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Health economic evaluation of universal HPV vaccination within the Swedish national vaccination programme for children

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Preface

The Public Health Agency of Sweden has conducted an investigation into whether the national vaccination programme for children against human papilloma virus (HPV), which today is limited to girls, should be extended to also include boys.

This report describes the health economic evaluation that together with 12 other factors make up the 13 factors that the Public Health Agency of Sweden accounts for when proposing changes in the national vaccination programme to the government. These 13 factors together constitute the basis for making a decision on whether to extend the HPV-vaccination programme to boys.

The main target group for this publication is the government of Sweden (the Ministry of Health and Social Affairs). It could also be of interest for health professionals, foreign ministries of health, and public health institutions contemplating universal vaccination programmes against HPV.

The report was composed by Ellen Wolff, health economist at the unit for Epidemiology and Health Economics at the Public Health Agency of Sweden, in collaboration with a working group consisting of both analysts from the Public Health Agency of Sweden and external experts (see Appendix 1).

The Public Health Agency of Sweden

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Table of contents

Abbreviations

DALY	Disability-Adjusted Life Year
EMA	European Medicines Agency
EQ-5D	Instrument used to measure health-related quality of life
HPV	Human Papilloma Virus
ICER	Incremental Cost Effectiveness Ratio, the difference in costs between two interventions divided by the difference in effect
IP	Inpatient care
KPP	Cost per patient
PET-CT	Positron emission tomography–computed tomography
MRI	Magnetic resonance imaging
MSM	Men who have sex with men
OP	Outpatient visit
QALY	Quality-Adjusted Life Year, a measure that combines two dimensions of health - length of life and quality of life
SCB	Statistics Sweden
SIR-model	An epidemiologic model often used when simulating infectious diseases in which individuals move between different health states (Susceptible, Infected, and Recovered) depending on the risk of disease

Glossary

Deterministic model	The values of the parameters in the model are pre-determined and thus not dependent on statistical likelihood functions
Dominant	Results from a health economic analysis (cost-effectiveness analysis) that imply that the investigated intervention has a better health effect at a lower cost compared to another intervention
Herd immunity	When a portion of a population is immunized against an infectious disease, unvaccinated members of the community may also be protected against the disease due to a reduction in transmission of the infection.
Incidence	Number of new cases of a disease in a population during a specific time period
Prevalence	Number of cases of a certain disease in a population at a given time

Summary

Vaccination against human papilloma virus (HPV) is currently included in the Swedish national vaccination programme for children, and offered to girls free of charge through the school health care service. Boys can receive HPV vaccinations through their primary health clinic, at their own expense.

This report presents a health economic evaluation of an introduction of universal HPV vaccination (for both boys and girls) in Sweden. Universal HPV vaccination would imply a cost of about 375,000 SEK per gained QALY compared to only vaccinating girls. The results from the analysis are in line with results from similar evaluations from comparable countries. If the price of the vaccine was about 85% lower than today's list price, similar to the 2017 procurement price of Gardasil 4 in Sweden, the introduction of universal vaccination would imply an increase in costs of about 12 million SEK annually, compared to only vaccinating females. In addition, the added cost of school nurses administrating the vaccine would be about 5.6 million SEK annually.

The health economic analysis compared health effects and costs of an introduction of universal HPV vaccination compared to a situation where only girls are being vaccinated. The model used is a so-called extended SIR-model, with a time horizon of 100 years. The analysis takes herd-immunity into account. Costs are made up of direct costs for vaccine and resource use within the healthcare sector and indirect costs in the form of productivity losses. The results are also presented without the inclusion of indirect costs.

This health economic analysis is part of the knowledge base that the Public Health Agency of Sweden accounts for when proposing changes in the national vaccination programme to the government.

Svensk sammanfattning

I denna rapport presenteras en hälsoekonomisk analys av att introducera HPV-vaccination för pojkar i det nationella allmänna vaccinationsprogrammet för barn. HPV-vaccination för flickor ingår redan i programmet.

Den hälsoekonomiska analysen visar att ett införande av HPV-vaccination av pojkar skulle leda till en kostnad om ungefär 375 000 kronor per vunnet QALY, i jämförelse med att endast vaccinera flickor. Om priset för vaccinet vore ungefär 85 procent lägre än dagens listpris, vilket är det upphandlade priset i Stockholms läns landsting 2017, skulle vaccination av pojkar kosta ungefär 12 miljoner kronor per år. Det skulle även tillkomma en årlig kostnad på ungefär 5,6 miljoner kronor för administrering av vaccinet.

Den hälsoekonomiska analysen jämförde hälsoeffekter och kostnader av vaccination av både pojkar och flickor jämfört med att endast vaccinera flickor. Modellen som användes var en så kallad utökad SIR-modell, med en tidshorisont på hundra år. Analysen tog hänsyn till flockimmunitet som uppstår till följd av vaccination. Kostnader utgörs av direkta kostnader för vaccin och resursutnyttjande inom hälso- och sjukvården, samt indirekta kostnader i form av produktionsförluster vid sjukdom. Resultaten presenteras även utan medräkning av indirekta kostnader.

Den hälsoekonomiska analysen ingår i kunskapsunderlaget som tagits fram av Folkhälsomyndigheten för att bedöma om HPV-vaccination för pojkar uppfyller smittskyddslagens kriterier för kunna omfattas av nationellt vaccinationsprogram.

