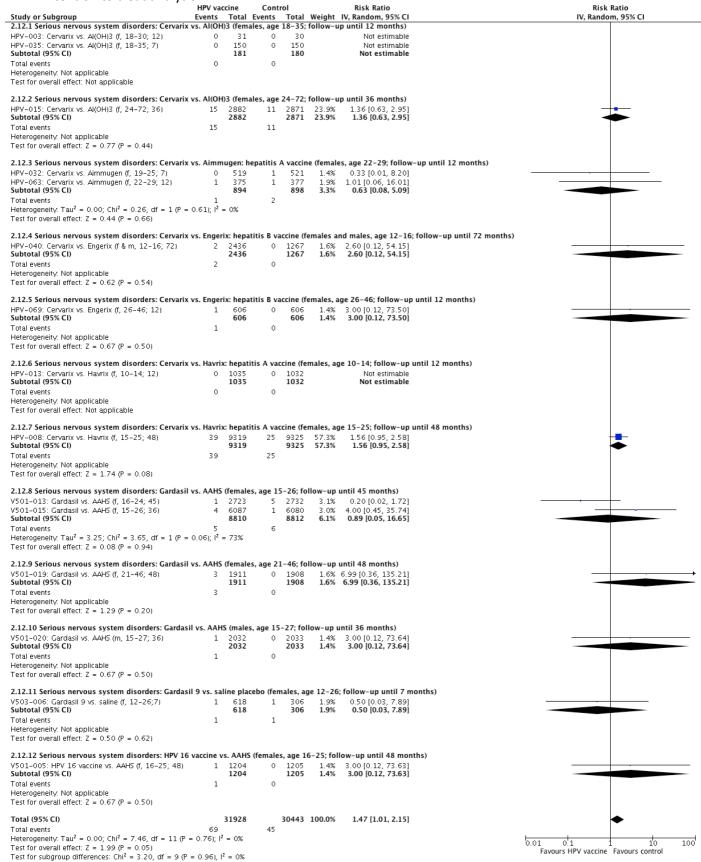
^{*2.10.} Risk ratio for GlaxoSmithKline studies (i.e., HPV-0xx): 1.52 [1.07, 2.18]; risk ratio for Merck Sharp & Dohme studies (i.e., V50x-xxx): 1.48 [0.56, 3.89]. We asked a physician with clinical expertise in CRPS to assess the reported MedDRA preferred terms as 'definitely,' 'probably,' 'probably not' or 'definitely not' associated with CRPS. We sent an Excel sheet to the physician with all the reported MedDRA terms. The physician was blinded, as the Excel sheet contained no outcome data. When the physician had assessed all the MedDRA terms, we synthesized the data for those MedDRA terms that the physician judged 'definitely' associated with CRPS and compared it to the reported serious harms.

2.11. Serious harms judged as 'definitely associated'* with postural orthostatic tachycardia syndrome (POTS): intention to treat analysis



*2.11. Risk ratio for GlaxoSmithKline studies (i.e., HPV-0xx): 2.06 [1.18, 3.60]; risk ratio for Merck Sharp & Dohme studies (i.e., V50x-xxx): 1.83 [0.68, 4.89]. We asked a physician with clinical expertise in POTS to assess the reported MedDRA preferred terms as 'definitely,' 'probably,' 'probably not' or 'definitely not' associated with POTS. We sent an Excel sheet to the physician with all the reported MedDRA terms. The physician was blinded, as the Excel sheet contained no outcome data. When the physician had assessed all the MedDRA terms, we synthesized the data for those MedDRA terms that the physician judged 'definitely' associated with POTS and compared it to the reported serious harms.

2.12. Serious harms reported within the MedDRA system organ class 'nervous system disorders (10029205)'*: intention to treat analysis



^{*2.12.} Risk ratio for GlaxoSmithKline studies (i.e., HPV-0xx): 1.48 [0.99, 2.22]; risk ratio for Merck Sharp & Dohme studies (i.e., V50x-xxx): 1.45 [0.43, 4.82].

2.13. New onset diseases ('medically significant conditions' and 'new medical history'*): intention to treat analysis

Study or Subgroup	HPV vaccine Events Total	Control	Weight	Risk Ratio IV, Random, 95% CI	,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,	Risk Ratio IV, Random, 95% CI
2.13.1 New onset diseases ('medically significant HPV-058: Cervarix vs. Al(OH)3 (f, 9-17; 12)					until 12 months)	IV, Kalidolli, 95% CI
Subtotal (95% CI) Total events	374 14	376 11	0.9%	1.28 [0.59, 2.78]		-
Heterogeneity: Not applicable Test for overall effect: Z = 0.62 (P = 0.53)	14	11				
2.13.2 New onset diseases (medically significant	conditions'): Cerva	arix vs. Al(OH)3 ((females.	age 15-25: follow-u	n until 7 months)	
HPV-038: Cervarix vs. Al(OH)3 (f, 15-25; 7) Subtotal (95% CI)	34 149 149	10 76 76	1.3% 1.3%	1.73 [0.91, 3.32] 1.73 [0.91, 3.32]	,	
Total events Heterogeneity: Not applicable	34	10	1.570	1.75 (0.51, 5.52)		
Test for overall effect: Z = 1.66 (P = 0.10)						
2.13.3 New onset diseases ('medically significant HPV-023: Cervarix vs. AI(0H)3 (f, 21-32; 36)	conditions'): Cerva	arix vs. Al(OH)3 ((females,		p until 7 months)	
HPV-031: Cervarix vs. Al(OH)3 (f, 18-35; 7)	13 176	24 178	1.3%	0.55 [0.29, 1.04]		
HPV-035: Cervarix vs. AI(OH)3 (f, 18-35; 7) Subtotal (95% CI)	0 150 549	0 150 541	5.1%	Not estimable 0.94 [0.35, 2.54]		-
Total events Heterogeneity: $Tau^2 = 0.44$; $Chi^2 = 7.27$, $chi = 1$ (P =	73 = 0.007); I ² = 86%	62				
Test for overall effect: Z = 0.12 (P = 0.91) 2.13.4 New onset diseases ('medically significant	conditions's Comm	aris us Al(OH)3 ((famalas	24 72 fellow u	n until 26 months)	
HPV-015: Cervarix vs. Al(OH)3 (f, 24-72; 36) Subtotal (95% CI)		1140 2871	34.8% 34.8 %	1.02 [0.96, 1.09] 1.02 [0.96, 1.09]	p until 30 months)	
Total events	1170	1140	34.0%	1.02 (0.90, 1.09)		
Heterogeneity: Not applicable Test for overall effect: Z = 0.69 (P = 0.49)						
2.13.5 New onset diseases ('medically significant	conditions'): Cerva				s, age 22-29; follow-up until 12 months)	
HPV-032: Cervarix vs. Aimmugen (f, 19-25; 7) HPV-063: Cervarix vs. Aimmugen (f, 22-29; 12) Subtotal (95% CI)	11 375 894	107 521 15 377 898	7.3% 0.9% 8.2%	0.85 [0.66, 1.10] 0.74 [0.34, 1.58] 0.84 [0.66, 1.07]		
Total events	102	122	0.270	0.84 [0.00, 1.07]		T
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.13$, $df = 1$ (P = Test for overall effect: Z = 1.41 (P = 0.16)	= 0.72j; l* = 0%					
2.13.6 New onset diseases ('medically significant HPV-030: Cervarix vs. Engerix (f, 9-15; 12)	conditions'): Cerva	arix vs. Engerix: h	hepatitis 1.9%	B vaccine (females as 1.27 [0.75, 2.15]	nd males, age 9-15; follow-up until 12 months)	
HPV-040: Cervarix vs. Engerix (f, 9-15; 12) HPV-040: Cervarix vs. Engerix (f & m, 12-16; 72) Subtotal (95% Cl)	47 643 890	76 1047 1293	4.1% 5.9%	1.27 [0.75, 2.15] 1.01 [0.71, 1.43] 1.08 [0.81, 1.45]		<u> </u>
Total events Heterogeneity: Tau ² = 0.00; Chi ² = 0.50, df = 1 (P =	75	98	3.370	1.00 [0.01, 1.43]		Ţ
Test for overall effect: Z = 0.52 (P = 0.61)	- J.70], I ⁻ = U%					
2.13.7 New onset diseases ('medically significant HPV-069: Cervarix vs. Engerix (f, 26-46; 12)	conditions'): Cerva	arix vs. Engerix: h	hepatitis		ge 26-46; follow-up until 12 months)	
Subtotal (95% CI) Total events	606	606	0.4%	0.71 [0.23, 2.24]		
Heterogeneity: Not applicable	,	,				
Test for overall effect: Z = 0.58 (P = 0.56) 2.13.8 New onset diseases ('medically significant	conditions'): Carv	ariy vs. Havriy: h	onatitis /	A vaccine (females an	se 9-15: follow-up until 12 months)	
HPV-013: Cervarix vs. Havrix (f, 10-14; 12) HPV-033: Cervarix vs. Havrix (f, 9-15; 7)	0 1035 0 160	0 1032 0 161	cputitis /	Not estimable Not estimable	e 3 13, follow up dittil 12 months)	
Subtotal (95% CI)	1195	1193		Not estimable		
Total events Heterogeneity: Not applicable	v	V				
Test for overall effect: Not applicable 2.13.9 New onset diseases ('medically significant	conditions'): Carv	ariy ve Havriy: h	onatitis /	A vaccine (females ac	ie 15–25: follow-un until 48 months)	
HPV-008: Cervarix vs. Havrix (f, 15-25; 48) Subtotal (95% CI)	3378 9319 9319	3298 9325			e 13 23, follow up ultil 40 months,	•
Total events Heterogeneity: Not applicable	3378	3298	71.770	1.02 (0.55, 1.07)		
Test for overall effect: Z = 1.25 (P = 0.21)						
2.13.10 New onset diseases ('medically significan HPV-029: Cervarix vs. Twinrix (f, 8-15; 12)	nt conditions'): Cerv	varix vs. Twinrix: 31 271	: hepatiti 2.0%	s A and B vaccine (fer 0.74 [0.45, 1.24]	nales, age 8-15; follow-up until 12 months)	
Subtotal (95% CI) Total events	23 270	31 271 31	2.0%	0.74 [0.45, 1.24]		•
Heterogeneity: Not applicable Test for overall effect: Z = 1.13 (P = 0.26)	23	31				
2.13.11 New onset diseases ('new medical history	v'): Gardasil vs. carr	rier solution (fen	nales and	t males age 9-16: fo	llow-up until 18 months)	
V501-018: Gardasil vs. carrier solu. (f&m,9-16;18) Subtotal (95% CI)	0 1184 1184	0 597 597	iares arie	Not estimable Not estimable	ap and to monday	
Total events Heterogeneity: Not applicable	0	0				
Test for overall effect: Not applicable						
2.13.12 New onset diseases ('new medical history V501-013: Gardasil vs. AAHS (f, 16-24; 45)	y'): Gardasil vs. AAF 0 2723	HS (females, age 0 2732	15-26; f	ollow-up until 45 mo	onths)	
V501-015: Gardasii vs. AAHS (f, 16-24, 45) V501-015: Gardasii vs. AAHS (f, 15-26; 36) Subtotal (95% Cl)	0 2723 0 6087 8810	0 6080 8812		Not estimable Not estimable		
Total events Heterogeneity: Not applicable	0	0				
Test for overall effect: Not applicable						
2.13.13 New onset diseases ('new medical history V501-019: Gardasil vs. AAHS (f, 21-46; 48)	y'): Gardasil vs. AAF 0 1911	HS (females, age 0 1908	21-46; f	ollow-up until 48 me	onths)	
Subtotal (95% CI) Total events	1911	1908		Not estimable		
Heterogeneity: Not applicable	v	V				
Test for overall effect: Not applicable 2.13.14 New onset diseases ('new medical history	v'): Gardasil ve 🗛 🗓	HS (males, and 1	5-27: fol	llow-up until 36 man	ths)	
V501-020: Gardasil vs. AAHS (m, 15-27; 36) Subtotal (95% CI)	0 2032 2032	0 2032 2032	, 101	Not estimable Not estimable	,	
Total events	0	0		HOL COLINADIO		
Heterogeneity: Not applicable Test for overall effect: Not applicable						
2.13.15 New onset diseases ('new medical history V503-006: Gardasil 9 vs. saline (f, 12-26;7)	y'): Gardasil 9 vs. sa 0 618	aline placebo (fe	males, aç	ge 12-26; follow-up Not estimable	until 7 months)	
V503-006: Gardasii 9 Vs. saiine (f, 12-26;7) Subtotal (95% Cl) Total events	0 618 618	306 306		Not estimable		
Heterogeneity: Not applicable Test for overall effect: Not applicable	v	~				
2.13.16 New onset diseases ('new medical history	y'): HPV 16 vaccine	vs. AAHS (female	es, age 1	6-25: follow-un unti	[48 months)	
V501-005: HPV 16 vaccine vs. AAHS (f, 16-25; 48) Subtotal (95% CI)		0 1205 1205	.,	Not estimable Not estimable		
Total events Heterogeneity: Not applicable	0	0		st communie		
Test for overall effect: Not applicable						
Total (95% CI) Total events	32887	32310	100.0%	1.02 [0.95, 1.10]		.
		4779				
Heterogeneity: Tau ² = 0.00; Chi ² = 16.14, df = 11 (Test for overall effect: Z = 0.49 (P = 0.63)	4874	4779 6			0.02_	0.1 10 50

^{*2.13.} Risk ratio for 'medically significant conditions' (GlaxoSmithKline): 1.02 [0.95, 1.10]; risk ratio for 'new medical history' (Merck Sharp & Dohme): not applicable.

2.14. New onset diseases most associated with the HPV vaccines ('medically significant conditions'*) - 'back pain': intention to treat analysis

and the state of t	HPV vacc		Contro			Risk Ratio		Risk Ratio
Study or Subgroup 2.14.1 New onset back pain ('medically significant o						V, Random, 95% CI age 18-35: follow-up	until 12 months)	IV, Random, 95% CI
PV-031: Cervarix vs. Al(OH)3 (f, 18-35; 7)	0	176	0	178	(remaies,	Not estimable		
V-035: Cervarix vs. Al(OH)3 (f, 18-35; 7)	0	150	0	150		Not estimable		
ototal (95% CI)	0	326	0	328		Not estimable		
al events erogeneity: Not applicable	U		U					
st for overall effect: Not applicable								
14.3 New areas has been using the adjustic simulficants		D. C	· •	L/OLINA	<i>(6</i>	24 72 fallam m		
L 4.2 New onset back pain ('medically significant (V-015: Cervarix vs. Al(OH)3 (f, 24-72; 36)		2882		2871	(remaies,	Not estimable	until 36 months)	
btotal (95% CI)		2882	0	2871		Not estimable		
tal events	0		0					
eterogeneity. Not applicable								
st for overall effect: Not applicable								
.14.3 New onset back pain ('medically significant o	conditions	'): Cervari	ix vs. A	immug	gen: hepat	itis A vaccine (females	, age 22-29; follow-up until 12 months)	
PV-063: Cervarix vs. Aimmugen (f, 22-29; 12)	0	375	0	377		Not estimable		
ibtotal (95% CI)		375		377		Not estimable		
otal events eterogeneity. Not applicable	0		0					
est for overall effect: Not applicable								
14.4 New onset back pain ('medically significant o					nepatitis A		10-14; follow-up until 12 months)	
PV-013: Cervarix vs. Havrix (f, 10-14; 12) ibtotal (95% CI)		1035 1035	0	1032 1032		Not estimable Not estimable		
otal events	0		0					
eterogeneity. Not applicable	-							
est for overall effect: Not applicable								
14.5 New onset back pain ('medically significant	conditions	'): Cervari	ix vs. H	lavrix: I	nepatitis A	vaccine (females, age	15-25; follow-up until 48 months)	
PV-008: Cervarix vs. Havrix (f, 15-25; 48)		9319		9325		Not estimable		
ubtotal (95% CI)		9319		9325		Not estimable		
otal events	0		0					
eterogeneity. Not applicable est for overall effect: Not applicable								
est for overall effect. Not applicable								
.14.6 New onset back pain ('new medical history'):					nales and		w-up until 18 months)	
501-018: Gardasil vs. carrier solu. (f&m,9-16;18)		1184	0	597		Not estimable		
ubtotal (95% CI) otal events	0	1184	0	597		Not estimable		
eterogeneity. Not applicable	v		•					
est for overall effect: Not applicable								
.14.7 New onset back pain ('new medical history'):	Cardasil	E AAHS	(famale		15-26: fo	llow-up until 45 mont	he)	
501-013: Gardasil vs. AAHS (f, 16-24; 45)		2723			100.0%	1.08 [0.77, 1.52]		_
501-015: Gardasii vs. AAHS (f, 15-26; 36)		6087		6080	200.000	Not estimable		
ubtotal (95% CI)		8810		8812	100.0%	1.08 [0.77, 1.52]		*
otal events	68		63					
eterogeneity. Not applicable est for overall effect: Z = 0.46 (P = 0.64)								
est for overall effect. 2 = 0. 10 (r = 0.01)								
14.8 New onset back pain ('new medical history'):					21-46; fo		hs)	
501-019: Gardasil vs. AAH5 (f, 21-46; 48) ubtotal (95% CI)		1911 1911	0	1908 1908		Not estimable Not estimable		
otal events	0	1311	0	1300		Not estimable		
eterogeneity. Not applicable	*		~					
est for overall effect: Not applicable								
14.9 New onset back pain ('new medical history'):	Gardasil	S AAHS	(maler	ane 11	5-27: falls	w-un until 36 manths	5)	
501–020: Gardasil vs. AAHS (m. 15–27; 36)		2032		2033	, e, ioile	Not estimable	••	
ibtotal (95% CI)		2032	~	2033		Not estimable		
otal events	0		0					
eterogeneity. Not applicable								
est for overall effect: Not applicable								
14.10 New onset back pain ('new medical history'): Gardasil		ine pla	cebo (f	emales, ag	je 12-26; follow-up ui	ntil 7 months)	
03-006: Gardasil 9 vs. saline (f, 12-26;7)	0	618	0	306		Not estimable		
ibtotal (95% CI)	^	618	^	306		Not estimable		
otal events eterogeneity: Not applicable	0		0					
est for overall effect: Not applicable								
	0. UDV 15	manic - :			laa a **	5 25. fallow	49	
14.11 New onset back pain ('new medical history'					ies, age 16		48 months)	
501–005: HPV 16 vaccine vs. AAHS (f, 16–25; 48) 1btotal (95% CI)		1204 1204	0	1205 1205		Not estimable Not estimable		
otal events	0	*	0	1203		commune		
eterogeneity. Not applicable	~		•					
est for overall effect: Not applicable								
otal (95% CI)	7	9696		28794	100.0%	1.08 [0.77, 1.52]		_
otal (93% CI)	68		63	-5,54	200.070	2.00 [0.77, 1.32]		
eterogeneity. Not applicable			-					0.1 0.2 0.5 1 2 5
est for overall effect: Z = 0.46 (P = 0.64)								Favours HPV vaccine Favours control
t for overall effect: 2 = 0.46 (P = 0.64) t for subgroup differences: Not applicable								Favours HPV vaccine Favours control

Test for subgroup differences: Not applicable

*2.14. Risk ratio for 'medically significant conditions' (GlaxoSmithKline): not applicable; risk ratio for 'new medical history' (Merck Sharp & Dohme): 1.08 [0.77, 1.52].

