Cost-effectiveness of HPV-vaccination of boys aged 12 in a Norwegian setting

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Background: Infection with high-risk human papilloma virus (HPV) types 16 and/or 18 is documented to be related to cervical, vulvar, vaginal, penile, anal and oropharyngeal cancer, while infection with low-risk HPV types 6 and/or 11 is documented to be related with genital warts. This economic evaluation examines the cost-effectiveness of vaccinating both 12-year-old boys and girls against HPV-infection compared to maintaining the current practice of vaccinating only 12-year-old girls. Two vaccines (both delivered in a 3-dose schedule) are available on the Norwegian market with documented effect against HPV-infection: the quadrivalent vaccine is directed at HPV 6, 11, 16 and 18 and the bivalent vaccine is directed at HPV 16 and 18. In this report, we estimated the cost-effectiveness of the quadrivalent vaccine for the target population, as this is the vaccine currently offered in the vaccine program for girls. The cost -effectiveness of the bivalent vaccine is discussed in a scenario analysis. Main findings: The main finding of the evaluation is the following: • From a societal perspective, vaccinating boys in addition to girls aged 12 with the *(continued)*

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Norwegian Knowledge Centre for the Health Services
Oslo, January 2015

Key messages

Infection with high-risk human papilloma virus (HPV) types 16 and/or 18 is documented to be related to cervical, vulvar, vaginal, penile, anal and oropharyngeal cancer, while infection with low-risk HPV types 6 and/or 11 is documented to be related with genital warts. This economic evaluation examines the cost-effectiveness of vaccinating both 12-year-old boys and girls against HPV-infection compared to maintaining the current practice of vaccinating only 12-year-old girls.

Two vaccines (both delivered in a 3-dose schedule) are available on the Norwegian market with documented effect against HPV-infection: the quadrivalent vaccine is directed at HPV 6, 11, 16 and 18 and the bivalent vaccine is directed at HPV 16 and 18. In this report, we estimated the cost-effectiveness of the quadrivalent vaccine for the target population, as this is the vaccine currently offered in the vaccine program for girls. The cost-effectiveness of the bivalent vaccine is discussed in a scenario analysis.

The main finding of the evaluation is the following:

- From a societal perspective, vaccinating boys in addition to girls aged 12 with the quadrivalent vaccine is probably not cost-effective. The incremental cost-effectiveness ratio (ICER) was NOK 1,626,261 for a quality-adjusted life-year (QALY).

Although there is no official cost-effectiveness threshold value in Norway, such high ICERs are generally associated with the intervention not being accepted for implementation in the Norwegian health sector.

Title:
Cost-effectiveness of HPV-vaccination of males aged 12 in a Norwegian setting ----------

Type of publication:
Economic evaluation

Health technology assessment (HTA) is a multidisciplinary process that summarizes information about the medical, social, economic and ethical issues related to the use of a health technology in a systematic, transparent, unbiased, robust manner. Its aim is to inform the development of safe, effective health policies that are patient focused and that seek to achieve best value.

Doesn't answer everything:

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

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Last search for studies: January, 2014 for vaccine effect and April 2014 for HRQoL-data.

Peer Review:
Aileen Neilson, Health Economics Research Unit, University of Aberdeen.

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Executive summary

Background

Infection with human papilloma virus (HPV) is documented to be related to cervical, vulvar, vaginal, penile, anal and oropharyngeal cancer and genital warts. The Norwegian Institute of Public Health is responsible for managing the publicly funded vaccination program against the human papillomavirus (HPV). Currently, this program covers the expenses of vaccinating only 12-year-old girls with the quadrivalent vaccine (directed at HPV 6, 11, 16 and 18), delivered in a 3-dose schedule.

Gender-neutral vaccination has been recommended in a few countries, e.g. United States (1) and Australia (2). In the European Union, only Austria (3) has recommended it. The UK government decided in 2014 to reconsider whether HPV vaccination should be offered to men who have sex with men and/or adolescent males (4).

In this economic evaluation, we evaluate the cost-effectiveness of vaccinating 12-year-old boys against HPV-infection in addition to the current practice of vaccinating 12-year-old-girls, compared to maintaining the current practice.

Objective

To evaluate the epidemiological impact, costs, health benefits and cost-effectiveness of administering the quadrivalent HPV-vaccine to 12-year-old-boys in addition to the current practice of vaccinating 12-year-old-girls, compared to maintaining the current practice. We evaluate in addition how alternative scenarios would influence results and conclusions.

Method

We used an already published American economic model consisting of a deterministic, dynamic population-based model that estimated the proportion of

people in every contemporary and future cohort having experienced infection with HPV 6/11, 16 and/or 18, from 2016-2115.

The model was adapted to the Norwegian setting with respect to incidence rates of HPV-related outcomes, costs and health related quality-of-life (HRQoL). In addition, the model was modified in order to incorporate the findings on clinical endpoints reported in our systematic reviews. Finally, the model was made probabilistic.

The focus in our base case analysis was on evaluating the consequences of HPV-vaccination of boys (using the quadrivalent vaccine in a 3-dose schedule) may have for 184 birth cohorts during the first 100 years: The 91 cohorts aged 8-99 at the moment of starting the vaccination of boys and the coming 93 cohorts of 8-year-old boys and girls.

We assumed that 82% of all boys and girls aged 12 would get on average 2.54 and 2.78 doses of the HPV-vaccine, respectively. Furthermore, we assumed that the vaccine would only have effect on genital warts, cervical, vulvar, vaginal and anal precancerous lesions and cancer as documented in our own systematic reviews (vaginal and anal outcomes were included only in sensitivity analyses). Finally, the price of the vaccine was set equal to the maximum pharmacy retail price (PRP) of the quadrivalent vaccine in December 2014, NOK 1,113.40/dose.

The economic evaluation was performed from two different costs perspectives: a health-care perspective focusing on costs to the National health system; and a societal perspective in which we excluded the value-added tax (VAT) from prices and included the deadweight loss of taxation, the costs to patients for time used under treatment and the work-related productivity costs due to disease.

For each perspective, an Incremental Cost Effectiveness Ratio (ICER) in terms of NOK per quality-adjusted life year (QALY) gained was calculated. To determine whether vaccinating boys aged 12 was cost-effective, the resulting ICER was compared to a range of potential willingness-to-pay (WTP) values between NOK 250 000 - 2 000 000/ QALY gained. ICERs lower than the chosen WTP value typically supports the hypothesis that vaccinating boys is cost-effective and therefore yields good value for money, while ICERs above the chosen WTP value suggest the opposite.

In addition, we assessed the uncertainty around the results and estimated the Expected Value of Perfect Information (EVPI).

We ascertained the impact on the base case results by changing the value of potentially important inputs and modelling assumptions. We did this by conducting the following sensitivity analyses (from a health care perspective):

1. Lower vaccine purchase prices per dose.
2. The exclusion of the effect of the vaccine on genital warts in order to examine the cost-effectiveness of using a bivalent vaccine.
3. Increasing the coverage among girls instead of vaccinating boys.
4. The exclusion of the HRQoL-impact of vaccination.
5. The inclusion of the vaccine effect on anal cancer (in both genders) and vaginal cancer and vaginal intraepithelial neoplasia grade 2 and 3 (VaIN 2+).
6. The exclusion of the effect of the vaccine in reducing the number of conization-related preterm births.
7. A 2-doses schedule providing the full vaccination effect reported in published studies.
8. The reduction in the incidence of several relevant outcomes under different vaccine coverage assumptions.

In addition, we conducted a series of one-way sensitivity analyses where we examined how the base case results changed when increasing or reducing certain groups of variables (epidemiologic, effect, costs, HRQoL) by 25%. We present the results in the form of a Tornado diagram.

Results

From a health-care perspective, the base case results showed that including boys in the current vaccination program would lead to a discounted, incremental cost of NOK 1.851 billion (1 billion = 1 thousand million) and a discounted, incremental health gain of 1,034.59 QALYs over the 100 years horizon of the model (2016-2115). This resulted in an ICER of NOK 1,789,463/QALY. The scatter-plot of the ICER showed that both the incremental costs and the health gain were positive for all iterations.

The ICER of vaccinating boys is lower from a societal perspective than from a public health perspective. The incremental costs were approximately 9% lower, NOK 1.677 billion vs. NOK 1.851 billion in the public health-care perspective, while the incremental effect was the same, leading to an ICER of NOK 1,626,261 /QALY.

The results of the scenario analyses were the following:

1. Using prices of NOK 250, 500 and 750/dose resulted in lower incremental costs and therefore lower ICERs of NOK 351,975/QALY, NOK 765,909/QALY and NOK 1,186,606/QALY, respectively.
2. Excluding the vaccine effect on genital warts resulted in both somewhat higher incremental costs and a considerably lower incremental health effect than in the base case. The resulting ICER was NOK 3,754,854/QALY.

Assuming these results apply to the bivalent vaccine, and that the price of the quadrivalent vaccine is equal to the public price of NOK 1,113.40/dose, we estimated that the price of the bivalent vaccine had to be approximately 550 NOK/dose or lower in order to be as cost-effective as the quadrivalent vaccine.

3. Increasing the first dose coverage among girls aged 12 from 82% to 92% (for at least one dose) instead of vaccinating boys of same age resulted in a 42% lower incremental effect and an 89% lower incremental costs than vaccinating boys. The ICER was NOK 336,755/QALY, considerably below the ICER of the vaccination program for boys.
4. Ignoring all HRQoL-gains (reduction of morbidity) and focusing exclusively on lifetime gains (reduction in mortality) in terms of life-years gained (LYG) resulted in a 71% decrease in the nominal incremental effect of the program, compared to the base case (where reductions in both morbidity and mortality are assessed). This is partly due to the large HRQoL-gain associated with preventing genital warts, an important outcome for males in our model. The lower incremental effect leads to a considerably higher ICER, NOK 6,188,344 /LYG.
5. When incorporating the potential effect of the vaccine in reducing the number of cases of VaIN 2+ and vaginal and anal cancer, the ICER decreased to NOK 1,538,578/QALY.
6. When excluding the vaccine effect in reducing the number of conization-related preterm births, the ICER increased to NOK 1,848,515/QALY.
7. Assuming all children get two vaccination doses led to an ICER of NOK 1,389,853 million/QALY, approximately 22% lower than in the base case.
8. Depending on the outcome, including boys in the vaccination program led to incidence reductions after 100 years that were 1-9 percentage points higher than increasing coverage among girls and 3-13 percentage points higher than vaccinating only girls at the current coverage rate. The greatest incidence reduction accomplished by vaccinating boys was registered for genital warts among males.

Finally, our one-way sensitivity analyses showed that changes in the incidence of HPV-related outcomes and the HRQoL-losses associated with these outcomes had a considerable impact on the cost-effectiveness results, although less than changes in the vaccine effect estimates. Changes in the HPV-acquisition rates and treatment costs had very limited impact on the results.

Conclusion

From both perspectives and given the current public price of NOK 1,113.4/dose of the quadrivalent vaccine, vaccinating boys in addition to girls aged 12 years is

probably not cost-effective. The incremental ICER was NOK 1,789,463/QALY from a health care perspective and NOK 1,626,261/QALY from a societal perspective.

Although there is no official cost-effectiveness threshold value in Norway, such high ICERs are generally associated with the intervention not being accepted for implementation in the Norwegian health sector.

The price scenario analysis shows that a lower price per vaccine dose has a major, positive effect on the cost-effectiveness of the program.

Increasing coverage among girls aged 12 from 82% to 92% seems to be more cost-effective than vaccinating boys and girls at a coverage rate of 82%.

The price of the bivalent vaccine should not be higher than approximately NOK 550/dose for it to be deemed as cost-effective as the quadrivalent vaccine.

Hovedfunn (norsk)

Det er dokumentert en sammenheng mellom infeksjon med humant papillomavirus (HPV) type 16 og 18 og livmorhals-, vulva-, vaginal, anal, penis- og munnsvelgkreft. HPV type 6 og 11 er assosiert med kjønnsvorter. I denne helseøkonomiske evalueringen har vi undersøkt kostnadseffektiviteten av å vaksinere 12-årige gutter og jenter, sammenlignet med å fortsette med dagens vaksinering av kun 12-årige jenter.

To ulike vaksiner, begge i et tre-doserregime, er per dags dato tilgjengelige i Norge: en bivalent vaksine som er rettet mot HPV-typene 16 og 18 og en kvadrivalent vaksine som er rettet mot HPV-typene 6, 11, 16 og 18. I denne rapporten har vi undersøkt kostnadseffektiviteten til den kvadrivalente vaksinen, siden det er denne vaksinen som nå tilbys 12-årige jenter. Kostnadseffektiviteten til den bivalente vaksinen er undersøkt i en scenarioanalyse.

Hovedfunnet er:

- Vaksinasjon av gutter i tillegg til jenter er sannsynligvis ikke kostnadseffektivt i et samfunnsperspektiv. Den inkrementelle kostnadseffektivitetsratioen (IKER) er kr 1,626,261 for et vunnet kvalitetsjustert leveår (QALY).

Det finnes ingen offisiell grenseverdi for IKER i Norge, men en IKER av en slik størrelsesorden er generelt assosiert med at tiltaket ikke implementeres i den norske helsetjenesten.

Tittel:
Økonomisk evaluering av å vaksinere 12-årige gutter mot HPV-infeksjon.

Publikasjonstype:

Metodevurdering

En metodevurdering er resultatet av å
- innhente
- kritisk vurdere og
- sammenfatte

relevante forskningsresultater ved hjelp av forhåndsdefinerte og eksplisitte metoder.

Minst ett av følgende tillegg er også med:
helseøkonomisk evaluering, vurdering av konsekvenser for etikk, jus, organisasjon eller sosiale forhold

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Svarer ikke på alt:

- Ingen studier utenfor de eksplisitte inklusjonskriteriene er inkludert.
- Ingen anbefalinger

Hvem står bak denne rapporten?

Kunnskapssenteret har skrevet rapporten på oppdrag fra Folkehelseinstituttet (FHI).

Når ble litteratursøket utført?

Søk etter effekstudier avsluttet januar 2014 og søk etter livskvalitetsdata ble avsluttet april 2014.

Fagfeller:

Aileen Neilson, Health Economics Research Unit, University of Aberdeen.

Eline Aas, Avdeling for helseledelse og helseøkonomi, Institutt for helse og samfunn, Universitet i Oslo.

Sammendrag (norsk)

Bakgrunn

Det er dokumentert sammenheng mellom infeksjon med humant papillomavirus (HPV) og kjønnsvorter, livmorhals-, vulva-, vaginal-, anal-, penis- og munnsvelgkreft. Nasjonalt folkehelseinstitutt (FHI) administrerer barnevaksinasjonsprogrammet i Norge, og jenter på 12-13 år (7. klasse) får gjennom vaksinasjonsprogrammet tilbud om tre doser av den kvadrivalente vaksinen (rettet mot HPV 6/11, 16 og 18). Gutter får ikke dette tilbudet i dag.

Utenfor Europa er kjønnsnøytral vaksinering anbefalt blant annet i USA (1) og Australia (2). Blant EU-landene er det kun Østerrike (3) som har anbefalt kjønnsnøytral vaksinering. I Storbritannia ble det i 2014 besluttet å revurdere om HPV-vaksinen bør tilbys menn som har sex med menn og/eller til unge gutter (4).

I denne helseøkonomiske evalueringen undersøkte vi kostnadseffektiviteten av å vaksinere 12-årige gutter og jenter mot HPV, sammenlignet med å fortsette med dagens vaksinering av kun 12-årige jenter.

Problemstilling

Å vurdere epidemiologiske konsekvenser, kostnader, helsegevinster og kostnadseffektivitet av å tilby HPV-vaksine til 12 år gamle gutter og jenter, sammenlignet med dagens praksis hvor vaksinen kun tilbys 12 år gamle jenter. I tillegg vurderte vi hvordan endringer i sentrale antagelser og variabler påvirket resultatene og konklusjonene.

Metode

En tidligere publisert, deterministisk, populasjonsbasert og dynamisk modell ble brukt for å utføre analysen. Modellen beregner andelen personer i nåværende og

fremtidige kohorter som har opplevd infeksjon med HPV 6/11, 16 og/eller 18, fra 2016 til 2115.

Modellen ble tilpasset norske forhold med tanke på forekomst av HPV-relaterte utfall, kostnader og helserelatert livskvalitet. Modellen ble i tillegg klargjort for bruk av effektdataene fra Kunnskapssenterets systematiske oversikter og for probabilistiske sensitivitetsanalyser.

Hovedanalysen så på kostnadseffektiviteten av de første 100 årene av et vaksinasjonsprogram hvor 12 år gamle gutter og jenter tilbys tre doser av den kvadrivalente vaksinen. Virkningene ble analysert for totalt 184 fødselskohorter: De 91 kohortene gutter og jenter med alder 8-99 ved starten av vaksinasjonsprogrammet, og de påfølgende 93 fødselskohortene med 8 år gamle gutter og jenter.

Vi antok at 82 prosent av alle gutter og jenter på 12 år i gjennomsnitt fikk henholdsvis 2.54 og 2.78 doser av HPV-vaksinen. Basert på funnene i de systematiske oversiktene var vaksinens effekt i hovedanalysen begrenset til livmor- og vulvakreft og forstadier til disse, samt kjønnsvorter. Resultatene av å inkludere effekt på vaginal- og analkreft, og forstadier til disse, vises i separate analyser. Den maksimale utsalgsprisen for apotek (AUP) på den kvadrivalente vaksinen per desember 2014 på kr. 1,113.40/dose ble brukt i hovedanalysen.

Hovedanalysen ble utført både i et helsetjenesteperspektiv og i et samfunnsperspektiv. Helsetjenesteperspektivet inkluderte kostnadene begrenset til det offentlige helsevesenet. I samfunnsperspektivet ekskluderte vi merverdiavgiften (MVA) fra prisene, men inkluderte i tillegg skattekostnaden, en verdsetting av pasientenes reise- og ventetid, samt mulige produksjonstap av sykdom.

For begge perspektiver ble det beregnet en inkrementell kostnadseffektivitetsratio (IKER) i form av kroner per vunnet kvalitetsjusterte leveår (QALY). Resultatene ble sammenliknet med et sett potensielle referanseverdier for verdien av en vunnet QALY, fra kr 250 000 til 2 000 000. Dersom IKER sannsynligvis er lavere enn en angitt referanseverdi, er det vanlig å konkludere at det nye tiltaket er kostnadseffektivt til den referanseverdien (motsatt dersom IKER er over en valgt referanseverdi).

Resultatene ble vurdert med utgangspunkt i den samlede usikkerheten i hovedanalysens parametere, og vi estimerte verdien av perfekt informasjon (EVPI).

Konsekvensene av å endre underliggende antakelser og sentrale parametere i hovedanalysen ble undersøkt i en rekke scenarioanalyser, under følgende betingelser (alle i helsetjenesteperspektiv):

1. Lavere pris per vaksinedose.
2. Ekskludere effekten av vaksinen på kjønnsvorter, for å vurdere kostnadseffektiviteten av den bivalente vaksinen.
3. Økt dekningsgrad for jenter som et alternativ til å vaksinere gutter.
4. Effekt beregnet som vunne leveår (det vil si uten livskvalitetsgevinster av vaksinering).
5. Inklusjon av vaksineeffekt på analkreft (begge kjønn) og vaginalkreft, inkludert forstadier til vaginalkreft.
6. Ekslusjon av koniseringsrelaterte tidligfødsler og konsekvensene av disse på kostnader og helsegevinster.
7. To doser i stedet for tre, uten å redusere vaksineeffekten.
8. Reduksjon i insidensen av sentrale utfall i modellen under ulike antakelser om dekningsgrad.

Som et supplement til de ovenstående scenarioanalysene ble det utført en serie med enveis- sensitivitetsanalyser, som viser hvordan hovedanalysens resultater endrer seg når sentrale grupper av parametere økes eller reduseres med 25 prosent. Disse resultatene presenteres i et Tornado-diagram.

Resultater

I et helsetjenesteperspektiv, og med en tidshorisont på 100 år (2016-2115), er den diskonterte inkrementelle kostnaden ved å inkludere 12 år gamle gutter i vaksinasjonsprogrammet 1.851 milliarder kroner, med en diskontert helsegevinst på 1,034.59 QALYs. Dette tilsvarer en IKER på 1,789,463 kr/QALY. Både de inkrementelle kostnadene og helsegevinstene er positive for alle iterasjoner i den probabilistiske sensitivitetsanalysen.

Å vaksinere gutter fremstår som noe mer kostnadseffektivt i et samfunnsperspektiv. De inkrementelle kostnadene er da omtrent 9 prosent lavere, kr. 1.677 milliarder mot 1.851 milliarder. Helsegevinsten av å vaksinere påvirkes ikke av perspektivet og derfor lik mellom de to perspektivene. I samfunnsperspektivet er IKER kr 1,626,261 kr/QALY.

Resultatene av scenarioanalysene er som følger:

1. Med en pris per vaksinedose på den kvadrivalente vaksinen på hhv. 250, 500 og 750 kr/dose er IKER 351,975 kr/QALY, 765,909 kr/QALY og 1,186,606 kr/QALY.

2. Å eksludere vaksineeffekten på kjønnsvorter gir betydelig lavere helsegevinst og noe høyere kostnader, som resulterer i en IKER på 3,754,854 kr/QALY. Dersom man antar at disse resultatene er gyldige for den bivalente vaksinen, og at prisen på den kvadrivalente vaksinen er lik den offentlige prisen på kr. 1,113.40 /dose, må den bivalente vaksinens pris være omtrent 550 kr/dose eller lavere for at den skal være like kostnadseffektiv som den kvadrivalente vaksinen.
3. Økt dekningsgrad fra 82 prosent til 92 prosent (minst en dose), uten å vaksinere gutter, resulterer i en 42 prosent lavere inkrementell effekt og 89 prosent lavere kostnader sammenlignet med å vaksinere gutter og jenter med 82 prosent dekningsgrad. Økt dekningsgrad for jenter gir en IKER på 336,755 kr/QALY, betydelig lavere enn IKER forbundet med å inkludere gutter i vaksinasjonsprogrammet.
4. Når livskvalitetsgevinstene av å vaksinere ikke inkluderes, blir den nominelle inkrementelle effekten av å vaksinere 12 år gamle gutter og jenter, redusert med 71 prosent, sammenlignet med hovedanalysen (som inkluderer både livskvalitetsgevinstene og levetidsgevinstene og av å vaksinere). Dette kan forklares med at livskvalitetsgevinstene knyttet til å forebygge kjønnsvorter er et viktig utfall for guttene i hovedanalysen. Resultatet er en IKER på 6,188,344 kr per vunnet leveår.
5. Inklusjon av vaksineeffekt på vaginale kreftforstadier (VaIN 2+), analkreft (begge kjønn) og vaginalkreft fører til en reduksjon i IKER til 1,538,578 kr/QALY.
6. Ekslusjon av konsekvensene ved koniseringsrelaterte tidligfødsler øker IKER til 1,848,515 kr/QALY.
7. Resultatet av å anta at alle barn som vaksineres får 2 doser, fører til en IKER på 1,389,853kr/QALY, omtrent 22% lavere enn i hovedanalysen.
8. Avhengig av hvilket utfall det er snakk om, gir vaksinasjon av gutter en reduksjon i insidensen av relevante utfall for alle aldersgrupper. Etter en 100-års periode var reduksjonen i insidens i ulike utfall 1 til 9 prosentpoeng høyere sammenlignet med kun økt dekningsgrad blant jenter, og 3 til 13 prosentpoeng høyere sammenlignet med å beholde dagens vaksinasjonsprogram for jenter med dagens dekningsgrad. Den største reduksjonen i insidens av utfall ved å vaksinere gutter er knyttet til kjønnsvorter hos gutter.

Enveis- sensitivitetsanalysene indikerer at insidensen av HPV-relaterte utfall og livskvalitetstapene forbundet med HPV-relaterte sykdommer har stor betydning for resultatene, men at effekten av vaksinen er den parameteren som har størst betydning. Endringene i sannsynlighetene for HPV-smitte og behandlingskostnadene har begrenset innvirkning på resultatene.

Konklusjon

Å vaksinere gutter ved 12 års alder med den kvadrivalente vaksinen til en pris på kr 1,113.40/dose, er sannsynligvis ikke kostnadseffektivt, uansett perspektiv. IKER var kr 1,789,463/QALY fra et helsetjenesteperspektiv og kr 1,626,261/QALY fra et samfunnsperspektiv.

Det finnes ingen offisiell grenseverdi for IKER i Norge, men en IKER av en slik størrelsesorden er generelt assosiert med at tiltaket ikke implementeres i den norske helsetjenesten.

Prisscenarioene viser at lavere vaksinepris har stor betydning for resultatene, i den forstand at det gir en betydelig lavere IKER.

Økt dekningsgrad for jenter fra 12 års alder fra 82 prosent til 92 prosent ser ut til å være mer kostnadseffektivt enn å vaksinere både gutter og jenter ved 12 års alder med en dekningsgrad på 82 prosent.

Prisen av den bivalente vaksinen bør ikke være høyere enn kr 550/dose, for å kunne anses som like kostnadseffektiv som den kvadrivalente vaksinen i hovedanalysen.

Glossary and abbreviations	
ICER	**Incremental cost-effectiveness ratio**. The ratio of the difference in costs between two alternative health technologies to the difference in effectiveness between these two technologies. $ICER = \frac{Cost_{\text{intervention}} - Cost_{\text{comparator}}}{Effect_{\text{intervention}} - Effect_{\text{comparator}}} = \frac{\Delta C}{\Delta E}$
CI	**Confidence interval.** A measure of uncertainty around the results of a statistical analysis that describes the range of values within which we can be reasonably sure that the true mean effect lies. Wider intervals indicate lower precision; narrow intervals, greater precision.
CUA	**Cost-utility analysis.** An economic evaluation where health consequences are measured in **QALY**s.
EVPI	**Expected value of perfect information.** The monetary value of reducing decision uncertainty around the costs and health gains of a project for society to a minimum. Can also be interpreted as the expected cost of uncertainty, jointly determined by the probability that a decision based on existing information will be wrong (i.e. that another alternative would have had higher net health/monetary benefit once our current uncertainties are resolved) and the consequences of a wrong decision.
HRQoL	**Health related quality of life.** See QALYs.
LYG	**Life-years gained**. When results are presented as LYG, the years are not weighted on the 0-1 scale. In QALY-terms, this is equivalent to assigning each gained life year a value of 1. See QALYs.
NHB	**Net Health Benefit.** In a decision-making process, a positive NHB suggests that the intervention represents good value for money $NHB = \Delta E - \frac{\Delta C}{\lambda}$
NMB	**Net Monetary Benefit.** In a decision-making process, a positive NMB suggests that the intervention represents good value for money. $NMB = \lambda \cdot \Delta E - \Delta C$
Odds	The odds of an event happening is defined as the probability that an event will occur, expressed as a proportion of the probability that the event will not occur.
OR	**Odds ratio.** The ratio of the odds of an outcome in one treatment group divided by the odds of the same outcome in a different treatment group.
PSA	**Probabilistic sensitivity analysis.** An analysis of the uncertainty related to all parameters in a decision analytic model. Typically performed by Monte Carlo simulation, hence by drawing values from probability distributions for all parameters simultaneously.

QALY	**Quality-adjusted life-year.** A measure of health outcomes that combines quantity and quality of life by assigning to each year of life a weight from 1 (perfect health) to 0 (state judged equivalent to death) dependent on the individual's health related quality of life during that year.
RCT	**Randomised controlled trial.** An experiment in which investigators use randomisation to allocate participants into the groups that are being compared. Usually allocation is made at the level of individuals, but sometimes it is done at group level e.g. by schools or clinics. This design allows assessment of the relative effects of interventions.
RR	**Relative risk / risk ratio.** The relative risk is the absolute risk (AR) in the intervention group divided by the AR in the control group. It is to be distinguished from odds ratio (OR), which is the ratio of events over non-events in the intervention group over the ratio of events over non-events in the control group.
SR	**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.
Statistically significant	The findings of a study are unlikely to have arisen because of chance. Significance at the commonly cited 5% level ($P < 0.05$) means that the observed difference or greater difference would occur by chance in only 1/20 similar cases. Where the word "significant" or "significance" is used without qualification in the text, it is being used in this statistical sense.
TTO	**Time trade-off**. A health utility valuation method that involves asking subjects to consider the time they would be willing to sacrifice to avoid a certain poorer health state.
WTP (λ)	**Willingness to pay**. A pre-specified limit of what society is willing to pay for a given health unit (e.g. QALY or life year).

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Preface

The Norwegian Knowledge Centre for the Health Services (NOKC) was commissioned by the Norwegian Institute of Public Health to undertake an assessment of the cost-effectiveness of administering boys aged 12 the HPV-vaccine in addition to the current practice of vaccinating 12 year-old girls compared to maintaining the current practice. The results contained in this report will be used as scientific documentation in preparation of national recommendations regarding the HPV-vaccination program.

