Effect of HPV-vaccination of boys

Report from Kunnskapssenteret (Norwegian Knowledge Centre for the Health Services)
No 1–2015
Systematic review

kunnskapssenteret
Norwegian Knowledge Centre for the Health Services

Background: Human papillomavirus (HPV) is the most common sexually transmitted agent worldwide and more than 100 types of HPV have been identified. This systematic review was carried out to assess whether vaccinating boys with the same HPV vaccines currently offered to 11 to 12-year-old girls in Norway would be effective in preventing HPV-related diseases among males. The five included references represent two different clinical trials. The efficacy data is from one large randomized study that examined the efficacy of prophylactic vaccination of males aged 16 to 26 with the quadrivalent HPV vaccine. **Main findings:** • This study shows that the quadrivalent vaccine is efficacious in preventing external genital lesions, caused by infection with HPV 6, 11, 16 or 18, in males aged 16-26 (moderate quality of evidence). • Genital warts are the main type of genital lesions prevented by vaccinating males (moderate quality evidence). • Effect data on precancerous lesions such as penile intraepithelial neoplasia (PIN2+) are sparse because of limited (three years) follow-up, and the results are not conclusive (low quality evidence). Assessement of pre-

(continued)

Norwegian Knowledge Centre for the Health Services (Kunnskapssenteret)
PO Box 7004, St. Olavs plass
N-0130 Oslo
(+47) 23 25 50 00
www.kunnskapssenteret.no
Report: ISBN 978-82-8121-937-3 ISSN 1890-1298

no 1–2015

kunnskapssenteret

(continued from page one) cancerous lesions probably needs longer follow-up time. • In the subpopulation of men who have sex with men, the vaccine reduced the risk of anal intraepithelial neoplasia (AIN2+) (low quality evidence). • Three years follow-up after HPV vaccination indicated little or no difference in the occurrence of serious adverse events in the vaccine group compared to the control group (moderate quality of evidence).• Long-term follow-up studies are required to demonstrate if there is an effect of HPV vaccination on cancer related mortality and cancer prevalence (i.e. penile, anal or oropharyngeal cancer).

Title	Effect of HPV-vaccination of boys
Norwegian title	Effekt av HPV-vaksinering av gutter
Institution	Norwegian Knowledge Centre for the Health Services (Nasjonalt kunnskapssenter for helsetjenesten) Magne Nylenna, *Director*
Authors	Juvet, Lene K., *researcher, Norwegian Knowledge Center for the Health Services* Sæterdal, Ingvil, *(Project leader), researcher, Norwegian Knowledge Center for the Health Services* Couto, Elisabeth, *researcher, Norwegian Knowledge Center for the Health Services* Harboe, Ingrid, *librarian, Norwegian Knowledge Center for the Health Services* Marianne, Klemp, *Research director, Norwegian Knowledge Center for the Health Services*
ISBN	978-82-8121-937-3
ISSN	1890-1298
Report	No. 1 – 2015
Project number	734
Type of report	Systematic review (systematisk oversikt)
No. of pages	45 (59 including appendices)
Client	Norwegian Institute of Public Health
Subject headings (MeSH)	Papillomavirus infection, Condyloma acuminata, Human papillomavirus (6, 11, 16, 18), Viral vaccines, Cancer vaccines, Immunization
Citation	Juvet LK, Sæterdal I, Couto E, Harboe I, Klemp M. Effect of HPV vaccination of boys. Report from Kunnskapssenteret no. 1–2015. Oslo: Norwegian Knowledge Centre for the Health Services, 2015.

Norwegian Knowledge Centre for the Health Services summarizes and disseminates evidence concerning the effect of treatments, methods, and interventions in health services, in addition to monitoring health service quality. Our goal is to support good decision making in order to provide patients in Norway with the best possible care. The Knowledge Centre is organized under The Norwegian Directorate of Health, but is scientifically and professionally independent. The Centre has no authority to develop health policy or responsibility to implement policies.

Norwegian Knowledge Centre for the Health Services
Oslo, January 2015

Key messages

Human papillomavirus (HPV) is the most common sexually transmitted agent worldwide and more than 100 types of HPV have been identified.

This systematic review was carried out to assess whether vaccinating boys with the same HPV vaccines currently offered to 11 to 12-year-old girls in Norway would be effective in preventing HPV-related diseases among males.

The five included references represent two different clinical trials. The efficacy data is from one large randomized study that examined the efficacy of prophylactic vaccination of males aged 16 to 26 with the quadrivalent HPV vaccine.

- This study shows that the quadrivalent vaccine is efficacious in preventing external genital lesions, caused by infection with HPV 6, 11, 16 or 18, in males aged 16-26 (moderate quality of evidence).
- Genital warts are the main type of genital lesions prevented by vaccinating males (moderate quality evidence).
- Effect data on precancerous lesions such as penile intraepithelial neoplasia (PIN2+) are sparse because of limited (three years) follow-up, and the results are not conclusive (low quality evidence). Assessement of precancerous lesions probably needs longer follow-up time.
- In the subpopulation of men who have sex with men, the vaccine reduced the risk of anal intraepithelial neoplasia (AIN2+) (low quality evidence).
- Three years follow-up after HPV vaccination indicated little or no difference in the occurrence of serious adverse events in the vaccine group compared to the control group (moderate quality of evidence).
- Long-term follow-up studies are required to demonstrate if there is an effect of HPV vaccination on cancer related mortality and cancer prevalence (i.e. penile, anal or oropharyngeal cancer).

Title:
Effect of HPV-vaccination of boys

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:

Norwegian Knowledge Centre for the Health Services

Updated:

Last search for studies: January 2014.

Executive summary

Background

Human papillomavirus (HPV) is the most common sexually transmitted agent worldwide and more than 100 types of HPV have been identified. The WHO International Agency for Research on Cancer concluded that there was sufficient evidence to support a causal role of certain types of HPV infection in carcinoma of the cervix, vulva, vagina, penis, anus and oropharynx. HPV16 and 18 cause more than 90% of the HPV-related cancers. Variable proportions of certain non-cervical cancers (e.g. anal, penis and oropharyngeal) are HPV-related. Oncogenic HPVs, particularly HPV 16, are associated with anogenital cancers (anus, vagina, vulva and penis), and oropharyngeal cancers.

Efficient prophylactic vaccines could possibly have an important public health impact. Under several plausible assumptions, an economic evaluation from 2007 suggested that introduction of HPV 16/18 type vaccination of 12-year-old girls in Norway may be a cost-effective strategy for further reductions in cervical cancer incidence and mortality. Norway introduced prophylactic HPV vaccination in the childhood immunization program in 2009. It is unclear whether vaccinating boys will also be beneficial, and The Norwegian Institute of Public Health requested a Health Technology Assessment to ascertain the potential effectiveness of vaccinating males aged 12.

Objective

To carry out a systematic review in order to assess whether vaccinating boys with the same HPV vaccines currently offered to 12-year-old girls in Norway would be effective in preventing HPV-related diseases among boys.

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 prespecified criteria. We retrieved full text publications of potentially eligible references, and 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. One review author extracted data from the included references and another review author verified the data.

We entered and analysed data using the Review Manager software and calculated risk ratios and associated 95% confidence intervals for the estimates 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 five included references represent two different clinical trials. One large randomized study (n=4055) that shows results of prophylactic administration of quadrivalent HPV vaccine is the basis for the efficacy data in this systematic review. This study shows that the HPV vaccine is efficacious in preventing external genital lesions with infection of HPV 6, 11, 16 and 18 in males aged 16 to 26 (RR 0.33 (CI 0.25-0.44). Among the external genital lesions, the outcome that predominates is genital warts, and a prevented by vaccinating was observed (RR 0.39 (CI 0.25-0.58). Other precancerous lesions probably need studies with a longer follow up time. So far with only 3 years follow up, there was very sparse data on the precancerous penile lesions (PIN2+) and the results are not conclusive (RR1.2 (CI 0.37-3.94). For the subpopulation of men who have sex with men, the vaccine reduced precancerous anal lesions (AIN2+) (RR 0.46 (CI 0.27-0.79) (low quality evidence).
Three years follow-up after HPV vaccination indicate little or no difference in the occurrence of serious adverse events in the vaccine group compared to the control group (RR 0.81 (CI 0.16-0.87) (moderate quality of evidence).

Discussion

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

There was no statistically significant difference in serious adverse events between the vaccination and the placebo groups. Nevertheless, the number of cases within the clinical studies is not sufficient to determine the occurrence of rarely occurring

(and potentially severe) adverse events in a reliable way. Future trials and possible follow-up publications of existing trials should assess long-term safety.

We have conducted a systematic review based on randomized controlled clinical trials. Randomized controlled trials have lower risk of bias than observational studies, and are therefore the preferred design to study the effects of an intervention. However, observational studies will be appropriate to assess long-term follow-up data and monitor outcomes related to harm.

Many countries have already started national vaccination programs for girls, but we will only have evidence on the true effect on cancer outcomes of these programs 20-30 years from now. It remains to be seen whether we will see a dramatic reduction in HPV- associated cancers, such as cervix, vulva, vagina, anus, and oropharyngeal because of the national vaccination program.

Conclusion

HPV vaccine is efficacious in preventing external genital lesions with infection of HPV 6, 11, 16 and 18 in boys and men aged 16-26 years. The main genital lesion prevented is genital warts. There are very sparse data on precancerous lesions (PIN2+) and the results are so far not conclusive with 3 years follow up. HPV vaccination reduced the risk of anal intraepithelial neoplasia (AIN2+) in a subpopulation of men who have sex with men. There is little or no difference in the occurrence of serious adverse events when compared to the control groups.

Further research is needed to demonstrate whether HPV vaccination reduces the incidence of HPV related cancers and cancer related mortality and to get data on long-term safety.

Hovedfunn (norsk)

Humant papillomavirus (HPV) er ansett som det vanligste seksuelt overførbare virus på verdensbasis. Mer enn 100 typer av HPV er identifisert.

Denne systematiske oversikten ble utført for å vurdere om HPV-vaksinene som i dag gis til 12 år gamle jenter i Norge, også forebygger HPV-relaterte sykdommer hvis den gis til gutter.

Dataene er hovedsakelig basert på én stor randomisert kontrollert studie som viser resultatet av å gi kvadrivalent HPV-vaksine, dvs. vaksine som beskytter mot humant papillomavirus type 6, 11, 16 og 18, til gutter og menn i alderen 16 til 26 år.

• HPV-vaksinasjon med kvadrivalent vaksine beskytter trolig mot lesjoner på ytre kjønnsorganer forårsaket av HPV 6, 11, 16 og 18 hos gutter og menn i alderen 16 til 26 år. Vaksinen beskytter særlig mot kjønnsvorter, som utgjør hovedtyngden av eksterne lesjoner. Dokumentasjonen er av moderat kvalitet.

• Vi kan ikke konkludere om vaksinen forebygger mot forstadier til kreft på penis, fordi det er meldt om få hendelser. Dokumentasjonen er av lav kvalitet.

• Blant menn som har sex med menn vil HPV-vaksinasjon muligens føre til færre forstadier til analkreft. Dokumentasjonen er av lav kvalitet.

• HPV-vaksinering av gutter gir trolig ingen alvorlige bivirkninger i løpet av tre år etter vaksinering, men antall studiedeltakere er for lavt til å oppdage sjeldne bivirkninger. Dokumentasjonen er av moderat kvalitet.

• For å kunne vurdere om HPV-vaksinasjon har effekt på kreftforekomst eller kreftdødelighet, trengs studier med lang oppfølgingstid.

Tittel:
Effekt av HPV-vaksinering av gutter

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 Nasjonalt folkehelseinstitutt

---

Når ble litteratursøket utført?

Søk etter studier ble avsluttet januar 2014.

Sammendrag (norsk)

Effekt av HPV-vaksinering av gutter

Bakgrunn

Humant papillomavirus (HPV) er ansett som det vanligste seksuelt overførbare virus på verdensbasis. Mer enn 100 typer av HPV er identifisert. Det internasjonale institutt for kreftforskning (IARC) som er del av WHO, mener at det er tilstrekkelig dokumentasjon for å si at infeksjon med HPV 16 forårsaker kreft på livmorhalsen, i vulva, skjeden, på penis, i endetarmen, i munnhulen, svelget og mandlene. Mer enn 90 prosent av HPV-relatert kreft er forårsaket av HPV 16 eller 18.

