Supplement. Evidence Table and Risk of Bias

KQ1. Is the 2-dose schedule of HPV preventive vaccine effective?

1) Quadrivalent vaccine

ID	Study design	Participant	Inclusion & exclusion criteria	Intervention	Result	Remark
Dobson et al. (2013) [10]	Randomized, phase 3, postlicensure, multicenter, age-stratified, noninferiority immunogenicity study	- 830 Girls (9–13 years) and young women (16–26 years) - 3 Provincial centers in Canada	1. Inclusion criteria - Age: girls: 9–13 years; young women: 16–26 years - ≤ 4 Lifetime sexual partners 2. Exclusion criteria - Pregnancy at enrollment or at vaccine visit - History of genital warts or CIN, or prior receipt of any HPV vaccine - Presence of HPV 16, 18, 6, and 11 antibodies (all participants) or virus infection (among sexually active women participants) at study enrollment- an exclusion from per-protocol study participant analysis for that genotype-specific outcome	1. Girls (9–13 years) - 3 Doses of quadrivalent HPV vaccine 0, 2, and 6 months (n=261) - 2 Doses at 0 and 6 months (n=259) 2. Young women (16–26 years) - 3 Doses at 0, 2, and 6 months (n=310)	1. The GMT ratios - Non-inferior for girls (2 doses) to women (3 doses) - 2.07 (95% CI, 1.62–2.65) for HPV 16 - 1.76 (95% CI, 1.41–2.19) for HPV 18 2. GMT responses 1 months after last vaccination in girls (3 doses) - HPV 16 of 7,736 mMU/mL (95% CI, 6,651–8,999) - HPV 18 of 1,730 mMU/mL (95% CI, 1,512–1,980) 3. The GMT ratios - Non-inferior for girls (2 doses) to girls (3 doses) - 0.95 (95% CI, 0.73–1.23) for HPV 16 - 0.68 (95% CI, 0.54–0.85) for HPV 18 4. The GMT ratios for girls (2 doses) to women (3 doses) - Non-inferior for all genotypes to 36 months 5. Antibody responses in girls - Non-inferior after 2 doses vs 3 doses for all 4 vaccine genotypes at month 7, but not for HPV 18 by month 24 or HPV 6 by month 36.	Quadrivalent
Hernandez-Avila et al. (2015) [11]	Open-label non-randomized clinical trial	- 9–10 years (n=150) and in 2 dose - 9–10 years (n=150) in 3 dose - 18–24 years (n=150) in 3 dose	-	1. 2 Dose (0–6 months) - Quadrivalent HPV vaccine - Aged 9–10 years (n=150) 2. 3 Doses (0, 2, and 6 months) - Quadrivalent HPV vaccine - Girls aged 9–10 years (n=150) 3. 3 Doses (0, 2, and 6 months) - Women 18–24 years (n=150)	1. At 7 months - All vaccines: seropositive for HPV 16 and HPV 18 antibodies 2. At month 21 - 18–24 years: HPV 16, 98.5%; HPV 18, 56.6% 3. 3 Doses for girls (9–10 years) - HPV 16, 99.3%; HPV 18, 86.3% seropositivity rates 4. 2 Doses for girls (9–10 years) - HPV 16, 99.3%; HPV 18, 70.2% seropositivity rates 5. The two doses schedule was non-inferior compared to the three doses schedule in same-age girls and to the group of adult women after 21 months of the first vaccine dose	Quadrivalent

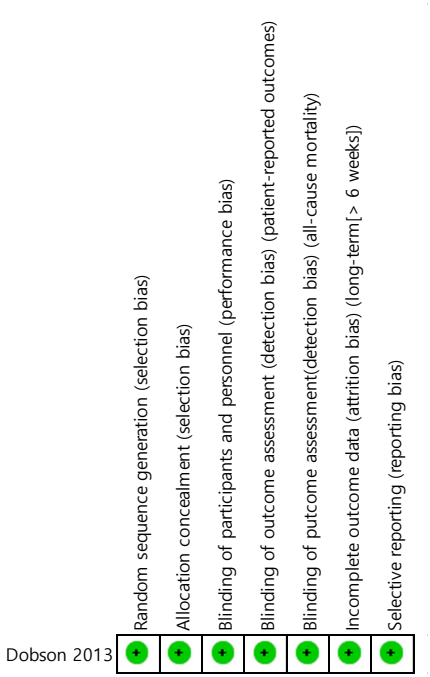
Question: The effect of quadrivalent HPV vaccine 2-dose

1. Dobson SR, McNeil S, Dionne M, Dawar M, Ogilvie G, Krajden M, et al. Immunogenicity of 2 doses of HPV vaccine in younger adolescents vs 3 doses in young women: a randomized clinical trial. JAMA 2013;309:1793-802 [10].
2. Hernandez-Avila M, Torres-Ibarra L, Stanley M, Salmeron J, Cruz-Valdez A, Munoz N, et al. Evaluation of the immunogenicity of the quadrivalent HPV vaccine using 2 versus 3 doses at month 21: an epidemiological surveillance mechanism for alternate vaccination schemes. Hum Vaccin Immunother 2015 Jul 25 [Epub]. http://dx.doi.org/10.1080/21645515.2015.1058458 [11].

Quality assessment						
Participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**
The effect of quadrivalent HPV vaccine 2-dose						
830 (1 study) 36 months	No serious risk of bias	No serious consistency	Serious*	No serious imprecision	Undetected	⊕⊕⊕O **MODERATE** due to indirectness

GMT, geometric mean antibody titer; HPV, human papillomavirus.

*Two studies using GMTs to confirm the efficacy of vaccine.



2) Bivalent vaccine

ID	Study design	Participant	Inclusion & exclusion criteria	Intervention	Result	Remark
Romanowski et al. (2011) [12]	Partially-blind, controlled, randomized trial	960 Healthy girls and young women	Inclusion criteria - 9–25 years old - Age stratified: 9–14, 15–19, 20–25 years	1. 2-Dose schedules - Using the licensed 20/20F/0, 6 month - Using an alternative 40 µg of each antigen (40/40F)/0, 2 month - Using an alternative 40 µg of each antigen (40/40F)/0, 6 month 2. 3-Dose schedule - Using the licensed 20/20F/0–1–6 month	1. At M7, the 3-dose schedule - Not immunologically superior to 2-dose schedules except in the 40/40F M0, 2 group for HPV 16 (lower limit of 95% CI GMT ratio [2D/3D] <0.5). 2. The 2-dose schedules for both HPV 16 and HPV 18 in girls 9–14 years - Immunologically non-inferior to the 3-dose schedule in women 15–25 years (upper limit of 95% CI for GMT ratio [3D/2D] <2). 3. At M24, non-inferiority was maintained for the 2-dose M0, 6 schedules in girls 9–14 years vs. the 3-dose schedule in women 15–25 years. 4. All formulations had acceptable reactogenicity and safety profiles.	Bivalent
Romanowski, et al. (2014) [13]	Partially-blind, controlled, randomized trial	960 Healthy girls and young women	Inclusion criteria - 9–25 years old - Age stratified: 9–14, 15–19, 20–25 years	1. 9–14 years old girls - 2-Dose schedule (0–6 month) 2. 15–25 years old women - 3-Dose schedule (0–1–6 month)	In the according-to-protocol immunogenicity cohort 1. All initially seronegative subjects seroconverted for HPV 16 and 18 antibodies and remained seropositive up to M48. 2. GMT ratios at M36 and M48 for both HPV 16 and 18 close to 1 → non-inferiority was demonstrated. 3. The kinetics of HPV 16, 18, 31, and 45 antibody responses were similar for both groups and HPV 16 and 18 GMTs were substantially higher than natural infection titers. 4. The vaccine had a clinically acceptable safety profile in both groups.	Bivalent

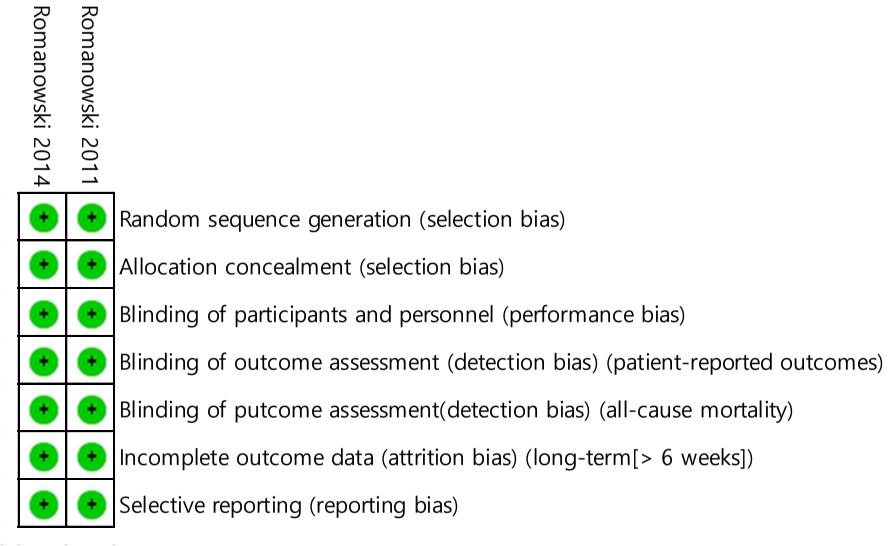
Question: The effect of bivalent HPV vaccine 2-dose

1. Romanowski B, Schwarz TF, Ferguson LM, Peters K, Dionne M, Schulze K, et al. Immunogenicity and safety of the HPV-16/18 AS04-adjuvanted vaccine administered as a 2-dose schedule compared with the licensed 3-dose schedule: results from a randomized study. Hum Vaccin 2011;7:1374-86 [12].
2. Romanowski B, Schwarz TF, Ferguson LM, Ferguson M, Peters K, Dionne M, et al. Immune response to the HPV-16/18 AS04-adjuvanted vaccine administered as a 2-dose or 3-dose schedule up to 4 years after vaccination: results from a randomized study. Hum Vaccin Immunother 2014;10:1155-65 [13].

Quality assessment						
Participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**
The effect of bivalent HPV vaccine 2-dose						
960 (2 studies)	No serious risk of bias	No serious inconsistency	Serious*	No serious imprecision	Undetected	⊕⊕⊕O **MODERATE** due to indirectness

2D, 2-dose; 3D, 3-dose; GMT, geometric mean antibody titer; HPV, human papillomavirus.

*Two randomized clinical trials using GMTs to confirm the efficacy of vaccine.


Romanowski 2014
Romanowski 2011
Random sequence generation (selection bias)
Allocation concealment (selection bias)
Blinding of participants and personnel (performance bias)
Blinding of outcome assessment (detection bias) (patient-reported outcomes)
Blinding of putcome assessment(detection bias) (all-cause mortality)
Incomplete outcome data (attrition bias) (long-term[> 6 weeks])
Selective reporting (reporting bias)

KQ2. Is the 3-dose schedule of HPV preventive vaccine effective in middle-aged women?

1) Quadrivalent vaccine

ID	Study design	Participant	Inclusion & exclusion criteria	Intervention	Result	Remark
Munoz et al. (2009) [15] Castellsague et al. (2011) [16]	Randomized, placebo-controlled, double-blind safety, immunogenicity, and efficacy study	- 3,819 Women - 38 Study sites in Colombia, France, Germany, Philippine, Spain, Thailand, and the USA - Final analysis	1. Inclusion criteria - 24–45 years of age - Not pregnant - Not hysterectomized 2. Exclusion criteria - Prior history of genital warts or cervical disease - Women with any previous cervical surgical procedure and those having undergone a cervical biopsy within the past 5 years - Women infected with HIV - Immunocompromised women	Quadrivalent vaccine or placebo: day 1, and at months 2, and 6	1. In the per-protocol population - Efficacy against the combined incidence of persistent infection, CIN/EGL related to HPV 6/11/16/18: 88.7% (95% CI, 78.1–94.8). - Efficacy for women who were seropositive and DNA negative for the relevant vaccine HPV type at the time of enrolment who received at least 1 dose: 66.9% (95% CI, 4.3–90.6). 2. Sero-positivity at month 48 - HPV 6: 91.5%; HPV 11, 92.0%; HPV 16, 97.4%; HPV 18, 47.9% 3. No serious vaccine-related adverse experiences	Quadrivalent
Luna et al. (2013) [17]	Randomized, placebo-controlled, double-blind safety, immunogenicity, and efficacy study	1. Base study (FUTURE III) - 3,819 Women 2. Follow-up study - 5 Sites in Colombia - 1,335 Women	- 24–45 years of age (in the original vaccine group during the base study; n=684) - 29–50 years of age (in the original placebo group during the base study; n=651)	The quadrivalent HPV vaccine 1. In women who were vaccinated at 24 to 45 years of age (for those enrolled in the original vaccine group during the protocol 019 base study) 2. In women who were vaccinated at 29 to 50 years of age (if they were in the original placebo group during the protocol 019 base study) 3. No placebo group	1. No cases of HPV 6/11/16/18-related CIN or EGL during the extended follow-up phase in the per-protocol population 2. Immunogenicity persists against vaccine-related HPV types 3. No evidence of HPV type replacement has been observed.	Quadrivalent

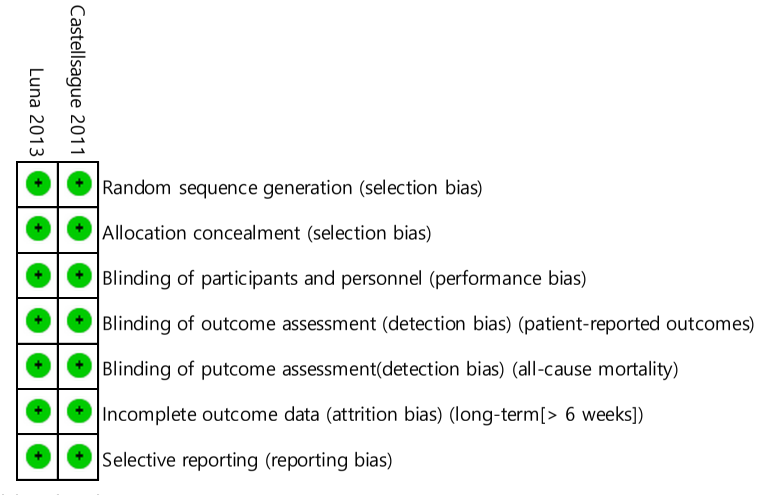
Question: The effect of quadrivalent HPV vaccine 3-dose in old aged women

1. Munoz N, Manalastas R Jr, Pitisuttithum P, Tresukosol D, Monsonego J, Ault K, et al. Safety, immunogenicity, and efficacy of quadrivalent human papillomavirus (types 6, 11, 16, 18) recombinant vaccine in women aged 24-45 years: a randomised, double-blind trial. Lancet 2009;373:1949-57 [15].
2. Castellsague X, Munoz N, Pitisuttithum P, Ferris D, Monsonego J, Ault K, et al. End-of-study safety, immunogenicity, and efficacy of quadrivalent HPV (types 6, 11, 16, 18) recombinant vaccine in adult women 24-45 years of age. Br J Cancer 2011;105:28-37 [16].
3. Luna J, Plata M, Gonzalez M, Correa A, Maldonado I, Nossa C, et al. Long-term follow-up observation of the safety, immunogenicity, and effectiveness of Gardasil in adult women. PLoS One 2013;8:e83431 [17].

Quality assessment						
Participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**
The effect of quadrivalent HPV vaccine 3-dose in old aged women						
3,819 (1 study)	No serious risk of bias	No serious inconsistency	Serious*	No serious imprecision	Undetected	⊕⊕⊕O MODERATE due to indirectness

CIN, cervical intraepithelial neoplasia; EGL, external genital lesions; FUTURE, Females United to Unilaterally Reduce Endo/Ectocervical Disease; GMT, geometric mean antibody titer; HIV, human immunodeficiency virus; HPV, human papillomavirus.

*One randomized clinical trial and 1 long-term follow-up study.


