Health Information and Quality Authority

An tÚdarás Um Fhaisnéis agus Cáilíocht Sláinte

Draft report for public consultation

Health technology assessment (HTA) of extending the national immunisation schedule to include HPV vaccination of boys

Appendices

24 July 2018

Appendix 2

Appendix 2A. Summary of HPV immunisation programmes and uptake, by country

Country and or region	Vaccine used	Programme format	Financing	Availability	Programme description	3 doses vaccination coverage (year)	Comments
EUROPE							
Austria	9-valent	Gender neutral		2014 (September) Recommendation given in 2007; funding & 2-dose schedule started in 2014	Target age: 9-14. Schools/ primary care-based delivery	62% for boys & girls (2015)	Recommendation given in 2007; funding & 2-dose schedule started in 2014
Belgium	4-valent	Females		Jun-05	Target age: 12-13; catch-up 13-18	Varies by region: 30%-83% (2012-2013). Lower coverage in Flanders region, higher coverage in Wallonian region	Lower coverage in Flanders region, higher coverage in Wallonian region
Bulgaria	4-valent	Females		Jul-05	Target age: 12		
Czech Republic	4-valent	Females	Reimbursed; no programme in place	Jul-05	Target age: 13, primary care provided. Reimbursed; no programme in place.	65% (Unknown)	Reimbursed – no official national immunisation programme
Denmark	9-valent	Females	Private	2006 (October)	Private vaccination: Girls and boys ≥ 9 yrs	Private vaccination: No information for total group of females. About 15% for those born in 1985-1992	
			Public	Nov-17	School-based programme changed to Gardasil®9 (2 dose schedule)		
				Jan-09	GP Childhood immunisation programme: Girls 12 yrs	Children immunisation programme by GPs: Girls 12 yrs: 79% (2012)	
Finland	4-	Females		Jul-05	Target age 11-	68% (2015)	

	valent				12; schools-based		
France	4-valent	Females		Jun-05	Target age: 11-14; catch-up: age 15-23; delivered in primary care or health centres	17% for 16 year olds (2014)	
Germany	9-valent	Gender neutral (Saxony)	Public	Mar-07	GP/community programme: Routine vaccination of girls aged 12-17 yrs	Girls 16-18: about 40% (2009). 2012: 16-56%. Coverage by age: 14 yo - 16.3%; 15 yo - 37.7%; 16 yo - 45.9%; 17 yo - 55.6%.	Initial recommendation was for a vaccination age of 12 to 17 and 3-dose vaccination; STIKO recommendation since 2014 has been 2-dose vaccination for girls between the ages of 9 – 14 years
Greece	4-valent	Females		Jun-05	Target age: 11-18; delivered in primary care or health centres	Varies by source: 5%-27% (2011)	
Greenland	4-valent	Females		Jun-05	Target age: 12; catch-up: 13-15 years. Mixed delivery		
Hungary	4-valent	Females		Jul-05	Target age: 12; schools-based	80% (2015) for 2-dose schedule	
Iceland	4-valent	Females		Jul-05	12; schools-based	88% (2014)	
Ireland	4-valent	Females	Public	Jul-05	Target age: 12–13; schools-based	85% for 12-13 yo, 45% for 18-19 yo (2014)	
Italy	9-valent	Gender neutral		2007–2008	Target age: 12; catch-up varies by region. Delivered by primary care/health centres	11-71% (2014). Coverage by age: 11 yo - 10.7%; 12 yo - 62.4%; 13 yo - 67.0%; 14 yo - 71.1%; 15 yo - 72.1%; 16 yo - 70.9%; 17 yo - 70.8%	
Latvia	4-valent	Females		Jul-05	Target age: 12. Mixed delivery	61% (2011)	
Liechtenstein	4-valent	Gender neutral			Target age: 11-14; catch up 15-19		

Luxembourg	4-valent	Females		Jun-05	Target age: 12-18' delivery by primary care/health centres	29% (2008)	
Republic of Macedonia (formerly the Yugoslav Republic of Macedonia)	4-valent	Females		Jul-05	Target age: 12; catch-up 13-16; schools-based delivery	65% (2012)	
Netherlands	4-valent	Females		Jul-05	Target age: 12; Catch-up: 13-16. Mixed delivery	61% (2014)	
Norway	4-valent	Females		Jul-05	Target age: 12. Schools-based delivery	79% (2014)	
Portugal	9-valent	Females		Jul-05	Target age: 13; Catch-up: 17. Primary care/health centre delivery	87% (2015)	
Romania	4-valent	Females		Jul-05	Target age: 12. Mixed delivery	<5%	
San Marino	4-valent	Females		Jul-05	Target age: 11		
Slovenia	9-valent	Females		Jul-05	Target age: 12. Schools-based delivery	49% (2012)	
Spain	4-valent	Females		Jun-05	Target age: 11–14. Delivery varies by region	73% (2014)	
Sweden	4-valent	Females	Partially subsidised	October 2006 (Opportunistic vaccination)	Opportunistic vaccination: Girls 13-20	2014 (Garland): 80%	
			Public	2012	School-based programme: Girls 11-12 yrs; School-based catch-up: Girls 13-18 yrs	NA	
UK - England	2-valent, switch to 4-valent in September 2012	Females	Public	Sep-08	School-based programme: Girls 12-13 yrs School-based/GP catch-up: Girls 14-17 yrs	School-based programme: Girls 12-13 yrs: 84% (2011) Catch-up: Girls 14-17 yrs: 56% (range from 39 to 76%) (2011)	2014 UK (Garland): 86%

UK - Scotland	2-valent, switch to 4-valent in September 2012	Females	Public	Sep-08	School-based programme: Girls 12-13 yrs School-based/GP catch-up: Girls 14-17 yrs	School-based programme: Girls 12-13 yrs: 90% (2011) Catch-up (in and out of school): Girls 13-17 yrs: 88% (33% among school leavers) (2011)	2014 UK (Garland): 86%
CENTRAL ASIA							
Uzbekistan	4-valent			Jul-05			
AMERICAS							
Argentina	4-valent	Gender neutral		Jul-05	Target age: 11. Mixed delivery	50% (2013)	
Barbados	4-valent			Jul-05	Target age: 11		
Bermuda	4-valent	Gender neutral		Jun-05	Target age: 11-13		
Brazil	4-valent	Gender neutral		Jul-05	Target age: 9. Also recommended in HIV+. Mixed delivery		Also recommended in HIV+ population
Canada	9-valent	Gender neutral	Private	August 2006 (vaccine available privately)	Private vaccination: Girls/women 9-26 yrs	Private vaccination: Girls/women 9-26 yrs: 3% at least one dose (2009)	
			Public	Sep-08	School-based programme: Girls Grade 6 (≈ 11-12 yrs)	School-based programme: Girls 11-12 yrs: about 50% (2009). 2013 (Garland): 60 to 85% by region	
Cayman Islands	4-valent	Females			Target age: 11-13		
Chile	4-valent	Females		Jul-05	Target age: 9. Catch-up age 11-12. Schools-based delivery. Also recommended in HIV+		Also recommended in HIV+ population
Colombia	4-valent	Females		Jul-05	Target age: 9-17. Mixed delivery	87% (2013)	
Ecuador	4-valent	Females		Jul-05	Target age: 9. Clinic delivery		
Guyana	4-valent	Females		Jul-05	Target age: 11		
Mexico	4-valent	Females		Jun-05	Target age: 10. Mixed delivery. Boys also vaccinated in Mexico City	0.67	Boys vaccinated in Mexico City

Panama	4-valent	Gender neutral		Jun-05	Target age: 10. Mixed delivery	67% (2010)	
Paraguay	4-valent	Females		Jul-05	Target age: 10. Mixed delivery		
Puerto Rico	4-valent	Gender neutral		Jun-05	Target age: 11-18 (females and males). Mixed delivery		
Peru	4-valent	Females		Jul-05	Target age: 10. Schools-based delivery		
Surinam	4-valent	Females		Jul-05	Target age: 9		
Trinidad & Tobago	4-valent	Females		Jul-05	Target age: 11-12		
Uruguay	4-valent	Females		Jul-05	Target age: 12. Clinic-based delivery		
US	9-valent	Gender neutral	Mix of public and private	Jun-06	Primary care providers vaccination: Girls/women 11 12 yrs routine and 13-26 yrs, if not previously vaccinated. Boys/men 11-12 yrs routine and 13-21 yrs if not previously vaccinated since October 2011 MSM 22-26years or immunocompromised since October 2011	Routine and catch-up vaccination: Girls 13-17 yrs: 33% (2012). Women 19-26 yrs: 21% at least one dose (2010). 2014 (Garland): 40% for females, 22% for males	School-based programme: Girls 12-13 yrs: 71% (2012); Boys 12-13: NA School-based catch-up: Girls 14-17 yrs:70% (2012); Boys 14-15 yrs: NA
ASIA-PACIFIC							
Australia	4-valent	Gender neutral	Public	2007 (April)	School-based programme: Girls 12-13 yrs Boys 12-13 yrs since February 2013 School-based catch-up: Girls 14-17 yrs (2007-2009) Boys 14-15 yrs (2013-2014)	School-based programme: Girls 12-13 yrs: 71% (2012) Boys 12-13: NA School-based catch-up: Girls 14-17 yrs:70% (2012) Boys 14-15 yrs: NA 2014 Garland: 73.1% girls (slightly lower boys)	
Bhutan	4-valent	Females		Jul-05	Target age: 12. Mixed delivery. Catch-up 13-18.	>90% (2014)	
Brunei	4-valent	Females		2012-2015	Target age: 12-13		

Malaysia	4-valent	Females		Jul-05	Target age: 13. Schools-based delivery. Catch-up 13-18	87% (2011)	
Japan	4-valent	Females		Jul-05	Target age: 13. Health centre delivery	0.6% (2014) (Sapporo)	
Philippines	4-valent	Females		Jul-05	Target age: 9 Health centre delivery		
WESTERN PACIFIC							
Fiji	4-valent	Females		Jun-05	Target age: 13		
Kiribati	4-valent	Females		Jul-05	NA		
Federated States of Micronesia	4-valent	Females		Jul-05	Target age: 9. Primary care/health centre delivery		
Marshall Islands	4-valent	Females		Jun-05	Target age: 11-12. Primary care/health centre delivery		
Palau	4-valent	Females		Jul-05	Target age: 9-26		
Singapore	4-valent	Females		Jul-05	Target age: 9–26. Primary care/health centre delivery.		
New Zealand	9-valent	Gender neutral	Public	Sep-08	School-based/GP/community programme: Girls 11-12 yrs; School-based/GP/community catch-up: Girls 13-20 yrs (2008-2010)	School-based/GP/community programme: Girls 11-12 yrs: around 55% (2012) (57% in Auckland) School-based/GP/community catch-up: Girls 13-20 yrs (2008-2010): 50% (2012). 2014 (Garland): 56%	
EASTERN MEDITERRANEAN							
Abu Dhabi, United Arab Emirates	4-valent	Females		Jun-05	Target age: 15–17. Schools-based delivery. Catch-up 18-26	59% (2011)	
Israel	4-valent	Gender neutral		2011 (females) & 2015 (males)	Target age: 14 (females) & 14(males). Schools-based/health centre delivery	~60% (2014)	
AFRICA							

Botswana	4-valent	Females		Jul-05	Target age: 9-13. Schools-based/health centre delivery. 2-dose programme; 3 doses for HIV positive		2-dose programme; 3 doses for HIV positives
Lesotho	4-valent			Jul-05	Target age: 9-13		
Libya	4-valent			Jul-05	Target age: 15		
Rwanda	4-valent			Jul-05	Target age: grade 6. Schools-based delivery. Catch up: 9th school year	99% (2013)	
South Africa	4-valent			Jul-05	Target age: 9 (grade 4). Schools-based delivery	87% (dose 1)	
Republic of Seychelles	4-valent			Jul-05	Target age: 10-12. Schools-based delivery		
Uganda	4-valent			Jul-05	Target age: 10. Schools-based delivery		

Sources:

Garland SM, Kjaer SK, Munoz N, Block SL, Brown DR, DiNubile MJ, et al. Impact and Effectiveness of the Quadrivalent Human Papillomavirus Vaccine: A Systematic Review of 10 Years of Real-world Experience. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2016;63(4):519-27.

Drolet M, Benard E, Boily MC, Ali H, Baandrup L, Bauer H, et al. Population-level impact and herd effects following human papillomavirus vaccination programmes: a systematic review and meta-analysis. The Lancet Infectious diseases. 2015;15(5):565-8

Appendix 4

Appendix 4.1 Search terms and results

1. Medline (PubMed)

A) Intervention

(HPV vaccin*) OR (human papillomavirus vaccin*) OR (HPV immuni*) OR (human papillomavirus immuni*) OR (gardasil*) OR (cervarix) OR (silgard)

B) Filters

Clinical Trials, Humans

= 355 Trials

2. Embase

A) Intervention

(HPV vaccin*) OR (human papillomavirus vaccin*) OR (HPV immuni*) OR (human papillomavirus immuni*) OR (gardasil*) OR (cervarix) OR (silgard)

B) Filters

Randomised Controlled Trials, Humans

= 435 Trials (of which 107 were unique to Embase)

3. Cochrane Register of Controlled Trials

A) Intervention

(HPV vaccin*) OR (human papillomavirus vaccin*) OR (HPV immuni*) OR (human papillomavirus immuni*) OR (gardasil*) OR (cervarix) OR (silgard)

B) Filters

Trials

= 597 Trials

4. Clinicaltrials.gov

A) Intervention

(HPV vaccin*) OR (human papillomavirus vaccin*) OR (HPV immuni*) OR (human papillomavirus immuni*) OR (gardasil*) OR (cervarix) OR (silgard)

B) Filters

Phase II / III / IV Trials

= 76 Trials (of which Merck Sharp and Dohme (2016) (Protocol V503-010) NCT01984697 was full text reviewed)

Appendix 4.2 Table v1.0 Studies excluded after full text review

Study	Reason for exclusion
Ault 2011[260]	Irrelevant study design (observed rates of AIS detection +/- HPV prevalence in two trials)
Barr 2008[261]	Irrelevant population
Draper 2013[262]	Irrelevant intervention (2-valent HPV vaccine)
Einstein 2009[263]	Irrelevant intervention (2-valent HPV vaccine)
Einstein 2011a[264]	Irrelevant intervention (2-valent HPV vaccine)
Einstein 2011b[265]	Irrelevant intervention (2-valent HPV vaccine)
Einstein 2014a[266]	Irrelevant intervention (2-valent HPV vaccine)
Einstein 2014b[267]	Irrelevant intervention (2-valent HPV vaccine)
Future II Study Group 2007b[268]	Irrelevant population (women with virological evidence of HPV infection at baseline)
Garland 2015[269]	Irrelevant population (Study population previously received 4-valent HPV vaccine)
Gilca 2015[270]	Irrelevant intervention (booster doses)
Joura 2012[271]	Irrelevant study design (retrospective pooled analysis)
Joura 2016[272]	Irrelevant publication (abstract)
Krajden 2011[273]	Irrelevant study design (comparison of antibody response detection techniques)
Krajden 2014[274]	Irrelevant study design (comparison of antibody response detection techniques)
Leung 2015[275]	Irrelevant intervention (2-valent HPV vaccine)
Luna 2013[276]	Irrelevant population (older women > 24 years)
Luxembourg 2015a[277]	Irrelevant study design (lot consistency study)
Luxembourg 2015b[278]	Duplication (phase II results; longer follow-up in Joura 2015 and Huh 2017)
Munoz 2009[279]	Irrelevant population (older women > 24 years)
Ogilvie 2017[280]	Irrelevant publication (research letter)
Olsson 2007[281]	Irrelevant intervention (booster dose)
Olsson 2009[282]	Irrelevant population (women with virological evidence of HPV infection at baseline)
Paavonen 2008[283]	Duplication (review article of Joura 2007)
Palefsky 2011[284]	Irrelevant population (MSM)
Perez 2008[285]	No response from author (to clarify results, timelines and methodology)
Petersen 2017[286]	Irrelevant study design (combined analysis of baseline covariate impact of five phase 3 trials)
Sankaranarayanan 2016[287]	Irrelevant study design (prospective cohort study)
Villa 2005[288]	Longer follow-up reported in Villa 2006

Wheeler 2008[289]	Irrelevant intervention (HBV vaccine co-administration)
Wheeler 2009[290]	Irrelevant population (mITT not reported; sexually-active women aged 16 to 26 years)
Merck Sharp and Dohme (2016) (Protocol V503-010)[291]	Duplication (trial results reported by Iversen 2016)

Abbreviations: HBV, hepatitis B vaccine; RCT, randomised controlled trial;

Appendix 4.2 Table v2.0 Studies excluded after full text review

Reason for exclusion	Study references
Irrelevant intervention (n=10)	(262-267, 270, 275, 281, 289)
Irrelevant population (n=8)	(261, 268, 269, 276, 279, 282, 284, 290)
Irrelevant study design (n=7)	(260, 271, 273, 274, 277, 286, 287)
Irrelevant publication (n=2)	(272, 280)
Duplication (n=3)	(278, 283, 291)
Longer follow-up reported (n=1)	(288)
No response from author (n=1)	(285)

Appendix 4.3 Forest plots

Figure 4.6 Estimate of effect on HPV 06/11/16 or 18-related persistent infection comparing the 4-valent HPV vaccine versus placebo in women 16-23 years at 60 months (unrestricted susceptible population).

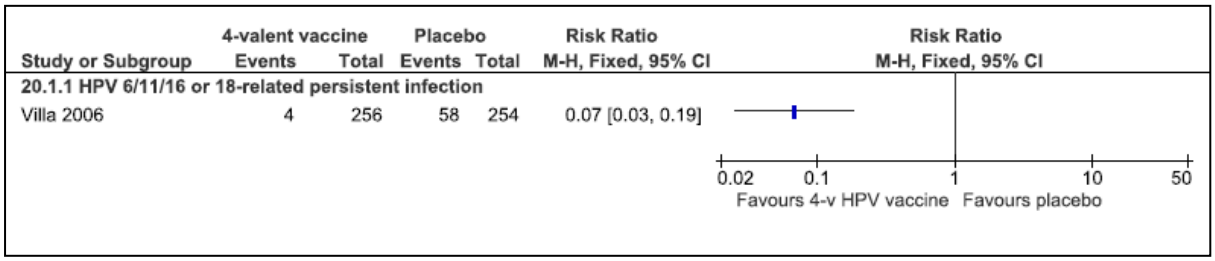


Figure 4.7 Estimate of effect on HPV 06/11/16 or 18-related CIN, external anogenital and vaginal lesions comparing the 4-valent HPV vaccine versus placebo in women aged 15 to 26 years at 42 months (generally HPV-naïve population)

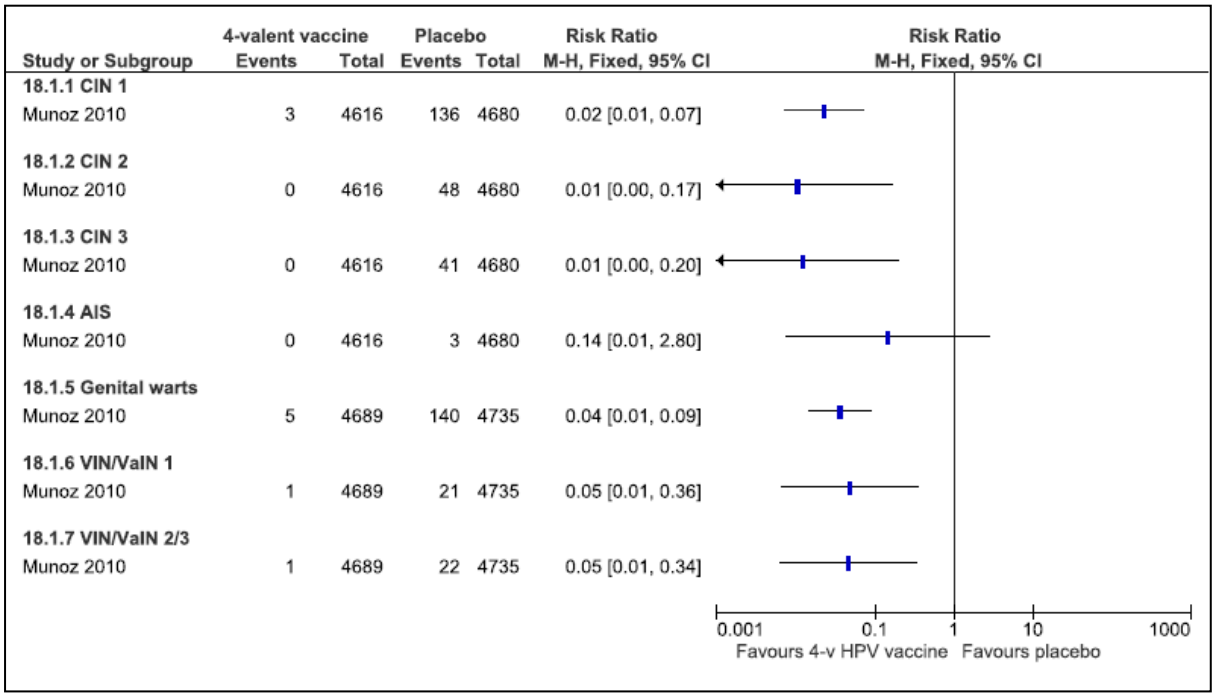


Figure 4.8 Estimate of effect on any HPV type-related CIN, external anogenital and vaginal lesions comparing the 4-valent HPV vaccine versus placebo in women 16-24 years at 36 months (generally HPV-naïve population)

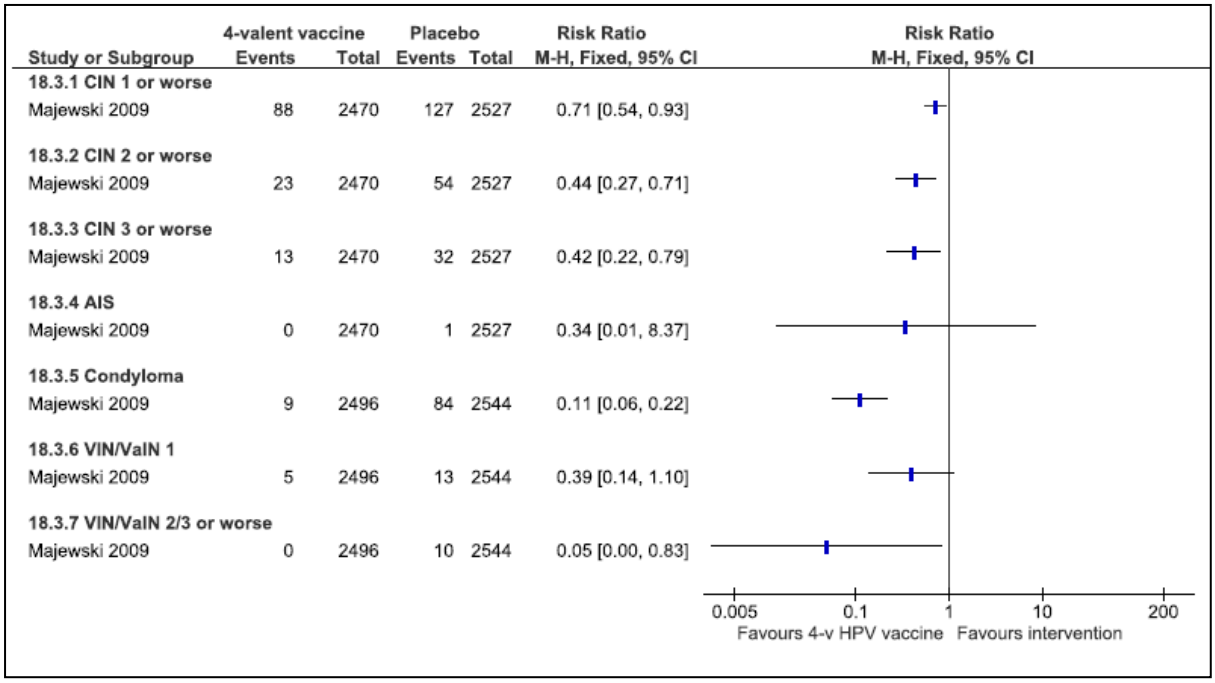


Figure 4.9 Estimate of effect on HPV 06/11/16 or 18-related CIN, external anogenital and vaginal lesions comparing the 4-valent HPV vaccine versus placebo in women 16-26 years at 36 and 42 months (unrestricted susceptible population)

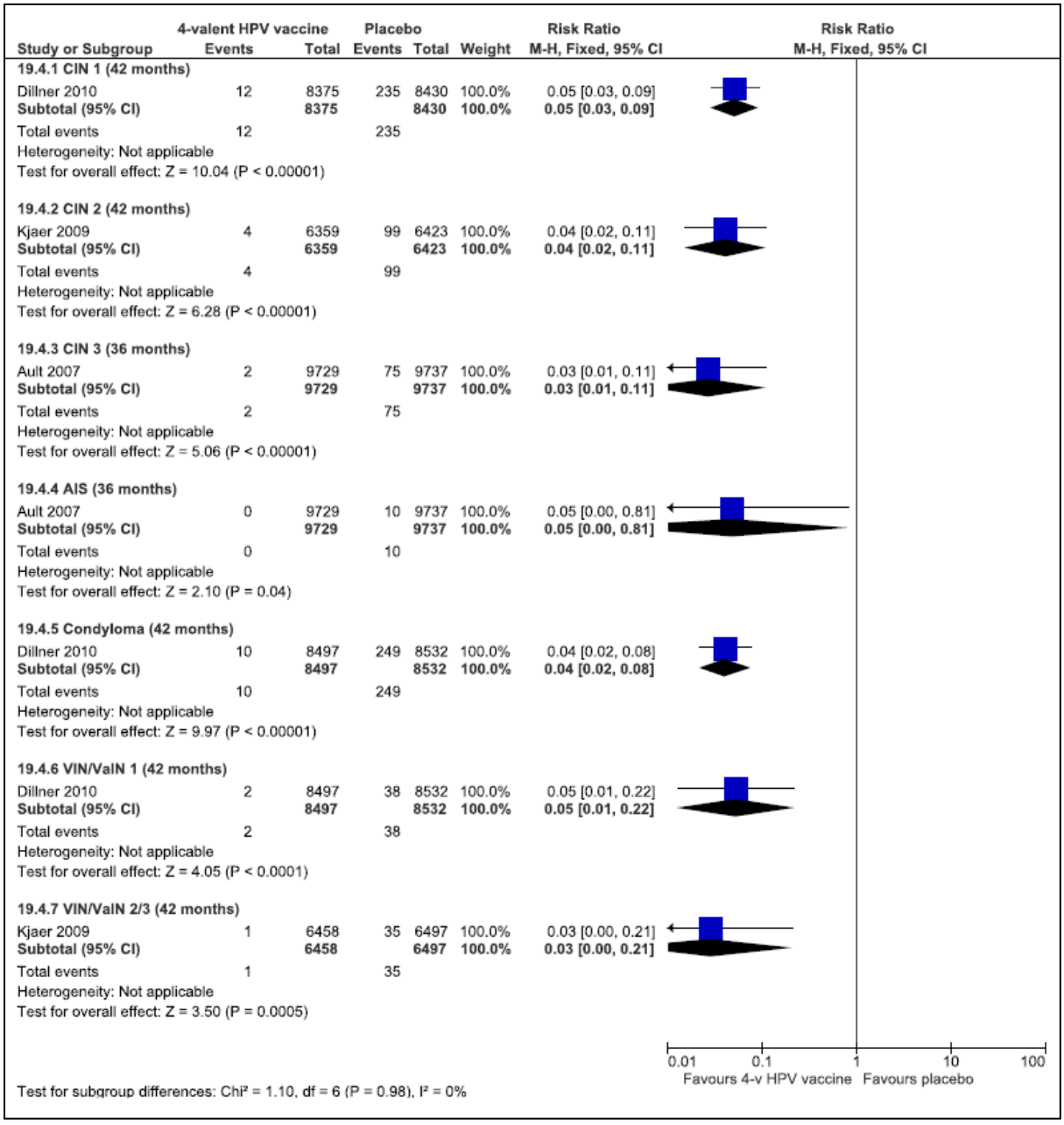


Figure 4.10 Estimate of effect on HPV 06/11/16 or 18-related persistent infections comparing the 4-valent HPV vaccine versus placebo in 16-26 year old males at 2.9 years (median) (Naïve-to-relevant type population)

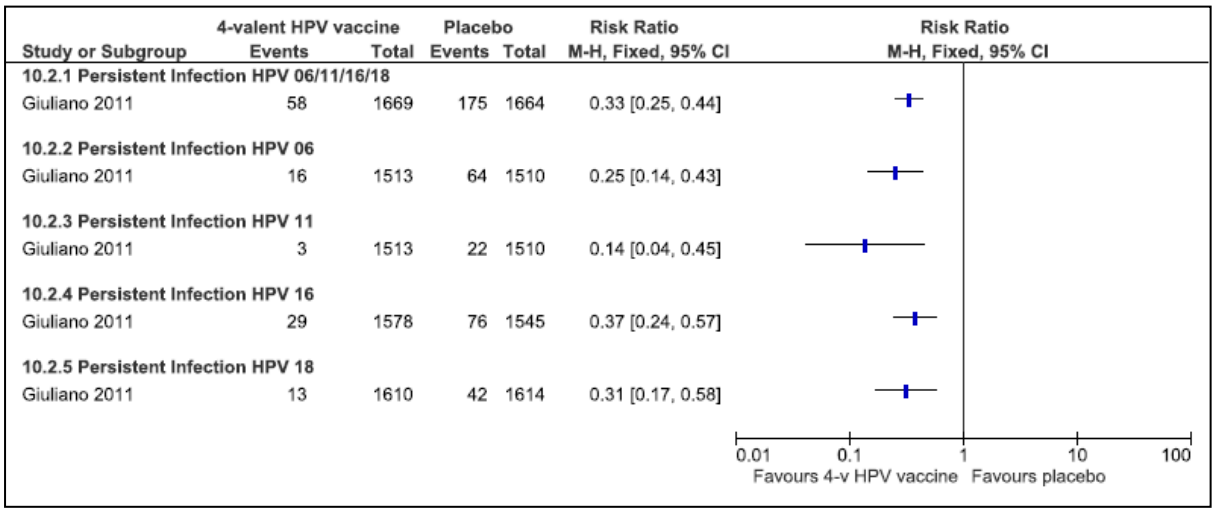


Figure 4.11 Estimate of effect on HPV 06/11/16 or 18-related lesions comparing the 4-valent HPV vaccine versus placebo in 16-26 year old males at 2.9 years (median) (Naïve-to-relevant type population)