Arna Desser and Signe Agnes Flottorp performed the internal review of this health economic evaluation, while Aileen Neilson (Health Economics Research Unit, University of Aberdeen) and Eline Aas (Institute of Health and Society, University of Oslo) performed the external peer review of the report. Bjarne Robberstad (University of Bergen) assisted along the process.

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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. We used data from the Cancer Registry of Norway. The interpretation and reporting of these data are the sole responsibility of the authors, and no endorsement by the Cancer Registry of Norway is intended nor should be inferred.

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Objective

To evaluate the epidemiological impact, costs, health benefits and cost-effectiveness of administering the quadrivalent HPV-vaccine to 12-year-old-boys in addition to the current practice of vaccinating 12-year-old-girls, compared to maintaining the current practice. In addition, to evaluate how alternative scenarios would influence results and conclusions.

Background

Human papillomavirus (HPV) is considered the most common sexually transmitted virus worldwide (5) and more than 100 types of HPV have been identified (6, 7). Several cancers are believed to be primarily HPV-related, among others 100% of all cervical cancers, 90% of all anal cancers (in both genders) and 40% of all vulvar and vaginal cancers (8). In addition, close to 100% of all anogenital warts are associated with low-risk HPV types (9).

The annual age-adjusted incidence rates per 100 000 person-years of these HPV-related outcomes vary widely: 540 for genital warts (average for ages 17-49 and for both genders, own calculations), 10 for cervical cancer, 1.7 for vulvar cancer, 1 for female anal cancer and 0.5 for male anal cancer (10).

Efficient prophylactic vaccines could have an important public health impact. As cancer takes a long time to develop, it would be difficult to conduct clinical trials ascertaining the efficacy of HPV vaccination on cervical cancer and other cancer types related to HPV. Furthermore, as screening for cervical cancer is available, conducting such trials would be unethical. For these reasons, the WHO and the US Food and Drug Administration recommended that phase III trials examining vaccination efficacy can use high-grade cervical intraepithelial neoplasia grades 2 and 3 (CIN 2+) as endpoints (11).

The Norwegian Institute of Public Health (FHI) is responsible for managing the vaccination program against HPV. Currently, this program covers the direct expenses of vaccinating 12-year-old girls with the quadrivalent vaccine through the public health-care system.

Although some countries, e.g. United States, Austria, and Australia, recommend gender-neutral vaccination, results from models of the cost-effectiveness of such policies vary widely according to model assumptions. Incorporating herd immunity and the burden of disease in men, male vaccination may be cost-effective depending upon coverage, vaccine price and other factors (12-16).

The target population of a potential male vaccination program in Norway would consist of each cohort of boys aged 12 born in 2004 or later, each consisting of approximately 31 000 individuals (17).

Introduction to Economic Evaluations of Health-care Programmes

The basic task of any economic evaluation is to identify, measure, value and compare costs and consequences of the alternatives being considered in an incremental analysis which means that the difference in cost is compared with the differences in consequences (18). Hence, results of economic evaluations can be expressed as an incremental cost-effectiveness ratio (ICER), which is defined by the following equation:

$$ICER = \frac{Cost_{\text{intervention}} - Cost_{\text{comparator}}}{Effect_{\text{intervention}} - Effect_{\text{comparator}}} = \frac{\Delta C}{\Delta E}$$

Because the health-care sector, as the society in general, is restricted by scarce resources and budget constraints, economic evaluations are tools for decision makers facing questions of how to prioritize and maximize benefits from scarce resources. For an economic evaluation to be meaningful in a decision making process, the ICER must be judged with regards to a ceiling ratio that reflects the decision maker's maximum willingness-to-pay (WTP) for a health gain. Such a ceiling ratio has not yet been established in Norway.

The decision rule for an economic evaluation can therefore be expressed as:

$$\frac{\Delta C}{\Delta E} < \lambda$$

where λ equals WTP, and means that if the ICER of an intervention is below the ceiling ratio, introducing the intervention represents good value for money. Because ICERs have poor statistical properties, they are often rearranged to express either net monetary benefit (NMB) or net health benefit (NHB), yielding the following decision rules related to NMB or NHB.

$$NMB: \lambda \cdot \Delta E - \Delta C > 0$$

$$NHB \quad : \Delta E - \frac{\Delta C}{\lambda} > 0$$

In other words, the intervention can be considered cost-effective if it yields a positive NHB or NMB.

Economic evaluations are often based on decision models (such as decision trees and Markov models) that calculate results based on various input parameters in the model. Because there are always uncertainties related to the values of these parameters, sensitivity analysis is an important feature of any economic evaluation using a decision model framework. In short, sensitivity analysis illustrates how much the results vary as model parameters are changed. Sensitivity analyses can be performed in various ways, with one-way or two-way sensitivity analysis being common approaches. This represents changing, respectively, one or two model-

parameters at a time while all other model-parameters are held constant, in order to see how much impact the variation in these parameters has on the results. One-way sensitivity analyses are often presented as tornado-diagrams, which identify and illustrate the model-parameters that have the highest impact on the results.

Another important kind of sensitivity analysis is referred to as probabilistic sensitivity analysis (PSA). The advantage of PSA is that it takes the uncertainties of all model-parameters into account simultaneously. The basic approach in PSA is to assign appropriate probability distributions to the model-parameters, i.e. replacing of the "fixed" values of the parameters with values generated by random draws from the distributions. Doing this repeatedly, with a large number of iterations, enables one to estimate probabilities of alternatives that would be cost-effective subject to different ceiling values of WTP. The calculation is based on the alternative that renders the highest values of NMB or NHB. PSA is often presented as scatter plots, which show point estimates of the ICER for all iterations in the cost-effectiveness plane, and also by cost-effectiveness acceptability curves (CEACs), that show the probability of the alternatives being cost-effective subject to changing values of WTP.

Another result from PSA is the expected value of perfect information (EVPI). This number indicates the upper bound on the returns to further research about the costs and effect of a health program (i.e. the returns of eliminating 100% of the uncertainties in the results of the analysis). It can also be interpreted as the expected cost of uncertainty, and is determined jointly by the probability that a decision based on existing information will be wrong (i.e. that another alternative would have had higher net-benefit once our current uncertainties are resolved) and the consequences of a wrong decision (19).

If EVPI for a given population seems large, it might be of interest to find out for which parameters it would be most useful to get new and improved data. Expected value of perfect information for parameters is a more time-consuming operation, but it can help determine for which single parameters or groups of parameters it is most cost-effective to conduct new research.

In short, making a model probabilistic means that it is possible to estimate the uncertainty in the decision of implementing alternative interventions, which allows estimating the value of collecting additional information from new research.

Priority setting criteria

According to Norwegian policy documents (20), a treatment should be prioritized only if the following criteria are met:

1. *The disease is severe:* A disease is considered severe to the degree that it causes pain and discomfort, loss of physical, psychological and social function and if it limits the individual in his or her daily activities. Severity is also evaluated according to the increase in the risk of death, disability and discomfort, if treatment is postponed.

2. *The treatment is effective:* the patient should be expected to benefit from treatment in terms of longevity or improved quality of life of certain duration. The treatment effectiveness should also be well documented.

3. *The treatment is cost-effective:* the additional costs of the treatment should be reasonable compared to the additional benefits.

The policy documents mentioned above give no guidance as to what constitutes a ”reasonable” relationship between costs and effectiveness. There exists no academic consensus regarding this threshold value, nor has it been subject to a political process in Norway.

Methods

Choice of Model

The cost-effectiveness of HPV-vaccination has been examined in a series of health-economic models for a large number of different patient groups, see for example Seto and colleagues (21). Due to the availability of already developed models, we decided to adapt one of them to the Norwegian setting.

In order to choose the most appropriate model, we required that it:

- *was not developed or financed by the pharmaceutical industry or other for-profit organizations (in order to avoid potential conflicts of interests),*
- *was accessible for examination, modification and publication,*
- *incorporated the effect of the vaccine on every outcome for which a link to HPV is well documented,*
- *incorporated herd immunity, and*
- *allowed for probabilistic sensitivity analysis (PSA) and value-of-information (VoI) analysis*

The chosen model was developed at the Centers for Disease Control and Prevention (CDC) by Harrell W. Chesson and colleagues (13). Harrel W. Chesson collaborated with us during the adaptation of the model, although the responsibility for the final choices in this analysis and the results are the authors' alone.

This model has been previously adapted to a Norwegian setting in order to assess the cost-effectiveness of administering a catch-up vaccine to females aged 26 or younger who were not offered the vaccine at age 12 (22).

General

The analysis consists of a cost-utility analysis (CUA) in which relevant costs were expressed in Norwegian kroner (NOK) and effects were expressed in QALYs. The analysis was conducted both from a public health-care and a societal cost

perspective. Both costs and effects were discounted as currently recommended by the Norwegian Ministry of Finance (23), i.e. a discount rate of 4% during the first 40 years of the program, 3% from year 41 to 75 and finally, 2% beyond year 75 of the program.

The model we use calculates the number of avoided HPV-related outcomes due to HPV vaccination. Each outcome is assumed to be associated with a loss of quality-adjusted life years (QALY) and a treatment cost. Therefore the incremental effect of the vaccination program would be represented by the net amount of avoided lost QALYs, while the incremental cost would consist of the difference in vaccination costs and avoided treatment costs. The screening program and its associated costs are assumed to remain unchanged, see Discussion for details.

The results were expressed as ICERs, and suggestions about cost-effectiveness were based on a range of potential willingness-to-pay values. Uncertainties in model-parameters were handled by making the decision model probabilistic and by performing one-way sensitivity and scenario analyses (i.e. analyses in which we tested alternative assumptions on some given parameters).

Model Structure

The original model is described in detail elsewhere (13, 24). Here we will highlight its main elements and, where relevant, the main differences between the original model and its Norwegian adaptation used in this report.

A discrete-time approach is used in the infection model, in which the impact of vaccination was modeled as a sequence of 1-year transitions among four mutually exclusive states. Differences in sexual activity level (that is, rate of sex partner change) were incorporated in the model by assuming age-specific probabilities of acquiring HPV 6/11, 16 and/or 18.

The transition from HPV acquisition to HPV-related health outcomes is not explicitly modeled. Instead, the impact of vaccination on health outcomes was calculated under the assumption that the percentage reduction in health outcomes attributable to a specific HPV-type, in a given year and for a given age cohort, was proportional to the percentage reduction in the cumulative acquisition rate of that HPV-type due to vaccination.

Although it is a simpler model compared to other existing models (15, 16, 25), in the sense that there was no need to model the possible progression from HPV infection to disease, the mixing of sex partners, and so forth, Chesson and colleagues reported results that were consistent with results of published studies based on more complex

models. This was particularly the case when key assumptions (e.g., vaccine duration, efficacy, and cost) were similar (24).

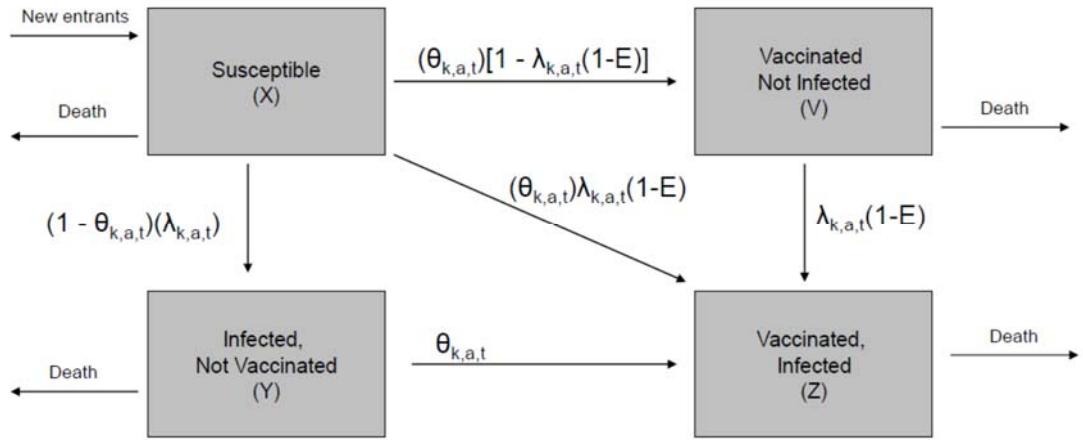
The cumulative acquisition rate at a given age is equivalent to the share of the cohort that has experienced infection (with the relevant HPV-type) for the first time at the age of interest or before. The focus is therefore on the first infection and not on reinfections.

The vaccine reduces the cumulative acquisition rate in two different ways: First, it protects the vaccinated individual against infection when exposed to the HPV-virus (the direct effect, which only vaccinated males and females benefit from); and second, it reduces the overall probability of exposure to HPV, independently of vaccination status (the indirect effect or herd immunity, which all females and males benefit from). See Appendix 3. Vaccine effect for more details on how the vaccine effect was incorporated in our analysis.

Cervical cancer screening was not explicitly modeled. Instead, we assumed that current cervical cancer screening in Norway was reflected in the observed rates of cervical intraepithelial neoplasia (CIN) and cervical cancer applied in the model. In other words, we assume that the current screening activities remain unchanged within the time frame of the model.

The model consists of six similar infection submodels, three for each gender: One for HPV 16, another for HPV 18 and the last one for HPV 6/11. For each submodel, each age cohort was divided into four groups, based on the individual's vaccination and HPV-exposure status, see Figure 1.

Figure 1. Vaccination and infection submodel used for each HPV-type and gender.



Each submodel reports the distribution of each cohort aged 8-99 among these four groups during the 100 year-period after implementation of the HPV-vaccination program for boys and girls aged 12. This means that:

- Our analysis focuses on the consequences that such a program may have for 184 specific cohorts of boys and girls, namely the 91 cohorts aged 8-99 at the start of the vaccination program and the future 93 cohorts of 8-year-olds.
- The statuses of cohorts aged 0-7 and 100 and older were ignored, as we assumed that the effect of the vaccine on the incidence rates of HPV-related diseases in these age groups would be negligible.
- Our analysis also ignores those transitions taking place before and after the 100 year-period after implementation of the HPV-vaccination.

In every submodel, each cohort of girls and each cohort of boys enters the model in the susceptible group (X), at age 8. These girls/boys are neither vaccinated nor infected with the relevant HPV-type. The infected group (Y) consists of those not vaccinated who have been infected in the years after age 8. Those infected with a specific HPV-type never return to the susceptible group for that type and receive no benefit if vaccinated. Furthermore, we assumed no children might experience infection with any HPV in age 8-12 (see the epidemiology section for details), although the model allows for alternative assumptions for these age groups (which we have not examined).

Those in the susceptible group (X) at the time of the vaccination (age 12) move to the "vaccinated, not infected" group (V), or, possibly to the "vaccinated, infected" group (Z), as vaccine does not prevent 100% of all future infections with HPV 6/11, 16 and/or 18. In any given year after vaccination, those in the "vaccinated, not infected" group (V) can also move to the "vaccinated, infected" group (Z).

Those in the infected group (Y) at the time of vaccination move to the "vaccinated after HPV infection" group (Z), and we assumed that those in this group remain here for life and do not receive any vaccine benefits in terms of protection against HPV 6/11, 16 or 18.

The rest of the population (i.e. cohorts aged 9 or older), were distributed among the four states based on earlier transitions (not reported in our analysis).

Furthermore:

- Individuals may die in any of the four classes. The same age- and sex-specific all-cause death rates (background mortality) from Statistics Norway were applied to all classes, such that the number of people in each cohort decreased from year to year due to death, but death did not influence the age and year-specific percentage of the population in each class. Differences in cervical, vulvar, vaginal and anal cancer mortality (the latter two only in sensitivity analyses) between vaccination strategies are incorporated in the model through the QALY-losses accumulated by each treatment group (more details in the section about the health related quality-of-life). Background mortality was not adjusted for HPV-related mortality.

- $\theta_{g,a,t}$ is the annual probability of receiving HPV vaccination, i.e. the corresponding coverage rate, for gender "g" (1 for female, 2 for male) at age "a" in year t (where $1 \leq t \leq 100$). In our case, $\theta_{g,a,t}$ is equal to 82% at age 12 for every vaccinated cohort of boys and girls, and zero otherwise.

- E_g is vaccine efficacy against HPV 6/11, 16 or 18 acquisition for gender "g". It is defined as the relative risk reduction (RRR) of persistent infection after 12 months for gender g (see the section about the efficacy of the vaccine for details).

- $\lambda_{g,a,t}$ is the annual probability of acquiring HPV 6/11, 16 or 18 for gender g at age a in year t. It is calculated by adjusting the probability of HPV acquisition in the absence of vaccination (P), for changes in HPV prevalence in the population due to HPV vaccination (see the epidemiology section for more details about P). The adjustment is calculated based on the changes in the cumulative acquisition rate (from age 8) for the relevant HPV type in the population, thus incorporating herd immunity in the model. See Chesson (13), appendix 1, pages 4, 5 and 6 for further details.

In both the original and the Norwegian model sexual behavior is incorporated through the adjusted probability of HPV acquisition in the absence of vaccination, by assuming an assortative sexual mixing across age groups such that 90% of individuals choose sexual partners within 5 years of their own age. The other 10% choose sexual partners without regard to the age difference.

The main outcome in the base case of the Norwegian model is the reduction of the following HPV 6/11, 16 and/or 18 related outcomes among men and/or women:
- Cancer (cervical and vulvar).
- Cervical intraepithelial neoplasias, grades 2 and 3 (CIN 2 and 3)
- Vulvar intraepithelial neoplasias, grades 2 and 3 (VIN 2 and 3)
- Genital warts
- Conization related preterm births (living babies born before week 33) due to previous CIN 2+ treatment of the mother
- Serious cases of adverse events due to vaccination

For more details about the calculation of the number of avoided outcomes, see Appendix 3. Vaccine effect.

The Norwegian model does not include vaginal, anal, penile or oropharyngeal cancer in its base case, all of which were included in the original model (13). Nevertheless, we conduct a scenario analysis in which the effect of vaccination on anal cancer (both genders) and vaginal cancer and precancerous lesions, are included. These

analyses are based on the effect estimates from our review (26) on precancerous anal lesions (VIN/VaIN and AIN 2+).

Finally, our model was made probabilistic, in the sense that most key input variables were assigned a probability distribution based on the available data. This allowed us to better assess the uncertainty around the results and to estimate the expected value of perfect information (EVPI).

Model Parameters

In order to consider the consequences of vaccinating both boys and girls aged 12, the analysis has to include different types of parameters to capture epidemiologic information, estimates of the effect of the vaccine on outcomes of interest, costs and health related quality-of-life (HRQoL).

Epidemiology

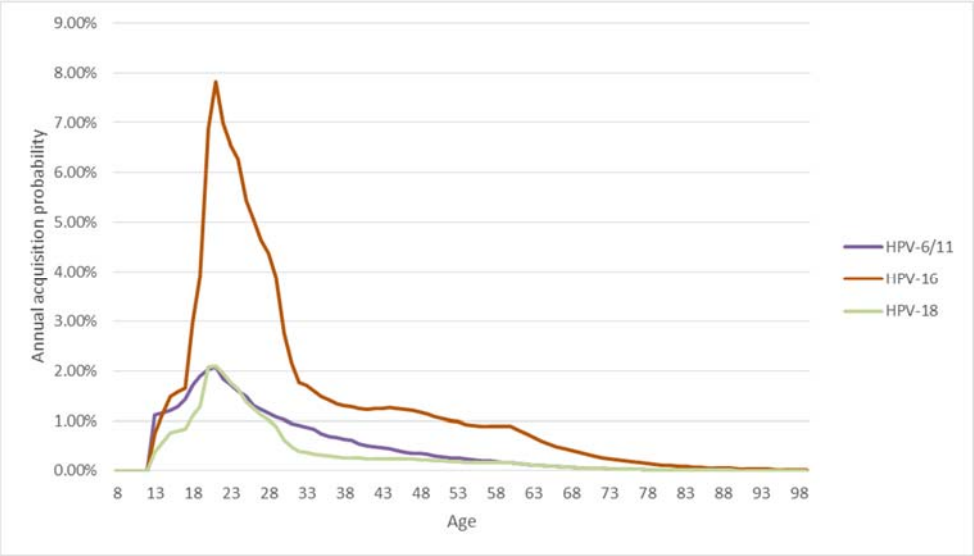
1. *HPV 6/11, 16 and 18 annual first-time acquisition probabilities for males and females in the absence of vaccination (P).*

   We only needed to estimate the annual probability of first-time infection in the absence of vaccination, i.e. P (see the section about model structure for details).

   To our knowledge, no such data are available for Norway, so we estimated them based on yet unpublished prevalence data from the Norwegian Institute of Public Health and the acquisition rates used by Chesson and colleagues for the United States. For more details, see Appendix 2. Epidemiological data.

   As mentioned above, we assumed no children aged 12 or younger would experience HPV-infection, as the median age of sexual debut in Norway has been estimated to be 17.1 for females and 17.9 for males (27). Furthermore, we assumed that the resulting probabilities would apply to both males and females, as we did not find any evidence supporting the hypothesis of acquisition differences between genders. We assumed as well that P for the different HPV-types would not change over time, as we did not expect these to be influenced by the implementation of any HPV vaccination program. Finally, our model applies only to a heterosexual population, so that the probabilities we estimated may not be representative for women (men) exclusively having sex with other women (men).

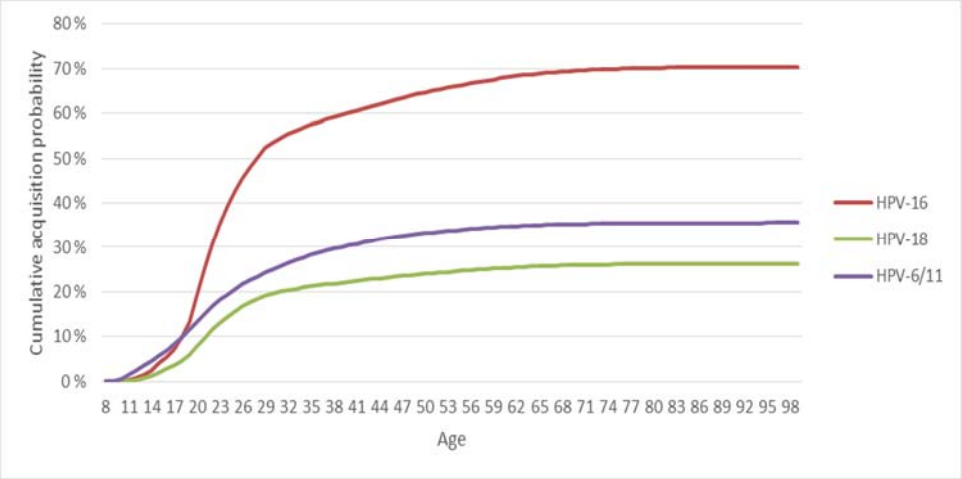
Figure 2. Estimated annual acquisition probabilities for HPV 6/11, 16 and 18 (both genders)



All three curves show rapid growth in the acquisition probabilities from young ages to a peak at approximately 20-22 years old, and then a rapid decline phase ending in the early thirties, followed by a phase of slow decline.

Figure 3 shows the cumulative HPV 6/11, 16 and 18 acquisition rates associated with our acquisition probability estimates. The cumulative acquisition rate at age "x" is the probability of having experienced infection at age "x" or before. At age 99, the cumulative acquisition rate may be interpreted as the lifetime probability of having experienced infection with the relevant HPV-type. Our data suggests for example that the lifetime probability of infection with HPV 6/11, 16 and 18 in Norway (and for both genders) is 35%, 26% and 70%, respectively.

Figure 3. Estimated HPV 6/11, 16 and 18 cumulative acquisition rate in Norway as a function of age.



2. *Cervical and vulvar intraepithelial neoplasia (CIN/VIN) 2 and 3*
The Cancer Registry of Norway provided data on the number of new CIN and VIN 2 and 3 cases (confirmed through biopsy) that occurred every year from 2002 to 2012 and by age group (for VIN the data was for the 2008-2012 period). There was no differentiated data according to VIN type, but since most of cases reported to the Cancer Registry of Norway are of high-grade, i.e. 2 or 3 (personal communication), we assumed that all VIN were 2+.

We combined these data with population data from Statistics Norway (17) to calculate average annual incidence rates per female for each age group. We then extrapolated the average for 2002/2008-2012 over the horizon of the model (100 years, beginning in 2016).

To calculate an annual incidence rate, data about the number of new cases of an outcome of interest occurring during a given time period and the total person-time observed in that period, are required. Over a fixed period, the latter is the average size of the population over the observed period. Therefore, we used the total number of females in each age group for the observed period for which we had case information.

The results are the following:

Table 1. Estimated annual incidence rate of CIN/VIN 2 and 3 in Norway, per person-year.

Age group	CIN 2*	CIN 3*	VIN 2+**	VaIN 2+***
15-19	0.000080	0.000080	0	0
20-24	0.000480	0.001420	0	0
25-29	0.000820	0.004030	0.000025	0
30-34	0.000540	0.003650	0.000036	0.000012
35-39	0.000500	0.002730	0.000018	0
40-44	0.000390	0.001970	0.000025	0
45-49	0.000310	0.001210	0.000018	0.000012
50-54	0.000210	0.000690	0.000049	0.000005
55-59	0.000150	0.000500	0.00008	0.000011
60-64	0.000120	0.000400	0.000132	0.000019
65-69	0.000100	0.000320	0.000079	0.000013
70+	0.000030	0.000100	0.000100	0.000021

* Average 2002-2012

** Average 2008-2012

*** Average 2008-2012, used only in sensitivity analyses

Incidence rates for CIN 3 seem to be consistently higher than for CIN 2 (except for age group 15-19, for which they were equal). This might be due to the medical practice in Norway, focused on carrying out biopsies only when

cytology indicates HSIL (High-grade Squamous Intraepithelial Lesion) or a positive HPV-test with either ASC-US (Atypical Squamous Cells of Undetermined Significance) or LSIL (Low-grade Squamous Intraepithelial lesions). In these cases, finding CIN 3 is more probable than finding CIN 2, as the latter may have resolved/spontaneously disappeared without further complications.

3. *Cancer*

The Cancer Registry of Norway provided data on annual incidence rates for cervical, vulvar, vaginal and anal cancer for the period 2002-2012, for specified age groups and gender. Because the data showed that incidence rates for most cancer forms were relatively stable over this period, we used average rates for 2002-2012 to extrapolate the annual incidence rates for the horizon of the model.

Table 2. Annual cancer incidence rates per 100 000 person-years in Norway (average 2002-2012).

Age	Cervical	Vulvar	Vaginal*	Anal (females)*	Anal (males)*
05-09	0	0	0.00	0	0
10-14	0	0	0.00	0	0
15-19	0.08	0	0.00	0	0
20-24	2.59	0.12	0.00	0.06	0
25-29	10.81	0.13	0.06	0.00	0
30-34	21.24	0.44	0.00	0.22	0
35-39	23.77	0.64	0.16	0.52	0.05
40-44	20.41	1.88	0.25	0.91	0.42
45-49	19.41	2.75	0.27	1.60	0.75
50-54	18.07	3.40	0.96	2.97	1.49
55-59	15.90	3.65	0.94	2.79	1.62
60-64	17.61	4.25	1.54	4.49	2.26
65-69	14.79	8.59	1.97	4.65	2.02
70-74	14.94	9.96	1.85	4.97	2.51
75-79	18.99	13.23	1.44	6.20	3.22
80-84	18.42	18.72	3.45	7.03	4.55
85+	13.28	23.58	4.25	7.47	5.31

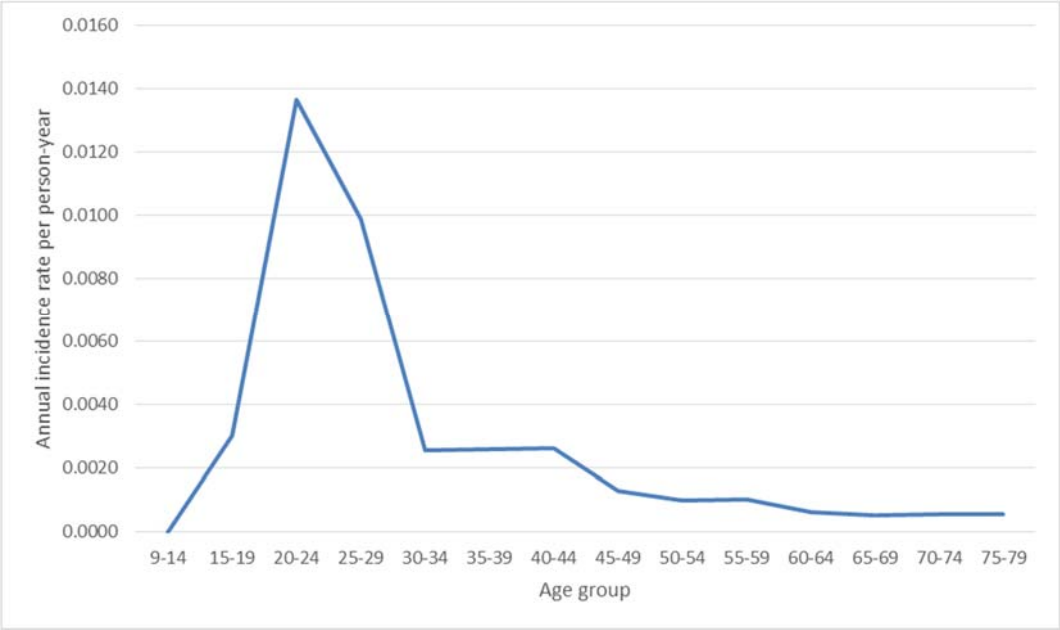
* Used only in sensitivity analyses

4. *Genital warts*

In our search for estimates for the incidence rates of genital warts in Norway, we examined a recent systematic review with data from several countries (28). In this review, the authors identified Norwegian data in one study (29), which reported cumulative incidence rates of self-reported,

clinically diagnosed genital warts among a sample of females in Norway (see Appendix 2. Epidemiological data for details). Lacking separate information for Norwegian men, we assumed that the estimated rates for women also applied to men.