2.15. New onset diseases most inversely associated with the HPV vaccines ('new medical history') - 'vaginal infection': intention to treat analysis

	HPV va	ccine	Cont	rol	Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight IV, Random, 95% CI	IV, Random, 95% CI
2.15.1 New onset vaginal infection ('new medical	nistory'): (Gardasil [•]	vs. carrie	er soluti	ion (females and males, age 9-16; follow-up until 18 months)	
V501-018: Gardasil vs. carrier solu. (f&m,9-16;18) Subtotal (95% CI)	0	1184 1184	0	597 597	Not estimable Not estimable	
Fotal events	0		0			
Heterogeneity: Not applicable						
Fest for overall effect: Not applicable						
2.15.2 New onset vaginal infection ('new medical	nistory'):	Gardasil	vs. AAHS	(femal	es, age 15-26; follow-up until 45 months)	
/501-013: Gardasil vs. AAHS (f, 16-24; 45)	0	2723	0	2732	Not estimable	
V501-015: Gardasil vs. AAHS (f, 15-26; 36)	0	6087	0	6080	Not estimable	
Subtotal (95% CI)		8810		8812	Not estimable	
Total events	0		0			
Heterogeneity: Not applicable						
Fest for overall effect: Not applicable						
2.15.3 New onset vaginal infection ('new medical	nistory'):	Gardasil	vs. AAHS	(femal	es, age 21–46; follow-up until 48 months)	
V501-019: Gardasil vs. AAHS (f, 21-46; 48)	0	1911	0	1908	Not estimable	
Subtotal (95% CI)		1911		1908	Not estimable	
Fotal events	0		0			
Heterogeneity. Not applicable						
Test for overall effect: Not applicable						
2.15.4 New onset vaginal infection ('new medical	nistory'):	Gardasil	9 vs. sal	ine plac	ebo (females, age 12-26; follow-up until 7 months)	
V503-006: Gardasil 9 vs. saline (f, 12-26;7)	0	618	0	306	Not estimable	
Subtotal (95% CI)		618		306	Not estimable	
Fotal events	0		0			
Heterogeneity: Not applicable						
Fest for overall effect: Not applicable						
Total (95% CI)		12523		11623	Not estimable	
Fotal events	0		0			
Heterogeneity. Not applicable					_	0.05 0.2 1 5 20
Test for overall effect: Not applicable						Favours HPV vaccine Favours control
						ravours rir v vaccine Favours control

Favours HPV vaccine Favours control Test for subgroup differences: Not applicable

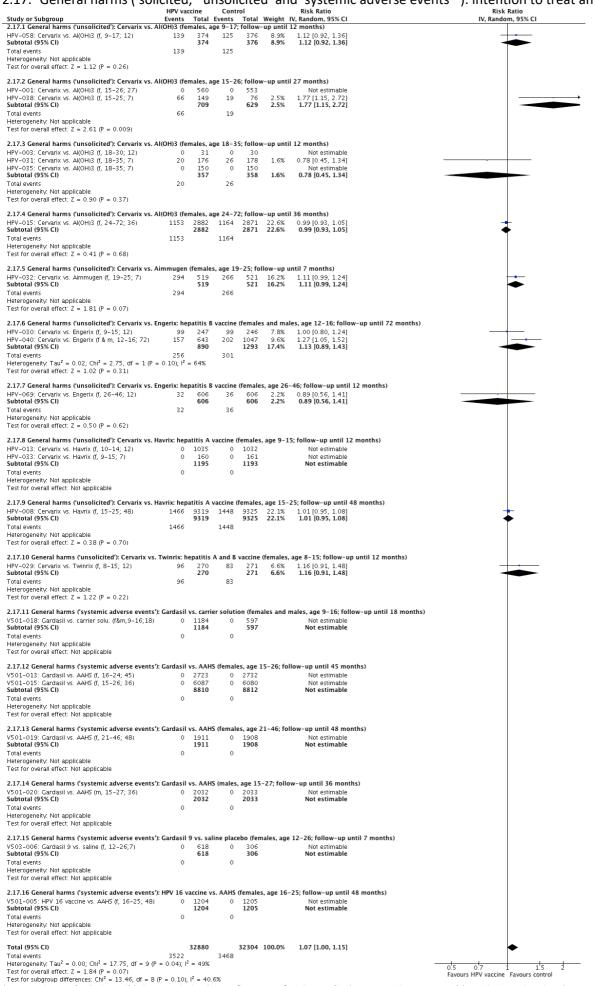
*2.15. Risk ratio for 'medically significant conditions' (GlaxoSmithKline): not applicable; risk ratio for 'new medical history' (Merck Sharp & Dohme): not applicable.

2.16. New onset diseases ('medically significant conditions' and 'new medical history') reported within the MedDRA system organ class 'vascular disorders (10047065)': intention to treat analysis

tudy or Subgroup	Events Total Eve		Risk Ratio ht IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI
16.1 New onset vascular disorders ('medically	significant conditions'):	Cervarix vs. Al(O	H)3 (females, age 24–72; follow-up until 36 months)	
V-015: Cervarix vs. Al(OH)3 (f, 24-72; 36)	0 2882	0 2871	Not estimable	
btotal (95% CI) al events	2882 0	2871	Not estimable	
ar events erogeneity. Not applicable	v	V		
st for overall effect: Not applicable				
			nugen: hepatitis A vaccine (females, age 22-29; follow-up until 12 mor	nths)
/-063: Cervarix vs. Aimmugen (f, 22-29; 12) ototal (95% CI)	0 375 375	0 377 377	Not estimable Not estimable	
al events	0	0		
erogeneity. Not applicable				
t for overall effect: Not applicable				
6.3 New onset vascular disorders ('medically	significant conditions'):	Cervarix vs. Havr	x: hepatitis A vaccine (females, age 10-14; follow-up until 12 months)	
/-013: Cervarix vs. Havrix (f, 10-14; 12)	0 1035	0 1032	Not estimable	
total (95% CI)	1035	1032	Not estimable	
al events	0	0		
terogeneity. Not applicable st for overall effect: Not applicable				
• •				
			x: hepatitis A vaccine (females, age 15-25; follow-up until 48 months)	
/-008: Cervarix vs. Havrix (f, 15-25; 48) ototal (95% Cl)	0 9319 9319	0 9325 9325	Not estimable Not estimable	
el events	0 9319	0	not estillable	
erogeneity. Not applicable	Ÿ	-		
st for overall effect: Not applicable				
6.5 New onset vascular disorders ('modically	significant conditions?	Cervariy ve Twin	rix: hepatitis A and B vaccine (females, age 8-15; follow-up until 12 m	onths)
/-029: Cervarix vs. Twinrix (f, 8-15; 12)	0 270	0 271	Not estimable	oning,
total (95% CI)	270	271	Not estimable	
al events	0	0		
erogeneity. Not applicable				
t for overall effect: Not applicable				
6.6 New onset vascular disorders ('new medi	cal history'): Gardasil vs.	carrier solution (females and males, age 9-16; follow-up until 18 months)	
01-018: Gardasil vs. carrier solu. (f&m,9-16;18		0 597	Not estimable	
ototal (95% CI)	1184	597	Not estimable	
al events erogeneity. Not applicable	0	0		
st for overall effect: Not applicable				
67.1	- I I :		45 26 fellow	
L6.7 New onset vascular disorders ('new medi	cai nistory'): Gardasii vs. 0 2723			
01-013: Gardasil vs. AAHS (f, 16-24; 45) 01-015: Gardasil vs. AAHS (f, 15-26; 36)	0 2/23	0 2732	Not estimable Not estimable	
ototal (95% CI)	8810	8812	Not estimable	
al events	0	0		
terogeneity. Not applicable st for overall effect: Not applicable				
st for overall effect. Not applicable				
6.8 New onset vascular disorders ('new medi				
01-019: Gardasil vs. AAHS (f, 21-46; 48)	0 1911	0 1908	Not estimable	
ototal (95% CI)	1911 0	1908 0	Not estimable	
arevents erogeneity. Not applicable	V	V		
t for overall effect: Not applicable				
6 O Nove operative coulon discorders (nove modified	aal history)). Cardaail wa	AAUS (males an	15 37 fellow up until 26 months)	
6.9 New onset vascular disorders ('new medi 01-020: Gardasil vs. AAHS (m, 15-27; 36)	cai nistory'): Gardasii vs. 0 2032	0 2033	15-27; Tollow-up until 36 months) Not estimable	
ot-020: Gardasii vs. AAH3 (III, 13-27, 30)	2032	2033	Not estimable	
al events	0	0		
terogeneity. Not applicable				
t for overall effect: Not applicable				
6.10 New onset vascular disorders ('new med	lical history'): HPV 16 va	ccine vs. AAHS (fe	males, age 16-25; follow-up until 48 months)	
01-005; HPV 16 vaccine vs. AAHS (f, 16-25; 48		0 1205	Not estimable	
ototal (95% CI)	1204	1205	Not estimable	
al events terogeneity: Not applicable	0	0		
erogeneity. Not applicable it for overall effect: Not applicable				
al (95% CI)	29022	28431	Not estimable	
al events erogeneity. Not applicable	0	0		
erogeneity: Not applicable t for overall effect: Not applicable				0.02 0.1 1 10
				Favours HPV vaccine Favours control

^{*2.16.} Risk ratio for 'medically significant conditions' (GlaxoSmithKline): not applicable; risk ratio for 'new medical history' (Merck Sharp & Dohme): not applicable.

2.17. General harms ('solicited,' 'unsolicited' and 'systemic adverse events'*): intention to treat analysis



^{*2.17.} Risk ratio for 'solicited' (GlaxoSmithKline): 1.07 [1.00, 1.15]; risk ratio for 'systemic adverse events' (Merck Sharp & Dohme): not applicable.

2.18. General harms most associated with the HPV vaccines ('solicited,' 'unsolicited' and 'systemic adverse events'*) - 'fatigue': intention to treat analysis

HPV vaccine Control Risk Ratio Events Total Events Total Weight IV, Random, 95% CI 2.18.1 General fatigue ('solicited'): Cervarix vs. Al(OH)/3 (Genales, age 9-17; follow-up until 12 months) Risk Ratio IV, Random, 95% CI HPV-058: Cervarix vs. Al(OH)3 (f, 9-17; 12) Subtotal (95% CI) 137 374 126 **374** 376 5.9% 1.09 [0.90, 1.33] 376 5.9% 1.09 [0.90, 1.33] Total events
Heterogeneity, Not applicable
Test for overall effect: Z = 0.89 (P = 0.37) 137 126 2.18.2 General fatigue ('solicited'): Cervarix vs. Al(OH)3 (females, age 15-26; follow-up until 27 months) 0 553 39 76 HPV-001: Cervarix vs. Al(OH)3 (f, 15-26; 27) HPV-038: Cervarix vs. Al(OH)3 (f, 15-25; 7) Subtotal (95% CI) 560 149 **709** 0 103 103 39 Total events Heterogeneity: Not applicable Test for overall effect: Z = 2.39 (P = 0.02) 2.18.3 General fatigue ('solicited'): Cervarix vs. Al(OH)3 (females, age 18-35; follow-up until 12 months) HPV-031: Cervarix vs. Al(OH)3 (f, 18-35; 7) HPV-031: Cervarix vs. Al(OH)3 (f, 18-35; 7) HPV-035: Cervarix vs. Al(OH)3 (f, 18-35; 7) Subtotal (95% CI) 30 178 4.8% 1.02 [0.82. 1.28] 150 357 150 358 4.8% 1.02 [0.82, 1.28] Total events
Heterogeneity: Not applicable
Test for overall effect: Z = 0.21 (P = 0.84) 2.18.4 General fatigue ('solicited'): Cervarix vs. Al(OH)3 (females, age 24-72; follow-up until 36 months) 1116 2882 916 2871 19.1% 1.21 [1.13, 1.30] 2882 2871 19.1% 1.21 [1.13, 1.30] HPV-015: Cervarix vs. Al(OH)3 (f, 24-72; 36) Subtotal (95% CI) 1116 916 Total events Heterogeneity: Not applicable Test for overall effect: Z = 5.39 (P < 0.00001) 2.18.5 General fatigue ('solicited'): Cervarix vs. Aimmugen: hepatitis A vaccine (females, age 19-29; follow-up until 12 months) HPV-032: Cervarix vs. Aimmugen (f, 19-25; 7) Subtotal (95% CI) 341 519 300 **519** 521 14.8% 1.14 [1.04, 1.26] 521 14.8% 1.14 [1.04, 1.26] Total events
Heterogeneity. Not applicable
Test for overall effect: Z = 2.68 (P = 0.007) 341 300
 2.18.6 General fatigue ('solicited'): Cervarix vs. Engerix: hepatitis 8 vaccine (females: and males: age 9-16; follow-up until 72 months)

 HPV-030: Cervarix vs. Engerix (f, 9-15; 12)
 107
 247
 104
 246
 5.5%
 1.02 [0.84, 1.26]

 HPV-040: Cervarix vs. Engerix (f & m, 12-16; 72)
 291
 643
 411
 1047
 12.4%
 1.15 [1.03, 1.29]

 Subtotal (95% Cl)
 800
 1293
 1.79%
 1.12 [1.02, 1.24]
 Total events 398
Heterogeneity, Tau² = 0.00; Chi² = 0.98, df = 1 (P = 0.32); l² = 0%
Test for overall effect: Z = 2.26 (P = 0.02) 5 1 5 2.18.7 General fatigue ('solicited'): Cervarix vs. Engerix: hepatitis B vaccine (females, age 26-46; follow-up until 12 months) HPV-069: Cervarix vs. Engerix (f, 26-46; 12) Subtotal (95% CI) 100 606 **606** 68 606 3.1% 1.47 [1.10, 1.96] 606 3.1% 1.47 [1.10, 1.96] Total events Heterogeneity. Not applicable Test for overall effect: Z = 2.64 (P = 0.008) 100

 2.18.8 General fatigue ('solicited'): Cervarix vs. Havrix: hepatitis A vaccine (females, age 9-15; follow-up until 12 months)

 HPV-013: Cervarix vs. Havrix (f, 10-14; 12)
 0
 1035
 0
 1032
 Not estimable

 HPV-033: Cervarix vs. Havrix (f, 9-15; 7)
 0
 160
 0
 161
 Not estimable

 0 1035 0 160 1195 HPV-013: Cervarix vs. Havrix (f, 10-14; 12) HPV-033: Cervarix vs. Havrix (f, 9-15; 7) Subtotal (95% CI) Total events Heterogeneity. Not applicable Test for overall effect: Not applicable 2.18.9 General fatigue ('solicited'): Cervarix vs. Havrix: hepatitis A vaccine (females, age 15-25; follow-up until 48 months) HPV-008: Cervarix vs. Havrix (f, 15-25; 48) Subtotal (95% CI) 1771 9319 1652 9325 20.9% 1.07 [1.01, 1.14] 9319 9325 20.9% 1.07 [1.01, 1.14] Total events
Heterogeneity. Not applicable
Test for overall effect: Z = 2.27 (P = 0.02) 1771 1652 2.18.10 General fatigue ('solicited'): Cervarix vs. Twinrix: hepatitis A and B vaccine (females, age 8-15; follow-up until 12 months) 133 270 119 **270** HPV-029: Cervarix vs. Twinrix (f, 8-15; 12) Subtotal (95% CI) 271 6.6% 1.12 [0.94, 1.34] 271 6.6% 1.12 [0.94, 1.34] 133 119 Total events Heterogeneity. Not applicable Test for overall effect: Z = 1.24 (P = 0.21) 2.18.11 General fatigue ('unsolicited'): Cervarix vs. Engerix: hepatitis B vaccine (females and males, age 9-16; follow-up until 72 months) HPV-030: Cervarix vs. Engerix (f, 9-15; 12) 0 247
HPV-040: Cervarix vs. Engerix (f & m, 12-16; 72) 0 1908
Subtotal (95% CI) 2155 0 246 0 3128 **3374** Not estimable Not estimable Total events Heterogeneity. Not applicable Test for overall effect: Not applicable Λ 2.18.12 General fatigue ('systemic adverse events'): Gardasil vs. carrier solution (females and males, age 9-16; follow-up until 18 months) V501-018: Gardasil vs. carrier solu. (f&m,9-16;18) Subtotal (95% Cl) 0 1184 1184 Total events Heterogeneity. Not applicable Test for overall effect: Not applicable 2.18.13 General fatigue ('systemic adverse events'): Gardasil vs. AAHS (males, age 15-27; follow-up until 36 months) V501-020: Gardasil vs. AAHS (m, 15-27; 36) Subtotal (95% CI) 13 2032 19 2033 0.6% 0.68 [0.34, 1.38] 2032 2033 0.6% 0.68 [0.34, 1.38] Total events 13 19 Heterogeneity. Not applicable
Test for overall effect: Z = 1.06 (P = 0.29) 2.18.14 General fatigue ('systemic adverse events'): Gardasil 9 vs. saline placebo (females, age 12-26; follow-up until 7 months) V503-006: Gardasil 9 vs. saline (f, 12-26;7) Subtotal (95% CI) 0 618 **618** 0 306 **306** Total events Heterogeneity: Not applicable Test for overall effect: Not applicable 2.18.15 General fatigue ('systemic adverse events'): HPV 16 vaccine vs. AAHS (females, age 16-25; follow-up until 48 months) V501-005: HPV 16 vaccine vs. AAHS (f, 16-25; 48) Subtotal (95% CI) 59 1204 1204 64 1205 2.2% 1205 2.2% 0.92 [0.65, 1.30] 0.92 [0.65, 1.30] 64 59 Total events Heterogeneity. Not applicable
Test for overall effect: Z = 0.46 (P = 0.65). Total (95% CI) 24314 24958 100.0% 1.13 [1.07, 1.19] Total events 2000; Total events 4255 3901 Heterogeneity, $Tau^2 = 0.00$, $Chi^2 = 17.23$, df = 11 (P = 0.10); $I^2 = 36\%$ Test for overall effect: Z = 4.58 (P < 0.00001) Test for osubgroup differences: $Chi^2 = 16.25$, df = 10 (P = 0.09), $I^2 = 38.5\%$

^{*2.18.} Risk ratio for 'solicited' (GlaxoSmithKline): **1.14 [1.08, 1.20]**; risk ratio for 'unsolicited' (GlaxoSmithKline): not applicable; risk ratio for 'systemic adverse events' (Merck Sharp & Dohme): 0.87 [0.64, 1.19]. To avoid double counting of participants in the total risk ratio estimate, we excluded the 'unsolicited' adverse events from total risk ratio estimate for studies that reported 'solicited' adverse events.

