Økonomisk evaluering av humant papillomavirus (HPV)-vaksinasjon i Norge

Rapport fra Kunnskapssenteret Nr 12–2007
Helseøkonomisk modell

Nasjonalt kunnskapssenter for helsetjenesten

Bakgrunn: HPV-vaksinasjon er svært effektivt mot utvikling av høyrisikotyper av humant papillomavirus (HPV 16/18-relaterte infeksjoner), som er den vanligste årsaken til livmorhalskreft. I Norge screenes nå kvinner i alderen 25 til 69 år hvert tredje år mot livmorhalskreft. Hvor effektiv og kostnadseffektiv HPV-vaksinasjon vil være i tillegg til screening over lengre tid, er de sentrale spørsmålene for beslutningstakere som skal vurdere om nye vaksiner skal inn i vaksinasjonsprogrammet. **Om metoden:** Formålet med denne rapporten var å estimere kostnadseffektiviteten av å vaksinere mot HPV type 16/18 i tillegg til å screene sammenlikna med bare å screene. En dynamisk modell for HPV-smitte ble brukt for å predikere antall forstadier til livmorhalskreft, nye tilfeller av livmorhalskreft og død. Resultatene ble sammenlikna med aldersspesifikke norske data i en situasjon uten vaksinering. Vi utforska den potensielle betydningen av å gi en vaksine til 12 år gamle jenter i perioden 2008–2060 under forutsetninger om 90 % effekt av vaksinen og 90 % dekning. Vi brukte utfall av modellen sammen med data for screeningprogrammet for å beregne kostnads-

(fortsetter på baksiden)

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(fortsettelse fra forsiden)

effektiviteten i et helsetjeneste- og samfunnsperspektiv. I analysene brukte vi norske data for ressursbruk og enhetskostnader. Kostnadseffektiviteten ble regnet ut både som kostnad per vunne leveår og kostnad per kvalitetsjusterte leveår (QALY). **Funn:** Det å introdusere vaksine og opprettholde screeningprogrammet resulterte i utgangsscenariet i NOK 477 000 per vunne leveår (NOK 399 000 per QALY) i et helsetjenesteperspektiv. I et samfunnsperspektiv ble dette redusert til NOK 141 000 per vunne leveår (NOK 118 000 per QALY). Estimatene var sensitive overfor antakelser om vaksinedekning, vaksinekostnader, diskonteringsrate og tidshorisonten til analysen. **Konklusjon:** Under diverse forutsetninger resulterte den økonomiske evalueringa i resultater som antyder at vaksinasjon mot HPV type 16/18 kan være en kostnadseffektiv strategi for å redusere antallet nye tilfeller og dødeligheten av livmorhalskreft ytterligere i Norge. Resultatene var imidlertid sensitive overfor valg av analyseperspektiv og andre antakelser i modellen.

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Nasjonalt kunnskapssenter for helsetjenesten
Oslo, 2007

Oppsummering

Økonomisk evaluering av humant papillomavirus (HPV)-vaksinasjon

Bakgrunn: HPV-vaksinasjon er svært effektivt mot utvikling av høyrisikotyper av humant papillomavirus (HPV 16/18-relaterte infeksjoner), som er den vanligste årsaken til livmorhalskreft. I Norge foretas det nå screening hvert tredje. år for kvinner i alderen 25 til 69 år. Hvor effektiv og kostnadseffektiv HPV-vaksinasjon vil være over lengre tid i tillegg til screening, er de sentrale spørsmålene for beslutningstakere som skal vurdere introduksjon av nye vaksiner i vaksinasjonsprogrammet

Metode: Formålet med denne rapporten var å estimere kostnadseffektiviteten av en HPV type 16/18-vaksinasjon i tillegg til screening sammenlikna med screening aleine. En dynamisk modell for HPV-smitte ble brukt for å predikere antall forstadier til livmorhalskreft, nye tilfeller av livmorhalskreft og død. Resultatene ble sammenlikna med aldersspesifikke norske data i en situasjon uten vaksinasjon. Vi utforska den potensielle betydninga av å gi en vaksine til 12 år gamle jenter under forutsetninger om 90% effekt av vaksinen og 90% dekning i perioden 2008–2060. Vi brukte utfall (som reduksjon i antall krefttilfeller og kreftdødsfall) av modellen sammen med data for screeningprogrammet for å beregne kostnadseffektiviteten i et helsetjeneste- og samfunnsperspektiv. I analysene brukte vi norske data for ressursbruk og enhetskostnader. Kostnadseffektivitet ble regnet ut både som kostnad per vunne leveår og kostnad per kvalitetsjusterte leveår (QALY).

Resultater: Det å introdusere vaksine og opprettholde screeningprogrammet resulterte i hovedscenariet i NOK 477 000 per vunne leveår (NOK 399 000 per QALY) i et helsetjenesteperspektiv, der kun kostnadene for helsetjenesten er tatt med. I et samfunnsperspektiv, der også besparelser grunnet lavere produksjonstap ved redusert dødelighet og sykdom er tatt med, ble dette redusert til NOK 141 000 per vunne leveår (NOK 118 000 per QALY). Estimatene var sensitive overfor antakelser om vaksinedekning, vaksinekostnader, diskonteringsrate og tidshorisonten til analysen.

Konklusjon: Under diverse forutsetninger indikerte den økonomiske evalueringa at HPV type 16/18-vaksinasjon kan være en kostnadseffektiv strategi for å redusere antallet nye tilfeller og dødeligheten av livmorhalskreft i Norge. Resultatene var imidlertid sensitive overfor valg av analyseperspektiv og andre antakelser i beregningene.

Sammendrag

Økonomisk evaluering av humant papillomavirus (HPV)-vaksinasjon

BAKGRUNN

Nasjonalt kunnskapssenter for helsetjenesten ble bedt av Nasjonalt folkehelseinstitutt om å lage en medisinsk metodevurdering av vaksiner mot humant papillomavirus (HPV) -infeksjon. En systematisk oversikt over effekt og bivirkninger har allerede blitt publisert (Rapport fra Kunnskapssenteret nr 5–2007). Formålet med denne andre rapporten er å estimere den potensielle kostnadseffektiviteten av en vaksine som inneholder HPV-typene 16 og 18 (de to mest vanlige årsakene til livmorhalskreft).

To vaksiner mot HPV er foreløpig utviklet; Gardasil® og Cervarix®. Gardasil er utviklet av Merck og markedsføres av Sanofi Pasteur MSD i Europa. Cervarix er utviklet av Glaxo-SmithKline. Den sistnevnte er forventet å få markedsføringstillatelse i løpet av 2007. Begge vaksinene er rettet mot type 16 og 18. Gardasil har i tillegg inkludert HPV 6 og 11, som er relatert til kjønnsvorter. Begge vaksiner har potensial til å oppnå ytterligere reduksjoner i tallet på nye tilfeller av livmorhalskreft, forstadier til livmorhalskreft og dødelighet av livmorhalskreft som skyldes infeksjoner relatert til HPV type 16/18.

FORMÅL

Formålet med denne rapporten var å bestemme kostnadseffektiviteten av å vaksinere 12-årige jenter med HPV-vaksine av typene 16 og 18 som tillegg til det eksisterende screeningprogrammet for livmorhalskreft sammenlikna med screening aleine.
Både den systematiske oversikten og denne økonomiske evalueringa vil inngå som deler av beslutningsgrunnlaget for ei arbeidsgruppe ved Folkehelseinstituttet. Denne arbeidsgruppa skal gi råd til Helse- og omsorgsdepartementet om hvorvidt HPV-vaksinasjon skal legges til dagens vaksinasjonsprogram.

METODE

Estimater på effekt av vaksinen fra den medisinske metodevurderingen ble kombinert med norske data på ressursbruk og enhetskostnader i en inkrementell, modellbasert helseøkonomisk analyse.
Vi evaluerte et program med HPV-vaksinasjon fra to perspektiver:

i) I et norsk helsetjenesteperspektiv, som inkluderer kostnader til vaksinasjon, diagnose og behandling av livmorhalskreft og forstadier til livmorhalskreft.

ii) I et samfunnsmessig perspektiv, som i tillegg til helsetjenestekostnadene inkluderer besparelser knyttet til lavere produksjonstap, som følge av redusert dødelighet av livmorhalskreft og redusert jobbfravær i forbindelse med kreftbehandling.

Vi delte den økonomiske evalueringa i to deler. I den første delen tilpassa vi en dynamisk modell for HPV-smitte fra en engelsk modell til en norsk setting. Dette involverte en syntese av kliniske data fra diverse kilder for å estimere virkningen av vaksinasjon på insidens og dødelighet i Norge. Den andre delen inneholdt den økonomiske modelleringa (i Microsoft Excel®) og syntetiseringa av de kliniske resultatene fra modellen med økonomiske data.

Vi genererte inkrementelle kostnadseffektivitets-ratioer (IKERe) både som kostnad per vunnet leveår og kostnad per vunnet kvalitetsjusterte leveår (QALY). I utgangsscenariet antok vi 90 % effekt av vaksinen og 90 % vaksinedekning. Et hypotetisk vaksinasjonsprogram med start i 2008 ble brukt, og kostnader ble simulert år-for-år i perioden 2008–2060. Framtidige kostnader, vunne leveår og QALYs ble diskontert med 4 % p.a. i forhold til dagens verdi (start i 2008). I sekundære analyser så vi på sensitiviteten til resultatene fra utgangsscenariet med tanke på endringer i effekten av vaksine, vaksinedekning, pris, diskonteringsrate og tidshorisonten til analysen.

RESULTATER

Resultatene fra den kliniske modellberegningen indikerte at årlig vaksinasjon av 12-årige jenter i perioden 2008–2060 (omtrent 1,5 million jenter) forhindra 2906 tilfeller av livmorhalskreft og 673 dødsfall relatert til livmorhalskreft. Innen 2060 ville den årlige reduksjonen i kreftinsidens være omtrent 50 %.

Fra et helsetjenesteperspektiv beløp de inkrementelle (netto) kostnadene over denne perioden seg til NOK 1,4 milliard (NOK 866 per vaksinerte jente).

Fra et samfunnsperspektiv var de totale inkrementelle kostnadene assosiert med vaksinasjon NOK 418 310 000 (NOK 271 per vaksinerte jente).

Den helseøkonomiske modellanalysen tyder på at vaksinasjon (i tillegg til screening) av 12-årige jenter, sammenliknet med et screeningprogram, ga totalt 2 962 vunne leveår ekstra (diskontert) og 3 539 kvalitetsjusterte leveår ekstra (diskontert). Dette ga 0,0019 vunne leveår og 0,0023 vunne kvalitetsjusterte leveår per vaksinert 12-åring, som resulterte i en kostnad per vunne leveår på NOK 477 000 og NOK 399 000 per vunne QALY i et helsetjenesteperspektiv. I et samfunnsperspektiv ble de tilsvarende resultatene NOK 141 000 per vunne leveår og NOK 118 000 per QALY.

Enkle enveis og toveis sensitivitetsanalyser antydet at resultatene er sensitive til forskjellige antakelser relatert til effekten av vaksine, vaksinedekning, diskonteringsrate og vaksinepris og til tidshorisonten for akkumulering av kostnader og helseeffekter. For eksempel vil de diskonterte inkrementelle kostnadseffektivitetsratioene, med en tidshorisont på 2008–2090, bli NOK 370 000 per vunne leveår og NOK 319 000 per kvalitetsjusterte leveår i et helsetjenesteperspektiv. Fra et samfunnsperspektiv er de tilsvarende kostnadseffektivitetsratioene NOK 87 000 og NOK 33 000. En reduksjon i vaksineprisen på 10 % ga ratioer på NOK 405 000 per vunne leveår og NOK 339 000 per QALY, sett i et helsetjenesteperspektiv. Fra et samfunnsperspektiv ga en 10 prosents prisreduksjon at

vaksinasjon i tillegg til screening resulterte i lavere kostnader og mer effekt enn screening aleine og kan derfor sies å være kostnadsbesparende (dominant strategi).

KONKLUSJON

Estimatene for kostnadseffektivitet var følsomme for både valg av perspektiv (helsetjeneste kontra samfunnsmessig) og andre antakelser i modellen. Det er behov mer og sikrere kunnskap om langtidseffekt av vaksinen og varigheten av immuniteten, vaksinekostnader og andre ekstra ressurser relatert til et fullt ut operasjonelt HPV-vaksinasjonsprogram.

Framtidige studier vil være informative med hensyn til en videre oppfølging av en HPV-vaksinert populasjon, for å bestemme mer presist overlevelseseffektene på kort og lang sikt og kostnadseffektiviteten når vaksinering blir brukt på flere enn bare 12 år gamle jenter og med forebygging av livmorhalskreft som hovedsiktemål.

Under diverse sannsynlige forutsetninger demonstrerte vår økonomiske evaluering at HPV-vaksinering (inkludert typene 16 og 18) kan være kostnadseffektivt sammenlikna med publiserte estimater for eksisterende vaksinasjonsprogrammer i Norge (for eksempel pneumokokkvaksinering av spedbarn).

Key messages

Cost-effectiveness of human papillomavirus (HPV) vaccination in Norway

Background: HPV vaccination is highly efficacious against the development of high risk HPV 16/18 type related infections, the most common cause of cervical cancer. In Norway, the current screening strategy (since 1995) is to screen every 3 years, woman aged 25 to 69. How effective and cost-effective HPV vaccination alongside screening would be over the long-term remain key issues for decision makers considering programme introduction.

Methods: The objective of this report was to estimate the potential cost-effectiveness of an HPV 16/18 type vaccination alongside screening compared to screening alone. A dynamic model of HPV transmission was used to predict cases of cervical dysplasia, cervical cancers and deaths and the results compared against age-specific Norwegian data representing a situation without vaccination. We then explored the potential impact of a vaccine given to 12-year-old girls under a base case assumption of 90% efficacy and 90% coverage for a hypothetical time period of 2008–2060. Model outputs (e.g. reductions in cancers and cancer deaths) together with screening programme data were used to perform cost-effectiveness calculations from the health care sector perspective and society. Analyses used available Norwegian data on resource consumption patterns and published unit costs. Cost-effectiveness was measured as the incremental cost per life year gained (LYG) and quality-adjusted life year (QALY) gained.

Results: Introduction of vaccination, and maintaining the screening programme unchanged yielded a base case incremental cost-effectiveness ratio (ICER) that varied from NOK 477,000/LY (NOK 399,00/ QALY) to NOK 141,000/ LY (NOK 118,000/QALY) from the healthcare sector and societal perspectives respectively. Estimates were sensitive to alternative assumptions relating to efficacy, coverage, vaccine cost, discount rate, and time horizon of the analysis.

Conclusion: Under several plausible assumptions, our economic evaluation suggest that introduction of HPV 16/18 type vaccination to current screening in Norway may be a cost-effective strategy for further reductions in cervical cancer incidence and mortality. However, the estimates were susceptible to both the perspective adopted, and assumptions used in the modelling analyses.

English summary

Cost-effectiveness of human papillomavirus (HPV) vaccination in Norway

BACKGROUND

The Norwegian Knowledge Centre for the Health Service (NOKC) was requested by the Norwegian Institute for Public Health to undertake a health technology assessment (HTA) for prophylactic vaccines against human papillomavirus (HPV infection). A systematic review in which the effectiveness and safety of such vaccines was evaluated has already been published (Report Nr 5-2007). The aim of this second report was to estimate the potential cost-effectiveness of a vaccine containing HPV types 16 and 18, the two most common causes of cervical cancer in terms of reducing the burden of disease from cervical cancer.