En helseøkonomisk evaluering fra 2007 utført av Kunnskapssenteret, viser at vaksinasjon mot HPV type 16 og 18- er en kostnadseffektiv strategi for å redusere antallet nye tilfeller og dødelighet av livmorhalskreft i Norge. HPV vaksinasjon av jenter ble introdusert i det norske barnevaksinasjonsprogrammet i 2009.

Problemstilling

Denne systematiske oversikten ble utført for å vurdere om HPV-vaksinene som i dag tilbys 11 til 12 år gamle jenter i Norge, også er effektiv for å forhindre HPV-relatert kreftsykdom hos gutter.

Metode

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

To oversiktsforfattere gjennomgikk alle referansene for å identifisere relevante publikasjoner i henhold til pre-spesifiserte kriterier. Vi innhentet fulltekst publikasjoner av potensielt relevante referanser, og vi vurderte alle inkluderte referanser for risiko for skjevhet i henhold til håndboken. Vi ekstraherte data ved hjelp av et pre-designet dataregistreringsskjema. Én forfatter hentet ut data og deretter ble dette kontrollert av en annen.

Vi analyserte resultatene ved hjelp Review Manager. Vi kalkulerte relativ risiko og tilhørende 95 prosent konfidensintervall for effektestimatene der det var mulig å sammenligne studier. Hvis dette ikke var mulig, fremstilte vi dataene narrativt. Vi brukte GRADE (Gradering of Recommendations Assessment, Development and Evaluation) for å vurdere samlet kvalitet på dokumentasjonen for hvert utfall.

Resultat

Vi gjennomførte litteratursøket etter randomiserte kontrollerte studier på HPV-vaksiner i januar 2014. Vi identifiserte 777 referanser. I tillegg fikk vi ni referanser fra de farmasøytiske selskapene som har markedsføringstillatelse for HPV-vaksiner i Norge. Etter å ha lest titler, sammendrag og fulltekster, inkluderte vi fem referanser basert på to randomiserte kontrollerte studier i denne systematiske oversikten.

De viktigste funnene fra denne systematiske oversikten er hovedsakelig basert på én stor randomisert kontrollert studie av kvadrivalent HPV-vaksine (vaksine mot HPV 6, 11, 16 og 18) til gutter i alderen 16 til 26 år.
Resultatene viste at HPV-vaksinasjon med kvadrivalent vaksine trolig beskyttet mot eksterne genitale lesjoner forårsaket av HPV 6, 11, 16 og 18 blant gutter og menn i alderen 16 til 26 år (RR 0.33 (KI 0.25-0.44). Hovedtyngden av lesjoner som HPV-vaksinen beskyttet mot var kjønnsvorter (kondylomer) (RR 0.39 (KI 0.25-0.58) (moderat kvalitet på dokumentasjonen). Vurderingen av om den kvadrivalente HPV-vaksinen beskytter mot forstadier til kreft på penis er preget av veldig få hendelser, og det er derfor vanskelig å konkludere om vaksinen forebygger forstadier til kreft på penis hos gutter (RR 1.2 (KI 0.37-3.94) (lav kvalitet på dokumentasjonen).
I en subpopulasjon av menn som har sex med menn førte HPV-vaksinasjon til færre forstadier til analkreft, sammenlignet med en kontrollgruppe som fikk placebo (RR 0.46 (KI 0.27-0.79) (lav kvalitet på dokumentasjonen).

Tre års oppfølging etter HPV-vaksinering viste liten eller ingen forskjell i alvorlige bivirkninger mellom de HPV-vaksinerte og kontrollgruppen som fikk placebo (moderat kvalitet på dokumentasjonen).

Diskusjon

HPV-vaksinasjon av gutter og menn i alderen 16 - 26 år beskytter trolig mot kjønnsvorter. Blant menn som har sex med menn gir HPV-vaksinasjon trolig færre tilfeller av forstadier til kreft i endetarmen. Vi vet ikke om HPV-vaksinasjon av gutter gir færre tilfeller av forstadier til analkreft eller peniskreft, fordi disse kreftformene er

sjeldne, og studiene som er gjennomført har for kort oppfølgingstid og veldig få hendelser. HPV-vaksinen gir trolig ingen alvorlige bivirkninger i løpet av tre år etter vaksinering, men antallet studiedeltakere er for lavt til å oppdage sjeldne bivirkninger.

Den langsiktige effekten av å gi HPV-vaksine til gutter er ukjent på grunn av relativt kort oppfølgingstid i de kliniske studiene. Siden vi først vil få vite den sanne effekten på kreftforekomst og kreftdødelighet om 20 - 30 år, er data fra langsiktig oppfølging av den vaksinerte befolkningen viktig.

Høygradige celleforandringer ble valgt som utfallsmål fordi de er direkte forløpere til aktuelle kreftformer hos menn (kreft på penis og kreft i endetarmen), og fordi de er beskrevet som det beste utfallsmålet når man skal undersøke effekten av HPV-vaksinasjon.

Sikkerhet over lang tid må vurderes i fremtidige studier eller i oppfølgingspublikasjoner av eksisterende studier.

Vi har gjennomført en systematisk oversikt basert på kliniske randomiserte kontrollerte studier. Randomiserte kontrollerte studier har lavere risiko for systematiske feil enn observasjonsstudier, og er derfor det foretrukne design for å undersøke effekten av en intervensjon. Observasjonsstudier og registerstudier kan imidlertid være mer hensiktsmessig for å undersøke sjeldne bivirkninger og langtidseffekter av vaksinen.

Nasjonale vaksinasjonsprogrammer av gutter er allerede startet i noen land.

Konklusjon

Denne systematiske oversikten ble utført for å vurdere om HPV-vaksinen som i dag gis til 12 år gamle jenter i Norge også forebygger HPV-relaterte sykdommer hvis den gis til gutter.

Dataene i denne systematiske oversikten baserer seg hovedsakelig på én stor randomisert kontrollert studie av kvadrivalent HPV-vaksine til gutter i alderen 16 til 26 år.

Kvadrivalent HPV-vaksine gitt til gutter og menn i alderen 16 til 26 år beskytter trolig mot kjønnsvorter (kondylomer) forårsaket av HPV 6, 11, 16 og 18 (moderat kvalitet på dokumentasjonen).

Blant menn som har sex med menn fører HPV-vaksinen til færre forstadier av kreft i endetarmen (lav kvalitet på dokumentasjonen).

HPV-vaksinering av gutter ser ikke ut til å medføre risiko for alvorlige bivirkninger, selv om vi ikke kan utelukke sjeldne bivirkninger (moderat kvalitet på dokumentasjonen).

Videre forskning er nødvendig for å undersøke om HPV-vaksinasjon reduserer forekomsten av HPV-relatert kreft, kreftdødelighet og for å få bedre data om sikkerhet ved HPV-vaksinasjon.

Table of contents

Contents

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 and a catch-up HPV vaccination of females up to 26 years of age.

We will perform a Health Technology Assessment (HTA) consisting of at least the three following elements: efficacy, safety and health economic evaluation. We will assess efficacy and safety through systematic reviews, and will perform the economic evaluation through a modelling analysis in separate reports.

This systematic review regarding the effect of HPV vaccination of males is one of four reports within the requested Health Technology Assessment of a potential expansion of the current HPV vaccination strategy also to include 12-year-old boys and catch-up vaccination of young women.

The project group for this report consisted of:

- Project leader: Ingvil Sæterdal, The Norwegian Knowledge Centre for the Health Services
- Other participants: Lene K Juvet, Elisabeth Couto, 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 and participation 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	Lene Kristine Juvet
Department director	*Head of Unit*	*Clinical evaluation*

Objective

To carry out a systematic review in order to assess whether vaccinating boys with the same HPV vaccines as currently offered to 11 to 12-year-old girls in Norway would be effective in preventing HPV-related diseases among boys.

Background

Human papilloma virus and cancer diseases

Human papillomavirus (HPV) is the most common sexually transmitted agent worldwide (1) and HPV-related cancers are a major public health concern. HPV is a family of DNA viruses that infect skin- or mucosal cells in epithelial tissues including the skin, cervix, anus, mouth and throat (2). The burden of HPV infection is considerable (3, 4). Most sexually active women and men will experience an HPV infection during their lifetime (3). HPV infections cause 5.2% of all cancers worldwide (3). Although more than 100 types of HPV have been identified (5, 6), a small number of HPV types contribute to a large proportion of HPV-related diseases. At least 13 of the more than 100 known HPV viruses are oncogenic “high-risk” genotypes. Cervical cancer is the most common cancer caused by HPV infections. Persistent infection with oncogenic HPV is 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 (3-5). The HPV-related cancers are dominated by cervical cancer worldwide, particularly in low income countries, where cervical cancer screening is limited (7). Industrialised countries control cervical cancer through cervical cancer screening. Current HPV vaccination can complement cervical screening in preventing cervical cancer and may permit the safe reduction of screening intensity in industrialised countries. In women HPV infection is also an established risk factor for vulvar (40% HPV related) and vaginal cancers (70% HPV related) (8) (9-11). Second-generation HPV vaccines (active against a broader array of HPV types related to cervical cancer) could possibly prevent an even higher proportion of cervical pre-cancers and cancers and might permit further reductions in screening intensity.

The World Health Organisation (WHO) International Agency for Research on Cancer concluded that there was sufficient evidence to support a causal role of HPV 16 infection in male carcinoma of the penis, anus and oropharynx (8). The virus is associated with 80% to 85% of anal cancers and 50% of penile cancers. In Europe, men account for approximately 30% of overall HPV-related cancers, mainly reflecting oropharyngeal cancer (12-15). The reported prevalence of HPV in oropharyngeal cancer has wide geographic variations; from 59,9% in the United states, 39,7 % in Europe and 32,5 % in the rest of the world (16). The studyalso indicate that the prevalence of HPV in oropharyngeal cancer has a faster increase rate in Europe (16).

Emerging evidence from Norway (17, 18), Sweden (19), Demark (20), the United States(21, 22), and Australia (23) highlights a significant increase in the incidence of HPV-related oropharyngeal cancers in males. The prevalence of HPV-16/18 in oropharyngeal cancer was lower in women (53%) than in men (66%) in the United States (22). An increase in the incidence of anal cancer has also been reported in several countries (24-27). Industrialised countries control cervical cancer by cervical cancer screening, but the incidence of other HPV-associated malignancies is increasing and the burden of HPV-associated disease in men is now increasing (28).

Two HPV vaccines targeting the two most oncogenic virus types (HPV16 and HPV18) are now commercially available. Controlled clinical trials have verified that the vaccines prevent incident anogenital infection and the associated neoplastic diseases that are induced by these HPV types in girls (29). Widespread uptake of current HPV vaccines by adolescent girls could reduce cancer incidence and mortality, while screening programs of adult women have the potential to reduce cervix cancer mortality more rapidly.

HPV vaccination of girls might also benefit the male population through herd immunity; however, in general, herd immunity will depend on high coverage rates among females. Vaccination of boys may have the potential to further reduce HPV-related diseases in both sexes. Furthermore, men who have sex with men, who are particularly susceptible to HPV related anal cancer, would only benefit from vaccination programs for boys.

Reducing HPV associated non-cervical cancers with HPV vaccination may have great importance in since there are no approved screening programs for these cancers. Preventing a substantial number of HPV related cancers in men will require either herd immunity through high coverage rates in females or the introduction of male vaccination (30).

Efficient vaccines could have an important public health impact. As cancer takes a long time to develop, it would be difficult, and probably also unethical, to conduct clinical trials to assess the efficacy of HPV vaccination on cancer types associated with HPV. For these reasons, the WHO and the US Food and Drug Administration recommended that phase III trials examine vaccination efficacy on high-grade intraepithelial neoplasia grades 2 and 3 (cervical intraepithelial neoplasia CIN2/3) (31).

Recent data demonstrate that human papilloma virus (HPV) plays a role in pathologies other than anogenital cancers, specifically head and neck malignancies, and non-cancerous conditions such as recurrent respiratory papillomatosis (RRP). High-risk HPV16 and 18, and low risk HPV6 and 11 play the main role in HPV-related pathologies. Increasing knowledge about the role of HPV infection in non-cervical diseases has led to questions about the effectiveness of HPV vaccination of boys in the prevention of these conditions.

Current policies of the European Medicines Agency (EMA) recommend HPV vaccines also for males. To provide direct protection to males, and to prevent HPV associated cancers for both females and males, several countries (Austria, Germany, the United States, Canada, and Australia) have recommended vaccinating males against HPV in addition to female vaccination (32).