2.19. General harms most associated with the HPV vaccines ('solicited,' 'unsolicited' and 'systemic adverse events'*)

- 'headache': intention to treat analysis

- 'headache': ı	HPV vac	cine	Cont	rol		Risk Ratio	5.5	Risk Ratio
19.1 General headache ('solicited'): Cervarix vs. Al(C PV-058: Cervarix vs. Al(OH)3 (f. 9-17: 12)	Events OH)3 (fe 123	Total males, a 374	Events ge 9-17 99	Total 7; follow 376	Weight -up until 3.4%	IV, Random, 95% CI 12 months) 1.25 [1.00, 1.56]		IV, Random, 95% CI
btotal (95% Ct) tal events terogeneity. Not applicable st for overall effect: Z = 1.96 (P = 0.05)	123	374	99	376	3.4%	1.25 [1.00, 1.56]		•
19.2 General headache ('solicited'): Cervarix vs. Al(C V-001: Cervarix vs. Al(OH)3 (f, 15-26; 27)	OH)3 (fe	males, a	ge 15-2	2 6; follo 553	w-up unt	il 27 months) Not estimable		
PV-038: Cervarix vs. Al(OH)3 (f, 15-25; 7) ibtotal (95% CI)	73	149 709	30	76 629	1.7% 1.7%	1.24 [0.90, 1.71] 1.24 [0.90, 1.71]		+
ital events eterogeneity: Not applicable est for overall effect: Z = 1.31 (P = 0.19)	73		30					
19.3 General headache ('solicited'); Cervarix vs. Al(C	OH)3 (fe	males, a	ge 18-3	35; follo	w-up unt	il 12 months)		
PV-003: Cervarix vs. Al(OH)3 (f, 18-30; 12) PV-031: Cervarix vs. Al(OH)3 (f, 18-35; 7)	72	31 176	71	30 178	2.7%	Not estimable 1.03 [0.80, 1.32]		+
PV-035: Cervarix vs. Al(OH)3 (f, 18-35; 7) ibtotal (95% CI) ital events	72	150 357	71	150 358	2.7%	Not estimable 1.03 [0.80, 1.32]		+
eterogeneity. Not applicable est for overall effect: Z = 0.20 (P = 0.84)								
19.4 General headache ('solicited'): Cervarix vs. Al(O PV-015: Cervarix vs. Al(OH)3 (f, 24-72; 36)	OH)3 (fe 1165	males, a				il 36 months)		L
ibtotal (95% CI) Ital events eterogeneity: Not applicable	1165	2882	1074	2871	19.3% 19.3%	1.08 [1.01, 1.15]		
st for overall effect: Z = 2.34 (P = 0.02) 19.5 General headache ('solicited'): Cervarix vs. Aim	ımugen	: hepatit	is A vac	cine (fer	nales, age	≥ 19-29; follow-up	until 12 months)	
PV-032: Cervarix vs. Aimmugen (f, 19-25; 7) ibtotal (95% CI)	250	519 519	222	521 521	8.0% 8.0 %	1.13 [0.99, 1.29] 1.13 [0.99, 1.29]		•
ital events eterogeneity: Not applicable est for overall effect: Z = 1,80 (P = 0.07)	250		222					
19.6 General headache ('solicited'): Cervarix vs. Eng	jerix: he	patitis B	vaccine	e (female	es and ma	iles, age 9–16; follov	w-up until 72 months)	
PV-030: Cervarix vs. Engerix (f, 9-15; 12) PV-040: Cervarix vs. Engerix (f & m, 12-16; 72) ibtotal (95% CI)	131 261	247 643	129 371	246 1047	5.6% 8.9%	1.01 [0.86, 1.20] 1.15 [1.01, 1.30]		ŧ
ibtotal (95% CI) ital events eterogeneity: Tau ² = 0.00; Chi ² = 1.37, df = 1 (P = 0.	392	890	500	1293	14.5%	1.09 [0.97, 1.23]		ľ
est for overall effect: Z = 1.42 (P = 0.15)								
19.7 General headache ('solicited'): Cervarix vs. Eng PV-069: Cervarix vs. Engerix (f, 26-46; 12) ibtotal (95% Cl)	erix: he	606 606	vaccine 46	606 606	es, age 26 1.4% 1.4%	-46; follow-up unti 1.54 [1.08, 2.20] 1.54 [1.08, 2.20]	I 12 months)	_
ibtotal (95% CI) ital events eterogeneity. Not applicable	71	606	46	906	1.4%	1.34 [1.08, 2.20]		
est for overall effect: Z = 2.41 (P = 0.02)						5.6.0.	2	
19.8 General headache ('solicited'): Cervarix vs. Hav PV-013: Cervarix vs. Havrix (f, 10-14; 12) PV-033: Cervarix vs. Havrix (f, 9-15; 7)	0	1035 160	0	(female: 1032 161	s, age 9-1	.5; follow-up until 1 Not estimable Not estimable	z months)	
PV-033: Cervarix vs. Havrix (f, 9-15; 7) ibtotal (95% CI) ital events	0	160 1195	0	161 1193		Not estimable Not estimable		
eterogeneity. Not applicable est for overall effect: Not applicable	-							
19.9 General headache ('solicited'): Cervarix vs. Hav PV-008: Cervarix vs. Havrix (f, 15-25; 48)	rix: hep		vaccine 1583	9325	19.9%	25; follow-up until 1.05 (0.99, 1.12)	48 months)	
ibtotal (95% CI) Ital events	1668	9319	1583	9325	19.9%	1.05 [0.99, 1.12]		ĺ
eterogeneity. Not applicable est for overall effect: Z = 1.66 (P = 0.10)	-							
19.10 General headache ('solicited'): Cervarix vs. Tv PV-029: Cervarix vs. Twinrix (f, 8-15; 12)	vinrix: h	270	A and B	271	4.3%		p until 12 months)	1
PV-029: Cervarix vs. Twinrix (f, 8-15; 12) ibtotal (95% CI) ital events	124	270	110	271	4.3%	1.13 [0.93, 1.37] 1.13 [0.93, 1.37]		<u></u>
eterogeneity. Not applicable st for overall effect: Z = 1.25 (P = 0.21)								
19.11 General headache ('unsolicited'): Cervarix vs. PV-058: Cervarix vs. A(OH)3 (f. 9-17: 12)	AI(OH)	374	s, age 9	9-17; fo	llow-up u	ntil 12 months) Not estimable		
PV-058: Cervarix vs. Al(OH)3 (f, 9-17; 12) ibtotal (95% CI) ital events	0	0	0	0		Not estimable		
aterogeneity. Not applicable est for overall effect: Not applicable								
19.12 General headache ('unsolicited'): Cervarix vs. PV-038: Cervarix vs. Al(OH)3 (f, 15-25; 7)	AI(OH)	149	s, age 1	76	ollow-up 0.0%	1.15 [0.37, 3.61]		
ibtotal (95% CI) Ital events	0	0	0	0		Not estimable		
eterogeneity: Not applicable est for overall effect: Not applicable								
19.13 General headache ('unsolicited'): Cervarix vs. PV-031: Cervarix vs. Al(OH)3 (f, 18-35; 7)	0	176	0	178	ollow-up	Not estimable		
PV-035: Cervarix vs. Al(OH)3 (f, 18-35; 7) ibtotal (95% CI) ital events	0	150 0	0	150 0		Not estimable Not estimable		
ital events eterogeneity. Not applicable est for overall effect: Not applicable	0		0					
19.14 General headache (unsolicited'): Cervarix vs.					(females,	age 19-29; follow-	up until 12 months)	
PV-032: Cervarix vs. Aimmugen (f, 19-25; 7) ibtotal (95% CI) ital events	19	519 0	27	521 0	0.0%	0.71 [0.40, 1.25] Not estimable		
eterogeneity. Not applicable est for overall effect: Not applicable								
19.15 General headache ('unsolicited'): Cervarix vs. PV-030: Cervarix vs. Engerix (f, 9-15; 12)	Engerix	: hepatit	is B vac		males and	I males, age 9-16; fo	ollow-up until 72 months)	
PV-040: Cervarix vs. Engerix (f & m, 12-16; 72) ibtotal (95% Cl)	ō	1908 0	0	3128 0		Not estimable Not estimable Not estimable		
ital events eterogeneity: Not applicable	0		0					
est for overall effect: Not applicable 19.16 General headache ('unsolicited'): Cervarix vs.	Havriv-	hepatiti	s A var	ine (fer	iales. ane	15-25; follow-up u	ntil 48 months)	
PV-008: Cenvarix vs. Havrix (f, 15-25; 48) sbtotal (95% CI)		9319 0		9325 0	0.0%	0.91 [0.76, 1.09] Not estimable		
ntal events eterogeneity. Not applicable	0		0					
st for overall effect: Not applicable 19.17 General headache ('unsolicited'): Cervarix vs.	Twinris	: hepatit	is A an	d B vacci	ine (fema	les, age 8-15: follow	r-up until 12 months)	
V-029: Cervarix vs. Twinrix (f, 8-15; 12) btotal (95% CI)	0	270 0	0	271 0	oema	Not estimable Not estimable		
tal events terogeneity. Not applicable	0		0					
st for overall effect: Not applicable 19.18 General headache ('systemic adverse events')): Garda	sil vs. ca	rrier so	lution (f	emales 21	nd males. age 9–16.	follow-up until 18 months)	
01-018: Gardasii vs. carrier solu. (f&m,9-16;18) ibtotal (95% CI)	0	1184 1184	0	597 597	ares di	Not estimable Not estimable	ap and to months)	
tal events terogeneity: Not applicable	0		0					
st for overall effect: Not applicable 19.19 General headache ('systemic adverse events')): Garda	sil vs. A	AHS (ma	iles, age	15-27: fe	ollow-up until 36 m	onths)	
01-020: Gardasii vs. AAHS (m, 15-27; 36) btotal (95% CI)	179	2032 2032	207	2033 2033	4.4% 4.4%	0.87 [0.72, 1.05] 0.87 [0.72, 1.05]	-	-
tal events eterogeneity. Not applicable	179		207					
est for overall effect: Z = 1.49 (P = 0.14) 19.20 General headache ('systemic adverse events')): Garda	sil 9 vs	saline n	lacebo (females :	age 12-26; follow-u	p until 7 months)	
i03-006: Gardasil 9 vs. saline (f, 12-26;7) ibtotal (95% CI)	318	618 618	150	306 306	7.6% 7.6 %	1.05 [0.91, 1.20] 1.05 [0.91, 1.20]	,	ţ
ital events eterogeneity. Not applicable	318		150					
est for overall effect: Z = 0.69 (P = 0.49) 19.21 General headache ('systemic adverse events')): HPV 1	6 vaccin	e vs. AA	HS (fem	ales. ane	16-25; follow-un ···	ntil 48 months)	
01-005: HPV 16 vaccine vs. AAHS (f, 16-25; 48) ibtotal (95% CI)	499	1204 1204	495	1205 1205	12.8% 12.8%	1.01 [0.92, 1.11] 1.01 [0.92, 1.11]	/	†
ital events eterogeneity. Not applicable	499		495					
est for overall effect: Z = 0.18 (P = 0.86)		22159		21584	100.0%	1.07 [1.03, 1.12]		
otal (95% CI)			4587					

^{*2.19.} Risk ratio for 'solicited' (GlaxoSmithKline): 1.09 [1.05, 1.13]; risk ratio for 'unsolicited' (GlaxoSmithKline): 0.90 [0.76, 1.06]; risk ratio for 'systemic adverse events' (Merck Sharp & Dohme): 0.99 [0.91, 1.09]. To avoid double counting of participants in the total risk ratio estimate, we excluded the 'unsolicited' adverse events from total risk ratio estimate for studies that reported 'solicited' adverse events.

2.20. General harms most associated with the HPV vaccines ('solicited,' 'unsolicited' and 'systemic adverse events'*) - 'myalgia': intention to treat analysis

- Iliyaigia . Ilitei	HPV vaccine	Control	Risk Ratio		Risk Ratio
tudy or Subgroup . 20.1 General myalgia ('solicited'): Cervarix vs. Al IPV-058: Cervarix vs. Al(OH)3 (f, 9-17; 12)	Events Total (OH)3 (females, a 110 374	Events Total ge 9-17; follow- 93 376			IV, Random, 95% CI
ubtotal (95% CI) otal events leterogeneity. Not applicable est for overall effect: Z = 1.44 (P = 0.15)	374 110	376 93		1.51	*
.20.2 General myalgia ('solicited'): Cervarix vs. Al	(OH)3 (females, a	ge 15-25; follow	v-up until 7 months)		
IPV-038: Cervarix vs. Al(OH)3 (f, 15-25; 7) ubtotal (95% CI) otal events	97 149 149 97	33 76 76 33		1.99] 1.99]	*
leterogeneity. Not applicable lest for overall effect: Z = 2.81 (P = 0.005)					
.20.3 General myalgia ('solicited'): Cervarix vs. Al PV-003: Cervarix vs. Al(OH)3 (f, 18-30; 12)	(OH)3 (females, a			mable	
PV-031: Cervarix vs. Al(OH)3 (f, 18-35; 7) PV-035: Cervarix vs. Al(OH)3 (f, 18-35; 7)	10 176 0 150	11 178 0 150	3.2% 0.92 [0.40, Not esti	mable	
ubtotal (95% CI) otal events eterogeneity. Not applicable est for overall effect: Z = 0.20 (P = 0.84)	357 10	358 11	3.2% 0.92 [0.40,	2.11]	
.20.4 General myalgia ('solicited'): Cervarix vs. Al	(OH)3 (females, a	ge 24-72; follow	v-up until 36 months)		
IPV-015: Cervarix vs. Al(OH)3 (f, 24-72; 36) ubtotal (95% Cl)	878 2882 2882	2871	12.7% 1.41 [1.29, 12.7% 1.41 [1.29,		i i
otal events leterogeneity. Not applicable est for overall effect: Z = 7.53 (P < 0.00001)	878	622			
.20.5 General myalgia ('solicited'): Cervarix vs. Ai					
PV-032: Cervarix vs. Aimmugen (f, 19-25; 7) ubtotal (95% CI) otal events	262 519 519 262	128 521 521	11.6% 2.05 [1.73, 11.6% 2.05 [1.73,	2.44] 2.44]	•
eterogeneity. Not applicable est for overall effect: Z = 8.16 (P < 0.00001)	202	120			
.20.6 General myalgia ('solicited'): Cervarix vs. En	ngerix: hepatitis B	vaccine (female:	s and males, age 9-16; i	follow-up until 72 months)	
PV-030: Cervarix vs. Engerix (f, 9-15; 12) PV-040: Cervarix vs. Engerix (f & m, 12-16; 72)	55 247 321 643	53 246 250 1047	12.2% 2.09 [1.83,	2.39]	†.
ubtotal (95% CI) otal events eterogeneity, Tau ² = 0,23; Chi ² = 14,80, df = 1 (P	890 376	303	20.9% 1.50 [0.75,	2.98]	
eterogeneity. Fau* = 0.23; Chi* = 14.80, df = 1 (P est for overall effect: Z = 1.14 (P = 0.25)	= 0.0001); I* = 9.	3%			
.20.7 General myalgia ('solicited'): Cervarix vs. En PV-069: Cervarix vs. Engerix (f, 26-46; 12)	ngerix: hepatitis B	vaccine (female:			
ubtotal (95% CI) otal events	606	606 42	8.2% 1.64 [1.14,	2.37]	•
eterogeneity. Not applicable est for overall effect: Z = 2.65 (P = 0.008)					
.20.8 General myalgia ('solicited'): Cervarix vs. Ha					
PV-013: Cervarix vs. Havrix (f, 10-14; 12) PV-033: Cervarix vs. Havrix (f, 9-15; 7) ubtotal (95% CI)	0 1035 0 160 1195	0 1032 0 161 1193	Not esti Not esti Not esti r	mable	
otal events eterogeneity. Not applicable	0	0			
est for overall effect: Not applicable					
.20.9 General myalgia ('solicited'): Cervarix vs. Ha PV-008: Cervarix vs. Havrix (f, 15-25; 48)	1607 9319	1381 9325	12.9% 1.16 [1.09,	1.24]	:
ubtotal (95% CI) oral events	9319 1607	9325 1381	12.9% 1.16 [1.09,	1.24]	,
eterogeneity. Not applicable est for overall effect: Z = 4.52 (P < 0.00001)					
.20.10 General myalgia ('solicited'): Cervarix vs. T PV-029: Cervarix vs. Twinrix (f, 8-15; 12)	Fwinrix: hepatitis	A and B vaccine 75 271	(females, age 8-15; follo 10.3% 1.32 [1.03,		-
ubtotal (95% CI) otal events	270 99	271 75	10.3% 1.32 [1.03,	1.70]	•
eterogeneity: Not applicable est for overall effect: Z = 2.22 (P = 0.03)					
.20.11 General myalgia ('unsolicited'): Cervarix vs IPV-038: Cervarix vs. AI(OH)3 (f, 15-25; 7)	s. Al(OH)3 (female	es, age 15-25; fo	llow-up until 7 months		
ubtotal (95% CI) otal events	149	76	Not estir		
eterogeneity. Not applicable est for overall effect: Not applicable					
.20.12 General myalgia ('unsolicited'): Cervarix v					
PV-031: Cervarix vs. Al(OH)3 (f, 18-35; 7) ubtotal (95% CI) otal events	0 176 176	0 178 178	Not estir Not estir	mable mable	
leterogeneity: Not applicable est for overall effect: Not applicable	Ť	•			
.20.13 General myalgia ('unsolicited'): Cervarix v					
PV-040: Cervarix vs. Engerix (f & m, 12-16; 72) ubtotal (95% CI) otal events	0 1908 1908	0 3128 3128	Not estir Not estir		
eterogeneity. Not applicable est for overall effect: Not applicable	v	•			
.20.14 General myalgia ('unsolicited'): Cervarix v					
PV-033: Cervarix vs. Havrix (f, 9-15; 7) ubtotal (95% CI)	0 160 160	0 161 161	Not estir Not esti r		
otal events eterogeneity. Not applicable	0	0			
est for overall effect: Not applicable .20.15 General myalgia ('systemic adverse event:	s'): Gardasil vs. ca	rrier solution (fe	males and males, age 9	-16: follow-up until 18 months)	
501-018: Gardasil vs. carrier solu. (f&m,9-16;18) ubtotal (95% CI)	0 1184 1184	0 597 597	Not estir Not estir	mable	
otal events eterogeneity. Not applicable	0	0			
est for overall effect: Not applicable	D 6 - 1 - 1 - 1			26	
. 20.16 General myalgia ('systemic adverse event: 501–020: Gardasil vs. AAHS (m, 15–27; 36) ubtotal (95% CI)	0 2032 2032	0 2033 2033	Not estir Not estir	mable	
otal events eterogeneity: Not applicable	0	0			
est for overall effect: Not applicable					
.20.17 General myalgia ('systemic adverse event: 503-006: Gardasil 9 vs. saline (f, 12-26;7)	0 618	0 306	Not estin	mable	
ubtotal (95% CI) otal events	618 0	3 06 0	Not estir	паріе	
eterogeneity. Not applicable est for overall effect: Not applicable					
.20.18 General myalgia ('systemic adverse event: 501-005: HPV 16 vaccine vs. AAHS (f, 16-25; 48)	0 1204	o 1205	Not estin	mable	
ubtotal (95% CI) otal events	1204	1205	Not estir		
eterogeneity: Not applicable est for overall effect: Not applicable					
	22002	24574	100.0% 1.44 [1.21,	1.71]	
otal (95% CI) otal events	23992 3508	2688	2001070 2001 (2022)	,	•

