Cost-effectiveness of a HPV-vaccination catch-up program for females aged 26 years or younger in a Norwegian setting

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Background: Infection with human papilloma virus (HPV) is documented to be associated with several precancerous lesions (CIN, VIN and VaIN), cancer and genital warts. In this economic evaluation, we evaluated the cost-effectiveness of administering a catch-up vaccine to females aged 26 years or younger in addition to the current practice of vaccinating 12 year-old- girls compared to maintaining the current practice. • Currently, two vaccines are available in the Norwegian market with documented effect against HPV-infection: the quadrivalent vaccine, directed at HPV 6, 11, 16 and 18, and the bivalent vaccine, directed at HPV 16 and 18. In this report, we estimated the cost-effectiveness of the quadrivalent vaccine for the target population. The cost-effectiveness of the bivalent vaccine is nevertheless discussed in one of the scenario analyses we conducted.
Main findings: • From a public health budget perspective and given the current public price of NOK 1 010.9/dose of the quadrivalent vaccine, introducing a catch-up vaccine for the target population is cost-effective if one is willing to pay NOK 578 391 for a gained quality-adjusted life-year (QALY). • For *(continued)*

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(continued from page one) a willingness-to-pay of NOK 578 391/QALY and from a public health budget perspective, the bivalent vaccine may be considered cost-effective if its price is no higher than approximately NOK 780/dose. • From a societal perspective, i.e. when costs to patients for time used under treatment and the work-related productivity costs due to disease are included, the catch-up vaccine is cost-effective if one is willing to pay NOK 553 691 per gained QALY.

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We would like to thank Ingvild Vistad, Turid Jorunn Thune, Harrell Chesson, Arna Desser, Signe Agnes Flottorp, Aileen Neilson and Bjarne Robberstad for their expertise in this project. Norwegian Knowledge Centre for the Health Services assumes final responsibility for the content of this report.

Norwegian Knowledge Centre for the Health Services
Oslo, March 2014

Key messages

Infection with human papillomavirus (HPV) is documented to be associated with several precancerous lesions (CIN, VIN and VaIN), cancer and genital warts. In this economic evaluation, we evaluated the cost-effectiveness of administering a catch-up vaccine to females aged 26 years or younger in addition to the current practice of vaccinating 12 year-old-girls compared to maintaining the current practice.

Currently, two vaccines are available in the Norwegian market with documented effect against HPV-infection: the quadrivalent vaccine, directed at HPV 6, 11, 16 and 18, and the bivalent vaccine, directed at HPV 16 and 18. In this report, we estimated the cost-effectiveness of the quadrivalent vaccine for the target population. The cost-effectiveness of the bivalent vaccine is nevertheless discussed in one of the scenario analyses we conducted.

The main results of the evaluation are the following:

- From a public health budget perspective and given the current public price of NOK 1 010.9/dose of the quadrivalent vaccine, introducing a catch-up vaccine for the target population is cost-effective if one is willing to pay NOK 578 391 for a gained quality-adjusted life-year (QALY).

- For a willingness-to-pay of NOK 578 391/QALY and from a public health budget perspective, the bivalent vaccine may be considered cost-effective if its price is no higher than approximately NOK 780/dose.

- From a societal perspective, i.e. when costs to patients for time used under treatment and the work-related productivity costs due to disease are included, the catch-up vaccine is cost-effective if one is willing to pay NOK 553 691 per gained QALY.

Title:
Cost-effectiveness of a HPV-vaccination catch-up program for females 26 years or younger in a Norwegian setting

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Type of publication:

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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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Aileen Neilson, Health Economics Research Unit, University of Aberdeen
Bjarne Robberstad, Department of Global Public Health and Primary Care, University of Bergen

Executive summary

Background

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 12-year-old girls with the quadrivalent vaccine (directed at HPV 6, 11, 16 and 18).

Catch-up vaccination programs for young women have been implemented in 10 out of the 29 EU/EEA countries (1). Due to this development and the interest shown by the Norwegian scientific community regarding this subject, the FHI commissioned the Norwegian Knowledge Centre for the Health Services (NOKC) an economic evaluation of administering a catch-up vaccine to those females aged 26 years or younger.

Objective

To evaluate the cost-effectiveness of administering a catch-up vaccine to females aged 26 years or younger in addition to the current practice of vaccinating 12 year-old- girls compared to maintaining the current practice.

Method

We used an already published economic model (2) consisting of a deterministic, dynamic population-based model that estimated the proportion of people in every future cohort infected with HPV 6, 11, 16 and/or 18.

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 efficacy reported in our systematic review (3). Finally, the model was made probabilistic in order to

assess the uncertainty around the results and to be able to perform Value-of-Information analysis.

The focus in our base case analysis was on evaluating the quadrivalent vaccine. We used the same vaccination coverage rates for the first dose reported for the Australian catch-up program, which on average were 54%.

Furthermore, the economic evaluation was performed from two different costs perspectives: a public health budget perspective focusing on costs to the National health system; and a societal perspective in which we also included the monetary value of patients' spent time on receiving treatment for HPV-related outcomes (travelling and waiting time) as well as the monetary value of changes in time use after receiving treatment.

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 the catch-up program was cost-effective, the resulting ICER was compared to a range of potential willingness-to-pay (WTP) values between NOK 250 000 - 1 000 000 per gained QALY. ICERs lower than the chosen WTP value typically supports the hypothesis that the catch-up vaccine is cost-effective and therefore yields good value for money, while ICERs above the chosen WTP value suggest the opposite.

We examined the uncertainty in our base case results and conducted value-of-information analysis by estimating the expected value of perfect information (EVPI).

The Norwegian Institute of Public Health is responsible for conducting open tender competitions regarding purchase of vaccine against human papillomavirus (HPV) for the Norwegian childhood immunization program. The current contract period is from 2013 through 2014, with the option of one to two additional years, and was awarded to Sanofi Pasteur MSD for its quadrivalent vaccine (4).

As the result of this tender process, the price per dose attained by the Norwegian Institute of Public Health may be lower than the public prices. We examined the cost-effectiveness of the quadrivalent vaccine in three different scenario analyses, using alternative prices of NOK 250, 500 and 750 per dose.

Finally, in addition to the price scenario analyses, we conducted a scenario analysis that excluded the effect on genital warts, in order to both estimate the cost-effectiveness of the only bivalent vaccine available in the market as of February 2014 (not protective against genital warts), and to ascertain the price level at which the bivalent vaccine achieved the same ICER as the quadrivalent vaccine.

Results

In our base case analysis we assumed that approximately 54% of all girls and young women in the target population would get on average 2.78 doses of the HPV-vaccine. Furthermore, we assumed that the vaccine would only have effect on the health outcomes in the model as documented in our own systematic review (3). Finally, the price of the vaccine was set equal to the public price of the quadrivalent vaccine, currently NOK 1010.9/dose.

From a public health budget perspective, the base case results showed that a catch-up program for females aged 26 years or younger would lead to a discounted, incremental cost of NOK 335.7 million and an incremental health gain of 580.4 QALYs. This resulted in an ICER of NOK 578 391/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 reached a maximum of approximately NOK 38.6 million at a WTP equivalent to the program's ICER 578 391/QALY. This means that if the expected costs of additional research are lower than NOK 38.6 million, then it is cost-effective to conduct further research given that the WTP is 578 391/QALY.

From a societal perspective the catch-up program had a lower ICER, NOK 553 691/QALY, mainly due to the large expected productivity costs associated with each case of cervical cancer and (to a lesser extent) conization-related, premature birth and late abortion.

Discussion

Several scenario analyses were conducted in order to ascertain the impact on the base case results of both the vaccine price and the exclusion of the vaccine effect on genital warts:

- Using prices of NOK 250, 500 and 750/dose resulted in lower incremental costs and therefore lower ICERs of NOK 111 772/QALY, NOK 265 327/QALY and NOK 417 659/QALY, respectively.
- Excluding the vaccine effect on genital warts from the analysis resulted in both higher incremental costs and lower incremental health effect than in the base case. The ICER was NOK 704 308/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 1010.9/dose, we estimated that the price of the bivalent vaccine had to be approximately 780 NOK/dose or lower in order to be as cost-effective as the quadrivalent vaccine.

Conclusion

Administering a catch-up (quadrivalent) vaccine at a price of NOK 1010.9/dose to females aged 26 years or younger may be considered cost-effective (regardless of perspective) for a willingness-to-pay value of NOK 578 391/QALY or higher.

The price of the bivalent vaccine should not be higher than approximately NOK 780/dose for it to achieve the same ICER as the quadrivalent vaccine.

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.
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

This project was commissioned by the Norwegian Institute of Public Health, who wanted us to assess the cost-effectiveness of administering females aged 26 years or younger the HPV-vaccine through a catch-up program in addition to the current practice of vaccinating 12 year-old girls compared to maintaining the current practice. The results 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 Bjarne Robberstad (University of Bergen) performed the external peer review of the report.

The project group consisted of:
Jon Mork, Rikshospitalet
Kjerstin Møllebakken, Kirkenes helsestasjon
Turid Jorunn Thune, Helse Bergen HF
Ingvild Vistad, Sørlandet sykehus HF

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.

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

Gro Jamtvedt	Marianne Klemp	Ingvild Sæterdal	Enrique Jiménez
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Objective

To evaluate the cost-effectiveness of administering a catch-up vaccine to females aged 26 years or younger in addition to the current practice of vaccinating 12 year-old- girls compared to maintaining the current practice.

Background

Human papillomavirus (HPV) is considered the most common sexually transmitted agent worldwide (5) and more than 100 types of HPV have been identified (6, 7). Persistent infection with oncogenic HPV types are recognized as a necessary cause of cervical cancer. Approximately 70% of cervical cancers in the world are attributed to two of the most common HPV types, 16 and 18 (6, 8, 9).

Efficient prophylactic vaccines could have an important public health impact. As cancer takes a long time to develop, it would be difficult to conduct clinical trials ascertaining the efficacy of HPV vaccination on cervical cancer and other cancer types associated with HPV. Furthermore, as screening for cervical cancer is available, conducting such trials would be unethical. For these reasons, the WHO and the US Food and Drug Administration recommended that phase III trials examine vaccination efficacy on high-grade cervical intraepithelial neoplasia grades 2 and 3 (CIN2/3) (10).

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

Catch-up vaccination programs for older girls/young women have been implemented in 10 out of the 29 EU/EEA countries (1). Due to this development and the interest shown by the Norwegian scientific community, the FHI commissioned the Norwegian Knowledge Center for the Health services to undertake an economic evaluation of implementing a catch-up vaccination program for females aged 19-26 years in 2015.

The total target population of such a catch-up program in Norway would consist of approximately 8 cohorts of females (those born 1989-1996), of 29 650 females each, i.e. 237 200 females.

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 Drummond 2005 (11). Hence, results of economic evaluations can be expressed as an incremental cost-effectiveness ratio (ICER), which is defined by the following equation:

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

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.

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

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

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 expected value of perfect information (EVPI). This is a number which indicates the value of reducing decision uncertainty for society to a minimum. It can also be interpreted as the expected cost of uncertainty, 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 (12).

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, wich allows estimating the value of collecting additional information from new research.

Priority setting criteria

According to Norwegian policy documents (ref: prioriteringsforskriften §2), a treatment should be prioritized 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 ac-

cording 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.

Economic evaluation - 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 Elbasha 2007 (13), Jit 2008 (14) and Kim 2009 (15). Due to the availability of already developed models, we decided to adapt one of them to a 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,*
- *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 Center for Disease Control and Prevention (CDC) by Harrell W. Chesson and colleagues (2), who collaborated with us during the adaptation of the model. Nevertheless, the responsibility for the final choices is the authors' alone.

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 from both a public health budget and a societal perspective, with both costs and effects discounted by an annual discount rate of 4%, as recommended by the Norwegian Ministry of Finance (16).

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 scenario analyses (i.e. analyses in which we tested alternative assumptions on some given parameters).

Model Structure

The original model has been described in detail elsewhere (2, 17). 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 model, in which the impact of vaccination was modeled as a sequence of 1-year transitions among four mutually exclusive states. The population was not classified according to sexual activity level (that is, rate of sex partner change). Instead, we assumed that each year the entire population was subject to a sex- and age-specific probability of acquiring a specific HPV type.

The transition from HPV acquisition to HPV-associated health outcomes is not explicitly modeled. Instead, in the original model the impact of vaccination on health outcomes was calculated under the assumption that the percentage reduction in health outcomes attributable to HPV-type in a given year for a given age cohort was equal to the percentage reduction in cumulative lifetime exposure to that HPV-type (i.e. the cumulative HPV-incidence) due to vaccination against that HPV-type in a given year for the given age cohort. In the Norwegian model the percentage reductions are not equal across outcomes, as reflected in the results from our systematic review (3). See section on efficacy for more details.