Background

Human papilloma virus

Infections with human papilloma virus (HPV) are common in humans, and it is considered the most prevalent sexually transmitted infection in both men and women (1, 2). HPV infects the basal epithelial cells of the skin and mucosa of the anogenital and upper aero-digestive tract (3). Over 200 types of HPV have been identified (4) of which 40 types are known to be sexually transmitted (5).

Over 90% of HPV infections are transient and are cleared within 1–2 years (6), but some infections persist and may cause a range of clinical states, including anogenital warts, precancerous lesions, and cancer (7).

HPV types are assigned numbers and are often categorized as “low risk” or “high risk” based on the association of that HPV type with cervical cancer, by far the most dominant HPV-associated cancer form (8). There are 13 high-risk HPV types (3) that in addition to causing cervical cancer also cause other cancer in the anogenital region, such as cancer of the vagina, vulva, anus, and penis as well as in the oropharyngeal region, predominantly tonsillar and base of tongue cancer. HPV types 16 and 18 cause around 70% of cervical cancer, and non-cervical HPV-associated cancer is mainly caused by HPV 16 (8, 9). Low-risk HPV types have not been associated with cancer but may cause other diseases; for example, HPV 6 and HPV 11 cause genital warts (condyloma acuminate) and recurrent respiratory papillomatosis (RRP) (10, 11).

In Sweden the incidence of anal cancer is currently more than three times higher in women than in men (14), and for oropharyngeal cancer it is the opposite situation with almost three times higher incidence in men (15, 16). The incidence of cervical cancer peaks between 35 and 45 years of age, while for the other HPV-associated cancers the peak is generally considerably higher and occurs after 60 years of age (17). Sweden has had a highly effective cervical screening programme since the 1960s, and a study has shown that in the absence of screening, the Nordic countries would be experiencing incidence rates on par with the high incidence rates in low-income countries (13).

Vaccines against HPV

Vaccines against HPV are prophylactic non-live vaccines and contain purified virus-like particles (VLPs) of the recombinant major (L1) capsid protein of different HPV types. Three different HPV vaccines have been developed so far – a bivalent vaccine containing HPV 16 and 18 (Cervarix®), a quadrivalent vaccine containing HPV 6, 11, 16, and 18 (Gardasil® also marketed as Silgard®) and a nonavalent vaccine containing HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 (Gardasil 9®).

The first HPV vaccine was approved for use and available in Sweden in 2006. In 2007 the vaccine was subsidized for girls 13–17 years of age. The subsidy was later extended to 26 years of age.

Vaccination programmes

In 2008 the National Board of Health and Welfare (NBHW) recommended including vaccination against HPV for all girls aged 10–12 years in the national vaccination programme, starting in 2010 with girls born in 1999 (25). However, due to procurement issues, the actual implementation was delayed until 2012. According to an update of the regulation of child vaccinations (HSLF-FS 2016:51), all girls should now be offered HPV vaccinations up to age 18. When the national vaccination programme started, the coverage reached around 80% and has been stable around this level since then. This is comparable to other Nordic countries (Figure 1), except notably in Denmark, where coverage has recently dropped dramatically due to fear of severe adverse events (26).

A few countries have implemented universal vaccination programmes against HPV, including Australia, Austria, Barbados, Canada, Israel, USA, Switzerland and Liechtenstein. Argentina and the UK have implemented risk-group vaccination programmes and offer HPV vaccination to MSM in their national programmes. Among the Nordic countries, only Norway has decided to include males, and universal vaccination within the national vaccination programme is planned to start in 2018.

Health economic model

We developed a health economic model to assess the consequences of including vaccination of boys against HPV in the national vaccination programme for children in Sweden.

Parameter estimates in the model are mainly based on the knowledge base that has been developed within the framework of this evaluation (20), as well as national guidelines. Where published data were missing, assumptions from clinical expertise have been used.

The model

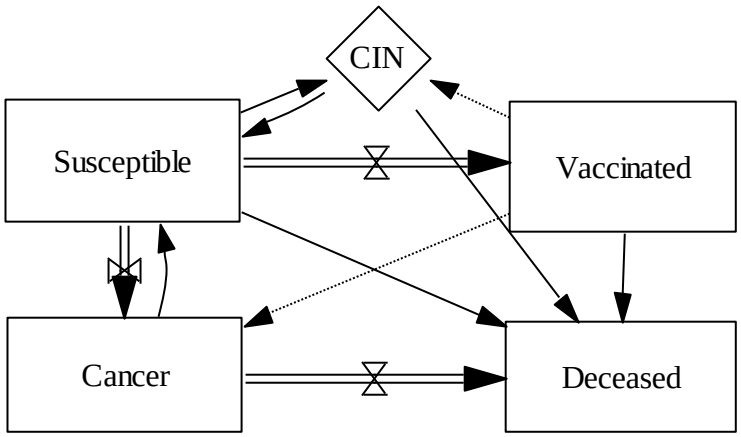
The epidemiological model used in the health economic analysis was developed in the software program Vensim, with data extracted to Excel for health economic calculations. The model was a so-called extended SIR (susceptible, infected, recovered) model, in which individuals moved between different health states depending on the risk of disease, which was sex and age group specific. The flow between health-states is illustrated in Figure 1 Quality of life weights and costs of treatment were linked to each of the health states.