^{*2.20.} Risk ratio for 'solicited' (GlaxoSmithKline): 1.37 [1.31, 1.43]; risk ratio for 'unsolicited' (GlaxoSmithKline): not applicable; risk ratio for 'systemic adverse events' (Merck Sharp & Dohme): not applicable. To avoid double counting of participants in the total risk ratio estimate, we excluded the 'unsolicited' adverse events from total risk ratio estimate for studies that reported 'solicited' adverse events.

3. <u>Journal publications</u>

3.1. All-cause mortality/deaths*: intention to treat analysis

t C-1	HPV vacci		Control	-1 1/2 1 1 1	Risk Ratio	Risk Ratio
tudy or Subgroup		Total Eve			IV, Random, 95% CI	IV, Random, 95% CI
1.1 All-cause mortality/deaths: Cervarix vs. A				-		
PV-015: Cervarix vs. Al(OH)3 (f, 24-72; 36) 1btotal (95% CI)		2882 2882		71 20.5% 71 20.5 %	4.65 [1.34, 16.16] 4.65 [1.34, 16.16]	
	14	2002	3	71 20.5%	4.03 [1.34, 10.10]	
ital events eterogeneity. Not applicable	14		3			
eterogeneity: Not applicable est for overall effect: Z = 2.42 (P = 0.02)						
(F = 0.02)						
1.2 All-cause mortality/deaths: Cervarix vs. A	limmugen: hep	atitis A v	accine (fe	males, age	19-25; follow-up until 7 mor	nths)
PV-032: Cervarix vs. Aimmugen (f, 19-25; 7)	0	519		21	Not estimable	
ubtotal (95% CI)	Ť	519		21	Not estimable	
otal events	0		0			
eterogeneity. Not applicable						
est for overall effect: Not applicable						
1.3 All-cause mortality/deaths: Cervarix vs. E	-				46; follow-up until 12 month	ns)
PV-069: Cervarix vs. Engerix (f, 26-46; 12)	0	606		06	Not estimable	
ubtotal (95% CI)		606		06	Not estimable	
otal events	0		0			
eterogeneity. Not applicable						
est for overall effect: Not applicable						
1.4 All-cause mortality/deaths: Cervarix vs. H	lavriv: bonaticio	A vaccin	ne (female	s and 15-2	S: follow-up uptil 48 months	5)
**		93 1 9			•	
PV-008: Cervarix vs. Havrix (f, 15-25; 48) ubtotal (95% CI)		9319 9 319		25 25.1% 25 25.1%		
otal events	9	,515	8	25.1/0	1.13 [0.73, 2.32]	
otal events eterogeneity. Not applicable	9		0			
est for overall effect: Z = 0.24 (P = 0.81)						
est for overall effect. 2 = 0.24 (1 = 0.01)						
.1.5 All-cause mortality/deaths: Gardasil vs. A	AHS (females,	age 15-2	26; follow	up until 45	5 months)	
501-013: Gardasil vs. AAHS (f, 16-24; 45)		2723	2 27			
501-015: Gardasii vs. AAHS (f, 15-26; 36)		5087	5 60			
ubtotal (95% CI)		8810		12 34.4%		
otal events	9		7			
leterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.08$, $df = 1$ ($P = 0.771$; $I^2 = 0$	0%				
est for overall effect: Z = 0.50 (P = 0.62)	, .					
.1.6 All-cause mortality/deaths: Gardasil vs. A	AAHS (females,	age 21-4	16; follow	up until 48-	8 months)	
501-019: Gardasil vs. AAHS (f, 21-46; 48)		1911	0 19		Not estimable	
ubtotal (95% CI)	1	1911	19	08	Not estimable	
otal events	0		0			
eterogeneity. Not applicable						
est for overall effect: Not applicable						
1 7 AU	AUG (- 15 27				
.1.7 All-cause mortality/deaths: Gardasil vs. A				-		_
501-020: Gardasil vs. AAHS (m, 15-27; 36) ubtotal (95% CI)		2032 2032	10 20 20			
		1032		33 19.9%	0.50 [0.06, 1.09]	
otal events	3		10			
eterogeneity. Not applicable						
est for overall effect: Z = 1.83 (P = 0.07)						
.1.8 All-cause mortality/deaths: HPV 16 vaccin	ne vs. AAHS (fei	males, an	ie 16-25:	follow-un i	until 48 months)	
501–005: HPV 16 vaccine vs. AAHS (f, 16–25; 4)		1204	0 12		Not estimable	
101-003. HPV 16 VALLINE VS. AAH3 (I, 16-23, 4)		1204 1 204	12		Not estimable Not estimable	
otal events	0		0		. Tot estimation	
otal events eterogeneity. Not applicable	V		~			
eterogenetty. Not applicable est for overall effect: Not applicable						
эл от олеган епесс. постаррисарие						
otal (95% CI)	27	7283	272	81 100.0%	1.20 [0.51, 2.80]	
otal events	35		28		,,	
eterogeneity: Tau² = 0.51; Chi² = 9.10, df = 4 (56%	20			
erogenery. Tau" = 0.51, Cm" = 9.10, df = 4 (est for overall effect: Z = 0.41 (P = 0.68)	, = 0.00), 1 = .	7 0 7 0				0.02 0.1 1 10 Favours HPV vaccine Favours control

Test for subgroup differences: Chi² = 9.02, df = 3 (P = 0.03), i² = 66.7%

*3.1. Risk ratio for GlaxoSmithKline studies (i.e., HPV-0xx): 2.16 [0.54, 8.61]; risk ratio for Merck Sharp & Dohme studies (i.e., V50x-xxx): 0.74 [0.27, 2.05].

3.2. Mortality/deaths from HPV-related cancers (anal, cervical, oropharyngeal, penile, vaginal and vulvar) irrespective of HPV type: intention to treat analysis

	HPV va	ccine	Cont	rol		Risk Ratio	Risk	Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI	IV, Rando	m, 95% CI	
3.2.1 Cervical cancer: Cervarix (females, age	24-72; fo	llow-u	p until 3	6 mon	ths)				
HPV-015: Cervarix vs. Al(OH)3 (f, 24-72; 36) Subtotal (95% CI)	0	2882 2882	0	2871 2871		Not estimable Not estimable			
Total events Heterogeneity: Not applicable	0		0						
Test for overall effect: Not applicable									
3.2.2 Oropharyngeal cancer: Cervarix (female	es, age 24	-72; fo	llow-up	until 3	6 month	is)			
HPV-015: Cervarix vs. AI(OH)3 (f, 24-72; 36) Subtotal (95% CI)	0	2882 2882	0	2871 2871		Not estimable Not estimable			
Total events	0		0						
Heterogeneity: Not applicable									
Test for overall effect: Not applicable									
3.2.3 Oropharyngeal cancer: Gardasil (female	es, age 21	-46; fo	llow-up	until 4	8 month	is)			
V501-019: Gardasil vs. AAHS (f, 21-46; 48) Subtotal (95% CI)	0	1911 1911	0	1908 1908		Not estimable Not estimable			
Total events	0		0						
Heterogeneity: Not applicable									
Test for overall effect: Not applicable									
Total (95% CI)		7675		7650		Not estimable			
Total events	0		0						
Heterogeneity: Not applicable							0.001 0.1	10	1000
Test for overall effect: Not applicable							Favours HPV vaccine		1000

Test for subgroup differences: Not applicable
*3.2. Risk ratio for 'medically significant conditions' (GlaxoSmithKline): not applicable; risk ratio for 'new medical history' (Merck Sharp & Dohme): not applicable.

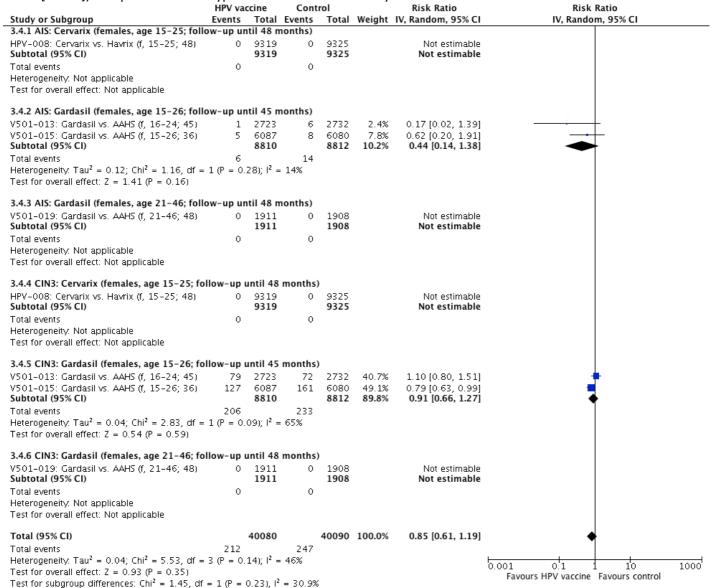
3.3. Incidence of HPV-related cancers (anal, cervical, oropharyngeal, penile, vaginal and vulvar) irrespective of HPV type*: intention to treat analysis

type . Intention to treat an	HPV vaccine	Contro		Risk Ratio	Risk Ratio
Study or Subgroup				IV, Random, 95% CI	
3.3.1 Cervical cancer: Cervarix (females, age				,	,
HPV-015: Cervarix vs. Al(OH)3 (f, 24-72; 36)	0 28		2871	Not estimable	
Subtotal (95% CI)	28		2871	Not estimable	
Total events	0	0			
Heterogeneity. Not applicable					
Test for overall effect: Not applicable					
3.3.2 Cervical cancer: Gardasil (females, age	21-46; follow-	up until 48 n	nonths)		
V501-019: Gardasil vs. AAHS (f, 21-46; 48)	0 19		1908	Not estimable	
Subtotal (95% CI)	19	11	1908	Not estimable	
Total events	0	0			
Heterogeneity. Not applicable					
Test for overall effect: Not applicable					
3.3.3 Oropharyngeal cancer: Cervarix (femal	es. age 24-72:	follow-up un	til 36 months)		
HPV-015: Cervarix vs. Al(OH)3 (f, 24-72; 36)	0 28		2871	Not estimable	
Subtotal (95% CI)	28		2871	Not estimable	
Total events	0	0			
Heterogeneity. Not applicable					
Test for overall effect: Not applicable					
3.3.4 Oropharyngeal cancer: Gardasil (femal	es. age 21-46:	follow-up un	til 48 months)		
V501-019: Gardasil vs. AAHS (f, 21-46; 48)	0 19		1908	Not estimable	
Subtotal (95% CI)	19		1908	Not estimable	
Total events	0	0			
Heterogeneity. Not applicable					
Test for overall effect: Not applicable					
3.3.5 Vaginal cancer: Cervarix (females, age	24-72: follow-	un until 36 m	onths)		
HPV-015: Cervarix vs. Al(OH)3 (f, 24-72; 36)	0 28		2871	Not estimable	
Subtotal (95% CI)	28		2871	Not estimable	
Total events	0	0			
Heterogeneity. Not applicable					
Test for overall effect: Not applicable					
3.3.6 Vulvar cancer: Cervarix (females, age 1	5-25: follow-u	n until 48 m	anthe)		
HPV-008: Cervarix vs. Havrix (f, 15-25; 48)	. 3-23, IOIIOW -0 0 93		9325	Not estimable	
Subtotal (95% CI)	93		9325 9325	Not estimable	
Total events	0	0			
Heterogeneity. Not applicable					
Test for overall effect: Not applicable					
3.3.7 Vulvar cancer: Gardasil (females, age 1	5-26: follow:	n until 45 m	anths)		
V501-013: Gardasil vs. AAHS (f, 16-24; 45)	is-26, idilow-1. 27	-	2732 100.0%	3.01 [0.12, 73.85]	
Subtotal (95% CI)	27		2732 100.0%	3.01 [0.12, 73.85]	
Total events	1	0		,	
Heterogeneity. Not applicable					
Test for overall effect: $Z = 0.67$ (P = 0.50)					
Total (95% CI)	245	10 3	4496 100 00/	2 01 [0 12 72 05]	
Total (95% CI) Total events	1	0	4486 100.0%	3.01 [0.12, 73.85]	
Heterogeneity. Not applicable	1	U			
Test for overall effect: Z = 0.67 (P = 0.50)					0.001 0.1 1 10 100
Test for subgroup differences: Not applicable					Favours HPV vaccine Favours control

Test for subgroup differences: Not applicable

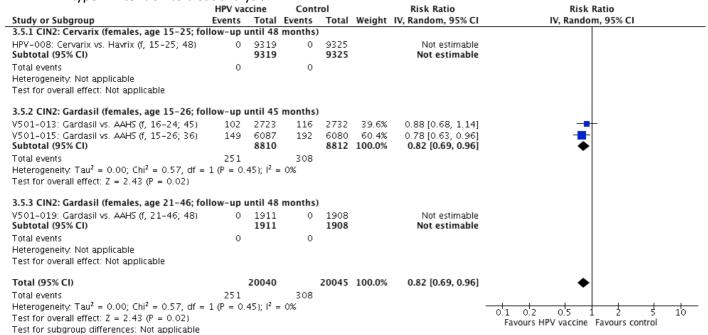
*3.3. Risk ratio for GlaxoSmithKline studies (i.e., HPV-0xx): not applicable; risk ratio for Merck Sharp & Dohme studies (i.e., V50x-xxx): 3.01 [0.12, 73.85].

3.4. Incidence of HPV-related carcinoma in situ (anal intraepithelial neoplasia grade 3 [AIN3], cervical adenocarcinoma in situ [AIS], cervical intraepithelial neoplasia grade 3 [CIN3], penile intraepithelial neoplasia grade 3 [PIN3], vaginal intraepithelial neoplasia grade 3 [VIN3] and vulvar intraepithelial neoplasia grade 3 [VaIN3]) irrespective of HPV type*: intention to treat analysis



^{*3.4.} Risk ratio for GlaxoSmithKline studies (i.e., HPV-0xx): not applicable; risk ratio for Merck Sharp & Dohme studies (i.e., V50x-xxx): 0.85 [0.61, 1.19].