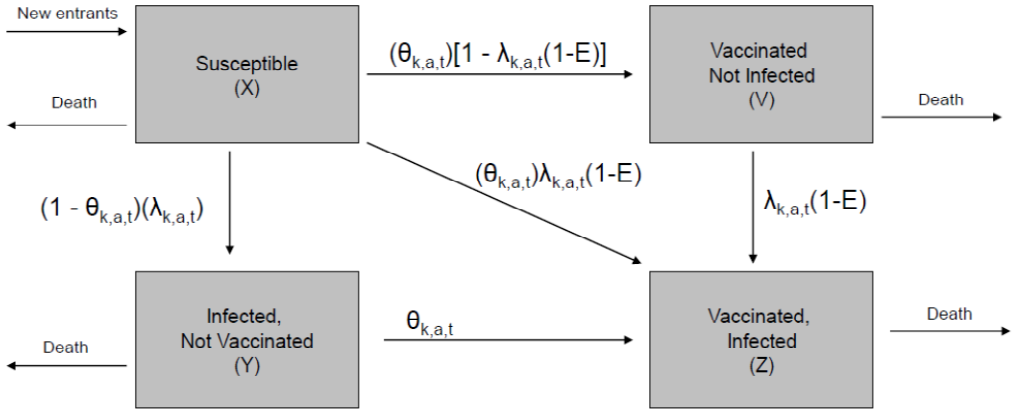
Cervical cancer screening was not explicitly modeled. Instead, we assumed that current cervical cancer screening in Norway was reflected in the observed rates of cervical intraepithelial neoplasia (CIN) and cervical cancer applied in the model. In other words, we assume that the current screening activities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

The model focuses on the first 100 years of an HPV-vaccination program by following the consequences that such a program may have for 191 birth cohorts: The 100 first cohorts of 8-year-olds, and the 91 cohorts above the age of 8 and below 100 years old. We did not include the consequences for those under age 8 years or over 99 years.

The model consists of three similar infection submodels: One for HPV-16, another for HPV-18 and the last one for HPV 6/11. For each submodel, each age and gender

cohort was divided into four classes, based on the individual's vaccination status and HPV-exposure, see Figure 1.

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



Every year a new cohort of 8-years-old girls/boys enters the model in the susceptible group (X). 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. We assumed that infection provides lifelong immunity, so that those infected with a HPV-type never return to the susceptible group for that type and receive no benefit if vaccinated.

Those in the susceptible group (X) and those in the infected (Y) group might be vaccinated in a given year (only females may be vaccinated in this model). Those in the susceptible group (X) at the time of the vaccination move to the "vaccinated, not infected" group (V), or, possibly to the "vaccinated, infected" group (Z), as vaccine efficacy is not 100%.

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. In any given year, those in the "vaccinated, not infected" group (V) can move to the "vaccinated, infected" group (Z), as vaccine efficacy is not 100%.

Furthermore:

- Individuals may die in any of the four classes. The same age- and sex-specific death rates 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. The model incorporates the differences in cervical, vaginal and vulvar cancer mortality between vaccination strategies through the QALY-losses accumu-

lated by each treatment group (more details in the section about the health related quality-of-life). Death rates for 2012 were obtained from Statistics Norway.

- $\theta_{k,a,t}$ is the annual probability of receiving HPV vaccination for sex k (1 for female, 2 for male) at age a in year t.
- E_k is vaccine efficacy against HPV 6, 11, 16 or 18 acquisition for sex k.
- $\lambda_{k,a,t}$ is the annual probability of acquiring HPV 6, 11, 16 or 18 for sex k at age a in year t.

$\lambda_{k,a,t}$ 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. The adjustment is calculated based on the changes in cumulative exposure to the relevant HPV type in the population, thus incorporating herd immunity in the model. See Chesson (2), appendix 1, pages 4, 5 and 6 for further details.

The vaccine reduces cumulative incidence in two different ways: First, it protects the vaccinated individual against infection when exposed to the HPV-virus (the direct effect, only enjoyed by vaccinated females); and second, it reduces the probability of exposure to HPV, independently of vaccination status (the indirect effect or herd immunity, enjoyed by all females and males).

Although the population was not classified according to sexual activity levels, 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 a 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 Norwegian model is the reduction of the following HPV 6, 11, 16 and/or 18 related outcomes among men and/or women:

- Cancer (cervical, vulvar and vaginal).
- Cervical intraepithelial neoplasias, grades 2 and 3 (CIN 2 and 3)
- Vulvar and vaginal intraepithelial neoplasias, grades 2 and 3 (VIN and VaIN 2 and 3)
- Genital warts
- Conization related events (preterm births and aborts) due to previous CIN 2+ treatment
- Serious cases of adverse events due to vaccination

The Norwegian model does not include either anal, penile or oropharyngeal cancer in its base case, all of which were included in the original model.

Finally, the original model was deterministic, but allowed for one-way, multi-way and probabilistic sensitivity analyses. We modified this by making the model proba-

bilistic, in the sense that the great majority of the included variables were assigned a probability distribution based on the available data. This allowed us to both assess the uncertainty around the results and perform of value-of-information (VoI) analysis.

Model Parameters

In order to consider the consequences of introducing a catch-up program for females aged 16 to 26 years, 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).

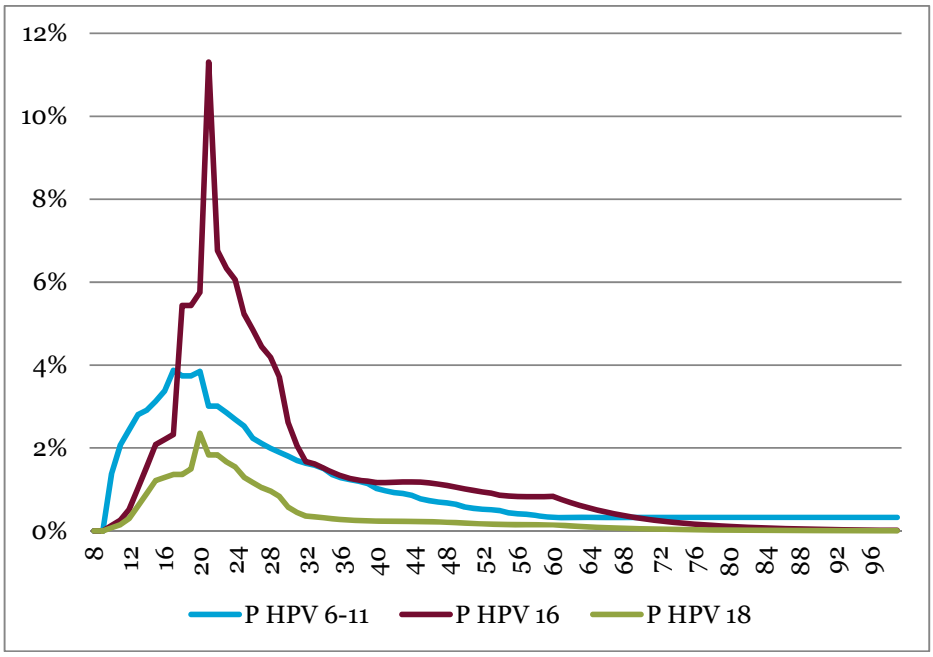
Epidemiology

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

   There are limited data on the annual incidence and prevalence of HPV in Norway. The Norwegian Institute of Public Health (FHI) provided us with yet unpublished data about HPV-prevalence in females aged 17 and 21 years. Based on these point estimates, and with the help of the prevalence data from Chesson (2), we extrapolated to obtain the prevalence for every age group between 8 and 16 and 22 and 85, and interpolated to obtain the prevalence for age groups 18, 19 and 20. In this way, we were able to obtain estimates of the prevalence rates for each age group.

   To obtain annual incidence rates for all age groups we then applied the method used by Chesson (2), appendix 1, pages 23 and 24. We thereby assumed that the relationship between prevalence and incidence rates in Norway is the same as in the USA. The results, presented in Figure 1, represent the probability of acquisition of a given HPV type at a given age, provided no acquisition of that HPV type had occurred previously.

Figure 2. Estimated annual incidence rates for HPV-6-11, 16 and 18



All three curves show fast growth in the incidence rates from young ages to a peak at approximately 20-21 years old, and then a fast decrease phase is observed ending in the thirties, followed by a phase of slow decrease.

2. *CIN 2 and 3*

The Cancer Registry of Norway provided data on the number of CIN 2 and 3 cases (confirmed through biopsy) that occurred every year from 2002 to 2010, by age group. We used these data to calculate average annual incidence rates per female for each age group based on population data from Statistics Norway.

To calculate an annual incidence rate, one need 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. Over a fixed period, the latter is the average size of the population over the observed period. We, therefore, 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 2 and 3 in Norway, per female (average 2002-2010, all females)

Age group	CIN 2	CIN 3
15-19	0.00009	0.00009
20-24	0.00050	0.00144
25-29	0.00079	0.00388
30-34	0.00054	0.00363
35-39	0.00048	0.00270
40-44	0.00037	0.00197
45-49	0.00031	0.00118
50-54	0.00021	0.00069
55-59	0.00015	0.00050
60-64	0.00012	0.00040
65-69	0.00010	0.00032
70+	0.00003	0.00010

Incidence rates for CIN 3 seem to be consistently greater than for CIN 2. 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 ASC-US or LSIL and positive HPV-test. In these cases, finding CIN 3 is more probable than finding CIN 1 or 2, as CIN 1 and 2 may have resolved/spontaneously disappeared without further complications.

3. *Cancer*

The Cancer Registry of Norway provided data on annual incidence rates for cervical, vaginal and vulvar cancer for the period between 2002 and 2010, for specified age groups and gender. The data showed that the incidence rate for most cancer forms was relatively stable over this period of time. We then extrapolated the average for 2002-2010 over the horizon of the model (100 years, beginning in 2015) for all rates in the base case.

Table 2. Annual incidence rates per 100 000 person-years (average 2002-2010).

Age	Vaginal	Vulvar	Cervical
05-09	0.00	0.00	0.00
10-14	0.00	0.00	0.00
15-19	0.00	0.00	0.08
20-24	0.00	0.14	2.59
25-29	0.08	0.16	10.81
30-34	0.00	0.40	21.24
35-39	0.20	0.58	23.77

40-44	0.20	2.00	20.41
45-49	0.27	2.78	19.41
50-54	0.90	3.38	18.07
55-59	0.86	3.51	15.90
60-64	1.72	3.77	17.61
65-69	1.98	8.61	14.79
70-74	2.00	10.19	14.94
75-79	0.99	13.86	18.99
80-84	3.52	20.10	18.42
85+	3.91	24.52	13.28

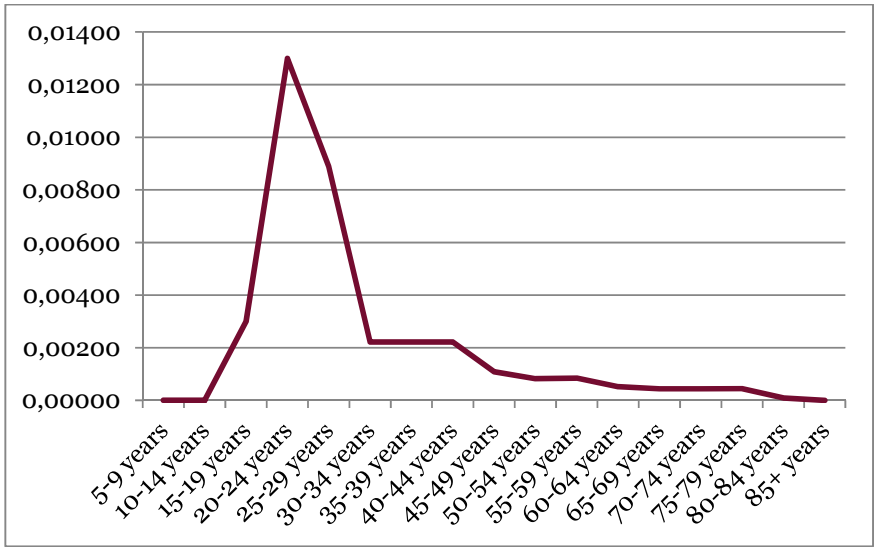
4. *Genital warts*

   Kjær (18) provided recent estimates for the cumulative incidence rates of self-reported, clinically-diagnosed genital warts among females in Norway. In order to calculate the annual incidence rates, we assumed that the annual incidence rate for a given age group was equal to the change in cumulative incidence from the year prior to the year of interest. Lacking separate information for Norwegian men, we assumed that the estimated rates for women also applied to men.

   Furthermore, we based our calculations on data for the youngest cohort in the dataset, 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 underestimate the future burden of genital warts as the cumulative incidence has grown rapidly over the last 30 years: For example, while the cumulative incidence in the cohort born between 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 (18).

   The 1979-86 cohort was followed only 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 is worth mentioning that this age profile, while hypothetical, yields a flatter profile than the ones registered for the older cohorts, i.e. it may be an optimistic forecast of the future burden of genital warts.

Figure 3 Estimated annual incidence rates (per person) of genital warts. Both male and female.



Source: Kjær (18) and own calculations

5. *Conizations*

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 and abortions (19-21). Since infection with HPV 16 and 18 has been reported to cause CIN 2 and 3 (22), we included in our analysis the potential reduction in preterm deliveries and abortions due to the vaccine. We limited our analysis to what we called critical preterm deliveries, i.e. deliveries before week 32 (as these children have the greatest possibility of experiencing serious lifetime-disabilities), and late abortions (no more than 24 weeks of gestation).

