Estimating uncertainties of HPV16/18 vaccination – a dynamic modelling approach

Report from Kunnskapssenteret (Norwegian Knowledge Centre for the Health Services)
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Health economic model

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Background: The National Council on Quality and Prioritisation in Health Care asked the Norwegian Knowledge Centre for the Health Services to quantify how several unresolved issues regarding long term efficacy may affect the future burden of cervical cancer and health economics of HPV 16/18 vaccination. **Method:** We used the dynamic natural history model and health economic approach as previously described in Report No. 12-2007. The analyses are made in a two-step approach: i) a natural history model is used to estimate the development in pre-cancerous and cancerous lesions in the time period 2008-2060, ii) health economic evaluations are performed based on the predicted burden of disease. Outcomes are compared to a base case vaccination-screening scenario assuming 90% vaccine coverage among 12-year old girls, 90% vaccine efficacy and a mean 3-yearly screening coverage of 80% among 25-69 year old women. **Results:** A more intensive screening strategy involving screening every year is comparable to the effectiveness of HPV 16/18 vaccination when compared to baseline screening. This increase in effectiveness comes with a high additional *(continued)*

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(continued from page one) estimated health sector cost of NOK 9,5 billion. We compared baseline screening to the strategy with the smallest effect. This combined strategy seems to be cost saving compared to baseline screening. Cost effectiveness of HPV 16/18 vaccination was relatively insensitive to reduced screening compliance among vaccinated women. **Conclusion:** Cytological screening is effective in reducing the burden of cervical cancer, and con-tinues to be important also after implementing HPV 16/18 vaccination. The inter-vention most likely to be selected given this evidence, is vaccination with increased screening intervals after 20 years. Cross protection and (slowly) waning vaccine efficacy is found to have minor positive and negative effects respectively on future incidence rates of cervical cancer and cost-effectiveness of the vaccine. A potential caveat is strain replacement of HPV 16 and 18 by other oncogenic HPV types, which may reduce the impact of HPV 16/18 vaccination significantly in a 50 year perspective.

Title Estimating uncertainties of HPV16/18 vaccination – a dynamic modelling approach

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Norwegian Knowledge Centre for the Health Services
Oslo, 2008

Norsk sammendrag

BAKGRUNN

Det diskuteres for tiden hvorvidt HPV16/18-vaksinasjon skal introduseres i det norske barnevaksinasjonsprogrammet. Nasjonalt råd for kvalitet og prioritering i helsetjenesten diskuterte saken i desember 2007, og Kunnskapssenteret ble forespurt om å bruke en dynamisk helseøkonomisk modell for å kvantifisere hvordan flere uløste spørsmål i forbindelse med langtidseffekt av HPV 16/18-vaksinasjon kan påvirke framtidig sykdomsbyrde av livmorhalskreft.

METODE

Vi brukte den samme modellen og helseøkonomiske framgangsmåten som beskrevet i Rapport 12-2007. Vi gjorde analysene i to steg: i) en modell for sykdomsutvikling ble brukt til å estimere forekomst av livmorhalskreft og forstadier til livmorhalskreft i perioden 2008-2060, ii) helseøkonomiske beregninger ble utført basert på de estimerte sykdomsbyrdene. Utfallene ble sammenlignet med et vaksinasjons-screenings-scenario hvor vi antok 90 % vaksinedekning blant 12-årige jenter, 90 % vaksineeffekt og en treårig screeningsdekning på 80 % blant 25-69-årige kvinner.

RESULTATER

I dette avsnittet presenteres ytterligere scenarier om HPV 16/18-vaksinens kostnadseffektivitet og innflytelse på sykdomsbildet. Dette er ment som et vedlegg til Rapport 12-2007.

Årlig screening uten HPV 16/18-vaksinasjon

En mer intensiv screeningsstrategi som involverer screening hvert år, er omtrent like effektiv som HPV 16/18-vaksinasjon kombinert med screening hvert tredje år med hensyn på vunne leveår og QALYs. Den økte effekten av årlig screening medfø-

rer imidlertid en høy tilleggskostnad for helsesektoren på 9,5 milliarder NOK. Ved en inkrementell analyse mellom HPV16/18-vaksine og screening hvert 3. år sammenliknet med årlig screening, viser det seg at årlig screening er dominert av vaksinestrategien. Fra et helseøkonomisk ståsted betyr dette at årlig screening ikke trenger å vurderes ytterligere fordi man kan oppnå tilsvarende helsegevinst ved å innføre HPV 16/18-vaksine i tillegg til dagens screeningprogram for en tilleggskostnad på bare 10 % av kostnaden ved årlig screening.

HPV 16/18-vaksinasjon med 5-årige screeningsintervaller f.o.m. 2028, 2038 eller 2048

Vi sammenliknet først dagens screeningprogram med det tiltaket som hadde minst effekt i forhold til vunne leveår og QALYs (vaksinasjon med 5-års screeningintervaller fra 2028). Denne kombinerte strategien er den mest kostnadseffektive sammenliknet med screening alene og sparer penger for samfunnet. Den inkrementelle analysen mellom de forskjellige tiltakene viser at hvis den 5-årlige screeningen utsettes til 2038 eller 2048 gir dette en ICER på henholdsvis 582 000 og 850 000 NOK per QALY sett fra et samfunnsperspektiv. Til slutt, hvis man sammenlikner vaksinasjon kombinert med 5-årlig screening fra 2048 med vaksinasjon kombinert med screening hvert 3. år for hele tidsperioden 2008-2060, vil det gi en ICER på 2.3 millioner NOK per QALY

Redusert deltagelse i screeningprogrammet blant vaksinerte kvinner

Kostnadseffektiviteten av HPV 16/18-vaksine er lite følsom for redusert deltagelse i screeningprogrammet blant vaksinerte kvinner.

Boostervaksinasjon

Analysen av endringer i kostnader og effekter mellom de forskjellige tiltakene, viser at hvis den 5-årlige screeningen utsettes til 2038 eller 2048, gir dette en ICER på henholdsvis 582 000 og 850 000 NOK per QAUALY sett fra et samfunnsperspektiv. Til slutt, hvis man sammenlikner vaksinasjon kombinert med 5-årlig screening fra 2048 med vaksinasjon kombinert med screening hvert 3. år for hele tidsperioden 2008 - 20 60, vil det gi en ICER på 2,3 millioner NOK per QUALY. Den inkrementelle analysen viser at et vaksinasjonsscenario med gradvis synkende immunitet er dominert av boostervaksinasjon fordi booster både er billigere og sparer flere liv. Av boostermulighetene ser det ut som 50 % dekning er den mest

optimale siden 80 % ICER er NOK 1,4 millioner per QALY fra et samfunnsmessig perspektiv.

HPV-virus type skift

Kostnadseffektiviteten av HPV 16/18-vaksine var følsom overfor virus type skift, både ved 50% og 55% hyppighet. Sammenliknet med baseline vaksinasjonsscreening-scenarioet økte ICER nesten 5 ganger ved 55 % virus type skift (samfunnsperspektiv).

Kryssbeskyttelse og HPV virus type skift

Kostnadseffektiviteten av HPV 16/18-vaksine var relativt lite følsom for kryssbeskyttelse mot andre HPV-virus, men da vi undersøkte et kombinert scenario med kryssbeskyttelse og virus type skift, var det bare en liten del av den negative effekten til virus type skift som kunne motvirkes. Sammenliknet med baseline vaksinasjonsscreening-scenarioet økte ICER fortsatt nesten 4 ganger ved 55 % virus type skift kombinert med 20 % kryssbeskyttelse (samfunnsperspektiv).