Two vaccines against HPV are currently developed, Gardasil® and Cervarix®. Gardasil is developed by Merck and is marketed in Europe by Sanofi Pasteur MSD, while Cervarix is developed by GlaxoSmith Kline. The latter is expected to receive market approval during 2007. Both vaccines are directed at type 16 and 18. Gardasil, in addition, included HPV 6 and 11 that are related to anogenital warts. Both vaccines hold the potential to achieve future reductions in the incidence of cervical cancers, pre-cancers and cervical cancer mortality arising from HPV type 16/18 specific infections.

OBJECTIVE

The aim of this report was to determine the cost-effectiveness of HPV vaccination including types 16/18 in 12-year-old girls alongside the existing cervical cancer screening programme in Norway compared to a progamme of screening alone.

Both the systematic review report and this economic evaluation report will form part of the basis for a working group at the Norwegian Institute of Public Health. The working group shall advise the Ministry of Health and Care Services on the issue of whether vaccines against HPV should be added to the Norwegian vaccination programme.

METHODS

Estimates of vaccine efficacy based on the systematic review were combined with Norwegian resource use and unit costs data in an incremental model based economic analysis.

A programme of HPV vaccination was evaluated from two perspectives:
i) from the Norwegian health sector perspective, incorporating an assessment of vaccination costs, diagnosis and treatment of cervical cancers and pre-cancers; and
ii) from a societal perspective, incorporating an assessment of productivity losses and gains associated with cervical cancer mortality and cancer treatment.

The economic evaluation was in two parts. The first was the adaption of a dynamic model of HPV transmission from a previous developed UK model (programmed in C+) to the Norwegian setting, involving the synthesis of clinical data from several sources, to estimate the relative impact on disease incidence and mortality in Norway. The second was the economic modeling part (in Microsoft Excel) and synthesized the clinical model outputs with economic data.

Incremental cost-effectiveness ratios (ICERs) were generated in terms of cost per life year (LY) gained and cost per quality adjusted life year (QALY) gained for a baseline "best case" under the assumption of 90% vaccine efficacy and 90% vaccine coverage. A hypothetical vaccination programme start date of 2008 was used and year-on-year costs and outcomes simulated for the period 2008–2060. Future costs, LYRS and QALYs were discounted at a rate of 4% per annum to present day values (the baseline start year of 2008). In secondary analysis we explored the sensitivity of the base case results to changes in vaccine efficacy, coverage, vaccine price, discount rate and time horizon of analysis.

RESULTS

The base case results from the clinical model estimated that annual vaccination of 12-year old girls over the period 2008–2060 (approx 1.5 million girls) averted 2906 cervical cancers and 673 cervical cancer related deaths. By 2060 the annual reduction in cancer incidence and cancer mortality were approx. 50%.

From the health sector perspective, the total estimated (net) incremental costs over this period amounted to NOK 1.4 billion (NOK 866 per girl vaccinated).
From the societal viewpoint, the total estimated incremental costs associated with vaccination were NOK 418,310, 000 (NOK 271 per girl vaccinated).

The economic modelling analyses suggested that compared with a programme of screening alone, vaccinating 12-year-old girls, yielded a total gain of 2,962 discounted life-years (0.0019 per vaccinated) and 3,539 discounted QALYs (0.0023 per vaccinated), at a cost of NOK 477,000 per LY gained and NOK 399,000 per QALY gained from the health sector perspective. From the societal perspective the corresponding ratios were NOK 141,000 per LY gained and NOK 118,000 per QALY gained.

Simple one- and two-way sensitivity analyses showed that results were sensitive to alternative assumptions relating to vaccine efficacy, coverage, discount rate, vaccine price and the time horizon over which costs and health benefits accumulate. For example, assuming a simulated time horizon of 2008–2090 (82 years as opposed to 52 years in the base case analysis), the discounted cost-effectiveness ratios from the health care sector perspective were NOK 370,000 per LY gained and NOK 319,000 per QALY gained. From the societal perspective the corresponding cost-effectiveness ratios were NOK 87,000 and NOK 33,000 respectively. Reducing the unit price of the vaccine by 10% yielded ratios of NOK 405,000 per LY and NOK 339,000 per QALY from the health sector perspective. From the societal viewpoint reducing vaccine price by 10% resulted in a situation where vacci-

nation was both more effective and cost-saving (i.e. - largely due to productivity gains from reduced cervical cancer incidence and mortality).

CONCLUSIONS

The cost-effectiveness estimates were sensitive to both the perspective taken in the analysis (health care sector versus societal) and the assumptions used in the economic model. Bounding more precisely the impact surrounding the current uncertainty of certain model parameter estimates such as vaccine efficacy and duration of immunity, vaccine costs and any extra resources associated with a fully operational HPV vaccination programme are needed.

Future studies would be informative with respect to the continued monitoring of an HPV vaccinated population, to determine more precisely the effects on short- and long-term survival and cost-effectiveness when used in a wider range of patients than just 12-year-old girls and with a primary focus on cervical cancer prevention.

Overall however, and under several plausible assumptions, our economic evaluation demonstrated that an HPV vaccine including types 16/18 may be considered potentially cost-effective, compared to published estimates of existing vaccination programmes in Norway (e.g. pneumococcal conjugate vaccine in infants) as well as being potentially cost-effective for a range of hypothetical decision makers' thresholds.

About the Norwegian Knowledge Centre for the Health Services

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

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Foreword

This report accompanies report Nr 5- 20007 commissioned by the Norwegian Institute for Public Health. The first report conducted a systematic review of the effectiveness of human papilloma virus (HPV) vaccination. The aim of the current report was to undertake a health economic evaluation of HPV vaccination, with a particular focus on assessing the potential impact of an HPV 16 and 18 type vaccination with regard to cervical cancer in the Norwegian healthcare setting.

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Professor Geoff P Garnett, Department of Infectious Disease Epidemiology, Imperial College, London. He developed the original HPV transmission model which is used in this study. Developed for the UK, the model has been further modified with the objective of reflecting Norwegian conditions. No restrictions on its use were applied. Professor Garnett provided brief comments and suggestions with respect to model fitting and validation of the disease model to Norwegian data.

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External:

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- Professor dr. philos. Jan Abel Olsen, Institutt for samfunnsmedisin, Universitetet i Tromsø.

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Contribution of authors:

- Aileen Rae Neilson (ARN) had overall responsibility for the economic modelling. ARN was responsible for the synthesis of clinical and economic data in order to generate estimates of costs-effectiveness for Norway. She was involved in the adaption of the previous UK model and leading in writing of the final report.
- Birgitte Freiesleben de Blasio (BFB) was responsible for further development of the HPV transmission model and modifications to the Norwegian setting. She led the calibration and validation of the model to Norwegian data. BFB carried out the simulations and scenarios investigated for this report and contributed to the writing and editing of this report.

The views expressed in this report are entirely those of the authors and do not necessarily reflect the reviews of the study sponsors/commissioners

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Problem to be addressed

Project mandate: To estimate the potential cost-effectiveness of a high-risk HPV 16/18 type vaccination in Norway.

1. Introduction

The recently published evidence from a systematic review of clinical trials of an HPV type specific vaccine by the Norwegian Knowledge Centre (Report Nr 5-2007) demonstrate vaccination to be highly efficacious against the development of incident/ persistent infections. In addition, the evidence is also suggestive of high efficacy for intermediate outcomes based on cytological and histological findings. Two vaccines against human papillomavirus are currently developed, Gardasil® and Cervarix®. Both vaccines are type specific and are directed against the two most common causes of cervical cancer in the world, type 16 and 18. Gardasil, in addition, includes HPV 6 and 11 that are related to anogenital warts. Gardisil has recently achieved a marketing authorization and it is expected that Cervarix will achieve market approval within 2007.
In both instances, however, the impact of HPV type specific vaccination was observed over a relatively short time horizon. How effective and cost-effective HPV vaccination alongside existing screening would be over the long-term remain key issues for decision makers considering programme introduction, as do related operational and monitoring systems necessary.

In Norway, the current strategy (since 1995) to prevent cervical cancer is screening every 3 years, woman aged 25 to 69. The coverage rate for the targeted age-range is around 76%, or almost 80% if crudely adjusted for hysterectomies the majority of cases of cervical cancer occur in the 20% of women from the non-participating population (1).

However, before HPV vaccination can be advocated as part of national health policy, and if so, how widely, its cost-effectiveness must be demonstrated. There are already a number of published economic evaluations of HPV vaccination, but these have some limitations, because they were based on mainly the North American or other European healthcare systems (2-7). These studies are briefly considered in the discussion. For the current study, we undertook an economic analysis constructed from the perspective of the Norwegian health care system commissioned by the Norwegian Institute for Public Health. The assessment sought to explore a range of scenarios under the assumption of vaccination annually all girls before the age of sexual debut. In Norway this age is around 16.3 years of age based on recent national sexual health surveys (8). All our analyses proceeded on the assumption of a vaccination strategy targeting 12-year-old girls.

The current report accompanies the first report (Report Nr 5-2007) in which a systematic review of the efficacy of HPV vaccines was undertaken, commissioned by the Norwegian Institute of Public Health. In this second report, cost-effectiveness estimates assuming an HPV vaccine containing type 16/18 and administered to 12-year-old girls alongside the current strategy for cervical cancer screening in Norway are presented. The economic evaluation was based on cost and outcome data combined with a previous dynamic mathematical model of HPV transmission developed for the UK NHS setting (G. Garnett, personal communication, a general modeling approach is discusssd in Garnett 2006(9))[1] adapted to the Norwegian healthcare setting and based on estimates of treatment effectiveness from the systematic review (Report Nr 5-2007).

[1] Full details of the transmission model programme code are available from the authors on request

2. Methods

2.1 Study question and perspective

In accordance with the original economic study plan http://www.kunnskapssenteret.no/index.php?artikkelid=562&back=2 , the first focus of our study question with respect to the primary viewpoint or frame of reference was from the perspective of the Norwegian health care system. Is HPV 16/18 vaccination alongside the current screening programme for the prevention of cervical cancer (compared with screening alone) cost-effective as judged by the incremental cost per life-year gained and the incremental cost per quality-adjusted life-year gained? An important art of any economic evaluation is that it should serve as a tool for decision-making regarding the allocation of scare resources, not least because of the relentless pressure on public healthcare budgets. However, it is also important to consider the societal perspective in economic evaluations, and is motivated by two main reasons (10). First, welfare changes need to be determined by assessing their full impact, and second a public (state) policy maker needs to be informed about the full consequences of implementing a certain programme. Again, not least on when the allocation of national budgets across different sectors are being determined. Such a broad view is appropriate from a societal perspective. Indeed, such a view is more closely related to the aim of maximizing social welfare. Therefore, as an important additional focus we also considered a broader viewpoint with respect to potential health benefits and costs. Thus the perspective(s) adopted in our economic evaluation of HPV16/18 vaccination may lend a potentially useful insight to decision makers from both a broad health care standpoint as well as a societal one.

We included the direct costs of screening, diagnostic and therapeutic workup of positive screening test results, treatment of pre-cancers and cancers, and vaccination costs. We also included assessment of any indirect economic costs, such as loss of work-related earnings, that is, productivity losses (e.g. due to premature death associated with cervical cancer). We did not include assessments of any indirect costs associated with capital and revenue costs of developing services to reach the intended targeted population to the point at which vaccination would be delivered across the whole national school based vaccination programme system to the standard required.

2.2 Study comparator

Because the present study is limited to focusing on cervical cancer and the potential impact that a high risk HPV specific type vaccine may have in a Norwegian population, we

have therefore assumed that the alternative health care intervention programmes being compared are that of screening alone and screening plus vaccination.

2.3 Form of Evaluation

We have adopted both a cost-effectiveness approach, assessing health gains in life-years as well a cost-utility approach, assessing health gains in quality-adjusted life years (QALYs). We have simulated costs and effectiveness over both short and long-term time horizons (e.g. assuming a hypothetical start date of 2008 for an HPV vaccine to be added to the existing school based vaccination schedule).

2.4 Steps to improve generalisability of results

The patients included in the trials of HPV vaccines containing HPV 16/18 types (report Nr 5- 2007) were highly selected and were largely recruited from non-Norwegian centres. In addition, the target age group in Norway currently under consideration is that of all 12-year old girls. This age differs to majority of the ages of the women included in the trials of HPV vaccine. For example, relating to basic study population characteristics the age range of women in the study by Villa 2006 of a quadrivalent HPV vaccine (including 16/18 types) was 16-23 years; in the studies by Harper 2004, Harper 2006 of a bivalent HPV 16/18 vaccine women were aged 15-25 years. So to produce results that were potentially more relevant to the Norwegian health care system, we undertook a modeling approach, applying data on efficacy from the trials (Report Nr 5-2007) to a population of 12-year old girls vaccinated within the national childhood vaccination schedule in Norway.(http://www.euvac.net/graphics/euvac/vaccination/norway.html)
For example, as part of the current schedule the MMR vaccine is administered at 11-12 years—a similar age to that being considered for including an HPV vaccine in the childhood vaccination programme.

2.5 Choice of Measure of Benefit

The use of life-years and QALYs as two useful measures of health benefits enabled us to encompass survival gains as well as potential utility values (or disutility) assigned to the different health states associated with cervical cancer. In the current analysis we associated a disutility with each of the 4 main stages of cancer which in general are: stage I, disease limited to the cervix uterus; stage II, malignant tumour invades beyond the uterus; stage III, malignancy extends to pelvic wall or lower vagina; stage IV: disease involves other organs, bladder, rectum and/or extends beyond the pelvic area and may be associated with distant metastasis.
In the case of QALYs, health gains refer to both a quantity part (prolonged life) and a quantity part (better quality of life).
Annual mortality rates from cervical cancer (age-cohort specific) were specified in the clinical model with consistency of model predictions of number of cancer deaths compared to published data (see appendix 5 later). Assessment of age-cohort specific life-years lost to premature cervical cancer mortality was based on Norwegian life-tables (Statistics Norway: http://www.ssb.no/emner/02/02/10/dode/tab-2006-04-27-05.html) and the mid-points for each 10-year age-cohort applied. For example, for women aged 16-25, we used the life expectancy associated with a 21-year-old, for a 26-35 cohort the life expectancy for a 31-year-old woman was used, and so on.

The source of quality of life weights for cervical cancer states used in the base case analysis were derived from the mid-points of the ranges reported by Goldie 2004 (4): Stage I 0.97 (0.73-0.99) midpoint=0.84; Stage II 0.90 (0.68-0.98)= 0.78; Stage III 0.9 (0.68-0.98)= 0.84; stage IV=0.62 (0.47-0.78) = 0.62. Alterative assumptions could be explored, but are not included in the sensitivity analyses of the current study.

2.6 Disease modelling

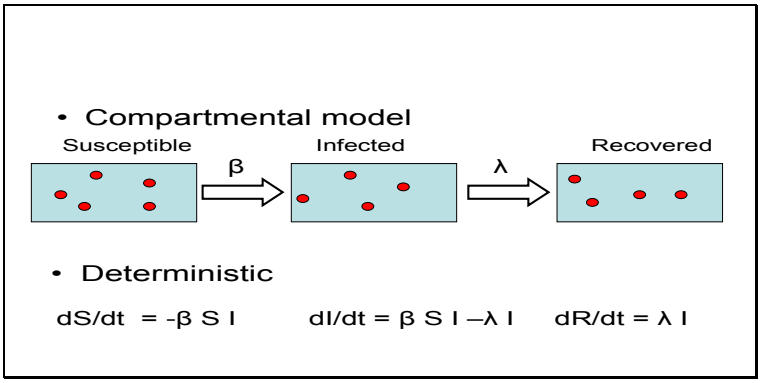
In terms of modeling methods, Markov models provide a convenient approach to model the natural history of HPV infection (11;12). The majority of models which have been developed (although potentially possible to do so) have generally not included transmission characteristics of the infection or built-in herd immunity which may actually underestimate benefits of vaccination (13,14). On the other hand "dynamic" models, permit the modeling of the sexual transmission characteristics of HPV infection (12;15). Although such models may be potentially more realistic, they also may introduce additional uncertainty (e.g. stability of assumed sexual behaviour patterns, average number of partners in different population sub-groups etc). The choice of modeling multiple versus single cohorts is also an important consideration. Modelling only a part of the relevant population can have a major affect on the effectiveness as well as cost-effectiveness estimates generated later (16;17). Multiple cohorts may produce higher cost-effectiveness ratios. Therefore, it is important to ensure the age distribution of the hypothetical baseline population modelled is similar to the one that would be affected by a specific policy decision if it were made tomorrow (17).