Two models were created, one for males and one for females, and the models affected each other through herd immunity. The models were in turn divided into eight sub models, where each sub model corresponded to one age group[1], and had the same structure as in Figure 1. Movement between the sub models occurred annually and was decided depending on the age structure of the age group – e.g. a tenth (1/10) of the individuals in the age group 10-19 moved on to the age group 20-29 each year (starting in t=10).

To include all relevant effects of the vaccination, the time horizon was set to 100 years, because some of the diseases that can arise as a consequence of HPV-infection occur decades after the time of infection (21). The cycle length was one year. Both health effects and costs were discounted by 3% annually, according to the general advice for health economic evaluations (21). Results are also presented without discounting, which is recommended in a European standard for health economic analyses of vaccination programmes (22).

[1] 10-19, 20-29, 30-39, 40-49, 50-59, 60-69, 70-84, 85+ years

Figure 1. Flowchart of the model



At the start of the model, the individuals enter the model in the health state of susceptible, and depending on the vaccination coverage, a proportion move on to the health state of vaccinated. Those who were vaccinated receive protection against infection corresponding to the effectiveness of the vaccine. The health state of cancer in Figure 1 represents all six different HPV-associated cancer types: cervical, vaginal, vulvar, anal, and oropharyngeal for females and penile, anal and oropharyngeal for males. In addition, each cancer type was divided into a number of health states depending on the severity of the disease. In the females´ model, precancerous cervical lesions, CIN (cervical intraepithelial neoplasia), were included. Each of the diseases was modelled separately, with separate effects of vaccination and burden of disease. In a share of the vaccinated individuals, the vaccine had no effect on cancer or CIN, and these are so-called non-responders. This could be due to cancer caused by an HPV-type that is not included in the vaccine, and this is illustrated by the dotted lines in the flowchart.

Individuals could move from one health state to another, stay in the same health state, or die – either as a consequence of cancer, or due to natural mortality in the population – in each model cycle. If an individual developed cancer and survived, he or she was assumed to stay in that health state for 5 years, before returning to the health state of susceptible.

The inflow in the model was based on a 2015 birth cohort. The outflow was either through cancer-related death or natural mortality. Because individuals entered the model at age 10, the age group 20-29 was unpopulated during the model's first 10 years, the age group 30-39 during the first 20 years, and so on.

Parameters and assumptions used in the model

Incidence

The model simulated HPV-associated cancer and CIN, because we have data on how much of these types of disease is caused by HPV infection. Data on the prevalence of HPV-infection in the population, however, are very limited.

To calculate the risk of HPV-associated cancer and CIN, we first extracted the average number of all cases of cervical, vaginal, vulvar, penile, anal and oropharyngeal cancer and CIN, by age group and sex, for the years 2010-2014 from the National Cancer registry (Table 1) (23, 24). We then estimated the proportion of cases that could be attributed to HPV, and thus be affected by vaccination (Table 2).

Table 1. Average number of cases 2010-2014, attributed to HPV, by age group and sex

	CIN	Cervical cancer	Vaginal cancer	Vulvar cancer	Anal cancer		Oropharyngeal cancer		Penile cancer
Age group	Female	Female	Female	Female	Female	Male	Female	Male	Male
0-19	82.2	0.6	0.6	0.2	0.0	0.0	0.0	0.2	0.0
20-29	7 519.5	43.0	0.0	0.5	0.2	0.2	0.0	0.0	0.1
30-39	4 964.4	112.8	0.5	0.5	1.1	0.5	0.7	1.0	0.8
40-49	2 690.1	104.8	1.6	3.4	4.9	1.8	5.8	16.4	1.7
50-59	969.3	57.8	2.0	5.7	20.9	8.1	18.7	56.1	6.1
60-69	361.0	57.0	5.6	5.4	29.0	13.2	27.8	70.2	14.4
70-84	119.0	75.2	9.5	9.1	29.0	13.9	14.2	33.7	17.4
85+	19.0	23.0	4.4	5.1	9.9	2.5	2.5	2.8	5.9

Table 2. Proportion of cases due to HPV (all types)

Health outcomes	Proportion of cases due to HPV (all types)	Source
CIN I	71.1%	(25)
CIN II	86.9%	(26)
CIN III	79%	(27)
Cervical cancer	100%	(28)
Vaginal cancer	78%	(28)
Vulvar cancer		
15-54 years	48%	(28)
55-64 years	28%	(28)
65+ years	15%	(28)
Anal cancer	88%	(28)
Tonsil and base of tongue cancer	74%	(29)
Penile cancer	51%	(28)

Distribution at diagnosis

The different cancer diseases and CIN were divided into two or three severity-states depending on the severity of disease. The definition of these severity-states, from here on denoted as A, B and C, where A is the least severe state and C the

most severe state, is presented in Table 3 below. Table 4 shows the distribution in the model at diagnosis, dependent on the age of the patient.