Genital warts

In the genital tract HPV (especially types 6 and 11) cause genital warts, the most common viral sexually transmitted disease. Genital warts (condyloma acuminate), associated with HPV types 6 and 11 in 90% of cases, are very common and recurrent benign lesions (33, 34). Although they do not lead to life-threatening diseases, genital warts affect patients' quality of life, especially due to emotional and sexual concerns (35, 36). It is estimated that around 300 000 new cases of genital warts occur annually among males in Europe as a consequence of HPV types 6 and 11 infection (14). The incidence of genital warts has increased over recent decades in Europe (14). Prevalence of genital warts peaks during the early years of sexual activity (37). A Nordic study reported that approximately 10% of women had been diagnosed with genital warts before the age of 45 (37). The treatment is expensive and recurrences of genital warts are common (35, 38, 39).

Situation in Norway

Norway introduced HPV vaccination in the childhood immunization program in 2009. 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). Some have argued that these programs should be expanded to also include boys, since 1) HPV also constitutes non-negligible health risks for boys, and 2) protected boys could indirectly also protect girls. Herd immunity for girls could come from vaccinating boys. However, the vaccination coverage of girls in Norway is relatively high (over 80 %) so the marginal change in herd immunity to girls from vaccinating boys is likely to be quite small.

An increase in the incidence of oropharyngeal cancer has been reported in Norway (40) while only a small increase in the incidence of anal cancer has been reported (40) (table 1). The incidence of penile cancer seems to be unchanged (40) (table 1).

Table 1. Number of new cancer cases per year for males (40).

	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
Oropharyngeal cancer	60	61	59	84	70	73	86	86	95	91	117	122
Anal cancer	17	11	23	16	22	13	18	18	20	29	19	24
Penile cancer	29	41	52	44	49	39	44	51	46	48	38	37

The five year survival rate for penile cancer is around 80 % in Norway, while the five year survival rate is lower for both anal cancer and oropharyngeal cancer (40) (table 2)

Table 2. Five year relative survival (males) in Norway in period 2008-2012 (40).

	2008-2012
Oropharyngeal cancer	60%
Anal cancer	65%
Penile cancer	80%

The Norwegian Institute of Public Health requested a Health Technology Assessment to ascertain the potential effectiveness of HPV vaccination of both catch up vaccination of girls up to 26 years and for vaccination of 12-year-old boys. A systematic review of effectiveness and an economic evaluation of catch-up vaccination were published in 2014. The aim of this report is to conduct a systematic review of studies assessing the effectiveness of HPV vaccination of 12-year-old boys. A health economic evaluation for Norway will be published separately at the same time.

Methods

Literature search

The research librarian, Ingrid Harboe, planned and executed the systematic literature searches in collaboration with the project group. We developed search strategies that combined selected index and free text terms. We provide the complete search strategy in Appendix 1. We conducted the last search for studies in January 2014.

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

We used a methodology search filter 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 excluded. We restricted the search to start at the year of publication 1999. The vaccines were introduced to the international market in 2006 and we did not expect to find relevant studies with publication date before 1999.

We also searched for ongoing trials in Clinical Trials.gov and WHO ICTRP in November 2014.

Furthermore, we contacted the pharmaceutical company with marketing authorization for the quadrivalent HPV vaccine in Norway (Sanofi Pasteur MSD) to obtain additional information.

Inclusion criteria

We included full-text references that fulfilled the following inclusion criteria:

Population:	Boys between 10 and 16
Interventions:	HPV vaccines
Control:	Placebo, no vaccine or other vaccines
Outcome:	Overall mortality Cancer related mortality Penile cancer Anal cancer Penile intraepithelial neoplasia grade 2 and higher (PIN2+) Anal intraepithelial neoplasia stage 2 and higher (AIN2+) Oropharyngeal cancer Genital warts/condyloma Persistent HPV infection Serious adverse events (SAE)
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.

Exclusion criteria

We excluded references that included both boys and girls if the studies did not present the results for the boys separately. We also excluded studies that only reported immunogenicity data for the vaccine.

Selection of articles and assessment of risk of bias

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.

Two of the review authors independently assessed risk of bias in publications that met predefined inclusion criteria according to the Handbook for the Norwegian Knowledge Centre (41). 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 analysed the data using the Review Manager software (RevMan) when possible. We performed the meta-analyses using the Mantel-Haenszel "random effects model", since we expected some differences in effect sizes between populations and settings. We calculated risk ratios (RR) and associated 95% confidence intervals for dichotomous outcomes. 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, as the included RCTs did not use this definition. Therefore, we have defined the intention-to-treat population matching the definition used. We conducted the analyses of serious adverse events based on the safety population as defined in each of the studies. We described the results in a narrative form when the outcome data could not be pooled.

We carried out analyses for HPV vaccination versus control. For all outcome we aimed at carrying out analysis based on both the HPV vaccine status in the lesions (HPV 6, 11, 16, 18 or all HPV types tested) and lesions unrelated to HPV status (all lesions).

Grading the quality of evidence

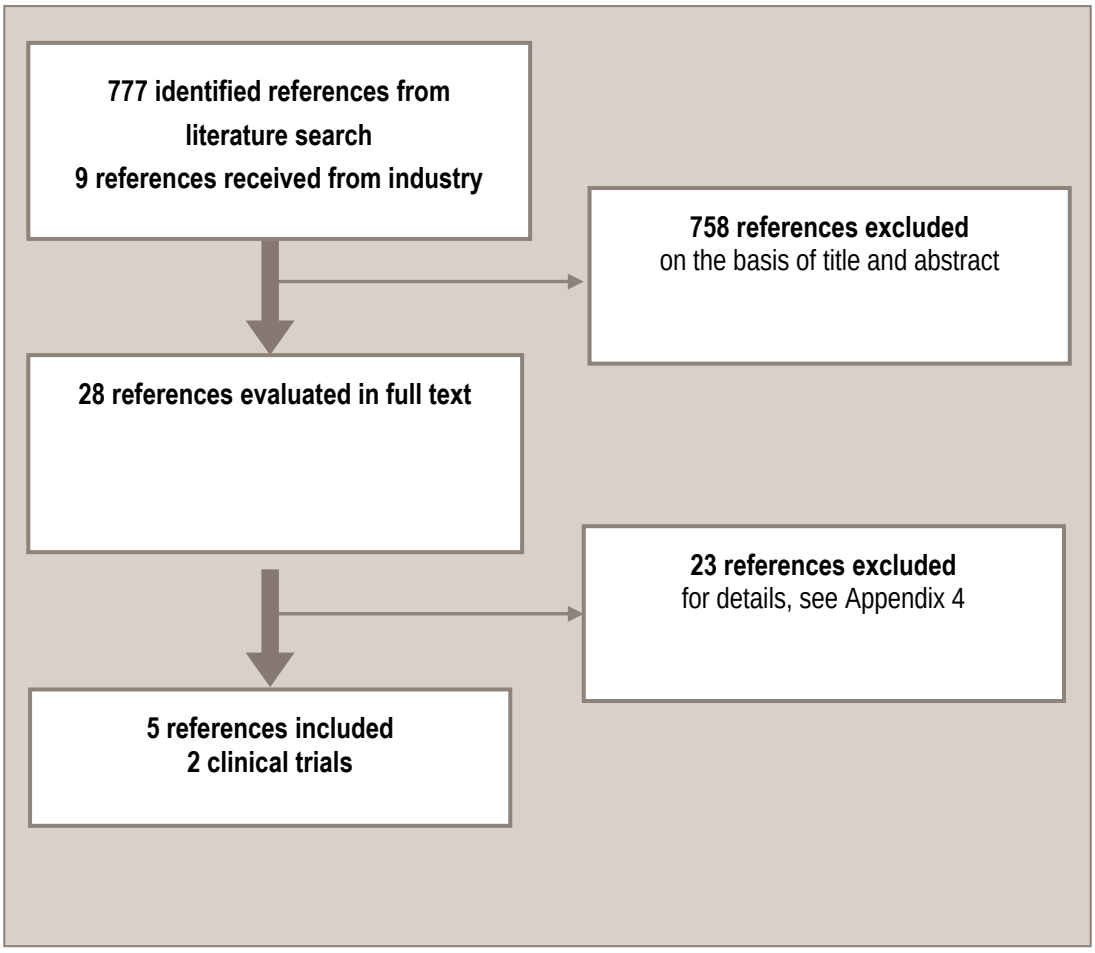
Two review authors assessed the overall quality of evidence for each outcome ascertained using GRADE (Grading of Recommendations Assessment, Development, and Evaluation). GRADE provides criteria for rating the quality of evidence considering study design, risk of bias, imprecision, inconsistency, indirectness, publication bias, effect size, 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

Result of literature search

We conducted the literature search for randomized controlled trials on HPV vaccines in October 2012 and an updated search in January 2014. We identified 777 (616 + 161) titles in the search for literature. We found 19 of these titles to be potentially relevant and reviewed full text copies. In addition, we received nine papers from the pharmaceutical company with marketing authorization for the quadrivalent HPV vaccine in Norway. Finally, five titles describing two studies met the prespecified inclusion criteria (Fig. 1).

Figure 1 *Flowchart of identification of documentation.*



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

Description of included literature

Studies included were randomized, controlled clinical trials. The five included references represent two different main clinical trials. Table 3 gives an overview of the included references, and characteristics of the included studies are shown in Appendix 2.

The participants in the two studies were healthy boys or young men with an age ranging from 10 to 18 years (N= 270) (42) or from 16 to 26 years (N= 4065) (43-46)including in total 4335 males. However, even if most of the males in the main study were at an older age than our inclusion criteria (boys aged 10 to 16 years), we included this study since this was the only study that evaluates efficacy in males.

The studies did not require a history of HPV infection or negative HPV tests for the males at entry. Fewer than six lifetime sex partners was a requirement in one of the two studies (43-46). One study was a multicenter study conducted in North America (USA and Canada), South America, Europe and Asia. The follow-up period was 36 months, and the study was carried out between 2004 and 2008 (43-46). The other study was conducted in Finland and was used to evaluate immunogenicity and safety of the vaccine. This study had a follow-up period of seven months and was carried out between April 2006 and January 2007 (42).

Vaccines used in the trials were the bivalent vaccine containing HPV 16 and 18 virus-like particles (VLP) from GlaxoSmithKline (42) and the quadrivalent vaccine containing HPV 6, 11, 16 and 18 from Merck (43-46). One trial used placebo as comparator (43-46) and the other trial used hepatitis B vaccine in both the intervention and the control groups (42). All vaccines were given as three doses within six months (Day 1, month 2 and month 6 or month 0, 1 and 6).

We assessed both studies as having low risk of bias. The risk of bias assessment for the included studies is shown in Appendix 2. We have summarized the results and assessed the quality of evidence for each outcome (the confidence we have in the results for each outcome) in the full GRADE evidence profiles shown in Appendix 3.

Table 3. Randomized controlled trials included in the systematic review

Studies	Vaccine	Population	Outcomes used in report	Follow-up
Giuliano 2011 Palefsky 2011 Moreira 2011 Goldstone 2013 (43-46)	HPV 6, 11, 16, 18	Randomized population N=4065 **Intention to treat (ITT) population** included all subjects who received one or more doses of vaccine or placebo and returned for follow up (N=4055). **HPV naïve ITT population** includes all subject who were HPV negative at studystart and recieived one or more doses vaccine or placebo for follow up (N=3333) **Per protocol population (PPP)** included only participants who were seronegative on day1 and received all 3 vaccinations within 1 year and with at least one follow-up visit post-dose 3 (N=2805) This population consist of a subgroup of men who have sex with men and some results are only for this population. N=551	PIN grade 1,2,3 Condyloma acuminatum SAE AIN grade 1,2,3	3 years (mean follow-up)
Petaja 2009 (47).	HPV 16, 18	**Total vaccinated cohort** Safety analysis were based on the total vaccinated cohort. N=270	SAE	7 months (mean follow-up)

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

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

Overall mortality

We did not find any references that reported results for overall mortality.

Cancer related mortality and penile, anal and oropharyngeal cancer incidence

Giulano 2011 and Palefsky 2011 (43, 46) intended to report on cancer mortality and incidence of penile and anal cancer. However, after 36 months follow-up there were no cases of penile or anal cancer or cancer-related deaths (43, 46). None of the included references reported on oropharyngeal cancer.

Persistent infection

One study reported effect of the HPV vaccine on persistent infection after six months (43). The outcome was reported both in HPV naïve population (naïve ITT) and in per protocol population (PPP), and persistent infection was presented as either HPV-unrelated or related to the HPV types included in the vaccine (table 4). We assessed the quality of evidence for these outcomes to be high and moderate.

