Health Information and Quality Authority

An tÚdarás Um Fhaisnéis agus Cáilíocht Sláinte

Appendices

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

4 December 2018

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Please note: Appendix numbers correspond to the relevant chapter of the full HTA report**.**

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-valent	Females		Jul-05	Target age 11-12; schools-based	68% (2015)	
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 4A 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 4B 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 4C 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 4D 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).

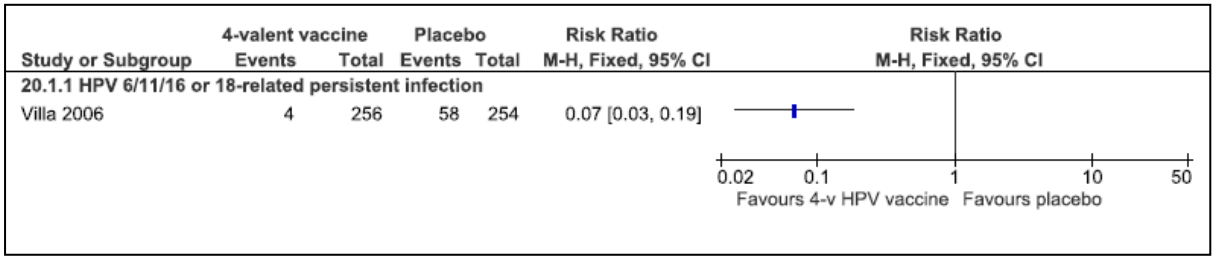


Figure 4.7 Estimate of effect on HPV 06/11/16 or 18-related CIN, external anogenital and vaginal lesions comparing the 4-valent HPV vaccine versus placebo in women aged 15 to 26 years at 42 months (generally HPV-naïve population)

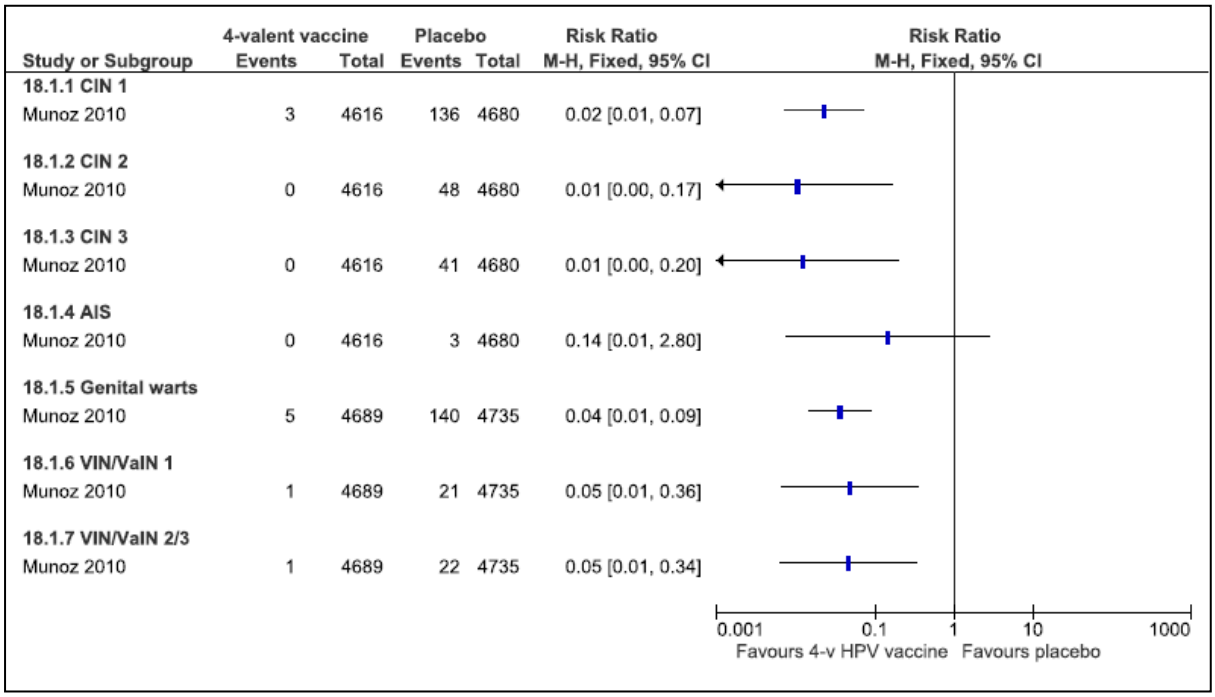


Figure 4.8 Estimate of effect on any HPV type-related CIN, external anogenital and vaginal lesions comparing the 4-valent HPV vaccine versus placebo in women 16-24 years at 36 months (generally HPV-naïve population)

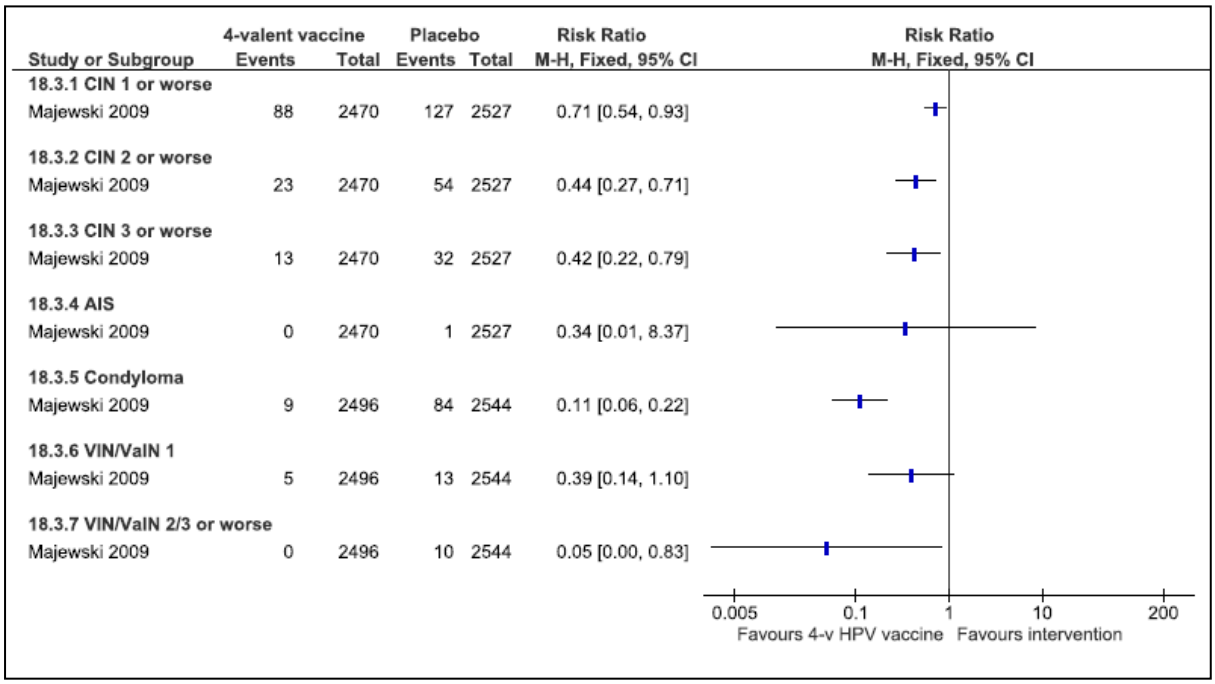


Figure 4.9 Estimate of effect on HPV 06/11/16 or 18-related CIN, external anogenital and vaginal lesions comparing the 4-valent HPV vaccine versus placebo in women 16-26 years at 36 and 42 months (unrestricted susceptible population)

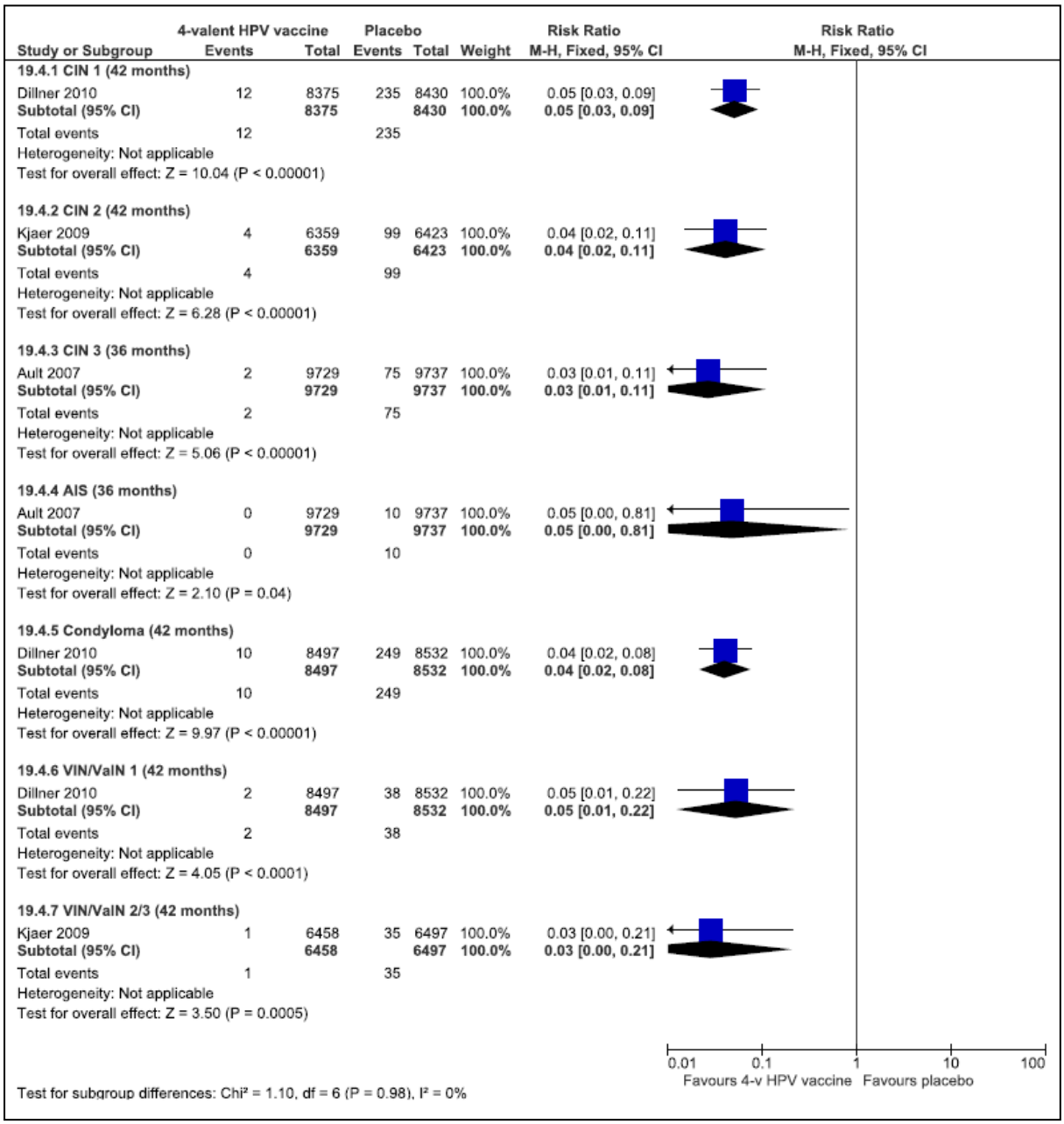


Figure 4.10 Estimate of effect on HPV 06/11/16 or 18-related persistent infections comparing the 4-valent HPV vaccine versus placebo in 16-26 year old males at 2.9 years (median) (Naïve-to-relevant type population)

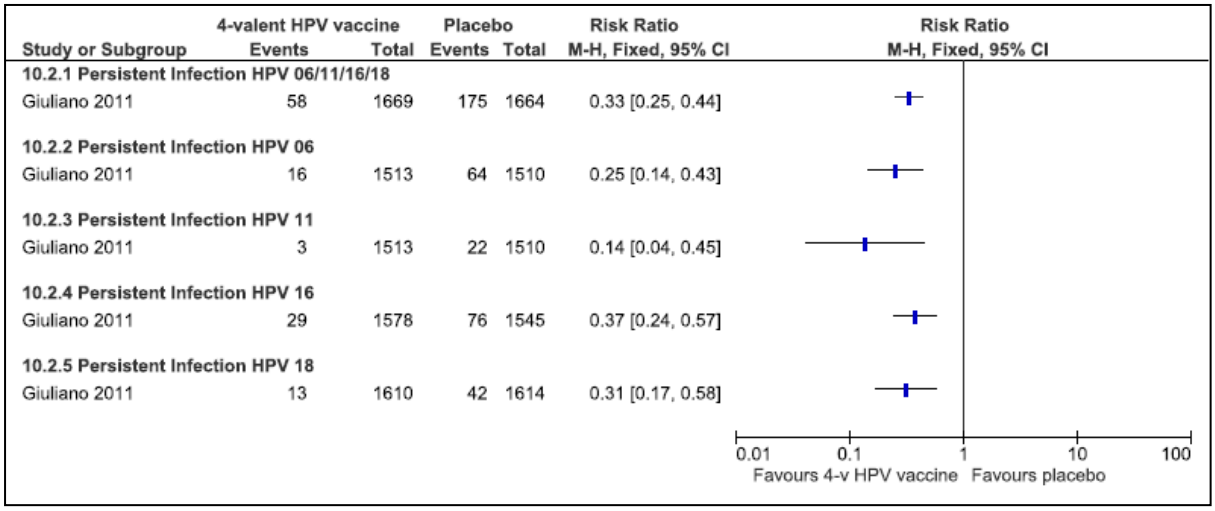


Figure 4.11 Estimate of effect on HPV 06/11/16 or 18-related lesions comparing the 4-valent HPV vaccine versus placebo in 16-26 year old males at 2.9 years (median) (Naïve-to-relevant type population)

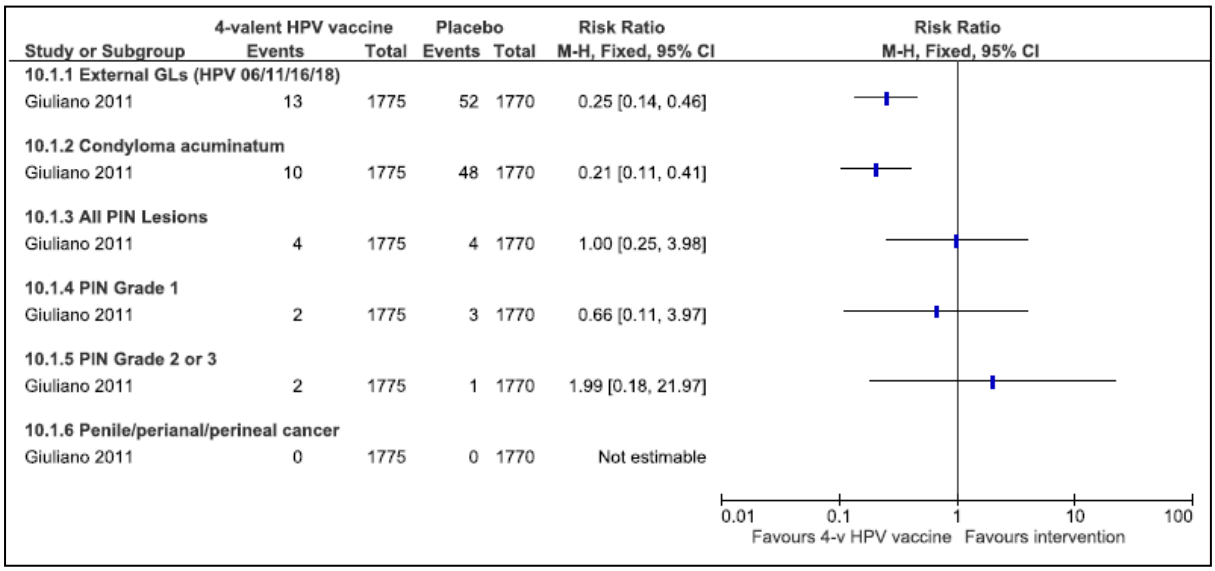


Figure 4.12 Estimate of effect on all-HPV type-related lesions comparing the 4-valent HPV vaccine versus placebo in 16-26 year old males at 36 months (HPV-naïve population)

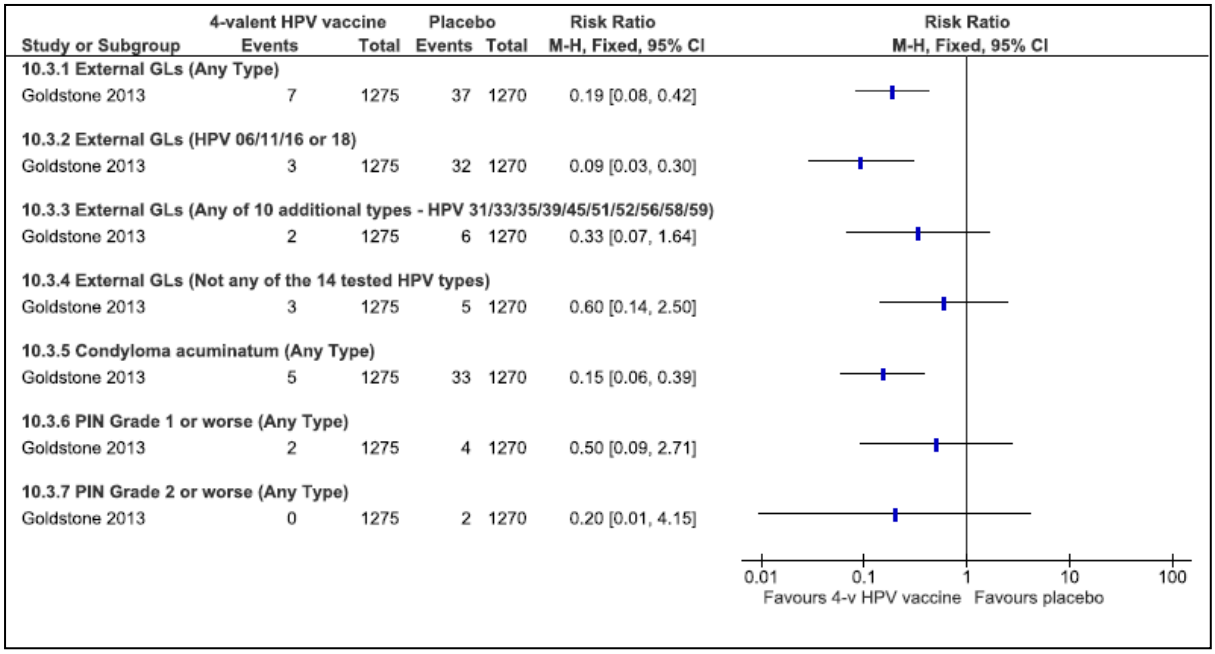


Figure 4.13 Estimate of effect on comparing 4-valent HPV vaccination in persistent infection and/or disease in boys versus girls aged 9 to 15 years from 42 to 96 months (Early Vaccination Group [EVG] ITT Population)

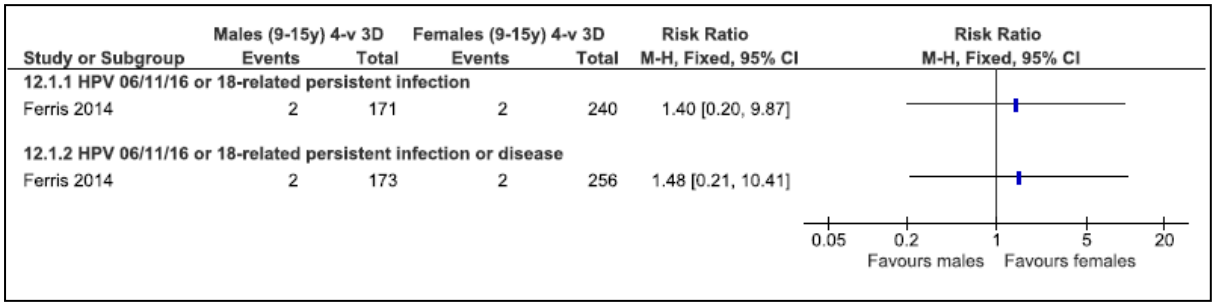


Figure 4.14 Estimate of effect on comparing 9-valent and 4-valent HPV vaccination in HPV 6, 11, 16 & 18-related low-grade and high-grade cervical, vaginal and vulvar disease in women 16-26 years at 48 months (modified intention-to-treat population)

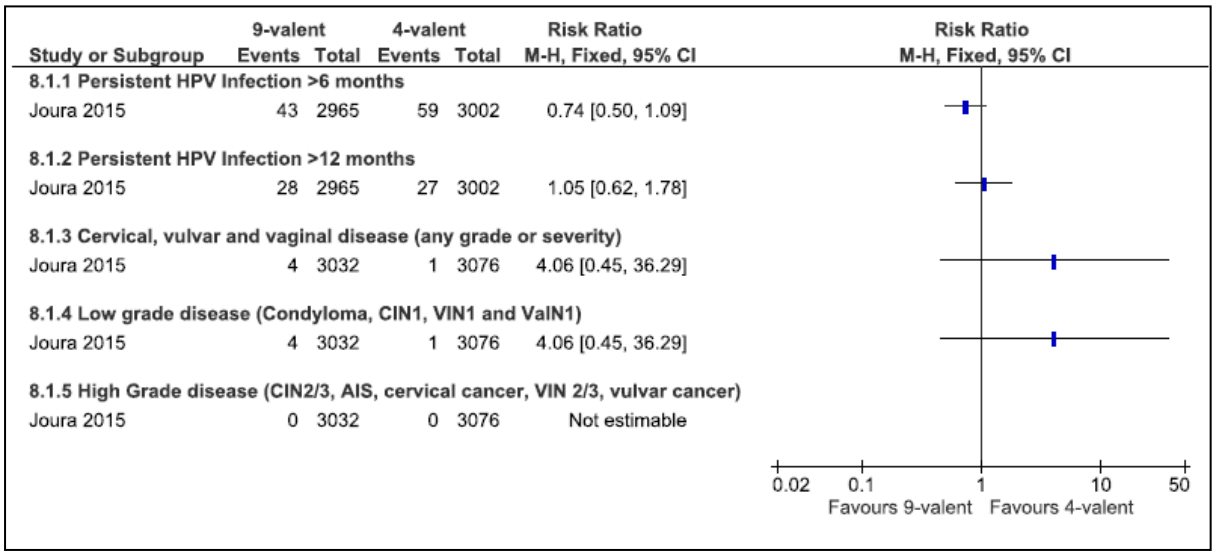


Figure 4.15 Estimate of effect on HPV 31/33/35/39/45/51/52/56/58 or 59-related CIN lesions and AIS comparing the 4-valent HPV vaccine versus placebo in women 16-26 years at 42 months (generally HPV-naïve population)