Figure 4. Estimated annual incidence rates of genital warts in Norway (per person-year), per age group and for both genders.



5. *Conization-related preterm births*

Conization (also known as cone biopsy) is a form of cervical biopsy, as well as a method of treating CIN 2 and 3. Women who have undergone conization before pregnancy have a greater risk of experiencing preterm deliveries (30-32). Since infection with HPV 16 and 18 has been reported to cause CIN 2+ (33), we included in our analysis the potential reduction in preterm deliveries due to the vaccine. We chose to limit our analysis to preterm deliveries of living babies before week 33 of gestation, as these children seem to have the greatest risk of experiencing serious lifetime-disabilities (communication with Ingvild Vistad). Late abortions (no more than 24 weeks of gestation) were also excluded from our analysis, this time due to ethical considerations.

Norwegian data from Albrechtsen (34) shows that, for the period 1967-2003, 769 preterm deliveries before week 33 took place among women having undergone conization prior to pregnancy. This represents 0.0344% of all deliveries in that period.

Since preterm deliveries may be caused by factors other than the conization status of the mother, we corrected for this when calculating the share of preterm births that may be avoided due to the HPV-vaccine (see Appendix 2.

Epidemiological data). Our calculations showed that HPV-infection-related critical preterm deliveries may account for 0.0248% of all births in a given year.

Although the effect of a reduction in the cumulative acquisition rate of HPV 16 and 18 on the annual number of conizations is likely to be relatively limited, every critical preterm delivery is associated with a potential for excess mortality, reduction in health-related quality of life, as well as need for health care throughout life. See the *Quality-adjusted life years* and *Costs* sections for more details. The impact on the results of excluding these preterm births was examined in a sensitivity analysis.

6. *Adverse effects of the vaccine*

The Norwegian Medicines Agency periodically reports the number of registered adverse events (AEs) attributed to the HPV-vaccine. Their report indicates that, as of August 2014 (35), 358 950 vaccine doses had been administered to girls born between 1997 and 2001. A total of 508 AEs were registered, of which 29 were considered serious, meaning that the patient experienced a reaction that required either admission to hospital or prolonged stay at the hospital. That represents approximately 8 serious AEs per 100 000 doses.

Table 3. Vaccination and related serious adverse events (AEs) in Norway, 2009-2014

Antall doser satt						
Dose	**Girls born 1997**	**Girls born 1998**	**Girls born 1999**	**Girls born 2000**	**Girls born 2001**	**Source**
First dose	22 174	24 402	25 268	25 737	25 350	Norwegian Medicines Agency (35)
Second dose	21 851	24 116	24 853	25 129	25 129	
Third dose	21 380	23 633	23 644	23 142	23 142	
Total per cohort	65 405	72 151	73 765	74 008	73 621	
Total since vaccination program	358 950					
Total # AEs	508					
Serious AEs	29					
Number of serious AEs (per 100 000 doses)	8					Own calculations

As the non-serious AEs lasted for a short period of time and probably had limited consequences for the patient, we did not include them in our model.

We only incorporated the rate of serious AEs cases per 100 000 doses to calculate the annual incidence rate per dose.

Furthermore, we did not have AEs data for boys: The data presented above apply only to girls, and the serious AEs registered in the effect studies for boys were considered by the authors to be unrelated to the study vaccination(26). Therefore, we assumed that the annual incidence rate per dose among boys was the same as among girls.

7. *Cohort size*
   In order to calculate the possible number of negative outcomes a HPV vaccine program may prevent, the model requires data not only on the incidence rates but also on the number of people in each cohort. We obtained population data from Statistics Norway showing that by 1st of January 2014 there were 60 940 (29 825 girls and 31 115 boys) eight-year-old children (17), and assumed that the size of future cohorts of eight-year-olds would remain unchanged.

8. *Birth rates*
   As explained above, the vaccine protects against HPV-infection, which may develop into CIN 2+ and then require conization later during a patient's life.

   To calculate the number of avoided conization-related events, we retrieved data from Statistics Norway for 2013 (36) on the number of live births, according to the mother's age, and the number of females in each age group (see Appendix *2*. Epidemiological data for details).

9. *Death rates for the general population*
   Finally, the number of people in each cohort may decrease as the cohort ages, due to all-cause mortality. To account for this in our model, we incorporated gender specific death rates (per 100 000) from Statistics Norway for 2013 (see Appendix 2. Epidemiological data for more details).

Efficacy of the HPV vaccine among boys and girls

We performed a systematic review to obtain data on the effect of the vaccine among boys in terms of protection against HPV 6/11, 16 and 18 infection, penile and anal precancerous lesions, cancer or cancer mortality and genital warts (26).

We only found reliable effect data for HPV-infection and genital warts, which we used together with the effect estimates for persistent infection, CIN 2+, VIN/VaIN

2+ and genital warts among females that we used in our economic evaluation of catch-up HPV vaccination of young women (22).

This means that our base case analysis does not include the effects of the vaccine on other outcomes linked to HPV-infection, such as vaginal, anal, penile and oropharyngeal cancer and juvenile onset recurrent respiratory papillomatosis (JoRRP). Nevertheless, we present below the effect estimates on anal and vaginal intraepithelial neoplasia, grade 2 and 3 (AIN and VaIN 2+) as these were used in a scenario analysis (see *Scenario Analyses*).

In order to reflect the effect of the vaccine on the general population in a more realistic manner, we used intention-to-treat (ITT) analysis and estimates for all lesions irrespective of HPV type.

Finally, we extrapolated the effect on precancerous vulvar lesions to vulvar cancer and the effect on precancerous cervical lesions on cervical cancer and conization-related preterm births. 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) (37), 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 (26). Furthermore, and according to the FDA, if efficacy trials using cervical cancer as the endpoint cannot be conducted, prevention of CIN 2+ or worse will most closely approximate the preventive efficacy of HPV vaccines for cervical cancer (38). This approach was also followed for VIN 2+ in our base case (as well as for VaIN and AIN 2+ in a scenario analysis).

<u>Vaccine effect on persistent infection with HPV 6/11, 16 and 18</u>

For boys, we used data from our systematic review (26), in which it is reported a six-month modified ITT relative risk (RR) estimate of persistent infection with HPV 16 and 18 among males of 0.33 (95% CI: 0.25, 0.44). This is equivalent to a relative risk reduction (RRR) of 67% (i.e. $E_2 = 0.67$ in the infection models presented earlier).

For girls, we used the same effect estimate as in our cost-effectiveness analysis of the catch-up vaccine for females (22), a RR of 0.26 (95% CI: 0.16, 0.41), equivalent to a RRR of 74% (i.e. $E_1 = 0.74$)

We did not find any evidence regarding the reduction in persistence infection with HPV 6/11 , but we assumed the RR for HPV 16 and 18 would also apply to infection with HPV 6 and 11.

Table 4. Relative risk (modified ITT) of persistent infection. Vaccination vs. no vaccination

Gender (follow-up)	Persistent infection (ITT), RR (95% CI)	Source
Boys (6 months)	0.33 (0.25, 0.44)	Juvet et al. (26)
Girls (12 months)	0.26 (0.16, 0.41)	Rambout et al. (39)

Vaccine effect on CIN 2 and 3 and cervical cancer

We used the four year follow-up, ITT, RR estimate of experiencing CIN 2+ lesions from our previous systematic review (40), which was 0.80 (95% CI: 0.62, 1.02). This is equivalent to a RRR of 20%.

Table 5. Relative risk (ITT) of experiencing CIN 2+. Vaccination vs. no vaccination

Gender (follow-up)	All CIN 2+ (ITT), RR (95% CI)	Source
Girls (4 years)	0.80 (0.62, 1.02)	Sæterdal et al. (40)

Vaccine effect on genital warts

For boys, we used the three-year follow-up, ITT, RR estimate of experiencing genital warts (all HPV types) from our systematic review (26), which in this case was 0.39 (95% CI: 0.25, 0.58), equivalent to a RRR of 61%. For girls we used the four-year follow-up, ITT RR estimate from our previous systematic review (40), which was 0.38 (95% CI: 0.31, 0.47), equivalent to a RRR of 62%.

Table 6. Relative risk (ITT) of experiencing genital warts (all HPV types). Vaccination vs. no vaccination

Gender (follow-up)	All genital warts (ITT), RR (95% CI)	Source
Boys (3 years)	0.39 (0.25, 0.58)	Juvet et al. (26)
Girls (4 years)	0.38 (0.31, 0.47)	Sæterdal et al. (40)

Vaccine effect on VIN/VaIN 2+ and vulvar cancer

We used the RR estimate for VIN/VaIN 2+ for the ITT population after a four-year follow-up (40). The estimate was 0.49 (95% CI: 0.32, 0.76), leading to a RRR of 51%.

Table 7. Relative risk (ITT) of experiencing VIN/VaIN 2+. Vaccination vs. no vaccination

Gender (follow-up)	All VIN/VaIN 2+ (ITT), RR (95% CI)	Source
Girls (4 years)	0.49 (0.32, 0.76)	Sæterdal et al. (40)

Vaccine effect on AIN and anal cancer

In one scenario analysis, we included the effect of the vaccine on anal cancer. For that purpose, we used the RR estimate for HPV 6, 11, 16 and 18-related AIN for the ITT population after a three-year follow-up (26). The estimate was 0.46 (95% CI: 0.27, 0.79), leading to a RRR of 54%.

The estimate was calculated from a male population, but due to the lack of data, we assumed it applied to females as well.

Table 8. Relative risk (ITT) of experiencing AIN 2+. Vaccination vs. no vaccination

Gender (follow-up)	AIN (ITT), RR (95% CI)	Source
Boys (3 years)	0.46 (0.27, 0.79)	Juvet et al. (26)

Costs

The total cost of vaccinating each cohort of 12-year-old boys starting in 2016 was calculated by summing the associated additional vaccine costs and then subtracting the savings from the reduction in HPV 6/11, 16 and 18-related health outcomes.

As mentioned earlier, we calculated total costs of the boys' vaccination program from two different perspectives:

- Public health-care perspective, which only includes costs to the National health budget (Value added tax, or VAT, included).
- Societal perspective, which includes both costs to the National health budget (after extraction of VAT and other transfer payments between economic agents, as they are not real economic costs),the deadweight loss of taxation, the costs to patients for time used under treatment and the work-related productivity costs due to disease.

Vaccine costs

We calculated vaccine costs by multiplying the price per dose by the number of vaccine doses administered.

The vaccine price in the base case was the maximum pharmacy retail price (PRP) of the quadrivalent vaccine in December 2014, NOK 1 113.4/dose (41). The model uses a scenario analysis to evaluate alternative, lower prices, probably closer to the actual tender price paid by the Norwegian health authorities, which is confidential.

To calculate the number of administered doses per girl we used the proportion of ITT- and PPP-participants in four of the main studies in the systematic review we conducted in connection with our report on catch-up HPV-vaccination program (40): Future I (42), Future II (43), Future protocol 19 (44) and Patricia (45) . The result was an average of 2.78 doses per girl.

For boys we conducted a similar analysis based on Giuliano (46), resulting in an estimate of 2.54 doses per boy. For more details, see Appendix 4. Costs.

Finally, we used a coverage rate of 82% for both boys and girls based on feedback from the Norwegian Institute of Public Health. These rates apply for those having received at least one dose, as we used the effect estimates of the vaccine in the intention-to-treat (ITT) population, i.e. those that received at least one vaccine dose.

Estimating cost savings due to vaccination

We estimated total savings by multiplying the number of prevented HPV-related health outcomes, which we obtained with the help of the infection models, by the respective cost per prevented outcome.

Each of the costs per prevented outcome consists of a series of inputs (diagnostic procedures, doctor payments, surgical procedures, medicines, patient travel time, etc.) classified according to disease and treatment stage. In most cases, the treatment stages were:

- medical assessment, where the right course of action was set,
- primary treatment,
- secondary/further treatment, in case of inadequate response to primary treatment, and
- follow-up, usually up to the patient's death (alternatively up to 10 years).

In order to obtain reliable estimates of resource use per case, we retrieved information from national and international treatment guidelines, the Cancer registry of Norway, the Directorate of Health and the Oncology Encyclopedia (ONCOLEX). We also contacted experts to obtain information about the course of disease treatment and/or costing of each of the health outcomes discussed earlier. The main sources of prices were the Norwegian hospital charges system, the Norwegian Medical Association, Norwegian Medicines Agency, and some private providers of diagnostic services (see Appendix 4. Costs).

Special issues regarding cost estimation from a societal perspective

1- *Excluding VAT from costs:*
   According to the Norwegian Ministry of Finance (23), when estimating costs from a societal perspective the value added tax (VAT) must be excluded from the purchase price of inputs as it represents a transfer of purchasing power from the purchaser (health-care providers, for example) to the State, and not a true cost.

The key cost drivers in the model are the public price of the vaccine and the health-care costs accrued at hospitals for treatment of HPV-related outcomes. Excluding VAT is straightforward for the public vaccine price but not for hospital-based health-care costs since only some costs (for example, purchase of certain consumable goods) are subject to VAT while others are not (for example, wages).

There is no published data specifying the share of health costs subject to VAT, so we estimated it by examining the operating costs reported by the four regional health trusts for 2011, and found that approximately 30% of costs may be considered VAT-liable (for more details, see Appendix 4. Costs). By assuming that this share also applied to the costs per HPV-related outcome in this model, we extracted the VAT from 30% of each outcome cost when evaluating the HPV-vaccine from a societal perspective.

2- *Deadweight loss due to tax funding:*
The Ministry of Finance has established that deadweight loss of taxation must be included in economic evaluations, regardless of sector (23). This loss is stated to be 20% of the net budget impact of implementation, which is calculated as the sum of necessary expenditures covered by the public budget minus all budgetary savings together with public sector's share of all associated productivity gains due to an increase in the number of working hours (currently set at 45%).

In order to estimate the deadweight loss in our model, we used the following formula to estimate the net budget impact (NBI) of each vaccination program:

- $NBI = IC_{Hcp} - 45\% * PG_{Sp}$

Where:

- IC_{Hcp} = Incremental costs from the health-care perspective (compared to a situation without vaccination), as estimated by our model.
- PG_{Sp} = Productivity gains from reduced number of cervical cancer and conisation-related preterm births cases (compared to a situation without vaccination).

Then we multiplied the NBI by 20% and added the result to the incremental costs from a societal perspective of each vaccination program.

3- *Monetary value of patient's time spent when receiving the vaccine or health treatment for HPV-related outcomes*
The monetary value of patient's time when receiving treatment for HPV-related outcomes was estimated by multiplying the number of spent hours

(according to the experts we consulted) by our estimate of the hourly after-tax wage rate for 2013, NOK 186. This figure is based on average monthly pre-tax income data for full-time employees, NOK 42 500 (47), a tax wedge to the employee of 26% (48) and some assumptions about the number of working hours (see Appendix 4. Costs for more details).

We used the after-tax wage rate as we assumed that the alternative usage of that time was leisure. This is a conservative assumption as some cervical cancer patients may be of working age and employed, so that they may have to spend working hours to receive treatment.

The value of the hours used by children in order to get the vaccine was not included in our analysis. Furthermore, as boys (and girls) will receive the vaccine during school hours, we assumed their parents would no experience loss of working time due to vaccination.

4- *The monetary value of lost working time after disease*

We included the monetary value of lost working time after disease (i.e. the productivity costs) caused by cancer mortality and conization-related preterm births. Since there are no requirements in Norway as to how to estimate this monetary value, we proceeded as follows:

- First, we estimated the annual total labor costs per employee per year in Norway based on data from Statistics Norway and the OECD. The result, NOK 653 850, reflects both the direct costs (wage before taxes) and the indirect costs (payroll tax, pension costs, insurance, job training, etc.).
- Then, we multiplied the result by the expected number of working years lost due to every HPV 16 and 18-related cervical cancer and preterm (living) birth before week 33.
- We discounted future income using the discount rates set by the Norwegian Ministry of Finance.
- Finally, the results were adjusted by reducing them by 50% in order to account for compensation mechanisms in the labor market, as proposed by the Norwegian Directorate of Health (49).

For further details, please see Appendix 4.

The costs per HPV-related outcome

Estimated costs are shown in Table 9:

Table 9. Estimated Norwegian cost per HPV-related outcome (2014-NOK)

Treatment	To public health budget	To society[a]	Source
CIN 2 - Conization	9,913	10,344	Ingvild Vistad, gynecologist, chief physician (Sørlandet sykehuset)
CIN 3 - Conization	9,913	10,344	Ingvild Vistad, gynecologist chief physician (Sørlandet sykehuset)
Conization-related costs	259,694[b]	436,112[c]	Ingvild Vistad, gynecologist, chief physician (Sørlandet sykehuset)
Genital warts	2,216	5,002	Turid Jorunn Thune, chief physician (Haukeland universitetssjukehus) and Ingvild Vistad, chief physician (Sørlandet sykehuset)
Cervical cancer	203,813	1,504,916	Ingvild Vistad, gynecologist, chief physician (Sørlandet sykehuset)
VIN 2 & 3	12,686	13,618	Ingvild Vistad, gynecologist, chief physician (Sørlandet sykehuset)
VaIN 2 & 3 [d]	12,686	13,618	Ingvild Vistad, gynecologist, chief physician (Sørlandet sykehuset)
Vulvar cancer	265,651	283,471	Ingvild Vistad, gynecologist, chief physician (Sørlandet sykehuset)
Vaginal cancer [d]	265,651	283,471	Ingvild Vistad, gynecologist, chief physician (Sørlandet sykehuset)
Anal cancer [d]	160,168	180,238	Åse Skår, oncologist (Kunnskapssenteret for helsetjenesten)
Serious adverse events of HPV-vaccine	40,650	42,684	Ingvild Vistad, gynecologist, chief physician (Sørlandet sykehuset)

[a] Deadweight loss due to tax funding excluded.

[b] Premature birth delivery costs at hospital only.

[c] Premature birth delivery costs at hospital plus long-term costs due to reduced productivity.

[d] Used in sensitivity analyses only, not the base case.

From a public health-care perspective, the costs of treating cancer are among the highest as these treatments require highly specialized services, usually over a long period of time.
From a societal perspective there are two costs estimates that experience a sharp increase:

- *Cervical cancer*. The treatment cost increases from approximately NOK 204,000 per case under the public health-care perspective, to approximately NOK 1,500,000 under the societal perspective. This is primarily because many of the patients are young (our calculations based on data from the Cancer Registry show a weighted average age at diagnosis of approximately 50) and still of working age, so that early cancer-related mortality may lead to a great expected loss of working years.
- *Conization-related costs.* It includes both the expected medical costs per premature living baby delivery, the expected long-term treatment costs of the newborn due to increased morbidity and the expected productivity costs due to life-time disability. The cost estimate increases from approximately NOK 260,000 to NOK 436,000 per case, also particularly because of the great expected productivity costs to the newborn.

For further details regarding cost estimation, please see Appendix 4. Costs.

Quality-adjusted life years

As in Chesson (13) and our previous report about catch-up vaccination (22), we calculated total age- and sex-specific numbers of discounted quality-adjusted life years (QALYs) lost per outcome. The outcomes in the model are associated with a loss of health-related quality of life (HRQoL) and/or life years. Each avoided outcome (e.g. cervical cancer or genital warts) thus yields a health gain.

Literature search for EQ-5D values

We did a systematic search for EQ-5D values in Medline and Embase in March and April 2014. Appendix 5. Health related quality-of-life (HRQL) data includes the search term combinations and results per search, for both the narrow and broader searches. In addition to the systematic search, we did some occasional reference list checking and searched in the EQ-5D reference database (50).

Choice of the EQ-5D instrument

For the time being, there are no requirements regarding the choice of HRQoL-instrument to use in health economic analysis in Norway. Since the generic preference based instrument EQ-5D is widely used and it is preferred by the National Institute for Health and Care Excellence (NICE) in its technology appraisals (51), we decided to use it in this report. Furthermore, since we expected

that values elicited with the same descriptive system and with index scores from the same tariff would be more consistent, we only included health state utility values from EQ-5D in the analysis.

General considerations

As in our previous report (22), we used a multiplicative approach to estimate the QALY-loss, assuming a fixed relative loss of HRQoL from a common general-population baseline across all age groups. This approach takes into consideration the natural decline in health due to age, and consequently the absolute decrement in HRQoL due to a health state falls with age. A baseline HRQoL-weight of one (perfect health) irrespective of age would lead to an overestimate of the QALY-loss (52, 53).

The outcomes in the Chesson model (13) were modeled independent of the natural history of disease. This is also the case for the QALY-calculations where we treat the precancerous lesions and associated cancers as independent events.

The calculation of the QALY-loss

We estimated the QALY-loss associated with the precancerous lesions and genital warts with the following formula:

$$QALY\ loss = T * B * k$$

Here, "T" is duration of the health state measured in years, adjusted for the probability of death using age- and sex- specific all-cause mortality rates from Statistics Norway (54). Ignoring all-cause mortality would have resulted in an overestimation of the QALY-loss, especially for the older age groups.

"B" is the age-dependent baseline HRQoL value used for both sexes. The table below shows the baseline EQ-5D value for each age group in the model. The data is from the 1998 public health survey in Stockholm County, Sweden (55). The use of a general-population baseline have support in the literature if one assumes that the patients also have comorbidities (53).

Finally, "k" is a multiplier we used in order to approximate a fixed relative HRQoL-loss caused by the health state across all age groups. The multiplier represents the percent loss of HRQoL due to the HPV-related outcome.

$$k = 1 - \frac{HRQoL\ value\ from\ study}{HRQoL\ reference\ group}$$

The reference group HRQL-value is the HRQoL of those without the health state in question, but otherwise having similar characteristics as the patients. To avoid under- or overestimation of the QALY-loss, differences between the groups with respect to age, sex or other variables should be controlled for statistically. But when

a reference value was missing in the study of interest, we chose to use the age-matched baseline data from Burström (55) as the reference value, see Table 10.

Table 10. Baseline EQ-5D values used in the model.

Age groups	HRQoL-weight – males and females (EQ-5D-3L)
12 to 19	0.890*
20 to 29	0.890
30 to 39	0.879
40 to 49	0.863
50 to 59	0.839
60 to 69	0.808
70 to 79	0.794
80 to 89	0.733
90 +	0.733*

* Values extrapolated from the adjacent age group.

The current discount rates specified by the Norwegian Ministry of Finance (23) were applied to outcomes with a duration of more than one year.

The QALY-loss for precancerous lesions and genital warts

Table 11 shows the QALY-losses for all age groups for the precancerous lesions and genital warts. Compared with the report on catch-up vaccination of women (22), the estimates are higher for CIN 2+ and lower for genital warts. This mainly reflects our decision to include only EQ-5D-data in the calculations. Appendix 5 includes tables with the calculation inputs and an overview of the included studies. Because we did not have data for VaIN, we used the QALY-loss associated with VIN as a proxy for that outcome. The choice was based on expert opinion (communication with Ingvild Vidstad).

We assumed an average duration of an episode of 0.5 years, equal to that used in both the Chesson model (13) and our economic evaluation of the catch-up vaccination of women (22). For genital warts, we used the estimate of 147 days from disease onset to end of treatment, reported in Woodhall (56).

Table 11. QALY-losses due to genital warts and HPV-related precancerous lesions, by age

Age group	CIN 2+	VIN	VaIN*	GW (women)	GW (men)
12 to 14	0.156	0.078	0.078	0.025	0.018
15 to 19	0.156	0.078	0.078	0.025	0.018
20 to 24	0.154	0.077	0.077	0.025	0.018
25 to 29	0.154	0.077	0.077	0.025	0.018
30 to 34	0.152	0.076	0.076	0.024	0.018
35 to 39	0.152	0.076	0.076	0.024	0.018
40 to 44	0.149	0.074	0.074	0.024	0.018
45 to 49	0.149	0.074	0.074	0.024	0.018
50 to 54	0.145	0.072	0.072	0.023	0.017
55 to 59	0.145	0.072	0.072	0.023	0.017
60 to 64	0.139	0.069	0.069	0.022	0.016
65 to 69	0.139	0.069	0.069	0.022	0.016
70 to 74	0.136	0.068	0.068	0.022	0.016
75 to 79	0.135	0.068	0.068	0.022	0.016
80 to 84	0.124	0.062	0.062	0.020	0.015
85 to 89	0.120	0.060	0.060	0.020	0.014
90 to 94	0.115	0.057	0.057	0.019	0.014
95 +	0.107	0.053	0.053	0.018	0.013

*The results for VaIN were only used in the scenario-analysis.

The QALY-loss for cancer health states

We describe the calculations for the cancer health states in appendix 5. The calculations generally follows the same formula as above, but also considering the excess mortality associated with cancer.

Table 12 shows the QALY-losses for all age groups for cervical cancer, vulvar cancer, vaginal cancer and anal cancer. The results for cervical and vulvar cancer were used both in the base case and in the scenario analyses, while the anal cancer and vaginal cancer results were used only in the scenario-analysis. The cancer survival data and disease stage at diagnosis for the different cancer types are the factors that influence the estimated QALY-losses the most. Tables with calculation inputs and an overview of the included studies are shown in appendix 5.

Due to the lack of data regarding the HRQoL-loss associated with vulvar cancer and vaginal cancer, we used the HRQoL-data on cervical cancer as a proxy for those outcomes. Compared with the report on catch-up vaccination (22), the QALY-losses

are however somewhat lower. This mainly reflects our decision only to include EQ-5D-data, and not changes in the survival data.

Table 12. QALY-loss due to HPV-related cancer, by age

Age group	Cervical cancer	Vulvar cancer	Anal (females)*	Anal (males)*	Vaginal cancer*
12 to 14	4.694	6.220	7.603	12.690	7.798
15 to 19	4.594	6.086	7.436	12.440	7.626
20 to 24	4.455	5.899	7.207	12.095	7.391
25 to 29	4.299	5.688	6.945	11.697	7.122
30 to 34	4.121	5.449	6.651	11.232	6.820
35 to 39	3.923	5.181	6.319	10.692	6.479
40 to 44	3.699	4.879	5.948	10.065	6.098
45 to 49	3.450	4.543	5.532	9.417	5.671
50 to 54	6.162	4.496	5.063	7.551	6.792
55 to 59	5.547	4.057	4.564	6.755	6.110
60 to 64	4.891	3.586	4.030	5.873	5.385
65 to 69	4.185	3.082	3.457	4.927	4.603
70 to 74	3.424	2.536	2.838	3.930	3.760
75 to 79	2.640	1.975	2.202	2.964	2.891
80 to 84	1.935	1.463	1.624	2.123	2.114
85 to 89	1.361	1.047	1.112	1.371	1.423
90 to 94	0.867	0.687	0.709	0.821	0.884
95 +	0.489	0.409	0.436	0.412	0.520

*The results for vaginal and anal cancer were only used in the scenario-analysis.

In one scenario analysis we examined the cost-effectiveness of vaccinating boys when excluding the effect on morbidity, that is when only including the effect on mortality. Table 13 shows the life-years lost estimates associated with cervical cancer and vulvar cancer we used in that scenario analysis.

Table 13. Life-years loss due to HPV-related cervical cancer and vulvar cancer, by age.