The modeling approach adopted to predict the health and economic outcomes of HPV 16/18 vaccination involved the adaptation of a previously developed UK academic model (see introduction) to the Norwegian setting. The dynamic model simulates the (sexual) transmission dynamics of HPV infection and (in some but not all cases) the onward progress to cervical cancer. We have followed the general lead of other evaluations and assumed that from an initial starting point, the natural history of HPV and cervical cancer is relatively consistent across countries in Europe. However it should be indicated that we then set about attempting to calibrate the disease process and related assumptions to data from Norway. The model was therefore essentially a clinical (disease) model and not an economic model, rather, the outputs from the clinical model provided an assessment of the likely (long-term) clinical impact of an HPV 16/18 type vaccine on future reductions in the incidence of cervical cancer, cervical dysplasia and cervical cancer mortality. These outputs in turn then provide necessary inputs to further undertake an analysis of the potential health economic impact of HPV 16/18 type vaccination. We had complete freedom to make any necessary changes to the clinical model parameter values, model structure, program (code—written in C+) in seeking to calibrate the clinical model to a Norwegian population and health care setting. A simple graphical illustration of the model is presented in Figure 2.1. Essentially, the model simulates yearly cohorts up to the age of sexual debut- age 16- allowing for age-specific vaccination which for the current analysis is for cohort vaccination at 12. The model then handles 6 x 10 year age groups at risk of infection and disease. The original model was developed to incorporate 4 viral types HPV 16, 18, 6/11 and other HR oncogenic types each with 3 or 4 infection states. The current analysis focuses on high risk types 16 and 18. There exists the possibility of occupying 1 of 3 vaccine statuses- unvaccinated; protected, vaccinated with loss of protection. Sexual activity classes are also grouped into 1 of 3 possibilities defined in

terms of the average number of sexual acts per partnership based on Norwegian data (low, medium, high). The number of possible disease or health states is 9. There exist 2 screening groups in the model, those women reached by programmes and those not.

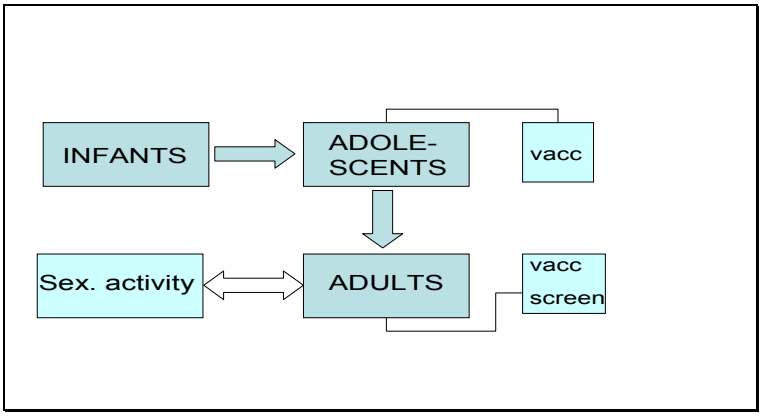
Figur 2.1 Basic illustration of disease transmission and epidemiological model of HPV infection

1. Population and primary sub-groups groups modelled:



The above three primary population groups are further described by:

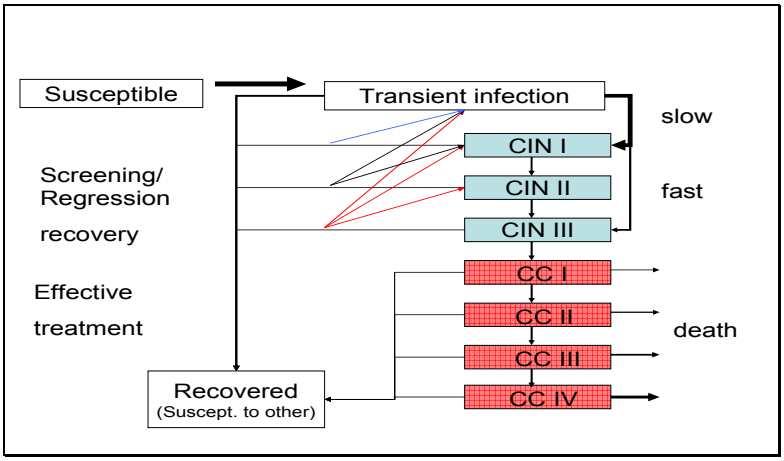
- **Children: (0-9y) in 10 yearly cohorts**
- **Adolescents: (10-15y) in 6 yearly cohorts**
- **Adults: (16-25y;26-35y; .. 66-75y) in 6 10-year age group**



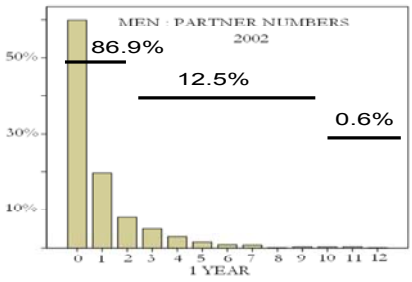
2. The original version of the model was developed to be able to handle 4 different HPV types:

- **Type 16, type 18, type 'other' (10 different), type 6 and 11 (related to genital warts)**

3. Modelling natural history of HPV, cervical cancer disease progression and sexual activity:



- Mixing(act. group, age, mix pref., partn.<time>)



Acts per partnership

	high	med.	low
high	2	12	104
med.	12	12	104
low	104	104	104

Mixing by age

- Mixing(act. group, age, mix pref., partn.<time>)
- 6 age groups

Age	16-25;	26-35;	36-45;	46-55;	56-65;	66-75
RA :	4.0	2.0	1.0	1.0	1.0	1.0

In the model various assumptions on the natural history of HPV (and progression to cervical cancer), clinical, population, screening, vaccine characteristics are specified. For example, re-setting the current screening strategy to every 3 years in women aged 25-69 yrs in line with the current strategy in Norway. Other modifications to parameters in the model included, those relating to sexual activity: categorized in the model into 3 classes and described in terms of the average number of sexual partners (low, medium, high) and based on data from the Norwegian Sexual Health Surveys (2002) to reflect more accurately actual sexual behaviour patterns currently typical in a Norwegian population. The disease model predicted annual incidence of disease and disease related deaths for the study arms (starting with the assumption of a vaccine introduction in 2008) projecting forward up to 52 years into the future (i.e. to 2060). Totals were computed for the accumulated health outcomes for various time horizons.

2.7 Assumptions about health care costs

We sought to assess the typical additional costs of incorporating HPV vaccination to the current childhood vaccination schedule in Norway and whilst assuming the current screening programme remained unchanged (detailed assumptions concerning resource use and unit costs applied are reported in APPENDIX 1). The identification, and measurement of resources utilized was informed both through discussion with clinicians involved in the care of cervical cancer patients in Norway (GBK) and based on descriptions in the literature (18;,21;,22;23) and based on Norwegian data (Norwegian Cancer Registry and National screening programme).

An assessment of the following resource use items associated with screening, diagnosis and treatment of cervical pre-invasive disease and cancers and vaccination were included in the present analysis:

- Screening programme costs: Routine cytology testing based with the Pap smear
- Work-up of positive test results: Including HPV testing, colposcopy with biopsy
- Management and treatment of cervical abnormalities: including ablation and resection procedures of the abnormal area
- Treatment of cervical cancers
- Vaccine (initial x 3 doses administered over 6 months, and booster x 1 dose after 10 years)

Some important disease management assumptions should be noted with respect to cost calculations:

- We assumed in line with current guidelines in Norway, all women with cytological findings of atypical squamous cells of undetermined significance (AS-CUS), low-grade squamous intraepithelial lesions (LSIL) would undergo HPV testing
- Women with high grade dysplasia (HSIL) were assumed to be referred for colposcopy with biopsy
- Treatment for high grade dysplasia (HSIL ≈ CIN 2/3) were assumed to include procedures such as conization, cryosurgery (freezing), LEEP excision (burning/laser treatment) of the abnormal cells area
- Cervical cancer treatments include surgical, radiotherapy and chemotherapy interventions

Available unit cost figures for the most recent price years 2005/2006 at the time of the analysis were based on official national tariffs (outpatient care) and hospital based DRG reimbursement rates (inpatient care).

2.8 Assumptions about productivity losses due to cervical cancer and cancer mortality

The inclusion of productivity losses in health economic evaluations is somewhat controversial and not always taken into account. For example, in the UK, the National Institute of Health and Clinical Excellence generally only considers direct healthcare costs. WHO guidelines also don't recommend their inclusion. However, for our analysis we have not presumed to favour one approach over the other, only that we present the two sets of results alongside each other for decision makers to then consider their relative importance.

We used the human capital approach to measure productivity losses—that is, by using forgone income attributable to cervical cancer morbidity (only in so far as an assessment relating to treatment costs) and premature mortality due to cervical cancer.

Assessment of productivity losses attributed to cervical cancer treatment

For an assessment of work absenteeism among women related to treatment of cervical cancer, we assumed that each outpatient radiotherapy (and/or chemotherapy) session results in 2 hours lost production. We valued this lost productivity according to average wage levels in Norway (average monthly earnings- across all working women of NOK 26,400 ≈ annual gross NOK 316,800, 2005) http://www.ssb.no/english/subjects/06/05/lonnansatt_en/ With an average working hours per week of 30.7 hours http://www.ssb.no/english/yearbook/tab/tab-210.html The cost of time for those women employed was set equal to the average national hourly rate (of approx NOK 198).

In addition not all women will be in employment (either full or part-time). According to official national statistics, approximately two-thirds of women aged 16-74 years were in employment in 2005 http://www.ssb.no/english/yearbook/tab/tab-206.html

Travel costs/expenses associated with cervical cancer treatment

Patient travel costs in relation to cervical cancer treatment were also considered. Time costs were applied for women undergoing radiotherapy/chemotherapy visits assuming an average 90 min round trip travel time, and as already mentioned above, a 2 hour treatment time. We did not assign any cost to lost leisure time to the third of women not employed. There is a lack of data on specific travel time costs associated with treatment visits to hospital amongst cervical cancer patients, however, the assumption of an average 90 min round trip travel time were based on the findings of a recent health survey conducted by Statistics Norway for the World Health Organisation. http://www.ssb.no/english/subjects/03/00/whs_en/main.html: In the survey, 330 persons answered questions about their last stay in hospital or a long time care facility. Estimations on travelling time to hospital give an average travel time of 44 minutes. Health region East has the shortest average travel time with 32 minutes, while region Mid-Norway and region North has the longest average travel time with 55 and 74 minutes, respectively (does not include ambulance transport).

Assessment of productivity losses due to cervical cancer mortality
The number of lost working days dues to cervical cancer deaths was reported in years and, similarly to cervical cancer treatment described above, valued according to the average national wage rate. For all women of working age and dying from cervical cancer, a production loss of NOK 316,800 per year was applied to the proportion of women in employment.

2.9 Adjustment for timing of costs and benefits

Although debate persists over the merits or otherwise of discounting survival gains in economic evaluations (19), the expected gains in out study were discounted at the same rate as costs. We accounted for the longer time horizon over which costs and health benefits may accrue by discounting outcomes and costs at a rate of 4% in line with recommended practice in Norway. Alternative assumptions on the discount rate applied were explored in sensitivity analyses (0%, 3% per year).

2.10 Scenarios modelled

To explore uncertainty in (parameter) estimates in health economic evaluations it is generally acknowledged that the technique known as probabilistic sensitivity analyses (PSA) is the methodology of choice (20). The procedure, essentially required in this instance involves undertaking Montecarlo simulation in which, for example 1000 iterations of the model are performed whereby parameter values are randomly sampled from specified distributions. However, for our economic analyses, it was not computationally practical to undertake such simulations (each simulation run of the model taking some 15-20 minutes to complete). Performing PSA on certain variables especially clinical ones such as vaccine efficacy and coverage was just not feasible. It was not therefore possible to determine how likely certain levels of cost-effectiveness were by simultaneously incorporating all ranges of values for a large number of model variables. We were thus limited to explore uncertainty in our results by performing a number of 1-way and multiway sensitivity analyses to explore the impact of varying key parameters in the model: vaccine efficacy; vaccine coverage; costs of vaccination, discount rate. This pragmatic approach adopted to sensitivity analyses is consistent with recent economic model based evaluations of HPV vaccination (6).

The baseline (base) scenario refers to the reference population of no vaccination (screening only). The costs and benefits (life years gained) generated from each alternative vaccination scenario alongside the current screening strategy in Norway (26-69 years of age every 3 years) are then compared to the reference population of screening alone. The primary vaccination scenario simulation: 12-year-old girls; 90% coverage; 90% efficacy.

3. Results

3.1 Model corroboration and calibration

Comparisons between each of the age-specific cohort model based predictions of cervical cancer, cancer mortality, CIN 2/3 (≈HSIL) with external benchmark data (based on data from the Norwegian Cancer Registry) were assessed (the results for cases of cervical cancer and cervical cancer deaths are presented in appendix 5). In most cases, age-specific model results for cervical cancer were found to lie within the 95% CIs of (actual) external benchmark (cancer registry based) data. However, it should be acknowledged that the model tends to underestimate somewhat, the number of cancers in each age-specific cohort (that is, the model predicted cancers lie closer to the lower limits in most cases).

3.2 Base case analysis

3.2.1 Costs and health benefits

Tables 1-5 present the costs and outcomes over various time horizons assuming annual vaccination of all 12-year- old girls (initial 3 doses) with a booster vaccination 10 years after the initial vaccination (i.e. at age 22 years). Table 1 and table 2 present estimated costs, effects and cost-effectiveness results at 10 year intervals (from 2008-2060) for the health care sector and societal perspective respectively. Tables 3-5 present total incremental costs, total incremental effectiveness and incremental cost-effectiveness ratios associated with an HP16/18 type vaccination. The base case analysis assumed a vaccine efficacy of 90% and vaccine coverage of 90%. Experience in Norway, suggest that a value of 90% coverage is not unrealistic, given that vaccine coverage rates are high in Norway at 90% or more for various childhood and adolescent vaccination programmes. http://www.fhi.no/tema/vaksine/dekning/. For example the recommended immunization schedule in Norway for MMR vaccine is targeted at adolescents aged 12-13 year-olds and has a national coverage rate of 90%. In the model, vaccination hypothetically starts in 2008 and the model simulations are run until the year 2060 (or the next 52 years) for 10 age-sex specific cohorts. Based on such a population modeling approach (and with multiple age-sex specific cohorts), the cumulative total gain for vaccinating all 12-year-old girls annually (around 1.5 million over a 52 year period) was estimated to be 2,962 discounted life years or 3,539 discounted QALYs. Distributed on a per patient/case basis this amounted to 0.00189 life years and 0.0023 QALYs respectively (table 3)
The estimated costs was NOK 5,006 (discounted) per vaccinated 12-year-old girl (NOK 6,761 including productivity losses due to productivity losses arising from cervical cancer mortality) and NOK 4,140 without vaccination (NOK 6,429 including productivity losses).