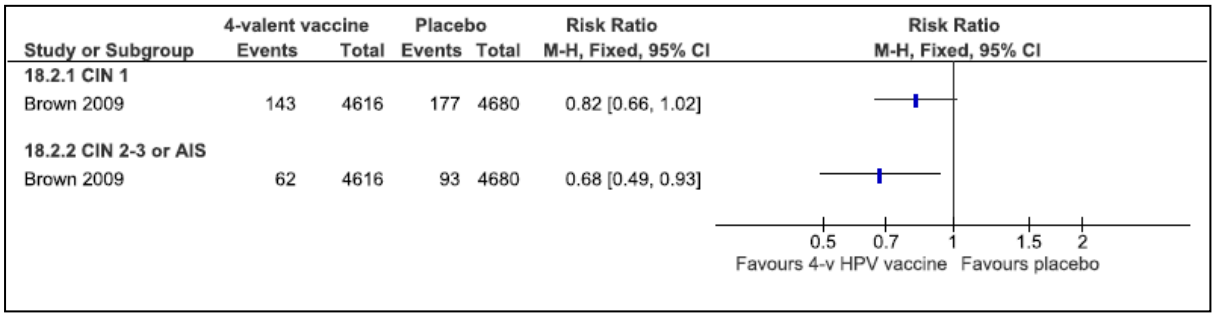


Figure 4.16 Estimate of effect on comparing 4-valent HPV vaccination in HPV 31/33/35/39/45/51/52/56/58 & 59-related persistent infection and external genital lesions in boys versus girls aged 9 to 15 years from 42 to 120 months (Early Vaccination Group [EVG] ITT Population)

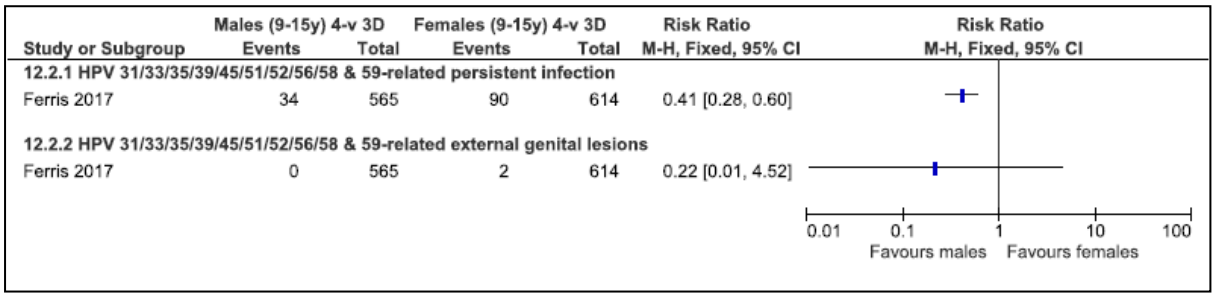


Figure 4.17 Estimate of effect on comparing 9-valent and 4-valent HPV vaccination in HPV 31, 33, 45, 52, 58-related low-grade and high-grade cervical, vaginal and vulvar disease in women 16-26 years at 48 months (modified intention-to-treat population)

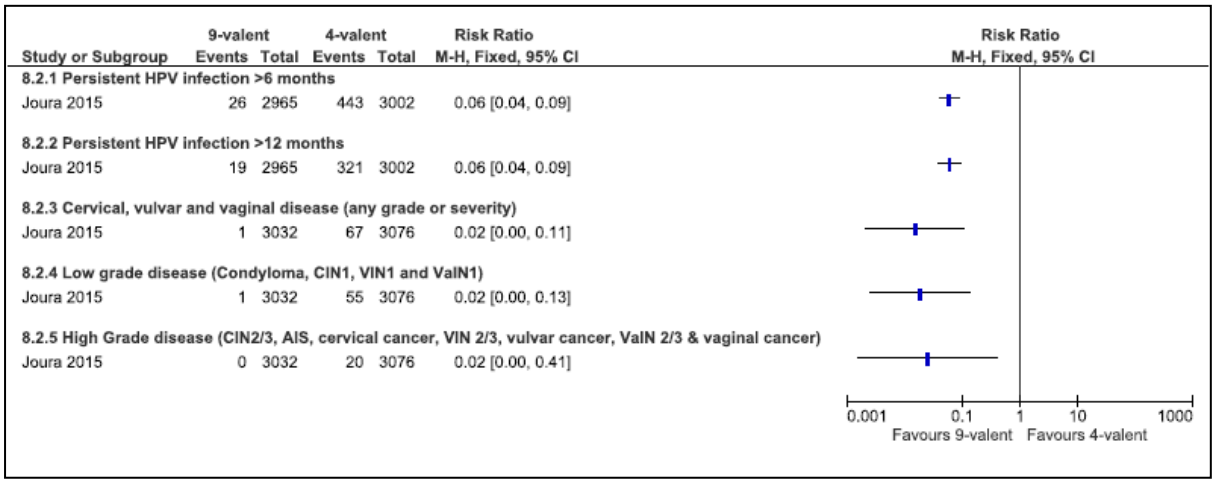


Figure 4.18 Estimate of effect on GMTs for common vaccine HPV types comparing 9-valent and 4-valent HPV vaccination in females 16-26 years from 7 to 42 months (per-protocol population)

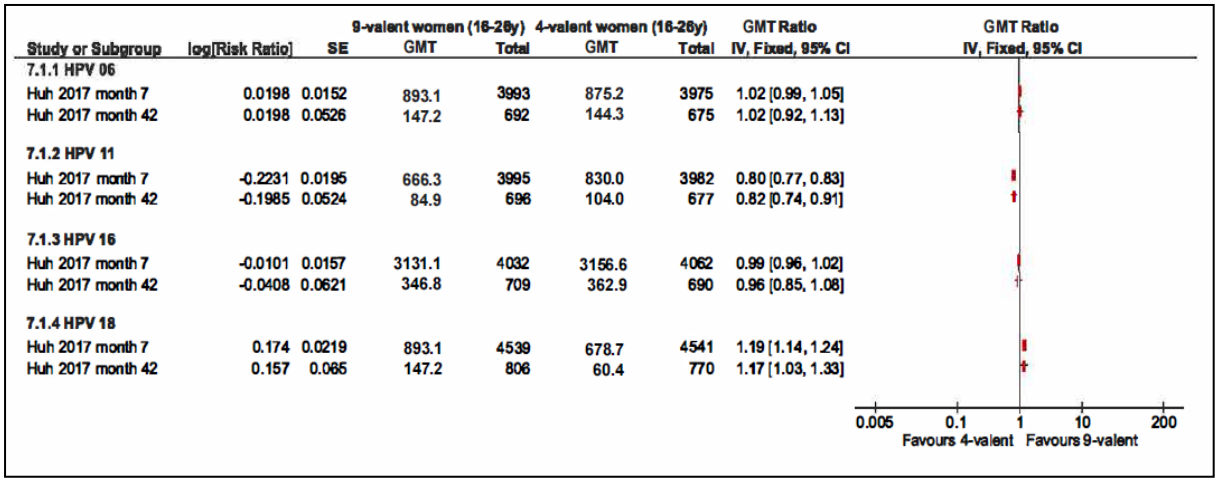


Figure 4.19 Estimate of effect on comparing seropositivity rates for 9-valent and 4-valent HPV vaccination in females 16-26 years from seven to 42 months (per-protocol population)

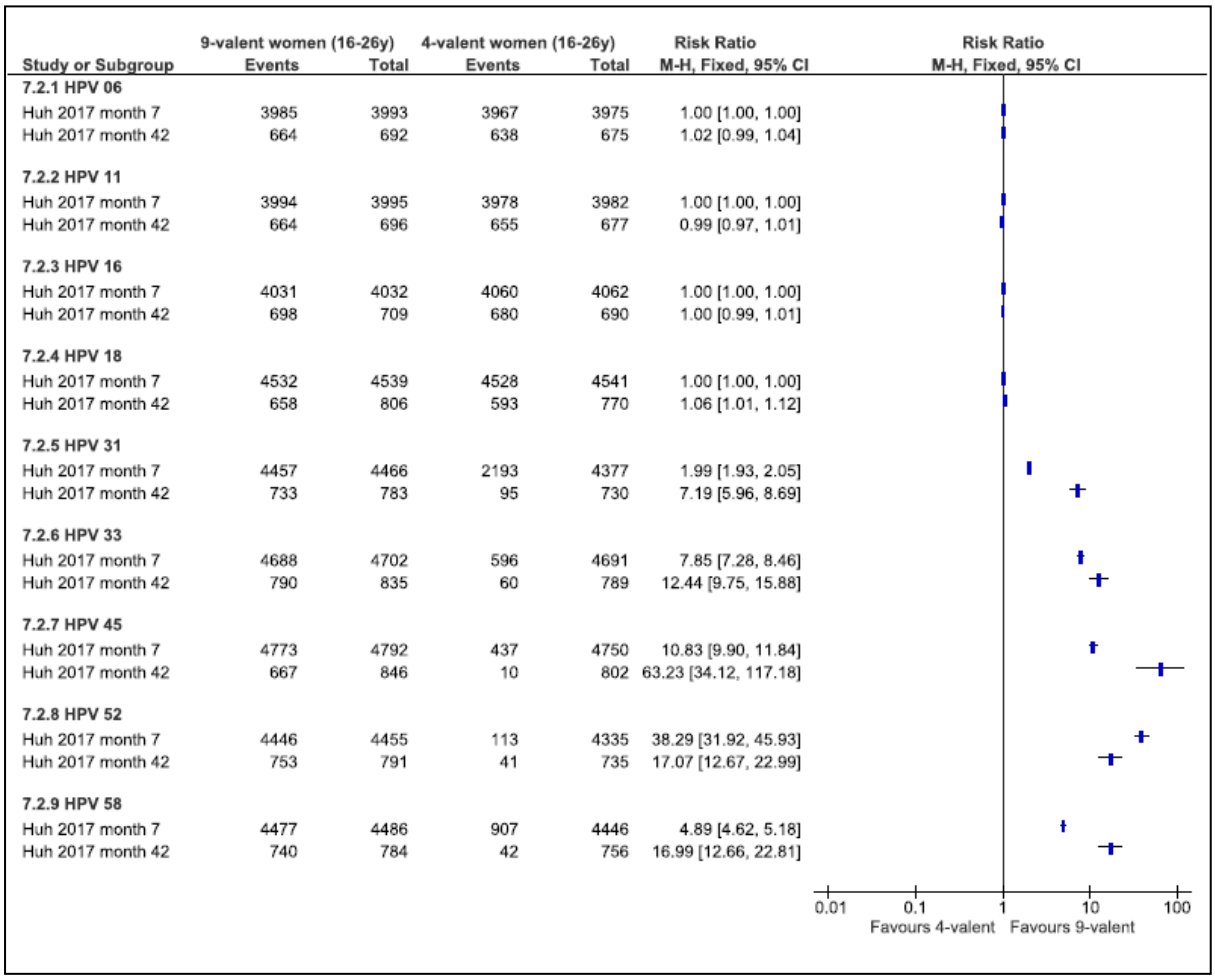


Figure 4.20 Estimate of effect on GMTs for all vaccine HPV types comparing 9-valent and 4-valent HPV vaccination in females aged nine to 15 years at seven months (per-protocol population)

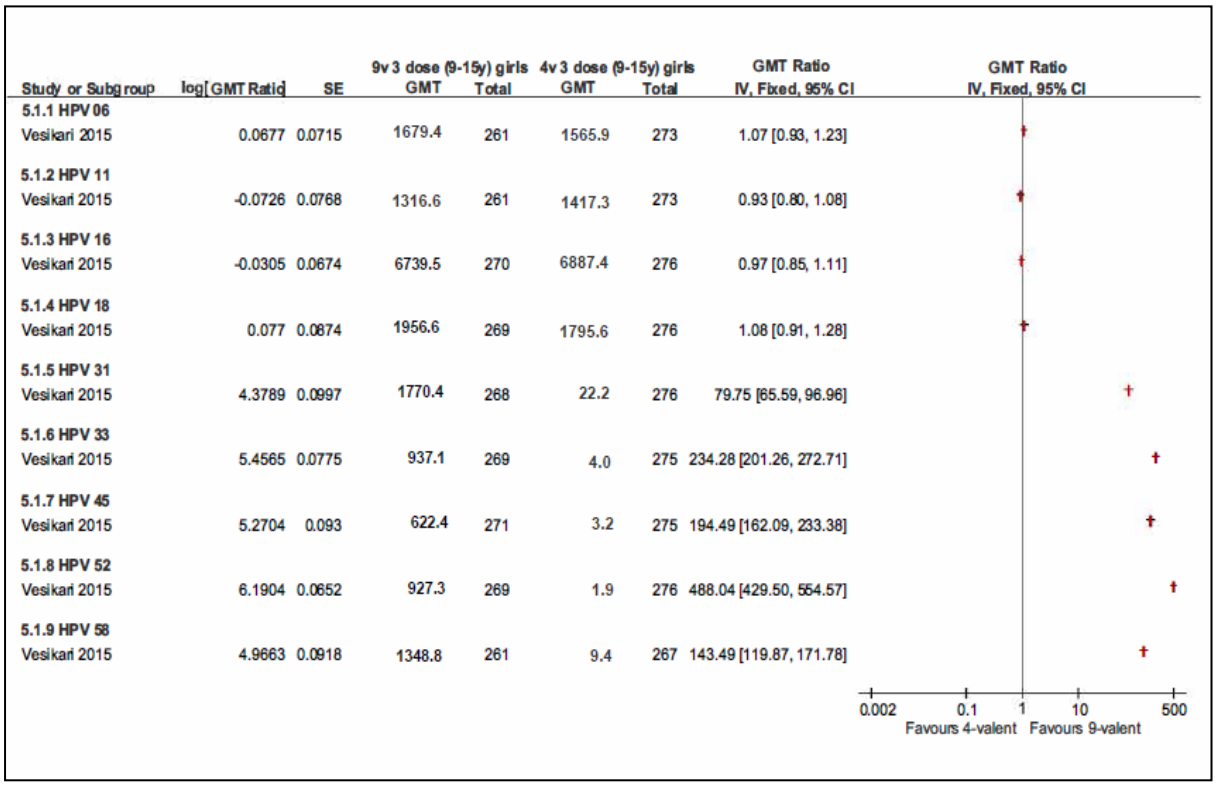


Figure 4.21 Estimate of effect on seropositivity rates for all vaccine HPV types comparing 9-valent and 4-valent HPV vaccination in females aged nine to 15 years at seven months (per-protocol population)

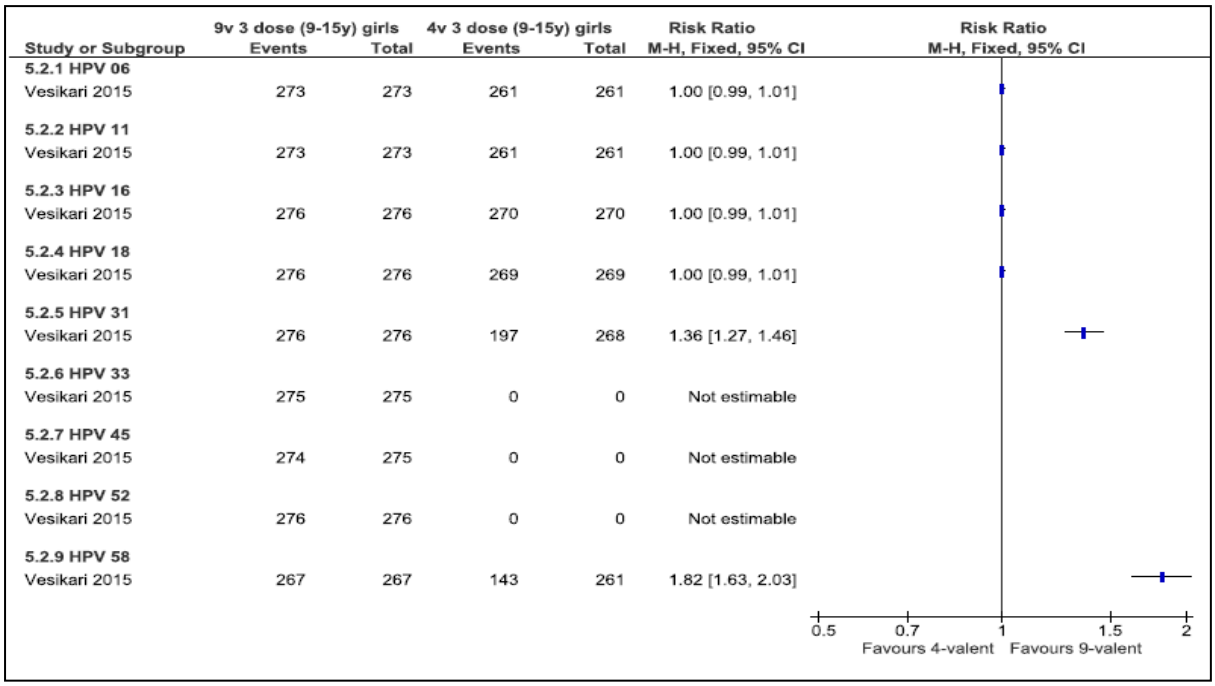


Figure 4.22 Estimate of effect on GMTs for all vaccine HPV types comparing 9-valent and 4-valent HPV vaccination in males 16-26 years at seven months (per-protocol population)

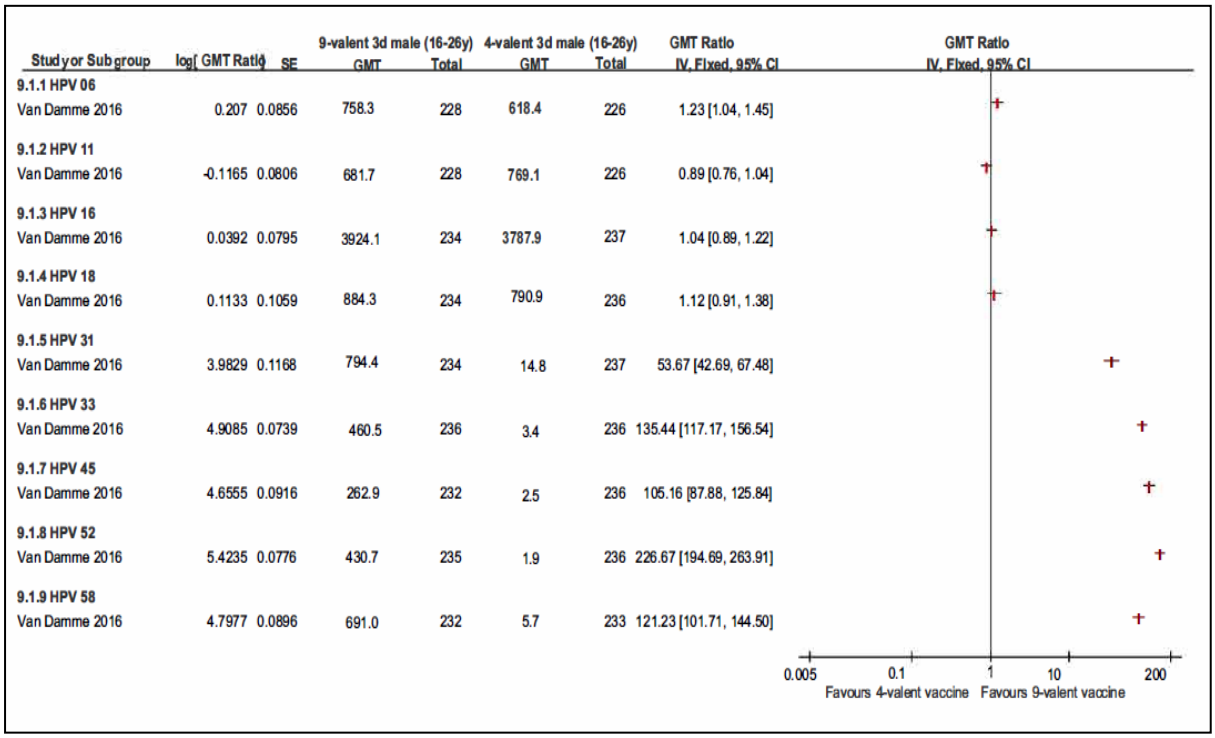


Figure 4.23 Estimate of effect on seropositivity rates for all vaccine HPV types comparing 9-valent and 4-valent HPV vaccination in males 16-26 years at seven months (per-protocol population)

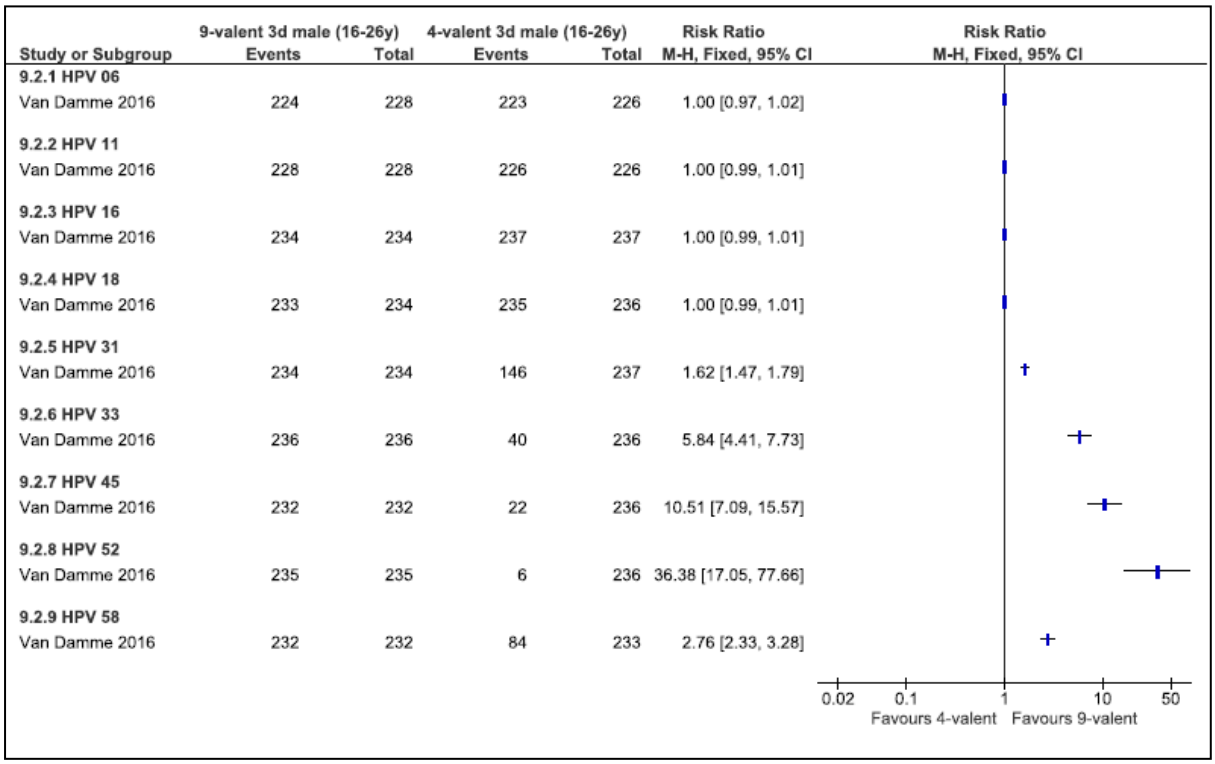


Figure 4.24 Estimate of effect on GMTs for the 4-valent HPV vaccine in males versus females aged nine to 15 years from seven to 96 months (per-protocol population)