Luna 2013
Castellsague 2011
Random sequence generation (selection bias)
Allocation concealment (selection bias)
Blinding of participants and personnel (performance bias)
Blinding of outcome assessment (detection bias) (patient-reported outcomes)
Blinding of putcome assessment(detection bias) (all-cause mortality)
Incomplete outcome data (attrition bias) (long-term[> 6 weeks])
Selective reporting (reporting bias)

2) Bivalent vaccine

ID	Study design	Participant	Inclusion & exclusion criteria	Intervention	Result	Remark
Skinner et al. (2014) [18]	Phase 3, multinational, double-blind, randomized controlled trial	- 5,777 Healthy women - Australia, Canada, Mexico, the Netherlands, Peru, Philippines, Portugal, Russia, Singapore, Thailand, the UK, and the USA	1. Inclusion criteria - ≥25 years old - 45% of participants in each of the 26–35 years and 36–45 years strata - About 10% in the 46 years and older stratum 2. Exclusion criteria - Women who were pregnant or breastfeeding - Women who had a chronic or autoimmune disease or immunodeficiency	1. HPV 16/18 AS04-adjuvanted vaccine 2. Control (aluminum hydroxide) 3. 0–1–6 month schedule	1. Vaccine efficacy against HPV 16/18-related 6-month persistent infection or CIN 1+: significant - In all age groups combined (81.1%; 97.7% CI, 52.1–94.0) - In the 26–35 years age group (83.5%; 97.7% CI, 45.0–96.8) - In the 36–45 years age group (77.2%; 97.7% CI, 2.8–96.9) - No cases in women aged 46 years and older 2. Vaccine efficacy against ≥ASC-US associated with HPV 16/18: significant 3. Significant cross-protective vaccine efficacy against 6-month persistent infection with HPV 31 (79.1%; 97.7% CI, 27.6–95.9) and HPV 45 (76.9%; 97.7% CI, 18.5–95.6) 4. Serious adverse events - 285 (10%) of 2,881 women in the vaccine group - 267 (9%) of 2,871 in the control group Five (<1%) and eight (<1%) of these events related to vaccination.	Bivalent
Schwarz et al. (2009) [9] Schwarz et al. (2011) [19] Schwarz et al. (2015) [20]	Multicentre, open-label, long-term follow-up (NCT00947115) of a primary phase-III study (NCT00196937)	- 488 Healthy women - Six centers in Germany and Poland	Inclusion criteria - Age: 15–55 years - Age-stratified into groups: 15–25, 26–45, and 46–55 years who received three vaccine doses in the primary study.	1. Immune responses in serum and CVS samples 6 years after dose 1 2. Anti-HPV 16/18 geometric mean titres by ELISA 3. SAEs	1. At 6 years after dose 1 - All women were seropositive for anti-HPV 16 - ≥97% were seropositive for anti-HPV 18 2. GMTs - 277.7–1,344.6 EU/mL for anti-HPV 16 - 97.6–438.2 EU/mL for anti-HPV 18 3. In all age groups, GMTs were higher (anti-HPV 16, 9.3–45.1-fold; anti-HPV 18, 4.3–19.4-fold) than levels associated with natural infection (29.8 EU/mL). 4. A strong correlation between serum and CVS anti-HPV 16/18 levels was observed, with correlation coefficients of 0.81–0.96 (anti-HPV 16) and 0.69–0.84 (anti-HPV 18).	Bivalent

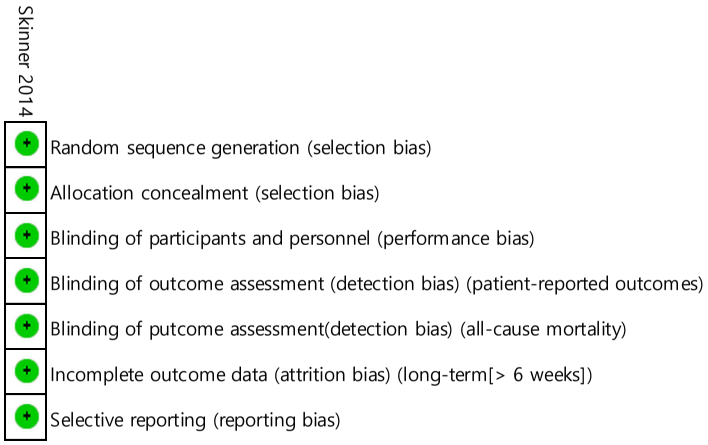
Question: The effect of bivalent HPV vaccine 3-dose in old aged women

1. Skinner SR, Szarewski A, Romanowski B, Garland SM, Lazcano-Ponce E, Salmeron J, et al. Efficacy, safety, and immunogenicity of the human papillomavirus 16/18 AS04-adjuvanted vaccine in women older than 25 years: 4-year interim follow-up of the phase 3, double-blind, randomised controlled VIVIANE study. Lancet 2014;384:2213-27 [18].
2. Schwarz TF, Spaczynski M, Schneider A, Wysocki J, Galaj A, Perona P, et al. Immunogenicity and tolerability of an HPV-16/18 AS04-adjuvanted prophylactic cervical cancer vaccine in women aged 15-55 years. Vaccine 2009;27:581-7 [9].
3. Schwarz TF, Spaczynski M, Schneider A, Wysocki J, Galaj A, Schulze K, et al. Persistence of immune response to HPV-16/18 AS04-adjuvanted cervical cancer vaccine in women aged 15-55 years. Hum Vaccin 2011;7:958-65 [19].
4. Schwarz T, Spaczynski M, Kaufmann A, Wysocki J, Galaj A, Schulze K, et al. Persistence of immune responses to the HPV-16/18 AS04-adjuvanted vaccine in women aged 15-55 years and first-time modelling of antibody responses in mature women: results from an open-label 6-year follow-up study. BJOG 2015;122:107-18 [20].

Quality assessment						
Participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**
The effect of bivalent HPV vaccine 3-dose in old-aged women						
5,777 (1 study)	No serious risk of bias	No serious inconsistency	Serious*	No serious imprecision	Undetected	⊕⊕⊕O MODERATE due to indirectness

ASC-US, atypical squamous cells of undetermined significance; CIN, cervical intraepithelial neoplasia; CVS, cervicovaginal secretion; ELISA, enzyme-linked immunosorbent assay; GMT, geometric mean antibody titer; HPV, human papillomavirus; SAE, serious adverse event.

*Three observational studies using GMTs.


Skinner 2014
Random sequence generation (selection bias)
Allocation concealment (selection bias)
Blinding of participants and personnel (performance bias)
Blinding of outcome assessment (detection bias) (patient-reported outcomes)
Blinding of putcome assessment(detection bias) (all-cause mortality)
Incomplete outcome data (attrition bias) (long-term[> 6 weeks])
Selective reporting (reporting bias)

KQ3. At what age should the 3-dose schedule of HPV preventive vaccine be administered?

1) Quadrivalent vaccine

ID	Study design	Participant	Inclusion & exclusion criteria	Intervention	Result	Remark
Koutsky et al. (2002) [21]	Randomly assigned in a 1:1 ratio according to a permuted-block design	- 2,392 Women - 16 Centers in the USA	Inclusion criteria - Female subjects - 16–23 years of age - Not pregnant - No prior abnormal Pap smears - No more than five male sex partners during their lifetime - Virgin seeking contraception	1. HPV 16 vaccine (40 µg of HPV-16 L1 virus-like particles formulated on 225 µg of aluminum adjuvant in a total carrier volume of 0.5 mL) 2. Placebo (225 µg of aluminum adjuvant in a total carrier volume of 0.5 mL) 3. Three intramuscular injections (day 0, 2, 6th months)	1. 100% efficacy (95% CI, 90–100; p<0.001) - The incidence of persistent HPV 16 infection - Placebo group: 3.8/100 woman-years at risk - Vaccine group: 0/100 woman-years at risk 2. HPV 16-related CIN among the placebo recipients: 9 cases	Quadrivalent
Ault et al. 2004 [22]	Double-blind, randomized, placebo-controlled phase I study	- 40 Women - 3 USA colleges	- 16–23 years of age Exclusion criteria - A prior abnormal Pap smear - ≥5 lifetime male sexual partners	1. HPV 18 vaccine (80 µg of HPV 18 L1 VLP formulated with 450 µg of amorphous aluminum hydroxyphosphate sulfate adjuvant in a buffered solution yielding a total injection volume of 0.5 mL) 2. Placebo (225 µg of aluminum adjuvant in a total carrier volume of 0.5 mL) 3. Three intramuscular injections (day 0, 2, 6th months)	1. The HPV 18 L1 VLP vaccine - Generally well-tolerated and highly immunogenic. 2. Peak anti-HPV 18 GMT in vaccines - 60-Fold greater than those observed in women following natural HPV 18 infection.	Quadrivalent
Villa et al. 2005 [23]	Randomized double-blind placebo-controlled phase II study	- 552 Women - Brazil, Europe, and the USA	1. Inclusion criteria - Female subjects - 16–23 years of age - Not pregnant - No prior abnormal Pap smears - No more than five male sex partners during their lifetime - Virgin ≤18 years old and seeking contraception 2. Exclusion criteria - Women with previous HPV infection	1. Quadrivalent HPV - 277 (mean age, 20.2±1.7 years) - 20 µg type 6, 40 µg type 11, 40 µg type 16, and 20 µg type 18 L1 VLP vaccine 2. Placebo - 275 (mean age, 20.0±1.7 years) 3. Vaccinated on 0, 2, 6th months	Combined incidence of persistent infection or disease with HPV 6, 11, 16, or 18 - Reduction of 90% (95% CI, 71–97; p<0.0001) in those assigned vaccine compared with those assigned placebo. HPV vaccine- generally well tolerated - Adverse event at the injection site: vaccine > placebo - Most common injection site event: pain - Most common systemic event: headache	Quadrivalent
Mao et al. 2006 [25]	Randomized, double-blind, placebo-controlled trial	- 2,391 Women, - 16 Centers in the US	Inclusion criteria - 16–23 years of age - No pregnant - No prior abnormal Pap smear - No more than 5 sexual partners - Virgin: seeking contraception	1. 40 Mug HPV 16 L1 VLP vaccine or placebo 2. Three intramuscular injection (day 1, month 2, and month 6)	1. 750 Placebo recipients in the per protocol population - 12 Women developed HPV 16-related CIN 2–3 (6 CIN 2 and 6 CIN 3) 2. 755 Vaccine recipients - No cases (vaccine efficacy 100%; 95% CI, 65–100) 3. Persistent HPV 16 infection - 111 Cases in placebo recipients - 7 Cases in vaccine recipients (vaccine efficacy 94%; 95% CI, 88–98).	Quadrivalent

Villa et al. (2006) [26]	Phase II, randomized, multicenter, double-blind, placebo-controlled study	- 1,158 Women - Brazil, Nordic countries (Finland, Sweden, Norway), the USA	1. Inclusion criteria - 16–23 years of age - Non-pregnant - No prior abnormal Pap smears - A lifetime history of four or fewer male sex partners - Virgin: ≥18 years of age and seeking contraception 2. Exclusion criteria - Subjects with prior HPV infection	1. The low-dose formulation which was subsequently approved as Gardasil 2. Two placebo arms with different adjuvant doses (225 or 450 μg)	At 5 years post enrolment 1. The combined incidence of HPV 6/11/16/18-related persistent infection or disease: reduced by 96% -Vaccine group, 2 cases; placebo group, 46 cases) 2. HPV 6/11/16/18-related precancerous cervical dysplasia or genital warts (efficacy, 100%; 95% CI, 12–100). -Vaccine group, 0 cases; placebo group, 6 cases	Quadrivalent
Garland et al. (2007) [27]	Randomized, placebo-controlled, double-blind trial (The FUTURE I study)	- 5,455 Women - 16 Countries	Inclusion criteria - 16–26 years of age - Not pregnant - No history of genital warts or abnormal Pap smear - No more than four sex partners in lifetime	1. The quadrivalent HPV 6/11/16/18 L1 virus-like-particle vaccine with amorphous aluminum hydroxyphosphate sulfate (Gardasil, Merck) as an adjuvant 2. The aluminum-containing placebo	1. In the per-protocol population - Vaccine efficacy: 100% for each of the co-primary end points 2. In an intention-to-treat analysis - Reduction of the rate of any vulvar or vaginal perianal lesions regardless of the causal HPV type by 34% (95% CI, 15–49) - Reduction of the rate of cervical lesions regardless of the causal HPV type by 20% (95% CI, 8–31) 3. Adverse event - Injection site: vaccine (87%) vs. placebo (77%) (most common: pain at the site) - Similar proportions ov vaccine and placebo recipient	Quadrivalent
Olsson et al. (2007) [28]	Randomized, multicenter, double-blind, placebo-controlled study	- 552 Women - Brazil, Finland, Sweden, Norway, and the USA	1. Inclusion criteria - 16–23 years - No prior abnormal Pap smears - ≤4 Male sex partners - Virgin: ≥18 years of age and seeking contraception - Prior HPV infection 2. Exclusion criteria - Pregnant - All subjects to use effective contraception during the trial	1. 3-Dose regimens of quadrivalent HPV (types 6, 11, 16, 18) L1 VLP vaccine or placebo 2. 3 years' follow-up	1. Serum anti-HPV levels declined post-vaccination, but reached a plateau at month 24 that remained stable through month 60. 2. Administration of a challenge dose of vaccine induced a classic anamnestic response, with anti-HPV levels 1 week post-challenge reaching levels observed 1 month following the completion of the 3-dose primary series. 3. At 1 month post-challenge, anti-HPV responses were higher than those observed 1-month post-dose 3. 4. A 3-dose regimen of quadrivalent HPV vaccine induces high efficacy and stable anti-HPV levels for at least 5 years. 5. Vaccination also induces robust immune memory	Quadrivalent
Ault et al. (2007) [4]	Double-blind, placebo-controlled, randomized trial (The FUTURE II study)	- 20,583 Women - 90 Study sites in 13 countries	Inclusion criteria - 16–26 years of age - Not pregnant - No prior abnormal Pap smear - No more than four sex partners	1. 3 Doses of either HPV 6/11/16/18 vaccine or placebo 2. Day 1, month 2, and month 6	1. Mean follow-up: 3.0 years (SD 0.66) 2. Vaccine efficacy for the prevention of the primary composite end point - 99% (95% CI, 93–100) in the per-protocol population - 44% (95% CI, 31–55) in an intention-to-treat population 3. The overall rate of CIN 2/3 or AIS due to any HPV type - 18% Reduction (95% CI, 7–29) in a second intention-to-treat analysis	Quadrivalent

Munoz et al. (2010) [30]	Two randomized, placebo-controlled, efficacy trials (FUTURE I and FUTURE II)	- 17,622 Women aged 15–26 years - Australia, Austria, Brazil, Canada, Colombia, Czech Republic, Denmark, Finland, Germany, Hong Kong, Iceland, Italy, Mexico, New Zealand, Norway, Peru, Poland, Puerto Rico, Russia, Singapore, Sweden, Thailand, the United Kingdom, and the United States	1. Negative to 14 HPV types 1) Inclusion criteria - At least one vaccination - Seronegative and PCR negative at day 1 to the vaccine HPV types (i.e., HPV 6, 11, 16, and 18), were PCR negative at day 1 to the nonvaccine high-risk HPV types that had available PCR assays (i.e., HPV 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59), and had a negative day 1 Pap test result - Any follow-up visit: endpoint counting began after day 1 2. Intention to treat 1) Inclusion criteria - At least one vaccination - Any follow-up visit	1. The HPV 6/11/16/18 vaccine or placebo - At day 1, month 2, and month 6 2. All women - Cervicovaginal sampling - Pap testing at day 1 and every 6–12 months thereafter 3. Outcomes - Any cervical intraepithelial neoplasia - Any external anogenital and vaginal lesions - Pap test abnormalities - Procedures such as colposcopy and definitive therapy	1. The average follow-up 3.6 years (maximum of 4.9 years) 2. In the population that was negative to 14 HPV types - Vaccination efficacy: up to 100% effective in reducing the risk of HPV 16/18-related high-grade cervical, vulvar, and vaginal lesions and of HPV 6/11-related genital warts 3. In the intention-to-treat group irrespective of causal HPV type Vaccination efficacy - The risk of any high-grade cervical lesions (19.0% reduction; rate vaccine 1.43, rate placebo 1.76, difference 0.33; 95% CI, 0.13–0.54) - The risk of vulvar and vaginal lesions (50.7% reduction; rate vaccine 0.10, rate placebo 0.20, difference 0.10; 95% CI, 0.04–0.16) - The risk of genital warts (62.0% reduction; rate vaccine 0.44, rate placebo 1.17, difference 0.72; 95% CI, 0.58–0.87) - The risk of Pap abnormalities (11.3% reduction; rate vaccine 10.36, rate placebo 11.68, difference 1.32; 95% CI, 0.74–1.90) - The risk of cervical definitive therapy (23.0% reduction; rate vaccine 1.97, rate placebo 2.56, difference 0.59; 95% CI, 0.35–0.83)	Quadrivalent
Block et al. (2006) [24]	- Non-inferiority immunogenicity study - A substudy within a randomized, double-blinded, multidose study	- 506 Girls and 510 boys (10–15 years of age) - 513 Females (16–23 years of age) - 61 Clinical center in Asia, Australia, Europe, Latin America, North America	Inclusion criteria 1. 10–15 years old girls and boys - Sexually naïve at enrollment and throughout the study 2. 16–23 years old females - Intact uterus - No evidence of gross purulent cervicitis - No history of genital warts - No previous abnormal Pap smear - No history of CIN - No more than four sexual partners during their lifetime	1. Three intramuscular injections (0, 1, 6th months) 2. Serology testing: day 1 and at months 3 and 7 on blinded samples. 3. Neutralizing antibody concentrations: using type-specific immunoassays and summarized as geometric mean titers and seroconversion rates	1. Seroconversion rates: ≥99% for all 4 human papillomavirus types in each group by month 7 2. Anti-human papilloma virus geometric mean titers in girls or boys: noninferior and 1.7- to 2.7-fold higher compared with women 3. Most (≥97%) injection-site adverse events were mild to moderate in intensity 4. Significantly more boys (13.8%) and girls (12.8%) than women (7.3%) reported fevers ≥37.8°C within 5 days of vaccination. Most (96.4%) fevers were mild (<39°C).	Quadrivalent

Reisinger et al. (2007) [29]	Randomized, double-blind, placebo-controlled, multicenter trial	- 1,781 Sexually naive children - 47 Study sites located in 10 countries in North America, Latin America, Europe, and Asia	Stratified by age (2:1 ratio of 9- to 12-year-old subjects and 13- to 15-year-old subjects) and by gender (1:1)	1. Quadrivalent HPV 6/11/16/18 vaccine 2. Saline placebo 3. 0, 2, 6 months 4. Serum neutralizing anti-HPV 6/11/16/18 responses: GMTs and seroconversion rates	1. Seroconversion rates at 7 months - ≥99.5% for the 4 vaccine-HPV-types 2. GMTs and seroconversion rates in boys - Non-inferior to those in girls ($p<0.001$) 3. Seropositive rates at month 18 - ≥91.5% of vaccine recipients regardless of gender 4. Injection site adverse event: vaccine>placebo - injection site erythema, pain, swelling 5. Most common systemic adverse event: headache, fever, pharyngeal pain (no significant difference)	Quadrivalent
Kang et al. (2008) [31]	- Randomized, double-blind, placebo-controlled study - 2:1 Ratio for randomization	-176 Volunteers aged 9–23 years -South Korea	1. Inclusion criteria - Non-pregnant - Aged 9–23 years at enrollment - Must not have had a febrile illness (fever more than 37.8˚C) at vaccination. - Subjects aged 9–15 years · Must have had no sexual experience before, and no plan to have sexual experience during the study period - Subjects aged 16–23 years · Must have had a history of less than four male and/or female sexual partners at enrollment · Use effective contraception during the study period · Not had a prior Pap test showing a squamous intraepithelial lesion or worse and/or a biopsy indicating CIN or worse 2. Exclusion criteria - Enrollment in studies of other investigational agents - History of any HPV vaccination - History of allergy to vaccine compound (including aluminum, yeast, and BENZONASE) - Thrombocytopenia - History of vaccination within 14 days from enrollment (previous 21 days for live vaccine) - Receipt of blood or blood-derived products within the 6 months preceding injection, and immunosuppression	1. 117 Women were assigned to quadrivalent HPV (20 µg type 6, 40 µg type 11, 40 µg type 16, and 20 µg type 18) vaccine 2. 59 Women to placebo - Individuals received vaccine at day 1, month 2, and month 6 - Blood samples for analysis at enrollment at month 7	Quadrivalent HPV vaccine was generally well tolerated with no vaccine-related serious adverse experiences. Quadrivalent HPV vaccine induced seroconversion for each vaccine-related HPV type. At month 7, vaccine-induced type-specific antibody titer was high.	Quadrivalent