KONKLUSJON

Cytologisk screening er effektivt for å redusere antall tilfeller av livmorhalskreft og vil fortsatt være viktig etter implementering av HPV 16/18-vaksinasjon. Det mest kostnadseffektive tiltaket gitt denne dokumentasjonen, vil være HPV 16/18-vaksinasjon i kombinasjon med økte screeningintervaller etter 20 år.

Kryssbeskyttelse mot andre HPV-virus vil ha en liten positiv effekt. Avtagende beskyttelse av vaksinen ser ut til å ha negativ effekt på fremtidig forekomst av livmorhalskreft og kostnadseffektiviteten av vaksinen. Det advares mot et mulig skifte fra HPV 16 og 18 til andre kreftfremkallende HPV-typer, noe som kan redusere effekten av HPV 16/18-vaksinasjon betraktelig i et 50-års perspektiv.

Executive summary

BACKGROUND

Whether HPV16/18 vaccination should be introduced into the Norwegian childhood vaccination programme is currently being discussed. The National Council on Quality and Prioritisation in Health Care discussed the matter in December 2007, and asked the Norwegian Knowledge Centre for the Health Services using a dynamic health economic model to quantify how several unresolved issues regarding long-term efficacy may affect the future burden of cervical cancer and health economics of HPV 16/18 vaccination.

METHOD

We used the same dynamic natural history model and health economic approach as previously described in Report No. 12-2007. The analyses are made in a two-step approach: i) a natural history model is used to estimate the development in pre-cancerous and cancerous lesions in the time period 2008-2060, ii) health economic evaluations are performed based on the predicted burden of disease. Outcomes are compared to a base case vaccination-screening scenario assuming 90% vaccine coverage among 12-year old girls, 90% vaccine efficacy and a mean 3-yearly screening coverage of 80% among 25-69 year-old women.

RESULTS

The potential disease impact and cost-effectiveness of HPV 16/18 vaccination as a result of performing a series of additional scenarios to accompany Report No. 12-2007 are presented in this section.

Screening once a year without HPV 16/18 vaccination

A more intensive screening strategy involving screening every year is comparable to the effectiveness of HPV 16/18 vaccination (LYG and QALYs) when compared to

baseline screening. This increase in effectiveness comes with a high additional estimated health sector cost of NOK 9,5 billion. When incremental analysis is performed between vaccination-screening and the improved screening program, it turns out that the latter is dominated by the vaccination based strategy. From a health economic point of view, this means that the more intensive screening programme should not be further considered for implementation since the health improvements can be achieved with vaccination for only one ninth of the additional costs of screening.

Screening 5-yearly from 2028, 2038 or 2048 together with HPV 16/18 vaccination

We first compared baseline screening to the strategy with the smallest effect (vaccination with 5-yearly screening after 20 years). This combined strategy seems to be cost-saving compared to baseline screening. If the 5-yearly screening is assumed to be delayed to 2038 or 2048, this would give ICERs of respectively 582 000 and 850 000 NOK per QALY gained from the societal perspective. Finally, moving from a strategy with vaccination and 5-yearly screening in 2048 to vaccination and screening every 3 years for the entire time horizon 2008-2060 would create an ICER of 2.3 million NOK per QALY gained.

Reduced screening compliance among vaccinated women

Cost-effectiveness of HPV 16/18 vaccination was relatively insensitive to reduced screening compliance among vaccinated women.

Booster vaccination

The incremental information shows that waning is dominated by booster because it averts less QALY loss at the same time as costing more compared to booster. Among booster options 50% coverage is more likely to be optimal since the ICER of 80% is as high as 1.4 million NOK per QALY from the societal perspective.

Strain replacement

Cost-effectiveness of HPV 16/18 vaccination was sensitive to strain replacement, both at a 50% and at a 55% rate. In comparison with the baseline vaccination screening scenario, the ICERs increased almost 5 times with a 55% rate of strain replacement (societal perspective).

Cross-protection and strain replacement

Cost-effectiveness was relatively insensitive to cross-protection, but when a combined scenario of cross-protection and strain replacement was modelled only some of the negative effect seen by replacement could be counteracted. In comparison with the baseline vaccination screening scenario, the ICERs still increased almost 4 times with a 55% rate of strain replacement combined with cross-protection of 20% (societal perspective).

CONCLUSIONS

Cytological screening is effective in reducing the burden of cervical cancer, and continues to be important also after implementing HPV 16/18 vaccination. The intervention most likely to be selected given this evidence, is vaccination with increased screening intervals after 20 years.

Cross-protection and (slowly) waning vaccine efficacy is found to have minor positive and negative effects respectively on future incidence rates of cervical cancer and cost-effectiveness of the vaccine. A potential caveat is strain replacement of HPV 16 and 18 by other oncogenic HPV types, which may reduce the impact of HPV 16/18 vaccination significantly in a 50 year perspective.

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Table of contents

Objective

Several questions regarding the long-term efficacy of HPV16/18 vaccination remain unanswered. How long is the duration of expected protection, when does one need a booster vaccination, what are the possible cross-protection gains and which possible shifts in HPV typology may be expected can only be answered some 10-15 years into the future.

We were therefore asked by the National Council for Quality and Prioritisation in Health Care to quantify how these unresolved issues may affect the future burden of cervical cancer and the health economics of introducing HPV 16/18 vaccination into the Norwegian childhood vaccination programme. Additionally, we were asked to make a health economic assessment of alternative set-ups of the national screening programme. The objective of this report was to assess some of the uncertainties regarding HPV 16/18 vaccination and for this purpose we used a dynamic compartmental disease model coupled with a health economic model, both of which were previously developed and applied in Report No. 12-2007. We have not estimated uncertainty concerning safety of such vaccination.

Background

In 2006 the Norwegian Institute for Public Health asked the Norwegian Knowledge Centre for the Health Service to undertake a health technology assessment (HTA) for prophylactic vaccines against human papillomavirus (HPV) infection. We completed our work in 2007 and delivered a systematic review in which the efficacy and safety of such vaccines were evaluated (Report No. 5-2007) and a health economic model where the cost-effectiveness of HPV 16/18 vaccination was evaluated (Report No. 12-2007).

Two vaccines against HPV have been developed to date, Gardasil® and Cervarix®. Gardasil is manufactured by Merck and is marketed in Europe by Sanofi Pasteur MSD, while Cervarix is manufactured by Glaxo Smith Kline. Both vaccines have received marketing authorisation in Norway and both vaccines are directed at HPV types 16 and 18. Both vaccines hold the potential to achieve future reductions in the incidence of cervical pre-cancers, cancers and cervical cancer mortality arising from HPV type 16/18 specific infections.

Whether HPV16/18 vaccinations should be introduced into the mass vaccination programme in Norway is currently being discussed. The National Council on Quality and Prioritisation in Health Care discussed the matter in December 2007. The Norwegian Knowledge Centre for the Health Service was asked to use our dynamic health economic model to estimate different uncertain factors regarding the long term efficacy of HPV16/18 vaccination and also to simulate alternative set-ups of the national screening programme. In this report we have explored the questions regarding how to improve the present screening programme in Norway. We have also estimated the impact of altering the screening intervals to once a year. Additionally, we have estimated the cost-effectiveness of HPV16/18 vaccination when the need for a booster vaccination, possible cross-protection and the possibility of virus strain replacement were taken into consideration.

Method

We used the same dynamic natural history model and health economic approach as previously described in Report Nr 12-2007.