Age group	Cervical cancer	Vulvar cancer
12 to 14	3.758	5.626
15 to 19	3.694	5.529
20 to 24	3.602	5.391
25 to 29	3.494	5.230
30 to 34	3.370	5.044
35 to 39	3.227	4.830
40 to 44	3.061	4.583
45 to 49	2.892	4.329
50 to 54	6.603	4.401
55 to 59	5.990	3.993
60 to 64	5.305	3.536
65 to 69	4.547	3.031
70 to 74	3.722	2.481
75 to 79	2.870	1.913
80 to 84	2.054	1.369
85 to 89	1.302	0.868
90 to 94	0.732	0.488
95 +	0.351	0.234

QALY-losses associated with HPV-related conization

As in the previous report (22), we included an expected lifetime QALY-loss for the premature newborns. The estimate does not include a QALY-loss for late abortions or premature births in week 33-36. We did not identify any HRQoL data related to conization-related complications in the literature search, so we based the estimate on an assumption of a lifetime loss of HRQoL of 25 % relative to the general population. See Appendix 5. Health related quality-of-life (HRQL) data for further explanation.

Table 14. QALY-losses associated with HPV-related conization

Outcome	Base case	Source
Lifetime QALY-loss per preterm delivery with complications due to previous conization of the mother	5.66	Assumption

QALY-losses associated with to HPV vaccination

For the QALY-loss associated with a serious adverse event due to vaccination we used the same estimate as in our report on catch-up vaccination, 0.01 QALYs.

Table 15. QALY-losses associated with serious adverse events due to vaccination

Outcome	Base case	Source
QALY-loss per serious adverse event due to vaccination	0.01	Assumption

Assigning distributions to the random variables in the model

As discussed earlier, we implemented a probabilistic model by assigning a probability distribution to most variables. An important exception was the probability of HPV 6/11, 16 and 18-infection, which were excluded because the model could not be run as their values changed for each simulation (their impact on the results was however examined in a one way sensitivity analysis, see Scenario Analyses)

The choice of distribution is based on the characteristics of the random variable at issue (range, confidence intervals) and the recommendations from the literature. We followed Briggs et al. (19).

Incidence rates of HPV-related outcomes

We assigned a beta distribution to most incidence rates. To fit the distribution we assumed that alpha (α) was equal to the average annual number of cases based on the 2002-2012 data by age group provided by the Cancer Registry of Norway. To calculate the beta (β) parameter, we substracted "α" from the average number of females in that age group in the period 2002-2012, available at the website of Statistics Norway (17).

The fit of the distribution for genital warts was performed differently since, as explained earlier, we only had incidence rates based on data from Kjær et al. (29). The mean in every distribution was assumed to be equal to the estimate, while the standard error of the incidence was assumed to be 50 % of the value of mean. We then used the method of moments to estimate "α" and "β" based on the values of the mean and variance (the latter being the square of the standard error).

Vaccine effect

Vaccine effect estimates (RR) were assigned a lognormal distribution. The mean in every distribution was assumed to be equal to the estimate, while the standard error was calculated using the values of the estimate's 95% confidence interval.

Costs

We assigned a gamma distribution to each cost item. The fit of the distribution was the same for all costs variables in the sense that our cost estimate was assumed to be the mean value and the standard error, 50% of that mean. Then we used the mean and the standard error to estimate both "α" and "β" (19).

QALY-losses

We used a lognormal distribution for the QALY-loss for each age group. Alternatively one could have directly assigned a distribution to the random

components of the QALY-losses, namely mortality (both the annual mortality for the general population and the five-year mortality for the cancer patients), HRQoL-weights (both for the general population and the cancer patients) and the patients cancer stage distribution at diagnosis. However that approach would have required knowledge of the specific distribution of each of these variables, something we did not have, so for simplicity we assumed that the uncertainty around all of these parameters would be captured by assigning a lognormal distribution to each of the QALY-losses.

The fit of the distribution was the same for all QALY-losses. We assumed the available estimate was the mean value (m) and then assigned the standard error (v) a value equivalent to 50% of that mean. Then we used “m” and “v” to estimate the μ and σ parameters of the lognormal distribution using the following expressions (57):

$$\mu = \ln\left(\frac{m^2}{\sqrt{v+m^2}}\right), \sigma = \sqrt{\ln(1+\frac{v}{m^2})}$$

Results

We calculated the epidemiologic impact, lifetime costs and HRQoL-gains of both vaccinating boys and girls aged 12 and of vaccinating only girls (current vaccination program), based on 1 000 simulations of the model (see Appendix 1. for more details).

We present the results using the Incremental Cost-Effectiveness Ratio (ICER). The ICER is the difference in costs between the two alternatives divided by the difference in QALYs or life-years gained, and is one of the factors decision makers may pay attention to when considering implementation/decommission of health-care programs.

We also present the results for Net Health Benefit (NHB), Net Monetary Benefit (NMB), Expected Value of Perfect Information (EVPI) and Cost Effectiveness Acceptability curves (CEAC) for a range of different willingness-to-pay values.

We present the results from our base case analysis first and then examine the different scenario analyses conducted to explore the robustness of the base case results. See Context of results section (in the Discussion section) for help when interpreting the results in this report.

Estimated epidemiologic impact of vaccination of boys against HPV infection

We estimated the total reduction in the incidence of the relevant HPV-related outcomes during the first hundred years after the implementation of vaccination of boys in addition to girls aged 12, compared to no vaccination. For the estimation and comparison of the reduction in incidence for different vaccination strategies, please see the Scenario Analyses section.

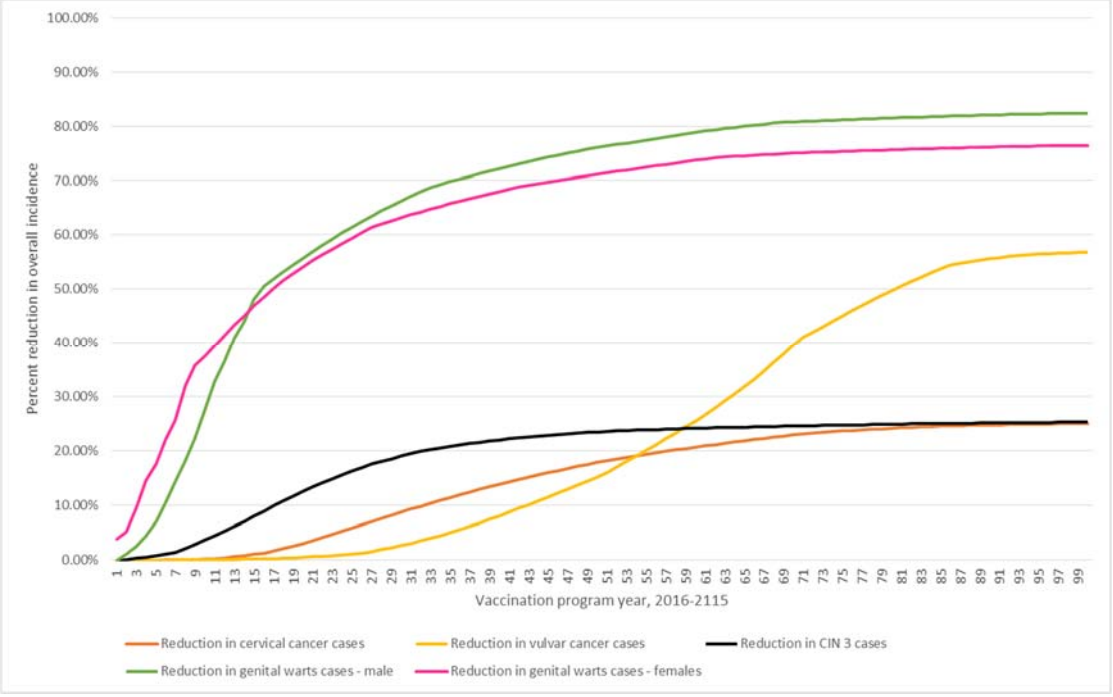
Our model predicts a gradual reduction in the population incidence rate of all relevant outcomes as the share of vaccinated cohorts increases over time. Other factors influencing the intensity and the time profile of the incidence reduction are the vaccine effect estimates and diseases' average onset age. In Table 5. Relative risk (ITT) of experiencing CIN 2+. Vaccination vs. no vaccinationTable 5 we show the

time profile of the percent reduction in population incidence rates a selection of the outcomes:

a. Genital warts incidence among males and females seems to be the outcome for which the greatest reduction after 100 years is estimated, approximately 82% and 76% respectively. The reduction among females is greater than zero already at first year of the program for boys because of the existence of the current vaccination for girls only. The genital warts incidence rates exhibit the most rapid decline among all outcomes, with a reduction of more than 50% within twenty years after implementation, probably due to the early onset of the disease.
b. The reduction in vulvar cancer incidence after 100 years would also be considerable, approximately 57%, but due to the late onset of this disease, it would take several decades before the reduction becomes noticeable.
c. The incidence reductions for cervical cancer and CIN 3 (and most probably CIN 2 as well) were considerably lower than for the other outcomes, reflecting the fact that the effect estimate on CIN 2+ from our systematic review also was considerably lower. The reduction becomes noticeable relatively quickly, especially for CIN 3, as data from Cancer Norway shows that the number of cases reach a maximum by age 25-39.

Figure 5 summarizes our results. For details on the calculation, see Appendix 3. Vaccine effect:

Figure 5. Time profile of the percent reduction in population incidence due to vaccination of males and females, compared to no vaccination.



Based on these results, the incidence rates presented in the Epidemiology section and population data for 2014 from Statistics Norway (17), we estimated the (undiscounted) number of avoided cases between 2016-2115 for vaccination of girls

only and for vaccination of both boys and girls, compared to a situation without vaccination. The results are presented in Table 16:

Table 16. Undiscounted number of avoided HPV-related outcomes between 2016-2115, compared to no vaccination

Vaccination program	Avoided cervical cancer cases	Avoided vulvar cancer cases	Avoided CIN 3 cases	Avoided genital warts (among males)	Avoided genital warts (among females)
I. Only girls (82% coverage)	4,355	1,488	49,508	192,883	219,851
II. Boys + girls (82% coverage)	4,955	1,739	56,257	257,222	257,222
Difference (II-I)	601	251	6,748	64,339	37,371
Difference (II-I as % of I)	14%	17%	14%	33%	17%

Our model predicts that vaccinating boys in addition to girls aged 12 will lead to additional avoided HPV-related outcomes every year between 2016-2115: On average 6 cervical cancer cases, 2.5 vulvar cancer cases, 67 CIN 3 cases and 1,016 genital warts (643 among males and 373 among females). The additional number of avoided cases ranges between 14% (cervical cancer and CIN 3) and 33% (genital warts among males) of the reduction attained by only vaccinating girls.

See Appendix 3. Vaccine effect for details on these calculations.

Base case Incremental Cost-effectiveness Estimates

Cost-effectiveness results when conducting the analysis from a public health-care perspective

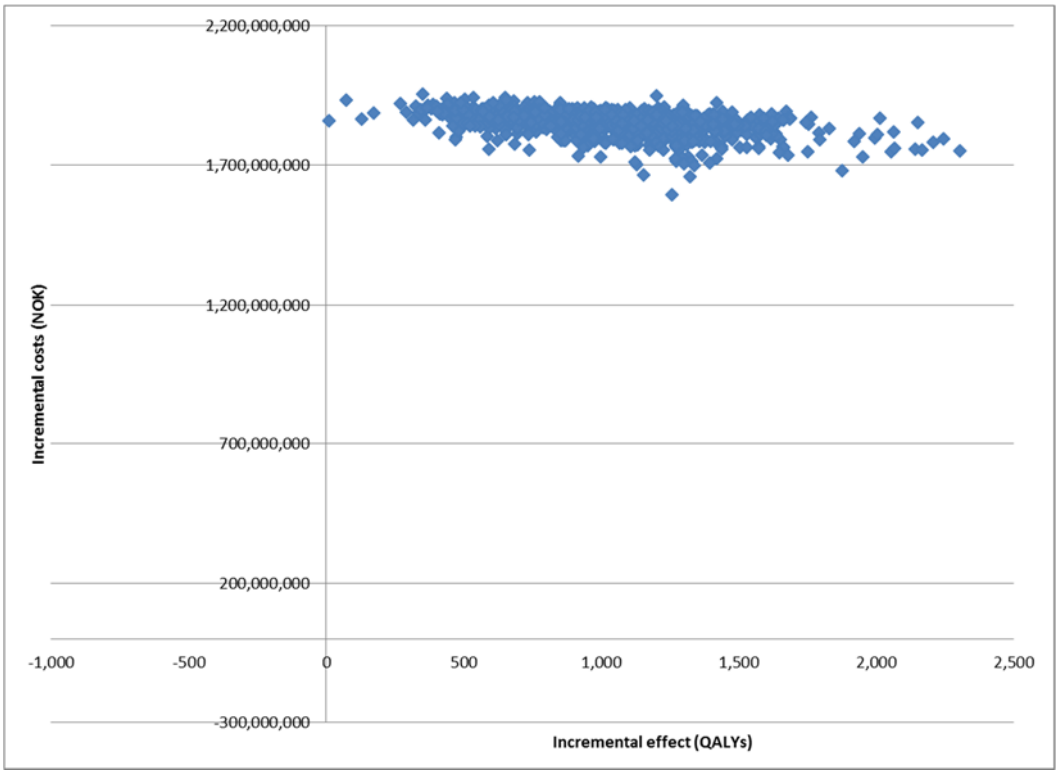
Below we present the results, based on the average of the costs and effects simulated of 1 000 iterations in the model. The incremental costs/effect of vaccinating both boys and girls aged 12 vs. the current program (vaccination of girls aged 12 only) were calculated by subtracting the incremental costs/effect of the current program vs. no vaccination from the incremental costs/effect of vaccinating both boys and girls aged 12 vs. no vaccination (labelled II-I in Table 17 below).

Table 17. Expected incremental costs and effects of vaccinating boys and girls vs. vaccinating girls aged 12 only. Public health-care perspective.

Intervention	Incre-mental cost vs. No vacc. (NOK)	Incre-mental effect vs. No vacc. (QALYs)	Incre-mental Cost (II-I, NOK)	Incre-mental effect (II-I, QALYs)	ICER (NOK / QALY)
I. Current program (12-year-old girls only)	1,485,262,929	7,363.02	1,851,367,320	1,034.59	**1,789,463**
II. 12- year-old boys + Current program	3,336,630,249	8,397.61			

Vaccinating boys and girls aged 12 (starting from 2016) instead of only vaccinating girls results in a discounted health gain of 1,034.59 QALYs and a discounted, incremental cost of NOK 1,85 billion in a 100 years perspective. This implies an ICER of NOK 1,789,463/QALY. This value was generally considered to high in several recent decisions by the Norwegian health authorities, suggesting that vaccination of boys is not cost-effective. See the Context of results section for help interpreting this result. Below we show the scatter plot of the 1 000 iterations of the model, where the incremental effect is displayed along the x-axis and the incremental costs along the y-axis:

Figure 6. Cost-effectiveness scatter plot of vaccinating boys and girls aged 12 vs. only vaccinating girls. Public health-care perspective.



All iterations were located in the upper right quadrant, where both the incremental costs and effect of the vaccination program are positive. This means that our model supports the hypothesis that adding the boys vaccination program results in better health outcomes (in the form of more QALYs) than keeping the current vaccination program, but at higher costs. Figure 6 also highlights a negative relationship between the incremental cost and the incremental effect, because an increase in the number of avoided cases leads to greater costs savings and, therefore, lower incremental costs. However, the relationship seems weak.

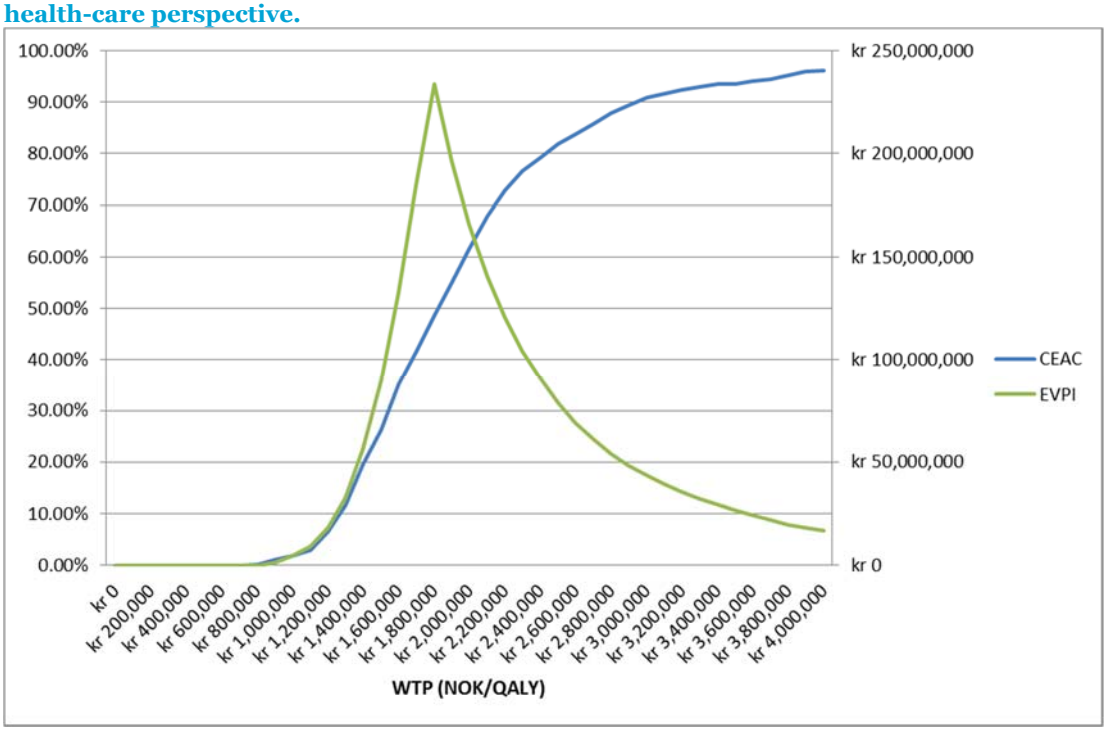
Table 18 reports both the incremental net health and monetary benefit (INHB and INMB) for different WTP values. Positive values for the INHB and INMB suggest that adding a vaccination program for boys to the current vaccination program would be cost-effective, while the opposite is true for negative values. For a WTP equal to the ICER of the program (1,789,463 NOK/QALY) both measures are equal to zero.

Table 18. Incremental net health and monetary benefit of adding the boy vaccination program to the current vaccination program. Public health-care perspective.

	WTP (NOK/QALY)			
Incremental Net Benefit	**500,000**	**1,000,000**	**1,500,000**	**2,000,000**
INHB	-2,668	-817	-200	109
INMB	-1,334,070,543	-816,773,766	-299,476,989	217,819,787

The probability that adding vaccination of boys to the current program is cost-effective as a function of the WTP can be examined in the cost-effectiveness acceptability curve (CEAC), in blue in figure 7.

Figure 7. CEAC (blue, left axis) and EVPI (green, right axis) in the base case. Public health-care perspective.



The CEAC indicates that the probability that boys vaccination program is cost-effective is 0%, 2%, 26% and 62% as willingness-to-pay (WTP) per QALY is, respectively, NOK 0.5, NOK 1, NOK 1.5 and NOK 2 million.

The expected value of perfect information (EVPI) curve can be interpreted as the upper bound on the returns to further research about the costs and effect of a health program (i.e. the returns of eliminating 100% of the uncertainties in the results of the analysis). For the vaccination program for boys and girls, the EVPI reached a maximum of approximately NOK 233 million at a WTP equivalent to the ICER. This means that if the expected costs of additional research were lower than NOK 233 million, it may at a WTP equivalent to the ICER be cost-effective to reduce uncertainty by conducting further research and wait for the new results before deciding whether the program vaccination for boys should be implemented or not.

For WTP values below NOK 800,000/QALY, on the other hand, the returns to further research are zero, as it seems fairly improbable that boy's vaccination is cost-effective at a price of 1,113.4/dose. In other words, more knowledge is not likely to change this fact for WTP values close to those shown by Norwegian health authorities in recent decisions (see Context of results).

The dispersion around the mean incremental cost in the scatter-plot seems to be relatively smaller than the dispersion around the mean incremental effect, which suggests that further research on the effect estimates may give most value for money. This is discussed further in *Scenario Analyses*.

Cost-effectiveness results from a societal perspective:
Below we present the average results, based on 1 000 iterations of the model, when conducting the analysis from a societal perspective.

Table 19. Expected incremental costs and effects of vaccinating boys and girls aged 12 vs. vaccinating girls only. Societal perspective.

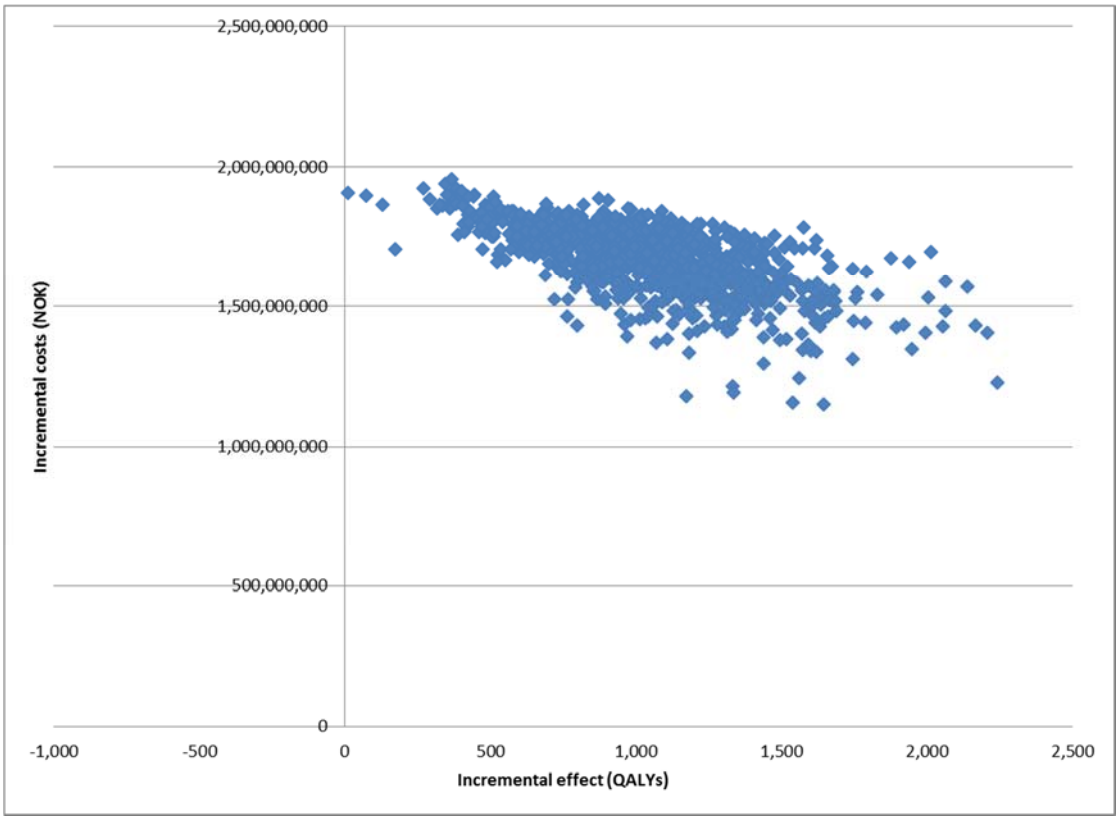
Intervention	Incremental cost vs. No vacc. (NOK)	Incre-mental effect vs. No vacc. (QALYs)	Incre-mental Cost (II-I, NOK)	Incre-mental effect (II-I, QALYs)	ICER (NOK / QALY)
I. Current program (12- year-old girls only)	247,059,107	7,366.21	1,677,319,569	1,031.40	**1,626,261**
II. 12- year-old boys + Current program	1,924,378,676	8,397.61			

The differences in the results between the two perspectives primarily reflects cost differences. From a societal perspective, the incremental costs were 9% lower, NOK 1.677 billion vs. NOK 1.851 billion in the public health-care perspective (the incremental effect was slightly lower from this perspective due to the way the model is built up, not to real effect differences between perspectives).

The ICER was NOK 1,626,261/QALY, which is lower than in the public health-care perspective. This is probably because the exclusion of VAT, together with the inclusion of productivity benefits of reducing the numbers of cervical cancer cases and premature births, more than outweighs the inclusion of deadweight costs of taxation associated with the need of public funding for the vaccination program.

Figure 8 shows the scatter-plot of the ICER from the societal perspective:

Figure 8. Cost-effectiveness scatter plot of vaccinating boys and girls aged 12 vs. vaccinating girls aged 12 only. Societal perspective.



The societal perspective scatter-plot shows that both the costs and effect of introducing boys to the vaccination program were positive in all iterations, and that the dispersion of the incremental cost was greater than in the health-care perspective. This is probably because dispersion in the incremental effect is to a certain degree incorporated in the incremental cost through the inclusion of productivity gains. This is also most probably the reason why the negative

correlation between the incremental effect and the incremental costs is now stronger than in the analysis from a health-care perspective.

Table 20 reports both the incremental net health and monetary benefit (INHB and INMB) for different WTP values.

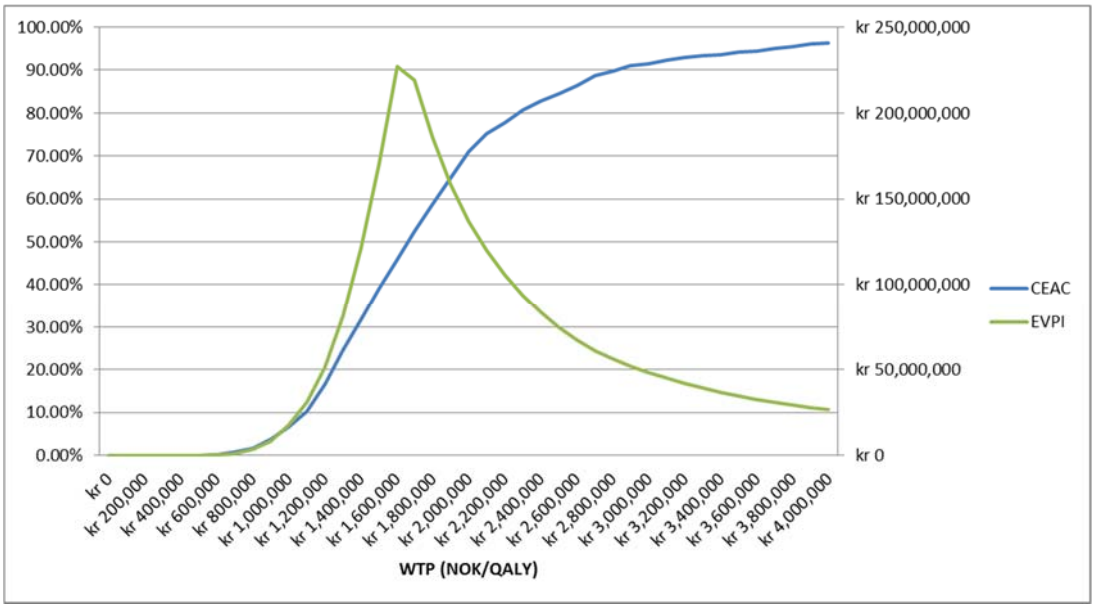
Table 20. Incremental net health and monetary benefit of adding the vaccination program for boys to the current vaccination program

	WTP (NOK/QALY)			
Incremental Net Benefit	**500,000**	**1,000,000**	**1,500,000**	**2,000,000**
INHB	-2,323	-646	-87	193
INMB	-1,161,621,465	-645,923,362	-130,225,259	385,472,844

The results from the CEAC (blue curve in Figure 9) show that the probability of the boys vaccination program to be cost-effective is 0%, 7%, 39% and 71% as WTP/ QALY is, respectively, NOK 0.5, NOK 1, NOK 1.5 and NOK 2 million.

The expected value of perfect information (EVPI) curve (in green in Figure 9) reaches a maximum value of approximately NOK 225 million from a societal perspective, for a willingness-to-pay of NOK 1,626,261/QALY. This means that if the expected costs of additional research were lower than NOK 225 million, it may be cost-effective to reduce uncertainty by conducting further research and wait for the new results before deciding whether the program vaccination for boys should be implemented or not.

Figure 9. CEAC (blue, left axis) and EVPI (green, right axis) in the base case, societal perspective.