We used data from Albrechtsen (23), which showed that 141 371 preterm deliveries were registered in Norway for the period 1967-2003, of which 995 took place after the mother underwent conization and therefore fall into the category "critical". This represents a 0.704% of all preterm deliveries in that period and 0.044% of all deliveries.

Since preterm deliveries can be caused by factors other than the conization status of the mother, we corrected for this before 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 16 and 18 infection-related critical preterm deliveries may account for 0.0154% of all births. Using it as an annual rate would result in approximately 9 births when using delivery figures for

2012. HPV 6 and 11 have no known link to CIN 2+ and therefore are assumed to have no effect on the number of conizations carried out.

Although the effect of a reduction in the cumulative incidence 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 very serious reduction in the newborn's expected HRQoL and an extensive need for health care throughout life. See the Health Related Quality-of-Life (HRQoL) and Costs sections for more details.

6. *Adverse effects of the vaccine*

The Norwegian Medicines Agency periodically reports the number of registered adverse events (AEs) cases attributed to the HPV-vaccine. Their report indicates that, as of August 2013 (24), 277 625 vaccine doses had been administered to girls born between 1997 and 2000. Among these doses 431 cases of AEs were registered, of which 25 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 9 cases of serious AEs per 100 000 doses.

As the non-serious AEs cases lasted for a short period of time and probably had limited consequences for the patient, we did not include them in our model. Nevertheless we used the rate of serious AEs cases per 100 000 doses to calculate the annual incidence rate per dose.

Table 4 Vaccination and related serious adverse events (AEs) in Norway, 2009-2013

	Number of doses (by August 2013)				
	Girls born 1997	**Girls born 1998**	**Girls born 1999**	**Girls born 2000**	**Source**
First dose	21 963	24 057	24 995	25 054	Norwegian Medicines Agency (24)
Second dose	21 644	23 747	24 573	23 936	
Third dose	21 125	23 166	23 065	20 300	
Total per cohort	*64 732*	*70 970*	*72 633*	*69 290*	
Total since vaccination program started	***277 625***				
Total # AEs	431				
Serious AEs	25				
Number of serious AEs (per 100 000)	**9**				Own calculations

7. *Cohort size*
   In order to calculate the possible number of negative outcomes a HPV vaccine catch-up 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 in 2013 there were 60 829 (29 703 girls and 31 126 boys) eight-year-old children, and assumed that the size of future cohorts of eight-year-olds would remain unchanged.

   Although this is a strong assumption, we considered that changes in the size of the cohort would have a rather small effect on the relationship between incremental costs and incremental effects of the program, and thus on the results in this report.

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 first needed data on the annual number of births in Norway. We retrieved data from Statistics Norway for 2012 on the number of live births, according to the mother's age, and the number of females in each age group. We were then able to calculate the number of live births per 1 000 women in each age group between 15 and 49 years (see Appendix 2. Epidemiological data).

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 2012 (see Appendix 2. Epidemiological data).

   The Norwegian population has experienced a large increase in life expectancy since the Second World War because of reduced mortality in most age groups, and recent data indicates that this is a continuing trend (http://ssb.no/dode). Incorporating this 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 therefore would be heavily discounted, limiting the effect of falling death rates on the relationship between total incremental costs and effects. For simplicity, we assumed that the 2012-mortality rates would apply for the coming 100 years.

Efficacy of the HPV vaccine

As explained earlier, we assumed that those infected with a specific HPV-type cannot return to the susceptible group for that type in the infection model, i.e. they experience lifelong natural immunity against that HPV-type for the rest of their lives and therefore receive no benefit if vaccinated (against that same HPV-type). This allowed us to track the share of people having experienced at least once infection with that type in each cohort over time and therefore to calculate the correspondent cumulative incidence.

Another key factor in our model was the assumption that the percentage reduction in health outcomes attributable to a given HPV type was proportional to the percentage reduction in cumulative incidence to that HPV type. The vaccine reduces cumulative incidence in two different ways: First, it protects the vaccinated individual against infection when exposed to the HPV-virus (the direct effect); and second, it reduces the probability of exposure to HPV, independently of vaccination status (the indirect effect or herd immunity).

The effect of the vaccine on HPV 6, 11, 16 and 18 infection was assumed to be equal to the estimate for persistent infection at 12 months from Rambout (25). For the vaccine effect on health related outcomes, on the other hand, we performed a systematic review to obtain data on the effect of the vaccine on precancerous lesions CIN 2+, VIN 2+ and VaIN 2+, as well as on genital warts (3). The results showed that the effect of the vaccine was different across HPV-related health outcomes, so we adjusted the results of the model as explained in Chesson (2), see Appendix 3. Vaccine effect. Because our systematic review did not uncover effectiveness data for cancer, cancer mortality or the conization-related long-term consequences for the newborn, we used available data to extrapolate these effects. We relied on CIN 2+ to extrapolate effects for cervical cancer and the conization-related long-term consequences, VIN 2+ for vulvar cancer and VaIN 2+ for vaginal cancer.

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

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

We used data from Rambout (25), which reported a twelve months modified ITT relative risk (RR) estimate of persistent infection with HPV 16 and 18 among females of 0.26 (95% CI: 0.16, 0.41). This is equivalent to a relative risk reduction of 74%. Our model included only one persistent infection reduction parameter, for HPV 6, 11, 16 and 18, so we assumed the same RR would also apply to infection with HPV 6 and 11.

Table 5. Relative risk (modified ITT) of persistent infection. vaccination vs. no vaccination

Effect estimate	Persistent infection at 12 months, RR (95% CI)
ITT	0.26 (0.16, 0.41)

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 systematic review (3), which was 0.80 (95% CI: 0.62, 1.02), see Table 6. This is equivalent to a relative risk reduction of 20%.

Table 6. Relative risk (ITT) of experiencing CIN 2+. catch-up-vaccine vs. no vaccine

Effect estimate	All CIN 2+, RR (95% CI)
ITT	0.80 (0.62, 1.02)

Vaccine effect on genital warts

We used the four to five year follow-up, ITT RR estimate of experiencing genital warts from our systematic review (3), which in this case was 0.38 (95% CI: 0.31, 0.47), equivalent to a relative risk reduction of 62%.

Table 7. Relative risk (ITT) of experiencing genital warts, catch-up-vaccine vs. no vaccine

Effect estimate	All genital warts, RR (95% CI)
ITT	0.38 (0.31, 0.47)

Vaccine effect on VIN 2+, VaIN 2+, vulvar and vaginal cancer

We used the RR estimate for VIN 2+ and/or VaIN 2+ for the ITT population after a four to five year follow-up (3). The estimate was 0.49 (95% CI: 0.32, 0.76), leading to a relative risk reduction of 51%.

Table 8. Relative risk (ITT) of experiencing VIN 2+, VaIN 2+, catch-up vaccine vs. no vaccine

Effect estimate	All VIN 2+, VaIN 2+, RR (95% CI)
ITT	0.49 (0.32, 0.76)

Vaccine effect on other HPV-related outcomes

The original model incorporates the effect of the vaccine on anal, penile and oropharyngeal cancer and juvenile onset recurrent respiratory papillomatosis (JoRRP) is incorporated. As our systematic review did not find studies reporting rel-

evant effect estimates, we decided not to include these outcomes in the base case analysis.

Costs

The total cost of the catch-up program 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 catch-up program from two different perspectives:

- Public health budget perspective, which only includes costs to the National health budget (Value added tax, or VAT, included).
- Societal perspective, which includes costs to the National health budget (VAT and other transfer payments between economic agents excluded, as they are not real economic costs), the monetary value to the patient of the time spent when receiving health treatment and the monetary value of lost working time after disease.

Vaccine costs

We calculated vaccine costs by multiplying the price per dose by the number of vaccine doses administered to females aged 26 years or younger.

The vaccine price in the base case was the public price of the quadrivalent vaccine in January 2014, NOK 1 010.9/dose (Norwegian Medicines Agency, NOMA). The model uses a scenario analysis to evaluate alternative, lower prices.

To calculate the number of administered doses per patient we used the proportion of ITT- and PPP-participants in four of the main studies in the systematic review: Future I (26), Future II (27), Future protocol 19 (28) and Patricia (29) . The result was an average of 2.78 doses per patient (for more details, see Appendix 4. Costs).

To determine the number of females in the target population of the catch-up program we chose to only include the female cohorts born 1989-1996, i.e. those females aged 13 or older when the current vaccination program for 12-year-old girls was introduced in 2009, but not older than 26 years-old at the beginning of the catch-up implementation, estimated to be Fall 2015.

Finally, we used the vaccination coverage rates reported in Australia for females aged 19-26, Brotherton 2011 (30). More specifically we used the rates for one dose, on average 54%, 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:

Table 9. Coverage rates (one dose) used in the Norwegian model.

Female's age in 2015 (year of birth)	Coverage rate in the model (one dose, females)
26 (1989)	30%
25 (1990)	49%
24 (1991)	56%
23 (1992)	57%
22 (1993)	58%
21 (1994)	59%
20 (1995)	61%
19 (1996)	62%

Estimating costs savings due to vaccination

We estimated total savings by multiplying the number of prevented HPV-related health outcomes, which we obtained from the infection model, 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 (16), 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. Tax on wages and payroll taxes are also transfers, this time from workers and employers to the State, but in this case we did not exclude these as this is not recommended by the Ministry of Finance.

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 because only some costs (for example, purchase of consumable goods) are subject to VAT while others are not (for example, wages).

There is no published data specifying the share 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 model from a societal perspective.

2- *Deadweight loss due to tax funding of the catch-up program:*
We have chosen to not include the potential cost imposed if extra tax revenues must be raised to fund the HPV catch-up program. Although the Ministry of Finance guidelines suggest including a cost of NOK 0.2 per NOK 1 of additional taxes to account for societal resources lost to tax collection, these guidelines are currently under review. In addition, current Directorate of Health recommendations for health economic evaluations do not include these costs (31).

3- *Monetary value of patient's time spent when receiving health treatment*
The experts we consulted during the costs estimating process provided us with an estimation of the number of hours of her/his time a patient would have to sacrifice in order to receive each vaccine dose as well as treatment for HPV-related outcomes.

We then multiplied the number of hours by our estimate of the hourly after-tax wage rate for 2012, NOK 121, based on the Norwegian average annual pre-tax income data from Statistics Norway (NOK 446 200, http://www.ssb.no/inntekt-og-forbruk) and some assumptions (see Appendix 4. Costs).

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 patients

may be of working age and employed, so that they may have to spend working hours to receive treatment.

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

- we multiplied the aforementioned average annual pre-tax income data from Statistics Norway (NOK 446 200, http://www.ssb.no/inntekt-og-forbruk) by the expected number of working years lost due to every HPV 16 and 18-related cancer, preterm birth and abortion case;
- future income was discounted using a real rate of 4%;
- the results were adjusted by reducing them 50% in order to account for compensation mechanisms in the labor market, as proposed by the Norwegian Directorate of Health (31).

For further details, please see Appendix 4.

The costs per HPV-related outcome

The results of the cost estimation process are shown in Table 10:

Table 10. Estimated Norwegian cost per HPV-related outcome (2014-NOK)

Treatment	To public health budget (NOK)	To society (NOK)	Experts consulted*
CIN 2 - Conization	8 326	8 492	Ingvild Vistad, gynecologist, chief physician (Sørlandet sykehuset)
CIN 3 - Conization	8 326	8 492	Ingvild Vistad, gynecologist, chief physician (Sørlandet sykehuset)
Conization-related long term costs	71 306	278 417	Ingvild Vistad, gynecologist, chief physician (Sørlandet sykehuset)
Genital warts	2 562	4 294	Turid Jorunn Thune, chief physician (Haukeland universitetssjukehus) and Ingvild Vistad, gynecologist, chief physician (Sørlandet sykehuset)
Cervical cancer	208 663	1 211 965	Ingvild Vistad, gynecologist, chief physician (Sørlandet sykehuset)
Vaginal cancer	280 402	285 516	Ingvild Vistad, gynecologist, chief physician (Sørlandet sykehuset)

Vulvar cancer	280 402	285 516	Ingvild Vistad, gynecologist, chief physician (Sørlandet sykehuset)
Serious adverse events of HPV-vaccine	42 158	42 537	Ingvild Vistad, gynecologist, chief physician (Sørlandet sykehuset)

* The responsibility for the final choices is the authors' alone.

The costs of treating cancer are 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 209 000 per case under the public health budget perspective, to approximately NOK 1.2 mill under the societal perspective. This is primarily because many of patients are young (weighted average age at diagnosis is 50.5, according to data from the Cancer Registry) and still of working age, so that early cancer-related mortality leads to a great expected loss of working years.
- *Conization-related long term costs to the newborn.* It includes both the expected medical costs per abortion and per premature living baby, the expected long-term treatment costs of the newborn due to disability, the expected productivity costs due to life-time disability and the expected productivity costs due to abortion. The cost estimate increases from approximately NOK 71 000 to NOK 278 000 per case, also particularly because of the great expected productivity costs to the newborn.