In terms of proportional costs (based on 2005 cancer registry and screening programme data), and a programme of screening alone (with total costs of approx NOK 246 million estimated for 2005), Pap smear testing were estimated to account for around 74% of total annual costs. The remainder being due to diagnostic workup of positive Pap smear test results, therapeutic workup of abnormal findings; diagnostic work-up associated with cervical cancers, and cancer treatment costs (including an assessment of long-term surveillance).
For a programme of vaccination alongside screening, an initial 3 dose regime would add approx. NOK 77 million (excl. VAT) --again based on a 2005 population
The total costs to society of including HPV 16/18 vaccine in the childhood vaccination program assumes three doses administered to all 12-year-old girls in school based settings as part of the regular schedule of vaccinations around the same age (e.g. MMR). With no administration costs, price including VAT (and pharmacy margins), acquisition of the vaccine will cost around NOK 103 million per year (based on 90% coverage, e.g. approx 27,300 12-year olds in 2008). In a booster year (in the base case assumed to be administered 10 years after the initial immunization) estimated costs would increase to around NOK 101 million. Without VAT, the annual vaccination cost as mentioned earlier would be NOK 77 million. Booster vaccinations would thus increase costs by approx. a further NOK 24 million.

In the base case, taking all vaccinated 12-year olds into account is estimated to cost NOK 866 per 12-year old more than an unvaccinated one when direct health care costs are included. Taking into account indirect costs arising from productivity losses due to cervical cancer mortality and treatment (table 2, table 3) the additional cost per 12-year old vaccinated girl (compared) to an unvaccinated one is much reduced at NOK 271.

3.2.2 Cost-effectiveness

Costs accrue in the short-term (e.g. associated with initial vaccination), whereas survival gains accumulate over a far longer period, and analyses performed say at 10 years therefore underestimate expected yields (e.g. in terms of life years or QALYs gained) relative to costs. Potential cost savings associated with e.g. reduced mortality (and hence increased survival) in a vaccinated population, are only seen to offset vaccination costs after some decades.

The base case analysis showed that running a programme of annual vaccination for 52 years alongside the current programme of screening was more effective (total gain in life years of 2,962, or equivalent to 0.0019 per girl vaccinated), but more expensive (NOK 866 per vaccinated girl) than a programme of screening alone. Vaccination resulted in a cost-effectiveness ratio of additional cost of NOK 477,000 per life-year gained (NOK 399,000 per QALY gained). On the other hand, including indirect costs (e.g. productivity losses due to premature death from cervical cancer- table 2) and re- calculating cost-effectiveness for the same time horizons, resulted in a reduced (improved) cost-effectiveness ratio of NOK 141,000 per life-year gained (NOK 118,000 per QALY gained).

Tabell 3.1 Results from clinical and economic model simulations of HPV vaccination, provisional results: Base case analysis: 90% efficacy, 90% coverage, direct costs only

		Screening alone (NOK '000)		Vaccination and screening (NOK '000)														
Specific programme period (year) Simulation results cover (only) age-groups 16-75 (e.g. 86-88% of incident cancers in 2003-2005)	Time period	programme costs	life-years (lost to cervical cancer)	programme costs	life-years (lost to cervical cancer)	rate reduction in cancer incidence	rate reduction in cancer mortality	rate reduction in CIN 2/3	rate reduction in HPV 16 prevalence	rate reduction in HPV 18 prevalence	Life-years gained (undiscounted)	Cumulative discounted life-years gained (to vaccination start date 2008)	QALYs gained	Cumulative discounted QALYs gained (to vaccination start date 2008)	Incremental costs	Cumulative discounted incremental costs	Incremental discounted cost per life-year gained	Incremental discounted cost per QALY gained
2008 pre vaccination (or start)	113	253,145	864.35	331,100	864.35	0.00	0.00	0.00	0.00	0.00	0.00		0.00		77,955			
2018 post vaccination + 10 years	123	276,890	796.12	348,777	778.65	0.05	0.02	0.00	0.28	0.37	17.47	**27.77**	24.45	**40.63**	74,537	**645,790**	**23,253**	**15,895**
2028 post vaccination + 20 years	133	287,663	819.86	337,437	664.42	0.24	0.17	0.02	0.52	0.61	155.45	**479.86**	189.42	**607.99**	54,820	**971,703**	**2,025**	**1,598**
2038 post vaccination +30 years	143	297,000	853.98	347,134	568.08	0.36	0.31	0.18	0.60	0.66	285.89	**1,320.98**	338.20	**1,612.81**	55,338	**1,175,715**	**890**	**729**
2048 post vaccination + 40 years	153	304,226	874.03	351,507	501.84	0.43	0.40	0.23	0.64	0.69	372.19	**2,155.45**	438.33	**2,595.03**	52,612	**1,310,940**	**608**	**505**
2058 post vaccination + 50 years	163	313,632	905.73	359,777	467.86	0.48	0.46	0.25	0.67	0.71	437.87	**2,843.15**	512.10	**3,400.37**	51,640	**1,398,336**	**492**	**411**
2060 post vaccination + 52 years	165	315,772	913.47	361,167	463.79	0.49	0.47	0.26	0.67	0.71	449.68	**2,961.70**	525.66	**3,538.96**	50,928	**1,411,896**	**477**	**399**

Tabell 3.2 Results from clinical and economic model simulations of HPV vaccination, provisional results: Base case analysis: 90% efficacy, 90% coverage, indirect costs (productivity losses due to cervical cancer mortality, cancer outpatient treatment attendances, travel expensed)

		Screening alone (NOK' 000)				Vaccination and screening (NOK '000)												
Specifc programme period (year) Simulation results cover (only) age-groups 16-75 (e.g 86% to 88% of incident cancers in 2003-2005)	Time period	direct programme costs	Productivity losses due to cervical cancer mortality	Productivity losses associated with cancer treatment and travel to hospital	Total costs	direct programme costs	Productivity losses due to cervical cancer mortality	Productivity losses associated with cancer treatment and travel to hospital	total costs	Productivity losses averted	incremental costs	Cumulative (discounted) incremental costs	Life-years gained (undis-counted)	Cumulative (discounted) life-years gained (to vaccination start date 2008)	QALYs gained	Cumulative (discounted) QALYs gained (to vaccination start date 2008)	Incremental discounted cost per life-year gained	Incremental discounted cost per QALY gained
2008 pre vaccina-tion (or start)	113	253,145	147,567	26,118	426,831	331,100	147,567	26,118	5,04,785	0	77,955		0.000		0.0			
2018 post vaccina-tion + 10 years	123	276,890	150,946	26,494	454,331	351,427	132,381	25,123	506,932	19,936	54,601	592,058	17.470	39	24.45	58	15,013	10,291
2028 post vaccina-tion + 20 years	133	287,663	156,293	27,801	471,757	342,483	112,621	21,131	476,235	50,342	4,478	639,956	155.447	479.86	189.42	607.99	1,334	1,053
2038 post vaccina-tion +30 years	143	297,000	163,611	28,821	489,431	352,338	95,948	18,550	466,836	77,934	-22,596	600,045	285.894	1,320.98	338.20	1,612.81	454	372
2048 post vaccina-tion + 40 years	153	304,226	166,049	29,452	499,727	356,838	84,408	16,801	458,047	94,292	-41,680	517,666	372.187	2,155.45	438.33	2,595.03	240	199
2058 post vaccina-tion + 50 years	163	313,632	172,188	30,508	516,328	365,272	78,936	15,932	460,140	107,828	-56,188	433,876	437.870	2,843.15	512.10	3,400.37	153	128
2060 post vaccina-tion + 52 years	165	315,772	173,794	30,740	520,306	366,700	78,320	15,822	460,841	110,392	-59,464	418,310	449.679	2,961.70	525.66	3,538.96	141	118

Table 3.3 Estimated incremental costs of an HPV vaccination programme (NOK '000)[1]

	Incremental heath sector costs- and cost savings, NOK '000			**HEALTH SECTOR PERSPECTIVE**	Incremental production losses and gains, NOK '000[2]		**SOCIETAL PERSPECTIVE**
Base case:	Initial vaccination	Booster vaccination	Future cost-savings due to avoided cervical cancer treatments, pre-cancers	Total incremental health sector costs	Averted production losses due to early cancer deaths	Averted production losses due to work absences whilst undergoing cervical cancer treatment	Total incremental health sector costs AND productivity losses
90% efficacy, 90% coverage	1,753,428	365,959	707,491	1,411,896	880, 308	113,277	418,310
cost per vaccinated case				866			271
Cost calculations repeated with VAT included on the vaccine unit cost[3]	2,337,905	487,945	707,491	2,118,359	*880,308*	*113,277*	*1,124,774*
cost per vaccinated case				1,370			*727*

1. Accumulated results over 52 years of vaccinating each annual cohort of 12-year-old girls. The analysis assumed a booster vaccination would be required at age 22 to maintain vaccine efficacy. The baseline time is 2008. All future costs are discounted at a rate of 4% per annum.

2. Lost production during booster vaccination not included. Calculations were based on the human capital approach and are simply based on gross income. An alternative approach, is to consider only that fraction, which represents a 'contribution to the rest of society', i.e. the tax part of the income. Our estimates, therefore, should be interpreted with caution since the human capital approach remains controversial for a number of reasons.

3. VAT is not strictly a societal cost and it may be argued that it should not be included in a baseline societal perspective. VAT could be excluded on the grounds that it's a transfer payment and doesn't reflect the opportunity cost of resources. On the otherhand, if a decision maker is interested in a financial budget impact analysis from the point of view of an organization VAT might then be included. However, the Norwegian Institute for Public Health pointed out that they wanted to have VAT included in the costing calculations, so estimates are also presented here with VAT included. However, some cautionary concerns should be mentioned, in that these latter estimates may not always be considered appropriate from a health economic methodological practice point of view.

Table 3.4 Total LYRs and QALYs gained according to discount rate,

	Total expected numbers			Discount rate per annum	LYRs gained			QALYs gained		
	vaccinated 12-year old girls	averted cervical cancers[2]	averted cervical cancer deaths[2]		Total	per vaccinated case	per averted cervical cancer	Total	per vaccinated case	per averted cervical cancer
Base case 90% efficacy, 90% coverage[1]	≈1.5 million	2906	673	5%	1,919	0.0012	0.6605	2,341	0.0015	0.8057
				4%	2,962	0.0019	1.0193	3,539	0.0023	1.2178
				3%	4,686	0.0031	1.6126	5,489	0.0036	1.8887
				2%	7,616	0.0049	2.6209	8,749	0.0057	3.0108
				1%	12,755	0.0082	4.3894	14,362	0.0093	4.9421
				0%	21,946	0.0142	7.5520	24,318	0.0157	8.3683

1. 52 years of annual vaccination of 12-year-old girls. Booster vaccination at age 22.
2. Totals accumulated by 2060, assuming 52 years of a fully operational vaccination programme. The baseline time is 2008.

Table 3.5 Incremental cost-effectiveness ratios[1]

Scenario/ simulation description	Health sector perspective (NOK '000)		Societal perspective (NOK '000)	
	Cost per LY gained	Cost per QALY gained	Cost per LY gained	Cost per QALY gained
Base case				
90% vaccine efficacy, 90% coverage[2]	477	399	141	118
with health benefits undiscounted	64	58	19	17
VAT included in vaccine unit cost[3]	715	599	*380*	*318*
With health benefits undiscounted[3]	97	87	*19*	*17*
Sensitivity analyses				
Lower vaccine efficacy: 85% efficacy, 90% coverage	514	430	172	144
with health benefits undiscounted	69	62	23	21
VAT included in vaccine unit cost	764	640	*108*	*91*
with health benefits undiscounted	103	93	*57*	*31*
Higher vaccine efficacy: 100% efficacy, 90% coverage	412	345	87	73
with health benefits undiscounted	56	50	12	11
VAT included in vaccine unit cost	629	526	*305*	*255*
with health benefits undiscounted	85	77	*41*	*37*
Lower vaccine coverage: 90% efficacy, 80% coverage	566	474	216	180
with health benefits undiscounted	76	68	29	26
VAT included in vaccine unit cost	834	698	*483*	*404*
with health benefits undiscounted	111	101	*65*	*58*
Combination of lower efficacy and lower coverage: 85% efficacy, 80% coverage	607	508	249	209
with health benefits undiscounted	81	73	33	30
VAT included in vaccine unit cost	887	743	*530*	*444*
with health benefits undiscounted	118	107	*71*	*64*
Vaccine price: Reduced by 10%	405	339	70	58
with health benefits undiscounted	116	105	Cost-saving, more effective	Cost saving, more effective
VAT included in vaccine unit cost[4]	356	301	*284*	*238*
with health benefits undiscounted	188	170	*37*	*33*
Future costs and benefits discounted at 3%	354	302	123	105
with health benefits undiscounted	537	458	*330*	*231*

1. Results for a vaccination programme period 2008-2060 ≈ 1.5 million girls vaccinated 2. With a × 3 dose initial vaccination at 12 years old, booster vaccination after 10 years. 3. VAT generally argued not to be societal cost and therefore should not be included in a baseline societal perspective. However, the Norwegian Institute for Public Health pointed out that they wanted to have VAT included in the costing calculations, so estimates are also presented here with VAT included (direct). However, some cautionary concerns should be mentioned, in that these latter estimates may not always be considered appropriate from a health economic methodological practice point of view, often depending on the viewpoint taken.

3.2.3 Sensitivity and scenario analysis

A similar set of summary results – as presented above for the base case analysis are reported for an additional set of sensitivity analyses (table 3.5). We investigated with a range of simple sensitivity analyses how influential were alternative assumptions with respect to varying vaccine efficacy, vaccine coverage, duration of protection, and vaccine price

In addition, we undertook a number of other sensitivity analyses. The time horizon of the base case simulation is 52 years. Some published (Markov) models run for the duration of the expected lifetime of the cohort, which, if are assumed to be all 12-year- old girls, would create a potential time horizon of around 70 years (the average life expectancy for women in Norway: Statistics Norway). Clearly, computing costs and outcomes over for a longer time horizon improves cost-effectiveness ratios. In the base case the model was run for the period 2008-2060 (52 years) and produced a cost per life year gained of NOK 477,000. Running the simulations for a longer period, for example 2008-2090 reduce (improve) the cost-effectiveness ratios further (table 3.5).

Tabell 3.6 Cost-effectiveness assessments with: i) including over 75s; ii) simulation run to 2090

	Cost LYR gained (NOK '000)		Cost QALY gained (NOK '000)	
	Health care sector perspective	Societal perspective	Healthcare perspective	Societal perspective
Base case[1]	477	141	399	118
Including population over the age of 75[2]	430	96	361	80
Simulation run to 2090[3]	370	87	319	33

1. 90% efficacy, 90% coverage
2. Compared to the base-case analysis, hypothetical costs and outcomes are simulated for an additional 30 years (2008-2090 as opposed to the period 2008-2060)
3. Productivity losses due to cervical cancer mortality and cancer outpatient attendances Incorporating an assessment of the cancer incidence and mortality occurring in the over 75s also improves the cost-effectiveness ratios somewhat compared to the base case.

4. Discussion

A number of challenges exist in order to fully achieve the potential population health benefits from implementing a vaccine targeting HPV. The results of this current evaluation should be viewed as providing an insightful analysis of the potential health economic consequences with respect to cervical cancer with an assessment of an HPV 16/18 type specific vaccination for Norway. However, there remain some important uncetainties relating to long-term effectiveness, costs and cost-effectiveness, not addressed within the resources and time-frame available for conducting the present evaluation.

