Effect of catch-up HPV vaccination of young women

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Systematic Review

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Background: Human papillomavirus (HPV) is considered the most common sexually transmitted agent worldwide and more than 100 types of HPV have been identified. Persistent infection with oncogenic HPV is recognized as a necessary cause of cervical cancer. Approximately 70% of cervical cancers in the world are attributed to two of the most common HPV types, 16 and 18.

Lessons: •The results show a protective effect of HPV vaccination against Cervical intraepithelial neoplasia grade 2 and higher (CIN2+) associated with the HPV types included in the vaccines. The evidence has high quality. •The results indicate a protective effect against all CIN2+ lesions independent of HPV types in the lesions. The evidence has moderate quality. •The quadrivalent HPV vaccine protects against genital warts. The evidence has high quality. •Long-term (up to 8 years) follow-up after HPV vaccination indicates little or no difference in the occurrence of serious adverse events when compared to the control groups . The evidence has moderate quality.

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Norwegian Knowledge Centre for the Health Services
Oslo, Mars 2014

Key messages

Human papillomavirus (HPV) is considered the most common sexually transmitted agent worldwide and more than 100 types of HPV have been identified. Persistent infection with oncogenic HPV is recognized as a necessary cause of cervical cancer. Approximately 70% of cervical cancers in the world are attributed to two of the most common HPV types, 16 and 18.

This systematic review was carried out to assess whether the HPV vaccines currently offered to 11 to 12 year-old girls in Norway are also effective as a catch-up vaccination for women up to age 26 in preventing HPV-related diseases.

For HPV vaccination of women aged 16 and older:

- The results show a protective effect of HPV vaccination against Cervical intraepithelial neoplasia grade 2 and higher (CIN2+) associated with the HPV types included in the vaccines (high quality of the evidence), and indicate a protective effect against all CIN2+ lesions (independent of HPV types in the lesions) (moderate quality of evidence).

- The quadrivalent HPV vaccine protects against genital warts (high quality evidence).

- Long-term (up to 8 years) follow-up after HPV vaccination indicates little or no difference in the occurrence of serious adverse events when compared to the control groups (moderate quality of evidence).

Title:
Effect of catch-up HPV vaccination of young women

Type of publication:

Systematic review

A review of a clearly formulated question that uses systematic and explicit methods to identify, select, and critically appraise relevant research, and to collect and analyse data from the studies that are included in the review. Statistical methods (meta-analysis) may or may not be used to analyse and summarise the results of the included studies.

Doesn't answer everything:

- Excludes studies that fall outside of the inclusion criteria
- No health economic evaluation
- No recommendations

Publisher:

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Last search for studies: October, 2012.

Peer review:

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Executive summary

Background

Human papillomavirus (HPV) is considered the most common sexually transmitted agent worldwide and more than 100 types of HPV have been identified. However, a small number of HPV types contribute to a large proportion of HPV-related diseases. Persistent infection with oncogenic HPV is recognized as a necessary cause of cervical cancer. Approximately 70% of cervical cancers in the world are attributed to two of the most common HPV types, 16 and 18.

Efficient prophylactic vaccines can have an important public health impact. Under several plausible assumptions, an economic evaluation suggest that introduction of HPV 16/18 type vaccination to current screening in Norway may be a cost-effective strategy for further reductions in cervical cancer incidence and mortality. Prophylactic HPV vaccination was introduced in the Norwegian childhood immunization program in 2009. It is unclear whether vaccinating older girls will also be beneficial, and The Norwegian Institute of Public Health requested a Health Technology Assessment to ascertain the potential effectiveness of a catch-up vaccination of females up to 26 years of age.

Objective

To carry out a systematic review in order to assess whether HPV vaccines currently offered to 11- to 12-year-old girls in Norway are also effective as a catch-up vaccination for women up to age 26 in preventing HPV-related diseases.

Method

We have conducted this systematic review in accordance with the Handbook for the Norwegian Knowledge Center for the Health Services.

Two review authors reviewed all citations to identify relevant publications according to pre-specified criteria. Full text publications of potentially eligible references were

retrieved, and we assessed all included references for risk of bias according to the Handbook. We extracted data from the included references using a pre-designed data recording form. These steps were done independently and then jointly by two review authors or by one of the review authors and then checked by one of the others.

We entered and analyzed data using the Review Manager software and calculated risk ratios and the associated 95 % confidence interval for the estimate of effect. We applied the GRADE method (Grading of Recommendations Assessment, Development and Evaluation) to assess the overall quality of evidence for each outcome.

Results

The literature search for randomized controlled trials on HPV vaccines was conducted in October 2012. We identified 616 references. In addition, we received 12 references from the pharmaceutical companies with marketing authorization for HPV vaccines in Norway. After reading titles and abstracts and full texts, we included 46 references in the present report.

The main findings of the review are:
The pooled estimate for cervical intraepithelial neoplasia grade 2 and higher (CIN2+) show a borderline statistically significant difference in CIN2+ risk between the vaccine and the control groups (intention-to treat population, four-year follow-up) (RR= 0.80; 95% CI= 0.62, 1.02). The quality of the evidence for this outcome is moderate.

The pooled estimate for CIN2+ lesions associated with the HPV types in the vaccine shows a statistically significant difference in the risk of these lesions between the vaccine and control groups (intention-to treat population, four-year follow-up) (RR= 0.54; 95 % CI= 0.44, 0.67). The quality of the evidence for this outcome is high.

The pooled estimate for serious adverse events shows that there is no statistically significant difference between the vaccine and the control groups (safety population, longest reported follow-up) (RR= 0.99; 95 % CI= 0.91, 1.08). The quality of the evidence for this outcome is moderate.

Discussion

When combining the data for all pre-cancerous cervical lesions (CIN2+) in young women our results indicated a protective effect of these lesions. However, there is some uncertainty about the effectiveness of prophylactic HPV vaccination. The uncertainty is due to borderline significant results for CIN2+ lesions in the intention-to-treat and the per protocol population after a four-year follow-up.

Examining CIN2+ lesions independent of HPV type may reflect the possible wider public health impact of a HPV vaccination. Previous meta-analyses presented mostly results for lesions containing the HPV types included in vaccines under study (64;65). In line with previous meta-analyses, we found that assumed risk in the placebo group for HPV type related CIN2+ lesions is 22 per 1000, and the corresponding risk in the vaccine group is 12 per 1000. The confidence in this estimate (quality of the evidence) is high. High grade cervical lesions were chosen as the outcome of interest because they are immediate precursors to cervical cancer, and because they were described as the best outcome to use when examining the effect of HPV vaccination.

There is some uncertainty regarding the long-term effect of the vaccines due to the relatively short follow-up periods of the clinical trials. Since we will only know the true effect of HPV vaccination on cervical cancer and mortality outcomes in 20-30 years, long-term follow-up data for the vaccinated populations are important.

No statistically significant difference in serious adverse events between the vaccination and the placebo groups were found. Nevertheless, the number of cases within the clinical studies is not sufficient to determine the occurrence of rarely occurring (severe) adverse events in a reliable way. Long-term safety needs to be assessed in future trials and in possible follow-up publications of existing trials.

We have conducted a systematic review based on primary clinical trials of a randomized controlled design. Randomized controlled trials are expected to be more robust against bias than observational studies, and are therefore the preferred design for studies of effect of an intervention. However, to assess long-term follow-up data and outcomes related to harm, observational and registry studies might be more appropriate.

National vaccination programs have already been started in many countries, but the true effect on cervical cancer outcomes of this vaccine will be observed 20-30 years from now. It remains to be seen whether we will see a dramatic reduction in HPV-associated diseases, such as cervix, vulva, vagina, anus, oral cavity, and oropharynx and tonsil cancers, as a result of a national vaccination programs.

Conclusion

Our systematic review of the effect of a catch-up HPV vaccination of young women demonstrates that:

There is a protective effect of HPV vaccination against CIN2+ lesions associated with the HPV types in the vaccines (high quality of the evidence) and against all CIN2+ lesions (independent of HPV types in the lesions) (moderate quality of evidence).

Long-term (up to 8 years) follow-up after HPV vaccination indicates little or no difference in the occurrence of serious adverse events in the vaccine group when compared to the control group (moderate quality of evidence).

Further research is needed to demonstrate if there is an association between HPV vaccination and incidence of HPV related cancers, cancer related mortality and long-term safety.

Hovedfunn

Humant papillomavirus (HPV) er ansett som det vanligste seksuelt overførbare virus på verdensbasis, og mer enn 100 typer av HPV er identifisert. Vedvarende infeksjon med kreftfremkallende HPV er en forutsetning for utvikling av livmorhalskreft, og ca. 70 % av livmorhalskreft i verden tilskrives to av de vanligste HPV-typene, 16 og 18.

Denne systematiske oversikten ble utført for å vurdere om HPV-vaksinene som i dag gis til 11 - 12 år gamle jenter i Norge for å forebygge HPV-relaterte sykdommer, også er effektive for kvinner opp til 26 år.

HPV-vaksinasjon av kvinner som er 16 år og eldre:

- Resultatene viser at HPV-vaksinasjon har en beskyttende effekt mot de forstadier til livmorhalskreft som er assosiert med HPV-typene i vaksinene. Dokumentasjonen har høy kvalitet.

- Resultatene indikerer en beskyttende effekt mot alle forstadiene til kreft, uavhengig av HPV- type. Dokumentasjonen har moderat kvalitet.

- Vaksine mot HPV-type 6, 11, 16 og 18 beskytter mot kjønnsvorter (kondylomer). Dokumentasjonen har høy kvalitet.

- Langtidsoppfølgning, inntil 8 år etter HPV-vaksinering, viser liten eller ingen forskjell i alvorlige bivirkninger sammenlignet med kontrollgruppen. Dokumentasjonen har moderat kvalitet.

Tittel:
Effekt av innhentingsvaksinering med HPV av unge kvinner

Publikasjonstype:

Systematisk oversikt

En systematisk oversikt er resultatet av å
- innhente
- kritisk vurdere og
- sammenfatte

relevante forskningsresultater ved hjelp av forhåndsdefinerte og eksplisitte metoder.

Svarer ikke på alt:

- Ingen studier utenfor de eksplisitte inklusjonskriteriene
- Ingen helseøkonomisk evaluering
- Ingen anbefalinger

Hvem står bak denne rapporten?

Kunnskapssenteret har skrevet rapporten på oppdrag fra Folkehelseinstituttet.

Når ble litteratursøket utført?

Søk etter studier ble avsluttet Oktober, 2012.

Fagfeller:

Ingvild Vistad, seksjonsoverlege, Sørlandet sykehus HF

Jon Mork, dr. med, Rikshospitalet

Sammendrag

Bakgrunn

Humant papillomavirus (HPV) er ansett som det vanligste seksuelt overførbare virus på verdensbasis, og mer enn 100 typer av HPV er identifisert. Vedvarende infeksjon med onkogene HPV er en forutsetning for utvikling av livmorhalskreft, og ca. 70 % av livmorhalskreft i verden tilskrives to av de vanligste HPV-typene, 16 og 18.

Gitt ulike forutsetninger har en økonomisk evaluering av HPV-type 16/18-vaksinasjon vist seg å være en kostnadseffektiv strategi for å redusere antall nye tilfeller og dødelighet av livmorhalskreft i Norge. Slik vaksinering ble introdusert i det norske barnevaksinasjonsprogrammet i 2009. Denne systematiske oversikten ble utført for å vurdere om HPV-vaksinering også er effektivt for kvinner opp til 26 år for å forebygge HPV-relaterte sykdommer.

Problemstilling

Å utarbeide en systematisk oversikt for å kunne vurdere om HPV-vaksinen som i dag tilbys 11 til 12 år gamle jenter i Norge for å forhindre HPV-relatert sykdom, også er effektiv ved innhentingsvaksinering av kvinner opp til 26 år.

Metode

Vi har utarbeidet denne systematiske oversikten i henhold til metodehåndboken til Nasjonalt kunnskapssenter for helsetjenesten.

To oversiktsforfattere gjennomgikk alle referansene for å identifisere relevante publikasjoner i henhold til spesifiserte kriterier. Fulltekst publikasjoner av potensielt relevante referanser ble innhentet, og i henhold til håndboken vurderte vi alle inkluderte referanser for risiko for skjevhet. Vi hentet ut data fra de inkluderte referansene ved hjelp av et dataregistreringsskjema. Dette ble først gjort uavhengig og deret-

ter i fellesskap med to av forfatterne, eller ved at data ble hentet ut av én forfatter og deretter kontrollert av en annen.

Vi analyserte resultatene ved hjelp Review Manager-programvaren og kalkulerte risiko og tilhørende 95 % konfidensintervall for effektestimatet. Vi brukte GRADE-metoden (Gradering of Recommendations Assessment, Development and Evaluation) for å vurdere den generelle kvaliteten på dokumentasjonen for hvert utfall.

Resultat

Vårt litteratursøk etter randomiserte kontrollerte studier på HPV-vaksiner ble gjennomført i oktober 2012. Vi identifiserte 616 referanser. I tillegg fikk vi 12 referanser fra de farmasøytiske selskapene som har markedsføringstillatelse for HPV-vaksiner i Norge. Etter å ha lest titler, sammendrag og fulltekster, inkluderte vi 46 referanser i denne systematiske oversikten.

De viktigste funnene er:
Det samlede effektestimatet for forstadier til livmorhalskreft (cervikal intraepitelial neoplasi, CIN2+, lesjoner) viser en statistisk grensesignifikant forskjell i CIN2+ risiko mellom vaksine- og kontrollgruppene (intention to treat-populasjonen, fire års oppfølging) (RR = 0,80, 95 % CI = 0.62, 1,02). Kvaliteten på dokumentasjonen for dette utfallet er moderat.

Det samlede effektestimatet for CIN2+ lesjoner som er assosiert med HPV-typene som er i vaksinene, viser en statistisk signifikant forskjell i risikoen for disse lesjonene mellom vaksine- og kontrollgruppene (intention to treat-populasjonen, fire år oppfølging) (RR = 0,54, 95 % CI = 0,44, 0,67). Kvaliteten på dokumentasjonen for dette resultatet er høy.

Det samlede effektestimatet for alvorlige bivirkninger, viser at det ikke er en statistisk signifikant forskjell mellom vaksine - og kontrollgruppene ("safety population", lengste rapporterte oppfølging) (RR = 0,99, 95 % CI = 0,91, 1,08). Kvaliteten på dokumentasjonen for dette utfallet er moderat.

Diskusjon

Når man kombinerer resultater for forstadier til livmorhalskreft (CIN2+) hos unge kvinner uavhengig av HPV- type i lesjonene, indikerer våre resultater en beskyttende effekt. Det er imidlertid en viss usikkerhet om effektiviteten av forebyggende HPV-vaksinasjon. Usikkerheten skyldes grensesignifikante estimater for CIN2 + lesjonene i intention-to-treat og per protokoll populasjonen etter fire års oppfølging.

Å undersøke CIN2 + lesjoner uavhengig av HPV-type gjenspeiler trolig folkehelse-

perspektivet for virkningen av HPV-vaksinering. Tidligere meta-analyser har hovedsakelig presentert resultater for lesjoner som er positive for de HPV-typene som inngår i vaksinene som studeres. I tråd med tidligere meta-analyser, har vi funnet at antatt risiko i placebogruppen for HPV relatert CIN2 + lesjoner er 22 per 1000, og tilsvarende risiko i vaksinegruppen er 12 per 1000. Kvaliteten på denne dokumentasjonen er høy. Høygradige celleforandringer ble valgt som utfallsmål fordi de er direkte forløpere til livmorhalskreft, og fordi de er beskrevet som det beste utfallsmålet å bruke når man skal undersøke effekten av HPV-vaksinasjon.

Det er en viss usikkerhet om den langsiktige effekten av vaksinene, på grunn av relativt kort oppfølgingstid i de kliniske studiene. Siden vi først vil vite den sanne effekten av HPV-vaksinasjon på livmorhalskreft og kreftdødelighet om 20-30 år, blir langsiktig oppfølgingsdata for den vaksinerte befolkningen viktig.

Ingen statistisk signifikant forskjell i alvorlige bivirkninger mellom vaksinasjons- og placebogruppen ble funnet. Antallet hendelser i de kliniske studiene er imidlertid ikke tilstrekkelig til å bestemme forekomsten av sjeldent forekommende alvorlige bivirkninger på en pålitelig måte. Sikkerhet over lang tid må vurderes i fremtidige studier og mulig oppfølgingspublikasjoner av eksisterende studier.

Vi har gjennomført en systematisk vurdering basert på primære kliniske studier av et randomisert kontrollert design. Randomiserte kontrollerte studier er forventet å være mer robust mot skjevhet enn observasjonsstudier, og er derfor den foretrukne design for studier av effekten av en intervensjon. Men for å vurdere langsiktig oppfølgingsdata og resultater relatert til skade, kan observasjonsstudier og registerstudier være mer hensiktsmessig.

Nasjonale vaksinasjonsprogrammer er allerede i gang i mange land, men den sanne effekt på livmorhalskreft utfall av denne vaksinen vil først komme 20-30 år fra nå. Det gjenstår å se om vi vil se en dramatisk reduksjon i HPV-assosierte sykdommer, for eksempel livmorhals, vulva, vagina, anus, munnhulen og orofarynx og mandel kreft, som et resultat av et nasjonalt vaksinasjonsprogram .