Scenario Analyses

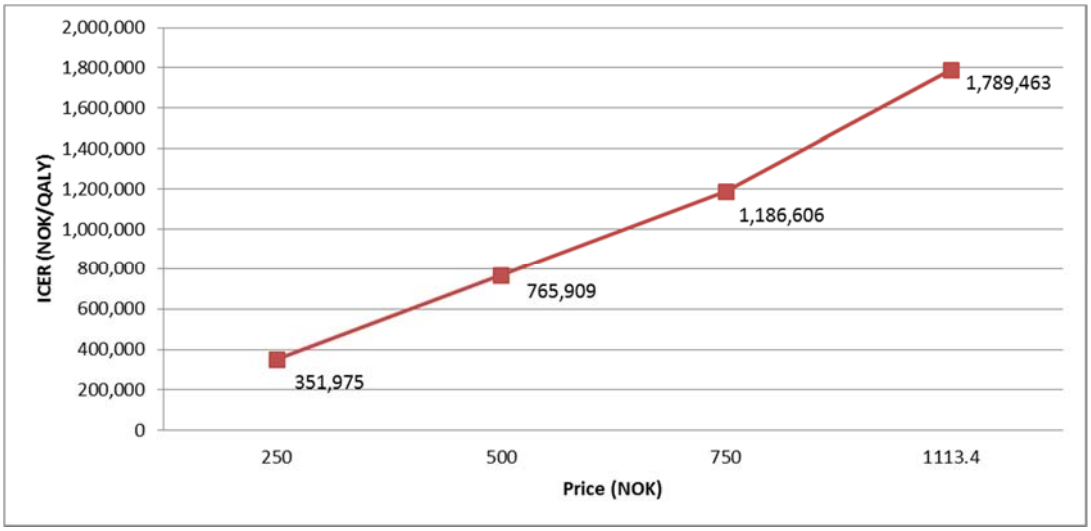
The scenario analyses make it possible to examine the impact on the results of changes in specific model assumptions and/or variable values.
We conducted eight scenario analyses: The first investigated the effect of a lower vaccine purchase price per dose. The second excluded the effect of the vaccine on genital warts in order to examine the cost-effectiveness of using a bivalent, rather than quadrivalent vaccine. The third evaluated the cost-effectiveness of increasing the coverage among girls instead of vaccinating boys. The fourth scenario analysis is the base case results in the public health perspective for life-years gained (LYG), i.e. without the HRQoL-impact of vaccination. In the fifth scenario analysis, we estimated the ICER when incorporating the vaccine effect on anal cancer (in both genders) and vaginal cancer, as well as on VaIN 2+. In the sixth scenario analysis, we excluded the effect of the vaccine in reducing the number of conization-related preterm births. In the seventh scenario analysis, we examined the cost-effectiveness of vaccinating boys when only administering two doses while obtaining the full vaccination effect reported in published studies. Finally, in the eight scenario analysis we estimated and compared the reduction in the incidence of the several relevant outcomes under different coverage assumptions.

In addition, we conducted a series of one-way analysis where we examined how the base case results changed when increasing or reducing certain groups of variable (epidemiologic, effect, costs, HRQoL) by 25%. We present the results in the form of a Tornado diagram.

Alternative prices
Our analysis assumes that the HPV vaccine is purchased at the maximum pharmacy retail price (PRP), NOK 1,113.40/dose in December 2014. We examined three alternative scenarios, with per dose prices of NOK 250, NOK 500 and NOK 750, from a public health-care perspective. The incremental costs declined 81%, 57% and 34% for a price of NOK 250, 500 and 750/dose, respectively. Since lower prices do not affect incremental health effect, lower incremental costs resulted in lower ICERs. These results show that in the price range NOK 250-1,113.4/dose, a 10% reduction in the dose price leads to a reduction in the ICER of approximately 10.3%.

Figure 10 illustrates the cost-effectiveness results for each vaccine price.

Figure 10. ICERs for base case and alternative quadrivalent vaccine price/dose scenarios



Excluding vaccine effect on genital warts

Although the quadrivalent vaccine used in the base case analyses is the one currently offered in the HPV vaccination program, a bivalent vaccine is also available. Both vaccines are administered following a 3-dose schedule. The bivalent vaccine, however, does not provide protection against genital warts.

We conducted a scenario analysis in which we excluded the vaccine's effect on genital warts and assumed that the bivalent and quadrivalent vaccines had the same price (NOK 1,113.40/dose) and effect. This allowed us to both estimate the cost-effectiveness of the bivalent vaccine and to ascertain the price at which the incremental cost-effectiveness ratios of the bivalent and quadrivalent vaccines were the same. All boys and girls aged 12 in both strategies were assumed to receive the bivalent vaccine in this scenario analysis. Table 21 provides results from a public health-care perspective.

Table 21. Estimated cost-effectiveness of the bivalent vaccine. Public health-care perspective.

Intervention	Incremental cost vs. No vacc. (NOK)	Incre-mental effect vs. No vacc. (QALYs)	Incremental Cost (II-I, NOK)	Incre-mental effect (II-I, QALYs)	ICER (NOK / QALY)
I. Current program (12-year-old girls only)	1,760,995,552	4,693.72	1,910,543,202	508.82	**3,754,854**
II. 12- year-old boys + Current program	3,671,538,754	5,202.54			

Compared to the base case, the incremental costs are slightly higher (NOK 1.910 vs. 1.851 billion) while the incremental effect is halved (gained QALYs 508.82 vs. 1,034.59 in base case). The result is an ICER of NOK 3.75 million/QALY, which means that the willingness-to-pay of the decision-maker has to increase considerably, from NOK 1.789 million/QALY to NOK 3.751 million/QALY, for the vaccination of boys with the bivalent vaccine to be considered cost-effective.

Based on these results, the price at which the bivalent vaccine reaches an ICER equivalent to the one of the quadrivalent vaccine, i.e. NOK 1.789 million/QALY, is approximately NOK 550/dose, equivalent to a price reduction of 50.6%.

These results are not surprising: Although the treatment costs and loss of quality of life associated with every genital wart episode are low compared to other HPV-related outcomes (e.g. cervical cancer), the condition occurs much more frequently. In addition, a top is reached at a younger age, so that the cost savings and HRQoL-gains are discounted less heavily than for other outcomes (e.g. cancer).

Increasing coverage among girls aged 12 instead of vaccinating boys

In this scenario analysis we evaluated the cost-effectiveness of increasing first dose coverage (currently at 82%) among girls aged 12 instead of vaccinating every cohort of boys and girls at the current coverage rate. As agreed with the Norwegian Institute of Public Health, we increased coverage from 82% to 92%.

This vaccination strategy led to a reduction in the number of HPV-related outcomes higher than when vaccinating girls only (at an 82% coverage rate) but lower than when vaccinating both boys and girls (also at an 82% coverage rate).

Table 22. Number of avoided HPV-related outcomes 2016-2115, compared to no vaccination

Vaccination program	Avoided cervical cancer cases	Avoided vulvar cancer cases	Avoided CIN 3 cases	Avoided genital warts (male) cases	Avoided genital warts (female) cases
Girls 82%	4,355	1,488	49,508	192,883	219,851
Girls 92%	4,680	1,613	53,035	208,038	234,721
Boys + girls 82%	4,955	1,739	56,257	257,222	257,222

The cost-effectiveness analysis was conducted assuming a health-care perspective and a public price of 1,113.4/dose. Table 23 provides the results.

Table 23. Estimated cost-effectiveness of increasing coverage among girls aged 12. Public health-care perspective.

Intervention	Incremental cost vs. No vacc. (NOK)	Incre-mental effect vs. No vacc. (QALYs)	Incremental Cost (II-I, NOK)	Incre-mental effect (II-I, QALYs)	ICER (NOK / QALY)
I. Current program (12-year-old girls, 82% cov.)	1,485,262,929	7,363.02	202,895,504	602.50	**336,755**
II. 12- year-old girls (92% cov.)	1,688,158,433	7,965.52			

Compared to the base case, the incremental costs decline sharply (approximately 89%, from NOK 1.851 to 0.203 billion) while the incremental effect does not fall as strongly (approximately 42%, from 1,034.59 to 602.50 gained QALYs). The result is an ICER of NOK 336,755/QALY, which suggests that increasing coverage among girls is more cost-effective than for vaccinating boys. However, our estimated incremental costs of increased coverage do not include the costs associated to such strategy (awareness campaigns, special targeting of left-out groups, etc.), so this ICER must be interpreted with caution (see also Discussion for more details on this).

Table 24 provides the results of comparing a vaccination program with 82% coverage of both boys and girls aged 12 to a girls-only vaccination program with 92% coverage. Incremental costs of vaccinating boys would almost the double compared to increasing coverage among girls aged 12 (NOK 1.648 billion), while the incremental effect would be approximately 6% higher (432.1 gained QALYs). Consequently, the ICER for adding boys to the vaccination program is substantially higher than in the base case (NOK 3,815,093/QALY vs. NOK 1,789,463/QALY).

Table 24. Estimated cost-effectiveness of vaccinating boys and girls aged 12 after having implemented an increase in coverage among girls first. Public health-care perspective.

Intervention	Incremental cost vs. No vacc. (NOK)	Incre-mental effect vs. No vacc. (QALYs)	Incremental Cost (II-I, NOK)	Incre-mental effect (II-I, QALYs)	ICER (NOK / QALY)
I. 92% coverage among 12-year-old girls	1,688,158,433	7,965.52	1,648,471,816	432.09	**3,815,093**
II. 12- year-old boys + Current program	3,336,630,249	8,397.61			

Base case results for life-years gained (LYG)
In this analysis, we use LYG as measure of effect instead of QALY, thus focusing only on the reductions in mortality associated with each HPV-related outcome while excluding the reduction in morbidity. The results in

Table 25 show that vaccinating boys aged 12 in addition to the current program yields 299 life-years gained, leading to an ICER of NOK 6.188 million/LYG from a health-care perspective.

Table 25. The results of the base case analysis, health-care perspective, LYG.

Intervention	Incremental cost vs. No vacc. (NOK)	Incre-mental effect vs. No vacc. (QALYs)	Incre-mental Cost (II-I, NOK)	Incre-mental effect (II-I, QALYs)	ICER (NOK / QALY)
I. Current program (12- year-old girls only)	1,484,994,556	2622.1	1,851,698,969	299.2	**6,188,344**
II. 12- year-old boys + Current program	3,336,693,525	2,921.4			

Assuming vaccine effect on anal cancer (both genders) and vaginal cancer
In our systematic review of the vaccine effect on boys, we estimated a relative risk reduction of 54% for HPV-16 and -18-related anal AIN 2+ cases. This effect estimate was not included in the base case because its relevance for the general population was questionable, as it was estimated among a population consisting exclusively of men who had sex with men.

We also excluded from the base case the effect estimate (taken from our previous systematic review) of a catch-up vaccination on VaIN 2+ and did not use it to extrapolate it to vaginal cancer as we did with the effect on VIN 2+ and vulvar cancer. We based this decision on expert opinion (personal communication with Ingvild Vistad) that VaIN 2+ is not considered a good predictor of future vaginal cancer on its own, as this cancer form often appears together with cervical and/or vulvar cancer.

However, because both anal and vaginal cancers often are included in HPV-vaccine models, we conducted a scenario analysis incorporating these cancers in order to facilitate comparison with other studies.

Table 26 provides the results from a health-care perspective and at a price of 1,113.4/dose.

Table 26. Estimated cost-effectiveness of boy vaccination, anal and vaginal cancer included. Public health-care perspective.

Intervention	Incremental cost vs. No vacc. (NOK)	Incre-mental effect vs. No vacc. (QALYs)	Incre-mental Cost (II-I, NOK)	Incre-mental effect (II-I, QALYs)	ICER (NOK / QALY)
I. Current program (12-year-old girls only)	1,450,724,656	8,272.87	1,845,774,621	1,199.66	**1,538,578**
II. 12- year-old boys + Current program	3,296,499,276	9,472.53			

The results show that vaccinating boys would yield very similar incremental costs to the ones in the base case (NOK 1.845 vs. NOK 1.851 billion), but also a 16% higher incremental effect (1,199.66 vs. 1,034.59 QALYs). This resulted in a 14% lower ICER, NOK 1.538 million/QALY.

Excluding the vaccine effect on conization-related preterm births

We assumed in our base case that vaccination against HPV may prevent a number of preterm births related to the conization status of the mother because women who have undergone conization before pregnancy, have a greater risk of experiencing preterm deliveries (30-32). As far as we know, incorporating this vaccine effect in HPV-models is not usual, so we examined how the base case results changed when we excluded it. The analysis was conducted from a health-care perspective and used the public price, 1,113.40/dose.

Table 27. Estimated cost-effectiveness when excluding the vaccine effect on conization-related preterm births. Public health-care perspective.

Intervention	Incremental cost vs. No vacc. (NOK)	Incre-mental effect vs. No vacc. (QALYs)	Incre-mental Cost (II-I, NOK)	Incre-mental effect (II-I, QALYs)	ICER (NOK / QALY)
Current program (12-year-old girls only)	1,497,528,961	7,098.14	1,852,962,887	1,002.41	**1,848,515**
12- year-old boys + Current program	3,350,491,848	8,100.54			

The incremental costs remained practically unchanged, while the incremental effect was reduced by approximately 3% (from 1,034.59 to 1,002.41 gained QALYs). This resulted in an ICER of NOK 1.848 million/QALY.

Administering two vaccine doses instead of three

The European Medicines Agency (EMA) endorsed in 2014 the introduction of a 2-dose schedule in individuals aged 9-13. The endorsement was based on data indicating that the immune responses to two doses of Gardasil given to girls aged 9-13 are at least as good as those in women aged 16-26 who were given three doses, which are the populations in which efficacy has been demonstrated (58).

We conducted a scenario analysis in which everyone getting the vaccine received two doses, while assuming that the estimated effect in our systematic reviews still applied. The analysis was conducted from a health-care perspective and used the public price, 1,113.40/dose.

Table 28. Estimated cost-effectiveness of a vaccination schedule of two doses. Public health-care perspective.

Intervention	Incremental cost vs. No vacc. (NOK)	Incre-mental effect vs. No vacc. (QALYs)	Incremental Cost (II-I, NOK)	Incremental effect (II-I, QALYs)	ICER (NOK / QALY)
I. Current program (12- year-old girls only)	912,889,441	7,363.10	1,441,571,988	1,037.21	**1,389,853**
II. 12- year-old boys + Current program	2,354,461,428	8,400.31			

Compared to the base case, the incremental costs are 22% lower, while the incremental effect remains unchanged. This resulted in an ICER of NOK 1.389 million/QALY, also approximately 22% lower than in the base case.

Comparison of the estimated epidemiologic impact of different HPV-vaccination strategies

We estimated and compared the reduction in the incidence of several HPV-related outcomes under different coverage assumptions:

1. Vaccination of girls aged 12 only, with 82% of every cohort receiving at least one dose (current situation).
2. Vaccination of girls aged 12 only, with 92% of every cohort receiving at least one dose.
3. Vaccination of boys and girls aged 12, with 82% of every cohort receiving at least one dose (the strategy in focus in this report).

The results are shown in the following table:

Table 29. Percentage reduction in the incidence rates of some HPV-related outcomes, 100 years horizon (2016-2115).

Outcome	Vaccination of girls aged 12 - 82% coverage	Vaccination of girls aged 12 - 92% coverage	Vaccination of girls and boys aged 12
Cervical cancer	22%	23%	25%
Vulvar cancer	48%	52%	57%
CIN 3	22%	24%	25%
Genital Warts (males)	69%	73%	82%
Genital Warts (females)	64%	69%	76%

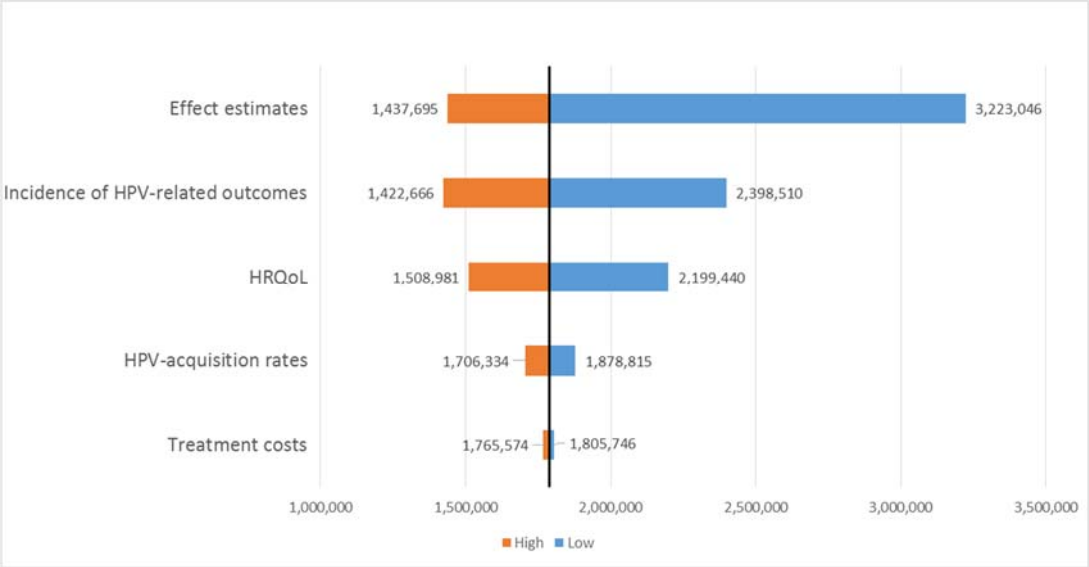
Depending on the outcome, including boys in the vaccination program led to incidence reductions after 100 years that were 1-9 percentage points higher than increasing coverage among girls and 3-13 percentage points higher than vaccinating only girls at the current coverage rate. The greatest incidence reduction accomplished by vaccinating boys was registered for genital warts among males, 82%. See Appendix 3. Vaccine effect for more results.

Tornado diagram

We examined how varying the values of groups of variables affected the ICER from a health-care perspective in one-way analyses.

The results of these analyses are plotted in Figure 11, in a Tornado diagram. The black, vertical line indicates the value of the base case ICER from a health-care perspective (NOK 1,789,463/QALY). The blue bars indicate the value of the ICER when the average value of all variables in a given group is reduced by 25%, while the orange bars indicate the value of the ICER when the average value of all variables in a given group are increased by 25%.

Figure 11. Tornado diagram. One-way analyses. Health-care perspective.



Changes in the vaccine effect estimates had the greatest impact on the base case results: When assuming a 25% higher relative risk (i.e. a lower vaccine effect in terms of relative risk reduction), the ICER experienced an 80% increase, while assuming a 25% lower relative risk led to a 20% decrease. This asymmetry is due to the fact that the ICER is the incremental cost times the reciprocal of the incremental effect, so that for a given positive incremental cost, a decrease in the positive incremental effect always has a greater (or at least equivalent) impact on the ICER than an increase.

The incidence rates of HPV-related outcomes was the next group of variables in this analysis with greatest effect on the ICER, with a 34% increase when assuming 25% lower incidence rates and a 20.5% decrease when assuming 25% greater incidence rates.

The HRQoL-loss relative to the general population baseline (k) had an impact on the ICER of approximately +23%/-16% for values of k 25% lower/greater than in the base case, while changes in the value of the HPV-acquisition rates and treatment costs had a substantially lower impact, +/- 5% and +/-1%, respectively.

Discussion

In this health-economic analysis we have evaluated the epidemiological impact and the cost-effectiveness of administering vaccination against HPV-infection to boys aged 12 in addition to the current practice of vaccinating girls aged 12, compared to maintaining the current practice.

Summary of results

In our base case analysis we assumed that 82% of all boys and girls aged 12 would get on average 2.54 and 2.78 doses of the HPV-vaccine, respectively. Furthermore, we assumed that the vaccine would only have an effect on the persistent infection, genital warts and precancerous lesions as documented in our own systematic reviews (26, 40), and extrapolated the effect on precancerous vulvar lesions to vulvar cancer and the effect on precancerous cervical lesions on cervical cancer and conization-related preterm births. Finally, the price of the vaccine was set equal to the maximum PRP of the quadrivalent vaccine, NOK 1,113.40/dose (NOMA, December 2014).

From a health-care perspective, the base case results showed that including boys in the current vaccination program would lead to a discounted, incremental cost of NOK 1.851 billion and an incremental health gain of 1,034.59 QALYs. This resulted in an ICER of NOK 1,789,463/QALY. The scatter plot of the ICER showed that both the incremental costs and the health gain were positive for all iterations.

The expected value of perfect information (EVPI) curve, which can be interpreted as the upper bound on the returns to further research about the costs and effect of a vaccination program for boys and girls, reached a maximum of approximately NOK 233 million at a WTP equivalent to the ICER. This means that if the expected costs of additional research are lower than these returns to the EVPI, then it could be cost-effective to conduct further research when the WTP is 1,789,463/QALY.

The ICER of vaccinating boys from a societal perspective is lower than from a health perspective. The incremental costs were approximately 9% lower, NOK 1.677 billion vs. NOK 1.851 billion in the public health-care perspective, while the incremental effect was the same, leading to an ICER of NOK 1,626,261 /QALY.

We conducted several scenario analyses to explore the effect of changing a variety of assumptions from the base case. The results were as follows:

- Using prices of NOK 250, 500 and 750/dose resulted in lower incremental costs and therefore lower ICERs of NOK 351,975/QALY, NOK 765,909/QALY and NOK 1,186,606/QALY, respectively.
- Excluding the vaccine effect on genital warts from the analysis resulted in both somewhat higher incremental costs and a considerably lower incremental health effect than in the base case. The ICER was then NOK 3,754,854/QALY. Assuming these results apply to the bivalent vaccine, and that the price of the quadrivalent vaccine is equal to the public price of NOK 1,113.40/dose, we estimated that the price of the bivalent vaccine had to be approximately NOK 550 /dose or lower in order to be as cost-effective as the quadrivalent vaccine.
- Increasing the first dose coverage among girls aged 12 from 82% to 92% instead of vaccinating boys of same age resulted in a 42% lower incremental effect and a 89% lower incremental cost than vaccinating boys. The ICER is then NOK 336,755/QALY, considerably lower than the ICER of the vaccination program for boys. The ICER of vaccinating boys and girls aged 12 at an 82% coverage rate vs. vaccinating girls only at a 92% coverage rate was approximately NOK 3.815 million/QALY.
- Ignoring all HRQoL-gains (reduction of morbidity) and focusing exclusively on lifetime gains (reduction in mortality) in terms of life-years gained (LYG) resulted in a 71% decrease in the nominal incremental effect of the program, compared to the base case (where reductions in both morbidity and mortality are taken into account). This may be due to the large HRQoL-gain associated preventing genital warts, an important outcome for males in our model. The lower incremental effect leads to a considerably higher ICER of approximately NOK 6.2 million/LYG.
- Incorporating the potential effect of the vaccine in reducing the number of cases of VaIN 2+ and vaginal and anal cancer, reduced the ICER to NOK 1,538,578/QALY.
- When excluding the vaccine effect in reducing the number of conization-related preterm births, the ICER increased to NOK 1,848,515/QALY.
- Assuming all vaccinated children get two vaccination doses each, led to an ICER of NOK 1,389,853/QALY, approximately 22% lower than in base case.
- Depending on the outcome, including boys in the vaccination program led to incidence reductions after 100 years that were 1-9 percentage points higher than increasing coverage among girls and 3-13 percentage points higher than vaccinating only girls at the current coverage rate. The greatest incidence reduction accomplished by vaccinating boys was registered for genital warts among males (82%).
- Finally, our one-way analyses showed that changes in the incidence of HPV-related outcomes and the HRQoL-losses associated with these outcomes had

a considerable impact on the cost-effectiveness results, although less than the impact of changes in the vaccine effect estimates. Changes in the HPV-acquisition rates and treatment costs had very limited impact on the results.

Context of results

As mentioned earlier (see Priority setting criteria), there is no official cost-effectiveness threshold value in Norway. This means that health authorities themselves, case-by-case have to ascertain whether the relationship between the costs and effectiveness of a health intervention/program are reasonable, and therefore whether they are willing to pay the required price per QALY or not.

In the course of this assessment, health authorities may choose to compare the resulting ICER-values with the values of other programs that previously have been subject of an economic evaluation and which were (or were not) implemented in the National Health Service. We have identified some recent decisions that may work as a basis for comparison:

- Dymista (flutikason) for the treatment of moderate to severe allergic rhinitis: The Norwegian Medicines Agency accepted in 2013 the uptake of Dymista in the list over preapproved medicines for outpatient treatment (blå resept) based on an ICER of NOK 72,000-124,000/QALY (59). The analysis was conducted from a limited societal perspective, i.e. when excluding the deadweight loss due to tax funding and the monetary value of lost working time due to sickness.
- Tasigna (nilotinib) for the treatment of chronic myeloid leukemia (CML): The Norwegian Medicines Agency accepted in 2013 the uptake of Tasigna in the list over preapproved medicines for outpatient treatment based on an ICER of approximately NOK 373,000/QALY, when evaluated from a limited societal perspective (60).
- Avastin (bevacizumab) for the treatment of advanced ovarian cancer: The four Norwegian Health trusts have in 2014 approved the use of Avastin (61). The ICER was between NOK 491,508-650,264/QALY (depending on the length of the follow-up in the clinical study) when evaluated from a limited societal perspective.
- Rotavirus vaccine: In 2014, the rotavirus vaccine was included in the children vaccination program in Norway, more specifically the monovalent vaccine (Rotarix). The ICER was NOK 687,000/QALY from a health-care perspective and NOK 27,500/QALY and from a societal perspective (62)
- Picato (ingenolmebutat) for the treatment of actinic keratoses on trunk and extremities: The Norwegian Medicines Agency rejected in 2014 the uptake of Picato in the list over preapproved medicines for outpatient treatment based on an ICER of approximately NOK 800,000/QALY, when evaluated from a limited societal perspective (63).

- Jevtana (kabazitaksel) for the treatment of metastatic, castration resistant prostate cancer: The four Norwegian Health trusts have in 2014 rejected the use of Jevtana based on an ICER of approximately NOK 1,400,000/QALY when evaluated from a limited societal perspective (64).

We made the list of examples in order to help the reader in contextualizing the results in this report. It is important to emphasize that this list must be interpreted with caution. The examples are not exhaustive as only decisions made in 2013-2014 are included. And perhaps most importantly, because other criteria than cost-effectiveness play an important role in the decision-making, the health gains of different patient groups may be valued differently by Norwegian health authorities.

An alternative approach when considering whether a health program is cost-effective or not is to compare the ICER of that program with an estimate of the actual cost per QALY in the health services. This alternative approach is closely linked to the concept of opportunity cost of scarce resources within a fixed health budget. Based on empirical data on health sector resource use and associated QALYs gain, researchers in the UK have estimated the NICE cost-effectiveness threshold to be £12,936/QALY (65). In this opportunity-cost framework, the implementation of an intervention with a cost per QALY gained higher than £12,936/QALY would lead to a net loss of QALYs because it would displace other interventions with a better cost per QALY ratio.

A similar cost-per-QALY value has not yet been estimated for the Norwegian health-care sector. The Norwegian Directorate of Health's conversion to the Norwegian setting of the UK estimate resulted in an ICER of approximately NOK 215,000/QALY (66). Thus, according to this approach, HPV-vaccination of boys and girls aged 12 at a price of NOK 1,113.4/dose, clearly would not be cost-effective compared to vaccination of girls only.

Strengths and weaknesses of this report

Data sources

Most of the epidemiological and costing data we used in this economic analysis were from Norwegian sources, strengthening the relevance of the results for a Norwegian setting. In addition, most of the data were retrieved from published literature or publicly available sources (such as the Cancer registry of Norway), which increases the transparency of our results.

Target population and sexual behavior

The results of our analyses are based on a simulated population in which sex with people of the same gender is not considered, i.e. the results may not apply to the same extent to women having sex with women and men having sex with men. The herd immunity effect may be particularly weak for unvaccinated men having sex exclusively with other unvaccinated men.

Mortality rates

We incorporated gender specific death rates (per 100 000-year) from Statistics Norway for 2013 and assumed that they would apply for the period 2016-2115. Alternatively, we may have assumed increasingly lower future mortality rates, as the Norwegian population has experienced a large increase in life expectancy since the Second World War (mainly because of reduced mortality in most age groups) and recent data indicates that this is a continuing trend (67).

Incorporating increasingly lower mortality rates in our model would mean that the number of persons in each age group would grow progressively, and the age at death, increase. This would imply a potentially higher number of prevented HPV-related health outcomes and therefore greater vaccine effect in the vaccinated cohorts.

However, the consequences of lower death rates would accrue far in the future and would be heavily discounted, limiting the effect on the relationship between total incremental costs and effects. Furthermore, the background mortality was slightly overestimated as we did not adjust it for HPV-related mortality (which is reflected in the QALY-losses caused by HPV-related outcomes). For example, cervical cancer mortality was 1.9 per 100,000 persons-year in 2012 (68).

Screening and vaccination

A key simplification of our model was to assume that current cervical cancer screening in Norway was reflected in the observed rates of cervical cancer that we applied in our model. We also assumed that vaccinated women would not change their behavior regarding compliance to the screening program.

HPV-acquisition probability rates

We lacked Norwegian data on the HPV 6/11, 16 and 18 acquisition probability rates among those experiencing infection for the first time. The only data we had was the prevalence rates for those same types, for females aged 17 and 21. To obtain acquisition rates we based our calculations on the Norwegian prevalence rates for those two age groups and the age profile of the acquisition probability rates in the original model (13).