3.5. Incidence of HPV-related moderate intraepithelial neoplasia (anal intraepithelial neoplasia grade 2 [AIN2], cervical intraepithelial neoplasia grade 2 [CIN2], penile intraepithelial neoplasia grade 2 [PIN2], vaginal intraepithelial neoplasia grade 2 [VIN2] and vulvar intraepithelial neoplasia grade 2 [VaIN2]) irrespective of HPV type*: intention to treat analysis



^{*3.5.} Risk ratio for GlaxoSmithKline studies (i.e., HPV-0xx): not applicable; risk ratio for Merck Sharp & Dohme studies (i.e., V50x-xxx): 0.82 [0.69, 0.96]. There were no reports of AIN2, PIN2, VIN2 or VaIN2 irrespective of HPV type.

3.6. Incidence of HPV-related moderate intraepithelial neoplasia or worse (AIN2+, CIN2+, PIN2+, VIN2+, VaIN2+) irrespective of HPV type*: intention to treat analysis

irrespective of the type . If	HPV vac		Cont	-		Risk Ratio	Risk Ratio
tudy or Subgroup	Events	Total		Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
6.6.1 CIN2+: Cervarix (females, age 15-25; fol	-			0225	30.300	0.70 (0.50 0.00)	-
PV-008: Cervarix vs. Havrix (f, 15-25; 48) ubtotal (95% Cl)	224	9319 9319	322	9325 9325	29.2% 29.2%	0.70 [0.59, 0.82] 0.70 [0.59, 0.82]	<u> </u>
otal events	224		322				•
eterogeneity. Not applicable							
est for overall effect: Z = 4.22 (P < 0.0001)							
.6.2 CIN2+: Cervarix (females, age 22-29; fol	llow-up up	til 12 m	onths)				
PV-063: Cervarix vs. Aimmugen (f, 22-29; 12)		375	41	377	8.4%	0.47 [0.28, 0.79]	
ubtotal (95% CI)	15	375		377		0.47 [0.28, 0.79]	•
otal events	19		41				
leterogeneity. Not applicable							
est for overall effect: Z = 2.85 (P = 0.004)							
.6.3 CIN2+: Cervarix (females, age 24-72; fol	llow-up un	til 36 m	onths)				
PV-015: Cervarix vs. Al(OH)3 (f, 24-72; 36)	0	2882	0	2871		Not estimable	
ubtotal (95% CI)		2882		2871		Not estimable	
otal events leterogeneity: Not applicable	0		0				
est for overall effect: Not applicable							
.6.4 CIN2+: Gardasil (females, age 15-26; fol	-						
501-013: Gardasil vs. AAHS (f, 16-24; 45)	183	2723	194	2732		0.95 [0.78, 1.15]	<u> </u>
501–015: Gardasil vs. AAHS (f, 15–26; 36) ubtotal (95% Cl)	219	6087 8810	266	6080 8812	28.5% 55.1%	0.82 [0.69, 0.98] 0.88 [0.76, 1.01]	
otal events	402		460		55.2,0		•
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.10$, $df = 1$		$1^2 = 9\%$					
est for overall effect: Z = 1.89 (P = 0.06)							
.6.5 CIN2+: Gardasil (females, age 21-46; fol	llow-un un	til 48 m	onths)				
'501-019: Gardasii vs. AAHS (f, 21-46; 48)	-	1911	0	1908		Not estimable	
ubtotal (95% CI)		1911		1908		Not estimable	
otal events	0		0				
leterogeneity. Not applicable							
est for overall effect: Not applicable							
3.6.6 PIN2+: Gardasil (males, age 15-27; follo	w-up until	36 mon	ths)				
(501-020: Gardasil vs. AAHS (m, 15-27; 36)	3	2032	2		0.9%	1.50 [0.25, 8.97]	
subtotal (95% CI)	_	2032	_	2033	0.9%	1.50 [0.25, 8.97]	
otal events Heterogeneity: Not applicable	3		2				
est for overall effect: Z = 0.44 (P = 0.66)							
C 7 MN2 : ValN2 : - Canda : 1 /f- males	15 26 6-1				- \		
8 .6.7 VIN2+ or VaIN2+: Gardasil (females, age /501–013: Gardasil vs. AAHS (f, 16–24; 45)	: 15-26; foi 17	2723	untii 45 23	2732	6.3%	0.74 [0.40, 1.38]	
/501-015: Gardasii vs. AAHS (f, 10-24, 45)	0	6087	0	6080		Not estimable	
Subtotal (95% CI)		8810		8812	6.3%	0.74 [0.40, 1.38]	-
otal events	17		23				
Heterogeneity: Not applicable							
est for overall effect: Z = 0.94 (P = 0.35)							
3.6.8 VaIN2+: Gardasil (females, age 15-26; fo	ollow-up u	ntil 45 n	nonths)				
/501-013: Gardasil vs. AAHS (f, 16-24; 45)	0	2723	0	2732		Not estimable	
(501-015: Gardasil vs. AAHS (f, 15-26; 36)	0	6087 8810	0	6080 8812		Not estimable Not estimable	
oubtotal (95% CI) Total events	0	0010	0	0012		NOT ESTIMABLE	
Heterogeneity. Not applicable	v		0				
est for overall effect: Not applicable							
6 Q VaIN2 + Cardasil (famales are 21 45 fo	allow ere co	ntil 40 -	ort				
5 .6.9 VaIN2+: Gardasil (females, age 21–46; fo (501–019: Gardasil vs. AAHS (f, 21–46; 48)	ollow-up ui O	ntii 48 n 1911	nonths) 0	1908		Not estimable	
iubtotal (95% CI)	U	1911	U	1908		Not estimable	
otal events	0		0				
leterogeneity. Not applicable							
est for overall effect: Not applicable							
.6.10 VIN2+ or VaIN2+: Cervarix (females, ag	e 15-25: fa	ollow-ur	until 4	8 monti	hs)		
HPV-008: Cervarix vs. Havrix (f, 15-25; 48)		9319	0			Not estimable	
ubtotal (95% CI)		9319		9325		Not estimable	
otal events	0		0				
Heterogeneity. Not applicable							
est for overall effect: Not applicable							
				5/182	100.0%	0.77 [0.65, 0.92]	•
otal (95% CI)		54179		34103	200.070		▼ 1
Fotal (95% CI) Fotal events	665		848	34103	2001070	,	Ť
				34103	1001070	,	0.05 0.2 1 5

^{*3.6.} Risk ratio for GlaxoSmithKline studies (i.e., HPV-0xx): 0.62 [0.43, 0.89]; risk ratio for Merck Sharp & Dohme studies (i.e., V50x-xxx): 0.87 [0.77, 0.99].

3.7. Number of treatment procedures (both surgical and non-surgical treatment) due to HPV-related diseases irrespective of HPV type*: intention to treat analysis

	HPV va	ccine	Cont	rol		Risk Ratio	Risk Ratio
Study or Subgroup						IV, Random, 95% CI	IV, Random, 95% CI
3.7.1 Treatment procedures: Cervarix (female	s, age 15	-25; fol	low-up	until 48	months)		_
HPV-008: Cervarix vs. Havrix (f, 15-25; 48) Subtotal (95% CI)	180	9319 9319	240		100.0% 100.0%	0.75 [0.62, 0.91] 0.75 [0.62, 0.91]	
Total events Heterogeneity: Not applicable Test for overall effect: Z = 2.94 (P = 0.003)	180		240				
3.7.2 Treatment procedures: Cervarix (female	s, age 24	-72; fol	low-up	until 36	months)		
HPV-015: Cervarix vs. Al(OH)3 (f, 24-72; 36) Subtotal (95% CI)	0	2882 2882	0	2871 2871		Not estimable Not estimable	
Total events Heterogeneity: Not applicable Test for overall effect: Not applicable	0		0				
3.7.3 Treatment procedures: Gardasil (female	s, age 15	-26; fol	low-up	until 45	months)		
V501-013: Gardasil vs. AAHS (f, 16-24; 45) V501-015: Gardasil vs. AAHS (f, 15-26; 36) Subtotal (95% CI)	0		0	2732 6080 8812		Not estimable Not estimable Not estimable	
Total events Heterogeneity: Not applicable Test for overall effect: Not applicable	0		0				
3.7.4 Treatment procedures: Gardasil (female	s, age 21	-46; fol	low-up	until 48	months)		
V501-019: Gardasil vs. AAHS (f, 21-46; 48) Subtotal (95% CI)	0	1911 1911	0	1908 1908		Not estimable Not estimable	
Total events Heterogeneity: Not applicable Test for overall effect: Not applicable	0		0				
3.7.5 Treatment procedures: Gardasil (males,	age 15-	27; follo	w-up ur	itil 36 m	onths)		
V501-020: Gardasil vs. AAHS (m, 15-27; 36) Subtotal (95% CI)	0	2032 2032	0	2033 2033		Not estimable Not estimable	
Total events Heterogeneity: Not applicable Test for overall effect: Not applicable	0		0				
Total (95% CI)		24954		24949	100.0%	0.75 [0.62, 0.91]	-
Total events Heterogeneity: Not applicable Test for overall effect: Z = 2.94 (P = 0.003) Test for subgroup differences: Not applicable	180		240				0.5 0.7 1 1.5 2 Favours HPV vaccine Favours control

^{*3.7.} Risk ratio for GlaxoSmithKline studies (i.e., HPV-0xx): **0.75 [0.62, 0.91]**; risk ratio for Merck Sharp & Dohme studies (i.e., V50x-xxx): not applicable.

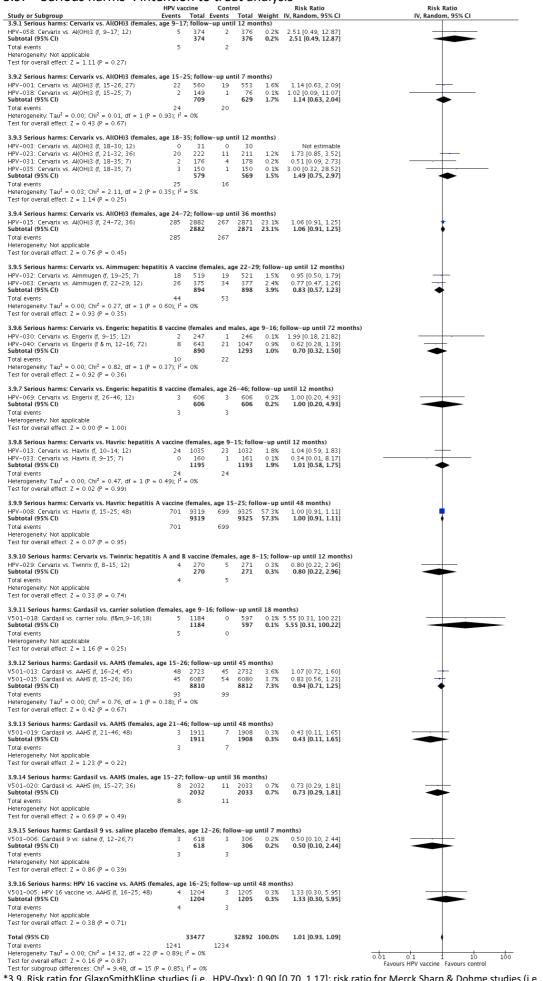
3.8. Fatal harms*: intention to treat analysis

.o. ratarnamis . intention to the	•		1	Dial. D	:-	Bi-l. B-ti-
Study or Subgroup	HPV vaccine Events To			Risk R eight IV, Randor		Risk Ratio IV, Random, 95% CI
3.8.1 Fatal harms: Cervarix vs. Al(OH)3 (females						
HPV-015: Cervarix vs. AI(OH)3 (f, 24-72; 36)				0.5% 4.65 [1.3		-
Subtotal (95% CI)		882	2871 20	0.5% 4.65 [1.3	34, 16.16]	-
otal events	14	3				
leterogeneity. Not applicable						
est for overall effect: Z = 2.42 (P = 0.02)						
.8.2 Fatal harms: Cervarix vs. Aimmugen: hepa	titis A vaccine (f	emales age 1	19-25: follo	ow-up until 7 m	onths)	
HPV-032: Cervarix vs. Aimmugen (f, 19-25; 7)		19 0	521	-	estimable	
IPV-063: Cervarix vs. Ainmagen (f, 19-29, 7)		75 0	377		estimable estimable	
ubtotal (95% CI)		94	898		stimable	
otal events	0	0				
Heterogeneity. Not applicable						
est for overall effect: Not applicable						
3.8.3 Fatal harms: Cervarix vs. Engerix: hepatitis						
HPV-069: Cervarix vs. Engerix (f, 26-46; 12)		06 0	606		estimable	
Subtotal (95% CI)		06	606	Not e	estimable	
Total events	0	0				
Heterogeneity. Not applicable						
est for overall effect: Not applicable						
3.8.4 Fatal harms: Cervarix vs. Havrix: hepatitis	A vaccine (femal	es, age 15-2	5; follow-u	up until 48 mont	hs)	
HPV-008: Cervarix vs. Havrix (f, 15-25; 48)				•	43, 2.92]	
ubtotal (95% CI)	93	19	9325 25		.43, 2.92]	*
otal events	9	8				
Heterogeneity. Not applicable						
Test for overall effect: $Z = 0.24$ (P = 0.81)						
OF Fatal harmer Cardasil vs. AAUS (famales a	as 15 36, follow					
3.8.5 Fatal harms: Gardasil vs. AAHS (females, a				3 40/ 4 00 10	4.4.7.47.1	
501-013: Gardasil vs. AAHS (f, 16-24; 45)		'23 2)87 5			14, 7.12]	
'501-015: Gardasil vs. AAHS (f, 15-26; 36) Jubtotal (95% CI)		987 5 9 10			44, 4.40] .48, 3.46]	
otal events	9	7	0012 5	4.470 1.20 [0	.40, 5.40)	
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.08$, $df = 1$ (Fig. 1)	$P = 0.771$: $I^2 = 09$					
est for overall effect: Z = 0.50 (P = 0.62)	,					
•						
3.8.6 Fatal harms: Gardasil vs. AAHS (females, a	ge 21–46; follov	v-up until 48	months)			
501-019: Gardasil vs. AAHS (f, 21-46; 48)			1908		estimable	
ubtotal (95% CI)		011	1908	Not e	estimable	
otal events	0	0				
leterogeneity. Not applicable						
est for overall effect: Not applicable						
.8.7 Fatal harms: Gardasil vs. AAHS (males, age	15-27; follow-	up until 36 n	nonths)			
'501-020: Gardasil vs. AAHS (m, 15-27; 36)		32 10		9.9% 0.30 [0.	08, 1.091	-
ubtotal (95% CI)		32			.08, 1.09]	-
otal events	3	10				
leterogeneity. Not applicable						
est for overall effect: Z = 1.83 (P = 0.07)						
0.0.5		6.11				
3.8.8 Fatal harms: HPV 16 vaccine vs. AAHS (fem						
'501–005: HPV 16 vaccine vs. AAHS (f, 16–25; 48		104 0	1205		estimable	
ubtotal (95% CI)		.04	1205	NOT 6	estimable	
otal events leterogeneity. Not applicable	0	0				
reterogeneity: Not applicable Test for overall effect: Not applicable						
esciol overali ellect. Not applicable						
otal (95% CI)	276	558	27658 100	0.0% 1.20 [0	.51, 2.80]	•
otal events	35	28				T
Heterogeneity: $Tau^2 = 0.51$; $Chi^2 = 9.10$, $df = 4$ (Fig. 1)	$P = 0.06$); $I^2 = 56$				0.0	01 0 1 1 10 10
Test for overall effect: Z = 0.41 (P = 0.68)	•				0.0	Favours HPV vaccine Favours control
est for subgroup differences: $Chi^2 = 9.02$, df = 3	$(P = 0.03), I^2 = 1$	66.7%				TAYOUTS THEY VACCINE FAVOURS CONTROL

Test for subgroup differences: Chi² = 9.02, df = 3 (P = 0.03), I² = 66.7%

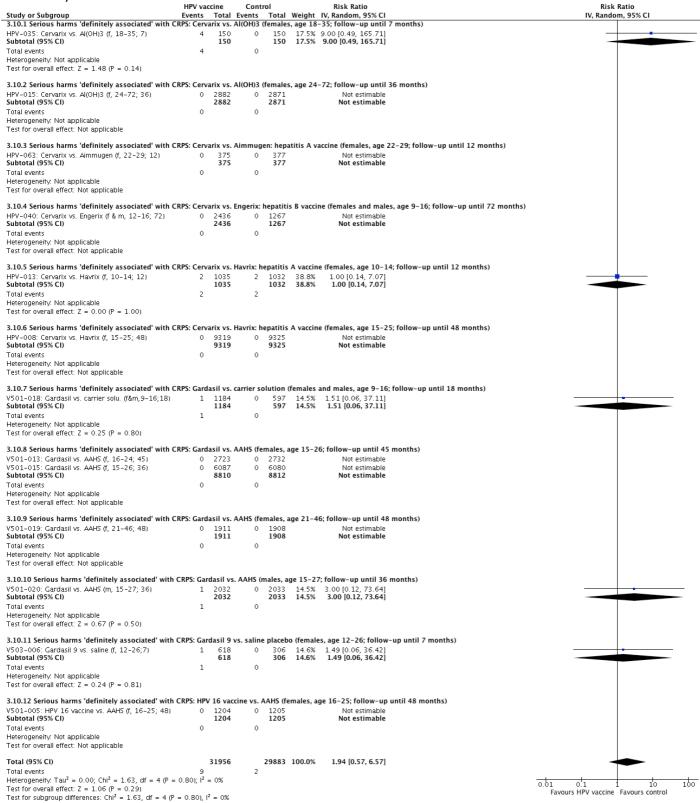
*3.8. Risk ratio for GlaxoSmithKline studies (i.e., HPV-0xx): 2.16 [0.54, 8.61]; risk ratio for Merck Sharp & Dohme studies (i.e., V50x-xxx): 0.74 [0.27, 2.05].