Konklusjon

Vår systematiske oversikt over effekt av innhentingsvaksinering med HPV av unge kvinner viser at:

Resultatene viser en beskyttende effekt av HPV-vaksinasjon mot CIN2 + lesjoner som er assosiert med HPV-typene som er i vaksinene (høy kvalitet på dokumentasjonen), og indikerer en beskyttende effekt mot alle CIN2+ lesjoner (moderat kvalitet på dokumentasjonen).

Langtidsoppfølgning (inntil 8 år) etter HPV vaksinering viser liten eller ingen forskjell i alvorlige bivirkninger sammenlignet med kontrollgruppen (moderat kvalitet på dokumentasjonen).

Videre forskning er nødvendig for å undersøke om det er en assosiasjon mellom HPV-vaksinasjon og insidens av HPV-relatert kreft, kreftdødelighet og langtids sikkerhet.

Nasjonalt kunnskapssenter for helsetjenesten fremskaffer og formidler kunnskap om effekt av metoder, virkemidler og tiltak og om kvalitet innen alle deler av helsetjenesten. Målet er å bidra til gode beslutninger slik at brukerne får best mulig helsetjenester. Kunnskapssenteret er formelt et forvaltningsorgan under Helsedirektoratet, men har ikke myndighetsfunksjoner og kan ikke instrueres i faglige spørsmål.

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Preface

The Norwegian Institute of Public Health requested a Health Technology Assessment from the Norwegian Knowledge Centre for the Health Services to ascertain the potential effectiveness of HPV vaccination of young boys, a catch-up HPV vaccination of females up to 26 years of age, as well as a catch-up HPV vaccination of older boys.

We will perform a Health Technology Assessment (HTA) consisting of at least the three following elements: efficacy, safety and health economic evaluation. Efficacy and safety will be assessed through systematic reviews, and the economic evaluation will be performed through a modeling analysis.

This systematic review of the effect of HPV vaccination of young women is the first deliverable of the Health Technology Assessment regarding a potential expansion of the current HPV vaccination strategy to include 12- year-old boys and catch-up vaccination of both young women and men.

The project group consisted of:

- Project coordinator: Ingvil Sæterdal, The Norwegian Knowledge Centre for the Health Services
- Other participants: Elisabeth Couto, Lene Juvet, Ingrid Harboe and Marianne Klemp, The Norwegian Knowledge Centre for the Health Services

We would like to thank Ingvild Vistad og Jon Mork for their expertise in this project.
Norwegian Knowledge Centre for the Health Services assumes final responsibility for the content of this report.

The aim of this report is to support well-informed decisions in health care that lead to improved quality of services. The evidence should be considered together with other relevant issues, such as clinical experience and patient preference.

Gro Jamtvedt	Marianne Klemp	Ingvil Sæterdal
Department director	*Unit director*	*Project coordinator*

Objective

To carry out a systematic review in order to assess whether HPV vaccines currently offered to 11 to 12-year-old girls in Norway are also effective as a catch-up vaccination for women up to age 26 in preventing HPV-related diseases.

Background

Human papillomavirus (HPV) is considered the most common sexually transmitted agent worldwide (1). The burden of HPV infection is considerable (2;3). More than 100 types of HPV have been identified (4;5). However, a small number of HPV types contribute to a large proportion of HPV-related diseases. Persistent infection with oncogenic HPV is recognized as a necessary cause of cervical cancer, with approximately 70% of cervical cancers in the world attributed to two of the most common HPV types, 16 and 18 (3) (2,5). The WHO International Agency for Research on Cancer judged that there was sufficient evidence to support a causal role of HPV 16 infection in carcinoma of the cervix, vulva, vagina, penis, anus, oral cavity, and oropharynx and tonsil (6). It was estimated that 5.2% of all cancers worldwide are attributed to HPV infections (2). Most sexually active women, and men, will experience an HPV infection during their lifetime (7).

Efficient prophylactic vaccines could have an important public health impact. As cancer takes a long time to develop, it would be difficult to conduct clinical trials ascertaining the efficacy of HPV vaccination on cervical cancer and other cancer types associated with HPV. Furthermore, as screening for cervical cancer is available, conducting such trials would be unethical. For these reasons, the WHO and the US Food and Drug Administration recommended that phase III trials examine vaccination efficacy on high-grade cervical intraepithelial neoplasia grades 2 and 3 (CIN2/3) (8). These dysplastic lesions are precursors of invasive cervical cancer, as shown in Figure 1. HPV 16 and 18 causes 50% of high-grade cervical intraepithelial neoplasia (CIN2/3) (9).

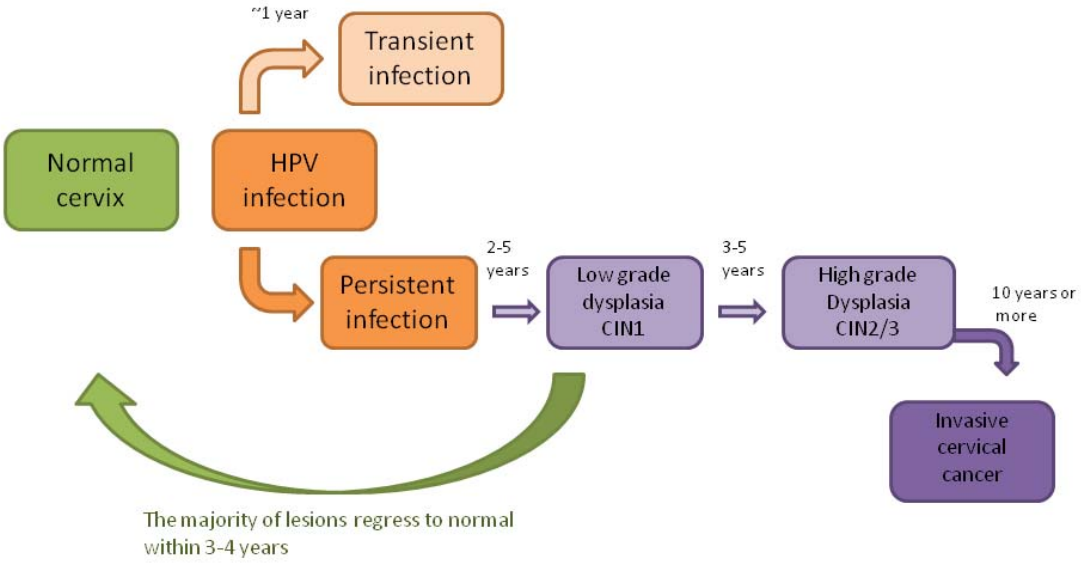

Figure 1: Natural history of cervical cancer

HPV infection is an established risk factor for vulvar and vaginal cancers (6). Vulvar intraepithelial neoplasia (VIN) and vaginal intraepithelial neoplasia (VaIN) are precursor lesions for vulva and vaginal cancers, respectively. Examining the possible association between HPV vaccination and VIN and VaIN lesions could give an insight into the possible association between such a vaccination and the incidence of vulvar and vaginal cancers.

The current cervical screening strategy in Norway is to take a cytological Pap-smear once every 3 years for women aged 25 to 69 (detailed algorithm for the Norwegian Cervical screening program can be found on the Cancer registry website (http://kreftregisteret.no/). A reduction in cervical cancer incidence was observed after screening program implementation (10). However, screening does not prevent HPV infection or development of pre-cancerous lesions. Identified pre-cancerous cells (CIN2+) are carefully followed and most commonly treated with excisional treatments, including loop electrosurgical excision procedures, laser conization and cold-knife conization.

Approximately 100% of genital warts (condyloma acuminate) are caused by either HPV 6 or 11 (11). An increasing incidence of genital warts has been described over recent decades in Europe (12). The prevalence of genital warts peaks in early sexually active years (13). A Nordic study reported that approximately 10% of women had been diagnosed with genital warts before the age of 45 (13). Diagnosis of genital warts can cause psychological stress and -sexual dysfunction; treatment is expensive and recurrences are common (14-16).

Under several plausible assumptions, an economic evaluation suggests that introduction of HPV 16/18 type vaccination to current screening in Norway may be a cost-effective strategy for further reductions in cervical cancer incidence and mortality (17), (18). Prophylactic HPV vaccination was introduced in the Norwegian childhood immunization program in 2009. In Norway, the vaccines Gardasil® (directed at HPV types 6, 11, 16 and 18) and Cervarix® (against 16 and 18 HPV types) were licensed for women aged 9 to 26, and currently Gardasil® is used to immunize 7th grade school girls (aged 11 to 12 years). These vaccines are non-infectious and contain virus-like particles. Because these vaccines were shown to be more effective among women who were not already infected with HPV, it is unclear whether vaccinating older women would be beneficial. Catch-up vaccination programs for older women have been implemented in 10 out of the 29 EU/EEA countries (19). However, the cost-effectiveness of a catch-up vaccination for females up to 26 years has not yet been established in Norway and needs assessment before a decision can be made regarding implementation.

The Norwegian Institute of Public Health requested a Health Technology Assessment to ascertain the potential effectiveness of a catch-up vaccination of females up to 26 years of age.

Method

This report presents a systematic review of the effect of a catch-up HPV vaccination of young women. It sheds light on whether HPV vaccines currently offered to 11 to 12-year-old girls in Norway are also effective as catch-up vaccination of women up to 26 years in preventing HPV-related cancers.

Literature search

We systematically searched for relevant literature in the following databases:

- Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present
- Embase 1980 to present
- Cochrane Central Register of Controlled Trials (Central)
- ISI web of Science
- PubMed (epub ahead of print)
- Google scholar

A methodology search filter was used to limit retrieval to randomized controlled trials. The search filter consisted of a combination of Randomized Controlled Trial.pt. (publication type), Randomized Controlled Trial (MeSH) and random*. as a text word (*=truncation). Studies about animals or animal experiments were removed. The year of publication was limited to 1999 to current (since the vaccines were introduced to the international market, including Norway, in 2006 we did not expect to find relevant studies with publication date before this).

The research librarian, Ingrid Harboe, planned and executed all the searches in collaboration with the project group. We developed search strategies that combined selected index and free text terms. The complete search strategy is shown in appendix 1. Last search for studies was carried out in October 2012.

We also looked for ongoing trials in Clinical Trials.gov and WHO ICTRP. We have listed all relevant trials in Appendix 5.

Furthermore, we contacted the pharmaceutical companies with marketing authorization for HPV vaccines in Norway (GlaxoSmithKline AS and Sanofi Pasteur MSD)

to obtain additional information and, if any, unpublished results that could be relevant to the reviewed topic and fulfilled the inclusion criteria. Supplemental information was considered.

Inclusion criteria

The inclusion criteria for the systematic review were defined using the following PICO:

Population:	Women aged 16 and older (this population is currently not included in the HPV vaccination program in Norway)
Interventions:	HPV vaccines
Control:	Placebo, no vaccine or other vaccines
Outcome:	Overall mortality Cancer related mortality Cervical cancer Cervical intraepithelial neoplasia grade 2 and higher (CIN2+) Vaginal intraepithelial neoplasia stage 2 and higher (VaIN2+) Vulval intraepithelial neoplasia stage 2 and higher (VIN2+) Serious adverse events (SAE) Genital warts/condyloma
Study design:	Randomized controlled trials
Languages:	No language restrictions was applied during the literature search, but we only included studies written in English, German, Italian, French, Portuguese and Spanish, or one of the Scandinavian languages.

We included full text references that assessed any of the predefined outcomes.

Article selection

The review authors worked independently and in pairs and reviewed all citations generated by the search to identify potentially relevant publications based on title and/or abstract. We retrieved the full text of all potentially eligible references and worked independently and in pairs to assess whether these references should be included based on the inclusion criteria. We resolved disagreements by discussion or, if required, we consulted one of the other review authors.

Assessment of risk of bias

Publications that met the predefined inclusion criteria were assessed for potential risk of bias according to the Handbook for the Norwegian Knowledge Centre (20). All assessments were performed and agreed upon by two of the review authors working independently. We resolved disagreements by discussion or, if required, by consulting one of the other review authors.

Data extraction and management

One review author extracted data from the included references and another review author verified the data.

We used a data extraction form that captured the following information: Identification details of the study (authors, year of publication, design and setting, clinical trial identification number or name, funding); Participant characteristics (gender, age); Intervention and control characteristics (type of vaccine and control, dose, vaccination schedule); Outcomes (outcome data (results)), methods for assessing/measuring the outcome data, length of follow-up, loss to follow-up).

We entered and analyzed the data using the Review Manager software (RevMan). We performed the meta-analyses using the Mantel-Haenszel "random effects model", since we expect some differences in effect sizes between populations and settings. However, if fewer than three studies reported the same clinical outcome we chose the "fixed effect model". We did this because we realized that the calculation of inter-study heterogeneity will be imprecise when the included studies show inconsistent results. If using fixed versus random effects models revealed significant results for one method and non-significant results for the other or if the results differed significantly, we have presented the results for both methods. For dichotomous outcomes we calculated risk ratios (RR) and associated 95% confidence intervals. For all outcomes, we conducted each analysis according to the "intention-to-treat" principle, when possible. However, the intention-to-treat principle in its strictest form (all randomized subjects) was not possible, so we have defined the intention-to-treat population matching best the definition used in included studies. In addition, we conducted analyses according to per-protocol, when possible. For assessment of serious adverse events we conducted the analyses based on the safety population as it was defined in each of the studies. When the outcome data could not be pooled in meta-analyses, we described the results in a narrative form.

Where data was reported in several publications, we used the publication with the longest follow-up. When a publication included several trials, preference was given to the publication that included the most trials in order to include the largest number of participants in the analysis.

We carried out analyses for HPV vaccination versus control. For the outcome CIN2+ and Condyloma we also carried out analysis based on the HPV DNA status in the lesions.

Grading the quality of evidence

Two review authors assessed the overall quality of evidence for each outcome ascertained using GRADE (Grading of Recommendations Assessment, Development, and Evaluation). GRADE provides criteria for rating the quality of evidence considering study design, risk of bias, imprecision, inconsistency, indirectness, publication bias, large effect, dose response gradient and confounding factors. We followed the GRADE guidelines and categorized our confidence in the effect estimates into four levels: high, moderate, low and very low. We have presented both the results from the meta-analyses (the estimate of effect) and the quality rating in the ”Summary of Findings” tables prepared using GRADE profiler software (GRADEpro) . For more details about the GRADE system we refer to publications by the GRADE Working Group (www.gradeworkinggroup.org).

Results

The literature search for randomized controlled trials on HPV vaccines was conducted in October 2012. We identified 616 references. In addition, we received 12 references from the pharmaceutical companies with marketing authorization for HPV vaccines in Norway. After reading titles and abstracts, 127 references were considered as possibly eligible and were read in full text. We excluded 81 references (these are listed in Appendix 4), and examined 46 references for the present report. A flow diagram of the selection process is shown in Figure 2.

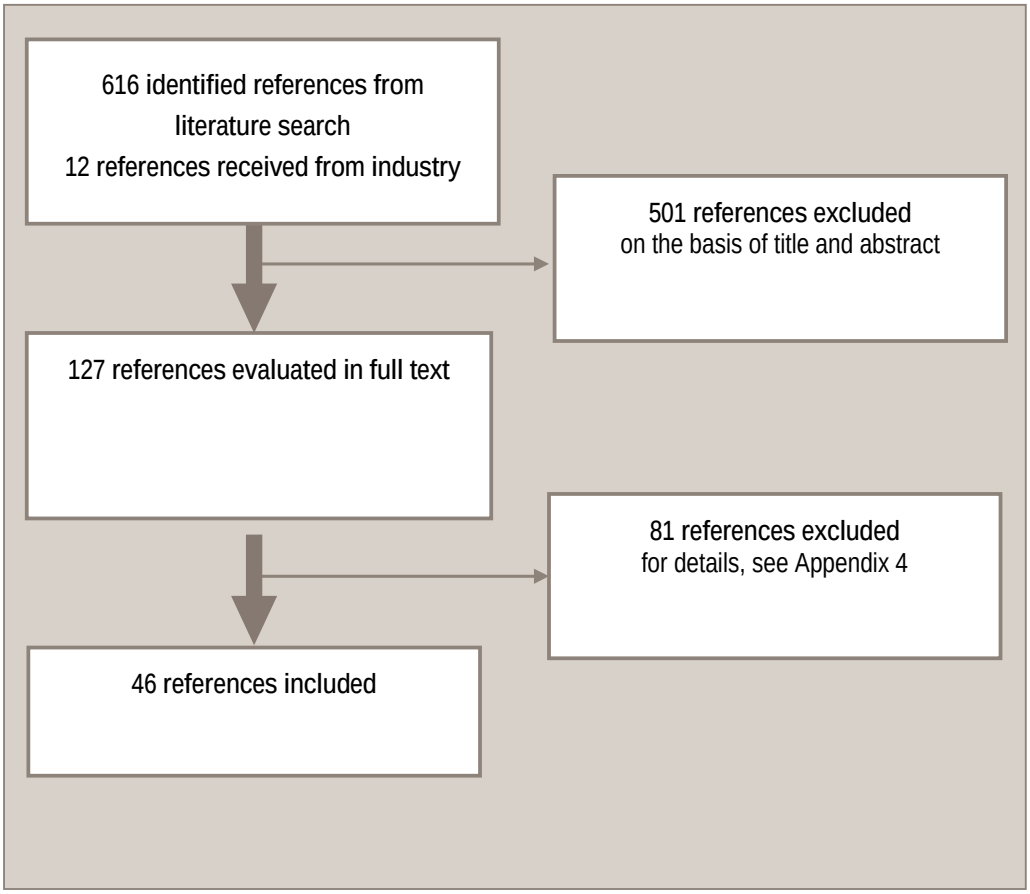

Figure 2. Flow diagram for selection of literature.