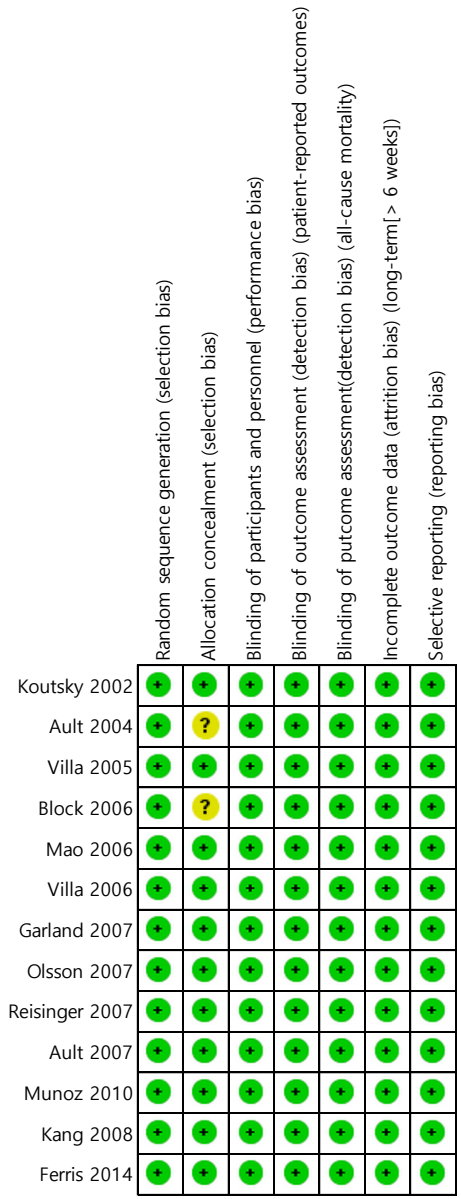
Ferris et al. (2014) [32]	- Randomized, double-blind, placebo-controlled study - Long-term safety, immunogenicity, and effectiveness study	Sexually naive boys and girls aged 9 to 15 years (n=1,781)	Inclusion criteria - Sexually naive boys and girls - Aged 9–15 years - Early vaccination group (n=1,179) - Catch-up vaccination group (n=482)	1. HPV 4 vaccine or saline placebo 2. Day 1 and months 2 and 6 - At month 30, the placebo group (n=482) received HPV 4 vaccine following the same regimen - Both cohorts were followed through month 96.	1. Vaccination-induced anti-HPV response - Persisted through month 96 for each of the HPV 4 vaccine types 2. Among 429 subjects who received HPV 4 vaccine at a mean age of 12, none developed HPV 6/11/16/18-related disease or persistent infection of ≥12 months' duration. 3. Acquisition of new sexual partners (among those ≥16 years) was ~1 per year. 4. Subjects receiving HPV 4 vaccine at month 30 (mean age 15 years) - A similar baseline rate of seropositivity to ≥1 of the 4 HPV types to those vaccinated at day 1 (mean age 12 years; 1.9% [9 of 474] vs. 1.7% [20 of 1,157]); 5. No new significant serious AEs were observed in both genders. 3 Serious AEs: - Fatal road traffic accident (EVG, 4.7 years postdose 3) → not vaccine-related - Tonic-clonic movement postphlebotomy (EVG, 7 years postdose 3) → not vaccine-related - Cranial nerve VII paralysis (CVG, 131 days postdose 3) → determined to be vaccine-related. 6. No significant pregnancy-related adverse outcome observed. - EVG (72%) and CVG (70%): live births - EVG (94%) and CVG (92%): normal infant outcome - 3 Congenital anomalies (2 cases of trisomy 21 and 1 choanal atresia)	Quadrivalent

Question: The effective range of age of quadrivalent HPV vaccine 3-dose

1. Koutsky LA, Ault KA, Wheeler CM, Brown DR, Barr E, Alvarez FB, et al. A controlled trial of a human papillomavirus type 16 vaccine. N Engl J Med 2002;347:1645-51 [21].
2. Ault KA, Giuliano AR, Edwards RP, Tamms G, Kim LL, Smith JF, et al. A phase I study to evaluate a human papillomavirus (HPV) type 18 L1 VLP vaccine. Vaccine 2004;22:3004-7 [22].
3. Villa LL, Costa RL, Petta CA, Andrade RP, Ault KA, Giuliano AR, et al. Prophylactic quadrivalent human papillomavirus (types 6, 11, 16, and 18) L1 virus-like particle vaccine in young women: a randomised double-blind placebo-controlled multicentre phase II efficacy trial. Lancet Oncol 2005;6:271-8 [23].
4. Mao C, Koutsky LA, Ault KA, Wheeler CM, Brown DR, Wiley DJ, et al. Efficacy of human papillomavirus-16 vaccine to prevent cervical intraepithelial neoplasia: a randomized controlled trial. Obstet Gynecol 2006;107:18-27 [25].
5. Villa LL, Costa RL, Petta CA, Andrade RP, Paavonen J, Iversen OE, et al. High sustained efficacy of a prophylactic quadrivalent human papillomavirus types 6/11/16/18 L1 virus-like particle vaccine through 5 years of follow-up. Br J Cancer 2006;95:1459-66 [26].
6. Garland SM, Hernandez-Avila M, Wheeler CM, Perez G, Harper DM, Leodolter S, et al. Quadrivalent vaccine against human papillomavirus to prevent anogenital diseases. N Engl J Med 2007;356:1928-43 [27].
7. Olsson SE, Villa LL, Costa RL, Petta CA, Andrade RP, Malm C, et al. Induction of immune memory following administration of a prophylactic quadrivalent human papillomavirus (HPV) types 6/11/16/18 L1 virus-like particle (VLP) vaccine. Vaccine 2007;25:4931-9 [28].
8. Ault KA; Future II Study Group. Effect of prophylactic human papillomavirus L1 virus-like-particle vaccine on risk of cervical intraepithelial neoplasia grade 2, grade 3, and adenocarcinoma in situ: a combined analysis of four randomised clinical trials. Lancet 2007;369:1861-8 [4].
9. Munoz N, Kjaer SK, Sigurdsson K, Iversen OE, Hernandez-Avila M, Wheeler CM, et al. Impact of human papillomavirus (HPV)-6/11/16/18 vaccine on all HPV-associated genital diseases in young women. J Natl Cancer Inst 2010;102:325-39 [30].
10. Block SL, Nolan T, Sattler C, Barr E, Giacoletti KE, Marchant CD, et al. Comparison of the immunogenicity and reactogenicity of a prophylactic quadrivalent human papillomavirus (types 6, 11, 16, and 18) L1 virus-like particle vaccine in male and female adolescents and young adult women. Pediatrics 2006;118:2135-45 [24].
11. Reisinger KS, Block SL, Lazcano-Ponce E, Samakoses R, Esser MT, Erick J, et al. Safety and persistent immunogenicity of a quadrivalent human papillomavirus types 6, 11, 16, 18 L1 virus-like particle vaccine in preadolescents and adolescents: a randomized controlled trial. Pediatr Infect Dis J 2007;26:201-9 [29].
12. Kang S, Kim KH, Kim YT, Kim YT, Kim JH, Song YS, et al. Safety and immunogenicity of a vaccine targeting human papillomavirus types 6, 11, 16 and 18: a randomized, placebo-controlled trial in 176 Korean subjects. Int J Gynecol Cancer 2008;18:1013-9 [31].
13. Ferris D, Samakoses R, Block SL, Lazcano-Ponce E, Restrepo JA, Reisinger KS, et al. Long-term study of a quadrivalent human papillomavirus vaccine. Pediatrics 2014;134:e657-65 [32].

Quality assessment						
Participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**
The effective range of age of quadrivalent HPV vaccine 3-dose						
45,815 (13 studies)	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	⊕⊕⊕⊕ HIGH

AE, adverse event; AIS, adenocarcinoma *in situ*; CIN, cervical intraepithelial neoplasia; CVG, catch-up vaccination group; EVG, early vaccination group; FUTURE, Females United to Unilaterally Reduce Endo/Ectocervical Disease; GMT, geometric mean antibody titer; HPV, human papillomavirus; PCR, polymerase chain reaction; VLP, virus-like particle.


Random sequence generation (selection bias)
Allocation concealment (selection bias)
Blinding of participants and personnel (performance bias)
Blinding of outcome assessment (detection bias) (patient-reported outcomes)
Blinding of putcome assessment(detection bias) (all-cause mortality)
Incomplete outcome data (attrition bias) (long-term[> 6 weeks])
Selective reporting (reporting bias)
Koutsky 2002
Ault 2004
Villa 2005
Block 2006
Mao 2006
Villa 2006
Garland 2007
Olsson 2007
Reisinger 2007
Ault 2007
Munoz 2010
Kang 2008
Ferris 2014

2) Bivalent vaccine

ID	Study design	Participant	Inclusion & exclusion criteria	Intervention	Result	Remark
Harper et al. (2004) [33]	Multicenter, randomized, double-blind, placebo-controlled trial	- 1,113 Women (15–25 years of age) - North America and Brazil	Inclusion criteria 1. Women eligible for the initial phase (months 0–18) - 15–25 years-old women - <6 Sexual partners - No history of abnormal Pap test - No ablative or excisional treatment of the cervix - No ongoing treatment for external condylomata - Cytologically negative, seronegative for HPV 16 and 18 antibodies by ELISA, and HPV-DNA-negative by PCR for 14 high-risk HPV types ≤90 days before study entry 2. Women eligible for extension phase (months 18–27) - Completed the initial phase - No ablative or excisional treatment of the cervix - No hysterectomy after enrollment	1. The bivalent HPV 16/18 VLP vaccine formulated with AS04 adjuvant (containing 20 μg each of HPV 16 and HPV 18 L1 VLP) or placebo 2. Three intramuscular injections (0, 1, 6th months)	1. In the according-to-protocol analysis - 91.6% Efficacy (95% CI, 64.5–98.0) against incident infection - 100% Against persistent infection (95% CI, 47.0–100) with HPV 16/18 2. In the Intention-to-treat analyses - 95.1% Efficacy (95% CI, 63.5–99.3) against persistent cervical infection with HPV 16/18 - 92.9% Efficacy (95% CI, 70.0–98.3) against cytological abnormalities associated with HPV 16/18 infection 3. Adverse event - The vaccine was generally safe, well tolerated, and highly immunogenic. - No serious adverse events related to vaccination - More injection site symptoms in vaccination group	Bivalent
Harper et al. (2006) [34]	Follow-up study of multicenter, double-blind, randomized, placebo-controlled trial reported in 2004	- Women who enrolled with initial study - 28 Sites in North America (Canada and the USA) and Brazil - Follow-up: up to 4.5 years	Women who originally received all three doses - Bivalent HPV 16/18 VLP vaccine (n=393) - Placebo (n=383)	1. HPV DNA, using cervical samples 2. Yearly cervical cytology assessments 3. The long-term immunogenicity and safety of the vaccine	1. ≥98% Seropositivity for HPV 16/18 2. Vaccine efficacy against HPV 16 and 18 endpoints: - Incident infection: 96.9% (95% CI, 81.3–99.9) - Persistent infection: 6-month definition, 94.3% (95% CI, 63.2–99.9); 12-month definition, 100% (95% CI, 33.6–100) 3. In a combined analysis of the initial efficacy and extended follow-up studies - Vaccine efficacy: 100% (95% CI, 42.4–100) against CIN lesions associated with vaccine types 4. Adverse event - More adverse events and new onset of chronic diseases in placebo group	Bivalent

Paavonen et al. (2007) [35]	Phase III double-blind, randomized controlled trial	- 18,644 Women - 14 Countries	1. Inclusion criteria - 15–25 years of age - <6 Lifetime sexual partners before study - Intact cervix 2. Exclusion criteria - Women with a history of colposcopy - Women were pregnant or breastfeeding - Women had chronic or autoimmune disease or immunodeficiency	1. HPV 16/18 vaccine (n=9,319) 2. Hepatitis A vaccine (n=9,325) 3. 0, 1, and 6 months	1. CIN 2+ associated with HPV 16 or HPV 18 DNA - 2 Cases in the HPV 16/18 vaccine group - 21 Cases in the control group: of the 23 cases, 14 (two in the HPV 16/18 vaccine group, 12 in the control group) contained several oncogenic HPV types - Vaccine efficacy against CIN 2+ containing HPV 16/18 DNA was 90.4% (97.9% CI, 53.4–99.3; p<0.0001). 2. Safety outcomes - No clinically meaningful differences between the study groups	Bivalent
Paavonen et al. (2009) [36]	Phase III randomized, double-blind, controlled	18,644 Women (15–25 years)	- ATP-E (vaccine, n=8,093; control, n=8,069) - TVC (included all women receiving at least one vaccine dose, regardless of their baseline HPV status; represents the general population, including those who are sexually active; vaccine, n=9,319; control, n=9,325) - TVC-naive (no evidence of oncogenic HPV infection at baseline; represents women before sexual debut; vaccine, n=5,822; control, n=5,819)	HPV 16/18 AS04-adjuvanted vaccine (months 0, 1, and 6)	1. Vaccine efficacy against CIN 2+ associated with HPV 16/18 - 92.9% (96.1% CI, 79.9–98.3) in the primary analysis - 98.1% (96.1% CI, 88.4–100) in an analysis in which probable causality to HPV type was assigned in lesions infected with multiple oncogenic types (ATP-E cohort) 2. Vaccine efficacy against CIN 2+ irrespective of HPV DNA - 30.4% (96.1% CI, 16.4–42.1) in the TVC - 70.2% (96.1% CI, 54.7–80.9) in the TVC-naïve 3. Corresponding values against CIN 3+ - 33.4% (96.1% CI, 9.1–51.5) in the TVC - 87.0% (96.1% CI, 54.9–97.7) in the TVC-naïve 4. Vaccine efficacy against CIN 2+ associated with 12 non-vaccine oncogenic types - 54.0% (96.1% CI, 34.0–68.4; ATP-E) 5. Individual cross-protection against CIN 2+ associated with HPV 31, 33, and 45 was seen in the TVC 6. Adverse event - Similar proportion of serious adverse events, medically significant conditions, new-onset chronic diseases, and new-onset autoimmune diseases in vaccine and control groups	Bivalent
GlaxoSmithKline Vaccine HPV-007 Study Group et al. (2009) [37]	Double-blind, randomized, placebo-controlled initial study	- 1,889 Women - 27 Sites (5 in Brazil, 5 in Canada, and 17 in the USA)	Inclusion criteria - 15–25 years old - Normal cervical cytology - HPV 16/18 seronegative and oncogenic HPV DNA-negative (14 types) - Participated in initial study (n=1,113) and follow-up study (n=776)	1. HPV 16/18 AS04-adjuvanted vaccine and placebo 2. Cervical samples for HPV DNA test every 6 months 3. Management of abnormal cytologies was pre-specified, and HPV 16/18 antibody titres were assessed.	1. Vaccine efficacy - Against incident infection with HPV 16/18 95.3% (95% CI, 87.4–98.7) - Against 12-month persistent infection 100% (95% CI, 81.8–100) 2. Vaccine efficacy against CIN 2+ - 100% (95% CI, 51.3–100) for lesions associated with HPV 16/18 - 71.9% (95% CI, 20.6–91.9) for lesions independent of HPV DNA 3. Antibody concentrations by ELISA - ≥12-Fold than after natural infection (both antigens) 4. Safety outcomes - Safety profiles of the HPV-16/18 vaccine and placebo: similar - Adverse events: a similar number of women in both the vaccine and placebo groups - None of the serious adverse events related or possibly related to vaccination, and no deaths.	Bivalent

Schwarz et al. (2009) [9]	Phase III, non-randomized, open-label, age-stratified study	666 Healthy women	1. Inclusion criteria - Women between 15 and 55 years of age - A negative pregnancy test on the day of vaccination 2. Exclusion criteria - An investigational drug or vaccine within 30 days - Chronic immune-modifying drugs within 6 months - Immunoglobulins or blood products within 3 months or planned to use any of these during the study period - Breastfeeding - Previously received HPV or AS04-based vaccines	1. HPV 16/18 AS04 vaccine (CervarixTM, Glaxo-SmithKline Biologicals, Rixensart, Belgium) contained 20 µg each of HPV 16 and HPV 18 L1 protein VLPs adjuvanted with AS04 - 0–1–6 Month schedule 2. Enrolment was stratified into three equally sized age strata: 15–25, 26–45, and 46–55 years of age. The second age group (26–45 years of age) was also stratified into equally sized age strata: 26–35 and 36–45 years of age.	1. The vaccine was well tolerated and 100% seropositivity was achieved 1 month after the third dose in all age groups. 2. There was a high correlation between HPV 16 and 18 antibody levels (IgG) in cervicovaginal secretions and sera, regardless of age. 3. The HPV 16/18 AS04-adjuvanted vaccine induces a robust and persistent immune response in women >26 years of age and generates antibodies that transudate through the cervix epithelium.	Bivalent
Schwarz et al. (2011) [19]	Multicenter, open-label, age-stratified phase III study (NCT00196937)	- 531 Healthy women - Six centers in Germany and Poland	Inclusion criteria - Age: 15–55 years - Age-stratified into groups: 15–25, 26–45, and 46–55 years) who received three vaccine doses in the primary study	1. 3 Doses of HPV 16/18 AS04-adjuvanted vaccine at 0, 1, and 6 months 2. Anti-HPV 16/18 seropositivity rates and GMTs - By ELISA in women - From the time of first vaccination through 48 months	1. Seropositivity at month 48 - Anti-HPV 16 antibodies: 100% - Anti-HPV 18 antibodies: 99.4% 2. Antibody kinetics - Peak response at month 7 followed by a gradual decline tending towards a plateau in all age groups - Anti-HPV 16/18 GMTs were sustained at month 48 in all age groups, including women aged 46–55 years in whom GMTs were respectively 11- and 5-fold higher than natural infection levels. 3. Clinically acceptable safety profile in all age groups	Bivalent
Lehtinen et al. (2012) [38]	Double-blind, randomized, controlled PATRICIA trial	- 18,644 Women aged 15–25 years - 14 Countries in Asia Pacific, Europe, Latin America, and North America	Inclusion criteria - 15–25 years old - <6 Lifetime sexual partners 1. TVC women - Received at least one vaccine dose - Approximate catch-up populations - Including sexually active women (vaccine n=9,319; control n=9,325) 2. TVC-naive women - No evidence of oncogenic HPV infection at baseline - Approximating early adolescent HPV exposure (vaccine n=5,824; control n=5,820).	1. HPV 16/18 AS04-adjuvanted vaccine 2. A control hepatitis A vaccine	1. Vaccine efficacy against CIN 3+ associated with HPV 16/18: - 100% (95% CI, 85·5–100) in the TVC-naive - 45.7% (95% CI, 22·9–62·2) in the TVC 2. Vaccine efficacy against all CIN 3+ (irrespective of HPV type in the lesion) - 93.2% (95% CI, 78·9–98·7) in the TVC-naive - 45·6% (95% CI, 28·8–58·7) in the TVC 3. Vaccine efficacy against all CIN 3+ - Higher than 90% in all age groups in the TVC-naïve - Highest in the 15–17 year age group in the TVC and progressively decreased in the 18–20 year and 21–25 year age groups 4. Vaccine efficacy against all AIS - 100% (95% CI, 31.0–100) in the TVC-naïve - 76·9% (95% CI, 16.0–95.8) in the TVC 5) Safety outcomes - A similar proportion of serious adverse events, new-onset chronic diseases, new-onset autoimmune diseases, and medically significant conditions in vaccine and placebo group - Pregnancy outcomes: also similar in both groups	Bivalent

