**Supplement 1. UK and US government information on HPV vaccination**

| Source | Comment |
|---|---|
| NHS website, UK (1) | 'It helps protect them against cervical cancer, which is the most common cancer in women under 35 in the UK. The HPV vaccine is effective at stopping girls getting the types of HPV that cause most cervical cancers, and some other anal and genital cancers and cancers of the head and neck.'<br><br>'Gardasil protects against 4 types of HPV: 6, 11, 16 and 18. Between them, types 16 and 18 are the cause of most cervical cancers in the UK (more than 70%)'. 'Studies have already shown that the vaccine protects against HPV infection for at least 10 years, although experts expect protection to last for much longer.' |
| Public Health England HPV vaccination guide(2) | 'Girls who have the vaccine will significantly reduce their chance of getting cervical cancer.' |
| CDC, 6 reasons to get HPV vaccine for your child(3) | **'**HPV vaccination is cancer prevention. HPV causes over 33,700 cases of cancer in men and women every year in the U.S. HPV vaccination can prevent over 90% (31,200) of these cancers from ever developing by preventing the infections that cause those cancers.' |

**References**

1. NHS. HPV vaccine - NHS: Department of Health; 2019 [Available from: https://www.nhs.uk/conditions/vaccinations/hpv-human-papillomavirus-vaccine/.
2. Public Health England. HPV vaccination guide. 2017.

3. CDC. 6 reasons to get HPV vaccine for your child: CDC; 2018 [Available from: https://www.cdc.gov/hpv/infographics/vacc-six-reasons.html.

| Database | Search strategy |
|---|---|
| Medline search criteria (02.01.15, then re-run on 10.05.16 and 30.07.18): | 'exp papillomavirus vaccines/' OR 'hpv vaccin*.mp' OR 'human papillomavirus vaccin*.mp' = 8,957<br>AND efficacy.mp (698,216) = 1,107<br>Limit to 'clinical trial-all, clinical trial, controlled clinical trial, meta-analysis, randomised controlled trial, systematic reviews = 204<br>Limit to English Language = 197 |
| Embase search criteria: (02.01.15, then re-run on 10.05.16 and 30.07.18) | (hpv/ OR hpv) AND vaccin* = 15,007<br>AND efficacy = 2,787<br>limit to randomised controlled trial, controlled clinical trial, meta analysis, Cochrane review, systematic review And English language<br>= 318 |
| Additional searches | Clinicaltrials.gov: 'hpv vaccine' limited to phase 2, 3, and 4 trials<br>EU Clinical Trials Database: 'hpv vaccine'<br>Search of GSK and Merck websites for registered trials<br>Additional papers were found through reviewing references of papers found and search updates from Embase and Medline. We included the results of one trial, V501-041, that was published after our last search.(1) A further search for |

| | |
|---|---|
| | observational and Phase 4 trials was run on 06.04.17. One study, Palmer et al, which was published after this search was included.(2) |

**Supplement 2. Search Strategy**

## References

1. Wei L, Xie X, Liu J, Zhao Y, Chen W, Zhao C, et al. Efficacy of quadrivalent human papillomavirus vaccine against persistent infection and genital disease in Chinese women: A randomized, placebo-controlled trial with 78-month follow-up. Vaccine. 2018.
2. Palmer T, Wallace L, Pollock KG, Cuschieri K, Robertson C, Kavanagh K, et al. Prevalence of cervical disease at age 20 after immunisation with bivalent HPV vaccine at age 12-13 in Scotland: retrospective population study. Bmj. 2019;365:l1161.

## Supplement 3. HPV systematic reviews and meta-analyses

| Paper | Systematic review or Meta-analysis | Focus | Included trials | Comments including any notable findings and problems with the review |
|---|---|---|---|---|
| Schmiedeskamp et al 2006(1) | Systematic review | Pharmacology, efficacy, safety, tolerability, and pharmacoeconomics | Brown 04 (post-hoc analysis of Phase I trials), Koutsky 02 (V501-005), Harper 04 (HPV-001), Villa 05 (V501-027), FUTURE I (interim results), FUTURE II (interim results) | • Early review so limited number of trials included and used interim results |

| | | | | |
|---|---|---|---|---|
| FUTURE II STUDY GROUP 2007(2) | Meta-analysis | Efficacy of Gardasil in Women with Virological Evidence of HPV Infection | FUTURE I, FUTURE II | • Only two Gardasil trials<br>• Post-hoc analysis |
| La Torre et al 2007(3) | Systematic review & meta-analysis | Persistent six-month cervical infection with HPV 16/18 | Villa 06 (V501-007), Harper 06 (HPV-001), Mao 06 (V501-005), Brown 04, Paavonen 07 (PATRICIA) | • Limited to five trials<br>• Included evidence from monovalent vaccine<br>• Did not discuss limitations of six-month persistent infection |
| Rambout et al 2007(4) | Systematic review & Meta-analysis | Main outcome vaccine HPV-type CIN2+ | FUTURE II, FUTURE I, HPV-001, V501-005, PATRICIA (Paavonen 07), V501-007 (Villa 05, Villa 06) | • Acknowledged short trial length, trial heterogeneity, high loss to follow up and high rates of participant exclusion in sub-groups |
| Ault et al 2007(5) | Meta-analysis | Gardasil efficacy against CIN2+ | V501-001, V501-007, FUTURE I, FUTURE II | • Combined results from monovalent vaccine<br>• Mean follow-up three years |
| Barr et al 2008(6) | Meta-analysis | Gardasil efficacy in North America in sexually active women | FUTURE I, FUTURE II, V501-005, V501-007, V501-016 (immunogenicity trial) | • Used ITT population but initial trial recruitment restricted number of previous partners |
| Harper et al 2008(7) | Meta-analysis | Impact of Cervarix on subsequent HPV-16/18 infection and cervical disease in women 15–25 years of age | HPV-007, PATRICIA- interim analysis | • Used CIN2+ lesion case assignment based on previous history of persistent HPV infection |
| Joura et al 2008(8) | Meta-analysis | Correlating immune response and efficacy | FUTURE I, FUTURE II | • No immune correlate with vaccine efficacy found |
| Perez et al 2008(9) | Meta-analysis | Safety, immunogenicity and efficacy of Gardasil in Latin America | FUTURE I, FUTURE II, V501-007, V501-018, V501-016 (immunogenicity) | |
| Tay et al 2008(10) | Meta-analysis | Safety, immunogenicity and efficacy of Gardasil in Asia-Pacific region | FUTURE I, FUTURE II | |

| | | | | |
|---|---|---|---|---|
| Brown et al 2009(11) | Meta-analysis | Gardasil efficacy on non-vaccine HPV in HPV-naïve women | FUTURE I, FUTURE II | • Used combined surrogate outcome of CIN1+ |
| Damm et al 2009(12) | Systematic review | Efficacy and cost-effectiveness | Did not specify which trials were considered | • Labelled as systematic review but no evidence of this in analysis |
| Kjaer et al 2009(13) | Meta-analysis | Efficacy of Gardasil against CIN2+ due to vaccine-HPV types | V501-007, FUTURE I, FUTURE II | • Combined lesions due to HPV 6 and 11 which are not known to be carcinogenic |
| Lazcano-Ponce et al 2009(14) | Meta-analysis | Impact of Gardasil in Mexican women | Post-hoc analysis of FUTURE I and FUTURE II | • Combined surrogate outcome of HPV6/11/16/18 CIN1+ |
| Majewski et al 2009(15) | Meta-analysis | Impact of Gardasil in European women<br>Efficacy against CIN and EGL by HPV6/11/16/18 in PPE, efficacy against CIN and EGL due to any HPV type in naïve group | V501-007,<br>FUTURE I,<br>FUTURE II,<br>V501-016 (immunogenicity study) | |
| Medeiros et al 2009(16) | Systematic review and Meta-analysis | Efficacy of Cervarix and Gardasil against all genital lesions in ITT sub-group | HPV-001 (Harper 06), CVT (Hildesheim 07), PATRICIA (Paavonen 07), V501-005 (Mao 06), FUTURE I (Garland), FUTURE II (FUTURE II) | • Reported they found inconsistency and heterogeneity among the trials |
| Olsson et al 2009(17) | Meta-analysis | Gardasil efficacy in women with previous HPV infection | V501-007, FUTURE I, FUTURE II | |
| Wheeler et al 2009(18) | Meta-analysis | Oncogenic non-vaccine HPV types in sexually active women | FUTURE I, FUTURE II | • Pre-specified analysis non-vaccine CIN1+ (combined surrogate outcome) |
| Dillner et al 2010(19) | Meta-analysis | Gardasil efficacy against low-grade cervical and genital lesions | FUTURE I, FUTURE II | • Focus on CIN1 and non-cervical genital lesions so less relevant to cervical cancer |

| | | | | |
|---|---|---|---|---|
| Munoz et al 2010(20) | Meta-analysis | Gardasil efficacy against all HPV-associated genital disease | FUTURE I, FUTURE II | |
| Ault et al 2011(21) | Meta-analysis | Quadrivalent efficacy against AIS | FUTURE I, FUTURE II | • Only 25 positive cases of AIS in two trials |
| Lu et al 2011(22) | Systematic review and Meta-analysis | Efficacy and safety. Primary endpoint CIN2+ | V501-005 (Koutsky, Mao 06), HPV-001 (Harper 06), HPV-007 (Harper 04), V501-007 (Villa 05, Villa 06), FUTURE I (Garland 07, Brown 09, Wheeler 09), FUTURE II (Future II Study Group, Brown 09, Wheeler 09), FUTURE III (Munoz 09), PATRICIA (Paavonen 07, Paavonen 09) | • Included Monovalent HPV-16 vaccine trial<br>• Seven trials included |
| Haupt et al 2011(23) | Impact of an HPV6/11/16/18 L1 viruslike particle vaccine on progression to cervical intraepithelial neoplasia in seropositive women with HPV16/18 infection | Gardasil efficacy against HPV16/18 CIN2+ in women with HPV16/18 DNA positivity prior to vaccination | FUTURE I, FUTURE II | • No impact on incidence of HPV 16/18 CIN2+ if already existing infection |
| Joura et al 2012(24) | Effect of the human papillomavirus (HPV) quadrivalent vaccine in a subgroup of women with cervical and vulvar disease: retrospective | Impact of Gardasil on a subgroup with vulvar and cervical disease | FUTURE I, FUTURE II | |