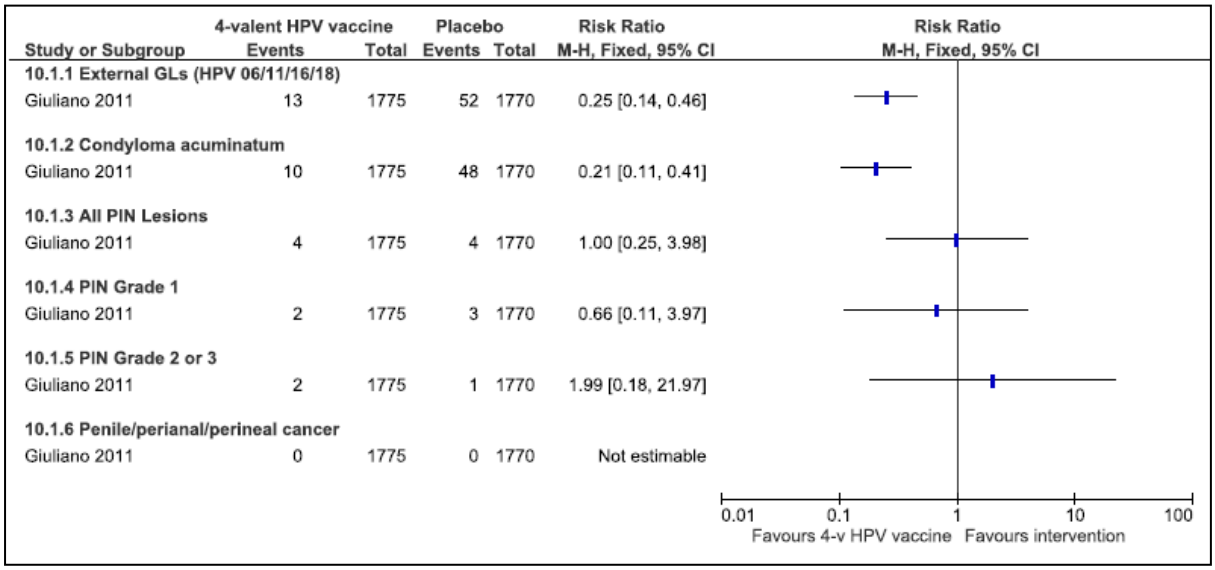


Figure 4.12 Estimate of effect on all-HPV type-related lesions comparing the 4-valent HPV vaccine versus placebo in 16-26 year old males at 36 months (HPV-naïve population)

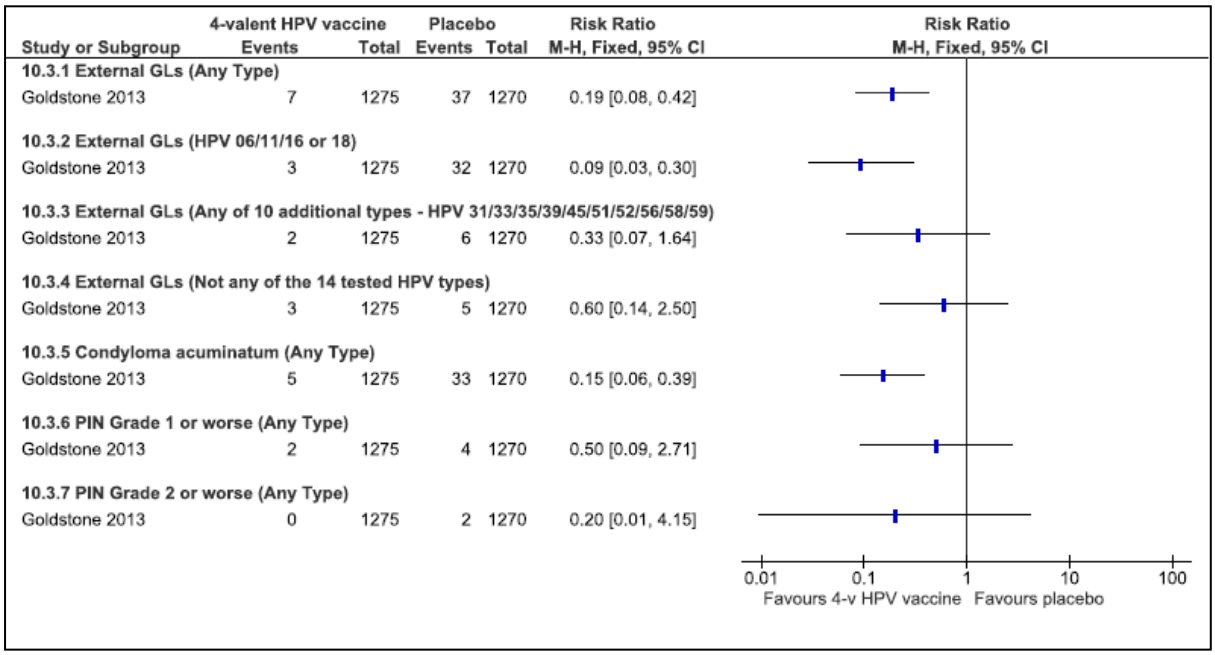


Figure 4.13 Estimate of effect on comparing 4-valent HPV vaccination in persistent infection and/or disease in boys versus girls aged 9 to 15 years from 42 to 96 months (Early Vaccination Group [EVG] ITT Population)

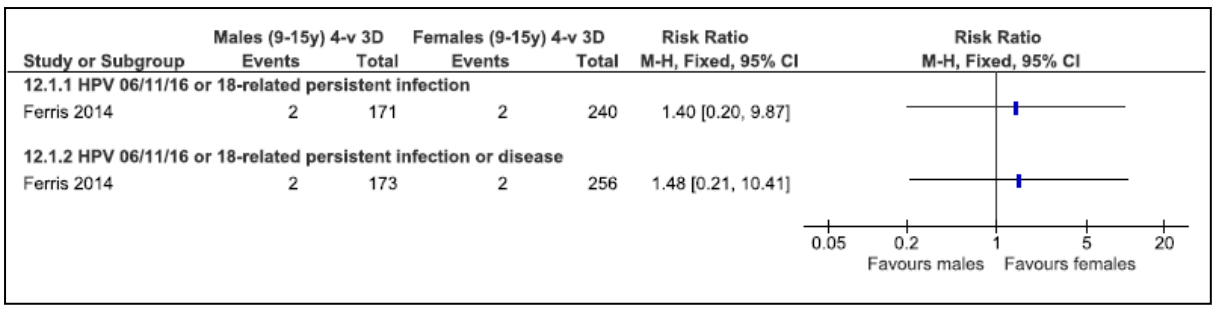


Figure 4.14 Estimate of effect on comparing 9-valent and 4-valent HPV vaccination in HPV 6, 11, 16 & 18-related low-grade and high-grade cervical, vaginal and vulvar disease in women 16-26 years at 48 months (modified intention-to-treat population)

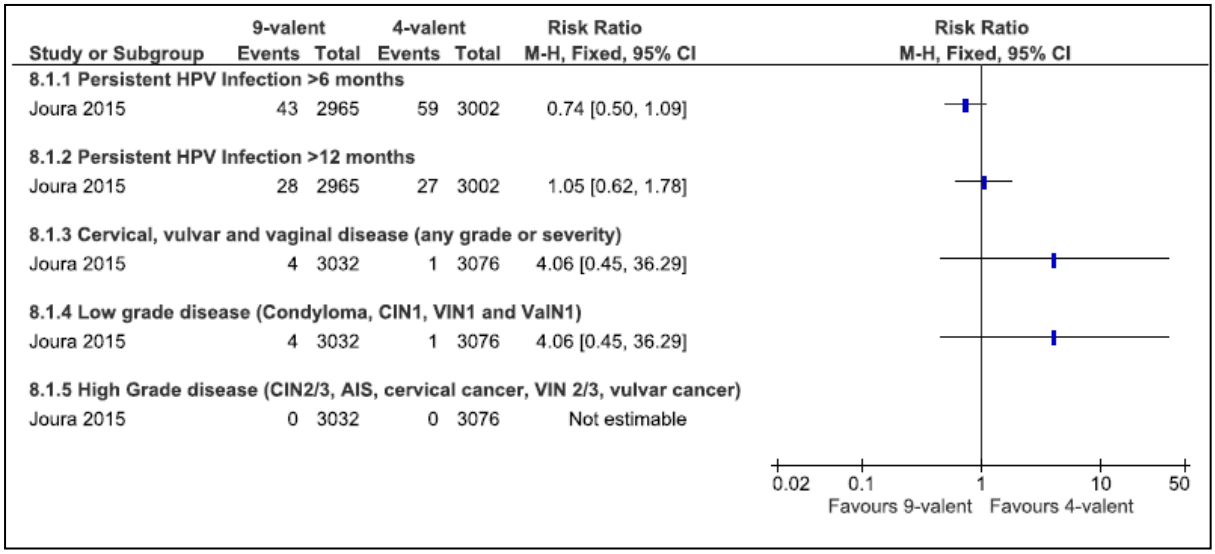


Figure 4.15 Estimate of effect on HPV 31/33/35/39/45/51/52/56/58 or 59-related CIN lesions and AIS comparing the 4-valent HPV vaccine versus placebo in women 16-26 years at 42 months (generally HPV-naïve population)

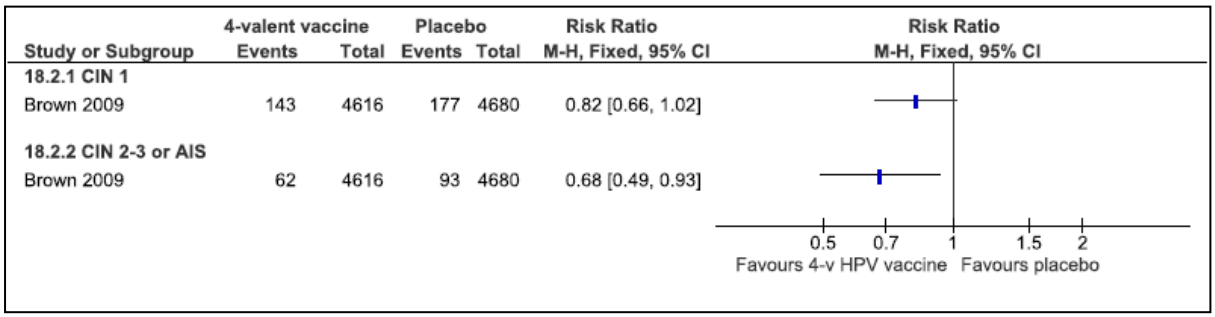


Figure 4.16 Estimate of effect on comparing 4-valent HPV vaccination in HPV 31/33/35/39/45/51/52/56/58 & 59-related persistent infection and external genital lesions in boys versus girls aged 9 to 15 years from 42 to 120 months (Early Vaccination Group [EVG] ITT Population)

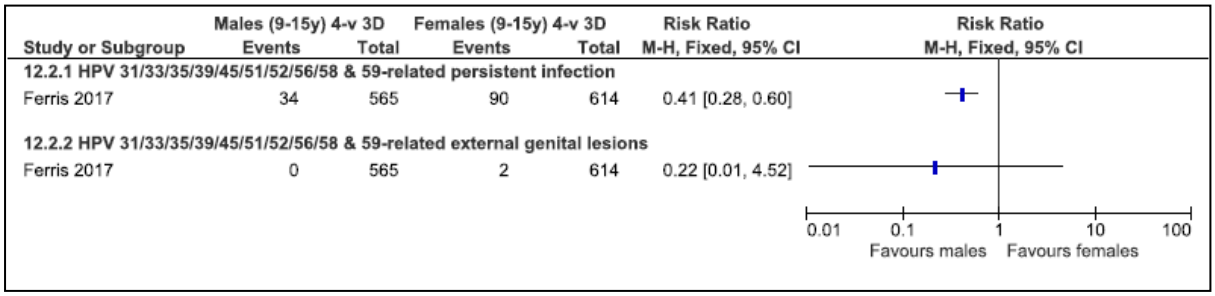


Figure 4.17 Estimate of effect on comparing 9-valent and 4-valent HPV vaccination in HPV 31, 33, 45, 52, 58-related low-grade and high-grade cervical, vaginal and vulvar disease in women 16-26 years at 48 months (modified intention-to-treat population)

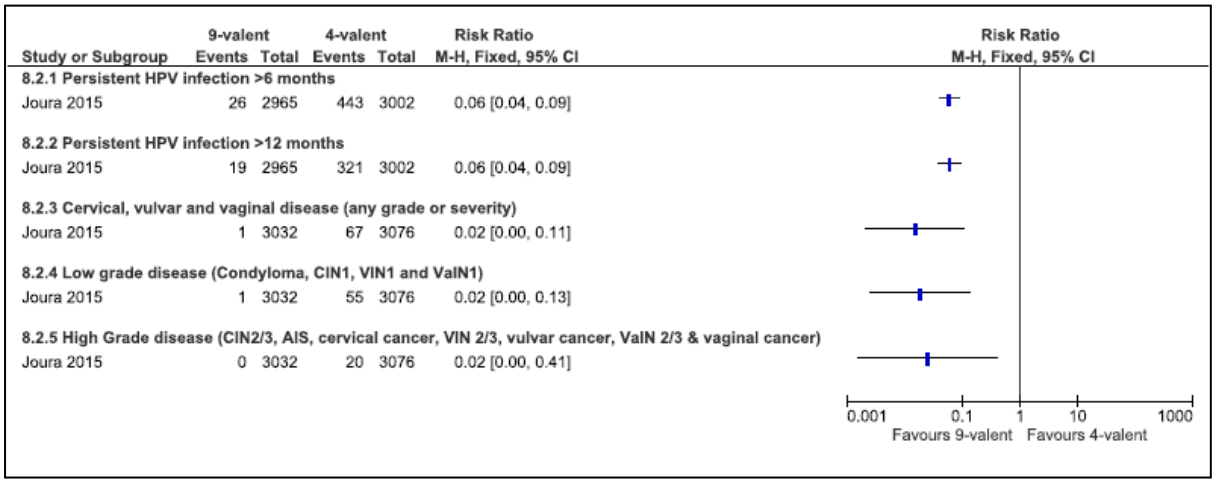


Figure 4.18 Estimate of effect on GMTs for common vaccine HPV types comparing 9-valent and 4-valent HPV vaccination in females 16-26 years from 7 to 42 months (per-protocol population)

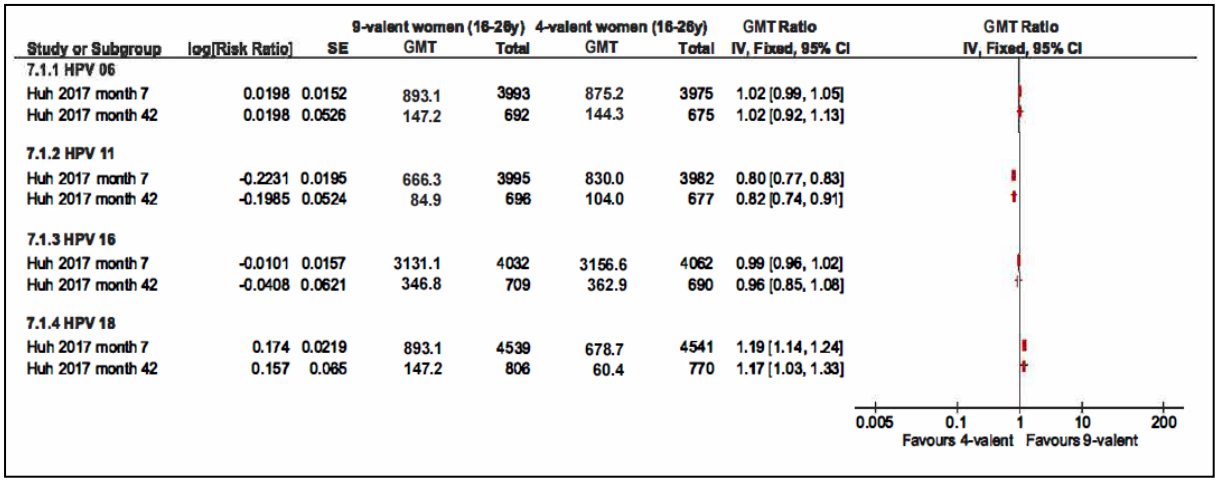


Figure 4.19 Estimate of effect on comparing seropositivity rates for 9-valent and 4-valent HPV vaccination in females 16-26 years from seven to 42 months (per-protocol population)

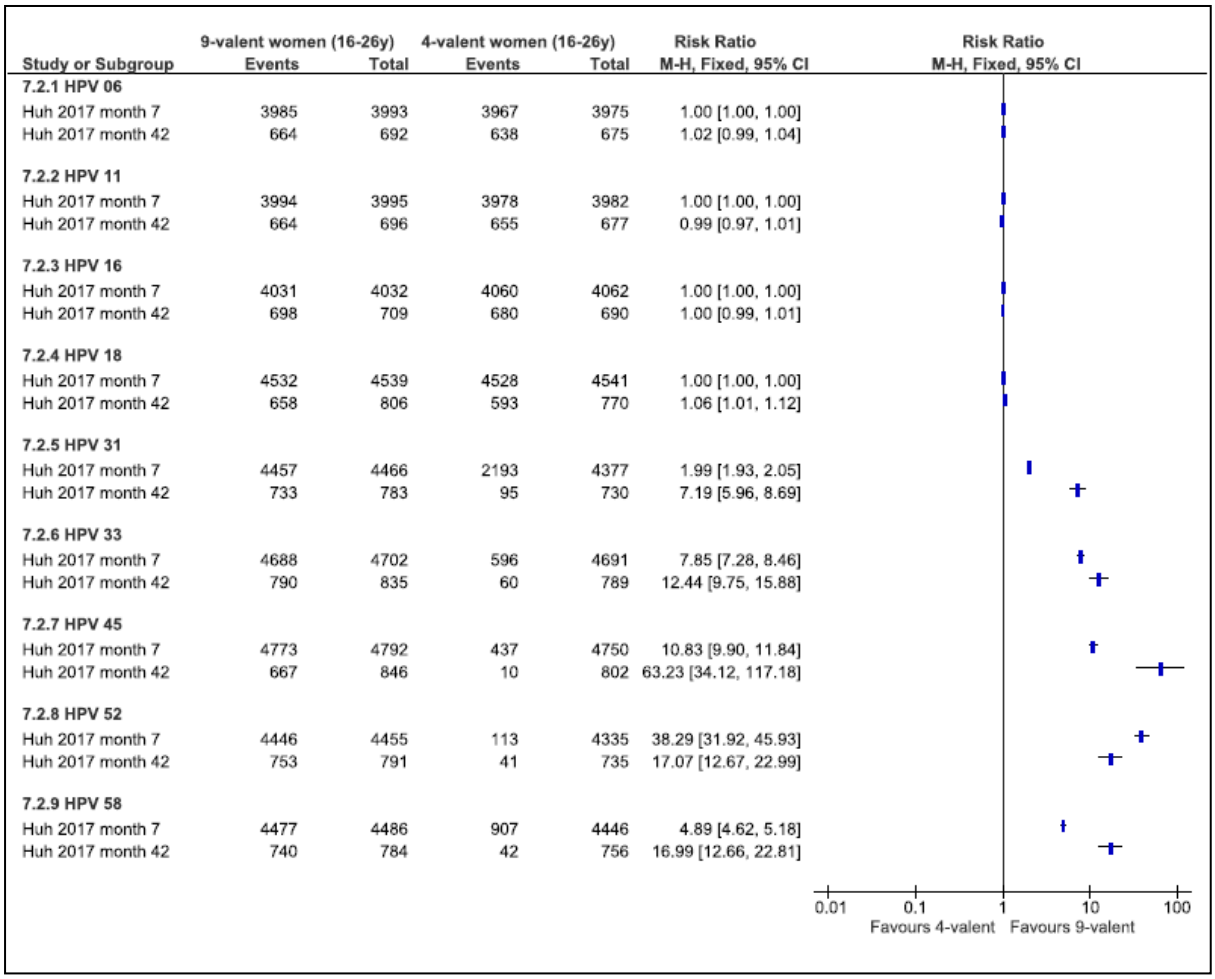


Figure 4.20 Estimate of effect on GMTs for all vaccine HPV types comparing 9-valent and 4-valent HPV vaccination in females aged nine to 15 years at seven months (per-protocol population)

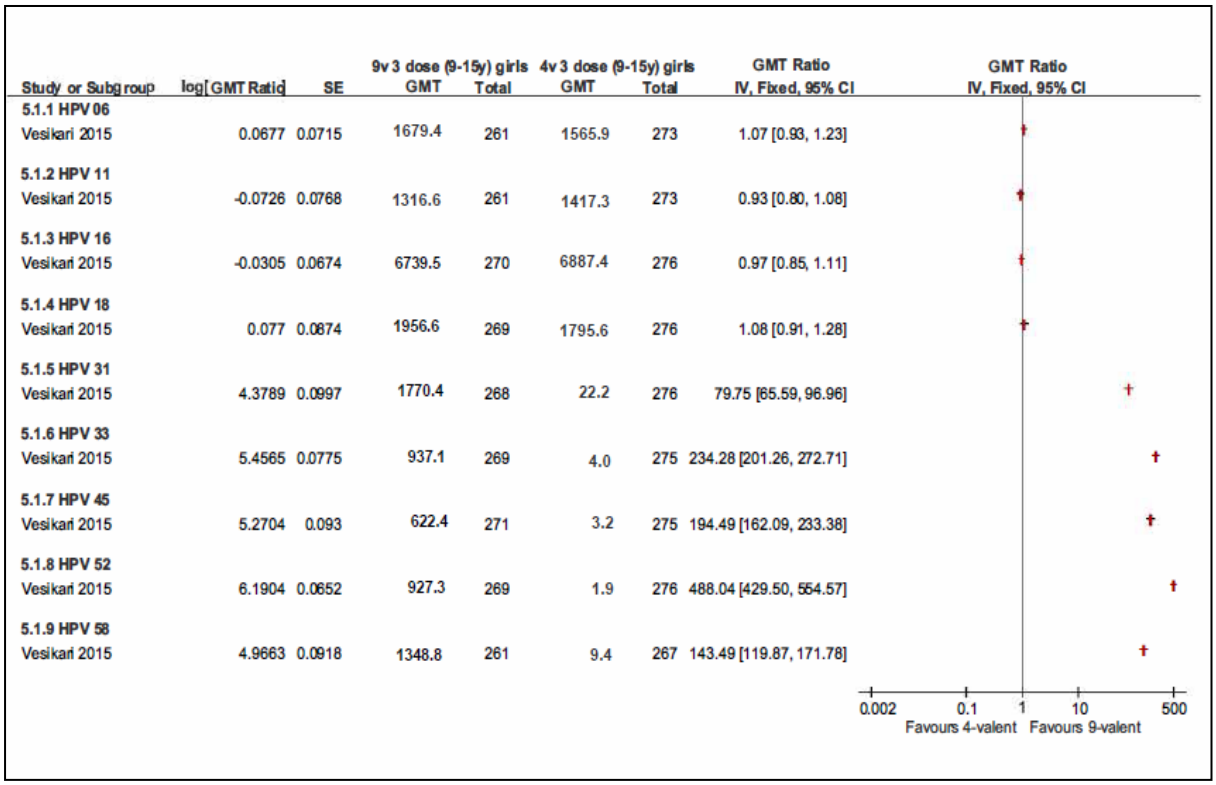


Figure 4.21 Estimate of effect on seropositivity rates for all vaccine HPV types comparing 9-valent and 4-valent HPV vaccination in females aged nine to 15 years at seven months (per-protocol population)

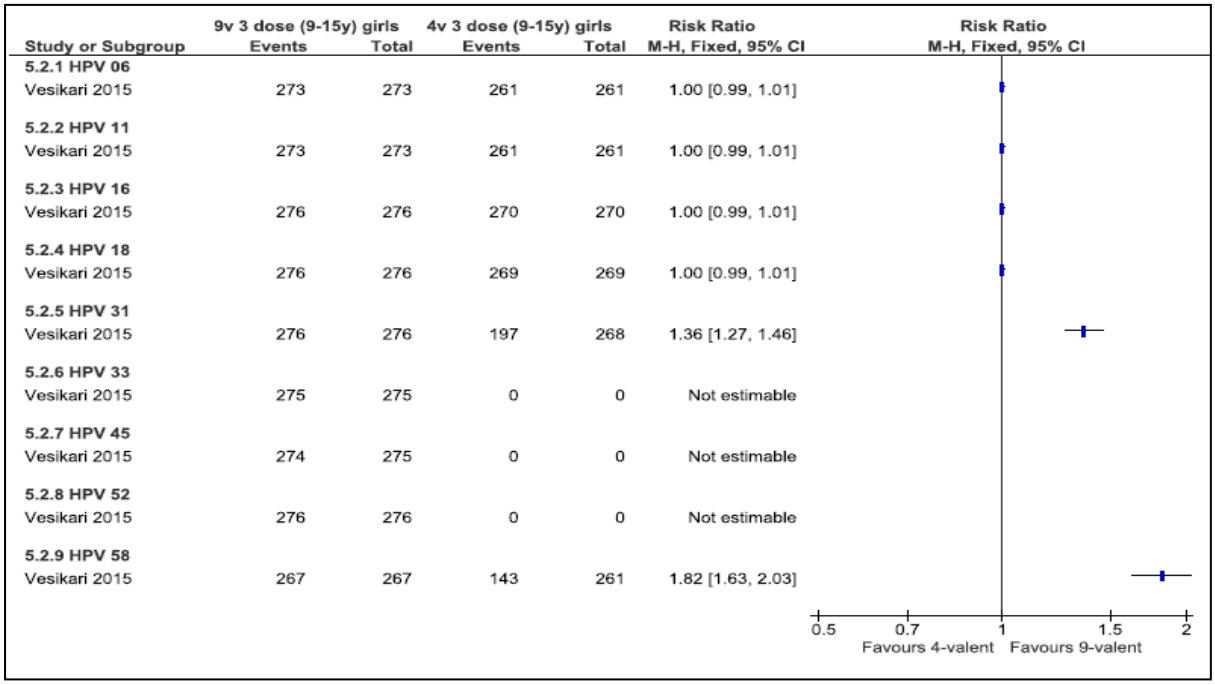


Figure 4.22 Estimate of effect on GMTs for all vaccine HPV types comparing 9-valent and 4-valent HPV vaccination in males 16-26 years at seven months (per-protocol population)

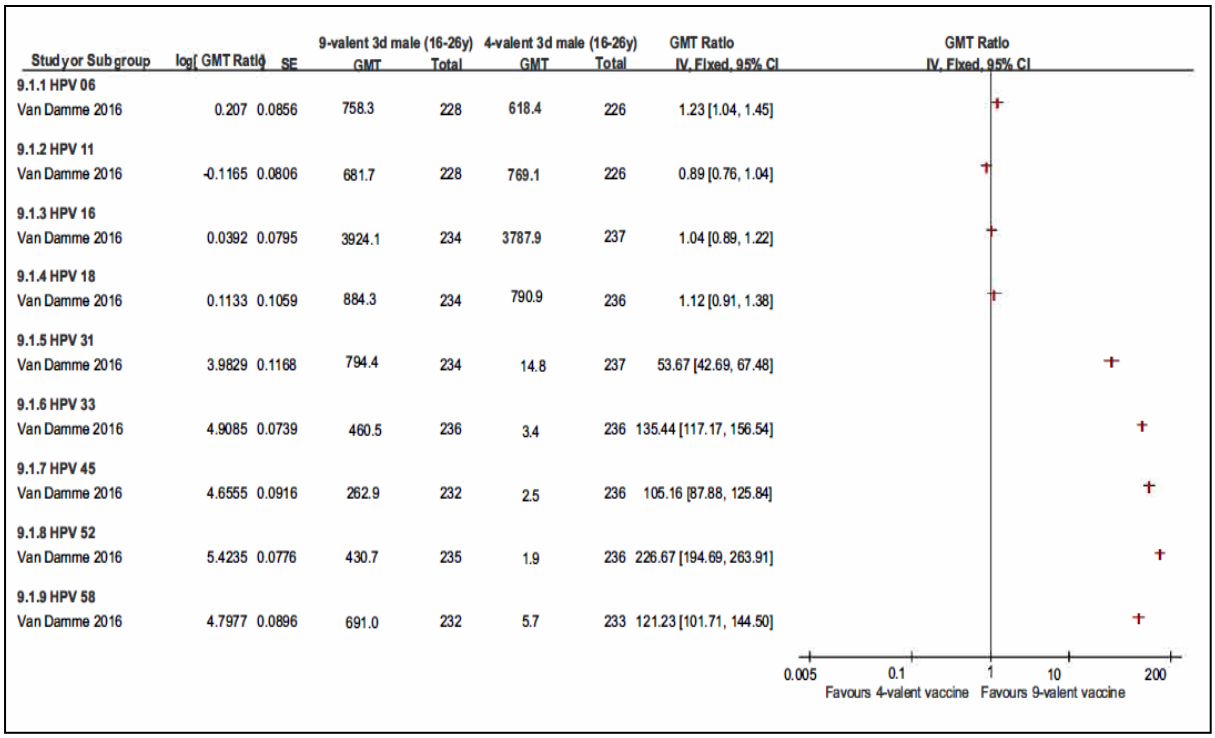


Figure 4.23 Estimate of effect on seropositivity rates for all vaccine HPV types comparing 9-valent and 4-valent HPV vaccination in males 16-26 years at seven months (per-protocol population)

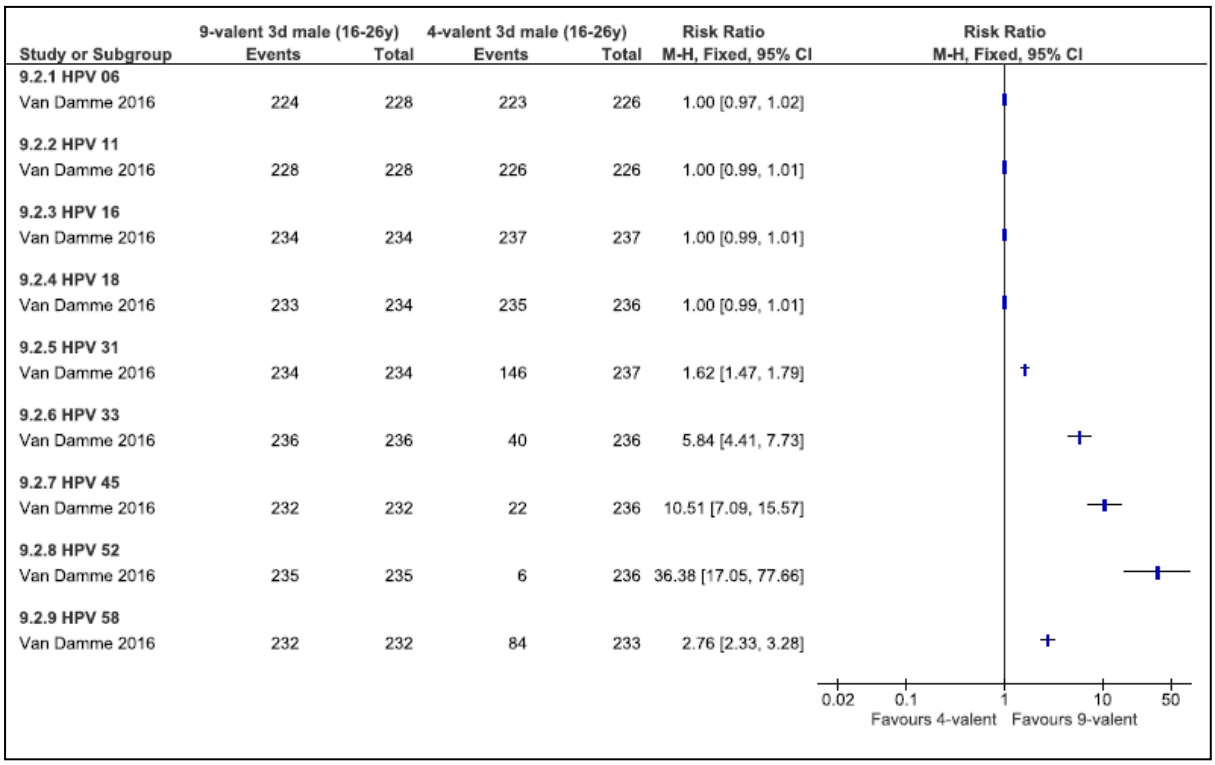


Figure 4.24 Estimate of effect on GMTs for the 4-valent HPV vaccine in males versus females aged nine to 15 years from seven to 96 months (per-protocol population)