Naud et al. (2014) [39]	Long-term follow-up of an initial double-blind, randomized (1:1), placebo-controlled study (HPV-001, NCT00689741)	1,113 Women	Inclusion criteria - 15–25 years old - Enrolled in HPV-001 and who participated in the follow-up study HPV-007	-	1. No new HPV 16/18-associated infections and cytohistopathological abnormalities occurred in the vaccine group. 2. Vaccine efficacy against HPV 16/18 incident infection - 100% (95% CI, 66.1–100) 3. Vaccine efficacy over the 113 months (9.4 years) - Against incident infection in vaccine and placebo groups: 95.6% (95% CI, 86.2–99.1; 3/50) - Against 6-month persistent infection: 100% (95% CI, 84.1–100; 0/21) - Against 12-month persistent infection: 100% (95% CI, 61.4–100; 0/10) - Against ≥ASC-US: 97·1% (95% CI, 82.5–99.9; 1/30) - Against ≥LSIL: 95·0% (95% CI, 68.0–99.9; 1/18) - Against CIN 1+: 100% (95% CI, 45.2–100; 0/8) - Against CIN 2+ associated with HPV 16/18: 100% (95% CI, –128.1 to 100; 0/3) 4. Safety result - The most common significant adverse events in the vaccine: 5/224 (2.2%) cases each for gastritis, incomplete spontaneous abortion, depression, and hypertension. - The most common significant adverse events in the placebo group: 3/213 (1.4%) for genital herpes. - No adverse events considered to be possibly related to the study vaccine or placebo.	Bivalent
Schwarz et al. (2015) [20]	Multicenter, open-label, long-term follow-up (NCT00947115) of a primary phase-III study (NCT00196937)	- 488 Healthy women - Six centers in Germany and Poland	Inclusion criteria - Age: 15–55 years - Age-stratified into groups: 15–25, 26–45, and 46–55 years) who received three vaccine doses in the primary study.	1. Immune responses in serum and CVS samples 6 years after dose 1 2. Anti-HPV 16/18 GMTs by ELISA 3. SAEs	1. At 6 years after dose 1 - All women were seropositive for anti-HPV 16. - ≥97% were seropositive for anti-HPV 18. 2. GMTs - 277.7–1,344.6 EU/mL for anti-HPV 16 - 97.6–438.2 EU/mL for anti-HPV-18 3. In all age groups, GMTs were higher (anti-HPV 16, 9.3–45.1-fold; anti-HPV 18, 4.3–19.4-fold) than levels associated with natural infection (29.8 EU/mL). 4. A strong correlation between serum and CVS anti-HPV 16/18 levels was observed, with correlation coefficients of 0.81–0.96 (anti-HPV 16) and 0.69–0.84 (anti-HPV 18).	Bivalent
Einstein et al. (2014) [40]	Observer-blind, randomized, age-stratified, head-to-head study	1,106 Healthy women aged 18–45 years old	1. TVC -Vaccinated with at least one dose of HPV 16/18 vaccine (n=553) or HPV 6/11/16/18 vaccine (n=553) 2. The month 60 TVC - 421 Women consented to participate in the extended month 60 visit (213 in the HPV 16/18 vaccine group and 208 in the HPV 6/11/16/18 vaccine group) 3. The month 60 according-to-protocol (ATP) cohort - 315 Women (159 women in the HPV 16/18 vaccine group and 156 in the HPV	1. Cervarix group -Subjects received 3 doses of HPV 16/18 vaccine at months 0, 1 and 6 and a dose of placebo at month 2 2. Gardasil group - Subjects received 3 doses of HPV 6/11/16/18 vaccine at months 0, 2 and 6 and a dose of placebo at month 1	1. The month 60 ATP cohort 1) Serum neutralizing antibody responses for HPV 16 - HPV 16/18 vaccine higher than HPV 6/11/16/18 vaccine: 7.8-fold (18–26-year stratum), 5.6-fold (27–35-year stratum), and 2.3-fold (36–45-year stratum) 2) Serum neutralizing antibody responses for HPV 18 - HPV 16/18 vaccine higher than HPV 6/11/16/18 vaccine: 12.1-fold (18–26-year stratum), 13.0-fold (27–35-year stratum), and 7.8-fold (36–45-year stratum) 2. Seropositivity at month 60 1) HPV 16 - All subjects (100%) in HPV 16/18 vaccine group The majority (95.7%–97.5%) in HPV 6/11/16/18 vaccine group 2) HPV 18 - The majority (98.1%–100%) of subjects in HPV 16/18 vaccine group - Decreased considerably (61.1%–76.9%) across the 3 age strata in HPV 6/11/16/18 vaccine group	Bivalent

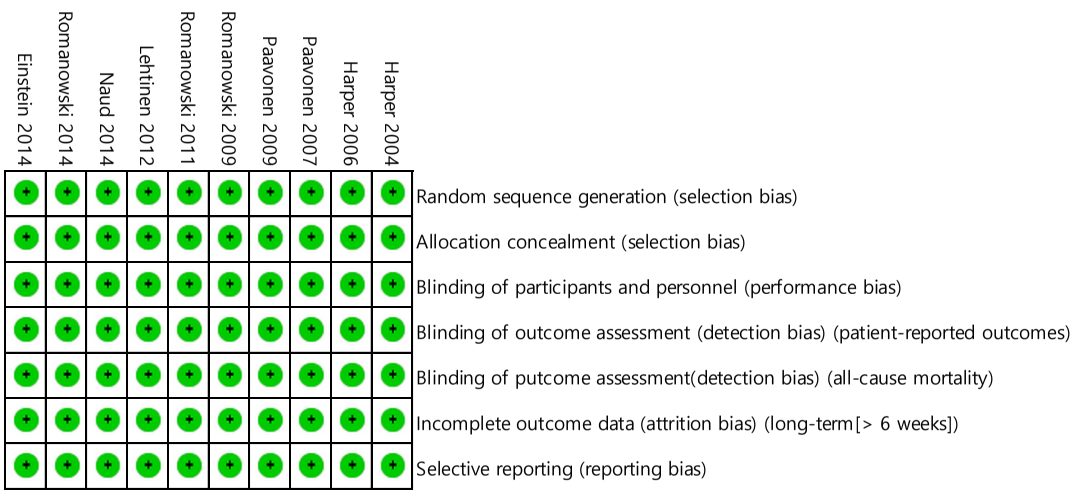
			6/11/16/18 vaccine group) - Met the eligibility criteria - Received a full series of 3-dose vaccination - Complied with the procedures defined in the protocol		3. TVC 1) GMTs for anti-HPV 16 and anti-HPV 18 nAb - Higher in HPV 16/18 vaccine group than in HPV 6/11/16/18 vaccine group 4. Longer durability of nAb response for HPV 16/18 vaccine compared to HPV 6/11/16/18 vaccine 5. Safety profile - Serious adverse events: 8% (n = 44) in HPV-16/18 vaccine group and 6.7% (n=37) in HPV-6/11/16/18 vaccine group - Medically significant conditions: 46.8% (n=259) in HPV-16/18 vaccine group and 40.9% (n=226) in HPV-6/11/16/18 vaccine group - New onset chronic diseases: 7.1% (n=39) in HPV-16/18 vaccine group and 7.8% (n=43) in HPV-6/11/16/18 vaccine group - New onset autoimmune disease: 1.3% (n=7) in HPV-16/18 vaccine group and 2.4% (n=13) in HPV-6/11/16/18 vaccine group - Pregnancy: similar outcomes between vaccine groups	
Romanowski et al. (2011) [12]	Partially-blind, controlled, randomized trial	960 Girls and young women	Inclusion criteria - 9–25 years old - Age stratified: 9–14, 15–19, 20–25 years	1. 2-Dose schedules - Using the licensed 20/20F/0, 6 month - Using an alternative 40 µg of each antigen (40/40F)/0, 2 month - Using an alternative 40 µg of each antigen (40/40F)/0, 6 month 2. 3-Dose schedule - Using the licensed 20/20F/0, 1, 6 month	1. At M7, the 3-dose schedule was not immunologically superior to 2-dose schedules except in the 40/40F M0,2 group for HPV 16 (lower limit of 95% CI GMT ratio [2D/3D] <0.5). 2. For both HPV 16 and 18, the 2-dose schedules in girls 9–14 years were immunologically non-inferior to the 3-dose schedule in women 15–25 years (upper limit of 95% CI for GMT ratio [3D/2D] <2). 3. At M24, non-inferiority was maintained for the 2-dose M0,6 schedules in girls 9–14 years vs. the 3-dose schedule in women 15–25 year. 4. All formulations had acceptable reactogenicity and safety profiles.	Bivalent
Romanowski et al. (2014) [13]	Randomized, partially-blind study	960 Healthy girls and young women	Inclusion criteria - 9–25 years old - Age stratified: 9–14, 15–19, 20–25 years	1. 9–14 years old girls - 2-Dose schedule (0–6 month) 2. 15–25 years old women - 3-Dose schedule (0–1–6 month)	In the according-to-protocol immunogenicity cohort 1. All initially seronegative subjects seroconverted for HPV 16 and 18 antibodies and remained seropositive up to M48 2. GMT ratios at M36 and M48 for both HPV 16 and 18 close to 1 → non-inferiority was demonstrated 3. The kinetics of HPV 16, 18, 31, and 45 antibody responses were similar for both groups and HPV 16 and 18 GMTs were substantially higher than natural infection titers. 4. The vaccine had a clinically acceptable safety profile in both groups.	Bivalent

Question: The effective range of age of bivalent HPV vaccine 3-dose

1. Harper DM, Franco EL, Wheeler C, Ferris DG, Jenkins D, Schuind A, et al. Efficacy of a bivalent L1 virus-like particle vaccine in prevention of infection with human papillomavirus types 16 and 18 in young women: a randomised controlled trial. Lancet 2004;364:1757-65 [33].
2. Harper DM, Franco EL, Wheeler CM, Moscicki AB, Romanowski B, Roteli-Martins CM, et al. Sustained efficacy up to 4.5 years of a bivalent L1 virus-like particle vaccine against human papillomavirus types 16 and 18: follow-up from a randomised control trial. Lancet 2006;367:1247-55 [34].
3. Paavonen J, Jenkins D, Bosch FX, Naud P, Salmeron J, Wheeler CM, et al. Efficacy of a prophylactic adjuvanted bivalent L1 virus-like-particle vaccine against infection with human papillomavirus types 16 and 18 in young women: an interim analysis of a phase III double-blind, randomised controlled trial. Lancet 2007;369:2161-70 [35].
4. Paavonen J, Naud P, Salmeron J, Wheeler CM, Chow SN, Apter D, et al. Efficacy of human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine against cervical infection and precancer caused by oncogenic HPV types (PATRICIA): final analysis of a double-blind, randomised study in young women. Lancet 2009;374:301-14 [36].
5. GlaxoSmithKline Vaccine HPV-007 Study Group, Romanowski B, de Borba PC, Naud PS, Roteli-Martins CM, De Carvalho NS, et al. Sustained efficacy and immunogenicity of the human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine: analysis of a randomised placebo-controlled trial up to 6.4 years. Lancet 2009;374:1975-85 [37].
6. Schwarz TF, Spaczynski M, Schneider A, Wysocki J, Galaj A, Perona P, et al. Immunogenicity and tolerability of an HPV-16/18 AS04-adjuvanted prophylactic cervical cancer vaccine in women aged 15-55 years. Vaccine 2009;27:581-7 [9].
7. Schwarz TF, Spaczynski M, Schneider A, Wysocki J, Galaj A, Schulze K, et al. Persistence of immune response to HPV-16/18 AS04-adjuvanted cervical cancer vaccine in women aged 15-55 years. Hum Vaccin 2011;7:958-65 [19].
8. Lehtinen M, Paavonen J, Wheeler CM, Jaisamrarn U, Garland SM, Castellsague X, et al. Overall efficacy of HPV-16/18 AS04-adjuvanted vaccine against grade 3 or greater cervical intraepithelial neoplasia: 4-year end-of-study analysis of the randomised, double-blind PATRICIA trial. Lancet Oncol 2012;13:89-99 [38].
9. Naud PS, Roteli-Martins CM, De Carvalho NS, Teixeira JC, de Borba PC, Sanchez N, et al. Sustained efficacy, immunogenicity, and safety of the HPV-16/18 AS04-adjuvanted vaccine: final analysis of a long-term follow-up study up to 9.4 years post-vaccination. Hum Vaccin Immunother 2014;10:2147-62 [39].
10. Schwarz T, Spaczynski M, Kaufmann A, Wysocki J, Galaj A, Schulze K, et al. Persistence of immune responses to the HPV-16/18 AS04-adjuvanted vaccine in women aged 15-55 years and first-time modelling of antibody responses in mature women: results from an open-label 6-year follow-up study. BJOG 2015;122:107-18 [20].
11. Einstein MH, Takacs P, Chatterjee A, Sperling RS, Chakhtoura N, Blatter MM, et al. Comparison of long-term immunogenicity and safety of human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine and HPV-6/11/16/18 vaccine in healthy women aged 18-45 years: end-of-study analysis of a phase III randomized trial. Hum Vaccin Immunother 2014;10:3435-45 [40].
12. Romanowski B, Schwarz TF, Ferguson LM, Peters K, Dionne M, Schulze K, et al. Immunogenicity and safety of the HPV-16/18 AS04-adjuvanted vaccine administered as a 2-dose schedule compared with the licensed 3-dose schedule: results from a randomized study. Hum Vaccin 2011;7:1374-86 [12].
13. Romanowski B, Schwarz TF, Ferguson LM, Ferguson M, Peters K, Dionne M, et al. Immune response to the HPV-16/18 AS04-adjuvanted vaccine administered as a 2-dose or 3-dose schedule up to 4 years after vaccination: results from a randomized study. Hum Vaccin Immunother 2014;10:1155-65 [13].

Quality assessment						
Participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**
The effective range of age of bivalent HPV vaccine 3-dose						
72,820 (10 studies)	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	⊕⊕⊕⊕ HIGH

2D, 2-dose; 3D, 3-dose; AIS, adenocarcinoma *is situ*; ASC-US, atypical squamous cells of undetermined significance; ATP-E, according-to-protocol cohort for efficacy; CIN, cervical intraepithelial neoplasia; ELISA, enzyme-linked immunosorbent assay; GMT, geometric mean antibody titer; HPV, human papillomavirus; IgG, immunoglobulin G; LSIL, low-grade squamous intraepithelial lesion; nAb, neutralizing antibodies; PATRICIA, PApilloma TRIal against Cancer in young Adults; PCR, polymerase chain reaction; SAE, serious adverse event; TVC, total vaccinated cohort; VLP, virus-like particle.


Einstein 2014
Romanowski 2014
Naud 2014
Lehtinen 2012
Romanowski 2011
Romanowski 2009
Paavonen 2009
Paavonen 2007
Harper 2006
Harper 2004
Random sequence generation (selection bias)
Allocation concealment (selection bias)
Blinding of participants and personnel (performance bias)
Blinding of outcome assessment (detection bias) (patient-reported outcomes)
Blinding of putcome assessment(detection bias) (all-cause mortality)
Incomplete outcome data (attrition bias) (long-term[> 6 weeks])
Selective reporting (reporting bias)

KQ4. Is the HPV preventive vaccine safe?