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

Health Related Quality-of-Life (HRQoL)

In Chesson (2) the authors calculated the expected, age-specific number of discounted lifetime quality-adjusted life years (QALY) lost per HPV-related health outcome by calculating the percent reduction in discounted quality-adjusted life expectancy (QALE) in the general population, associated with that outcome.

To calculate the discounted QALE in the general Norwegian population we used the gender-neutral EQ-5D -weights at each age in Burström (32); the gender-specific death rate per 100 000 at each age group in 2012 (Statistics Norway); and a real discount rate of 4%.

To calculate the percent reduction in QALE, we used HRQoL-weights associated with each health outcome before and after treatment. The QALE was calculated

based on the EQ-5D-weights in Burström (32). For consistency we used data based on EQ-5D (and TTO) throughout the model. Not all weights in Chesson (2) were EQ-5D or time trade-off (TTO)-based, so we conducted our own systematic literature search to find relevant weights which were transferable to a Norwegian setting (see Appendix 5. Health related quality-of-life (HRQL) data for more details).

There were two other important elements for calculating the percent reduction in QALE were the durations of the QALY-losses: First, the duration of the QALY-losses, which were assumed to be the same as in Chesson (2). And second, for cancer, the 5-year survival (i.e. the percentage of patients still alive five years after the date of diagnosis) for every disease stage and the disease stage at diagnosis (separately for those aged 50 or younger and for those over 50), data we obtained from the Cancer Registry of Norway. See the Appendix 5. Health related quality-of-life (HRQL) data

The resulting number of expected QALYs lost by HPV-related health outcome, gender and age group are presented in Table 11:

Table 11. Expected number of discounted lost QALYs per case by age, females and males

Age group	CIN 2	CIN 3	GW - Female	GW - Men	Cervical cancer	Vaginal cancer	Vulvar cancer
12 to 14	0.110	0.110	0,047	0,0431	6.795	8.272	6.945
15 to 19	0.110	0.110	0,047	0,0431	6.670	8.115	6.817
20 to 24	0.109	0.109	0,046	0,0426	6.495	7.896	6.636
25 to 29	0.109	0.109	0,046	0,0426	6.293	7.641	6.426
30 to 34	0.107	0.107	0,046	0,0421	6.058	7.346	6.183
35 to 39	0.107	0.107	0,046	0,0421	5.785	7.002	5.900
40 to 44	0.105	0.105	0,045	0,0413	6.046	6.959	5.670
45 to 49	0.105	0.105	0,045	0,0413	7.004	7.313	5.516
50 to 54	0.102	0.102	0,043	0,0402	7.212	7.193	5.206
55 to 59	0.102	0.102	0,043	0,0402	6.539	6.509	4.718
60 to 64	0.099	0.098	0,042	0,0387	5.804	5.766	4.187
65 to 69	0.098	0.098	0,042	0,0387	5.019	4.969	3.618
70 to 74	0.097	0.097	0,041	0,0380	4.172	4.110	3.005
75 to 79	0.096	0.096	0,041	0,0380	3.270	3.198	2.352
80 to 84	0.089	0.089	0,038	0,0351	2.413	2.338	1.733
85 to 90	0.088	0.088	0,038	0,0351	1.695	1.616	1.215
91 to 94	0.088	0.087	0,038	0,0351	1.100	1.024	0.787
95 +	0.085	0.085	0,038	0,0351	0.518	0.462	0.372

The QALY-weights for the different cancer types are quite similar so differences in lost QALYs between cancer types to a large degree are associated primarily with the cancer specific mortality rates and the patient distribution among disease stages at diagnosis (see Appendix 5. Health related quality-of-life (HRQL) data for details).

The estimation method used yielded smoothly decreasing QALY-loss values with respect to age for all outcomes except for cervical and vaginal cancer, for which there

is an increase around age 45. This increase mainly reflects the fact that the disease stage at diagnosis is considerably more unfavorable for patients older than 50 than it is for those aged 50 or younger, as a substantially larger share of these older patients are diagnosed with regional and distant cancers, which are associated with far lower 5-years survival probabilities than local cancers (source: Data from Cancer Registry of Norway).

CIN and genital warts lead to a relatively low number of lost QALYs, mainly due to the nature of these conditions, which are of short duration and relatively limited severity.

For serious episodes of AEs and conization related outcomes the QALY-losses were calculated as one-time losses, as AEs may only take place during the year of vaccination, while QALY-losses due to conization related outcomes are all discounted to birth, as if they only took place at birth and not later on in life.

Table 12 Number of QALYs lost per case, females and males (discounted)

Outcome	Base case	Source
Serious AEs of vaccination	0.01	Assumption
Expected loss (for the newborn) per critical preterm delivery due to previous conization	3.56	Own calculations

In order to estimate the HRQoL-loss due to serious AE episodes, we went through all 25 serious adverse event notifications, provided to us by the Norwegian Medicines Agency. Most patients experienced several symptoms at the same time, some of them quite severe, as for example loss of consciousness and convulsions. Nevertheless, for most of patients the notifications did not reveal the exact duration of each symptom, making it difficult to calculate an average estimate of a HRQoL-loss per serious AE episode. For simplicity we assumed that the total loss would be 0,01 QALYs, approximately equivalent to an annual loss per episode of three days in full health.

Assigning distributions to the random variables in the model

As discussed earlier, we implemented a probabilistic model by assigning a probability distribution to most included 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.

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 primarily followed Briggs (12).

Incidence rates of the 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 data per age group between 2002 and 2010 provided to us 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 between 2002 and 2010, available at the website of Statistics Norway (http://ssb.no/befolkning).

The fit of the distribution for genital warts was performed differently because, as explained earlier, we only had incidence rates based on data from Kjær (18). We then assumed that the standard error of the incidence would be 50 % the value of the estimated incidence rate and used the method of the moments to estimate α and β based on the values of the mean and the variance (i.e. the square of the standard error).

Vaccine effect
The 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 the available cost estimate was assumed to be the mean value and the standard error, 50% of that mean.

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-loses, 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 patient cancer stage distribution at diagnosis. However that approach would have required knowledge about 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 in the sense that the available estimate was assumed to be the mean value and the standard error, 50% of that mean.

Economic evaluation – Results

We calculated lifetime costs and effectiveness in terms of QALYs, for both the current vaccination program and catch-up in addition to the current program based on 1 100 simulations of the model (for more details, see Appendix 1. General information about the model).

Based on the difference in costs between the two alternatives divided by the difference in health effect we calculated then a Incremental Cost-Effectiveness Ratio (ICER) which is one of the factors decision makers may pay attention to when considering the implementation/decommissioning of health care programs. We also calculated the Net Health Benefit (NHB) based on a range of 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.

Base case Incremental Cost-effectiveness Estimates

Results when conducting the analysis from a public health budget perspective
Below we present the average results, based on 1 100 iterations of the model. The incremental costs/effect are calculated by subtracting the costs/effect of the current program from the costs/effect of adding the catch-up program to the current program.

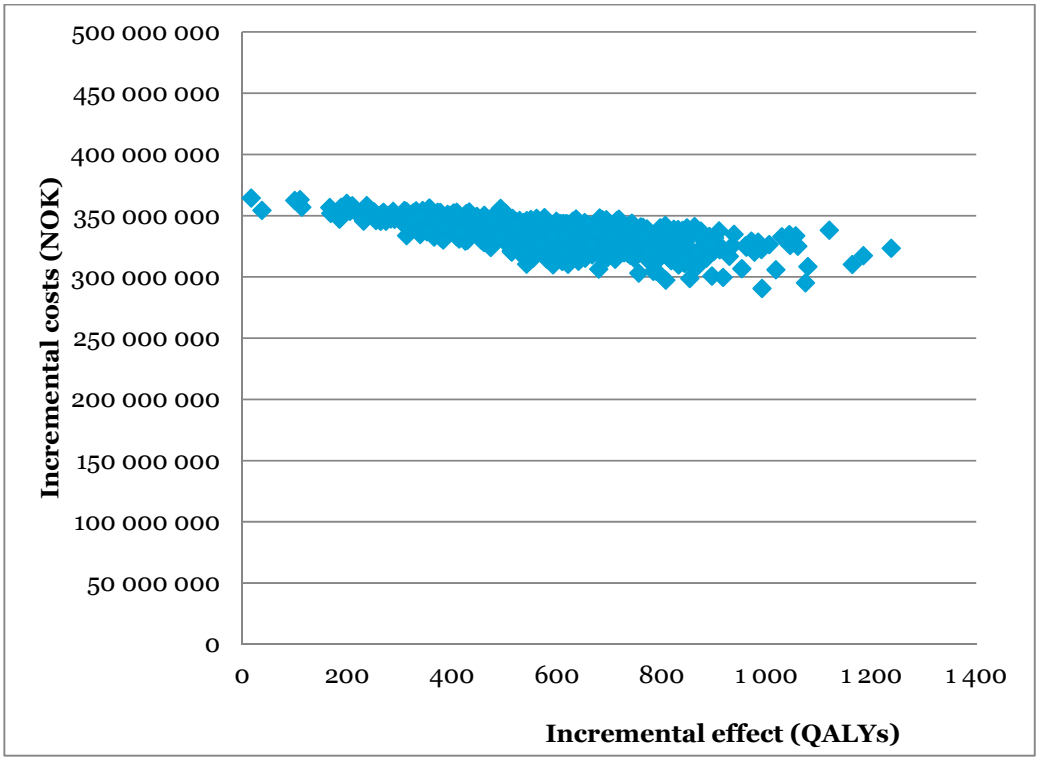
Table 13. Expected incremental costs and effects of catch-up vaccine vs. Current vaccination program. Public health care budget perspective.

Intervention	Costs (NOK)	Effect (QALYs)	Incremental Cost (NOK)	Incremental effect (QALYs)	ICER (NOK / QALY)
Current program (12-year-old girls only) vs. No vaccination	1 720 399 478	10 256.46	335 734 785	580.46	**578 391**
Catch-up + Current program vs. No vaccination	2 056 134 263	10 836.92			

Adding a catch-up vaccination program in 2015 for females aged 26 years or younger to the current vaccination program for 12-years-old girls alone, results in a discounted health gain of 580.46 QALYs and a discounted, incremental cost of NOK 335.7 million, providing an ICER of 578 391 NOK/QALY. Dividing the incremental costs and the incremental health gain by the estimated number of females that would receive at least one dose of the catch-up vaccine (approximately 128 100, i.e. 54 % of the target population, 237 200 females), we obtained an expected incremental cost of NOK 2 620/vaccinated female and an expected incremental health gain of 0.0045 QALYs/vaccinated female.

Below we show the scatter plot of the 1 100 iterations of the model, where the incremental effect is displayed along the x-axis and the incremental costs along the y-axis:

Figure 3. Cost-effectiveness scatter plot of adding the catch-up program to the current vaccination program. Public health budget perspective.



All iterations were located in the upper right quadrant, where both the incremental costs and effect of the catch-up program were positive, i.e. our model supports the hypothesis that the catch-up program results in better health outcomes (in the form of QALYs) than keeping the current vaccination program but at higher costs.

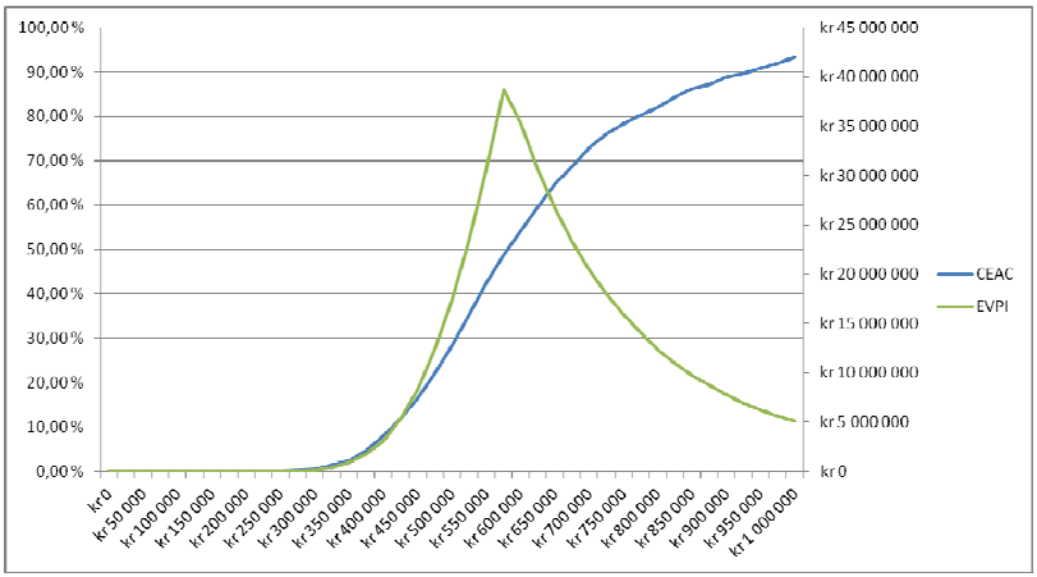
Table 14 reports both the incremental net health and monetary benefit (INHB and INMB) for different WTP values. Positive values for the INHB and INMB suggest that adding the catch-up program to the current vaccination program would be cost-effective, while the opposite is true for negative values. For a WTP of 578 391 NOK/QALY, both measures are equal to zero.