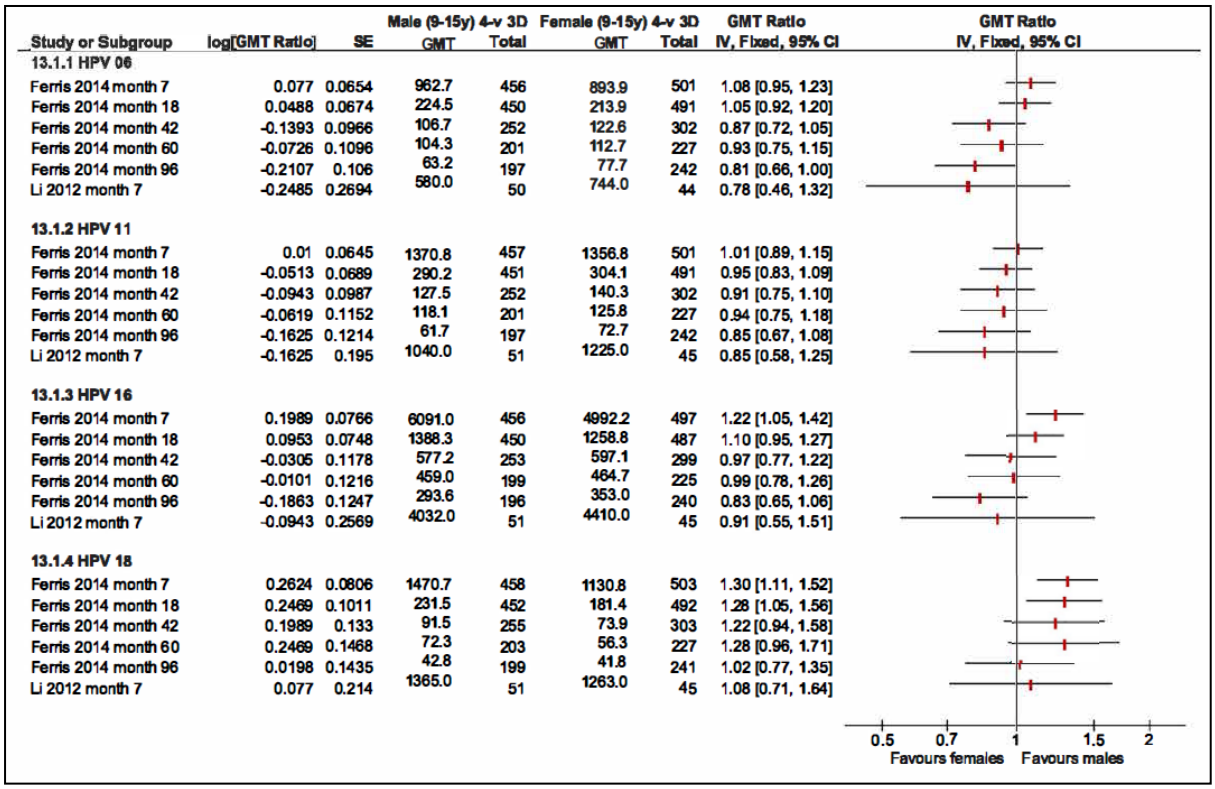


Figure 4.25 Estimate of effect on seropositivity rates for the 4-valent HPV vaccine in males versus females aged nine to 15 years from seven to 18 months (per-protocol population)

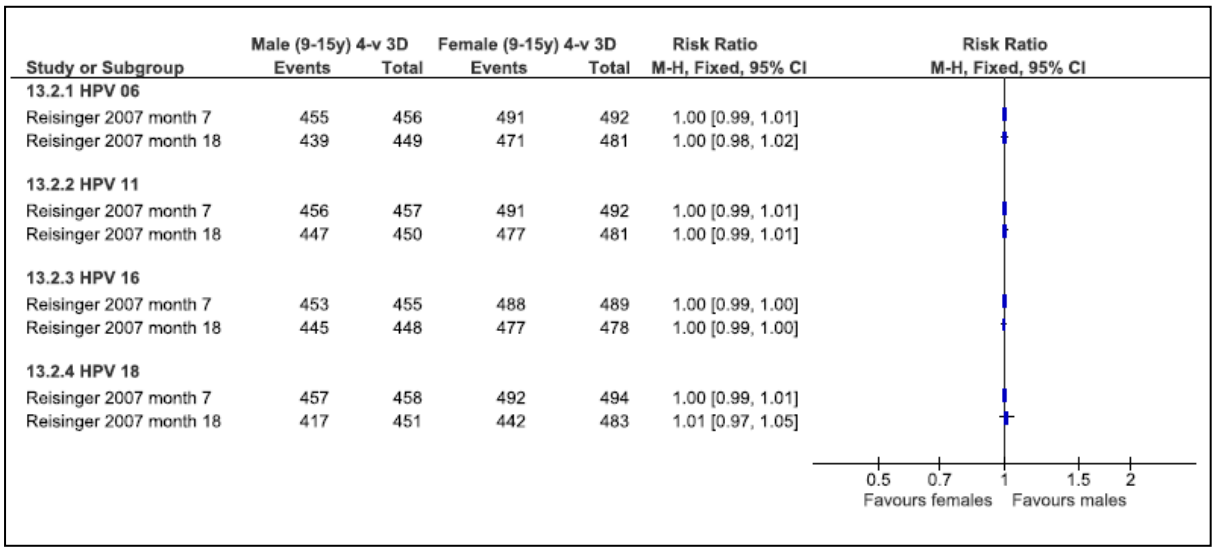


Figure 4.26 Estimate of effect on GMTs for the 9-valent HPV vaccine in males versus females 16-26 years at seven months (per-protocol population)

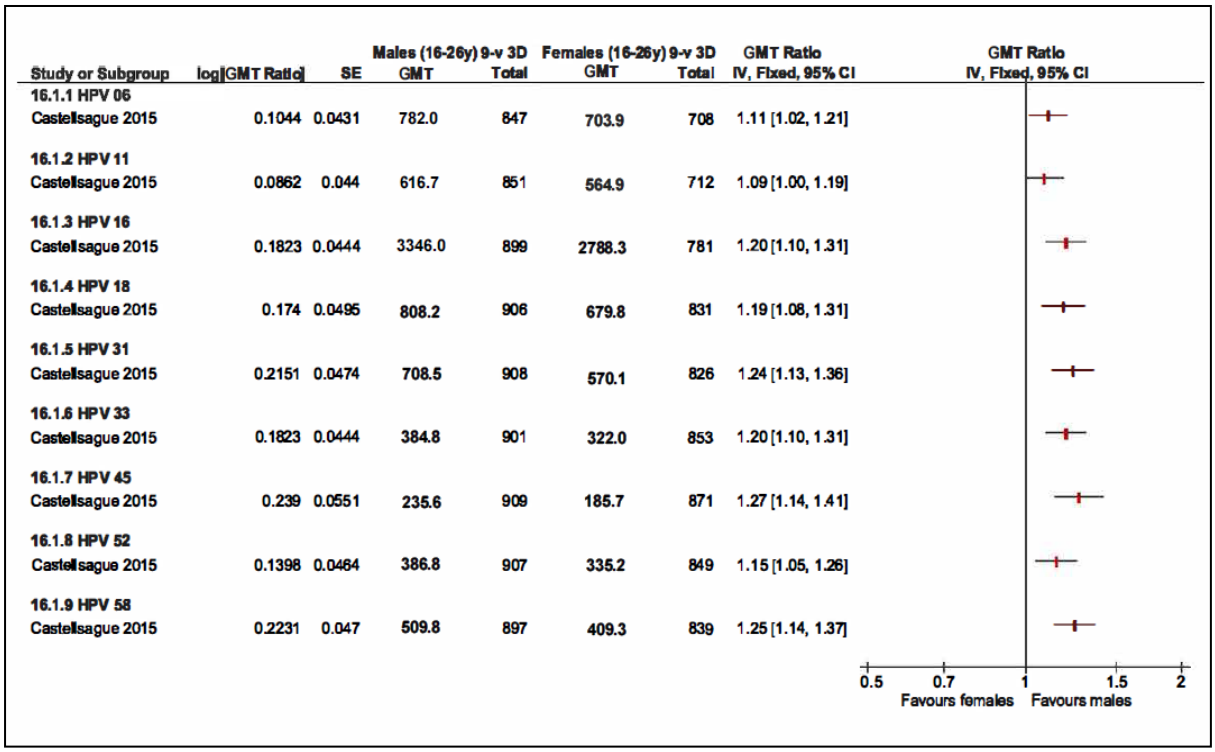


Figure 4.27 Estimate of effect on seropositivity rates for the 9-valent HPV vaccine in males versus females 16-26 years at seven months (per-protocol population)

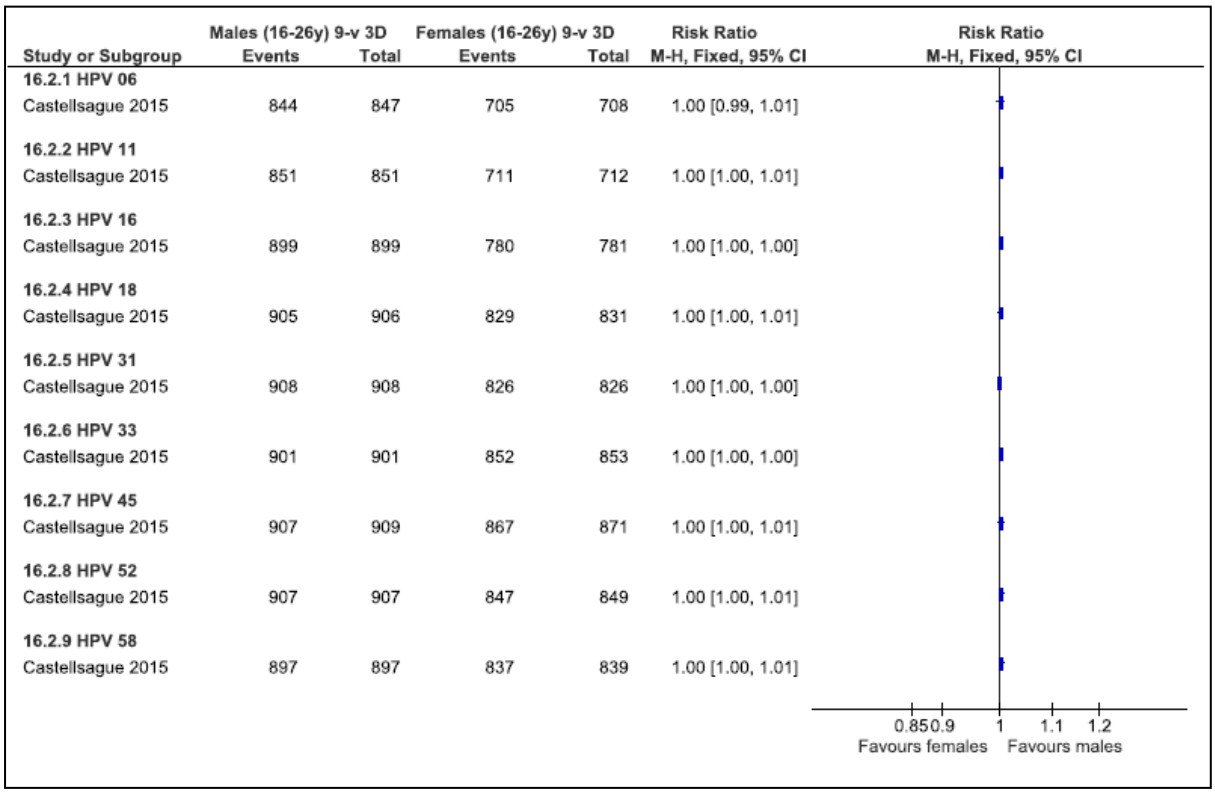


Figure 4.28 Estimate of effect on GMTs for the 9-valent HPV vaccine in males versus females aged nine to 15 years from seven to 36 months (per-protocol population)

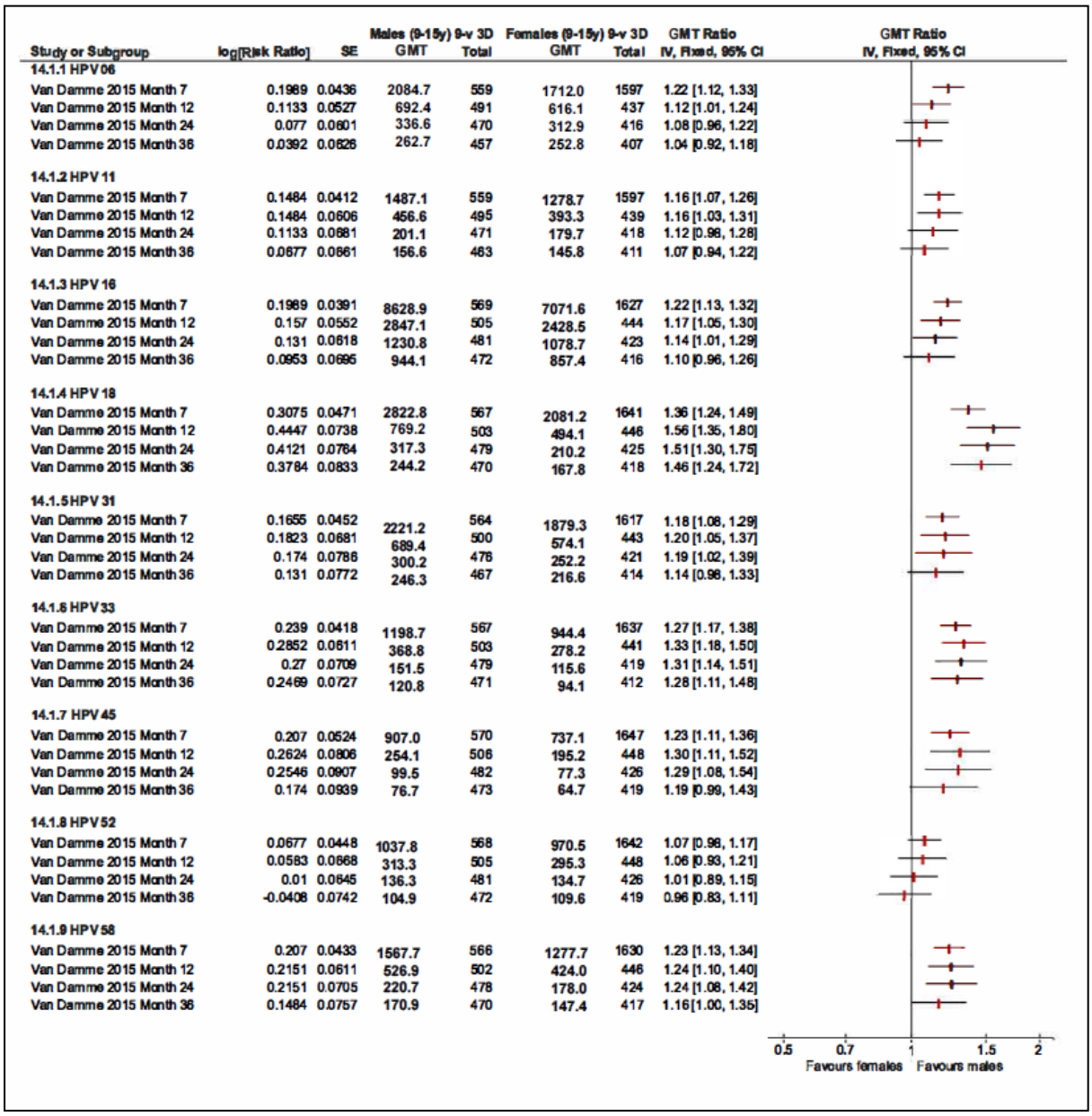


Figure 4.29 Estimate of effect on seropositivity rates for the 9-valent HPV vaccine in males versus females aged nine to 15 years from seven to 36 months (per-protocol population)

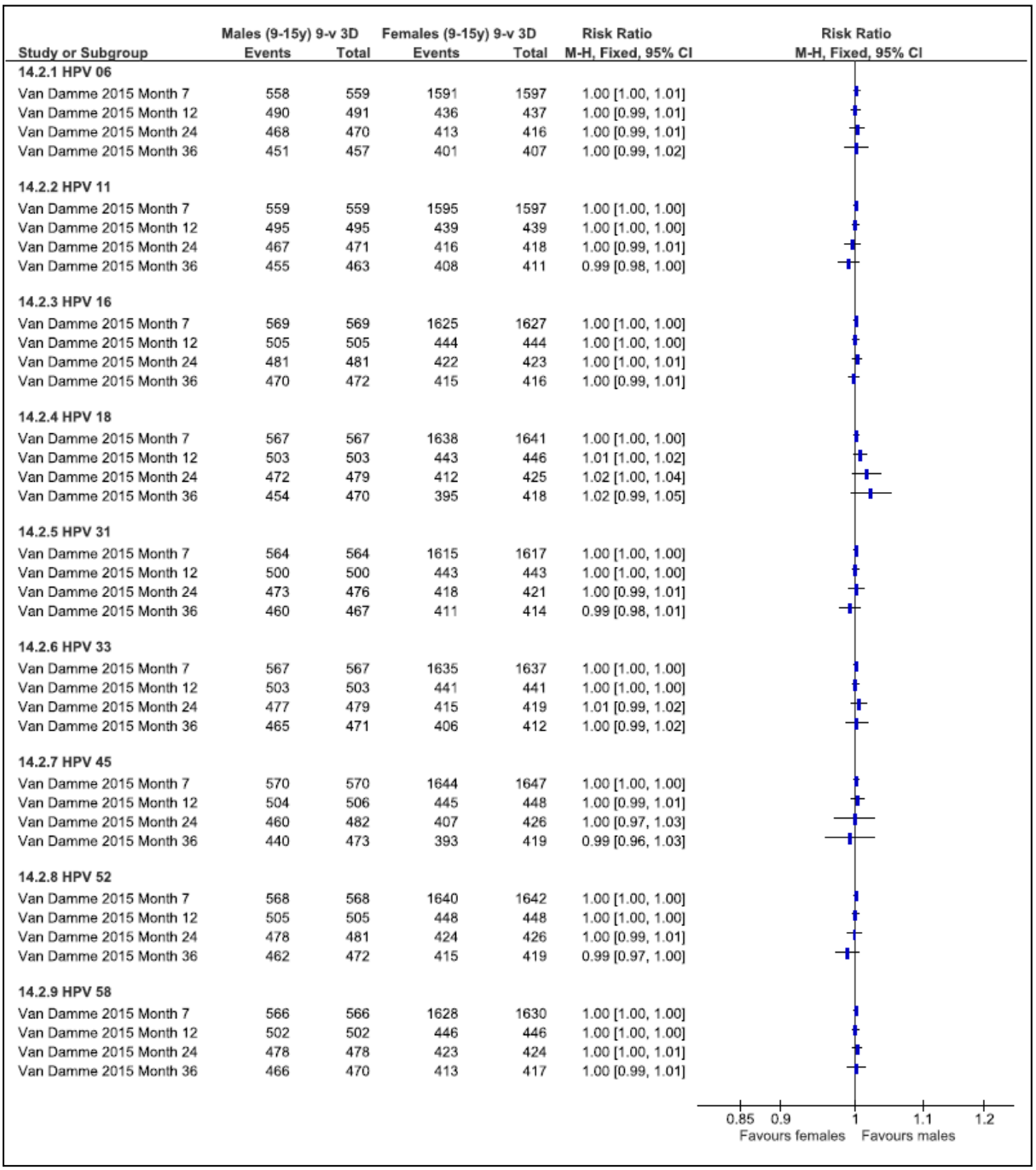


Figure 4.30 Estimate of effect on GMTs comparing two-dose HPV vaccine schedules (females nine-15 years) versus three-dose HPV vaccine schedules (females 15-26 years) at seven months (per-protocol population)

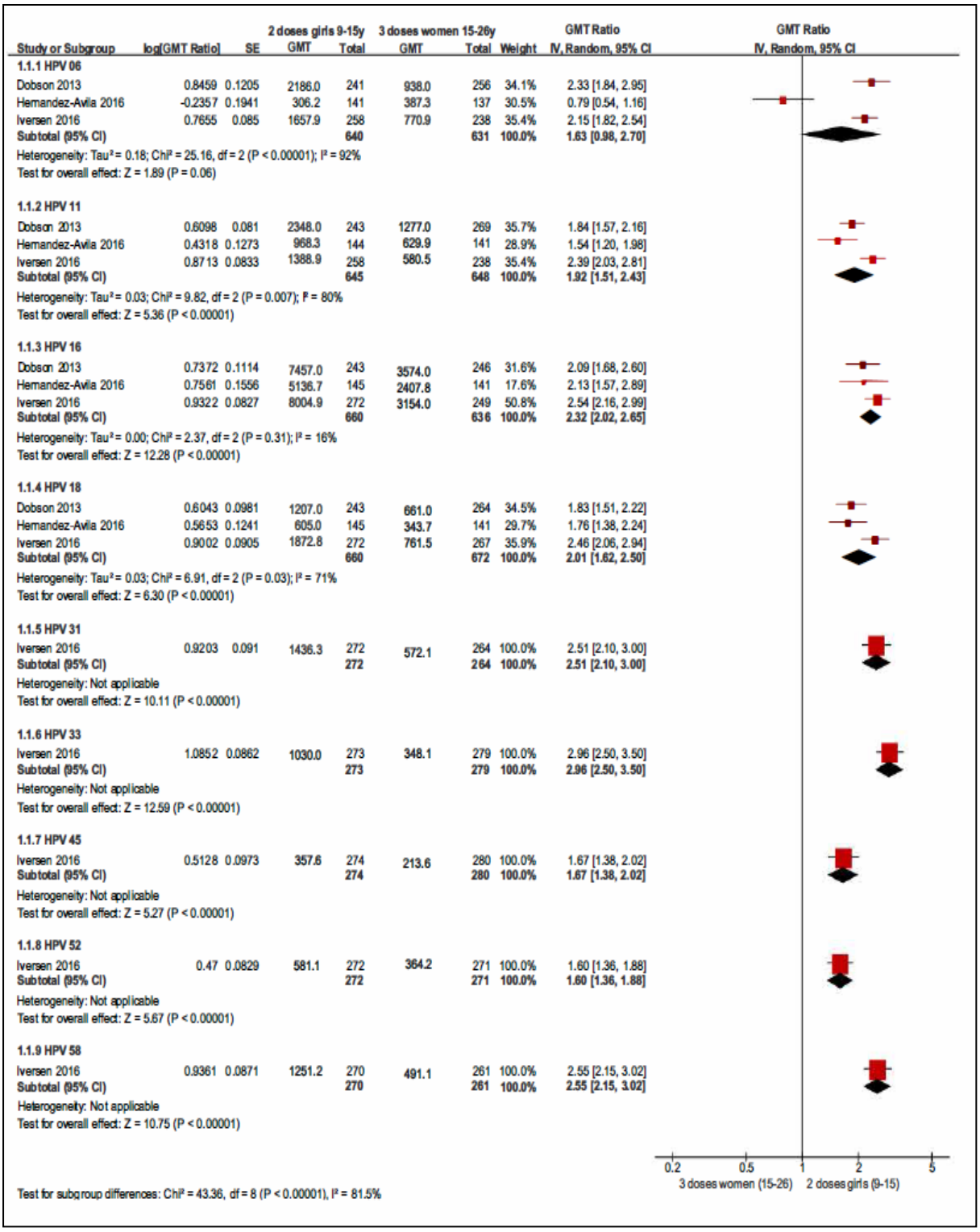


Figure 4.31 Estimate of effect on seropositivity rates comparing two-dose HPV vaccine schedules (females nine-15 years) versus three-dose HPV vaccine schedules (females 15-26 years) at seven months (per-protocol population)

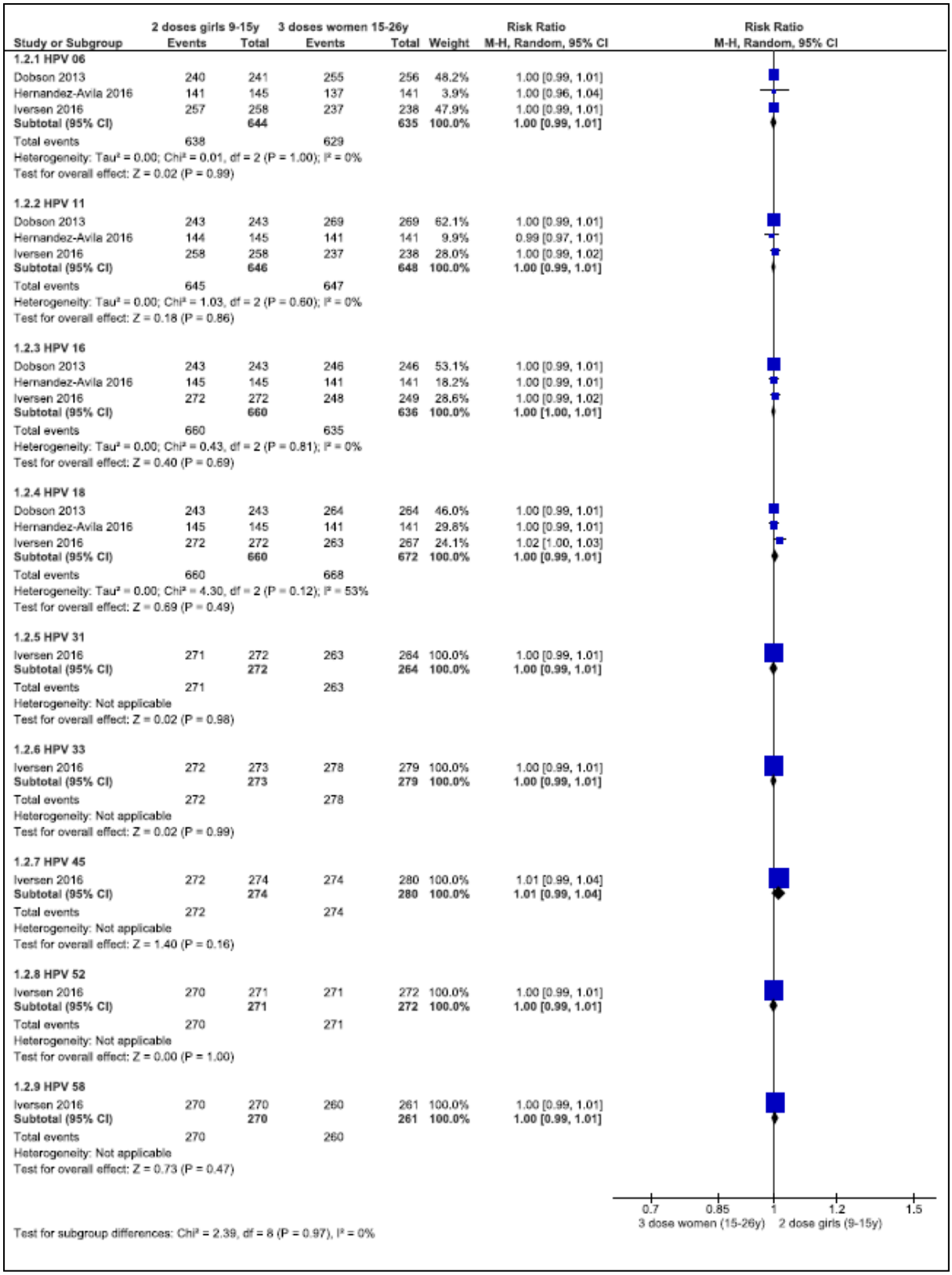

2 doses girls 9-15y
3 doses women 15-26y
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
1.2.1 HPV 06
Dobson 2013 240 241 255 256 48.2% 1.00 [0.99, 1.01]
Hernandez-Avila 2016 141 145 137 141 3.9% 1.00 [0.96, 1.04]
Iversen 2016 257 258 237 238 47.9% 1.00 [0.99, 1.01]
Subtotal (95% CI) 644 635 100.0% 1.00 [0.99, 1.01]
Total events 638 629
Heterogeneity: Tau² = 0.00; Chi² = 0.01, df = 2 (P = 1.00); I² = 0%
Test for overall effect: Z = 0.02 (P = 0.99)
1.2.2 HPV 11
Dobson 2013 243 243 269 269 62.1% 1.00 [0.99, 1.01]
Hernandez-Avila 2016 144 145 141 141 9.9% 0.99 [0.97, 1.01]
Iversen 2016 258 258 237 238 28.0% 1.00 [0.99, 1.02]
Subtotal (95% CI) 646 648 100.0% 1.00 [0.99, 1.01]
Total events 645 647
Heterogeneity: Tau² = 0.00; Chi² = 1.03, df = 2 (P = 0.60); I² = 0%
Test for overall effect: Z = 0.18 (P = 0.86)
1.2.3 HPV 16
Dobson 2013 243 243 246 246 53.1% 1.00 [0.99, 1.01]
Hernandez-Avila 2016 145 145 141 141 18.2% 1.00 [0.99, 1.01]
Iversen 2016 272 272 248 249 28.6% 1.00 [0.99, 1.02]
Subtotal (95% CI) 660 636 100.0% 1.00 [1.00, 1.01]
Total events 660 635
Heterogeneity: Tau² = 0.00; Chi² = 0.43, df = 2 (P = 0.81); I² = 0%
Test for overall effect: Z = 0.40 (P = 0.69)
1.2.4 HPV 18
Dobson 2013 243 243 264 264 46.0% 1.00 [0.99, 1.01]
Hernandez-Avila 2016 145 145 141 141 29.8% 1.00 [0.99, 1.01]
Iversen 2016 272 272 263 267 24.1% 1.02 [1.00, 1.03]
Subtotal (95% CI) 660 672 100.0% 1.00 [0.99, 1.01]
Total events 660 668
Heterogeneity: Tau² = 0.00; Chi² = 4.30, df = 2 (P = 0.12); I² = 53%
Test for overall effect: Z = 0.69 (P = 0.49)
1.2.5 HPV 31
Iversen 2016 271 272 263 264 100.0% 1.00 [0.99, 1.01]
Subtotal (95% CI) 272 264 100.0% 1.00 [0.99, 1.01]
Total events 271 263
Heterogeneity: Not applicable
Test for overall effect: Z = 0.02 (P = 0.98)
1.2.6 HPV 33
Iversen 2016 272 273 278 279 100.0% 1.00 [0.99, 1.01]
Subtotal (95% CI) 273 279 100.0% 1.00 [0.99, 1.01]
Total events 272 278
Heterogeneity: Not applicable
Test for overall effect: Z = 0.02 (P = 0.99)
1.2.7 HPV 45
Iversen 2016 272 274 274 280 100.0% 1.01 [0.99, 1.04]
Subtotal (95% CI) 274 280 100.0% 1.01 [0.99, 1.04]
Total events 272 274
Heterogeneity: Not applicable
Test for overall effect: Z = 1.40 (P = 0.16)
1.2.8 HPV 52
Iversen 2016 270 271 271 272 100.0% 1.00 [0.99, 1.01]
Subtotal (95% CI) 271 272 100.0% 1.00 [0.99, 1.01]
Total events 270 271
Heterogeneity: Not applicable
Test for overall effect: Z = 0.00 (P = 1.00)
1.2.9 HPV 58
Iversen 2016 270 270 260 261 100.0% 1.00 [0.99, 1.01]
Subtotal (95% CI) 270 261 100.0% 1.00 [0.99, 1.01]
Total events 270 260
Heterogeneity: Not applicable
Test for overall effect: Z = 0.73 (P = 0.47)
Test for subgroup differences: Chi² = 2.39, df = 8 (P = 0.97), I² = 0%
0.7
0.85
1
1.2
1.5
3 dose women (15-26y)
2 dose girls (9-15y)