Description of included literature

The 46 included references represent 13 different main clinical trials, with some of the main clinical trials included in several studies. An overview of the included references is given in Table 1 and characteristics of the included studies are shown in Appendix 2.

The participants in the studies were healthy, non-pregnant women with an age ranging from 15 to 45 years. One of the studies included women aged 9 to 23 years, but the mean age was 17 years, so we decided to include the study (21). FUTURE protocol 19 (22;23) included women aged 24 to 45, mean age 34 years. However, we included this study since our inclusion criterion was women aged 16 and older. For some of the studies, there was a requirement of no history of HPV infection and negative HPV tests at entry into the study (24). In addition, fewer than four to six lifetime sex partners was also a requirement in some of the studies (21;24-26). The studies were conducted in North America (USA and Canada), South America, Europe and Asia.

Vaccines used in the trials were the bivalent vaccine containing HPV 16 and 18 virus-like particles (VLP) from GlaxoSmithKline, and the monovalent vaccine containing HPV 16 VLP and quadrivalent vaccine containing HPV 6, 11, 16 and 18 both from Merck. All trials used placebo as comparator except for one that used hepatitis B vaccine in both the intervention and the control groups (27), and another that compared the bivalent and the quadrivalent vaccines (28). All vaccines were given as three doses within six months (Day 1, month 2 and month 6 or month 0, 1 and 6).

The studies were generally assessed as having low risk of bias; however some of the studies had unclear allocation concealment and unclear blinding. The risk of bias assessment for the included references is shown in Appendix 2.

Table 1. Randomized controlled trials included in the review

Studies	Vaccine	Population	Outcomes used in report	Follow-up
FUTURE (protocol 5,7,13,15) (29)	HPV 6, 11, 16, 18 Protocol 5 is only HPV16	Intention to treat (ITT) population included all subjects who received at least one dose and had at least one follow-up visit post-dose 1. Per protocol population (PPP) included only participants with at least one follow-up visit post-dose 3	CIN2+	3 years (mean follow-up)
FUTURE (protocol 7,13,15)	HPV 6, 11, 16, 18	Intention to treat (ITT) population included all subjects who received at least one dose and had at least one follow-up	VIN2+ VaIN2+	3 years (mean follow-up)

(30;31)		visit post-dose 1. Per protocol population (PPP) subjects who were PCR negative and seronegative to HPV 6, HPV 11, HPV 16, or HPV 18 at enrollment; remained PCR negative to the same vaccine HPV type (s), to which they were naïve at enrollment, through 1 month post dose 3; received three doses of vaccine or placebo within 1year; and did not violate the protocol.		
FUTURE (protocol 13,15) (32-37)	HPV 6, 11, 16, 18	Intention to treat (ITT) population included all subjects who received at least one dose and had at least one follow-up visit post-dose 1. Per protocol population (PPP) Defined as subjects who Received all 3 doses of vaccine or placebo within 12 months. Were seronegative and HPV DNA negative on PCR analysis for HPV-6, HPV-11, HPV-16, or HPV-18 at day .Remained negative on PCR analysis for the same HPV type (to which they were negative at day 1 through 1 month after the third dose.	CIN2+ Condyloma VIN2+ VaIN2+	3 years (mean follow-up)
FUTURE (protocol 13) (38)	HPV 6, 11, 16, 18	Safety population included all randomized participants with follow-up information	SAE	3 years (mean follow-up)
FUTURE (protocol 15) (39)	HPV 6, 11, 16, 18	Safety population included all subjects who completed the vaccination report card from day 1 through day 15 after each vaccination	SAE	3 years (mean follow-up)
FUTURE (protocol 7) (40)	HPV 6, 11, 16, 18	Intention to treat (ITT) population included all subjects who were naıve to the relevant HPV type(s) at enrolment and had received at least one vaccination. Per protocol population (PPP) consisted of subjects who were PCR and seronegative to HPV 6, 11, 16, or 18 at enrolment, remained PCR-negative to the same vaccine-HPVtype (s) (to which they were naı¨ve at enrolment) through 1 month postdose three, received three doses of vaccine or placebo within 1year, and did not violate the protocol.	Condyloma SAE	
FUTURE (protocol 19) (22;23)	HPV 6, 11, 16, 18	Intention to treat (ITT) population subjects who received X1 dose of vaccine or placebo and returned for follow-up. Per protocol population (PPP) subjects who were seronegative at day 1 and PCR-negative (swab and biopsy specimens) from day 1 through month 7 to the relevant vaccine HPV type(s) and did	CIN2 Condyloma VIN2+ VaIN2+	

		not violate the protocol. The PPE-eligible participants received all 3 vaccinations within 1 year, and had 1 or more follow-up visits after month 7.		
FUTURE Protocol 7, 13,15,16 (41) Protocol 13,15,16 (42-45)	HPV 6, 11, 16, 18 HPV 6, 11, 16, 18	Intention to treat (ITT) population included all subjects who received at least 1 dose of vaccine or placebo and returned for follow-up. Per protocol population (PPP) includes all subjects aged 9–24 who were not general protocol violators; received all 3 vaccinations within acceptable day ranges; were seronegative at day 1 and (for all subjects except those <16 years old in protocols 016 and 018) negative for HPV DNA via PCR assay from day 1 through month 7 for the relevant HPV type(s); and had a month 7 serum sample collected within an acceptable day range.		
FUTURE (protocol 5) (25;46;47)	HPV 16	Intention to treat (ITT) population included all subjects who received at least one vaccination, included all protocol violators as well as subjects who tested positive for HPV-16 infection at enrollment. Per protocol population (PPP) included only participants who tested seronegative for HPV16 at the first study visit, tested negative for HPV16 DNA at all visits between day 1 and month 7 inclusive, and completed the entire three dose vaccine series. Safety population included all randomized participants	CIN2+ SAE	4 years (incl 7 months); ~8 years (Seattle centers)
PATRICIA (48-52)	HPV16/18	ITT population called total vacine cohort (TVC) included all women who received at least one vaccine dose and were evaluable for efficacy, irrespctive of baseline HPV status, cytological status, and serostatus. PPP Called according to protocol for efficacy (ATP-E) included all participants that received three doses of vaccine or placebo with a negative HPV DNA test, seronegative for HPV16 and/or 18 and with normal or low-grade cytology on day 1. Safety population included all randomized participants	CIN2+	End of study 48 month (in addition 15 and 35 month)
Harper	HPV 16/18	ITT population included all women who	Overall	Up to 6,4 years

(24;53-56)		had received at least one dose of study vaccine or placebo in the initial efficacy study, and who had any data available for outcome measurement in the extended follow-up phase. PPP included all women in the extended follow up phase who received three doses of HPV 16/18 vaccine or placebo, and who were negative for high-risk HPV DNA and seronegative for HPV 16 and HPV 18 at month 0, and negative for HPV 16 and HPV 18 DNA at month 6 in the initial efficacy study. Safety population included all assessible women who did not use any investigational or non-registered product or any HPV vaccine other than study vaccine during the study period.	mortality CIN2+ SAE	(incl 27 months and 4,5 years); up to 8.4 years (Brazilian centers)
Bhatla 2010 (57)	HPV16/18	Safety population included all vaccinated subjects with at least one vaccine/placebo dose administration documented.	SAE	7 months
Kang 2008 (21)	HPV 6, 11, 16, 18	Safety population included all subjects who received at least one injection	Overall mortality SAE	7 months
Kim 2011 (58)	HPV 16/18	Safety population included all participants with at least one vaccine/placebo dose administered.	SAE	7 months
Konno (59;60) (Konno 2009, Konno 2010)	HPV16/18	Safety population included all	SAE	24 months (incl 7 and 12 months)
Leroux-Roels 2011 (27)	HPV 16/18 and hepatitis B	Safety population included all women who received the fourth hepatitis B vaccine dose at month 12 (total vaccinated cohort up to month 13).	SAE	12 months
Ngang 2010 (61)	HPV 16/18	Safety population included all subjects who received at least one dose of the vaccine.	Total mortality SAE	7 months
Poland 2005 (62)	HPV 16	Safety population included all subjects who received at least one dose of the vaccine or placebo.	SAE	24 months
Yoshikawa (26)	HPV 6, 11, 16, 18	Safety population included all subjects who received at least one study vaccination and had follow-up data.	SAE SAE	7 months
Einstein (28;63)	Cervarix vs Gardasil	Safety population included all vaccinated participants (total vaccinated cohort)	Overall mortality	24 months

			SAE	

HPV vaccine versus control (placebo, no vaccine or other vaccine)

We summarized results for HPV vaccine group versus control (placebo, no vaccine or other vaccine) irrespective of the HPV status of the participants at study entry.

Overall mortality

Overall mortality was reported by FUTURE I and II, FUTURE protocol 19, PATRICIA, Harper, Kang 2008 and Ngang 2010 (21;22;24;38;39;48;61) . The authors reported that none of the deaths were considered to be related to the vaccination in either the vaccine or control groups.

Cancer related mortality and cervical cancer

We did not find any references that reported results for cancer related mortality or cervical cancer for this comparison.

CIN2+

For the outcome CIN2 and higher grade lesions (CIN2+), we present data for all CIN2+ lesions and for CIN2+ lesions associated with the HPV types in the vaccine. HPV CIN2+ lesions associated with the HPV types in the vaccine are those for which the HPV type in the lesion is the same as in the vaccine. Results are presented for a follow-up period of four years for both the intention-to-treat and the per protocol populations. We also present results for the intention-to-treat population for up to eight years.

All types of CIN2+ lesions (in intention-to-treat- and per protocol-populations)

We included five studies that reported on all CIN2+ lesions for the intention-to-treat population after a four-year follow-up. The pooled estimate for this outcome showed a borderline statistically significant difference in CIN2+ risk between the vaccine and the control groups (RR= 0.80; 95% CI= 0.62, 1.02), Figure 3. The quality of the evidence for this outcome is moderate due to inconsistency, Table 2.

If the fixed effect model was used, there was a 23% reduction in CIN2+ risk in the vaccine groups compared with the control groups (RR= 0.77; 95% CI= 0.70, 0.84).

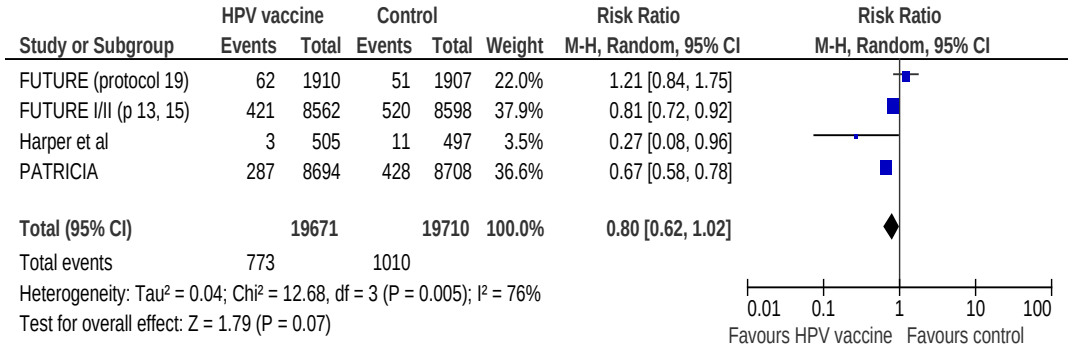

Figure 3. HPV vaccine versus control. Outcome: CIN2+, intention-to-treat (follow-up 4 years)

Additionally, we identified one relevant study that reported on all CIN2+ for the per protocol population after a four-year follow-up. The estimate for this outcome showed a statistically non-significant difference in CIN2+ lesions between the vaccine and the control groups (RR= 0.49; 95% CI= 0.21, 1.14), Figure 4. The quality of the evidence for this outcome is low due to imprecision, Table 2.

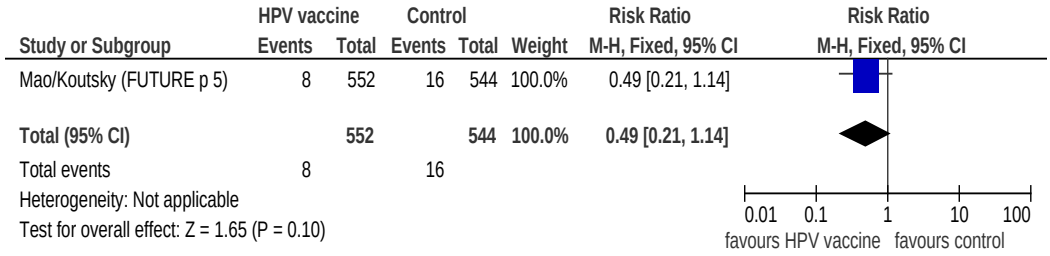

Figure 4. HPV vaccine versus control. Outcome: CIN2+, per protocol (4-year follow-up)

One of the studies also reported results for all CIN2+ lesions for the intention-to-treat population after a six-year follow-up. The estimate for this outcome showed a 71% reduction of all CIN2+ lesions in the vaccine group compared with the control group (RR= 0.29; 95% CI= 0.11, 0.78), Figure 5. The quality of the evidence for this outcome is moderate due to imprecision, Table 2.

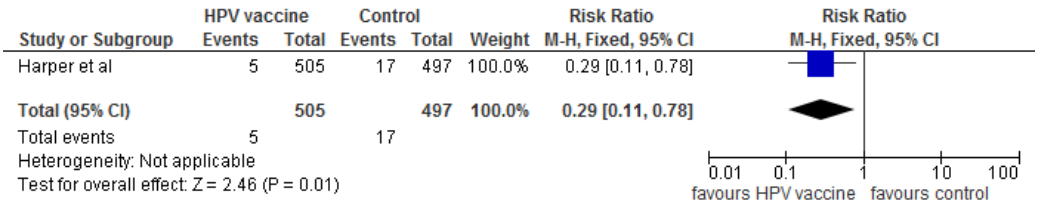

Figure 5. HPV vaccine versus control. Outcome: CIN2+, intention-to-treat (6-year follow-up)

One of the studies reported on all CIN2+ lesions for the intention-to-treat population after an eight-year follow-up. The estimate for this outcome showed a statistically non-significant difference between the vaccine and the control groups (RR= 0.64; 95% CI= 0.27, 1.52), Figure 6. The quality of the evidence for this outcome is low due to high risk of bias and imprecision, Table 2.

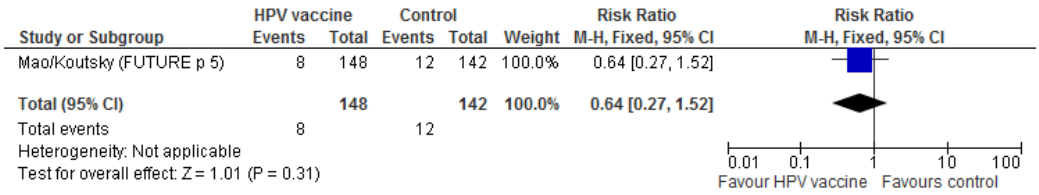

Figure 6. HPV vaccine versus control. Outcome: CIN2+, intention-to-treat (8-year follow-up)

CIN2+ lesions associated with the HPV types in the vaccine (in intention-to-treat- and per protocol populations)

We included seven studies that reported on CIN2+ lesions associated with the HPV types in the vaccines for the intention-to-treat population after a four-year follow-up. The pooled estimate for this outcome showed a 46% reduction in the risk for these lesions in the vaccine compared with the control groups (RR= 0.54; 95% CI= 0.44, 0.67), Figure 7. The quality of the evidence for this outcome is high, Table 2.

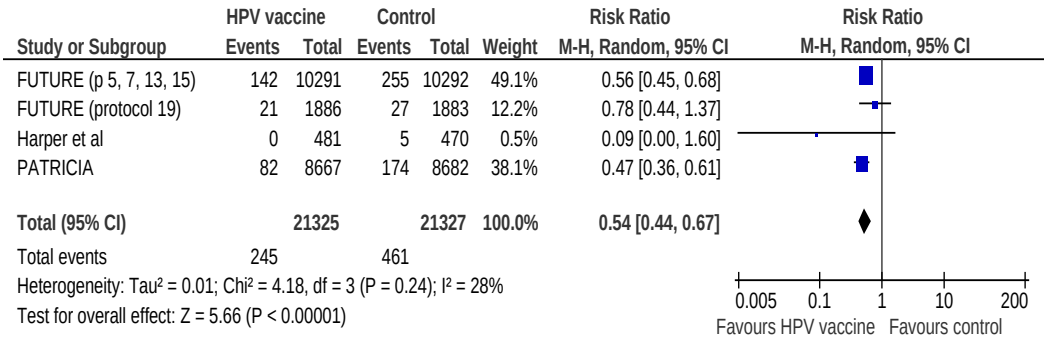

Figure 7. HPV vaccine versus control. Outcome: CIN2+ (HPV type related), intention-to-treat population (4-year follow-up)

We also included six studies that reported on CIN2+ lesions associated with the HPV types in the vaccines for the per protocol population after a four-year follow-up. The pooled estimate for this outcome showed a statistically significant difference in risk of these lesions between the vaccine and the control groups (RR= 0.05; 95% CI= 0.01, 0.16), Figure 8. The quality of the evidence for this outcome is high, Table 2.