Table 4. Estimates of effect for six months persistent infection after HPV vaccination in boys 16-26 years.

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (Studies)	Quality of the evidence (GRADE)
	Risk with placebo	Risk with HPV vaccination			
Persistent infection, **ITT naive**	105 per 1000	35 per 1000 (26 to 46)	**RR 0.33** (0.25 to 0.44)	3333 (1 RCT) [1]	⨁⨁⨁⨁ HIGH [2]
Persistent infection, **PPP**	72 per 1000	11 per 1000 (6 to 19)	**RR 0.15** (0.09 to 0.26)	2790 (1 RCT) [1]	⨁⨁⨁◯ MODERATE [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 intervention (and its 95% CI). 1. Guiliano 2011. 2. Funded by vaccine provider (we did not downgrade), 3. Few events.

External genital lesions

One study (43) reported on the outcome external genital lesions, which is a combination of all kind of external genital lesions: condylomata acuminata, PIN1, PIN2 and PIN3 in addition to penile/perianal/perineal cancer. The outcome was reported both as HPV-unrelated or related to the HPV types included in the vaccine (Table 5). The study found fewer males with external genital lesions in the vaccine group compared to the control group, both for ITT and PPP population. The pooled estimate for this outcome showed a 67% reduction in the risk for total external genital lesions (any HPV type) in the vaccine group compared with the control groups (RR= 0.33; 95% CI=0.25, 0.44) in the intention to treat population. The quality of the evidence is moderate.

Table 5. Estimates of RRs for total external genital lesions (condylomata acuminata, PIN, and penile/perianal/perineal cancer) after HPV vaccination in boys 16-26 years.

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (Studies)	Quality of the evidence (GRADE)
	Risk with placebo	Risk with HPV vaccination			
External genital lesions - any HPV type **ITT**	44 per 1000	18 per 1000 (12 to 26)	**RR 0.33** (0.25 to 0.44)	4055 (1 RCT) [1]	⊕⊕⊕◯ MODERATE [2,3]
External genital lesions - HPV 6,11,16,18 **ITT**	38 per 1000	13 per 1000 (3 to 20)	**RR 0.35** (0.23 to 0.54)	4055 (1 RCT) [1]	⊕⊕⊕◯ MODERATE [2,3]
External genital lesions - any HPV type **PPP**	28 per 1000	5 per 1000 (2 to 11)	**RR 0.17** (0.07 to 0.39)	2545 (1 RCT) [1]	⊕⊕⊕◯ MODERATE [2,3]
External genital lesions - HPV 6,11,16,18 **PPP**	22 per 1000	2 per 1000 (1 to 17)	**RR 0.10** (0.03 to 0.32)	2805 (1 RCT) [1]	⊕⊕⊕◯ MODERATE [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 intervention (and its 95% CI). 1. Guiliano 2011. 2. Funded by vaccine provider (we did not downgrade), 3. Few events.

Penile, perianal or perineal intraepithelial neoplasia (PIN)

One study reported on the outcome PIN 2/3 lesions (PIN; penile/perianal/perineal intraepithelial neoplasia) (43). The outcome was reported related to the HPV types included in the vaccine (table 6). There was no significant difference in PIN cases between the vaccine and the placebo group in the ITT population. The pooled estimate for this outcome showed RR= 1.20; 95% CI=0.37, 3.94). The quality of the evidence for this outcome is low, Table 6.

Although there were no cases of PIN in the PPP vaccine group, there was no statistically significant difference in the incidence of PIN between the PPP vaccine group and the placebo group. The pooled estimate for this outcome was RR= 0.14; 95% CI=0.01, 2.79). The quality of the evidence for this outcome is low, Table 6. In general, very few PIN cases were observed in both groups and the results were inconclusive.

Table 6. Estimates of effect for HPV 6,11,16,18 related PIN lesions after HPV vaccination in boys 16-26 years.

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (Studies)	Quality of the evidence (GRADE)
	Risk with placebo	Risk with HPV vaccination			
All PIN lesions HPV 6,11,16,18 ITT	2 per 1000	3 per 1000 (1 to 10)	**RR 1.2** (0.37 to 3.94)	4055 (1 RCT) [1]	⨁⨁◯◯ LOW [2 3 4]
PIN 2/3 lesions HPV 6,11,16,18 ITT	1 per 1000	1 per 1000 (0 to 9)	**RR 1.5** (0.25 to 8.99)	4055 (1 RCT) [1]	⨁⨁◯◯ LOW [2 3 4]
All PIN lesions HPV 6,11,16,18 PPP	2 per 1000	0 per 1000 (0 to 6)	**RR 0.14** (0.01 to 2.78)	2805 (1 RCT) [1]	⨁⨁◯◯ LOW [2 3 4]
PIN 2/3 lesions HPV 6,11,16,18 PPP	1 per 1000	0 per 1000 (0 to 6)	**RR 0.34** (0.01 to 8.24)	2805 (1 RCT) [1]	⨁⨁◯◯ LOW [2 3 4]

*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). 1. Guiliano 2011. 2. Funded by vaccine provider (we did not downgrade), 3. Few events, 4. Wide confidence interval crossing the line of no effect.

Genital warts (Condyloma acuminata)

One study reported on the outcome condyloma (43). Results were reported both as HPV-unrelated or related to the HPV types included in the vaccine (table 7). The study found fewer males with genital warts in the vaccine group compared to the control group, both in ITT and PPP population. The pooled estimate for this outcome (condyloma, all HPV types) showed a 61% reduction in the risk for total external genial lesions in the vaccine compared with the control groups (RR= 0.39; 95% CI=0.25, 0.58). The quality of the evidence for this outcome is moderate, Table 7.

Table 7: Estimates of effect for genital warts (condyloma acuminata) after HPV vaccination in boys 16-26 years.

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (Studies)	Quality of the evidence (GRADE)
	Risk with placebo	Risk with HPV vaccination			
Condyloma all HPV types ITT	41 per 1000	16 per 1000 (10 to 24)	**RR 0.39** (0.25 to 0.58)	4055 (1 RCT) [1]	⊕⊕⊕◯ MODERATE [2 3]
Condyloma HPV 6,11,1618 ITT	35 per 1000	12 per 1000 (7 to 19)	**RR 0.33** (0.21 to 0.53)	4055 (1 RCT) [1]	⊕⊕⊕◯ MODERATE [2 3]
Condyloma HPV 6,11,16,18 PPP	20 per 1000	2 per 1000 (1 to 7)	**RR 0.1** (0.03 to 0.35)	2805 (1 RCT) [1]	⊕⊕⊕◯ MODERATE [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 intervention (and its 95% CI). 1. Guiliano 2011. 2. Funded by vaccine provider (we did not downgrade), 3. Few events.

Serious adverse effect

Both included studies reported on serious adverse events (SAE) (45, 47). 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 entire study period for each study; 3 years (45) and 7 month. An SAE was defined as an untoward occurrence that resulted in death, was life-threaten, required hospitalization, resulted in disability or incapacity (47). SAE consist of serious disease (eg. appendicitis, hypersenitivity, myocardial infarction, new onset diseases) and accidents (eg. car accident, gun shot). Authors of both studies consider all reported SAE to be unrelated to the study vaccination (45, 47). The pooled estimate for this outcome showed no statistically significant difference between the vaccine and the control groups (RR= 0.81; 95% CI= 0.35, 1.87), Figure 2. The quality of the evidence for this outcome is moderate, Table 8.

Figure 2. Pooled analysis of serious adverse events after HPV vaccination in boys 16-26 years.

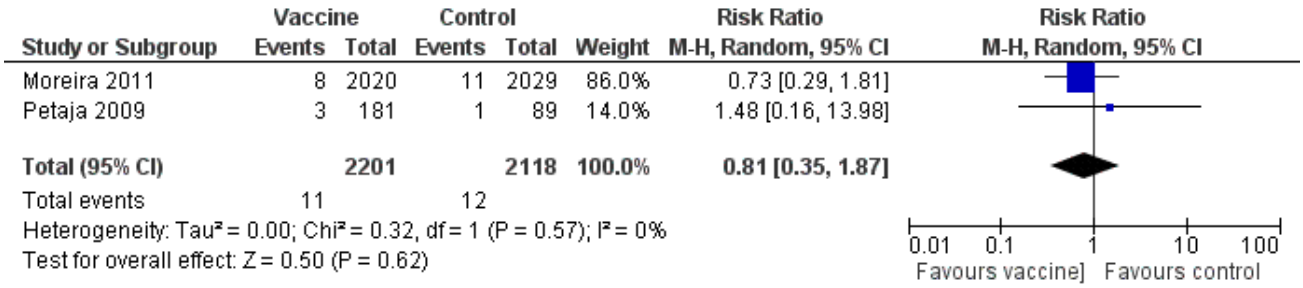


Table 8. Estimates of effects for serious adverse events after HPV vaccination in boys 16-26 years.

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (Studies)	Quality of the evidence (GRADE)
	Risk with placebo	Risk with HPV vaccination			
Serious adverse events	6 per 1000	5 per 1000 (1 to 11)	**RR 0.81** (0.16 to 1.87)	4319 (2 RCTs) [1,2]	⊕⊕⊕◯ MODERATE [3,4]

*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). 1. Moreira 2011. 2. Peataja 2009 3. Funded by vaccine provider (we did not downgrade), 4. Few events.

HPV vaccine versus control in men who have sex with men (MSM)

Anal intraepithelial neoplasia (AIN)

The study by Palefsky et al 2011, analysed data from a subgroup of men who have sex with men. This subgroup analysis was in accordance with the study protocol (46). Palefsky et al. reported on the outcome AIN lesions (AIN; anal intraepithelial neoplasia) in MSM population (46). Results were reported either as all AIN or AIN related to the HPV types included in the vaccine (Table 7). There were fewer total AIN cases in the vaccine group compared to the control group, both in ITT and PPP populations. The pooled estimate for this outcome showed a 28% reduction in the risk for total AIN due to any HPV type in the vaccine compared with the control groups (RR= 0.72; 95% CI=0.56, 0.92) in the ITT population. A higher relative risk reduction was observed when only AIN lesions related to the HPV vaccine type

(HPV 6,11,16,18) were assessed (RR= 0.49; 95% CI=0.34, 0.69). For the AIN2/3 lesion, the most developed lesions, a risk reduction was also observed in the vaccine group of the MSM population (RR= 0.46; 95% CI=0.27, 0.79). The PPP population had an even higher risk reduction for AIN2/3 lesions. The quality of the evidence for these outcomes are low, Table 9. The vaccine seemed to be more efficacious for outcomes related to the HPV vaccine types of virus than for outcomes regardless of HPV-type. There was no evidence that the vaccine protected against disease caused by non-vaccine HPV-types (44).

Table 9. HPV vaccination in MSM 16-26 years – effects on AIN after three years follow up.

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (Studies)	Quality of the evidence (GRADE)
	Risk with placebo	Risk with HPV vaccination			
All AIN lesions all HPV ITT	373 per 1000	269 per 1000 (209 to 343)	**RR 0.72** (0.56 to 0.92)	551 (1 RCT) [2]	⨁⨁◯◯ LOW [3 4 5]
AIN 2/3 lesions HPV 6,11,16,18 ITT	141 per 1000	65 per 1000 (38 to 112)	**RR 0.46** (0.27 to 0.79)	551 (1 RCT) [1]	⨁⨁◯◯ LOW [3 4 5]
AIN 2/3 lesions HPV 6,11,16,18 PPP	63 per 1000	16 per 1000 (4 to 54)	**RR 0.25** (0.07 to 0.86)	402 (1 RCT) [1]	⨁⨁◯◯ LOW [3 4 5]

*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). 1. Palefski 2011. 2. Goldstone 2013. 3.Funded by vaccine provider (we did not downgrade), 4. Few events. 5. Population comprise only men who have sex with men. Downgrade AIN since there is uncertainty about transferability to the full population.

Genital warts (Condyloma acuminata)

The study by Palefsky 2011 (46) also reported on condylomas. There were fewer cases of condyloma in the vaccine group compared to the control group, both in the ITT and PPP population. In the ITT population the pooled estimate showed a 58 % reduction in the risk for condylomas in the vaccine compared with the control groups (RR= 0.42; 95% CI=0.22, 0.79) (Table 10). The quality of the evidence for this outcome is moderate. In the PPP population, the risk reduction was higher, but not statistically significant. The quality of the evidence for this outcome is low.