Figure 4.32 Estimate of effect on GMTs comparing two-dose 4-valent HPV vaccine schedules (females nine-13 years) versus three-dose 4-valent HPV vaccine schedules (females 16-26 years) from seven to 36 months (per-protocol population)

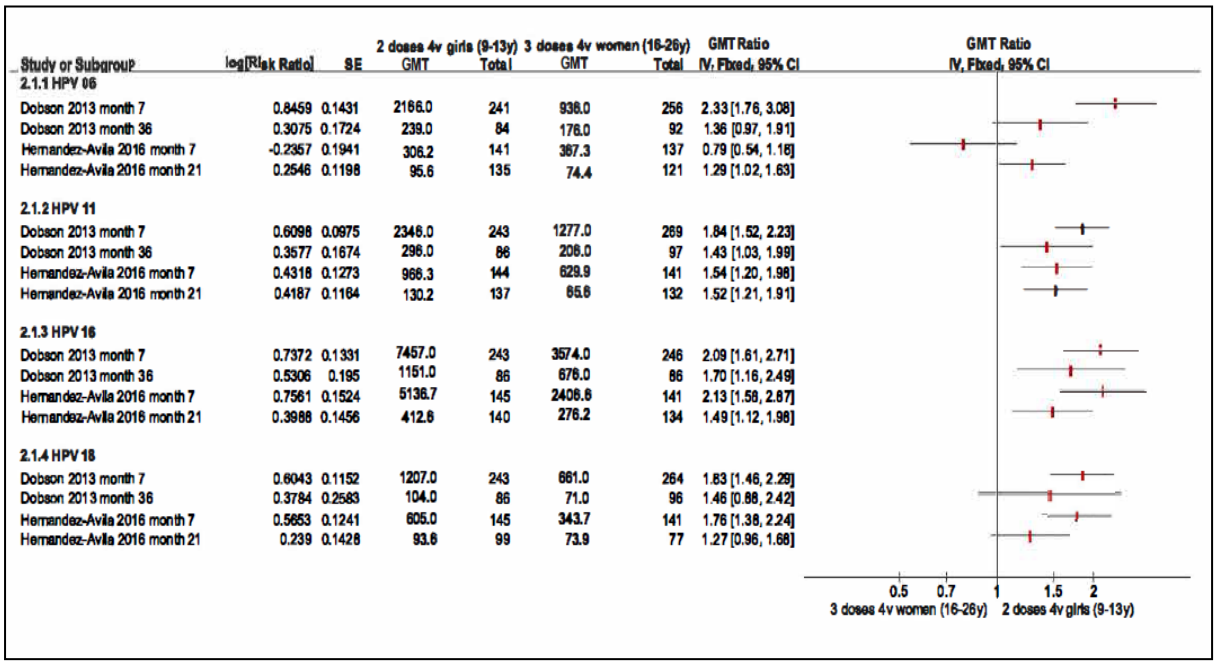


Figure 4.33 Estimate of effect on seropositivity rates comparing two-dose 4-valent HPV vaccine schedules (females nine-13 years) versus three-dose 4-valent HPV vaccine schedules (females 16-26 years) from seven to 36 months (per-protocol population)

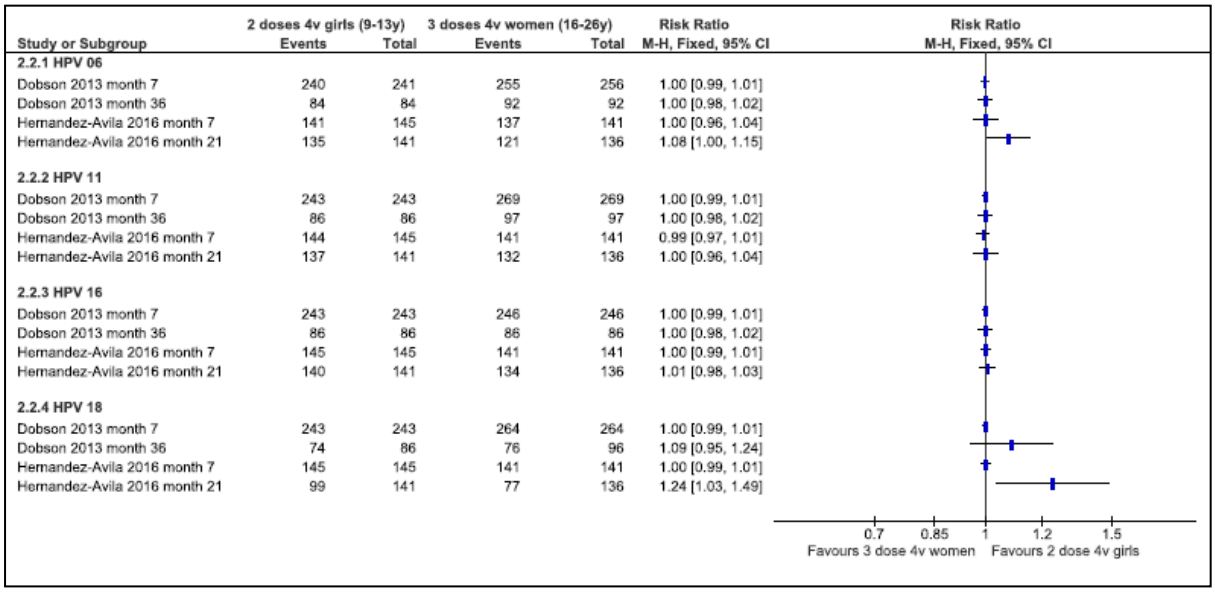


Figure 4.34 Estimate of effect on GMTs comparing two-dose versus three-dose HPV vaccine schedules (females nine-14 years) at seven months (per-protocol population)

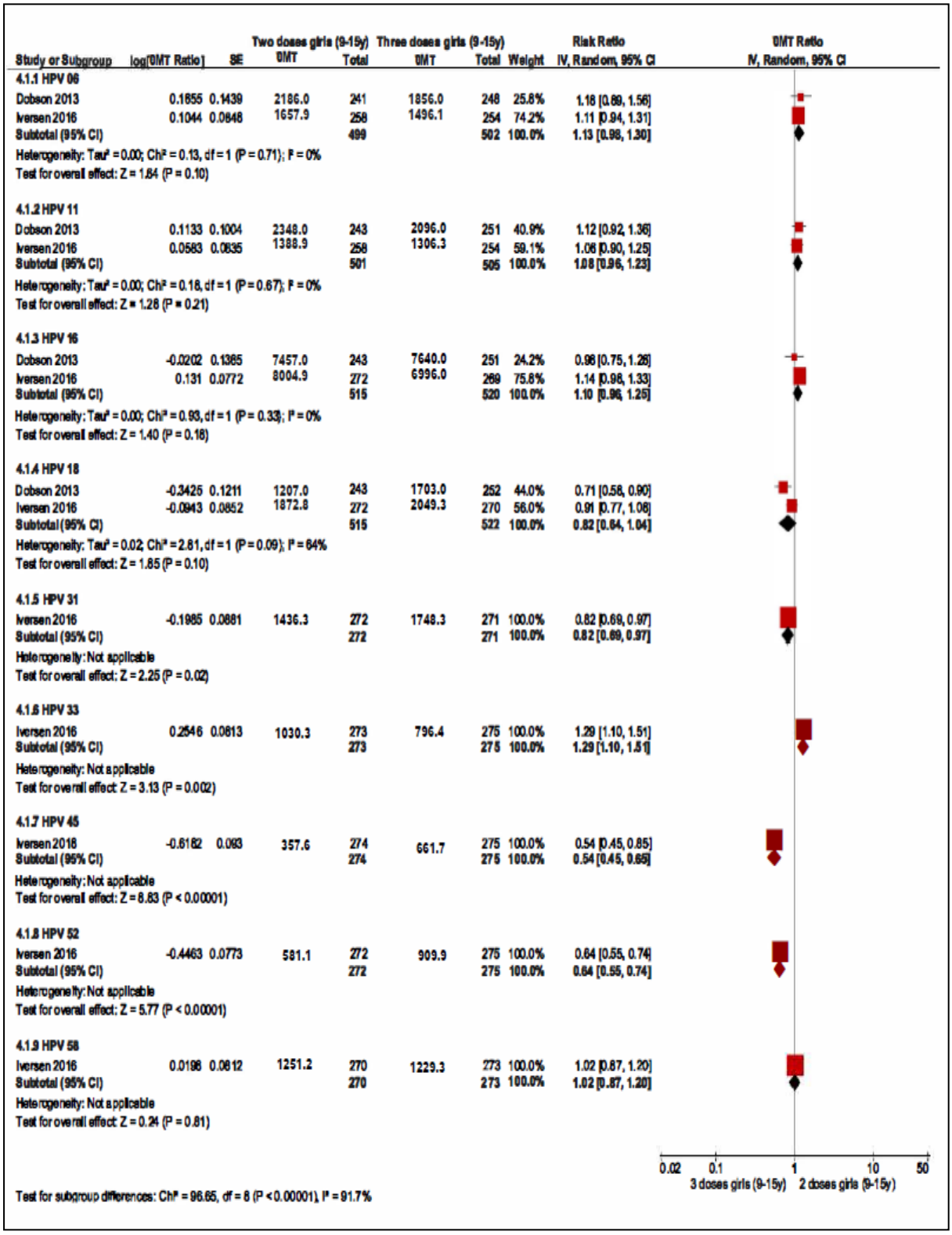


Figure 4.35 Estimate of effect on seropositivity rates comparing two-dose versus three-dose HPV vaccine schedules (females nine-14 years) at seven months (per-protocol population)

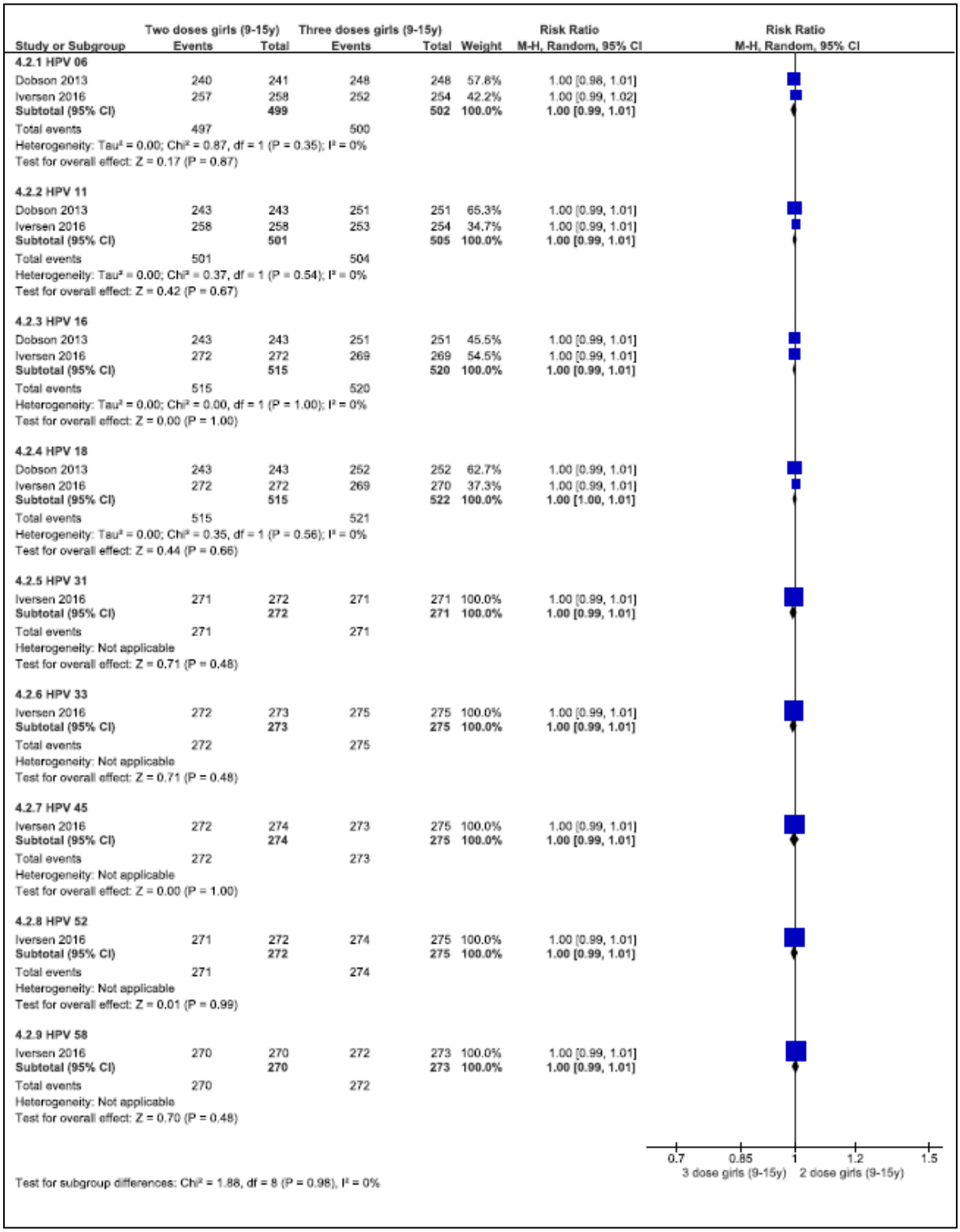


Figure 4.36 Estimate of effect on GMTs comparing two-dose versus three-dose HPV vaccine schedules (females nine-13 years) from seven to 36 months (per-protocol population)

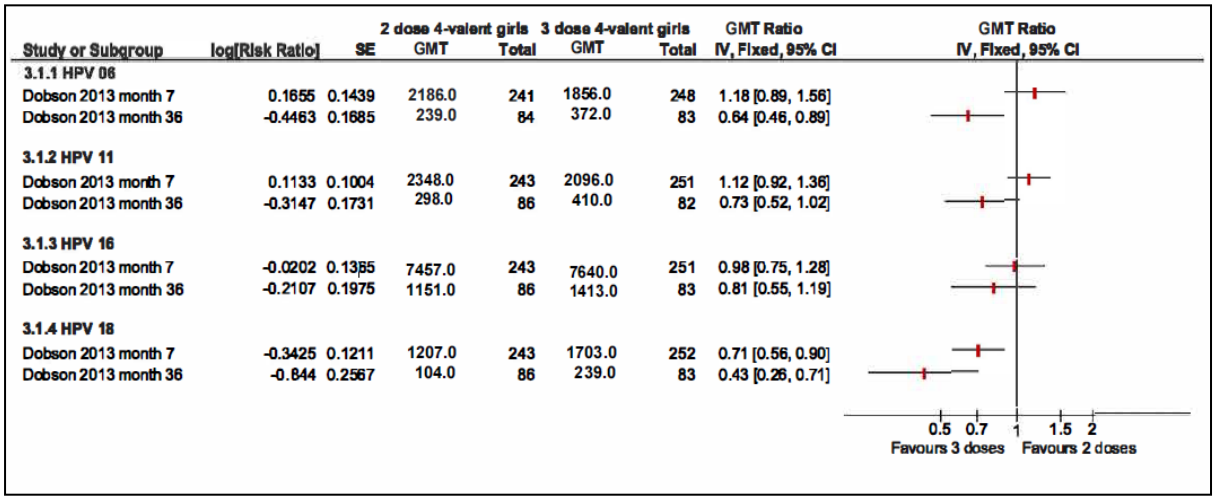
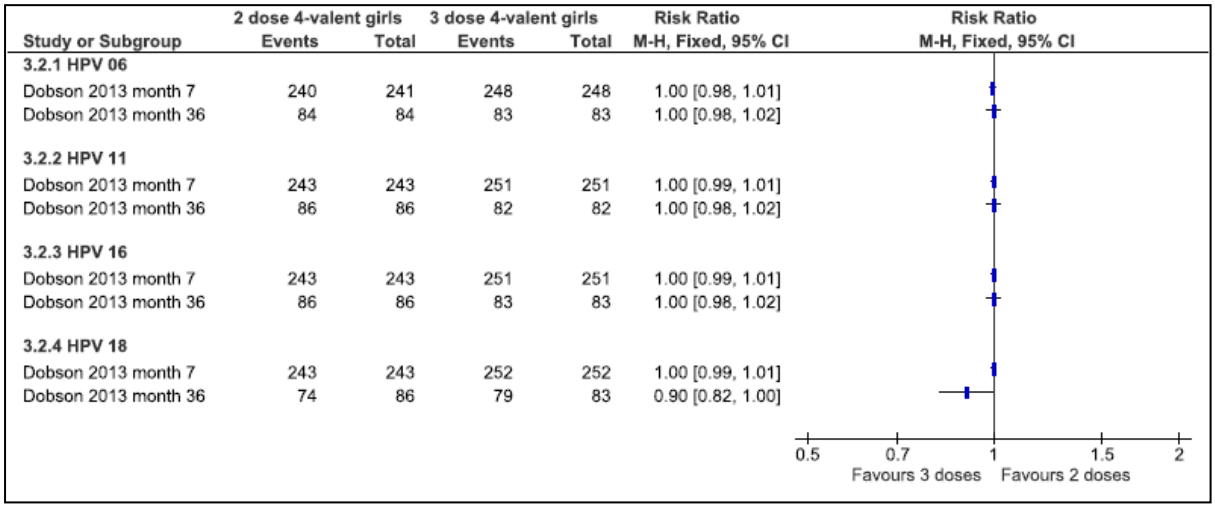


Figure 4.37 Estimate of effect on seropositivity rates comparing two-dose versus three-dose HPV vaccine schedules (females nine-13 years) from seven to 36 months (per-protocol population)



Appendix 4.4 Supplementary summary of findings tables

Table 4.33 Immunogenicity outcomes (GMTs and seropositivity rates) for 9-valent HPV vaccine compared to 4-valent HPV vaccine in 16 to 26 year old females at seven and 42 months

Outcomes		Absolute effects (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
		4-valent vaccine	9-valent vaccine			
GMTs - HPV 06	Huh 2017 month 7	875.2 mMU/mL (854.2 – 896.8)	893.1 mMU/mL (871.7 – 915.1)	GMT Ratio 1.02 (0.99 to 1.05)	7968 (1 RCT)[222]	⊕⊕⊕⊕ HIGH
	Huh 2017 month 42	144.3 mMU/mL (134.5 – 154.8)	147.2 mMU/mL (137.3 – 157.8)	GMT Ratio 1.02 (0.92 to 1.13)	1367 (1 RCT)[222])	⊕⊕⊕◯ MODERATE [a]
GMTs - HPV 11	Huh 2017 month 7	830.0 mMU/mL (809.2 – 851.4)	666.3 mMU/mL (649.6 – 683.4)	GMT Ratio 0.80 (0.77 to 0.83)	7977 (1 RCT)[222]	⊕⊕⊕⊕ HIGH
	Huh 2017 month 42	104.0 mMU/mL (96.7 – 111.9)	84.9 mMU/mL (79.0 – 91.3)	GMT Ratio 0.82 (0.74 to 0.91)	1373 (1 RCT)[222]	⊕⊕⊕◯ MODERATE [a]
GMTs - HPV 16	Huh 2017 month 7	3156.6 mMU/mL (3082.3 – 3232.7)	3131.1 mMU/mL (3057.1 – 3206.9)	GMT Ratio 0.99 (0.96 to 1.02)	8094 (1 RCT)[222]	⊕⊕⊕⊕ HIGH
	Huh 2017 month 42	362.9 mMU/mL (333.8 – 394.6)	346.8 mMU/mL (319.3 – 376.7)	GMT Ratio 0.96 (0.85 to 1.08)	1399 (1 RCT)[222]	⊕⊕⊕◯ MODERATE [a]
GMTs - HPV 18	Huh 2017 month 7	678.7 mMU/mL (660.2 – 697.7)	804.6 mMU/mL (782.7 – 827.1)	GMT Ratio 1.19 (1.14 to 1.24)	9080 (1 RCT)[222]	⊕⊕⊕⊕ HIGH
	Huh 2017 month 42	60.4 mMU/mL (55.2 – 66.1)	70.8 mMU/mL (64.8 – 77.3)	GMT Ratio 1.17 (1.03 to 1.33)	1576 (1 RCT)[222]	⊕⊕⊕◯ MODERATE [a]
GMTs - HPV 31	Huh 2017 month 7	9.7 mMU/mL (9.4 – 10.1)	658.4 mMU/mL (636.7 – 680.9)	GMT Ratio 67.88 (64.6 to 71.3)	8843 (1 RCT)[222]	⊕⊕⊕⊕ HIGH
	Huh 2017 month 42	<4 mMU/mL (<4 – <4)	70.4 mMU/mL (65.3 – 75.9)	Not estimable	1513 (1 RCT)[222]	⊕⊕⊕◯ MODERATE [a]
GMTs - HPV 33	Huh 2017 month 7	<4 mMU/mL (<4 – <4)	415.9 mMU/mL (405.6 – 426.4)	Not estimable	9393 (1 RCT)[222]	⊕⊕⊕⊕ HIGH
	Huh 2017 month 42	<4 mMU/mL (<4 – <4)	44.3 mMU/mL (41.6 – 47.1)	Not estimable	1624 (1 RCT)[222]	⊕⊕⊕◯ MODERATE [a]
GMTs - HPV 45	Huh 2017 month 7	<3 mMU/mL (<3 – <3)	252.8 mMU/mL (246.2 – 259.6)	Not estimable	9542 (1 RCT)[222]	⊕⊕⊕⊕ HIGH
	Huh 2017 month 42	<3 mMU/mL (<3 – <3)	21.1 mMU/mL (19.8 – 22.5)	Not estimable	1648 (1 RCT)[222]	⊕⊕⊕◯ MODERATE [a]

Outcomes		Absolute effects (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
		4-valent vaccine	9-valent vaccine			
GMTs - HPV 52	Huh 2017 month 7	<3 mMU/mL (<3 – <3)	379.7 mMU/mL (371.6 – 388.0)	Not estimable	8790 (1 RCT)[222]	⊕⊕⊕⊕ HIGH
	Huh 2017 month 42	<3 mMU/mL (<3 – <3)	43.2 mMU/mL (40.6 – 46.0)	Not estimable	1526 (1 RCT)[222]	⊕⊕⊕◯ MODERATE [a]
GMTs - HPV 58	Huh 2017 month 7	<4 mMU/mL (<4 – <4)	482.5 mMU/mL (469.9 – 495.3)	Not estimable	8932 (1 RCT)[222]	⊕⊕⊕⊕ HIGH
	Huh 2017 month 42	<4 mMU/mL (<4 – <4)	52.0 mMU/mL (48.7 – 55.6)	Not estimable	1540 (1 RCT)[222]	⊕⊕⊕◯ MODERATE [a]
Seropositivity - HPV 06	Huh 2017 month 7	3967/3975 (99.8%) (99.7 – 99.9%)	3985/3993 (99.8%) (99.6 – 99.9%)	RR 1.00 (1.00 to 1.00)	7968 (1 RCT)[222]	⊕⊕⊕⊕ HIGH
	Huh 2017 month 42	638/675 (94.5%) (92.5 – 96.1%)	664/692 (95.5%) (93.7 – 96.9%)	RR 1.02 (0.99 to 1.04)	1367 (1 RCT)[222]	⊕⊕⊕◯ MODERATE [a]
Seropositivity - HPV 11	Huh 2017 month 7	3978/3982 (99.9%) (99.8 – 100%)	3994/3995 (100%) (99.9 – 100%)	RR 1.00 (1.00 to 1.00)	7977 (1 RCT)[222]	⊕⊕⊕⊕ HIGH
	Huh 2017 month 42	655/677 (96.8%) (95.1 – 98.0%)	664/696 (95.4%) (93.6 – 96.8%)	RR 0.99 (0.97 to 1.01)	1373 (1 RCT)[222]	⊕⊕⊕◯ MODERATE [a]
Seropositivity - HPV 16	Huh 2017 month 7	4060/4062 (100%) (99.8 – 100%)	4031/4032 (100%) (99.9 – 100%)	RR 1.00 (1.00 to 1.00)	8094 (1 RCT)[222]	⊕⊕⊕⊕ HIGH
	Huh 2017 month 42	680/690 (98.6%) (97.4 – 99.3%)	698/709 (98.4%) (97.2 – 99.2%)	RR 1.00 (0.99 to 1.01)	1399 (1 RCT)[222]	⊕⊕⊕◯ MODERATE [a]
Seropositivity - HPV 18	Huh 2017 month 7	4528/4541 (99.7%) (99.5 – 99.8%)	4532/4539 (99.8%) (99.7 – 99.9%)	RR 1.00 (1.00 to 1.00)	9080 (1 RCT)[222]	⊕⊕⊕⊕ HIGH
	Huh 2017 month 42	593/770 (77.0%) (73.9 – 79.9%)	658/806 (81.6%) (78.8 – 84.3%)	RR 1.06 (1.01 to 1.12)	1576 (1 RCT)[222]	⊕⊕⊕◯ MODERATE [a]
Seropositivity - HPV 31	Huh 2017 month 7	2193/4377 (50.1%) (48.7 – 51.6%)	4457/4466 (99.8%) (99.6 – 99.9%)	RR 1.99 (1.93 to 2.05)	8843 (1 RCT)[222]	⊕⊕⊕⊕ HIGH
	Huh 2017 month 42	95/730 (13.0%) (10.7 – 15.7%)	733/783 (93.6%) (91.7 – 95.2%)	RR 7.19 (5.96 to 8.69)	1513 (1 RCT)[222]	⊕⊕⊕◯ MODERATE [a]
Seropositivity - HPV 33	Huh 2017 month 7	596/4691 (12.7%) (11.8 – 13.7%)	4688/4702 (99.7%) (99.5 – 99.9%)	RR 7.85 (7.28 to 8.46)	9393 (1 RCT)[222]	⊕⊕⊕⊕ HIGH
	Huh 2017 month 42	60/789 (7.6%) (5.9 – 9.7%)	790/835 (94.6%) (92.9 – 96.0%)	RR 12.44 (9.75 to 15.88)	1624 (1 RCT)[222]	⊕⊕⊕◯ MODERATE [a]

Outcomes		Absolute effects (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
		4-valent vaccine	9-valent vaccine			
Seropositivity - HPV 45	Huh 2017 month 7	437/4750 (9.2%) (8.4 – 10.0%)	4773/4792 (99.6%) (99.4 – 99.8%)	RR 10.83 (9.90 to 11.84)	9542 (1 RCT)[222]	⊕⊕⊕⊕ HIGH
	Huh 2017 month 42	10/802 (1.2%) (0.6 – 2.3%)	667/846 (78.8%) (75.9 – 81.5%)	RR 63.23 (34.12 to 117.18)	1648 (1 RCT)[222]	⊕⊕⊕◯ MODERATE [a]
Seropositivity - HPV 52	Huh 2017 month 7	113/4335 (2.6%) (2.2 – 3.1%)	4446/4455 (99.8%) (99.6 – 99.9%)	RR 38.29 (31.92 to 45.93)	8790 (1 RCT)[222]	⊕⊕⊕⊕ HIGH
	Huh 2017 month 42	41/735 (5.6%) (4.0 – 7.5%)	753/791 (95.2%) (93.5 – 96.6%)	RR 17.07 (12.67 to 22.99)	1526 (1 RCT)[222]	⊕⊕⊕◯ MODERATE [a]
Seropositivity - HPV 58	Huh 2017 month 7	907/4446 (20.4%) (19.2 – 21.6%)	4477/4486 (99.8%) (99.6 – 99.9%)	RR 4.89 (4.62 to 5.18)	8932 (1 RCT)[222]	⊕⊕⊕⊕ HIGH
	Huh 2017 month 42	42/756 (5.6%) (4.0 – 7.4%)	740/784 (94.4%) (92.5 – 95.9%)	RR 16.99 (12.66 to 22.81)	1540 (1 RCT)[222]	⊕⊕⊕◯ MODERATE [a]

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). [222] Huh 2017. a. Downgraded one level for risk of bias: high loss to follow up

Table 4.34 Immunogenicity outcomes (GMTs and seropositivity rates) for 9-valent HPV vaccine compared to 4-valent HPV vaccine in 9 to 15 year old females at seven months

Outcomes	*Absolute effects (95% CI)*		*Relative effect (95% CI)*	*№ of participants (studies)*	*Certainty of the evidence (GRADE)*
	4-valent vaccine	*9-valent vaccine*			
GMTs - HPV 06 Follow up: 7 months	1565.9 mMU/mL (1412.2 – 1736.3)	*1679.4 mMU/mL* *(1518.9 – 1856.9)*	RR 1.07 (0.93 to 1.23)	534 (1 RCT)[249]	⊕⊕⊕⊕ HIGH
GMTs - HPV 11 Follow up: 7 months	1417.3 mMU/mL (1274.2 – 1576.5)	*1315.6 mMU/mL* *(1183.8 – 1462.0)*	RR 0.93 (0.80 to 1.08)	534 (1 RCT)[249]	⊕⊕⊕⊕ HIGH
GMTs - HPV 16 Follow up: 7 months	6887.4 mMU/mL (6220.8 – 7625.5)	*6739.5 mMU/mL* *(6134.5 – 7404.1)*	RR 0.97 (0.85 to 1.11)	546 (1 RCT)[249]	⊕⊕⊕⊕ HIGH
GMTs - HPV 18 Follow up: 7 months	1795.6 mMU/mL (1567.2 – 2057.3)	*1956.6 mMU/mL* *(1737.3 – 2203.7)*	RR 1.08 (0.91 to 1.28)	545 (1 RCT)[249]	⊕⊕⊕⊕ HIGH
GMTs - HPV 31 Follow up: 7 months	22.2 mMU/mL (18.9 – 26.1)	*1770.4 mMU/mL* *(1585.7 – 1976.6)*	RR 79.75 (65.59 to 96.96)	544 (1 RCT)[249]	⊕⊕⊕⊕ HIGH
GMTs - HPV 33 Follow up: 7 months	4 mMU/mL (3.6 – 4.5)	*937.1 mMU/mL* *(845.3 – 1038.9)*	RR 234.28 (201.26 to 272.71)	544 (1 RCT)[249]	⊕⊕⊕◯ MODERATE [a]
GMTs - HPV 45 Follow up: 7 months	3.2 mMU/mL (2.8 – 3.6)	*622.4 mMU/mL* *(545.4 – 710.2)*	RR 194.49 (162.09 to 233.38)	546 (1 RCT)[249]	⊕⊕⊕◯ MODERATE [a]
GMTs - HPV 52 Follow up: 7 months	1.9 mMU/mL (1.8 – 2.1)	*927.3 mMU/mL* *(837.5 – 1026.9)*	RR 488.04 (429.50 to 554.57)	545 (1 RCT)[249]	⊕⊕⊕◯ MODERATE [a]
GMTs - HPV 58 Follow up: 7 months	9.4 mMU/mL (8.1 – 10.9)	*1348.8 mMU/mL* *(1218.3 – 1493.2)*	RR 143.49 (119.87 to 171.78)	528 (1 RCT)[249]	⊕⊕⊕⊕ HIGH
Seropositivity - HPV 06 Follow up: 7 months	261/261 (100%)	*273/273 (100%)*	RR 1.00 (0.99 to 1.01)	534 (1 RCT)[249]	⊕⊕⊕⊕ HIGH
Seropositivity - HPV 11 Follow up: 7 months	261/261 (100%)	*273/273 (100%)*	RR 1.00 (0.99 to 1.01)	534 (1 RCT)[249]	⊕⊕⊕⊕ HIGH
Seropositivity - HPV 16 Follow up: 7 months	270/270 (100%)	*276/276 (100%)*	RR 1.00 (0.99 to 1.01)	546 (1 RCT)[249]	⊕⊕⊕⊕ HIGH
Seropositivity - HPV 18 Follow up: 7 months	269/269 (100%)	*276/276 (100%)*	RR 1.00 (0.99 to 1.01)	545 (1 RCT)[249]	⊕⊕⊕⊕ HIGH

Outcomes	*Absolute effects (95% CI)*		*Relative effect (95% CI)*	*№ of participants (studies)*	*Certainty of the evidence (GRADE)*
	4-valent vaccine	*9-valent vaccine*			
Seropositivity - HPV 31 Follow up: 7 months	197/268 (73.5%)	*276/276 (100%)*	RR 1.36 (1.27 to 1.46)	544 (1 RCT)[249]	⊕⊕⊕⊕ HIGH
Seropositivity - HPV 33 Follow up: 7 months	Not reported	*275/275 (100%)*	Not estimable	275 (1 RCT)[249]	⊕⊕⊕◯ MODERATE [a]
Seropositivity - HPV 45 Follow up: 7 months	Not reported	*274/275 (99.6%)*	Not estimable	275 (1 RCT)[249]	⊕⊕⊕◯ MODERATE [a]
Seropositivity - HPV 52 Follow up: 7 months	Not reported	*276/276 (100%)*	Not estimable	276 (1 RCT)[249]	⊕⊕⊕◯ MODERATE [a]
Seropositivity - HPV 58 Follow up: 7 months	143/261 (54.8%)	*267/267 (100%)*	RR 1.82 (1.63 to 2.03)	528 (1 RCT)[249]	⊕⊕⊕⊕ HIGH

**The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).* [249] Vesikari 2015 a. Downgraded one level for risk of bias: selective reporting of results. The paper did not report the complete set of seropositivity rates for non-vaccine HPV types of the 4-valent vaccine, i.e. no results provided for HPV 33/45/52 and only text results provided for HPV 31 and 58.