4.1 Current study methodological limitations

The model performance is less than perfect, but we consider it acceptable compared to the available data. Appendix 5 demonstrated that for example, model results for annual age-specific cancers fell within the 95% confidence limits of external data based on cancer registry cases in Norway. However, it should be pointed out that their remain some problems with fitting the model to Norwegian data including:

(1) the data does not reflect the screening / vaccination setting: The cin1-3 LSIL/HSIL values are TOTAL numbers, including data from individuals who are screened outside the recommended screening setting.
(2) The cin1-cin2 is likely underestimated in the data, since more severe cell changes are likely to undergo further investigation (biopsy).
(3) There is a tendency for women with high risk behaviour not to attend the screening programme. Thus, there will be an overweight of un-detected cin-cases.

(1) implies that the model will underestimate the amount of screenings performed. This is also found, approximately 25% lower values of predicted screenings compared to data. It should be pointed out that our analysis does not use the model results for number of screening tests performed as the basis for estimating screening costs, but uses data on the actual number of Pap smear tests performed and women screened in Norway from the screening programme (Cancer Registry, 2005 which amounts to approx 450,000 tests annually in Norway).
(2) implies that we should expect the model to produce higher cin 1- cin 2 cases than what is being reported. This tendency is also observed, as the model predicts higher cin 2 cases compared to data. However, how large should the estimated deviation be remains uncertain. There are less CIN2 than CIN3 detected in Norway so the observed data are

correct. One possible reason, maybe that pathologists tend to use either CIN1 or CIN3 for classifying pre-malignancy cervical dysplasia and that CIN2 is more often left out/not diagnosed. Our assumption, then of the CIN3 data being more realistic of the real incidence of precancerous findings in Norway is probably correct and we have thus concentrated on fitting the CIN3 data (but in any case have also included CIN 2 in our comparisons- especially as a basis for number of cases/ quantities used in the cost estimation associated with high grade cervical abnormalities). There was no available data on CIN 1 in Norway for us to run consistency checks with our model results.
(3) The model takes account of current sexual behaviour patterns in the Norwegian population, but does not separate the sexual behaviour of women attending the screening programme from those who do not. The bias could result in the model underestimating the cancer incidence, but by how much again, is unclear. More concrete data will be needed on this issue to discuss the importance.

4.2 Health policy implications of HPV vaccination

Comparison of the range of our HPV vaccine cost-effectiveness results with those recently published Norwegian cost-effectiveness estimates of 7-valent pneumoccocal conjugate (PCV-7) vaccine (24). The range of cost-effectiveness estimates reported in this economic evaluation was taken into account in the recent government decision to include PCV-7 in the Norwegian childhood vaccination program.

Tabell 4.1 Comparison with cost-effectiveness assessments of adding 7-valent pneumococcal conjugate vaccine (PCV-7) vaccine to the Norwegian childhood vaccination program

	Cost LYR gained (NOK '000)		Cost QALY gained (NOK '000)	
	Health care costs	Including productivity losses	Health care costs	Including productivity losses
Base case HPV 16/18 vaccine[1]	477	117	399	98
PCV-7: x 4 vaccine doses, no herd immunity	2,603	1,038	1,172	469
PCV-7: x 4 vaccine doses, herd immunity included	1,281	485	803	310
PCV-7: x 3 vaccine doses, no herd immunity	1,541	dominant	695	dominant
PCV-7: x 3 vaccine doses, herd immunity included	753	dominant	477	dominant

1. 90% efficacy, 90% coverage

Norway at present does not have any official cost-effectiveness threshold. However, Norwegian guidelines for priority setting state that cost-effectiveness is a legitimate criterion for priority setting, and the Ministry of Finance has issued guidelines for economic evaluation of public programmes including health care (Norwegian Ministry of Finance. Guidelines for social economics analyses, Norway: 2005). Here, NOK 425,000 is mentioned as a threshold of the cost per life year. Such judgements are very much value

based however, Our base case estimates, which we considered to be on the conservative side, are close to this threshold. However, alternative assumptions resulted in cost-effectiveness considerably lower than this hypothetical threshold value.

Our analyses, based on an up-to-date estimate of the effectiveness of HPV 16/18 vaccine and modeled on the Norwegian health care setting, suggests that HPV 16/18 vaccine might well be cost-effective, over the long-term. In the base-case analysis HPV vaccination was associated with an additional cost of NOK 477,000 per LYR gained and NOK 399,000 per QALY gained over a simulated 52 year time horizon. This estimate, under current assumptions, is also within the published estimates for other vaccination programmes in Norway.. For example, pneumococcal conjugate vaccine (26).

When the clinical model was run for a longer time horizon cost-effectiveness estimates were lower (improved). However, both the short-term and long-term cost-effectiveness estimates have to be regarded as somewhat imprecise. At 52 years the impact on costs ranged from an additional (annual) cost of NOK (+) 50,928,000 (table 3.1) to a cost saving of NOK(-) 59,464,000 (table 3.2) when costs associated with productivity losses costs were included. There was therefore considerable uncertainty about the exact size of the incremental cost-effectiveness ratio for HPV vaccine in cervical cancer prevention. Furthermore, the findings point to the significant consequences of including "indirect" costs in estimating the potential 'value for money' of an HPV 16/18. type specific vaccination. The relative importance given to these different cost perspectives by decision-makers' in making valued judgments on the efficiency of HPV vaccination is likely to have a key role in planning any potential programme introduction.
The cost-effectiveness estimates were also sensitive to vaccine efficacy, duration of immunity, coverage and cost of HPV vaccination.

Summary of previous work
Our results are not as optimistic as some earlier estimates. However, as already mentioned the overall approach is more conservative.Tabel 4.2 provides some insight into the range of cost-effectiveness of HPV vaccination in published studies compared to the current study. The majority of recent studies have been undertaken from the perspective of the North American health care system. More studies from European and other countires would therefore be informative. Although not presented here, studies also vary with respect to their asssumptions on e.g. quality of life weights assigned to different health states, resource use and unit costs applied, and the time horizon over which costs and outcomes are simulated.

Tabell 4.2 Comparison with some other recent cost-effectiveness analyses of HPV vaccine introduction

Study	Model type (disease/epidemiologial model)	Perspective(s) presented	Country	Key base case assumptions				ICERS[4]		
				Target population	Vaccine coverage	Efficacy	Duration of protection	Discount rate	Cost per LY gained	Cost per QALY gained
Present analysis	transmission model	Healthcare sector Societal[1]	Norway	12-year-old girls	90%	90% against HPV 16/18 type infections	10 years, booster at 10 years	4%	NOK 117,000 to NOK 477,000	NOK 98,000 to NOK 399,00
Sanders 2003	State-transition Markov	Healthcare sector	US	12-year-old girls	70%	75% against 13 high-risk type HPV types	10 years, Booster every 10 years	3%	-	$22,755 to $52,398 (NOK 222,000 to NOK 510,000)
Kulasingam 2003	State-transition Markov	Healthcare sector Societal[2]	US	12-year-old girls	100%	90% against 70% of high-risk HPV types 16/18 infections	10 years	3%?	$44,889 to $236,889 (NOK 383,000 to NOK 2,019,000)	-
Goldie 2004	State-transition Markov	Societal[2]	US	12-year-old girls	100%	90% against HPV 16/18 type infections	Lifelong (no booster)	3%	-	$24,300 to $4,863,000 (NOK 207,000 to NOK 41,435,000)
Taira 2004	Hybrid (dynamic/ Markov)	Healthcare sector	US	12-year-old girls and boys	70%	90% against HPV 16/18 type infections	10 years, Booster every 10 years	3%	-	$14,583 to $442,039 (NOK 125,000 to NOK 3,767,000)
Elbasha 2007	Dynamic HPV transmission	Healtcare sector	US	12-year old girls and boys	Up to 70%[3]	90% against incident HPV 16/18 or 6/11 infection, 100% against associated disease	Lifelong (no booster)	3%	-	$4,666 (girls only) $45,056 (girls and boys) (NOK 31,000 to NOK 297,000)
Kulasingam 2005	Markov	Healthcare sector	UK	12-year-old girls	87%	90% agains HPV type 16,18 6 and 11 infection	20 years	3%	£20,600 to £28,200 (NOK249,000 to NOK 341,000)	£16,000 to £22,000 (NOK 194,000 to NOK 255,000)

1. Productivity losses due to premature death from cervical cancer, time and travel costs associated with cervical cancer treatment

2. Time costs 3. Increasingly linearly from 0% to 70% during first 5 yeas of the programme and 70% thereafter. Catch-up program for 12- to 24-year-olds

4. ICERs (updated) to their approximate 2006 prices accoding to the consumer price index (Satistics Norway).

In 2 recent reviews Newall 2007 (14) and Dansbach 2006 (13) the authors indicate that though HPV vaccination could be cost-effective their remain considerable uincertainty around key variables and model validation in a number of models this could be further improved. We consider this also to be the case in our own analysis. The reviews noted that amongst the most influential varianbles on cost-effectiveness were vaccine effectiveness, coverage, cancer screening strategy, model type.

It should be pointed out that the fixed costs of developing and maintaining a capability to register and monitor vaccinated population(s) and provide vaccination would need to be taken into account in a more comprehensive analysis.

Generalisability of these results

Another uncertainty relates to the generalisability of the findings. It is likely that both actual resource use (e.g. number of colposcopies performed, other procedures and treatments) and the valuation of resources (e.g. unit cost per investigation, procedure, treatment) will vary considerably within the Norwegian health care system. Hence, we used national official figure to "average out" local differences in unit costs and we believe that the resources used by patients registered at Radiumhospital and, other cancer centres are reasonably representative of the resources used by patients managed by other Norwegian hospitals. Our analysis did not include the costs of implementing HPV vaccine in Norwegian schools, vaccination registration and monitoring systems or any public educational campaigns that may be necessary. We assumed that there were no capacity constraints in the healthcare system and that there were no extra costs with giving annual HPV vaccination to all 12-year-old girls, or of giving HPV vaccine to more of the population if this was considered required, for example to include a catch-up vaccination programme for other age-groups.

We also assumed that HPV vaccinations were "equal", regardless of where they occur (rural, city schools, size of cohort of 12-year-old girls to be vaccinated, or any other intended age-group in the future), that vaccine supply, delivery and storage equipment was always readily available, and that the correct number and mix of healthcare professionals were always in place to administer the vaccine.

It remains difficult to assess the additional costs of developing specific service components likely to be required to deliver HPV vaccine in Norwegian schools, over and above those required for adding an HPV vaccine as a "standard" vaccine to the existing vaccine programme schedule in schools.

5. Conclusion

Implications for Practice

Our economic modeling analysis, constructed from the perspective of the Norwegian healthcare setting, suggests that an HPV 16/18 vaccine for cervical cancer holds the promise, under favourable assumptions, of being cost-effective in terms of LYRs and QALYs gained, particularly when longer-term cost and health outcomes were considered. In the situation were direct costs are considered, a time horizon of 80+ years demonstrated cost-effectiveness ratios below hypothetical potential decision makers thresholds in Norway. On the other hand, HPV vaccination alongside screening, a time horizon of 30 years, and including procuctivity losses showed to be cost saving when compared to screening alone.

However, the range of possible ICERs was quite considerable, the bounding of which, being limited, in the current evaluation, by not performing probabilistic sensitivity analyses to explore the impact of parameter uncertainty on our results. The conclusions from the economic modeling were sensitive to assumptions made on a number of parameters, including the effectiveness of HPV vaccination

For the limited number of analyses undertaken in the current economic evaluation, the results suggested that HPV vaccine to be potentially cost-effectiveness or even cost-savings (when productivity losses were included). However, in view of the lack of precision of the estimates and lack of data on the cost of "rolling out" vaccination to the many schools that (assuming) will need some degree of extra resources to give HPV vaccination, we were unable to model the widespread use of HPV vaccination for cancer prevention in Norway.

Implications for Research

The cost-effectiveness of HPV vaccine could not be assessed reliably because of e.g. imprecise estimates of (long-term, post trial time horizon) efficacy. Long-term follow-up, observational studies may provide sufficiently precise estimates of long-term effects (as well as any side effects or adverse events) from HPV vaccination. If (longer-term) studies established reliably that HPV vaccination was effective in the longer-term, then better estimates of the cost of implementing HPV vaccination in the Norwegian healthcare setting will be needed. A more "dynamic systems approach" to explore the relationships between different systems components and their impact on patient treatment strategies would be informative. For example, we have assumed that the current screening strategy would remain unchanged over the longer-term in the advent of the introduction of an

HPV vaccination programme. Because the cost-effectiveness estimates were sensitive to a relatively small set of parameters, future research could focus on the relationship between HPV vaccination, resource consequences, and heath effects. More data are needed, for example, on the duration of vaccine derived immunity, beyond trial lifetime and the effect (reductions) on the burden of cervical cancers and cervical precancerous dysplasia and on subsequent survival.

In summary, from the set of results presented in this present economic evaluation, the following conclusions might be proposed:

- The preliminary results from the base case analysis suggest that in terms of cost per life year gained it will be many years, if not decades, before the accumulated costs and health benefits of an HPV vaccination programme may be considered cost-effective. When the health care sector direct costs are considered, and for a programme time horizon of 52 years (2008 to 2060), the cost per life year of over NOK 400,000 is close to some commonly reported cost-effectiveness thresholds in the literature, but not necessarily outside what some decision makers would consider to be cost-effective.

- When the viewpoint for the analysis is societal, cost-effectiveness ratios are considerably lower (improved). In the base case to NOK 141, 000 per life year gained and NOK 118, 000 per QALY gained when productivity losses due to cervical cancer mortality are accounted for.

- Any savings in direct health care costs (e.g. cancer treatment costs) arising due to reductions in the incidence of cervical cancers and pre-cancers and the reduction in cancer deaths are likely to be relatively small (≈ in the order of maybe 5-10%). The base case results make it quite clear that there is a wide gap between the expenses of the vaccination program (under the given assumptions). Therefore any substantial offset or "recovery" of vaccination program costs due to these types of costs may be negligible. On the other hand, and from a societal perspective, potential gains in productivity (e.g. from averted cancers and cancer related deaths) resulting from a programme of vaccination appear to be considerable.

- Our population based approach using a number of age-sex specific cohorts, calculates cost-effectiveness ratios for various time horizons. Running our simulation calculations for a longer time horizon reduce (improve) the cost-effectiveness ratios of HPV vaccination further. Running the clinical and economic models for the period 2008 to 2090 resulted in a cost per life year gained of NOK 370,000 and cost per QALY gained of NOK 319,000 (direct cost only).

- Cost-effectiveness ratios are lower when costs associated with potential productivity gains are included, and when cost-effectiveness is measured in terms of cost per quality adjusted life year, rather than cost per life year.

- No barriers or system capacity constraints are assumed in our analysis with respect to introducing an HPV vaccination programme, assumed to be targeted at all 12.year old girls in Norway. However, it is realistic to expect at least some additional resources will be required in introducing an HPV vaccination programme to the existing school-based schedule. Additional investment may include (but is not limited to) public health education and promotion, setting up running the vaccination monitoring systems (e.g. population tracking of initial and booster vaccinations, recording of effects, side-effects etc).

- HPV is sexually transmitted infection, the impact of any changes in sexual behaviour in the population in the long-term (e.g. number of partners), or the role of other sexually transmitted infections may have (e.g. HIV) is uncertain.

- The design of targeted health education and health promotion strategies are likely to have an important role to play in optimizing the success of rolling out any HPV vaccination programme. The response of suggesting to parents that their 12-year-old daughter might need a vaccine against a sexually transmitted infection remains somewhat uncertain. The present analysis assumes that acceptance (public, clinician etc) will not be a barrier to implementation.