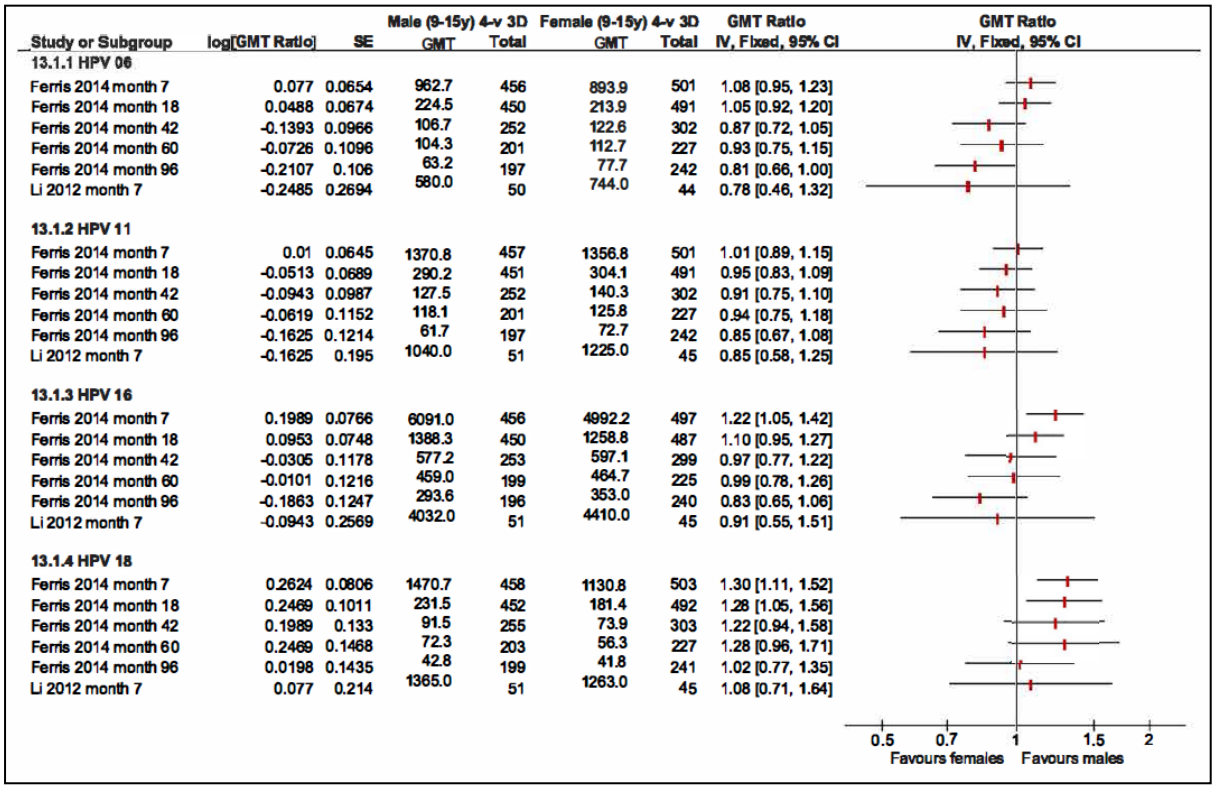


Figure 4.25 Estimate of effect on seropositivity rates for the 4-valent HPV vaccine in males versus females aged nine to 15 years from seven to 18 months (per-protocol population)

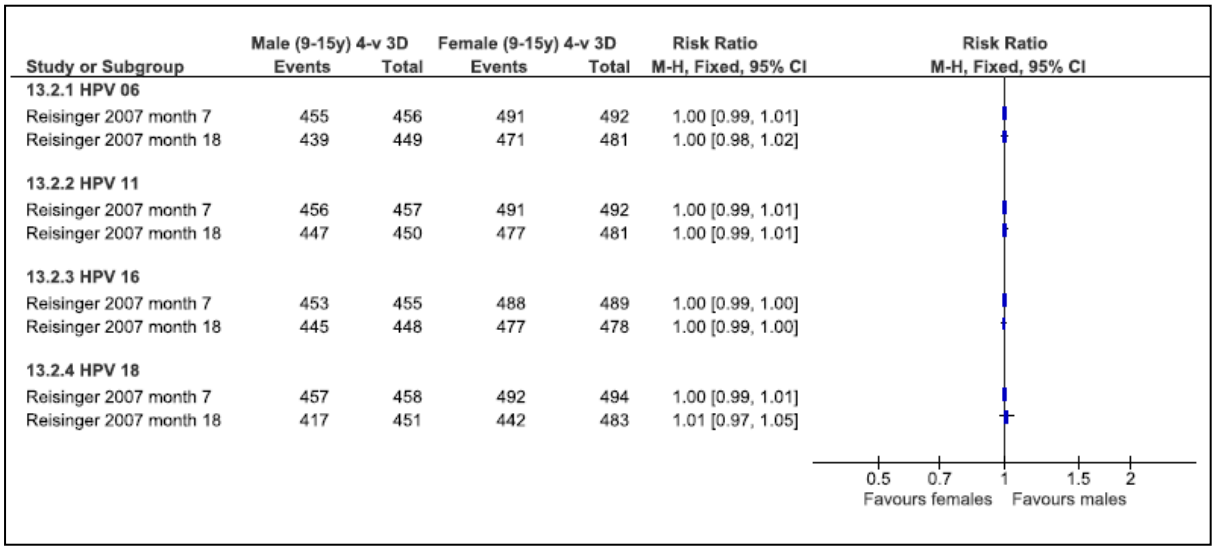


Figure 4.26 Estimate of effect on GMTs for the 9-valent HPV vaccine in males versus females 16-26 years at seven months (per-protocol population)

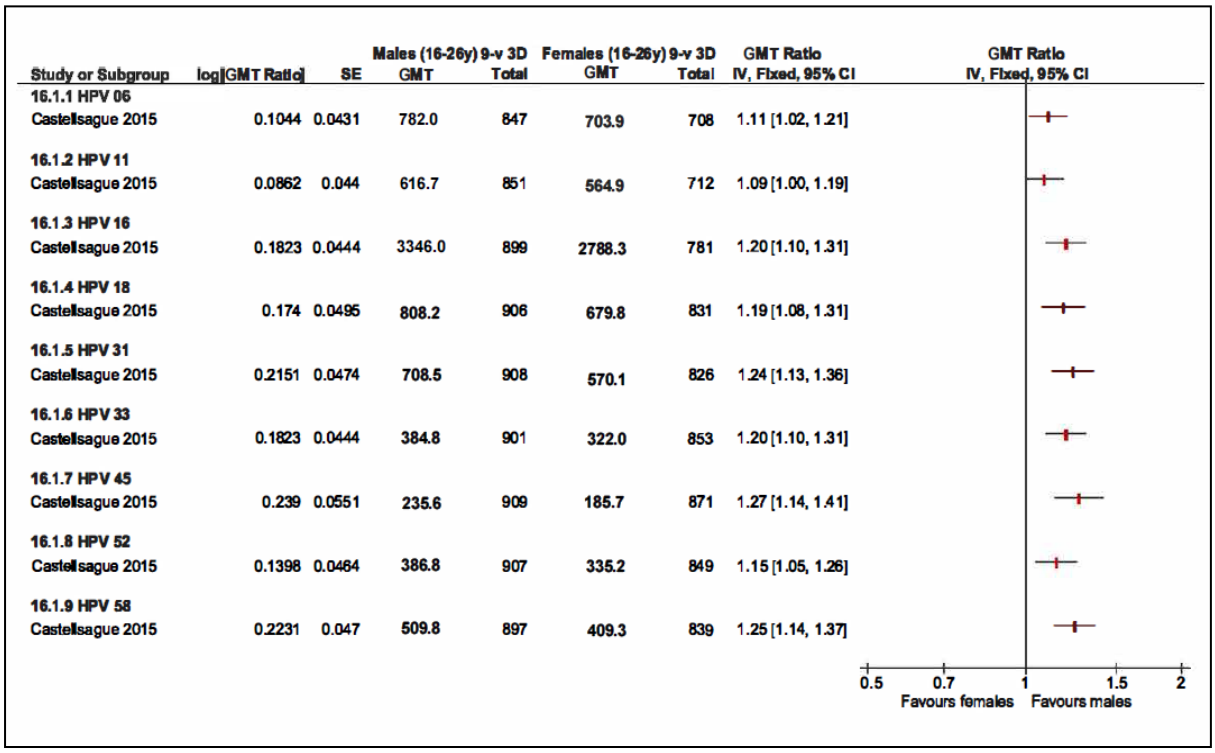


Figure 4.27 Estimate of effect on seropositivity rates for the 9-valent HPV vaccine in males versus females 16-26 years at seven months (per-protocol population)

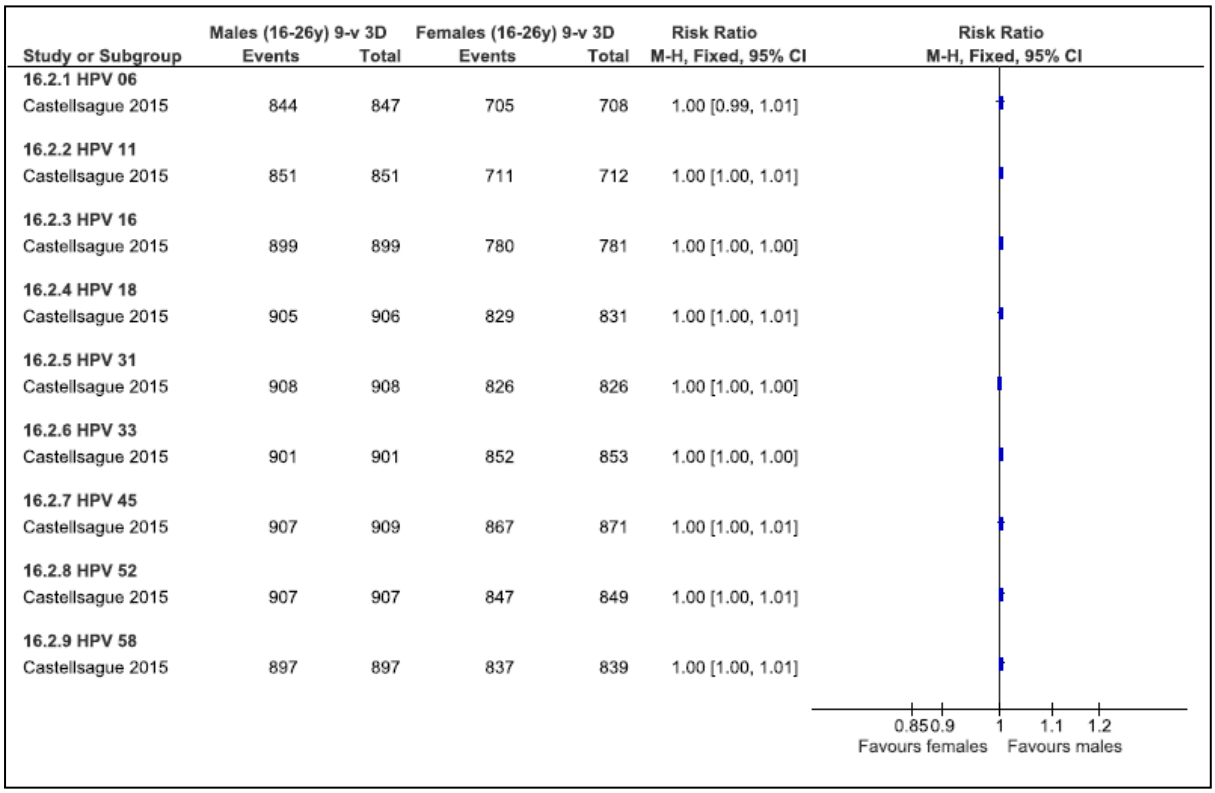


Figure 4.28 Estimate of effect on GMTs for the 9-valent HPV vaccine in males versus females aged nine to 15 years from seven to 36 months (per-protocol population)

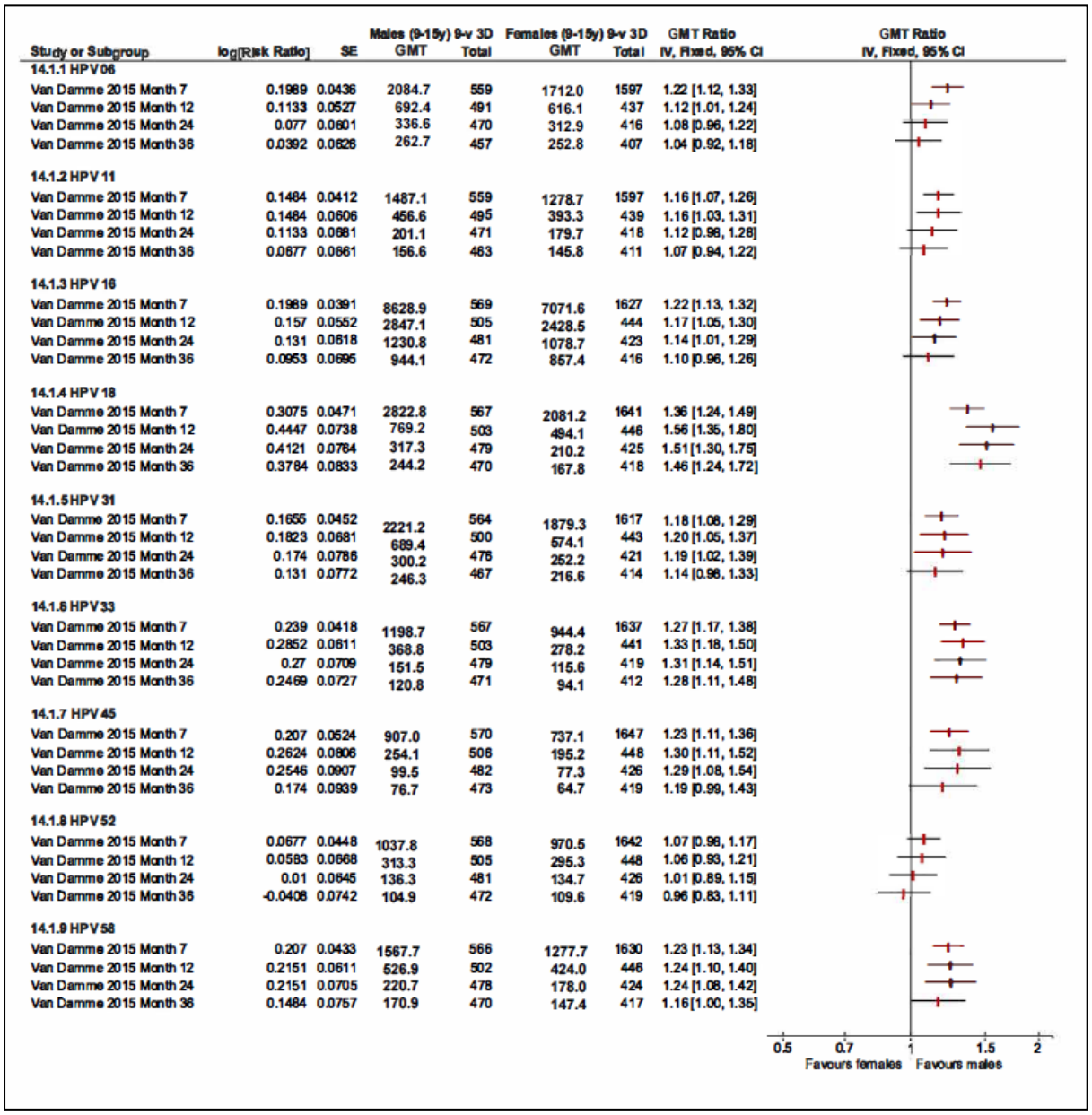


Figure 4.29 Estimate of effect on seropositivity rates for the 9-valent HPV vaccine in males versus females aged nine to 15 years from seven to 36 months (per-protocol population)

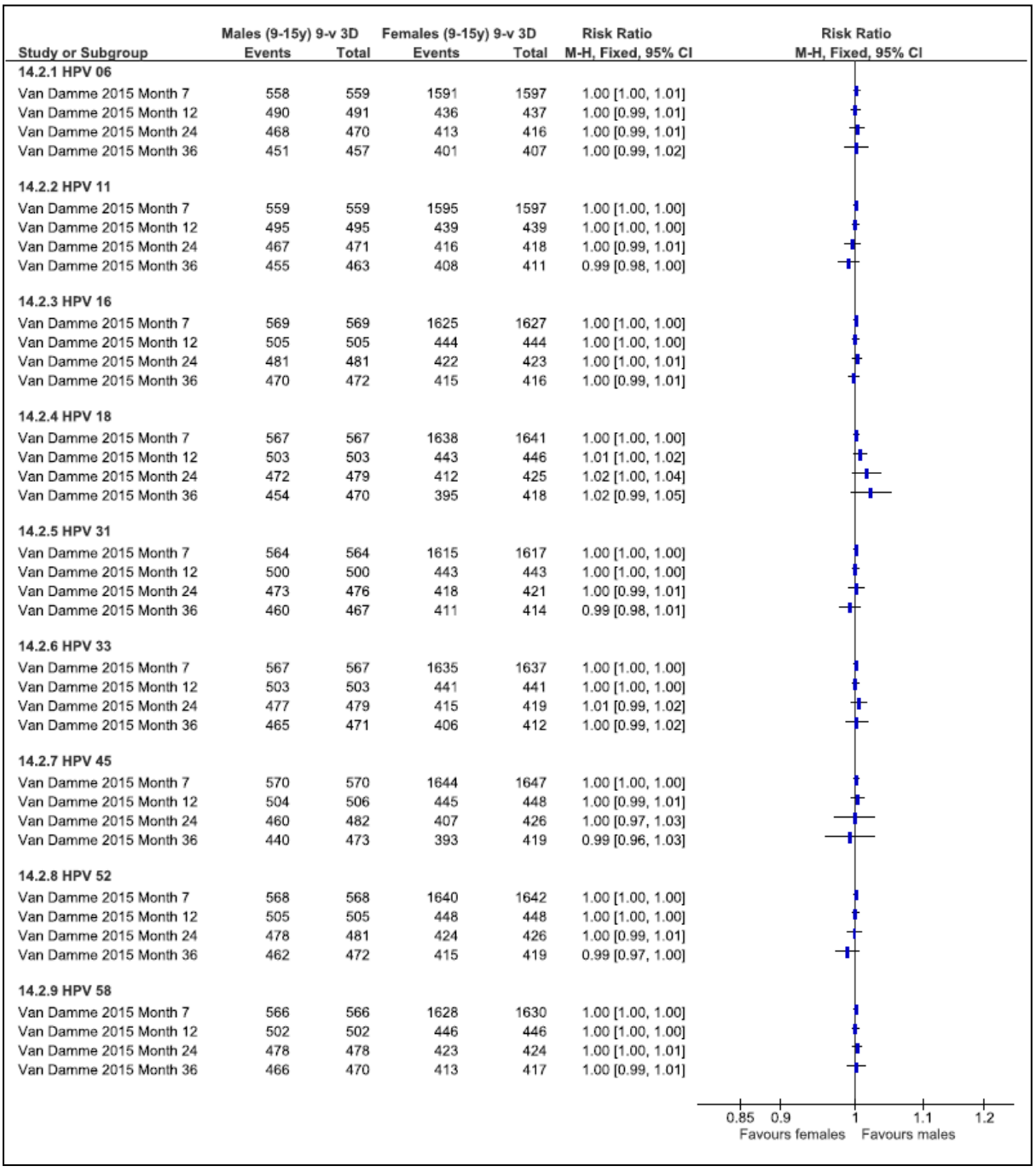


Figure 4.30 Estimate of effect on GMTs comparing two-dose HPV vaccine schedules (females nine-15 years) versus three-dose HPV vaccine schedules (females 15-26 years) at seven months (per-protocol population)

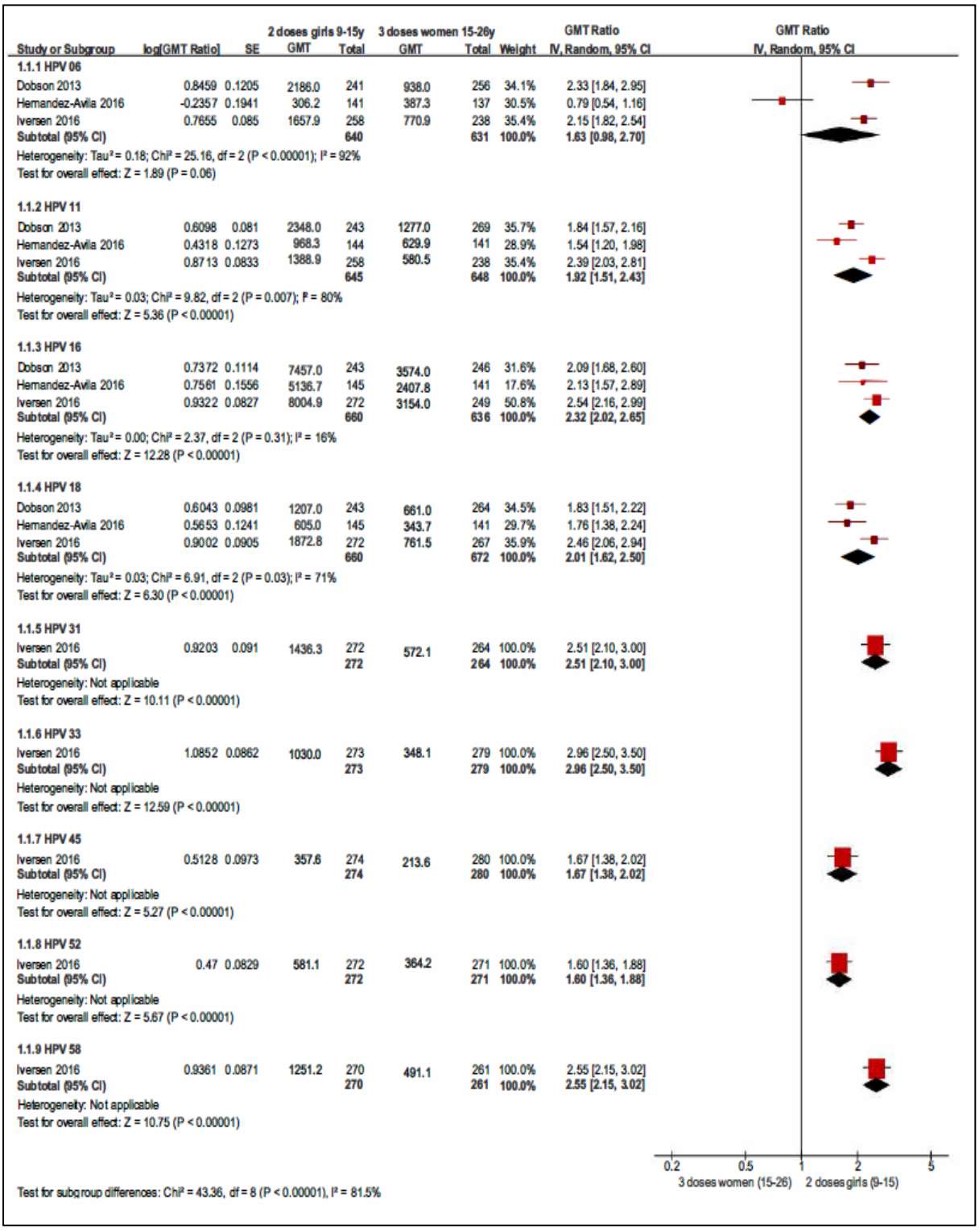


Figure 4.31 Estimate of effect on seropositivity rates comparing two-dose HPV vaccine schedules (females nine-15 years) versus three-dose HPV vaccine schedules (females 15-26 years) at seven months (per-protocol population)