1) Quadrivalent vaccine

ID	Study design	Participant	Inclusion & Exclusion criteria	Intervention	Result	Remark
Villa et al. (2005) [23]	Randomized double-blind placebo-controlled phase II study	- 552 Women - Brazil, Europe, USA	1. Inclusion criteria - Female subjects - 16–23 years of age - Not pregnant - No prior abnormal Pap smears - No more than five male sex partners during their lifetime - Virgin ≤18 years old and seeking contraception 2. Exclusion criteria - Women with previous HPV infection	1. Quadrivalent HPV - 277 (mean age, 20.2 years [SD, 1–7]) - 20 µg type 6, 40 µg type 11, 40 µg type 16, and 20 µg type 18 L1 VLP vaccine 2. Placebo (aluminum adjuvant only) - 275 (mean age, 20.0 years [SD, 1–7]) 3. Vaccinated on 0, 2, 6th months	Follow-up time: up to 36 months 1. Injection site AEs: vaccine (86%) vs. placebo (77%) 2. Systemic AEs: vaccine (69%) vs. placebo (69%) 3. Vaccine-related injection site AEs: vaccine (86%) vs. placebo (77%) 4. Vaccine-related systemic AEs: vaccine (38%) vs. placebo (33%) 5. Serious AEs: vaccine (1%) vs. placebo (1%)	Quadrivalent
Block et al. (2006) [24]	Non-inferiority immunogenicity study A substudy within a randomized, double-blinded, multidose study	- 506 Girls and 510 boys (10–15 years of age) - 513 Females (16–23 years of age). - 61 Clinical center in Asia, Australia, Europe, Latin America, North America	Inclusion criteria 1. 10–15 years old girls and boys - Sexually naïve at enrollment and throughout the study 2. 16–23 years old females - Intact uterus - No evidence of gross purulent cervicitis - No history of genital warts - No previous abnormal Pap smear - No history of CIN - No more than four sexual partners during their lifetime	1. Three intramuscular injections (0, 2, 6th months) 2. Serology testing: day 1 and at months 3 and 7 on blinded samples 3. Neutralizing antibody concentrations: using type-specific immunoassays and summarized as geometric mean titers and seroconversion rates. 4. Any systemic or local AEs occurred within 14 days of injection were recorded on vaccination report card. 5. Each AE were classified according to symptom as mild, moderate, or severe.	1. Proportion of reporting at least 1 injection-site or systemic AE were lower among girls and boys than older women. 2. Vaccine-related AE: girls (84.4%), boys (79.2%) vs. women (89.3%) 3. Vaccine-related injection-site AE: girls (80.8%), boys (74%) vs. women (87.5%) 4. Vaccine-related systemic AE: girls (30.7%), boys (27.2%) vs. women (32.2%) 5. Most (≥97%) injection-site adverse events were mild to moderate in intensity and transient 6. Significantly more boys (13.8%) and girls (12.8%) than women (7.3%) reported fevers ≥37.8°C within 5 days of vaccination. Most (96.4%) fevers were mild (<39°C).	Quadrivalent
Garland et al. (2007) [27]	Randomized, placebo-controlled, double-blind trial (The FUTURE I study)	- 5,455 Women - 16 Countries	Inclusion criteria 1. 16–26 years of age 2. Not pregnant 3. No history of genital warts or abnormal Pap smear 4. No more than four sex partners in lifetime	1. The quadrivalent HPV 6/11/16/18 L1 virus-like-particle vaccine with amorphous aluminum hydroxyphosphate sulfate (Gardasil, Merck) as an adjuvant 2. The aluminum-containing placebo 3. Oral temperature recorded on vaccination report card 4. AEs recorded on vaccination report card for 15 days after vaccination	Mean follow-up time: 3 years 1. Injection-site events - Vaccine (86.8%) vs. placebo (77.4%) (95% CI, 9.4 [7.3–11.5]) - Erythema, pain, swelling: more common in vaccine group than in placebo group 2. Systemic events - Vaccine (65.3%) vs. placebo (63.7%) (95% CI, 1.6 [–1.0 to 4.2]) 3. Serious events - Vaccine (1.8%) vs. placebo (1.7%) (95% CI, 0.1 [–0.6 to 0.8]) - Death: vaccine (0.1%) vs. placebo (0.1%) (95% CI, 0 [–0.2 to 0.2])	Quadrivalent

Reisinger et al. (2007) [29]	Randomized, double-blind, placebo-controlled, multicenter trial	- 1,781 Sexually naive children - 47 Study sites located in 10 countries in North America, Latin America, Europe, and Asia	Stratified by age (2:1 ratio of 9- to 12-year-old subjects and 13- to 15-year-old subjects) and by gender (1:1)	1. Quadrivalent HPV 6/11/16/18 vaccine 2. Non-aluminum placebo (0, 2, 6 months) 3. Serum neutralizing anti-HPV 6/11/16/18 responses: GMTs and seroconversion rates 4. Oral temperature recorded on vaccination report card 5. AEs recorded on vaccination report card for 15 days after vaccination	Follow-up time: up to 18 months 1. 1 or more AEs: vaccine (82.7%) vs. placebo (67.1%) 2. Injection site AEs: vaccine (75.3%) vs. placebo (50.0%) - Erythema: vaccine (20.3%) vs. placebo (13.2%) - Pain: vaccine (73.2%) vs. placebo (45.4%) - Swelling: vaccine (20.7%) vs. placebo (7.7%) 3. Systemic AEs: vaccine (46.4%) vs. placebo (44.5%) 4. Serious AEs: vaccine (0.4%) vs. placebo (0.0%) 5. Serious vaccine-related AEs: vaccine (0.0%) vs. placebo (0.0%)	Quadrivalent
Munoz et al. (2009) [15]	Multicenter, randomized, placebo-controlled, double-blind safety, immunogenicity, and efficacy study	- 3,819 Women - 38 Study sites in Colombia, France, Germany, Philippine, Spain, Thailand, and the USA	1. Inclusion criteria - 24–45 years of age - Not pregnant - Not hysterectomized 2. Exclusion criteria - Prior history of genital warts or cervical disease - Women with any previous cervical surgical procedure and those having undergone a cervical biopsy within the past 5 years - Women infected with HIV - Immunocompromised women	1. Quadrivalent HPV vaccine (n=1,911) or aluminum-containing placebo (n=1,908) 2. Day 1, and months 2 and 6	Mean follow-up 2.2 years 1. One or more AEs - Injection site: vaccine (76.8%) vs. placebo (64.3%) - Systemic: vaccine (59.2%) vs. placebo (60%) 2. Serious AEs: vaccine (0.2%) vs. placebo (0.4%) - No vaccine-related serious adverse events 3. Withdrawal due to vaccine-related serious AEs: vaccine (0%) vs. placebo (0%)	Quadrivalent
Castellsague et al. (2011) [16]	Randomized, placebo-controlled, double-blind safety, immunogenicity, and efficacy study	- 3,819 Women - 38 Study sites in Colombia, France, Germany, Philippine, Spain, Thailand, and the USA	1. Inclusion criteria - 24–45 years of age - Not pregnant - Not hysterectomized 2. Exclusion criteria - Prior history of genital warts or cervical disease - Women with any previous cervical surgical procedure and those having undergone a cervical biopsy within the past 5 years - Women infected with HIV - Immunocompromised women	1. Quadrivalent vaccine or aluminum-containing placebo 2. Day 1, and at months 2 and 6 3. AEs were recorded using vaccine report card.	Median follow-up 4.0 years 1. Vaccine-related AEs: vaccine (82.8%) vs. placebo (73.7%) 2. Injection-site AEs: vaccine (76.7%) vs. placebo (64.2%) 3. Systemic AEs: vaccine (39.5%) vs. placebo (36.9%) 4. Serious AEs: vaccine (0%) vs. placebo (0%) 5. Discontinued due to vaccine-related AE: vaccine (0.3%) vs. placebo (0.1%) - No discontinuation due to vaccine-related serious AE 6. Who died: vaccine (0.4%) vs. placebo (0.1%) - Not related to vaccine	Quadrivalent
Luna et al. (2013) [17]	Long-term follow-up study of original randomized, placebo-controlled, double-blind safety, immunogenicity, and efficacy study (Protocol 019)	1. Base study (FUTURE III) - 3,819 Women 2. Follow-up study - 5 Sites in Colombia - 1,335 Women	- 24–45 years of age (in the original vaccine group during the base study [n=684]) - 29–50 years of age (in the original placebo group during the base study [n=651])	The quadrivalent HPV vaccine 1. In women who were vaccinated at 24 to 45 years of age (for those enrolled in the original vaccine group during the protocol 019 base study): EVG 2. In women who were vaccinated at 29 to 50 years of age (if they were in the original placebo group during the protocol 019 base study): CVG 3. No placebo group	1. Median follow-up 6.3 years 2. No new serious adverse experiences 3. Most commonly reported new medical conditions: bacterial vaginitis, hypothyroidism, uterine myoma 4. Of the 4 known pregnancy outcomes, all have normal live births.	Quadrivalent

Ferris et al. (2014) [32]	Randomized, double-blind, placebo-controlled study Long-term safety, immunogenicity, and effectiveness study	Sexually naive boys and girls aged 9–15 years (n=1,781)	Inclusion criteria - Sexually naive boys and girls - Aged 9 to 15 years - Early vaccination group (n=1,179) - Catch-up vaccination group (n=482)	1. HPV 4 vaccine or saline placebo 2. Day 1 and months 2 and 6 3. At month 30, the placebo group (n=482) received HPV 4 vaccine following the same regimen 4. Both cohorts were followed through month 96.	1. No new significant serious AEs were observed in both genders. 1) 3 Serious AEs - Fatal road traffic accident (EVG, 4.7 years postdose 3) → not vaccine-related - Tonic-clonic movement postphlebotomy (EVG, 7 years postdose 3) → not vaccine-related - Cranial nerve VII paralysis (CVG, 131 days postdose 3) → determined to be vaccine-related. 2. No significant pregnancy-related adverse outcome observed. - EVG (72%) and CVG (70%): live births - EVG (94%) and CVG (92%): normal infant outcome - 3 Congenital anomalies (2 cases of trisomy 21 and 1 choanal atresia)	Quadrivalent
Ojha et al. (2014) [45]	Post marketing surveillance study	14,822 Adverse events reported, among them 4,670 AEs were qHPV vaccine-related.	Analysis data from VAERS in USA from Jan 2010 to Dec 2012	1. Types of vaccine noted in VAERS 2. Hepatitis A, B, DPT, qHPV, influenza, MMR, pneumococcal, SmallPox, rotavirus, poliovirus, VZV, rabies, yellow fever	Reports of AEs 1. Overall: qHPV (0.19%) vs. all other vaccine (0.35%), RR 0.54 (95% CI, 0.26–1.1) 2. Female: qHPV (0.14%) vs. all other vaccine (0.25%), RR 0.55 (95% CI, 0.2–1.5) 3. Male: qHPV (0.39%) vs. all other vaccine (0.49%), RR 0.8 (95% CI, 0.27–2.3) 4. Age 9–17 years: qHPV (0.21%) vs. all other vaccine (0.32%), RR 0.`64 (95% CI, 0.27–1.5) 5. Age 18–26 years: qHPV (0.15%) vs. all other vaccine (0.4%), RR 0.39 (95% CI, 0.09–1.7)	Quadrivalent
Arnheim-Dahlstrom et al. (2013) [46]	Cohort study	- 296,826 Girls - Denmark and Sweden registry	- 10–17 years old - qHPV vaccination in Denmark and Sweden	Among 997,585 girls, 296,826 received a total of 696,420 qHPV vaccine doses	1. Rate ratios for 5 neurological events (Bell's palsy, epilepsy, narcolepsy, optical neuritis, paralysis) were not significantly increased 2. Inverse association with epilepsy and paralysis 3. No association between qHPV vaccination and venous thromboembolism 4. No association between qHPV vaccination and increased risk of autoimmune disease	Quadrivalent
Scheller et al. (2015) [44]	Prospective cohort study	- 3,983,824 Women - Sweden and Denmark	1. Inclusion criteria - Data from National Registration System in Denmark and Sweden - Aged 10–44 years - Follow up 2006–2013 2. Exclusion criteria - History of multiple sclerosis and other central nervous system demyelinating disease	3 Doses of qHPV vaccine (day 1, month 2, and month 6)	Crude incidence rate (events/100,000 person-years) 1. Multiple sclerosis: unvaccinated (21.54) vs. vaccinated (6.12), adjusted RR 0.90 (95% CI, 0.70–1.15) 2. Other demyelinating disease: unvaccinated (16.14) vs. vaccinated (7.54), adjusted RR 1.00 (95% CI, 0.80–1.26)	Quadrivalent

Grimaldi-Bensouda et al. (2014) [47]	Case-control study	- 113 Specialized centers in France - Cases (n=269), age-matched control (n=1,096)	- 14–26 years old female - Cases: 6 types of AD (ITP, MS, GBS, connective tissue disorder (SLE, rheumatoid arthritis), type 1 DM, autoimmune thyroiditis)	qHPV vaccination	1. Adjusted OR for qHPV vaccine: 0.9 (95% CI, 0.5–1.5) 2. Adjusted OR for ITP: 1.0 (95% CI, 0.4–2.6) 3. Adjusted OR for MS: 0.3 (95% CI, 0.1–0.9) 4. Adjusted OR for connective disorder: 0.8 (95% CI, 0.3–2.4) 5. Adjusted OR for type 1 DM: 1.2 (95% CI, 0.4–3.6) - No evidence of increase in the risk of AD following vaccination with qHPV vaccine	Quadrivalent
Leung et al. (2015) [43]	Observer-blind, randomized, age-stratified study with three parallel groups	- 1,075 Girls aged 9–14 years old - 21 Sites in France, Hong Kong, Singapore, and Sweden	Inclusion criteria - Healthy girls aged 9–14 years - Negative pregnancy test on the day of each vaccination - Agree to continue contraception	1. HPV 16/18 L1 VLP ASO4-adjuvanted vaccine at M0,6 (HPV 16/18 [2D] group) 2. HPV 6/11/16/18 L1 VLP vaccine at M0,6 (HPV 6/11/16/18 [2D] group) 3. HPV 6/11/16/18 L1 VLP vaccine at M0,2,6 (HPV 6/11/16/18 [3D] group)	Safety profile 1. At least one medically significant adverse event up to M12 - HPV 16/18 (2D): 14% - HPV 6/11/16/18 (2D): 16% - HPV 6/11/16/18 (3D): 13% 2. SAEs - HPV 16/18 (2D): 13 (3.6%) - HPV 6/11/16/18 (2D): 2 (0.6%) - HPV 6/11/16/18 (3D): 1 (0.3%) - None of the SAEs to have a causal relationship to vaccination 3. Potential immune-mediated diseases - HPV 16/18 (2D): 3 (0.8%) - HPV 6/11/16/18 (2D): 3 (0.8%) - Reactive arthritis, juvenile idiopathic arthritis, erythema nodosum, alopecia areata, ulcerative colitis, and coeliac disease - Among them, a possible causal relationship to vaccination: -Serious event: erythema nodosum and juvenile idiopathic arthritis Non-serious event: reactive arthritis	Bivalent & Quadrivalent
Kang et al. (2008) [31]	Randomized, double-blind, placebo-controlled study 2:1 Ratio for randomization	- 176 Volunteers aged 9–23 years - South Korea	1. Inclusion criteria - Non-pregnant - Aged 9–23 years at enrollment - Must not have had a febrile illness (fever more than 37.8˚C) at vaccination. - Subjects aged 9–15 years: · Must have had no sexual experience before, and no plan to have sexual experience during the study period - Subjects aged 16–23 years · Must have had a history of less than four male and/or female sexual partners at enrollment · Use effective contraception during the study period · Not had a prior Pap test showing a squamous intraepithelial lesion or worse and/or a biopsy indicating CIN	1. 117 Women were assigned to quadrivalent HPV (20 µg type 6, 40 µg type 11, 40 µg type 16, and 20 µg type 18) vaccine (59 women to placebo) 2. Individuals received vaccine at day 1, month 2, and month 6 3. Blood samples for analysis at enrollment at month 7	Quadrivalent HPV vaccine was generally well tolerated with no vaccine-related serious adverse experiences Quadrivalent HPV vaccine induced seroconversion for each vaccine-related HPV type. At month 7, vaccine-induced type-specific antibody titer was high.	Quadrivalent

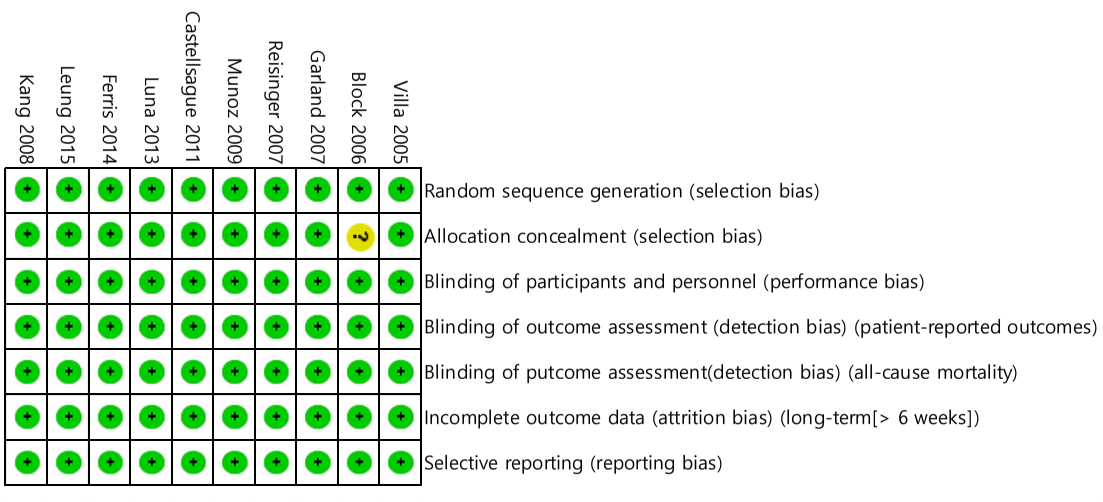
			or worse 2. Exclusion criteria - Enrollment in studies of other investigational agents - History of any HPV vaccination - History of allergy to vaccine compound (including aluminum, yeast, and BENZONASE) - Thrombocytopenia - History of vaccination within 14 days from enrollment (previous 21 days for live vaccine) - Receipt of blood or blood-derived products within the 6 months preceding injection, and immunosuppression			