| | | | | |
|---|---|---|---|---|
| | pooled analysis of trial data | | | |
| Malagon et al 2012(25) | Systematic review and Meta-analysis | Cross-protection against CIN2+ and 6 month persistent infection due to non-vaccine HPV types | FUTURE I, FUTURE II, PATRICIA, HPV-001/007/023 | • Higher cross-protection for Cervarix but admitted this could be due to difference in study design. |
| Clark et al 2013(26) | Meta-analysis | Gardasil efficacy in Black women | FUTURE I, FUTURE II | |
| Tomljenovic et al 2013(27) | Systematic review | Comparison of efficacy and safety of Cervarix and Gardasil | FUTURE I, FUTURE II, V501-007, | • No meta-analysis done<br>• Raised concerns about use of surrogate markers, selective reporting of results. |
| Couto et al 2014(28) | Systematic review and meta-analysis | Impact of catch-up vaccination on girls aged 16+ | Monovalent HPV-16 vaccine, PATRICIA, FUTURE III, HPV-001/007/023, V501-007, FUTURE I, FUTURE II | • Acknowledges important differences in inclusion criteria for the different trials, limiting generalizability of the findings to the target population for catch-up vaccination<br>• Borderline protective effect of a HPV catch-up vaccination on all CIN2+, with a pooled RR of 0.80 (95% CI: 0.62-1.02) for a follow-up period of 4 years |
| Delere et al 2014(29) | Systematic Review and Meta-analysis | Short- and long-term efficacy | FUTURE I, FUTURE II, HPV-001/007/023, CVT, Konno, PATRICIA, V501-007 | • Based on just seven trials<br>• Combined CIN2+ associated with any HPV type and vaccine types in the same analysis |
| Miltz et al 2014(30) | Systematic review and Meta-analysis | Women with evidence of prior exposure, CIN3+ | PATRICIA (Lehtinen 12), FUTURE III (Castellsague), Olsson 2009 meta-analysis, Joura 2007 (non-cervical outcomes) | • No evidence that vaccination prevents vaccine type HPV cervical pre-cancer in women with evidence of prior HPV exposure<br>• Reviewers did not separate women with seropositive status (indicating past infection) from those DNA positive (indicating on-going infection) |
| DiMario et al 2015(31) | Systematic review and Meta-analysis | Comparison of Cervarix and Gardasil | PATRICIA, Konno, FUTURE I, FUTURE II, HPV-001/007 | • Noted a difference in efficacy between the two vaccines in the TVC-naïve cohort against CIN2+ due to any HPV type (higher efficacy with Cervarix). |

| | | | | |
|---|---|---|---|---|
| | | | | • The authors requested single patient data from both GSK and Sanofi Pasteur MSD but these requests were not met.<br>• Noticed significant heterogeneity between the trials, that data were often "differently and poorly reported" and length of follow-up was insufficient.<br>• Only considered five trials |
| Kreimer et al 2015(32) | Meta-analysis | Cervarix efficacy with 1 vs. 2 vs. 3 doses | PATRICIA, CVT | • Post-hoc analysis<br>• Primary endpoint incident infection (not considered adequate surrogate endpoint) |
| Angioli et al 2016(33) | Systematic review | Vaccine efficacy and safety | HPV-001/007/023, V501-007, PATRICIA, CVT, FUTURE I, FUTURE II, Gardasil 9 trial | • Only considered seven trials<br>• Did not discuss the issues raised by the heterogeneity of the trials. |
| Skinner et al 2016(34) | Systematic review | Efficacy of Cervarix | HPV-001/007/023, PATRICIA, CVT, VIVIANE, Konno, Zhu | • Paper funded by GSK<br>• Discussed challenges of proving cross-protection as many lesions contained multiple HPV types |
| Tota et al 2017(35) | Meta-analysis | Risk of type-replacement with Cervarix | PATRICIA, CVT | • Looked at incident infection<br>• Only looked at data from two trials |
| Haghshenas et al 2017(36) | Meta-analysis | Efficacy against CIN1+ | V501-005 (Monovalent HPV-16 vaccine, Mao), Perex meta-analysis (see above), | • Looked at combined surrogate endpoint of CIN1+<br>• Did not include all relevant studies |
| Mousavi et al 2017(37) | Meta-analysis | Efficacy against persistent HPV infection | V501-007, V501-027, HPV-001, PATRICIA (Paavonen 07), V501-005 (monovalent HPV-16 vaccine), Perez meta-analysis (see above), Majewski meta-analysis (see above) | • Did not include all relevant studies<br>• Did not take heterogeneity into account |
| WHO Position Paper 2017 (38) | Systematic review | Efficacy, and safety | FUTURE I, FUTURE II, V501-007, HPV-001/007/023, PATRICIA (Interim analysis), Schiller 12 review | • Acknowledge that definition of persistent infection of six months is not universally accepted<br>• 'Current evidence suggests the 3 licensed HPV vaccines have relatively similar effectiveness in preventing cervical cancer'- no trials have shown impact on cervical cancer rates.<br>• 'WHO recommends all countries proceed with nationwide introduction of HPV vaccination' |

| | | | | |
|---|---|---|---|---|
| | | | | • 'Low confidence of scientific evidence that HPV vaccination provides long term protection' |
| Arbyn et al 2018(39) | Cochrane Systematic review and Meta-analysis | Efficacy against CIN2+ and CIN3+ for vaccine-type HPV and irrespective of HPV type | V501-005 (monovalent HPV-16 vaccine), HPV-001/007/023, Konno, PATRICIA, CVT, VIVIANE, Zhu, V501-007, FUTURE I, FUTURE II, FUTURE III, V501-027 | • Included all efficacy trials<br>• Focussed on CIN2+ but did not discuss the concerns with this surrogate marker<br>• Did not discuss the issue of type-replacement<br>• Acknowledged that there was trial heterogeneity and that this affected efficacy<br>• Considered the results of the HPV-16 monovalent vaccine trial which we have excluded<br>• For CIN3+ in HPV-naïve women included results from non-blinded follow-up of Konno<br>• For CIN3+ in women regardless of HPV status did not acknowledge restrictions on trial eligibility which mean women in trials likely less HPV exposure than general population<br>• Did not comment on the small remaining number of participants in the trials used as evidence of prolonged vaccine efficacy. |

**References**


1. Schmiedeskamp MR, Kockler DR. Human papillomavirus vaccines. Ann Pharmacother. 2006;40(7-8):1344-52.
2. Group FIS. Prophylactic efficacy of a quadrivalent human papillomavirus (HPV) vaccine in women with virological evidence of HPV infection. J Infect Dis. 2007;196(10):1438-46.
3. La Torre G, de Waure C, Chiaradia G, Mannocci A, Ricciardi W. HPV vaccine efficacy in preventing persistent cervical HPV infection: a systematic review and meta-analysis. Vaccine. 2007;25(50):8352-8.
4. Rambout L, Hopkins L, Hutton B, Fergusson D. Prophylactic vaccination against human papillomavirus infection and disease in women: a systematic review of randomized controlled trials. Cmaj. 2007;177(5):469-79.
5. Ault KA. 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. The Lancet. 2007;369(9576):1861-8.
6. Barr E, Gause CK, Bautista OM, Railkar RA, Lupinacci LC, Insinga RP, et al. Impact of a prophylactic quadrivalent human papillomavirus (types 6, 11, 16, 18) L1 virus-like particle vaccine in a sexually active population of North American women. Am J Obstet Gynecol. 2008;198(3):261 e1-11.

7. Harper DM. Impact of vaccination with Cervarix (trade mark) on subsequent HPV-16/18 infection and cervical disease in women 15-25 years of age. Gynecol Oncol. 2008;110(3 Suppl 1):S11-7.
8. Joura EA, Kjaer SK, Wheeler CM, Sigurdsson K, Iversen OE, Hernandez-Avila M, et al. HPV antibody levels and clinical efficacy following administration of a prophylactic quadrivalent HPV vaccine. Vaccine. 2008;26(52):6844-51.
9. Perez G, Lazcano-Ponce E, Hernandez-Avila M, Garcia PJ, Munoz N, Villa LL, et al. Safety, immunogenicity, and efficacy of quadrivalent human papillomavirus (types 6, 11, 16, 18) L1 virus-like-particle vaccine in Latin American women. Int J Cancer. 2008;122(6):1311-8.
10. Tay EH, Garland S, Tang G, Nolan T, Huang LM, Orloski L, et al. Clinical trial experience with prophylactic HPV 6/11/16/18 VLP vaccine in young women from the Asia-Pacific region. Int J Gynaecol Obstet. 2008;102(3):275-83.
11. Brown DR, Kjaer SK, Sigurdsson K, Iversen OE, Hernandez-Avila M, Wheeler CM, et al. The impact of quadrivalent human papillomavirus (HPV; types 6, 11, 16, and 18) L1 virus-like particle vaccine on infection and disease due to oncogenic nonvaccine HPV types in generally HPV-naive women aged 16-26 years. J Infect Dis. 2009;199(7):926-35.
12. Damm O, Nocon M, Roll S, Vauth C, Willich S, Greiner W. Human papillomavirus (HPV) vaccination for the prevention of HPV 16/18 induced cervical cancer and its precursors. GMS Health Technol Assess. 2009;5:Doc04.
13. Kjaer SK, Sigurdsson K, Iversen OE, Hernandez-Avila M, Wheeler CM, Perez G, et al. A pooled analysis of continued prophylactic efficacy of quadrivalent human papillomavirus (Types 6/11/16/18) vaccine against high-grade cervical and external genital lesions. Cancer Prev Res (Phila). 2009;2(10):868-78.
14. Lazcano-Ponce E, Perez G, Cruz-Valdez A, Zamilpa L, Aranda-Flores C, Hernandez-Nevarez P, et al. Impact of a quadrivalent HPV6/11/16/18 vaccine in Mexican women: public health implications for the region. Arch Med Res. 2009;40(6):514-24.
15. Majewski S, Bosch FX, Dillner J, Iversen OE, Kjaer SK, Munoz N, et al. The impact of a quadrivalent human papillomavirus (types 6, 11, 16, 18) virus-like particle vaccine in European women aged 16 to 24. J Eur Acad Dermatol Venereol. 2009;23(10):1147-55.
16. Medeiros LR, Rosa DD, da Rosa MI, Bozzetti MC, Zanini RR. Efficacy of human papillomavirus vaccines: a systematic quantitative review. Int J Gynecol Cancer. 2009;19(7):1166-76.
17. Olsson SE, Kjaer SK, Sigurdsson K, Iversen OE, Hernandez-Avila M, Wheeler CM, et al. Evaluation of quadrivalent HPV 6/11/16/18 vaccine efficacy against cervical and anogenital disease in subjects with serological evidence of prior vaccine type HPV infection. Hum Vaccin. 2009;5(10):696-704.
18. Wheeler CM, Kjaer SK, Sigurdsson K, Iversen OE, Hernandez-Avila M, Perez G, et al. The impact of quadrivalent human papillomavirus (HPV; types 6, 11, 16, and 18) L1 virus-like particle vaccine on infection and disease due to oncogenic nonvaccine HPV types in sexually active women aged 16-26 years. J Infect Dis. 2009;199(7):936-44.