Table 10: HPV vaccination in MSM population age 16-26 years – effects on genital warts after three years follow up.

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (Studies)	Quality of the evidence (GRADE)
	Risk with placebo	Risk with HPV vaccination			
Condyloma HPV 6,11,16,18 ITT	113 per 1000	47 per 1000 (26 to 89)	**RR 0.42** (0.23 to 0.79)	550 (1 RCT) [1]	⨁⨁⨁◯ MODERATE [2 3]
Condyloma HPV 6,11,16,18 PPP	29 per 1000	2 per 1000 (0 to 42)	**RR 0.08** (0.005 to 1.45)	402 (1 RCT) [1]	⨁⨁◯◯ LOW [2 3 4]

*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). 1. Palefski 2011. 2.Funded by vaccine provider (we did not downgrade), 3. Few events. 4. Wide confidence interval crossing the line of no effect.

Discussion

While this review indicates a protective effect of HPV vaccination on genital warts in vaccinated boys, we still do not know whether the HPV vaccines lower cancer incidence and cancer mortality in men. HPV vaccination protected against anal pre-cancerous lesions in men who have sex with men. There are very sparse data on precancerous HPV vaccine-related penile pre-cancerous lesions in males and the results are not conclusive. Due to the relatively short follow-up period of published clinical trials, the long-term effect of HPV vaccination for boys remains unclear. Penile and anal cancer are rare conditions and the cancers develop slowly. To demonstrate an effect of HPV vaccination on these rare conditions need follow up for decades. This systematic review can therefore not demonstrate any prevention of HPV-related cancer or reduction in overall mortality.

Main findings

The very small number of precancerous lesions reported in the studies examined for this review and the short follow-up period makes it impossible to conclude if HPV vaccine of boys protects against pre-cancerous lesions for penile (PIN) and anal cancers (AIN) in men (43, 46).

This systematic review included two studies that provided results on efficacy and safety of prophylactic administration of quadrivalent HPV vaccine in boys. The efficacy results are mainly from one large, multicentre randomized controlled trial, including more than 4000 boys/men (43, 46).

The study included boys aged 16 and older. We used this study to estimate the efficacy of vaccinating younger boys as we did not identify any studies involving boys aged 10-12.

The large multicentre study showed that the HPV vaccine was efficacious in preventing external genital lesions with infection of HPV 6, 11, 16 and 18 in boys and men aged 16 to 26. The study also demonstrated a lower incidence of genital warts (condyloma acuminata) in HPV-vaccinated men. Among all men 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 was 41 per 1000, and the corresponding risk in the vaccine group was 16 per 1000. Confidence in these estimates (quality of the evidence) is moderate. Since HPV-related cancers usually develop very slowly, the data from this trial are too recent to provide any long-term evidence on either penile cancer or precancerous penile lesions. High grade precancerous lesions were chosen as the outcome of interest since they are immediate pre-cursors to cancers and because they have been described as the best outcome to use when examining the effect of HPV vaccination on cervical cancer in girls (31). So far, with only three years follow up, there are very sparse data on precancerous HPV vaccine-related lesions PIN2+ in males and the results are not conclusive.

For a subgroup of the population, men who have sex with men, HPV vaccination reduced the rate of AIN, including grade 2 and 3, after three years of follow-up. For grade AIN2+ associated with the HPV types in the vaccine, the assumed risk in the placebo group was 141 per 1000, and the corresponding risk in the vaccine group was 65 per 1000. The study also found a corresponding lower incidence of genital warts in HPV-vaccinated men who have sex with men. The efficacy of the vaccine regardless of HPV-type seems to be less than the efficacy of the vaccine for the specific vaccine HPV type related lesions. We did not find any evidence that the vaccine was efficacious against diseases due to non-vaccine HPV types (44). Many anal cancers and pre-cancers seem to be caused by other HPV types than the HPV types that the current vaccines cover, and this may decrease wider public health impact of HPV vaccination of boys (44).

The RCT by Guiliano et al. (43, 46) did not have oropharyngeal cancer as an outcome. Since there is an absence of detectable precancerous lesions in oropharynx (48), this outcome was not an option for these trials with a relative short follow up.

There was no statistically significant difference in serious adverse events between the vaccination and the placebo groups. This corresponds well with data from studies of young women (49, 50). However, the small number of cases within the clinical trials are not sufficient to determine the occurrence of rarely occurring (severe) adverse events in a reliable way. We need long-term safety data from future trials and from possible follow-up of existing trials.

The ultimate goal for these vaccines is the prevention of cancer. When combining the data for all pre-cancerous cervical lesions (CIN2+) in young women catch up population a protective effect for these lesions was found in the vaccine group compared to a placebo group (49, 50). Among all young women in the intention-to-treat analysis, the quadrivalent HPV vaccine provided also protects against genital warts associated with the HPV types included in the vaccine (49, 50).

Since infection with an oncogenic HPV type is thought to be a necessary step in the pathogenesis of HPV-related cancer, a number of potential endpoints are considered (31). The choice of endpoints in clinical efficacy trials of prophylactic HPV vaccines will be affected by the sample sizes, trial designs, duration of the trial, resources needed, choice of study populations, and the indication in the vaccine label (31). When preventive efficacy trials using cervical cancer as the outcome are deemed not feasible or not appropriate, then endpoints based on high-grade CIN pathologic criteria appear to be the most clinically relevant and most accurate in predicting and quantifying the preventive efficacy of HPV vaccines for cervical cancer (31). Both the precancerous lesions CIN 2 and 3 are considered high-grade cervical lesions. Thus, it is reasonable to consider CIN 2/3 or worse (CIN2+) as a single entity for the purpose of selection of efficacy endpoints for HPV vaccine trials for female. If efficacy trials using cervical cancer as the endpoint cannot be conducted, prevention of CIN 2/3 or worse will most closely approximate the preventive efficacy of HPV vaccines for cervical cancer (31). This similar approach has been done in the studies predicting preventive efficacy for the vaccine in anogenital cancer in males. Prevention of cancer would be the most clinically relevant endpoint for a preventive HPV vaccine comprising oncogenic types. However, there appears to be significant feasibility issues for conducting a vaccine study using cervical cancer as the endpoint. Standard of care in the industrialised countries is that women enrolled in HPV vaccine trials would be followed closely by means of Pap screening and other interventions, as appropriate. Given the relatively protracted duration of carcinogenesis following HPV infection (median time from HPV infection to carcinoma in situ has been estimated to be 7-12 years) (51), and the relatively low frequency of cervical cancer due to screening and early treatment, clinical studies using cervical cancer as an endpoint could require a prolonged duration of follow-up to identify sufficient cases to establish efficacy.

A recent meta-analysis showing the distribution of HPV types in European men showed that the HPV prevalence in the general population was significantly higher in studies published after 2000 than in earlier studies (52). HPV prevalence differed between the general and the high-risk male populations, but HPV16 and HPV18 were among the most common HPV types detected in both groups (52). This increase might be due to better detection methods and not to a change in HPV prevalence over time (52).

There is still some uncertainty regarding the long-term effect of the vaccines for boys due to the relatively short follow-up period of the clinical trials. Since we will only know the true effect of HPV vaccination on cancer incidence and mortality outcomes in 20-30 years from now, 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 design to study long-term effects after HPV vaccination (53).

HPV vaccination of girls might also potentially benefit the male population through herd immunity. Vaccinating boys could reduce HPV-related disease both in girls and boys to a greater extent than herd immunity, which are dependent of high vaccination coverage among female (52). In Norway, we have a vaccine coverage above 80% and the gain for girls by herd immunity is potentially not so high. While men who have sex with men, who are particularly susceptible to HPV-related anal-cancer, would only benefit from vaccination programs for boys (52, 54, 55)

Early data from Australia and Sweden are already showing high efficacy in preventing genital warts in immunized cohorts of females and a significant but lower efficacy in unimmunized males from the same population, which illustrates the impact of herd immunity (56). The cohort 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 (56). For heterosexual men under 21 years there was a large reduction in the incidence of genital warts in the vaccination period from 12.1% in 2007 to 2.2% in 2011. A large cohort study in Sweden reported similar results among girls (57). Genital warts have a shorter incubation time after incident HPV infection and, might therefore be a good measure for early evaluations of HPV vaccine effectiveness (58), although we still do not know if a similar vaccine effect will occur on more serious outcomes as cancer. The study concluded that young age at first vaccination is imperative for maximizing the effectiveness of quadrivalent HPV vaccine (57). A decrease in both oral and cervical HPV prevalence were found in a follow up study after gradual introduction of public HPV vaccination in a youth clinic in Sweden (59). In HPV vaccinated girls a reduced prevalence of oral HPV infection was observed compared to a control group of girls without vaccination (60). A recent study did not find significant serious adverse events after eight years of follow up in both genders (61). A large cohort study examined the safety of the vaccine and found no evidence supporting associations between exposure to HPV vaccine and autoimmune, neurological, or venous thromboembolic adverse events (62).

Recent studies have shown a reduced-dose scheduling can translate to greater public health benefits in resource-poor settings. Although the data do not allow conclusions about a 1-dose schedule, we can offer a robust quantification of the difference in risk with 2 vs. 3 doses as well as solid evidence for the importance of early vaccination in a real-life health care environment and for a disease end point (63). Although maximum reduction in risk of condyloma was seen after three doses of quadrivalent HPV vaccine, two vaccine doses were also associated with a considerable reduction in condyloma risk. The implication of these findings for the relationship between number of vaccine doses and cervical cancer risk requires further investigation (64).

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 more robust against bias than observational studies, and are therefore the preferred design for studies of the effect of an intervention. Observational and registry studies might be more appropriate to assess long-term follow-up data and outcomes related to harm.

The vaccine producers have sponsored all included studies. This can be a source of bias since studies funded by the pharmaceutical industry have been found to be more likely to present outcomes in favour of the sponsor (65). To limit the risk of reporting 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. The outcomes reported in these studies is according to the protocol.

Implications for practice and research

HPV vaccination is a public health intervention and its effects will only be demonstrated years or decades after the implementation of the program. It is still unclear if implementation of the vaccine will benefit future generations, and there is not a consensus on this topic despite extended debates (66). Many countries have not recommended male vaccination because it is not cost-effective. USA, Canada, Austria, and Australia have recommended gender-neutral vaccination (52, 67). Denmark has decided not to recommend vaccination of boys (68). Careful health economic modelling will guide the decisions on whether to vaccinate boys in Norway. A separate report will cover cost-effectiveness of HPV vaccination in males for Norway.

Many countries have already started national vaccination programs for girls, but the true effect on cancer outcomes of HPV vaccination will first be evident 20-30 years from now. Expanding the vaccination program to also include males would further control the transmission of HPV and provide direct protection to males. The European Centre for Disease Prevention and Control (ECDC) says that while the vaccine is effective, current economic models have not yet found it to be cost-effective to include boys in HPV vaccination programmes. ECDC will update the economic models as more data begins to emerge.

Conclusion

This systematic review is based on data from two randomized controlled studies. The efficacy data in our review are from a single large RCT that examined the effect of prophylactic vaccination of males aged 16 to 26 years using the quadrivalent HPV vaccine. Finding from this randomized study showed that the HPV vaccine was efficacious in preventing external genital lesions caused by infection with HPV 6, 11, 16 or 18 in males aged 16 to 26. The vaccine prevents genital warts in males (moderate quality evidence).

A longer follow-up time is necessary to assess effects on precancerous lesions in males. So far, with only three years follow up, there are very sparse data on the precancerous lesions PIN2+ and the results are not conclusive (low quality evidence).

In a subpopulation of men who have sex with men, the vaccine reduced anal precancerous lesions (AIN2+) (low quality evidence).

There were no difference in serious adverse events after three years follow-up of HPV vaccination (moderate quality of evidence).

Need for further research

The present systematic review found no results for the effects of the vaccine on the incidence of penile or anal cancer or cancer-related mortality. Long-term follow-up studies are needed to demonstrate whether there is an effect of HPV vaccination on cancer outcomes or not.

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

We suggest the following research question for long-term studies to demonstrate effects on cancer incidence, cancer related mortality and safety:

Design: Prospective observational studies (vaccinated versus non-vaccinated cohorts) and registry studies.
Population: Male vaccination age 10-16 years

Intervention and comparator: HPV vaccines versus placebo or other vaccines.
Outcomes: Cancer related mortality, penile cancer, anal cancer, oropharyngeal cancer other cancer types, pre-cancerous lesions unrelated to HPV status in the lesions, serious adverse events.