Table 4.35 Immunogenicity outcomes (GMTs and seropositivity rates) for 9-valent HPV vaccine compared to 4-valent HPV vaccine in 16 to 26 year old males at seven months

Outcomes	Absolute effects (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
	4-valent vaccine	9-valent vaccine			
GMTs - HPV 06 Follow up: 7 months	618.4 mMU/mL (554.0 – 690.3)	758.3 mMU/mL (665.9 – 863.4)	GMT Ratio 1.23 (1.04 to 1.45)	454 (1 RCT)[248]	⨁⨁⨁⨁ HIGH
GMTs - HPV 11 Follow up: 7 months	769.1 mMU/mL (683.5 – 865.3)	681.7 mMU/mL (608.9 – 763.4)	GMT Ratio 0.89 (0.76 to 1.04)	454 (1 RCT)[248]	⨁⨁⨁⨁ HIGH
GMTs - HPV 16 Follow up: 7 months	3787.9 mMU/mL (3378.4 – 4247.0)	3924.1 mMU/mL (3513.8 – 4382.3)	GMT Ratio 1.04 (0.89 to 1.21)	471 (1 RCT)[248]	⨁⨁⨁⨁ HIGH
GMTs - HPV 18 Follow up: 7 months	790.9 mMU/mL (683.0 – 915.7)	884.3 mMU/mL (766.4 – 1020.4)	GMT Ratio 1.12 (0.91 to 1.37)	470 (1 RCT)[248]	⨁⨁⨁⨁ HIGH
GMTs - HPV 31 Follow up: 7 months	14.8 mMU/mL (12.5 – 17.5)	794.4 mMU/mL (694.2 – 909.2)	GMT Ratio 53.67 (42.69 to 67.48)	471 (1 RCT)[248]	⨁⨁⨁⨁ HIGH
GMTs - HPV 33 Follow up: 7 months	3.4 mMU/mL (3.1 – 3.7)	460.5 mMU/mL (410.6 – 516.4)	GMT Ratio 135.44 (117.17 to 156.54)	472 (1 RCT)[248]	⨁⨁⨁⨁ HIGH
GMTs - HPV 45 Follow up: 7 months	2.5 mMU/mL (2.3 – 2.8)	262.9 mMU/mL (226.2 – 305.5)	GMT Ratio 105.16 (87.88 to 125.84)	468 (1 RCT)[248]	⨁⨁⨁⨁ HIGH
GMTs - HPV 52 Follow up: 7 months	1.9 mMU/mL (1.8 – 2.1)	430.7 mMU/mL (377.8 – 491.0)	GMT Ratio 226.67 (194.69 to 263.91)	471 (1 RCT)[248]	⨁⨁⨁⨁ HIGH
GMTs - HV 58 follow up: 7 months	5.7 mMU/mL (5.0 – 6.5)	691.0 mMU/mL (614.9 – 776.5)	GMT Ratio 121.23 (101.71 to 144.50)	465 (1 RCT)[248]	⨁⨁⨁⨁ HIGH
Seropositivity - HPV 06 Follow up: 7 months	223/226 (98.7%) (96.2 – 99.7%)	224/228 (98.2%) (95.6 – 99.5%)	RR 1.00 (0.97 to 1.02)	454 (1 RCT)[248]	⨁⨁⨁⨁ HIGH
Seropositivity - HPV 11 Follow up: 7 months	226/226 (100%) (98.4 – 100%)	228/228 (100%) (98.4 – 100%)	RR 1.00 (0.99 to 1.01)	454 (1 RCT)[248]	⨁⨁⨁⨁ HIGH
Seropositivity - HPV 16 Follow up: 7 months	237/237 (100%) (98.5 – 100%)	234/234 (100%) (98.4 – 100%)	RR 1.00 (0.99 to 1.01)	471 (1 RCT)[248]	⨁⨁⨁⨁ HIGH
Seropositivity - HPV 18 Follow up: 7 months	235/236 (99.6%) (97.7 – 100%)	233/234 (99.6%) (97.6 – 100%)	RR 1.00 (0.99 to 1.01)	470 (1 RCT)[248]	⨁⨁⨁⨁ HIGH
Seropositivity - HPV 31 Follow up: 7 months	146/237 (61.6%) (55.1 – 67.8%)	234/234 (100%) (98.4 – 100%)	RR 1.62 (1.47 to 1.79)	471 (1 RCT)[248]	⨁⨁⨁⨁ HIGH

Outcomes	Absolute effects (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
	4-valent vaccine	9-valent vaccine			
Seropositivity - HPV 33 Follow up: 7 months	40/236 (16.9%) (12.4 – 22.4%)	236/236 (100%) (98.4 – 100%)	RR 5.84 (4.41 to 7.73)	472 (1 RCT)[248]	⊕⊕⊕⊕ HIGH
Seropositivity - HPV 45 Follow up: 7 months	22/236 (9.3%) (5.9 – 13.8%)	232/232 (100%) (98.4 – 100%)	RR 10.51 (7.09 to 15.57)	468 (1 RCT)[248]	⊕⊕⊕⊕ HIGH
Seropositivity - HPV 52 Follow up: 7 months	6/236 (2.5%) (0.9 – 5.5%)	235/235 (100%) (98.4 – 100%)	RR 36.38 (17.05 to 77.66)	471 (1 RCT)[248]	⊕⊕⊕⊕ HIGH
Seropositivity - HPV 58 Follow f up: 7 months	84/233 (36.1%) (29.9 – 42.6%)	232/232 (100%) (98.4 – 100%)	RR 2.76 (2.33 to 3.28)	465 (1 RCT)[248]	⊕⊕⊕⊕ HIGH

The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect of the intervention (and its 95% CI).* [248] Van Damme 2016

Table 4.36 Immunogenicity outcomes for the 4-valent HPV vaccine in nine to 15 year old males compared to nine to 15 year old females to seven, 18 and 96 months

Outcomes		Absolute effects (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
		9 to 15 year old females	9 to 15 year old males			
GMTs - HPV 6	Ferris 2014 month 7	893.9 mMU/mL (818.7 – 976.0)	962.7 mMU/mL (874.2 – 1060.1)	GMT Ratio 1.08 (0.95 to 1.23)	957 (1 RCT)[219]	⨁◯◯◯ VERY LOW [b, d, e]
	Ferris 2014 month 96	77.7 mMU/mL (67.9 – 89.0)	63.2 mMU/mL (53.9 – 74.0)	GMT Ratio 0.81 (0.66 to 1.00)	439 (1 RCT)[219]	⨁◯◯◯ VERY LOW [d, e]
GMTs - HPV 11	Ferris 2014 month 7	1356.8 mMU/mL (1245.1 – 1478.6)	1370.8 mMU/mL (1249.6 – 1503.8)	GMT Ratio 1.01 (0.89 to 1.15)	958 (1 RCT)[219]	⨁◯◯◯ VERY LOW [b, d, e]
	Ferris 2014 month 96	72.7 mMU/mL (61.8 – 85.5)	61.7 mMU/mL (51.6 – 73.8)	GMT Ratio 0.85 (0.67 to 1.08)	439 (1 RCT)[219]	⨁◯◯◯ VERY LOW [d, e]
GMTs - HPV 16	Ferris 2014 month 7	4992.2 mMU/mL (4501.9 – 5535.9)	6091.0 mMU/mL (5447.0 – 6811.0)	GMT Ratio 1.22 (1.05 to 1.42)	953 (1 RCT)[219]	⨁◯◯◯ VERY LOW [b, e]
	Ferris 2014 month 96	353.0 mMU/mL (303.1 – 411.0)	293.6 mMU/mL (240.5 – 358.4)	GMT Ratio 0.83 (0.65 to 1.06)	436 (1 RCT)[219]	⨁◯◯◯ VERY LOW [d, e]
GMTs - HPV 18	Ferris 2014 month 7	1130.8 mMU/mL (1018.3 – 1255.7)	1470.7 mMU/mL (1311.2 – 1649.5)	GMT Ratio 1.30 (1.11 to 1.52)	961 (1 RCT)[219]	⨁◯◯◯ VERY LOW [b, e]
	Ferris 2014 month 96	41.8 mMU/mL (35.0 – 49.9)	42.8 mMU/mL (34.5 – 53.2)	GMT Ratio 1.02 (0.77 to 1.35)	440 (1 RCT)[219]	⨁◯◯◯ VERY LOW [d, e]
Seropositivity - HPV 06	Reisinger 2007 month 7	491/492 (99.8%)	455/456 (99.8%)	RR 1.00 (0.99 to 1.01)	948 (1 RCT)[246]	⨁⨁⨁◯ MODERATE [a]
	Reisinger 2007 month 18	471/481 (97.9%)	439/449 (97.8%)	RR 1.00 (0.98 to 1.02)	930 (1 RCT)[246]	⨁⨁⨁◯ MODERATE [a]
Seropositivity - HPV 11	Reisinger 2007 month 7	491/492 (99.8%)	456/457 (99.8%)	RR 1.00 (0.99 to 1.01)	949 (1 RCT)[246]	⨁⨁⨁◯ MODERATE [a]
	Reisinger 2007 month 18	477/481(99.2%)	447/450 (99.3%)	RR 1.00 (0.99 to 1.01)	931 (1 RCT)[246]	⨁⨁⨁◯ MODERATE [a]
Seropositivity - HPV 16	Reisinger 2007 month 7	488/489 (99.8%)	453/455 (99.5%)	RR 1.00 (0.99 to 1.00)	944 (1 RCT)[246]	⨁⨁⨁◯ MODERATE [a]
	Reisinger 2007 month 18	477/478 (99.8%)	445/448 (99.3%)	RR 1.00 (0.99 to 1.00)	926 (1 RCT)[246]	⨁⨁⨁◯ MODERATE [a]

Outcomes		Absolute effects (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
		9 to 15 year old females	9 to 15 year old males			
Seropositivity - HPV 18	Reisinger 2007 month 7	442/483 (91.5%)	417/451 (92.5%)	RR 1.01 (0.97 to 1.05)	934 (1 RCT)[246]	⊕⊕⊕◯ MODERATE [a]
	Reisinger 2007 month 18	492/494 (99.6%)	457/458 (99.8%)	RR 1.00 (0.99 to1.01)	952 (1 RCT)[246]	⊕⊕⊕◯ MODERATE [a]

The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect of the intervention (and its 95% CI).* [219] Ferris 2014, [246] Reisinger 2007. a. Downgraded one level for risk of bias: non-randomised comparison. b. Downgraded one level for inconsistency: heterogeneity between the studies at 7 months c. Downgraded one level for imprecision: very small sample size d. Downgraded one level for imprecision: the 95% CI overlaps line of no effect e. Downgraded two levels for risk of bias: non-randomised comparison with cross-over of placebo group to catch up vaccination group; suspected reporting bias in presentation of results and high loss to follow up at later timepoint (attrition bias).

Table 4.37 Immunogenicity outcomes for the 9-valent HPV vaccine in nine to 15 year old males compared to nine to 15 year old females at seven and 36 months

Outcomes		Absolute effects (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
		9 to 15 year old females	9 to 15 year old males			
GMTs - HPV 06	Van Damme 2015 month 7	1712.0 mMU/mL (1638.9–1788.4)	2084.7 mMU/mL (1940.9 – 2239.2)	GMT Ratio 1.22 (1.12 to 1.33)	2156 (1 RCT)[247]	⨁⨁◯◯ LOW [a]
	Van Damme 2015 month 36	252.8 mMU/mL (232.1 – 275.3)	262.7 mMU/mL (241.4 – 285.8)	GMT Ratio 1.04 (1.92 to 1.18)	864 (1 RCT)[247]	⨁⨁◯◯ LOW [a]
GMTs - HPV 11	Van Damme 2015 month 7	1278.7 mMU/mL (1223.1–1336.8)	1487.1 mMU/mL (1385.0 – 1596.7)	GMT Ratio 1.16 (1.07 to 1.26)	2156 (1 RCT)[247]	⨁⨁◯◯ LOW [a]
	Van Damme 2015 month 36	145.8 mMU/mL (132.6 – 160.2)	156.6 mMU/mL (142.4 – 172.1)	GMT Ratio 1.07 (0..94 to 1.22)	874 (1 RCT)[247]	⨁◯◯◯ VERY LOW [a,b]
GMTs - HPV 16	Van Damme 2015 month 7	7071.6 mMU/mL (6776.1–7380.1)	8628.9 mMU/mL (8077.5 – 9218.0)	GMT Ratio 1.22 (1.13 to 1.32)	2196 (1 RCT)[247]	⨁⨁◯◯ LOW [a]
	Van Damme 2015 month 36	857.4 mMU/mL (779.8 – 942.8)	944.1 mMU/mL (856.4 – 1040.8)	GMT Ratio 1.10 (0.96 to 1.26)	888 (1 RCT)[247]	⨁◯◯◯ VERY LOW [a,b]
GMTs - HPV 18	Van Damme 2015 month 7	2081.2 mMU/mL (1978.8–2188.9)	2822.8 mMU/mL (2609.0 – 3054.2)	GMT Ratio 1.36 (1.24 to 1.49)	2208 (1 RCT)[247]	⨁⨁◯◯ LOW [a]
	Van Damme 2015 month 36	167.8 mMU/mL (149.5 – 188.3)	244.2 mMU/mL (219.1 – 272.2)	GMT Ratio 1.46 1.24 to 1.72)	888 (1 RCT)[247]	⨁⨁◯◯ LOW [a,b]
GMTs - HPV 31	Van Damme 2015 month 7	1879.3 mMU/mL (1791.3–1971.6)	2221.2 mMU/mL (2056.4 – 2399.1)	GMT Ratio 1.18 (1.08 to 1.29)	2181 (1 RCT)[247]	⨁⨁◯◯ LOW [a]
	Van Damme 2015 month 36	216.6 mMU/mL (194.0 – 241.8)	246.3 mMU/mL (221.4 – 274.1)	GMT Ratio 1.14 (0.98 to 1.33)	881 (1 RCT)[247]	⨁◯◯◯ VERY LOW [a,b]
GMTs - HPV 33	Van Damme 2015 month 7	944.1 mMU/mL (904.3–985.7)	1198.7 mMU/mL (1117.3 – 1285.9)	GMT Ratio 1.27 (1.17 to 1.38)	2204 (1 RCT)[247]	⨁⨁◯◯ LOW [a]
	Van Damme 2015 month 36	94.1 mMU/mL (84.9 – 104.2)	120.8 mMU/mL (109.3 – 133.6)	GMT Ratio 1.28 (1.11 to 1.48)	883 (1 RCT)[247]	⨁⨁◯◯ LOW [a,b]
GMTs - HPV 45	Van Damme 2015 month 7	737.1 mMU/mL (698.4–777.8)	907.0 mMU/mL (830.0 – 991.2)	GMT Ratio 1.23 (1.11 to 1.38)	2217 (1 RCT)[247]	⨁⨁◯◯ LOW [a]
	Van Damme 2015 month 36	64.7 mMU/mL (57.1 – 73.4)	76.7 mMU/mL (67.4 – 87.1)	GMT Ratio 1.19 (0.99 – 1.43)	892 (1 RCT)[247]	⨁◯◯◯ VERY LOW [a,b]

Outcomes		Absolute effects (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
		9 to 15 year old females	9 to 15 year old males			
GMTs - HPV 52	Van Damme 2015 month 7	970.5 mMU/mL (927.1–1016.0)	1037.8 mMU/mL (962.9 – 1118.6)	GMT Ratio 1.07 (0.98 to 1.17)	2210 (1 RCT)[247]	⊕◯◯◯ VERY LOW [a,b]
	Van Damme 2015 month 36	109.6 mMU/mL (99.7 – 120.4)	104.9 mMU/mL (94.9 – 115.8)	GMT Ratio 0.96 (0.83 to 1.11)	891 (1 RCT)[247]	⊕◯◯◯ VERY LOW [a,b]
GMTs - HPV 58	Van Damme 2015 month 7	1277.7 mMU/mL (1222.0–1336.0)	1567.7 mMU/mL (1461.2 – 1682.0)	GMT Ratio 1.23 (1.13 to 1.34)	2196 (1 RCT)[247]	⊕⊕◯◯ LOW [a]
	Van Damme 2015 month 36	147.4 mMU/mL (133.0 – 163.2)	170.9 mMU/mL (154.5 – 189.0)	GMT Ratio 1.16 (1.00 to 1.35)	887 (1 RCT)[247]	⊕◯◯◯ VERY LOW [a,b]
Seropositivity - HPV 06	Van Damme 2015 month 7	1591/1597 (99.6%) (99.2 – 99.9)	558/559 (99.8%) (99.0 – 100)	RR 1.00 (1.00 to 1.01)	2156 (1 RCT)[247]	⊕⊕◯◯ LOW [a]
	Van Damme 2015 month 36	401/407 (98.5%) (96.8 – 99.5)	451/457 (98.7%) (97.2 – 99.5)	RR 1.00 (0.99 to 1.02)	864 (1 RCT)[247]	⊕⊕◯◯ LOW [a]
Seropositivity - HPV 11	Van Damme 2015 month 7	1595/1597 (99.9%) (99.5 – 100)	559/559 (100%) (99.3 – 100)	RR 1.00 (1.00 to 1.00)	2156 (1 RCT)[247]	⊕⊕◯◯ LOW [a]
	Van Damme 2015 month 36	408/411 (99.3%) (97.9 – 99.8)	455/463 (98.3%) (96.6 – 99.3)	RR 0.99 (0.98 to 1.00)	874 (1 RCT)[247]	⊕⊕◯◯ LOW [a]
Seropositivity - HPV 16	Van Damme 2015 month 7	1625/1627 (99.9%) (99.6 – 100)	569/569 (100%) (99.4 – 100)	RR 1.00 (1.00 to 1.00)	2196 (1 RCT)[247]	⊕⊕◯◯ LOW [a]
	Van Damme 2015 month 36	415/416 (99.8%) (98.7 – 100)	470/472 (99.6%) (98.5 – 99.9)	RR 1.00 (0.99 to 1.01)	888 (1 RCT)[247]	⊕⊕◯◯ LOW [a]
Seropositivity - HPV 18	Van Damme 2015 month 7	1638/1641 (99.8%) (99.5 – 100)	567/567 (100%) (99.4 – 100)	RR 1.00 (1.00 to 1.00)	2208 (1 RCT)[247]	⊕⊕◯◯ LOW [a]
	Van Damme 2015 month 36	395/418 (94.5%) (91.9 – 96.5)	454/470 (96.6%) (94.5 – 98.0)	RR 1.02 (0.99 to 1.05)	888 (1 RCT)[247]	⊕⊕◯◯ LOW [a]
Seropositivity - HPV 31	Van Damme 2015 month 7	1615/1617 (99.9%) (99.7 – 100)	564/564 (100%) (99.3 – 100)	RR 1.00 (1.00 to 1.00)	2181 (1 RCT)[247]	⊕⊕◯◯ LOW [a]
	Van Damme 2015 month 36	411/414 (99.3%) (97.9 – 99.9)	460/467 (98.5%) (96.9 – 99.4)	RR 0.99 (0.98 to 1.01)	881 (1 RCT)[247]	⊕⊕◯◯ LOW [a]
Seropositivity - HPV 33	Van Damme 2015 month 7	1635/1637 (99.9%) (99.6 – 100)	567/567 (100%) (99.4 – 100)	RR 1.00 (1.00 to 1.00)	2204 (1 RCT)[247]	⊕⊕◯◯ LOW [a]
	Van Damme 2015 month 36	406/412 (98.5%) (96.9 – 99.5)	465/471 (98.7%) (97.2 – 99.5)	RR 1.00 (0.99 to 1.02)	883 (1 RCT)[247]	⊕⊕◯◯ LOW [a]

Outcomes		Absolute effects (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
		9 to 15 year old females	9 to 15 year old males			
Seropositivity - HPV 45	Van Damme 2015 month 7	1644/1647 (99.8%) (99.5 – 100)	570/570 (100%) (99.4 – 100)	RR 1.00 (1.00 to 1.00)	2217 (1 RCT)[247]	⨁⨁◯◯ LOW [a]
	Van Damme 2015 month 36	393/419 (93.8%) (91.0 – 95.9)	440/473 (93.0%) (90.3 – 95.1)	RR 0.99 (0.96 to 1.03)	892 (1 RCT)[247]	⨁⨁◯◯ LOW [a]
Seropositivity - HPV 52	Van Damme 2015 month 7	1640/1642 (99.9%) (99.6 – 100)	568/568 (100%) (99.4 – 100)	RR 1.00 (1.00 to 1.00)	2210 (1 RCT)[247]	⨁⨁◯◯ LOW [a]
	Van Damme 2015 month 36	415/419 (99.0%) (97.6 – 99.7)	462/472 (97.9%) (96.1 – 99.0)	RR 0.99 (0.97 to 1.00)	891 (1 RCT)[247]	⨁⨁◯◯ LOW [a]
Seropositivity - HPV 58	Van Damme 2015 month 7	1628/1630 (99.9%) (99.6 – 100)	566/566 (100%) (99.4 – 100)	RR 1.00 (1.00 to 1.00)	2196 (1 RCT)[247]	⨁⨁◯◯ LOW [a]
	Van Damme 2015 month 36	413/417 (99.0%) (97.6 – 99.7)	466/470 (99.1%) (97.8 – 99.8)	RR 1.00 (0.99 to 1.01)	887 (1 RCT)[247]	⨁⨁◯◯ LOW [a]

**The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).* [247] Van Damme 2015. a. Downgraded two levels for risk of bias: non-randomised comparison with allocation concealment for girls only. Unblinded participants and staff for the immunogenicity study. Difference in approach to populations selected for reporting immunogenicity outcome vs. antibody persistence (selection, performance, detection and reporting bias). Also: High loss to follow up (attrition bias). b. Downgraded one level for imprecision: the 95% CI overlaps line of no effect

Table 4.38 Immunogenicity comparison of 2 doses of the 4-valent HPV vaccine in younger females (9 to 13 year old) versus 3 doses of the 4-valent HPV vaccine in older females (15 to 26 year old) at multiple timepoints

Outcomes		Absolute effects (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
		Older (15 to 26 year old) females	Younger (9 to 13 year old) females			
GMTs - HPV 06	Dobson 2013 month 7	938 mMU/mL (796 – 1105)	2186 mMU/mL (1846 – 2588)	GMT Ratio 2.33 (1.76 to 3.09)	497 (1 RCT)[218]	⨁◯◯◯ VERY LOW [a, b]
	Dobson 2013 month 36	176 mMU/mL (145 – 213)	239 mMU/mL (195 – 292)	GMT Ratio 1.36 (0.97 to 1.90)	176 (1 RCT)[218]	⨁◯◯◯ VERY LOW [a, b, c, d, e]
	Hernandez-Avila 2016 month 7	387.3 mMU/mL (305.4 – 491.2)	306.2 mMU/mL (228.3 – 410.7)	GMT Ratio 0.79 (0.54 to 1.15)	278 (1 RCT [221])	⨁◯◯◯ VERY LOW [a, b, e]
	Hernandez-Avila 2016 month 21	74.4 mMU/mL (63.3 – 87.3)	95.6 mMU/mL (81.0 – 112.8)	GMT Ratio 1.29 (1.02 – 1.62)	256 (1 RCT [221])	⨁◯◯◯ VERY LOW [a, b]

Outcomes		Absolute effects (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
		Older (15 to 26 year old) females	Younger (9 to 13 year old) females			
GMTs - HPV 11	Dobson 2013 month 7	1277 mMU/mL (1144 – 1427)	2348 mMU/mL (2090 – 2638)	GMT Ratio 1.84 (1.52 to 2.23)	512 (1 RCT)[218]	⨁⨁◯◯ LOW [a]
	Dobson 2013 month 36	208 mMU/mL (172 – 251)	298 mMU/mL (244 – 364)	GMT Ratio 1.43 (1.03 to 1.99)	183 (1 RCT)[218]	⨁◯◯◯ VERY LOW [a, c, d]
	Hernandez-Avila 2016 month 7	629.9 mMU/mL (540.4 – 734.2	968.3 mMU/mL (800.1 – 1171.9)	GMT Ratio 1.54 (1.20 to 1.96)	285 (1 RCT [221])	⨁⨁◯◯ LOW [a]
	Hernandez-Avila 2016 month 21	85.8 mMU/mL (73.9 – 99.6)	130.2 mMU/mL (109.3 – 155.0)	GMT Ratio 1.52 (1.21 – 1.91)	269 (1 RCT [221])	⨁⨁◯◯ LOW [a]
GMTs - HPV 16	Dobson 2013 month 7	3574 mMU/mL (3065 – 4169)	7457 mMU/mL (6388 – 8704)	GMT Ratio 2.09 (1.61 to 2.71)	489 (1 RCT)[218]	⨁⨁◯◯ LOW [a]
	Dobson 2013 month 36	678 mMU/mL (540 – 850)	1151 mMU/mL (918 – 1444)	GMT Ratio 1.70 (1.16 to 2.49)	172 (1 RCT)[218]	⨁◯◯◯ VERY LOW [a, c, d]
	Hernandez-Avila 2016 month 7	2408.8 mMU/mL (2003.5 – 2896.1)	5136.7 mMU/mL (4035.8 – 6538.0)	GMT Ratio 2.13 (1.58 to 2.89)	286 (1 RCT [221])	⨁⨁◯◯ LOW [a]
	Hernandez-Avila 2016 month 21	276.2 mMU/mL (226.0 – 337.7)	412.8 mMU/mL (338.1 – 504.1)	GMT Ratio 1.49 (1.12 to 1.98)	274 (1 RCT [221])	⨁⨁◯◯ LOW [a]
GMTs - HPV 18	Dobson 2013 month 7	661 mMU/mL (580 – 754)	1207 mMU/mL (1054 – 1384)	GMT Ratio 1.83 (1.46 to 2.29)	507 (1 RCT)[218]	⨁⨁◯◯ LOW [a]
	Dobson 2013 month 36	71 mMU/mL (53 – 95)	104 mMU/mL (77 – 141)	GMT Ratio 1.46 (0.88 to 2.41)	182 (1 RCT)[218]	⨁◯◯◯ VERY LOW [a, b, c, d]
	Hernandez-Avila 2016 month 7	343.7 mMU/mL (291.9 – 404.7)	605.0 mMU/mL (503.2 – 727.4)	GMT Ratio 1.76 (1.38 to 2.25)	286 (1 RCT [221])	⨁⨁◯◯ LOW [a]
	Hernandez-Avila 2016 month 21	73.9 mMU/mL (61.3 – 89.1)	93.8 mMU/mL (76.4 – 115.3)	GMT Ratio 1.27 (0.96 to 1.67)	176 (1 RCT [221])	⨁◯◯◯ VERY LOW [a, e]
Seropositivity - HPV 06	Dobson 2013 month 7	255/256 (>99%)	240/241 (>99%)	RR 1.00 (0.99 to 1.01)	497 (1 RCT)[218]	⨁⨁◯◯ LOW [a]
	Dobson 2013 month 36	92/92 (100%)	84/84 (100%)	RR 1.00 (0.98 to 1.02)	176 (1 RCT)[218]	⨁◯◯◯ VERY LOW [a, c, d]
	Hernandez-Avila 2016 month 7	137/141 (97.1%)	141/145 (97.2%)	RR 1.00 (0.96 to 1.04)	286 (1 RCT [221])	⨁⨁◯◯ LOW [a]