Table 14. Incremental net health and monetary benefit of adding the catch-up program to the current vaccination program

	WTP (NOK/QALY)			
Incremental Net Benefit	**250 000**	**500 000**	**750 000**	**1 000 000**
INHB (QALYs)	-762	-91	133	245
INMB (NOK)	-190 618 903	-45 503 022	99 612 859	244 728 740

The probability that adding the catch-up-vaccine 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 4.

Figure 4. CEAC (blue, left axis) and EVPI (green, right axis) in the base case, public health budget perspective.



The figure indicates that the probability that catch-up program is cost-effective is 0%, 28.2% 78.3% and 93.2% as willingness-to-pay (WTP) per QALY is, respectively, NOK 250 00, NOK 500 000, NOK 750 000 and NOK 1 000 000.

The expected value of perfect information (EVPI) curve, which can be interpreted as the upper bound on the returns to further research regarding the costs and effect of the catch-up program, reached a maximum of approximately NOK 38.6 million at a WTP equivalent to the program's ICER 578 391/QALY. If the expected costs of additional research are lower than these returns to the EVPI, then it is cost-effective to conduct further research when the WTP is 578 391/QALY.

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.

Results when conducting the analysis from a societal perspective:
Below we present the average results, based on 1 100 iterations of the model from a societal perspective.

Table 15. Expected total costs and effects of catch-up vaccine vs. Current vaccination program. Societal perspective.

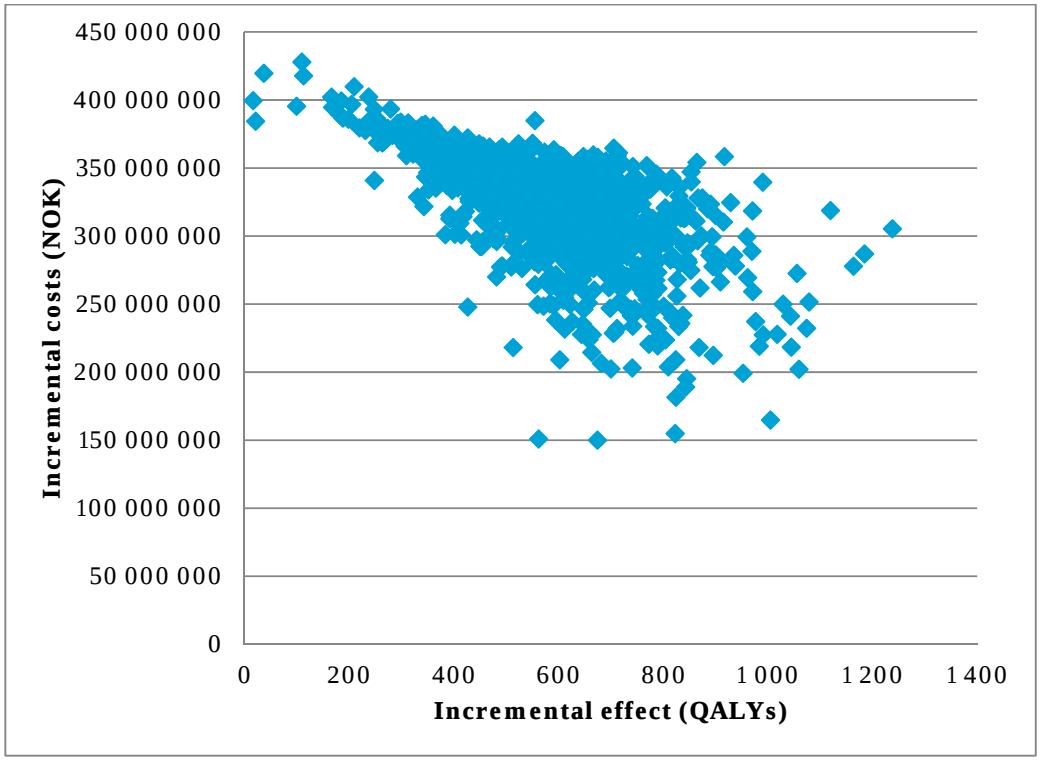
Intervention	Costs (NOK)	Effect (QALYs)	Incremental Cost (NOK)	Incremental effect (QALYs)	ICER (NOK/ QALY)
Current program (12-year-old girls only) vs. No vaccination	1 292 475 294	10 257.65	321 356 298	580.39	**553 691**
Catch-up + Current program vs. No vaccination	1 613 831 592	10 838.04			

From a societal perspective the incremental costs were approximately 4.3% lower than from a public health budget perspective, NOK 321.3 million vs. NOK 335.7 million, while the incremental effect was practically the same, resulting in an ICER of NOK 553 691/QALY, an improvement compared with the ICER from a public health budget perspective, NOK 578 391/QALY.

The difference in the results between the two perspectives primarily reflects the costs that differ most between perspectives, namely the cost per cervical cancer case and per premature birth and late abortion due to HPV-related conization. As described earlier, these cost inputs included large expected productivity costs because patients suffer these outcomes and the resulting serious health consequences at a young age. The cost per cervical cancer is particularly important, because it occurs more frequently than premature births due to HPV-related conizations (see Method for details).

The scatter-plot of the ICER from this perspective is shown in Figure 5:

Figure 5. Cost-effectiveness scatter-plot of adding the catch-up program to the current vaccination program. Societal perspective.



The societal perspective scatter-plot shows that both the costs and effect of introducing the catch-up program were positive in all iterations, and that the dispersion of the incremental cost was greater than in the public budget perspective scatter-plot.

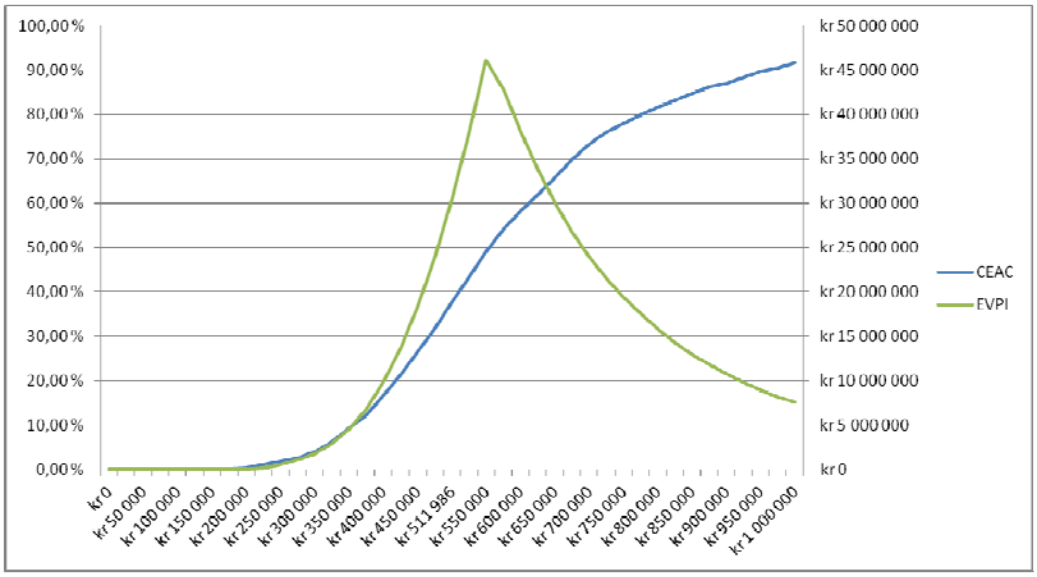
Table 16 reports both the incremental net health and monetary benefit (INHB and INMB) for different WTP values.

Table 16. Incremental net health and monetary benefit of adding the catch-up program to the current vaccination program. Societal perspective.

	WTP (NOK/QALY)			
Incremental Net Benefit	**250 000**	**500 000**	**750 000**	**1 000 000**
INHB (QALYs)	-705	-62	152	259
INMB (NOK)	-176 259 049	-31 161 799	113 935 450	259 032 699

The results from the CEAC (blue curve in Figure 6) show that the probability of the catch-up program to be cost-effective is approximately 1.91%, 37.6%, 77.9% and 91.7% as WTP per QALY is, respectively, NOK 250 000, NOK 500 000, NOK 750 000 and NOK 1 000 000.

Figure 6. CEAC (blue, left axis) and EVPI (green, right axis) in the base case. Societal perspective.



The expected value of perfect information (EVPI) curve (in green in Figure 6) from a societal perspective was approximately NOK 47 million for a willingness-to-pay equivalent to the ICER, NOK 553 691/QALY.

For a willingness-to-pay equivalent to the ICER from a public health budget perspective, NOK 578 391/QALY, the EVPI was NOK 42.5 million, approximately NOK 4 million higher than from a public health budget perspective. This suggests that the returns to further research regarding the costs and effect of the catch-up program are greater as the costs of uncertainty (determined jointly by the probability that a decision based on existing information will be wrong and the consequences of a wrong decision) seem to be higher from a societal perspective.

Scenario Analyses

Scenario analyses make it possible to examine the impact of specific model assumptions on the results. We conducted two types of scenario analyses: The first investigated the effect of a lower vaccine purchase price. The second excluded the estimated effect of the vaccine on genital warts in order to examine the cost-effectiveness of using a bivalent, rather than quadrivalent vaccine.

Alternative prices

Our analysis assumes that the HPV vaccine is purchased at market price, currently NOK 1010.9/dose. We examined three alternative scenarios, with per dose prices of NOK 250, NOK 500 and NOK 750. All prices were evaluated in the model from a

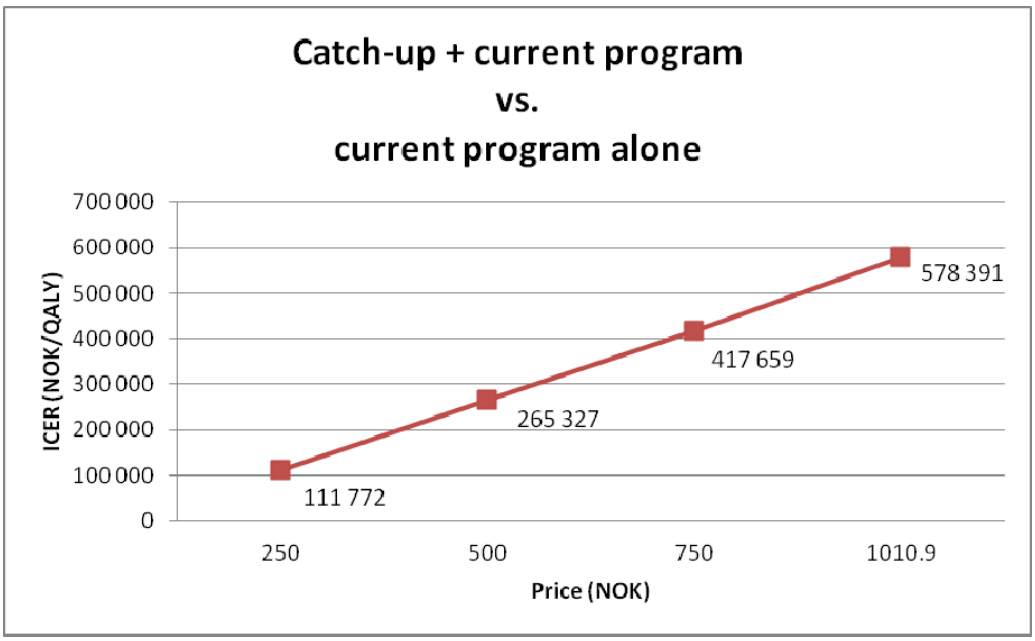
public health budget perspective. Table 17 reports cost-effectiveness results for each price, while Figure 7 illustrates the information graphically:

Table 17. ICERs and NHBs of adding the catch-up program, compared to current program alone when using vaccine prices below the current public price

	Incremental Cost (NOK)	Incremental effect (QALYs)	ICER (NOK/QALY)
NOK 1010.9 / dose	335 734 785	580.46	578 391
NOK 750 / dose	242 885 930	581.54	417 659
NOK 500 / dose	153 916 157	580.10	265 327
NOK 250 / dose	64 946 384	581.06	111 772

The incremental costs fell 80.6%, 54.1% and 27.6% for, a price of, respectively, NOK 250, 500 and 750/dose. As the incremental health effect remained practically unchanged (with very small variations), lower incremental costs resulted in lower ICERs.

Figure 7. ICERs for base case and alternative quadrivalent vaccine price 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. The bivalent vaccine, however, does not provide protection against genital warts.

We conducted a scenario analysis, which excluded the vaccine's effect on genital warts and assumed that the price of the bivalent vaccine would be equal to the price of the quadrivalent, i.e. NOK 1010.9/dose. We did this in order to both estimate the cost-effectiveness of the bivalent vaccine and to ascertain the price at which the cost-effectiveness of the bivalent and quadrivalent vaccines were the same. All females, aged 12 or older, were assumed to receive the bivalent vaccine in this scenario analysis.

Table 18 provides results from a public health budget perspective:

Table 18. Estimated cost-effectiveness of the bivalent vaccine. Public health budget perspective.