Table 3. Definition of severity states

	A	B	C	Source
CIN	I	II	III	Expert opinion
Cervical cancer	1A+1B*	2*	3+*	Expert opinion
Vaginal cancer	1A+1B*	2	3+	Expert opinion
Vulvar cancer	1A+1B*	2	3+	Expert opinion
Penile cancer	Non-invasive, without lymph node metastasis	Invasive, without lymph node metastasis	With lymph node metastasis	(30) + Expert opinion
Anal cancer	-	T1-T2 (<4cm)N+M0**	T2(>4cm)-T4N0/N+M0**	Expert opinion
Oropharyngeal cancer	-	I+II	III+IV	Expert opinion

*Based on FIGO staging, **Based on TNM staging

Table 4. Distribution of cases by severity-state at diagnosis, depending on age, by disease and sex

	Age at diagnosis<50 years			Age at diagnosis>50 years			Source
	A	B	C	A	B	C	
CIN	35%	34%	32%	44%	27%	30%	(24)
Cervical cancer	82%	12%	6%	40%	25%	35%	Expert opinion
Vaginal cancer	40%	20%	40%	31%	27%	41%	(23)
Vulvar cancer	66%	19%	15%	35%	31%	33%	(23)
Penile cancer	54%	32%	14%	32%	53%	15%	(31)
Anal cancer	-	25%	75%	-	25%	75%	Expert opinion
Oropharyngeal cancer							
Males	-	10%	90%	-	13%	87%	(32)
Females	-	13%	87%	-	13%	87%	(32)

Five-year relative survival

We estimated the 5-year relative survival, dependent on cancer type, age at diagnosis and severity state (Table 5).

Table 5. 5-year relative survival by cancer type, age at diagnosis and severity state

	Age at diagnosis<50 years			Age at diagnosis>50 years			Source
	A	B	C	A	B	C	
Cervical cancer	94%	72%	38%	84%	54%	24%	Expert opinion
Vaginal cancer	31%	33%	18%	31%	33%	18%	(23)
Vulvar cancer	45%	33%	18%	45%	33%	18%	(23)
Penile cancer	98%	94%	46%	99%	81%	46%	(31)
Anal cancer	-	75%	60%	-	75%	60%	Expert opinion
Oropharyngeal cancer	-	88%	66%	-	86%	68%	Expert opinion

Vaccination coverage

The health economic analysis compared a situation with universal vaccination to a situation where only females are being vaccinated. Because individuals entered the model when they were 10 years old, we assumed that they were not yet sexually active, and thus had not been infected with HPV. We also assumed that the whole population entering the model was unvaccinated. Thus, all of the individuals in the model were eligible for vaccination, and the inflow in the model was therefore one birth cohort.

We assumed a vaccination coverage of about 80% among males, which is similar to that of females in Sweden since the start of the vaccination programme against HPV (33).

Vaccine effectiveness

The vaccine effectiveness in the model is HPV-type specific, and vaccination was assumed to provide life-long protection. We assumed that the vaccine is 100% effective against HPV types 16 and 18, i.e. everyone that was vaccinated developed protective antibody levels against HPV 16 and 18, while the total vaccine effectiveness against each HPV-associated cancer or CIN is dependent on the proportion that is due to HPV 16 and 18 (Table 6).

Table 6. Vaccine effectiveness applied in model, dependent on disease

Disease	Proportion related to HPV 16 and 18	Source
CIN I	26%	(5, 25)
CIN II	43%	(5, 26)
CIN III	61%	(5, 27)
Cervical cancer	70%	(5, 28)
Vaginal cancer	55%	(34)
Vulvar cancer	54%	(35)
Anal cancer	84%	(28, 36)
Tonsil and base of tongue cancer	60%	(29, 34)
Penile cancer	48%	(28, 34)

Herd immunity

To account for the changes in HPV prevalence in the population due to HPV vaccination, we applied a method earlier used by Chesson et al (37), where an adjustment term is applied to the probability of acquiring an HPV-infection and ultimately developing HPV-associated cancer or CIN. The risk of HPV-associated cancer was calculated as $\varphi_{k,a,t} = P_{k,a}\left(1 - A_{k,a,t}\right)$, where $P_{k,a}$ is the age and sex-specific risk of HPV-associated cancer or CIN in the absence of vaccination, and $A_{k,a,t}$ is the adjustment term to account for changes in HPV prevalence in the population due to HPV vaccination. The adjustment term was calculated based on data from a previously published study (38). We assumed an 80% vaccination coverage among 10-25 year-olds, 20% among 26-49 year-olds, and no vaccination

in older age groups, in line with unpublished analyses of vaccination registries. The reduction in cumulative exposure was calculated as $C = 1 - (\hat{e}_{k,a,t}/e_{k,a,t})$, where $e_{k,a,t}$ is the cumulative exposure to HPV for sex k at age a years at time t in the absence of a vaccination programme, and $\hat{e}_{k,a,t}$ is the cumulative exposure to HPV for sex k at age a in years in year t of the vaccination programme.

The adjustment term was calculated as $A = (1 - \varepsilon)\dot{C}_{k',a,t} + \varepsilon\hat{C}_{k',a,t}$, where $\dot{C}_{k',a,t}$ is the average value of C for those of the opposite sex within 10 years of age, whereas $\hat{C}_{k',a,t}$ is the average value of C for the whole population of the opposite sex. The term Ɛ reflects the sexual mixing patterns in the population. We assumed that Ɛ was equal to 10%, implying that 90% of the individuals in the population have sexual contacts within 10 years of their own age (39).