DISEASE MODEL

The natural history model is adapted from a compartmental model developed by Geoff Garnett (1) and follows a population through HPV infection, development of cervical lesions and cervical cancer. HPV infection may be of type 16, type 18, or type 'other', comprising ten non-specified oncogenic HPV types not included in the vaccine. The population size is 4,75 million and is stratified into three classes: children (aged 0-9 years), adolescents (aged 10-15 years) followed in 1-year cohorts and adults (aged 16-75 years) aggregated in 10-year cohorts. Individuals are assumed to become sexually active at the age of 16.

Individuals are divided into compartments based on their value of state parameters: age, infection status and sexual activity class; for women also screening compliance and 8 pathogenic disease stages CIN 1-3, carcinoma in situ and cervical cancer stage I-IV. Susceptible persons become infected according to the sexual mixing patterns with the opposite gender, which are formulated on the basis of Norwegian survey data. The model simulates a time period of 200 years with weekly updating, and systematic screening is implemented in year 100 (corresponding to 1995). Vaccination is scheduled for 12-year old girls and initiated in year 113 (corresponding to 2008).

The model was fitted to Norwegian age-specific incidence of cervical cancer and mortality data from 1995-2004 and data on CIN 2/3 from 2002-2004 (Report No 12-2007).

Model limitations

- Sexual behaviour and mixing patterns are fitted to current data and are assumed not to change during the period of simulation.

- The population structure is static and fitted to the present Norwegian population. It is expected that changes in birth rates and life expectancy may impact on both the total and the age-specific burden of disease during the decades to follow.
- We made no adjustment with regard to the density of co-infections (16-18; 16-other; 18-other, 16-18-other).

Deviations from Report No 12-2007:

Due to some minor adjustments of model parameters, the present and former base case scenarios are slightly different. Consequently, the incidence and mortality outcome may differ with 1-2% from estimates described in the Report No 12-2007. However, the relative impacts of vaccine interventions are not affected noticeably.

HEALTH ECONOMIC ASSESSMENT

A cost-effectiveness approach, assessing health gains in life-years as well as a cost-utility approach, assessing health gains in quality-adjusted life years (QALYs) is adopted, similar to the procedures in the main report. A detailed description of the assumptions about health care costs, health state utility assessment, productivity losses due to cervical cancer, cervical cancer treatment and cancer mortality is provided in Report 12-2007.

Outcomes are compared to a base case vaccination-screening scenario assuming 90% vaccine coverage among 12-year old girls, 90% vaccine efficacy and a mean 3-yearly screening coverage of 80% among 25-69 year old women. Results are presented for both healthcare sector and societal perspectives over a time horizon of 52 years (2008-2060). Future costs and outcomes are discounted at a rate of 4% per annum to their present day values (base year 2008).

SCENARIOS MODELLED

A description of the different scenarios modelled is given below:

	Description
	Baseline screening 80% average 3-yearly coverage of Pap smear cytological screening; age-specific coverage from (2)
	Baseline vaccination-screening Screening parameters as in baseline screening; 90% vaccination coverage 90% vaccination efficacy; vaccination programme is implemented over a 5 year period 2008-2013 assuming a

	linear increase in the coverage to reach 90%; no waning
	Vaccination-screening waning immunity Screening parameters as in baseline screening; 90% vaccination coverage 90% vaccination efficacy, waning efficacy with a constant loss of 0.0079/year is applied to all vaccinated population segments.
	Screening 1 year Screening parameters as in baseline screening; from 2008 a 1-yearly screening programme is initiated; age specific coverage as before.
	5yearly-screening initiated in 2028, 2038, 2048 Primary screening and vaccination parameters as in baseline vaccination-screening; from year 2028, 2038 or 2048 a 5yearly screening programme is implemented with coverage as before.
	Reduced screening compliance among vaccinated women Screening parameters as in baseline screening for non-vaccinated women; in vaccinated women the 3-yearly screening compliance is changed to 50-60%.
	Booster 50%, 80% Screening parameters as in baseline screening; 90% vaccination coverage, 90% vaccination efficacy, waning efficacy with a constant loss of 0.0079/year is applied to all vaccinated population segments. This gives a vaccine efficacy of 80% after 15 years, and 60% efficacy after 50 years. Booster vaccination is given to the age group 16-25 years corresponding to coverage of 50-80% for a single 1-year cohort starting from 2023.
	Replacement 0.5, 0.55 Screening and vaccination parameters as in baseline vaccination-screening. In a 20 year period following the implementation of vaccination from 2013-2033 the progression rate of HPV type 'other' relative to type 16/18 increases linearly from 0.4 to 0.5-0.55. The progression rate of HPV type 'other' is usually set to 0.4 of the progression rate of type 16/18 which is 1 in the model.
	Cross-protection 20% Screening and vaccination parameters as in baseline vaccination-screening. Vaccine efficacy of 20% for HPV type other is implemented.
	Cross-protection 20% replacement 0.55 Screening and vaccination parameters as in replacement 0.55. Vaccine efficacy of 20% for HPV type other is implemented.

Results

A series of additional scenarios to accompany Report No. 12-2007 are presented in this section. The estimated disease impact and cost-effectiveness are reported in the individual simulation sections below.

IMPROVING THE PRESENT SCREENING PROGRAMME WITHOUT VACCINATION

In Finland, organised mass screening has resulted in a substantial decrease in the incidence of cervical cancer from 14 per 100,000 women in 1960 to 4 per 100,000 by 1990. During the last decade the incidence has been relatively stable in the country, but in recent years there has been a trebling of women between 30-39 years developing cervical cancer (3), and a high HPV-DNA prevalence of 33% among young females has been reported (4). A study of HPV type time trends points to an epidemic spread of HPV-16 throughout the 1980s and 1990s (5). This tendency of rising HPV-16 exposure may potentially lead to an increase in cervical carcinoma in Finland in the years to come.

The Finnish screening programme targets women aged 30-60 years in 5-year screening intervals. Based on the Finnish Cancer Registry (6), the coverage of the target population is ~70%. However, the official figures are probably not representative of the true screening frequency, as many women, on their own initiative, are screened at private clinics on a yearly basis.

The present Norwegian screening programme targets women between 25-69 years of age in 3-yearly intervals and the current coverage lies around ~80% (7). Hence, Norway has already high coverage and elevated screening frequency compared to the official figures from Finland. To study the impact of reducing the screening interval from 3 to 1 year, simulations were performed with respect to implementing a 1-year screening interval in 2008.