- Although not considered in the current analysis, the case for vaccinating boys (as well as girls) has been evaluated in the literature). A few studies suggest that the marginal benefits from vaccinating boys as well as girls may be negligible compared to the invested vaccination expenditure. (Taira 2004) However more precise longer term costs and outcomes may be informative

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Appendix

Appendix 1

Detailed assumptions on key cost events, resource use and unit costs in screening, diagnosis and treatment of cervical cancers and pre-cancers

Main cost events/items in screening, diagnosis and treatment of cervical pre-invasive disease and cancers	**Resource use**	**Unit costs (i.e. cost per case, procedure or episode of care)**	**Source/ Comments**	
Routine cytology screening with the Pap smear	The total number of tests performed annually in Norway under the current strategy of screening of every 3 years, woman aged 25 to 69 is in the	**Estimate of the cost of screening** (based on an assessment including GP visit + Pap smear testing proce-	Resource use: Norwegian Cancer Registry (resource use) Unit costs: Normaltariff	**Note**. The clinical model permits simulations to be undertaken for the inclusion of age-specific cohorts **up to the age of**

Main cost events/items in screening, diagnosis and treatment of cervical pre-invasive disease and cancers	Resource use	Unit costs (i.e. cost per case, procedure or episode of care)	Source/ Comments	
	region of **500, 000 (initial and any repeated test)**. For example for years: 2002 (510 628); 2003 (495 448); 2004 (484 225) tests were performed. An average a rate of approx 1.08 tests per women tested. Assume annual number of tests performed in women **up to age of 75 years = 476,000**	dure + consumable items + path/lab processing) =125+170+25+65+ 22 = **NOK 407** Legwood 2006 (25) estimated the cost of a conventional cytology for the UK of £23.6 (£23.4-£23.8) 2001-02 prices (NOK 352.24 NOK) ≈ 381 in NOK 2006 prices Brown (2006), UK £21.68 in 2003 prices (NOK 318.82) ≈ NOK 325 in NOK 2006 prices	for privat allmenpraksis 2006-2007 GP visit/consultation. Takst 2ad page 16, Konsultasjon hos allmennpraktiserende lege **= NOK 125 (GPs fee)** **"visit" fee assumed covered in Takst 214c?** *plus* Gynekologi og fødselshjelp Takst 214c page 25 Endometriebiopsi/cytologisk prøvetaking fra uterinhulen **=NOK 170** *plus ?*Consumables/disposables, Satser for forbruksmateriell Takst 10a. Materiallgruppe 1, Utstyr til gynekologisk undersokelse herunder tupfere, engangsspekulum,	**75 years.** Potential events occurring in cohorts older than this age are not included. Data from the Norwegian Cancer Registry (Screening Programme), suggest that 1.7% of tests are performed annually in women aged over the age of 75.

Main cost events/items in screening, diagnosis and treatment of cervical pre-invasive disease and cancers	Resource use	Unit costs (i.e. cost per case, procedure or episode of care)	Source/ Comments	
			etc. **NOK 34** Takst 10b. Materiallgruppe 2, Utsyr til prøvetaking fra livmorhulen. **NOK 65** R Laboratorieundersøkelser og prøver **705e** Cervico-vaginalutstryk Interpretation, investigation of cytological test Cervical-vaginal "streak culture" **NOK 22**	
1. Estimated total annual cervical cancer screening costs	**≈ NOK 183,260,000 (193,723,200)**			
Diagnostic workup of positive test results based on main types of smear diagnosis/cytology findings--pre-invasive disease SEE ALSO NOTE A (BELOW) **Mild abnormalities:** ➢ Atypical squamous cells of undetermined signifi-	The total number of abnormal (positive) tests requiring medical follow-up is approx **25,000 per year**. For example, for years: 2002 (25,950);2003 (24, 723); 2004 (23,500) representing as a percentage of the total number of adequate tests performed 5.3%, 5.3%, and	Clinic visit and HPV test for ASCUS and LSIL and Inadequate/ unfit tests (assumed to be now commonly applied in practice on suspicion of HPV infection for index cytological diagnosis of	Resource use: Norwegian Cancer Registry (resource use) Unit costs: **HPV testing** Outpatient Tariff: R Laboratorieundersøkelser of prøver, 1. Generelle teknikker	Assumed that women with moderate or severe cytology results are recommended for colposcopy (≈HSIL) Women with mild cytology results are assumed to undergo repeat Pap smear testing and HPV

Main cost events/items in screening, diagnosis and treatment of cervical pre-invasive disease and cancers	Resource use	Unit costs (i.e. cost per case, procedure or episode of care)	Source/ Comments	
cance **(AS-CUS)** ➢ - Low.grade squamous intraepithelial lesion **(LSIL)** **Mod/severe abnormalities:** ➢ High-grade squamous intraepithelial lesion **(HSIL)** -Other abnormal results? (Atypical glandular cells). Inadequate/unfit Pap smear tests? Carcinoma in situ--also a form of HSIL. Other abnormal results, e.g. atypical glandular cells? Note. The outcome in the follow-up after a positive test will in some cases be a false positive smear.	5.1% respectively The total number of **ASCUS** per year is approx **9,700**. For example for years: 2002 (10, 821); 2003 (9, 757); 2004 (8,587) representing 41.7%, 39.5% and 36.5% of abnormal tests respectively. The total number of new **LSIL** cases reported per year is approx **5,600**. For example in years: 2002 (5,564); 2003 (5,645); 2004 (5,604) Representing 21.4%, 22.8%, and 23.8% of abnormal tests respectively. Approx a total number of **3,500 HSIL** cases are reported per year. For example in 2002: 3 643, 2003: 3369: 2004: 3416. Representing 14.0%, 13.6% and 14.5% of abnormal tests. Other positive results (includ-	ASC-US, LSIL or for unsuitable cytology)[3] **=** NOK 301+ NOK 265 **= NOK 566** Referral to gynecologic oncology clinic, outpatient visit and colposcopy with biopsy for HSIL = 278 + 265 **= NOK 543** ***(NOK 1,300)**	Takst 701k, **NOK 301** Merknad R3bb Takst 701k *plus* patient co-payment per visit of NOK 265 (Takstnummer 201b) RTV. Oupatient schedule Section H.Onkologi. Takstgruppe 3 Takst nr **H03a** Procedure for Punksjoncytology for taking av representative materiale **NOK 278 OR** Section B Kirurgiske specialiteter, Takstgruppe 3 Takst nr **B20** Portiobiopsi,, cervical abrasion. Biopsi fra vagina/ vulva/ perineum. **NOK 278.** *Note. A colposcopy procedure probably takes around 15-20 mins to per-	testing (≈LSIL) Inadequate tests are re-tested Normal results return to routine screening. ****Note.** Where the index cytology finding is considered **inadequate/unfit** (which may or may not be abnormal – only that a result cannot be determined) it may be reasonable to assume routine recommendation for all women to undergo HPV-testing in addition to a repeat smear test. This would generate an approx. further **24,000** cases to receive HPV testing at a cost of

Main cost events/items in screening, diagnosis and treatment of cervical pre-invasive disease and cancers	Resource use	Unit costs (i.e. cost per case, procedure or episode of care)	Source/ Comments	
	ing those that go on to be considered false positives) account for 22.1%, 23.5% and 24.6% of all positive tests Resource use assumptions: Smear diagnoses of **ASCUS** or **LSIL** assumed to receive minimum of **HPV-testing + repeat Pap test.** Note: A measure of any additional Pap tests performed are assumed to be already captured in the total number of annual tests performed (i.e. in the approx 500 000 per year)—this assumption is also applied to cases of inadequate tests etc. The number of **HSIL** diagnoses is used to approximate to the number of women recom-		form. However, the above estimate for colposcopy appears to be somewhat on the low side compared published estimates, e.g. a range of US$101-US$136 for colposcopy was reported in 4 European countries (Kim 2005) all figures in 2004 US$. Legwood (2006) reported for the UK a cost of £122 (£98-£147) in 2001/02 prices. Brown (2006) quoted a colposcopy cost of £130 in 2003 prices. » Thus assuming a tariff equivalent to that of a long consultation (1 hr), Takstgruppe 5 might be a more reasonable estimate colposcopy (in place of Takstgruppe 3?) **NOK 757**	**NOK 13,584,000** Additionally, there are an approx **5,800** cases of reported findings of other types of abnormalities tin which women might also reasonably receive HPV-testing at a cost of **NOK 3,282,000** **Private Physcian's fee schedule: Normaltariff for privat spesiaslistpraksis 2006-2007 for Kolposkopi Takst 208, NOK 12 !! LESS than a PAP test!!**

Main cost events/items in screening, diagnosis and treatment of cervical pre-invasive disease and cancers	Resource use	Unit costs (i.e. cost per case, procedure or episode of care)	Source/ Comments	
	mended for referral for **colposcopy**. As a conservative estimate all HSIL cases are assumed to result in **biopsy** taken **on colposcopy.**		In which case, the cost estimate for performing a colposcopy = NOK 757+278+265 **= NOK 1,300**	
Estimated annual workup costs for abnormal findings (diagnostic)	**≈ NOK 25,525,800? 16,224,500**			
Management/treatment of cervical pre-cancers (on an outpatient/day-case or inpatient basis?) Treatment for dysplasia (or cancer) is not usually done at the time of the initial colposcopy, since the treatment depends on the analysis of the biopsies done during colposcopy and the resulting pathology report.	As is generally reported in the literature, on follow-up of positive tests, CIN or cancer is detected in more cases with HSIL compared to LSIL. HSIL diagnoses (approximates to actual numbers of CIN2/3 based on Cancer Registry data. For example in 2004: 3,416 HSIL versus 3536 CIN2/3). A proportion of the approx. annual 3,500 HSIL (CIN2/3) cases are likely to be treated by conisation, but not all.	Based on data from the Norwegian Cancer Registry in 2005, **669** women were admitted to hospital for surgical procedures associated with D&C, conization, for non-malignancy S **(DRG364) NOK 11,381.** Assume this number as a basis for estimating CIN 2/3 cases (or approx **19 % of all CIN 2/3 annual cases**) that undergo hospitalizations for conization pro-	Two general types of treatment assumed: - Destruction **(ablation)** of the abnormal area and - Removal (resection). Both types of treatment are highly curative with only a small proportion of women experiencing a recurrence of their abnormality after treatment. Generally, destruction (**ablation**) procedures are used for **milder dysplasia** and **removal (resection)** is recommended for more **severe**	Several alternatives are usually available, including follow up frequent pap tests, repeat colposcopy, cryosurgery or the freezing of abnormal cells, LEEP or the burning off of abnormal cells, laser or conization (cone biopsy).

Main cost events/items in screening, diagnosis and treatment of cervical pre-invasive disease and cancers	Resource use	Unit costs (i.e. cost per case, procedure or episode of care)	Source/ Comments	
	Ongoing periodic surveillance of HSIL? For example additional clinic visit, HPV-testing repeated at 6, or 12 months?	cedures- cost apportioned accordingly. The others (**81**%are assumed to have abnormal cells "destroyed" with other procedures such as cryosurgery (freezing), LEEP excision, burning/laser treatment. **applying an estimate of NOK 716?** The above estimate is considerably lower than published estimates. Loop electrosurgical excision procedures (LOOP) reported by Brown (2006) £280 – private insurer fee schedule in 2003 figures. Legwood colpo-	**dysplasia or cancer.** Treatment for **HSIL (or equivalent to 20% of CIN2/3 cases)** assumed to include conisation. **DRG 364** reimbursement 40%=NOK 4,552 (wt=0,36) 100%=**NOK 11,381** Treatments for other HSIL cases (CIN2/3) are also assumed to include day surgical outpatients' procedures. RTV Outpatients Schedule. B Kirugiske spesialiteter . Dagkirurgiske takster. Takstgruppe 6 (individual fee). **Tg 4? NOK 451** **P. bet 25. Plus patient co-payment NOK 265** Gynekologi/obstetrikk. Takstgruppe 3. B20b Kryo-eller laserbehandling, evaporise-	

Main cost events/items in screening, diagnosis and treatment of cervical pre-invasive disease and cancers	Resource use	Unit costs (i.e. cost per case, procedure or episode of care)	Source/ Comments	
		scopy and treatment for CIN of £624 (£415-£833). Kim 2005, treatment of CIN 2/3 US$678-$2,168- includes patient time costs.	ring på cervix, av mindre forandringer I vagina/ vulva/ perineum/ perinalt NOK 278 Alternatively the lowest reported DRG wkt for any given day surgical procedure is 0.18, and non-surgical day case 0.1. If latter is applied: NOK **3161.4** this estimate is more line with estimates in the published literature for less invasive procedures for treatment of CIN. Overall the weighted average cost estimate for treating CIN2/3 (HSIL) ***NOK 4,723 (rather than NOK 2,742)***	
Estimated total annual workup costs for abnormal cytology findings (therapeutic, HSIL-CIN2/3)	**≈ 16,530,500**			
Estimated total annual costs of pre-invasive disease	**≈ NOK 40 867 800? 32,755,000**			

Main cost events/items in screening, diagnosis and treatment of cervical pre-invasive disease and cancers	Resource use	Unit costs (i.e. cost per case, procedure or episode of care)	Source/ Comments	
Invasive cancer workup and treatment (diagnostic and therapeutic) **See NOTE B (below)**	**See NOTE B (below)**	**See NOTE B (below)** » estimated total cost per case ≈ **NOK 5,400**	**Poliklinikksystemet** (RTV outpatients clinic tarriff)	
Estimated total annual cancer workup costs (diagnostic)	**≈ NOK 1,458,000** **(based on 270 incident cervical cancer cases in 2005)**			
Invasive Cancer Treatment (including inpatient and outpatient care and routine post-treatment follow-up/surveillance) The number of newly diagnosed cancers in Norway in 2005 was 270: Case diagnosed annually in previous years show declining trend in incidence: 2002 (306); 2003 (296); 2004 (268) The overall stage distribution is relatively similar from year to year with around 60% of cases detected in early cancer stage 1. For example (based on years	Assumed around 50% of patients with invasive cancer will be surgically managed **(all in Stage 1)** • 71% radical hysterectomy • 14% conisation • 10% hysterectomy • 4% trachelectomy **Additionally:** Around 5% of patients treated with radical hysterectomy will receive adjuvant radiotherapy afterward. The scheme for this treatment is: 27 fractions of external radiation [takst nr.	Vekt 3,44 40% DRG reimbursement = NOK 43,501 100% = NOK 108,752.16	Annual cancer cases: Norwegian Cancer Registry **ISF** HDG 13: Diseases and disorders of the female reproductive system DRG353 Pelvic evisceration, radical hysterectomy Other DRG360 Vagina, cervix & vulva procedures Vekt 0,53. 40% DRG reimbursement = NOK 6,702; 100% = 16,755.42	In actual practice a few patients will experience a pelvic relapse after radical hysterectomy and will have external radiation. We assume this to be only a small proportion of women and therefore not included in our cost estimation calculations.