In the model, the proportion of the male population that are men who have sex with men (MSM) were not protected by herd immunity from vaccinating girls. In line with previous reports from our agency, we assume that 2.5% of men are MSM (40).

Resource use

The vaccine is given in two doses, and we assumed that a school nurse would have to spend 15 minutes on each dose. The total cost of vaccination included both the price for two doses of the vaccine as well as the average costs for 30 minutes of a school nurses work day.

Resource use for cancer and CIN in the analysis was dependent on cancer type and severity state. Resource use for the first 5 years after diagnosis was extracted from national guidelines or based on expert opinion (Table7).

Table 7. Resource use (number of visits) during the first five years after diagnosis, divided by severity state

Year	1					2			3		4		5	
Type of visit	**IP**	**OP**	**PET-CT**	**MRI**	**Cytostatic**	**IP**	**OP**	**X-ray**	**IP**	**OP**	**IP**	**OP**	**IP**	**OP**
CIN														
1	0	3	0	0	0	0	1	0	0	1	0	0	0	0
2	0	3	0	0	0	0	1	0	0	1	0	0	0	0
3	0	3	0	0	0	0	1	0	0	1	0	0	0	0
Cervical cancer														
A	2	5	1	1	0	0	2	0	0	2	0	1	0	1
B	2	5	2	2	0	0	2	0	0	2	0	1	0	1
C	6.5	9	2	2	5	0	2	0	0	2	0	1	0	1
Vaginal cancer														
A	1	7	0	0	0	0	2	0	0	1	0	1	0	1
B	1.5	6	0	1	0	0	2	0	0	1	0	1	0	1
C	1.5	6	0	1	0	0	2	0	0	1	0	1	0	1
Vulvar cancer														
A	1	7	0	0	0	0	2	0	0	1	0	1	0	1
B	1.5	6	0	1	0	0	2	0	0	1	0	1	0	1
C	1.5	6	0	1	0	0	2	0	0	1	0	1	0	1
Penile cancer														
A	1	6	0	0	0	0	4	0	0	2	0	2	0	2
B	1	6	0	0	0	0	4	0	0	2	0	2	0	2
C	1	6	2	0	0	0	4	0	0	2	0	2	0	2
Anal cancer														
A	1.5	8	0	0	1	0	3.5	0	0	2	0	2	0	2
B	2.5	8	0	0	2	0	3.5	0	0	2	0	2	0	2
Oropharyngeal cancer														
A	2	8	0	1	0	0	4	1	0	2.5	0	2.5	0	2.5
B	2.5	12	0	1	6	0	4	1	0	2.5	0	2.5	0	2.5

IP: inpatient care. OP: outpatient visit. PET-CT: positron emission tomography–computed tomography. MRI: magnetic resonance imaging.

Costs

Direct costs

Costs were extracted from the KPP database (cost per patient) from 2014 and 2015, and the table below shows the ICD-10 codes that were used (Table 8). We used the average of 2014 and 2015 when we were able to, and if there were no observations for one of the years we chose the year that had data. The costs of the vaccine and medical resources were taken from Apoteket.se. The cost per dose of the vaccine was set to 852 SEK in the base-case analysis.

Table 8. Average cost per visit in the health care sector, in SEK

	Average cost per visit	
Disease	**Inpatient care**	**Outpatient visits**
CIN	38,176	4,146
Cervical cancer	52,705	3,121
Vaginal cancer	42,449	3,882
Vulvar cancer	58,427	3,231
Penile cancer	63,805	2,631
Anal cancer	76,000	3,660
Oropharyngeal cancer	52,818	3,065

Indirect costs

The health economic analysis had a societal perspective in the base-case analysis, implying that indirect costs were included in the analysis in the form of productivity losses in case of illness. In the analysis, it was assumed that 90% of the population between the ages of 20 and 65 were working.

The cost of productivity losses was calculated based on the average monthly salary in 2014 of 31,400 SEK (41) and the statutory employers' fee of 31.42% (42). This inferred a productivity loss of 41,266 SEK per month, or 1,769 SEK per working day. The length of the productivity loss in the model was dependent on disease and on the severity state. We used data from the Swedish Social Insurance Agency for the length of sick leave due to tumours (43). In the model, those with severity state A were assumed to be part of the lowest 25th percentile, those in severity state B were assumed to be the median, and those in severity state C were assumed to be the highest 25th percentile (Table 9). People with CIN were assumed to have no sick leave due to the disease, thus only productivity losses due to outpatient visits were calculated.

The assumed length of sick leave with the associated costs is presented in Table 9. We also included cost per outpatient visits, calculated as hours lost in productivity (Table 10).

Table 9. Indirect costs due to treatment by severity state

Group	**A (25th percentile)**	**B (median)**	**C (75th percentile)**
Absence from work (working days)	23 working days	56 working days	209 working days
Costs (SEK)	44,915	110,885	411,255

Table 10. Indirect costs (in SEK) per outpatient visit by disease and severity state.