3.9. Serious harms*: intention to treat analysis



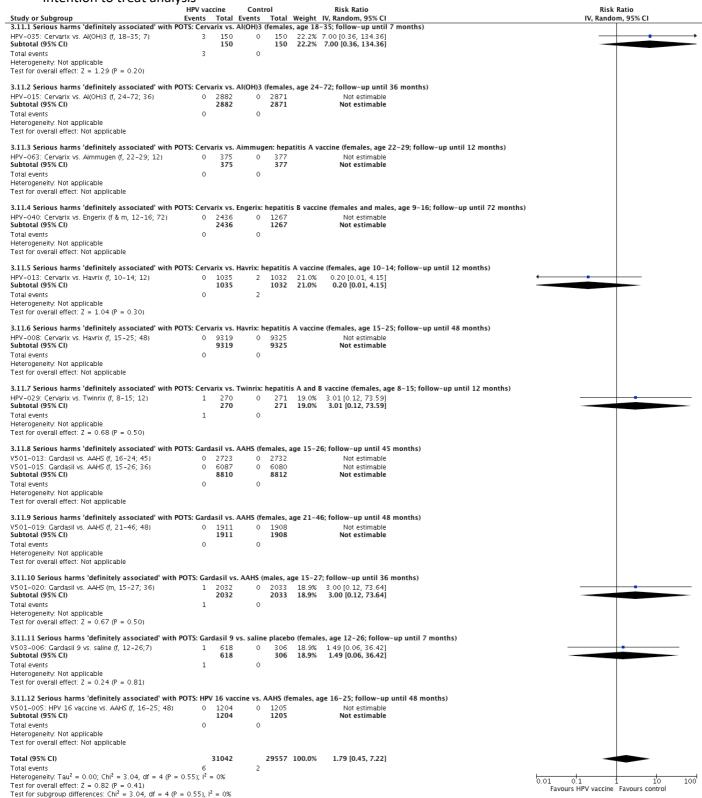
^{*3.9.} Risk ratio for GlaxoSmithKline studies (i.e., HPV-0xx): 0.90 [0.70, 1.17]; risk ratio for Merck Sharp & Dohme studies (i.e., V50x-xxx): 1.02 [0.94, 1.10].

3.10. Serious harms judged as 'definitely associated'* with chronic regional pain syndrome (CRPS): intention to treat analysis



*3.10. Risk ratio for GlaxoSmithKline studies (i.e., HPV-0xx): 2.27 [0.28, 18.35]; risk ratio for Merck Sharp & Dohme studies (i.e., V50x-xxx): 1.89 [0.30, 11.99]. We asked a physician with clinical expertise in CRPS to assess the reported MedDRA preferred terms as 'definitely,' 'probably, 'probably not' or 'definitely not' associated with CRPS. We sent an Excel sheet to the physician with all the reported MedDRA terms. The physician was blinded, as the Excel sheet contained no outcome data. When the physician had assessed all the MedDRA terms, we synthesized the data for those MedDRA terms that the physician judged 'definitely' associated with CRPS and compared it to the reported serious harms.

3.11. Serious harms judged as 'definitely associated'* with postural orthostatic tachycardia syndrome (POTS): intention to treat analysis



^{*3.11.} Risk ratio for GlaxoSmithKline studies (i.e., HPV-0xx): 1.62 [0.19, 13.68]; risk ratio for Merck Sharp & Dohme studies (i.e., V50x-xxx): 2.11 [0.22, 20.29]. We asked a physician with clinical expertise in POTS to assess the reported MedDRA preferred terms as 'definitely,' 'probably, 'probably not' or 'definitely not' associated with POTS. We sent an Excel sheet to the physician with all the reported MedDRA terms. The physician was blinded, as the Excel sheet contained no outcome data. When the physician had assessed all the MedDRA terms, we synthesized the data for those MedDRA terms that the physician judged 'definitely' associated with POTS and compared it to the reported serious harms.

3.12. Serious harms reported within the MedDRA system organ class 'nervous system disorders (10029205)'*: intention to treat analysis

Study or Subgroup		Total		Total		Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI
.12.1 Serious nervous system disorders: Cervarix HPV-003: Cervarix vs. A(OH)3 (f, 18-30; 12) HPV-035: Cervarix vs. A(OH)3 (f, 18-35; 7) Jubtotal (95% CI)	v s. Al(OH) 0 2	3 (fema 31 150 181	les, age O O	30	11.0%	p until 12 months) Not estimable 5.00 [0.24, 103.28] 5.00 [0.24, 103.28]	
otal events leterogeneity. Not applicable est for overall effect: Z = 1.04 (P = 0.30)	2		0				
.12.2 Serious nervous system disorders: Cervarix IPV-015: Cervarix vs. Al(OH)3 (f, 24-72; 36) ubtotal (95% CI) otal events leterogeneity. Not applicable est for overall effect: Not applicable	0	3 (fema 2882 2882	les, age 0 0	24-72 ; 2871 2871	follow-u	p until 36 months) Not estimable Not estimable	
.12.3 Serious nervous system disorders: Cervarix IPV-063: Cervarix vs. Aimmugen (f, 22-29; 12) ubtotal (95% CI) otal events leterogeneity. Not applicable est for overall effect: Not applicable	v s. Aimmu 0 0	gen: he 375 375	e patitis o	4 vaccin 377 377	e (female	s, age 22–29; follow-up until 12 months) Not estimable Not estimable	
.12.4 Serious nervous system disorders: Cervarix PV-040: Cervarix vs. Engerix (f & m, 12-16; 72) ubtotal (95% CI) otal events eterogeneity. Not applicable est for overall effect: Not applicable	0	: hepat 2436 2436	itis B va O O	ccine (fo 1267 1267	emales ai	nd males, age 12-16; follow-up until 72 m Not estimable Not estimable	nonths)
12.5 Serious nervous system disorders: Cervarix PV-069: Cervarix vs. Engerix (f, 26-46; 12) ubtotal (95% CI) otal events eterogeneity. Not applicable est for overall effect: Not applicable	vs. Engerix O O	: hepat 606 606	itis B va O O	606 606	emales, a	ge 26-46; follow-up until 12 months) Not estimable Not estimable	
.12.6 Serious nervous system disorders: Cervarix PV-013: Cervarix vs. Havrix (f, 10-14; 12) ubtotal (95% CI) otal events eterogeneity. Not applicable est for overall effect: Z = 0.00 (P = 1.00)	1	hepatit 1035 1035		1032	13.1%	e 10-14; follow-up until 12 months) 1.00 [0.06, 15.92] 1.00 [0.06, 15.92]	
.12.7 Serious nervous system disorders: Cervarix PV-008: Cervarix vs. Havrix (f, 15-25; 48) ubtotal (95% CI) otal events eterogeneity. Not applicable est for overall effect: Not applicable	0	hepatit 9319 9319	0 0	9325 9325 9325	males, ag	e 15-25; follow-up until 48 months) Not estimable Not estimable	
.12.8 Serious nervous system disorders: Gardasii 501-013: Gardasii vs. AAH5 (f, 16-24; 45) 501-015: Gardasii vs. AAH5 (f, 15-26; 36) ubtotal (95% CI) otal events eterogeneity. Tau ² = 2.58; Chi ² = 3.07, df = 1 (P = est for overall effect: Z = 0.00 (P = 1.00)	1 4 5	2723 6087 8810		2732 6080	21.0% 21.0% 21.0% 42.0 %	until 45 months) 0.25 [0.03, 2.24] 4.00 [0.45, 35.74] 1.00 [0.07, 15.09]	-
.12.9 Serious nervous system disorders: Gardasil 501-019: Gardasil vs. AAH5 (f, 21-46; 48) ubtotal (95% CI) otal events eterogeneity. Not applicable est for overall effect: 2 = 1.04 (P = 0.30)	2	females 1911 1911		1908	10.9%	until 48 months) 4.99 [0.24, 103.91] 4.99 [0.24, 103.91]	
.12.10 Serious nervous system disorders: Gardas 501–020: Gardasil vs. AAH5 (m, 15–27; 36) ubtotal (95% CI) otal events leterogeneity. Not applicable est for overall effect: Z = 0.67 (P = 0.50)	1	(males, 2032 2032	, age 15 0 0		low-up u 9.8% 9.8%	ntil 36 months) 3.00 [0.12, 73.64] 3.00 [0.12, 73.64]	
.12.11 Serious nervous system disorders: Gardas 503-006: Gardasil 9 vs. saline (f, 12-26;7) ubtotal (95% CI) otal events leterogeneity. Not applicable est for overall effect: Z = 0.50 (P = 0.62)	i il 9 vs. sal ii 1 1	618 618 618	ebo (fen 1 1		ge 12-26; 13.1% 13.1%	follow-up until 7 months) 0.50 [0.03, 7.89] 0.50 [0.03, 7.89]	
12.12 Serious nervous system disorders: HPV 16 501-005: HPV 16 vaccine vs. AAHS (f, 16-25; 48) ubtotal (95% Cf) otal events eterogeneity. Not applicable est for overall effect: Not applicable	0	. AAHS 1204 1204	(female: 0	s, age 10 1205 1205	6-25; foll	ow-up until 48 months) Not estimable Not estimable	
otal (95% CI)	3	1409		29922	100.0%	1.45 [0.53, 3.94]	

Test for subgroup differences: Chi² = 2.14, df = 5 (P = 0.83), I² = 0%

*3.12. Risk ratio for GlaxoSmithKline studies (i.e., HPV-0xx): 2.08 [0.27, 16.05]; risk ratio for Merck Sharp & Dohme studies (i.e., V50x-xxx): 1.31 [0.37, 4.60].

3.13. New onset diseases ('medically significant conditions' and 'new medical history'*): intention to treat analysis

Study or Subgroup	HPV vaccine	Control	Weight	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI
3.13.1 New onset diseases ('medically significant of HPV-058: Cervarix vs. Al(OH)3 (f, 9-17; 12)		varix vs. Al(OH)3	(females		14, nandin, 93% er
Subtotal (95% CI) Total events Heterogeneity. Not applicable	37 4 14			1.28 [0.59, 2.78]	*
Test for overall effect: Z = 0.62 (P = 0.53)					
3.13.2 New onset diseases ('medically significant of HPV-038; Cervarix vs. Al(OH)3 (f. 15-25; 7)	conditions'): Cen			age 15-25; follow-up until 7 months) 1.73 [0.91, 3.32]	
Subtotal (95% CI) Total events	1 49 34		1.6%	1.73 [0.91, 3.32]	•
Heterogeneity. Not applicable Test for overall effect: Z = 1.66 (P = 0.10)					
3.13.3 New onset diseases ('medically significant o	conditions'): Cer	varix vs. Al(OH)3	(females	age 18-35; follow-up until 7 months)	
HPV-023: Cervarix vs. Al(OH)3 (f, 21-32; 36) HPV-031: Cervarix vs. Al(OH)3 (f, 18-35; 7)	60 222 13 176			1.50 [1.05, 2.15] 0.55 [0.29, 1.04]	
HPV-035: Cervarix vs. Al(OH)3 (f, 18-35; 7) Subtotal (95% CI)	42 150 548			1.75 [1.12, 2.74] 1.19 [0.66, 2.13]	•
Total events Heterogeneity: $Tau^2 = 0.20$; $Chi^2 = 9.20$, $df = 2$ (P =	115 = 0.01); I ² = 78%	86			
Test for overall effect: Z = 0.58 (P = 0.56)					
3.13.4 New onset diseases ('medically significant of HPV-015: Cervarix vs. Al(OH)3 (f, 24-72; 36)	1169 2882	1136 2871	23.8%	1.03 [0.96, 1.09]	·
Subtotal (95% CI) Total events	2882 1169	1136	23.8%	1.03 [0.96, 1.09]	† .
Heterogeneity: Not applicable Test for overall effect: Z = 0.77 (P = 0.44)					
3.13.5 New onset diseases ('medically significant of HPV-032; Cervarix vs. Aimmugen (f. 19-25; 7)				itis A vaccine (females, age 22-29; follo	w-up until 12 months)
HPV-032: Cervarix vs. Ammugen (f, 19-25; 7) HPV-063: Cervarix vs. Aimmugen (f, 22-29; 12) Subtotal (95% CI)	91 519 98 375 894	115 377	9.3%	0.85 [0.66, 1.10] 0.86 [0.68, 1.08] 0.86 [0.72, 1.01]	-
Total events	189	222	17.4%	0.60 [0.72, 1.01]	1
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.00$, $df = 1$ (P = Test for overall effect: Z = 1.81 (P = 0.07)	v.98), if = 0%				
3.13.6 New onset diseases ('medically significant of HPV-030: Cervarix vs. Engerix (f, 9-15; 12)	conditions'): Cen			B vaccine (females and males, age 9-15, 1.30 [0.78, 2.17]	; follow-up until 12 months)
HPV-030: Cervarix vs. Engerix (f, 9-15; 12) HPV-040: Cervarix vs. Engerix (f & m, 12-16; 72) Subtotal (95% CI)	47 643 890	76 1047	4.9%	1.30 [0.78, 2.17] 1.01 [0.71, 1.43] 1.09 [0.82, 1.46]	-
Total events Heterogeneity, Tau ² = 0.00; Chi ² = 0.64, df = 1 (P =	77	99	/0	,, 20103	Ť
Test for overall effect: Z = 0.59 (P = 0.55)	1⊆ _{1,1} 1 = 0/6				
3.13.7 New onset diseases ('medically significant of HPV-069: Cervarix vs. Engerix (f, 26-46; 12)	conditions'): Cen			B vaccine (females, age 26-46; follow-u 0.71 [0.23, 2.24]	up until 12 months)
Subtotal (95% CI) Total events	5			0.71 [0.23, 2.24]	
Heterogeneity. Not applicable Test for overall effect: Z = 0.58 (P = 0.56)					
3.13.8 New onset diseases ('medically significant o	conditions'): Cer	varix vs. Havrix: h	epatitis	A vaccine (females, age 9-15; follow-up	until 12 months)
HPV-013: Cervarix vs. Havrix (f, 10-14; 12) HPV-033: Cervarix vs. Havrix (f, 9-15; 7)	166 1035 11 160		11.8%	0.85 [0.70, 1.02] 1.11 [0.48, 2.53]	<u> </u>
Subtotal (95% CI) Total events	1195 177	205 205	12.8%	0.86 [0.72, 1.03]	•
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.38$, $df = 1$ (P = Test for overall effect: Z = 1.61 (P = 0.11)	: 0.54); I ² = 0%				
3.13.9 New onset diseases ('medically significant o					p until 48 months)
HPV-008: Cervarix vs. Havrix (f, 15-25; 48) Subtotal (95% CI)	2960 9319 9319	9325		0.98 [0.94, 1.02] 0.98 [0.94, 1.02]	•
Total events Heterogeneity. Not applicable	2960	3025			
Test for overall effect: Z = 0.99 (P = 0.32)	t conditions's Co	monity are. Taningia	hanatit	s A and B vassing (famales age 9, 15, fo	bllow un until 13 months)
3.13.10 New onset diseases ('medically significant HPV-029: Cervarix vs. Twinrix (f, 8-15; 12) Subtotal (95% CI)	0 270 270	0 271		Not estimable Not estimable	now-up until 12 months)
Total events	0	0		Not estimable	
Heterogeneity: Not applicable Test for overall effect: Not applicable					
3.13.11 New onset diseases ('new medical history'), V501-018: Gardasil vs. carrier solu. (f&m,9-16;18)	'): Gardasil vs. ca 0 1184			I males, age 9-16; follow-up until 18 m Not estimable	onths)
Subtotal (95% CI)	1184			Not estimable	
Heterogeneity: Not applicable Test for overall effect: Not applicable	v	v			
3.13.12 New onset diseases ('new medical history')	'): Gardasil vs. A/	AHS (females, auc	15-26:	ollow-up until 45 months)	
V501-013: Gardasil vs. AAHS (f, 16-24; 45) V501-015: Gardasil vs. AAHS (f, 15-26; 36)	0 2723	0 2732		Not estimable Not estimable	
Subtotal (95% CI) Total events	8810			Not estimable	
Heterogeneity: Not applicable Test for overall effect: Not applicable	, and the second	,			
3.13.13 New onset diseases ('new medical history'	'): Gardasil vs. A/	AHS (females, age	21-46;	ollow-up until 48 months)	
V501-019: Gardasil vs. AAHS (f, 21-46; 48) Subtotal (95% CI)	0 1911 1911	0 1908		Not estimable Not estimable	
Total events Heterogeneity: Not applicable	0	0			
Test for overall effect: Not applicable					
3.13.14 New onset diseases ('new medical history'), V501-020: Gardasil vs. AAHS (m. 15-27; 36)	"): Gardasil vs. AA 0 2032			low-up until 36 months) Not estimable	
Subtotal (95% CI) Total events	2032			Not estimable	
Heterogeneity: Not applicable Test for overall effect: Not applicable					
3.13.15 New onset diseases ('new medical history'					
V503-006: Gardasil 9 vs. saline (f, 12-26;7) Subtotal (95% CI)	0 618 618	306		Not estimable Not estimable	
Total events Heterogeneity: Not applicable	0	0			
Test for overall effect: Not applicable	D. LIMIT -			e as fallow w	
3.13.16 New onset diseases ('new medical history'), V501-005: HPV 16 vaccine vs. AAHS (f, 16-25; 48)	0 1204	0 1205		Not estimable	
Subtotal (95% CI) Total events	1204	0 1205		Not estimable	
Heterogeneity: Not applicable Test for overall effect: Not applicable					
Total (95% CI)	32886		100.0%	1.00 [0.92, 1.09]	+
Total events	4740	4801			
Heterogeneity: Tau ² = 0.01; Chi ² = 26.25, df = 13 (P Test for overall effect: Z = 0.02 (P = 0.98)	$P = 0.02$; $I^2 = 50$				0.02 0.1 10

^{*3.13.} Risk ratio for 'medically significant conditions' (GlaxoSmithKline): 1.00 [0.92, 1.09]; risk ratio for 'new medical history' (Merck Sharp & Dohme): not applicable.