19. Group FIIS, Dillner J, Kjaer SK, Wheeler CM, Sigurdsson K, Iversen OE, et al. Four year efficacy of prophylactic human papillomavirus quadrivalent vaccine against low grade cervical, vulvar, and vaginal intraepithelial neoplasia and anogenital warts: randomised controlled trial. Bmj. 2010;341:c3493.
20. 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(5):325-39.
21. Ault KA, Joura EA, Kjaer SK, Iversen OE, Wheeler CM, Perez G, et al. Adenocarcinoma in situ and associated human papillomavirus type distribution observed in two clinical trials of a quadrivalent human papillomavirus vaccine. Int J Cancer. 2011;128(6):1344-53.
22. Lu B, Kumar A, Castellsague X, Giuliano AR. Efficacy and safety of prophylactic vaccines against cervical HPV infection and diseases among women: a systematic review & meta-analysis. BMC Infect Dis. 2011;11:13.
23. Haupt RM, Wheeler CM, Brown DR, Garland SM, Ferris DG, Paavonen JA, et al. Impact of an HPV6/11/16/18 L1 virus-like particle vaccine on progression to cervical intraepithelial neoplasia in seropositive women with HPV16/18 infection. Int J Cancer. 2011;129(11):2632-42.
24. Joura EA, Garland SM, Paavonen J, Ferris DG, Perez G, Ault KA, et al. Effect of the human papillomavirus (HPV) quadrivalent vaccine in a subgroup of women with cervical and vulvar disease: retrospective pooled analysis of trial data. Bmj. 2012;344:e1401.
25. Malagón T, Drolet M, Boily M-C, Franco EL, Jit M, Brisson J, et al. Cross-protective efficacy of two human papillomavirus vaccines: a systematic review and meta-analysis. The Lancet Infectious Diseases. 2012;12(10):781-9.
26. Clark LR, Myers ER, Huh W, Joura EA, Paavonen J, Perez G, et al. Clinical trial experience with prophylactic human papillomavirus 6/11/16/18 vaccine in young black women. J Adolesc Health. 2013;52(3):322-9.
27. Tomljenovic L, Spinosa JP, Shaw CA. Human papillomavirus (HPV) vaccines as an option for preventing cervical malignancies: (how) effective and safe? Current pharmaceutical design. 2013;19(8):1466-87.
28. Couto E, Saeterdal I, Juvet LK, Klemp M. HPV catch-up vaccination of young women: a systematic review and meta-analysis. BMC Public Health. 2014;14:867.
29. Delere Y, Wichmann O, Klug SJ, van der Sande M, Terhardt M, Zepp F, et al. The Efficacy and Duration of Vaccine Protection Against Human Papillomavirus: A Systematic Review and Meta-analysis. Dtsch Arztebl Int. 2014;111(35-36):584-91.
30. Miltz A, Price H, Shahmanesh M, Copas A, Gilson R. Systematic review and meta-analysis of L1-VLP-based human papillomavirus vaccine efficacy against anogenital pre-cancer in women with evidence of prior HPV exposure. PLoS One. 2014;9(3):e90348.
31. Di Mario S, Basevi V, Lopalco PL, Balduzzi S, D'Amico R, Magrini N. Are the Two Human Papillomavirus Vaccines Really Similar? A Systematic Review of Available Evidence: Efficacy of the Two Vaccines against HPV. J Immunol Res. 2015;2015:435141.

32. Kreimer AR, Struyf F, Del Rosario-Raymundo MR, Hildesheim A, Skinner SR, Wacholder S, et al. Efficacy of fewer than three doses of an HPV-16/18 AS04-adjuvanted vaccine: combined analysis of data from the Costa Rica Vaccine and PATRICIA Trials. Lancet Oncol. 2015;16(7):775-86.
33. Angioli R, Lopez S, Aloisi A, Terranova C, De Cicco C, Scaletta G, et al. Ten years of HPV vaccines: State of art and controversies. Critical reviews in oncology/hematology. 2016;102:65-72.
34. Skinner SR, Apter D, De Carvalho N, Harper DM, Konno R, Paavonen J, et al. Human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine for the prevention of cervical cancer and HPV-related diseases. Expert Rev Vaccines. 2016;15(3):367-87.
35. Tota JE, Struyf F, Merikukka M, Gonzalez P, Kreimer AR, Bi D, et al. Evaluation of Type Replacement Following HPV16/18 Vaccination: Pooled Analysis of Two Randomized Trials. J Natl Cancer Inst. 2017;109(7).
36. Haghshenas MR, Mousavi T, Kheradmand M, Afshari M, Moosazadeh M. Efficacy of Human Papillomavirus L1 Protein Vaccines (Cervarix and Gardasil) in Reducing the Risk of Cervical Intraepithelial Neoplasia: A Meta-analysis. Int J Prev Med. 2017;8:44.
37. Mousavi T, Moosazadeh M, Afshari M, Davoodi L, Haghshenas M. Efficacy of L1 protein vaccines against cervical and vaginal cancer: A systematic review and meta-analysis. Iranian Red Crescent Medical Journal. 2017;19(4).
38. World Health Organization. Human papillomavirus vaccines: WHO position paper. WHO Weekly epidemiological record [Internet]. 2017 [cited 2018 04 August]; 92(19):[241-68 pp.]. Available from: http://apps.who.int/iris/bitstream/handle/10665/255353/WER9219.pdf;jsessionid=F3DCFC97BAD6862E5437EFDAE3B58E2E?sequence=1.
39. Arbyn M, Xu L, Simoens C, Martin-Hirsch PP. Prophylactic vaccination against human papillomaviruses to prevent cervical cancer and its precursors. The Cochrane database of systematic reviews. 2018;5:CD009069.

**Supplement 4. Efficacy against CIN3/AIS in HPV-naïve women**

| Vaccine / Trial | Paper | Subgroup | CIN3/AIS due to HPV 16/18 | CIN3/AIS due to any HPV type |
|---|---|---|---|---|

| | | | **Specific outcome** | **Number with outcome/ vaccinated cohort** | **Number with outcome/ placebo cohort** | **VE = Vaccine Efficacy (95%CI)** | **Specific outcome** | **Number with outcome/vaccinated cohort** | **Number with outcome/placebo cohort** | **VE = Vaccine Efficacy (95%CI)** |
|---|---|---|---|---|---|---|---|---|---|---|
| Cervarix / PATRICIA | Lehtinen 12(30) | TVC-naive | CIN3/AIS | 0/5466 | 27/5452 | 100% (85.5, 100) | CIN3/AIS | 3/5466 | 44/5452 | 93.2% (78.9, 98.7) |
| Cervarix / PATRICIA | Lehtinen 12(30) | TVC-naive | AIS | 0/5466 | 6/5452 | 100% (15.5, 100) | AIS | 0/5466 | 7/5452 | 100% (31.0, 100) |
| Gardasil / Meta-analysis of FUTURE I and FUTURE II | Munoz 10(56) | Negative to 14 HPV types population | CIN3 | 0/4616 vs | 41/4680 | 100% (90.5, 100) | CIN3 | 36/4616 | 64/4680 | 43% (13, 63.2) |
| | | | AIS | 0/4616 | 3/4680 | 100% (<0 , 100) | AIS | 0/4616 | 3/4680 | 100% (<0, 100) |
| FUTURE II | FUTURE II Study Group(49) | Per-protocol susceptible population | CIN3 | 1/5305 | 29/5260 | 97 (79, 100) | Results not given | Results not given | Results not given | Results not given |
| FUTURE II | FUTURE II Study Group(49) | Per-protocol | AIS | 0/5305 | 1/5260 | 100 (<0, 100) | Results not given | Results not given | Results not given | Results not given |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | susceptible population | | | | | | | | |

Supplement 4 Footnote: We have included the Munoz meta-analysis of FUTURE I and FUTURE II as it presents outcomes not given in the original trial papers.(48, 49) FUTURE I only gave results for CIN3 and AIS due to HPV6/11/16/18 combined, in both FUTURE I and FUTURE II papers results for CIN3+ due to any HPV type were only given for ITT subgroup.