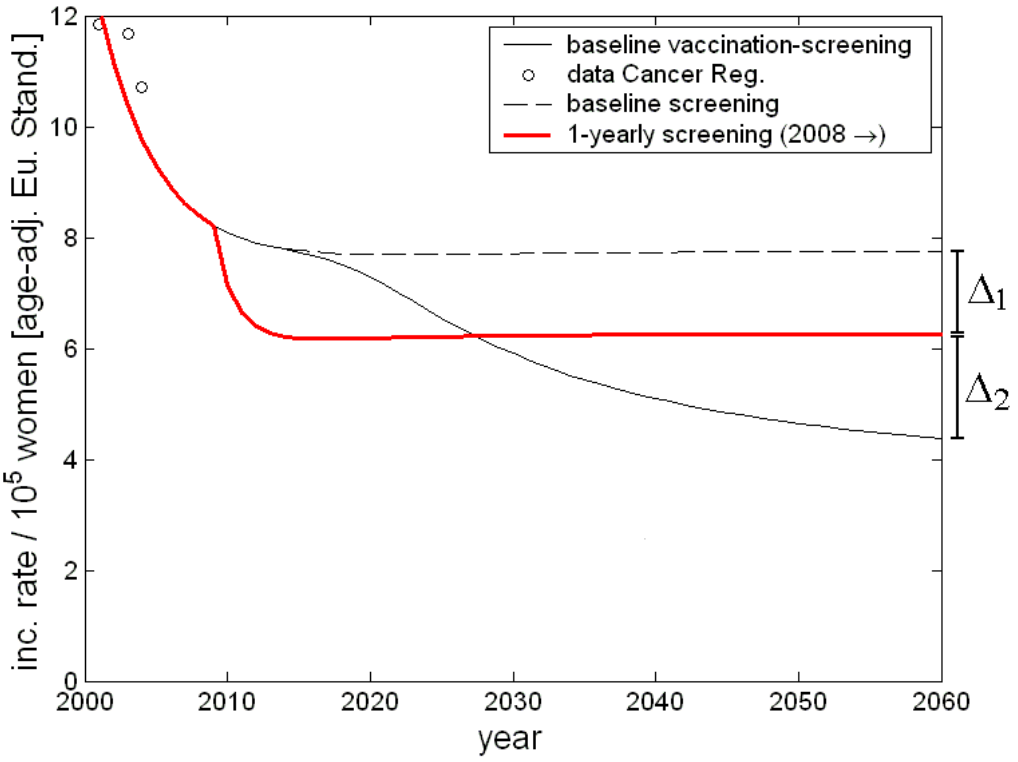

Fig 1: Impact of changing screening guidelines from 3-yearly to 1-yearly Pap smear testing. The screening coverage is assumed to be 80% in all cases.

Disease impact

The effect of reducing the screening interval (Fig. 1) is seen in a 10-year interval to decrease the incidence of cervical cancer by $\Delta_1 = 20\%$ compared to the expected incidence obtained by maintaining the present screening guidelines. In a long-term perspective, however, improved screening practice alone is far less efficient in reducing cervical cancer compared to conjoint screening and HPV 16/18 vaccination. By 2060 the cervical cancer incidence is roughly $\Delta_2 = 1.4$ times higher than the level obtained in the baseline vaccination-screening scenario. On the other hand, the accumulated incidence of 1-yearly screening without vaccination is only ~1.07 times larger than vaccination, since improved screening has a more immediate effect.

In the model it is assumed that the sexual behaviour of women - and their risk of developing cervical cancer - is independent of their participation in the screening programme. In Norway women outside the organized screening programme are found to have an increased risk of developing cervical cancer (8). Hence, the reduction in incidence of cervical cancer predicted as a result of increasing the

screening frequency is likely to be overestimated by the model. For health economic calculations see table 1.

Table 1 Costs, effects and cost-effectiveness of yearly Pap smear testing

Scenario	Effects				Costs (NOK '000)			Health sector perspective Cost effectiveness (ICERs NOK '000)			Societal perspective- Cost effectiveness (ICERs NOK '000)	
	Life-years lost to cervical cancer	QALYs lost to cervical cancer	Incremental life-years	Incremental QALYs	Health sector costs	Production losses due to cancer treatment and death	Incremental health sector costs	Production losses averted	Cost per life-year gained	Cost per QALY gained	Cost per life-year gained	Cost per QALY gained
Baseline screen	19 104	22 311	-	-	6 401 424	4 258 910	-			-		-
Baseline vaccination-screening [1]	16 245	18 898	2 859	3 413	7 478 986	3 281 014	1 077 562	977 896	377	316	35	29
Screen 1 year [2]	16 247	18 907	2	9	15 882 216	3 262 422	9 481 194	996 488	Dominated		Dominated	

1) no waning assumption = no loss in vaccine immunity and therefore no booster costs are applied in this scenario

2) Screening more intensively is assumed to increase proportionally the total number of screening tests performed (i.e. an approx three-fold increase)

Health economic impact

A more intensive screening strategy involving screening every year is comparable to the effectiveness of HPV 16/18 vaccination (LYG and QALYs) when compared to baseline screening. This increase in effectiveness comes with a high additional estimated health sector cost of NOK 9,5 billion. When incremental analysis is performed between vaccination-screening and the improved screening program, the latter is dominated by the vaccination based strategy. From a health economic point of view, this means that the more intensive screening programme should not be further considered for implementation since the health improvements can be achieved with vaccination for only one ninth of the additional costs of screening.

INCREASING THE SCREENING INTERVAL COMBINED WITH VACCINATION

In our report No. 12-2007, impact and cost-effectiveness of HPV vaccination were estimated assuming that vaccination occurs in addition to current cervical screening practice. One option with regard to decreasing the costs of running a combined vaccination/screening programme would be to reduce the total annual Pap volume, e.g. by increasing the interval between consecutive Pap smears.

Simulations were performed by changing screening intervals from 3 to 5-years in the entire target population 20, 30 and 40 years after introducing HPV vaccination, while maintaining 80% screening coverage among the women.

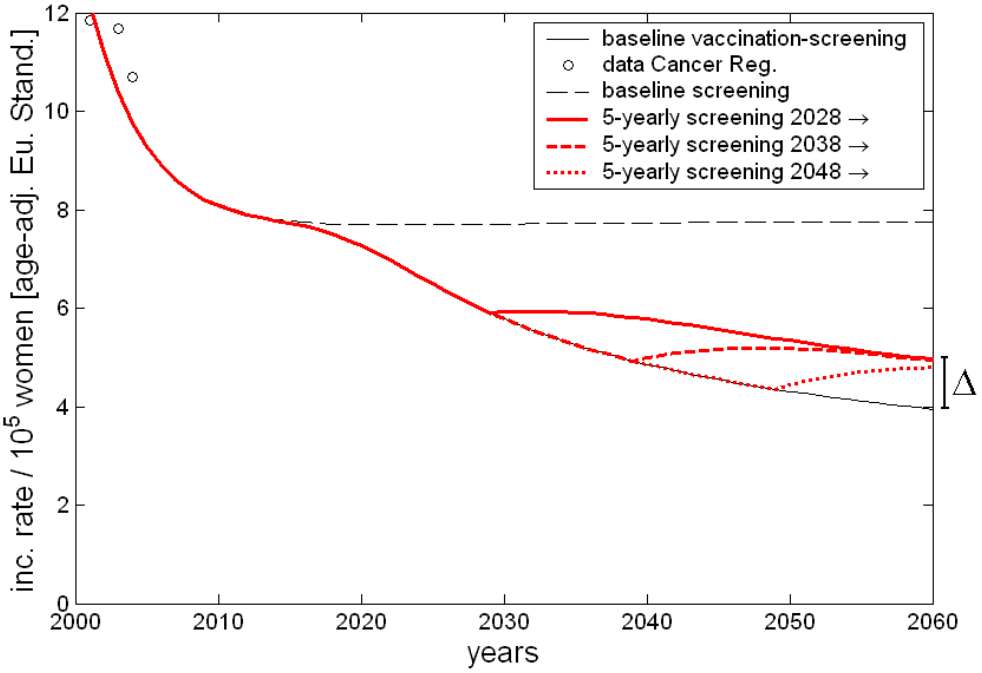

Fig 2: Effect of reducing the screening frequency from 3-yearly to 5-yearly intervals; screening coverage 80%

Disease impact

The model estimates the incidence of cervical cancer to increase by $\Delta = 20\%$ in 2060 compared to maintaining the current screening programme after vaccination has been implemented.

Changing the screening interval in 2028-2048 causes the incidence curves to increase and collapse onto a single line. This line is identical to the one obtained from running a 5-yearly screening practice starting in 2028. By 2060, both the total and age-specific incidence is the same for the three scenarios. Thus, screening affects the women who are already diseased, but it does not change the underlying HPV infection exposure (no herd effect). For health economic calculations see table 2.