3.14. New onset diseases most associated with the HPV vaccines ('medically significant conditions') - 'back pain': intention to treat analysis

Study or Subgroup		Total		Total W	Risk Ratio eight IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI
4.1 New onset back pain ('medically significa V-031: Cervarix vs. Al(OH)3 (f. 18-35: 7)	nt conditions	'): Cerv 176	arix vs. A	178 178	males, age 18-35; follow-up until 12 months) Not estimable	
V-031: Cervarix vs. Al(OH)3 (f, 18-35; 7) V-035: Cervarix vs. Al(OH)3 (f, 18-35; 7)	0	150	0	150	Not estimable Not estimable	
ototal (95% CI)	Ť	326		328	Not estimable	
al events	0		0			
erogeneity. Not applicable						
st for overall effect: Not applicable						
14.2 New onset back pain ('medically significa	nt conditions	'): Cerv	arix vs. A	AI(OH)3 (f	males, age 24–72; follow-up until 36 months)	
V-015: Cervarix vs. Al(OH)3 (f, 24-72; 36)		2882	0	2871	Not estimable	
ibtotal (95% CI)	0	2882	0	2871	Not estimable	
eterogeneity. Not applicable	v		v			
est for overall effect: Not applicable						
14.2 New onset back pain (modically significa	nt conditions	h Con	ariv ve /	Vimmuaa	: hepatitis A vaccine (females, age 22-29; follow-up until 12 m	onths)
PV-063: Cervarix vs. Aimmugen (f, 22-29; 12)	0	375	0	377	Not estimable	ionais)
ıbtotal (95% CI)	-	375		377	Not estimable	
otal events	0		0			
eterogeneity. Not applicable est for overall effect: Not applicable						
escrot overall effect. Not applicable						
					atitis A vaccine (females, age 10-14; follow-up until 12 month	is)
PV-013: Cervarix vs. Havrix (f, 10-14; 12) ubtotal (95% CI)		1035 1035	0	1032 1032	Not estimable Not estimable	
ntal events	0	1023	0	1032	not estimable	
eterogeneity. Not applicable	•		~			
est for overall effect: Not applicable						
14.5 New onset back pain ('medically significa	nt conditions	'r Cerv	ariv vs I	lavriv he	atitis A vaccine (females, age 15-25; follow-up until 48 month	(2)
.14.3 New onset back pain (medically significa PV-008: Cervarix vs. Havrix (f, 15-25; 48)		9319	arix vs. r 0	9325	Not estimable	13)
ubtotal (95% CI)	Ť	9319		9325	Not estimable	
otal events	0		0			
leterogeneity. Not applicable est for overall effect: Not applicable						
est for overall effect. Not applicable						
					es and males, age 9-16; follow-up until 18 months)	
501-018: Gardasil vs. carrier solu. (f&m,9-16;18		1184 1184	0	597 597	Not estimable Not estimable	
ubtotal (95% CI) ntal events	0	1184	0	397	NOT estimable	
leterogeneity. Not applicable	v		•			
est for overall effect: Not applicable						
.14.7 New onset back pain ('new medical histor	n''r Cardasil y	ε ΔΔΗ	S (famal	os ano 15	-26: follow-up until 45 months)	
501-013: Gardasil vs. AAHS (f, 16-24; 45)		2723		2732	Not estimable	
501-015: Gardasil vs. AAHS (f, 15-26; 36)	0	6087	0	6080	Not estimable	
ubtotal (95% CI)		8810		8812	Not estimable	
otal events leterogeneity. Not applicable	0		0			
est for overall effect: Not applicable						
.14.8 New onset back pain ('new medical histor						
501-019: Gardasil vs. AAHS (f, 21-46; 48) ubtotal (95% CI)		1911 1911	0	1908 1908	Not estimable Not estimable	
otal events	0		0			
eterogeneity. Not applicable						
est for overall effect: Not applicable						
.14.9 New onset back pain ('new medical histor	ry'): Gardasil v	s. AAH	S (males	, age 15-	7; follow-up until 36 months)	
501-020: Gardasil vs. AAHS (m, 15-27; 36)	0	2032	0	2033	Not estimable	
ubtotal (95% CI)		2032		2033	Not estimable	
otal events eterogeneity: Not applicable	0		0			
eterogeneity: Not applicable est for overall effect: Not applicable						
**		_				
14.10 New onset back pain ('new medical histo						
503-006: Gardasil 9 vs. saline (f, 12-26;7) ubtotal (95% CI)	0	618 618	0	306 306	Not estimable Not estimable	
otal events	0	- 10	0	- 30		
eterogeneity. Not applicable						
est for overall effect: Not applicable						
14.11 New onset back pain ('new medical histo	ory'): HPV 16 v	/accine	vs. AAH	S (female:	, age 16-25; follow-up until 48 months)	
501-005: HPV 16 vaccine vs. AAHS (f, 16-25; 48		1204	0	1205	Not estimable	
ubtotal (95% CI)		1204		1205	Not estimable	
otal events	0		0			
leterogeneity: Not applicable est for overall effect: Not applicable						
otal (95% CI)		9696		28794	Not estimable	
otal events eterogeneity. Not applicable	0		0			
						0.1 0.2 0.5 1 2 5 1
est for overall effect: Not applicable						Favours HPV vaccine Favours control

^{*3.14.} Risk ratio for 'medically significant conditions' (GlaxoSmithKline): not applicable; risk ratio for 'new medical history' (Merck Sharp & Dohme): not applicable.

3.15. New onset diseases most inversely associated with the HPV vaccines ('new medical history') - 'vaginal infection': intention to treat analysis

	HPV va	ccine	Cont	rol	Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight IV, Random, 95% CI	IV, Random, 95% CI
3.15.1 New onset vaginal infection ('new medical h	nistory'): (Gardasil	vs. carrie	er solut	ion (females and males, age 9-16; follow-up until 18 months)	
V501-018: Gardasil vs. carrier solu. (f&m,9-16;18) Subtotal (95% CI)	0	1184 1184	0	597 597	Not estimable Not estimable	
Fotal events	0		0			
Heterogeneity: Not applicable						
Fest for overall effect: Not applicable						
3.15.2 New onset vaginal infection ('new medical h	history'): (Gardasil	vs. AAHS	S (fema	es, age 15-26; follow-up until 45 months)	
/501-013: Gardasil vs. AAHS (f, 16-24; 45)	0	2723	0	2732	Not estimable	
V501-015: Gardasil vs. AAHS (f, 15-26; 36)	0	6087	0	6080	Not estimable	
Subtotal (95% CI)		8810		8812	Not estimable	
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
3.15.3 New onset vaginal infection ('new medical h	history'): (Gardasil	vs. AAHS	S (fema	es, age 21-46; follow-up until 48 months)	
V501-019: Gardasil vs. AAHS (f, 21-46; 48) Subtotal (95% CI)	0	1911 1911	0	1908 1908	Not estimable Not estimable	
Fotal events	0		0			
Heterogeneity. Not applicable						
Test for overall effect: Not applicable						
3.15.4 New onset vaginal infection ('new medical h	history'): (Gardasil	9 vs. sal	ine pla	ebo (females, age 12-26; follow-up until 7 months)	
V503-006: Gardasil 9 vs. saline (f, 12-26;7) Subtotal (95% CI)	0	618 618	0	306 306	Not estimable Not estimable	
Fotal events	0	010	0	300	not estimable	
Heterogeneity. Not applicable	•		0			
Fest for overall effect: Not applicable						
Total (95% CI)		12523		11623	Not estimable	
Total events	0		0			
Heterogeneity: Not applicable						0.05 0.2 5 20
Fest for overall effect: Not applicable						Favours HPV vaccine Favours control
Fest for subgroup differences: Not applicable						. a.

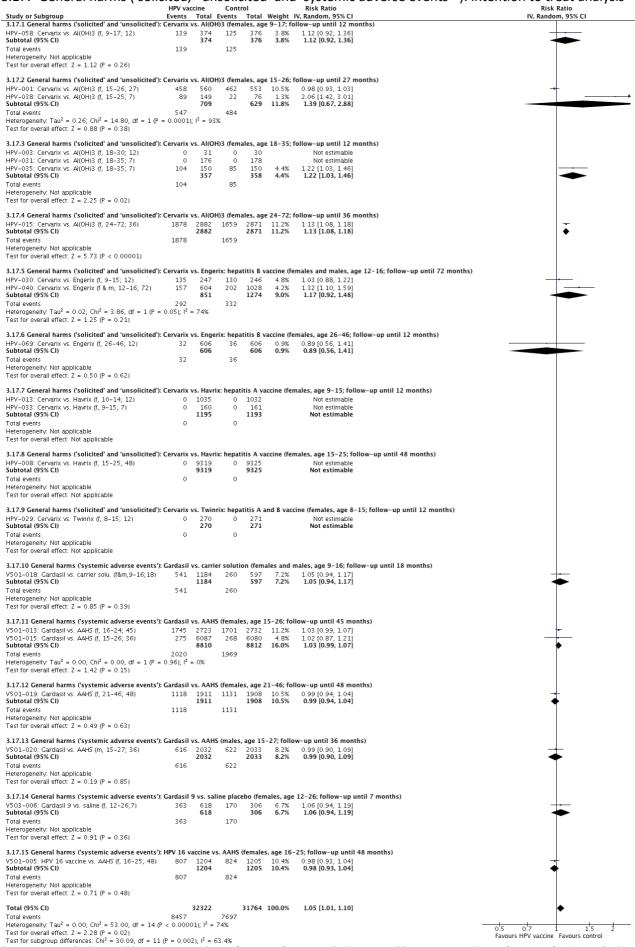
^{*3.15.} Risk ratio for 'medically significant conditions' (GlaxoSmithKline): not applicable; risk ratio for 'new medical history' (Merck Sharp & Dohme): not applicable.

3.16. New onset diseases ('medically significant conditions' and 'new medical history') reported within the MedDRA system organ class 'vascular disorders (10047065)': intention to treat analysis

Study or Subgroup	HPV vaccine Events Total E		Risk Ratio Veight IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI
			N(OH)3 (females, age 24-72; follow-up until 36 months)	
V-015: Cervarix vs. Al(OH)3 (f, 24-72; 36) btotal (95% CI)	0 2882 2882	0 2871 2871	Not estimable Not estimable	
tal events	0	0	Not estimable	
terogeneity. Not applicable	*	*		
st for overall effect: Not applicable				
16.2 New onset vascular disorders ('medically	significant condition	'): Cervarix vs. A	himmugen: hepatitis A vaccine (females, age 22-29; follow-up until 12 months)	
V-063: Cervarix vs. Aimmugen (f, 22-29; 12)	0 375	0 377	Not estimable	
ibtotal (95% CI)	375	377	Not estimable	
otal events eterogeneity. Not applicable	0	0		
est for overall effect: Not applicable				
.16.3 New onset vascular disorders ('medically	significant condition	i'): Cervarix vs. I	lavrix: hepatitis A vaccine (females, age 10-14; follow-up until 12 months)	
PV-013: Cervarix vs. Havrix (f, 10-14; 12)	0 1035	0 1032	Not estimable	
ubtotal (95% CI)	1035	1032	Not estimable	
otal events	0	0		
leterogeneity: Not applicable est for overall effect: Not applicable				
.16.4 New onset vascular disorders ('medically	significant condition	'): Cervarix vs	lavrix: hepatitis A vaccine (females, age 15-25; follow-up until 48 months)	
PV-008: Cervarix vs. Havrix (f, 15-25; 48)	0 9319	0 9325	Not estimable	
ubtotal (95% CI)	9319	9325	Not estimable	
otal events	0	0		
leterogeneity: Not applicable est for overall effect: Not applicable				
	-1	D. Camardon	Colorius benefitie A and B construction (formulae and 0.15; follows on 1972)	
.16.5 New onset vascular disorders ('medically IPV-029: Cervarix vs. Twinrix (f, 8-15; 12)	0 270	0 271	winrix: hepatitis A and B vaccine (females, age 8-15; follow-up until 12 months) Not estimable	
ubtotal (95% CI)	270	271	Not estimable	
otal events	0	0		
leterogeneity. Not applicable lest for overall effect: Not applicable				
.16.6 New onset vascular disorders ('new medi 501-018: Gardasil vs. carrier solu. (f&m,9-16;18		vs. carrier soluti 0 597	on (females and males, age 9–16; follow-up until 18 months) Not estimable	
iubtotal (95% CI)	1184	597	Not estimable	
otal events	0	0		
leterogeneity: Not applicable est for overall effect: Not applicable				
3.16.7 New onset vascular disorders ('new medi 7501-013: Gardasii vs. AAHS (f. 16-24; 45)	cal history'): Gardasil 0 2723	vs. AAHS (femal 0 2732	es, age 15-26; follow-up until 45 months) Not estimable	
501-015: Gardasii vs. AAH5 (f, 16-24, 45) 501-015: Gardasii vs. AAH5 (f, 15-26; 36)	0 2723	0 6080	Not estimable Not estimable	
ubtotal (95% CI)	8810	8812	Not estimable	
otal events	0	0		
leterogeneity. Not applicable est for overall effect: Not applicable				
• • • • • • • • • • • • • • • • • • • •				
.16.8 New onset vascular disorders ('new medi 501-019: Gardasil vs. AAHS (f, 21-46; 48)	cal history'): Gardasil 0 1911	vs. AAHS (femal 0 1908	es, age 21–46; follow-up until 48 months) Not estimable	
ubtotal (95% CI)	1911	1908	Not estimable	
otal events	0	0		
eterogeneity. Not applicable				
est for overall effect: Not applicable				
.16.9 New onset vascular disorders ('new medi				
501-020: Gardasil vs. AAHS (m, 15-27; 36) ubtotal (95% CI)	0 2032 2032	0 2033 2033	Not estimable Not estimable	
ubtotal (95% CI) ntal events	0	0	NOT ESTIMABLE	
otal events leterogeneity: Not applicable	٧	V		
est for overall effect: Not applicable				
.16.10 New onset vascular disorders ('new med	dical history'): HPV 16	vaccine vs. AAH	5 (females, age 16-25; follow-up until 48 months)	
501-005: HPV 16 vaccine vs. AAHS (f, 16-25; 48	3) 0 1204	0 1205	Not estimable	
ubtotal (95% CI)	1204	1205	Not estimable	
otal events	0	0		
leterogeneity. Not applicable est for overall effect: Not applicable				
otal (95% CI)	29022	28431	Not estimable	
otal (95% CI) otal events	0	0	HACE COUNTRY IN	
eterogeneity: Not applicable	~	~	-	0.02 0.1 10
est for overall effect: Not applicable est for subgroup differences: Not applicable			'	Favours HPV vaccine Favours control

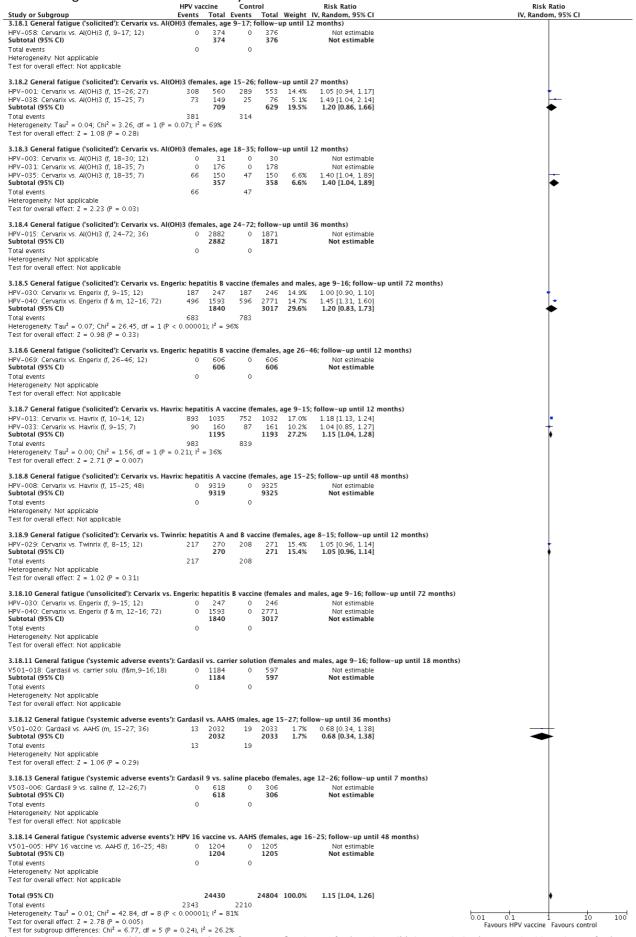
^{*3.16.} Risk ratio for 'medically significant conditions' (GlaxoSmithKline): not applicable; risk ratio for 'new medical history' (Merck Sharp & Dohme): not applicable.

3.17. General harms ('solicited,' 'unsolicited' and 'systemic adverse events'*): intention to treat analysis



*3.17. Risk ratio for 'solicited' (GlaxoSmithKline): **1.14 [1.03, 1.26]**; risk ratio for 'unsolicited' (GlaxoSmithKline): **1.01** [0.98, 1.03]; risk ratio for 'systemic adverse events' (Merck Sharp & Dohme): **1.01** [0.97, **1.04**]. To avoid double counting of participants in the total risk ratio estimate, we only included 'solicited' adverse events if the journal publication also had reported 'unsolicited' adverse events.

3.18. General harms most associated with the HPV vaccines ('solicited,' 'unsolicited' and 'systemic adverse events'*) - 'fatigue': intention to treat analysis



^{*3.18.} Risk ratio for 'solicited' (GlaxoSmithKline): **1.16 [1.05, 1.28]**; risk ratio for 'unsolicited' (GlaxoSmithKline): not applicable; risk ratio for 'systemic adverse events' (Merck Sharp & Dohme): 0.68 [0.34, 1.38]. To avoid double counting of participants in the total risk ratio estimate, we excluded the 'unsolicited' adverse events from total risk ratio estimate for studies that reported 'solicited' adverse events.