Main cost events/items in screening, diagnosis and treatment of cervical pre-invasive disease and cancers	Resource use	Unit costs (i.e. cost per case, procedure or episode of care)	Source/ Comments	
2002-2004): Stage 1 (60.3%, 61.8%, 59.5%) Stage 2 (17.8%, 15.7%, 21.8%) Stage 3 (13.1%, 12.5 %, 9.7%) Stage 4 (9.7%, 10.7%, 9.5%) Assumed stage distribution used in the present analysis of: 60%,18%:12% 10% In brief, the distribution of treatments for cervical cancer are assumed to be approx: 50% surgically intervention 40% curative radiotherapy 10% palliative treatment (e.g. assumed around half of patients get full curative radiotherapy, the other half will not receive cancer specific treatment but palliative treatment/radiotherapy) **SURGERY**	**H05c**, Ekstern strålebehandling per felt, **NOK 412 = NOK 11,124 and patient co-payment per visit of NOK 265 x 27 = NOK 7,155** (Takstnummer 201b)] plus 6 courses of weekly **cisplatin** (40 mg/m2)National Register for Chemotherapy Treatments database http://www.oncolex.no/nasjonaltRegister/cureDef.aspx?id=161106, Pris NOK 732 » once a week for 6 weeks = **NOK 4,392** Full radiation and concomitant weekly cisplatin with curative intention: Assumed for the standard treatment	Radiotherapy outpatient consultations: RTV Outpatient Tarrifs: H Onkologi. Takst-	DRG 366 Malignancy, female reproductive system m/bk (with complications) Vekt 1,26 40% DRG rembursement = NOK 15,933; 100%= NOK 39,833.64 DRG 367 Malignancy female reproductive system u/bk (w/out complications) Vekt 0,55 40% reimbursement= NOK 6,955, 100% NOK 17,387.7 DRG 368 Infections, female reproductive system, wekt 0.58 40% reimbursement = NOk 7,334, 100% reimbursement NOK 18,336.12 ISF HDG 17 Myeloproliferative diseases and disorders,	

Main cost events/items in screening, diagnosis and treatment of cervical pre-invasive disease and cancers	Resource use	Unit costs (i.e. cost per case, procedure or episode of care)	Source/ Comments	
Surgical interventions may include: Radical hysterectomy (LCD30) or Trachelecotmy (LCD96) in a few selected cases Hysterectomy (LDC000), Conisation (LDC00-LDC03) **RADIOTHERAPY (RT)** Palliative or radical RT? External beam Intracavitary Combination of external beam & high dose intracavitary brachytherapy Note. Radiotherapy for gynaecological cancers can be given externally or internally. Whilst external is given as an out-patient, internal may also be given as an in-patient (overnight stays in	algorithm for cancer in **Stages 2-IV(a)** as follows: **External radiation**: 27 sessions/fractions takst nr. **H05c**, Ekstern strålebehandling per felt, **NOK 412 = NOK 11,124 and patient co-payment per visit of NOK 265 x 27 = NOK 7,155** **External radiation total = NOK 18,279** - **Brachytherapy**: 5 treatment sessions/fractions Intracavitary brachytherapy: Takst nr **H06a**, Interstitiell strålebehandling, per felt, NOK **757= 5×757 =3,785 and patient co-payments of NOK 265 x 5 = NOK 1,325** **Intracavitary brachytherapy total = NOK 5,110** -**Cisplatin** weekly: 6 courses	gruppe 5 External radiotherapy. Takst nr. **H05c**, Ekstern strålebehandling per felf, NOK 412 Intracavitary brachytherapy: Takst nr **H06a**, Interstitiell strålebehandling, per felt, NOK 757 **H05a** Intravenøs infusjon av særlig vevstoksiske cytostatika Takstgruppe 5, NOK 757 (infusion and adminstration costs included in costs in the national chemotherapy data bases?) PLUS patient co-payment per visit of NOK 265 (Takstnum-	poorly differentiated neoplasm's DRG410A Chemotherapy w/o acute Leukemia as secondary, tumour unspecified. Vekt 0.17 40% reimbursement = NOK 2,150; 100% reimbursement = NOK 5,374.38 DRG410B Chemotherapy w/o acute Leukemia as secondary, tumour group 1(treatment codes with Z51.11 max ≈ NOK 18K) vekt 0.29 40% reimbursement = NOK 3,667; 100%= NOK 9,168.06 DRG410C Chemotherapy w/o acute Leukemia as secondary, tumour group 2 Vekt 0.53 40% reimbursement = NOK 6,702; 100% reimbursement = 16,755.42 DRG410D Chemotherapy w/o acute Leukemia as secondary,	

Main cost events/items in screening, diagnosis and treatment of cervical pre-invasive disease and cancers	Resource use	Unit costs (i.e. cost per case, procedure or episode of care)	Source/ Comments	
hospital taking 1 to 5 days). For our cost calculations we assumed (all) radiotherapy is delivered on an outpatient basis. **CHEMOTHERAPY** Concomitant (with full radiation) weekly cisplatin	with 40 mg/m2. NOK 732 » once a week for 6 weeks = **NOK 4,392** *Plus* Some measure of an assessment of potential additional resources involved with actual administration of intravenous infusion of a chemotherapeutic drug, we apply a tariff equivalent for an oncologic fullstendig undersøkelse**. H02 NOK 138 = 6 × 138 =NOK 828 and patient co-payment per outpatient treatment session of NOK 265 x 6 = NOK 1,536 (or using tariff H05a, NOK 757 = NOK 4,542)** **Course of Cisplatin total =NOK 6,756** **(or using tariff H05a = NOK 10,524)**	mer 201b) In addition we assume that long-term follow-up of cervical cancer patients to consist of post treatment surveillance involving some minimum of annual review with (e.g. physical with pelvic exam, PAP test and chest X-ray) for 5 years. There may be greater frequency of actual patient follow-up the first few years after primary treatment, in which case actual resource use may be an underestimate. If follow-up assessments are performed by patients' own GP then tariff applied = **NOK 170** If follow-up assessments	tumour group 2 Vekt 1,07 40 % reimbursement = NOK 13,531; 100% reimbursement = NOK 33,826.98 **Outpatient visits** according to a national price list covered by the individual patient (in the form of co-payments) and the National Insurance Administration (NIA) Refs. National Insurance Administration, Rikstrygdeverket [cited 2004 Dec 15]; Available from: URL : http://www.trygdeetaten.no The National Health Administration: The tariff of public out-patient treatment valid from January 1st 2004. Oslo, The national	Some women with terminal illness disease (e.g. stage IVb) are likely to be unsuitable to receive standard treatment. In practice they will either receive no treatment, some palliative radiotherapy or both. For the purposes of cost calculations, we have assumed to calculate the cost for curative radiotherapy for half of these patients. The remainder we

Main cost events/items in screening, diagnosis and treatment of cervical pre-invasive disease and cancers	Resource use	Unit costs (i.e. cost per case, procedure or episode of care)	Source/ Comments	
	» Total estimated cost of a course of treatment involving full radiation and weekly cisplatin ≈ **NOK 33,913**	performed at hospital pollklinisk: H. Onkologi Takstrguppe 3. H03a. Punksjonscytologi for taking av representativt material. **NOK 278.** If chest x-ray perfomed + PK113 RG thorax vekt 0.155= NOK 54.095 + PK 002, vekt 0.186 = 64.914 NOK = **NOK 119.009** Hospital outpatient total = NOK 397.09 » **approx range 170-400 NOK** PLUS patient co-payment per visit of NOK 265 (Takstnummer 201b) Year 1: three (four) hospital outpatient	Health Administration, 2003 Patient co-payment of NOK 265 (Takstnummer 201b) Tariff of the NIA for prolonged treatment (H06e NOK 757/hour) A Indremedisinske spesialiteter, p11 Takstrgruppe 6, Dagkirurgiske takster A62a Intravenøs infusjon av særlig vevstoksiske cytostatika. Kan benyttes hver gang behandlingen gis ? Takstgruppe 6 = 898 or ?Takstgruppe 5= 757 ISF code Z51.50, treatment at a palliative centre Døgnopphold 0.66 DRG-	have assumed will not receive cancer specific treatment but palliative treatment until they die (?). We have not included an estimate of the costs associated with palliative treatment to relieve symptoms/ pain management (?) The proportion of women experiencing a relapse/recurrence of their disease after initial treatment is estimated to be up to 40% (GBK) The treatment strategy for most patients with a relapse is 6 course of chemotherapy (using cisplatin and 5FU). This may still be somewhat

Main cost events/items in screening, diagnosis and treatment of cervical pre-invasive disease and cancers	Resource use	Unit costs (i.e. cost per case, procedure or episode of care)	Source/ Comments	
		visits? e.g. (at 6 weeks) post-treatment, 3 mo, 6 mo, 12 mo Year 2 and 3: two visits Years 4 and 5: annually ≈ 5 year cost of NOK 5637.585 (discounted 4% p.a.)	poeng (inpatient) Dagbehandling 0.03 DRG-poeng (not inpatient)	of an underestimate as some patients will receive additional chemotherapy after the 6 course with further targeted treatment an eventually in some cases
HPV 16/18 vaccine	**Vaccine is assumed to be administered annually to all 12-year old girls in Norway in the base case analysis:** The simulation of an HPV 16/18 vaccination program is assumed to begin in 2008. The total number of 12-year old girls vaccinated is based on population projections per 01.01, by sex, age, time and contents (Source: Statistics Norway).	Maximum price = NOK 1259.40 per 1 x 0,5 ml or with 25% VAT excluded = NOK 945 Estimate for an initial 3 dose injection course assumed: = NOK 2,835 (base case) and booster shot of NOK 945 (delivered for example	There is currently no published price in Norway for an HP16/18 vaccine. It is reasonable to argue however, that the vaccination price of an HPV16/18 vaccination when available will at least be similar to the currently published price of the quadrivalent vaccine: Legemiddelverket Official (maximum) pharmacy	Source: Based on maximum price from Legemiddelverket subtracted are 25% VAT For analysis conducted from the societal perspective VAT (25%) is excluded on on the grounds that it's a transfer payment and doesn't reflect the opportunity cost of resources. If

Main cost events/items in screening, diagnosis and treatment of cervical pre-invasive disease and cancers	Resource use	Unit costs (i.e. cost per case, procedure or episode of care)	Source/ Comments	
	For example in 2008: **30 567 12-year old girls** would be potentially targeted A vaccination **coverage/**uptake of **90%** is applied in the **base case,** thus **27,510 12**-year old girls would be vaccinated Estimated annual costs of associate with associated with: » initial vaccination **NOK 77,990,850** (excl. VAT) NOK 103,938,282 (incl. VAT) » booster vaccination (e.g. 10 years following initial vaccination) **NOK 25,996,950** (excl. VAT) NOK 34,646,094 (incl. VAT)	at 10 years after initial vaccination) Cost estimates rounded to the nearest NOK 10	sales price for Gardasil (HPV types 6,11,16, 18), www. legemiddelverket.no/pia/refpris.asp	however, we had been carrying out a financial budget impact from the point of view of an organization that would be a different story. VAT included if perspective adopted is the healthcare sector?

1. Norwegian National Insurance Administration Reimbursement Fees (effective from July 1, 2006)
http://rundskriv.trygdeetaten.no/rtv/lpext.dll/Infobase9/f20001201nr1389?fn=main-j.htm&f=templates
2. Veileder I samfunnsøkonomise analyzer. Finansdepartementet

3. http://www.kreftregisteret.no/om_kreftregisteret/registrering/masseundersokelser_etc/kvalitetsmanual.pdf

- Life tables, 2005. Statistics Norway http://www.ssb.no/emner/02/02/10/dode/tab-2006-04-27-05.html
- Veileder I samfunnsøkonomise analyzer. Finansdepartementet, Finansavdelingen p 42, section 5.11 Oppsummering, note 2 (effective as of September 2005). Recommended discount rates in Norway. Discounting of future costs is applied only to those costs occurring after the first year the HPV vaccination is introduced. That is, to any costs which may be incurred during the second and subsequent years of the vaccination programme.
- GB Kristensen (Consultant Gynaecologist, Radiumhospital, Oslo. Personal communication, Dec20006/January2007).
- Norwegian National Insurance Administration Reimbursement Fees (effective from July 1, 2006) http://rundskriv.trygdeetaten.no/rtv/lpext.dll/Infobase9/f20001201nr1389?fn=mainj.htm&f=templates
- Enhetsrefusjonen for 2006 er fastsatt til 31 614 kroner (Innsatsstyrt finansiering 2006, Helse-Og Omsorgsdepartementet, Oslo, 2006)
- It is feasible that not all patients will continue to receive (annual) follow-up post initial treatment. However, we have assumed that patients continue to receive routine follow-up on an annual basis. Consequently, this will tend to bias the results against ongoing cervical cancer surveillance practice (i.e. to over, rather than underestimate the true costs of long-term follow-up)
- OEDC Statistics. Country-specific consumer price indices. http://stats.oecd.org/wbos/default.aspx?querytype=view&queryname=221

NOTE A.

Diagnostic workup of positive cytology results (for premalignant dysplastic changes, the CIN (cervical intraepithelial neoplasia) grading is used)

- Processing, investigation of cytological test (i.e. Pap smear). Outpatient Tariff Schedule: R. Laboratorieundersøkelser og prøver. 5 Patologi R1. Takst nr 705e Cervico-vaginalstryk (cervical-vaginal culture) **NOK 24**
- Tissue biopsy taken on colposcopy examination. Outpatient Tariff Schedule: B. Kirugiske spesialiteter. Gynekologi/obstetrikk, Takstgruppe 3. Takst nr. B20a Portiobiopsi, cervical abrasion. Biopsi fra vagina/vulva/perineum. **NOK 278**. R. Laboratorieundersøkelser og prøver. 5 Patologi R1. Fremstilling og granskning av cyrtologiske prøver. Takst nr **705g** Punksjonscytologi, prøvetaking og hurtigfarging **NOK 168 .** Patient co-payment**,** takstnummer **201b =NOK 265**
- **Treatments/ procedures for HSIL:** B. Kirugiske spesialiteter. Gynekologi/obstetrikk, Takstgruppe 3. Takst nr. B20a Kryo- eller laserbehandling, evaporisering på cervix, av mindre forandringer i vagina/vulva/perineum/perianlt **NOK=278.** Takstgrupped 6 (individual tariffs for day surgery & procedures performed on an outpatient basis). Dagki-rurgiske takster . Takst nr. B21d konisering, Takst nr. B21e Laserevaporisering av utbredte forandringer I vagina/vulva/perineum/ cervix. B23h Andre gynekolgiske inngrep i narkose/spinal/epidural. Plus patient co-payment**,** takstnummer **201b =NOK 265**
- Surveillance for women treated for high-grade dysplasia (e.g. with loop excision) assumed to have a follow-up outpatient consultation. Including e.g. pelvic exam / Pap smear at 6 months? B Kirurgiske spesialiteter Gynekologi/obstetrikk Takstgruppe 3 (Generell kirurgi) **NOK 278.** Patient co-payment**,** takstnummer **201b =NOK 265**

NOTE B.

With respect to cervical cancer, the main treatment centre in Norway is at Radium hospital (DNR) and in 2004; 150-160 patients were treated out of a total of about 270 cases nationally that year.