Intervention	Costs (NOK)	Effect (QALYs)	Incremental Cost (NOK)	Incremental effect (QALYs)	ICER (NOK/ QALY)
Current program (12-year-old girls only) vs. No vaccination	1 938 508 269	6 910.49	342 151 615	485.80	**704 308**
Catch-up + Current program vs. No vaccination	2 280 659 884	7 396.28			

Compared to the base case, the incremental costs are slightly higher (NOK 342.1 vs. 335.7 million) while the incremental effect is considerably lower (485.8 gained QALYs vs. 580.46 in base case). The result is an ICER of NOK 704 308/QALY, which means that the willingness-to-pay of the decision-maker has to increase from NOK 578 391/QALY to NOK 704 308/QALY for the catch-up program to be considered cost-effective.

Furthermore, and based on the abovementioned results, the price at which the bivalent vaccine reaches an ICER equivalent to the one of the quadrivalent vaccine, i.e. 578 391/QALY, is approximately NOK 780/dose.

Discussion

In this health economic analysis we have evaluated the cost-effectiveness in the Norwegian setting of administering a catch-up vaccine to females aged 26 years or younger compared to maintaining the current practice of vaccinating 12-year-old girls.

Summary of results

In our base case analysis we assumed that approximately 54% of all girls and young women in the target population would get on average 2.78 doses of the HPV-vaccine. Furthermore, we assumed that the vaccine would only have effect on the health outcomes in the model as documented in our own systematic review (3). Finally, the price of the vaccine was set equal to the public price of the quadrivalent vaccine, currently NOK 1010.9/dose.

From a public health budget perspective, the base case results showed that a catch-up program for females aged 26 years or younger would lead to a discounted, incremental cost of NOK 335.7 million and an incremental health gain of 580.4 QALYs. This resulted in an ICER of NOK 578 391/QALY. The probability that the catch-up program was both less effective and more expensive than keeping the current vaccination program was zero. In addition, 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 reached a maximum of approximately NOK 38.6 million at a WTP equivalent to the program's ICER 578 391/QALY. This means that if the expected costs of additional research are below NOK 38.6 million, it is cost-effective to conduct further research when the WTP is 578 391/QALY.

From a societal perspective the catch-up program had a lower ICER, NOK 553 691 /QALY, mainly due to the expected productivity costs associated with each case of cervical cancer case and (to a lesser extent) of premature birth and late abortion.

Several scenario analyses were conducted in order to ascertain the impact on the base case results of both the vaccine price and the exclusion of the vaccine effect on genital warts:

- Using prices of NOK 250, 500 and 750/dose resulted in lower incremental costs and therefore lower ICERs of NOK 111 772/QALY, NOK 265 327/QALY and NOK 417 659/QALY, respectively.
- Excluding the vaccine effect on genital warts from the analysis resulted in both higher incremental costs and a lower incremental health effect than in the base case. The ICER was NOK 704 308/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 1010.9/dose, we estimated that the price of the bivalent vaccine had to be approximately 780 NOK/dose or lower in order to be as cost-effective as the quadrivalent vaccine.

Strengths and weaknesses of this report

Choice of model
We chose to adapt an existing model to the Norwegian setting instead of developing an all-new one. 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,*
- *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*

We acknowledge that setting too many requirements may could have reduced the probability of finding an adequate model. Nevertheless, in order to answer the questions posed by the Norwegian Institute of Public Health, and to assure the impartiality of our assessment, we considered that all five requirements were necessary.

The model we finally chose, Chesson (2), was considered fit-for-purpose as it fulfilled all these requirements. Although it is as simpler model compared to other existing models (13-15), in the sense that there was no need to model the probability of HPV acquisition, the possible progression from HPV infection to disease, the mixing of sex partners, the probability of HPV transmission, and so forth, Chesson and col-

leagues 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 (17).

Data sources

Most of the epidemiological and costing data we used in this economic analysis were from Norwegian sources, strengthening the transferability of the results to a Norwegian setting. In addition, most of the data were retrieved from published literature or publicly available sources (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 men having sex exclusively with other men, as vaccine coverage among males in Norway (not a part of the current, publicly funded vaccination program) is believed to be well below coverage among females.

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. In doing so, we implicitly assumed that vaccinated and unvaccinated women would have the same cervical cancer screening rates. If vaccinated women are more likely to be screened than unvaccinated women, then the cost-effectiveness of female vaccination could be less favorable than we estimated, and the cost-effectiveness of increased vaccine coverage of females could be more favorable than we estimated (2).

We also assumed that vaccinated women would not change their behavior regarding compliance to the screening program. If women decided to attend screening less frequently as a result of having received the vaccine, the ICER of the catch-up program may be higher than in our base-case results.

HPV-incidence rates

We lacked data on the incidence rates of the HPV 6, 11, 16 and 18. The only data we had was the prevalence rates for females aged 17 and 21 years old for those same

types. To obtain incidence rates we based our calculations on the Norwegian values for those two age groups and the age profile of the incidence rates in the original model (2). More specifically, we assumed that the age profile of HPV-infection in Norway is similar to the one in the USA. Lower prevalence and incidence rates would most probably result in fewer avoided HPV-related outcomes and therefore higher incremental costs and a smaller health gain.

Effect estimates in the target population

We used the vaccine effect estimates on relevant HPV-related outcomes from our own systematic review (3), which included the latest findings in the literature for females in the target population. These findings showed that the vaccine had effect on cervical, vaginal and vulvar precancerous lesions as well as on genital warts, so we incorporated these effects in our analysis. In addition, we assumed that the effect on precancerous lesions (CIN2+, VIN 2+ and VaIN 2+) also applied to cervical, vaginal and/or 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 catch-up program may be overestimated, and the ICER higher.

Furthermore, as we did not find any evidence regarding the effect of the vaccine on neither anal, penile or oropharyngeal lesions or cancers, nor on JoRRP in our systematic review, we did not include these outcomes in the model analysis. The inclusion of potential prevented anal, oropharyngeal, penile lesions or cancer and/or JoRRP cases would most probably lead to greater cost savings and a higher incremental effect and thus to lower ICERs.

The time horizon of the model is a vital 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 any new 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 was long enough to capture all relevant consequences of introducing the catch-up program for the public health budget and society. Several, earlier analysis of catch-up programs have as well used a time horizon of 100 years (33).

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. This may primarily reflect a weaker effect on those outcomes taking place

early in patient's life (genital warts and CIN 2+ lesions), as the corresponding costs and HRQoL-losses would not be heavily discounted.

Finally, we did not incorporate cross-protection against other HPV-types than the ones targeted at by the quadrivalent vaccine, as our systematic review did not find evidence in this regard. If cross-protection did exist and were incorporated in our model, it might increase the number of HPV-related events prevented by the vaccine, thus increasing the effect and reducing the incremental costs of the catch-up program, which in turn would result in a lower ICER. On the other hand, 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 (17).

Costs

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

The vaccination costs are based on two main assumptions: First, that the coverage rates for one dose in Norway will be the same as the rates in the existing Australian catch-up program; and second, that the average number of vaccine doses each female will receive is equivalent to the weighted average of four studies included in our systematic review. The uncertainty around these parameters may be resolved as the catch-up program is implemented and we gather more data.

The model does not include the cost to the public health system of administering the vaccine, since we did not know at the moment of writing this report how the eventual catch-up program would be implemented. All other things held constant, including the costs of vaccine administration in our analysis would result in increased costs and (most probably) no change in the incremental effect, so that the ICERs of the catch-up program from both analysis perspectives would increase.

The model also 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 the catch-up program.

We excluded from our model the costs and QALY-losses associated with VIN and VaIN 2+ in order to compensate for the assumption of vaccine effect on vaginal and vulvar cancer. Incorporating the avoided costs and QALY-losses associated with VIN and VaIN 2+ may reduce the ICER of the catch-up program.

The calculation of costs from the societal perspective is based on several assumptions. Among other things 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 this, our analysis is, to our knowledge, one of the few that includes such productivity costs, probably giving a more accurate picture of the consequences for society of introducing a catch-up program.

The exclusion of the VAT from the 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.

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

To calculate the discounted QALE in the general Norwegian population we used the gender-neutral EQ-5D -weights at each age in Burström 2006 (32). As these weights were calculated using the EQ-5D method, we used data exclusively based on EQ-5D (or TTO) throughout the model for the sake of consistency. In order to find relevant EQ-5D or TTO weights we conducted and presented the results of a systematic literature search, which made our model more transparent.

Because we did not find 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. Furthermore we did not find Norwegian HRQoL-data, which may limit the transferability of the model results to a Norwegian setting.

All these factors together may have increased the uncertainty around our results. In order to take this into account, we assigned distributions with wide confidence intervals to all QALY-losses (as we did with the average cost estimates). This may ex-

plain the large variation of the incremental effect across model iterations, shown in Figure 3 and Figure 5, which resulted in lower probabilities of the catch-up program being cost-effective, as well as higher EVPI, for every potential willingness-to-pay per-gained-QALY.

Our results compared to other findings/other reviews

We found a systematic literature review of the different methodological approaches and underlying assumptions of models assessing the cost-effectiveness of vaccination catch-up strategies, de Peuter (33). The cost-effectiveness results of catch-up programs for females aged 12 to 26 compared with vaccination of 12-years-old girls is presented for three of these models, and in all three cases the ICER of the catch-up program was substantially lower than in our base case: In Elbasha (13) the ICER was NOK 28 000/QALY ($ 1 = NOK 6), while in Dasbach (34) it was NOK 69 500/QALY (€ 1 = NOK 8.4) and in Insinga (35), NOK 18 300/QALY.

One factor that may explain the difference in ICERs is the inclusion of younger cohorts in the catch-up programs they examined, as this may result in more prevented HPV-related outcomes and therefore more gained QALYs and greater costs savings.

Conclusion

Administering a catch-up (quadrivalent) vaccine at a price of NOK 1010.9/dose to females aged 26 years or younger may be considered cost-effective (regardless of perspective) for a willingness-to-pay value of NOK 578 391/QALY or higher.

On the other hand, the price of the bivalent vaccine should not be higher than NOK 780/dose for it to be deemed as cost-effective as the quadrivalent.

Need for further research

The incidence and prevalence of the different HPV-types are especially important variables when estimating the number of HPV-related outcomes a vaccination program may help to avoid. Nevertheless, Norwegian incidence and prevalence data are very limited, which suggests that more research in this area may result in useful inputs for the estimation of the cost-effectiveness of the HPV-vaccine.

Implications for practice

The total target population of the catch-up program in Norway consists of approximately 237 200 females (8 cohorts, born 1989-1996, of approximately 29 650 females each). If the mean coverage rate reach 54% for the first dose, 50% for the second dose and 46% for all three doses, approximately 356 000 additional doses will be required to implement the catch-up program for females aged 19 to 26 years in 2015.

For more details regarding this calculation, see Appendix 6. Estimation of the vaccine expenditures associated with the implementation of the catch-up program.

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Appendixes

Appendix 1. General information about the model

On the Excel-model inner workings
The model calculates the differences in health effects and costs between the chosen intervention and no vaccination (as it was the case in Norway before 2009). This means that in order to examine the differences between the current situation in Norway, with a vaccination program for 12-year-old girls since 2009, and the catch-up program from 2015, the model had first to be run 1 100 times for each of these interventions against no vaccination. 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 incidence (annual acquisition probabilities) in the absence of vaccination.

> Chesson (2) 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, to estimate type-specific acquisition probabilities.
>
> Furthermore, they used a combined probability of infection for HPV 6 and 11. 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.

Percentage of health outcomes attributable to different HPV types
Table 19 shows the attributable percentages that were used in the original model (for those outcomes we included in the Norwegian adaptation). These determine to what degree the number of total cases of each outcome may be reduced due to vaccination. Totals below 100% indicate that these four HPV types are not the sole reason for these outcomes.

Table 19. 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%*
Vaginal cancer	-	49.20%	6.80%	*56.00%*
Vulvar cancer	-	39.60%	4.40%	*44.00%*
Genital warts	90.00%	-	-	*90.00%*

We did not, however, use these percentages as the effect estimates used in the Norwegian model informed about the effect on all outcomes in the table above, i.e. not only the HPV 6/11, 16 or 18-related, as in the original model.

This means that the totals we used did sum to 100%. In order to adjust the original percentages, we took into account the proportions between the HPV-16 and 18 percentages. The results are shown below:

Table 20. 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%*
Vaginal cancer	-	87.86%	12.14%	*100%*
Vulvar cancer	-	90.00%	10.00%	*100%*
Genital warts	100%	-	-	*100%*

Conizations

Albrechtsen (23) reports data from Norway showing that 141 371 births were registered as preterm births in the period 1967-2003. Among these births, 995 took place after the mother underwent conization so that they may be categorized as critical (delivery before week 32 and late abortions with less than 24 weeks of gestation), equivalent to 0,704% of all preterm births or 0,044% of all births. 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 21 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**	**Total preterm deliveries**
Late Abortion	209	226	8 501	**8 936**	**141 371**
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**	

Source: Source: Albrechtsen (23). Tables 1 and 2

Total critical preterm deliveries after cervical conization (1967-2003)	995 = (226 + 234 + 535)
As% of total number of preterm deliveries	0.704%
As% of total number of deliveries	0.044%

In Table 22 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 22 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 (23). Tables 1 and 2

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 23:

Table 23 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**
14 164	93.75%
59	0.39%
55	0.36%
160	1.06%
670	4.43%
15 108	**100%**

Source: Own calculations

In this hypothetical case, the number of preterm deliveries would be 274, equivalent to 0,194% of all preterm deliveries or 0,012% of all births. This means that only 0,032% (= 0,044% - 0,012%) of all preterm births may be attributed to the fact that the mother had a conization before giving birth. Using births data for Norway, 60 248 births in 2012, 0,032% of all births results in approximately 20 births.