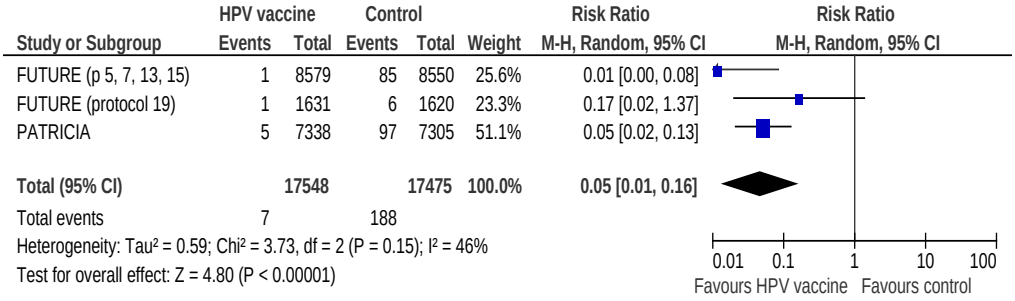

Figure 8. HPV vaccine versus control. Outcome: CIN2+ (HPV type related), per protocol population (4-year follow-up)

We included two studies that reported on CIN2+ lesions associated with the HPV types in the vaccines for the intention to treat population after an eight-year follow-up. The pooled estimate for this outcome showed a 71% reduction in the risk of these lesions in the vaccine group compared with the control group (RR= 0.29; 95% CI= 0.09, 0.96) (Figure 9). However, the confidence interval was large, and the quality of the evidence for this outcome is moderate due to imprecision, Table 2.

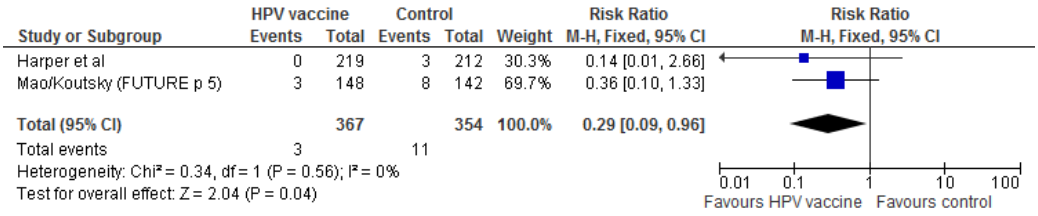

Figure 9. HPV vaccine versus control. Outcome: CIN2+ (HPV type related), intention-to-treat population (8-year follow-up)

Genital warts (Condyloma)

We included two studies that reported on genital warts (condyloma) for the intention-to-treat population after a four-year follow-up. The pooled estimate for this outcome showed a 62% reduction in the risk of genital warts in the vaccine group

compared with the control group (RR= 0.38; 95% CI= 0.31, 0.47), Figure 10. The quality of the evidence for this outcome is high, Table 2.

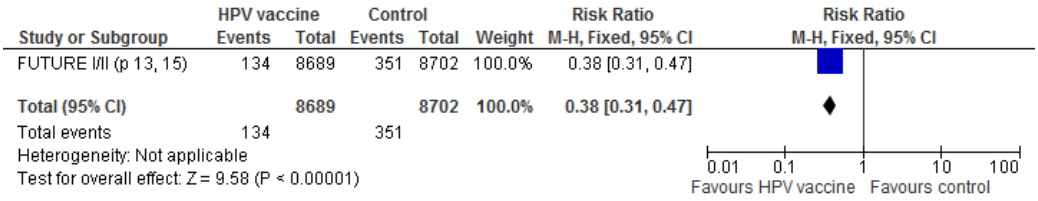

Figure 10. HPV vaccine versus control. Outcome: Genital warts, intention-to-treat population (4-year follow-up)

We included four studies that reported on genital warts associated with the HPV types in the vaccines for the intention-to-treat population after four to five-year follow-up. The pooled estimate for this outcome showed a statistically significant difference between the vaccine groups and the control groups (RR= 0.28; 95% CI= 0.12, 0.65), Figure 11. The quality of the evidence for this outcome is high, Table 2.

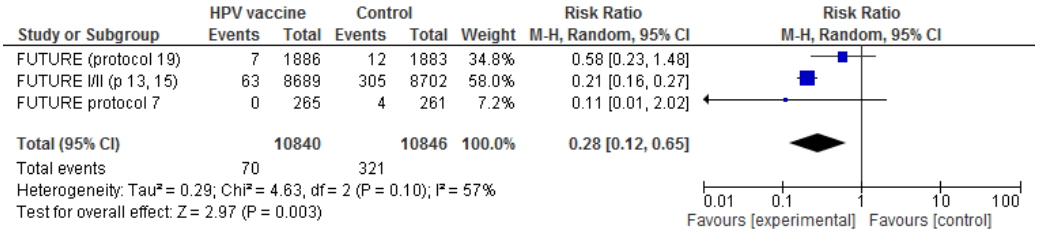

Figure 11. HPV vaccine versus control. Outcome: Genital warts, HPV type related, intention-to-treat population (4 to 5-year follow-up)

VIN2+, VaIN2+

We included two studies that reported on VIN2+ or VaIN2+ for the intention-to-treat population after a four-year follow-up. The pooled estimate for this outcome showed a 51% reduction in the risk of VIN2+ or VaIN2+ in the vaccine group compared with the control group (RR= 0.49; 95% CI= 0.32, 0.76), Figure 12. The quality of the evidence for this outcome is moderate due to imprecision, Table 2.

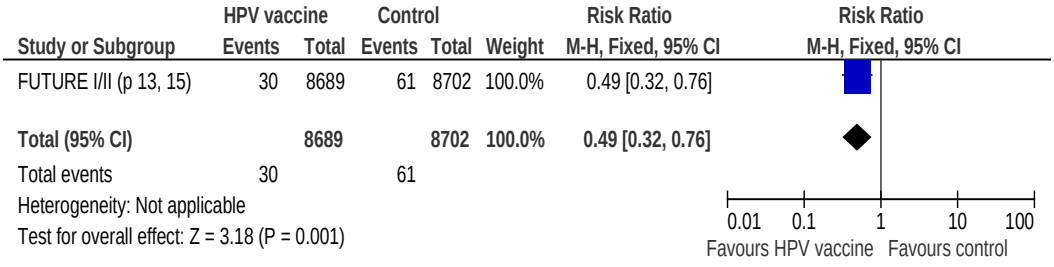

Figure 12. HPV vaccine versus control. Outcome: VIN2+, VaIN2+, intention-to-treat population (4-year follow-up)

We included four studies that reported on VIN2+ or VaIN2+ associated with the HPV types in the vaccines for the intention-to-treat population after four to five years follow-up. The pooled estimate for this outcome showed a non-statistically significant difference between the vaccine group and the control group (RR= 0.72; 95% CI= 0.03, 15.02), Figure 13. The quality of the evidence for this outcome is low due to imprecision and inconsistency, Table 2.

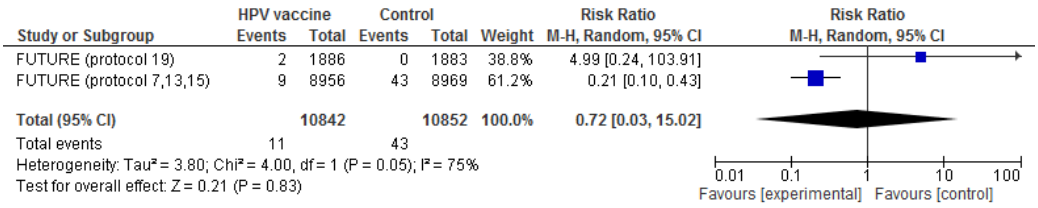

Figure 13. HPV vaccine versus control. Outcome: VIN2+, VaIN2+, HPV related, intention-to-treat population (4 to 5-year follow-up)

Serious Adverse Events

We included 14 studies that reported on serious adverse events. We have reported the results for the safety population as it was defined in each of the studies. The outcome was ascertained using estimates reported for the longest follow-up for each study. The pooled estimate for this outcome showed no statistically significant difference between the vaccine and the control groups (RR= 0.99; 95% CI= 0.91, 1.08), Figure 14. The quality of the evidence for this outcome is moderate due to high risk of bias, Table 2.

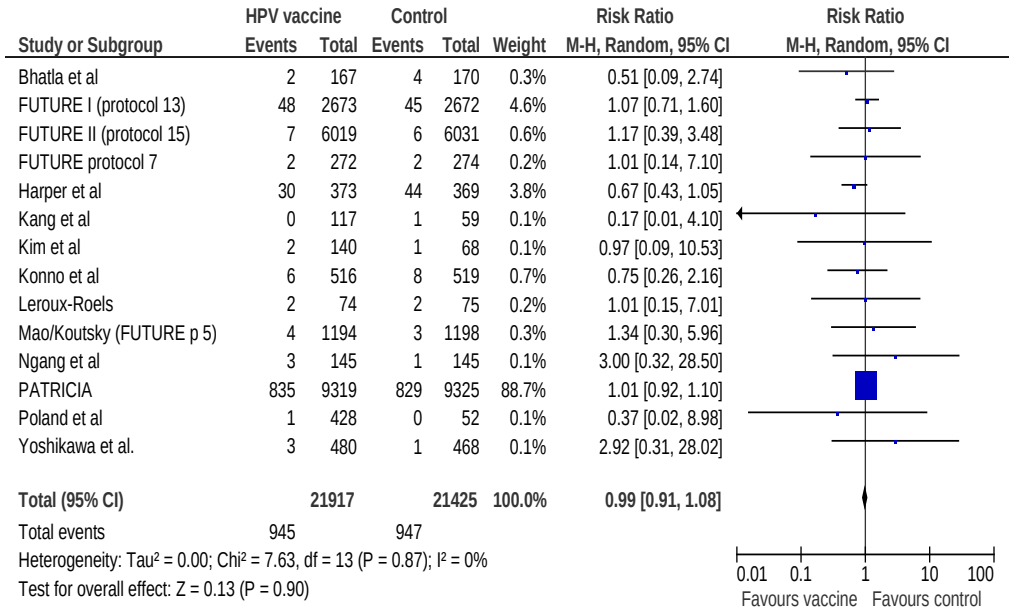

Figure 14. HPV vaccine versus control. Outcome: Serious Adverse Events, safety population (longest reported follow up)

Summary of findings table

The results for the comparison of HPV vaccines versus control are summarized in Table 2. The "Summary of Findings" table also presents our assessment of the quality of the evidence or the confidence we have in the results for each of the outcomes. The full GRADE evidence profile is shown in Appendix 3.

Table 2. Summary of fidings table for HPV vaccine versus placebo or no vaccine

HPV vaccines compared to placebo, no vaccine or other vaccines for women aged 16 years and older

Patient or population: women aged 16 years and older
Settings: community
Intervention: HPV vaccines
Comparison: placebo, no vaccine or other vaccines

Outcomes	Illustrative comparative risks* (95% CI) Assumed risk **Placebo, no vaccine or other vaccines**	Corresponding risk **HPV vaccines**	Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
Cancer related mortality			No studies were found that reported results for cancer related mortality or cervical cancer			
Cervical cancer						
CIN 2+ ITT (any HPV type**)** (4-year follow-up)	**51 per 1000**	**41 per 1000** (32 to 52)	**RR 0.8** (0.62 to 1.02)	39381 (5 studies)	⊕⊕⊕⊖ **moderate**[1,2]	
CIN2+ PPP (any HPV type) (4-year follow-up)	**29 per 1000**	**14 per 1000** (6 to 34)	**RR 0.49** (0.21 to 1.14)	1096 (1 study)	⊕⊕⊖⊖ **low**[2,3]	
CIN2+ ITT (any HPV type) (6-year follow-up)	**34 per 1000**	**10 per 1000** (4 to 27)	**RR 0.29** (0.11 to 0.78)	1002 (1 study)	⊕⊕⊕⊖ **moderate**[2,4]	
CIN2+ ITT (any HPV type) (8-year follow-up)	**85 per 1000**	**54 per 1000** (23 to 128)	**RR 0.64** (0.27 to 1.52)	290 (1 study)	⊕⊕⊖⊖ **low**[2,5,6]	
CIN2+ lesions ITT (HPV 16 and/or 18 related) (4-year follow up)	**22 per 1000**	**12 per 1000** (10 to 14)	**RR 0.54** (0.44 to 0.67)	42652 (7 studies)	⊕⊕⊕⊕ **high**[2]	
CIN2+ ITT (HPV 16 and/or 18 related) (8-year follow-up)	**31 per 1000**	**9 per 1000** (3 to 30)	**RR 0.29** (0.09 to 0.96)	721 (2 studies)	⊕⊕⊕⊖ **moderate**[4,7]	
CIN2+ PPP (HPV (16 and/or 18 related) (4-year follow up)	**11 per 1000**	**1 per 1000** (0 to 2)	**RR 0.05** (0.01 to 0.16)	35023 (6 studies)	⊕⊕⊕⊕ **high**[2]	
Genital warts ITT(any HPV type**)** (4-year follow-up)	**40 per 1000**	**15 per 1000** (13 to 19)	**RR 0.38** (0.31 to 0.47)	17391 (2 studies)	⊕⊕⊕⊕ **high**[2]	
Genital warts ITT (HPV 6 and/or 11 related) (4-5 year follow up)	**30 per 1000**	**8 per 1000** (4 to 19)	**RR 0.28** (0.12 to 0.65)	21686 (4 studies)	⊕⊕⊕⊕ **high**[2]	
VIN2+ and VaIN2+ ITT (any HPV type)(4-year follow-up)	**7 per 1000**	**3 per 1000** (2 to 5)	**RR 0.49** (0.32 to 0.76)	17391 (2 studies)	⊕⊕⊕⊖ **moderate**[2,4]	
VIN2+ and VaIN 2+ ITT (HPV related) (4-5-year follow-up)	**4 per 1000**	**3 per 1000** (0 to 60)	**RR 0.72** (0.03 to 15.02)	21694 (4 studies)	⊕⊕⊖⊖ **low**[1,6]	
Serious Adverse Events (Follow-up: >7 months[8], longest reported follow	**44 per 1000**	**44 per 1000** (40 to 48)	**RR 0.99** (0.91 to 1.08)	43342 (14 studies)	⊕⊕⊕⊖ **moderate**[2,9]	

up)

*The basis for the **assumed risk** is the median control group risk across studies. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] I-square >75%
[2] Funded by vaccine provider (we did not downgrade)
[3] Few events, high number of loss to follow-up
[4] Few events
[5] Participants were not blinded in this extended follow-up study.
[6] Few events and wide confidence interval. Both estimates of relative and absolute effects have wide confidence intervals.
[7] Participants were not blinded in one of the extended follow-up studies.
[8] We used the longest reported follow-up for each trial
[9] We have reported the results for the safety population as it was defined in each of the studies. Might have led to uncertain loss to follow up. Serious adverse events are defined differently in the studies.

HPV 16/18 vaccine versus HPV 6/11/16/18 vaccine

We summarized results for the HPV 16/18 vaccine (*Cervarix*™) versus the HPV 6/11/16/18 vaccine (*Gardasil*®). Only one study was included for this comparison (28;63). The study participants were healthy women, aged 18 to 45, recruited from 40 centers in the US. To date, two publications have reported results from the study, one after seven months follow-up and one after 24 months.

Overall mortality, cancer related mortality, cervical cancer and CIN2+

We did not find any references that reported results for cancer related mortality, cervical cancer or CIN2+ lesions for this comparison. The study we included reported one death due to metastatic renal cancer, but it is unknown which of the vaccines the participant received.

Serious Adverse Events

The included study reported on serious adverse events. We have reported the results for the total vaccinated cohort as it was defined in the study after 24-month follow-up. The estimate for this outcome showed no statistically significant difference between the HPV 16/18 vaccine and the HPV 6/11/16/18 vaccine groups (RR= 1.05; 95% CI= 0.59, 1.05), Figure 15. The quality of the evidence for this outcome is low due to high risk of bias and imprecision, Table 3.

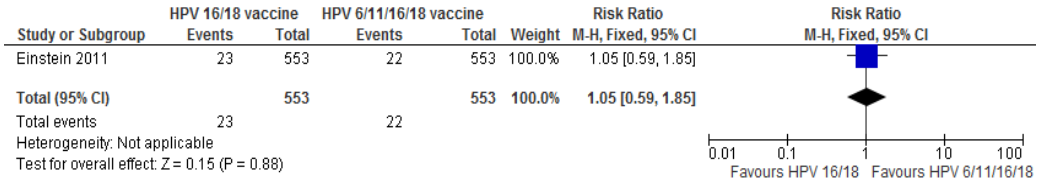

Figure 15. HPV vaccine versus control. Outcome: Serious Adverse Events, safety population (24 months follow-up)

Summary of findings table

The results for the comparison of the HPV 16/18 vaccine versus the HPV 6/11/16/18 vaccine are summarized in Table 3. The "Summary of Findings" table also presents our assessment of the quality of the evidence or the confidence we have in the results for each of the outcomes. The full GRADE evidence profile is shown in Appendix 3.