Diagnostic workup of cervical cancer (to determine stage- FIGO definitions and staging system)

Concerning the tests and procedures in the diagnostic workup of cervical cancer we assumed the following would be included as general practice in Norway (on guidance from Dr Gunnar Balle Kristensen, Rikshospitalet-Radiumhospitalet HF, Oslo):

- MRI. RTV, Primaæerkategori(s). PK001 Gransking CT MR of angio = **NOK 64.914**. Takstnummer PK402 kontrast region/rekonstr.= **NOK 671**. insentivsats 15? **Patient co-payment,** takstnummer 202= **NOK 200, 201b =NOK 265**

= NOK 1200.914

- Chest X-ray (thorax). Primaæerkategori(s). **PK002** Gransking RG og UL **= NOK 64.914**. Takstnummer PK113 **RG thorax =NOK 54.1, Patient co-payment,** takstnummer 202= **NOK 200, 201b =NOK 265**

= NOK 584.014

- Gynecologic examination under general anesthesia. With **cystoscopy**. Outpatient Tariff Schedule: B. Kirugiske spesialiteter. Takstgruppe 4, Takst nr. B11d. Urethra-cytoskopi **NOK 451.** Takstgruppe 6, Dagkirurgiske takster, Takst nr B23h. Andre gynekologiske inngrep i narkose/spinal/epidural at **NOK 1 444?** with additional patient co-payment of **NOK 75 + patient co-payment NOK 278**

= NOK 791

- Tissue biopsy of the tumour. Outpatient Tariff Schedule: B. Kirugiske spesialiteter. Gynekologi/obstetrikk, Takstgruppe 3. Takst nr. B20a Portiobiopsi, cervical abrasion. Biopsi fra vagina/vulva/perineum. **NOK 278,** plus patient co-payment NOK 265

= NOK 543

- Full blood count with test of hematologic values, liver and renal function. Outpatient Tariff Schedule: A. Indremedisinske Spesialiteter.Takstgruppe 4, Takst nr. A51a Full utredning innen infeksjonsmedisin (full investigation for infection/ infectious disease) **NOK 408**. Takstrgruppe 6, Takst nr A62b Full utrending innen hematology **NOK 898**. Liver function test with Kreatinin clearance. R. Laboratorieundersøkelser og prøver 7 Klinisk kjemi R1 (Clinical Chemistry), Takst nr. 707b Mer komplisterte eller sammensatte analyser, Kreatin clearance NOK 14. **Liver function test?** Plus patient co-payment **NOK 265**

= NOK 1163

- Recommending a PET-CT as a diagnostic investigation standard is slowly emerging into practice (GBK). An appropriate outpatient tariff??. Performing Positron-Emission Tomography is considerably more expensive than conventional imaging with CT and MRI. For example, in the UK the cost per FDG-PET scan is in the order of £800-£1000 (Cook 2001, British Journal of Radiology 74:399-401). Applying the highest Radiology Outpatient Tariff (from section S): PK009 Stentinnleggelse PK009 wt 6,795, NOK=2,371 is likely to significantly underestimate the actual cost per case. In the first instance, apply an estimate ≈ NOK 8,000 to represent reimbursement value for a PET-CT scan?
- As for women treated for HSIL, post-treatment surveillance is assumed to occur in practice. A number of periodic outpatient follow-up consultations after the initial treatment episode including e.g. pelvic exam/ x-ray B Kirurgiske spesialiteter Gynekologi/obstetrikk Takstgruppe 3 (Generell kirurgi) **NOK 278.** Patient co-payment**,** takstnummer **201b =NOK 265. For example at 6, 12 months then annually? If no recurrence, routine smear at 3 yearly intervals. Assume a minimum of 2 surveillance outpatient visits post-treatment.**

= NOK 1,086

» Total cost per case ≈ NOK 5,400

Appendix 2

Cost analysis: cervical cancer treatment

	Total incident cervical cancers in 2005:				270
	Cancers by stage distribution				
		stage 1	stage 2	stage 3	stage 4
	proportion	0.6	0.18	0.12	0.1
	cases	162	48.6	32.4	27
Main standard treatments for cervical cancer:	**Unit cost applied**				
	(NOK)				
Surgically managed (approx 50% at Radiumhospital)					
Predominantly with radical hysterectomy, stage I	108,752	17,617,850			
consisation also assumed to be peformed in some women preceding hysterectomy (e.g approx 10/70 surgical patients treated at Radium, 2005)	12,646	307,298			
Radiotherapy with curative intention following a standard scheme of:					
External radiation: 27 treatment sessions (fractions)[1]	677	2,961,198	888,359	592,240	493,533
Intracavitary brachytherapy: 5 sessions (sometimes 6)[1]	1,022	99,338	298,015	198,677	165,564
weekly cisplatin: 6 courses with 40 mg / m2[1,2]	1,754	170,489	511,466	340,978	284,148
1.radio-/ chemotherapy outpatient visits: patient co-payment	265				
2.administration of intravenous infusion of chemotherapy drugs (Tkst nr. H06a)	757				
Treatment for disease Recurrence/Relapse (approx 40% of women)					
6 courses (1 course = 2 days) of chemotherapy (cisplatin and 5FU)	6,124	396,835	119,051	79,367	66,139
Post-treatment outpatient surveillance (over 5 years)	5,637	913,194	273,958	182,639	152,199
Total estimated costs (by stage)		22,466,202	2,090,850	1,393,900	1,161,583
		NOK			
Overall total estimated cancer treatment costs		27,112,535			
Total estimated cancer diagnostic workup costs		1,458,000			
Total cervical cancer costs		28,570,535			

Average cost per case		105,817			
Example of cervical cancer cost estimates in the published literature:					
UK: Brown (2006) cost per case for first year mangement of new cervical cancer in the UK, 2003 of £10,464 (excl. indirect)					
≈ NOK 153,882 (or NOK 160,567 in 2006 prices).					
Switzerland: Gerber 2005 (24) based on expert opinion, CHF 20,000 per case, 2005 prices (NOK 102,111 100 CHF = 513.47 NOK)					
≈ NOK 105,089 in 2006 prices					
UK, NL, France: Kim (2005) prices in 2004 US$					
Cancer stage (applying a similar distibribution as our study)	Proportion	UK	NL	France	
Local	0.6	11,171	3,985	2,236	
Regional	0.3	9,169	4,122	4,335	
Distant	0.1	3,242	2,147	3,412	
		23,582	10,254	9,983	
Approx cost per case (2006 NOK)		147,993	64,348	62,650	

Appendix 3

DRG codes most likely to apply to women admitted to hospital for the treatment of pre-invasive and invasive cancer (data source: Norwegian patient register, 2005)

Hospital admissions*	DRG Reimbursement	Total Number registered in 2005	Tumours	Elective	Emergency	16-49	50-66	67-79	80+	ALOS (all)	ALOS (tumours)
DRG353 pelvic evisceration, radical hysterectomy S (LCD30)**	40%=43 501 (wt=3,44) 100%=**108 752**	277	275	269	8	99	100	63	15	10.3	10.3
DRG360 Vagina, cervix & vulva procedures S	40%=6 702 (wt=0,53) 100%=**16 755**	600	172	395	205	318	136	70	57	2.9	6.4
DRG363 D&C, conization & radio-implant, for mal S	40%=5 058 (wt=0,40) 100%=**12 646**	368	368	307	61	76	111	105	75	3.3	3.3
DRG364 D&C, conization, for non-malignancy S	40%=4 552 (wt=0,36) 100%=**11 381**	669	52	422	247	219	165	140	145	1.8	2.6
DRG365 other female reproductive system o.r.p? S	40%=12 266 (wt = 0,97) 100%=**30,666**	438	142	296	142	318	73	29	16	5.8	16.3
DRG366 malignancy, female reproductive system (with complications) M	40%=15 933 (wt=1,26) 100%=**39 834**	2961	2961	1730	1231	419	1146	940	456	6.7	6.7
DRG 367 malignancy, female reproductive	40%=6,955 (wt =0,55)	1330	1330	801	529	281	514	327	197	3.8	5.2

system (without complications) M	100%=**17,140**										

* MDC: Diseases and disorders of the female reproductive system (data were not available for a further breakdown according to ICD-10 codes: C53 malignant neoplasm of the cervix uteri (or its subclassifications), N87 dysplasia of the cervix uteri, D06, carcinoma in situ). ALOS: mean length of hospital inpatient stay. M: medical. S: surgical procedures. ** NOMESCO Classification of Surgical procedures

Non surgical cancer treatment is assumed to be managed in the outpatients/day patient clinic setting. DRGs relevant for day surgery: Treatments and procedures for HSIL. Diagnostic workup for cancers.

Appendix 4

Source of unit cost information for estimating travel expenses associated with cancer treatment

Based data from the Norwegian Labour and Welfare Organisation (NAV) at: http://www.nav.no/805316850.cms; http://www.nav.no/1073750869.cms

NAV was established on July 1, 2006, and is a comprehensive welfare reform)

NAV is a merger of three former organisations:

- The National Insurance organisation (state)
- The National Employment Service (state)
- The Social Welfare System (municipal)

Eigendelar og satser ved reise til behandling

Satsane som er gitte opp gjeld per 1. januar 2007.

Type	Beløp i kr	Merknad
Reise i samband med undersøking og behandling éin veg	kr 120,-	
Reise i samband med undersøking og behandling tur-retur	kr 240,-	
Bruk av eige transportmiddel	kr 1,75 per km	
Reise i samband med fritt sjukehusval (kvar veg)	kr 400,-	Kan ikkje førast på eigendelskortet
Kostgodtgjering	kr 165,- per døgn	
Overnattingsgodtgjering inntil	kr 285,- per døgn	
Dekning av tapt arbeidsinntekt for eventuelt følgje	inntil kr 80,- per time	

Eigendel ved kjøp av lækjemiddel/medisinsk utstyr på blå resept

Gjeld frå 1. januar 2007

Appendix 5. Model validation

1. Provisional results for model predicted versus external data based cervical cancers

2005

age-group	resident women	cancer based on external incidence data	cancers predicted by model	95% CI		model estimates within 95% CI (y/n?)	Proportion of cancers predicted by the model	absolute difference (±) in cancer cases
				lower limit	upper limit			
16-25yr	273,604	8.800	4.550	2.486	15.11	y	0.52	4.250
26-35yr	320,527	61.800	39.411	45.894	77.706	n	0.62	22.389
36-45yr	330,860	66.400	50.170	49.931	82.869	y	0.77	16.230
46-55yr	301,050	47.400	45.160	33.407	61.393	y	0.91	2.240
56-65yr	250,189	41.800	33.112	28.629	54.971	y	0.82	8.688
66-75yr	168,339	34.425	22.686	22.427	46.423	y	0.67	11.739
overall	1,644,569	260.625	195.089	228.486	292.764	n	0.75	65.536
*75+	204,635	32.375	27.577	20.724	44.026	y	0.85	

- estimated if applying the (same) cancer incidence rate for age-group 65-75 yr

2004

age-group	resident women	cancer based on external incidence data	cancers predicted by model	95% CI		model estimates within 95% CI (y/n?)	Proportion of cancers predicted by the model	absolute difference (±) in cancer cases
				lower limit	upper limit			
16-25yr	275,539	2.000	4.659	-1.272	5.272	y	2.33	-2.659
26-35yr	313,000	46.400	39.684	32.55	60.25	y	0.86	6.716
36-45yr	334,993	64.000	53.091	47.822	80.178	y	0.83	10.909
46-55yr	303,543	55.600	45.160	40.487	70.713	y	0.81	10.440
56-65yr	259,812	45.800	36.115	32.037	59.563	y	0.79	9.685
66-75yr	171,506	26.075	24.122	15.567	36.583	y	0.93	1.953
overall	1,658,393	239.875	202.831	209.021	270.729	n	0.85	37.044

2003

age-group	resident women	cancer based on external incidence data	cancers predicted by model	95% CI		model estimates within 95% CI (y/n?)	Proportion of cancers predicted by the model	absolute difference (±) in cancer cases
				lower limit	upper limit			
16-25yr	271,295	5.800	4.691	0.58	11.02	y	0.81	1.109
26-35yr	318,492	57.000	47.042	41.704	72.296	y	0.83	9.958
36-45yr	330,391	73.400	55.329	56.61	90.19	n	0.75	18.071
46-55yr	301,534	53.200	47.329	38.406	67.994	y	0.89	5.871
56-65yr	251,559	43.400	37.031	29.989	56.311	y	0.85	6.369
66-75yr	170,731	27.325	25.150	16.58	38.07	y	0.92	2.175
overall	1,644,002	260.125	216.572	228.016	292.234	n	0.83	43.553

2002

age-group	resident women	cancer based on external incidence data	cancers predicted by model	95% CI		model estimates within 95% CI (y/n?)	Proportion of cancers predicted by the model	absolute difference (±) in cancer cases
				lower limit	upper limit			
16-25yr	267,921	267,921	267,921	267,921	267,921	267,921	267,921	267,921
26-35yr	267,921	267,921	267,921	267,921	267,921	267,921	267,921	267,921

36-45yr	267,921	267,921	267,921	267,921	267,921	267,921	267,921	267,921
46-55yr	267,921	267,921	267,921	267,921	267,921	267,921	267,921	267,921
56-65yr	267,921	267,921	267,921	267,921	267,921	267,921	267,921	267,921
66-75yr	267,921	267,921	267,921	267,921	267,921	267,921	267,921	267,921
overall	267,921	267,921	267,921	267,921	267,921	267,921	267,921	267,921

2. Provisional results for model predicted versus data based cervical cancer deaths

2004

age-group	resident women	deaths based on external incidence data	deaths predicted in the model	95% CI		model estimates within 95% CI of data (y/n)?	proportion deaths predicted by model	absolute difference (±) in deaths
				lower limit	upper limit			
16-25yr	275,539	0.000	0.549	-0.5	0.5	n?	na	-0.549
26-35yr	313,000	2.800	5.412	-0.98	6.58	y	1.93	-2.612
36-45yr	334,993	8.000	10.626	1.956	14.044	y	1.33	-2.626
46-55yr	303,543	12.800	16.665	5.288	20.312	y	1.30	-3.865
56-65yr	259,812	18.800	9.802	27.798	54.971	y	0.52	8.998
66-75yr	171,506	14.100	15.339	6.241	21.959	y	1.09	-1.239
overall	1,658,393	56.500	58.393	41.268	71.732	y	1.03	-1.893

* To consider some possible assessment for the over 75s. Restults may be estimated assuming e.g. the cancer incidence rate from the next oldest age-group: 65-75 yr was applied.Total actual cervical cancer deaths in 2004 (including over 75s): **81** (Norwegian Ca cer Registry) na = calculation is not applicable in this context

2003

age-group	resident women	deaths based on external incidence data	deaths predicted in the model	95 % CI		model estimates within 95% CI of data (y/n)?	proportion deaths predicted by model	absolute difference (±) in deaths
				lower limit	upper limit			
16-25yr	271,295	2.200	0.562	-1.411	2.573	y	0.26	1.638
26-35yr	318,492	2.600	5.478	-1.06	6.26	y	2.11	-2.878
36-45yr	330,391	11.400	11.315	4.283	18.517	y	0.99	0.085
46-55yr	301,534	17.000	17.867	8.419	25.581	y	1.05	-0.867
56-65yr	251,559	18.200	16.282	9.339	27.061	y	0.89	1.918
66-75yr	170,731	18.225	16.282	9.358	27.092	y	0.89	1.943
overall	1,644,002	69.625	67.786	52.771	86.479	y	0.97	1.839

2003

age-group	resident women	deaths based on external incidence data	deaths predicted in the model	95% CI		model estimates within 95% CI of data (y/n)?	proportion deaths predicted by model	absolute difference (±) in deaths
				lower limit	upper limit			
16-25yr	267,921	0.000	0.581	-1.207	5.607	y	na	-0.581
26-35yr	324,148	2.800	5.996	-0.98	6.58	y	2.14	-3.196
36-45yr	326,101	12.200	12.123	4.854	19.546	y	0.99	0.077
46-55yr	242,423	18.800	19.182	9.802	27.798	y	1.02	-0.382
56-65yr	171,352	14.000	16.736	6.167	21.833	y	1.20	-2.736
66-75yr	220,895	22.325	16.582	12.565	32.085	y	0.74	5.743
overall	1,552,840	70.125	71.200	52.213	87.037	y	1.02	-1.075

3. Provisional results for model predicted versus histology and cytology based data (CIN 2/3 and HSIL/LSIL respectively)

Overall results

	CIN 2/3		HSIL		LSIL	
	Histology data	model	Cytology data	model	Cytology data	model
2002	3,555	4,458	3,643	4,458	5,564	2,526
2003	3,578	4,122	3,369	4,122	5,645	2,490
2004	3,536	3,869	3,416	3,869	5,604	2,465
2005	-	3,680	-	3,680	-	2,449
2006	-	3,540	-	3,540	-	2,441
2007	-	3,438	-	3,438	-	2,438
2008 (theoretical simulation start year for vaccination)	-	3,364	-	3,364	-	2,439

The most recent 'actual data' year of 2004 and the number of cases reported are used as the initial basis for calcualtion of (annual) costs associated with the diagnosis, management and treatment of CIB 2/3, HSIL, LSIL. (the current situation without vaccination). Detailed cost assumptions and resource use are presented earlier in Appendix 1