Table 2 Costs, effects and cost-effectiveness of 5-yearly Pap smears

Scenario	Effects				Costs (NOK '000)				Health sector perspective Cost effectiveness (ICERs NOK '000)		Societal perspective- Cost effectiveness (ICERs NOK '000)	
	Life-years lost to cervical cancer	QALYs lost to cervical cancer	Incremental life-years	Incremental QALYs	Health sector costs	Production losses due to cancer treatment and death	Incremental health sector costs	Production losses averted	Cost per life-year gained	Cost per QALY gained	Cost per life-year gained	Cost per QALY gained

Baseline screen	19 104	22 311			6 401 424	4 258 910						
Vaccination + 5y screen 2028 [1]	16 849	19 634	2 255	2 677	6 735 921	3 409 312	334 497	849 598	148	125	Cost-saving	
Vaccination + 5y screen 2038 [1]	16 521	19 174	328	460	7 059 141	3 353 611	323 220	55 701	985	703	816	582
Vaccination + 5y screen 2048 [1]	16 322	18 974	199	200	7 284 531	3 298 288	225 390	55 323	1 132	1 127	855	850
Baseline vaccination-screening [1]	16 245	18 898	77	76	7 478 986	3 281 014	194 455	17 274	2 525	2 559	2 301	2 331

1= no waning assumption = no loss in vaccine immunity and therefore no booster costs are applied in this scenario

Health economic impact

We first compared baseline screening to the strategy with the smallest effect (vaccination with 5-yearly screening after 20 years). This combined strategy seems to be cost-saving compared to baseline screening. If the 5-yearly screening is assumed to be delayed to 2038 or 2048, this would give ICERs of respectively 582 000 and 850 000 NOK per QALY gained.

Finally, moving from a strategy with vaccination and 5-yearly screening in 2048 to vaccination and screening every 3 years for the entire time horizon 2008-2060 would create an ICER of 2.3 million NOK per QALY gained.

EFFECT OF REDUCED SCREENING COMPLIANCE AMONG VACCINATED WOMEN

It has been speculated that vaccinated women may be less compliant to participate in the national screening programme. If this situation should occur, it may have a negative impact on the overall health gain from introducing the vaccine. We tested this scenario by assuming a lowered participation in the 3-yearly screening programme after vaccination had been implemented. In the sub-group of vaccinated women we reduced the screening compliance to respectively 50 or 60%, while keeping the baseline screening participation of 80% among non-vaccinated women.

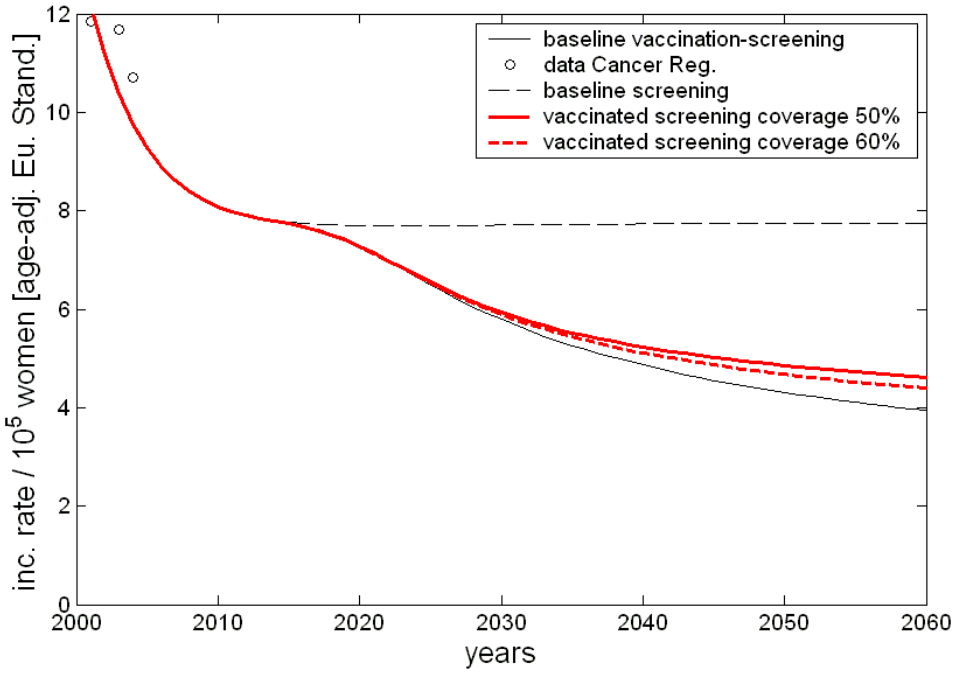

Fig 3: Impact of reduced screening among vaccinated women

Disease impact

The model predicts the incidence of cervical cancer to increase by 17% (50% coverage) and 11% (60% coverage) among vaccinated women in 2060. The effect will develop from around 2030, and it is assumed that the risk behaviour among vaccinated and non-vaccinated women is equal. The health economic assessment is shown in table 3.

Table 3 Sensitivity analysis: reduced screening compliance among vaccinated women

Scenario	Effects				Costs (NOK '000)			Health sector perspective Cost effectiveness (ICERs NOK '000)			Societal perspective- Cost effectiveness (ICERs NOK '000)	
	Life-years lost to cervical cancer	QALYs lost to cervical cancer	Incremental life-years	Incremental QALYs	Health sector costs	Production losses due to cancer treatment and death	Incremental health sector costs	Production losses averted	Cost per life-year gained	Cost per QALY gained	Cost per life-year gained	Cost per QALY gained
Baseline screen	19 104	22 311			6 401 424	4 258 910						
Baseline vaccination-screening [1]	16 245	18 898	2 859	3 413	7 478 986	3 281 014	1 077 562	977 896	377	316	35	29
Reduced screening 60%	16 435	19 131	2 669	3 180	7 276 067	3 323 147	874 643	935 763	328	275	Cost-saving	
Reduced screening 50%	16 530	19 248	2 574	3 063	7 277 077	3 344 280	875 653	914 630	340	286	Cost-saving	

1) no waning assumption = no loss in vaccine immunity and therefore no booster costs are applied in this scenario

Health economic impact

Cost-effectiveness of HPV 16/18 vaccination was relatively insensitive to reduced screening compliance among vaccinated women.

BOOSTER VACCINATION / DURATION OF PROTECTION

It will take years before the long-term protection of HPV vaccines can be documented. In the report No. 12-2007, waning efficacy was not considered in the natural history model. Instead, the base case scenario assumed a 90% vaccine efficacy with a booster vaccine after 10 years to sustain the level of protection.

Current efficacy studies include 5-6 years follow-up, and there is no evidence of significant waning immunity during this time period. For this reason we tested for a slowly waning efficacy by assuming the vaccine efficacy to decrease with a constant rate from 90-80% during a 15 year period after the vaccination. It was further assumed that vaccine potency would continue to decay with the same constant rate throughout lifetime. One booster dose is given to the 16-25 year age group corresponding to a coverage of 50-80% among 22-year old women, who are previously vaccinated.