Table 3. Summary of fidings table for HPV 16/18 vaccine versus HPV 6/11/16/18 vaccine

HPV 16/18 compared to HPV 6/11/16/18 for women aged 16 years and older

Patient or population: Women aged 16 years and older
Settings: Community
Intervention: HPV 16/18
Comparison: HPV 6/11/16/18

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Partici-pants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk **HPV 6/11/16/18**	Corresponding risk **HPV 16/18**				
Serious Adverse Events (24-month follow up)	**40 per 1000**	**42 per 1000** (23 to 74)	**RR 1.05** (0.59 to 1.85)	1106 (1 study)	⨁⨁⨀⨀ **low**[1,2,3]	

*The basis for the **assumed risk** is the median control group risk across studies). The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the inter-vention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Unclear randomization and allocation concealment
[2] few events, only one study
[3] Funded by one of the vaccine providers (we did not downgrade)

Discussion

The objective of this review was to assess whether HPV vaccines currently offered to 11 to 12-year old girls in Norway are also effective as a catch-up vaccination strategy for women up to age 26 in preventing HPV-related diseases. The cost-effectiveness of such a vaccination will be covered in a separate report. Since cervical cancer usually develops very slowly, HPV vaccine data are still too recent to provide long-term evidence on cervical cancer and cancer related mortality. While this review indicates a protective effect of HPV vaccination on cervical pre-cancerous lesions, it is still unknown whether the HPV vaccines lower cervical cancer incidence. Due to the relatively short follow-up periods of published clinical trials up, the long term effect of HPV vaccination remains unclear. This systematic review can therefore not demonstrate any prevention of cervical cancer or reduction in overall mortality from the included studies.

Main findings

When combining the data for all pre-cancerous cervical lesions (CIN2+) in young women our results indicated a protective effect of these lesions. However, there is some uncertainty about the effectiveness of prophylactic HPV vaccination. The uncertainty is due to borderline significant results for CIN2+ lesions in the intention-to-treat and the per protocol population after a four-year follow-up.

Examining CIN2+ lesions independent of HPV type may reflect the possible wider public health impact of an HPV vaccination. Previous meta-analyses presented mostly results for lesions containing the HPV types included in vaccines under study (64;65). In line with previous meta-analyses, we found that assumed risk in the placebo group for HPV type related CIN2+ lesions is 22 per 1000, and the corresponding risk in the vaccine group is 12 per 1000. The confidence in this estimate (quality of the evidence) is high. High grade cervical lesions were chosen as the outcome of interest because they are immediate precursors to cervical cancer, and because they were described as the best outcome to use when examining the effect of HPV vaccination (8).

The intention-to-treat analysis is the most relevant from a public health perspective since it reflects the expected results if the HPV vaccine was offered to a broader pop-

ulation (the population would include people who will not take the vaccine or not take all the required doses). The studies varied in their inclusions criteria regarding previous HPV status. We have not analyzed separately the results for HPV naïve women and women with a previous history of HPV infection. However, the combined analysis might better reflect the general population, and, in particular, the population that would be targeted by a potential catch-up HPV vaccination.

There is some uncertainty regarding the long term effect of the vaccines due to the relatively short follow-up periods of the clinical trials. Since we will only know the true effect of HPV vaccination on cervical cancer and mortality outcomes in 20-30 years, long term follow-up data for the vaccinated populations are important. Using population registry data matched to vaccination information has been described as the best study design for studying long-term effects after HPV vaccination (66).

Evidence from clinical trials has shown lower incidence of genital warts (condyloma acuminata) in HPV vaccinated women. Among all women in the intention-to-treat analysis, the quadrivalent HPV vaccine provided protection against genital warts associated with the HPV types included in the vaccine. For genital warts, associated with the HPV types in the vaccine, the assumed risk in the placebo group is 30 per 1000, and the corresponding risk in the vaccine group is 8 per 1000. The confidence in these estimates (quality of the evidence) is high. Large cohort studies in Sweden and in Australia reported similar results (67) (69). Genital warts has a shorter incubation time after incident HPV infection and, as such, is an ideal measure for early evaluations of HPV vaccine effectiveness (68). The follow-up period of vaccinated cohorts in Sweden is still too short to assess the effectiveness against pre-cancerous lesions or invasive HPV-related cancers (67). Cohorts in Australia showed the same trend (69). An analysis of 85 770 new patients from six Australian sexual health clinics showed a remarkable reduction in the proportion of women under 21 years of age presenting with genital warts—from 11.5 % in 2007 to 0.85 % in 2011 (69).

No statistically significant difference in serious adverse events between the vaccination and the placebo groups were found. Nevertheless, the number of cases within the clinical studies is not sufficient to determine the occurrence of rarely occurring (severe) adverse events in a reliable way. Long-term safety needs to be assessed in future trials and in possible follow-up publications of existing trials.

Strengths and limitations of this review

We have conducted a systematic review based on primary clinical trials of a randomized controlled design. Randomized controlled trials are expected to be more robust against bias than observational studies, and are therefore the preferred design for studies of the effect of an intervention. However, to assess long-term follow-up data

and outcomes related to harm, observational and registry studies might be more appropriate.

Since data from the same clinical trial are published in many different publications within the field of HPV vaccination, we choose to prepare our own systematic review rather than building on others. We did this in order to get an overview of all the data, and also to assure, as far as possible, that all the data is compiled.

All included studies are sponsored by the vaccine producers. This can be a source of bias since drug studies funded by the pharmaceutical industry have been found to be more likely to present outcomes in favor of the sponsor (70). To limit the risk of publication bias, protocols for clinical trials are supposed to be registered in international databases so that it will be more transparent to follow what was planned and what is published.

Implications for practice and research

In 2007, Australia became one of the first countries to implement a nationally funded HPV vaccination program for girls and young women with the quadrivalent vaccine (71). It started with the vaccination in schools of girls aged 12 years and was followed by a catch-up program of girls and women aged 13-26 years. Quadrivalent vaccine protects against HPV types 6 and 11, which cause more than 90% of genital warts, in addition to HPV types 16 and 18, which are strongly associated with an increased risk of cervical cancer. Australian vaccination coverage rates were almost 80% for all three doses. Both Sweden and Denmark from the Nordic countries have already implemented catch-up programs, while Finland has not made the decision at the time of this report's publication.

Most women have positive attitudes and high intentions toward HPV vaccination as stated by a recent systematic review (72). Modeling the impact of screening policy and screening compliance on incidence and mortality of cervical cancer has shown that greatest health gains were accomplished by ensuring a high vaccine uptake (73). It still needs to be assessed whether the HPV vaccine program could lead to a reduction in attendance at cervical cancer screening programs. The model showed that screening of young women <30 years remains important and that increasing the screening interval to 5 years might lead to 4.7-11,3% additional cancers per year (73).

HPV distribution varies a bit geographically. Our review includes studies from South and North America and from Europe. In North America HPV 16 and 53 are the most common HPV types, in South America HPV 16 and 58 are most frequent and in northern Europe HPV 16 and 18 are the most prevalent types (1). Since the vaccine seems to be effective for the lesions that are HPV related to the vaccines, the results

might be even better for the northern Europe population than was demonstrated in the trials.

National vaccination programs have already been started in many countries, but the true effect on cervical cancer outcomes of this vaccine will first come 20-30 years from now. It remains to be seen whether we will see a dramatic reduction in HPV-associated diseases, such as cervix, vulva, vagina, anus, oral cavity, and oropharynx and tonsil cancers, as a result of a national vaccination programs.

Conclusion

Our systematic review of the effect of a catch-up HPV vaccination of young women demonstrates that:

There is a protective effect of HPV vaccination against CIN2+ lesions associated with the HPV types in the vaccines (high quality of the evidence) and all CIN2+ lesions (independent of HPV types in the lesions) (moderate quality of evidence).

Long-term (up to 8 years) follow-up after HPV vaccination indicates little or no difference in the occurrence of serious adverse events in the vaccine group when compared to the control group (moderate quality of evidence).

Need for further research

The present systematic review found no results for incidence of cervical cancer or cancer related mortality. Long-term follow –up studies are required to demonstrate if there is an effect of HPV vaccination on cancer outcomes.

Long-term follow-up studies are also required to generate more data on the safety aspects of the vaccine.

We suggest the following PICO for long-term studies to demonstrate effect on cancer, cancer related mortality and safety:

Design: Prospective observational studies (vaccinated versus non-vaccinated cohorts) and registry studies.
Population: Women
Intervention and comparator: HPV vaccines versus placebo or other HPV vaccines.
Outcomes: Cancer related mortality, cervical cancer, other cancer types, pre-cancerous lesions unrelated of HPV status in the lesions, serious adverse events

International collaboration is essential in order to generate sufficient data and avoid duplication of work.

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Appendixes

Appendix 1. Literature search

Databases: Embase, Ovid Medline, Cochrane Library; Central, ISI web of Science, PubMed, Clinical Trials.gov, WHO ICTRP, Google scholar
Study design: RCT; search filter based on Ovid's filter "Therapy Maximizes specificity", extended with "random*.tw"
Time limit: 1999 - 2012
Result: 615 RCT (868 including dupl.)
Searched by: Ingrid Harboe, research librarian

Search strategies:
Database: Embase 1980 to 2012 Week 38, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present
Date: 04.10.2012
Result: 448 RCT

#	Searches	Results
1	Papillomavirus infections/ use prmz	13426
2	Papillomavirus infections/ use emez	2854
3	Papillomaviridae/ use prmz	18154
4	Papilloma virus/ use emez	9369
5	Warts/ use prmz	3806
6	Wart virus/ use emez [Underordnet emneord for Papilloma virus/]	21446
7	Condylomata acuminata/ [U e for Wart virus]	10074
8	Human papillomavirus 6/ use prmz	252
9	Human papillomavirus type 6/ use emez	1121
10	Human papillomavirus 11/ use prmz	232
11	Human papillomavirus type 11/ use emez	1026
12	Human papillomavirus 16/ use prmz	2127
13	Human papillomavirus type 16/ use emez	5375
14	Human papillomavirus 18/ use prmz	891
15	Human papillomavirus type 18/ use emez	2782
16	papillomavir*.tw. [= -virus/ -viridae]	48019
17	papilloma vir*.tw.	8898

18	hpv*.tw.	51345
19	wart virus*.tw.	257
20	condylomata acuminat*.tw.	2151
21	genital wart*.tw.	3684
22	venereal wart*.tw.	145
23	or/1-22	87192
24	Papillomavirus Vaccines/ use prmz [= human papilloma virus vaccines i Medline]	3229
25	Viral Vaccines/ use prmz	18904
26	Wart virus vaccine/ use emez [= hpv vaksine i Embase]	5437
27	Virus vaccine/ use emez	16768
28	Cancer vaccines/ use prmz	9149
29	Cancer vaccine/ use emez	9689
30	*Vaccines/ use prmz	10142
31	*Vaccine/ use emez	17399
32	vaccin*.tw.	421906
33	Immunization/	112477
34	(immuni?e or immuni?ation*).tw.	165835
35	or/24-34	570950
36	23 and 35	14897
37	Animals/ or Animal/ or Animal Experiment/	8367690
38	Humans/	26303234
39	37 not (37 and 38)	6438647
40	36 not 39 [resultat uten animals]	13742
41	limit 40 to yr="1999 -Current"	12793
42	Randomized Controlled Trial.pt.	337758
43	Randomized Controlled Trial/	667268
44	random*.tw.	1372370
45	or/42-44	1549338
46	41 and 45	863
47	remove duplicates from 46 [RCT]	530
48	47 use emez [RCT]	480
49	limit 48 to embase	398
50	47 use prmz [RCT]	50

Database: Cochrane Library
Date: 03.10.2012
Result: 185 clinical trials

ID Search

#1 MeSH descriptor: [Papillomavirus Infections] this term only
#2 MeSH descriptor: [Papillomaviridae] explode all trees
#3 MeSH descriptor: [Warts] this term only
#4 MeSH descriptor: [Condylomata Acuminata] this term only
#5 MeSH descriptor: [Human papillomavirus 6] explode all trees
#6 MeSH descriptor: [Human papillomavirus 11] this term only
#7 MeSH descriptor: [Human papillomavirus 16] this term only
#8 MeSH descriptor: [Human papillomavirus 18] this term only
#9 papillomavir*:ti,ab,kw
#10 papilloma vir*:ti,ab,kw
#11 hpv*:ti,ab,kw
#12 wart virus*:ti,ab,kw
#13 condylomata acuminat*:ti,ab,kw
#14 genital wart*:ti,ab,kw
#15 venereal wart*:ti,ab,kw
#16 MeSH descriptor: [Papillomavirus Infections] this term only
#17 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16
#18 MeSH descriptor: [Papillomavirus Vaccines] this term only
#19 MeSH descriptor: [Viral Vaccines] this term only
#20 MeSH descriptor: [Cancer Vaccines] this term only
#21 MeSH descriptor: [Vaccines] this term only
#22 vaccin*:ti,ab,kw
#23 MeSH descriptor: [Immunization] this term only
#24 (immuni?e or immuni?ation*):ti,ab,kw
#25 MeSH descriptor: [Papillomavirus Infections] this term only and with qualifiers: [Prevention & control - PC]
#26 #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25
#27 #17 and #26
#28 limit #27 to 1999-2012

Database: ISI Web of Science

Date: 03.10.2012
Result: 233 RCT
Search: Topic=(HUMAN PAPILLOMAVIRUS 6 or HUMAN PAPILLOMAVIRUS 11 or HUMAN PAPILLOMAVIRUS 16 or HUMAN PAPILLOMAVIRUS 18) AND Topic=(vaccine or vaccination) AND Topic=(randomized controlled trial) NOT Topic=(review)
Refined by: Document Types=(ARTICLE)
Timespan=1999-01-01 - 2012-09-27. Databases=SCI-EXPANDED

Database: PubMed

Date: 04.10.2012
Search: human papillomavirus vaccine and publisher [sb] (epub ahead of print)
Result: 1 unike

WHO ICTRP:

Date: 03.10.2012
Search: Condition: human papillomavirus OR human papilloma virus OR hpv
AND
Intervention: vaccine OR vaccination
Result: 34 trials (44 records) (referanser i eget dok.)

Clinical Trials.gov:
Date: 03.10.2012
Search: Condition: human papillomavirus OR human papilloma virus OR hpv
AND
Intervention: vaccine OR vaccination
Result: 219 (se referanser i eget dok. "Clinical Trials 219 ref")

Google scholar
Date: 03.10.2012
Search: vaccine "human papilloma virus" "randomized controlled trial"
Limit: 2011-2012 (ferdig med 2012, ikke 2011-resultat, kan sjekke et år av gangen)
Result: 0

Appendix 2. Characteristics of included studies and Risk of Bias tables

Details of study	Citation
Ref ID	200
Protocol number	NCT00344032
Study name	
First author of study, year of publication	Bhatla 2010
Title of study	Immunigenicity and safety of human papillomavirus-16/18 AS04-adjuvant cervical cancer vaccine in healthy Indian women
Study design	RCT
Year(s) study was conducted	July 2006 - December 2007
Follow up period	1 month post completion of the vaccination course (7 months)
Geographical location	India (4 centers across India)
Funding source	GlaxoSmithKline Biologicals
Population	
Gender	Women
Age of participants (mean/median)	28.4 years (18-35)
Inclusion criteria	Generally healthy, not taking any other investigational products or steroids and not pregnant or planning to become pregnant. Subjects with child-bearing potential were required to be taking effective

	contraception or abstinent from sexual relations.
Exclusion criteria	
Intervention and comparison	
Intervention	GlaxoSmithKline's HPV (16/18) L1 virus-like particle (VLP) cervical cancer vaccine, containing AS04 adsorbed on aluminum hydroxide adjuvant system. Vaccinated on months 0, 1 and 6.
Comparison(s)	Placebo, months 0, 1 and 6
Outcomes	
	Immunogenicity (Seroconversion/seropositivity rates for anti-HPV-16 and anti-HPV-18 antibodies
	Safety/reactogenicity (Local and general symptoms)
	Serious adverse events (as classified by the medical Dictionary for Regulatory Activities)
	New-onset chronic disorders
	Other medical significant conditions

Risk of Bias table for Bhatla 2010

Entry/Domain	Judgement	Description
Random sequence generation?	Low risk	"The randomization was performed at GSK Biologicals, …, using a standard Statistical Analysis System"
Allocation concealment?	High risk	"The investigator at the study center enrolled the participants, assigning them to their groups according to the randomization
Blining of participants and personnel?	Unclear risk	State that it is a double-blind study, but method not mentioned
Blinding of outcome assessments?	Unclear risk	State that it is a double-blind study, but method not mentioned
Incomplete outcome data?	Unclear risk	
Selective reporting?	Unclear risk	
Other sources of bias?	Unclear risk	
Conclusion	High risk of bias	

Details of study	Citation
Ref ID	280
Protocol number	
Study name	
First author of study, year of publication	Kang 2008
Title of study	Safety and immunigenicity of a vaccine targeting human papillomavirus types 6, 11, 16 and 18: a randomized, placebo-controlled trial in 176 Korean subjects
Study design	RCT
Year(s) study was conducted	October 2005 - May 2006
Follow up period	7 months
Geographical location	Korea, ten medical institutions reqruited females
Funding source	Merck & Company Inc
Population	
Gender	Women
Age of participants (mean/median)	16.6 (9 - 23)
Inclusion criteria	Non pregnant, aged 9-23 years at enrollment, and must not hace had a febrile illness (fever more than 37,8 °C) at vaccination. Subjects aged 9-15 years: no sexual experience, and no plan to have sexual experience during the study period. Subjects aged 16-23 years: histoy of less than four sexula partners at enrollment, and required to use effective contraception during the study period.
Exclusion criteria	Enrollment in studies of other investigational agents, history of any HPV vaccination, history of allergy to vaccine compound, history of vaccination within 14 days from enrollment, receipt of blood or blood-derived products within the 6 months preceding imjection, and immunosuppression. Subjects who were 16-23 years: no prior Papinocolaou test showing a squamous intraepithelial lesion or worse and/or a biopsy indicating CIN or worse.
Intervention and comparison	
Intervention	GARDASIL; 20 µg type 6, 40 µg type 11, 40µg type 16, 20 µg type 18, and 225 µg amorphous aluminum hydroxyphosphate sulfate adjuvant. 0.5 ml at day 1, month 2 and month 6.