Outcomes		Absolute effects (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
		Older (15 to 26 year old) females	Younger (9 to 13 year old) females			
	Hernandez-Avila 2016 month 21	121/136 (89%)	135/141 (95.7%)	RR 1.08 (1.00 to 1.15)	277 (1 RCT [221])	⊕⊕◯◯ LOW [a]
Seropositivity - HPV 11	Dobson 2013 month 7	269/269 (100%)	243/243 (100%)	RR 1.00 (0.99 to 1.01)	512 (1 RCT)[218]	⊕⊕◯◯ LOW [a]
	Dobson 2013 month 36	97/97 (100%)	86/86 (100%)	RR 1.00 (0.98 to 1.02)	183 (1 RCT)[218]	⊕◯◯◯ VERY LOW [a, c, d]
	Hernandez-Avila 2016 month 7	141/141 (100%)	144/145 (99.3%)	RR 0.99 (0.97 to 1.01)	286 (1 RCT [221])	⊕⊕◯◯ LOW [a]
	Hernandez-Avila 2016 month 21	132/136 (97.1%)	137/141 (97.2%)	RR 1.00 (0.96 to 1.04)	277 (1 RCT [221])	⊕⊕◯◯ LOW [a]
Seropositivity - HPV 16	Dobson 2013 month 7	246/246 (100%)	243/243 (100%)	RR 1.00 (0.99 to 1.01)	489 (1 RCT)[218]	⊕⊕◯◯ LOW [a]
	Dobson 2013 month 36	86/86 (100%)	86/86 (100%)	RR 1.00 (0.98 to 1.02)	172 (1 RCT)[218]	⊕◯◯◯ VERY LOW [a, c, d]
	Hernandez-Avila 2016 month 7	141/141 (100%)	145/145 (100%)	RR 1.00 (0.99 to 1.01)	286 (1 RCT [221])	⊕⊕◯◯ LOW [a]
	Hernandez-Avila 2016 month 21	134/136 (98.5%)	140/141 (99.3%)	RR 1.01 (0.98 to 1.03)	277 (1 RCT [221])	⊕⊕◯◯ LOW [a]
Seropositivity - HPV 18	Dobson 2013 month 7	264/264 (100%)	243/243 (100%)	RR 1.00 (0.99 to 1.01)	507 (1 RCT)[218]	⊕⊕◯◯ LOW [a]
	Dobson 2013 month 36	76/96 (79%)	74/86 (86%)	RR 1.09 (0.95 to 1.24)	182 (1 RCT)[218]	⊕◯◯◯ VERY LOW [a, c, d]
	Hernandez-Avila 2016 month 7	141/141 (100%)	145/145 (100%)	RR 1.00 (0.99 to 1.01)	286 (1 RCT)[221]	⊕⊕◯◯ LOW [a]
	Hernandez-Avila 2016 month 21	77/136 (56.6%)	99/141 (70.2%)	RR 1.24 (1.03 to 1.49)	277 (1 RCT)[221]	⊕⊕◯◯ LOW [a]

The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect of the intervention (and its 95% CI).* [218] Dobson 2013, [221] Hernandez-Avila 2016. a. Downgraded two levels for risk of bias: non-random sequence generation; open-label trials with unclear allocation concealment. b. Downgraded one level for inconsistency: heterogeneity between studies for HPV 6. c. Downgraded one level for imprecision: low sample size. d. Downgraded one level for risk of bias: high loss to follow up. e. Downgraded one level for imprecision: the 95% CI overlaps line of no effect

Table 4.39 Immunogenicity comparison of 2 doses versus 3 doses of the 4-valent HPV vaccine in younger females (9 to 13 year old) at multiple timepoints (7 and 36 months)

Outcomes		Absolute effects (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
		Three doses	Two doses			
GMTs - HPV 06	Dobson 2013 month 7	1856 mMU/mL (1571 – 2192)	2186 mMU/mL (1846 – 2588)	GMT Ratio 1.18 (0.89 to 1.56)	489 (1 RCT)[218]	⊕◯◯◯ VERY LOW [a, b]
	Dobson 2013 month 36	372 mMU/mL (304 – 456)	239 mMU/mL (195 – 292)	GMT Ratio 0.64 (0.46 to 0.90)	167 (1 RCT)[218]	⊕◯◯◯ VERY LOW [a, c]
GMTs - HPV 11	Dobson 2013 month 7	2096 mMU/mL (1869 – 2350)	2348 mMU/mL (2090 – 2638)	GMT Ratio 1.12 (0.92 to 1.36)	494 (1 RCT)[218]	⊕◯◯◯ VERY LOW [a, b]
	Dobson 2013 month 36	410 mMU/mL (335 – 503)	298 mMU/mL (244 – 364)	GMT Ratio 0.73 (0.52 to 1.02)	168 (1 RCT)[218]	⊕◯◯◯ VERY LOW [a, b, c]
GMTs - HPV 16	Dobson 2013 month 7	7640 mMU/mL (6561 – 8896)	7457 mMU/mL (6388 – 8704)	GMT Ratio 0.98 (0.75 to 1.27)	494 (1 RCT)[218]	⊕◯◯◯ VERY LOW [a, b]
	Dobson 2013 month 36	1413 mMU/mL (1122 – 1780)	1151 mMU/mL (918 – 1444)	GMT Ratio 0.81 (0.55 to 1.20)	169 (1 RCT)[218]	⊕◯◯◯ VERY LOW [a, b, c]
GMTs - HPV 18	Dobson 2013 month 7	1703 mMU/mL (1489 – 1946)	1207 mMU/mL (1054 – 1384)	GMT Ratio 0.71 (0.56 to 0.89)	495 (1 RCT)[218]	⊕⊕◯◯ LOW [a]
	Dobson 2013 month 36	239 mMU/mL (175 – 327)	104 mMU/mL (77 – 141)	GMT Ratio 0.43 (0.26 to 0.73)	169 (1 RCT)[218]	⊕◯◯◯ VERY LOW [a, c]
Seropositivity - HPV 06	Dobson 2013 month 7	248/248 (100%)	240/241 (99.6%)	RR 1.00 (0.98 to 1.01)	489 (1 RCT)[218]	⊕⊕◯◯ LOW [a]
	Dobson 2013 month 36	83/83 (100%)	84/84 (100%)	RR 1.00 (0.98 to 1.02)	167 (1 RCT)[218]	⊕◯◯◯ VERY LOW [a, c]
Seropositivity - HPV 11	Dobson 2013 month 7	251/251 (100%)	243/243 (100%)	RR 1.00 (0.99 to 1.01)	494 (1 RCT)[218]	⊕⊕◯◯ LOW [a]
	Dobson 2013 month 36	82/82 (100%)	86/86 (100%)	RR 1.00 (0.98 to 1.02)	168 (1 RCT)[218]	⊕◯◯◯ VERY LOW [a, c]
Seropositivity - HPV 16	Dobson 2013 month 7	251/251 (100%)	243/243 (100%)	RR 1.00 (0.99 to 1.01)	494 (1 RCT)[218]	⊕⊕◯◯ LOW [a]
	Dobson 2013 month 36	83/83 (100%)	86/86 (100%)	RR 1.00 (0.98 to 1.02)	169 (1 RCT)[218]	⊕◯◯◯ VERY LOW [a, c]
Seropositivity - HPV 18	Dobson 2013 month 7	252/252 (100%)	243/243 (100%)	RR 1.00 (0.99 to 1.01)	495 (1 RCT)[218]	⊕⊕◯◯ LOW [a]

Outcomes		Absolute effects (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
		Three doses	Two doses			
	Dobson 2013 month 36	79/83 (95%)	74/86 (86%)	RR 0.90 (0.82 to 1.02)	169 (1 RCT)[218]	⊕◯◯◯ VERY LOW [a, c]

The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect of the intervention (and its 95% CI).* [218] Dobson 2013. a. Downgraded two levels for risk of bias: non-random sequence generation; open-label trial with unclear allocation concealment; high loss to follow up (attrition bias at 36 months). b. Downgraded one level for imprecision: the 95% CI overlaps line of no effect. c. Downgraded one level for imprecision: low sample size

Appendix 5

Appendix 5A: Search terms and results

Embase

Embase 06/07/2017		Search Strings	Results
Searches	#1	(papillomavirus vaccine) OR (papillomavirus vaccination) OR (HPV vaccine) OR (HPV vaccination)	13,822
	#2	(condylomata AND acuminata) OR (anogenital AND warts) OR (cervical AND intraepithelial AND neoplasia) OR (cervical AND dysplasia) OR (uterine AND cervical AND neoplasm) OR (hpv AND related AND diseases) OR (papillomavirus AND infection)	45,818
	#3	(program AND evaluation) OR (population AND surveillance) OR (sentinel AND surveillance) OR incidence OR prevalence	1,825,623
	#4	1 AND 2 AND 3	3,226
	#5	Publication year 2014 to 2017	1,179

PubMed

Search string: *((((papillomavirus vaccine) OR (papillomavirus vaccination) OR (hpv vaccine) OR (hpv vaccination))) AND ((condylomata AND acuminata) OR (anogenital AND warts) OR (cervical AND intraepithelial AND neoplasia) OR (cervical AND dysplasia) OR (uterine AND cervical AND neoplasm) OR (hpv AND related AND diseases) OR (papillomavirus AND infection))) AND ((program AND evaluation) OR (population AND surveillance) OR (sentinel AND surveillance) OR incidence OR prevalence)*

Filter: publications from 1/1/2014 to 6/7/2017

(= 982 results)

Appendix 5B: AMSTAR 2

The following is the quality appraisal of the systematic review by Drolet et al.[295] using the AMSTAR 2 quality appraisal tool.[292]

Item 1. Did the research questions and inclusion criteria for the review include the components of PICO?

Answer: Yes

Item 2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?

Answer: Partial yes. Protocol registration was not identified for this review. This systematic review was conducted prior to the conception of AMSTAR 2, and protocol registration was not commonplace in the past. Nonetheless, authors report that an a priori design was used without significant deviations from the protocol.

Item 3. Did the review authors explain their selection of the study designs for inclusion in the review?

Answer: Yes

Item 4. Did the review authors use a comprehensive literature search strategy?

Answer: Yes

Item 5. Did the review authors perform study selection in duplicate?

Answer: Yes

Item 6. Did the review authors perform data extraction in duplicate?

Answer: Yes

Item 7. Did the review authors provide a list of excluded studies and justify the exclusions?

Answer: Partial yes. Authors provided justifications for the exclusions, however a reference list not given.

Item 8. Did the review authors describe the included studies in adequate detail?

Answer: Yes

Item 9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?

Answer: Yes

Item 10. Did the review authors report on the sources of funding for the studies included in the review?

Answer: Yes

Item 11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?

Answer: Yes

Item 12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?

Answer: Yes

Item 13. Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review?

Answer: Yes

Item 14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?

Answer: Yes. Meta-regression was employed to deal with issue of heterogeneity foundacross studies.

Item 15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?

Answer: No. Publication bias appears not to have been assessed. However, for the purposes of updating this review, estimates from the meta-analysis were not used as we decided a priori not to pool results from individual studies.

Item 16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?

Answer: Yes

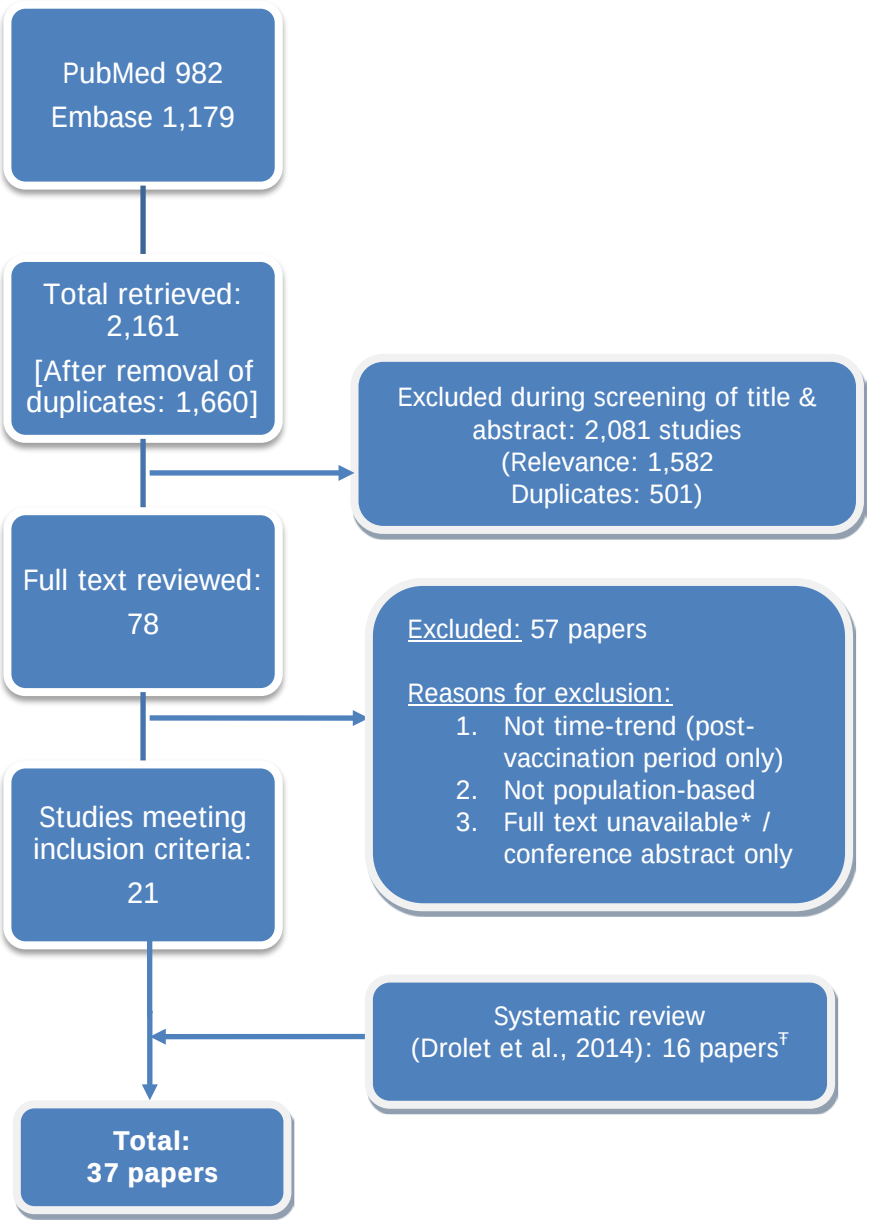
Conclusion: All items received a positive rating with the exception of items 2, 7 and 15.

Item 2 was rated as a 'partial yes'. AMSTAR 2 now specifies that a protocol for the systematic review must have been registered to receive a 'yes' for this item. However, authors do report that an *a priori* design was followed and there were no major deviations to the planned methods. Additionally, the systematic review was conducted prior to the conception of AMSTAR 2 when registering procols for systematic reviews was not commonplace.

Item 7 received a partial yes. Authors provided justifications for the exclusions, however a reference list not given.

Item 15 received a 'no' with relation to the identification and consideration of publication bias. In terms of updating this systematic review, however, we did not judge this to be of major concern as estimates from the meta-analysis were not used in our updated review. It was decided *a priori* not to pool results from individual studies due to the high levels of heterogeneity noted across studies due to large differences in vaccination programmes.

Appendix 5C: Flow diagram for study selection



*Since our initial search, the full text of Cocchio et al. 2017 has become available (item 13 in excluded list – Appendix 5E)
[Ŧ]While Drolet et al. 2014 included 20 papers, full text was unavailable for three (conference proceedings) and one study was otherwise excluded (see appendix 5E)

Appendix 5D: Risk of bias in included studies

D.1 HPV infection

Study	Cameron , 2016[300]	Chow , 2015[298]	Chow , 2017[299]	Cummings , 2012[296]	Dunne , 2015[310]
Funding	Monitoring and evaluation of the HPV immunisation programme in Scotland is funded by the Scottish government.	The Australian National Health and Medical Research Council Program	The Australian National Health and Medical Research Council Program	National Institutes of Health	Division of STD Prevention, CDC.
Risk of selection bias					
Subjects included in the study	Women aged 20–21 years participating in routine cervical cancer screening in Scotland	Women aged 25 years or younger who attended the Melbourne Sexual Health Centre (Melbourne, VIC, Australia) diagnosed with chlamydia	Heterosexual men aged 25 years or younger attending the Melbourne Sexual Health Centre between July 1, 2004, and June 30, 2015, who tested positive for Chlamydia trachomatis	Clinic-based: Women attending 1 of 3 urban primary care clinics in Indianapolis	Population based: Residual specimens from women attending routine cervical screening at Kaiser Permanente Northwest
Potential for selection bias: Changes in the study population characteristics between the pre- and post-vaccination periods	Low Unlikely changes in the attendees between the pre- and post-vaccination periods	Low Unlikely changes in the attendees between the pre- and post-vaccination periods	Low Unlikely changes in the attendees between the pre- and post-vaccination periods	Low Unlikely changes in the clientele of primary care clinics between the pre- and post-vaccination periods	Low Unlikely changes in the women attending routine screening between the pre- and post-vaccination periods
Risk of information bias					
HPV testing	HPV+ Multimetrix HPV assay (Diamex, Heidelberg, Germany; 18 types)	PCR: HPV amplification and detection using the PapType high-risk HPV detection and genotyping kit	PCR [PapType assay (Genera Biosystems,Scoresby, VIC, Australia)]	PCR Roche Linear Array test which detects 37 different HPV types	Linear Array (LA) HPV Genotyping Test (Roche Molecular Diagnostics) and HPV-52 quantitative polymerase chain reaction
Performance of the HPV test used	Unreported	Unreported	Unreported	Unreported	Unreported
Outcome used in publication	Odds and adjusted odds ratios reported, along with	Both frequency of infection and adjusted	Both frequency of infection and adjusted	Odds ratios of HPV prevalence (crude)	Odds ratios of HPV prevalence (adjusted)

	frequencies	prevalence ratios reported	prevalence ratios reported		
Potential for information bias: Errors in the identification of HPV+ during the pre and post-vaccination period	Medium Potential for masking by HPV16/18, particularly in the pre-vaccine period	Medium Potential for masking by HPV16/18, particularly in the pre-vaccine period	Medium Potential for masking by HPV16/18, particularly in the pre-vaccine period	Medium Potential for masking by HPV16/18, particularly in the pre-vaccine period	Medium Potential for masking by HPV16/18, particularly in the pre-vaccine period
Risk of confounding					
Potential confounders considered	Adjusted odds reported: adjust for birth year, number of doses of vaccine received, SIMD score, and age at vaccination	Adjustment for confounders also included (number of sexual partners, condom use, and anatomical sampling sites).	Also adjusted for number of female partners and 100% condom use.	Analysis matched on age at enrollment, clinic site and reported sexual activity (yes, never) at time of enrollment	Confounders considered including recent STI and recent pregnancy testing.
Potential for confounding: Changes in HPV infection between the pre and post-vaccination periods could be diluted/exacerbated by other variables	Low	Low	Low	Medium. Changes in sexual activity not accounted for except yes/never	Low
External validity					
External validity: Results can be generalised to the population at the country/region level†	High. Population-based surveillance	Medium. Young women attending STI clinic testing positive for chlamydia may not represent overall population.	Medium. Men attending STI clinic testing positive for chlamydia may not represent overall population.	Medium. Young women attending to urban primary care clinics may not represent the overall population (e.g., different vaccination coverage)	High. Attendees of routine screening

Study	Kahn , 2012[301]	Kahn , 2016[302]	Kavanagh , 2014[309]	Markowitz , 2013[308]
Funding	National Institutes of Health	National Institute of Allergy and Infectious Diseases, National Institutes of Health	Scottish government, Chief Scientist Office	Centers for Disease Control and Prevention
Risk of selection bias				
Subjects included in the study	Clinic-based: Young women attending 2 primary care clinics in Cincinnati who had had sexual contact. Great proportion of minority and low-income women	Clinic-based: Three sites that provide primary care to adolescents and young adults: a hospital-based teen health center and 2 health department sites (a community health center and sexually transmitted disease clinic)	Population based: Women attending their cervical screening appointment across Scotland	Population-based: Participants in NHANES which is designed to be nationally representative of the civilian, non-institutionalised US population
Potential for selection bias: Changes in the study population characteristics between the pre- and post-vaccination periods	Low. Unlikely changes in the clientele of primary care clinics between the pre- and post-vaccination periods	Low. Unlikely changes in the clientele of primary care clinics between the pre- and post-vaccination periods	Low. No documented changes in screening rates of women aged 20-24 years old between the pre- and post-vaccination periods	Low Unlikely changes in the NHANES participants between the pre- and post-vaccination periods
Risk of information bias				
HPV testing	PCR Roche Linear Array test which detects 37 different HPV types	PCR Roche Linear Array test which detects 36 different HPV types.	Multimetrix HPV Assay which detects 18 high-risk types	PCR Roche Linear Array test which detects 37 different HPV types
Performance of the HPV test used	Unreported	Unreported	Low	Unreported
Outcome used in publication	HPV prevalence difference (adjusted)	HPV prevalence difference (adjusted)	HPV prevalence over time	HPV prevalence ratio (crude)
Potential for information bias: Errors in the identification of HPV+ during the pre and post-vaccination period	Medium Potential for masking by HPV16/18, particularly in the pre-vaccine period	Medium Potential for masking by HPV16/18, particularly in the pre-vaccine period	Medium Potential for masking by HPV16/18, particularly in the pre-vaccine period	Medium Potential for masking by HPV16/18, particularly in the pre-vaccine period
Risk of confounding				

Potential confounders considered	Analysis adjusted for demographic characteristics (race, health insurance plan etc), gynecologic history (number of times pregnant, history of Chlamydia, AGW), behaviors (age at first sexual intercourse, number male sexual partners, condom use, smoking etc) using propensity scores	Adjusted with Propensity Scores (logistic regression). Adjusted for demographic characteristics, gynecologic history, sexual history, and enrollment site, independent of the study outcome.	No adjustment in the analysis of changes of HPV prevalence over time	Analysis adjusted for race/ethnicity, lifetime number of sex partners for girls aged 14-19 years old. No adjustment for the other age groups, but all analysis weighted to represent the U.S population
Potential for confounding: Changes in HPV infection between the pre and post-vaccination periods could be diluted/exacerbated by other variables	Low/Medium Several risk factors were considered. However, residual confounding by other factors associated with HPV vaccination and infection may still be present	Low/Medium Several risk factors were considered. However, residual confounding by other factors associated with HPV vaccination and infection may still be present	Medium No adjusted analysis of changes in HPV prevalence over time. Confounding by factors associated with HPV vaccination and infection may be present (e.g., changes in sexual activity)	Low/medium Few factors considered for girls aged 14-19 years old
External validity				
External validity: Results can be generalised to the population at the country/region level†	Low/medium Women attending to the 2 primary care clinics may not be representative of the overall population (e.g., different vaccination coverage). Minorities and women from low socio-economic status are overrepresented	Low/medium Women attending to the 3 sites may not be representative of the overall population (e.g., different vaccination coverage). Also, possible overrepresentation of minorities and women from low socio-economic status	Medium/high Women participating in screening may not represent to overall population (e.g., different vaccination coverage)	Medium/high The survey was designed to be representative of the general population but non-participants could still be different than participants with respect to variables not considered in the sampling design.

Study	Markowitz , 2016[307]	Mesher , 2013[306]	Mesher , 2016[303]	Soderlund-Strand , 2014[311]
Funding	Centers for Disease Control and Prevention	Public Health England	Public Health England	Public Health Agency of Sweden
Risk of selection bias				
Subjects included in the study	Population-based: Participants in NHANES which is designed to be nationally representative of the civilian, non-institutionalized US population	Clinic-based: Women undergoing chlamydia screening at community sexual health services, general practice and youth clinics in 7 regions around England	Girls and women aged 16–24 years undergoing chlamydia screening in community sexual health services, general practice, youth clinics in 7 regions around England	Samples from the Chlamydia trachomatis screening in Skane Sweden
Potential for selection bias: Changes in the study population characteristics between the pre- and post-vaccination periods	Low Unlikely changes in the NHANES participants between the pre- and post-vaccination periods	Medium Documented changes in the clientele receiving chlamydia testing between the pre- and post-vaccination periods	Medium Analyses compare data from repeat cross-sectional surveys. Therefore, unrecorded changes in the population characteristics may have resulted in a change in HPV prevalence which is unrelated to HPV vaccination.	Low Unlikely change in participants in Chlamydia screening programme
Risk of information bias				
HPV testing	PCR Roche Linear Array test which detects 37 different HPV types	2008: Hybrid Capture 2 and Roche Linear Array 2010-2012: HPV+ In-house multiplex PCR and Luminex-based genotyping test (13 HPV types)	Post-vaccination: using in-house multiplex PCR and Luminex-based genotyping test with pyruvate dehydrogenase (PDH) detection for sample integrity. Pre-vaccination specimens were tested by Hybrid Capture 2 (HC2) HPV DNA test using the Combined Probe Cocktail Method to detect HR and possible HR types (as above) and five LR types (6, 11, 42, 43 and 44) and genotyped by the Linear Array HPV Genotyping (LA) test (Roche Molecular Systems) if HC2 positive. Logistic regresion then used to account for different testing platforms	PCR with genotyping by matrix-assisted laser desorption ionization time-of-flight (MALDI-TOF) mass spectrometry. Secondary HPV DNA analysis on the Luminex platform
Performance of the HPV test used	Unreported	Unreported	Unreported	Unreported
Outcome used in	Adjusted prevalence ratio	Odds ratios of HPV prevalence	Prevalence, odds ratios and adjust	HPV prevalence over time

publication	comparing NHANES 2003–2006 and 2009–2012	(adjusted)	odds ratios	
Potential for information bias: Errors in the identification of HPV+ during the pre and post-vaccination period	Medium Potential for masking by HPV16/18, particularly in the pre-vaccine period	Medium/high Potential for masking by HPV16/18, particularly in the pre-vaccine period; different tests used in the pre- and post-vaccination periods Which may have contributed to higher prevalence of non-vaccine types in the post-vaccination period	Low Adjusted for different testing platform in pre- and post-vaccination periods	High Authors found a "strong increasing trend over time in the use of genital swabs for Chlamydia screening"; it has been well documented that this sample type is better for HPV detection that urine samples
Risk of confounding				
Potential confounders considered	Adjusted for race/ethnicity and lifetime and past year number of sex partners. All estimates were weighted by using sample weights to account for unequal probabilities of selection and adjustment for nonresponse.	Analysis adjusted for sexual history, age, venue type, ethnicity and chlamydia positivity	Adjusted ORs were calculated adjusting for age,testing venue type and chlamydia positivity (as a marker for sexual behaviour).	Analysis by age and gender
Potential for confounding: Changes in HPV infection between the pre and post-vaccination periods could be diluted/exacerbated by other variables	Low/medium	Medium. Several risk factors were considered. However, residual confounding by other factors associated with HPV vaccination and infection can still be present (e.g., changes in sexual activity)	Low	High Other confounders not considered such as sexual behaviour patterns
External validity				
External validity: Results can be generalized to the population at the country/region level†	Medium/high The survey was designed to be representative of the general population but non-participants could still be different than participants with respect to variables not considered in the sampling design.	Medium Chlamydia screening recommended for all sexually-active young women and uptake was 40% in 2011. However, women undergoing chlamydia screening may not be representative of the overall population (e.g., different vaccination coverage)	High Attendees of screening	High The Skane region in Southern Sweden has 1.27 million inhabitants). During a single year 23% of all 19-year-old girls undergo Chlamydia screening

Study	Sonnenberg , 2013[304]	Tabrizi , 2012[297]	Tabrizi , 2014[313]
Funding	UK Medical Research Council, Wellcome Trust, Economic and Social Research Council and the Department of Health	Australian National Health and Medical Research Council, and AntiCancer Council for Victoria	Australian National Health and Medical Research Council, and AntiCancer Council for Victoria
Risk of selection bias			
Subjects included in the study	Population-based: Participants in NATSAL which is designed to be nationally representative of the British population	Clinic-based: Women recruited from participating family planning clinics for Pap screening in Sydney, Melbourne, and Perth	Clinic-based: Women recruited from participating family planning clinics for Pap screening in Sydney, Melbourne, and Perth
Potential for selection bias: Changes in the study population characteristics between the pre- and post-vaccination periods	Medium Possible changes in the NATSAL participants between the pre- and post-vaccination periods (> 10 yrs between the 2 periods). Both surveys are weighted to Census data from the time.	Low Unlikely changes in the clientele of family planning clinics between the pre- and post-vaccination periods	Low Women in the postvaccine implementation sample were more likely to be using hormonal contraception but were similar with respect to other characteristics
Risk of information bias			
HPV testing	In-house Luminex-based genotyping assay (20 HPV types) in urine samples	Amplicor HPV test kit (Roche Molecular system) (13 HPV types) and PGMY09-PGMY11 PCR-ELISA Roche Linear Array HPV Genotyping test	Amplicor HPV test kit (Roche Molecular system) (13 HPV types) and PGMY09-PGMY11 PCR-ELISA Roche Linear Array HPV Genotyping test
Performance of the HPV test used	Unreported	Unreported	Unreported
Outcome used in publication	Odds ratios of HPV prevalence (adjusted)	Odds ratios of HPV prevalence (adjusted)	Odds ratios of HPV prevalence (adjusted)
Potential for information bias: Errors in the identification of HPV+ during the pre and post-vaccination period	High. Potential for masking by HPV16/18, particularly in the pre-vaccine period; Urine is a suboptimum specimen for the detection of HPV; Differences in methods of sample collection, preparation and storage between the pre- and post-vaccination periods	Medium Potential for masking by HPV16/18, particularly in the pre-vaccine period	Medium Potential for masking by HPV16/18, particularly in the pre-vaccine period
Risk of confounding			
Potential confounders considered	No adjustment in the comparison of HPV prevalence between the pre- and post-vaccination periods, but all analysis weighted to represent the British population	Analysis adjusted for age, contraceptive use, region, socioeconomic group and smoking status (these variables differed significantly between the 3 groups of women)	Analysis adjusted for confounding by sociodemographic characteristics (age, hormonal contraceptive use, education, country of birth), and the number of sexual partners in the past 12 months

Potential for confounding: Changes in HPV infection between the pre and post-vaccination periods could be diluted/exacerbated by other variables	Medium/high No adjusted analysis of changes in HPV prevalence over time and likely changes over a 10-year period in factors associated with HPV vaccination and infection (e.g., changes in sexual activity documented when comparing NATSAL-2 and -3	Medium Few sexual behavior factors considered and residual confounding by other factors associated with HPV vaccination and infection is possible (e.g., changes in sexual activity)	Low
External validity			
External validity: Results can be generalized to the population at the country/region level†	Medium The survey was designed to be representative of the general population. However, participants and those providing urine samples might not be fully representative of the general population, despite efforts to adjust for known biases and the use of additional weights for urine selection and urine non-response	Medium Young women attending family planning clinics may not represent the overall population (e.g., different vaccination coverage)	Medium Young women attending family planning clinics may not represent the overall population (e.g., different vaccination coverage)

†For external validity, high is good.