**Supplement 5. Vaccine efficacy against 12-month persistent infection in HPV-naïve women**

| **Vaccine/Trial** | **Paper** | **Subgroup** | **12-month persistent infection due to HPV 16/18** | | | **12-month persistent infection due to any oncogenic type** | | |
|---|---|---|---|---|---|---|---|---|
| | | | **Number with outcome/ vaccinated cohort** | **Number with outcome/ placebo cohort** | **VE = Vaccine Efficacy (95%CI) p-value where given** | **Number with outcome/ vaccinated cohort** | **Number with outcome/ placebo cohort** | **VE = Vaccine Efficacy (95%CI) p-value where given** |
| Cervarix/ Konno | Konno Jul 10(27) | TVC-E | 0/406 | 9/411 | 100% (47.4, 100) p=0.0037 | 19/443 | 37/441 | 50.1% (9.8, 73.2) p=0.013 |
| Cervarix/ Zhu | Zhu 17(45) | ATP-E | 1/2425 | 32/2455 | 96.9% (81.1, 99.9) | 192/2703 | 215/2714 | 10.4% (-9.3, 26.7) |
| Cervarix/ PATRICIA | Szarewski 12(33) | TVC stratified by HPV 16/18 PCR negative and seronegative | 51/7844 | 341/7854 | 85.3% (80.0, 89.5) | Not given | Not given | Not given |
| Cervarix/ PATRICIA | Paavonen 09(29) | ATP-E | Not given | Not given | Not given | 549/7509 | 760/7488 | 28.9% (20.1, 36.8) p<0.0001 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Cervarix/ HPV-023 | Naud 14(25) | ATP-E | 0/193 | 10/175 | 100% (61.4, 100) | 36/179 | 36/158 | 12.9% (-42.3, 46.7) |

## Supplement 6. Results from trials testing cross-protection against non-vaccine HPV types

## Statistically significant results given in bold

| Vaccine | Trial, Sub-group, Outcome | HPV type | Number with outcome/ vaccinated cohort | Number with outcome/ placebo cohort | VE = Vaccine Efficacy (95%CI) |
|---|---|---|---|---|---|
| Cervarix | CVT(1) Herrero et al, 11 supplementary analysis, ATP, 12 month persistent infection | **31** | **21/2525** | **39/2546** | **45.7% (8.2, 68.6)** |
| | | 33 | 8/2596 | 13/2645 | 37.3% (-51.4, 75.3) |
| | | 35 | 11/2593 | 13/2631 | 14.1% (-94.0, 62.5) |
| | | 52 | 60/2456 | 51/2505 | -20.0% (-74.9, 17.4) |
| | | 58 | 23/2551 | 22/2595 | -6.3% (-92.4, 41.1) |
| | | 39 | 24/2528 | 23/2581 | -6.5% (-90.2, 40.2) |
| | | 45 | 8/2573 | 17/2622 | 52.0% (-9.8, 80.4) |
| | | 59 | 17/2576 | 10/2637 | -74.0% (-295.1, 20.1) |
| | | 68-73 | 19/2519 | 18/2576 | -7.9% (-108.1, 43.8) |
| | | **51** | **57/2453** | **36/2539** | **-63.9% (-150.7, -8.2)** |
| | | 56 | 22/2524 | 30/2564 | 25.5% (-29.2, 57.5) |
| | | 66 | 32/2521 | 33/2565 | 1.3% (-61.1, 39.6) |
| | PATRICIA Wheeler et al 12-supplementary analysis(2), ATP, 12 month persistent infection | **31** | **30/7295** | **136/7309** | **78.1% (67.2, 85.7)** |
| | | **33** | **38/7426** | **59/7404** | **35.8% (1.9, 58.5)** |
| | | 35 | 37/7468 | 26/7462 | -42.6% (-145.2, 16.0) |
| | | 52 | 200/7185 | 205/7134 | 3.0% (-18.5, 20.6) |
| | | **58** | **83/7411** | **54/7403** | **-54.1% (-121.3, -8.1)** |
| | | 39 | 86/7322 | 86/7322 | -0.2% (-36.7, 26.6) |
| | | **45** | **13/7485** | **32/7445** | **59.6% (20.8, 80.5)** |
| | | 59 | 27/7425 | 20/7422 | -35.2% (-154.3, 26.9) |

| | | | | | |
|---|---|---|---|---|---|
| | | 68 | 76/7344 | 75/7321 | -1.1% (-41.1, 27.5) |
| | | 51 | 149/7089 | 192/7061 | **22.8% (3.8, 38.1)** |
| | | 56 | 104/7357 | 91/7343 | -14.4% (-53.3, 14.5) |
| | | 66 | 92/7307 | 92/7266 | 0.4% (-34.5, 26.2) |
| | VIVIANE(3),<br>ATP,<br>6 month persistent infection | **31** | **10/2073** | **29/2090** | **65.8% (24.9, 85.8)** |
| | | 33 | 12/2105 | 9/2094 | -32.0% (-275.2, 51.5) |
| | | 35 | 11/2112 | 17/2101 | 36.2% (-50.8, 74.3) |
| | | 52 | 54/2060 | 56/2058 | 4.9% (-44.0, 37.2) |
| | | 58 | 24/2098 | 19/2092 | -25.3% (-151.0, 35.5) |
| | | 39 | 34/2097 | 26/2078 | -28.8% (-130.7, 27.1) |
| | | **45** | **9/2106** | **30/2088** | **70.7% (34.2, 88.4)** |
| | | 59 | 22/2105 | 21/2083 | -3.0% (-104.0, 47.9) |
| | | 68 | 31/2084 | 33/2085 | 7.0% (-61.3, 46.5) |
| | | 51 | 48/2071 | 42/2072 | -13.6% (-80.6, 28.3) |
| | | 56 | 28/2100 | 30/2081 | 8.4% (-63.6, 48.9) |
| | | 66 | 45/2089 | 49/2080 | 9.2% (-9.3, 24.4) |
| | Zhu(4)<br>ATP-E, 12 month persistent infection | **31** | **3/2671** | **16/2676** | **81.2% (34.4, 96.5)** |
| | | 33 | 8/2663 | 9/2675 | 10.6% (-161.2, 70.0) |
| | | 35 | 11/2686 | 9/2695 | -22.9% (-235.5, 53.7) |
| | | 52 | 70/2553 | 63/2569 | -12.4% (-60.5, 21.2) |
| | | 58 | 15/2656 | 18/2661 | 16.4% (−75.8, 60.8) |
| | | 39 | 15/2641 | 22/2664 | −14.8% (−113.6, 37.9) |
| | | 45 | 5/2674 | 2/2694 | −152.3% (−2549.9, 58.7) |
| | | 59 | 7/2694 | 2/2687 | −250.2 % (−3355.0, 33.3) |
| | | 68 | 12/2659 | 12/2675 | −0.8% (−145.3, 58.6) |
| | | 51 | 28/2639 | 24/2647 | −17.6% (−112.0, 34.3) |
| | | 56 | 14/2665 | 11/2672 | −27.9% (−211.3, 46.1) |
| | | 66 | 17/2662 | 10/2657 | −70.3% (−316.2, 26.4) |
| Gardasil | FUTURE I & FUTURE II – meta-analysis by Brown et al 09(5),<br>Efficacy population negative for 14 HPV types,<br>6 month persistent infection | **31** | **31/cohort total not given** | **57/ cohort total not given** | **46.2% (15.3, 66.4)** |
| | | 33 | 15/ cohort total not given | 21/ cohort total not given | 28.7% (-45.1, 65.8) |
| | | 35 | 14/ cohort total not given | 17/ cohort total not given | 17.8% (-77.1, 62.5) |
| | | 45 | 24/ cohort total not given | 26/ cohort total not given | 7.8% (-67.0, 49.3) |
| | | 58 | 35/ cohort total not given | 37/ cohort total not given | 5.5% (-54.3, 42.2) |

| | | | | | |
|---|---|---|---|---|---|
| | | 52 | 50/ cohort total not given | 61/ cohort total not given | 18.4% (-20.6, 45.0) |
| | | 59 | 45/ cohort total not given | 55/ cohort total not given | 18.7 (-22.8, 46.4) |

**References**


1. Herrero R, Wacholder S, Rodriguez AC, Solomon D, Gonzalez P, Kreimer AR, et al. Prevention of persistent human papillomavirus infection by an HPV16/18 vaccine: a community-based randomized clinical trial in Guanacaste, Costa Rica. Cancer Discov. 2011;1(5):408-19.
2. Wheeler CM, Castellsague X, Garland SM, Szarewski A, Paavonen J, Naud P, et al. Cross-protective efficacy of HPV-16/18 AS04-adjuvanted vaccine against cervical infection and precancer caused by non-vaccine oncogenic HPV types: 4-year end-of-study analysis of the randomised, double-blind PATRICIA trial. Lancet Oncol. 2012;13(1):100-10.
3. Wheeler CM, Skinner SR, Del Rosario-Raymundo MR, Garland SM, Chatterjee A, Lazcano-Ponce E, et al. Efficacy, safety, and immunogenicity of the human papillomavirus 16/18 AS04-adjuvanted vaccine in women older than 25 years: 7-year follow-up of the phase 3, double-blind, randomised controlled VIVIANE study. Lancet Infect Dis. 2016;16(10):1154-68.
4. Zhu FC, Hu SY, Hong Y, Hu YM, Zhang X, Zhang YJ, et al. Efficacy, immunogenicity, and safety of the HPV-16/18 AS04-adjuvanted vaccine in Chinese women aged 18-25 years: event-triggered analysis of a randomized controlled trial. Cancer medicine. 2017;6(1):12-25.
5. Brown DR, Kjaer SK, Sigurdsson K, Iversen OE, Hernandez-Avila M, Wheeler CM, et al. The impact of quadrivalent human papillomavirus (HPV; types 6, 11, 16, and 18) L1 virus-like particle vaccine on infection and disease due to oncogenic nonvaccine HPV types in generally HPV-naive women aged 16-26 years. J Infect Dis. 2009;199(7):926-35.