Comparison(s)	Placebo with same adjuvant. 0.5 ml at day 1, month 2 and 6.
Outcomes	
	Immunogenicity. Serum anti HPV-6, 11, 16 and 18 responses.
	Injection site adverse experiences on days 1-5 post vaccination

Risk of Bias table for Kang 2008

Entry/Domain	Judgement	Description
Random sequence generation?	Unclear	"We randomly allocated participants in a 2:1 ratio to either vaccination group or the placebo group. Randomization was performed by the study centers using the block method with decreasing block sizes"
Allocation concealment?	Unclear	Method not described
Blining of participants and personnel?	Low risk	"The placebo consisted of the same adjuvant and was visually indistinguishable from the vaccine"
Blinding of outcome assessments?	Unclear	Method not described
Incomplete outcome data?	Low risk	All subjects were included in the safety analysis
Selective reporting?	Low risk	
Other sources of bias?	Low risk	
Conclusion	High risk of bias?	

Details of study	Citation
Ref ID	120
Protocol number	Study ID: 107291
Study name	
First author of study, year of publication	Kim 2011

Title of study	Human papillomavirus 16/18 AS04-adjuvanted cervical cancer vaccine: immunigenicity and safety in 15-25 years old healthy Korean women
Study design	RCT
Year(s) study was conducted	June 2007 to March 2008
Follow up period	7 months
Geographical location	Korea, six Korean centres
Funding source	GlaxoSmithKline Biologicals
Population	
Gender	Women
Age of participants (mean/median)	Mean age 22 ±2.37 years (15-25)
Inclusion criteria	Negative urine pregnancy test before each vaccination and agree to use adequate contraceptive precautions over the vaccination period.
Exclusion criteria	If the women had used any investigational or non-registered drug or vaccine, were pregnant or lactating or planning/likely to conceive during the study. History of HPV vaccination, monophosphoryl lipid A (MPL) or AS04-adjuvant administration, and those with history of chronic diseases.
Intervention and comparison	
Intervention	HPV-16/18 vaccine containing 20 μg each of HPV-16 and -18 L1 (structural protein of HPV) virus like particle and adjuvanted with proprietary immunostimulatory AS04 adjuvant system. 0.5 ml administered intramuxcularly at 0, 1, and 6 months schedule
Comparison(s)	Placebo containing 500 μg of aluminium as $AL(OH)_3$ without viral agent. Administered as adove
Outcomes	
	Antibody response against HPV-16 and HPV-18
	Solicited local symptoms
	Solicited general symptoms
	Unsolicited adverse events
	Serious adverse events
	New onset chronic diseases (NOCD)
	Medically significant conditions (MSD)
	Pregnancy outcomes

Risk of Bias table for Kim 2011

Entry/Domain	Judgement	Description
Random sequence generation?	Low risk	"The randomisation of the study vaccine/placebo was performed at GSK Biologicals, using a standard statistical analysis system programme. "
Allocation concealment?	Low risk	"Random allocation of participants was done with a 2:1 blocking scheme using an internet based randomisation system (SBIR) at the investigator site."
Blining of participants and personnel?	Low risk	"All participants and study personnel involved in the study conduct were blinded throught the study until the last subject and last visit and the database was frozen"
Blinding of outcome assessments?	Unclear	Not specified
Incomplete outcome data?	Low risk	All drop outs are accounted for
Selective reporting?	Low risk	
Other sources of bias?	Low risk	
Conclusion	Low risk of bias	

Details of study	Citation
Ref ID	481
Protocol number	Study number: 106001, NCT00306241
Study name	
First author of study, year of publication	Ngang 2010
Title of study	Human papillomavirus-16/18 AS04-adjuvanted cervical cancer vaccine: immunigenicity and safety in healthy Chinese women from Hong Kong
Study design	RCT
Year(s) study was conducted	March 2006 - June 2007
Follow up period	7 months
Geographical location	Hong Kong

Funding source	GlaxoSmithKline Biologicals
Population	
Gender	Women
Age of participants (mean/median)	Mean age 26 (SD=4)
Inclusion criteria	Healthy women aged 18 to 35 years
Exclusion criteria	Women who were reciving any investigational or non-registered drug or vaccine were excluded, as were those who had received AS04-adjuvant or HPV vaccine. Those having a chronic disease, or were pregnant, breasfeeding or planning to conceive were also excluded.
Intervention and comparison	
Intervention	0.5 ml HPV-16/18 vaccine containing 20 μg each of HPV-16 and -18 L1 virus like particle (VLP) and adjuvanted with a proprietary AS04 adsorbed on aluminum hydroxide, 500 μg. Three doses were administered intramuscularly at months 0, 1 and 6.
Comparison(s)	Placebo consisting of 500 μg aluminum hydroxide without any viral antigen. Administered as the vaccine.
Outcomes	
	Immunigenicity; serum antibody responses to HPV-16 and -18.
	Solicited local symptoms
	Solicited general symptoms
	Serious adverse events
	Medically significant conditions (events that promted emergency room or physician visits unrelated to common diseases or routine visits for physical examination or vaccination)
	New-onset chronic diseases (based on a review of the subject's pre-vaccination medical history)
	Pregnancies

Risk of Bias table for Ngang 2010

Entry/Domain	Judgement	Description
Random sequence generation?	Low risk	Randomization procedure is explained. Age stratification (18-25 and 26-35 years was used. Both randomisation of vaccine and randomisation of subjects were performed.
Allocation concealment?	Low risk	See above

Blining of participants and personnel?	Unclear risk	Method not described
Blinding of outcome assessments?	Unclear risk	Method not described
Incomplete outcome data?	Low risk	Drop outs are accounted for
Selective reporting?	Low risk	
Other sources of bias?	Low risk	
Conclusion	Low risk of bias	

Details of study	Citation
Ref ID	408
Protocol number	
Study name	
First author of study, year of publication	Poland 2005
Title of study	Immunigenicity and Reactogenicity of a Novel Vaccine for Human Papilloomavirus 16: A 2-year Randomized Controlled Trial
Study design	RCT
Year(s) study was conducted	October 12, 1998 to September 30, 2001
Follow up period	24 months
Geographical location	US, 15 centers
Funding source	Merck Research Laboratories, Rahway, NJ
Population	
Gender	Women
Age of participants (mean/median)	21.5 (SD 2.1)
Inclusion criteria	Healthy non pregnant women 18 to 26 years of age. Subjects were instructed to use effective contraceptive measures for the first 7 months of the trial and were discontinued if they became pregnant during the vaccination phase.

Exclusion criteria	Allergic to any vaccine component, had received any blood product or component in the previous 6 months, had any know immune or coagulation disorder, or had received any other vaccination in the previous 30 days.
Intervention and comparison	
Intervention	1 of 4 doses of HPV 16 L1 VLP vaccine at day 1, at month 2, and at month 6. The vaccine consists of highly purified (>97 %) recombinant VLP of HPV 16 L1 capsid polypeptide adsorbed onto and aluminum adjuvant. Each O.5 ml dose contained 225 μg aluminum adjuvant and 10, 20, 40 or 80 μg of HPV 16 L1 VLP. Administered via intramuscular injection into the upper arm.
Comparison(s)	O.5 ml placebo containing 225 μg of aluminum adjuvant in the same carrier as the vaccine.
Outcomes	
	Serum anti- HPV 16 L1 antibody
	Adverse ecperiences
	Serious adverse experiences predefined as any AE that resulted in death, was deemed by the investigator to be life threatning, or resulted in a persistent or severe diability or incapacity.

Risk of Bias table for Poland 2005

Entry/Domain	Judgement	Description
Random sequence generation?	Low risk	"..assigned to study groups using a computer-generated randomization schedule (blocking factor of 9) in a 2:2:2:2:1 ratio to receive 1 of 4 doses…"
Allocation concealment?	Unclear	Method not described
Blining of participants and personnel?	Unclear	Method not described, state to be double blinded
Blinding of outcome assessments?	Unclear	See above
Incomplete outcome data?	Low risk	Drop outs are accounted for
Selective reporting?	Low risk	
Other sources of bias?	Low risk	
Conclusion	High risk of bias??	

Details of study	Citation	Citation
Ref ID	475	29
Protocol number		
Study name	Konno	
First author of study, year of publication	Konno 2009	Konno 2010
Title of study	Immunogenicity, reactivity, and safety of human papillomavirus 16/18 AS04-adjuvanted vaccine in Japanese women	Effecacy of human papillomavirus 16/18 AS04-adjuvanted vaccine in Japanese women Aged 20 to 25 years
Study design	RCT	
Year(s) study was conducted		
Follow up period	7 months	12, 24 months
Geographical location	Japan	
Funding source	GlaxoSmith Kline Biologicals	
Population		
Gender	Female	
Age of participants (mean/median)	20-25 (mean)	
Inclusion criteria	Healthy women , agreed to contraception, intact cervix	
Exclusion criteria	history of vaccine reaction, , chronic or autoimmune disaease	
Intervention and comparison		
Intervention	HPV16/18 SA04-adjuvanted vaccine (20 μg) on 0,1 and 6 month schedule	
Comparison(s)	Hepatitt A vaccine (inactivaed HAV antigen) (0,5 μg) on 0,1 and 6 month schedule	
Outcomes		
	Immonugenicity	
	reactivity	

	safety	

Risk of Bias table for Konno 2009/2010

Entry/Domain	Judgement	Description
Random sequence generation?	Low risk	Randomized 1:1 fasion, not more stated
Allocation concealment?	Unclear risk	Not stated
Blining of participants and personnel?	Low risk	Phase II , double blinded (observer blinded)
Blinding of outcome assessments?	Low risk	To ensure blinding, the interim analysis was performed by an independent and external statistician. Therefor the study blinding is maintained for GlaxoSmithKline personnel, investigators, study collaborators, and subjects.
Incomplete outcome data?	High risk	5 out of 1035 lost to follow up
Selective reporting?	Low risk	Reporting ITT and ATP
Other sources of bias?	Low risk	Funding GSK
Conclusion	Low risk of bias	

Details of study	Citation
Ref ID	119
Protocol number	
Study name	Leroux-Roels
First author of study, year of publication	Leroux-Roels 2011
Title of study	Ramdomized trial of the immunogenecity and safety of the Hepatitis B vaccine given in a accelerated schedule coadministrated with the

	human papillomavirus 16/18 L1 AS-04 adjuvanted cervical cancer vaccine.
Study design	RCT
Year(s) study was conducted	
Follow up period	12 month
Geographical location	Belgium
Funding source	GlaxoSmith Kline Biologicals
Population	
Gender	Female
Age of participants (mean/median)	20-25 (mean 22.2)
Inclusion criteria	Healthy women , agreed to contraception, no pregnant, no breastfeeding,
Exclusion criteria	history of vaccine reaction, , chronic or autoimmune disaease
Intervention and comparison	
Intervention	Hepatitis B vaccine given at 0,1,2, and 12 months and the HPV16/18 L1 virus like vaccine Cervarix (20 μg) on 0,1 and 6 month schedule
Comparison(s)	Hepatitt B vaccine (HBV) Havrix (20 μg) on 0,1 and 12 month schedule
Outcomes	
	HPV infections
	Safety

Risk of Bias table for Leroux-Roels 2011

Entry/Domain	Judgement	Description
Random sequence generation?	Low risk	Women were randomized (1:1 ratio) to receive the hepatitis B vaccine and the HPV-16/18 vaccine (HepB_HPV group) or the hepatitis B vaccine alone given at. A randomization blocking scheme was used, with the randomization list generated at GSK Biologicals using a standard Statistical Analysis System (SAS) program
Allocation concealment?	Low risk	Treatment allocation at each study center was performed using an

		Internet-based randomization system with an algorithm using a minimization procedure accounting for center.
Blining of participants and personnel?	Unclear risk	not stated
Blinding of outcome assessments?	Unclear risk	not stated
Incomplete outcome data?	Yes	5 of 76 all in the combined vaccine group were lost to follow up
Selective reporting?	Yes	Reporting ITT (TCV) and ATP
Other sources of bias?	Low risk	Funding GSK
Conclusion	Unclear risk of bias	

Details of study	Citation
Ref ID	
Protocol number	
Study name	
First author of study, year of publication	Yoshikawa 2013
Title of study	Efficacy of quadrivalent human papillomavirus (types 6, 11, 16 and 18) vaccine (GARDASIL) in Japanese women aged 18-26 years
Study design	
Year(s) study was conducted	
Follow up period	30 months
Geographical location	Japan
Funding source	Not stated
Population	
Gender	Women
Age of participants (mean/median)	18 to 26 years (mean age 23)
Inclusion criteria	Healthy women who were not pregnant, had no previous abnormal pap smears and reported lifetime history of four or fewer male sex partners. The study did not exclude women with previous HPV infection. Participants were required to use effective contraception during the vaccination phase.

Exclusion criteria	
Intervention and comparison	
Intervention	20 μg of HPV type 6, 40 μg of HPV type 11, 40 μg of HPV type 16 and 20 μg of HPV type 18 with 225 μg aluminum adjuvant. Intramuscular injection at day 1, month 2 and month 6
Comparison(s)	Placebo consisting of same adjuvant without VLP. Intramuscular injection at day 1, month 2 and month 6
Outcomes	
	Persistent infection
	Cervical end external genital disease
	Adverse events
	Serious adverse events

Risk of Bias table for Yoshikawa 2013

Entry/Domain	Judgement	Description
Random sequence generation?	Unclear risk	Method not described. State to be randomized.
Allocation concealment?	Unclear risk	Method not described
Blining of participants and personnel?	Unclear risk	Method not described. State to be double blind.
Blinding of outcome assessments?	Unclear risk	Method not described. State to be double blind
Incomplete outcome data?	Low risk	
Selective reporting?	Low risk	
Other sources of bias?	Low risk	
Conclusion	High risk of bias	

Details of study	Citation	Citation
Ref ID	110	227
Protocol number	NCT00423046	
Study name		
First author of study, year of publication	Einstein 2011	Einstein 2009
Title of study	Comparative immunogenicity and safety of human papillomavirus (HPV)-16/18 vaccine and HPV-6/11/16/18 vaccine	
Study design	RCT	
Year(s) study was conducted	not stated	
Follow up period	24 months (long term follow up through 48 months is ongoing)	7 months
Geographical location	USA, 40 centers	USA, 40 centers
Funding source	GlaxoSmithKline Biologicals, Belgium	GlaxoSmithKline Biologicals, Belgium
Population		
Gender	Women	
Age of participants (mean/median)	18-45, 30.7 ±8,02 (Cervarix); 30,2 ±7,67 (Gardasil)	
Inclusion criteria	Healthy women, intact cervix, a negative urine pregnancy test. If of childbearing potential, participants were required to be abstinent or use adequate contraception for 30 days prior to vaccination and to agree to continue such precautions for two months after the final vaccine dose.	
Exclusion criteria	Women who had previously received any HPV vaccine or vaccine/product containing MPL or AS04 where excluded.	
Intervention and comparison		
Intervention	0.5 ml doses of Cervarix administered into the deltoid muscle of the non-dominant arm according to their recommended three-dose schedules (Months 0,1,6)	

Comparison(s)	0.5 ml doses of Gardasil administered into the deltoid muscle of the non-dominant arm according to their recommended three-dose schedules (Months 0,2,6)	
Outcomes		
	Antibody response in serum	
	Antibody response in cervicovaginal secretions	
	Memory B-cell responses	
	CD4+ T-cell responses	
	Safety	

Risk of Bias table for Einstein 2009/2011

Entry/Domain	Judgement	Description
Random sequence generation?	Unclear	"Women were stratified by age (16-26, 27-35, 36-45 years) and randomized (1:1 in each age group)"
Allocation concealment?	Unclear	Not descibed
Blining of participants and personnel?	Low risk	"The study was conducted in an observer-blind manner (i.e., vaccines were prepared and administered by qualified medical personnel not otherwise involved in the conduct of the study, with study personnel involved in the clinical evaluation of the subjects and subjects themselves remaining blinded to treatment group). To maintain the blind, women received one dose of placebo at either month 1 or 2 as appropriate.
Blinding of outcome assessments?	Low risk	See above
Incomplete outcome data?	Low risk	All participants in the total vaccinated cohort are included in the safety assessment
Selective reporting?	Low risk	
Other sources of bias?	Low risk	
Conclusion	Low risk of bias	

Details of study	Citation	Citation	Citation	Citation	Citation
Ref ID	416	393	256	208	667
Protocol number			NCT00120848	NCT00518336	NCT00518336
Study name					
First author of study, year of publication	Harper 2004	Harper 2006	GlaxoSmithKline study group 2009	Carvalho 2010	Roteli-Martins 2012
Title of study	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	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	Sustained efficacy and immunigenicity of the human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine: analysis of a randomised placebo-controlled trial up to 6.4 years	Sustained efficacy and immunigenicity of the HPV-16/18 AS04-adjuvanted vaccine up to 7.3 years in young adult women	Sustained immunogenicity and efficacy of the HPV-16/18 AS04-adjuvanted vaccine
Study design	RCT	Follow-up of RCT	Follow-up RCT	Follow-up RCT	Follow-up RCT
Year(s) study was conducted	Not mentioned	November 2003 - July 2004	November 2003 - Aug 2007	November 2007 and 3 years	
Follow up period	27 months. Initial phase concluded at month 18, follow-up extension phase concluded at month 27.	mean follow-up time 47.7 months, SD 3.4	6.4 years	mean follow-up time was 7.0 years (2561.6 days, SD 70.3 days)	mean follow-up time was 7.9 years (2902.6 days, SD 102.5 days.)