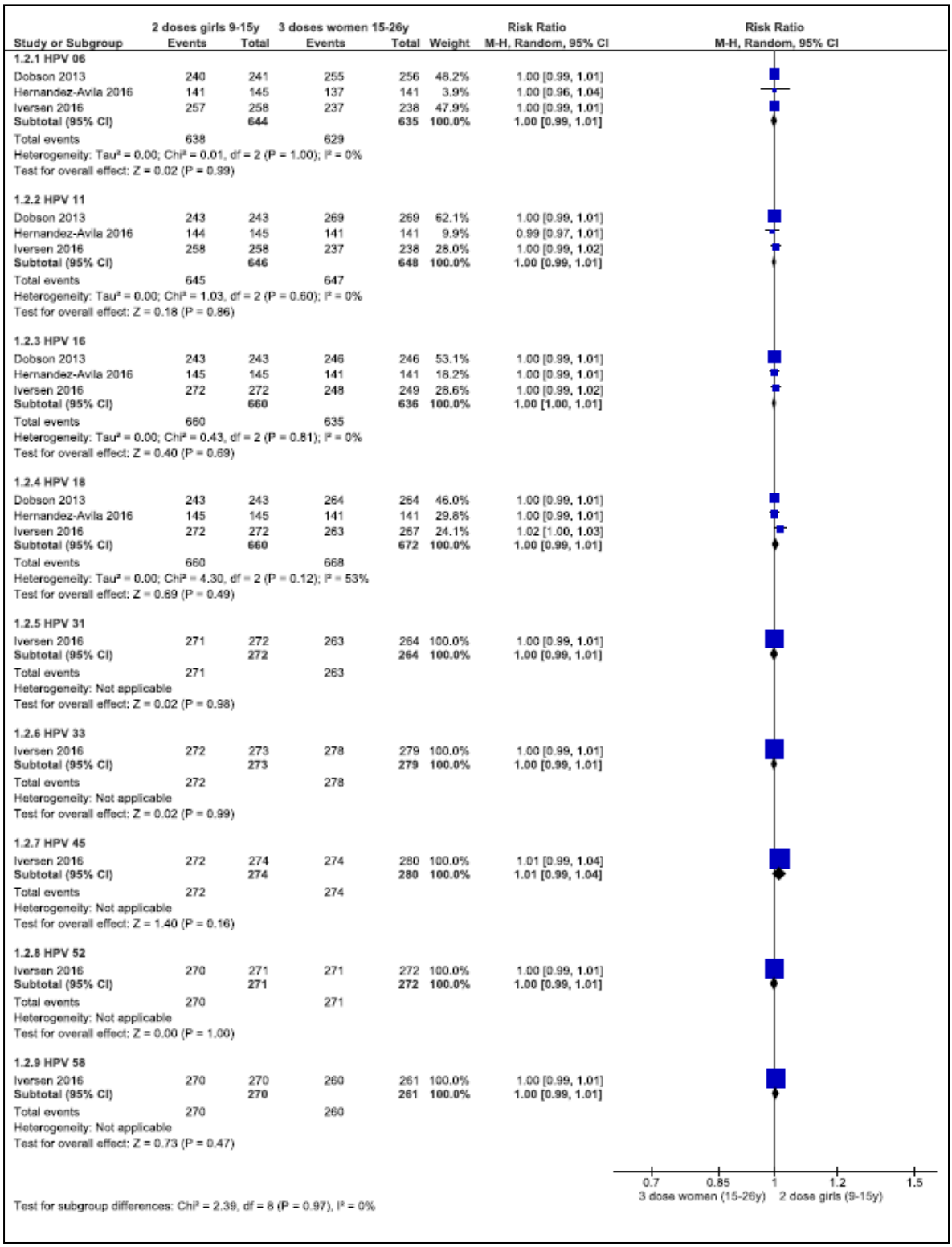


Figure 4.32 Estimate of effect on GMTs comparing two-dose 4-valent HPV vaccine schedules (females nine-13 years) versus three-dose 4-valent HPV vaccine schedules (females 16-26 years) from seven to 36 months (per-protocol population)

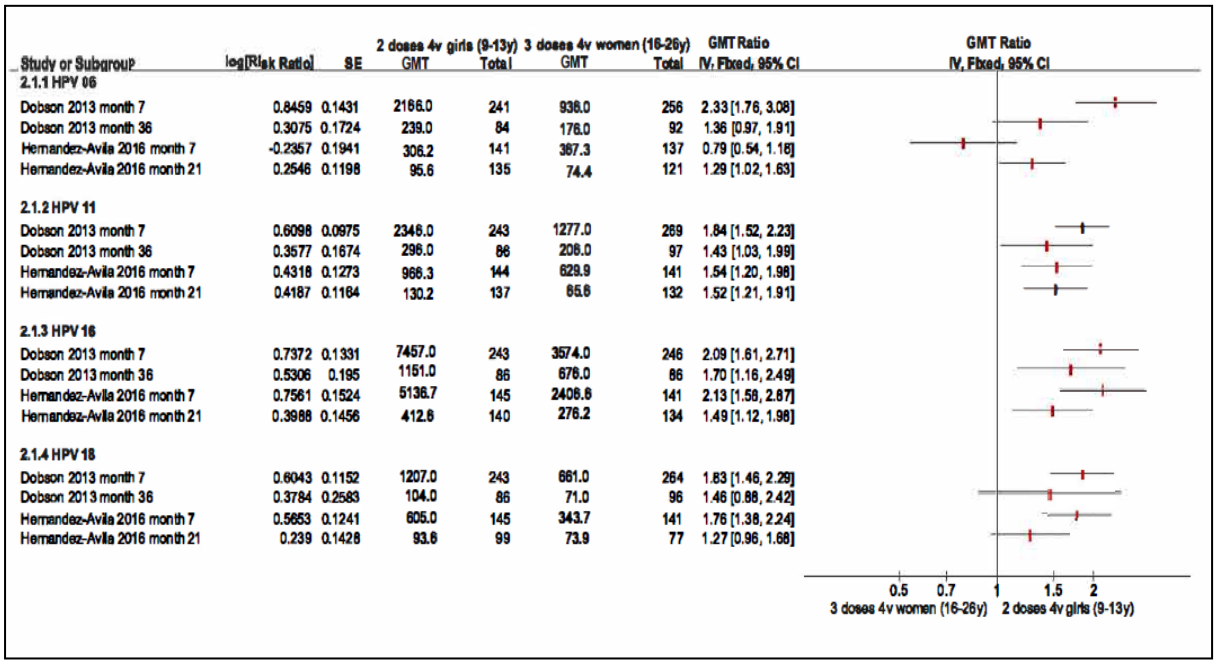


Figure 4.33 Estimate of effect on seropositivity rates comparing two-dose 4-valent HPV vaccine schedules (females nine-13 years) versus three-dose 4-valent HPV vaccine schedules (females 16-26 years) from seven to 36 months (per-protocol population)

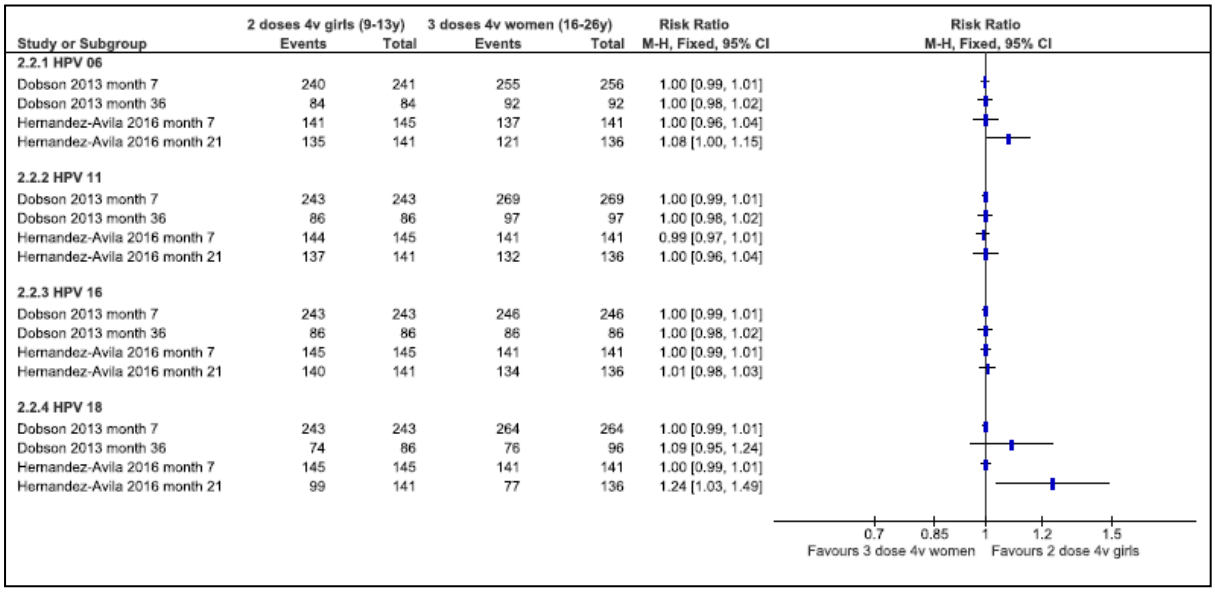


Figure 4.34 Estimate of effect on GMTs comparing two-dose versus three-

dose HPV vaccine schedules (females nine-14 years) at seven months (per-protocol population)

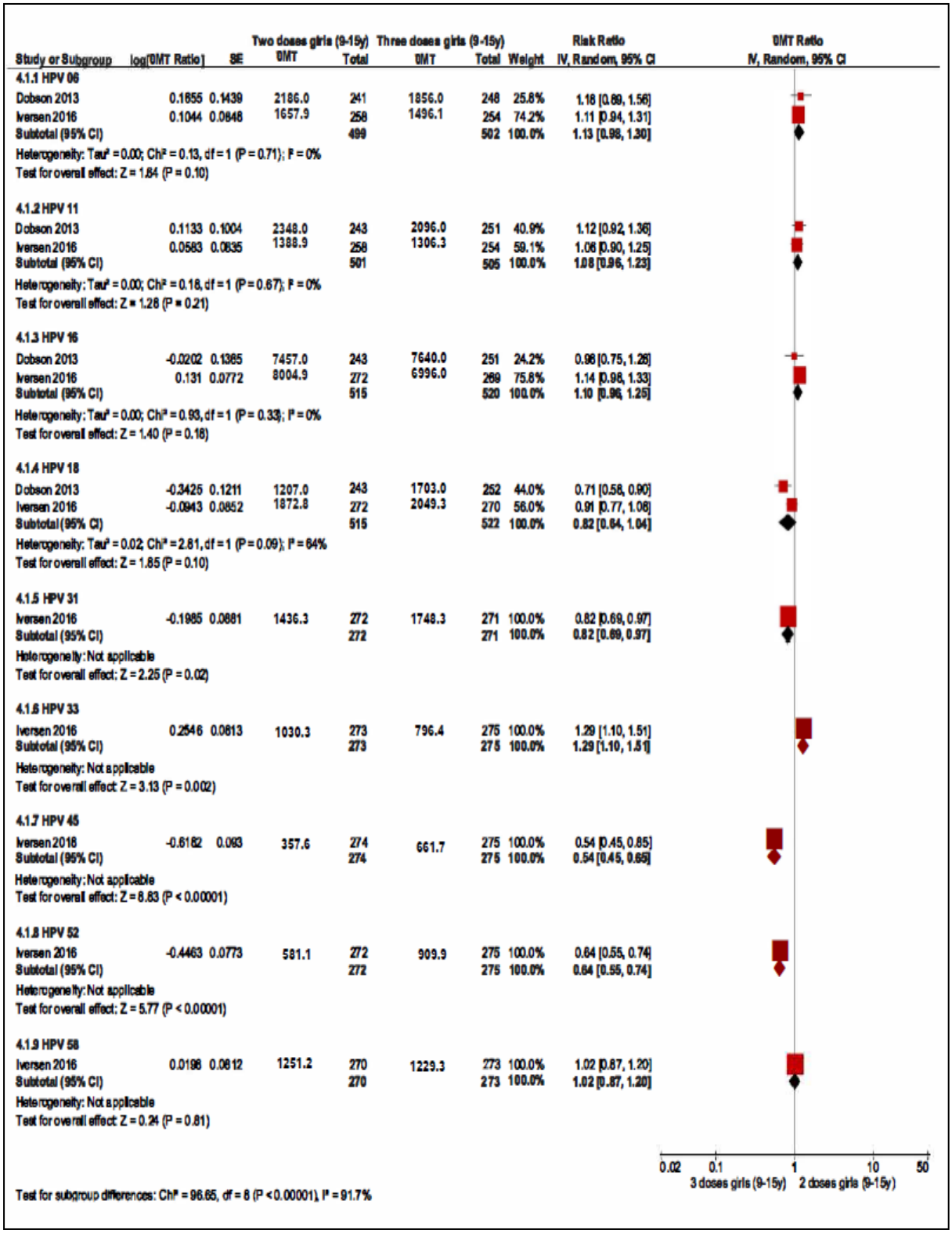


Figure 4.35 Estimate of effect on seropositivity rates comparing two-dose

versus three-dose HPV vaccine schedules (females nine-14 years) at seven months (per-protocol population)

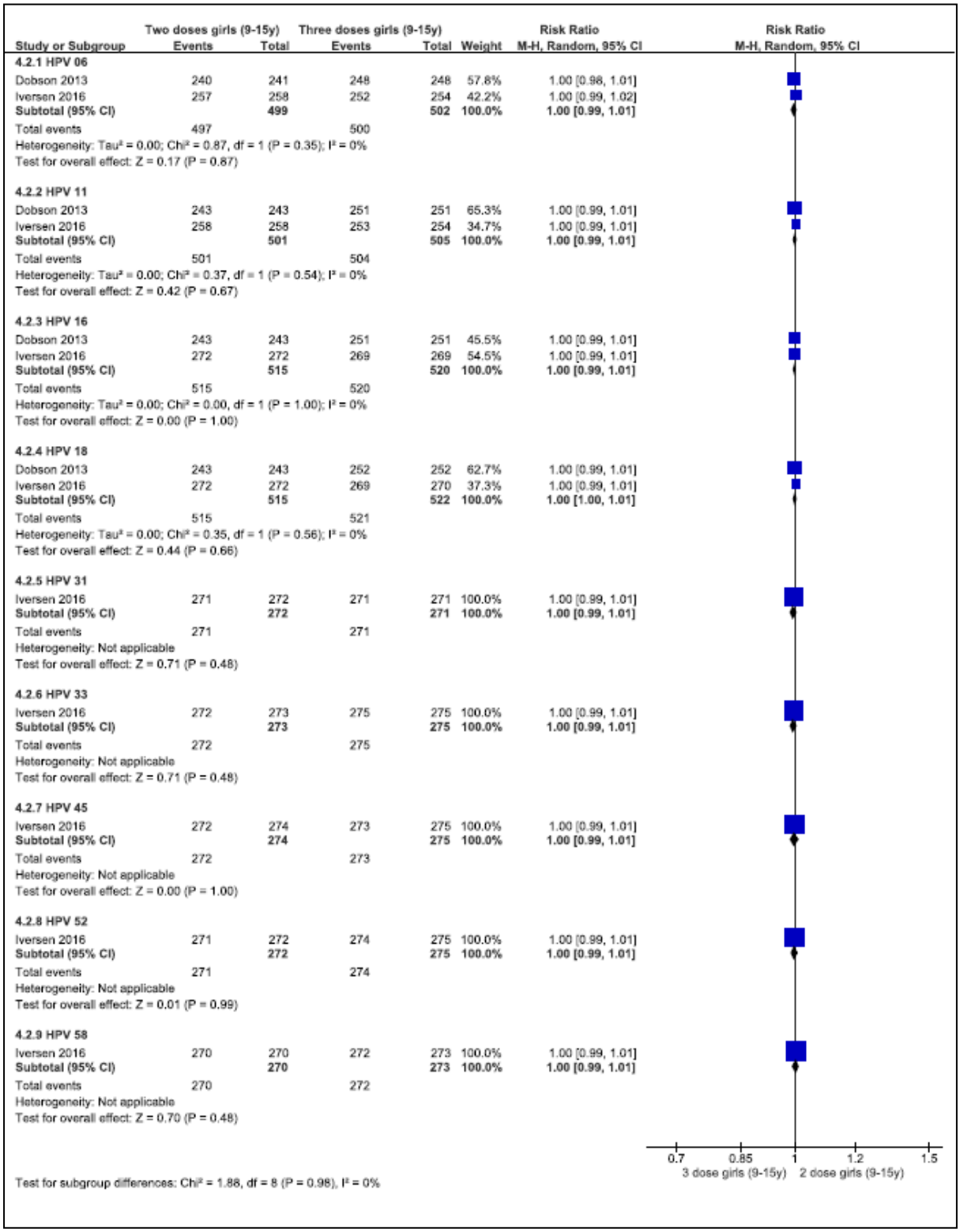


Figure 4.36 Estimate of effect on GMTs comparing two-dose versus three-dose HPV vaccine schedules (females nine-13 years) from seven to 36 months (per-protocol population)

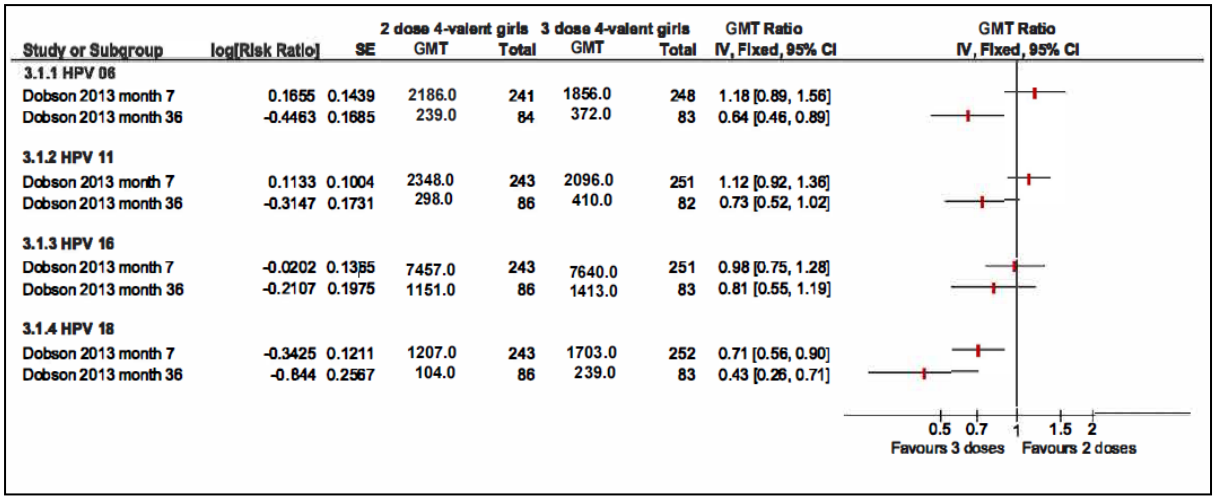
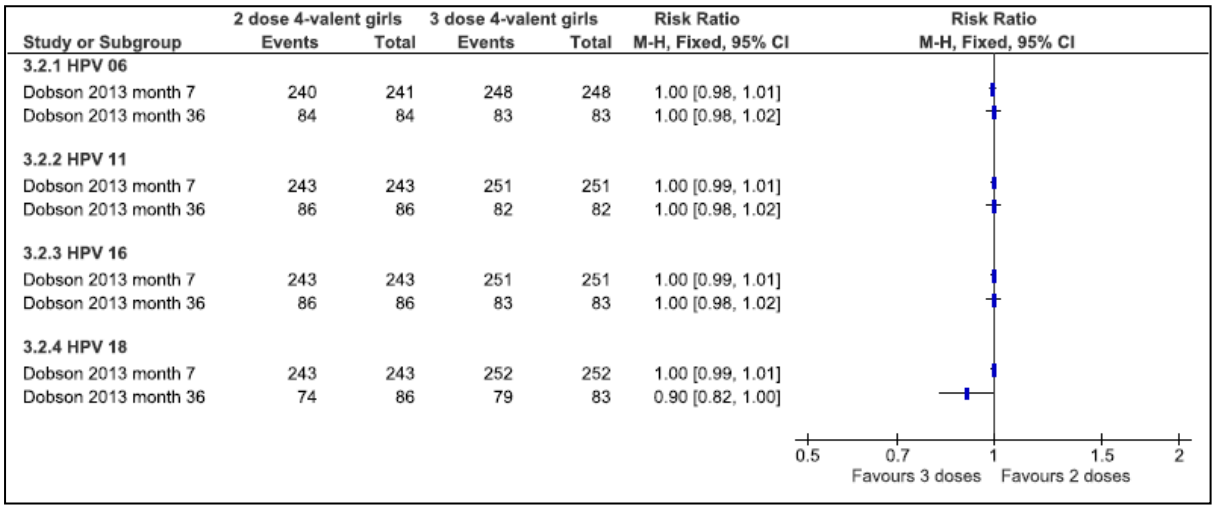


Figure 4.37 Estimate of effect on seropositivity rates comparing two-dose versus three-dose HPV vaccine schedules (females nine-13 years) from seven to 36 months (per-protocol population)



Appendix 4E 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]
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]

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 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]
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
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]

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 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
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

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 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]
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]
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]

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 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]
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]
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]

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	**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]
	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]
	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.