**Supplement 7. Definition of trial sub-groups and sub-groups used in each trial**

| Sub-group | Trials using sub-group (papers using sub-group referenced) In bold where sub-group used for powered outcomes | Characteristics of subgroup | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Negative on PCR on day 1 for relevant HPV type | Remained PCR negative to relevant HPV type to month 7 (1 mth after third dose) | Remained PCR negative to relevent HPV type on month 6 | Negative on serology on day 1 for relevant HPV type | Received 3 doses within a year | No protocol violations | Included even if abnormal cytology on day 1 | Other criteria | Start of case counting |
| **Total Vaccine Cohort (TVC)** | CVT(1) | - | n/a | n/a | - | - | - | + | Sexually active or became sexually active during the trial; Provided cervical samples | Not specified |
| **NRT-Unrestricted susceptible population (known as HNRT in V501-041)** | FUTURE I(2), FUTURE II(3), FUTURE III(4, 5), V501-041(6) | + | - | - | + | - | - | + | | Day after first vaccine (V501-005 Day 1) |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Modified Intention To Treat** | V501-007(7, 8) | + | - | - | + | - | - | + | | 30 days after day 1 |
| **Primary analysis** | CVT(9) | + | - | - | - | - | - | + | | Month 6 |
| **TVC-E (1)** | Zhu(10, 11), Konno(12), VIVIANE(13, 14) | + | - | - | + (Skinner + for HPV16/18) | - | | Excluded if high-grade or missing cytology | | Day after first vaccine |
| **TVC-E (2)** | Konno(15), **PATRICIA**(16, 17) | - | n/a | n/a | - | - | - | Excluded if high-grade or missing cytology | | Day affter first vaccine (? Day after first vaccine- Konno Apr 10) |
| **Other** | PATRICIA(18) | + | - | - | - | Not specified | Not specified | Not specified | | ?Day after first vaccine |
| **Naïve cohort** | CVT(1) | + | n/a | + | + | - | - | Excluded if CIN2+at baseline | No biopsy or treatment before 6 month visit; sexually active or became sexually active during the trial | ?Month 6 |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **TVC-naïve** | PATRICIA(17, 19, 20) | DNA negative for all 14 oncogenic types at month 0 | - | - | Seronegative for HPV 16 and 18 | - | | Normal cytology at month 0 | | Day after first vaccine |
| **ITT (1)** | **HPV-001(21). HPV-007**(22, 23), HPV-023(24-26) | DNA negative for HR HPV DNA at month 0 | - | - | - | - | - | + | | Month 6 |
| **ITT (2) (Known as Full Analysis Set (FAS) Population in V501-041)** | FUTURE I(2), FUTURE II(27), FUTURE III(4, 5), **CVT(28)**, VIVIANE(13, 14), VPATRICIA(17, 19, | - | n/a | n/a | - | - | - | + | | Day after first vaccine (V501-005 Day 1) Herrero- not documented) |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | 20, 29), V501-041(6) | | | | | | | | | |
| **ATP-E (1)** | **PATRICIA(17, 20)** | + | - | - | + | + | + | Excluded if high-grade or missing cytology | | Day after third vaccine |
| **ATP- Per-protocol efficacy analysis (2)** | **FUTURE I(2)**, **FUTURE II(27)**, FUTURE III(4, 5), V501-007(7, 8), **V501-027(30), V501-041(6)** | + | + | n/a | + | + | + | + | | Month 7 |
| **ATP cohort for efficacy (ATP-E) (3)** | **Zhu(10, 11)**, **Konno(12, 15), VIVIANE (13, 14)** | + | n/a | + | + (Skinner + for vaccine types, - for non-vaccine types) | + | + | Excluded if high-grade or missing cytology | | Month 6 |
| **According to Protocol** | **CVT(28, 31)** | + | n/a | + | - | + | + | + | | Month 6 |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **(ATP) cohort (1)** | | | | | | | | | | |
| **ATP (2)** | **HPV-001(21), HPV-007(22, 23), HPV-023(24-26)** | DNA negative for HR HPV DNA at month 0 | n/a | Negative to HPV 16/18 DNA | Seronegative for HPV 16/18 | + | + | Normal cytology at month 0 | | Month 6 |

This table gives the inclusion criteria for each of the sub-groups included in the trials and the list of trials that use each sub-group.

**References**


1. Rodriguez AC, Solomon D, Herrero R, Hildesheim A, Gonzalez P, Wacholder S, et al. Impact of human papillomavirus vaccination on cervical cytology screening, colposcopy, and treatment. Am J Epidemiol. 2013;178(5):752-60.
2. 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(19):1928-43.
3. Future II Study Group. Quadrivalent vaccine against human papillomavirus to prevent high-grade cervical lesions. N Engl J Med. 2007;356(19):1915-27.
4. 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(9679):1949-57.
5. 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(1):28-37.
6. Wei L, Xie X, Liu J, Zhao Y, Chen W, Zhao C, et al. Efficacy of quadrivalent human papillomavirus vaccine against persistent infection and genital disease in Chinese women: A randomized, placebo-controlled trial with 78-month follow-up. Vaccine. 2018.
7. 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(11):1459-66.
8. Villa LL, Costa RLR, 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. The Lancet Oncology. 2005;6(5):271-8.
9. Kreimer AR, Rodriguez AC, Hildesheim A, Herrero R, Porras C, Schiffman M, et al. Proof-of-principle evaluation of the efficacy of fewer than three doses of a bivalent HPV16/18 vaccine. Journal of the National Cancer Institute. 2011;103(19):1444-51.
10. Zhu F-C, Chen W, Hu Y-M, Hong Y, Li J, Zhang X, et al. Efficacy, immunogenicity and safety of the HPV-16/18 AS04-adjuvanted vaccine in healthy Chinese women aged 18-25 years: Results from a randomized controlled trial. International Journal of Cancer. 2014;135(11):2612-22.
11. Zhu FC, Hu SY, Hong Y, Hu YM, Zhang X, Zhang YJ, et al. Efficacy, immunogenicity, and safety of the HPV-16/18 AS04-adjuvanted vaccine in Chinese women aged 18-25 years: event-triggered analysis of a randomized controlled trial. Cancer medicine. 2017;6(1):12-25.
12. Konno R, Tamura S, Dobbelaere K, Yoshikawa H. Efficacy of human papillomavirus type 16/18 AS04-adjuvanted vaccine in Japanese women aged 20 to 25 years: final analysis of a phase 2 double-blind, randomized controlled trial. Int J Gynecol Cancer. 2010;20(5):847-55.
13. 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(9961):2213-27.
14. Wheeler CM, Skinner SR, Del Rosario-Raymundo MR, Garland SM, Chatterjee A, Lazcano-Ponce E, et al. Efficacy, safety, and immunogenicity of the human papillomavirus 16/18 AS04-adjuvanted vaccine in women older than 25 years: 7-year follow-up of the phase 3, double-blind, randomised controlled VIVIANE study. Lancet Infect Dis. 2016;16(10):1154-68.

15. Konno R, Tamura S, Dobbelaere K, Yoshikawa H. Efficacy of human papillomavirus 16/18 AS04-adjuvanted vaccine in Japanese women aged 20 to 25 years: interim analysis of a phase 2 double-blind, randomized, controlled trial. Int J Gynecol Cancer. 2010;20(3):404-10.
16. 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(9580):2161-70.
17. 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(9686):301-14.
18. Palmroth J, Merikukka M, Paavonen J, Apter D, Eriksson T, Natunen K, et al. Occurrence of vaccine and non-vaccine human papillomavirus types in adolescent Finnish females 4 years post-vaccination. Int J Cancer. 2012;131(12):2832-8.
19. 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(1):89-99.
20. Wheeler CM, Castellsague X, Garland SM, Szarewski A, Paavonen J, Naud P, et al. Cross-protective efficacy of HPV-16/18 AS04-adjuvanted vaccine against cervical infection and precancer caused by non-vaccine oncogenic HPV types: 4-year end-of-study analysis of the randomised, double-blind PATRICIA trial. Lancet Oncol. 2012;13(1):100-10.
21. 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. The Lancet. 2004;364(9447):1757-65.
22. 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(9518):1247-55.
23. Romanowski B, de Borba PC, Naud PS, Roteli-Martins CM, De Carvalho NS, Teixeira JC, 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(9706):1975-85.
24. De Carvalho N, Teixeira J, Roteli-Martins CM, Naud P, De Borba P, Zahaf T, et al. Sustained efficacy and immunogenicity of the HPV-16/18 AS04-adjuvanted vaccine up to 7.3 years in young adult women. Vaccine. 2010;28(38):6247-55.
25. 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(8):2147-62.
26. Roteli-Martins CM, Naud P, De Borba P, Teixeira JC, De Carvalho NS, Zahaf T, et al. Sustained immunogenicity and efficacy of the HPV-16/18 AS04-adjuvanted vaccine: up to 8.4 years of follow-up. Hum Vaccin Immunother. 2012;8(3):390-7.
27. Group FIS. Prophylactic efficacy of a quadrivalent human papillomavirus (HPV) vaccine in women with virological evidence of HPV infection. J Infect Dis. 2007;196(10):1438-46.
28. Herrero R, Wacholder S, Rodriguez AC, Solomon D, Gonzalez P, Kreimer AR, et al. Prevention of persistent human papillomavirus infection by an HPV16/18 vaccine: a

community-based randomized clinical trial in Guanacaste, Costa Rica. Cancer Discov. 2011;1(5):408-19.
29. Szarewski A, Skinner SR, Garland SM, Romanowski B, Schwarz TF, Apter D, et al. Efficacy of the HPV-16/18 AS04-adjuvanted vaccine against low-risk HPV types (PATRICIA randomized trial): an unexpected observation. J Infect Dis. 2013;208(9):1391-6.
30. Yoshikawa H, Ebihara K, Tanaka Y, Noda K. Efficacy of quadrivalent human papillomavirus (types 6, 11, 16 and 18) vaccine (GARDASIL) in Japanese women aged 18-26 years. Cancer Sci. 2013;104(4):465-72.
31. Hildesheim A, Wacholder S, Catteau G, Struyf F, Dubin G, Herrero R, et al. Efficacy of the HPV-16/18 vaccine: final according to protocol results from the blinded phase of the randomized Costa Rica HPV-16/18 vaccine trial. Vaccine. 2014;32(39):5087-97.

## Supplement 8. Type assignment in disease endpoints

| Vaccine and Trial | Method used |
|---|---|
| **Cervarix**<br>**HPV-001/ 007/ 023** | HPV 16/18 infection detected in cytology specimen prior to colposcopy. Positive if contained HPV16 or 18 regardless of whether other HPV types detected.(1) |
| **Cervarix**<br>**Konno** | DNA testing from cytology specimen.(2) |
| **Cervarix**<br>**PATRICIA** | In PATRICIA trial primary analysis was on the basis of HPV16/18 being found in a lesion, they also did an additional analysis in Szarewski's paper where they attributed causality in specimens where more than one HPV type was found based on finding the same HPV in one of two preceding cytological samples.(3) |
| **Cervarix**<br>**Costa Rica Vaccine Trial (CVT)** | Attributed causality when more than one HPV type was found in a lesion as an exploratory analysis(4) |
| **Cervarix**<br>**VIVIANE** | Tried to attribute causality when more than one HPV type was found in a lesion(5) |

| | |
|---|---|
| **Cervarix**<br>**Zhu** | Tried to attribute causality when more than one HPV type was found in a lesion(6) |
| **Gardasil**<br>**V501-007** | Required evidence of persistent rather than incident infection with HPV DNA of the same type found in previous samples(7) |
| **Gardasil**<br>**FUTURE I** | HPV DNA to be found in an adjacent histologic section of the same biopsy site(8) |
| **Gardasil**<br>**FUTURE II** | HPV DNA to be found in an adjacent histologic section of the same biopsy site(9) |
| **Gardasil**<br>**FUTURE III** | HPV DNA to be found in an adjacent histologic section of the same biopsy site(10) |
| **Gardasil**<br>**V501-027** | HPV DNA detected in tissue from cervicovaginal samples or from biopsy.(11) |
| **Gardasil**<br>**V501-041** | HPV type 6/11/16/18 DNA detected in same tissue block(12) |

## References


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. The Lancet. 2004;364(9447):1757-65.
2. Konno R, Tamura S, Dobbelaere K, Yoshikawa H. Efficacy of human papillomavirus 16/18 AS04-adjuvanted vaccine in Japanese women aged 20 to 25 years: interim analysis of a phase 2 double-blind, randomized, controlled trial. Int J Gynecol Cancer. 2010;20(3):404-10.
3. Szarewski A, Poppe WAJ, Skinner SR, Wheeler CM, Paavonen J, Naud P, et al. Efficacy of the human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine in women aged 15-25 years with and without serological evidence of previous exposure to HPV-16/18. International Journal of Cancer. 2012;131(1):106-16.
4. Hildesheim A, Wacholder S, Catteau G, Struyf F, Dubin G, Herrero R, et al. Efficacy of the HPV-16/18 vaccine: final according to protocol results from the blinded phase of the randomized Costa Rica HPV-16/18 vaccine trial. Vaccine. 2014;32(39):5087-97.
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(9961):2213-27.
6. Zhu F-C, Chen W, Hu Y-M, Hong Y, Li J, Zhang X, et al. Efficacy, immunogenicity and safety of the HPV-16/18 AS04-adjuvanted vaccine in healthy Chinese women aged 18-25 years: Results from a randomized controlled trial. International Journal of Cancer. 2014;135(11):2612-22.