Geographical location	North America (Canada and USA) and Brazil, 32 study sites	North America (Canada and USA) and Brazil, 28 study sites	North America (Canada and USA) and Brazil, 27 study sites	Brazil, 5 centers	Brazil, 5 centers
Funding source	GlaxoSmithKline Biologicals	GlaxoSmithKline Biologicals	GlaxoSmithKline Biologicals	GlaxoSmithKline Biologicals	GlaxoSmithKline Biologicals
Population					
Gender	Women	Women	Women	Women	Women
Age of participants (mean/median)	mean 20 years (SD=3)	mean 23.2 years (SD 2.9 (vaccine group); SD 2.8 (placebo group))	mean age 23 at entry into the follow up study	mean age 26.5 years at entry to teh study	mean age 26.5 years at entry to the study
Inclusion criteria	The initial phase (months 0-18) included healthy women aged 15-25 years, who had had no more than six sexualt partners, no history of an abnormal Pap test or ablative or extensional treatment for external condylomata; who were cytologically negative, seronegative for HPV-16 and HPV-18 antibodies by ELISA, and HPV-DNA negative by PCR for 14 high risk HPV types, no more than 90 days before study entry. Women who completed the	Those who participated in the initial efficacy study, received all three doses of vaccine or placebo, and for whom treatment allocation remained double blinded.	Women who received all three doses of study vaccine or palcebo and for whom treatment allocation remained masked were eligible for the 3-year follow-up study, which included seven scheduled visits.	Women participating at Brazilian study centers, who received all three doses of vaccine or placebo and whose treatment allocatoion remained blinded from the original study (Harper 2004)	Women participating at Brazilian study centers, who received all three doses of vaccine or placebo and whose treatment allocatoion remained blinded from the original study (Harper 2004)

	initial phase of the study earliest, and who did not have ablative or excisional therapy of the cervix, or hysterectomy after enrollment, wer eligible to participate in the extension phase of the study (months 18-27).				
Exclusion criteria					
Intervention and comparison					
Intervention	HPV-16/18 virus-like particle (VLP) vaccine containing 20 μg of HPV-16 L1 VLP and 20 μg of HPV-18 L1 VLP with AS04 adjuvant containing 500 μg aluminum hydroxide and 50 μg 3-deacylated monophosphoryl lipid A provided in a monodose vial. 0.5 ml dose at months 0, 1 and 6.	See Harper 2004	See Harper 2004	See Harper 2004	See Harper 2004

Comparison(s)	0.5 ml placebo at months 0, 1 and 6.	See Harper 2004	See Harper 2004	See Harper 2004	See Harper 2004
Outcomes					
	Immunogenicity	Immunigenicity	Immunigenicity	Immunigenicity	Immunigenicity
	Incident HPV-16 and HPV-16/18 infections	Incident HPV-16/18 infections	Incident HPV-16/18 infections	Incident HPV-16/18 infections	Incident HPV-16/18 infections
	Persistent HPV-16 and HPV-16/18 infections. (Detected in both cervical and cervicovaginal samples)	Persistent HPV-16 and HPV-16/18 infections. (Detected in both cervical and cervicovaginal samples)	Persistent HPV-16 and HPV-16/18 infections. (Detected in both cervical and cervicovaginal samples)	Persistent HPV-16 and HPV-16/18 infections. (Detected in both cervical and cervicovaginal samples)	Persistent HPV-16 and HPV-16/18 infections. (Detected in both cervical and cervicovaginal samples)
	Cytological abnormalities	Cytological and histological outcomes	Cytological and histological outcomes	Cytological and histological outcomes	Cytological and histological outcomes
	Adverse events and serious adverse events. Measured with diary cards and interviews.	Incident infection with HPV 45, 31, 52, 33 and 58	Adverse events and serious adverse events. Measured with diary cards and interviews.	Adverse events and serious adverse events. New onset chronic diseases, new onset autoimmune diseases, medically significant adverse events.	Adverse events and serious adverse events. New onset chronic diseases, new onset autoimmune diseases, medically significant adverse events.
		Adverse events and serious adverse events. Measured with diary cards and interviews.		Pregnancies and their outcomes	Pregnancies and their outcomes

Risk of Bias table for Harper 2006/ GlaxoSmithKline study group 2009

Entry/Domain	Judgement	Description
Random sequence generation?	Low risk	"Stratified, block randomisation according to validated algorithm was centralised with an internet randomisation system. Stratification was according to age (15-17, 18-21, and 22-25 years) and region (North america and Brazil)"
Allocation concealment?	Low risk	"Treatment allocation remained concealed from investigators and the women participating in a long-term follow-up study"
Blining of participants and personnel?	Low risk	Placebo and vaccine was identical in appearance.
Blinding of outcome assessments?	Unclear risk	Not reported
Incomplete outcome data?	Low risk	Loss to follow up reported
Selective reporting?	Low risk	
Other sources of bias?	Low risk	Funding GSK
Conclusion	Low risk of bias	

Details of study	Citation	Citation	Citation	Citation	Citation
Ref ID	380	432	259		
Protocol number					
Study name	FUTURE (protocol 5)	FUTURE (protocol 5)			
First author of study, year of publication	Mao 2006	Koutsky 2002	Rowhani-Rahbar 2009		
Title of study	Efficacy of Human Papillomavirus-16 Vaccine to Prevent cervical Intraepithelial Neoplasia	A controlled trial of a human pappilomavirus type 16 vaccine	Longer-term prophylactic monovalent human papillomavirus type 16 vaccine		
Study design	RCT	RCT			
Year(s) study was conducted	October 1998 to November 1999	October 1998 to November 1999	March 2006 - May 2008		
Follow up period	48 months	7 months	8.5 years (range: 7.2 - 9.5 years)		
Geographical location	US, 16 centers		US, Seattle		
Funding source	Merck Research Laboratories	Merck Research Laboratories	Merck Research laboratories, West Point, USA		
Population					

Gender	Women				
Age of participants (mean/median)	20 years old, range 16-25				
Inclusion criteria	Not pregnant, reporting no prior Pap tests and lifetime history of 0-5 male sex partners were eligible. Virgins were enrolled if they were seeking contraception.		The 500 women from Seattle that took part in the original trial		
Exclusion criteria					
Intervention and comparison					
Intervention	HPV 16 vaccine containing 40 μg of HPV 16 L1 virus-like particle formulated on 225 μg of aluminum adjovant in a total carrier volume of 0.5 ml. The participants received 3 intramuscular injections at day 1, month 2 and month 6.				
Comparison(s)	Placebo containing 225 μg of aluminum adjovant in a total carrier volume of 0.5 ml. Administered as the				

	vaccine.				
Outcomes					
	Persistent HPV infection	Serious adverse events	Adverse events that occured within 14 days after vaccination		
	HPV 16 related CIN	Adverse events	Adverse events that oc Rowhani-Rahbar cured within 14 days after vaccination		
	HPV 16 antibodies				

Risk of Bias table for Koutsky/Mao/Rowhani-Rahbar

Entry/Domain	Judgement	Description
Random sequence generation?	Low risk	"Women underwent randomization according to a permuted block design. They were randomly assigned in a 1:1 ratio within study centres."
Allocation concealment?	Unclear	Method not described
Blining of participants and personnel?	Low risk	"Vaccine and placebo were visually indistinguishable". Participant were unblinded in the Rowhani-Rahbar follow-up trial.

Blinding of outcome assessments?	Unclear	Method not described
Incomplete outcome data?	High risk	More loss to follow up in the intervention group
Selective reporting?	Low risk	
Other sources of bias?	Low risk	
Conclusion	Low risk of bias (High risk of bias for long-term follow up trial)	

Details of study	Citation	Citation	Citation	Citation	Citation
Ref ID	354	243	470	105	19

Protocol number					
Study name					
First author of study, year of publication	Paavonen 2007	Paavonen 2009	Lehtinen 2012	Wheeler 2012	Szarewski 20011
Title of study	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	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	Overall efficacy of HPV-16/18 AS04-adjuvanted vaccine against grade 3 cervical intraepithelial neoplassia: 4-year end of study ananlysisi of the randomized doulble blind PATRICIA trial	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	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
Study design	RCT				
Year(s) study was conducted	May 2004-June 2005				
Follow up period	14.8 months (SD 4.9) (Interim)	34,9 months	48 months	48 months	
Geographical location	Australia, Belgium,Brazil, Cananda, Finland, Germany, Italy, Mexico, Phillipines, Spain, Taiwan, Thailand, UK and USA				

Funding source	GlaxoSmith Kline Biologicals				
Population					
Gender	Female				
Age of participants (mean/median)	15-25 (mean 20.0)				
Inclusion criteria	Healthy women who reported no more than six sexual partners, agreed to contraception, intact cervix,				
Exclusion criteria	history of coloposcopy, pregnant, breestfeeding, chronic or autoimmune disaease				
Intervention and comparison					
Intervention	HPV16/18 L1 virus like vaccine (20 µg) on 0,1 and 6 month schedule				
Comparison(s)	Hepatitt A vaccine (HAV) Havrix (720 EU) on 0,1 and 6 month schedule				
Outcomes					
	CIN1+				

	CIN2+				
	CIN3+				
	immunogenicity				
	safety				

Risk of Bias table for PATRICIA (Paavonen 2007)

Entry/Domain	Judgement	Description
Random sequence generation?	Low risk	Internet-based centralised randomisation system
Allocation concealment?	Low risk	Allocation of treatment numbers was stratified by study site and by age
Blining of participants and personnel?	Low risk	Dobble blinded. Because the study is continuing, individual vaccine allocation remains blinded
Blinding of outcome assessments?	Low risk	All CIN endpoints were confirmed by an expert histopathology review panel taht was blinded to vaccine status
Incomplete outcome data?	Low risk	5% dropped out of the study, shown in table 1.
Selective reporting?	Low risk	Reporting total vaccine cohorts

Other sources of bias?	Low risk	Funding by GlaxoSmithKline Biologicals
Conclusion	Low risk of bias	

Risk of Bias table for FUTURE protocol 7

Entry/Domain	Judgement	Description
Random sequence generation?	unclear	
Allocation concealment?	yes	Both the subject and the investigator and his/her staff were blinded to who received vaccine and who received placebo
Blining of participants and personnel?	yes	Mentionned fully double-blind trial
Blinding of outcome assessments?	unclear	Mentionned fully double-blind trial
Incomplete outcome data?		260 Vaccine group: 241 with completed follow-up, 275 placebo: 242 complete FU
Selective reporting?	NO	
Other sources of bias?	no	
Conclusion		

Risk of Bias table for FUTURE protocol 13

Entry/Domain	Judgement	Description
Random sequence generation?	YES	A computer-generated randomized allocation schedule within each study center in a 1:1 ratio to receive three 0.5-ml intradeltoid injections of either quadrivalent vaccine or placebo at day 1, months 2 and 6.
Allocation concealment?		
Blining of participants and personnel?	YES	The subject, investigator and Sponsor were blinded to the identity of the clinical material
Blinding of outcome assessments?	YES	All biopsy specimens were read in a blinded fashion
Incomplete outcome data?		
Selective reporting?	NO	per-protocol, unrestricted population, intention-to-treat
Other sources of bias?	NO	
Conclusion		

Risk of Bias table for FUTURE protocol 15

Entry/Domain	Judgement	Description
Random sequence generation?	YES	Subjects were allocated to treatment assignment using a computer-generated randomized allocation schedule within each study center (1:1 ratio) to receive three 0.5-ml intradeltoid injections of either quadrivalent vaccine or placebo at day 1
Allocation concealment?	unclear	not clarify
Blining of participants and personnel?	unclear	double-blind study, but no further clarification
Blinding of outcome assessments?	YES	clinical management by pathologists unaware of treatment-group assignments
Incomplete outcome data?		total population=6087 (vaccine), 6080 (control). PPP= 5305 (V), 5260 (C),unrestricted=5865 (V), 5863 (C), ITT=6087 (V), 6080 (C)
Selective reporting?	NO	per-protocol, unrestricted population, intention-to-treat
Other sources of bias?	no	
Conclusion		

Details of study	Citation
Ref ID	365
Protocol number	PROTOCOL 13: NCT00092521
Study name	FUTURE
First author of study, year of publication	Garland
Title of study	
Study design	Double blind RCT
Year(s) study was conducted	2001-2007
Follow up period	Post-dose 3 follow-up: 2.5 years
Geographical location	International
Funding source	Merck
Population	
Gender	Female
Age of participants (mean/median)	16-23
Inclusion criteria	Healthy women who were not pregnant and had no history of genital warts or abnormal results on cervical cytologic testing and had a lifetime number of no more than four sex partners were eligible
Exclusion criteria	Enrolled subjects with clinical evidence of genital HPV disease at day 1 were discontinued from the study before randomization
Intervention and comparison	
Intervention	HPV 6, 11, 16, 18
Comparison(s)	Placebo
Outcomes	

	CIN, AIS, condyloma acuminata, VIN, or VaIN

Details of study	Citation
Ref ID	463
Protocol number	PROTOCOL 15: NCT00092534
Study name	FUTURE
First author of study, year of publication	FUTURE II study group
Title of study	
Study design	Double blind RCT
Year(s) study was conducted	2002-2007
Follow up period	Post-dose 3 follow-up: 2.5 years
Geographical location	International
Funding source	Merck
Population	
Gender	Female
Age of participants (mean/median)	16-26
Inclusion criteria	
Exclusion criteria	
Intervention and comparison	
Intervention	HPV 6, 11, 16, 18

Comparison(s)	Placebo
Outcomes	

Details of study	Citation
Ref ID	377, 379, 410
Protocol number	PROTOCOL 7: NCT00365716
Study name	FUTURE
First author of study, year of publication	Villa (for all 3 publications)
Title of study	
Study design	Double blind RCT
Year(s) study was conducted	2002-2007
Follow up period	Post-dose 3 follow-up: 2.5 years
Geographical location	International
Funding source	Merck
Population	
Gender	Female
Age of participants (mean/median)	16-23
Inclusion criteria	#377 nonpregnant, healthy women who had no prior abnormal Pap smears, and reported a lifetime history of four or fewer male sex partners. Among virgins, enrolment was limited to those women who were X18 years of age and seeking contraception. #379 only non-pregnant, healthy women who reported no prior abnormal Pap smears of low-grade squamous intraepithelial lesion (LSIL) or worse, and reported a lifetime history of four or fewer male sex partners were enrolled.