More specifically, we assumed that the age profile of HPV-infection in Norway (although not the level) is similar to the one in the United States. If HPV-incidence for the vaccine types in Norway turns out to be lower than our estimates, we would expect higher incremental costs and a smaller health gain, resulting in a slightly higher ICER, as suggested by our results in the Tornado diagram.

Incidence rates of genital warts

The incidence rates for genital warts on which we based our calculations may underestimate the real incidence rates, as the original data in Kjær et al. (29) do not take into account recurrent genital warts episodes. This may underestimate the cost-effectiveness of the quadrivalent vaccines as recurrence rates observed in clinical trials of anogenital warts therapies range among studies and treatments, from 9% to 80% (28).

Effect estimates in the target population

We used the vaccine effect estimates for relevant HPV-related outcomes from our systematic review on catch-up HPV vaccination of young females (40) and on vaccination of boys (26), both of which included the latest findings in the literature for females and males. These findings showed that the vaccine had effect on cervical and vulvar precancerous lesions as well as on genital warts, and we incorporated these effects in our analysis. In addition, we assumed that the effect on precancerous lesions (CIN 2+ and VIN 2+) also applied to cervical and vulvar cancer despite not having found any evidence on this. This assumption is based on the expected relationship between precancerous lesions and cancer cases. If this relation does not exist or is weaker than assumed in our model, then the costs savings and the health

gain from the vaccination program for boys may be overestimated, and the ICER higher.

The effect estimates for precancerous lesions and genital warts are based on results from clinical trials that mainly included young women and men aged 16 and older. The effect estimates for these outcomes may be more favorable in our target population (boys and girls aged 12), in which the vast majority of the individuals not yet have been exposed to HPV infection. It is difficult to predict the impact on the ICER of vaccinating boys and girls: Although most probably it will result in a higher health gain among boys compared to no vaccination, it may as well lead to a lower incremental gain compared to vaccinating girls only.

The inclusion of potential prevented oropharyngeal, penile cancer and/or JoRRP cases most probably would lead to greater cost savings and a higher incremental effect, and thus to lower ICERs.

The time horizon of the model is an important variable when assessing vaccine programs as their consequences may take years to unfold, for example through the development of herd immunity. Short time horizons may ignore the long-term effects and consequences of the program while very long time horizons may not add relevant information beyond a certain point in time as the accrued effects and costs would be heavily discounted. We chose the same time horizon as in Chesson, i.e. 100 years, as we considered it long enough to capture all relevant consequences of introducing vaccination of boys from either a public health-care or societal perspective.

We assumed that the vaccine provided lifelong immunity, as we did not find any data indicating a waning effect. If the effect of the vaccine did decrease some years after vaccination, the incremental effect would probably fall and the incremental costs increase.

Finally, we did not incorporate cross-protection against other HPV-types than the ones targeted by the quadrivalent vaccine. If cross-protection does exist and is incorporated in our model, it would increase the number of HPV-related events prevented by the vaccine, thus increasing the effect and reducing the incremental costs of the vaccination program for boys, which in turn would result in a lower ICER. Alternatively, the ICER estimates would have been higher if we had included the potential increase in negative health outcomes caused by HPV types not protected against by vaccination, Chesson (24).

Costs

Ideally, resource use data and costs should come from studies following those who were vaccinated and those who were not in order to ascertain the differences between these groups. We were however unable to find such data. Instead, we based the average costs of treating lesions, cancer, genital warts and conization related outcomes in the model on the recommendations from Norwegian experts, public price lists, etc., which strengthens the transferability of the estimates to a Norwegian setting.

The number of doses per vaccinated female in our model is 2.78, lower than the average number of doses per female that results from using the actual, average vaccine coverage rates in Norway (for female cohorts born 1998-2001), currently at 2.91 doses. We did not however use 2.91 because 2.78 was the average number of doses that every vaccinated female received in the studies included in our systematic review (40), so that our effect estimates were associated to this particular vaccine consumption pattern and no other.

The model does not include the cost to the public health system of vaccine wastage or of administering each vaccine dose (in a recent economic evaluation of second generation pneumococcal conjugate vaccines in Norway (69), the authors used a vaccine administration cost of NOK 81/per dose). It does not include either the cost associated with increasing coverage among girls in that particular scenario. Nevertheless, one may use our price sensitivity analysis to approximate how the inclusion of these costs may affect the base case results for prices per dose between NOK 250 and 1,113.4). Suppose that these costs lead to a 10% higher cost per dose. Then, our model estimates that the ICER would be increased by 10.3% NOK/QALY (see Scenario Analyses for details).

The model does not incorporate the value of time spent by the patient's caregiver, which in the case of terminal cancer patients or newborns with serious sequelae due to a preterm birth, may be substantial. Incorporating the value of the saved caregiver's time in the analysis from a societal perspective may reduce the ICER of vaccinating boys from a societal perspective.

The calculation of costs from the societal perspective is based on several assumptions. We assumed that the alternative use of the time spent by the patient receiving treatment was leisure and not work. Furthermore, we did not include the productivity costs due to cancer morbidity, only those due to cancer mortality. Both assumptions may lead to an underestimation of the productivity costs due to HPV-related events. On the other hand, the productivity costs we included in our model assumed full employment in the relevant patient groups, which may overestimate the true productivity costs. Despite all these shortcomings, our analysis is, to our

knowledge, one of the few that includes such productivity costs in the assessment of HPV-vaccination of boys, giving a more accurate picture of the consequences for society of introducing a vaccination program for boys.

The exclusion of the VAT from treatment costs was made based on our own assessment of the size of the VAT-liable share, as we did not find nationwide data. More precise data on this share would increase the precision of the costs estimates.

We did not include transportation costs (car usage, train tickets, etc.) to patients and the health-care system, neither patient copayments when undergoing health treatment. Including these would reduce the ICER so that boy vaccination would appear to be more cost-effective.

Finally, in order to take all uncertainty around our estimates into account, we assigned distributions with wide confidence intervals to all average cost estimates.

HRQoL

With no published age or gender-specific EQ-5D data from the general Norwegian population, we chose to use the gender-neutral EQ-5D -weights from a Swedish population (55) as the baseline for the loss of HRQoL. For those studies that did not report a reference value, we used the baseline data in the calculation of the relative loss of HRQoL due to the health state. Consequently, the baseline data have a high impact on our calculations of the relative HRQoL-losses associated with different HPV-related outcomes. Although we did control for age by using the age-matched data for the reference population, our calculations did not statistically control for other potential sources of variation in HRQoL between the patients and the reference population. This adds to the uncertainty of the calculation of the relative loss of HRQoL, and may lead to an over- or underestimation of the QALY-loss associated with the HPV-related outcome. The strength of our approach is however that it is consistent across the different outcomes.

Since we did not find relevant weights for either VIN 2+, VaIN 2+, vaginal or vulvar cancer, the adverse events of the vaccine or the conization-related long-term consequences of preterm births, we made assumptions regarding the HRQoL-losses associated with these outcomes.

We did not identify any Norwegian HRQoL-data in the literature search, which may limit the transferability of the model results to a Norwegian setting.

The relative loss of HRQoL associated with a health state may vary with age (53). Our assumption of a fixed relative loss across all age strata, for all the outcomes may

as a result lead to an over- or underestimation of the QALY-loss for the young and old age groups. If one assume that the error is random across all the outcomes, the assumption may not lead to wrong estimates, but with no information regarding this relationship for our outcomes it is uncertain how large the error is and how we should have corrected for it.

All these factors taken together contribute to the uncertainty around our results. In order to consider this great uncertainty, we assigned distributions with wide confidence intervals to all QALY-losses (as we did with the average cost estimates). This may be one of several factors explaining the large variation of the incremental effect across model iterations, shown in Figure 6 and Figure 8**.**

Our results compared to other findings/other reviews

Several publications have examined the cost-effectiveness of male vaccination in different settings when taking into account both the direct and indirect (herd immunity) effect of the HPV vaccine.

One of these publications is a recent cost-effectiveness analysis of vaccinating boys in Norway by Burger and colleagues (12). They reported an ICER (from a societal perspective) of approximately NOK 363 000/QALY ($60,100/QALY) when using a price of NOK 450/dose ($75/dose) and NOK 706 000/QALY ($116,700/QALY) for a price of NOK 900 ($150/dose). These results are 41% and 45% (respectively) lower than our results for similar prices.

Several factors may explain why our ICER-estimates are higher (not exhaustive list):

- Burger et al. includes some outcomes in their base case we do not include, specifically, vaginal, anal, oropharyngeal and penile cancer, as well as juvenile recurrent respiratory papillomatosis.
- Burger and colleagues used ATP (According to Protocol), RRR estimates on HPV 6/11/16/18-related disease of 100% for females and 90% for males, considerably higher than the ITT estimates we used, with the lowest being 20% for CIN 2+ and the highest, 62% for genital warts among females.
- Burger et al. do not seem to include vaccination adverse events, while we do.

On the other hand, there are several factors suggesting that our ICER estimates should be lower than in Burger and colleagues (not exhaustive list):

- Burger et al. do not seem to include conization-related preterm births, while we do.

- Our estimates of the cost savings per avoided HPV-related outcome were generally higher.
- We applied our (lower) effect estimates on a greater share of each cohort, 82% vs. 71% in Burger et al.

The net impact of all these choices may explain why the ICER-results in Burger et al. were lower than in our analysis.

Kim and colleagues (16) assessed the cost-effectiveness of including boys in the HPV-vaccination program in the United States in addition to vaccination of girls and screening with cytology. Assuming a three-dose schedule and a price of approximately NOK 720/dose ($120/dose), they estimated that vaccinating 75% of all boys and girls aged 12 resulted in a ICER close to NOK 1.2 million/QALY ($200,000/QALY). This result applied from a societal perspective and is higher than ours for a similar dose price (approximately NOK 1 million/QALY).

Chesson and colleagues developed and used the model we adapted for Norway when they examined the cost-effectiveness of male HPV vaccination in the United States (13). They estimated that for a total cost (price per dose, administration and wastage) of approximately NOK 1,000/dose ($167/dose) and a coverage rate for all three doses of 75% (for both genders), the ICER of male vaccination in addition to vaccination of girls aged 12 was approximately NOK 2.6 million/QALY ($436,000/QALY) from a societal perspective. This result almost doubles ours for a similar price (approximately NOK 1.4 million/QALY), although it should be noted that their result was based on the assumption of no vaccine effect on outcomes other than cervical cancer, cervical precancerous lesions and genital warts (in both genders).

Elbasha and colleagues (14) assessed the cost-effectiveness of vaccinating boys and men age 9-26 compared to vaccinating girls and women only. For a price of approximately NOK 800/dose ($133/dose) and a coverage rate for the first dose of 80% by age 26 among women and 48% among men, the ICER of male vaccination in addition to female vaccination was approximately NOK 414,000/QALY ($69,000/QALY). This result applies when only including vaccine effect on cervical, vaginal and vulvar disease in addition to genital warts (in both genders), and it is considerably lower than ours for a similar price per dose (approximately NOK 1.1 million/QALY).

Based on the model by Elbasha and colleagues, a cost-effectiveness analysis of gender-neutral vaccination in Austria was published in 2014 (70). As mentioned earlier, Austria is the only country in the European Union where gender-neutral vaccination has been recommended. The results show that for a total cost per

vaccine dose (price and administration cost) of NOK 960 (€ 120), the ICER of vaccinating 65% of girls and boys aged 9 alongside cervical screening was NOK 126,560 (€ 15,820) compared to cervical screening alone (no vaccination). This result applied when including the effect of the vaccine on cervical, vaginal and vulvar cancer as well as genital warts.

Jit and colleagues (15) assessed the cost-effectiveness of vaccination of boys at age 12 in addition to girls. They estimated that for a total cost of approximately NOK 700/dose (£70/dose) and a coverage rate for the three doses of 80% among boys and girls aged 12, the ICER was approximately NOK 5.2 million/QALY (£520,255 /QALY) from a healthcare provider perspective. This ICER applies when including only the vaccine effect on cervical disease and genital warts (in both genders), and is considerably higher than our result for a similar price (approximately NOK 1.1 million/QALY).

Pearson and colleagues (71) examined the cost-effectiveness of adding vaccination of boys aged 12 to the girls vaccination program in New Zealand. Their results show that for a total cost per vaccine dose (price and administration cost) of NOK 1,362-1,448 (NZD 239-254), the ICER of vaccinating 45-56% of girls and boys aged 12 vs. only vaccinating 45-56% of girls aged 12, was NOK 672,600 (NZD 118,000). The ICER of vaccinating 73% of girls and boys aged 12 vs. only vaccinating 73% of girls aged 12, was NOK 1,407,000 (NZD 247,000). These results applied when including the effect of the vaccine on cervical, vulvar, oropharyngeal and anal cancer, as well as CIN 1, 2 and 3 and genital warts.

Conclusion

From both perspectives and given the current public price of NOK 1,113.4/dose of the quadrivalent vaccine, vaccinating boys in addition to girls aged 12 years is probably not cost-effective. The incremental ICER was NOK 1,789,463/QALY from a health care perspective and NOK 1,626,261/QALY from a societal perspective.

Although there is no official cost-effectiveness threshold value in Norway, such high ICERs are generally associated with the intervention not being accepted for implementation in the Norwegian health sector.

The price scenario analysis shows that a lower price per vaccine dose has a major, positive effect on the cost-effectiveness of the program.

Increasing coverage among girls aged 12 from 82% to 92% seems to be more cost-effective than vaccinating both boys and girls at coverage rate of 82% (when only taking into account the cost of purchasing additional vaccine doses).

Finally, the price of the bivalent vaccine should not be higher than approximately NOK 550/dose for it to be deemed as cost-effective as the quadrivalent.

Need for further research

Our systematic review revealed the lack of reliable data regarding the effect of the vaccine on cancer. In addition, the knowledge we have on the duration of the vaccine effect on precancerous lesions and genital warts is limited. Furthermore, new studies enrolling participants of ages closer to that of the target population in the Norwegian HPV-vaccination program (12 years old) would help to reduce the uncertainty around the transferability of our results. These are very important issues, as our one-way analyses showed that changes in vaccine effect estimates had a great impact on the cost-effectiveness results.

Finally, there is a need for more EQ-5D data of high quality on the HRQoL of HPV-related outcomes as well as Norwegian general population data with the EQ-5D instrument.

Implications for practice

The annual target population of a vaccination program for boys consists of approximately 25 420 boys (82% of each cohort, which by January 2014 consisted of approximately 31 000 boys).

If the mean coverage rate reaches 82% for the first dose, 69.3% for the second dose and 56.7% for all three doses, approximately 121 000 additional doses will be required every year to implement HPV-vaccination of boys aged 12, starting in 2016.

At the current maximum PRP (NOK 1,113.4/dose), that implies an additional expense of approximately NOK 135 million per year. For more details regarding this calculation, see Appendix 6. Estimation of the vaccine expenditures associated with the implementation .

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Appendices

Appendix 1. On the inner workings of the Excel model

The model calculates the differences in health effects and costs between the chosen intervention and no vaccination (the situation in Norway before 2009). This means that in order to examine the differences between the current situation in Norway and a potential program of vaccinating boys beginning in 2016, the model had first to be run 1 000 times the comparison of each of these interventions against the "no vaccination" option. Then the results for these two separate comparisons were collected and compared to calculate the relevant ICER.

Appendix 2. Epidemiological data

HPV 6/11, 16 and 18 annual acquisition probabilities in the absence of vaccination used in the original model

To estimate type-specific acquisition probabilities, Chesson and colleagues (13) used age-specific probabilities of acquisition of high risk HPV types from previously published models, smoothed the data to allow for gradual changes and finally used US-data about the percentage of high risk HPV infection attributable to HPV 16 and 18.

For HPV 6 and 11 they used a combined probability of infection. The annual probability of HPV 6/11 acquisition has previously been estimated at approximately 2% for women aged 18 to 35 years, and the annual probability of HPV 6 acquisition has been estimated at approximately 2.5% for sexually-active, college-aged women. Chesson and colleagues then applied these estimates as follows: They assumed that the annual probability of HPV 6/11 infection would be 0% for ages 9 years and younger, 2% for ages 10 to 16 years and ages 24 to 29 years, and 3% for ages 17 to 23 years. They assumed that the annual probability of HPV 6/11 acquisition for ages 30-34 years would be 25% less than that of ages 25-29 years, and that the same 25% reduction would hold for subsequent five-year age groups. This 25% reduction in

HPV 6/11 acquisition probabilities was based on the approximate relative reduction in the probability of genital warts with age.

They then smoothed these HPV acquisition probabilities to allow for gradual changes in the probability of HPV acquisition with age, using a process similar to that described above for HPV 16 and HPV 18. Age-specific acquisition probabilities for women over age 60 years were estimated by assuming that the probability of HPV 6/11 acquisition would decrease by 10% annually after age 60.

HPV 6/11, 16 and 18 annual acquisition probabilities in the absence of vaccination used in the Norwegian model

Because we did not have access to the data that Chesson and colleagues used to estimate these probabilities for the United States, we estimated the acquisition probabilities for Norway through the prevalence rate of the respective HPV-type in Norway.

The only Norwegian prevalence data we had was yet unpublished data about HPV-prevalence in females aged 17 and 21 years in 2014 from the Norwegian Institute of Public Health. In order to estimate the prevalence rates for all age groups we first estimated the prevalence of each HPV-type in the United States as described in Chesson (13). Then, based on the relationship between our two Norwegian point estimates and the estimated prevalence in the United States at age 17 and 21, we extrapolated to obtain the Norwegian prevalence for age group between 8 and 16 and 22 and 85, and interpolated to obtain the prevalence for age group 18, 19 and 20.

Once we had estimated the Norwegian prevalence rates per age group, we were able to calculate the acquisition probabilities by reversing the calculations in the original model. We thereby assumed that the HPV 6/11, 16 and 18 infection time-profile and the relationship between prevalence and incidence rates in Norway is the same as in the United States, more specifically that the annual probability of infection clearance was 0.45 for HPV 16 and 18 and 0.75 for HPV 6/11.

Percentage of health outcomes attributable to different HPV types

Table 30 shows the percentages attributable to different HPV types that were used in the original model (for those outcomes included in the Norwegian adaptation). These determine to the degree to which the number of total cases of each outcome

may be reduced by vaccination. Totals below 100% indicate that these four HPV types are not the sole reason for these outcomes.

Table 30. Percentages of health outcomes attributable to HPV 6/11, 16 and 18. Original model

Health outcome	HPV 6/11	HPV 16	HPV 18	Total
CIN 2	-	53.80%	4.80%	*58.60%*
CIN 3	-	53.80%	4.80%	*58.60%*
Cervical cancer	-	58.00%	12.00%	*70.00%*
Vulvar cancer	-	39.60%	4.40%	*44.00%*
Vaginal cancer	-	39.60%	4.40%	*44.00%*
Anal cancer (both genders)	-	79.80%	7.20%	*87.00%*
Genital warts	90.00%	-	-	*90.00%*

In our model, we used other percentages, see Table 31:

- For cervical cancer, CIN 2 and 3 and genital warts we used 100%, because all these outcomes are HPV-related (8, 72) and our effect estimates applied independently of which HPV-type caused them.
- For vulvar cancer we used 90% because it is the share of vulvar cancers that are squamous cell carcinomas (73), close to 100% of all squamous cell carcinomas take place after development of VIN (personal communication with Ingvild Vistad) and our effect estimate on VIN applies to all types of VIN (not only to those HPV-related, which are approximately 60% (73).
- For vaginal cancer (only examined in a sensitivity analysis) we used the same percentage as for vulvar cancer, due to similar etiologies.
- For anal cancer (only examined in a sensitivity analysis) we used 82.8%, based on data from the United States suggesting that 90% of all anal cancers are due to previous HPV-infection, of which 92% were due to HPV 16 and 18 (8). We multiplied 90% by 92% because our effect estimate on precancerous anal lesions (AIN 2+) applied only to those which were HPV 16 and 18-related.

In order to estimate the percentages attributable to HPV 6/11, 16 and 18, we took into account the proportions between these HPV-types in Chesson (13). The results are shown in Table 31.

Table 31. Percentages of health outcomes attributable to HPV 6/11, 16 and 18. Norwegian model

Health outcome	6 and 11	16	18	*Total*
CIN 2	-	91.81%	8.19%	*100%*
CIN 3	-	91.81%	8.19%	*100%*
Cervical cancer	-	82.86%	17.14%	*100%*
Vulvar cancer	-	81.00%	9.00%	*90%*
Vaginal cancer*	-	79%	11%	*90%*
Anal cancer (both genders)*	-	76%	6.8%	*82.8%*
Genital warts (both genders)	100%	-	-	*100%*

* Used only in scenario analysis

Incidence rates of genital warts

We based our calculations on data for the youngest cohort in the dataset from Kjær (29), i.e. those born between 1979 and 1986, as we assumed that their infection time-profile would reflect the pattern for future cohorts in the most accurate way. This may overestimate the burden of genital warts among cohorts born before 1979. On the other hand, we may underestimate the burden among future cohorts, as the cumulative incidence has grown rapidly over the last 30 years: For example, while the cumulative incidence in the cohort born 1964-68 first reached 12% at an average age of 42, that value was reached in the cohort born between 1979-86 at an average age of 27.

We had data on the 1979-86 cohort until they reached age 27. From this point, we assumed the cumulative incidence curve would level out as the cohort aged, as was the case for the previous cohorts, reaching 16% at age 45. We then assumed the cumulative incidence grew at an annual rate of 0.5% from age 45-60, then at 0.25% from age 61-80, with no further growth beyond age 80. It should be noted that this age profile, while hypothetical, yields a flatter time profile than the ones registered for the older cohorts, i.e. it may be an optimistic forecast of the burden of genital warts among future cohorts.

In order to estimate the incidence rates of genital warts, we first calculated the survival curve S(t) from the cumulative incidence rate in age group in Kjær (29). This is possible because the cumulative incidence can be defined as F(t), the cumulative distribution function, which is the complement of S(t). Based on the literature (74), we then assumed that the incidence rate in every age group was equivalent to the hazard function h(t) for that age group, defined by the formula:

$$h(t) = -\frac{d}{dt}[log\ S(t)]$$

Conization-related preterm births

Albrechtsen (34) reported data from Norway showing that 141 371 births were registered as preterm births in the period 1967-2003. Of these, 769 took place before week 33 of gestation and among mothers having undergone conization prior to pregnancy. This is equivalent to 0.0344% of all births in that period. Although a woman may have given birth to several of these children, this fact does not change the conclusions of this analysis, as what we are interested in is the consequences for the newborn.

Table 32. Births in Norway, 1967-2003

	Births before cervical conization	Births after cervical conization	No cervical conization	TOTAL
Normal	53,326	12,514	2,029,039	**2,094,879**
Late Abortion	209	226	8,501	**8,936**
week 24-27	263	234	7,757	**8,254**
week 28-32	614	535	22,945	**24,094**
week 33-36	2,724	1,599	95,764	**100,087**
TOTAL	**57,136**	**15,108**	**2,164,006**	**2,236,250**

In Table 33 we present the distribution of births per outcome, according to the mother's conization status, in order to examine whether there is a correlation between these two variables:

Table 33. Share of births per outcome, according to mother's conization status

	Births before cervical conization	Births after cervical conization	No cervical conization
Normal	93.33%	82.83%	93.76%
Late Abortion	0.37%	1.50%	0.39%
week 24-27	0.46%	1.55%	0.36%
week 28-32	1.07%	3.54%	1.06%
week 33-36	4.77%	10.58%	4.43%
TOTAL	**100%**	**100%**	**100%**

Source: Albrechtsen (34). Tables 1 and 2

Table 34. Preterm deliveries before week 33 and after conization, 1967-2003

Number of deliveries before week 33 and after cervical conization	769 = (234 + 535)
As % of total number of deliveries	0.0344%

The data show an increased frequency of preterm births among mothers that underwent conization before giving birth, while the two other groups' shares are almost identical. Were the frequency among births after conization equivalent to the frequency in for example the no conization group, the shares would have looked more as shown in Table 35:

Table 35. Births after conization if shares were similar to the situation without conization

	Births after cervical conization (1967-2003)	**Shares from births other than after conization**
Normal	14 164	93.75%
Late Abortion	59	0.39%
week 24-27	55	0.36%
week 28-32	160	1.06%
week 33-36	670	4.43%
TOTAL	**15 108**	**100%**

Source: Own calculations

In this hypothetical case, the number of deliveries before week 33 would be 215 (late abortions not included), equivalent to 0.0096% of all births. This means that only 0.0248% (= 0.0344% - 0.0096%) of all preterm births may with some certainty be attributed to the fact that the mother had a conization before pregnancy. Given that 58 991 births were registered in Norway in 2013 (SSB), 0.0248% of these means approximately 15 births.

Table 36. Estimated annual number of preterm deliveries exclusively due to conization

Excess share of preterm delivery due to previous conization	0.0248%
Expected annual number of living babies delivered before week 33 exclusively due to conization (2013)	14.62

Source: Own calculations

Furthermore, we assumed that all conizations are carried out to exclusively treat CIN 2 and 3, which is a simplification as other females, e.g. some cervical cancer patients may have conizations.

Based on the percentages of health outcomes attributable to HPV 16 and 18 mentioned earlier, we assumed that approximately 0.0228% of all births in a given year are preterm births or late abortions due to HPV-16 infection and 0.0020% due to HPV-18 infection.

Table 37. Estimated annual share of total deliveries resulting in conization-related preterm delivery, due to infection with HPV 16 or 18

Preterm critical deliveries due to conization before pregnancy, as % of total yearly deliveries	0.0248%
Share of CIN 2 and 3 cases due to HPV-16 infections	91.81%
Share of CIN 2 and 3 cases due to HPV-18 infections	8.19%
Share of total deliveries that result in conization-related preterm deliveries due to HPV-16 infections	0.0228% = 91.81% * 0.0248%
Share of total deliveries that result in conization-related preterm deliveries due to HPV-18 infections	0.0020% = 8.19% * 0.0248%

Source: Own calculations

Birth rates

Population and birth data from Statistics Norway for 2013 allowed us to calculate the birth rate per 1 000 women-year:

Table 38. Birth rates (living babies) per 1 000 women-year. Norway, 2013

Age	Rate
< 14	0
14	0
15	0.45
16	1.19
17	3.80
18	8.03
19	14.67
20	25.12
21	35.28
22	46.91
23	60.07
24	74.20
25	90.71
26	103.62
27	118.08
28	129.14
29	136.54
30	135.29
31	132.36
32	125.46
33	111.71
34	101.90
35	84.49
36	68.28
37	54.88
38	44.58
39	34.36
40	21.62
41	14.22
42	8.97
43	5.52
44	3.07
45	1.34
46	0.51
47	0.11
48	0.12
49	0.18
50 +	0.00

Death rates

Table 39 contains the death rates (number of per 100 000) that were used in the model (54).

Table 39. Death rates (all causes) per 100 000 in Norway by gender and age (2013).

AGE	male	female
8	0.000096	0.000067
9	0.000064	0.000067
10	0.000065	0.000068
11	0.000098	0.000068
12	0.000095	0
13	0.000031	0.000032
14	0.000031	0.000033
15	0.000092	0.000065
16	0.000208	0.000063
17	0.000382	0.000251
18	0.000562	0.000284
19	0.000503	0.000315
20	0.000612	0.000219
21	0.000401	0.000245
22	0.00071	0.000208
23	0.000454	0.000206
24	0.000857	0.000236
25	0.000698	0.000267
26	0.000643	0.000181
27	0.000786	0.000182
28	0.000587	0.000304
29	0.000872	0.000152
30	0.000687	0.000273
31	0.00072	0.000273
32	0.000634	0.000335
33	0.000715	0.000427
34	0.001122	0.000369
35	0.000934	0.00053
36	0.00102	0.000622
37	0.000795	0.000453
38	0.001018	0.000493
39	0.001016	0.000597
40	0.000994	0.000782
41	0.001391	0.000819
42	0.001474	0.000739
43	0.001387	0.000598
44	0.001429	0.001134

45	0.001298	0.00099
46	0.001498	0.001206
47	0.001771	0.00142
48	0.002419	0.001181
49	0.002528	0.001532
50	0.002561	0.001824
51	0.002728	0.002144
52	0.002893	0.002673
53	0.003383	0.001961
54	0.004341	0.00285
55	0.004715	0.00352
56	0.00439	0.002985
57	0.005818	0.003135
58	0.006434	0.002978
59	0.007366	0.004895
60	0.007311	0.0045
61	0.008175	0.004714
62	0.008529	0.006021
63	0.009378	0.006425
64	0.009898	0.006584
65	0.011225	0.006609
66	0.013434	0.008739
67	0.014621	0.009125
68	0.015681	0.010619
69	0.017909	0.01104
70	0.017038	0.010893
71	0.019852	0.012732
72	0.022663	0.015816
73	0.02568	0.015062
74	0.030465	0.018348
75	0.030049	0.021472
76	0.03769	0.023291
77	0.039534	0.023382
78	0.047437	0.030397
79	0.050946	0.033258
80	0.057326	0.037995
81	0.064659	0.044925
82	0.077209	0.047989
83	0.082587	0.048556
84	0.098683	0.062748
85	0.101422	0.077072
86	0.118107	0.085463
87	0.126848	0.095172
88	0.134726	0.104406

89	0.168743	0.122018
90	0.173041	0.13587
91	0.195858	0.156155
92	0.224793	0.168204
93	0.237834	0.194634
94	0.218281	0.216784
95	0.280574	0.252001
96	0.333555	0.256672
97	0.31365	0.299806
98	0.310407	0.311992
99	0.36691	0.314446

Appendix 3. Vaccine effect

Calculation of the number of avoided HPV-related outcomes in the model

We calculated the number of avoided HPV-related outcomes (N) for each independent cohort (of males or females) at age "a" and year "t" of the vaccination program using the following formula:

$$N_{a,t,x,lag} = R_a * \left(\frac{POP_{a,t}}{100{,}000}\right) * (ATTRIB_X) * \left(C_{g,a-lag,t-lag}\right) * AR$$

Where:

- R_a is the rate of the outcome (per 100,000-year) in age group "a" in the absence of vaccination,
- $POP_{a,t}$ is the number of females/males in age group "a" at time "t",
- $ATTRIB_X$ is the percentage of the outcome attributable to the relevant HPV type,
- $C_{g,a,t}$ is the reduction (for gender "g") in the cumulative acquisition of the relevant HPV type due to vaccination as estimated by the infection model,
- "Lag" is a disease-specific lag term.
- AR is the adjustment ratio, used to adjust the effect of the vaccine.