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

References

1. DeSanjose S, Diaz M, Castellsague X, Clifford G, Bruni L, Munoz N, et al. Worldwide prevalence and genotype distribution of cervical human papillomavirus DNA in women with normal cytology: a meta-analysis. Lancet InfectDis 2007;7(7):453-459.

2. Schiller JT, Day PM, Kines RC. Current understanding of the mechanism of HPV infection. Gynecol Oncol 2010;118(1 Suppl):S12-17.

3. Parkin DM. The global health burden of infection-associated cancers in the year 2002. IntJCancer 2006;118(12):3030-3044.

4. WHO Information Centre on HPV and Cervical cancer. HPV and cervical cancer in the world: 2007 report. Vaccine 2013;25 Suppl 3:C1-C230.

5. IARC working group on the evaluation of carcinogenic risks to humans. A review of human carcinogenesis. Part B: Biological agents. Lyon, France: 2009

6. IARC. Human papillomaviruses. 2007

7. Lowy DR, Schiller JT. Reducing HPV-associated cancer globally. Cancer Prev Res 2012;5(1).

8. Bouvard V, Baan R, Straif K, Grosse Y, Secretan B, El GF, et al. A review of human carcinogens--Part B: biological agents. Lancet Oncol 2009;10(4):321-322.

9. De Vuyst H, Clifford Gm Fau - Nascimento MC, Nascimento Mc Fau - Madeleine MM, Madeleine Mm Fau - Franceschi S, Franceschi S. Prevalence and type distribution of human papillomavirus in carcinoma and intraepithelial neoplasia of the vulva, vagina and anus: a meta-analysis. Int J Cancer 2009;124(7):1626-1636.

10. Gillison M. HPV and its effect on head and neck cancer prognosis. Clin Adv Hematol Oncol 2010;8(10):680-682

11. Gillison ML BT, Pickard RK, Tong ZY, Xiao W, Kahle L, Graubard BI, Chaturvedi AK. Prevalence of oral HPV infection in the United States, 2009-2010. JAMA 2012;307(7):693-703.

12. Bonanni P LM, Latham NB, Bechini A, Tiscione E, Lai P, Panatto D, Gasparini R, Boccalini S. An overview on the implementation of HPV vaccination in Europe. Hum Vaccin 2011;7:Suppl:128-135.

13. Goon PK, Stanley MA, Ebmeyer J, Steinstrasser L, Upile T, Jerjes W, et al. HPV & head and neck cancer: a descriptive update. Head Neck Oncol 2009;1:36.

14. Hartwig S, Syrjanen S, Dominiak-Felden G, Brotons M, Castellsague X. Estimation of the epidemiological burden of human papillomavirus-related cancers and non-malignant diseases in men in Europe: a review. BMC Cancer 2012;12:30.

15. Syrjanen S, Lodi G, von Bultzingslowen I, Aliko A, Arduino P, Campisi G, et al. Human papillomaviruses in oral carcinoma and oral potentially malignant disorders: a systematic review. 2011(Suppl 1:58-72).

16. Mehanna H, Beech T, Nicholson T, El-Hariry I, McConkey C, Paleri V, et al. Prevalence of human papillomavirus in oropharyngeal and nonoropharyngeal head and neck cancer--systematic review and meta-analysis of trends by time and region. Head Neck 2013;35(5):747-755.

17. Nygard M, Aagnes B, Bray F, Moller B, Mork J. Population-based evidence of increased survival in human papillomavirus-related head and neck cancer. Eur J Cancer 2012;48(9):1341-1346.

18. Mork J, Moller B, Dahl T, Bray F. Time trends in pharyngeal cancer incidence in Norway 1981-2005: a subsite analysis based on a reabstraction and recoding of registered cases. Cancer Causes Control 2010;21(9):1397-1405.

19. Nasman A, Attner P, Hammarstedt L, Du J, Eriksson M, Giraud G, et al. Incidence of human papillomavirus (HPV) positive tonsillar carcinoma in Stockholm, Sweden: an epidemic of viral-induced carcinoma? Int J Cancer 2009;125(2):362-366.

20. Blomberg M, Nielsen A, Munk C, Kjaer SK. Trends in head and neck cancer incidence in Denmark, 1978-2007: focus on human papillomavirus associated sites. Int J Cancer 2011;129(3):733-741.

21. Marur S, D'Souza G, Westra WH, Forastiere AA. HPV-associated head and neck cancer: a virus-related cancer epidemic. Lancet Oncol 2010;11(8):781-789.

22. Steinau M, Saraiya M, Goodman MT, Peters ES, Watson M, Cleveland JL, et al. Human papillomavirus prevalence in oropharyngeal cancer before vaccine introduction, United States. Emerg Infect Dis 2014;20(5):822-828.

23. Hocking JS, Stein A, Conway EL, Regan D, Grulich A, Law M, et al. Head and neck cancer in Australia between 1982 and 2005 show increasing incidence of potentially HPV-associated oropharyngeal cancers. British Journal of Cancer 2011;104(5):886-891.

24. 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. Obstetrical and Gynecological Survey 2005;60(5):303-305.

25. Brewster DH, Bhatti LA. Increasing incidence of squamous cell carcinoma of the anus in Scotland, 1975-2002. Br J Cancer 2006;95(1):87-90.

26. Jin F, Stein AN, Conway EL, Regan DG, Law M, Brotherton JM, et al. Trends in anal cancer in Australia, 1982-2005. Vaccine 2011;29(12):2322-2327.

27. Nielsen A, Munk C, Kjaer SK. Trends in incidence of anal cancer and high-grade anal intraepithelial neoplasia in Denmark, 1978-2008. Int J Cancer 2012;130(5):1168-1173.

28. Stanley M. HPV vaccination in boys and men. Hum Vaccin Immunother 2014;10(7):2109-2111.

29. Schiller JT, Lowy DR. Understanding and learning from the success of prophylactic human papillomavirus vaccines. Nat Rev Microbiol 2012;10(10):681-692.

30. Burger EA, Sy S, Nygard M, Kristiansen IS, Kim JJ. Prevention of HPV-related cancers in Norway: cost-effectiveness of expanding the HPV vaccination program to include pre-adolescent boys. PLoS One 2014;9(3):e89974.

31. Pratt D, Goldenthal K, Geber A. Preventive Human Papillomavirus (HPV) Vaccines- Regulatory Briefing Document on Endpoints. Vaccines and Related Biological Products Advisory Committee Meeting November 28 and 29, 2001. http://www.fda.gov/ohrms/dockets/ac/01/briefing/3805b1_01.htm (accessed 2013 june 14). 2001.

32. Jiang Y, Gauthier A, Postma MJ, Ribassin-Majed L, Largeron N, Bresse X. A critical review of cost-effectiveness analyses of vaccinating males against human papillomavirus. Hum Vaccin Immunother 2013;9(11):2285-2295.

33. Lacey CJ, Lowndes CM, Shah KV. Chapter 4: Burden and management of non-cancerous HPV-related conditions: HPV-6/11 disease. Vaccine 2006;24 Suppl 3:S3/35-S33/41.

34. von Krogh G. Management of anogenital warts (condylomata acuminata). Eur J Dermatol 2001;11(6):598-603; quiz 604.

35. Maw RD, Reitano M, Roy M. An international survey of patients with genital warts: perceptions regarding treatment and impact on lifestyle. IntJSTD AIDS 1998;9(10):571-578.

36. Woodhall S, Ramsey T, Cai C, Crouch S, Jit M, Birks Y, et al. Estimation of the impact of genital warts on health-related quality of life. Sex Transm Infect 2008;84(3):161-166.

37. Kjaer SK, Tran TN, Sparen P, Tryggvadottir L, Munk C, Dasbach E, et al. The burden of genital warts: a study of nearly 70,000 women from the general female population in the 4 Nordic countries. JInfectDis 2007;196(10):1447-1454.

38. Brown RE, Breugelmans JG, Theodoratou D, Benard S. Costs of detection and treatment of cervical cancer, cervical dysplasia and genital warts in the UK. CurrMedResOpin 2006;22(4):663-670.

39. Mortensen GL, Larsen HK. The quality of life of patients with genital warts: a qualitative study. BMCPublic Health 2010;10:113.

40. Cancer Registry of Norway. Cancer in Norway 2012 - Cancer incidence, mortality, survival and prevalence in Norway. Oslo, Norway: Cancer Registry of Norway; 2014

41. Nasjonalt kunnskapssenter for helsetjenesten. Slik oppsummerer vi forskning. Håndbok for Nasjonalt kunnskapssenter for helsetjenesten. 3.2. reviderte utg. 2013. 2013

42. Petaja T, Pedersen C, Poder A, Strauss G, Catteau G, Thomas F, et al. Long-term persistence of systemic and mucosal immune response to HPV-16/18 AS04-adjuvanted vaccine in preteen/adolescent girls and young women. IntJCancer 2011;129(9):2147-2157.

43. Giuliano AR, Palefsky JM, Goldstone S, Moreira J, E.D, Penny ME, et al. Efficacy of quadrivalent HPV vaccine against HPV infection and disease in males. New England Journal of Medicine 2011;364(5):401-411.

44. Goldstone SE, Jessen H, Palefsky J, Giuliano A, Jr ME, Vardas E, et al. Quadrivalent HPV vaccine efficacy against disease related to vaccine and non-vaccine HPV types in males. Vaccine 2013;31(37):3849-3855.

45. Moreira ED, Palefsky JM, Giuliano AR, Goldstone S, Aranda C, Jessen H, et al. Safety and reactogenicity of a quadrivalent human papillomavirus (types 6, 11, 16, 18) L1 viral-like-particle vaccine in older adolescents and young adults. Human Vaccines 2011;7(7):768-775.

46. Palefsky JM, Giuliano AR, Goldstone S, Moreira ED, Aranda C, Jessen H, et al. HPV vaccine against anal HPV infection and anal intraepithelial neoplasia. The New England journal of medicine 2011;365(17):1576-1585.

47. Petaja T, Keranen H, Karppa T, Kawa A, Lantela S, Siitari-Mattila M, et al. Immunogenicity and safety of human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine in healthy boys aged 10-18 years. JAdolescHealth 2009;44(1):33-40.

48. Chaturvedi AK. Epidemiology and clinical aspects of HPV in head and neck cancers. Head Neck Pathol 2012;6 Suppl 1:S16-24.

49. Couto E, Saeterdal I, Juvet L, Klemp M. HPV catch-up vaccination of young women: a systematic review and meta-analysis. BMC Public Health 2014;14:867.

50. Sæterdal I CE, Juvet L, Harboe I, Klemp M Effect of catch-up HPV vaccination of young women. Rapport fra Kunnskapssenteret nr 4 - 2014 2014.

51. Ylitalo N, Josefsson A, Melbye M, Sorensen P, Frisch M, Andersen PK, et al. A prospective study showing long-term infection with human papillomavirus 16 before the development of cervical carcinoma in situ. Cancer Res 2000;60(21):6027-6032.

52. Hebnes J, Olesen T, Duun-Henriksen A, Munk C, Norrild B, Kjaer S. Prevalence of Genital Human Papillomavirus among Men in Europe: Systematic Review and Meta-Analysis. J Sex Med 2014;11:2630-2644.

53. Rana MM, al e. Understanding long-term protection of human papillomavirus vaccination against cervical carcinoma: Cancer registry-based follow-up. Int J Cancer 2013;132(12):2833-2838.

54. Frisch M, Smith E, Grulich A, Johansen C. Cancer in a population-based cohort of men and women in registered homosexual partnerships. Am J Epidemiol 2003;157(11):966-972.

55. Heck JE, Berthiller J, Vaccarella S, Winn DM, Smith EM, Shan'gina O, et al. Sexual behaviours and the risk of head and neck cancers: a pooled analysis in the International Head and Neck Cancer Epidemiology (INHANCE) consortium. Int J Epidemiol 2010;39(1):166-181.

56. Ali.H, al e. Genital warts in young Australians five years into national human papillomavirus vaccination programme: national surveillance data. BMC Public Health 2013;13(18):1-9.

57. Leval A, Herweijer E, Ploner A, Eloranta S, Fridman SJ, Dillner J, et al. Quadrivalent human papillomavirus vaccine effectiveness: a Swedish national cohort study. JNatlCancer Inst 2013;105(7):469-474.

58. Levin MJ, Moscicki AB, Song LY, Fenton T, Meyer WA, Read JS, et al. Safety and immunogenicity of a quadrivalent human papillomavirus (types 6, 11, 16, and 18) vaccine in HIV-infected children 7 to 12 years old. Journal of acquired immune deficiency syndromes (1999) 2010;55(2):197-204.