Question: The safety profile of quadrivalent HPV vaccine 3-dose

1. Villa LL, Costa RL, Petta CA, Andrade RP, Ault KA, Giuliano AR, et al. Prophylactic quadrivalent human papillomavirus (types 6, 11, 16, and 18) L1 virus-like particle vaccine in young women: a randomised double-blind placebo-controlled multicentre phase II efficacy trial. Lancet Oncol 2005;6:271-8 [23].
2. Block SL, Nolan T, Sattler C, Barr E, Giacoletti KE, Marchant CD, et al. Comparison of the immunogenicity and reactogenicity of a prophylactic quadrivalent human papillomavirus (types 6, 11, 16, and 18) L1 virus-like particle vaccine in male and female adolescents and young adult women. Pediatrics 2006;118:2135-45[24].
3. Garland SM, Hernandez-Avila M, Wheeler CM, Perez G, Harper DM, Leodolter S, et al. Quadrivalent vaccine against human papillomavirus to prevent anogenital diseases. N Engl J Med 2007;356:1928-43 [27].
4. Reisinger KS, Block SL, Lazcano-Ponce E, Samakoses R, Esser MT, Erick J, et al. Safety and persistent immunogenicity of a quadrivalent human papillomavirus types 6, 11, 16, 18 L1 virus-like particle vaccine in preadolescents and adolescents: a randomized controlled trial. Pediatr Infect Dis J 2007;26:201-9 [29].
5. Munoz N, Manalastas R Jr, Pitisuttithum P, Tresukosol D, Monsonego J, Ault K, et al. Safety, immunogenicity, and efficacy of quadrivalent human papillomavirus (types 6, 11, 16, 18) recombinant vaccine in women aged 24-45 years: a randomised, double-blind trial. Lancet 2009;373:1949-57 [15].
6. Castellsague X, Munoz N, Pitisuttithum P, Ferris D, Monsonego J, Ault K, et al. End-of-study safety, immunogenicity, and efficacy of quadrivalent HPV (types 6, 11, 16, 18) recombinant vaccine in adult women 24-45 years of age. Br J Cancer 2011;105:28-37 [16].
7. Luna J, Plata M, Gonzalez M, Correa A, Maldonado I, Nossa C, et al. Long-term follow-up observation of the safety, immunogenicity, and effectiveness of Gardasil in adult women. PLoS One 2013;8:e83431 [17].
8. Ferris D, Samakoses R, Block SL, Lazcano-Ponce E, Restrepo JA, Reisinger KS, et al. Long-term study of a quadrivalent human papillomavirus vaccine. Pediatrics 2014;134:e657-65 [32].
9. Ojha RP, Jackson BE, Tota JE, Offutt-Powell TN, Singh KP, Bae S. Guillain-Barre syndrome following quadrivalent human papillomavirus vaccination among vaccine-eligible individuals in the United States. Hum Vaccin Immunother 2014;10:232-7 [24].
10. Arnheim-Dahlstrom L, Pasternak B, Svanstrom H, Sparen P, Hviid A. Autoimmune, neurological, and venous thromboembolic adverse events after immunisation of adolescent girls with quadrivalent human papillomavirus vaccine in Denmark and Sweden: cohort study. BMJ 2013;347:f5906 [46].
11. Scheller NM, Svanstrom H, Pasternak B, Arnheim-Dahlstrom L, Sundstrom K, Fink K, et al. Quadrivalent HPV vaccination and risk of multiple sclerosis and other demyelinating diseases of the central nervous system. JAMA 2015;313:54-61 [44].
12. Grimaldi-Bensouda L, Guillemot D, Godeau B, Benichou J, Lebrun-Frenay C, Papeix C, et al. Autoimmune disorders and quadrivalent human papillomavirus vaccination of young female subjects. J Intern Med 2014;275:398-408 [47].
13. Leung TF, Liu AP, Lim FS, Thollot F, Oh HM, Lee BW, et al. Comparative immunogenicity and safety of human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine and HPV-6/11/16/18 vaccine administered according to 2- and 3-dose schedules in girls aged 9-14 years: Results to month 12 from a randomized trial. Hum Vaccin Immunother 2015;11:1689-702 [43].
14. Kang S, Kim KH, Kim YT, Kim YT, Kim JH, Song YS, et al. Safety and immunogenicity of a vaccine targeting human papillomavirus types 6, 11, 16 and 18: a randomized, placebo-controlled trial in 176 Korean subjects. Int J Gynecol Cancer 2008;18:1013-9 [31].

Quality assessment						
Participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**
The safety profile of quadrivalent HPV vaccine 3-dose						
14,387 (10 studies)	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	⊕⊕⊕⊕ HIGH

2D, 2-dose; 3D, 3-dose; EVG, early vaccination group; FUTURE, Females United to Unilaterally Reduce Endo/Ectocervical Disease; GBS, Guillain-Barre syndrome; GMT, geometric mean antibody titer; HIV, human immunodeficiency virus; HPV, human papillomavirus; ITP, idiopathic thrombocytopenic purpura; MMR, Measles/Mumps/Rubella Vaccine; MS, central demyelination/multiple sclerosis; OR, odds ratio; qHPV, quadrivalent human papillomavirus; RR, risk ratio; SAE, serious adverse event; SLE, systemic lupus erythematosus; VAERS, vaccine adverse event reporting system; VLP, virus-like particle; VZV, varicella zoster vaccine.


Kang 2008
Leung 2015
Ferris 2014
Luna 2013
Castellsague 2011
Munoz 2009
Reisinger 2007
Garland 2007
Block 2006
Villa 2005
Random sequence generation (selection bias)
Allocation concealment (selection bias)
Blinding of participants and personnel (performance bias)
Blinding of outcome assessment (detection bias) (patient-reported outcomes)
Blinding of putcome assessment(detection bias) (all-cause mortality)
Incomplete outcome data (attrition bias) (long-term[> 6 weeks])
Selective reporting (reporting bias)

2) Bivalent vaccine

ID	Study Design	Participant	Inclusion & Exclusion criteria	Intervention	Result	Remark
Harper et al. (2004) [33]	Multicenter, randomized, double-blind, placebo-controlled trial HPV-001	-1,113 Women (15–25 years of age) -North America and Brazil	Inclusion criteria 1. Women eligible for the initial phase (months 0–18) - 15–25 years-old women - <6 Sexual partners - No history of abnormal Pap test - No ablative or excisional treatment of the cervix - No ongoing treatment for external condylomata - Cytologically negative, seronegative for HPV 16 and 18 antibodies by ELISA, and HPV-DNA-negative by PCR for 14 high-risk HPV types ≤90 days before study entry. 2. Women eligible for extension phase (months 18–27) - Completed the initial phase - No ablative or excisional treatment of the cervix - No hysterectomy after enrollment	1. The bivalent HPV 16/18 VLP vaccine formulated with AS04 adjuvant or placebo ($Al(OH)_3$) 2. Three intramuscular injections (0, 1, 6th months)	Follow-up time: 18 months (extension phase 18–27 months) 1. Injection-site symptoms (i.e., pain, swelling, redness): vaccine (94%) vs. placebo (87.7%) - More common in vaccine group, but transient and mild 2. General symptoms (i.e., headache, fatigue, itching, etc.): vaccine (86.3%) vs. placebo (85.9%) 3. Serious AEs: vaccine (4%) vs. placebo (3.5%) 4. Withdrawal from the study due to serious AE: vaccine (0.1%) vs. placebo (0%) - Not related to vaccine	Bivalent
Harper et al. (2006) [34]	Follow-up study of multicenter, double-blind, randomized, placebo-controlled trial reported in 2004	- Women who enrolled with initial study - 28 Sites in North America (Canada and the USA) and Brazil - Follow-up: up to 4.5 years	Women who originally received all three doses - Bivalent HPV 16/18 VLP vaccine (n=393) - Placebo (n=383)	1. The bivalent HPV 16/18 VLP vaccine formulated with AS04 adjuvant or placebo ($Al(OH)_3$) 2. HPV DNA, using cervical samples 3. Yearly cervical cytology assessments 4. The long-term immunogenicity and safety of the vaccine	Mean follow-up time: 47.7 months (SD 3.4) (maximum 4.5 years) 1. AEs: vaccine (14%) vs. placebo (22%) 2. New-onset chronic disease: vaccine (3%) vs. placebo (5%) 3. Serious AEs: vaccine (4%) vs. placebo (5%) - None was related to vaccination	Bivalent

GlaxoSmithKline Vaccine HPV-007 Study Group et al. (2009) [37]	Double-blind, randomized, placebo-controlled initial study	- 1,113 Women - 27 Sites (5 in Brazil, 5 in Canada, and 17 in the USA)	Inclusion criteria - 15–25 years old - Normal cervical cytology - HPV 16/18 seronegative and oncogenic HPV DNA-negative (14 types) - Participated in initial study (n=1,113) and follow-up study (n=776)	1. HPV 16/18 AS04-adjuvanted vaccine and placebo ($Al(OH)_3$) 2. Cervical samples for HPV DNA test every 6 months 3. Management of abnormal cytologies was pre-specified, and HPV 16/18 antibody titres were assessed.	Median follow-up time: 5.9 years (maximum 6.4 years) 1. AEs: vaccine (28%) vs. placebo (33%) 2. Serious AEs: vaccine (8%) vs. placebo (10%) - None of the serious AEs was related to vaccination 3. New onset chronic disease (i.e., diabetes mellitus, autoimmune disease): vaccine (5%) vs. placebo (6%) 4. Pregnancies reported: vaccine (131 cases) vs. placebo (131 cases) - No imbalance in outcomes between groups	Bivalent
Paavonen et al. (2009) [36]	Phase III randomized, double-blind, controlled PATRICIA trial	18,729 Women (15–25 years)	1. ATP-E (vaccine, n=8,093; control, n=8,069) 2. TVC (included all women receiving at least one vaccine dose, regardless of their baseline HPV status; represents the general population, including those who are sexually active; vaccine, n=9,319; control, n=9,325) 3. TVC-naive (no evidence of oncogenic HPV infection at baseline; represents women before sexual debut; vaccine, n=5,822; control, n=5,819).	1. Vaccine group (n=9,319): 3 injections of bHPV vaccine at day 1, months 1, and 6 2. Placebo (hepatitis A vaccine) group (n=9,325): 3 injections of placebo at day 1, months 1, and 6	Mean follow-up time: 39.4 months (SD 9.5) 1. Serious AEs: vaccine (8%) vs. placebo (8%) 2. Medically significant condition: vaccine (32%) vs. placebo (32%) 3. New-onset chronic disease: vaccine (3%) vs. placebo (3%) 4. New-onset autoimmune disease: vaccine (<1%) vs. placebo (<1%) 5. Congenital anomalies: vaccine (<1%) vs. placebo (<1%) 6. Spontaneous abortion: vaccine (9%) vs. placebo (9%) - No significant difference between vaccine and placebo	Bivalent
Lehtinen et al. (2012) [38]	Double-blind, randomized, controlled PATRICIA trial (4-year end-of-study analysis)	- 30,288 Women aged 15–25 years - 14 Countries in Asia Pacific, Europe, Latin America, and North America	Inclusion criteria - 15–25 years old - <6 Lifetime sexual partners 1. TVC women - Received at least one vaccine dose, - Approximate catch-up populations - Including sexually active women (vaccine, n=9,319; control, n=9,325) 2. TVC-naive women - No evidence of oncogenic HPV infection at baseline, - Approximating early adolescent HPV exposure (vaccine, n=5,824; control, n=5,820).	1. Vaccine group (n=9,319): 3 injections of bHPV vaccine at day 1, months 1, and 6 2. Placebo (hepatitis A vaccine) group (n=9,325): 3 injections of placebo at day 1, months 1, and 6	Median follow-up time: 47.4 months (range, 0–62) 1. Serious AEs: vaccine (9%) vs. placebo (8.9%) 2. Vaccine-related serious AEs: vaccine (0.1%) vs. placebo (0.1%) 3. Medically significant condition: vaccine (35.4%) vs. placebo (36.2%) 4. New-onset chronic disease: vaccine (3.1%) vs. placebo (3.3%) 5. New-onset autoimmune disease: vaccine (1.1%) vs. placebo (1.0%) 6. Abnormal infant: vaccine (1.2%) vs. placebo (1.0%) 7. Spontaneous abortion: vaccine (9.1%) vs. placebo (8.6%)	Bivalent

Naud et al. (2014) [39]	Final analysis of long-term follow-up of an initial double-blind, randomized (1:1), placebo-controlled study (HPV-001, NCT00689741)	1,113 Women (15–25 years of age)	Inclusion criteria - 15–25 years old - Enrolled in HPV-001 and who participated in the follow-up study HPV-007	1. An initial double-blind, randomized, multicenter vaccination study (HPV-001; NCT00689741): 1,113 women followed for up to 27 months 2. A long-term follow-up study of the entire cohort (HPV-007; NCT00120848): 776 women followed for up to 77 months (6.4 years) post initial vaccination 3. A long-term follow-up study (HPV-023): 113 months (9.4 years) 4. 3 Doses of either the vaccine formulated with AS04 adjuvant or placebo on a 0, 1, and 6 months schedule	Mean follow-up time: 107 months (maximum duration 113 months) 1. Medically significant AEs: vaccine (26.8%) vs. placebo (17.8%) - Vaccine: gastritis, spontaneous abortion, depression, hypertension - Placebo: genital herpes 2. Serious AEs: vaccine (8.9%) vs. placebo (5.2%) 3. New onset chronic disease: vaccine (2.7%) vs. placebo (1.4%) 4. New onset autoimmune disease (hypothyroidism, RA, vitiligo): vaccine (1.8%) vs. placebo (0.5%) 5. Pregnancy outcome - Ectopic pregnancy: 2% vs. 0% - Normal live births: 82.4% vs. 86.5% - Spontaneous abortion: 15.7% vs. 7.7% - Stillbirth: 0% vs. 1.9%	Bivalent
Schwarz et al. (2015) [20]	Multicenter, open-label, long-term follow-up (NCT00947115) of a primary phase-III study (NCT00196937)	- 488 Healthy women - Six centers in Germany and Poland	Inclusion criteria - Age: 15–55 years - Age-stratified into groups: 15–25, 26–45, and 46–55 years) who received three vaccine doses in the primary study	1. Immune responses in serum and CVS samples 6 years after dose 1 2. Anti-HPV 16/18 GMTs by ELISA 3. Record any local and systemic AEs on diary cards	Follow-up up to 6 years 1. Local AEs - Pain: 15–25 years (96.9%) vs. 26–45 years (92.9%) vs. 46–55 years (82.6%) - Swelling: 15–25 years (42.3%) vs. 26–45 years (44.2%) vs. 46–55 years (40.1%) 2. Systemic AEs: 15–25 years (10.5%) vs. 26–45 years (12.8%) vs. 46–55 years (12.3%) 3. Serious AEs: 15–25 years (1.7%) vs. 26–45 years (1.3%) vs. 46–55 years (3.3%) - 46–55 years: 1 suicide, 1 road accident	Bivalent
Skinner et al. (2014) [18]	Phase 3, multinational, double-blind, randomized controlled trial (VIVIANE study-interim 4 year analysis)	- 5,777 Healthy women - Australia, Canada, Mexico, the Netherlands, Peru, Philippines, Portugal, Russia, Singapore, Thailand, the UK, and the USA	1. Inclusion criteria - ≥25 years old - 45% of participants in each of the 26–35 years and 36–45 years strata - About 10% in the 46 years and older stratum 2. Exclusion criteria - Women who were pregnant or breastfeeding - Women who had a chronic or autoimmune disease or immunodeficiency	1. Vaccine group (n=2,881): 3 injections of bHPV vaccine at day 1, months 1, and 6 2. Placebo ($Al(OH)_3$) group (n=2,871): 3 injections of placebo at day 1, months 1, and 6	Follow-up time: up to 48 months 1. Injection-site AEs: vaccine (85%) vs. placebo (67%) 2. Serious AEs: vaccine (10%) vs. placebo (9%) 3. Medically significant conditions: vaccine (41%) vs. placebo (40%) 4. New-onset chronic disease: vaccine (5%) vs. placebo (6%) 5. Death: vaccine (<1%) vs. placebo (<1%) 6. Pregnancy outcome - Congenital anomalies: vaccine (1%) vs. placebo (2%) - Spontaneous abortion: vaccine (19%) vs. placebo (19%)	Bivalent

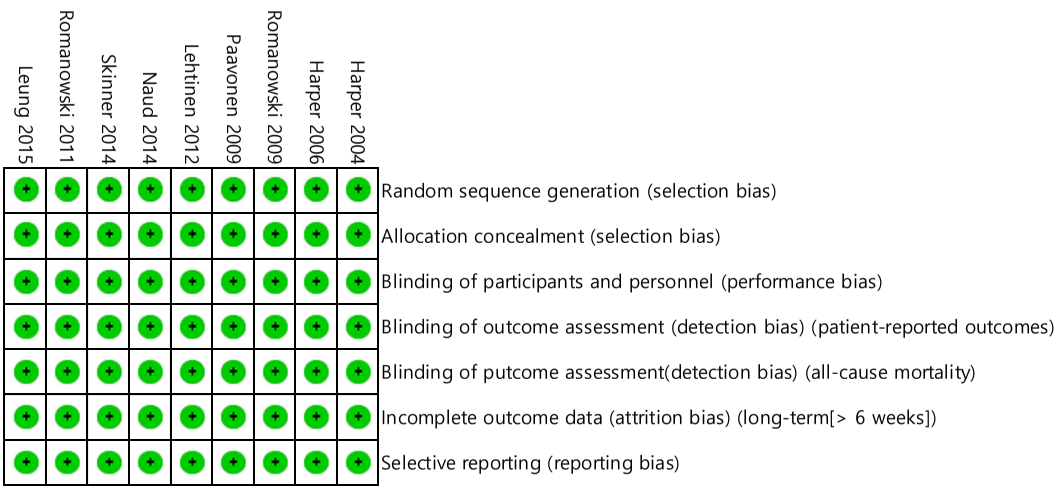
Romanowski et al. (2011) [12]	Partially-blind, controlled, randomized trial	960 Girls and young women	Inclusion criteria - 9–25 years old - Age stratified: 9–14, 15–19, 20–25 years	1. 2-Dose schedules - Using the licensed 20/20F/0, 6 month - Using an alternative 40 µg of each antigen (40/40F)/0, 2 month - Using an alternative 40 µg of each antigen (40/40F)/0, 6 month 2. 3-Dose schedule - Using the licensed 20/20F/0, 1, 6 month	1. At M7, the 3D schedule was not immunologically superior to 2D schedules except in the 40/40F M0,2 group for HPV 16 (lower limit of 95% CI GMT ratio [2D/3D] <0.5). 2. For both HPV 16 and 18, the 2D schedules in girls 9–14 years were immunologically non-inferior to the 3D schedule in women 15–25 years (upper limit of 95% CI for GMT ratio [3D/2D] <2). 3. At M24, non-inferiority was maintained for the 2D M0,6 schedules in girls 9–14 years vs. the 3D schedule in women 15–25 years. 4. All formulations had acceptable reactogenicity and safety profiles.	Bivalent
Leung et al. (2015) [43]	Observer-blind, randomized, age-stratified study with thee parallel groups	- 1,075 Girls women aged 9–14 years old - 21 Sites in France, Hong Kong, Singapore, and Sweden	Inclusion criteria - Healthy girls aged 9–14 years - Negative pregnancy test on the day of each vaccination - Agree to continue contraception	1. HPV 16/18 L1 VLP ASO4-adjuvanted vaccine at M0,6 (HPV 16/18 [2D] group) 2. HPV 6/11/16/18 L1 VLP vaccine at M0,6 (HPV 6/11/16/18 [2D] group) 3. HPV 6/11/16/18 L1 VLP vaccine at M0,2,6 (HPV 6/11/16/18 [3D] group) - Girls in the 2D groups: placebo [$Al(OH)_3$] at M2	1. Antibody responses at M7 for HPV 16/18 (2D) - Superior to those for HPV 6/11/16/18 (2D) and HPV 6/11/16/18 (3D) 1) Lower limit of 95% CI for GMR >1: - HPV 16/18 (2D)/HPV 6/11/16/18 (2D) for anti-HPV 16: 1.69 (1.49–1.91) - HPV 16/18 (2D)/HPV 6/11/16/18 (2D) for anti-HPV 18: 4.52 (3.97–5.13) - HPV 16/18 (2D)/HPV 6/11/16/18 (3D) for anti-HPV 16: 1.72 (1.54–1.93) - HPV 16/18 (2D)/HPV 6/11/16/18 (3D) for anti-HPV 18: 3.22 (2.82–3.68) 2. Among initially seronegative girls in the ATP-I, neutralizing antibody titers were at least 1.8-fold higher for HPV 16/18 (2D) vs. HPV 6/11/16/18 (2D) and HPV 6/11/16/18 (3D) at M7 and M12. 3. Frequencies of HPV 16/18-specific T- and B-cells were in similar ranges between groups. Safety profile 1) At least one medically significant adverse event up to M12 - HPV 16/18 (2D): 14% - HPV 6/11/16/18 (2D): 16% - HPV 6/11/16/18 (3D): 13% 2) SAEs - HPV 16/18 (2D): 13 (3.6%) - HPV 6/11/16/18 (2D): 2 (0.6%) - HPV 6/11/16/18 (3D): 1 (0.3%) - None of the SAEs to have a causal relationship to vaccination - No discernible pattern in the nature and time to onset of the SAEs 3) Potential immune-mediated diseases - HPV 16/18 (2D): 3 (0.8%) - HPV 6/11/16/18 (2D): 3 (0.8%) - Reactive arthritis, juvenile idiopathic arthritis, erythema nodosum, alopecia areata, ulcerative colitis, and coeliac disease - Among them, a possible causal relationship to vaccination - Serious event: erythema nodosum and juvenile idiopathic arthritis Non-serious event: reactive arthritis	Bivalent