7. Villa LL, Costa RLR, 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. The Lancet Oncology. 2005;6(5):271-8.
8. 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(19):1928-43.
9. Future II Study Group. Quadrivalent vaccine against human papillomavirus to prevent high-grade cervical lesions. N Engl J Med. 2007;356(19):1915-27.
10. 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(9679):1949-57.
11. Yoshikawa H, Ebihara K, Tanaka Y, Noda K. Efficacy of quadrivalent human papillomavirus (types 6, 11, 16 and 18) vaccine (GARDASIL) in Japanese women aged 18-26 years. Cancer Sci. 2013;104(4):465-72.
12. Wei L, Xie X, Liu J, Zhao Y, Chen W, Zhao C, et al. Efficacy of quadrivalent human papillomavirus vaccine against persistent infection and genital disease in Chinese women: A randomized, placebo-controlled trial with 78-month follow-up. Vaccine. 2018.

## Supplement 9. Non-vaccine HPV type outcomes by trial

| Trial | Paper | Non-vaccine HPV outcomes considered |
|---|---|---|
| HPV-001 | Harper 04(1) | None considered |
| V501-007 | Villa 06(2) | None considered |
| FUTURE I | Garland 07(3) | CIN1+ due to any HPV type* |
| FUTURE II | Future II Study Group 07(4) | CIN2+ due to any HPV type* |
| HPV-007 | Harper 06(5) | CIN1+ and CIN2+ due to oncogenic HPV type** and due to any HPV type*** (includes if HPV DNA negative) |
| | Romanowski 09(6) | CIN1+ and CIN2+ due to any HPV type*** (includes if HPV DNA negative) |
| HPV-023 | De Carvalho 10(7) | Incident infection, 6-month and 12-month persistent infection |

| | | |
|---|---|---|
| | | (PI), CIN1+ and CIN2+ due to any oncogenic HPV type** |
| | Roteli-Martins 12(8) | CIN1+ and CIN2+ due to any oncogenic HPV type** |
| | Naud 14(9) | Incident infection any oncogenic HPV type**, HPV 45, 31,33, 51 separately; 6 and 12-month PI oncogenic HPV types**, CIN1+ and CIN2+ oncogenic types** |
| Konno | Konno Jul 10(10) | Incident infection, 12-month PI, CIN1+ and CIN2+ due to any oncogenic type** |
| FUTURE III | Castellsague 11(11) | CIN2+ due to non-vaccine types 31, 33, 35, 39, 45, 51, 52, 56, 58, or 59. |
| V501-027 | Yoshikawa 13(12) | None considered |
| PATRICIA | Paavonen 07(13) | 6 and 12-month PI due to HPV 31, 33, 45, 52, 58 (separately and combined), any oncogenic type**, non-vaccine oncogenic type[#] |
| | Paavonen 09(14) | 6-month PI, 12-month PI , CIN2+ due to HPV 31, 33, 45, 52, 58 (separately and combined), any oncogenic type**, non-vaccine oncogenic type[#] |

| | | |
|---|---|---|
| | Lehtinen 12(15) | CIN1+, CIN2+ CIN3+, AIS due to any HPV type*** |
| CVT | Herrero 11(16) | 12-month PI with HPV 31/33/45, other oncogenic types and any oncogenic type**** |
| | Hildesheim 14(17) | CIN2+ due to any oncogenic HPV type and non-vaccine oncogenic HPV types[##] |
| VIVIANE | Skinner 14(18) | 6-month PI due HPV types 31/33/35/52/58 (separately and combined), types 39/45/58/68 (separately and combined), types 51, 56, 66, to non-vaccine oncogenic types and any oncogenic HPV types** |
| | Wheeler 16(19) | 6-month PI, 12-month PI, CIN1+, CIN+ due to non-vaccine oncogenic types[#] individually or in combination; CIN1+and CIN2+ irrespective of HPV infection |
| Zhu | Zhu 14(20) | None considered |
| | Zhu 17(21) | Incident infection, 6 and 12-month PI with oncogenic HPV types** and non-vaccine oncogenic types[#] |
| V501-041 | Wei 18(22) | None considered |

* Not clear if tested for HPV presence or if so, what types tested for

** HPV types 16,18, 31,33,35,39,45,51,52,56, 58, 59, 66, and 68

*** Irrespective of HPV-DNA type and includes if HPV DNA negative

**** HPV types 16,18, 31,33,35,39,45,51,52,56, 58, 59, 66, 68 and 73- specifies that cannot differentiate between types 68 and 73

[#] Non-vaccine oncogenic types: 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, or 68

[##] HPV types 31,33,35,39,45,51,52,56, 58, 59, 66, 68 and 73- specifies that cannot differentiate between types 68 and 73

**References**


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. The Lancet. 2004;364(9447):1757-65.
2. 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(11):1459-66.
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(19):1928-43.
4. Future II Study Group. Quadrivalent vaccine against human papillomavirus to prevent high-grade cervical lesions. N Engl J Med. 2007;356(19):1915-27.
5. 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(9518):1247-55.
6. Romanowski B, de Borba PC, Naud PS, Roteli-Martins CM, De Carvalho NS, Teixeira JC, 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(9706):1975-85.
7. De Carvalho N, Teixeira J, Roteli-Martins CM, Naud P, De Borba P, Zahaf T, et al. Sustained efficacy and immunogenicity of the HPV-16/18 AS04-adjuvanted vaccine up to 7.3 years in young adult women. Vaccine. 2010;28(38):6247-55.
8. Roteli-Martins CM, Naud P, De Borba P, Teixeira JC, De Carvalho NS, Zahaf T, et al. Sustained immunogenicity and efficacy of the HPV-16/18 AS04-adjuvanted vaccine: up to 8.4 years of follow-up. Hum Vaccin Immunother. 2012;8(3):390-7.
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(8):2147-62.
10. Konno R, Tamura S, Dobbelaere K, Yoshikawa H. Efficacy of human papillomavirus type 16/18 AS04-adjuvanted vaccine in Japanese women aged 20 to 25 years: final analysis of a phase 2 double-blind, randomized controlled trial. Int J Gynecol Cancer. 2010;20(5):847-55.
11. 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(1):28-37.

12. Yoshikawa H, Ebihara K, Tanaka Y, Noda K. Efficacy of quadrivalent human papillomavirus (types 6, 11, 16 and 18) vaccine (GARDASIL) in Japanese women aged 18-26 years. Cancer Sci. 2013;104(4):465-72.
13. 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(9580):2161-70.
14. 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(9686):301-14.
15. 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(1):89-99.
16. Herrero R, Wacholder S, Rodriguez AC, Solomon D, Gonzalez P, Kreimer AR, et al. Prevention of persistent human papillomavirus infection by an HPV16/18 vaccine: a community-based randomized clinical trial in Guanacaste, Costa Rica. Cancer Discov. 2011;1(5):408-19.
17. Hildesheim A, Wacholder S, Catteau G, Struyf F, Dubin G, Herrero R, et al. Efficacy of the HPV-16/18 vaccine: final according to protocol results from the blinded phase of the randomized Costa Rica HPV-16/18 vaccine trial. Vaccine. 2014;32(39):5087-97.
18. 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(9961):2213-27.
19. Wheeler CM, Skinner SR, Del Rosario-Raymundo MR, Garland SM, Chatterjee A, Lazcano-Ponce E, et al. Efficacy, safety, and immunogenicity of the human papillomavirus 16/18 AS04-adjuvanted vaccine in women older than 25 years: 7-year follow-up of the phase 3, double-blind, randomised controlled VIVIANE study. Lancet Infect Dis. 2016;16(10):1154-68.
20. Zhu F-C, Chen W, Hu Y-M, Hong Y, Li J, Zhang X, et al. Efficacy, immunogenicity and safety of the HPV-16/18 AS04-adjuvanted vaccine in healthy Chinese women aged 18-25 years: Results from a randomized controlled trial. International Journal of Cancer. 2014;135(11):2612-22.
21. Zhu FC, Hu SY, Hong Y, Hu YM, Zhang X, Zhang YJ, et al. Efficacy, immunogenicity, and safety of the HPV-16/18 AS04-adjuvanted vaccine in Chinese women aged 18-25 years: event-triggered analysis of a randomized controlled trial. Cancer medicine. 2017;6(1):12-25.
22. Wei L, Xie X, Liu J, Zhao Y, Chen W, Zhao C, et al. Efficacy of quadrivalent human papillomavirus vaccine against persistent infection and genital disease in Chinese women: A randomized, placebo-controlled trial with 78-month follow-up. Vaccine. 2018.