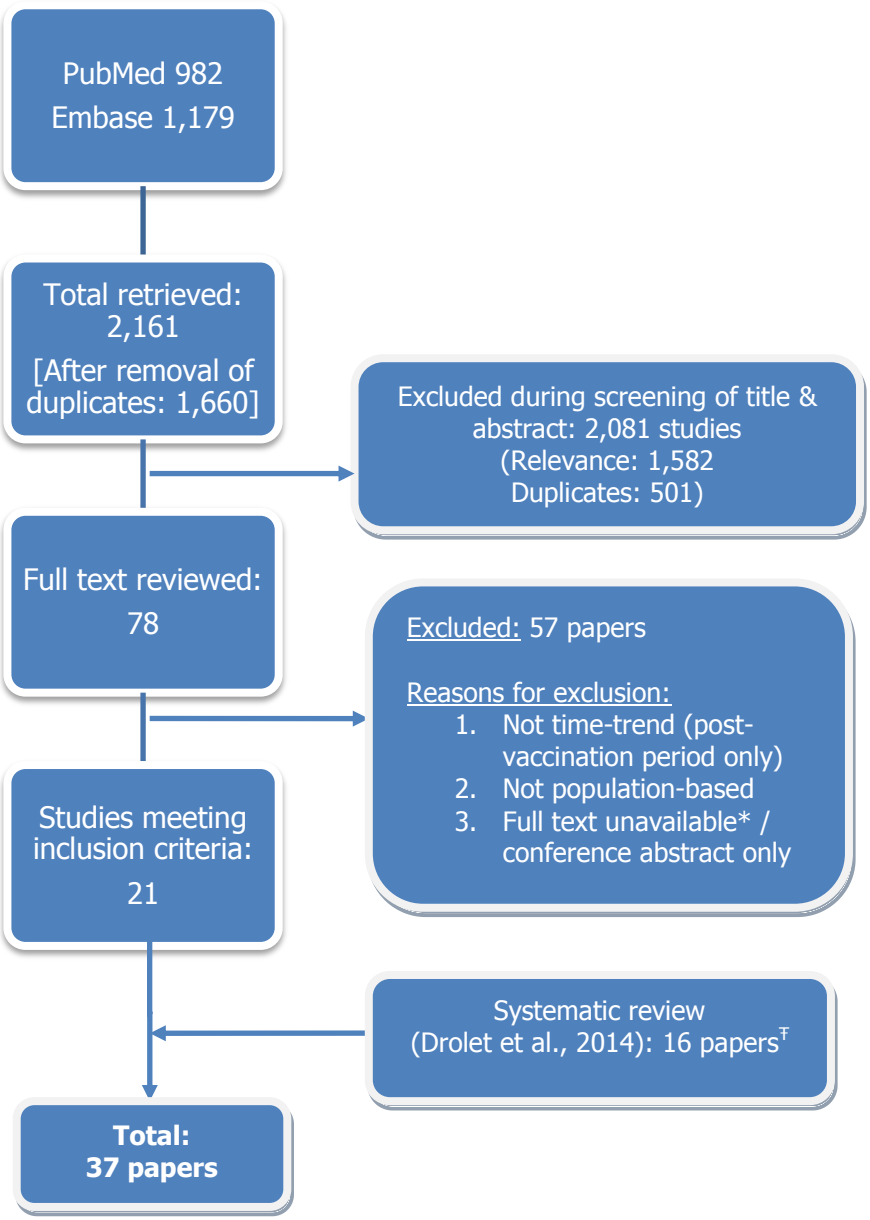
Item 2 was rated as a 'partial yes'. AMSTAR 2 now specifies that a protocol for the systematic review must have been registered to receive a 'yes' for this item. However, authors do report that an *a priori* design was followed and there were no major deviations to the planned methods. Additionally, 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)
†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

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 frequencies	Both frequency of infection and adjusted prevalence ratios reported	Both frequency of infection and adjusted prevalence ratios reported	Odds ratios of HPV prevalence (crude)	Odds ratios of HPV prevalence (adjusted)
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 publication	Adjusted prevalence ratio comparing NHANES 2003–2006 and 2009–2012	Odds ratios of HPV prevalence (adjusted)	Prevalence, odds ratios and adjust odds ratios	HPV prevalence over time
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.

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 identification of diagnosed AGW cases during the pre and post-vaccination period	Low	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
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

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.

19. Howell-Jones R, Soldan K, Wetten S, Mesher D, Williams T, Gill ON, et al. Declining genital Warts in young women in england associated with HPV 16/18 vaccination: an ecological study. The Journal of infectious diseases. 2013;208(9):1397-403.

20. Kahn JA, Brown DR, Ding L, Widdice LE, Shew ML, Glynn S, et al. Vaccine-type human papillomavirus and evidence of herd protection after vaccine introduction. Pediatrics. 2012;130(2):e249-56.

21. Kahn JA, Widdice LE, Ding L, Huang B, Brown DR, Franco EL, et al. Substantial Decline in Vaccine-Type Human Papillomavirus (HPV) among Vaccinated Young Women during the First 8 Years after HPV Vaccine Introduction in a Community. Clinical Infectious Diseases. 2016;63(10):1281-7.

22. Kavanagh K, Pollock KG, Potts A, Love J, Cuschieri K, Cubie H, et al. Introduction and sustained high coverage of the HPV bivalent vaccine leads to a reduction in prevalence of HPV 16/18 and closely related HPV types. British journal of cancer. 2014;110(11):2804-11.

23. Leval A, Herweijer E, Arnheim-Dahlstrom L, Walum H, Frans E, Sparen P, et al. Incidence of genital warts in Sweden before and after quadrivalent human papillomavirus vaccine availability. The Journal of infectious diseases. 2012;206(6):860-6.

24. Liu B, Donovan B, Brotherton JM, Saville M, Kaldor JM. Genital warts and chlamydia in Australian women: comparison of national population-based surveys in 2001 and 2011. Sexually transmitted infections. 2014;90(7):532-7.

25. Lurie S, Mizrachi Y, Chodick G, Katz R, Schejter E. Impact of quadrivalent human papillomavirus vaccine on genital warts in an opportunistic vaccination structure. Gynecologic Oncology. 2017;146(2):299-304.

26. Markowitz LE, Hariri S, Lin C, Dunne EF, Steinau M, McQuillan G, et al. Reduction in human papillomavirus (HPV) prevalence among young women following HPV vaccine introduction in the United States, National Health and Nutrition Examination Surveys, 2003-2010. The Journal of infectious diseases. 2013;208(3):385-93.

27. Mesher D, Panwar K, Thomas SL, Beddows S, Soldan K. Continuing reductions in HPV 16/18 in a population with high coverage of bivalent HPV vaccination in England: An ongoing cross-sectional study. BMJ Open. 2016;6(2).

28. Mesher D, Soldan K, Howell-Jones R, Panwar K, Manyenga P, Jit M, et al. Reduction in HPV 16/18 prevalence in sexually active young women following the introduction of HPV immunisation in England. Vaccine. 2013;32(1):26-32.

29. Mikolajczyk RT, Kraut AA, Horn J, Schulze-Rath R, Garbe E. Changes in incidence of anogenital warts diagnoses after the introduction of human papillomavirus vaccination in Germany-an ecologic study. Sexually transmitted diseases. 2013;40(1):28-31.

30. Ogilvie GS, Naus M, Money DM, Dobson SR, Miller D, Krajden M, et al. Reduction in cervical intraepithelial neoplasia in young women in British Columbia after introduction of the HPV vaccine: An ecological analysis. International Journal of Cancer. 2015;137(8):1931-7.

31. Sando N, Kofoed K, Zachariae C, Fouchard J. A reduced national incidence of anogenital warts in young Danish men and women after introduction of a national quadrivalent human papillomavirus vaccination programme for young women--an ecological study. Acta dermato-venereologica. 2014;94(3):288-92.

32. Smith MA, Liu B, McIntyre P, Menzies R, Dey A, Canfell K. Fall in genital warts diagnoses in the general and indigenous Australian population following implementation of a national human papillomavirus vaccination program: analysis of routinely collected national hospital data. The Journal of infectious diseases. 2015;211(1):91-9.

33. Söderlund-Strand A, Uhnoo I, Dillner J. Change in population prevalences of human papillomavirus after initiation of vaccination: The high-throughput HPV monitoring study. Cancer Epidemiology Biomarkers and Prevention. 2014;23(12):2757-64.

34. Sonnenberg P, Clifton S, Beddows S, Field N, Soldan K, Tanton C, et al. Prevalence, risk factors, and uptake of interventions for sexually transmitted infections in Britain: findings from the National Surveys of Sexual Attitudes and Lifestyles (Natsal). Lancet (London, England). 2013;382(9907):1795-806.

35. Tabrizi SN, Brotherton JM, Kaldor JM, Skinner SR, Cummins E, Liu B, et al. Fall in human papillomavirus prevalence following a national vaccination program. The Journal of infectious diseases. 2012;206(11):1645-51.

36. Tanton C, Mesher D, Beddows S, Soldan K, Clifton S, Panwar K, et al. Human papillomavirus (HPV) in young women in Britain: Population-based evidence of the effectiveness of the bivalent immunisation programme and burden of quadrivalent and 9-valent vaccine types. Papillomavirus research (Amsterdam, Netherlands). 2017;3:36-41.

37. Wilson AR, Welch RJ, Hashibe M, Greenwood J, Jackson B, She RC. Surveillance of human papilloma virus using reference laboratory data for the purpose of evaluating vaccine impact. Online journal of public health informatics. 2014;6(3):e194.

Appendix 5F List of studies excluded from this review

1. Arbyn M, Broeck DV, Benoy I, Bogers J, Depuydt C, Praet M, et al. Surveillance of effects of HPV vaccination in Belgium. Cancer Epidemiology. 2016;41:152-8.
Justification: comparison is vaccinated versus unvaccinated in postvaccination period

2. Bianchi S, Boveri S, Igidbashian S, Amendola A, Urbinati AM, Frati ER, et al. Chlamydia trachomatis infection and HPV/Chlamydia trachomatis co-infection among HPV-vaccinated young women at the beginning of their sexual activity. Archives of gynecology and obstetrics. 2016;294(6):1227-33. *Justification: comparison is vaccinated versus unvaccinated*

3. Brisson M, Bénard É, Drolet M, Bogaards JA, Baussano I, Vänskä S, et al. Population-level impact, herd immunity, and elimination after human papillomavirus vaccination: a systematic review and meta-analysis of predictions from transmission-dynamic models. The Lancet Public Health. 2016;1(1):e8-e17. *Justification: not time-trend study; meta-analysis*

4. Brotherton JM, Gertig DM, May C, Chappell G, Saville M. HPV vaccine impact in Australian women: ready for an HPV-based screening program. The Medical journal of Australia. 2016;204(5):184-e1. *Justification: full text unavailable; insufficient information in abstract*

5. Brotherton JML, Giuliano AR, Markowitz LE, Dunne EF, Ogilvie GS. Monitoring the impact of HPV vaccine in males-Considerations and challenges. Research. 2016;2:106-11. *Justification: not time-trend study – a review*

6. Bruni L, Diaz M, Barrionuevo-Rosas L, Herrero R, Bray F, Bosch FX, et al. Global estimates of human papillomavirus vaccination coverage by region and income level: A pooled analysis. The Lancet Global Health. 2016;4(7):e453-e63. *Justification: not time-trend study*

7. Canfell K. HPV vaccination in Australia: Impact on cervical screening. Acta Cytologica. 2016;60:56. *Justification: conference abstract only*

8. 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. *Justification: Post-vaccination period only*

9. Capra G, Giovannelli L, Matranga D, Bellavia C, Guarneri MF, Fasciana T, et al. Potential impact of a nonavalent HPV vaccine on HPV related low-and high-grade cervical intraepithelial lesions: A referral hospital-based study in Sicily. Human Vaccines and Immunotherapeutics. 2017:1-5. *Justification: not time-trend study; 9-versus 4-valent*

10. Carozzi FM, Ocello C, Burroni E, Faust H, Zappa M, Paci E, et al. Effectiveness of HPV vaccination in women reaching screening age in Italy. Journal of Clinical Virology. 2016;84:74-81. *Justification: not time-trend study*

11. Chanal J, Fouere S, Yassir-Oria F, Spenatto N, Bouscarat F, Picot E, et al. [CONDYDAV: A multicentre observational study of patients presenting external genital warts in France]. Annales de dermatologie et de venereologie. 2016;143(11):675-81. *Justification: postvaccination period only*

12. Chandler EL, Ding L, Widdice L, Thomas R, Bernstein DI, Brown DR, et al. Epidemiology of anogenital human papillomavirus (HPV) among 13-26 year-old young men after HPV vaccine introduction. Journal of Adolescent Health. 2016;58(2):S117-S8. *Justification: postvaccination period only*

13. Cocchio S, Baldovin T, Bertoncello C, Buja A, Furlan P, Saia M, et al. Decline in hospitalization for genital warts in the Veneto region after an HPV vaccination program: an observational study. BMC infectious diseases. 2017;17(1):249. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5382454/

    This citing was retrieved during our initial search, however only the abstract was located. It has come to our knowledge that since our initial search, the study has now been published in full.

14. Coleman H, O'Farrell N, Kapembwa M, Brook G, McSorley J. The impact of an HPV vaccination programme in young men who have sex with men (MSM) on clinical presentations with genital warts. Sexually Transmitted Infections. 2017;93:A3-A4. *Justification: MSM only*

15. Daugherty M, Byler T. HPV prevalence in males in the United States from penile swabs: Results from NHANES. Journal of Urology. 2017;197(4):e137-e8. *Justification: postvaccination period only*

16. Donken R, Bogaards JA, van der Klis FRM, Meijer CJLM, de Melker HE. An exploration of individual- and population-level impact of the 2-dose HPV vaccination schedule in pre-adolescent girls. Human Vaccines and Immunotherapeutics. 2016;12(6):1381-93. *Justification: not time-trend study*

17. Fischer S, Bettstetter M, Becher A, Lessel M, Bank C, Krams M, et al. Shift in prevalence of HPV types in cervical cytology specimens in the era of HPV vaccination. Oncology Letters. 2016;12(1):601-10. *Justification: postvaccination period only*

18. Flagg EW, Torrone E, Weinstock H. Prevalence of low-and high-grade cervical intraepithelial lesions among female participants in private health plans in the United States, 2007-2013: Ecologic evidence of population effectiveness of human papillomavirus vaccination. Sexually Transmitted Infections. 2015;91:A167-A8. *Justification: Paper unobtainable*

19. Flagg EW, Torrone EA, Weinstock H. Ecological Association of Human Papillomavirus Vaccination with Cervical Dysplasia Prevalence in the United States, 2007-2014. American journal of public health. 2016;106(12):2211-8. *Justification: Paper unobtainable*

20. Gargano JW, Unger ER, Liu G, Steinau M, Meites E, Dunne E, et al. Prevalence of genital human papillomavirus in males, United States, 2013-2014. Journal of Infectious Diseases. 2017;215(7):1070-9. *Justification: not time-trend study*

21. Grün N, Ährlund-Richter A, Franzén J, Mirzaie L, Marions L, Ramqvist T, et al. Follow-up on oral and cervical human papillomavirus prevalence 2013-2015 in youth at a youth clinic in Stockholm, Sweden. Infectious Diseases. 2016;48(2):169-70. *Justification: Paper unobtainable*

22. Guerra FM, Rosella LC, Dunn S, Wilson SE, Chen C, Deeks SL. Health service utilisation for anogenital warts in Ontario, Canada prior to the human papillomavirus (HPV) vaccine programme introduction: A retrospective longitudinal population-based study. BMJ Open. 2016;6(3). *Justification: prevaccination period only*

23. Han JJ, Beltran TH, Song JW, Klaric J, Choi YS. Prevalence of Genital Human Papillomavirus Infection and Human Papillomavirus Vaccination Rates Among US Adult Men: National Health and Nutrition Examination Survey (NHANES) 2013-2014. JAMA oncology. 2017;3(6):810-6. *Justification: postvaccination period only*

24. Hariri S, Johnson ML, Bennett NM, Bauer HM, Park IU, Schafer S, et al. Population-based trends in high-grade cervical lesions in the early human papillomavirus vaccine era in the United States. Cancer. 2015;121(16):2775-81. *Justification: Post-vaccination period only*

25. Heard I, Tondeur L, Arowas L, Demazoin M, Falguieres M, Parent Du Chatelet I. Effectiveness of Human Papillomavirus Vaccination on Prevalence of Vaccine Genotypes in Young Sexually Active Women in France. The Journal of infectious diseases. 2017;215(5):757-63. *Justification: comparison is vaccinated versus unvaccinated*

26. Herweijer E, Sundström K, Ploner A, Uhnoo I, Sparén P, Arnheim-Dahlström L. Quadrivalent HPV vaccine effectiveness against high-grade cervical lesions by age at vaccination: A population-based study. International Journal of Cancer. 2016;138(12):2867-74. *Justification: not time-trend study*

27. Hirth J, Laz TH, Kuo YF, McGrath C, Starkey J, Rupp R, et al. Regional variations in vaginal HPV prevalence and vaccination among females across time in NHANES (2003-2012). Journal of Women's Health. 2016;25(4):A16. *Justification: Paper unobtainable*

28. Judlin P, Jacquard AC, Carcopino X, Aubin F, Dahlab A, Mistretta F, et al. Potential impact of the human papillomavirus vaccine on the incidence proportion of genital warts in French women (EFFICAE study): A multicentric prospective observational study. Sexual Health. 2016;13(1):49-54. *Justification: Paper unobtainable*

29. Kliewer E MS, Demers AA, Lambert P, Musto G. Quadrivalent HPV vaccination and the incidence of anogenital warts in Manitoba, Canada.. 28th International Papillomavirus Conference; San Juan, Puerto Rico. Nov 30–Dec 6, 2012; Abstract E07-663. 2012. *Justification: full text unavailable (conference proceeding); included in Drolet 2014*

30. Ladner J, Besson MH, Audureau E, Rodrigues M, Saba J. Experiences and lessons learned from 29 HPV vaccination programs implemented in 19 low and middle-income countries, 2009-2014. BMC health services research. 2016;16(1):575. *Justification: mixed methods postvaccination survey*

31. Lamb F, Herweijer E, Ploner A, Uhnoo I, Sundström K, Sparén P, et al. Timing of two versus three doses of quadrivalent HPV vaccine and associated effectiveness against condyloma in Sweden: A nationwide cohort study. BMJ Open. 2017;7(6). *Justification: timing of vaccination in a cohort study*

32. Largeron N, Petry KU, Jacob J, Bianic F, Anger D, Uhart M. An estimate of the public health impact and cost-effectiveness of universal vaccination with a 9-valent HPV vaccine in Germany. Expert review of pharmacoeconomics & outcomes research. 2017;17(1):85-98. *Justification: modelling study*

33. Liaw KL, Kjaer SK, Nygard M, Dillner J. Utilization of nordic countries national registries to monitor the impact of HPV vaccination. Pharmacoepidemiology and Drug Safety. 2014;23:356. *Justification: postvaccination period only*

34. Luxembourg A, Kjaer SK, Nygard M, Ellison MC, Group T, Marshall JB, et al. Design of a long-term follow-up effectiveness, immunogenicity and safety study of women who received the 9-valent human papillomavirus vaccine. Contemporary clinical trials. 2017;52:54-61. *Justification: design for a RCT*

35. Markowitz LE, Liu G, Hariri S, Steinau M, Dunne EF, Unger ER. Prevalence of HPV After Introduction of the Vaccination Program in the United States. Pediatrics. 2016;137(3):e20151968. *Justification: paper unobtainable*

36. McCarthy WA, Hui Y, Diaz-Gomez BL, Ou J, Paquette C, Sung CJ, et al. Usual type endocervical adenocarcinoma/AIS incidence and distribution of high-risk HPV genotypes between 2007-2010 and 2011-2015. Laboratory Investigation.

2017;97:300A. *Justification: Conference abstract only, unclear link to vaccination programme.*

37. Meites E, Gorbach PM, Gratzer B, Panicker G, Steinau M, Collins T, et al. Monitoring for human papillomavirus vaccine impact among gay, bisexual, and other men who have sexwith men-United States, 2012-2014. Journal of Infectious Diseases. 2016;214(5):689-96. *Justification: MSM only*

38. Merckx M, Broeck DV, Benoy I, Depuydt C, Weyers S, Arbyn M. Early effects of human papillomavirus vaccination in Belgium. European Journal of Cancer Prevention. 2015;24(4):340-2. *Justification: Data from the postvaccination period only. Vaccine was introduced in 2007 Belgium, fully reimbursed 2008. Opportunistic until 2010 school-based programme*

39. Merckx M, Weyers S, Benoy I, Arbyn M, Van Den Broeck D. Surveillance of the effects of vaccination against HPV. European Journal of Contraception and Reproductive Health Care. 2014;19:S36. *Justification: Abstract only*

40. Mesher D, King E, Sonnenberg P, Linley E, Beddows S, Soldan K, et al. HPV 16 and 18 seropositivity and DNA detection among men who have sex with men: Evidence for the potential benefit of vaccination. Sexually Transmitted Infections. 2017;93:A3. *Justification: MSM only*

41. Moscicki AB, Karalius B, Tassiopoulos K, Jacobson D, Patel K, Purswani MU, et al. HPV4 vaccine immunogenicity/effectiveness in perinatally HIV-infected (PHIV) youth. Topics in Antiviral Medicine. 2017;25(1):342s. *Justification: HIV positive only*

42. Navarro-Illana E, López-Lacort M, Navarro-Illana P, Vilata JJ, Diez-Domingo J. Effectiveness of HPV vaccines against genital warts in women from Valencia, Spain. 2017;35(25):3342-6. *Justification: Comparison is vaccinated vs unvaccinated in postvaccination period only*

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)*

45. Nsouli-Maktabi H, Ludwig SL, Yerubandi UD, Gaydos JC. Incidence of genital warts among U.S. service members before and after the introduction of the quadrivalent human papillomavirus vaccine. Msmr. 2013;20(2):17-20. *Justification: full text unavailable (conference proceeding); included in Drolet 2014*

46. Oliphant J, Perkins N. Impact of the human papillomavirus (HPV) vaccine on genital wart diagnoses at Auckland Sexual Health Services. The New Zealand medical journal. 2011;124(1339):51-8. *Justification: full text unavailable (conference proceeding); included in Drolet 2014*

47. Oliphant J, Stewart J, Saxton P, Lo M, Perkins N, Ward D. Trends in genital warts diagnoses in New Zealand five years following the quadrivalent human papillomavirus vaccine introduction. The New Zealand medical journal. 2017;130(1452):9-16. *Justification: paper unobtainable*

48. Ozawa N, Ito K, Tase T, Metoki H, Yaegashi N. Beneficial effects of human papillomavirus vaccine for prevention of cervical abnormalities in Miyagi, Japan. Tohoku Journal of Experimental Medicine. 2016;240(2):147-51. *Justification: comparison is vaccinated versus unvaccinated*

49. Palmer TJ, McFadden M, Pollock KGJ, Kavanagh K, Cuschieri K, Cruickshank M, et al. HPV immunisation and cervical screening-confirmation of changed performance of cytology as a screening test in immunised women: A retrospective population-based cohort study. British Journal of Cancer. 2016;114(5):582-9. *Justification: comparison is vaccinated versus unvaccinated*

50. Perkins RB, Lin M, Wallington SF, Hanchate A. Impact of number of human papillomavirus vaccine doses on genital warts diagnoses among a National Cohort of U.S. Adolescents. Sexually Transmitted Diseases. 2017;44(6):365-70. *Justification: comparison is vaccinated versus unvaccinated*

51. Saccucci M, Ding L, Franco E, Bernstein DI, Brown D, Kahn JA. Epidemiologic trends in non-vaccine-type hpv after vaccine introduction: No evidence for type replacement but evidence for cross-protection. Journal of Adolescent Health. 2017;60(2):S18-S9. *Justification: paper unobtainable*

52. Silverberg M, Leyden W, Gregorich S, Huchko M, Kulasingam S, Kuppermann M, et al. Effectiveness of "catch-up" HPV vaccination on incident cervical neoplasia in a U.S. healthcare setting. Journal of Lower Genital Tract Disease. 2017;21(2):S16. *Justification: comparison is vaccinated versus unvaccinated*

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*

54. Tanaka H, Shirasawa H, Shimizu D, Sato N, Ooyama N, Takahashi O, et al. Preventive effect of human papillomavirus vaccination on the development of uterine cervical lesions in young Japanese women. The journal of obstetrics and gynaecology research. 2017. *Justification: comparison is vaccinated versus unvaccinated*

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*

56. Tarney CM, Pagan M, Klaric J, Beltran T, Han JJ. Population impact of HPV vaccination in the United States. Gynecologic Oncology. 2016;141:24-5. *Justification: paper unobtainable*