	Health state		
	A	B	C
CIN	737	737	737
Cervical cancer	1,228	1,228	2,211
Vaginal cancer	1,719	1,474	1,474
Vulvar cancer	1,719	1,474	1,474
Penile cancer	1,474	1,474	1,474
Anal cancer		1,965	1,965
Oropharyngeal cancer		1,965	2,948

Health related quality of life

Table 11 below presents the QALY-weights used in the model for the respective disease and severity state. Because the modelled cohorts reflected the general population, we have assumed that everyone was healthy in the population unless they have HPV-associated cancer or CIN. Thus, they were assumed to have full health, corresponding to a QALY weight of 1 in the susceptible and vaccinated health states of the model.

Table 11. QALY-weights used in the model, by disease and severity state

	QALY-weight used in model	Source
Healthy	1.00	Assumption
CIN		
1	0.93	(44)
2	0.86	(44, 45)
3	0.86	(44, 45)
Cervical cancer		
A	0.76	(44)
B	0.67	(44)
C	0.48	(44)
Vaginal cancer		
A	0.64	(46)
B	0.59	(46)
C	0.54	(46)
Vulvar cancer		
A	0.70	(46)
B	0.65	(46)
C	0.60	(46)
Penile cancer		
A	0.84	(46)
B	0.79	(46)
C	0.74	(46)
Anal cancer		
A	0.57	(46)
B	0.52	(46)
Oropharyngeal cancer		
A	0.58	(46)
B	0.53	(46)
Deceased	0.00	Assumption

Results

We conducted a health economic evaluation of introducing a universal HPV vaccination programme in Sweden, compared to only vaccinating females. The results are valid given the parameters and assumptions that have been presented in previous sections.

Base-case analysis

The introduction of universal HPV-vaccination in the national vaccination programme for children in Sweden would imply an increase in costs of about 2 billion SEK over 100 years. This is mainly due to the increased costs of vaccination that occurs immediately after an introduction of a universal programme, while the positive effects of vaccination, in the form of reduced resource use in the health care sector due to reduced burden of disease, occur many years after the time of infection.

A universal vaccination programme would also lead to about 5,600 gained QALYs. This implies a cost per gained QALY of about 375,000 SEK (Table 12).

Table 12. Results from the base-case analysis, with inclusion of indirect costs

	No vaccination	Vaccination	Difference
Cost of vaccine	- SEK	2,818,335,907 SEK	2,818,335,907 SEK
Direct costs	1,114,785,793 SEK	541,078,299 SEK	-573,707,495 SEK
Indirect costs	279,233,855 SEK	137,167,643 SEK	- 142,066,212 SEK
Total costs	1,394,019,648 SEK	3,496,581,848 SEK	2,102,562,200 SEK
QALY	62,399 875	62,405,479	5,604
ICER (incremental cost-effectiveness ratio)			**375,163 SEK**

In Table 13 below, the results from the base-case analysis are presented without the inclusion of indirect costs. The cost per gained QALY increased slightly, to about 400,000 SEK, because the decrease in productivity losses as a consequence of a decreased burden of disease were not accounted for.

Table 13. Results from the base-case analysis, without the inclusion of indirect costs

	No vaccination	Vaccination	Difference
Cost of vaccine	- SEK	2,818,335,907 SEK	2,818,335,907 SEK
Direct costs	1,114,785,793 SEK	541,078 299 SEK	-573,707,495 SEK
Total costs	1,114,785,793 SEK	3,359,414,206 SEK	2,244,628,412 SEK
QALY	62,399,875	62,405,479	5,604
ICER (incremental cost-effectiveness ratio)			**400,512 SEK**

Sub-analysis: Inclusion of genital warts

One of the vaccines against HPV that is available on the Swedish market provides protection against HPV 6 and 11 in addition to HPV 16 and 18. HPV causes about 94% of all genital warts, of which HPV 6 and 11 are responsible for 90%.

Therefore, we also conducted a sub-analysis that, in addition to cancer and CIN, included the effect of vaccination on HPV-associated genital warts. The flowchart of the transmission model in which we modelled genital warts was similar to that described in the section above (Figure 1), with the same assumptions regarding population, herd immunity, and vaccination coverage. The number of cases of genital warts and assumptions of the model are listed in Table 14 and Table 15 below.

Table 14. Average number of cases of genital warts per year, dependent on age group and sex (2006-2010)

	Sex		
Age group	**Females**	**Males**	**Source**
0-19	766	311	(47)
20-29	4,714	6,283	(47)
30-39	1,214	2,071	(47)
40-49	663	766	(47)
50-59	219	285	Assumption
60-69	74	105	Assumption
70-84	21	32	Assumption
85+	2	2	Assumption

Table 15. Parameters and assumptions in the sub-analysis

		Source
Vaccination coverage	80%	Assumption
Vaccine effectiveness	90%	(48)
Share of genital warts attributable to HPV infection	94%	(48)
Cost of treatment	2,401 SEK	(49)
Indirect cost	221 SEK	Assumption
QALY-weight	0,93	(44)

The results from the sub-analysis are presented in Table 16 below. When the effect of the vaccine on the incidence of genital warts was included, the cost per gained QALY decreased to 290,000 SEK. The decrease was a consequence of decreased differences in total costs and an increase in the number of gained QALYs.