C.2. Risk of Bias: Anogenital warts

Study	Ali, 2013[314]	Baandrup, 2013[315]	Bauer, 2012[316]	Bollerup, 2016[317]
Funding	CSL Biotherapies	Aragon Foundation, Aase and Ejnar Danielsen Foundation, Mermaid II Project	CDC, California Department of Public Health	Mermaid II Project
Risk of selection bias				
Subjects included in the study	Clinic-based: New clients of 8 sexual health services across Australia (Australian born)	Population-based: Denmark population from Statistics Denmark	Health provider/insurance-based: Clients of the California Family Planning access care & treatment (FPACT) program	Data from 2 nationwide registries: the Danish National Patient Register and the National Prescription Registry. Both are nationwide registers based on individual-level data.
Potential for selection bias: Changes in the study population characteristics between the pre- and post-vaccination periods	Medium/High Possible changes in the clientele of the sexual health services in the pre- and post-vaccination periods as reflected by increasing annual number of clients and % of clients with chlamydia after 2006	Low Entire population of Denmark	Low Unlikely change in the FPACT (family planning program for low-income individuals) clientele between the pre- and post-vaccination periods	Low Entire population of Denmark
Risk of information bias				
Data source	Medical records	National patient register	FPACT database (clinical encounter claims data)	National patient registries
Anogenital wart case definition	Clinical diagnosis	ICD-10 code A63.0	ICD-9 codes 078.10, 078.11 OR prescription of Imiquimod or Podophyllotoxin	ICD diagnostic code A63.0; for Podophyllin prescriptions: Anatomical Therapeutic Chemical code D06BB04
Outcome used in publication	Annual proportion of new clients with diagnosed AGW	Annual incidence rate of diagnosed AGW in the population	Annual proportion of FPACT clients diagnosed with AGW	Annual incidence rate in the population
Numerator	Number of newly diagnosed AGW cases per year	Number of newly diagnosed AGW cases each year (washout period of 12 months)	Number of first ever cases diagnosed after 2007 (cases prior to 2007 excluded) per year	Number of new AGW cases each year (clinical or Podophyllin GP prescription)

Denominator	Total number of new patients per year	Annual population estimates	All clients registered in the FPACT each year	Annual population estimates covering all of Denmark obtained from Statistics Denmark
Potential for information bias: Errors in the identification of diagnosed AGW cases during the pre and post-vaccination period	Low AGW are directly diagnosed by physicians	Medium Sensitivity/specificity of algorithm to correctly identify diagnosed AGW not specified. AGW treated by GP not included. However, unlikely to change over time	Medium Sensitivity/specificity of algorithm to correctly identify diagnosed AGW not specified, unlikely to change over time unless awareness is associated with likelihood of including code	Low/Medium Sensitivity/specificity of algorithm to correctly identify diagnosed AGW not specified. However, unlikely to change over time
Risk of confounding				
Potential confounders considered	Analysis stratified by age, gender, sexual orientation and residential status	Stratified by age and sex	Analysis stratified by age and gender	Stratified by age and sex
Potential for confounding: Changes in AGW between the pre and post-vaccination periods could be diluted/exacerbated by other variables	High Other factors could potentially cause changes in AGW frequency over time (e.g., changes in sexual activity, health seeking behaviour) and data suggested increasing proportion of clients with chlamydia after 2007	Medium Other factors may have altered disease rates in population	Medium Other factors could potentially cause changes in AGW frequency over time (e.g., changes in sexual activity)	Medium Other factors could potentially cause changes in AGW frequency over time (e.g., changes in sexual activity, health seeking behaviour). However, authors note other STIs have increased in Denmark over study timeframe.
External validity				
External validity: Results can be generalized to the population at the country/region level†	Low Clients of 8 sexual health clinics possibly representative of sexual health clinic clients in Australia, may not represent the overall population (e.g., different vaccination coverage)	High Entire population, contains all cases of AGW admitted to hospital or in outpatient clinics	Medium FPACT is a program for low-income individuals and 87% of participants are females. Results could be different for medium/high-income individuals (e.g., different vaccination coverage)	High Entire population of Denmark analysed

Study	Chow, 2014[318]	Dominiak, 2015[319]	Flagg, 2013[320]	Guerra, 2016[321]
Funding	National Health and Medical Research Council (NHMRC) programme grant	Sanofi Pasteur MSD	Centers for Disease Control and Prevention	Public Health Ontario
Risk of selection bias				
Subjects included in the study	Clinic-based. New patients attending Melbourne Sexual Health Centre from July 2004 to June 2014	All women and men aged 16–59 years in Belgium	Health provider/insurance-based : Enrollees in approximately 100 private health insurance plans across US	Entire population Ontario aged over 15
Potential for selection bias: Changes in the study population characteristics between the pre- and post-vaccination periods	Medium/High Authors note change (increase) in presentations at MSHC over time.	Low	Low Unlikely change in enrollees of insurance plans between the pre and post-vaccination periods. No decrease in Pap test or pelvic examination (opportunities to diagnose AGW) over time	Low
Risk of information bias				
Data source	Medical records	Database (reimbursement database)	Truven Health Analytics MarketScan Commercial Claims and Encounters Database	Health administrative data to identify incident AGWs and total health service utilization (HSU) for AGWs
Anogenital wart case definition	Clinical diagnosis	First prescription of imiquimod with a level of reimbursement specific for AGWs	1) ICD-9 codes 078.11 OR 2) ICD-9 code 078.1, 078.10, 078.19 and therapeutic procedure or diagnosis of benign anogenital neoplasm OR 3) ≥ 1 prescription for AGW treatment and therapeutic procedure or diagnosis of benign anogenital neoplasm	OHIP database provides diagnostic and procedural codes from physician office visits that can be combined into algorithms to generate a probable outcome definition for AGWs
Outcome used in publication	Annual proportion of new clients with diagnosed AGW and adjust Odds Ratios for diagnosis of AGW in post-vaccination period	Incidence Rate Ratios and 95% CI's by age category	Annual proportion of insured individuals with diagnosed AGW	Average annual incidence of diagnosed anogenital warts in the population (by physician office visits) and RR of anogenital warts proportion (crude)

Numerator	Number of newly diagnosed AGW cases per year	Rates per 100,000 reported (unestimable by age category)	Number of patients with AGW diagnosis each year	Rates per 100,000 reported (unestimable numerator by age category)
Denominator	Total number of new patients per year	Rates per 100,000 reported (unestimable by age category)	Total number of clients enrolled in in health insurance plans each year	Rates per 100,000 reported (unestimable denominator by age category)
Potential for information bias: Errors in the identification of diagnosed AGW cases during the pre and post-vaccination period	Low AGW are directly diagnosed by physicians	High Surrogate measure used. Changes in presciption patterns may have altered identification of AGWs	Medium Sensitivity/specificity of algorithm to correctly identify diagnosed AGW not specified However, unlikely to change over time	Low
Risk of confounding				
Potential confounders considered	Analysis stratified by vaccination period, age, gender, MSM and risk groups; logistic regression adjusted for number of sexual partners in past 12 months.	Only stratified by age and sex. Other confounders not controlled for.	Analysis stratified by age, gender, region, and insurance plan type	A number of factors that could have influenced the observed trends aside from the HPV vaccine program. For example, the increasing use of urine screening for chlamydia as opposed to gynecological exam with swabs may have reduced the number of AGW cases diagnosed incidentally.
Potential for confounding: Changes in AGW between the pre and post-vaccination periods could be diluted/exacerbated by other variables	Low/medium. Other factors may be unaccounted for including changing demographics, however attempt made at controlling for confounders**.**	Medium/High	Medium Other factors could potentially cause changes in AGW frequency over time (e.g., changes in sexual activity, health seeking behaviour)	Medium/High
External validity				
External validity: Results can be generalized to the population at the country/region level†	Low. MSHC primarily targets individuals at high risk of STIs; absolute proportion of individuals with AGW may not reflect community as a whole	High Nationally representative sample	Medium/High The Truven Health Analytics contains data from 100 health insurance plan throughout the US (n=13 million in 2010). Results could be different for uninsured individuals	High Nationally representative sample

Study	Harrison, 2014[322]	Howell-Jones, 2013[323]	Leval, 2012[324]	Liu, 2014[325]
Funding	BEACH project - funded by the Australian Government Department of Health and Ageing along with many other co-funders (including industry funding)	Public Health England	National Research School in Health Care Sciences, Strategic Research Program (Karolinska Institutet), Erasmus Programme	Australian National Health and Medical Research Council (NHMRC)
Risk of selection bias				
Subjects included in the study	Primary care encounters	Health provider/based: Women diagnosed at Genitourinary medicines (GUM) and England population from national statistics	Population-based: Sweden population from Statistics Sweden	An Australia-wide survey of women
Potential for selection bias: Changes in the study population characteristics between the pre- and post-vaccination periods	Medium While a nationally representative sample, authors note change (increase) in chlamydia over time.	Low/Medium Possible changes in GUM services clientele in the pre- and post-vaccination periods	Low Entire population of Sweden	Medium While a nationally representative sample, protocols between two sampling periods not identical (e.g., mobile telephone calling in later period and fixed line in earlier period)
Risk of information bias				
Data source	Continuous cross-sectional study	Genitourinary Medicine Clinic Activity Dataset (GUMCAD) (diagnoses at GUM clinics nationally	National patient register, Prescribed drug register	Survey
Anogenital wart case definition	Genital warts were defined as ICPC 2 codes Y76 for males and X91 for females.	Clinical diagnosis	ICD-10 code A63 OR prescription of Imiquimod or Podophyllotoxin	Self-reported AGW
Outcome used in publication	Reduction in genital warts per 100,000 encounters	Annual incidence rate of GUM-diagnosed AGW in the population	Annual incidence rate of diagnosed AGW in the population	OR's from logistic regression adjusting for age and other factors in addition to frequencies.

Numerator	Number of newly diagnosed AGW cases	Number of first diagnosed AGW cases since 2006, each year	Number of newly diagnosed AGW cases each year, (washout period of 6 months)	Number of women ever-diagnosed AGW
Denominator	Total number of encounters	Annual population estimates	Annual population estimates	Total number of women surveyed
Potential for information bias: Errors in the identification of diagnosed AGW cases during the pre and post-vaccination period	Low AGW are directly diagnosed by physicians	Low AGW are directly diagnosed by physicians in GUM clinics	Medium Sensitivity/specificity of algorithm to correctly identify diagnosed AGW not specified, unlikely to change over time unless awareness is associated with likelihood of including code	Medium/high Self-reported data
Risk of confounding				
Potential confounders considered	Stratified by age, sex, vaccination period. Large increase in other STI diagnoses	Analysis stratified by age and gender, and adjusted for chlamydia diagnoses and area	Analysis stratified by age and gender	Adjustments made. ORs were adjusted for age, country of birth, state of residence, education, Aboriginality; ORs for warts were additionally adjusted for chlamydia.
Potential for confounding: Changes in AGW between the pre and post-vaccination periods could be diluted/exacerbated by other variables	Medium/high. Other factors unaccounted for	Medium Other factors could potentially cause changes in AGW frequency over time (e.g., changes in sexual activity, health seeking behaviour)	Medium Other factors could potentially cause changes in AGW frequency over time (e.g., changes in sexual activity); data suggesting increasing sexual activity over time in Sweden	Low
External validity				
External validity: Results can be generalized to the population at the country/region level†	High Nationally representative sample.	Medium/High About 95% of AGW diagnoses are made in GUM clinics (~85% sample of national data used)	High Entire population	High Nationally representative sample.

Study	Lurie, 2017[326]	Mikolajczyk, 2013[327]	Smith, 2015[329]
Funding	Unclear (Conflict of Interests include honoraria from GSK and MSD)	Sanofi-Pasteur MSD	National Health and Medical Research Council Australia
Risk of selection bias			
Subjects included in the study	Entire Maccabi Healthcare Services population (one of four publicly funded insurance providers in Israel)	Health provider/insurance-based : Enrollees in 1 large health insurance company across Germany	All hospital admissions in Australia
Potential for selection bias: Changes in the study population characteristics between the pre- and post-vaccination periods	Low (complete population)	Low Unlikely change in enrollees of insurance plans between the pre- and post-vaccination periods	Medium Possible increase in out-of-hospital treatment of AGW over time period reported by authors.
Risk of information bias			
Data source	Medical records database (includes all outpatient encounters)	German Pharmaco-epidemiological research database	National Hospital Morbidity Database (a comprehensive data set of admissions to virtually all public and private hospitals in Australia)
Anogenital wart case definition	Diagnosis of AGW	ICD-10 code A63.0	All NHMD admissions between 1 July 1999 and 30 June 2011 that included ICD-10-AM code A63.0 (anogenital warts) as a main or contributory diagnosis were included.
Outcome used in publication	Frequency of AGW	Annual incidence rate of diagnosed AGW among insured individuals	EAPC AGW diagnosis (Poisson and negative binomial regression); crude frequency of AGW rate and rate per 100,000
Numerator	Number of AGW diagnoses	Number of newly diagnosed case each year, (washout period of 12 months)	Frequency of AGW hospital admission
Denominator	Total population covered	Total number of clients of 1 large insurance company each year	Rate per 100,000
Potential for information bias: Errors in the	Low	Medium Sensitivity/specificity of algorithm to	Low

identification of diagnosed AGW cases during the pre and post-vaccination period		correctly identify diagnosed AGW not specified, unlikely to change over time unless awareness is associated with likelihood of including code	
Risk of confounding			
Potential confounders considered	Stratified by age and sex	Analysis stratified by age and gender	Stratified by age and sex. Subgroup analysis by ethnicity, MSM and cervical screening
Potential for confounding: Changes in AGW between the pre and post-vaccination periods could be diluted/exacerbated by other variables	Medium. Other factors may have altered disease rates in population	Medium Other factors could potentially cause changes in AGW frequency over time (e.g., changes in sexual activity, health seeking behaviour)	Medium/high. A possible explanation for the observed decline is that treatments for warts (eg, topical treatments or other nonsurgical methods) may have been increasingly performed outside of hospital settings over the period after NHVP implementation
External validity			
External validity: Results can be generalized to the population at the country/region level†	High Complete population.	Medium/High The insurance plan includes > 6million individuals, 8% of the German population and is demographically representative. Results could be different in uninsured individuals	High Complete national data

†For external validity, high is good

C.3. Risk of Bias: Cervical Intraepithelial Neoplasia (CIN) 2+

Study	Brotherton, 2011[331]	Ogilvie, 2015[330]	Baldur-Felskov, 2014[332]	Baldur-Felskov, 2015[333]
Funding	None	Grant sponsor: BC Centre for Disease Control Foundation for Public and Population Health	Mermaid project (MERMAID II)	Mermaid project (MERMAID II)
Risk of selection bias				
Subjects included in the study	Population-based: Women included in the Victorian Cervical Cytology Registry	Population-based: Cervical Cancer Screening Programme database (British Columbia state)	Nationwide Pathology Data Bank: all cervical specimens in Denmark	Danish Cancer Registry (nationwide database)
Potential for selection bias: Changes in the study population characteristics between the pre- and post-vaccination periods	Low	Low	Low	Low
Risk of information bias				
CIN2+ diagnosis	Histopathological. The registry receives data from almost all cytology and cervical histopathology taken in Australia	Histopathological.	Histopathological. The data bank receives data from almost all cytology and cervical histopathology taken in Denmark	Histopathological.
Outcome used in publication	Annual incidence of high grade lesions	Incidence rate ratios comparing pre- and post-vaccination periods	EAPC from Poisson model of CIN2+ or Atypia	EAPC from Poisson regression model
Potential for information bias: Errors in the identification of pre-cancerous cervical lesions during the pre and post-vaccination period	Medium Sensitivity/specificity may change after vaccination	Medium Sensitivity/specificity may change after vaccination	Medium Sensitivity/specificity may change after vaccination	Low Histopathological diagnosis of carcinoma would not have changed
Risk of confounding				

Potential confounders considered	Analysis stratified by age	Analysis stratified by age	Analysis stratified by age	Analysis stratified by age
Potential for confounding: Changes in precancerous between pre and post-vaccination periods could be diluted/exacerbated by other variables	Medium/High: Other factors could potentially cause changes in the incidence of precancerous cervical lesions (e.g., changes in screening guidelines, sexual activity). Changes in screening guidelines documented in 2006	Medium/High: Other factors could potentially cause changes in the incidence of precancerous cervical lesions (e.g., changes in screening guidelines, sexual activity).	Medium/High: Other factors could potentially cause changes in the incidence of precancerous cervical lesions (e.g., changes in screening guidelines, sexual activity). No information on individual women's HPV vaccination status or risk factors	Medium/High: Other factors could potentially cause changes in the incidence of cancer and CIN3
External validity				
External validity: Results can be generalized to the population at the country/region level†	Medium/High. Women participating in screening may not be representative of the overall population (e.g., different vaccination coverage)	Medium/High. Women participating in screening may not be representative of the overall population (e.g., different vaccination coverage)	Medium/High. Women participating in screening may not be representative of the overall population (e.g., different vaccination coverage).	Medium/High. Women participating in screening may not be representative of the overall population (e.g., different vaccination coverage)

†For external validity, high is good

Appendix 5E:

List of studies included in this review

1. Ali H, Donovan B, Wand H, Read TR, Regan DG, Grulich AE, et al. Genital warts in young Australians five years into national human papillomavirus vaccination programme: national surveillance data. BMJ (Clinical research ed). 2013;346:f2032.

2. Baandrup L, Blomberg M, Dehlendorff C, Sand C, Andersen KK, Kjaer SK. Significant decrease in the incidence of genital warts in young Danish women after implementation of a national human papillomavirus vaccination program. Sexually transmitted diseases. 2013;40(2):130-5.

3. Baldur-Felskov B, Dehlendorff C, Junge J, Munk C, Kjaer SK. Incidence of cervical lesions in Danish women before and after implementation of a national HPV vaccination program. Cancer Causes and Control. 2014;25(7):915-22.

4. Baldur-Felskov B, Munk C, Nielsen TS, Dehlendorff C, Kirschner B, Junge J, et al. Trends in the incidence of cervical cancer and severe precancerous lesions in Denmark, 1997-2012. Cancer causes & control : CCC. 2015;26(8):1105-16.

5. Bauer HM, Wright G, Chow J. Evidence of human papillomavirus vaccine effectiveness in reducing genital warts: an analysis of California public family planning administrative claims data, 2007-2010. American journal of public health. 2012;102(5):833-5.

6. Bollerup S, Baldur-Felskov B, Blomberg M, Baandrup L, Dehlendorff C, Kjaer SK. Significant reduction in the incidence of genital warts in young men 5 years into the danish human papillomavirus vaccination program for girls and women. Sexually transmitted diseases. 2016;43(4):238-42.

7. Brotherton JM, Fridman M, May CL, Chappell G, Saville AM, Gertig DM. Early effect of the HPV vaccination programme on cervical abnormalities in Victoria, Australia: an ecological study. Lancet (London, England). 2011;377(9783):2085-92.

8. Cameron RL, Kavanagh K, Pan J, Love J, Cuschieri K, Robertson C, et al. Human papillomavirus prevalence and herd immunity after introduction of vaccination program, Scotland, 2009–2013. Emerging Infectious Diseases. 2016;22(1):56-64.

9. Canvin M, Sinka K, Hughes G, Mesher D. Decline in genital warts diagnoses among young women and young men since the introduction of the bivalent HPV (16/18) vaccination programme in England: An ecological analysis. Sexually Transmitted Infections. 2017;93(2):125-8.

10. Chow EP, Read TR, Wigan R, Donovan B, Chen MY, Bradshaw CS, et al. Ongoing decline in genital warts among young heterosexuals 7 years after the Australian human papillomavirus (HPV) vaccination programme. Sexually transmitted infections. 2015;91(3):214-9.

11. Chow EPF, Danielewski JA, Fehler G, Tabrizi SN, Law MG, Bradshaw CS, et al. Human papillomavirus in young women with Chlamydia trachomatis infection 7 years after the Australian human papillomavirus vaccination programme: A cross-sectional study. The Lancet Infectious Diseases. 2015;15(11):1314-23.

12. Chow EPF, Machalek DA, Tabrizi SN, Danielewski JA, Fehler G, Bradshaw CS, et al. Quadrivalent vaccine-targeted human papillomavirus genotypes in heterosexual men after the Australian female human papillomavirus vaccination programme: a retrospective observational study. The Lancet Infectious Diseases. 2017;17(1):68-77.

13. Cummings T, Zimet GD, Brown D, Tu W, Yang Z, Fortenberry JD, et al. Reduction of HPV infections through vaccination among at-risk urban adolescents. Vaccine. 2012;30(37):5496-9.

14. Dominiak-Felden G, Gobbo C, Simondon F. Evaluating the early benefit of quadrivalent HPV vaccine on genital warts in Belgium: A cohort study. PLoS ONE. 2015;10(7).

15. Dunne EF, Naleway A, Smith N, Crane B, Weinmann S, Braxton J, et al. Reduction in human papillomavirus vaccine type prevalence among young women screened for cervical cancer in an integrated US healthcare delivery system in 2007 and 2012-2013. Journal of Infectious Diseases. 2015;212(12):1970-5.

16. Flagg EW, Schwartz R, Weinstock H. Prevalence of anogenital warts among participants in private health plans in the United States, 2003-2010: potential impact of human papillomavirus vaccination. American journal of public health. 2013;103(8):1428-35.

17. Guerra FM, Rosella LC, Dunn S, Wilson SE, Chen C, Deeks SL. Early impact of Ontario's human papillomavirus (HPV) vaccination program on anogenital warts (AGWs): A population-based assessment. 2016;34(39):4678-83.

18. Harrison C, Britt H, Garland S, Conway L, Stein A, Pirotta M, et al. Decreased management of genital warts in young women in Australian general practice post introduction of national HPV vaccination program: results from a nationally representative cross-sectional general practice study. PLoS One. 2014;9(9):e105967.

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Justification: comparison is vaccinated versus unvaccinated in postvaccination period

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43. Niccolai LM, Julian PJ, Meek JI, McBride V, Hadler JL, Sosa LE. Declining rates of high-grade cervical lesions in young women in Connecticut, 2008-2011. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology. 2013;22(8):1446-50. *Justification: All samples from post-vaccine era; vaccine available since 2006 (although uptake increased over time); included in Drolet 2014*

44. Niccolai LM, Meek JI, Brackney M, Hadler JL, Sosa LE, Weinberger DM. Declines in HPV-associated high-grade cervical lesions after introduction of HPV vaccines in Connecticut, US, 2008-2015. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2017. *Justification: All samples from post-vaccine era; vaccine available since 2006 (although uptake increased over time)*

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53. Smith MA, Liu B, McIntyre P, Menzies R, Dey A, Canfell K. Trends in genital warts by socioeconomic status after the introduction of the national HPV vaccination program in Australia: Analysis of national hospital data. BMC Infectious Diseases. 2016;16(1). *Justification: Secondary analysis of Smith 2015 by socioeconomic status*

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55. Tarney C, Pagan M, Klaric J, Beltran T, Han J. HPV vaccination does not provide herd immunity for unvaccinated women or cross-protection for nonvaccine HPV types. Obstetrics and Gynecology. 2016;127:4S. *Justification: paper unobtainable*

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Appendix 5F: Summary of Findings (GRADE) tables

Question: Is there evidence of a population-level reduction in HPV-related disease following HPV immunisation programme implementation, comparing the pre- and post-vaccination periods?

Setting: Any population for whom a HPV immunisation programme was implemented

Summary of Findings

Certainty assessment							Sample size		Effect	Certainty
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Pre-vaccination**	**Post-vaccination**		
1. HPV 16/18 infection in girls (less than 20 years of age)										
13	observational studies	serious [a]	not serious	not serious	not serious	publication bias not suspected	10,167	13,013	**RR[b] ranged from** 0.04 to 0.50	⊕⊕◯◯ LOW[c]
2. HPV 16/18 infection in women (20 to 24 years of age)										
11	observational studies	serious [a]	not serious	not serious	not serious	publication bias not suspected	14,696	17,337	**RR[b] ranged from** 0.12 to 1.40	⊕◯◯◯ VERY LOW
3. HPV types 31/33/45/52/58 in girls (less than 20 years of age)										
12	observational studies	serious [a]	not serious	not serious	not serious	publication bias not suspected	9,796	12,613	**RR[b] ranged from** 0.67 to 1.62	⊕◯◯◯ VERY LOW
4. HPV types 31/33/45/52/58 in women (20 to 24 years of age)										
11	observational studies	serious [a]	not serious	not serious	not serious	publication bias not suspected	14,696	17,337	**RR[b] ranged from** 0.74 to 1.42	⊕◯◯◯ VERY LOW
5. Anogenital warts in girls (less than 20 years of age)										
10	observational studies	serious [a]	not serious	not serious	not serious	publication bias not suspected	9,140,390	12,917,924	**RR ranged from** 0.08 to 1.00	⊕◯◯◯ VERY LOW

Certainty assessment							Sample size		Effect	Certainty
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Pre-vaccination**	**Post-vaccination**		
6. Anogenital warts in women (20 +)										
11	observational studies	serious [a]	not serious	not serious	not serious	publication bias not suspected	13,542,421	27,609,812	**RR ranged from** 0.42 to 1.29	⊕◯◯◯ VERY LOW
7. Anogenital warts in boys (less than 20 years of age)										
10	observational studies	serious [a]	not serious	not serious	not serious	publication bias not suspected	4,221,196	7,608,638	**RR ranged from** 0.21 to 1.57	⊕◯◯◯ VERY LOW
8. Anogenital warts in men (20 +)										
10	observational studies	serious [a]	not serious	not serious	not serious	publication bias not suspected	12,062,360	22,961,127	**RR ranged from** 0.63 to 1.55	⊕◯◯◯ VERY LOW
9. CIN2+ in women (less than 20 years of age)										
3	observational studies	serious [a]	not serious	not serious	not serious	publication bias not suspected	11,656,905	18,032,926	**RR ranged from** 0.14 to 0.69	⊕◯◯◯ VERY LOW

RR: Risk ratio

Explanations

a. In all studies, there was risk of confounding (changes in outcome between pre and post-vaccination periods could be diluted/exacerbated by other variables) and potential for selection bias (changes in the study population characteristics between the pre- and post-vaccination periods).

b. Prevalence ratios of HPV infection were obtained by dividing the prevalence of HPV infection in the post-vaccination period by that of the pre-vaccination period.

c. This outcome was upgraded from 'very low' to 'low' due to large magnitude of effect

Appendix 5G. EAPC from Guerra et al. 2016

The estimated annual percentage change (EAPC) in anogenital warts by sex and age groups from Guerra et al. 2016 is presented below.

Average annual percentage change in AGW incidence (pre-vaccination / post-vaccination era)	
Females	
15-17	-5.9 (p=0.20)
18-20	-6.5 (p=0.03)
21-23	-3.3 (p=0.18)
24-26	+4.1 (p=0.15)
Males	
15-17	+12 (p=0.04)
18-20	+5.9 (p=0.33)
21-23	+4.8 (p=0.11)
24-26	+1.0 (p=0.77)

Appendix 6

Appendix 6A: Search terms and results

Search terms related to safety were guided by published literature.[345]

PubMed

Date of search: 12.4.18

Search string: (((ae OR co OR de) OR safe OR safety OR side effect* OR tolerability OR toxicity OR adrs OR (adverse adj2 (effect OR effects OR reaction OR reactions OR event OR event OR outcome OR outcomes))) AND ((HPV vaccin*) OR (human papillomavirus vaccin*) OR (HPV immuni*) OR (human papillomavirus immuni*) OR (4-valent vaccine*) OR (2-valent vaccine))

[Results = 2,745]

[Filters applied: Systematic reviews, humans = 133 results]

Embase

Embase 12/4/18		Search Strings	Results
Searches	#1	('**hpv**' OR '**hpv**'/exp OR **hpv**) AND **vaccin*** OR (('**hpv**' OR '**hpv**'/exp OR **hpv**) AND **immuni***) OR '**4-valent vaccine**' OR '**4-valent vaccine**'/exp OR **4-valent vaccine** OR '**silgard**' OR '**silgard**'/exp OR **silgard** OR '**2-valent vaccine**' OR '**2-valent vaccine**'/exp OR **2-valent vaccine**	19,072
	#2	'**safety**'/exp OR **safety** OR '**adverse event***' OR '**adverse drug reaction***' OR '**adrs**' OR '**side effect***' OR '**monitor***' OR '**toxicity**'/exp OR **toxicity** OR **complication***	6,373,204
	#3	1 AND 2	5,524
	#4	#3 AND '**systematic review**'/de	126

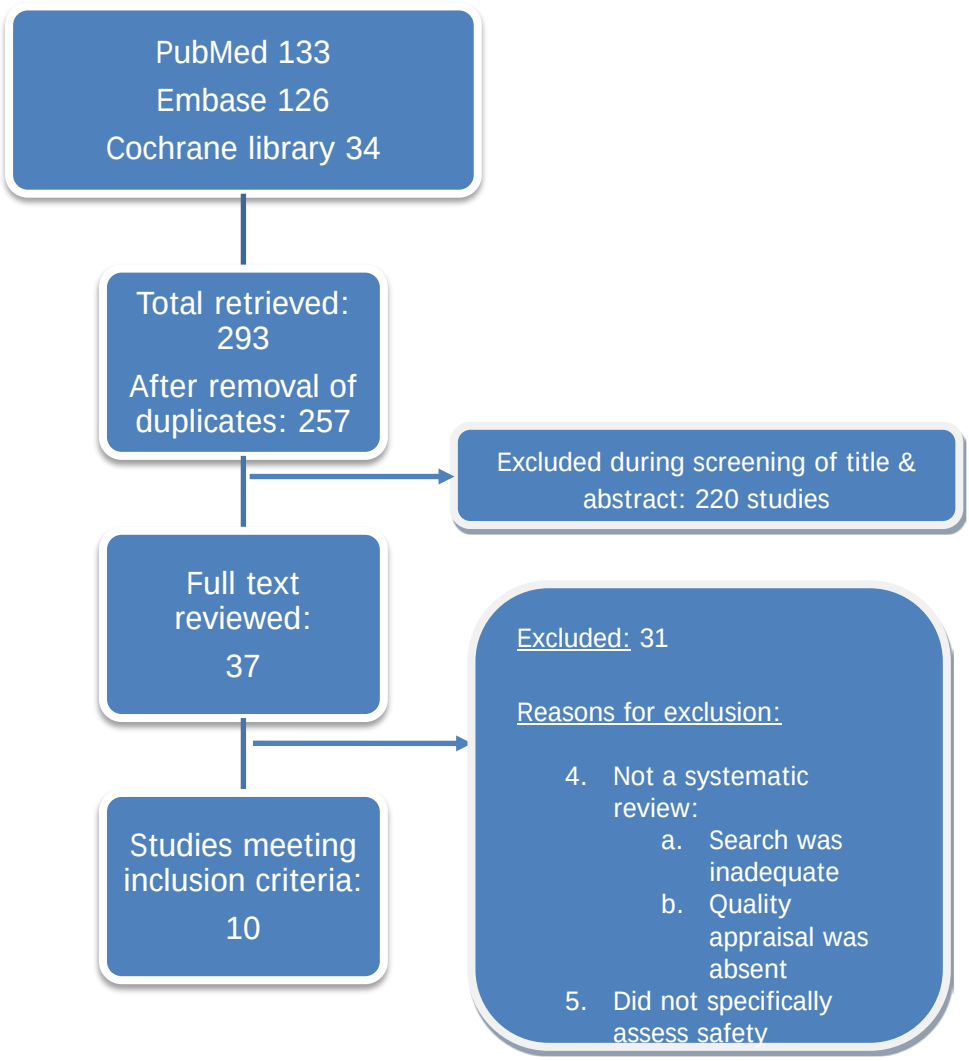
[Query(('safety'/exp OR safety OR 'adverse event*' OR 'adverse drug reaction*' OR 'adrs' OR 'side effect*' OR 'monitor*' OR 'toxicity'/exp OR toxicity OR complication*) AND (('hpv' OR 'hpv'/exp OR hpv) AND vaccin* OR (('hpv' OR 'hpv'/exp OR hpv) AND immuni*) OR '4-valent vaccine' OR '4-valent vaccine'/exp OR 4-valent vaccine OR 'silgard' OR 'silgard'/exp OR silgard OR '2-valent vaccine' OR '2-valent vaccine'/exp OR 2-valent vaccine)) AND 'systematic review'/exp

Mapped terms"systematic review" mapped to 'systematic review', term is exploded]

Cochrane library

Cochrane library 12/4/18		Search Strings	Results
Searches	#1	(HPV vaccine) or (HPV vaccination) or (human papillomavirus vaccine) or (human papillomavirus vaccation) or (HPV immunisation) or (HPV immunisation) or (human papillomavirus immunisation) or (human papillomavirus immunisation) or (4-valent vaccine) or (2-valent vaccine)	760
	#2	safety or safe or 'adverse event' or 'adverse drug reaction' or 'adrs' or 'side effect' or 'monitor' or 'toxicity' or toxic or complication	272,220
	#3	1 AND 2	272 [Cochrane reviews: 27 Other reviews: 4 HTAs: 3]

Appendix 6B: Flow diagram for study selection



Appendix 6C: List of studies included in this review

1. Arbyn M, Xu L, Simoens C, Martin-Hirsch PPL. Prophylactic vaccination against human papillomaviruses to prevent cervical cancer and its precursors. Cochrane Database of Systematic Reviews. 2018(5).