Question: The safety profile of bivalent HPV vaccine 3-dose in 15–25 young women

1. Harper DM, Franco EL, Wheeler C, Ferris DG, Jenkins D, Schuind A, et al. Efficacy of a bivalent L1 virus-like particle vaccine in prevention of infection with human papillomavirus types 16 and 18 in young women: a randomised controlled trial. Lancet 2004;364:1757-65 [33].
2. Harper DM, Franco EL, Wheeler CM, Moscicki AB, Romanowski B, Roteli-Martins CM, et al. Sustained efficacy up to 4.5 years of a bivalent L1 virus-like particle vaccine against human papillomavirus types 16 and 18: follow-up from a randomised control trial. Lancet 2006;367:1247-55 [34].
3. GlaxoSmithKline Vaccine HPV-007 Study Group, Romanowski B, de Borba PC, Naud PS, Roteli-Martins CM, De Carvalho NS, et al. Sustained efficacy and immunogenicity of the human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine: analysis of a randomised placebo-controlled trial up to 6.4 years. Lancet 2009;374:1975-85 [37].
4. Paavonen J, Naud P, Salmeron J, Wheeler CM, Chow SN, Apter D, et al. Efficacy of human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine against cervical infection and precancer caused by oncogenic HPV types (PATRICIA): final analysis of a double-blind, randomised study in young women. Lancet 2009;374:301-14 [36].
5. Lehtinen M, Paavonen J, Wheeler CM, Jaisamrarn U, Garland SM, Castellsague X, et al. Overall efficacy of HPV-16/18 AS04-adjuvanted vaccine against grade 3 or greater cervical intraepithelial neoplasia: 4-year end-of-study analysis of the randomised, double-blind PATRICIA trial. Lancet Oncol 2012;13:89-99 [38].
6. Naud PS, Roteli-Martins CM, De Carvalho NS, Teixeira JC, de Borba PC, Sanchez N, et al. Sustained efficacy, immunogenicity, and safety of the HPV-16/18 AS04-adjuvanted vaccine: final analysis of a long-term follow-up study up to 9.4 years post-vaccination. Hum Vaccin Immunother 2014;10:2147-62 [39].
7. Schwarz T, Spaczynski M, Kaufmann A, Wysocki J, Galaj A, Schulze K, et al. Persistence of immune responses to the HPV-16/18 AS04-adjuvanted vaccine in women aged 15-55 years and first-time modelling of antibody responses in mature women: results from an open-label 6-year follow-up study. BJOG 2015;122:107-18 [20].
8. Skinner SR, Szarewski A, Romanowski B, Garland SM, Lazcano-Ponce E, Salmeron J, et al. Efficacy, safety, and immunogenicity of the human papillomavirus 16/18 AS04-adjuvanted vaccine in women older than 25 years: 4-year interim follow-up of the phase 3, double-blind, randomised controlled VIVIANE study. Lancet 2014;384:2213-27 [18].
9. Romanowski B, Schwarz TF, Ferguson LM, Peters K, Dionne M, Schulze K, et al. Immunogenicity and safety of the HPV-16/18 AS04-adjuvanted vaccine administered as a 2-dose schedule compared with the licensed 3-dose schedule: results from a randomized study. Hum Vaccin 2011;7:1374-86 [12].
10. Leung TF, Liu AP, Lim FS, Thollot F, Oh HM, Lee BW, et al. Comparative immunogenicity and safety of human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine and HPV-6/11/16/18 vaccine administered according to 2- and 3-dose schedules in girls aged 9-14 years: Results to month 12 from a randomized trial. Hum Vaccin Immunother 2015;11:1689-702 [43].

Quality assessment						
Participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**
The safety profile of bivalent HPV vaccine 3-dose						
58,718 (9 studies)	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	⊕⊕⊕⊕ HIGH

2D, 2-dose; 3D, 3-dose; AE, adverse event; ATP-E, according-to-protocol cohort for efficacy; ATP-I, according-to-protocol immunogenicity cohort; bHPV, bivalent human papillomavirus; CVS, cervicovaginal secretion; ELISA, enzyme-linked immunosorbent assay; GMT, geometric mean antibody titer; HPV, human papillomavirus; PATRICIA, PApilloma TRIal against Cancer In young Adults; PCR, polymerase chain reaction; RA, rheumatoid arthritis; SAE, serious adverse event; TVC, total vaccinated cohort; VIVIANE, Human PapillomaVIrus: Vaccine Immunogenicity aNd Efficacy; VLP, virus-like particle.


Leung 2015
Romanowski 2011
Skinner 2014
Naud 2014
Lehtinen 2012
Paavonen 2009
Romanowski 2009
Harper 2006
Harper 2004
Random sequence generation (selection bias)
Allocation concealment (selection bias)
Blinding of participants and personnel (performance bias)
Blinding of outcome assessment (detection bias) (patient-reported outcomes)
Blinding of putcome assessment(detection bias) (all-cause mortality)
Incomplete outcome data (attrition bias) (long-term[> 6 weeks])
Selective reporting (reporting bias)

Special situation

(1) Pregnant women

To date, in phase 3 clinical trials, the vaccination group has shown no statistically significant differences from the placebo group in pregnancy/childbirth-related data, such as newborn survival rate, congenital birth defects rate, delivery type (vaginal or cesarean), miscarriage, stillbirth rates, or ectopic pregnancy rates. No intervention is required when the vaccine is administered during pregnancy. However, since studies of the impact of the vaccine on pregnancy are currently limited, human papillomavirus vaccination during pregnancy is not recommended.

(2) Breast-feeding women

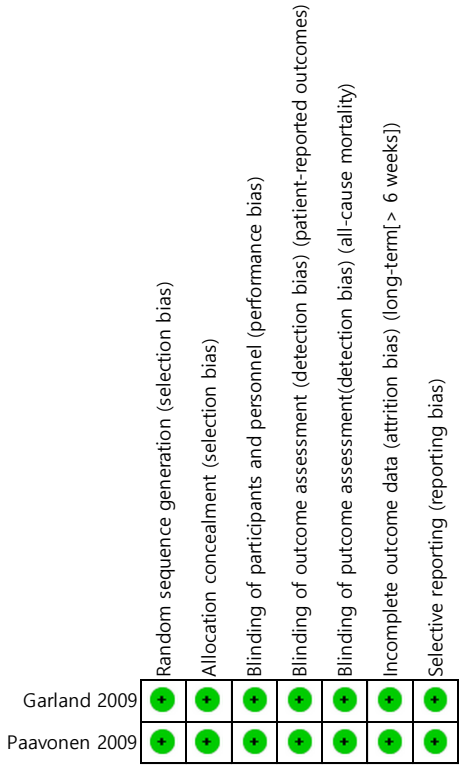
ID	Study design	Participant	Inclusion & exclusion criteria	Intervention	Result	Remark
Garland et al. (2009) [42]	Combined analysis of 5 RCTs	20,551 Women aged 15–45 years	-	1. Vaccine group (n=10,126): 3 injections of qHPV vaccine at day 1, months 2, and 6 2. Placebo group (n=10,425): 3 injections of placebo at day 1, months 2, and 6	1. Live births: vaccine (72.1%) vs. placebo (70.2%) 2. Congenital anomalies: vaccine (2.1%) vs. placebo (1.4%) 3. Cesarean delivery: vaccine (27.9%) vs. placebo (26.6%) 4. Vaginal delivery: vaccine (72.1%) vs. placebo (73.3%) 5. Fetal loss: vaccine (27.8%) vs. placebo (29.7%) 6. Ectopic pregnancy: vaccine (0.1%) vs placebo (0.15%) 7. AEs during lactation: vaccine (16 neonates) vs. placebo (4 neonates) - Vaccine: pneumonia, bronchiolitis - Placebo: hematemesis, bronchiolitis, pyrexia, hyperbilirubinemia	Quadrivalent
Paavonen et al. (2009) [36]	Phase III randomized, double-blind, controlled	18,729 Women (15–25 years)	1. ATP-E (vaccine, n=8,093; control, n=8,069) 2. TVC (included all women receiving at least one vaccine dose, regardless of their baseline HPV status; represents the general population, including those who are sexually active; vaccine, n=9,319; control, n=9,325) 3. TVC-naive (no evidence of oncogenic HPV infection at baseline; represents women before sexual debut; vaccine, n=5,822; control, n=5,819)	HPV 16/18 AS04-adjuvanted vaccine (months 0, 1, and 6)	1. Pregnancies: vaccine (n=1,804) vs. placebo (n=1,802) 2. Ongoing pregnancies: vaccine (11%) vs. placebo (12%) 3. Normal infant: vaccine (62%) vs. placebo (63%) 4. Abnormal infant - Congenital anomaly: vaccine (<1%) vs. placebo (<1%) - Medically significant condition: vaccine (<1%) vs. placebo (<1%) 5. Spontaneous abortion: vaccine (9%) vs. placebo (9%) 6. Elective termination: vaccine (10%) vs. placebo (11%)	Bivalent

Question: The safety profile of quadrivalent HPV vaccine in breastfeeding women and neonate

1. Garland SM, Ault KA, Gall SA, Paavonen J, Sings HL, Ciprero KL, et al. Pregnancy and infant outcomes in the clinical trials of a human papillomavirus type 6/11/16/18 vaccine: a combined analysis of five randomized controlled trials. Obstet Gynecol 2009;114:1179-88 [42].
2. Paavonen J, Naud P, Salmeron J, Wheeler CM, Chow SN, Apter D, et al. Efficacy of human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine against cervical infection and precancer caused by oncogenic HPV types (PATRICIA): final analysis of a double-blind, randomised study in young women. Lancet 2009;374:301-14 [36].

Quality assessment						
Participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**
The safety profile of quadrivalent HPV vaccine						
39,280 (2 studies)	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	⊕⊕⊕⊕ HIGH

AE, adverse event; ATP-E, according-to-protocol cohort for efficacy; HPV, human papillomavirus; qHPV, quadrivalent human papillomavirus; RCT, randomized controlled trial; TVC, total vaccinated cohort.



(3) 2-Dose vaccination

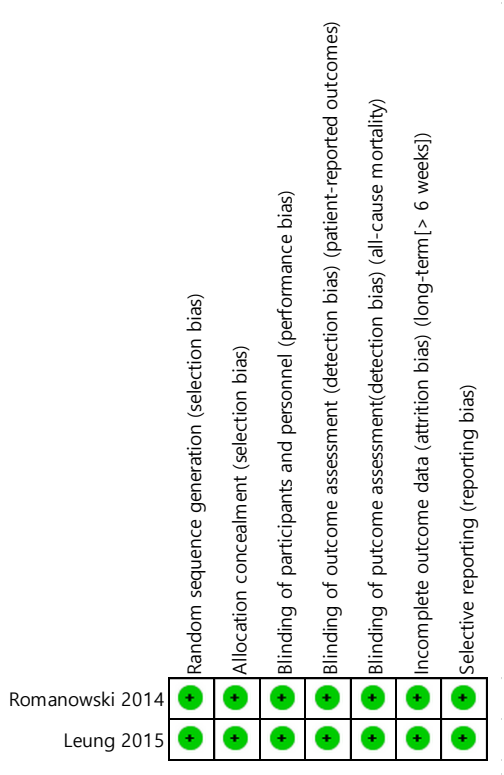
ID	Study design	Participant	Inclusion & exclusion criteria	Intervention	Result	Remark
Romanowski et al. (2014) [13]	Randomized, partially-blind study	960 Healthy girls and young women	Inclusion criteria - 9–25 years old - Age stratified: 9–14, 15–19, 20–25 years	1. 2 Doses group (n=240): 2 injections of bHPV vaccine at day 1 and month 6 2. 3 Doses group (n=239): 3 injections of bHPV vaccine at day 1, months 1 and 6	Follow-up time: up to 48 months 1. AEs leading to withdrawal: 2D (0%) vs. 3D (0%) 2. Serious AEs: 2D (7.9%) vs. 3D (5.4%) 3. Medically significant condition: 2D (36.7%) vs. 3D (34.3%) 4. New onset chronic disease: 2D (5.4%) vs. 3D (2.5%) 5. New onset autoimmune disease: 2D (2.1%) vs. 3D (1.7%) 6. Ectopic pregnancy: 2D (0%) vs. 3D (0%) 7. Elective termination: 2D (12.5%) vs. 3D (25%) 8. Normal live infant: 2D (62.5%) vs. 3D (60%) 9. Spontaneous abortion: 2D (12.5%) vs. 3D (5%) 10. Ongoing pregnancy: 2D (8.3%) vs. 3D (10%)	Bivalent
Leung et al. (2015) [43]	Observer-blind, randomized, age-stratified study with three parallel groups	- 1,075 Girls aged 9–14 years old - 21 Sites in France, Hong Kong, Singapore, and Sweden	Inclusion criteria - Healthy girls aged 9–14 years - Negative pregnancy test on the day of each vaccination - Agree to continue contraception	1. HPV 16/18 L1 VLP ASO4-adjuvanted vaccine at M0,6 (HPV 16/18 [2D] group) 2. HPV 6/11/16/18 L1 VLP vaccine at M0,6 (HPV 6/11/16/18 [2D] group) 3. HPV 6/11/16/18 L1 VLP vaccine at M0,2,6 (HPV 6/11/16/18 [3D] group) - Girls in the 2D groups: placebo [$Al(OH)_3$] at M2	Safety profile 1. At least one medically significant adverse event up to M12 - HPV 16/18 (2D): 14% - HPV 6/11/16/18 (2D): 16% - HPV 6/11/16/18 (3D): 13% 2. SAEs - HPV 16/18 (2D): 13 (3.6%) - HPV 6/11/16/18 (2D): 2 (0.6%) - HPV 6/11/16/18 (3D): 1 (0.3%) - None of the SAEs to have a causal relationship to vaccination 3. Potential immune-mediated diseases - HPV 16/18 (2D): 3 (0.8%) - HPV 6/11/16/18 (2D): 3 (0.8%) - Reactive arthritis, juvenile idiopathic arthritis, erythema nodosum, alopecia areata, ulcerative colitis, and coeliac disease - Among them, a possible causal relationship to vaccination -Serious event: erythema nodosum and juvenile idiopathic arthritis Non-serious event: reactive arthritis	Bivalent & Quadrivalent

Question: The safety profile of HPV vaccine 2-dose

1. Romanowski B, Schwarz TF, Ferguson LM, Ferguson M, Peters K, Dionne M, et al. Immune response to the HPV-16/18 AS04-adjuvanted vaccine administered as a 2-dose or 3-dose schedule up to 4 years after vaccination: results from a randomized study. Hum Vaccin Immunother 2014;10:1155-65 [13].
2. Leung TF, Liu AP, Lim FS, Thollot F, Oh HM, Lee BW, et al. Comparative immunogenicity and safety of human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine and HPV-6/11/16/18 vaccine administered according to 2- and 3-dose schedules in girls aged 9-14 years: Results to month 12 from a randomized trial. Hum Vaccin Immunother 2015;11:1689-702 [43].

Quality assessment						
Participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**
The safety profile of quadrivalent HPV vaccine						
2,035 (2 studies)	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	⊕⊕⊕⊕ HIGH

2D, 2-dose; 3D, 3-dose; AE, adverse event;; bHPV, bivalent human papillomavirus; HPV, human papillomavirus; SAE, serious adverse event; VLP, virus-like particle.



KQ5. Does the HPV preventive vaccine provide cross-protection against HPV types not included in the vaccine?