Table 24 Estimated annual number of preterm deliveries exclusively due to conization

Total critical preterm deliveries after cervical conization (1967-2003)	274
% of total number of preterm deliveries	0.194%
% of total number of deliveries	0.012%
Excess share of preterm delivery due to previous conization	0.032%
Expected annual number of preterm deliveries exclusively due to conization (2012)	19.42

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, also may have conizations.

Based on the percentages of health outcomes attributable to HPV 16 and 18 mentioned earlier, we assumed that approximately 0,0296% of all births in a given year are preterm births or late abortions due to HPV-16 infection and 0,0026% due to HPV 18 infection.

Table 25 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	0.032%
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	0.0296% = 91.81% * 0.032%
Share of total deliveries that result in conization-related preterm deliveries due to HPV-18 infections	0.0026% = 8.19% * 0.032%

Source: Own calculations

Birth rates

Population and birth data from Statistics Norway for 2012 allowed us to calculate the birth rate (number of newborns per 1 000):

Table 26. Birth rates in Norway, 2012

Age	Base case (newborns per 100 000)
14	0.00
15	0.22
16	1.31
17	4.13
18	8.26
19	16.34
20	27.01
21	40.72
22	50.15
23	66.31
24	82.58
25	96.67
26	111.50
27	121.58
28	133.29
29	134.44
30	140.84
31	137.32

32	126.44
33	115.77
34	104.37
35	87.01
36	69.97
37	57.38
38	44.95
39	33.24
40	22.07
41	14.34
42	8.41
43	5.19
44	2.94
45	1.30
46	0.72
47	0.52
48	0.39
49	0.15
50 +	0.00

Death rates

Table 19 contains the death rates (number of per 100 000) that were used in the model (Statistics Norway, 2012).

Table 27. Death rates per 100 000 in Norway (2012), by gender and age.

AGE	male	female
8	0.000097	0.000102
9	0.000033	0.000137
10	0.000132	0.000137
11	0.000095	0.000133
12	0.000093	0.000065
13	0.000062	0.000196
14	0.000216	0.000097
15	0.00018	0.000127
16	0.000267	0.000221
17	0.000209	0.000159
18	0.000537	0.000127
19	0.000295	0.000126
20	0.000667	0.000279

21	0.000694	0.000212
22	0.000726	0.000211
23	0.000499	0.000091
24	0.00057	0.000184
25	0.000815	0.000218
26	0.000632	0.000376
27	0.000575	0.000156
28	0.00066	0.00025
29	0.000648	0.000248
30	0.001035	0.000308
31	0.000649	0.00034
32	0.000907	0.000248
33	0.000734	0.000187
34	0.000862	0.000348
35	0.00077	0.000346
36	0.000979	0.000487
37	0.000779	0.000644
38	0.001163	0.000516
39	0.001241	0.000422
40	0.001013	0.000467
41	0.001432	0.000852
42	0.000982	0.000874
43	0.001308	0.000949
44	0.001303	0.000772
45	0.001713	0.000899
46	0.001908	0.001452
47	0.002047	0.001414
48	0.001921	0.001387
49	0.0019	0.001612
50	0.002816	0.001865
51	0.003011	0.001762
52	0.00374	0.001834
53	0.003913	0.002312
54	0.003841	0.00291
55	0.004437	0.002915
56	0.004511	0.003867
57	0.005082	0.003102
58	0.005618	0.003211
59	0.006924	0.004142
60	0.007663	0.005259
61	0.009314	0.00452
62	0.008594	0.005787
63	0.009691	0.005906
64	0.010727	0.007012

65	0.010956	0.00777
66	0.014015	0.008064
67	0.015429	0.009143
68	0.015938	0.011125
69	0.016023	0.011141
70	0.018458	0.011869
71	0.021341	0.014402
72	0.025047	0.016139
73	0.025468	0.016285
74	0.026124	0.01914
75	0.032494	0.021409
76	0.033274	0.022293
77	0.041045	0.025807
78	0.047307	0.03137
79	0.054768	0.03305
80	0.058195	0.037045
81	0.068343	0.044952
82	0.079529	0.050365
83	0.088712	0.062505
84	0.096434	0.062888
85	0.105321	0.07257
86	0.116649	0.087642
87	0.132591	0.095146
88	0.145341	0.113199
89	0.169266	0.119733
90	0.19462	0.154562
91	0.200273	0.153723
92	0.239318	0.191977
93	0.248707	0.194145
94	0.260306	0.227292
95	0.30096	0.251671
96	0.313095	0.283759
97	0.319717	0.309819
98	0.381843	0.327848
99	0.302252	0.347939

Appendix 3. Vaccine effect

As mentioned earlier, we performed a systematic review where we obtained data on the effect of the vaccine on precancerous lesions CIN 2+, VIN 2+ and VaIN 2+, as well as on genital warts (3). 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 (2), 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 ratio by the outcome related cost savings and avoided QALY-losses in that iteration. For example, if in a give 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) would be multiplied by the cost savings and QALY-losses due to the reduction in the number of CIN 3 cases, as calculated by the infection model.

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

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 was the public price (NOK 1010.9/dose by February 2014). For the calculation of the number of administered doses per patient we used the number of ITT- and PPP-participants in four of the main studies in the systematic review. We did this to match the effect estimate as reported in the studies with the estimated number of doses needed to achieve that effect.

More specifically, 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 28. Share of ITT-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 (26)	5 455	3 745	69%	12.7%	8.7%
Future II (27)	16 805	15 261	91%	39.1%	35.5%
Patricia (29)	18 644	16 162	87%	43.4%	37.6%
Future p 19 (28)	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 vaccine doses per female as follows:

Table 29. Estimated share of the 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		***2.78***

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, assisted us in cost estimation process, but we are responsible for the final choice of values. The same applies to all other unit costs used in this model.

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 lession (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 30. 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	590	590
Visit to gynecologist	1.00	1 174	1 174
Colposcopy	1.00	1019	1019
Biopsy	1.00	938	938
Patient time (hours)	3.00	121	364
Total (NOK)			**4 423**

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 31. Medical assessment after cervical cancer diagnosis.

Resource	Number	Price/DRG (NOK)	Cost (NOK)
Visit to gynecologist	1.00	1 174	1 174
Colposcopy	0.33	1 019	340
Biopsy	0.10	938	94
Blood tests	1.00	112	112
MR	1.00	4 165	4 165
CT-pelvis	1.00	4 250	4 250
PET	0.25	19 550	4 888
Cervix sample collection	1.00	5 912	5 912
Biopsy of the lymph node	0.20	1 305	261
Ultrasound	1.00	1 305	1 305
Examination under general anesthesia	0.50	5 137	2 569
Cytoscopy	0.50	5 137	2 569
Patient time (hours)	4.25	121	515
Total			**28 152**

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 (36).

Table 32. Patient distribution among cancer stages at the beginning of primary treatment (Norway).

Cervix cancer stage IA	59%
Cervix cancer stage IA1	
Cervix cancer stage IA2	
Cervix cancer stage IB1	
Cervix cancer stage IB2	
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 33. Treatment costs in primary treatment, by stage

Plateepitelcarcinom stage IA1			
Resource	**Number**	**Price/DRG (NOK)**	**Cost (NOK)**
Conization procedure	1	5 912	5 912
Patient time	1.50	121	182
Total (NOK)			**6 094**
Plateepitelcarcinom stage IA2			
Resource	**Number**	**Price/DRG (NOK)**	**Cost (NOK)**
Radical hysterectomy	0.50	144 047	72 024
Pelvic lymphadenectomy	1.00	72 452	72 451
Trachelectomy	0.50	21 933	11 335
Patient time (hours)	41.00	121	4 969
Total (NOK)			**160 779**
Adenocarcinom stage IA			
Resource	**Number**	**Price/DRG (NOK)**	**Cost (NOK)**
Hysterectomy	0.25	144 047	36 012
Radical hysterectomy	0.25	144 047	36 012
Trachelectomy	0.50	22 669	10 966
Lymphadenectomy	1.00	72 452	72 452
Patient time (hours)	73.00	121	8 847
Total (NOK)			**164 289**
Cervix cancer stage IB1			
Resource	**Number**	**Price/DRG (NOK)**	**Cost (NOK)**
Radical hysterectomy	1.00	144 047	144 047
Pelvic lymphadenectomy	1.00	72 452	72 452
Patient time (hours)	73.00	121	8 847
Total (NOK)			**225 346**
Cervix cancer stage IB2			
Resource	**Number**	**Price/DRG**	**Cost**

		(NOK)	(NOK)
Radical hysterectomy	0.33	144 047	48 011
Pelvic lymphadenectomy	0.33	72 452	24 148
Internal radiotherapy	0.67	31 435	20 955
External radiotherapy	0.67	51 984	34 653
Patient time (hours)	91.75	121	11 119
Total (NOK)			**139 516**
Cervix cancer stage IIA			
Resource	**Number**	**Price/DRG (NOK)**	**Cost (NOK)**
Same treatment as in stage IB2	0.50	127 767	63 883
Internal radiotherapy	0.25	157 176	39 294
External radiotherapy	0.25	51 984	12 996
Chemotherapy	0.50	57 081	28 540
Patient time (hours)	64.63	121	7 832
Total (NOK)			**152 546**
Cervix cancer stage IIB			
Resource	**Number**	**Price/DRG (NOK)**	**Cost (NOK)**
Internal radiotherapy	0.50	157 176	78 588
External radiotherapy	0.50	51 984	25 992
Chemotherapy	1.00	57 081	57 081
Patient time (hours)	37.50	121	4 545
Total (NOK)			**166 206**
Cervix cancer stage IIIA, IIIB			
Resource	**Number**	**Price/DRG (NOK)**	**Cost (NOK)**
Internal radiotherapy	0.50	157 176	78 588
External radiotherapy	0.50	51 984	25 992
Chemotherapy	1.00	57 081	57 081
Patient time (hours)	37.50	121	4 545
Total (NOK)			**166 206**
Cervix cancer stage IVA and IVB			
Resource	**Number**	**Price/DRG (NOK)**	**Cost (NOK)**
Internal radiotherapy	0.50	157 176	78 588
External radiotherapy	0.50	51 984	25 992
Chemotherapy	1.00	57 081	57 081
Patient time (hours)	37.50	121	4 545
Total (NOK)			**166 206**

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 34. 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	652	652
Patient time (hours)	1.50	121	182
Total (NOK)			**2 008**
Inadequate clinical response/residual disease - Surgery			
Resource use	**Number**	**Price/DRG (NOK)**	**Cost (NOK)**
MR	1.00	4 165	4 165
CT-pelvis and -thorax	1.00	4 250	4 250
Radical hysterectomy	0.25	144 047	36 012
Pelvic lymphadenectomy	0.10	72 452	7 245
Internal radiotherapy	0.35	31 435	11 002
External radiotherapy	0.40	51 984	20 794
Patient time (hours)	48.63	121	5 893
Total (NOK)			**89 361**
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	4 165	4 165
CT-pelvis and -thorax	1.00	4 250	4 250
PET	0.25	19 550	4 888
Patient time (hours)	3.75	121	454
Total (NOK)			**14 931**
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	121	4 363
Total (NOK)			**23 639**
Total – discounted (NOK)			**19 173**

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.

Treatment phase	Cost item	Expected cost (NOK)
1. Medical assessment	Testing and diagnosing	31 695
	Patient time costs	878
2. Primary treatment	Cervix cancer stage IA	697
	Cervix cancer stage IA1	18 385
	Cervix cancer stage IA2	18 342
	Cervix cancer stage IB1	25 546
	Cervix cancer stage IB2	15 076
	Cervix cancer stage IIA	14 471
	Cervix cancer stage IIB	16 166
	Cervix cancer stage IIIA and IIIB	17 782
	Cervix cancer stage IVA and IVB	16 166
	Patient time costs	6 200
3. Follow-up / secondary treatment	New medical assessment 6 w. after radiotherapy (all patients)	1 826
	Inadequate clinical response - Surgery	10 618

	Good tumor response, but not total remission - Intensive surveillance	3 719
	Total tumor remission - Surveillance	18 170
	Patient time costs	10 068
Total expected costs per cervical cancer case	*To the public health budget*	*208 664*
	To the patient	*17 146*

The total expected costs to the public health budget are NOK 208 664 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 add 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 35 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 budget perspective.