## Supplement 10. Phase 4, observational and follow-up studies considering efficacy/ effectiveness outcomes

| | Study<br><br>Sponsor | Type of study | Country/ timeframe/ gender/ age/ size | Details | Primary efficacy/ effectiveness outcome(s) | Study status<br><br>Results | Which reasons for uncertainty does this address? |
|---|---|---|---|---|---|---|---|
| CERVARIX | | | | | | | |
| 1 | NCT00534638<br><br>GSK | Phase IV trial | Finland Oct 2007-Dec 2014 Male and female 12-15yrs 34206 enrolled | Randomized non-blinded. Three groups- Cervarix 90% boys & girls vaccinated, 10% Energix-B ; Cervarix 90% girls vaccinated, 10% girls & 100% boys Energix B; 100% Energix-B | Effectiveness against incident genital infection with HPV 16/18 in females at 18.5 years of age. | Completed<br><br>Results published: Incident HPV infection, VE against HPV 16/18 incident infection varied from 89.2 to 95.2% across different birth cohorts in groups where some received Cervarix vaccination.(1) | None |
| 2 | NCT02296255<br><br>Cancer Prevention and Research Institute, Italy | Phase IV study | Italy Apr 2010 – Jul 2013 (30 months) Female 25 yrs 832 enrolled | This study included a control group | Incident HR-HPV infection, cytological abnormalities | Completed<br><br>Results published: There was a reduction in abnormal cytology in the vaccinated group but this was not statistically significant.(2) | None due to the short follow-up, small study population, and the outcome. |
| 3 | NCT01393470<br><br>University of Tampere (FinnMedi Oy and GSK as collaborators) | Observational cohort study | Finland May 2011 –Dec 2024 (est.) Female 16-19 yrs 10,000 (est.) | Following up Finnish participants of the GSK-run PATRICIA trial, HPV-008 is due to continue until 2024. Estimated enrollment 10,000. Includes a comparison | CIN3+ | Enrolling participants<br><br>Interim results published, follow-up of 4.5 to 10 years. Intention-to-treat VE against any CIN3+ 66% (95% CI 8, 88).(3) | Longer follow-up and more stringent outcome of CIN 3+ but based on vaccination of a trial cohort not general population. |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | | | against a non-vaccinated cohort | | | |
| 4 | NCT00929526<br><br>GSK | Follow-up of Konno<br><br>Phase III | Japan<br>Jun 2009 – Feb 2011<br>Female<br>20-25 yrs<br>752 included | Follow-up of Konno study (initial study 2 years) for additional 2 years, non-blinded. | CIN1+ cases associated with HPV 16 and/or HPV 18 | Completed<br><br>Results published: In TVC-naïve group, vaccine efficacy regardless of HPV type to CIN3+ was 100% but insignificant confidence intervals (−417.0–100) and only two cases in control group.(4)<br><br>Note: any HR -HPV type – was a secondary outcome | None- Too small, short follow-up, insignificant results for CIN3+ irrespective of HR-HPV type |
| 5 | Pollock et al<br><br>Independent, funding from Chief Scientist Office grant | Observational cohort study | Scotland<br>2008-May 2013<br>Female<br>Aged 20-21 in 2008-2012<br>106,052 | Registry based cohort study analysing colposcopy data of women born between 1988-1992 who entered cervical screening and were aged 20-21 from 2008-2012, comparing rates of CIN1, 2 and 3 between those immunised and not immunised. | CIN1, CIN2 and CIN3 incidence rates per 1000 person-years and relative risk reduction amongst those vaccinated. | Completed<br><br>RR of CIN3 for those receiving 3 doses adjusted for age, deprivation and cohort year 0.45 95%CI (0.35, 0.58) p<0.0001. RR of CIN3 for those receiving 1 or 2 doses not statistically significant but small numbers.(5) | Considers CIN3 alone, and considers CIN3 regardless of HPV type, considers women in Scottish national screening programme so usual rate of screening.<br><br>Authors acknowledge they could not adjust for whether participants stayed in school- those who did would have been part of catch-up vaccination cohort |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 6 | Cameron et al | Observational study | Scotland Cervical screening samples from 2009-2013 Female Age 20-21 at time of cervical screening 5,715 women | HPV testing on cervical screening samples from 2009-2013, prevalence of incident infection by HPV type | HPV type (16 or 18; 31, 33 or 45; other non-vaccine high risk types (35, 39, 51, 52, 56, 58, 59, 68) prevalence for those receiving three doses of Cervarix vs none, potential herd immunity with trends over time in those not vaccinated. | Decrease in HPV 16 and 18 in vaccinated vs non-vaccinated women 11.0% vs 29.4%, adjusted OR 0.30 95%CI (0.25, 0.35) Annual prevalence of HPV 16 and 18 decreased over time, 10. 1% (8.4, 12.2) in 2009 vs. 28.8% 95%CI (26.7, 31) in 2013. Prevalence of 31, 33 and 45 decreased in vaccinated vs unvaccinated. Prevalence of non-vaccine non-cross protective high-risk HPV types significantly increased from 29.1% 95%CI(26.9, 31.3) in 2009 to 33.9% 95%CI(31.0, 36.8) in 2013. Prevalence of HPV 51 was marginally and non-significantly increased in vaccinated compared to non-vaccinated women.(6) | Uses incident infection. Raises concerns about potential for type replacement. |
| 7 | Cruickshank et al | Observational ecological study | Scotland Colposcopy referrals from 2008-2014 Female Age 20 or 21 at time of colposcopy and born 1 Jan | Ecological study of women referred for colposcopy and outcomes. | Referral criteria, positive predictive value of colposcopy, default rates, and rates of cervical biopsies and treatments. | Completed<br><br>Reduction in the proportion of those referred for colposcopy due to abnormal cytology, 91% in 2008-09 to 90.3% | Ecological study so not causal and results not linked to immunisation status. Uses usual frequency of testing as includes results from |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | | 1985 or later 7,372 women | | | in 2013-14, p=0.03 Reduction in rates of CIN2+ of those referred for colposcopy 39.21% in 2008-09 and 25.81% in 2013-14.(7) | cervical screening programme. |
| 8 | Palmer et al<br><br>Health Protection Scotland | Observational study | Scotland Smear test results aged 20 of women born between 1 Jan 1988 and 5 Jun 1996 138,692 women | Retrospective population study of results on first cervical screening linked to immunisation status and date of birth | Cytology and histology findings on cervical screening | Completed<br><br>For fully immunized women, first vaccinated aged 12-13, vaccine effectiveness against CIN3+ due to any HPV type 86% 95%CI(75, 92). For women first vaccinated aged 17, vaccine effectiveness against CIN3+ 45% 95%CI(17, 64)(8) | Observational study so cannot establish causality, see main text for more information |
| GARDASIL | | | | | | | |
| 8 | NCT00092534/ Nordic Cancer Registry Study/ V501-015<br><br>Merck | Follow-up of FUTURE II<br><br>Post-marketing commitment (EMA, US FDA) | Denmark, Norway, Sweden, Iceland OrIginal study Jun 2002 – Jul 2007, 2 extension studies until Mar 2017 Female 16-23 yrs 12167 enrolled | First extension study V501-015-10 Second extension study V501-015-20 Registry based follow-up | CIN2+ due to HPV 16/18 | Completed.<br><br>Preliminary data published in conference abstract in 2013.<br><br>No cases in vaccinated cohort at 9 years but figures not given for placebo cohort or for CIN due to any oncogenic type.(9) | Unknown, as full results not yet published, and not clear whether figures for any oncogenic types will be presented. Unlikely due to composite endpoints and short follow-up |
| 9 | NCT00092547 Adolescent Sentinel Cohort Study/ V501-018 | Immunogenicity trial<br><br>Phase III | Columbia, Denmark, Mexico, Norway, Portugal, | Extended with a secondary outcome to assess | Primary outcome was regarding immunogenicity. | Completed.<br><br>Preliminary results have been | Considers girls of target vaccination age |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | Merck | Post-marketing commitment (EMA, US FDA) | Spain, Taiwan, Thailand, UK, US Oct 2003 – Jun 2015 Male and female 9-15 yrs 1781 enrolled | effectiveness up to 126 months. Comparing early (EVG) and catch-up (CVG) vaccination groups. | | presented up to 96 months.(10)<br><br>Secondary outcome looking at effectiveness - CIN1+ due to HPV6/11/16/18 or persistent infection of 4 months duration.<br><br>EVG 2 cases of persistent HPV 16 infection out of 256 girls. In CVG, 2 cases of HPV 16 persistent infection, 4 cases of HPV-18 persistent infection, 1 case of HPV-18 CIN1. Small numbers for effectiveness outcomes. | however multicountry study – small numbers at country level; combined endpoints, small numbers for effectiveness outcomes. |
| 10 | NCT01077856 Vaccine Impact in Population study/ V501-033<br><br>Merck (collaborators: Danish Cancer Society Union for International Cancer Control Cancer Registry of Norway Karolinska Institute) | Observational cohort study<br><br>Post-marketing commitment (EMA, US FDA) | Norway, Sweden and Denmark May 2007- Dec 2014 Female 18-45 yrs 54,516 enrolled | Registry based incidence rates of HPV-related genital disease in pre-vaccine era (2004-2006) and post vaccination periods (2007-2011) | Incidence of CIN1+, incidence of HPV 6/11/16/18 and other than 16/18 HR -HPV type related CIN2+, incidence of HPV-related female genital diseases (incl. vulvar and vaginal cancer and their high grade precursors), prevalence of HPV 6/11/16/18 and other than 16/18 HR -HPV type infection | Completed.<br><br>Results obtained through FOI request through EMA, not published.(11)<br><br>Incidence of CIN2+ increased in Denmark and Sweden across all ages during the study period. In Danish data, When stratified by vaccination status, incidence of CIN2+ showed a | Large study cohort but short duration and use of combined endpoints |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | | | | | significant decrease in the youngest age group with high vaccination coverage. No appreciable changes in rates of cervical cancer in any of the countries during the follow-up period. | |
| 11 | NCT01544478/V501-110<br><br>Merck | Phase IV study | Japan<br>Nov 2011 to Aug 2016<br>Female<br>16-26 yrs<br>1,030 participants enrolled | Open label descriptive study | Combined incidence of CIN2+ related to HPV 6/11/16/18 up to month 48 post-vaccination | Completed.<br><br>Results not published | Unknown but unlikely given use of combined endpoint |
| 12 | Rana et al<br><br>Grant sponsors: Finnish Cancer Organizations and Nordic Cancer Union, Merck& Co. Inc., GSK Biologicals | Cohort cancer registry-based follow-up | Finland<br>2007-2011<br>Female<br>16 to 17 yrs (at the time of vaccination)<br>866 vaccinated subjects, 861 placebo subjects (50% cross-vaccinated in 2007), 15,719 unvaccinated reference cohort. | Four year passive follow-up of Finnish cohort from FUTURE II (involved in active follow-up from 2002-2007). | Incidence of CIN3+ | Completed.<br><br>Results published: Incidence rates of CIN3 for the three groups were 0/100,000, 87.1/100,000 and 93.8/100,000. "We identified zero cases of CIN3 or ICC in the HPV6/11/16/18 cohort, three cases of CIN3 in the original placebo cohort (with or without cross-vaccination) and 59 CIN3 and 3 ICC cases in the unvaccinated reference cohort." (note: first two CI wide, the third one | Some evidence for more stringent endpoint of CIN3+ regardless of HPV type, however short follow-up |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | | | | | tight)(12) | |
| 13 | NCT00090220/ V501-019/ FUTURE III<br><br>Merck | Long-term follow-up study | Colombia Jun 2004 – Nov 2015 Female 24-45 yrs (age at vaccination of EVG), 29-50 yrs (age at vaccination of CVG) 3819 enrolled in original study (contribute to analysis of first 4 years), rest of analysis just for Colombia cohort 1360 participants (1335 vaccinated). | No control group. Included early vaccination group and catch-up vaccination group. Extension study of FUTURE III trial including women from Colombia study sites to look at safety, effectiveness and immunogenicity. | HPV6/11/16/18 related CIN1+ or genital warts; and HPV 16/18 CIN2+ | Completed.<br><br>Results of interim analysis to Year 6 post-start of base study published, details of Year 8 analysis in conference abstract, further analysis planned at Year 10.<br><br>Secondary outcomes of non-HPV 6/11/16/18 related genital warts or cervical dysplasia, and of non-HPV 16/18-related CIN2+<br><br>At Year 6, no new cases since base study of HPV6/11/16/28 CIN1+ or genital warts. 2 cases of HR non-vaccine HPV type CIN2+ in EVG full-analysis population.(13)<br>At Year 8, no cases of HPV6/11/16/18 CIN1+ or genital warts in EVG.(14) | Some supporting evidence for effectiveness in older women and looking at cross-protection but short follow-up, no control and results reported only for the combined endpoint |
| 14 | NCT00834106 / V501-041<br><br>Merck | Phase III | China Dec 2008-Sept 2016 (78 months follow-up) Female 20-45 yrs 3006 enrolled | Randomised placebo-controlled blinded trial of Gardasil | Persistent HPV 6/11/16/18 infection or related genital disease (up to month 30); CIN2+ (up to month 78) | Completed.<br><br>No results published or posted on clinicaltrials.gov | Unlikely-although placebo-controlled, using combined endpoints, small numbers |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | | | | | | and short follow-up |
| 15 | NCT02653118/ V503-021<br><br>Merck | Observational study<br><br>(Registry-based extension of protocol V503-001) | Denmark, Norway, Sweden<br>Original study period- Sept 2007- July 2016 (up to 54 months)<br>Extension Jan 2016- Jan 2024<br>Female<br>16-26 yrs at time of vaccination<br>4453 (est.) | Long-term observational follow-up of participants from Nordic countries of original V503-001 trial of Gardasil 9 vs. Gardasil. Gardasil subjects were offered cross-vaccination with Gardasil 9. | Combined incidence of HPV 16/18/31/33/45/52/58 related CIN2+ up to 16 years after vaccination in V503-001 base study | Ongoing, not recruiting. | May address long-term efficacy given length of follow-up however unlikely as combined endpoints and small study numbers |
| 16 | NCT02934724<br><br>Oslo University Hospital<br><br>(Collaborator: University Hospital, Akershus) | Observational study | Norway<br>Nov 2016- est Dec 2018<br>Female born in 1997<br>18-20 yrs<br>317 participants | . | Vaginal and oral HPV 6/11/16/18 prevalence in vaccinees and non-vaccinees. | Ongoing, not recruiting | None, small size and looking at vaccine type HPV incidence |
| 17 | Baldur-Felskov et al.<br><br>Funding: Mermaid Project (MERMAID2) | Observational cohort study | Denmark<br>Oct 2006- March 2012<br>Female<br>Included all girls born in Denmark from 1989 to 1999<br>399,244 women | Information on vaccination status from registries, linked to information on cervical lesions. | Risk of atypia+; CIN2+ and CIN3+ in vaccinated vs. unvaccinated | Completed. Results published: Birth cohorts 1989-1990 statistically significant reduced risk of atypia+, reduced risk of CIN2+ but not statistically significant. Birth cohorts 1991-1994 statistically reduced risk of atypia+ and CIN2+. No events in birth cohort 1997-1999.(15) | Some supporting evidence for girls in target vaccination group but follow up too short with low incidence rates and use of combined endpoints |
| 18 | NCT03105856<br>FASTER-Tlalpan Study (FASTER)<br><br>Instituto Nacional de Salud Publica, Mexico | Phase IV<br><br>Cervarix<br>Gardasil | Mexico<br>Jan 2017 – unclear (10 years duration)<br>Female | Three groups- bivalent vaccine +HR-HPV screening, quadrivalent | Incidence 6-month persistent infection of HPV 16 or HPV 18<br><br>Secondary outcome CIN2+ | Ongoing, not recruiting | May help answer questions about cross-protection as |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | | 25-45 Yrs 18,000 (est.) | + HR HPV screening, HR HPV screening alone. 2-dose HPV vaccination | | | comparing two vaccines, included control group. May help answer uncertainties regarding disease outcome regardless of HPV type. May provide information on longer term follow-up. |
| 19 | Drolet et al.<br><br>Funding: The Canadian Institutes of Health Research | Systematic review and meta-analysis of population based time-trend ecological studies. | 20 eligible studies conducted in 8 high-income countries (US, UK, Australia, New Zealand, Canada, Sweden, Denmark, Germany). Studies looked at period from 1985 to 2012 Male and female Study participants ranged from 13-39 Variable sample sizes | Included population-based and clinic-based studies, some looked at herd-immunity post-female vaccination programmes. | Assessed prevalence of HPV infection, genital warts and cervical dysplasia pre and post-immunization screening programmes. | Completed.<br><br>Results published Evidence from one study (Brotherton) of a reduction in prevalence of CIN2+ in girls <18 years three years after vaccination programme introduction.(16) | Ecological studies so not directly addressing the uncertainties raised but provides supportive evidence for impact in general population. |