2. Coelho PLS, Da Silva Calestini GL, Alvo FS, De Moura Freitas JM, Castro PMV, Konstantyner T. Safety of human papillomavirus 6, 11, 16 and 18 (recombinant): Systematic review and meta-analysis. Revista Paulista de Pediatria. 2015;33(4):474-82.

3. Costa APF, Cobucci RNO, Da Silva JM, Da Costa Lima PH, Giraldo PC, Gonçalves AK. Safety of human papillomavirus 9-valent vaccine: A meta-analysis of randomized trials. Journal of Immunology Research. 2017;2017.

4. Jacqueline Parsons PTM, Prof Michael Gold. Serious adverse events associated with HPV vaccination. Adelaide Health Technology Assessment, University of Adelaide. 2017.

5. Lu B, Kumar A, Castellsagué X, Giuliano AR. Efficacy and Safety of Prophylactic Vaccines against Cervical HPV Infection and Diseases among Women: A Systematic Review & Meta-Analysis. BMC Infectious Diseases. 2011;11.

6. Medeiros LR, Rosa DD, Da Rosa MI, Bozzetti MC, Zanini RR. Efficacy of human papillomavirus vaccines a systematic quantitative review. International Journal of Gynecological Cancer. 2009;19(7):1166-76.

7. Meggiolaro A, Migliara G, La Torre G. Association between Human Papilloma Virus (HPV) vaccination and risk of Multiple Sclerosis: A systematic review. Human vaccines & immunotherapeutics. 2018:1-9.

8. Ogawa Y, Takei H, Ogawa R, Mihara K. Safety of human papillomavirus vaccines in healthy young women: a meta-analysis of 24 controlled studies. Journal of pharmaceutical health care and sciences. 2017;3:18.

9. Rambout L, Hopkins L, Hutton B, Fergusson D. Prophylactic vaccination against human papillomavirus infection and disease in women: A systematic review of randomized controlled trials. CMAJ. 2007;177(5):469-79.

10. Setiawan D, Luttjeboer J, Pouwels KB, Wilschut JC, Postma MJ. Immunogenicity and safety of human papillomavirus (HPV) vaccination in Asian populations from six countries: A meta-analysis. Japanese Journal of Clinical Oncology. 2017;47(3):265-76.

Appendix 6D: List of studies excluded from this review

1. Angelo MG, David MP, Zima J, Baril L, Dubin G, Arellano F, et al. Pooled analysis of large and long-term safety data from the human papillomavirus-16/18-AS04-adjuvanted vaccine clinical trial programme. Pharmacoepidemiol Drug Saf. 2014;23(5):466-79. *Justification: not a Systematic Review*

2. Angioli R, Lopez S, Aloisi A, Terranova C, De Cicco C, Scaletta G, et al. Ten years of HPV vaccines: State of art and controversies. Critical Reviews in Oncology/Hematology. 2016;102:65-72. *Justification: not a Systematic Review*

3. Bonde U, Joergensen JS, Lamont RF, Mogensen O. Is HPV vaccination in pregnancy safe? Human Vaccines and Immunotherapeutics. 2016;12(8):1960-4. *Justification: not a Systematic Review*

4. Brinth L, Theibel AC, Pors K, Mehlsen J. Suspected side effects to the quadrivalent human papilloma vaccine. Danish Medical Journal. 2015;62(4):1-5. *Justification: not a Systematic Review*

5. Chandler RE, Juhlin K, Fransson J, Caster O, Edwards IR, Norén GN. Current Safety Concerns with Human Papillomavirus Vaccine: A Cluster Analysis of Reports in VigiBase®. Drug Safety. 2017;40(1):81-90. *Justification: not a Systematic Review*

8. De Vincenzo R, Conte C, Ricci C, Scambia G, Capelli G. Long-term efficacy and safety of human papillomavirus vaccination. International journal of women's health. 2014;6:999-1010. *Justification: not a Systematic Review*

9. Descamps D, Hardt K, Spiessens B, Izurieta P, Verstraeten T, Breuer T, et al. Safety of human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine for cervical cancer prevention: a pooled analysis of 11 clinical trials. Human vaccines. 2009;5(5):332-40. *Justification: not a Systematic Review*

10. Forinash AB, Yancey AM, Pitlick JM, Myles TD. Safety of the HPV Bivalent and Quadrivalent Vaccines During Pregnancy. The Annals of pharmacotherapy. 2011;45(2):258-62. *Justification: not a Systematic Review*

11. Gonçalves AK, Cobucci RN, Rodrigues HM, De Melo AG, Giraldo PC. Safety, tolerability and side effects of human papillomavirus vaccines: A systematic quantitative review. Brazilian Journal of Infectious Diseases. 2014;18(6):651-9. *Justification: Insufficient detail regarding quality appraisal of included studies given.*

12. Hawkes D, Benhamu J, Sidwell T, Miles R, Dunlop RA. Revisiting adverse reactions to vaccines: A critical appraisal of Autoimmune Syndrome Induced by Adjuvants (ASIA). Journal of Autoimmunity. 2015;59:77-84. *Justification: not HPV safety review (adjuvant)*

13. Huygen F, Verschueren K, McCabe C, Stegmann JU, Zima J, Mahaux O, et al. Investigating Reports of Complex Regional Pain Syndrome: An Analysis of HPV-16/18-

Adjuvanted Vaccine Post-Licensure Data. EBioMedicine. 2015;2(9):1114-21. *Justification: Analysis of adverse event reports database (GSK)*

15. Jara LJ, García-Collinot G, Medina G, Cruz-Dominguez MP, Vera-Lastra O, Carranza-Muleiro RA, et al. Severe manifestations of autoimmune syndrome induced by adjuvants (Shoenfeld's syndrome). Immunologic Research. 2017;65(1):8-16. *Justification: not HPV safety review (adjuvant)*

16. Konstantyner T, Coelho PLS, Calestini GLDS, Alvo FS, Freitas JMDM, Castro PMV. Revista Paulista de Pediatria. 2015. *Justification: Duplicate of Coelho 2015 (Portuguese)*

17. La Torre G, de Waure C, Chiaradia G, Mannocci A, Capri S, Ricciardi W. The Health Technology Assessment of bivalent HPV vaccine 2-valent vaccine ® in Italy. Vaccine. 2010;28(19):3379-84. *Justification: HTA with SR of efficacy but not safety*

18. Loharikar A, Suragh TA, MacDonald NE, Balakrishnan MR, Benes O, Lamprianou S, et al. Anxiety-related adverse events following immunization (AEFI): A systematic review of published clusters of illness. Vaccine. 2018;36(2):299-305. *Justification: no quality appraisal; general review*

20. Luo W, Zhang SH, Zhou YZ, Wang C, Yang L, Qiu J. Safety and immunogenicity of quadrivalent HPV vaccine: A meta-analysis. Chinese Journal of Evidence-Based Medicine. 2015;15(1):47-53. *Justification: Cannot locate English text*

21. Macartney KK, Chiu C, Georgousakis M, Brotherton JML. Safety of human papillomavirus vaccines: A review. Drug Safety. 2013;36(6):393-412. *Justification: Not a systematic review with formal quality appraisal. General discussion of this paper included.*

22. Macki M, Dabaja AA. Literature review of vaccine-related adverse events reported from HPV vaccination in randomized controlled trials. Basic and clinical andrology. 2016;26:16. *Justification: not a Systematic Review (only 1 database searched and no quality appraisal)*

23. Mailand MT, Frederiksen JL. Vaccines and multiple sclerosis: a systematic review. Journal of Neurology. 2017;264(6):1035-50. *Justification: not a Systematic Review (only 1 database searched and no quality appraisal)*

24. Martínez-Lavín M, Amezcua-Guerra L. Serious adverse events after HPV vaccination: a critical review of randomized trials and post-marketing case series. Clinical Rheumatology. 2017;36(10):2169-78. *Justification: not a Systematic Review (only 1 database searched and no quality appraisal)*

26. Moreira ED, Jr., Block SL, Ferris D, Giuliano AR, Iversen OE, Joura EA, et al. Safety Profile of the 9-Valent HPV Vaccine: A Combined Analysis of 7 Phase III Clinical Trials. Pediatrics. 2016;138(2). *Justification: not a Systematic Review; Pooled analysis of 7 completed or ongoing studies*

27. Niyibizi J, Zanre N, Mayrand MH, Trottier H. The association between adverse pregnancy outcomes and maternal human papillomavirus infection: a systematic review protocol. Syst Rev. 2017;6(1):53. *Justification: protocol*

28. Noronha AS, Markowitz LE, Dunne EF. Systematic review of human papillomavirus vaccine coadministration. Vaccine. 2014;32(23):2670-4. *Justification: not a Systematic Review; unknown databases, no quality appraisal*

30. Pellegrino P, Radice S, Clementi E. Immunogenicity and safety of the human papillomavirus vaccine in patients with autoimmune diseases: A systematic review. Vaccine. 2015;33(30):3444-9. *Justification: not a Systematic Review; 1 database, no quality appraisal*

31. Rey-Ares L, Ciapponi A, Pichon-Riviere A. Efficacy and safety of human papilloma virus vaccine in cervical cancer prevention: Systematic review and meta-analysis. Archivos Argentinos de Pediatria. 2012;110(6):483-9. *Justification: Cannot locate English translation; no formal quality appraisal*

32. Sangar VC, Ghongane BB, Mathur G, Chowdhary AS. Safety and adverse events of prophylactic HPV vaccines among healthy women: A systematic review & meta analysis. International Journal of Pharmaceutical Sciences and Research. 2015;6(4):1779-91. *Justification: inadequate quality appraisal*

34. Signorelli C, Odone A, Ciorba V, Cella P, Audisio RA, Lombardi A, et al. Human papillomavirus 9-valent vaccine for cancer prevention: A systematic review of the available evidence. Epidemiology and Infection. 2017;145(10):1962-82. *Justification: inadequate quality appraisal*

35. Tan P, Wang X, Wei S, Liu Y, Wei Q, Dong Q. Efficacy and safety of prophylactic human papillomavirus vaccination in healthy males: A meta-analysis. Reviews in Medical Microbiology. 2015;26(4):143-53. *Justification: Cannot access full paper*

36. Tomljenovic L, Spinosa JP, Shaw CA. Human papillomavirus (HPV) vaccines as an option for preventing cervical malignancies: (How) effective and safe? Current Pharmaceutical Design. 2013;19(8):1466-87. *Justification: No details of search used*

37. Wacholder S, Chen BE, Wilcox A, Macones G, Gonzalez P, Befano B, et al. Risk of miscarriage with bivalent vaccine against human papillomavirus (HPV) types 16 and 18: pooled analysis of two randomised controlled trials. BMJ (Clinical research ed). 2010;340:c712. *Justification: not a Systematic Review*

Appendix 6E: Additional information on AMSTAR 2 appraisal tool

AMSTAR (A MeaSurement Tool to Assess systematic Reviews), originally published in 2007, is one of the most widely used instruments used to assess the quality of systematic reviews.[398] AMSTAR was designed as a practical critical appraisal tool for use by health professionals and policy makers who do not necessarily have advanced training in epidemiology, to enable them to carry out rapid and reproducible assessments of the quality of conduct of systematic reviews of randomised controlled trials of interventions. A modified version was validated externally and performed well against the global judgments of a panel of content experts.[399]

AMSTAR underwent further development to enable appraisal of systematic reviews of randomised and non-randomised studies of healthcare interventions. The revised instrument (AMSTAR 2) has an overall rating based on weaknesses in critical domains; AMSTAR 2 is not intended to generate an overall score.

Appendix 6E lists all items included in the AMSTAR 2 assessment tool.

Seven of the domains assessed in AMSTAR 2 have been highlighted as critical in the appraisal of study quality:[292]

- Protocol registered before commencement of the review
- Adequacy of the literature search
- Justification for excluding individual studies
- Risk of bias from individual studies being included in the review
- Appropriateness of meta-analytical methods
- Consideration of risk of bias when interpreting the results of the review)
- Assessment of presence and likely impact of publication bias.

The authors further propose a scheme for interpreting weaknesses detected in critical and non-critical items:

Rating overall confidence in the results of the review

1. High

   No or one non-critical weakness: the systematic review provides an accurate and comprehensive summary of the results of the available studies that address the question of interest

2. Moderate

   *More than one non-critical weakness**: the systematic review has more than one weakness but no critical flaws. It may provide an accurate summary of the results of the available studies that were included in the review

3. Low

   One critical flaw with or without non-critical weaknesses: the review has a critical flaw and may not provide an accurate and comprehensive summary of the available studies that address the question of interest

4. Critically low

   More than one critical flaw with or without non-critical weaknesses: the review has more than one critical flaw and should not be relied on to provide an accurate and comprehensive summary of the available studies

*Additionally, multiple non-critical weaknesses may diminish confidence in the review and it may be appropriate to move the overall appraisal down from moderate to low confidence.

Appendix 6F: Additional information on GRADE quality of evidence assessment

GRADE identifies five key elements that can be used to rate confidence in the estimates of intervention effects. The criteria are:

- risk of bias
- inconsistency of results indirectness of evidence
- imprecision
- publication bias.

Assessing and combining these components determines the quality of evidence for each outcome of interest as:

- ‘high’ - further research is very unlikely to change our confidence in this estimate of effect
- ‘moderate’ - (further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
- ‘low’ - further research is likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
- ‘very low’ - any estimate of effect is very uncertain.

Appendix 6G: Quality appraisal of included reviews using the AMSTAR 2 tool

	Arbyn 2018	ADELAIDE HTA (Parsons 2017)	Coelho 2015	Costa 2017	Lu 2011
OVERALL RESULT	**HIGH**	**LOW**	**CRITICALLY LOW**	**CRITICALLY LOW**	**CRITICALLY LOW**
1. Did the research questions and inclusion criteria for the review include the components of PICO?	Yes	Yes	Yes	Yes	No
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?*	Yes	Yes/partial yes.	Yes	Yes	No
3. Did the review authors explain their selection of the study designs for inclusion in the review?	No - did not explain why only RCTs	Yes	Yes	Yes	No
4. Did the review authors use a comprehensive literature search strategy?*	Yes	Partial yes	Partial yes	Yes	Yes
5. Did the review authors perform study selection in duplicate?	Yes	Unreported	Yes	Yes	Yes
6. Did the review authors perform data extraction in duplicate?	Yes	Unreported	Yes	Unreported	Yes
7. Did the review authors provide a list of excluded studies and justify the exclusions?*	Yes	No	No	No	No
8. Did the review authors describe the included studies in adequate detail?	Yes	Yes	Partial yes	No – little information on comparator	Yes
	Arbyn 2018	**ADELAIDE HTA (Parsons 2017)**	**Coelho 2015**	**Costa 2017**	**Lu 2011**

9.	Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?*	Yes	Yes	Yes: Jadad scale	Yes: Jadad scale	Partial yes; Tool not specified; Allocation concealment and Blinding assessed
10.	Did the review authors report on the sources of funding for the studies included in the review?	Yes	Yes	No	No	Yes
11.	If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?*	Yes	Yes	No – heterogeneity not tested although mentioned in discussion	Yes (included only low risk of bias RCTs)	Yes (included only low risk of bias RCTs)
12.	If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	Yes	Yes: Overall low RoB RCTs	Yes, by Jadad scale	Yes (included only low risk of bias RCTs)	Yes (included only low risk of bias RCTs)
13.	Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review?*	Yes	Yes: Overall low RoB RCTs	Yes, by Jadad scale	Yes (included only low risk of bias RCTs)	Yes (included only low risk of bias RCTs)
14.	Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Yes	Yes	Yes	Yes	Yes
15.	If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?*	Yes	Yes - as a part of GRADE evidence synthesis	No	Yes	Yes
16.	Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes	Yes	Yes	Yes	Unreported

*** = indicates a critical domain.**

	Meggiolaro 2018	Medeiros 2009	Ogawa 2017	Rambout 2007	Setiawan 2017
OVERALL RESULT	**CRITICALLY LOW**	**CRITICALLY LOW**	**CRITICALLY LOW**	**CRITICALLY LOW**	**CRITICALLY LOW**
1. Did the research questions and inclusion criteria for the review include the components of PICO?	No	Yes	Yes	Yes	Yes
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?*	No	No	No	Yes	No
3. Did the review authors explain their selection of the study designs for inclusion in the review?	Yes	Yes	No	No	No
4. Did the review authors use a comprehensive literature search strategy?*	Yes	Partial Yes	Yes	Yes	Yes
5. Did the review authors perform study selection in duplicate?	Yes	Yes	Yes	Yes	Yes
6. Did the review authors perform data extraction in duplicate?	Yes	Yes	Unreported	Yes	Yes
7. Did the review authors provide a list of excluded studies and justify the exclusions?*	No	Yes	No	No. List created and documented reason for exclusion, but this list not provided in publication	No / partial yes: reasons given, but list not given
8. Did the review authors describe the included studies in adequate detail?	Yes	Yes	Yes	Yes	Yes
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?*	Yes - Newcastle-Ottowa for observational, AMSTAR for Systematic Review	Yes. Cochrane Gynaecological Cancer Group & Oxford Level of Evidences Classification	Yes: Cochrane RoB tool	Yes. Jadad scale.	Yes

	Meggiolaro 2018	Medeiros 2009	Ogawa 2017	Rambout 2007	Setiawan 2017
10. Did the review authors report on the sources of funding for the studies included in the review?	Yes	No	No	Yes. Jadad scale.	Yes
11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?*	No Meta-analysis	Yes	No - heterogeneity identified but not taken into consideration / interrogated	Yes	Yes
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	No Meta-analysis	Yes	Yes Overall low RoB RCTs	Yes	No
13. Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review?*	No Meta-analysis	Yes	Yes Overall low RoB RCTs	Yes; all trials 5/5 Jadad	No
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	N/A	Yes	No	Yes; all trials 5/5 Jadad	Yes
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?*	No Meta-analysis	No	No	Yes	Yes
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes	Yes	Yes	No	Yes

*=indicates a critical domain.

Appendix 6H: Serious adverse events and deaths (all included reviews)

Study	Relative Risk (RR) / Odds Ratio (OR); 95% Confidence Interval (CI)
Arbyn. 2018	• Serious adverse events: RR 0.98; 95% CI: 0.92 to 1.05 (data from 71,597 participants in 23 RCTs; high-quality evidence) • Deaths: RR 1.29; 95% CI: 0.85 to 1.98 (data from 71,176 participants in 23 RCTs; low-quality evidence)
Adelaide HTA 2017 (Parsons et al.)	• Serious adverse events: o 4-valent versus placebo: RR 0.93 (95% CI 0.72 to 1.21) o 4-valent versus control: RR 0.87 (95% CI 0.43 to 1.78) o 2-valent versus placebo: RR 0.87 (95% CI 0.60 to 1.25) o 2-valent versus control: RR 1.01 (95% CI 0.95 to 1.07) • Deaths: RR not calculated. In the trials that did report causality, no deaths were judged to be related to vaccination o In the 4-valent vaccine trials, no deaths were considered vaccine-related o In the 2-valent vaccine trials, two studies reported deaths. They did not assess their causality but did report the causes, which were: suicide, car accidents, assault, cancer, Crohn's disease, systemic lupus erythematosus, HIV-related condition and acute myocardial infarction
Coelho et al. 2015	• Meta-analysis was only performed on minor outcomes. • From the study authors: "among the analyzed studies, there was only one case of severe adverse event related to the vaccine, which was bronchospasm. The others showed no reports of vaccine-related severe adverse effects or deaths."
Costa et al. 2017	• Serious adverse events were not common, and there was no significant difference between 9- and 4-valent vaccines. Out of more than 27,000 vaccine recipients, a total of 29 and 23 recipients from the 9-valent and 4-valent groups, respectively, experienced a serious vaccine-related adverse event. • A total of 6 deaths were recorded from each group but none was judged to be vaccine related.
Lu et al.2011	• Serious Adverse Events*: RR 1.00 (95% CI: 0.91 to 1.09); n=7 studies. • Injection-related Serious Adverse Events**: RR 1.82 (95% CI: 0.79 to 4.20); n=7 studies. • Deaths: unreported.
Medeiros et al. 2009	• Serious Adverse Events: OR 1.05 (95% CI: 0.91 to 1.21); n=2 trials, both 2-valent vaccine trials. • Deaths: Not estimable (0 in intervention, 0 in control).

Meggiolaro et al. 2018	• Serious adverse events other than multiple sclerosis were not assessed. • Multiple Sclerosis was deemed not associated with HPV vaccine.
Ogawa et al. 2017	Serious adverse events or deaths were not considered. Only solicited and unsolicited local or systemic symptoms were investigated.
Rambout et al. 2007	• Greater than one serious adverse events: Peto odds ratio 1.00 (95% CI: 0.87 to 1.14) n=6 trials. • Death: Peto odds ratio 0.91 (95% CI: 0.39 to 2.14), n=4 trials. Most deaths were reported as accidental, and none of the deaths were considered attributable to the vaccine. *Note: Medeiros 2009 and Rambout 2007 systematic reviews were very similar in design; difference in outcomes partly explained by model used (fixed effects in Rambout, random effects in Medeiros) and number of included studies.*
Setiawan et al. 2017	Serious adverse events or deaths were not considered. Only local or systemic adverse events were investigated.

RR=relative risk. OR=odds ratio. CI=confidence interval

*'Serious Adverse Events' in Lu et al. included abnormal pregnancy outcomes, blood and lymphatic system disorder, hepatobiliary disorder, immune system disorder, cardiac and vascular disorder, gastrointestinal disorder, musculoskeletal and connective tissue disorder, nervous system disorder, psychiatric disorder, renal and urinary disorder, reproductive system and breast disorder, respiratory, thoracic and mediastinal disorder, skin and subcutaneous tissue disorder, neoplasm, infection and infestation, injury, poisoning and procedural complications

**'Injection-related Serious Adverse Events' in Lu et al. included bronchospasm, gastroenteritis, headache, hypertension, injection-site pain, decrease in joint movement at injection site, hypersensitivity to injection, chills, headache and fever

Appendix 7

Appendix 7A: Search terms and results

Pubmed 20/11/2017		Search Strings	Results
Searches	#1	(human papillomavirus vaccines[MeSH Terms]) OR HPV vaccin* OR HPV immun*	8,087
	#2	((((((((((((((((((models, economic[mesh]) OR "economics, pharmaceutical"[mesh]) OR "economics, medical"[mesh]) OR "health care costs"[mesh]) OR "decision support techniques"[mesh]) OR "cost-benefit analysis"[mesh]) OR "Cost of illness"[mesh]) OR "cost savings"[mesh]) OR "Hospital costs"[mesh]) OR "economic"[ti]) OR ("costs and cost analysis"[mesh])) OR economic evaluation*[ti]) OR economic analy*[ti]) OR cost analy*[ti]) OR cost eff*[ti]) OR cost benefit*[ti]) OR cost utilit*[ti]) OR ("economics"[mesh])) OR cost*[ti/ab])	666,270
	#3	((letter[Publication Type] OR editorial[Publication type] OR historical article[Publication Type]) OR animals)	7,823,160
	#4	(#1 AND #2) NOT #3	**643**

EMBASE 20/11/2017		Search Strings	Results
Searches	#1	('hpv'/exp OR hpv) AND ('vaccine'/exp OR vaccine)	12,146
	#2	HPV AND vaccin*	12,132
	#3	wart AND virus AND vaccine	13,173
	#4	human AND papillomavirus AND vaccine	10,637
	#5	(hpv OR human) AND papillomavirus AND (immunization OR immunisation)	3,059
	#6	#1 OR #2 OR #3 OR #4 OR #5	17,477
	#7	models, AND economic OR 'economics'/exp OR 'economics, pharmaceutical'/exp OR 'economics, medical'/exp OR 'health care costs'/exp OR 'cost benefit analysis'/exp OR 'cost of illness'/exp OR 'cost	1,414,469

		savings'/exp OR 'hospital costs'/exp OR 'economic':ab,ti OR 'costs and cost analysis'/exp OR cost*:ab,ti OR (economic AND evaluation*:ab,ti) OR (economic AND analy*:ab,ti) OR (cost AND analy*:ab,ti) OR (cost AND eff*:ab,ti) OR (cost AND benefit*:ab,ti) OR (cost AND utilit*:ab,ti)	
	#8	#6 AND #7	3,626
	#9	#8 AND 'human'/de AND [embase]/lim NOT [medline]/lim	1,014
	#10	#8 AND 'human'/de AND [embase]/lim NOT [medline]/lim AND ('letter'/it OR 'note'/it OR 'short survey'/it)	116
	#11	#9 NOT #10	898

EBSCOhost (CINAHL + EconLit) 20/11/2017		**Search Strings**	**Results**
Searches	#1	SU models, economic	12,444
	#2	SU economics OR SU economics, pharmaceutical OR SU economics, medical	770,452
	#3	SU Health Care Costs OR SU Decision Support Techniques OR SU Cost-Benefit Analysis OR SU Cost of Illness OR SU Cost Savings OR SU Hospital Costs	77,705
	#4	TI economic OR AB economic	347,877
	#5	SU costs AND cost analysis	26,827
	#6	TI cost* OR AB cost*	259,919
	#7	TI economic evaluation* OR AB economic evaluation*	6,341
	#8	TI economic analy* OR AB economic analy*	25,267
	#9	TI cost analy* OR AB cost analy*	20,637
	#10	TI cost eff* OR AB cost eff*	53,276
	#11	TI cost benefit* OR AB cost benefit*	17,241
	#12	TI cost utilit* OR AB cost utilit*	3,024
	#13	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12	1,129,338
	#14	TI human papillomavirus vaccine OR AB human	1,068

		papillomavirus vaccine	
	#15	TI HPV vaccine OR AB HPV vaccine	1,982
	#16	SU HPV vaccine	2,812
	#17	SU human papillomavirus vaccine	9,120
	#18	TI HPV immunisation OR AB HPV Immunisation	148
	#19	TI HPV immunization OR AB HPV immunization	150
	#20	TI human papillomavirus immunization OR AB human papillomavirus immunization	69
	#21	TI human papillomavirus immunisation OR AB human papillomavirus immunisation	58
	#22	HPV vaccine	2,044
	#23	human papillomavirus vaccine	1,145
	#24	#14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23	2,683
	#25	S13 AND S24	**440**

Cochrane Collaboration 21/11/2017		**Search Strings**	**Results**
Searches	#1	human papillomavirus vaccine	555
	#2	HPV vaccine:ti,ab,kw	547
	#3	HPV immunisation OR HPV immunization	146
	#4	human papillomavirus immunisation OR human papillomavirus immunization	145
	#5	#1 OR #2 OR #3 OR #4	672
	#6	economic:ti,ab,kw	13,157
	#7	cost*:ti,ab,kw	58,209
	#8	economic evaluation*:ti,ab,kw	6,896
	#9	economic analy*:ti,ab,kw	23,012
	#10	cost analy*:ti,ab,kw	44,367
	#11	cost eff*:ti,ab,kw	42,424
	#12	cost benefit*:ti,ab,kw	25,928
	#13	cost utilit*:ti,ab,kw	2,698
	#14	MeSH descriptor: [Economics, Pharmaceutical] explode all trees	244
	#15	MeSH descriptor: [Economics] explode all trees	27,751
	#16	MeSH descriptor: [Economics, Medical] explode all trees	105

	#17	MeSH descriptor: [Health Care Costs] explode all trees	7,471
	#18	MeSH descriptor: [Decision Support Techniques] explode all trees	3,671
	#19	MeSH descriptor: [Cost-Benefit Analysis] explode all trees	18,506
	#20	MeSH descriptor: [Cost of Illness] explode all trees	1,349
	#21	MeSH descriptor: [Cost Savings] explode all trees	1,021
	#22	MeSH descriptor: [Hospital Costs] explode all trees	1,527
	#23	MeSH descriptor: [Costs and Cost Analysis] explode all trees	25,599
	#24	#6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23	75,688
	#25	#5 and #24	**229**