59. Grun N, Ahrlund-Richter A, Franzen J, Mirzaie L, Marions L, Ramqvist T, et al. Oral human papillomavirus (HPV) prevalence in youth and cervical HPV prevalence in women attending a youth clinic in Sweden, a follow up-study 2013-2014 after gradual introduction of public HPV vaccination. Scand J Infect Dis 2014:1-5.

60. Herrero R, Quint W, Hildesheim A, Gonzalez P, Struijk L, Katki HA, et al. Reduced prevalence of oral human papillomavirus (HPV) 4 years after bivalent HPV vaccination in a randomized clinical trial in Costa Rica. PLoS One 2013;8(7):e68329.

61. Ferris D, Samakoses R, Block SL, Lazcano-Ponce E, Restrepo JA, Reisinger KS, et al. Long-term study of a quadrivalent human papillomavirus vaccine. Pediatrics 2014;134 (3)(e657-65).

62. Arnheim-Dahlstrom L, Pasternak B, Svanstrom H, Sparen P, Hviid A. Autoimmune, neurological, and venous thromboembolic adverse events after immunisation of adolescent girls with quadrivalent human papillomavirus vaccine in Denmark and Sweden: cohort study. BMJ 2013;347:f5906.

63. Ploner A, Herweijer E, Arnheim-Dahlstrom L. Number of Human Papillomavirus Vaccine Doses and Condyloma Reply. JAMA 2014;311(23):2439-2440.

64. Herweijer E, Leval A, Ploner A, Eloranta S, Simard JF, Dillner J, et al. Association of varying number of doses of quadrivalent human papillomavirus vaccine with incidence of condyloma. JAMA 2014;311(6):597-603.

65. Higgins J, Green S. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011. The Cochrane Collaboration; 2011.

66. Weatherly H, Drummond M, Claxton K, Cookson R, Ferguson B, Godfrey C, et al. Methods for assessing the cost-effectiveness of public health interventions: key challenges and recommendations. Health Policy 2009;93(2-3):85-92.

67. Australian Goverment. Vaccinating against Human Papillomavirus (HPV) is the best way to prevent HPV-related cancers and disease. The HPV vaccine is

being provided free in schools as part of the National Immunisation Program. Available from: http://hpv.health.gov.au/.

68. Sundhedstyrrelsen. HPV-vaccination. Sundhedstyrrelsen [Accessed 12 november]. Available from: http://sundhedsstyrelsen.dk/da/sundhed/vaccination/hpv-vaccination/spoergsmaal-og-svar-ved-hpv-vaccinen#A.

Appendix

Appendix 1. Search methods

Prosjekt 734 HVP vaksine gutter

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: 616 RCT (868 including dupl.)

Update search: Date: 09.01.2014
Result: 161 RCT/CCT
58 SR

Searched by: Ingrid Harboe, research librarian

Searchstrategies:
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

Characteristic of Giuliano 2011, Palefsky 2011, Moreira 2011, Goldestone 2013 (43-46).

Details of study	Citation	Citation	Citation	Citation
Protocol number	NTC00090285	NTC00090285	NTC00090285	NTC00090285
Study name	Protocol V501-20	Protocol V501-20	Protocol V501-20	Protocol V501-20
First author of study, year of publication	**Giuliano 2011**	**Palefsky 2011**	**Moreira 2011**	**Goldestone 2013**
	Efficacy of quadrivalent HPV vaccine against infection against HPV infection and disease in males.	HPV vaccine against Anal HPV infection and Anal intraepithelial Neoplasia	Safety and reactivity of a Quadrivalent human papillomavirus (types 6,11,16,18) L1 viral-like-particle vaccine in older adolescent and young adults	Quadrivalent HPV vaccine efficacy against disease related to vaccine and non-vaccine HPV types in males
Study design	RCT	RCT	RCT	RCT
Year(s) study was conducted	September 2004-August 2008			
Follow up period	36 months	36 months	36 months	36 months
Geographical location	18 countries			
Funding source	Merck			
Population				
Gender	Male			
Age of participants (mean/median)	16-23 (mean 20.5)			
Inclusion criteria	Healthy male who reported no more than five female sexual partners, MSM 16-26 years one to five male or female partners during lifetime			
Exclusion criteria	Detectable anogenital warts or genital lesion at screening that were suggestive of infection with non-HPV sexually transmitted disease or had history of such findings were excluded.			
Intervention and comparison				
Intervention	(Gardasil™) human papillomavirus (types 6, 11, 16, 18) recombinant vaccine on 0,2 and 6 month schedule			

Comparison(s)	placebo (unspecified) on 0,2 and 6 month schedule			
Outcomes			**Outcome assessed within:**	
	Human Papillomavirus (HPV) Related External Genital Warts		**Giuliano**	
	Perineal Intraepithelial Neoplasia (PIN), Penile, Perianal or Perineal Cancer		**Giuliano**	
	Anal Intraepithelial Neoplasia (AIN), Anal Cancer		**Palefsky** **Goldstone**	
	Serious Adverse Events (SAEs)		**Moreira**	

Risk of Bias table for Giuliano 2011, Palefsky 2011, Moreira 2011, Goldestone 2013 (43-46).

Entry/Domain	**Judgement**	**Description**
Random sequence generation?	Low risk	Randomized (1:1 ratio) to receive either the HPV-6,11,16,18 vaccine or a placebo control vaccine. A computer-generated allocation was produced by sponsor
Allocation concealment?	Low risk	A computer-generated allocation was produced by sponsor
Blining of participants and personnel?	Low risk	observer-blind
Blinding of outcome assessments?	Low risk	observer-blind
Incomplete outcome data?	High risk	4065 were inrolled, 4055 received on or more doses of vaccine (intention to treat populatin ; ITT)
Selective reporting?	Low risk	Reporting ITT and PPP
Other sources of bias?	Low risk	Funding Merck
Conclusion	Low risk of bias	

Characteristic of Petaja 2009 (47).

Details of study	**Citation**

Protocol number	NTC00309166
Study name	Petaja
First author of study, year of publication	**Petaja 2009**
Title of study	Immunogenicity and safety of human papillomavirus (HPV)-16/18 AS-04-adjuvanted Vaccine in healthy boys 10-18 years
Study design	RCT
Year(s) study was conducted	April 2006-January 2007
Follow up period	
Geographical location	Finland
Funding source	GlaxoSmith Kline Biologicals
Population	
Gender	Male
Age of participants (mean/median)	10-18 years
Inclusion criteria	Healthy male
Exclusion criteria	other vaccine, immunoglobulins or blood products the last 30 days
Intervention and comparison	
Intervention	Cervarix Randomized 2:1 HPV16/18 SA04-adjuvanted vaccine (20 μg) on 0,1 and 6 month schedule
Comparison(s)	Hepatitt B vaccine (Engerix-B) (10 μg) on 0,1 and 6 month schedule
Outcomes	
	Safety, Immunogenicity
	Serious adverse events

Risk of Bias table for Petaja 2009 (47).

Entry/Domain	Judgement	Description
Random sequence generation?	Low risk	randomized (2:1 ratio) to receive either the HPV- 16/18 AS04-adjuvanted vaccine or a HBV control vaccine (A randomization blocking scheme was used to ensure that balance between treatments (2:1) and approximately equal distribution across the three age strata was maintained.)
Allocation concealment?	Low risk	All study personnel were blinded to the vaccines used, except the study nurse administrating the vaccines
Blining of participants and personnel?	Low risk	observer-blind
Blinding of outcome assessments?	Low risk	observer-blind

Incomplete outcome data?	Low risk	5/181 lost of follow-up in HPV16/18 group and 3/89 in HBV group
Selective reporting?	Low risk	Reporting ITT
Other sources of bias?	Low risk	Funding GSK
Conclusion	Low risk of bias	

Appendix 3. GRADE profiles

Author(s): Lene K Juvet, Ingvil Sæterdal, Elisabeth Couto
Date: October 2214
Question: Should HPV vaccination vs. placebo be used for prevention of cancer lesions in males?
Settings: Community
Bibliography (systematic reviews): Effect of HPV vaccination of boys, Juvet et al 2014.

Quality assessment							№ of patients		Effect		Quality
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	HPV vaccination	placebo	Relative (95% CI)	Absolute (95% CI)	
Persistent infection ITT naive (follow up: mean 6 months; assessed with: DNA detection in anogenital swab or biopsy specism collected in two or more consecutive visits)											
1 [1]	randomised trial [1]	not serious	not serious	not serious	not serious	none [2]	58/1669 (3.5%)	175/1664 (10.5%)	**RR 0.33** (0.25 to 0.44)	70 fewer per 1000 (from 59 fewer to 79 fewer)	⊕⊕⊕⊕ HIGH
Pesistent infection PPP (follow up: mean 6 months; assessed with: DNA detection in anogenital swab or biopsy specism collected in two or more consecutive visits)											
1 [1]	randomised trial [1]	not serious	not serious	not serious	serious [3]	none [2]	15/1390 (1.1%)	101/1400 (7.2%)	**RR 0.15** (0.09 to 0.26)	61 fewer per 1000 (from 53 fewer to 66 fewer)	⊕⊕⊕◯ MODERATE
all PIN lesions HPV 6,11,16,18??? ITT (follow up: mean 3 years; assessed with: PCR assay of biopsy)											
1 [1]	randomised trial [1]	not serious	not serious	not serious	very serious [3,4]	none [2]	6/2025 (0.3%)	5/2030 (0.2%)	**RR 1.2** (0.37 to 3.94)	0 fewer per 1000 (from 2 fewer to 7 more)	⊕⊕◯◯ LOW
PIN 2/3 lesions HPV 6,11,16,18??? ITT (follow up: mean 3 years; assessed with: PCR assay of biopsy)											
1 [1]	randomised trial [1]	not serious	not serious	not serious	very serious [3,4]	none [2]	3/2025 (0.1%)	2/2030 (0.1%)	**RR 1.5** (0.25 to 8.99)	0 fewer per 1000 (from 1 fewer to 8 more)	⊕⊕◯◯ LOW
all PIN lesions HPV 6,11,16,18??? PPP (follow up: mean 3 years; assessed with: PCR assay of biopsy)											
1 [1]	randomised trial [1]	not serious	not serious	not serious	very serious [3,4]	none [2]	0/1397 (0.0%)	3/1408 (0.2%)	**RR 0.14** (0.01 to 2.78)	2 fewer per 1000 (from 2 fewer to 4 more)	⊕⊕◯◯ LOW
PIN 2/3 lesions HPV 6,11,16,18 ????PPP (follow up: mean 3 years; assessed with: PCR assay of biopsy)											
1 [1]	randomised trial [1]	not serious	not serious	not serious	very serious [3,4]	none [2]	0/1397 (0.0%)	1/1408 (0.1%)	**RR 0.34** (0.01 to 8.24)	0 fewer per 1000 (from 1 fewer to 5 more)	⊕⊕◯◯ LOW
Condyloma all HPV types ITT (follow up: mean 3 years)											
1 [1]	randomised trial [1]	not serious	not serious	not serious	serious [3]	none [2]	32/2025 (1.6%)	83/2030 (4.1%)	**RR 0.39** (0.25 to 0.58)	25 fewer per 1000 (from 17 fewer to 31 fewer)	⊕⊕⊕◯ MODERATE
Condyloma HPV 6,11,1618 ITT (follow up: mean 3 years)											
1 [1]	randomised trial [1]	not serious	not serious	not serious	serious [3]	none [2]	24/2025 (1.2%)	72/2030 (3.5%)	**RR 0.33** (0.21 to 0.53)	24 fewer per 1000 (from 17 fewer to 28 fewer)	⊕⊕⊕◯ MODERATE
Condyloma HPV 6,11,16,18 PPP (follow up: mean 3 years)											
1 [1]	randomised trial [1]	not serious	not serious	not serious	serious [3]	none [2]	3/1397 (0.2%)	28/1408 (2.0%)	**RR 0.1** (0.03 to 0.35)	18 fewer per 1000 (from 13 fewer to 19 fewer)	⊕⊕⊕◯ MODERATE
MSM AIN 2/3 lesion HPV 6,11,16,18?? ITT (follow up: mean 3 years; assessed with: PCR assay of biopsy)											
1 [5]	randomised trial [5]	not serious	not serious	not serious [6]	serious [3]	none [2]	18/275 (6.5%)	39/276 (14.1%)	**RR 0.46** (0.27 to 0.79)	76 fewer per 1000 (from 30 fewer to 103 fewer)	⊕⊕⊕◯ MODERATE
MSM AIN 2/3 lesions HPV 6,11,16,18?? PPP (follow up: mean 3 years; assessed with: PCR assay of biopsy)											