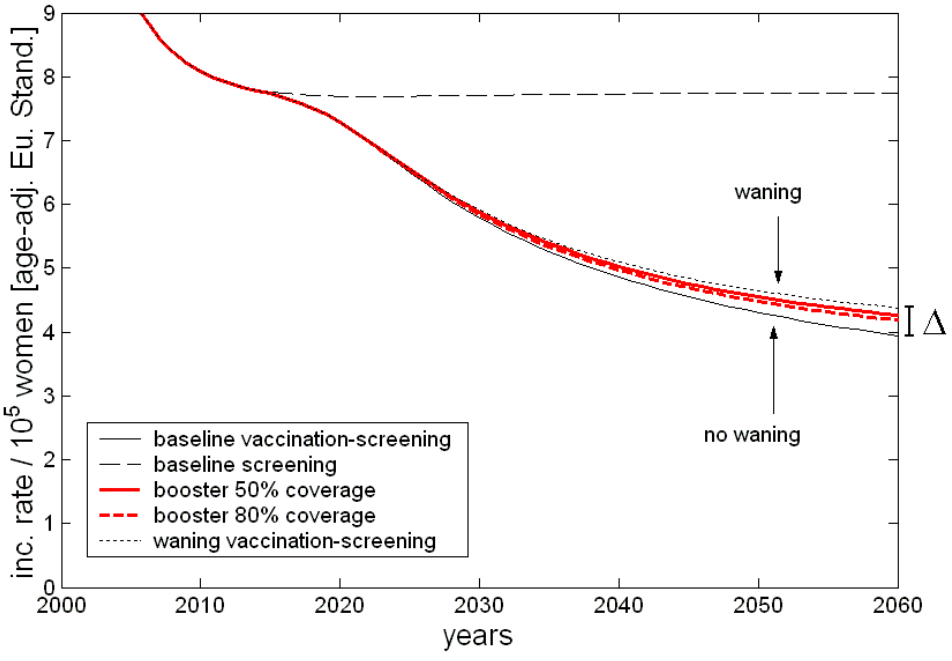

Fig 4: Impact of booster vaccination by assuming waning efficacy

Disease impact

The modelled difference between the baseline vaccination-screening scenario and the waning efficacy scenario is small and varies by Δ ~11% in 2060. The impact of waning efficacy is a slowly developing process, and the deviation from the asumption of constant vaccine efficacy will continue to develop until the end of the century.

The booster scenarios are found to lie closer to the waning scenario, giving a 3% (50% coverage) and 5% (80% coverage) overall reduced incidence compared to the waning scenario. This tendency becomes more prominent as time passes. Thus, the simulations indicate that given a slowly waning efficacy, a booster vaccination is not efficient in reducing cervical cancer incidence or is actually not needed in sustaining vaccine protection over time.

It should be noted that the model is not designed to study booster vaccination. Adults are grouped into 10-year cohorts, and thus, it is not possible to vaccinate a single 22-year old age cohort. Instead, the booster dose is applied to the entire 16-25 year age group, but assuming a lower coverage. The average vaccine efficacy in the 16-25 year age group is larger than the average efficacy in the 22-year cohort because the mean duration time since vaccination is shorter for the group as a whole compared to the 22-year old women. Therefore, the model tends to underestimate the effect of booster vaccination. Details of health economic calculations are assembled in table 4.

Table 4 Costs, effects and cost-effectiveness of booster vaccination

Scenario	Effects				Costs (NOK '000)			Health sector perspective Cost effectiveness (ICERs NOK '000)			Societal perspective- Cost effectiveness (ICERs NOK '000)	
	Life-years lost to cervical cancer	QALYs lost to cervical cancer	Incremental life-years	Incremental QALYs	Health sector costs	Production losses due to cancer treatment and death	Incremental health sector costs	Production losses averted	Cost per life-year gained	Cost per QALY gained	Cost per life-year gained	Cost per QALY gained
Baseline screen	19 104	22 311			6 401 424	4 258 910						
Vaccination-screening waning [1]	16 470	19 122			7 895 770	3 328 639			Dominated		Dominated	
Booster 50%[1,2,]	16 413	19 100	2 691	3 211	7 693 870	3 316 621	1 292 446	942 289	480	403	130	109
Booster 80%[1,2]	16 364	19 041	49	59	7 787 740	3 306 115	93 870	10 506	1 916	1 591	1 701	1 413

1) vaccination scenario comparison includes waning 2) booster costs applied

Health economic impact

The incremental information shows that waning is dominated by booster because it averts less QALY loss at the same time as costing more compared to booster. Among booster options 50% coverage is more likely to be optimal since the ICER of 80% is as high as 1.4 million NOK per QALY from the societal perspective.

STRAIN REPLACEMENT

Removal of the prevailing 16/18 infections may possibly create an ecological niche where other HPV strains can expand. It has been hypothesized that strain removal could take place both by mutations in the HPV genome—or indirectly—mediated by the host women.

In the latter case the dominant HPV infections may change among the group of women who are highly susceptible to infection and development of cervical lesions. The previous dominance of HPV 16/18 strains could be taken over by other HPV types not included in the vaccine. Consequently, it will appear *as if* the oncogenic potential of these strains are increased. The oncogenic potential may also increase by introduction of new strains with different phenotypes from current prevailing strains.

The impact of strain replacement was tested by increasing the progression rate for HPV type 'other' compared to the corresponding rates of HPV 16/18. During a 20 year period following the introduction of vaccination, the relative progression rate for HPV type 'other' increases from o.4 to 0.5 or 0.55. The choice of parameter variation was arbitrary; even modest changes in the relative progression rate may have a large impact on the disease dynamics, as the group represents an aggregate of 10 strains.

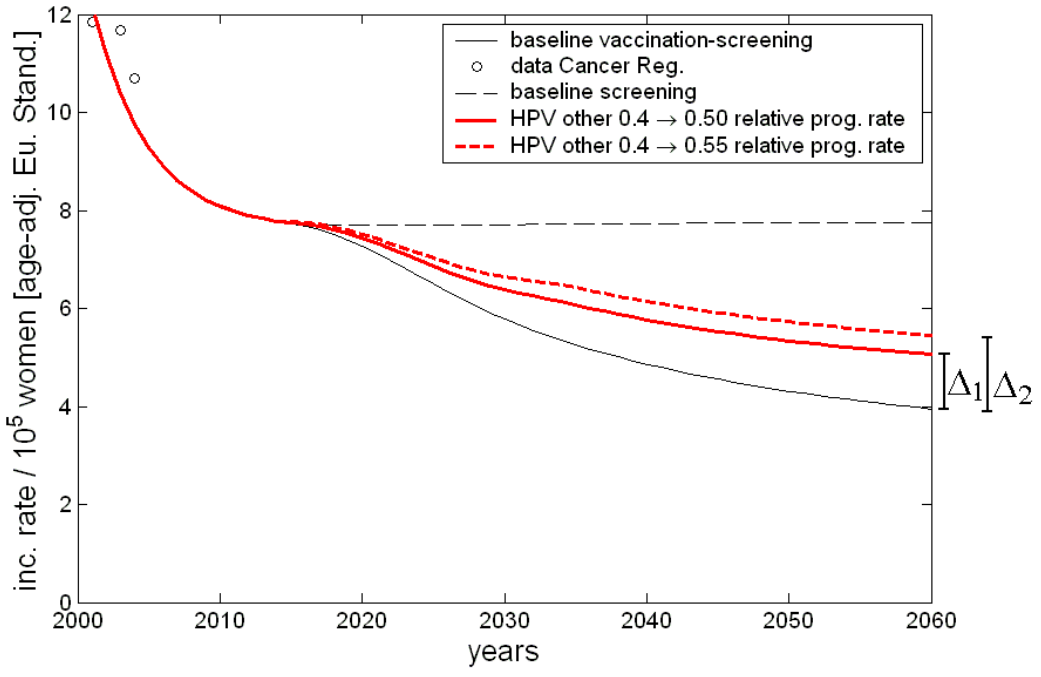

Fig 5: Impact of strain replacement

Disease impact

The model estimates an increased cervical cancer incidence of ~18% (2040) and Δ_1 ~29% (2060) for a relative progression rate of 0.5 compared to the baseline vaccination-screening scenario; the corresponding values for 0.55 relative progression rate are ~25% (2040) and Δ_2 ~38% (2060). Hence, strain replacement is found to have a strong impact on the predicted burden of disease. The high sensitivity is expected due to the abundance of HPV 'other' infections, which is a collection of ten HPV types. A more realistic scenario would be to increase the relative progression rate of only a few oncogenic HPV types, but this is unfortunately not possible to study with the present model. It may also be argued that the chosen time frame of 20 years may be too short as the HPV genome is quite stable and replicates slowly. Health economic calculations are provided in table 5.