Table 16. Results, sub-analysis with the inclusion of genital warts

	No vaccination	**Vaccination**	**Difference**
Cost of vaccine	- SEK	2,818,335,907 SEK	2,818,335,907 SEK
Direct costs	1,594,721,987 SEK	705,851,413 SEK	- 888,870,574 SEK
Indirect costs	359,352,959 SEK	169,263,287 SEK	- 190,089,672 SEK
Total costs	1,954,074,945 SEK	3,693,450,607 SEK	1,739,375,662 SEK
QALY	62,399,875	62,405,888	6,013
ICER			**289,247 SEK**

Sensitivity analyses

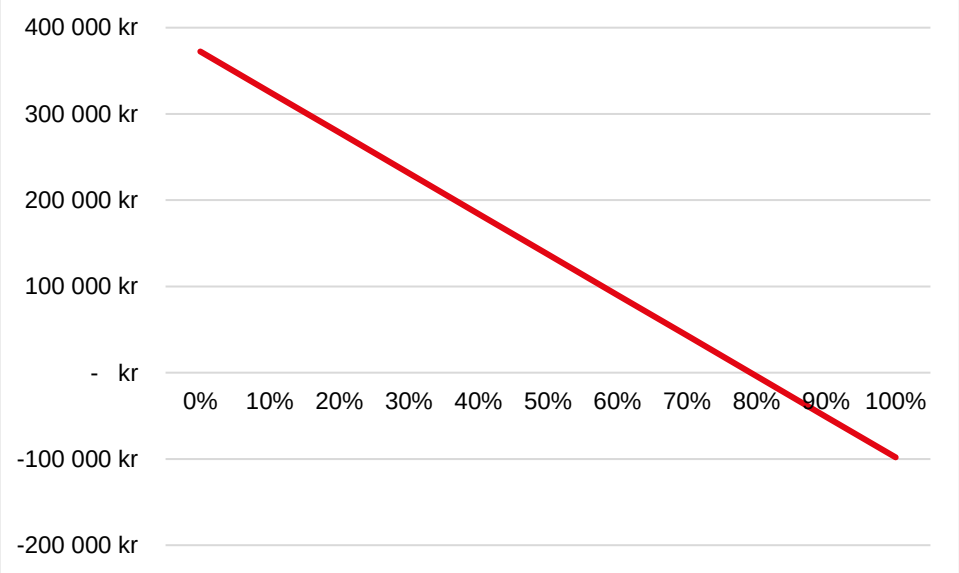
In order to investigate the robustness of the results from the base-case analysis, we conducted several sensitivity analyses. What appears to have the greatest impact on the results are assumptions about the discount rate and time horizon, and what diseases are included in the analysis.

The following parameters were varied in the sensitivity analyses:

1. Price of the vaccine
2. Vaccination coverage
3. Risk of infection
4. Effect of the vaccine
5. Time horizon
6. Discount rate

To take into account the potential rebates that can be negotiated between county councils and vaccine producers, so-called procurement prices, we conducted a sensitivity analysis where we demonstrate the effect of the vaccine price on the cost per gained QALY (ICER), given the assumptions made in the model. This is presented in Figure 22 below, where the values on the X-axis are the rebate of the original list price expressed as a percentage. The cost per gained QALY decreases by about 50,000 SEK for each 10% increase in the rebate on the vaccine price. When only 20% of the list price remains, a universal vaccination programme appears to be a dominant strategy, i.e. it has a better health effect at a lower cost compared to only vaccinating females.

Figure 2. Cost per gained QALY as the price of vaccine changes



The results from the sensitivity analyses are presented in Table 17 below. The results are not greatly affected by a decrease in vaccination coverage among males because the cost of the vaccine decreases at the same time as the effect on resource

use decreases, i.e. the two effects work in opposite directions. However, if the vaccination coverage among females were to decrease, the herd immunity from universal vaccination would make male vaccination more efficacious. The chosen discount rate also has a significant impact on the results as a consequence of the long time horizon.

Table 17. Results from sensitivity analyses

Variable(s) varied	Difference in cost	Difference in QALY	ICER
Base-case analysis	2,102,562,200 SEK	5,604	375,163 SEK
Discount rate (health effects): 0 %	2,102,562,200 SEK	30,720	69,536 SEK
Discount rate (health effects and costs): 0 %	4,337,855,885 SEK	30,720	143,462 SEK
Time horizon 50 years	1,967,637,393 SEK	3,005	654,881 SEK
Excluding the effect on CIN (1, 2, and 3)	2,515,622,548 SEK	1,485	1,694,140 SEK
50 % vaccination coverage, males	1,327,669,638 SEK	3,111	426,734 SEK
50 % vaccination coverage, females	1,123,557,542 SEK	14,035	80,052 SEK
50 % vaccination coverage, all sexes	894,186,673 SEK	6,251	143,055 SEK

We did not conduct a sensitivity analysis on the effect of the vaccine. Nevertheless, an increase in the vaccine effectiveness (through, for instance, cross protection of the vaccine against other HPV-types than 16 and 18 or through including more HPV-types in the vaccine), given the same price of the vaccine, would lead to more favourable results from the cost-effectiveness analysis.

Budget impact

The budget impact is presented as costs during the first year following an introduction of universal HPV vaccination in the national vaccination programme for children in Sweden. In other words, the added costs of vaccinating males.