3.19. General harms most associated with the HPV vaccines ('solicited,' 'unsolicited' and 'systemic adverse events'*)

- 'headache': intention to treat analysis Study or Subgroup Risk Ratio

Study or Subgroup Risk Ratio

Subgroup Events Total Events Total Weight IV, Random, 95% CI

3.19.1 General headache ('Solicited'): Cervarix vs. AlfOH13 (females, age 9-17; follow-up until 12 months)

HPV-058 Cervarix vs. AlfOH13 (f. 9-17; 12) Risk Ratio IV, Random, 95% CI HPV-058: Cervarix vs. Al(OH)3 (f, 9-17; 12) Subtotal (95% CI) 0 374 0 376 374 376 Total events
Heterogeneity: Not applicable
Test for overall effect: Not applicable 3.19.2 General headache ('Solicited'): Cervarix vs. Al(OH)3 (females, age 15-26; follow-up until 27 months)

HPV--001: Cervarix vs. Al(OH)3 (f, 15-26; 27) 331 560 329 553 149% 0.99 [0.90, 1.10]

HPV--038 (Cervarix vs. Al(OH)3 (f, 15-25; 7) 44 149 16 76 18% 1.40 [0.85, 2.21]

Subtotal (95% CI) 797 278 348 3.19.3 General headache ('solicited'): Cervarix vs. Al(OH)3 (females, age 18-35; follow-up until 12 months) HPV-003: Cervarix vs. Al(OH)3 (f, 18-30; 12) HPV-031: Cervarix vs. Al(OH)3 (f, 18-35; 7) HPV-035: Cervarix vs. Al(OH)3 (f, 18-35; 7) Subtotal (95% CI) 3.19.4 General headache ('solicited'): Cervarix vs. Al(OH)3 (females, age 24-72; follow-up until 36 months)
HPV-015: Cervarix vs. Al(OH)3 (f, 24-72; 36) 0 2882 0 2871 Not estir
Subtotal (95%CI) 2882 2871 Not estir
Total events 0 0 Total events
Heterogeneity. Not applicable
Test for overall effect: Not applicable 3.19.5 General headache ('solicited'): Cervarix vs. Engerix: hepatitis B vaccine (females and males, age 9-16; follow-up until 72 months) Subtotal (95% CI) 1840 Total events 607 Heterogeneity, $Tau^2 = 0.01$; $Chi^2 = 6.34$, Chi = 1 (P = 0.01); $Chi^2 = 84\%$ Test for overall effect: Chi = 1.73 (P = 0.08) 3.19.6 General headache ('solicited'): Cervarix vs. Engerix: hepatitis B vaccine (females, age 26-46; follow-up until 12 months) HPV-069: Cervarix vs. Engerix (f, 26-46; 12) Subtotal (95% CI) O 606 0 606 Not estimable
 O 606 Not estimable
 O 0 0 3.19.7 General headache ('solicited'): Cervarix vs. Havrix: hepatitis A vaccine ('solicited'): Cervarix vs. Havrix (10-14; 12) 891 1035 778 1032 19.3% 1.14 [1.09, 1.19] HPV-033: Cervarix vs. Havrix (7, 9-15; 7) 62 160 76 161 5.7% 0.82 [0.64, 1.06] Subtotal (95%) 0.91 [0.72, 1.37] 1034 [0.64, 1.06] Subtotal (95% 3.19.8 General headache ('solicited'): Cervarix vs. Havrix: hepatitis A vaccine (females, age 15-25; follow-up until 48 months) HPV-008: Cervarix vs. Havrix (f, 15-25; 48)
Subtotal (95% CI)
Total events
Heterogeneity. Not applicable
Test for overall effect: Not applicable 0 9319 0 9325 Not estimable 9319 9325 Not estimable 0 0
 3.19.9 General headache ('solicited'): Cervarix vs. Twinrix: hepatitis A and B vaccine (females, age 8-15; follow-up until 12 months)

 HEY-.029: Cervarix vs. Twinrix (f, 8-15; 12)
 210
 270
 180
 271
 142%
 1.17 [1.05, 1.30]

 Subtotal (9% CI)
 210
 180
 271
 142%
 1.17 [1.05, 1.30]

 Total events
 210
 180
 Total events Heterogeneity: Not applicable Test for overall effect: Z = 2.92 (P = 0.004) 3.19.10 General headache ('unsolicited'): Cervarix vs. Al(OH)3 (females, age 9-17; follow-up until 12 months)
HPV--058: Cervarix vs. Al(OH)3 (f. 9-17; 12) 0 374 0 376 Not estima
Subtotal (95%) 0 0 Not estima Total events
Heterogeneity, Not applicable
Test for overall effect: Not applicable 3.19.11 General headache ('unsolicited'): Cervarix vs. Al(OH)3 (females, age 15-25; follow-up until 7 months) S-19-11 Deletain Included (Cervality S. AllOH) 8 (HV-038: Cervarity S. AllOH) 8 (H5-25; 7) Subtotal (95% Ct) 10 dal events 0 Heterogeneity Not applicable 1 Heterogeneity Not applicable 3.19.12 General headache ('unsolicited'): Cervarix vs. Al(OH)3 (females, age 18-35; follow-up until 7 months)

HPV-031: Cervarix vs. Al(OH)3 (f, 18-35; 7) 0 176 0 178 Not estimal

HPV-035: Cervarix vs. Al(OH)3 (f, 18-35; 7) 0 150 150 Not estimal

Subtotal (95% CI) 0 0 Not estimal 3.19.13 General headache ('unsolicited'): Cervarix vs. Engerix: hepatitis B vaccine (females and males, age 9-16; follow-up until 72 months)
 HPV-040: Cervarix vs. Engerix (f, 9-15; 12)
 0
 247
 0
 246
 Not estimable

 HPV-040: Cervarix vs. Engerix (f & m, 12-16; 72)
 23
 1593
 16
 2771
 0.0%
 2.50 [1.33, 4.72]

 Subtotal (95%)
 0
 0
 Not estimable
 3.19.14 General headache ('unsolicited'): Cervarix vs. Twinrix: hepatitis A and B vaccine (females, age 8-15; follow-up until 12 months) HPV-029: Cervarix vs. Twinrix (f, 8-15; 12) 0 270 0 271 Not estimable
Subtotal (95% CI) 0 0 Not estimable
Total events 0 0 Heterogeneity: Not applicable Test for overall effect: Not applicable
 3.19.15 General headache ('systemic adverse events'): Gardasil vs. carrier solution (females and males, age 9-16; follow-up until 18 months)

 V501-018: Cardasil vs. carrier solut. (f&m, 9-16;18)
 0
 1184
 0
 597
 Not estimable

 Subtotal (95% CI)
 1184
 597
 Not estimable

 Total events
 0
 0
 0
 Total events Heterogeneity: Not applicable Test for overall effect: Not applicable
 3.19.16 General headache (*systemic adverse events'): Gardasil vs. AAHS (males, age 15-27; follow-up until 36 months)

 V501-020: Cardasil vs. AAHS (m, 15-27; 36)
 179
 2032
 207
 2033
 8.3%
 0.87 (0.72, 1.05)

 Subtotal (95% CI)
 2032
 2033
 8.3%
 0.87 (0.72, 1.05)

 Total events
 179
 207
 Total events
Heterogeneity: Not applicable
Test for overall effect: Z = 1.49 (P = 0.14)
 3.19.17 General headachec ("systemic adverse events"): Gardasill 9 vs. saline placebo ("emales, age 12-26; follow-up until 7 months)

 V503-006: Cardasill 9 vs. saline (", 12-26,7)
 119
 618
 55
 306
 4.7%
 1.07 (0.80, 1.43)

 Subtotal (9% CI)
 618
 55
 306
 4.7%
 1.07 (0.80, 1.43)

 Total events
 119
 55
 V503-006: Gardasil 9 vs. saline (f, 12-26,7) Subtotal (95% Cl) Total events Heterogeneity. Not applicable Test for overall effect: Z = 0.47 (P = 0.64)
 3.19.18 General headache (*systemic adverse events*): HPV 16 vaccine vs. AAHS (females, age 16-25; follow-up until 48 months)

 V501-005: HPV 16 vaccine vs. AAHS (f, 16-25; 48)
 0 1204
 0 1205
 Not estimable

 Subtotal (95% CI)
 Not estimable

 Total events
 0
 0
 Total events
Heterogeneity: Not applicable
Test for overall effect: Not applicable

0.02 0.1 1 Favours HPV vaccine Favours con

Total (95% CI) 22590 22787 100.0% 1.08 [1.01, 1.16]

Total events 2443 2372

Heterogeneity, Tau² = 0.01; Chi² = 26.92, df = 8 (P = 0.0007); i² = 70%

Test for overall effect: Z = 2.13 (P = 0.03)

Test for subgroup differences: Chi² = 8.77, df = 5 (P = 0.14), i² = 39.5%

**3 1 9 Rich vishif for (Cartistic March 10.14), i² = 39.5% *3.19. Risk ratio for 'solicited' (GlaxoSmithKline): 1.11 [1.03, 1.19]; risk ratio for 'unsolicited' (GlaxoSmithKline): 2.50 [1.33, 4.72]; risk ratio for 'systemic adverse events' (Merck Sharp & Dohme): 0.94 [0.76, 1.14]. To avoid double counting of participants in the total risk ratio estimate, we excluded the 'unsolicited' adverse events from total risk ratio estimate for studies that reported 'solicited' adverse events.

3.20. General harms most associated with the HPV vaccines ('solicited,' 'unsolicited' and 'systemic adverse events'*) - 'myalgia': intention to treat analysis

Study or Subgroup	HPV vaco Events	Total		Total	Weight	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI
ii.20.1 General myalgia (solicited): Cervarix vs. Al(O HV) – O58: Cervarix vs. Al(OH)3 (f, 9–17; 12) iubtotal (95% Cl) Total events Heterogeneity, Not applicable est for overall effect. Not applicable	H)3 (fema ○ ○	ales, age 374 374	9-17; 0 0	follow- 376 376	up until 1	2 months) Not estimable Not estimable	
.20.2 General myalgia ('solicited'): Cervarix vs. Al(O PV-038: Cervarix vs. Al(OH)3 (f, 15-25; 7) ubtotal (95% CI) utal events eterogeneity. Not applicable est for overall effect: Z = 2.45 (P = 0.01)	H)3 (fem 66 66	ales, age 149 149	20 20 20		up until 11.1% 11.1%	7 months) 1.68 [1.11, 2.55] 1.68 [1.11, 2.55]	-
20.3 General myalgia (solicited'): Cervarix vs. Al(O PV-003: Cenvarix vs. Al(OH)3 (f, 18-30; 12) PV-031: Cervarix vs. Al(OH)3 (f, 18-35; 7) PV-035: Cervarix vs. Al(OH)3 (f, 18-35; 7) bubtal (95% C) dial events eterogeneity. Not applicable eterogeneity. Not applicable	0 0 0 60	31 176 150 357	0 0 0 38 38	30 178 150 358	-up until 12.4% 12.4%	12 months) Not estimable Not estimable 1.58 [1.13, 2.21] 1.58 [1.13, 2.21]	•
20.4 General myalgia ('solicited'): Cervarix vs. Al(O 92-0.15: Cenvarix vs. Al(OH)3 (f, 24-72; 36) biotal (95% Cl) tial events eterogeneity. Not applicable st for overall effect. Not applicable		ales, age 2882 2882	2 4-72 0	; follow 2871 2871	-up until	36 months) Not estimable Not estimable	
20.5 General myalgia ('solicited'): Cervarix vs. Enge PV-030: Cervarix vs. Engerix (f, 9-15, 12) PV-040: Cervarix vs. Engerix (f & m, 12-16; 72) bitotal (95% Cl) tale events eterogeneity. Tau ² = 0.54; Chi ² = 47.37, df = 1 (P < st for overall effect. Z = 0.90 (P = 0.37)	70 539 609	247 1593 1840	74 347 421		and male 13.5% 15.6% 29.1 %	es, age 9-16; follow 0.94 [0.72, 1.24] 2.70 [2.40, 3.05] 1.61 [0.57, 4.51]	-up until 72 months)
20.6 General myalgia (sollicited'): Cervarix vs. Enge PV-069: Cervarix vs. Engerix (f, 26-46, 12) libitati 195% CI) tatal events sterogeneity. Not applicable stor overall effect: Not applicable	erix: hepa O	606 606	accine (0 0	females 606 606	, age 26	46; follow-up until Not estimable Not estimable	12 months)
20.7 General myalgia ('solicited'); Cervarix vs. Havre PV-013: Cervarix vs. Havrix (f. 10-14; 12) PV-033: Cervarix vs. Havrix (f. 9-15; 7) bibotal (9% Cl) pital events eterogeneity. Tau ² = 0.01; Chi ² = 1.72, df = 1 (P = 0 est for overall effect. 2 = 5.86 (P < 0.00001)	890 79 969	1035 160 1195	552 40 592	emales, 1032 161 1193	age 9-15 16.1% 12.9% 28.9%	; follow-up until 12 1.61 [1.51, 1.71] 1.99 [1.46, 2.71] 1.69 [1.42, 2.01]	
20.8 General myalgia ('solicited'): Cervarix vs. Havr PV-008: Cervarix vs. Havrix (f, 15-25; 48) bitotal (95% Cl) stal events eterogeneity. Not applicable staf for overall effect. Not applicable		itis A va 9319 9319	occine (f	9325 9325 9325	age 15-2	5; follow-up until 4 Not estimable Not estimable	18 months)
20.9 General myalgia ('solicited'): Cervarix vs. Twin t%-0.92 · Cenarix vs. Twinrix (f, 8-15; 12) thotal (95% CI) trai events eterogeneity. Not applicable st for overall effect. Z = 4.00 (P < 0.0001)	160 160	270 270 270	113	271 271 271	emales, ag 15.0% 15.0 %	ge 8-15; follow-up 1.42 [1.20, 1.69] 1.42 [1.20, 1.69]	until 12 months)
20.10 General myalgia ('unsolicited'); Cervarix vs. A 0°/L-038: Cervarix vs. Al(OH)3 (f, 15-25; 7) bitotal (95% Cl) otal events eterogeneity. Not applicable st for overall effect: Not applicable	AI(OH)3 (1 0 0	females 149 149	, age 15 0 0	-25; fol 76 76	low-up u	ntil 7 months) Not estimable Not estimable	
20.11 General myalgia ('unsolicited'); Cervarix vs. A V-0.31: Cervarix vs. Al(OH)3 (f, 18-35; 7) btotal (95% Cl) tal events terogeneity. Not applicable st for overall effect: Not applicable	AI(OH)3 (1 0 0	176 176	, age 18 0 0	-35; fol 178 178	low-up u	ntil 7 months) Not estimable Not estimable	
20.12 General myalgia ('unsolicited'); Cervarix vs. E PV-040' Cervarix vs. Engerix (f & m, 12-16; 72) bitotal (95% Cl) Ital events terogeneity. Not applicable st for overall effect: Not applicable		1593 1 593	B vacci O O	ne (fem 2771 2771	ales and r	nales, age 12–16; fo Not estimable Not estimable	ollow-up until 72 months)
20.13 General myalgia ('unsolicited'): Cervarix vs. I 97–033: Cervarix vs. Havrix (f, 9–15, 7) btotal (95% Cl) Ital events sterogeneity. Not applicable st for overall effect: Not applicable	Havrix: he	160 160	A vaccir 0 0	161 161	les, age 9	–15; follow-up unti Not estimable Not estimable	il 7 months)
20.14 General myalgia ('systemic adverse events'): 501–018: Gardasil vs. carrier solu. ('&m,9–16;18) bibotal (95%CI) stal events eterogeneity. Not applicable sts for overall effect. Not applicable		vs. carr 1184 1184	ier solu 0 0	597 597 597	nales and	males, age 9-16; fo Not estimable Not estimable	ollow-up until 18 months)
20.15 General myalgia ('systemic adverse events'): 601-015: Gardasil vs. AAH5 (f, 15-26; 36) bital (95% Cl) tal events sterogeneity. Not applicable st for overall effect. Z = 1,35 (F = 0,18)		vs. AAH 6087 6087	IS (fema 9 9	6080 6080	15-26; fo 3.4% 3.4%	0.44 [0.14, 1.44] 0.44 [0.14, 1.44] 0.44 [0.14, 1.44]	nonths)
20.16 General myalgia ('systemic adverse events'): 01-020: Gardasil vs. AAH5 (m, 15-27; 36) btotal (95% Cl) tal events terogeneity, Not applicable st for overall effect. Not applicable		vs. AAH 2032 2032	d S (male 0	es, age 1 2033 2033	5-27; fol	low-up until 36 mo Not estimable Not estimable	nths)
20.17 General myalgia ('systemic adverse events'): 03-006: Gardasil 9 vs. saline (f, 12-26;7) btotal (95% CI) tal events terogeneity, Not applicable st for overall effect: Not applicable	Gardasil O O	9 vs. sa 618 618	aline pla O	306 306	emales, ag	e 12-26; follow-up Not estimable Not estimable	ountil 7 months)
20.18 General myalgia ('systemic adverse events'): 01-005: HPV 16 vaccine vs. AAH5 (f, 16-25, 48) btotal (95% CI) dat events terogeneity, Not applicable st for overall effect: Not applicable		1204 1 204	0 0	5 (femal 1205 1205	es, age 16	5–25; follow-up unt Not estimable Not estimable	til 48 months)
otal (95% CI) otal events eterogeneity, Tau ² = 0.10; Chi ² = 88.28, df = 7 (P < est for overall effect: Z = 3.60 (P = 0.0003)	1868	3 0195); I ² = 9;	1193	31500	100.0%	1.57 [1.23, 2.01]	001 01 1 10

^{*3.20.} Risk ratio for 'solicited' (GlaxoSmithKline): **1.64 [1.29, 2.10]**; risk ratio for 'unsolicited' (GlaxoSmithKline): not applicable; risk ratio for 'systemic adverse events' (Merck Sharp & Dohme): 0.44 [0.14, 1.44]. To avoid double counting of participants in the total risk ratio estimate, we excluded the 'unsolicited' adverse events from total risk ratio estimate for studies that reported 'solicited' adverse events.