The lag term and AR are explained more in detail below.

The lag term

The lag term was included by Chesson and colleagues in the original model to establish a minimum time between vaccination and the prevention of a given health

outcome. Although protection against the HPV vaccine types was assumed to begin after completion of the vaccine series, the authors applied the lag term so that the adverse health outcomes averted by vaccination would accrue over a plausible time frame.

For cervical and other cancers, the authors used a minimum lag time of 5 years such that reductions in cancer for a given age cohort would not be observed in the first 5 years in which members of that cohort were vaccinated. The lag term applied was 1 for CIN 1, 2 for CIN 2, 3 for CIN 3, and 0 for genital warts. We have used these same lags in the Norwegian model,

Chesson and colleagues examined the impact of alternative lags on the results for the cost-effectiveness of male vaccination and they did not change substantially when no lag term was applied or when the lag terms for all health outcomes were doubled.

Adjusting the vaccine effect with AR

As mentioned earlier, we performed a systematic review to obtain data on the effect of the vaccine on persistent infection with HPV 6/11, 16 and 18 as well as precancerous lesions and genital warts. The results showed that the effect of the vaccine was different across health outcomes, so we adjusted the results of the model as explained in Chesson (13), appendix 1, page 11. This adjustment allowed us to approximate the value of avoided costs and QALY-losses associated with the reduction in HPV-related health outcomes.

More specifically, we calculated the ratio of relative risk reductions (RRR) between the vaccine effect on each health outcome and on persistent HPV 6/11, 16 and 18-infection for every iteration of the model, and then multiplied this adjustment ratio (AR) by the number of avoided HPV-related outcomes in that iteration. For example, if in a given iteration of the model, the vaccine leads to a RRR for persistent infection of 70% but only 25% for CIN 3, then the ratio (0.25/0.7 = 0.3571) would be multiplied by the number of avoided CIN 3 cases, as calculated by the infection model (see above).

Moreover, the effect estimate on persistent infection applied for a one-year period, while the estimates of the vaccine effect on CIN 2+, VIN 2+ and genital warts are all calculated at three to four years. In order to apply the adjustment we assumed that the latter effect estimates also applied to annual periods of time.

Diagrams of the estimated yearly epidemiologic impact of vaccination of boys

We estimated the yearly percent reduction in the population incidence of several HPV-related outcomes (cervical and vulvar cancers, CIN 3 and genital warts) during the first hundred years after the implementation of vaccination of boys in addition to girls aged 12. For this analysis, all variables were assumed to be deterministic.
In order to estimate the yearly percent reduction for each relevant HPV-related outcome, we used the following formula:

$$Reduction_t = \sum_b \left[\sum_a \left[CI_{g,a,b} * AR * Age\ incidence\ share_{g,a} \right] * (HPV\ incidence\ share_b) \right]$$

Where:
- **t:** Program year (1 ≤ t ≤ 100)
- **a:** Age.
- **g:** Gender.
- **b:** HPV-type (6/11, 16 or 18).
- **CI:** Reduction in cumulative exposure to HPV type "b", given age “a” and gender “g”.
- **AR:** Outcome-dependent adjustment of the vaccine effect on HPV-acquisition (see discussion above).
- **Age incidence share:** Gender-dependent share of the total average number of cases (2002-2012) registered in the group of age “a”.
- **HPV-incidence share:** Share of the number of cases of the relevant outcome caused by HPV-type "b".

Comparison of the estimated epidemiologic impact of different HPV-vaccination strategies

Following the method above, we estimated the reduction in several HPV-related outcomes under three different vaccination strategies, in the 100 years period after introduction (2016-2115):

1. Vaccination of girls aged 12 only, with 82% of every cohort receiving at least one dose (current situation).
2. Vaccination of girls aged 12 only, with 92% of every cohort receiving at least one dose.
3. Vaccination of boys and girls aged 12, with 82% of every cohort receiving at least one dose (the strategy in focus in this report).

Our results show that most of the vaccine effect (in terms of incidence rate reduction) of vaccinating boys aged 12 would be obtained by increasing coverage

among girls aged 12. The only exception to this observation is the incidence of genital warts among males, which experiences a greater reduction, probably thanks to the direct protective effect of vaccination among males (see figures below):

Figure 12. Reduction in genital warts incidence among females from year 1 to 100

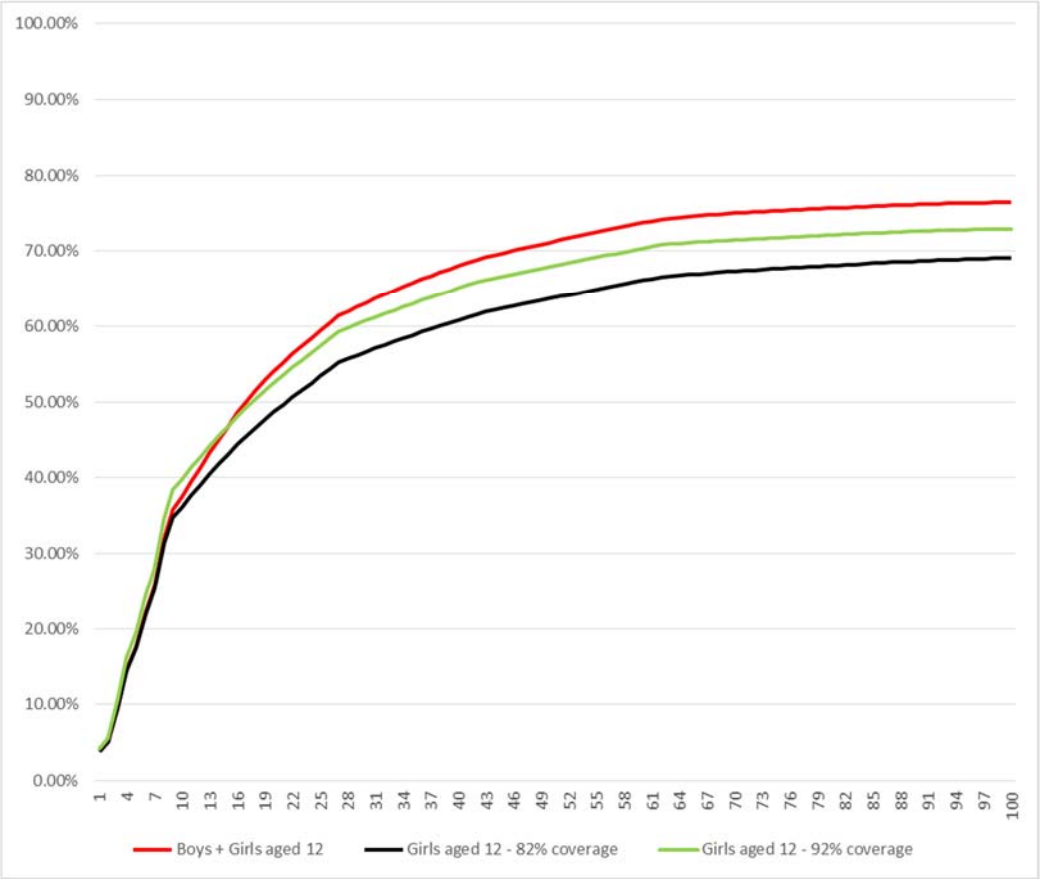


Figure 13. Reduction in genital warts incidence among males from year 1 to 100

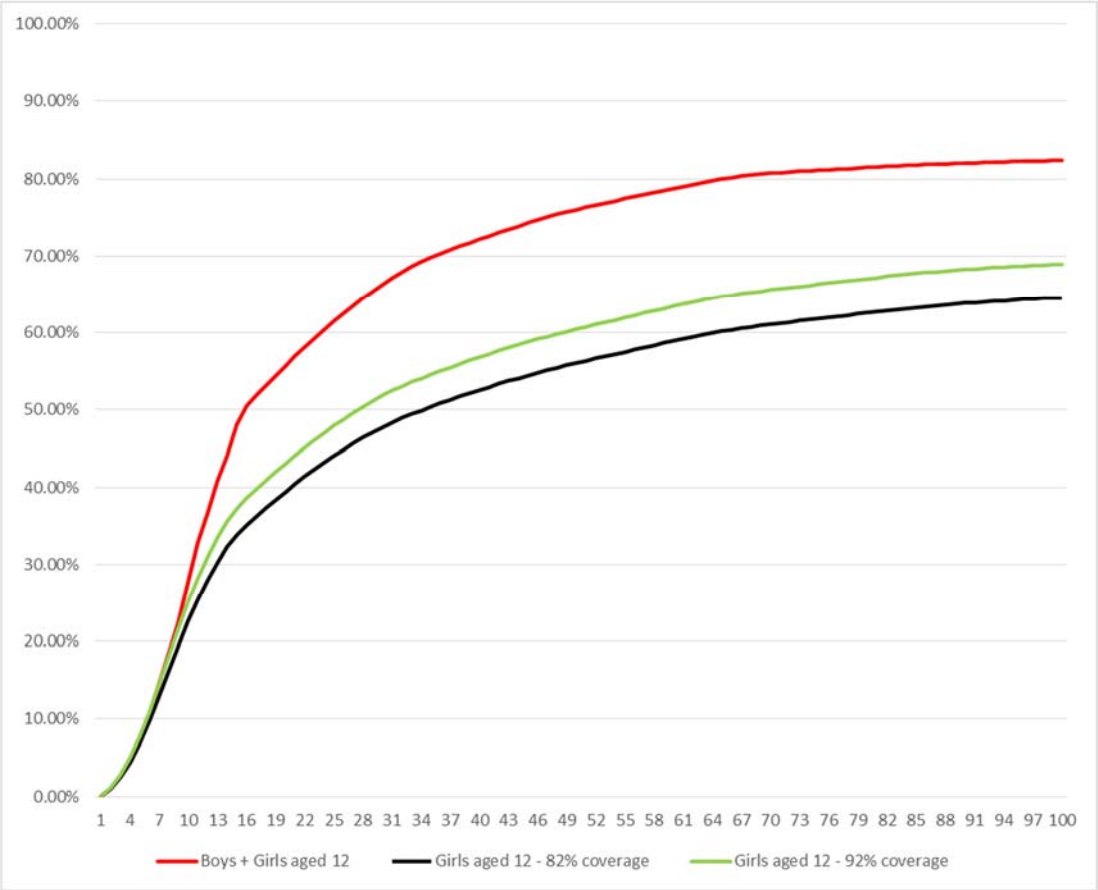


Figure 14. Reduction in vulvar cancer incidence from year 1 to 100

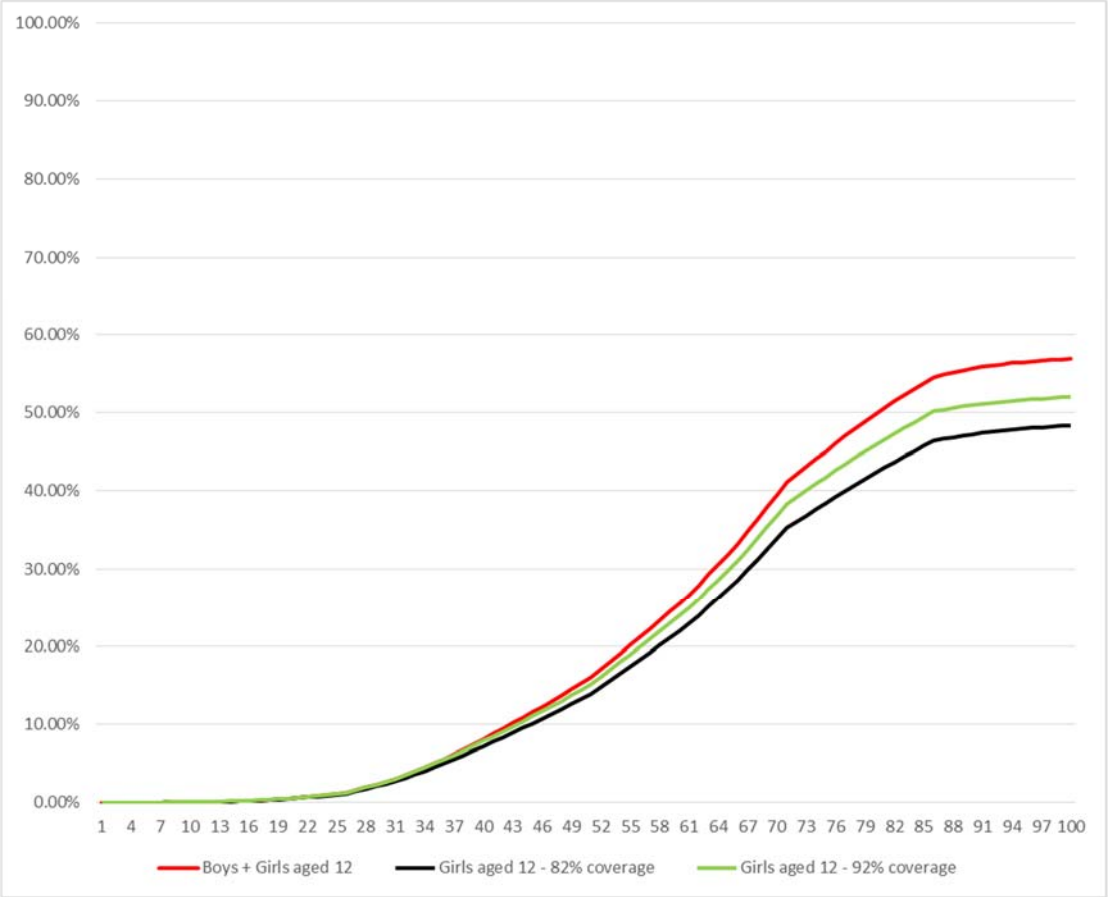


Figure 15. Reduction in cervical cancer incidence from year 1 to 100

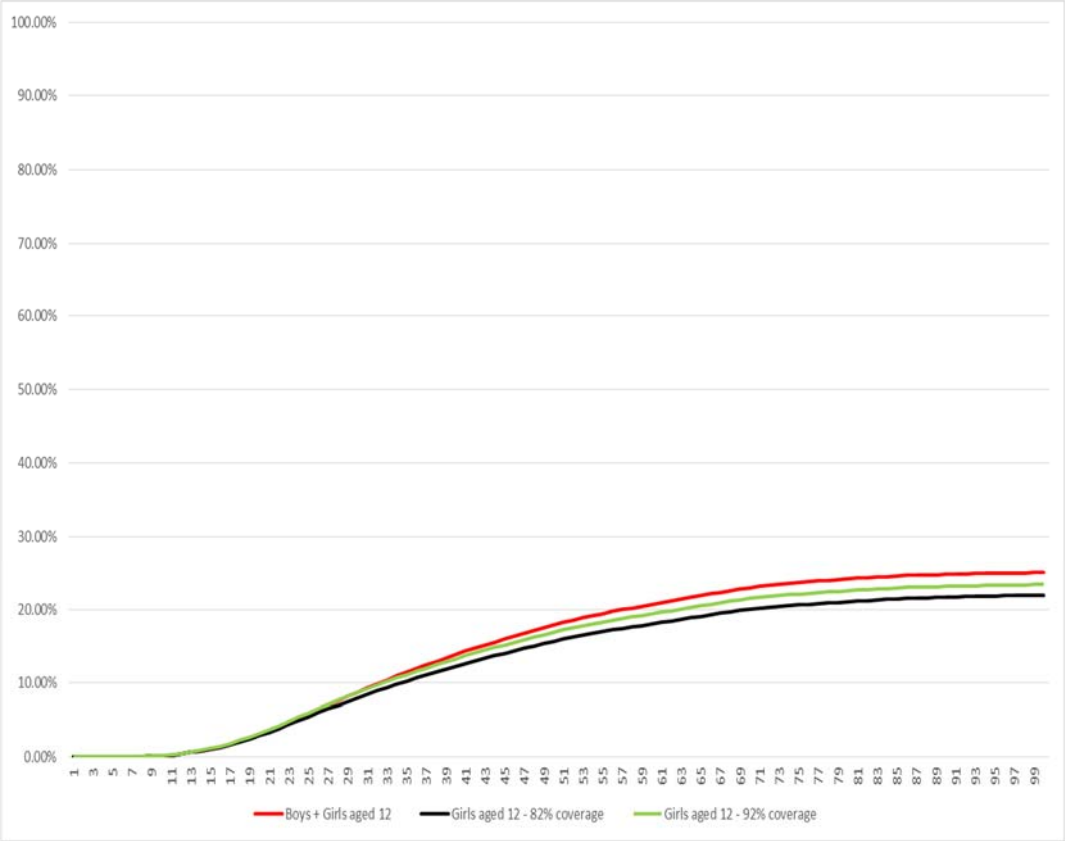
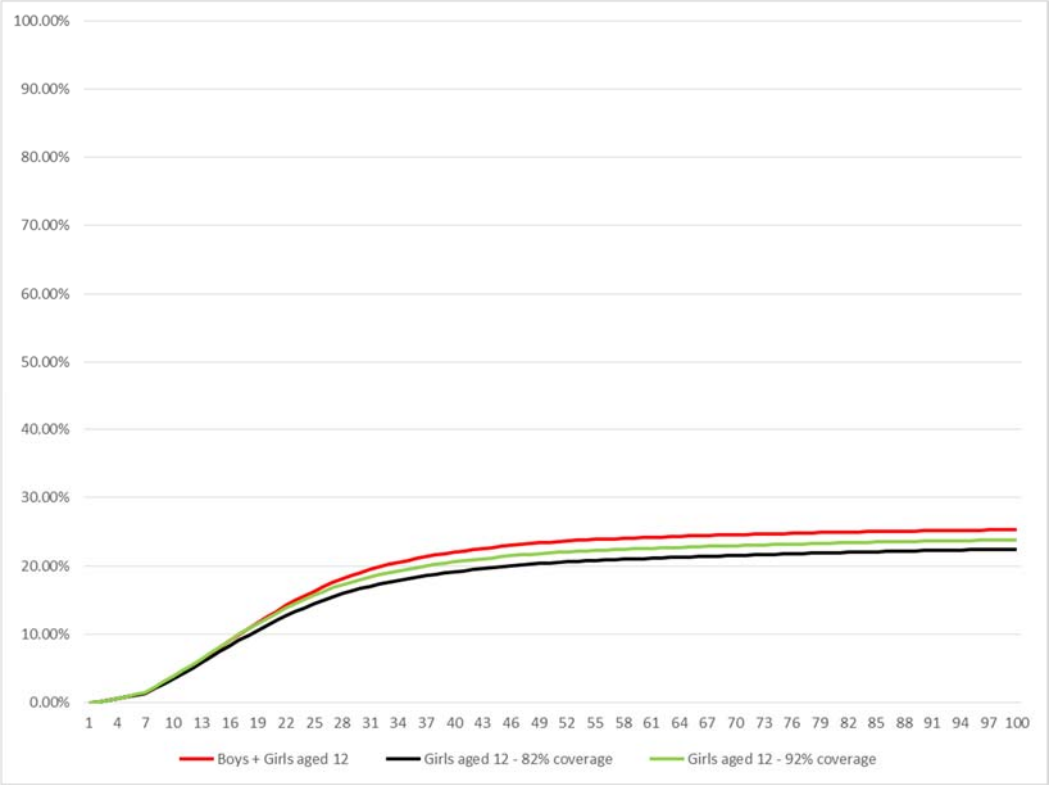


Figure 16. Reduction in CIN 3 incidence from year 1 to 100



Appendix 4. Costs

Vaccination costs

As described earlier, the vaccination costs are calculated as the product of the vaccine price per dose and the number of doses administered. The price used in the base case from a public health-care perspective was the maximum pharmacy retail price (PRP) of the quadrivalent vaccine in December 2014, NOK 1,113.4/dose (41) . From a societal perspective, we excluded the VAT from the public price (i.e., the price was divided by 1.25).

For the calculation of the number of administered doses per patient we used the number of ITT- and PPP-participants in the main studies in our systematic reviews (26, 40). We did this to match the effect estimates as reported in the studies with the estimated number of doses needed to achieve that effect.

More specifically, for girls we retrieved from these studies the share of the ITT-population that received three doses (i.e. the PPP-population) and calculated a weighted average of these shares, with the weights being the number of patients in

the ITT-population in each study. The result was 85.3%. The rest of the ITT-population, 14.7%, was assumed to be equally distributed between those that received one or two doses only, i.e. 7.35%.

Table 40. Share of ITT-female population receiving all three doses in a selection of studies

Study	ITT-population	PPP	Share of ITT population receiving 3 doses	Weight	Weighted share
Future I (42)	5 455	3 745	69%	12.7%	8.7%
Future II (43)	16 805	15 261	91%	39.1%	35.5%
Patricia (45)	18 644	16 162	87%	43.4%	37.6%
Future p 19 (44)	2 067	1 505	73%	4.8%	3.5%
SUM	***42 971***	***36 673***	***SUM***	***100.0%***	***85.3%***

We calculated then the average number of doses per vaccinated female as follows:

Table 41. Estimated share of the female ITT-population receiving one, two or three doses

Number of doses	Share of ITT-population	Weighted number of doses
1	7.35%	0.07
2	7.35%	0.15
3	85.3%	2.56
SUM	***100%***	***2.78***

For boys we conducted a similar analysis as for girls, this time based on data from Giuliano (46), which was identified when conducting our systematic review of male HPV-vaccination studies. Giuliano and colleagues reported that 69% of the ITT population received all three vaccine doses.

Table 42. Share of ITT-male population receiving all three doses in a selection of studies

Study	ITT-population	PPP	Share of ITT population receiving 3 doses
Giuliano (46)	4 055	2 805	69%

The rest of the ITT-population, 31% was assumed to be equally distributed between those that received one or two doses only, i.e. 15.5%. This resulted in an average of 2.54 doses per boy:

Table 43. Estimated share of the male ITT-population receiving one, two or three doses

Number of doses	Share of ITT-population	Weighted number of doses
1	15.5%	0.16
2	15.5%	0.31
3	69%	2.07
SUM	***100%***	***2.54***

Average cost per HPV-related outcome

We calculated an average cost per patient and outcome, so that both the differences in treatment course and the probability of diagnosis and treatment outcomes were taken into account.

As described earlier, each of the costs per prevented outcome consists of a series of inputs (diagnostic procedures, doctor payments, surgical procedures, medicines, patient travel time, etc.) classified according to disease and treatment stage. As the detailed explanation of how the cost of each outcome was estimated would be too lengthy to be included in this report, we decided for the sake of brevity to go through the estimation of the cost per cervical cancer case and use it as example of how the rest of the costs per outcome were estimated.

The choice of outcome is not arbitrary as cervical cancer is one the most important outcomes to consider when evaluating a HPV-vaccination program. Additionally, the estimation of the costs per cervical cancer case proved to be the most complicated in the model, due to the heterogeneity of the course of the disease and its treatment.

Ingvild Vistad, gynecologist at the Sørlandet sykehus HF, provided assistance in estimating costs, although we are responsible for the final choice of values.

For cervical cancer, as for all other cancer forms included in the model, we divided the treatment into four consecutive phases: Medical assessment, primary treatment, secondary treatment and follow-up.

i. *Medical assessment:*
   This phase starts after the patient has tested positive for atypical squamous cells of undetermined significance (ASC-US)/Low grade squamous intraepithelial lesion (LSIL) at the mass cervical cancer screening program.

The patient would undergo cytology and an HPV-test, which requires a visit to her general practitioner (GP). If the results show high-grade cytology (regardless the result of the HPV-test) or AS-US/LSIL and positive HPV-test result, the patient would undergo a colposcopy and a biopsy, both undertaken by a gynecologist. Up to this point, we assumed the patient would have used 3 hours of her time travelling to both the GP and gynecologist and undertaking the procedures.

The total cost per item is calculated by multiplying the unit cost and the number of units required. The unit cost for health services at the hospital is the corresponding share of the value of a Diagnose Related Group (DRG) point, NOK 40 772 in 2014.

Table 44. Medical assessment after mass screening

Treatment path after testing positive for ASC-US and LSIL at the cancer screening			
Resource	**Number**	**Price/DRG (NOK)**	**Cost (NOK)**
Visit to GP	1.00	284	284
Cytology	1.00	54	54
HPV-test	1.00	610	610
Visit to gynecologist	1.00	986	986
Colposcopy	1.00	1,264	1,264
Gynecologic biopsy	1.00	1,182	1,182
Patient time (hours)	3.00	186	559
Total (NOK)			**4,939**

When the existence of cancer is confirmed, the patient will visit the gynecologist one more time and under undergo a new set of tests, some of them not common to all patients, as for example biopsy of the lymph node, which is undertaken only in case of swollen lymph nodes (approximately 20% of all patients at this stage):

Table 45. Medical assessment after cervical cancer diagnosis.

Resource	Number	Price/DRG (NOK)	Cost (NOK)
Visit to gynecologist	1.00	986	986
Colposcopy	0.33	1,264	421
Biopsy	0.10	1,182	118
Blood tests	1.00	112	112
MR	1.00	1,530	1,530
CT-pelvis	1.00	1,108	1,108
PET	0.25	3,245	811
Cervix sample collection	1.00	1,182	1,182
Biopsy of the lymph node	0.20	2,120	424
Ultrasound	1.00	855	855
Examination under general anesthesia	0.50	1,182	591
Cytoscopy	0.50	1,182	591
Patient time (hours)	4.25	186	792
Total			**9,522**

ii. Primary treatment:

Once the medical assessment of the patient is completed and the cancer stage is determined, the primary treatment phase starts. Data on cancer stage distribution at this point was obtained from Haldorsen (75).

Table 46. Patient distribution among cancer stages at the beginning of primary treatment (Norway).

Cervix cancer stage IA	11.8%
Cervix cancer stage IA1	11.8%
Cervix cancer stage IA2	11.8%
Cervix cancer stage IB1	11.8%
Cervix cancer stage IB2	11.8%
Cervix cancer stage IIA	10%
Cervix cancer stage IIB	10%
Cervix cancer stage IIIA and IIIB	11%
Cervix cancer stage IVA and IVB	10%
Total	***100%***

The treatment plan will depend on both the stage of the patient's cancer and on other factors such as patient's life situation (e.g. fertility-preserving surgery or trachelectomy for young patients in stage IA2 or IA planning to have children) and adequacy of treatment to patient's clinical picture (e.g. giving chemotherapy or not together with radiotherapy to patients in stage IIA).

Table 47. Treatment costs in primary treatment, by stage.