Table 5 Sensitivity analysis: strain replacement

Scenario	Costs (NOK '000)		Costs (NOK '000)		Health sector perspective (NOK '000)		Societal perspective (NOK '000)	
	Life-years lost to cervical cancer	QALYs lost to cervical cancer	Health sector costs	Production losses due to cancer treatment and death	Cost per life-year gained	Cost per QALY gained	Cost per life-year gained	Cost per QALY gained
Baseline vaccination-screening [1]	16 245	18 898	7 478 986	3 281 014	377	316	35	29
Replacement 0.5 [2]	16 926	19 579	7 479 119	3 423 944	495	394	111	89
Replacement 0.55 [2]	17 297	19 950	7 479 242	3 501 805	591	457	176	136

1) no waning assumption = no loss in vaccine immunity and therefore no booster costs are applied in this scenario

Health economic impact

Cost-effectiveness of HPV 16/18 vaccination was sensitive to strain replacement, both at a 50% and at a 55 % rate. In comparison with the baseline vaccination screening scenario, the ICERs increased almost 5 times with a 55% rate of strain replacement (societal perspective).

CROSS-PROTECTION

It is still an open question whether prophylactic HPV vaccines provide cross-protection against other oncogenic HPV types. Recent data from Sanofi Pasteur (Gardasil) shows a 38% protection against the development of CIN 2/3 lesions for 10 HPV strains (31,33,35,39,45,51,52,566,58,59) in a 3-year follow-up period (9). These strains account for around 16% of cervical cancer cases in Europe. However, the

follow-up period is short (only 3 years) and the events averted are few. Future research and follow-up will probably give a more certain answer to this question.

Model simulations were performed adding a cross-protection of 20% to HPV type 'other', to take into account that the data material relates to only half of the cervical cancer cases caused by HPV strains, which are not included in the vaccines.

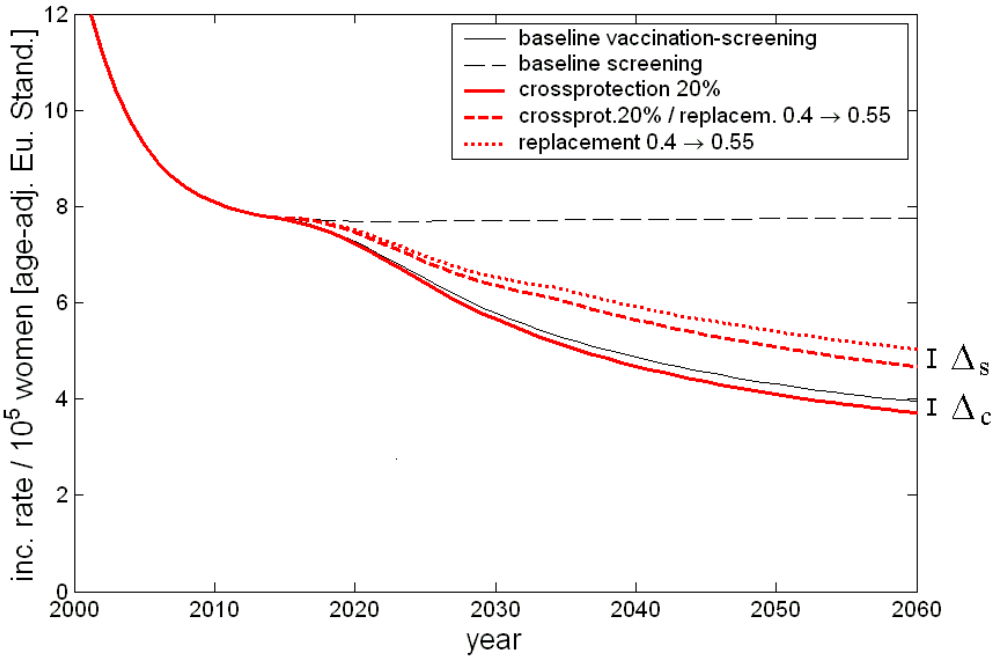

Fig 6: Impact of cross-protection of 20% in HPV type 'other', and in combination with strain replacement

Disease impact

The model predicts a Δ_C ~7% reduction in cervical cancer incidence compared to the baseline vaccination-screening by 2060 and a further decline of 1-2% is expected by the end of the century. The influence of cross protection on cervical cancer development evolves slowly. A combined scenario with cross protection and strain replacement 0.55 results in a reduction of Δ_S ~8% compared to the predicted to the replacement only outcome. The model indicates that if both cross protection and strain replacement influence the infection dynamics, the overall outcome will be dominated by the process of strain replacement. Hence, the effect of the vaccine intervention will decrease compared to the base case assumptions. Detailed health economic calculations are shown in table 6.

Table 6 Sensitivity analysis: cross-protection 2008-2060

Scenario	Effects		Costs (NOK '000)		Health sector perspective (NOK '000)		Societal perspective (NOK '000)	
	Life-years lost to cervical	QALYs lost to cervical	Health sector	Production losses due to cancer treat-	Cost per life-year	Cost per QALY	Cost per life-year	Cost per QALY

	cancer	cancer	costs	ment and death	gained	gained	gained	gained
Baseline screen	19 104	22 311	6 401 424	4 258 910				
Baseline vaccination-screening [1]	16 245	18 898	7 478 986	3 281 014	377	316	35	29
Cross-protection 20% [1]	16 092	18 745	7 478 768	3 247 261	358	302	22	18
Cross-protection 20%- Replacement 055 [1]	17 074	19 895	7 479 078	3 453 530	531	446	134	113

1) no waning assumption = no loss in vaccine immunity and therefore no booster costs are applied in this scenario

Health economic impact

Cost-effectiveness was relatively insensitive to cross-protection, but when a combined scenario of cross-protection and strain replacement was modelled only some of the negative effect seen by replacement could be counteracted. In comparison with the baseline vaccination screening scenario, the ICERs still increased almost 4 times with a 55% rate of strain replacement combined with cross-protection of 20% (societal perspective).

Discussion

In this report we have explored the long-term impact of a number of important unresolved issues related to HPV 16/18 vaccination and screening practice to help inform policy decisions and recommendations. The current modelling study supports the conclusion in Report No. 12-2007 indicating that vaccinating 12-year old girls against HPV 16/18 is likely to be cost-effective.