57. Thompson LH, Nugent Z, Blanchard JF, Ens C, Yu BN. Increasing incidence of anogenital warts with an urban-rural divide among males in Manitoba, Canada, 1990-2011. BMC public health. 2016;16:219. *Justification: Comparison is rural vs urban divide, prevaccination period for boys only*

58. Willows K, Bozat-Emre S, Kliewer E, Mahmud S. Effectiveness of the Quadrivalent Human Papillomavirus Vaccine (QHPV) against Anogenital Warts (AGWs) in Manitoba, Canada: A population-based study. Pharmacoepidemiology and Drug Safety. 2016;25:473-4. *Justification: paper unobtainable*

59. Woestenberg PJ, King AJ, van der Sande MA, Donken R, Leussink S, van der Klis FR, et al. No evidence for cross-protection of the HPV-16/18 vaccine against HPV-6/11 positivity in female STI clinic visitors. The Journal of infection. 2017;74(4):393-400. *Justification: postvaccination period only*

60. Wrenn A, Tracht J, Eltoum IE. Assessing trends in the prevalence of HPV infection: A five year retrospective analysis of women screened at a large academic institution. Journal of the American Society of Cytopathology. 2016;5(5):S36. *Justification: conference abstract only*

61. Zeybek B, Rodriguez A. Comparison of long term impact and clinical outcomes of reduced dose vs standard dose quadrivalent human papillomavirus vaccine in the United States: A database study. Gynecologic Oncology. 2017;145:3-4. *Justification: conference abstract only*

Appendix 5G 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)										

Certainty assessment							Sample size		Effect	Certainty
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Pre-vaccination**	**Post-vaccination**		
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
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 5H 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

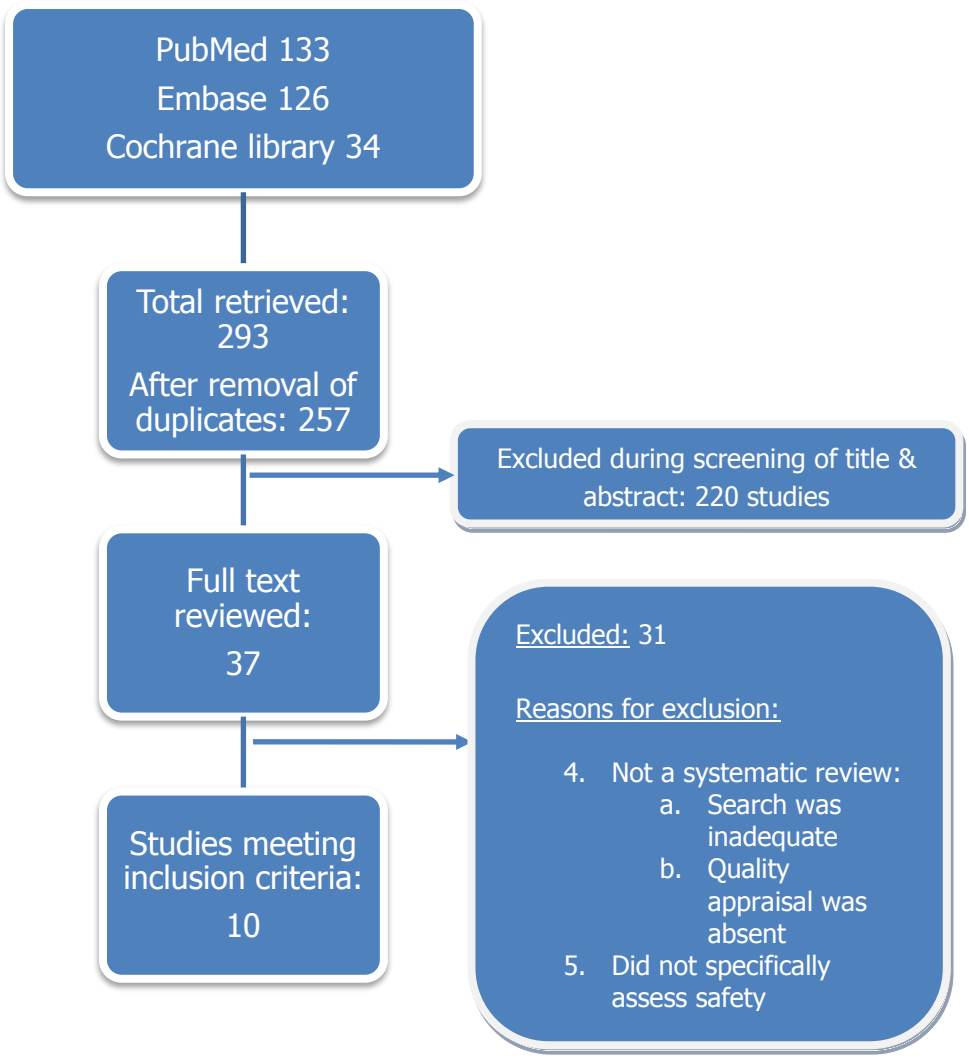
vaccine'/exp OR 2-valent vaccine)) AND 'systematic review'/exp

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:
	  ○ 4-valent versus placebo: RR 0.93 (95% CI 0.72 to 1.21)
	  ○ 4-valent versus control: RR 0.87 (95% CI 0.43 to 1.78)
	  ○ 2-valent versus placebo: RR 0.87 (95% CI 0.60 to 1.25)
	  ○ 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
	  ○ In the 4-valent vaccine trials, no deaths were considered vaccine-related
	  ○ 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 6I Summary of products characteristics and patient information leaflet

Please follow the following links to access the publicly available Summary of Product Characteristics (SPC) and Patient Information Leaflet (PIL) for Gardasil®, provided by the manufacturer and published on both the European Medicines Agency (EMA) and Health Products Regulatory Authority (HPRA) websites.

Summary of Product Characteristics (SPC): https://www.ema.europa.eu/documents/product-information/gardasil-epar-product-information_en.pdf

Patient Information Leaflet (PIL): http://www.hpra.ie/docs/default-source/vaccine-pils/gardasil-pil.pdf?sfvrsn=2

Further information materials are available on the HSE website: https://www.hse.ie/eng/health/immunisation/pubinfo/schoolprog/hpv/hpv-information-materials/

Appendix 6J Suspected adverse events reported to HPRA by System-Organ-Class

The following table is a summary of suspected adverse reactions or events reported to the HPRA in association with Gardasil® between 01 Jan 2006 and 31 Dec 2017.* Please also note the statement that accompanies adverse reaction data released by the HPRA (below).

System-Organ-Class (SOC)	Number of reactions/cases	
Blood and lymphatic system disorders	No. reactions	32
	No. cases	28
Cardiac disorders	No. reactions	73
	No. cases	59
Congenital, familial and genetic disorders	No. reactions	3
	No. cases	3
Ear and labyrinth disorders	No. reactions	33
	No. cases	27
Endocrine disorders	No. reactions	11
	No. cases	6
Eye disorders	No. reactions	141
	No. cases	104
Gastrointestinal disorders	No. reactions	472
	No. cases	326
General disorders and administration site conditions	No. reactions	969
	No. cases	496

Immune system disorders	No. reactions	63
	Of which anaphylactic: 11	
	No. cases	60
Infections and infestations	No. reactions	129
	No. cases	84
Injury, poisoning and procedural complications	No. reactions	63
	No. cases	58
Investigations	No. reactions	83
	No. cases	72
Metabolism and nutrition disorders	No. reactions	51
	No. cases	49
Musculoskeletal and connective tissue disorders	No. reactions	430
	No. cases	225
Neoplasms benign, malignant and unspecified (including cysts and polyps)	No. reactions	2
	No. cases	2
Nervous system disorders	No. reactions	1298
	No. cases	694
Pregnancy, puerperium and perinatal conditions	No. reactions	3
	No. cases	3
Psychiatric disorders	No. reactions	257
	No. cases	130
Renal and urinary disorders	No. reactions	13
	No. cases	11
Reproductive system and breast disorders	No. reactions	87
	No. cases	60
Respiratory, thoracic and mediastinal disorders	No. reactions	175
	No. cases	126
Skin and subcutaneous tissue disorders	No. reactions	361
	No. cases	254
Social circumstances	No. reactions	39
	No. cases	29
Surgical and medical procedures	No. reactions	6
	No. cases	5
Vascular disorders	No. reactions	135
	No. cases	116
Total number of reactions		**4929**
Total number of cases		**1119**

*Data retrieved with permission from the Health Products Regulatory Authority (HPRA)

Statement to accompany adverse reaction data released by the HPRA

Introduction

This document provides background information on the HPRA adverse reaction reporting system and provides advice on interpretation of information collected through this system.

Spontaneous adverse reaction reports

The spontaneous monitoring system was established in 1968. Reports of suspected adverse reactions are received from patients and consumers, healthcare professionals and pharmaceutical companies through the online reporting options accessible from the HPRA website, in hardcopy format via freepost or by telephone. Anonymised report details are included on a computerised database to facilitate processing and evaluation of reports.

Information collected through this system is an important method of monitoring drug safety in normal clinical practice, by increasing knowledge about known adverse reactions and also by acting as an early warning system for the identification of previously unrecognised adverse reactions. Such information is one of the tools used by the HPRA in its ongoing safety evaluation of marketed drugs and is vital in identifying drugs where a change in their authorisation (licence) status is required such as the addition of warnings and precautions for use, restriction in usage, or rarely, withdrawal from the marketplace.

The HPRA issues a Drug Safety Newsletter (DSN) which is distributed through professional organisations to healthcare professionals approximately six times a year, providing updated information on adverse reactions and providing advice on safe use of specific medicines. Copies of these newsletters are available from the HPRA website (www.hpra.ie) or from the Pharmacovigilance Department, Health Products Regulatory Authority, Kevin O'Malley House, Earlsfort Centre, Earlsfort Terrace, Dublin 2, Ireland. Phone 01-6764971, Fax 01-6767836.

Adverse reaction listings

- Lists all the reactions reported to have occurred in association with a suspected drug substance/product.
- Lists all reactions included on the original report (please note that many reports contain more than one reaction, therefore the total number of reactions may exceed the number of reports received for the drug). Each report relates to an individual patient.
- Lists reactions for a specific drug substance irrespective of whether the reporter provided the approved drug substance name or a brand name of that substance. Brand names are included in the listing if they have been provided.
- Includes data for reports when the drug substance is given either as a single constituent or combination (multi-constituent product). In the case of the latter it may not be always possible to identify which (if any) of the drug

substances in the combination product was responsible for a particular reaction.
- Uses adverse reaction terms known as 'preferred terms'. This system is used in order to ensure consistency of terminology and facilitate exchange of information with pharmaceutical companies and international bodies.

Guidance on interpretation of adverse reaction listings

- Interpretation of the data in an adverse reaction listing should take into account the following:
- Reports submitted to the HPRA in many instances arise from suspicions occurring during observation of an unexpected and/or unwanted event.
- In many cases only limited details about each suspected adverse reaction report are received.
- Numerical comparisons should not be made between reactions associated with different drugs on the basis of the data included in listings alone. Comparisons may be misleading because of the limitations of the data.
- The inclusion of a particular reaction on the listing does not necessarily mean it has been caused by the suspect drug. Many factors have to be taken into account in assessing a causal relationship including temporal association, the possible contribution of concomitant medication, and the underlying disease.
- Interpretation of reactions to medicines in cases where multiple other therapies have been used requires special care. This is particularly relevant for vaccines as many are administered in combination. In these circumstances it may be difficult to ascribe a causal reaction to an individual vaccine or drug.
- Certain reported reactions are conditions which often occur spontaneously. In these cases there may be a temporal relationship between the medicine and the reaction which is not necessarily causal. This applies particularly to vaccines.
- The number of reports received should not be used as a basis for determining the incidence of a reaction as neither the total number of reactions occurring, nor the number of patients using the drug is known. Adverse reaction reporting rates are influenced by the seriousness of the reactions, their ease of recognition and the extent of use of a particular drug. Report rates may also be stimulated by promotion and publicity about a drug.
- Reporting tends to be highest for newly authorised medicines during the first one or two years on the market and then falls off over time.

Appendix 7

Appendix 7A Search terms and results

Pubmed

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

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 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)	1,414,469
	#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

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 papillomavirus vaccine	1,068
	#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

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**

Appendix 7B Applicability of studies

The applicability of cost-effectiveness studies to the policy question being addressed in this HTA was assessed using two questionnaires: Philips and ISPOR. Both questionnaires consider applicability under a number of headings including modelling approach, input data, internal and external validity, and conflict of interest. The results of the questionnaires do not give an overall summary finding and although they do address aspects of quality, they do not clearly guide a judgement of quality. The review of evaluations may be carried out to address two distinct questions:

Is a study likely to accurately address their stated aim? (Issue of quality and risk of bias.)

Are the findings of the study likely to address our policy question? (Applicability.)

Analogous to risk of bias tools, the questionnaires assist the reviewer in identifying study characteristics that might bias the results in both contexts. In relation to the systematic review undertaken in this HTA, economic evaluations were considered in terms of their applicability to the Irish setting. As such, applicability was considered in relation to the design of the programme (e.g., age at vaccination, number of doses), key input data (e.g., efficacy, vaccine uptake, and vaccine price), and choice of health outcomes.

As with any such tool, while the supporting materials for the questionnaires give general guidance on how to address the questions, two reviewers may interpret the questions differently. Hence the questionnaires were used primarily as a means to highlight potential issues of applicability or risk of bias in the economic evaluations reviewed. Rather than report on every questionnaire item, we highlight the key issues identified for each study that raise questions about risk of bias and applicability (Table A7.x).

Table A7.x Applicability issues in studies included in systematic review

Study	Applicability issues
Bresse (2014)	Three dose schedule. 3.0% discount rate. Included oropharyngeal cancer. Conflict of interest in study team.
Brisson (2016)	Societal perspective. Three dose schedule. 3.0% discount rate. Included oropharyngeal cancer. Data sources poorly referenced.
Burger (2014)	Societal perspective. Three dose schedule. 4.0% discount rate. Included oropharyngeal cancer. Conflict of interest in study team.
Chanthavilay (2016)	Outcome measured as DALYs rather than QALYs. 2-valent vaccine only. Three dose schedule. 3.0% discount rate. Overly restricted set of health outcomes.
Chesson (2011)	Societal perspective. Three dose schedule. 3.0% discount rate. Included oropharyngeal cancer. Conflict of interest in study team.
Damm (2017)	Three dose schedule. 3.0% discount rate. Overly restricted set of health outcomes. Where data were pooled, unclear what methods were used.
Elbasha (2007)	Three dose schedule. 3.0% discount rate. Overly restricted set of health outcomes. Conflict of interest in study team. Unclear where vaccine efficacy data sourced from.
Elbasha (2010)	Three dose schedule. 3.0% discount rate. Included oropharyngeal cancer. Conflict of interest in study team.
Graham (2015)	Three dose schedule. Included oropharyngeal cancer. Conflict of interest in study team. Model is possibly over-simplified. Poorly reported.
Haeussler (2015)	Unclear perspective. Three dose schedule. 3.0% discount rate. Included oropharyngeal cancer. Conflict of interest in study team. Unclear inclusion of risk groups.
Insinga (2007)	Three dose schedule. 3.0% discount rate. Overly restricted set of health outcomes. Conflict of interest in study team.
Jit (2008)	Three dose schedule. 3.5% discount rate. Overly restricted set of health outcomes. Many parameters are not described in sufficient detail.
Kim (2007)	Cost-effectiveness analysis. 2-valent vaccine only. Societal perspective. Three dose schedule. 3.0% discount rate. Overly restricted set of health outcomes.
Kim (2009)	Societal perspective. Three dose schedule. 3.0% discount rate. Included oropharyngeal cancer.
Kotsopoulos (2015)	Cost-benefit analysis. 1.4% discount rate. Conflict of interest in study team.
Kulsingam (2007)	2-valent vaccine only. Three dose schedule. Overly

	restricted set of health outcomes. Conflict of interest in study team. Methods are poorly described.
Laprise (2014)	3.0% discount rate. Included oropharyngeal cancer. Conflict of interest in study team.
Largeron (2017)	3.0% discount rate. Conflict of interest in study team.
Mennini (2017)	3.0% discount rate. Conflict of interest in study team.

Study	Applicability issues
NOKC (2015)	Three dose schedule. 4% discount rate (with step-down).
Olsen (2010)	Three dose schedule. 3.0% discount rate. Overly restricted set of health outcomes. Limited information on certain key assumptions and parameters.
Olsen (2015)	Three dose schedule. 3.0% discount rate. Included oropharyngeal cancer. Conflict of interest in study team.
Pearson (2014)	Three dose schedule. 3.0% discount rate. Included oropharyngeal cancer. Conflict of interest in study team.
Qendri (2017)	Cost-effectiveness analysis. 2-valent vaccine only. 3.0% discount rate. Included oropharyngeal cancer. Conflict of interest in study team. Model not clearly described. Efficacy assumptions probably unsupported.
Sharma (2015)	Societal perspective. Three dose schedule. 3.0% discount rate. Overly restricted set of health outcomes. Many parameters not clearly described.
Taira (2004)	2-valent vaccine only. Unclear perspective. Three dose schedule. Unclear discount rate. Overly restricted set of health outcomes. Short time horizon.
Tay (2017)	3.0% discount rate. Overly restricted set of health outcomes. Conflict of interest in study team.
Wolff (2017)	2-valent vaccine only. 3.0% discount rate. Included oropharyngeal cancer.
Zechmeister (2009)	Cost-effectiveness analysis. 2-valent vaccine only. Three dose schedule. Overly restricted set of health outcomes. Poorly reported.

It is worth noting some common issues impacting on study applicability. The intervention of interest is a vaccination programme where there may be a substantial lag between receipt of the vaccine and onset of adverse health outcomes associated with persistent HPV infection. As such discounting is likely to play an important role. Three of the studies were based on vaccination at age nine years, thereby increasing the lag between vaccination and accrual of health benefits, potentially reducing cost-effectiveness relative to a programme for 12 year olds. Only two of the studies included the same 5% discount rate as applies in Ireland. Lower discount rates may generate substantially lower ICERs given the lengthy time horizons used in the evaluations. The standard for the base case in Ireland is a cost-utility analysis from the perspective of the publicly-funded healthcare system. Adoption of a societal perspective could substantially alter the cost-effectiveness depending on the additional costs incorporated. It was noted in a number of evaluations that the ICER is very sensitive to vaccine uptake in girls, so clearly the applicability of findings will be questionable if a very different uptake rate is used to what applies in Ireland. Early studies were published before efficacy data were

available, and so the risk reductions used in the model were based on assumptions rather than observed data. Finally, the choice of outcomes is important. Later evaluations were more likely to include oropharyngeal and penile cancers, even though to date efficacy has not be demonstrated for these outcomes, thereby overestimating the benefits based on current knowledge. Earlier evaluations tended to include only CIN, cervical cancer and possible anogenital warts, thereby underestimating the benefits based on current knowledge.

From a study quality point of view, an important consideration is the substantial uncertainty regarding a number of the key parameters. Many of the models were deterministic and included univariate sensitivity analyses based on a very limited subset of parameters. As many of the models are based on a differential equations approach, there is justification for not employing a fully probabilistic approach to sensitivity analysis. However, from a decision making perspective it is important to understand how parameter uncertainty translates into decision uncertainty, and the choice of modelling approach can therefore limit the exploration of uncertainty.

Appendix 7C Excluded studies

Fifty nine studies were excluded on review of full text articles. In some cases the articles was only published as an abstract. Some articles were excluded for multiple reasons. The excluded articles are listed below categorised according to the first reason for exclusion.

Comparator

1. Boiron L, Joura E, Largeron N, Prager B, Uhart M. Estimating the cost-effectiveness profile of a universal vaccination programme with a nine-valent HPV vaccine in Austria. BMC Infect Dis. 2016;16:153.
2. Brisson M, Laprise JF, Chesson HW, Drolet M, Malagon T, Boily MC, et al. Health and Economic Impact of Switching from a 4-Valent to a 9-Valent HPV Vaccination Program in the United States. Journal of the National Cancer Institute [Internet]. 2016; 108(1) (no pagination)
3. Chesson HW, Markowitz LE, Hariri S, Ekwueme DU, Saraiya M. The impact and cost-effectiveness of nonavalent HPV vaccination in the United States: Estimates from a simplified transmission model. Hum Vaccin Immunother. 2016;12(6):1363-72.
4. Dee A, Howell F, O'Connor C, Cremin S, Hunter K. Determining the cost of genital warts: a study from Ireland. Sexually transmitted infections. 2009;85(5):402-3.
5. Durham DP, Ndeffo-Mbah ML, Skrip LA, Jones FK, Bauch CT, Galvani AP. National- and state-level impact and cost-effectiveness of nonavalent HPV vaccination in the United States. Proceedings of the National Academy of Sciences of the United States of America. 2016;113(18):5107-12.
6. Jit M, Brisson M, Laprise JF, Choi YH. Comparison of two dose and three dose human papillomavirus vaccine schedules: cost effectiveness analysis based on transmission model. Bmj. 2015;350:g7584.
7. Jit M, Chapman R, Hughes O, Choi YH. Comparing bivalent and quadrivalent human papillomavirus vaccines: economic evaluation based on transmission model. Bmj. 2011;343:d5775.
8. Laprise JF, Drolet M, Boily MC, Jit M, Sauvageau C, Franco EL, et al. Comparing the cost-effectiveness of two- and three-dose schedules of human papillomavirus vaccination: A transmission-dynamic modelling study. Vaccine [Internet]. 2014; 32(44):[5845-53 pp.]

Study type (including irrelevant reviews)

9. Audisio RA, Icardi G, Isidori AM, Liverani CA, Lombardi A, Mariani L, et al. Public health value of universal HPV vaccination. Critical reviews in oncology/hematology. 2016;97:157-67.
10. Barnabas RV, Kulasingam SL. Economic evaluations of human papillomavirus vaccines. Expert Review of Pharmacoeconomics and Outcomes Research. 2007;7(3):251-67.
11. Bogaards JA, Wallinga J, Brakenhoff RH, Meijer CJ, Berkhof J. Direct benefit of vaccinating boys along with girls against oncogenic human papillomavirus: bayesian evidence synthesis. Bmj. 2015;350:h2016.
12. Bosch X, Cortés Bordoy J, Gil De Miguel A, López Belmonte JL, Bresse X, Serip S, et al. Estimation of the epidemiological and economic impact of the quadrivalent HPV vaccination in girls and boys in Spain. Value in Health. 2013;16(7):A407-A8.