Exclusion criteria	
Intervention and comparison	
Intervention	HPV 6, 11, 16, 18
Comparison(s)	Placebo
Outcomes	

Risk of Bias table for

Entry/Domain	Judgement	Description
Random sequence generation?		
Allocation concealment?		
Blining of participants and personnel?		
Blinding of outcome assessments?		
Incomplete outcome data?		
Selective reporting?		
Other sources of bias?		
Conclusion		

Appendix 3 GRADE evidence Profiles

HPV vaccine versus control

Author(s):
Date: 2013-05-30
Question: Should HPV vaccines vs placebo, no vaccine or other vaccines be used in women aged 16 years and older?
Settings: Community
Bibliography: Effect of catch-up HPV vaccination of young women

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	HPV vaccines	Placebo, no vaccine or other vaccines	Relative (95% CI)	Absolute		
CIN 2+ (ITT (follow-up 4 years) (follow-up mean 4 years)												
5	randomised trials	no serious risk of bias	serious[1]	no serious indirectness	no serious imprecision	none[2]	773/19671 (3.9%)	1010/19710 (5.1%)	RR 0.8 (0.62 to 1.02)	10 fewer per 1000 (from 19 fewer to 1 more)	⊕⊕⊕O MODERATE	
CIN2+ PPP (follow-up 4 years) (follow-up mean 4 years)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3]	none[2]	8/552 (1.4%)	16/544 (2.9%)	RR 0.49 (0.21 to 1.14)	15 fewer per 1000 (from 23 fewer to 4 more)	⊕⊕OO LOW	
CIN2+ ITT (follow up 6 years) (follow-up mean 6 years)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[4]	none[2]	5/505 (0.99%)	17/497 (3.4%)	RR 0.29 (0.11 to 0.78)	24 fewer per 1000 (from 8 fewer to 30 fewer)	⊕⊕⊕O MODERATE	
CIN2+ ITT (follow-up 8 years) (follow-up mean 8 years)												
1	randomised trials	no serious risk of bias[5]	no serious inconsistency	no serious indirectness	very serious[6]	none[2]	8/148 (5.4%)	12/142 (8.5%)	RR 0.64 (0.27 to 1.52)	30 fewer per 1000 (from 62 fewer to 44 more)	⊕⊕OO LOW	
HPV 6,11,16 or 18 related CIN2+ lesions 4 years follow ITT (follow-up mean 4 years)												
7	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none[2]	245/21325 (1.1%)	461/21327 (2.2%)	RR 0.54 (0.44 to 0.67)	10 fewer per 1000 (from 7 fewer to 12 fewer)	⊕⊕⊕⊕ HIGH	

HPV 16 and/or 18 CIN2+ lesions follow up 8 years ITT (follow-up mean 8 years)												
2	randomised trials	no serious risk of bias[7]	no serious inconsistency	no serious indirectness	serious[4]	none	3/367 (0.82%)	11/354 (3.1%)	RR 0.29 (0.09 to 0.96)	22 fewer per 1000 (from 1 fewer to 28 fewer)	⊕⊕⊕O MODERATE	
HPV 6,11,16 or 18 related CIN2+ lesions, 4 years follow up, PPP (follow-up mean 4 years)												
6	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none[2]	7/17548 (0.04%)	188/17475 (1.1%)	RR 0.05 (0.01 to 0.16)	10 fewer per 1000 (from 9 fewer to 11 fewer)	⊕⊕⊕⊕ HIGH	
Condyloma, any HPV type, 4-year follow-up ITT (follow-up 4 years)												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none[2]	134/8689 (1.5%)	351/8702 (4%)	RR 0.38 (0.31 to 0.47)	25 fewer per 1000 (from 21 fewer to 28 fewer)	⊕⊕⊕⊕ HIGH	
Condyloma, HPV related (follow-up 4-5 years)												
4	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none[2]	70/10840 (0.65%)	321/10846 (3%)	RR 0.28 (0.12 to 0.65)	21 fewer per 1000 (from 10 fewer to 26 fewer)	⊕⊕⊕⊕ HIGH	
VIN2+ and VaIN2+, any HPV type related follow up 4 year ITT (follow-up mean 4 years)												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[4]	none[2]	30/8689 (0.35%)	61/8702 (0.7%)	RR 0.49 (0.32 to 0.76)	4 fewer per 1000 (from 2 fewer to 5 fewer)	⊕⊕⊕O MODERATE	
VIN2+ and VaIN 2+ HPV related (follow-up 4-5 years)												
4	randomised trials	no serious risk of bias	serious[1]	no serious indirectness	serious[6]	none	11/10842 (0.1%)	43/10852 (0.4%)	RR 0.72 (0.03 to 15.02)	1 fewer per 1000 (from 4 fewer to 56 more)	⊕⊕OO LOW	
Serious Adverse Events (longest reported follow up) (follow-up >7 months[8])												
14	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[9]	none[2]	945/21917 (4.3%)	947/21425 (4.4%)	RR 0.99 (0.91 to 1.08)	0 fewer per 1000 (from 4 fewer to 4 more)	⊕⊕⊕O MODERATE	

[1] I-square >75 %
[2] Funded by vaccine provider
[3] Few events, high number of loss to follow-up
[4] Few events
[5] Participants were not blinded in this extended follow-up study.
[6] Few events and wide confidence interval. Both estimates of relative and absolute effects have wide confidence intervals.
[7] Participants were not blinded in one of the extended follow-up studies.

[8] We used the longest reported follow-up for each trial
[9] We have reported the results for the safety population as it was defined in each of the studies. Might have led to uncertain loss to follow up. Serious adverse events are defined differently in the studies.

HPV 16/18 vaccine versus HPV 6/11/16/18 vaccine

Author(s):
Date: 2013-06-12
Question: Should HPV 16/18 vs HPV 6/11/16/18 be used in women aged 16 years and older?
Settings: Community
Bibliography:

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	HPV 16/18	HPV 6/11/16/18	Relative (95% CI)	Absolute		
Serious Adverse Events (follow-up mean 24 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none[3]	23/553 (4.2%)	22/553 (4%)	RR 1.05 (0.59 to 1.85)	2 more per 1000 (from 16 fewer to 34 more)	⊕⊕OO LOW	

[1] Unclear randomization and allocation concealment
[2] few events, only one study
[3] Funded by one of the vaccine providers

Appendix 4. List of excluded studies

(1) Overall efficacy of HPV-16/18 AS04-adjuvanted vaccine against cervical intraepithelial neoplasia: 4-year end-of-study analysis of the randomised, double-blind PATRICIA trial]. *Akush Ginekol (Sofiia)* 2012; 51(1):63-64. *Reason for exclusion:* No full text available.

(2) Efficacy of a bivalent L1 virus-like particle vaccine in prevention of infection with human papillomavirus types 16 and 18 in young women: A randomized, controlled trial - Commentary. *Obstet Gynecol Surv* 2005; 60(5):303-305.
Reason for exclusion: Editorial

(3) HPV vaccine prevents CIN. *J Fam Pract* 2006; 55(4):285.
Reason for exclusion: Commentary

(4) Adams M, Jasani B, Fiander A. Prophylactic HPV vaccination for women over 18 years of age. *Vaccine* 2009; 27(25-26):3391-3394.
Reason for exclusion: Non systematic review

(5) Ali.H, et al. Genital warts in young Australians five years into national human papillomavirus vaccination programme: national surveillance data. *BMC Public Health* 2013; 13(18):1-9.
Reason for exclusion: Not RCT

(6) Anderson JS, Hoy J, Hillman R, Barnden M, Eu B, McKenzie A et al. A randomized, placebo-controlled, dose-escalation study to determine the safety, tolerability, and immunogenicity of an HPV-16 therapeutic vbaccine in HIV-positive participants with oncogenic HPV infection of the anus. *J Acquir Immune Defic Syndr* 2009; 52(3):371-381.
Reason for exclusion: Not relevant population

(7) Ault KA, Giuliano AR, Edwards RP, Tamms G, Kim L-L, Smith JF et al. A phase I study to evaluate a human papillomavirus (HPV) type 18 L1 VLP vaccine. *Vaccine* 2004; 22(23-24):3004-3007.
Reason for exclusion: Not relevant outcome

(8) Barton S, O'Mahony C. HPV vaccination-reaping the rewards of the appliance of science. National programmes could virtually eliminate certain diseases and substantially reduce costs. *BMJ* 2013; 346(12):1-2.
Reason for exclusion: Not RCT

(9) Beceiro BB. Bivalent vaccine in view of human papillomavirus types 16 and 18 is effective for lowering the incidence of intraepithelial cervical neoplasia in women who previously were not infected by these genotypes. *FMC Formacion Medica Continuada en Atencion Primaria* 2007; 14(9):595.
Reason for exclusion: Abstract

(10) Block SL, Brown DR, Chatterjee A, Gold MA, Sings HL, Meibohm A et al. Clinical trial and post-licensure safety profile of a prophylactic human papillomavirus (Types 6, 11, 16, and 18) L1 virus-like particle vaccine. *Pediatr Infect Dis J* 2010; 29(2):95-101.
Reason for exclusion: Non systematic review

(11) Block SL, Nolan T, Sattler C, Barr E, Giacoletti KED, 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(5):2135-2145.
Reason for exclusion: Comparison of different vaccine doses

(12) Brown B, Blas M, Cabral A, Carcamo C, Gravitt P, Halsey N. Randomized trial of HPV4 vaccine assessing the response to HPV4 vaccine in two schedules among Peruvian female sex workers. *Vaccine* 2012; 30(13):2309-2314.
Reason for exclusion: Not relevant outcome

(13) Budenholzer B. HPV-16/18 AS04-adjuvanted vaccine prevented cervical intraepithelial neoplasia >= grade 3 in young women. *Ann Intern Med* 2012; 157(2):JC2-JC7.
Reason for exclusion: Commentary

(14) Capri S, Gasparini R, Panatto D, Demarteau N. Cost-consequences evaluation between bivalent and quadrivalent HPV vaccines in Italy: The potential impact of different cross-protection profiles. *Gynecol Oncol* 2011; 121(3):514-521.
Reason for exclusion: Not RCT (model)

(15) Chesson HW, et al. Modeling the impact of quadrivalent HPV vaccination on
Reason for exclusion: Not RCT (model)

(16) De CN, Roteli-Martins C, Teixeira J, Naud P, De BP, Zahaf T et al. Sustained levels of total and neutralising antibodies and favourable long term safety with the HPV-16/18 AS04-adjuvanted vaccine (Cervarix): Follow-up to 7.3 years. *International Journal of Gynecology and Obstetrics* 2009; Conference(var.pagings):S357-S358.
Reason for exclusion: Abstract

(17) Donovan B, Grulich AE. The quadrivalent HPV vaccine is effective prophylaxis against HPV-related external genital lesions in young men. *Evidence-Based Medicine* 2011; 16(5):157-158.
Reason for exclusion: Not relevant population

(18) Einstein MH, Baron M, Levin MJ, Chatterjee A, Fox B, Scholar S et al. Comparison of the immunogenicity of the human papillomavirus (HPV)-16/18 vaccine and the HPV-6/11/16/18 vaccine for oncogenic non-vaccine types HPV-31 and HPV-45 in healthy women aged 18-45 years. *Human Vaccines* 2011; 7(12):1359-1373.
Reason for exclusion: Not relevant outcome

(19) Elbasha EH, Dasbach EJ. Impact of vaccinating boys and men against HPV in the United States. *Vaccine* 2010; 28(42):6858-6867.
Reason for exclusion: Not relevant population

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Reason for exclusion: Safety, vaccine dose schedule

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Reason for exclusion: Vaccine dose schedule

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Reason for exclusion: Not RCT

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Reason for exclusion: Vaccine dose schedule

Appendix 5. List of ongoing trials

Title: Evaluation of Safety and Immunogenicity of Co-administering Human Papillomavirus (HPV) Vaccine With Other Vaccines in Healthy Female Subjects
URL: http://ClinicalTrials.gov/show/NCT00426361

Title: Efficacy, Immunogenicity and Safety of GSK Biologicals' HPV GSK 580299 Vaccine in Healthy Chinese Female Subjects
URL: http://ClinicalTrials.gov/show/NCT00779766

Title: Safety Study of GSK Biologicals' Human Papillomavirus Vaccine in 580299/008 Subjects From Brazil, Taiwan or Thailand
URL: http://ClinicalTrials.gov/show/NCT00849381

Title: Extended Follow-Up of Young Women in Costa Rica Who Received Vaccination Against Human Papillomavirus Types 16 and 18 and Unvaccinated Controls
URL: http://ClinicalTrials.gov/show/NCT00867464

Title: Evaluation of Safety and Immunogenicity of Co-administering HPV Vaccine With Other Vaccines in Healthy Female Subjects
URL: http://ClinicalTrials.gov/show/NCT00369824

Title: Safety Study of GSK Biologicals' HPV Vaccine (GSK-580299) in Healthy Female Subjects.
URL: http://ClinicalTrials.gov/show/NCT00811798

Title: Immunogenicity and Safety of a Commercially Available Vaccine Co-administered With GSK HPV Vaccine (580299)
URL: http://ClinicalTrials.gov/show/NCT00637195

Title: Cervical Intraepithelial Neoplasm (CIN) in Women (Gardasil)(V501-015 AM5; EXT1; EXT2(AM1))
URL: http://ClinicalTrials.gov/show/NCT00092534

Title: Human Papilloma Virus (HPV) Vaccine Immunogenicity and Safety Trial in Young and Adult Women With GSK Biologicals' HPV-16/18
URL: http://ClinicalTrials.gov/show/NCT00196937

Title: Primary and Secondary Prevention of Human Papillomavirus (HPV) Disease in China
URL: http://ClinicalTrials.gov/show/NCT01021904

Title: Immunogenicity and Safety of GlaxoSmithKline Biologicals' Huma Papillomavirus (HPV) Vaccine 580299 in Healthy Females 15 - 25 Years of Age
URL: http://ClinicalTrials.gov/show/NCT00552279

Title: Study to Assess Immune Responses and Safety of the GSK-580299 Vaccine in Healthy Women (26 to 45 Years)
URL: http://ClinicalTrials.gov/show/NCT01277042

Title: Human Papillomavirus (HPV) Vaccine (Cervarix TM) Efficacy, Immunogenicity & Safety Trial in Adult Japanese Women With GSK Biologicals HPV-16/18 Vaccine
URL: http://ClinicalTrials.gov/show/NCT00316693

Title: A Study to Evaluate the Immune Response and Safety of GSK Biologicals' HPV-16/18 L1 VLP AS04 Vaccine/Cervarix TM Vaccine in Healthy Females Aged 15-25 Years
URL: http://ClinicalTrials.gov/show/NCT00485732

Title: Safety Study of GSK Biologicals' Human Papillomavirus Vaccine in 580299/008 Subjects From Canada or the US
URL: http://ClinicalTrials.gov/show/NCT00799825

Title: Vaccine To Prevent Cervical Intraepithelial Neoplasia or Cervical Cancer in Younger Healthy Participants
Recruitment: Completed
URL: http://ClinicalTrials.gov/show/NCT00128661

Title: Human Papilloma Virus (HPV) Vaccine Trial in Young Adolescent Women With GlaxoSmithKline Biologicals' (GSK Bio) HPV-16/18 Vaccine
URL: http://ClinicalTrials.gov/show/NCT00316706

Title: A Study to Evaluate the Immunogenicity and Safety of GSK Biologicals' HPV Vaccine in Healthy Women Aged 18-35 Years
URL: http://ClinicalTrials.gov/show/NCT00306241

Title: Study to Evaluate the Immune Response and Safety of GSK Biologicals' HPV Vaccine in Healthy Women Aged 18-35 Years
URL: http://ClinicalTrials.gov/show/NCT00345878

Title: Multivalent HPV (Human Papillomavirus) Vaccine Study in 16- to 26-Year Old Men and Women (V503-003 AM5)
URL: http://ClinicalTrials.gov/show/NCT01651949

Title: Study to Test the Safety of HPV Vaccine in Women (V501-011)(COMPLETED)
URL: http://ClinicalTrials.gov/show/NCT00517309

Title: Human Papilloma Virus Vaccine Safety and Immunogenicity Trial in Young Adolescent Women With GSK Bio HPV-16/18.
URL: http://ClinicalTrials.gov/show/NCT00196924

Title: Safety and Immunogenicity of GlaxoSmithKline Biologicals' HPV Vaccine 580299 (Cervarix TM) in HIV Infected Females
URL: http://ClinicalTrials.gov/show/NCT00586339

Title: Broad Spectrum HPV (Human Papillomavirus) Vaccine Study in 16-to 26-Year-Old Women (V503-001 AM3)
URL: http://ClinicalTrials.gov/show/NCT00543543

Title: Follow-up Study to Evaluate the Long-term Efficacy of the HPV Vaccine (580299) in Healthy Young Adult Women in Brazil
URL: http://ClinicalTrials.gov/show/NCT00518336

Title: V501 Safety and Efficacy Study in Japanese Women Aged 16 to 26 Years (V501-110)
URL: http://ClinicalTrials.gov/show/NCT01544478

Title: Cervical Intraepithelial Neoplasm (CIN)-Warts Efficacy Trial in Women (Gardasil)
URL: http://ClinicalTrials.gov/show/NCT00092521

Title: Effectiveness Study of Gardasil on Condyloma
URL: http://ClinicalTrials.gov/show/NCT01553994

NCT01651949 Multivalent HPV (Human Papillomavirus) Vaccine Study in 16- to 26-Year Old Men and Women (V503-003 AM5)

JPRN-UMIN000007128 Efficacy of HPV vaccination in Japanese women

EUCTR2004-001325-14-ES
Estudio en fase III, doble ciego, aleatorizado, controlado, multicéntrico para evaluar la eficacia de la vacuna HPV-16/18 VLP/AS04 de GlaxoSmithKline Biologicals comparada con la vacuna antihepatitis A como control en la prevención de la infección cervical persistente por el HPV-16 o HPV-18 y del cáncer de cérvix, administrada por vía intramuscular conforme a la pauta de vacunación 0, 1 y 6 meses, en mujeres sanas entre 15 y 25 años A phase III, double-blind, randomized, controlled study to evaluate the efficacy of Glax-oSmithKline Biologicals' HPV-16/18 VLP/AS04 vaccine compared to hepatitis A vaccines as control in prevention of persistent HPV-16 or HPV-18 cervical infection and cervical neoplasia, administered intramuscularly according to a 0, 1, 6 month schedule in healthy female subjects aged 15 – 25 years or age. - HPV-008

NCT00779766 Efficacy, Immunogenicity and Safety of GSK Biologicals' HPV GSK 580299 Vaccine in Healthy Chinese Female Subjects

NCT00378560
V501 Efficacy Study in Women Aged 18 to 26 (V501-027)

NCT00365378
Study of Human Papillomavirus (HPV) 16 Vaccine in the Prevention of HPV 16 Infection in 16- to 23-Year-Old Females

Appendix 6. Abbreviations

HPV	Human papilloma virus
CIN2+	Cervical intraepithelial neoplasia grade 2+
VaIN2+	Vaginal intraepithelial neoplasis stage 2+

VIN2+	Vulval intraepithelial neoplasia stage 2+
SAE	Serious adverse events
RCT	Randomized Controlled Trials

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