Plateepitelcarcinom stage IA1			
Resource	**Number**	**Price/DRG (NOK)**	**Cost (NOK)**
Conization procedure	1	6,524	6,524
Patient time	1.50	186	280
Total (NOK)			**6,803**
Plateepitelcarcinom stage IA2			
Resource	**Number**	**Price/DRG (NOK)**	**Cost (NOK)**
Radical hysterectomy	0.50	147,105	73,552
Pelvic lymphadenectomy	1.00	54,920	54,920
Trachelectomy	0.50	82,849	41,424
Patient time (hours)	41.00	186	7,641
Total (NOK)			**177,538**
Adenocarcinom stage IA			
Resource	**Number**	**Price/DRG (NOK)**	**Cost (NOK)**
Hysterectomy	0.25	147,105	36,776
Radical hysterectomy	0.25	147,105	36,776
Trachelectomy	0.50	82,849	41,424
Lymphadenectomy	1.00	54,920	54,920
Patient time (hours)	73.00	186	13,605
Total (NOK)			**183,502**
Cervix cancer stage IB1			
Resource	**Number**	**Price/DRG (NOK)**	**Cost (NOK)**
Radical hysterectomy	1.00	147,105	147,105
Pelvic lymphadenectomy	1.00	54,920	54,920
Patient time (hours)	73.00	186	13,605
Total (NOK)			**215,630**
Cervix cancer stage IB2			
Resource	**Number**	**Price/DRG (NOK)**	**Cost (NOK)**

Radical hysterectomy	0.33	147,105	49,030
Pelvic lymphadenectomy	0.33	54,920	18,305
Internal radiotherapy	0.67	161,049	107,356
External radiotherapy	0.67	51,047	34,028
Patient time (hours)	91.75	186	17,099
Total (NOK)			**225,818**
Cervix cancer stage IIA			
Resource	**Number**	**Price/DRG (NOK)**	**Cost (NOK)**
Same treatment as in stage IB2	0.50	208,718	104,359
Internal radiotherapy	0.25	161,049	40,262
External radiotherapy	0.25	51,047	12,762
Chemotherapy	0.50	27,970	13,985
Patient time (hours)	64.63	186	12,044
Total (NOK)			**183,412**
Cervix cancer stage IIB			
Resource	**Number**	**Price/DRG (NOK)**	**Cost (NOK)**
Internal radiotherapy	0.50	161,049	80,525
External radiotherapy	0.50	51,047	25,523
Chemotherapy	1.00	27,970	27,970
Patient time (hours)	37.50	186	6,989
Total (NOK)			**141,006**
Cervix cancer stage IIIA, IIIB			
Resource	**Number**	**Price/DRG (NOK)**	**Cost (NOK)**
Internal radiotherapy	0.50	161,049	80,525
External radiotherapy	0.50	51,047	25,523
Chemotherapy	1.00	27,970	27,970
Patient time (hours)	37.50	186	6,989
Total (NOK)			**141,006**
Cervix cancer stage IVA and IVB			
Resource	**Number**	**Price/DRG (NOK)**	**Cost (NOK)**
Internal radiotherapy	0.50	161,049	80,525
External radiotherapy	0.50	51,047	25,523
Chemotherapy	1.00	27,970	27,970
Patient time (hours)	37.50	186	6,989
Total (NOK)			**141,006**

iii. Secondary/further treatment.

The result of the primary treatment is assessed within three months after ended treatment by a gynecologist or a gynecologic oncologist, by means of clinical examination, ultrasound and occasionally imaging examinations.

It is expected that 80% of all patients will experience a total tumor remission, followed by control visits to the gynecologist or gynecologic oncologist every three months for two years, then every six months for three years, and finally yearly control visits to the GP for ten years.

Some other 10% of patients are expected to experience a partial tumor remission. A gynecologist or a gynecologic oncologist would then examined the patient conducting a magnetic resonance imaging (MR), a computed tomography (CT) and in some cases a positron emission tomography (PET).

The final 10% of patients are expected to suffer residual disease or inadequate clinical response. After assessing patient's disease, secondary treatment consisting mainly of surgery and/or radiotherapy will be advised. The results of this secondary treatment will then be evaluated in a similar way to the primary treatment.

Table 48 Treatment course in the follow-up phase, cervical cancer.

New medical assessment within 3 months (all patients)			
Resource use	***Number***	***Price/DRG (NOK)***	***Cost (NOK)***
Visit to gynecologist or gynecologic oncologist	1.00	1,174	1,174
Ultrasound	1.00	2,120	2,120
Patient time (hours)	1.50	186	280
Total (NOK)			**3,574**
Inadequate clinical response/residual disease - Surgery			
Resource use	**Number**	**Price/DRG (NOK)**	**Cost (NOK)**
MR	1.00	1,530	1,530
CT-pelvis and -thorax	1.00	2,325	2,325
Radical hysterectomy	0.25	147,105	36,776
Pelvic lymphadenectomy	0.10	54,920	5,492
Internal radiotherapy	0.35	161,049	56,367
External radiotherapy	0.40	51,047	20,419
Patient time (hours)	48.63	186	9,062
Total (NOK)			**131,971**
Good tumor response, but not total remission - Intensive surveillance			

Resource use	Number	Price/DRG (NOK)	Cost (NOK)
Visit to gynecologist or gynecologic oncologist	1.00	1,174	1,174
MR	1.00	1,530	1,530
CT-pelvis and -thorax	1.00	2,325	2,325
PET	0.25	3,245	811
Patient time (hours)	3.75	1,174	1,174
Total (NOK)			**6,539**
Total tumor remission - Standard surveillance			
Resource use	**Number**	**Price/DRG (NOK)**	**Cost (NOK)**
Visit to gynecologist or gynecologic oncologist	14.00	1,174	16,436
Visit to GP	10.00	284	2,840
Patient time (hours)	36.00	186	6,709
Total (NOK)			**25,985**
Total – discounted (NOK)			**21,076**

iv. Expected costs per treatment phase

Based on the estimated costs per treatment phase and the patient distribution among cancer stages and treatment outcomes, we calculated the following expected costs per treatment phase.

Table 49. Expected costs per treatment phase.

Treatment phase	Cost item	Expected cost (NOK)
1. Medical assessment	Testing and diagnosing	13,110
	Patient time costs	1,351
2. Primary treatment	Cervix cancer stage IA	769
	Cervix cancer stage IA1	20,047
	Cervix cancer stage IA2	20,047
	Cervix cancer stage IB1	23,838
	Cervix cancer stage IB2	24,628
	Cervix cancer stage IIA	17,136
	Cervix cancer stage IIB	13,401
	Cervix cancer stage IIIA and IIIB	14,741
	Cervix cancer stage IVA and IVB	13,401
	Patient time costs	9,534
3. Follow-up / secondary treatment	New medical assessment within 3 months (all patients)	3,294
	Inadequate clinical response - Surgery	14,943

	Good tumor response, but not total remission - Intensive surveillance	3,236
	Total tumor remission - Surveillance	21,215
	Patient time costs	6,698
Total expected costs per cervical cancer case	*To the public health budget*	*203,813*
	To the patient	*17,583*

The total expected costs to the public health budget are NOK 203,813 per cervical cancer case. In order to calculate the expected costs to society, one has to add to this estimate the time costs to the patient as well as to correct for VTA and the deadweight loss due to tax funding, as well as the associated productivity costs. These two latter elements are discussed (on a general basis) below.

Extracting VAT when estimating costs from a societal perspective:

The following table shows the share of total operating costs that each cost item represents in the four health regional trusts' annual report and accounts for 2011. The last column shows the (arithmetic) average for all trusts:

Table 50. Reported shares of operating costs per regional health trust, 2011.

Year 2011	Regional health trust				Arithmetic average
Cost category	**South-East**	**West**	**North**	**Central**	
Purchase of health services	13.4%	14.6%	12.3%	12.3%	13.1%
Costs of goods sold	10.0%	10.3%	11.1%	11.2%	10.7%
Wages and other personnel costs	60.5%	59.7%	58.7%	60.0%	59.7%
Ordinary depreciation	5.2%	4.7%	5.1%	4.8%	4.9%
Write-downs	0.2%	0.2%	0.4%	0.0%	0.2%
Other operating costs	10.7%	10.5%	12.5%	11.7%	11.3%
TOTAL OPERATING COSTS	**100%**	**100%**	**100%**	**100%**	**100%**

We considered "Purchase of health services", "Costs of goods sold" and "Other operating costs" as the VAT-liable cost categories. Their shares were summed up, resulting in a total share of 35.1%. Nevertheless, as "Purchase of health services" in its turn consisted of both VAT-liable and not liable components (for example, wages paid by subcontractors), for simplicity we just rounded down the share to 30%. Then to calculate the cost without VAT we used the following relationship:

$$Y = X*(1-0.3) + X*(0.3/1.25) = X*(0.7+0.24) = X*0.94$$

Which expresses that by extracting the VAT from 30% of the cost per outcome was equivalent to considering 94% of the total expense from a public health-care perspective.

Monetary value of patient's time spent when receiving health treatment

We multiplied the number of hours spent by patient to get health treatment by our estimate of the hourly after-tax wage rate for 2013, NOK 186, based on Norwegian average monthly pre-tax income data from Statistics Norway, NOK 42 500 (47), and some assumptions. More specifically we assumed that the number of working hours per month was 169 (= 4.5 weeks x 37.5 working hours/week) and that the average income tax rate was 26%. This last rate was based on the rate reported at the OECD database (48).

Productivity costs in the analysis from a societal perspective:

We calculated the productivity costs (i.e. the monetary value of the expected loss of working years) associated with early cancer-related mortality and preterm births (i.e. births before week 33).

For early cancer-related death, we did as follows:

- First, we calculated the average age at diagnosis by means of a weighted average, the weights being the shares of patients diagnosed at the respective ages.
- Then we subtracted this average age from 67, the expected retirement age.
- We subtracted five additional years from the result, based on the assumption that no patient dies due to the cancer during the first five years after diagnose.
- We then multiplied the result (only if positive) by the average five-years mortality rate for that particular cancer type, which yielded the expected loss of working years due to early death, five years after cancer diagnosis (Cancer registry of Norway). Assuming, that all diagnosed patients survive until year five and that thereafter the survivors experience the same mortality rates as the rest of the population may be considered conservative.
- We assumed that the monetary value of every lost working year would be equal to the annual average pre-taxes total labor costs in Norway for 2013 (NOK 653 850), multiplied by the correction factor proposed by the Norwegian Directorate of Health to account for compensation mechanisms in the labor market (50%). The total labor costs were calculated by adding together the direct and indirect costs to the employer: The direct costs are the annual average pre-taxes wage from SSB, NOK 510 000 (47), while the indirect costs include the

payroll taxes, pension costs, insurance, in kind benefits, job training, etc. Data from SSB shows that the indirect costs' share of the total costs in Norway was 22% in 2008 (SSB).

- Finally, we discounted each of the corrected values and added them up, obtaining an approximation of the true discounted monetary value of the expected loss of working years due to early cancer-related death.

The formulas for the calculation are:

- $X = 50\% * \sum_{t=0}^{N} \frac{W_t}{(1+r)^t}$
- $N = (67 - A - 5) * M_{5\text{-year}}$

Where:

- X = Discounted, expected monetary value of lost working years due to cancer mortality
- W_t = Average pre-taxes annual wage at year t.
- r = Discount rate (4%, as the time horizon was shorter than 40 years)
- N = Expected loss of working years per cancer case, five years after diagnosis
- A = Weighted mean age at diagnosis (own calculations based on data from the Cancer registry of Norway)
- $M_{5\text{-year}}$ = Average 5-year mortality rate for all stages among patients aged > 50

Table 51. Estimation of productivity costs due to early cancer mortality.

Disease	(67-5)	Weighted average age at diagnosis (A)	Diffe-rence (years)	5-year mortality rate at diagnosis ($M_{5\text{-year}}$)	Expected lost working-years time due to cancer mortality, five years after diagnosis (N)	Discounted monetary value of lost working years time due to cancer mortality (X)
Cervical cancer	62	50.36	11.64	36.20%	4.21	1 295 750
Vulvar cancer	62	70.36	No expected loss of working years	-	-	-
Vulvar cancer	62	70.36	No expected loss of working years	-	-	-
Anal cancer (female)	62	66.55	No expected loss of working years	-	-	-
Anal cancer (male)	62	65.43	No expected loss of working years	-	-	-

Each cervical cancer results in an expected loss of approximately 4.21 years in the labor force while the losses caused by other cancers are expected to be zero. Given the average annual pre-taxes income in Norway for 2013, the expected loss caused by cervical cancer would represent a discounted loss of approximately NOK 1.3 million per case (corrected for compensation mechanisms in the labor market).

In addition, we calculated the productivity costs due to preterm births. Soergel (76) presents German estimates of the long-term costs of conization-related preterm deliveries. In order to be conservative, we chose to use the estimate for mild disabilities, 40,000 euro, which we converted to NOK by applying a rate of NOK 8 /euro, resulting in 320,000 NOK. We assumed that 60% of these costs would represent productivity costs due to late abortion, i.e. 192,000 NOK, and 40% health costs of different treatments through life, i.e. 128,000 NOK.

Appendix 5. Health related quality-of-life (HRQL) data

The HRQoL-data for precancerous lesions and genital warts

The HRQoL data for CIN 2+ came from a study, Galante (77), that compared the HRQoL-weights for pneumococcal and HPV-related diseases for different EQ-5D tariffs. Seventy-three non-patient study participants valued HPV-related health states using vignettes. The vignette description of the CIN 2+ health state included the screening procedures, the conization procedure and possible complications for future pregnancies. Values obtained through valuation of vignettes do not necessarily give a good approximation of how it is to live with the condition from a patient perspective (78). Because Galante did not report the HRQoL of a reference population, we used age-matched baseline data as a proxy (55). Despite these limitations, we accepted the use of the data because we did not identify any other EQ-5D data for CIN 2+ in our literature search.

The HRQoL data for VIN 2+ came from a multicenter, observational, cross sectional study of 42 patients with a confirmed diagnosis of VIN (79). The study found that women with VIN 2+ had a lower mean EQ-5D value than the age-matched UK general population. Because we did not have any HRQoL-data for VaIN, we used the data for VIN as a proxy for the HRQoL-loss associated with VaIN.

The CIN 2+ vignettes included a description of the conization procedure, and the QALY-losses due to CIN2+ can therefore be argued to include the impact of conization. The HRQoL-loss associated with ablative treatment or surgical excision of high-grade VIN lesions may however not be included in those estimates, because the patients asked were not necessarily under treatment for their condition. Those estimates may as a result be an underestimate of the actual QALY-loss. At the same time, respondents perceptions about the future with regards to fear of cancer and associated symptoms and treatments can bias the results in the opposite direction. A direct comparison of the CIN 2+ and VIN/VaIN values is however difficult, since the former study derived EQ-5D values from non-patients with vignettes, and the latter study reported values from actual patients.

The HRQoL data for genital warts came from two studies. Woodhall (56) was a questionnaire based study of 895 patients aged 16 or over with a current diagnosis of genital warts, attending eight sexual clinics in England and Northern Ireland. Dominiak-Felden (79) reported EQ-5D values derived from 186 patients with genital warts that attended specific health centers across the UK. The data reported for younger adults (18-34 year olds) suggested a significant loss of HRQoL. Both studies included new and recurrent episodes of genital warts, and both studies compared the patients EQ-5D values with age- and sex matched general UK population values.

Table 52. Inputs and results of the QALY-calculations for the precancerous outcomes and genital warts

Outcome	Health state HRQoL-value	Reference population HRQoL	Duration of episode	Value of k
Cervical intraepithelial neoplasia (CIN 2+)	*0,58* (44)	0,88 (55)	0,50 years (80)	0,346
Vulvar intraepithelial neoplasia (VIN 2+) (Used as proxy for vaginal intraepithelial neoplasia VaIN 2+)	0,72 (79)	0,89 (79)		0,172
Genital warts	**Women:** 0,87 (56) 0,87 (79) **Men:** 0,88 (56) 0,87 (79)	**Women:** 0,93 (56) 0,94 (79) **Men:** 0,92 (56) 0,94 (79)	0,40 years (56)	Women: 0,069 Men: 0,051

The HRQoL-data for cervical cancer, vulvar cancer, vaginal cancer and anal cancer

We used data from the aforementioned study by Galante and colleagues for the cervical cancer treatment, post-treatment and long-term post-cancer phase. The same limitations concerning the sample size and elicitation method apply here. The vignette for cervical cancer included a description of the most likely treatment options, possible complications following treatment (including the ability to have children), as well as the possibility of recurrence. For survivors the descriptions included the possibility for sexual problems, screening activities and the risk of recurrence.

After controlling for background variables, Korfage (81) found that the cervical cancer survivors (n=291) reported EQ-5D values that were not significantly different from the reference population (n=349) without history of disease. Lang (82) reported HRQoL values for 454 “disease free” cervical cancer patients that were

comparable to our age-matched baseline data (55). Consequently, the data from both studies suggest that the patients did not experience a HRQoL-loss as measured with the EQ-5D. The values for the post-treatment and long-term post-cancer phase in Table 53 are the arithmetic mean across the three studies Galante, Lang and Korfage.

As in the previous report (30), we divided the cancer health states into two different phases, each contributing to the total QALY-loss:

1. 0-3 years: The short-term phase: Treatment and post-treatment.
2. 3 years and up to patient's death: The long term post-cancer phase.

We assumed an average treatment phase that lasted for 4 months, followed by a post-treatment phase that lasted for 2 years and 8 months. As before, we assumed a loss of HRQoL, but no excess mortality when in treatment and post-treatment in the short-term phase.

In year three, we split the population into survivors and deceased according to the 5-year relative survival data from the Cancer Registry of Norway (CRN) (10). Survival according to disease stage (local, regional, distant) were complete only for cervical cancer. In order to be able to complete the QALY-calculations, we assumed that the cancer survival rate would be equal to the survival rate for the respective cervical cancer stage, after adjusting for differences in total survival between the relevant cancer and cervical cancer. In other words, we multiplied the survival rate for the respective cervical cancer stage with the ratio of total survival of the relevant cancer to the total survival of cervical cancer.

For those patients who die at year three, we calculated the quality-adjusted life expectancy lost (QALE). In the long-term post-cancer phase, we assumed a life-long HRQoL-loss for the proportion who survived, based on our findings in the literature.

Assuming, as we do, that all patients survive until year three and that thereafter the survivors experience the same mortality rates as the rest of the population may be considered conservative.

Finally, in the calculations of life-years lost, each life year lost is assigned a value of one and the HRQoL-loss associated with treatment or the post-treatment phases are not included. The net effect of those factors contribute to comparable results for QALY-losses and life-years lost.

Table 53. Inputs and results of the QALY-calculations for the cancer outcomes

Outcome	HRQoL-values	HRQoL-reference population	Value of k (percent reduction in HRQol)
Cervical cancer (Used as proxy for vulvar cancer, vaginal cancer, anal cancer)	**Treatment phase:** 0,152 (77) **Post-treatment and long term post-cancer phase:** 0,785 (77, 81, 82)	**Treatment phase:** 0,839 (55) **Post-treatment and long term post-cancer phase:** 0,851 (55, 81, 82)	**Treatment phase:** 0,819 **Post-treatment phase:** 0,059

QALY-losses associated with HPV-related conization

Our estimate of QALY-loss associated with premature births, was based on an assumption of a lifetime reduction in HRQoL only. The excess mortality associated with a premature birth before week 32 and 30 have been estimated by others to be approximately 1.35 and 2.16 QALYs (83). This potential for excess mortality was not included in our estimate of the potential QALY-loss associated with premature births.

The literature search

The tables below describes the narrow searches for CIN, VIN, VaIN, PIN, AIN, cervical cancer, vulvar cancer, vaginal cancer, penile cancer, anal cancer, oropharyngeal cancer, genital warts, conization and serious adverse events. The search included more outcomes than we included in the main analysis, because we a priori did not know which outcomes we would find effect data for and therefore include in the analysis.

Table 54. Common search terms for all the narrow searches.

#	Searches	Results
1	eq5d.mp.	521
2	eq-5d.mp.	5374
3	euroqol.mp.	3490
4	euro qol.mp.	158

5	tto.mp.	959
6	time trade off.mp.	1100
7	time tradeoff.mp.	242
8	euroqol-eq-5d.mp.	709
9	eq-5d-euroqol.mp.	58
10	or/1-9	8761

Table 55. CIN.

CIN	**Searches**	**Results**
11	uterine cervix carcinoma in situ/ or cervi* dysplasia.mp. or cervical intraepithelial neoplasia.mp. or cervical intraepithelial dysplasia.mp. or "cin".mp.	21375
12	10 and 11	13

Table 56. VIN

#	**Searches**	**Results**
11	(vulva* cancer-in-situ or vulva* neoplasia or vulva* dysplasia or vulva* carcinoma in situ or vulva* precancer or vulva* precarcinoma or "vin").mp.	1607
12	10 and 11	1

Table 57. VaIN.

#	**Searches**	**Results**
11	vaginal intraepithelial neoplasia/ or vagin* neoplasia.mp or vagin* dysplasia.mp or vagin* carcinoma in situ.mp or vagin* precancer.mp or vagin* precarcinoma.mp or "vain".mp or vagine*.mp	1434
12	10 and 11	0

Table 58. PIN.

#	**Searches**	**Results**

11	(peni* dysplasia or peni* intraepithelial neoplasia or peni* intra-epithelial neoplasia or peni* precancer or peni* precarcinoma or peni* carsinoma in situ or peni* neoplasia or "pin").mp.	13646
12	10 and 11	4

Table 59. AIN.

#	Searches	Results
11	(anal cancer-in-situ or anal neoplasia or anal dysplasia or anal intra-epithelial neoplasia or anal carcinoma in situ or anal precancer or anal precarcinoma or "ain").mp.	3884
12	10 and 11	0

Table 60. Cervical cancer.

#	Searches	Results
11	uterine cervix cancer/ or uterine cervix tumor/ or uterus cancer/ or uterine cervix carcinoma/ or trachelectomy.mp. or cervicectomy.mp. or hysterectomy.mp.	144205
12	10 and 11	58

Table 61. Vulvar cancer.

#	Searches	Results
11	vulva cancer/ or vulva tumor/ or vulva carcinoma/ or vulvect*.mp.	8872
12	10 and 11	1

Table 62. Vaginal cancer.

#	Searches	Results

11	vagina cancer/ or vagina tumor/ or vagina carcinoma/ or vagine*.mp.	5914
12	10 and 11	1

Table 63. Penis cancer.

#	Searches	Results
11	penis cancer/ or male genital tract cancer/ or penis tumor/ or penis carcinoma/ or penis/	17222
12	10 and 11	58

Table 64. Anal cancer.

#	Searches	Results
11	anus cancer/ or anus tumor/ or large intestine cancer/ or anus carcinoma/	7187
12	10 and 11	3

Table 65. Oropharyngeal cancer.

#	Searches	Results
11	oropharynx cancer/ or oropharynx tumor/ or pharynx cancer/ or oropharynx carcinoma/ or orophar* cancer.mp. or "head and neck cancer".mp.	47941
12	10 and 11	19

Table 66. Genital warts.

#	Searches	Results
11	condyloma acuminatum/ or wart virus*.mp. or genital wart*.mp. or venereal wart*.mp. or genital.mp.	257956
12	10 and 11	29

Table 67. Conization.

#	Searches	Results
11	(conis* or coniz* or cold knife coniz* or cold knife conis* or cervical coniz* or cervical conis* or cervix conis* or cervix coniz* or pap smear or loop electrical excision procedure or simple trachelectomy).mp.	8004
12	10 and 11	8

Table 68. Serious adverse events from vaccination.

#	Searches	Results
11	wart virus vaccine/ or vaccination reaction/	7661
12	10 and 11	1

Table 69. Wide searches for VIN, VaIN, PIN, AIN, vulvar cancer, vaginal cancer, penile cancer, anal cancer, oropharyngeal cancer, genital warts and conization.

#	Searches	Results
1	eq5d.mp.	175
2	eq-5d.mp.	2853
3	euroqol.mp.	2153
4	euro qol.mp.	53
5	tto.mp.	612
6	time trade off.mp.	757
7	time tradeoff.mp.	204
8	euroqol-eq-5d.mp.	467
9	eq-5d-euroqol.mp.	36
10	(quality adjusted life or quality-adjust-life).mp.	9732
11	(qaly* or qald* or qale* or qtime* or qali*).mp.	5216
12	(hql or hqol or h qol or hrqol).mp.	7475
13	(Sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).mp.	15865

14	(sf6D or sf 6D or short form 6D or shortform 6D or sf six D or sfsixD or shortform six D or short form six D).mp.	424
15	(sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).mp.	335
16	(hui or hui 2 or hui 3).mp.	691
17	standard gamble.mp.	663
18	or/1-17	35177
19	(vulva* cancer-in-situ or vulva* neoplasia or vulva* dysplasia or vulva* carcinoma in situ or vulva* precancer or vulva* precarcinoma or "vin").mp.	942
20	penis cancer/ or male genital tract cancer/ or penis tumor/ or penis carcinoma/ or penis/ or penectomy.mp.	19106
21	(peni* dysplasia or peni* intraepithelial neoplasia or peni* intra-epithelial neoplasia or peni* precancer or peni* precarcinoma or peni* carsinoma in situ or peni* neoplasia or "pin").mp.	10210
22	(conis* or coniz* or cold knife coniz* or cold knife conis* or cervical coniz* or cervical conis* or cervix conis* or cervix coniz* or pap smear or loop electrical excision procedure or simple trachelectomy).mp.	5295
23	anus cancer/ or anus tumor/ or large intestine cancer/ or anus carcinoma/ or colectomy.mp.	20974
24	(anal cancer-in-situ or anal neoplasia or anal dysplasia or anal intra-epithelial neoplasia or anal carcinoma in situ or anal precancer or anal precarcinoma or "ain").mp.	2653
25	vaginal intraepithelial neoplasia/ or vagin* neoplasia.mp. or vagin* dysplasia.mp. or vagin* carcinoma in situ.mp. or vagin* precancer.mp. or vagin* precarcinoma.mp. or "vain".mp. or vagine*.mp.	806
26	vagina cancer/ or vagina tumor/ or vagina carcinoma/ or vagine*.mp. or vaginectomy.mp.	4815
27	vulva cancer/ or vulva tumor/ or vulva carcinoma/ or vulvect*.mp.	7082
28	or/19-27	69313
29	18 and 28	115

Appendix 6. Estimation of the vaccine expenditures associated with the implementation HPV-vaccination of boys aged 12

We assumed in our analysis that the mean coverage rate for the first vaccine dose among boys would be the same as among girls, 82%. Furthermore, we assumed that 84.5% of those boys receiving at least one dose also would receive two and 69% all three (see Table 43).

Based on these assumptions we calculated that 69.3% (=84.5%*82%) of every boy cohort would receive two doses, while 56.6% (=69%*82%) would receive all three doses.

Given an estimated population size of 31,000 boys per cohort, this would mean that approximately 121,000 additional doses will be required every year to implement HPV-vaccination of boys.

Table 70. Estimated annual need of vaccine doses for boys aged 12.

Number of doses per boy	Share of target population	Total number of doses
1	82.0%	25,420
2	69.3%	42,960
3	56.6%	52,619
SUM		**120,999**

14	(sf6D or sf 6D or short form 6D or shortform 6D or sf six D or sfsixD or shortform six D or short form six D).mp.	424
15	(sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).mp.	335
16	(hui or hui 2 or hui 3).mp.	691
17	standard gamble.mp.	663
18	or/1-17	35177
19	(vulva* cancer-in-situ or vulva* neoplasia or vulva* dysplasia or vulva* carcinoma in situ or vulva* precancer or vulva* precarcinoma or "vin").mp.	942
20	penis cancer/ or male genital tract cancer/ or penis tumor/ or penis carcinoma/ or penis/ or penectomy.mp.	19106
21	(peni* dysplasia or peni* intraepithelial neoplasia or peni* intra-epithelial neoplasia or peni* precancer or peni* precarcinoma or peni* carsinoma in situ or peni* neoplasia or "pin").mp.	10210
22	(conis* or coniz* or cold knife coniz* or cold knife conis* or cervical coniz* or cervical conis* or cervix conis* or cervix coniz* or pap smear or loop electrical excision procedure or simple trachelectomy).mp.	5295
23	anus cancer/ or anus tumor/ or large intestine cancer/ or anus carcinoma/ or colectomy.mp.	20974
24	(anal cancer-in-situ or anal neoplasia or anal dysplasia or anal intra-epithelial neoplasia or anal carcinoma in situ or anal precancer or anal precarcinoma or "ain").mp.	2653
25	vaginal intraepithelial neoplasia/ or vagin* neoplasia.mp. or vagin* dysplasia.mp. or vagin* carcinoma in situ.mp. or vagin* precancer.mp. or vagin* precarcinoma.mp. or "vain".mp. or vagine*.mp.	806
26	vagina cancer/ or vagina tumor/ or vagina carcinoma/ or vagine*.mp. or vaginectomy.mp.	4815
27	vulva cancer/ or vulva tumor/ or vulva carcinoma/ or vulvect*.mp.	7082
28	or/19-27	69313
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Appendix 6. Estimation of the vaccine expenditures associated with the implementation HPV-vaccination of boys aged 12

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(continued from page one) quadrivalent vaccine is probably not cost-effective. The incremental cost-effectiveness ratio (ICER) was NOK 1,626,261 for a quality-adjusted life-year (QALY). Although there is no official cost-effectiveness threshold value in Norway, such high ICERs are generally associated with the intervention not being accepted for implementation in the Norwegian health sector.