Because many of the positive effects of the vaccine will not occur until many years after the introduction of the vaccine, cost savings in the form of decreased burden of disease are not presented in this section. The introduction of universal vaccination would imply an increase in costs of about 81 million SEK compared to only vaccinating females. This is based on the assumptions in the base-case analysis, i.e. vaccination coverage among males of 80% and the list price of the vaccine, without the additional cost of administrating the vaccine.

If the price of the vaccine was about 85% lower than today's list price, similar to the 2017 procurement price of Gardasil 4 in Sweden (50), the introduction of universal vaccination would imply an increase in costs of about 12 million SEK annually, compared to only vaccinating females.

In addition, the added cost of school nurses administrating the vaccine would be about 5.6 million SEK annually.

Discussion

We have conducted a health economic analysis of introducing universal HPV-vaccination in the national vaccination programme for children in Sweden in comparison to vaccinating only females. The national HPV-vaccination programme aims to decrease HPV-associated cancer in the population, and the model therefore focused on cancer and precancerous lesions of cervical cancer (CIN). The results from the base-case analysis suggests that the cost per gained QALY by introducing universal HPV vaccination would be about 375,000 SEK. The results are mostly affected by assumptions regarding which diseases that are included in the model, the discount rate, and the price of the vaccine.

There is as of yet no health economic data from implemented universal HPV-vaccination programs, since only a few countries have recently started implementation (such as Australia, Italy and Canada). Among the Nordic countries, only Norway has decided to include HPV-vaccination in the national program, and implementation will start in 2018. Therefore, the decision to introduce HPV-vaccine into national programmes is most often based (together with other criteria) on health economic evaluations like the one presented in this report.

There is a large degree of uncertainty in several of the assumptions in the analysis, especially regarding future vaccination coverage among both males and females, and the proportion attributable to HPV types 16 and 18, and the price of the vaccine following procurement. As is evident from the sensitivity analyses, these assumptions have a large impact on the results. The results that are presented in the base case analysis were based on available data and expert opinion and thus the most realistic outcome. Nevertheless, as in all economic analyses of the costs and benefits of introducing vaccines, the results are dependent on the assumptions that are made and the data that are available.

A systematic review of economic evaluations of HPV vaccination that included both cervical and non-cervical HPV-associated disease has recently been published (51). The review included 18 studies, out of which 14 had a similar approach to ours: dynamic transmission model taking herd immunity into account. Only two studies explicitly reported the transmission of HPV-infection among MSM. Six of the studies had a time horizon of 100 years or longer. Five of the studies were conducted from a societal perspective, but the included indirect costs varied between studies and sometimes included much more detailed calculations than our analysis, which was based on productivity losses. Sixteen of the studies used QALY-weights to measure health effects, whereas the remaining two had a disability-adjusted life years (DALY) approach. The results from the analyses varied due to assumptions in the models.

The comparison also varied between the studies. Eight of them compared universal vaccination to only vaccinating females, which is in line with our analysis. Of these, and as expected, analyses that included more HPV-associated diseases had a lower ICER than analyses only including cervical cancer. The ICERs of the

analyses that included all HPV-associated diseases ranged between 13,700 euro and 261,866 euro, with an average of approximately 50,000 euros, which is in line with the results from our analysis, with an exchange rate of 100 SEK=9,67 EUR. The single parameter that had the greatest influence on the results in the analyses, was the expected price of the vaccine (51).

This is the first health economic evaluation of universal HPV-vaccination that has been conducted in Sweden. The results from the analysis are in line with results from similar evaluations from countries that are more or less comparable to the Swedish setting. We conclude that the results are the most reasonable outcome of an introduction of universal HPV vaccination in the Swedish vaccination programme for children.

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Appendix 1. Contributing experts

The health economic evaluation has been developed by the following working group:

- Tina Dalianis, professor of tumor virology, Department of Oncology-pathology, Karolinska Institutet
- Miriam Elfström, epidemiologist at the Department of Laboratory Medicine, Karolinska Institutet and operations developer for cancer prevention at the Regional Cancer Center of Stockholm-Gotland
- Hélène Englund, analyst (epidemiologist), Unit for Vaccination Programmes, The Public Health Agency of Sweden
- Hedda Haugen Cange, Senior consultant, Department of Oncology, Sahlgrenska University Hospital
- Adam Roth, analyst (medical doctor), Unit for Vaccination Programmes, The Public Health Agency of Sweden
- Pär Sparén, professor of medical epidemiology, Department of Medical Epidemiology and Biostatistics, Karolinska Institutet
- Ellen Wolff, analyst (health economist), Unit for Epidemiology and Health Economics, The Public Health Agency of Sweden

The following experts were not part of the working group, but have been consulted on specific issues:

- Marie-Louise Lydrup, Senior Consultant, Department of surgery, Skåne University Hospital *(anal cancer)*
- Peter Kirrander, Senior Consultant, Urologic Department, Örebro University hospital *(penis cancer)*

This report describes a health economic evaluation that investigates the potential cost-effectiveness of an extension of the national vaccination programme for children against human papilloma virus to also include boys.

The main target group for this publication is the government of Sweden (the Ministry of Health and Social Affairs). It could also be of interest for health professionals, foreign ministries of health, and public health institutions contemplating universal vaccination programmes against HPV.

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