Quality assessment							№ of patients		Effect		Quality
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	HPV vaccination	placebo	Relative (95% CI)	Absolute (95% CI)	
1 [5]	randomised trial [5]	not serious	not serious	not serious [8]	serious [3]	none [2]	3/194 (1.5%)	13/208 (6.3%)	**RR 0.25** (0.07 to 0.86)	47 fewer per 1000 (from 9 fewer to 58 fewer)	⊕⊕⊕◯ MODERATE
MSM all AIN all HPV types ITT (follow up: mean 3 years)											
1 [9]	randomised trial [9]	not serious	not serious	not serious	serious [3]	none [3]	74/275 (26.9%)	103/276 (37.3%)	**RR 0.72** (0.56 to 0.92)	104 fewer per 1000 (from 30 fewer to 164 fewer)	⊕⊕⊕◯ MODERATE
MSM Condyloma HPV 6,11,16,18 ITT (follow up: mean 3 years)											
1 [5]	randomised trial [5]	not serious	not serious	not serious [8]	serious [3]	none [2]	13/275 (4.7%)	31/275 (11.3%)	**RR 0.42** (0.23 to 0.79)	65 fewer per 1000 (from 24 fewer to 87 fewer)	⊕⊕⊕◯ MODERATE
MSM Condyloma HPV 6,11,16,18 PPP (follow up: mean 3 years)											
1 [5]	randomised trial [5]	not serious	not serious	not serious [8]	very serious [3,4]	none [2]	0/194 (0.0%)	6/208 (2.9%)	**RR 0.08** (0.005 to 1.45)	27 fewer per 1000 (from 13 more to 29 fewer)	⊕⊕◯◯ LOW
Serois adverse events (follow up: median 3 years)											
2 [6,7]	randomised trials [6,7]	not serious	not serious	not serious	serious [3]	none [2]	11/2201 (0.5%)	12/2118 (0.6%)	**RR 0.81** (0.16 to 1.87)	1 fewer per 1000 (from 5 fewer to 5 more)	⊕⊕⊕◯ MODERATE
External genital lessions type - any HPV type ITT (follow up: mean 3 years)											
1 [1]	randomised trial [1]	not serious	not serious	not serious	serious [3]	none [2]	36/2025 (1.8%)	89/2030 (4.4%)	**RR 0.41** (0.28 to 0.59)	26 fewer per 1000 (from 18 fewer to 32 fewer)	⊕⊕⊕◯ MODERATE
External genital lessions type - HPV 6,11,16,18 ITT (follow up: mean 3 years)											
1 [1]	randomised trial [1]	not serious	not serious	not serious	serious [3]	none [2]	27/2025 (1.3%)	77/2030 (3.8%)	**RR 0.35** (0.23 to 0.54)	25 fewer per 1000 (from 17 fewer to 29 fewer)	⊕⊕⊕◯ MODERATE
External genital lessions type - any HPV type PPP (follow up: mean 3 years)											
1 [1]	randomised trial [1]	not serious	not serious	not serious	serious [3]	none [3]	6/1275 (0.5%)	36/1270 (2.8%)	**RR 0.17** (0.07 to 0.39)	24 fewer per 1000 (from 17 fewer to 26 fewer)	⊕⊕⊕◯ MODERATE
External genital lessions type - HPV 6,11,16,18 (follow up: mean 3 years)											
1 [1]	randomised trial [1]	not serious	not serious	not serious	serious [3]	none [2]	3/1397 (0.2%)	31/1408 (2.2%)	**RR 0.1** (0.03 to 0.32)	20 fewer per 1000 (from 15 fewer to 21 fewer)	⊕⊕⊕◯ MODERATE

MD – mean difference, RR – relative risk

1. Guiliano 2011
2. Funded by Merck
3. Few events
4. Wide confidence intervall crossing the line of no effect
5. Palefsky 2001
6. Moreira 2011
7. Petaja 2009
8. Population comprise only men who have sex with men. Decided not to downgrade for condyloma since the results ar similar to the main population. Downgrade AIN since there is uncertainty about transferability to the full population
9. Goldstone 2013

Appendix 4. Excluded studies

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.

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.

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.

Bosch FX, Broker TR, Forman D et al. Comprehensive Control of Human Papillomavirus Infections and Related Diseases. Vaccine 31S(2013) I1–I31.

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.

Elbasha EH, Dasbach EJ. Impact of vaccinating boys and men against HPV in the United States. *Vaccine* 2010; 28(42):6858-6867.

Garnock-Jones KP, Giuliano AR. Quadrivalent Human Papillomavirus (HPV) types 6, 11, 16, 18 vaccine: For the prevention of genital warts in males. *Drugs* 2011; 71(5):591-602.

Genden EM, Sambur IM, de Almeida JR, Posner M, Rinaldo A, Rodrigo JP, Strojan P, Takes RP, Ferlito A.Human papillomavirus and oropharyngeal squamous cell carcinoma: what the clinician should know. Eur Arch Otorhinolaryngol (2013) 270:405–416

Goldstone S. Efficacy of the quadrivalent hpv vaccine to prevent anal intraepithelial neoplasia among young men who have sex with men. *Sex Transm Infect* 2011; Conference(var.pagings):A352.

Hannisdal K, Schjølberg A, De Angelis PM, Boysen M, Clausen OP.Human papillomavirus (HPV)-positive tonsillar carcinomas are frequent and have a favourable prognosis in males in Norway. Acta Otolaryngol. 2010 Feb;130(2):293-9.

Hillman RJ, Giuliano AR, Palefsky JM, Goldstone S, Moreira J, E.D et al. Immunogenicity of the quadrivalent human papillomavirus (type 6/11/16/18) vaccine in males 16 to 26 years old. *Clinical and Vaccine Immunology* 2012; 19(2):261-267.

Hillman RJ. The effficacy of quadrivalent HPV (types 6/11/16/18) vaccine against HPV-related genital disease and infection in HIV negative young men. *Sexual Health* 2009; Conference(var.pagings):357.

Jessen H. HPV-Impfung bei Mannern. *JDDG - Journal of the German Society of Dermatology* 2012; Conference(var.pagings):30.

Levin MJ, Moscicki AB, Song LY, Fenton T, Meyer WA, Read JS et al. Safety and immunogenicity of a quadrivalent human papillomavirus (types 6, 11, 16, and 18) vaccine in HIV-infected children 7 to 12 years old. *Journal of acquired immune deficiency syndromes (1999)* 2010; 55(2):197-204.

Li R, Li Y, Radley D, Liu Y, Huang T, Sings HL et al. Safety and immunogenicity of a vaccine targeting human papillomavirus types 6, 11, 16 and 18: A randomized, double-blind, placebo-controlled trial in Chinese males and females. *Vaccine* 2012; 30(28):4284-4291.

Moreira ED Jr, Giuliano AR, Palefsky J, Flores CA, Goldstone S, Ferris D, Hillman RJ, Moi H, Stoler MH, Marshall B, Vuocolo S, Guris D, Haupt RM. Incidence, clearance, and disease progression of genital human papillomavirus infection in heterosexual men. J Infect Dis. 2014 Jul 15;210(2):192-9.

Reisinger KS, Block SL, Lazcano-Ponce E, Samakoses R, Esser MT, Erick J et al. Safety and persistent immunogenicity of a quadrivalent human papillomavirus types 6, 11, 16, 18 L1 virus-like particle vaccine in preadolescents and adolescents: A randomized controlled trial. *Pediatr Infect Dis J* 2007; 26(3):201-209.

Reisinger KS, Block SL, Collins-Ogle M, Marchant C, Catlett M, Radley D et al. Safety, tolerability, and immunogenicity of gardasil given concomitantly with Menactra and Adacel. *Pediatrics* 2010; 125(6):1142-1151.

Swedish KA, Factor SH Goldstone GE. Prevention of Recurrent High-Grade Anal Neoplasia With Quadrivalent Human Papillomavirus Vaccination of Men Who Have Sex With Men: A Nonconcurrent Cohort Study. Clinical Infectious Diseases 2012;54(7):891–8

Thompson HS, Davies ML, Holding FP, Fallon RE, Mann AE, O'N T, et al. Phase I safety and antigenicity of TA-GW: a recombinant HPV6 L2E7 vaccine for the treatment of genital warts. Vaccine 1999;17(1):40-9

Vesikari T, Van DP, Lindblad N, Pfletschinger U, Radley D, Ryan D et al. An open-label, randomized, multicenter study of the safety, tolerability, and immunogenicity of quadrivalent human papillomavirus (types 6/11/16/18) vaccine given concomitantly with diphtheria, tetanus, pertussis, and poliomyelitis vaccine in healthy adolescents 11 to 17 years of age. *Pediatr Infect Dis J* 2010; 29(4):314-318

Cause of exclusion.

Study First author year	Cause for exclusion of study
Anderson 2009	Therapeutic vaccine til HIVpositive participants
Block 2010	No RCT.
Block 2006	No gender specific outcome for males.
Bosch 2013	Review article
Donovan 2011	Comemtary to Guiliano study
Elbasha 2010	Economic model
Garnock-Jones 2011	Review article
Genden 2013	Review article
Goldstone 2011	Conference abstract

Hannisdal 2010	Case-control study
Hillman 2012	Conference abstract
Hillman 2009	Conference abstract
Jessen 2012	Conference abstract
Levin 2010	No gender specific outcome for males.
Li 2012	No gender specific safety data for males.
Moreira 2014	Result from placebo group only
Reisinger 2007	No gender specific safety data for males.
Reisinger 2010	No placebo group
Swedish 2012	Cohort study
Thompson 1997	Phase 1 study
Vesikari 2010	No placebo group

Appendix 5. Ongoing trials

We identified 13 ongoing trials whith a search on HPV vaccination and male on in WHO ICTRP Search Portal (http://apps.who.int/trialsearch/). Six of these were RCTs; two are already inculded in the review, one RCT was on educating pre/teens and their parents on the importance of HPV vaccination.

List of three ongoing trials including a population consiting of both male and female.

Study	*Design*	*N / age*	*Intervention*	*Period*
A phase III/IV, community-randomized, controlled study to evaluate the effectiveness of two vaccination strategies using GlaxoSmithKline Biologicals' HPV-16/18 L1 VLP AS04 vaccine in reducing the p... Phase 3 NCT00534638 http://apps.who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2007-001731-55-FI	Randomized, : Partially blind Primary Purpose: Prevention Safety/Efficacy	36 000 12 – 15 years Female and male	GlaxoSmithKline Biologicals' HPV-16/18 L1 VLP AS04 vaccine in reducing the prevalence of HPV-16/18 infection when administered intramuscularly according to a 0, 1, 6-month schedule Number of treatment arms in the trial: 3	Date of first enrolment: 09/08/2007 This study is recruiting participants
An Immunogenicity and Safety Study of Quadrivalent HPV (Types 6, 11, 16, 18) Virus-Like Particle (VLP) Vaccine in Chinese Female Subjects Aged 9 to 45 Years and Male Subjects Aged 9 to 15 Years Phase 3 NCT00496626 http://apps.who.int/trialsearch/Trial2.aspx?TrialID=NCT00496626	Randomized, : Double Blind (Subject, Investigator), Primary Purpose: Prevention Safety/Efficacy	600 Male 9 to 15 Years and female 9 to 45 Years	Quadrivalent Human Papillomavirus (HPV, Types 6, 11, 16, 18) Recombinant Vaccine (Gardasil®) vs placebo	Study Start Date: July 2008 Study Completion Date: February 2009
A Randomized, Double-Blinded, Placebo-Controlled, Phase III Trial of the Quadrivalent HPV Vaccine to Prevent Anal Human Papillomavirus Infection in HIV-Infected Men and Women Phase 3 NCT01461096 http://apps.who.int/trialsearch/Trial2.aspx?TrialID=NCT01461096	Randomized, Double Blind (Subject, Caregiver, Investigator, Outcomes Assessor), Primary Purpose: Prevention Endpoint Classification: Efficacy Study,	564 27 Years and older HIV positive	Quadrivalent Human Papillomavirus (HPV, Types 6, 11, 16, 18) Recombinant Vaccine (Gardasil®) vs placebo	Date of first enrolment: March 2012 Active, not recruiting