Monetary value of patient's time spent when receiving health treatment
We multiplied the number of hours spent by patient to get vaccinated and other health treatment by our estimate of the hourly after-tax wage rate for 2012, NOK 121, based on Norwegian average annual pre-tax income data from Statistics Norway (NOK 446 200, http://www.ssb.no/inntekt-og-forbruk) and some assumptions. More specifically we assumed that equal shares of this pre-tax income would be perceived once a month, 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 45%. This last rate was based on the rate recommended by the Ministry of Finance for estimation of the proportion of additional income accruing to the public sector. Our assumption is thus conservative, as the 45%-rate actually applies for all kind of income to the public budget (income tax, VAT, payroll taxes, public fees, etc) and not only income tax.

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 (abortions and 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 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).
- We assumed that the monetary value of every lost working year would be equal to the average pre-taxes annual income in Norway for 2012 (NOK 446 200), multiplied by the correction factor proposed by the Norwegian Directorate of Health to account for compensation mechanisms in the labor market (50%).
- 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:

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

Where:

- X = Discounted, expected monetary monetary value of lost working years time due to cancer mortality
- W_t = Average pre-taxes annual wage at year t ($1 \leq t \leq 4.255$)
- r = Discount rate (4%)
- 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

Table 36. Estimation of productivity costs due to early cancer mortality

Disease	(67-5)	Weighted average age at diagnosis (A)	Difference (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	50.5	11,5	37%	4.255	998 676
Vaginal cancer	62	69.19	No expected loss of working years	-	-	-
Vulvar cancer	62	70.78	No expected loss of working years	-	-	-

Each cervical cancer results in an expected loss of approximately 4.255 years in the labor force. Given the average annual income in Norway for 2012, this would represent a discounted loss of approximately NOK 1 million per cervical cancer case (corrected for compensation mechanisms in the labor market).

In addition to the productivity costs due to early cancer-related death, we calculated the loss due to preterm births:

- *Living baby, born before week 33*: Soergel (37) presents German estimates of the long term costs of conization-related preterm deliveries. In order to be conservative, we chose to used 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.

- *Late abortions:* Each abortion is assumed to lead to a loss equivalent to the monetary value of the expected number of years a newborn will expend in the working force, assumed to be 42 years (from age 25 to 67). This is equal to NOK 1 772 995, discounted to the moment of birth and corrected for compensation mechanisms in the labor market.

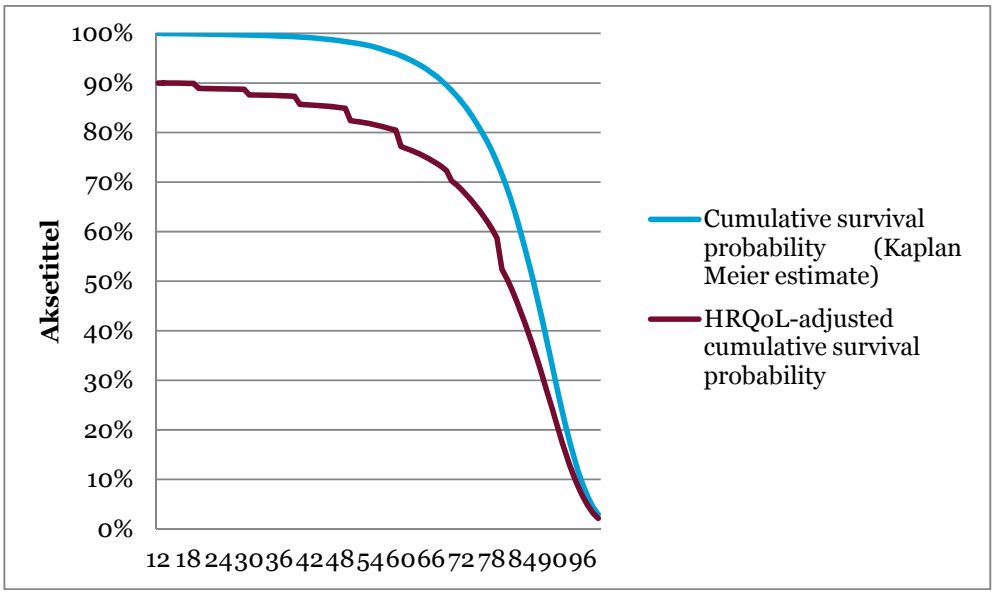
Appendix 5. Health related quality-of-life (HRQL) data

QALE, HRQoL-weights and HRQoL-losses per HPV-related outcome
The HRQoL-losses used in the economic model were calculated in a separate Excel sheet, based on the following factors:

i. Gender-specific death rates (per 100 000) in Norway.
ii. Discount factor of 4%.
iii. QALY weights for the general population, Burström (32).
iv. QALY weights of the different HPV-related health states, obtained from both the original model and our own literature search.
v. Duration of the health state the weight informs about.
vi. Distribution of cancer patients among cancer stage (local, regional or distant) for two age groups (those younger than 50 and those aged 50 or older).
vii. 5-years cancer survival rate at each cancer stage, also for both age groups mentioned above.

The three first factors are used to calculate the QALE (Quality-adjusted life expectancy) in the general population. For illustration purposes we show the QALE-results for women aged 12 to 99 years (i.e. the age range where we expect most HPV-related outcomes would find place):

Figure 8. QALE for Norwegian females 12-99



The upper curve shows the undiscounted, cumulative survival probability of an average female in Norway in 2012, when using the Kaplan-Meier estimate and the death rates (per 100 000) from Statistics Norway; while the lower curve shows the results from multiplying the relevant HRQoL-weight for each age group to the undiscounted, cumulative survival probability.

The area under the upper curve represents women's expected lifetime at age 12, which added to the previous 11 years is equal to 83.14 years, very close to Statistics Norway's own estimate of 83.41 years. On the other hand, the area under the lower curve represents women's expected lifetime, adjusted for HRQoL, i.e. the quality-adjusted life expectancy (QALE) at age 12. This is equal to approximately 61 QALYs if undiscounted (or 20 QALYs if discounted). This value expresses the maximal HRQoL-loss a 12-years-old female may experience due to a HPV-related outcome.

The QALY-weights of the different HPV-related health states and the duration of each health state are then combined with the QALE-results to calculate the HRQoL-loss for CIN- and genital warts episodes. For cancers we also used the distribution of cancer patients among cancer stage and the 5-years cancer survival rate at each cancer stage, for those younger than 50 and those aged 50 or older.

Health related quality-of-life in the general population:
Table 2 in Burström (32) gives the HRQoL-weights we used for the general population. The multi-attribute health status classification system used by the authors was the EQ-5D-3L (five dimensions and three levels at each dimension):

Table 37. Assumed HRQoL in the Norwegian general population, by age group.

Age groups	HRQoL-weight – males and females (EQ-5D-3L)
0 to 19	0.9
20 to 29	0.89
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 to 99	0.733

The literature search:
As pointed out earlier, in order to calculate the percent reduction in QALE, we needed HRQoL-weights associated with each health outcome before and after treatment. The QALE was calculated based on the EQ-5D weights in Burström (32), so for the sake of consistency we rejected the use of non-EQ-5D or at least TTO-based weights elsewhere in the model. As not all weights in Chesson (2) were EQ-5D or TTO-based, we conducted our own systematic literature search in Embase to find other relevant weights for each of the HPV-related outcomes, and in this way complement the TTO-based weights in Chesson (2). The search was conducted in December 2013.

Below we present the results of the literature search for the QALY-weights showed earlier, both in terms of search term combination and results per search term. We did not find results for either adverse events (AEs) of the vaccine, vaginal or vulvar cancer.

<u>CIN 2, 3</u>

#	Searches	Results
1	"eq-5d".mp.	4 667
2	15d.mp.	1 692
3	sf-6d.mp.	598
4	sf6d.mp.	47

5	eq5d.mp.	439
6	"15-d".mp.	2 688
7	"tto".mp.	855
8	"time-trade-off".mp.	1 004
9	1 or 5	5 026
10	2 or 6	4 350
11	3 or 4	639
12	7 or 8	1 395
13	9 or 10 or 11 or 12	10 746
14	"cervical intraepithelial neoplasia".mp. or uterine cervix carcinoma in situ/	12 462
15	"cin".mp.	9 505
16	14 or 15	16 634
17	13 and 16	7

Cervical cancer

#	Searches	Results
1	"eq-5d".mp.	4667
2	15d.mp.	1692
3	sf-6d.mp.	598
4	sf6d.mp.	47
5	eq5d.mp.	439
6	"15-d".mp.	2688
7	"time-trade-off".mp.	1004
8	"tto".mp.	855
9	1 or 5	5026
10	2 or 6	4350
11	3 or 4	639
12	7 or 8	1395
13	"cervical cancer".mp.	35512
14	"cervix cancer".mp.	34341
15	13 or 14	49923
16	10 or 11 or 12	6316
17	15 and 16	17

Genital warts

#	Searches	Results
1	"eq-5d".mp.	4667
2	15d.mp.	1692
3	sf-6d.mp.	598
4	sf6d.mp.	47
5	eq5d.mp.	439
6	"15-d".mp.	2688
7	"tto".mp.	855
8	"time-trade-off".mp.	1004
9	1 or 5	5026
10	2 or 6	4350
11	3 or 4	639
12	7 or 8	1395
13	9 or 10 or 11 or 12	10746
14	"genital wart".mp.	144
15	"genital warts".mp.	2319
16	genital.mp.	204336
17	wart*.mp.	40484
18	16 and 17	5839
19	14 or 15 or 18	5839
20	13 and 19	7

Conization related outcomes

#	Searches	Results
1	"eq-5d".mp.	4667
2	15d.mp.	1692
3	sf-6d.mp.	598
4	sf6d.mp.	47
5	eq5d.mp.	439
6	"15-d".mp.	2688
7	"time-trade-off".mp.	1004
8	"tto".mp.	855
9	1 or 5	5026
10	2 or 6	4350
11	3 or 4	639
12	7 or 8	1395
13	9 or 10 or 11 or 12	10746
14	conis*.mp.	523
15	coniz*.mp.	2600
16	14 or 15	2928
17	13 and 16	1

EQ-5D or TTO-based HRQoL-weights for the HPV-related outcomes obtained in the literature search:

In the following tables we show the QALY-weights we used for the different HPV-related outcomes in the model, as well as the source from which they were extracted. For every outcome, we calculated an arithmethic average of all obtained weights.

Table 38. HRQoL-weights for CIN

CIN 1	CIN 2	CIN 3	Sources
0.9100	0.8700	0.8700	*Kulasingam (38)*
0.8900	0.8900	0.8900	*Insinga (39)*
0.7963	0.6146	0.6146	*Galante (40)*

According to Insinga (39), each CIN 1-episode would last for 19,4 months, CIN 2 for 19,7 months and CIN 3 for 20,9 months. The duration of each CIN was 6 months in Kulasingham. Since duration was not stated in Galante (40), we assumed 6 months for these weights as well.

Table 39. Gender specific HRQoL-weights for genital warts

GW - Male	GW - Female	Sources
0.9010	0.9010	*Senecal (41)*
0.9570	0.9370	*Woodhall (42)*
0.8000	0.8000	*Mennini (43)*
0.6900	0.6870	*Favato (44)*
0.8700	0.8230	*Shi (45)*

The only source stating the duration of each genital warts episode was Woodhall (42), 111 days. This value was then assumed to apply for the weights from the other sources.

Our search for HRQoL-weights detected several published weight sets specifically for cervical cancer, but none for vaginal or vulvar cancer. We decided then to extrapolate the weights for cervical cancer to all of other cancer forms.

Table 40. HRQoL-weights for cervical cancer, per stage, before and after treatment

Cervical cancer stage	Favato (44)	Korfage (46)	Mennini (43)	Lang (47)	Galante (40)
local	0.5850	-	-	-	0.1520
regional	0.5485	-	-	-	0.1520
distant	0.4510	-	-	-	0.1520
post-local	-	0.9390	-	0.7550	0.6910
post-regional	-	0.9390	-	0.7550	0.6910
post-distant	-	0.9390	-	0.7550	0.6910

Distribution of cancer patients among cancer stage and 5-years cancer survival rate at each cancer stage:
Cancer Registry of Norway (CRN) provided us with all data we needed to calculate the distribution of cancer patients among stages and most of the five-year relative cancer survival rates.

For the survival rates for which CRN did not have data, we assumed that they would be equal to the survival rate for the respective cervical cancer stage (as this cancer form was the only one for which data for all stages was available), after adjusting for differences in overall survival between the relevant cancer and cervical cancer. In other words, the survival rate for the respective cervical cancer stage was multiplied by the ratio of overall survival of the relevant cancer form to the overall survival of cervical cancer.

Appendix 6. Estimation of the vaccine expenditures associated with the implementation of the catch-up program

We assumed in our analysis that 85.3% of those receiving at least one dose also received the last two (see Table 29), and that the mean coverage rate for the first vaccine dose would be the same as the rate reported in Australia, 54% (30).

Based on these assumptions we calculated that 50% of the target population of the catch-up program would receive two doses, and 46%, three doses. Given an estimated total target population of 237 200 females, this would mean that approximately 356 000 additional doses will be required to carry out the catch-up program for females aged 19 to 26 years in 2015.

Table 41. Estimated vaccine expenditures associated with the catch-up program

Number of doses per female	Share of target population	Total number of doses
1	54%	128 088
2	50%	118 701
3	46%	109 315
SUM		***356 104***