Sources: The information on type of study, country, duration, participants and primary efficacy objectives was collected from clinicaltrials.gov on 13-14th June 2017.
Results were sourced from published studies
* final report received from the EMA (FOI request)
Abbreviations: EVG=Early Vaccination Group, CVG= Catch-up Vaccination group, HR-HPV type = high risk HPV type

## References

1. Lehtinen M, Soderlund-Strand A, Vanska S, Luostarinen T, Eriksson T, Natunen K, et al. Impact of gender-neutral or girls-only vaccination against human papillomavirus-Results of a community-randomized clinical trial (I). Int J Cancer. 2018;142(5):949-58.

2. Carozzi FM, Ocello C, Burroni E, Faust H, Zappa M, Paci E, et al. Effectiveness of HPV vaccination in women reaching screening age in Italy. J Clin Virol. 2016;84:74-81.
3. Lehtinen M, Lagheden C, Luostarinen T, Eriksson T, Apter D, Harjula K, et al. Ten-year follow-up of human papillomavirus vaccine efficacy against the most stringent cervical neoplasia end-point-registry-based follow-up of three cohorts from randomized trials. BMJ open. 2017;7(8):e015867.
4. Konno R, Yoshikawa H, Okutani M, Quint W, V Suryakiran P, Lin L, et al. Efficacy of the human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine against cervical intraepithelial neoplasia and cervical infection in young Japanese women. Human Vaccines & Immunotherapeutics. 2014;10(7):1781-94.
5. Pollock KG, Kavanagh K, Potts A, Love J, Cuschieri K, Cubie H, et al. Reduction of low- and high-grade cervical abnormalities associated with high uptake of the HPV bivalent vaccine in Scotland. Br J Cancer. 2014;111(9):1824-30.
6. Cameron RL, Kavanagh K, Pan J, Love J, Cuschieri K, Robertson C, et al. Human Papillomavirus Prevalence and Herd Immunity after Introduction of Vaccination Program, Scotland, 2009-2013. Emerg Infect Dis. 2016;22(1):56-64.
7. Cruickshank ME, Pan J, Cotton SC, Kavanagh K, Robertson C, Cuschieri K, et al. Reduction in colposcopy workload and associated clinical activity following human papillomavirus (HPV) catch-up vaccination programme in Scotland: an ecological study. Bjog. 2017;124(9):1386-93.
8. Palmer T, Wallace L, Pollock KG, Cuschieri K, Robertson C, Kavanagh K, et al. Prevalence of cervical disease at age 20 after immunisation with bivalent HPV vaccine at age 12-13 in Scotland: retrospective population study. Bmj. 2019;365:l1161.
9. 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(3):e657-65.
10. Nygard M KS, Dillner J, Marshall B, Hansen BT, Sigurdardottir LG, et al., editor Long-term effectiveness and immunogenicity of Gardasil in the Nordic countries. EUROGIN; 2013.
11. VIP Study Investigators. Vaccine Impact in Population (VIP) Study for Gardasil in Four Nordic Countries. Final Study Report.; 2014 December.
12. Rana MM, Huhtala H, Apter D, Eriksson T, Luostarinen T, Natunen K, et al. Understanding long-term protection of human papillomavirus vaccination against cervical carcinoma: Cancer registry-based follow-up. Int J Cancer. 2013;132(12):2833-8.
13. 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(12):e83431.
14. Das R, Plata M, Gonzalez M, Correa A, Maldonado I, Nossa C, et al., editors. Long-term effectiveness of Gardasil among adult women in Colombia. EUROGIN; 2015 4-7 February 2015; Sevilla, Spain.
15. Baldur-Felskov B, Dehlendorff C, Munk C, Kjaer SK. Early impact of human papillomavirus vaccination on cervical neoplasia--nationwide follow-up of young Danish women. J Natl Cancer Inst. 2014;106(3):djt460.
16. Drolet M, Benard E, Boily MC, Ali H, Baandrup L, Bauer H, et al. Population-level impact and herd effects following human papillomavirus vaccination programmes: a systematic review and meta-analysis. Lancet Infect Dis. 2015;15(5):565-80.