13. Brisson M, van de Velde N, Franco EL, Drolet M, Boily MC. Incremental impact of adding boys to current human papillomavirus vaccination programs: role of herd immunity. J Infect Dis. 2011;204(3):372-6.
14. Brotherton JM, Ogilvie GS. Current status of human papillomavirus vaccination. Current opinion in oncology. 2015;27(5):399-404.
15. de Peuter MA, Littlewood KJ, Annemans L, Largeron N, Quilici S. Cost-effectiveness of catch-up programs in human papillomavirus vaccination. Expert review of vaccines. 2010;9(10):1187-201.
16. Fesenfeld M, Hutubessy R, Jit M. Cost-effectiveness of human papillomavirus vaccination in low and middle income countries: a systematic review. Vaccine. 2013;31(37):3786-804.
17. Fonseca AJ, de Lima Ferreira LC. Systematic review of the cost-effectiveness of the vaccination against HPV in Brazil. Hum Vaccin Immunother. 2014;10(12):3484-90.
18. Jeurissen S, Makar A. Epidemiological and economic impact of human papillomavirus vaccines. International journal of gynecological cancer : official journal of the International Gynecological Cancer Society. 2009;19(4):761-71.
19. Khatibi M, Rasekh HR. Applying a Simple Model of Cost Effectiveness Study of HPV Vaccine for Iran. Iranian journal of pharmaceutical research : IJPR. 2015;14(2):635-49.
20. Newall AT, Beutels P, Wood JG, Edmunds WJ, MacIntyre CR. Cost-effectiveness analyses of human papillomavirus vaccination. The Lancet Infectious diseases. 2007;7(4):289-96.
21. Song X, Mao F, Zhou Z, Zhao Q, Fang Y. [Health economic evaluation of human papillomavirus vaccines in the developing countries: systematic reviews]. Zhonghua yu fang yi xue za zhi [Chinese journal of preventive medicine]. 2016;50(1):85-90.
22. Stupiansky NW, Alexander AB, Zimet GD. Human papillomavirus vaccine and men: what are the obstacles and challenges? Current opinion in infectious diseases. 2012;25(1):86-91.

No abstract/ paper/conference abstract

23. Universal HPV vaccine coverage would be cost-effective. Contemporary Pediatrics. 2008;25(9):36-.
24. HPV vaccine might be a cost-effective barrier to oropharyngeal cancer in males. Nursing Standard. 2015;29(35):14-.
25. Anansushatgul J, Vichaichanakul K. Predicting the potential cost and effects of prophylactic HPV vaccination in males in Thailand. Value in Health. 2012;15(7):A656.
26. Boiron L, Joura E, Largeron N, Prager B, Nikoglou T. Estimating the cost-effectiveness profile of a universal vaccination programme with a nine-valent HPV vaccine in Austria. Value in Health. 2015;18(7):A585.
27. Callejo D, Lopez-Polin A, Blasco JA. Cost utility of human papiloma virus vaccine in Spain. Value in Health. 2010;13(7):A258.
28. Haussler K, Marcellusi A, Mennini FS, Favato G, Picardo M, Garganese G, et al. The effect of herd immunity in different human papillomavirus vaccination strategies: An economic evaluation of the best ii study. Value in Health. 2014;17(3):A85.
29. Hren R. Cost-effectiveness of a human papillomavirus vaccination of boys. Value in Health. 2011;14(7):A449.
30. Mennini FS, Bianic F, Baio G, Largeron N, Plazzotta G, Rinaldi A, et al. Estimating the cost-effectiveness profile of a vaccination programme with a nine-valent HPV vaccine in Italy. Value in Health. 2015;18(7):A457.

31. Prue G. Vaccinate boys as well as girls against HPV: it works, and it may be cost effective. Bmj. 2014;349:g4834.
32. Sæterdal I, Juvet L, Jimenez E, Couto E, Klemp M, Torkilseng EB. Expansion of the norwegian HPV vaccination program. Value in Health. 2014;17(7):A636.
33. Tay SK, Hsu T, Shcheprov A, Walia A, Kulkarni AS. The clinical and economic impact of school-based quadrivalent human papillomavirus vaccine on female or both genders in Singapore. Value in Health. 2016;19(7):A888.
34. Van Kriekinge G, Starkie-Camejo H, Li X, Demarteau N. Potential monetary value of human papillomavirus vaccination on human papillomavirus-related cancers and genital warts in the United Kingdom. Value in Health. 2014;17(7):A634.

Study population

35. Dasbach EJ, Insinga RP, Elbasha EH. The epidemiological and economic impact of a quadrivalent human papillomavirus vaccine (6/11/16/18) in the UK. BJOG : an international journal of obstetrics and gynaecology. 2008;115(8):947-56.
36. Insinga RP, Dasbach EJ, Elbasha EH. Structural differences among cost-effectiveness models of human papillomavirus vaccines. Expert review of vaccines. 2008;7(7):895-913.
37. Laprise J-F, Markowitz LE, Chesson HW, Drolet M, Brisson M. Comparison of 2-Dose and 3-Dose 9-Valent Human Papillomavirus Vaccine Schedules in the United States: A Cost-effectiveness Analysis. Journal of Infectious Diseases. 2016;214(5):685-8.
38. Setiawan D, Luttjeboer J, Westra TA, Wilschut JC, Suwantika AA, Daemen T, et al. The cost-effectiveness of HPV vaccination in addition to screening: a Dutch perspective. Expert review of vaccines. 2015;14(4):589-604.
39. Termrungruanglert W, Khemapech N, Havanond P, Pillsbury M, Shcheprov A, Numuang K, et al. Impact of vaccination: Health impact and cost-effectiveness to make informed policy decision on the introduction of human papillomavirus (HPV) vaccine to the national immunization program (NIP) in Thailand. Value in Health. 2014;17(7):A737.

Outcomes

40. Baussano I, Dillner J, Lazzarato F, Ronco G, Franceschi S. Upscaling human papillomavirus vaccination in high-income countries: Impact assessment based on transmission model. Infectious Agents and Cancer. 2014;9(1).
41. Brown VL, Jane White KA. The role of optimal control in assessing the most cost-effective implementation of a vaccination programme: HPV as a case study. Mathematical biosciences. 2011;231(2):126-34.
42. French KM, Barnabas RV, Lehtinen M, Kontula O, Pukkala E, Dillner J, et al. Strategies for the introduction of human papillomavirus vaccination: modelling the optimum age- and sex-specific pattern of vaccination in Finland. Br J Cancer. 2007;96(3):514-8.
43. Kotsopoulos N, Connolly M, Remy V. Assessing the fiscal consequences of immunizing the female and male population against human papillomavirus (HPV) in Germany. Value in Health. 2013;16(7):A363.
44. Moodley I, Tathiah N, Sartorius B. The costs of delivering human papillomavirus vaccination to Grade 4 learners in KwaZulu-Natal, South Africa. South African medical journal = Suid-Afrikaanse tydskrif vir geneeskunde. 2016;106(5):60.

Study design

45. Brisson M, Van de Velde N, Boily MC. Economic evaluation of human papillomavirus vaccination in developed countries. Public health genomics. 2009;12(5-6):343-51.
46. Demarteau N, Standaert B. Modelling the economic value of cross- and sustained-protection in vaccines against cervical cancer. J Med Econ. 2010;13(2):324-38.
47. Ryser MD, McGoff K, Herzog DP, Sivakoff DJ, Myers ER. Impact of coverage-dependent marginal costs on optimal HPV vaccination strategies. Epidemics. 2015;11:32-47.
48. Seto K, Marra F, Raymakers A, Marra CA. The Cost Effectiveness of Human Papillomavirus Vaccines. Drugs. 2012;72(5):715-43.
49. Siebert U, Sroczynski G, Baker P, Borget I, Castellsagué X, Chapman R, et al. Framework for evidence assessment based on grade and application to HPV vaccination in males in the European health care context. Value in Health. 2013;16(7):A327.
50. Ward G, Mehta V, Moore M. Morbidity, mortality and cost from HPV-related oropharyngeal cancer: Impact of 2-, 4- and 9-valent vaccines. Hum Vaccin Immunother. 2016;12(6):1343-7.

MSM population

51. Deshmukh AA, Cantor SB, Chiao EY, Nyitray AG, Das P, Chhatwal J. Expansion of current HPV vaccination guidelines to include men who have sex with men who are 27 years or older-a value of information analysis. Value in Health. 2015;18(3):A259.
52. Deshmukh AA, Chhatwal J, Chiao EY, Nyitray AG, Das P, Cantor SB. Long-Term Outcomes of Adding HPV Vaccine to the Anal Intraepithelial Neoplasia Treatment Regimen in HIV-Positive Men Who Have Sex With Men. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2015;61(10):1527-35.
53. Deshmukh AA, Chiao EY, Das P, Cantor SB. Clinical effectiveness and cost-effectiveness of quadrivalent human papillomavirus vaccination in HIV-negative men who have sex with men to prevent recurrent high-grade anal intraepithelial neoplasia. Vaccine. 2014;32(51):6941-7.
54. English KM, Marra F, Davoudi B, Gilbert M, Pourbohloul B. Evaluating the cost effectiveness of targeted vaccination strategies to reduce incidence of HPV-Related cancer and other clinical outcomes in men who have sex with Men (MSM) in British Columbia, Canada. Sexually transmitted infections. 2013;89.
55. Jiang Y, Gauthier A, Preaud E, Largeron N. Critical review of cost-effectiveness analyses of human papillomavirus vaccine in boys. Value in Health. 2012;15(7):A396.
56. Kim JJ. Targeted human papillomavirus vaccination of men who have sex with men in the USA: a cost-effectiveness modelling analysis. The Lancet Infectious diseases. 2010;10(12):845-52.
57. Lin A, Ong KJ, Hobbelen P, King E, Mesher D, Edmunds WJ, et al. Impact and cost-effectiveness of selective human papillomavirus vaccination of men who have sex with men. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2016.
58. Sauvageau C, Dufour-Turbis C. HPV vaccination for MSM: Synthesis of the evidence and recommendations from the Québec Immunization Committee. Human Vaccines and Immunotherapeutics. 2016;12(6):1560-5.
59. Vargas Parada C, Lennert Veerman J. Cost-Effectiveness Study of HPV Vaccination as a Primary Prevention Strategy for Anal Cancer in HIV-Positive Men in Chile. Value Health Reg Issues. 2016;11:17-23.

Appendix 8 Economic model parameter data

This appendix outlines the parameters included in cost-effectiveness and budget impact models. The data sources for the parameter values are listed in Chapter 8.

Appendix A8.1 HPV vaccine-related parameters

The model included a variety of parameters in relation to the uptake, cost, and effectiveness of the vaccine (Table A8.1).

The reduced risk of adverse health outcomes such as invasive cancer are calculated using a number of parameters taking into account the reduced risk of persistent HPV infection, the reduced risk of adverse health outcomes, and the proportion of those adverse health outcomes that can be attributed to persistent HPV infection (see Tables A8.1 to A8.6).

All data on attributable proportions were modelled using dirichlet distributions taking into account that a proportion of cases was not attributable to the nine HPV strains included in the model (Tables A8.3 to A8.6). In other words, the attributable proportions across the nine HPV strains would not sum to one for a given adverse health outcome. Use of a dirichlet distribution ensured that the sum of attributable proportions did not exceed one.

Appendix A8.2 Cost parameters

Cost parameters were defined by log normal distributions to reflect the right skew often observed in cost data (Table A8.7). The cost of treating anogenital warts was split into a number of cost components to facilitate the appropriate incorporation of VAT as part of the budget impact model.

Table A8.1 Miscellaneous vaccine-related parameters

Description	Distribution	Mean	LCI	UCI
Vaccine uptake in females	beta	0.800	0.718	0.871
Vaccine uptake in males (relative to uptake in females)	beta	0.877	0.770	0.952
Epsilon (sexual mixing across age groups)*	normal	0.100	0.080	0.119
Proportion medical card holders	beta	0.381	0.371	0.390
Uncertainty around infection acquisition (HPV 6/11)	normal	1.000	0.817	1.185
Uncertainty around infection acquisition (HPV 16)	normal	1.001	0.799	1.204
Uncertainty around infection acquisition (HPV 18)	normal	0.999	0.651	1.343
Uncertainty around infection acquisition (HPV 31/33/45/52/58)	normal	1.001	0.847	1.150
Cost of 4-valent vaccine (€ per dose)	gamma	27.18	24.78	34.09
Relative cost of 9-valent vaccine	normal	1.10	1.06	1.18
Cost of administering the vaccine (€ per dose)	log normal	15.95	13.87	18.30
Proportion completing two doses (females)	beta	0.978	0.942	0.997
Proportion completing two doses (males)	beta	0.978	0.942	0.997
Relative risk reduction of persistent infection with vaccination (HPV 6/11, females)	log normal	0.937	0.723	0.995
Relative risk reduction of persistent infection with vaccination (HPV 6/11, males)	log normal	0.781	0.569	0.904
Relative risk reduction of persistent infection with vaccination (HPV 16, females)	log normal	0.899	0.728	0.974
Relative risk reduction of persistent infection with vaccination (HPV 16, males)	log normal	0.623	0.438	0.761
Relative risk reduction of persistent infection with vaccination (HPV 18, females)	log normal	0.861	0.393	0.988
Relative risk reduction of persistent infection with vaccination (HPV 18, males)	log normal	0.679	0.432	0.833
Relative risk reduction of persistent infection with vaccination (HPV 31/33/45/52/58, females)	log normal	0.938	0.905	0.962
Relative risk reduction of persistent infection with vaccination HPV 31/33/45/52/58, males)	log normal	0.939	0.905	0.962

* Epsilon = 1 corresponds to random mixing by age group and epsilon = 0 corresponds to assortative mixing by age group such that all of a person's sex partners are within 5 years of age of that person. Epsilon = 0.1 reflects mixing by age group tending to be assortative.

Table A8.2 Risk reduction in adverse health outcomes

Condition	Distribution	HPV 6/11			HPV 16/18/31/33/45/52/58		
		Mean	LCI	UCI	Mean	LCI	UCI
CIN 1	log normal				0.027	0.007	0.072
CIN 2/3	log normal				0.009	0.001	0.042
Cervical cancer	log normal				0.009	0.001	0.042
Anal cancer	log normal				0.479	0.266	0.800
VaIN 2/3	log normal				0.078	0.007	0.324
Vaginal cancer	log normal				0.078	0.007	0.324
VIN 2/3	log normal				0.078	0.007	0.324
Vulvar cancer	log normal				0.078	0.007	0.324
Oropharyngeal cancer*	log normal				0.511	0.338	0.740
Penile cancer*	log normal				0.511	0.338	0.747
Anogenital warts (females)	log normal	0.040	0.015	0.089			
Anogenital warts (males)	log normal	0.220	0.104	0.412			
Recurrent respiratory papillomatosis	log normal	0.040	0.015	0.089			

* No risk reduction applied in the base case model – the reductions listed here were only applied in a scenario analysis.

Table A8.3 Proportion cases attributable to persistent HPV 6/11 infection

Condition	Females			Males		
	Mean	LCI	UCI	Mean	LCI	UCI
CIN 1	0.001	0.000	0.004	0	0	0
CIN 2/3	0	0	0	0	0	0
Cervical cancer	0	0	0	0	0	0
Anal cancer	0	0	0	0	0	0
VaIN 2/3	0	0	0	0	0	0
Vaginal cancer	0	0	0	0	0	0
VIN 2/3	0	0	0	0	0	0
Vulvar cancer	0	0	0	0	0	0
Oropharyngeal cancer	0	0	0	0	0	0
Penile cancer	0	0	0	0	0	0
Anogenital warts	0.900	0.881	0.918	0.900	0.881	0.918
Recurrent respiratory papillomatosis	0.900	0.881	0.918	0	0	0

Table A8.4 Proportion cases attributable to persistent HPV 16 infection

Condition	Females			Males		
	Mean	LCI	UCI	Mean	LCI	UCI
CIN 1	0.206	0.181	0.231	0	0	0
CIN 2/3	0.467	0.436	0.497	0	0	0
Cervical cancer	0.623	0.592	0.653	0	0	0
Anal cancer	0.833	0.810	0.856	0.833	0.810	0.856
VaIN 2/3	0.580	0.550	0.611	0	0	0
Vaginal cancer	0.643	0.613	0.673	0	0	0
VIN 2/3	0.796	0.770	0.820	0	0	0
Vulvar cancer	0.712	0.684	0.741	0	0	0
Oropharyngeal cancer	0.469	0.245	0.695	0.410	0.304	0.522
Penile cancer	0	0	0	0.739	0.712	0.766
Anogenital warts	0	0	0	0	0	0
Recurrent respiratory papillomatosis	0	0	0	0	0	0

Table A8.5 Proportion cases attributable to persistent HPV 18 infection

Condition	Females			Males		
	Mean	LCI	UCI	Mean	LCI	UCI
CIN 1	0.035	0.024	0.047	0	0	0
CIN 2/3	0.079	0.063	0.096	0	0	0
Cervical cancer	0.105	0.087	0.125	0	0	0
Anal cancer	0	0	0	0.038	0.027	0.050
VaIN 2/3	0.061	0.047	0.076	0	0	0
Vaginal cancer	0.068	0.053	0.084	0	0	0
VIN 2/3	0.026	0.017	0.037	0	0	0
Vulvar cancer	0.024	0.015	0.034	0	0	0
Oropharyngeal cancer	0.001	0.000	0.003	0.000	0.000	0.002
Penile cancer	0	0	0	0.008	0.003	0.014
Anogenital warts	0	0	0	0	0	0
Recurrent respiratory papillomatosis	0	0	0	0	0	0

Table A8.6 Proportion cases attributable to persistent HPV 31/33/45/52/58 infection

Condition	Females			Males		
	Mean	LCI	UCI	Mean	LCI	UCI
CIN 1	0.250	0.223	0.277	0	0	0
CIN 2/3	0.307	0.279	0.336	0	0	0
Cervical cancer	0.162	0.140	0.186	0	0	0
Anal cancer	0.027	0.018	0.038	0.027	0.018	0.038
VaIN 2/3	0.135	0.115	0.157	0	0	0
Vaginal cancer	0.144	0.123	0.167	0	0	0
VIN 2/3	0.122	0.102	0.143	0	0	0
Vulvar cancer	0.104	0.086	0.124	0	0	0
Oropharyngeal cancer	0.018	0.000	0.111	0.008	0.000	0.035
Penile cancer	0	0	0	0.104	0.086	0.123
Anogenital warts	0	0	0	0	0	0
Recurrent respiratory papillomatosis	0	0	0	0	0	0

Table A8.7 Cost parameters

Description	Distribution	mean	LCI	UCI
Cost of treating case of CIN1 (€)	log normal	352.32	288.11	423.59
Cost of treating case of CIN2/3 (€)	log normal	471.57	386.05	570.51
Cost of treating case of cervical cancer (€)	log normal	18,590	15,208	22,471
Cost of treating case of anal cancer (€)	log normal	26,368	21,539	31,951
Cost of treating case of VIN/VaIN (€)	log normal	472.74	387.20	574.27
Cost of treating case of vaginal cancer (€)	log normal	16,445	13,449	19,916
Cost of treating case of vulvar cancer (€)	log normal	13,063	10,733	15,784
Cost of treating case of oropharyngeal cancer (€)	log normal	29,487	24,135	35,644
Cost of treating case of penile cancer (€)	log normal	7,278	5,972	8,793
Cost of medicines to treat case of ano-genital warts (€)	log normal	32.30	26.50	39.03
Cost of non-medicine consumables to treat case of ano-genital warts (€)	log normal	16.58	13.58	19.95
Average number of GP visits to treat ano-genital warts	log normal	0.93	0.76	1.12
Cost of STI clinic staff to treat case of ano-genital warts (€)	log normal	324.52	265.38	392.14
Proportion ano-genital warts cases treated through GP	beta	0.50	0.33	0.67
Cost per annum of treating patient with recurrent respiratory papillomatosis (€)	log normal	1,563	1,278	1,889
Proportion patients with private health insurance cover	beta	0.10	0.06	0.15
Cost of treating case of serious adverse event (€)	log normal	1,574	1,285	1,910
Opportunity cost of a GP visit (€)	log normal	55.36	44.99	67.27
Proportion of non-serious adverse reactions resulting in GP visit	beta	0.05	0.02	0.10
Cost of outpatients appointment (€)	log normal	144.42	118.36	174.84
Cost of a smear test (€)	log normal	79.28	65.18	95.82
Cost of palliative care (€)	log normal	38,361	31,388	46,377

Appendix A8.3 Incidence data

Incidence data were expressed using beta distributions (Table A8.8 to A8.14).

Table A8.8 Incidence of CIN 1 and CIN 2/3 (per 10,000)

Age	CIN 1		CIN 2/3	
	Mean	(95% CI)	Mean	(95% CI)
0-14	0.00	(0.00, 0.00)	0.00	(0.00, 0.00)
15-19	0.20	(0.04, 0.48)	0.01	(0.00, 0.07)
20-24	4.33	(3.28, 5.52)	0.81	(0.40, 1.35)
25-29	377.01	(367.80, 386.44)	71.59	(67.49, 75.94)
30-34	181.70	(175.82, 187.67)	35.98	(33.34, 38.73)
35-39	136.80	(131.83, 141.94)	23.39	(21.31, 25.58)
40-44	117.80	(112.84, 122.69)	16.49	(14.66, 18.40)
45-49	89.05	(84.56, 93.61)	10.04	(8.61, 11.61)
50-54	42.34	(39.17, 45.58)	6.26	(5.06, 7.57)
55-59	26.26	(23.63, 28.99)	5.87	(4.65, 7.20)
60-64	13.21	(11.22, 15.38)	2.91	(2.03, 3.96)
65-69	5.45	(4.18, 6.89)	1.13	(0.59, 1.87)
70-74	1.69	(0.93, 2.69)	0.24	(0.03, 0.67)
75-79	0.65	(0.18, 1.41)	0.16	(0.00, 0.61)
80-84	0.00	(0.00, 0.00)	0.00	(0.00, 0.00)
85+	0.00	(0.00, 0.00)	0.00	(0.00, 0.00)

Table A8.9 Incidence of VIN 2/3 and VaIN 2/3 (per 10,000)

Age	VIN 2/3		VaIN 2/3	
	Mean	(95% CI)	Mean	(95% CI)
0-14	0.00	(0.00, 0.00)	0.00	(0.00, 0.00)
15-19	0.15	(0.04, 0.32)	0.00	(0.00, 0.00)
20-24	0.24	(0.09, 0.46)	0.09	(0.01, 0.25)
25-29	0.12	(0.02, 0.28)	0.00	(0.00, 0.00)
30-34	0.15	(0.04, 0.32)	0.00	(0.00, 0.00)
35-39	0.10	(0.02, 0.24)	0.08	(0.01, 0.21)
40-44	0.30	(0.14, 0.52)	0.04	(0.00, 0.14)
45-49	0.51	(0.27, 0.80)	0.08	(0.01, 0.23)
50-54	0.79	(0.49, 1.17)	0.13	(0.03, 0.31)
55-59	0.48	(0.25, 0.79)	0.09	(0.01, 0.25)
60-64	0.58	(0.32, 0.92)	0.14	(0.03, 0.35)
65-69	0.38	(0.15, 0.71)	0.25	(0.07, 0.54)
70-74	0.49	(0.20, 0.91)	0.40	(0.14, 0.83)
75-79	0.55	(0.23, 1.03)	0.31	(0.08, 0.74)
80-84	0.18	(0.02, 0.49)	0.21	(0.02, 0.58)
85+	0.23	(0.05, 0.55)	0.09	(0.00, 0.32)

Table A8.10 Incidence of anogenital warts (per 10,000)