1) Quadrivalent vaccine

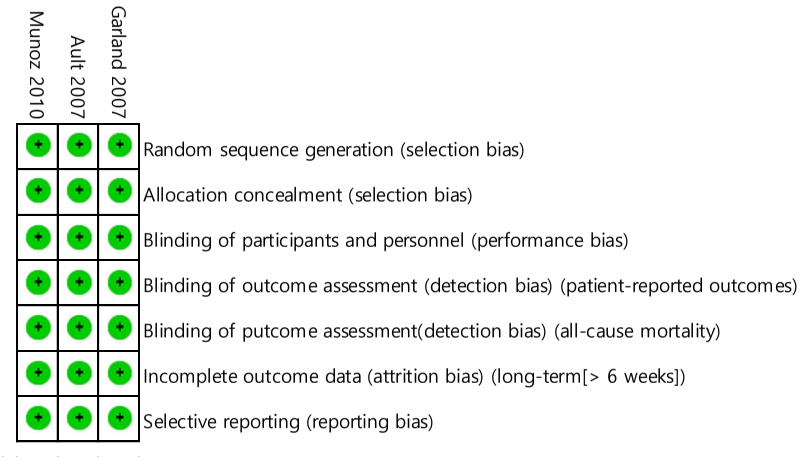
ID	Study design	Participant	Inclusion & exclusion criteria	Intervention	Result	Remark
Garland et al. (2007) [27]	Randomized, placebo-controlled, double-blind trial: The FUTURE I study	- 5,455 Women - 16 Countries	Inclusion criteria - 16–26 years of age - Not pregnant - No history of genital warts or abnormal Pap smear - No more than four sex partners in lifetime	- The quadrivalent HPV 6/11/16/18 L1 virus-like-particle vaccine with amorphous aluminum hydroxyphosphate sulfate (Gardasil, Merck) as an adjuvant - The aluminum-containing placebo	1. In the per-protocol population - Vaccine efficacy: 100% for each of the co-primary end points 2. In an intention-to-treat analysis - Reduction of the rate of any vulvar or vaginal perianal lesions regardless of the causal HPV type by 34% (95% CI, 15–49) - Reduction of the rate of cervical lesions regardless of the causal HPV type by 20% (95% CI, 8–31)	Quadrivalent
Ault et al. (2007) [4]	Double-blind, placebo-controlled, randomized trial: The FUTURE II study	- 20,583 Women - 90 Study sites in 13 countries	Inclusion criteria - 15–26 years of age - Not pregnant - No prior abnormal Pap smear - No more than four sex partners	- Quadrivalent HPV 6/11/16/18 vaccine (n=9,087), its HPV 16 vaccine component (n=1,204), or placebo (n=10 292) - Day 1, month 2, and month 6	1. Mean follow-up: 3.0 years (SD 0.66) 2. Vaccine efficacy for the prevention of the primary composite end point - 99% (95% CI, 93–100) in the per-protocol population - 44% (95% CI, 31–55) in an intention-to-treat population 3. The overall rate of CIN 2/3 or AIS due to any HPV type - 18% reduction (95% CI, 7–29) in a second intention-to-treat analysis	Quadrivalent
Munoz et al. (2010) [30]	Two randomized, placebo-controlled, efficacy trials (FUTURE I and FUTURE II)	- 17 622 Women aged 15–26 years - Australia, Austria, Brazil, Canada, Colombia, Czech Republic, Denmark, Finland, Germany, Hong Kong, Iceland, Italy, Mexico, New Zealand, Norway, Peru, Poland, Puerto Rico, Russia, Singapore, Sweden, Thailand, the United Kingdom, and the United States	1. Negative to 14 HPV types 1) Inclusion criteria - At least one vaccination -Seronegative and PCR negative at day 1 to the vaccine HPV types (i.e., HPV 6, 11, 16, and 18), were PCR negative at day 1 to the nonvaccine high-risk HPV types that had available PCR assays (i.e., HPV 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59), and had a negative day 1 Pap test result - Any follow-up visit. 2) Endpoint counting began after day 1 2. Intention to treat 1) Inclusion criteria - At least one vaccination - Any follow-up visit.	1. The HPV 6/11/16/18 vaccine or placebo - At day 1, month 2, and month 6 2. All women - Cervicovaginal sampling - Pap testing at day 1 and every 6–12 months thereafter 3. Outcomes - Any cervical intraepithelial neoplasia - Any external anogenital and vaginal lesions - Pap test abnormalities - Procedures such as colposcopy and definitive therapy	The average follow-up 3.6 years (maximum of 4.9 years) 1. In the population that was negative to 14 HPV types - Vaccination efficacy: up to 100% effective in reducing the risk of HPV 16/18-related high-grade cervical, vulvar, and vaginal lesions and of HPV 6/11-related genital warts 2. In the intention-to-treat group: irrespective of causal HPV type Vaccination efficacy: - The risk of any high-grade cervical lesions: 19.0% reduction (rate vaccine 1.43; rate placebo 1.76; difference 0.33; 95% CI, 0.13–0.54) - The risk of vulvar and vaginal lesions: 50.7% reduction (rate vaccine 0.10; rate placebo 0.20; difference 0.10; 95% CI, 0.04–0.16) - The risk of genital warts: 62.0% reduction (rate vaccine 0.44; rate placebo 1.17; difference 0.72; 95% CI, 0.58–0.87) - The risk of Pap abnormalities: 11.3% reduction (rate vaccine 10.36; rate placebo 11.68; difference 1.32; 95% CI, 0.74–1.90) - The risk of cervical definitive therapy: 23.0% reduction (rate vaccine 1.97; rate placebo 2.56; difference 0.59; 95% CI, 0.35–0.83)	Quadrivalent

Question: The cross-protection of quadrivalent HPV vaccine

1. Garland SM, Hernandez-Avila M, Wheeler CM, Perez G, Harper DM, Leodolter S, et al. Quadrivalent vaccine against human papillomavirus to prevent anogenital diseases. N Engl J Med 2007;356:1928-43 [27].
2. Ault KA; Future II Study Group. Effect of prophylactic human papillomavirus L1 virus-like-particle vaccine on risk of cervical intraepithelial neoplasia grade 2, grade 3, and adenocarcinoma in situ: a combined analysis of four randomised clinical trials. Lancet 2007;369:1861-8 [4].
3. Munoz N, Kjaer SK, Sigurdsson K, Iversen OE, Hernandez-Avila M, Wheeler CM, et al. Impact of human papillomavirus (HPV)-6/11/16/18 vaccine on all HPV-associated genital diseases in young women. J Natl Cancer Inst 2010;102:325-39 [30].

Quality assessment						
Participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**
The cross-protection of quadrivalent HPV vaccine						
17,622 (3 studies)	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	⊕⊕⊕⊕ HIGH

AIS, adenocarcinoma *in situ*; CIN, cervical intraepithelial neoplasia; FUTURE, Females United to Unilaterally Reduce Endo/Ectocervical Disease; HPV, human papillomavirus; PCR, polymerase chain reaction.


Munoz 2010
Ault 2007
Garland 2007
Random sequence generation (selection bias)
Allocation concealment (selection bias)
Blinding of participants and personnel (performance bias)
Blinding of outcome assessment (detection bias) (patient-reported outcomes)
Blinding of putcome assessment(detection bias) (all-cause mortality)
Incomplete outcome data (attrition bias) (long-term[> 6 weeks])
Selective reporting (reporting bias)

2) Bivalent vaccine

ID	Study design	Participant	Inclusion & exclusion criteria	Intervention	Result	Remark
Paavonen et al. (2009) [36]	Phase III randomized, double-blind, controlled	18,729 Women (15–25 years)	1. ATP-E (vaccine, n=8,093; control, n=8,069) 2. TVC (included all women receiving at least one vaccine dose, regardless of their baseline HPV status; represents the general population, including those who are sexually active; vaccine, n=9,319; control, n=9,325) 3. TVC-naive (no evidence of oncogenic HPV infection at baseline; represents women before sexual debut; vaccine, n=5,822; control, n=5,819)	HPV 16/18 AS04-adjuvanted vaccine (months 0, 1, and 6)	1. Vaccine efficacy against CIN 2+ associated with HPV 16/18 - 92.9% (96.1% CI, 79.9–98.3) in the primary analysis - 98.1% (96.1% CI, 88.4–100) in an analysis in which probable causality to HPV type was assigned in lesions infected with multiple oncogenic types (ATP-E cohort) 2. Vaccine efficacy against CIN 2+ irrespective of HPV DNA - 30.4% (96.1% CI, 16.4–42.1) in the TVC - 70.2% (96.1% CI, 54.7–80.9) in the TVC-naïve 3. Corresponding values against CIN 3+ - 33.4% (96.1% CI, 9.1–51.5) in the TVC - 87.0% (96.1% CI, 54.9–97.7) in the TVC-naïve 4. Vaccine efficacy against CIN 2+ associated with 12 non-vaccine oncogenic types - 54.0% (96.1% CI, 34.0–68.4; ATP-E) 5. Individual cross-protection against CIN 2+ associated with HPV 31, 33, and 45 was seen in the TVC 6. Adverse event - Similar proportion of serious adverse events, medically significant conditions, new-onset chronic diseases, and new-onset autoimmune diseases in vaccine and control groups.	Bivalent
GlaxoSmithKline Vaccine HPV-007 Study Group et al. (2009) [37]	Double-blind, randomized, placebo-controlled initial study	-1,113 Women - 27 Sites (5 in Brazil, 5 in Canada, and 17 in the USA)	Inclusion criteria - 15–25 years old - Normal cervical cytology - HPV 16/18 seronegative and oncogenic HPV DNA-negative (14 types) - Participated in initial study (n=1,113) and follow-up study (n=776)	1. HPV 16/18 AS04-adjuvanted vaccine and placebo 2. Cervical samples for HPV DNA test every 6 months 3. Management of abnormal cytologies was pre-specified, and HPV 16/18 antibody titres were assessed.	1. Vaccine efficacy - Against incident infection with HPV 16/18: 95.3% (95% CI, 87.4–98.7) - Against 12-month persistent infection: 100% (95% CI, 81.8–100) 2. Vaccine efficacy against CIN 2+ - 100% (95% CI, 51.3–100) for lesions associated with HPV 16/18 - 71.9% (95% CI, 20.6–91.9) for lesions independent of HPV DNA 3. Antibody concentrations by ELISA - ≥12-fold than after natural infection (both antigens) 4. Safety outcomes - Safety profiles of the HPV-16/18 vaccine and placebo: similar - Adverse events: a similar number of women in both the vaccine and placebo groups - None of the serious adverse events related or possibly related to vaccination, and no deaths.	Bivalent

Lehtinen et al. (2012) [38]	Double-blind, randomized, controlled PATRICIA trial	-30,288 Women aged 15–25 years - 14 Countries in Asia Pacific, Europe, Latin America, and North America	Inclusion criteria - 15–25 years old - <6 Lifetime sexual partners 1. TVC women - Received at least one vaccine dose - Approximate catch-up populations - Including sexually active women (vaccine, n=9,319; control, n=9,325) 2. TVC-naive women - No evidence of oncogenic HPV infection at baseline, - Approximating early adolescent HPV exposure (vaccine, n=5,824; control, n=5,820).	1. HPV 16/18 AS04-adjuvanted vaccine 2. A control hepatitis A vaccine	1. Vaccine efficacy against CIN 3+ associated with HPV 16/18 - 100% (95% CI, 85.5–100) in the TVC-naive - 45.7% (95% CI, 22.9–62·2) in the TVC 2. Vaccine efficacy against all CIN 3+ (irrespective of HPV type in the lesion) - 93.2% (78.9–98·7) in the TVC-naive - 45.6% (28.8–58·7) in the TVC 3. Vaccine efficacy against all CIN 3+ - Higher than 90% in all age groups in the TVC-naïve - Highest in the 15–17 year age group in the TVC and progressively decreased in the 18–20 year and 21–25 year age groups 4. Vaccine efficacy against all AIS - 100% (31.0–100) in the TVC-naïve - 76.9% (16.0–95.8) in the TVC 5) Safety outcomes - A similar proportion of serious adverse events, new-onset chronic diseases, new-onset autoimmune diseases, and medically significant conditions in vaccine and placebo group - Pregnancy outcomes: also similar in both groups	Bivalent
Draper et al. (2013) [52]	A computerized block randomization (phase IV trial)	- 198 Girls aged 12–15 years old -England (Gloucestershire and Hertfordshire)	1. Inclusion criteria - 12–15 Year old girls - Written informed consent from a parent or guardian of the subject 2. Exclusion criteria - Already received or were currently receiving HPV vaccination - Pregnant or become pregnant during the study - Breast-feeding mothers - Allergic to vaccine components	1. Randomized (1:1) to receive three doses of either the bivalent (Cervarix) or quadrivalent: (Gardasil) HPV vaccine at month (M) 0, 1 and 6 2. Blood samples were collected at M0 (prior to vaccination), M2 (1 month post second dose), M7 (1 month post third dose) and M12 (6 months post third dose)	1. Serum-neutralizing antibody responses against non-vaccine HPV types - Broader and of higher magnitude in the Cervarix compared to the Gardasil vaccinated individuals 2. Levels of neutralizing and binding antibodies in genital secretions - Closely associated with those found in the serum (r=0.869) - Cervarix having a median 2.5-fold (interquartile range, 1.7–3.5) higher geometric mean HPV-specific IgG ratio in serum and genital samples than Gardasil (p=0.0047) 2. Strong positive association between cross-neutralizing antibody seropositivity and available HPV vaccine trial efficacy data against non-vaccine types	Bivalent

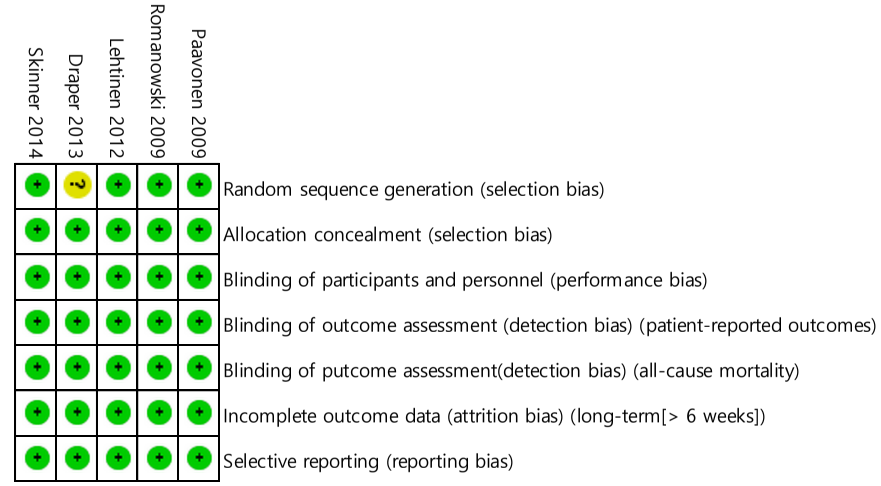
Skinner et al. (2014) [18]	Phase 3, multinational, double-blind, randomized controlled trial	- 5,777 Healthy women -Australia, Canada, Mexico, the Netherlands, Peru, Philippines, Portugal, Russia, Singapore, Thailand, the UK, and the USA	1. Inclusion criteria - ≥25 years old - 45% of participants in each of the 26–35 years and 36–45 years strata - About 10% in the 46 years and older stratum 2. Exclusion criteria - Women who were pregnant or breastfeeding - Women who had a chronic or autoimmune disease or immunodeficiency	1. HPV 16/18 AS04-adjuvanted vaccine 2. Control (aluminium hydroxide) 3. 0–1–6 Month schedule	1. Vaccine efficacy against HPV 16/18-related 6-month persistent infection or CIN 1+: significant - In all age groups combined (81.1%; 97.7% CI, 52.1–94.0) - In the 26–35 years age group (83.5%; 97.7% CI, 45.0–96.8) - In the 36–45 years age group (77.2%; 97.7% CI, 2.8–96.9) - No cases in women aged 46 years and older 2. Vaccine efficacy against ≥ASC-US associated with HPV 16/18: significant 3. Significant cross-protective vaccine efficacy against 6-month persistent infection with HPV 31 (79.1%; 97.7% CI, 27.6–95.9) and HPV 45 (76.9%; 97.7% CI, 18.5–95.6) 4. Serious adverse events - 285 (10%) of 2,881 women in the vaccine group - 267 (9%) of 2,871 in the control group - Five (<1%) and eight (<1%) of these events: related to vaccination	Bivalent

Question: The cross-protection of bivalent HPV vaccine

1. Paavonen J, Naud P, Salmeron J, Wheeler CM, Chow SN, Apter D, et al. Efficacy of human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine against cervical infection and precancer caused by oncogenic HPV types (PATRICIA): final analysis of a double-blind, randomised study in young women. Lancet 2009;374:301-14 [36].
2. GlaxoSmithKline Vaccine HPV-007 Study Group, Romanowski B, de Borba PC, Naud PS, Roteli-Martins CM, De Carvalho NS, et al. Sustained efficacy and immunogenicity of the human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine: analysis of a randomised placebo-controlled trial up to 6.4 years. Lancet 2009;374:1975-85 [37].
3. Lehtinen M, Paavonen J, Wheeler CM, Jaisamrarn U, Garland SM, Castellsague X, et al. Overall efficacy of HPV-16/18 AS04-adjuvanted vaccine against grade 3 or greater cervical intraepithelial neoplasia: 4-year end-of-study analysis of the randomised, double-blind PATRICIA trial. Lancet Oncol 2012;13:89-99 [38].
4. Draper E, Bissett SL, Howell-Jones R, Waight P, Soldan K, Jit M, et al. A randomized, observer-blinded immunogenicity trial of Cervarix((R)) and Gardasil((R)) Human Papillomavirus vaccines in 12-15 year old girls. PLoS One 2013;8:e61825 [51].
5. Skinner SR, Szarewski A, Romanowski B, Garland SM, Lazcano-Ponce E, Salmeron J, et al. Efficacy, safety, and immunogenicity of the human papillomavirus 16/18 AS04-adjuvanted vaccine in women older than 25 years: 4-year interim follow-up of the phase 3, double-blind, randomised controlled VIVIANE study. Lancet 2014;384:2213-27 [18].

Quality assessment						
Participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**
The cross-protection of bivalent HPV vaccine						
56,105 (5 studies)	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	⊕⊕⊕⊕ HIGH

AIS, adenocarcinoma *in situ*; ASC-US, atypical squamous cells of undetermimed significance; ATP-E, according-to-protocol cohort for efficacy; CIN, cervical intraepithelial neoplasia; ELISA, enzyme-linked immunosorbent assay; HPV, human papillomavirus; IgG, immunoglobulin G; PATRICIA, PApilloma TRIal against Cancer in young Adults; TVC, total vaccinated cohort.


Skinner 2014
Draper 2013
Lehtinen 2012
Romanowski 2009
Paavonen 2009
Random sequence generation (selection bias)
Allocation concealment (selection bias)
Blinding of participants and personnel (performance bias)
Blinding of outcome assessment (detection bias) (patient-reported outcomes)
Blinding of putcome assessment(detection bias) (all-cause mortality)
Incomplete outcome data (attrition bias) (long-term[> 6 weeks])
Selective reporting (reporting bias)