We have used a dynamic disease model, which has the advantage of tracking dynamically the effects of changing HPV exposure in the population (herd effect).The model is highly complex as it combines sexual interaction, HPV infection dynamics and cervical cancer development, and as such it is subject to uncertainties. First, some of the epidemiological parameters, particularly those related to pre-cancerous progression and regression, are uncertain. Second, the dynamic model presents the problem of representing age-specific sexual mixing and activity, which to a large degree is unknown. We have used sexual behavioural data from population based Norwegian studies to gauge the sexual parameters (10). Third, the abundance of HPV co-infections was not controlled for in the model. In another on-going work, we have fitted the density of co-infections to Norwegian and Swedish data. In this case the model predicts that a 50% cervical cancer incidence reduction will be obtained some 10-20 years later compared to the present results.
Other limiting factors include the assumption of static age- and sexual activity structures. Changes in the general sexual behaviour will affect the disease dynamics, but in a 50-years perspective other factors like implementation of multi-strain HPV vaccines may have even larger influence on future disease burden.
Despite these limitations, we believe the model is able to give a reasonable presentation of the HPV infection dynamics and development of cervical cancer. The model has been fitted to age-specific incidence and mortality rates during the past decade as well as to CIN 2/3 incidence rates, and it performs well on current disease data.

Improving the present cervical cancer screening programme in Norway in order to be as effective as the Finnish programme is not possible by altering the screening coverage, since we already have ~ 80 % coverage in the programme. This coverage is

slightly better than the official Finnish programme (which is ~ 70 %). Thus, the low cervical cancer incidence rates in Finland have to be explained by other mechanisms such as sexual behaviour, HPV-infection patterns, smoking habits and other co-factors. Finnish women also practice wild screening on a yearly basis in private clinics. The simulations underline the effect of a broad coverage screening programme in preventing cervical cancer. However, results show that intensified 1-year screening without HPV 16/18 vaccination is very costly, and it will not reduce the Norwegian incidence to values comparable to the current Finnish incidence rates of 4 per 100.000 women. The effect of 1-year screening would be relatively immediate and stabilize itself after approximately 10 years. In a long-term perspective an improved screening practice is less efficient than screening combined with vaccination in terms of long-term infection rate. However, 1-year screening is equally efficient in averting loss of life years, but is dominated by the combined vaccination and screening scenario and not of relevance in health economic terms.

Another option for improvement would be to try to increase the coverage of the current screening programme beyond ~ 80% (data not shown). We know from Norwegian studies that women outside the organized screening programme have an increased risk of developing cervical cancer (9). Approximately one third of new cervical cancers arise among the 20 % of women that do not take part in the screening programme. Therefore, to put more effort into screening these women is expected to yield lower cervical cancer incidence rates in the future.

We also tried to model an increase in the screening intervals from 3 to 5 years 20, 30 and 40 years after introducing HPV 16/18 vaccination. The effect of a general reduction in the screening frequency was a less costly programme but also a significant loss in health effect for the women (~20% in the time horizon 2008-2060). The most cost-saving alternative however, according to our health economic calculations, would be to implement HPV 16/18 vaccination together with todays screening programme and after 20 years increase the screening intervals from 3 to 5 years.

The long-term efficacy of HPV 16/18 vaccination is much debated. Since it will take years before long-term protection can be documented we have tried to model some of the uncertain issues in this report. One unresolved question is how long the protection against HPV-infection will last and when it will be necessary to give a booster vaccine to sustain the protection. Under the assumption of a slowly waning vaccine efficacy, booster vaccination is found to have little effect. Most women are still protected when the booster dose is given. However, if the vaccine effect were to wane more rapidly, booster vaccinations would be required to sustain protection against

HPV-infection. Today there is follow-up data for HPV16/18 vaccination for approximately 5 years and the data support the assertion of slowly waning efficacy (11). The health economic calculations show that introducing booster vaccinations with either 50 or 80% coverage would be slightly more effective and less costly than the vaccination/screening/waning scenario. The incremental analysis tells that waning is dominated by booster because it averts less QALY loss at the same time as costing more. Among booster options the 50% coverage seems to be the most cost-effective. However, the model is not well adapted to handle the issue of booster vaccination because adults are grouped in 10-year age groups. The model can therefore not be used to present data separately for each age cohort.

Provisional HPV vaccine recommendations from the American Centre for Disease Control (CDC) include catch-up vaccination for 13-26 year-old women. Given a slowly waning vaccine efficacy it may be considered to use resources to identify and vaccinate young women who for some reason avoided vaccination at the age of 12 years. Although, the documented vaccine efficacy on CIN 2/3 cervical disease among young, sexually active women is lower, ~ 45% (12), it may still be favourable in a population health perspective to vaccinate young women compared to running a booster vaccination programme if the average duration of vaccine protection can be extended.

In recent US based modeling studies, herd immunity is found to have a large impact on the estimated costs per QALY gained (13-14). The present dynamic model supports this general picture. Our preliminary results indicate that the herd effect (i.e. prevented infections in the susceptible population) accounts for ~20-30% prevented infections during the time period 2008-2060 (data now shown). The effect is largest during the first 10-25 years after starting the programme.

The model indicates that strain replacement may have significant negative influence on the prospective incidence of cervical cancer. However, the model simulates strain replacement for all the 'other' oncogenic HPV types and not only for one or two types that might have high oncogenic potential to proliferate when HPV 16 and 18 have disappeared. If strain replacement is to occur, it is likely that it can more than outbalance the potential positive influence achieved from cross-protection. In the simulations, strain replacement was implemented over a period of 20 years; this chosen time period is quite short, and accordingly, the results represent a "worst case" scenario. Other simulations have been performed where strain replacement is introduced over a period of 100 years. In combination with cross-protection, the results still point to a weak negative influence on cervical cancer incidence rates in

2060 compared to the baseline vaccination-screening scenario (data not shown). However, it should be noted that at present there is no support in the literature for strain replacement among HPV virus strains. The risk of a new HPV infection is higher for women with one or several HPV infections compared to non-infected women (14). This finding is supportive of a co-operative rather than competitive interaction among HPV virus strains. In addition, new multiple-strain HPV vaccines are expected to be on the market in the forthcoming years, and this may reduce the possibility for other high-oncogenic HPV strains to proliferate.

In our previous Report No. 12-2007, we showed that HPV 16/18 vaccination would reduce the amount of new CIN 2/3 precancerous lesions among vaccinated women compared to screening alone. After 52 years of HPV 16/18 vaccination and screening, an estimated reduction of 26 % in CIN 2/3 lesions was predicted. A decrease in CIN 2/3 lesions would probably lead to a reduced amount of annual conisation procedures in Norway, which are associated with premature births due to cervical insufficiency. Hence, savings attributable to treating complications after conisation procedures would further improve overall cost-effectiveness ratios of HPV 16/18 vaccination.

Taken together, we have explored several uncertain issues that may influence the efficacy and cost-effectiveness of HPV 16/18 vaccination. Sensitivity analysis demonstrated that cost-effectivness of HPV 16/18 vaccination was stable, but was most sensitive to HPV virus strain replacement. One major outstanding issue, which we have not modelled or taken into consideration in this report, is the long-term safety of HPV 16/18 vaccination. Post-licensure evaluation will need to further determine the long-term efficacy and safety of HPV 16/18 vaccination and a coordination between vaccine monitoring and cancer control programmes will be critical to assess the impact of the vaccine an its benefits compared with other existing prevention interventions such as screening in the future.

Conclusions

Cytological screening is effective in reducing the burden of cervical cancer, and will still be important after implementing HPV 16/18 vaccination. The intervention most likely to be selected given this evidence, is vaccination with increased screening intervals after 20 years.

Cross-protection and (slowly) waning vaccine efficacy is found to have minor positive and negative effects respectively on future cervical cancer incidence rates and cost-effectiveness of the vaccine. A potential caveat is strain replacement of HPV 16 and 18 by other oncogenic HPV types, which may reduce the impact of HPV 16/18 vaccination significantly in a 50 year perspective.

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