Age	Females		Males	
	Mean	(95% CI)	Mean	(95% CI)
0-14	2.00	(1.35, 2.77)	2.00	(1.37, 2.75)
15-19	34.41	(31.54, 37.45)	9.30	(7.86, 10.83)
20-24	62.09	(57.97, 66.17)	34.08	(31.11, 37.19)
25-29	49.42	(45.94, 52.91)	43.98	(40.69, 47.48)
30-34	31.10	(28.63, 33.69)	33.37	(30.73, 36.12)
35-39	24.14	(22.04, 26.32)	22.65	(20.53, 24.83)
40-44	19.26	(17.29, 21.39)	16.09	(14.28, 17.99)
45-49	14.97	(13.14, 16.94)	11.39	(9.81, 13.11)
50-54	9.79	(8.28, 11.40)	7.99	(6.61, 9.48)
55-59	6.99	(5.65, 8.46)	7.20	(5.83, 8.71)
60-64	5.80	(4.51, 7.24)	6.00	(4.70, 7.52)
65-69	4.39	(3.19, 5.76)	4.61	(3.40, 5.99)
70-74	3.50	(2.33, 4.89)	3.70	(2.49, 5.15)
75-79	2.19	(1.18, 3.53)	2.40	(1.28, 3.83)
80-84	0.00	(0.00, 0.00)	0.00	(0.00, 0.00)
85+	0.00	(0.00, 0.00)	0.00	(0.00, 0.00)

Table A8.11 Incidence of vaccine-related adverse events

Condition	Mean	LCI	UCI
4-valent vaccine			
Non-serious adverse events (proportion)	0.692	0.684	0.700
Serious adverse events (per 100,000)	8.1	5.4	11.2
9-valent vaccine			
Non-serious adverse events (proportion)	0.761	0.685	0.841
Serious adverse events (per 100,000)	8.9	5.9	12.6

Table A8.12Incidence of recurrent respiratory papillomatosis (per 100,000)

Condition	Mean	LCI	UCI
Recurrent respiratory papillomatosis (per 100,000)	0.98	0.47	1.78

Table A8.13 Incidence of invasive cancer in females (per 10,000)

Age	Cervical cancer		Vulvar cancer		Vaginal cancer		Anal cancer		Oropharyngeal cancer	
	Mean	(95% CI)	Mean	(95% CI)	Mean	(95% CI)	Mean	(95% CI)	Mean	(95% CI)
0-14	0.00	(0.00, 0.00)	0.00	(0.00, 0.00)	0.00	(0.00, 0.00)	0.00	(0.00, 0.00)	0.00	(0.00, 0.00)
15-19	0.01	(0.00, 0.05)	0.00	(0.00, 0.00)	0.00	(0.00, 0.00)	0.00	(0.00, 0.00)	0.00	(0.00, 0.00)
20-24	0.11	(0.05, 0.20)	0.01	(0.00, 0.05)	0.00	(0.00, 0.01)	0.00	(0.00, 0.01)	0.00	(0.00, 0.01)
25-29	1.34	(1.12, 1.59)	0.00	(0.00, 0.00)	0.00	(0.00, 0.01)	0.01	(0.00, 0.04)	0.01	(0.00, 0.04)
30-34	2.05	(1.78, 2.35)	0.02	(0.00, 0.06)	0.01	(0.00, 0.04)	0.01	(0.00, 0.04)	0.02	(0.00, 0.05)
35-39	2.46	(2.15, 2.80)	0.13	(0.07, 0.22)	0.01	(0.00, 0.04)	0.10	(0.05, 0.18)	0.06	(0.02, 0.11)
40-44	2.59	(2.26, 2.95)	0.11	(0.05, 0.19)	0.01	(0.00, 0.05)	0.05	(0.01, 0.11)	0.07	(0.03, 0.14)
45-49	1.99	(1.69, 2.32)	0.26	(0.16, 0.39)	0.04	(0.01, 0.09)	0.04	(0.01, 0.10)	0.14	(0.07, 0.24)
50-54	2.37	(2.01, 2.75)	0.13	(0.06, 0.23)	0.04	(0.01, 0.11)	0.10	(0.04, 0.19)	0.37	(0.24, 0.52)
55-59	2.50	(2.12, 2.92)	0.23	(0.13, 0.36)	0.07	(0.02, 0.14)	0.35	(0.21, 0.51)	0.41	(0.27, 0.58)
60-64	1.84	(1.49, 2.22)	0.30	(0.17, 0.46)	0.07	(0.02, 0.16)	0.44	(0.29, 0.63)	0.46	(0.30, 0.67)
65-69	1.50	(1.16, 1.89)	0.32	(0.18, 0.51)	0.09	(0.02, 0.21)	0.35	(0.19, 0.54)	0.35	(0.19, 0.54)
70-74	1.66	(1.25, 2.12)	0.71	(0.45, 1.02)	0.18	(0.07, 0.35)	0.18	(0.06, 0.34)	0.41	(0.23, 0.65)
75-79	1.30	(0.91, 1.76)	0.69	(0.42, 1.04)	0.29	(0.13, 0.52)	0.29	(0.12, 0.53)	0.36	(0.17, 0.62)
80-84	1.11	(0.70, 1.60)	1.16	(0.74, 1.67)	0.34	(0.13, 0.64)	0.19	(0.05, 0.42)	0.19	(0.06, 0.43)
85+	1.36	(0.90, 1.91)	1.01	(0.62, 1.49)	0.15	(0.03, 0.37)	0.25	(0.08, 0.52)	0.25	(0.08, 0.52)

Table A8.14 Incidence of invasive cancer in males (per 10,000)

Age	Penile cancer		Anal cancer		Oropharyngeal cancer	
	Mean	(95% CI)	Mean	(95% CI)	Mean	(95% CI)
0-14	0.00	(0.00, 0.00)	0.00	(0.00, 0.00)	0.00	(0.00, 0.00)
15-19	0.00	(0.00, 0.00)	0.00	(0.00, 0.00)	0.00	(0.00, 0.00)
20-24	0.00	(0.00, 0.01)	0.00	(0.00, 0.01)	0.01	(0.00, 0.05)
25-29	0.01	(0.00, 0.04)	0.00	(0.00, 0.01)	0.01	(0.00, 0.04)
30-34	0.01	(0.00, 0.04)	0.01	(0.00, 0.04)	0.01	(0.00, 0.04)
35-39	0.01	(0.00, 0.04)	0.02	(0.00, 0.06)	0.04	(0.01, 0.10)
40-44	0.08	(0.03, 0.15)	0.05	(0.01, 0.11)	0.16	(0.08, 0.25)
45-49	0.12	(0.06, 0.21)	0.07	(0.02, 0.13)	0.66	(0.49, 0.86)
50-54	0.25	(0.14, 0.38)	0.09	(0.03, 0.17)	0.95	(0.74, 1.20)
55-59	0.36	(0.23, 0.53)	0.13	(0.06, 0.23)	1.36	(1.08, 1.66)
60-64	0.28	(0.16, 0.43)	0.17	(0.07, 0.29)	1.82	(1.48, 2.20)
65-69	0.25	(0.13, 0.43)	0.14	(0.05, 0.27)	1.60	(1.25, 2.01)
70-74	0.47	(0.26, 0.74)	0.22	(0.09, 0.42)	1.17	(0.83, 1.57)
75-79	0.90	(0.56, 1.33)	0.26	(0.10, 0.50)	1.21	(0.80, 1.70)
80-84	1.26	(0.74, 1.92)	0.42	(0.15, 0.81)	0.63	(0.29, 1.10)
85+	0.77	(0.31, 1.44)	0.11	(0.00, 0.40)	0.56	(0.18, 1.15)

A8.4 Cancer stage at diagnosis by age

As part of the model it was necessary to estimate survival associated with invasive cancers. The model incorporated data on stage at diagnosis by age. Proportions by stage at diagnosis were modelled using dirichlet distributions for each of five age bands. Survival by stage at diagnosis and age were modelled using individual beta distributions.

Table A8.15 Cervical cancer: incidence in females by stage at diagnosis

Age	Stage I		Stage II		Stage III		Stage IV	
	Mean	(95% CI)	Mean	(95% CI)	Mean	(95% CI)	Mean	(95% CI)
15_44	0.676	(0.642, 0.709)	0.092	(0.072, 0.113)	0.166	(0.140, 0.194)	0.066	(0.050, 0.085)
45-54	0.469	(0.416, 0.525)	0.162	(0.125, 0.204)	0.264	(0.217, 0.314)	0.105	(0.073, 0.141)
55_64	0.393	(0.334, 0.453)	0.197	(0.151, 0.248)	0.231	(0.182, 0.284)	0.179	(0.135, 0.228)
65_74	0.176	(0.114, 0.249)	0.195	(0.129, 0.270)	0.345	(0.262, 0.431)	0.284	(0.208, 0.369)
75+	0.104	(0.051, 0.173)	0.259	(0.176, 0.353)	0.299	(0.210, 0.396)	0.338	(0.245, 0.437)

Table A8.16 Cervical cancer: survival in females by stage at diagnosis

Age	Stage I		Stage II		Stage III		Stage IV	
	Mean	(95% CI)	Mean	(95% CI)	Mean	(95% CI)	Mean	(95% CI)
15_44	0.970	(0.954, 0.983)	0.864	(0.776, 0.933)	0.602	(0.516, 0.684)	0.250	(0.141, 0.378)
45-54	0.952	(0.912, 0.980)	0.755	(0.629, 0.861)	0.608	(0.500, 0.708)	0.335	(0.188, 0.497)
55_64	0.864	(0.791, 0.924)	0.514	(0.376, 0.649)	0.480	(0.356, 0.604)	0.294	(0.173, 0.435)
65_74	0.714	(0.511, 0.881)	0.778	(0.595, 0.916)	0.292	(0.165, 0.436)	0.104	(0.028, 0.226)
75+	0.649	(0.345, 0.902)	0.288	(0.130, 0.478)	0.285	(0.135, 0.463)	0.050	(0.004, 0.145)

Table A8.17 Vulvar cancer: incidence in females by stage at diagnosis

Age	Stage I		Stage II		Stage III		Stage IV	
	Mean	(95% CI)	Mean	(95% CI)	Mean	(95% CI)	Mean	(95% CI)
15_44	0.638	(0.441, 0.809)	0.227	(0.088, 0.408)	0.090	(0.014, 0.224)	0.046	(0.002, 0.149)
45-54	0.622	(0.447, 0.776)	0.206	(0.089, 0.359)	0.069	(0.010, 0.178)	0.103	(0.025, 0.232)
55_64	0.465	(0.295, 0.641)	0.143	(0.045, 0.284)	0.250	(0.115, 0.418)	0.143	(0.046, 0.282)
65_74	0.466	(0.316, 0.623)	0.166	(0.068, 0.296)	0.268	(0.144, 0.413)	0.100	(0.028, 0.211)
75+	0.307	(0.204, 0.422)	0.270	(0.172, 0.379)	0.288	(0.189, 0.399)	0.135	(0.064, 0.226)

Table A8.18 Vulvar cancer: survival in females by stage at diagnosis

Age	Stage I		Stage II		Stage III		Stage IV	
	Mean	(95% CI)	Mean	(95% CI)	Mean	(95% CI)	Mean	(95% CI)
15_44	0.975	(0.873, 1.000)	0.925	(0.633, 1.000)	0.830	(0.261, 1.000)	0.708	(0.036, 1.000)
45-54	0.982	(0.895, 1.000)	0.815	(0.478, 0.990)	0.555	(0.051, 0.981)	0.456	(0.053, 0.908)
55_64	1.000	(1.000, 1.000)	0.896	(0.525, 1.000)	0.877	(0.595, 0.997)	0.523	(0.116, 0.910)
65_74	0.809	(0.612, 0.949)	0.873	(0.554, 0.998)	0.430	(0.165, 0.719)	0.317	(0.021, 0.778)
75+	0.600	(0.386, 0.793)	0.278	(0.104, 0.501)	0.284	(0.113, 0.492)	0.000	(0.000, 0.000)

Table A8.19 Vaginal cancer: incidence in females by stage at diagnosis

Age	Stage I		Stage II		Stage III		Stage IV	
	Mean	(95% CI)	Mean	(95% CI)	Mean	(95% CI)	Mean	(95% CI)
15_44	0.624	(0.297, 0.899)	0.125	(0.004, 0.413)	0.126	(0.004, 0.407)	0.125	(0.003, 0.412)
45-54	0.099	(0.003, 0.336)	0.252	(0.050, 0.547)	0.248	(0.051, 0.531)	0.401	(0.140, 0.706)
55_64	0.092	(0.002, 0.310)	0.094	(0.003, 0.308)	0.093	(0.003, 0.315)	0.721	(0.437, 0.934)
65_74	0.173	(0.032, 0.397)	0.274	(0.084, 0.525)	0.071	(0.002, 0.243)	0.481	(0.234, 0.733)
75+	0.339	(0.161, 0.538)	0.279	(0.117, 0.477)	0.102	(0.018, 0.251)	0.280	(0.123, 0.472)

Table A8.20 Vaginal cancer: survival in females by stage at diagnosis

Age	Stage I		Stage II		Stage III		Stage IV	
	Mean	(95% CI)	Mean	(95% CI)	Mean	(95% CI)	Mean	(95% CI)
15_44	0.735	(0.317, 0.981)	0.570	(0.005, 1.000)	0.343	(0.000, 0.988)	0.181	(0.000, 0.927)
45-54	0.978	(0.664, 1.000)	0.684	(0.140, 0.995)	0.471	(0.036, 0.948)	0.322	(0.024, 0.782)
55_64	1.000	(1.000, 1.000)	0.896	(0.184, 1.000)	0.568	(0.004, 1.000)	0.441	(0.139, 0.777)
65_74	0.789	(0.220, 1.000)	0.755	(0.285, 0.993)	0.239	(0.000, 0.962)	0.110	(0.001, 0.406)
75+	0.650	(0.308, 0.918)	0.196	(0.011, 0.552)	0.135	(0.000, 0.682)	0.030	(0.000, 0.217)

Table A8.21 Penile cancer: incidence in males by stage at diagnosis

Age	Stage I		Stage II		Stage III		Stage IV	
	Mean	(95% CI)	Mean	(95% CI)	Mean	(95% CI)	Mean	(95% CI)
15_44	0.428	(0.155, 0.727)	0.284	(0.064, 0.588)	0.144	(0.011, 0.400)	0.144	(0.011, 0.406)
45-54	0.300	(0.143, 0.484)	0.451	(0.268, 0.640)	0.200	(0.073, 0.370)	0.049	(0.003, 0.156)
55_64	0.343	(0.201, 0.503)	0.343	(0.202, 0.504)	0.218	(0.101, 0.363)	0.095	(0.024, 0.208)
65_74	0.364	(0.200, 0.548)	0.409	(0.235, 0.592)	0.181	(0.067, 0.341)	0.046	(0.002, 0.152)
75+	0.361	(0.233, 0.500)	0.278	(0.162, 0.414)	0.278	(0.162, 0.413)	0.083	(0.024, 0.177)

Table A8.22 Penile cancer: survival in males by stage at diagnosis

Age	Stage I		Stage II		Stage III		Stage IV	
	Mean	(95% CI)	Mean	(95% CI)	Mean	(95% CI)	Mean	(95% CI)
15_44	0.932	(0.607, 1.000)	0.796	(0.281, 0.999)	0.921	(0.315, 1.000)	0.768	(0.095, 1.000)
45-54	0.994	(0.929, 1.000)	0.637	(0.354, 0.875)	0.854	(0.480, 0.998)	0.947	(0.429, 1.000)
55_64	0.990	(0.911, 1.000)	0.588	(0.319, 0.827)	0.535	(0.208, 0.837)	0.665	(0.184, 0.981)
65_74	0.442	(0.165, 0.740)	0.304	(0.085, 0.584)	0.188	(0.006, 0.581)	0.133	(0.000, 0.838)
75+	0.415	(0.197, 0.648)	0.396	(0.159, 0.657)	0.651	(0.385, 0.874)	0.231	(0.006, 0.684)

Table A8.23 Anal cancer: incidence in males and females by stage at diagnosis

Age	Stage I		Stage II		Stage III		Stage IV	
	Mean	(95% CI)	Mean	(95% CI)	Mean	(95% CI)	Mean	(95% CI)
15_44	0.354	(0.185, 0.543)	0.259	(0.114, 0.439)	0.347	(0.182, 0.538)	0.039	(0.001, 0.137)
45-54	0.384	(0.202, 0.578)	0.250	(0.103, 0.440)	0.212	(0.077, 0.389)	0.154	(0.043, 0.320)
55_64	0.200	(0.113, 0.304)	0.336	(0.226, 0.453)	0.413	(0.297, 0.535)	0.051	(0.012, 0.116)
65_74	0.239	(0.123, 0.382)	0.331	(0.198, 0.481)	0.268	(0.143, 0.414)	0.162	(0.066, 0.288)
75+	0.115	(0.035, 0.236)	0.432	(0.277, 0.590)	0.339	(0.198, 0.494)	0.114	(0.033, 0.233)

Table A8.24 Anal cancer: survival in males and females by stage at diagnosis

Age	Stage I		Stage II		Stage III		Stage IV	
	Mean	(95% CI)	Mean	(95% CI)	Mean	(95% CI)	Mean	(95% CI)
15_44	0.973	(0.819, 1.000)	0.958	(0.742, 1.000)	0.888	(0.624, 0.997)	0.404	(0.000, 0.993)
45-54	0.834	(0.555, 0.986)	0.646	(0.268, 0.938)	0.870	(0.510, 0.999)	0.126	(0.000, 0.540)
55_64	0.984	(0.882, 1.000)	0.938	(0.809, 0.996)	0.734	(0.557, 0.879)	0.145	(0.000, 0.595)
65_74	0.811	(0.515, 0.978)	0.864	(0.638, 0.985)	0.540	(0.250, 0.819)	0.052	(0.000, 0.295)
75+	0.650	(0.200, 0.966)	0.274	(0.090, 0.513)	0.452	(0.197, 0.721)	0.021	(0.000, 0.210)

Table A8.25 Oropharyngeal cancer: incidence in males and females by stage at diagnosis

Age	Stage I		Stage II		Stage III		Stage IV	
	Mean	(95% CI)	Mean	(95% CI)	Mean	(95% CI)	Mean	(95% CI)
15_44	0.134	(0.044, 0.264)	0.157	(0.058, 0.295)	0.147	(0.053, 0.279)	0.562	(0.399, 0.719)
45-54	0.071	(0.036, 0.115)	0.050	(0.022, 0.091)	0.171	(0.116, 0.234)	0.708	(0.634, 0.778)
55_64	0.077	(0.047, 0.114)	0.076	(0.046, 0.114)	0.152	(0.109, 0.201)	0.695	(0.635, 0.752)
65_74	0.091	(0.049, 0.143)	0.042	(0.015, 0.081)	0.173	(0.116, 0.239)	0.694	(0.617, 0.768)
75+	0.019	(0.001, 0.061)	0.115	(0.053, 0.197)	0.193	(0.108, 0.293)	0.673	(0.560, 0.777)

Table A8.26 Oropharyngeal cancer: survival in males and females by stage at diagnosis

Age	Stage I		Stage II		Stage III		Stage IV	
	Mean	(95% CI)	Mean	(95% CI)	Mean	(95% CI)	Mean	(95% CI)
15_44	0.963	(0.713, 1.000)	0.962	(0.734, 1.000)	0.680	(0.269, 0.962)	0.882	(0.711, 0.982)
45-54	0.923	(0.713, 0.999)	0.696	(0.353, 0.940)	0.676	(0.492, 0.833)	0.590	(0.498, 0.680)
55_64	0.857	(0.670, 0.972)	0.533	(0.310, 0.757)	0.603	(0.440, 0.755)	0.437	(0.361, 0.514)
65_74	0.180	(0.032, 0.418)	0.290	(0.036, 0.673)	0.283	(0.128, 0.472)	0.412	(0.317, 0.508)
75+	0.738	(0.066, 1.000)	0.646	(0.310, 0.915)	0.543	(0.286, 0.792)	0.094	(0.029, 0.194)

Appendix A8.5 Quality of life/utility data

Disutility is the loss of health-related quality of life due to adverse health outcomes. The cost-effectiveness model required both the magnitude of the disutility and the length of time for which the disutility applied. For example, it was assumed that a woman with CIN 1 would have a disutility of 0.09 (that is, their quality of life was 91% of it's normal value) for an average of six months. All disutilities were modelled using beta distributions. Durations for in situ cancers and anogenital warts were modelled using normal distributions, while for adverse events they were modelled using log normal distributions.

Table A8.27 Disutility and duration of disuility associated with adverse health outcomes

Condition	Disutility			Duration (years)		
	Mean	LCI	UCI	Mean	LCI	UCI
CIN 1	0.090	0.042	0.152	0.500	0.399	0.597
CIN 2/3	0.130	0.073	0.200	0.501	0.403	0.598
VIN 2/3	0.191	0.119	0.272	0.500	0.401	0.597
VaIN 2/3	0.191	0.120	0.272	0.499	0.402	0.596
Ano-genital warts	0.036	0.025	0.049	0.500	0.403	0.596
Non-serious adverse events	0.034	0.014	0.063	0.006	0.004	0.007
Serious adverse events	0.100	0.049	0.164	0.078	0.052	0.114
Terminal cancer	0.635	0.538	0.726			
Recurrent respiratory papillomatosis	0.054	0.020	0.121			

Disutility associated with invasive cancers was defined, where possible, by stage at diagnosis (Table A8.28). Disutility was also given separately for the 'in treatment' phase and the long-term 'post-treatment' phase which extends to life-expectancy.

Table A8.28 Utilities associated with invasive cancers (during and after treatment)

	Cervical cancer		Vulvar cancer		Vaginal cancer		Anal		Oropharyngeal		Penile	
	Mean	(95% CI)	Mean	(95% CI)	Mean	(95% CI)	Mean	(95% CI)	Mean	(95% CI)	Mean	(95% CI)
During treatment												
Stage I	0.240	(0.214, 0.267)	0.240	(0.214, 0.267)	0.240	(0.214, 0.267)	0.430	(0.335, 0.527)	0.349	(0.259, 0.443)	0.291	(0.206, 0.383)
Stage II	0.330	(0.302, 0.357)	0.330	(0.302, 0.358)	0.330	(0.302, 0.357)	0.430	(0.335, 0.527)	0.046	(0.015, 0.095)	0.371	(0.284, 0.464)
Stage III	0.330	(0.302, 0.357)	0.330	(0.302, 0.358)	0.330	(0.302, 0.357)	0.430	(0.335, 0.527)	0.113	(0.059, 0.182)	0.451	(0.364, 0.539)
Stage IV	0.520	(0.493, 0.547)	0.520	(0.493, 0.547)	0.520	(0.493, 0.547)	0.430	(0.335, 0.527)	0.091	(0.043, 0.153)	0.451	(0.364, 0.539)
Post-treatment												
Stage I	0.160	(0.096, 0.236)	0.160	(0.095, 0.236)	0.160	(0.096, 0.238)	0.180	(0.113, 0.259)	0.280	(0.196, 0.372)	0.240	(0.163, 0.330)
Stage II	0.160	(0.096, 0.236)	0.160	(0.095, 0.236)	0.160	(0.096, 0.238)	0.180	(0.113, 0.259)	0.280	(0.196, 0.372)	0.240	(0.163, 0.330)
Stage III	0.160	(0.096, 0.236)	0.160	(0.095, 0.236)	0.160	(0.096, 0.238)	0.180	(0.113, 0.259)	0.280	(0.196, 0.372)	0.330	(0.245, 0.423)
Stage IV	0.160	(0.096, 0.236)	0.160	(0.095, 0.236)	0.160	(0.096, 0.238)	0.180	(0.113, 0.259)	0.280	(0.196, 0.372)	0.330	(0.245, 0.423)