

Background to
a vaccination programme
for the human papilloma
virus in Sweden 2007

Socialstyrelsen klassificerar sin utgivning i olika dokumenttyper. Detta är *Underlag för rekommendationer*. Det innebär att den innehåller strategidokument från Tillsynsavdelningens smittskydds-enhet som utgör underlag för nationella och regionala handlingsplaner. Socialstyrelsen svarar för innehåll och slutsatser.

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Förord

Det första HPV vaccinet godkändes för försäljning i Sverige hösten 2006. Möjligheten att med vaccination skydda kvinnor mot livmoderhalscancer krävde bedömning av många av de myndigheter som arbetar med de svenska vaccinationsprogrammen. Dessa inledde därför utifrån sina uppdrag och mandat utredningar av vaccinet och vaccinationseffekt(er). Ytterligare ett vaccin mot HPV försäljningsgodkändes hösten 2007. Läkemiddelsverket och dess motsvarighet på EU nivå, EMEA, har utvärderat vaccinernas effekt och säkerhet samt producenternas uppföljningsprogram efter godkännandet. Smittskyddsinstitutet och dess motsvarande myndighet på EU-nivå, ECDC har analyserat de förväntade medicinska effekterna och vilka övervakningsstrategier som behövs efter introduktion av HPV-vaccin i ett vaccinationsprogram. Läkemiddelsförmånsnämnden har efter ansökan från en av tillverkarna utrett om vaccinet har de effekter som krävs för att samhället ska subventionera det. SBU har utifrån sitt uppdrag utrett kvaliteten av det publicerade vetenskapliga underlaget och vilka slutsatser man kan dra härav.

Socialstyrelsen tillsatte i januari 2007 en expertgrupp, med uppdrag att utarbeta ett kunskapsunderlag till grund för Socialstyrelsens bedömning om och hur HPV vaccination ska kunna inkluderas i barnvaccinationsprogrammet. Deltagarna i expertgruppen finns listade i slutet av dokumentet. De representerar personligen de olika kunskaper som behövs för att på ett allsidigt sätt belysa alla aspekter på sjukdomen, nuvarande profylax, vaccinfrågor och hur ett vaccinationsprogram skulle kunna utformas. Deltagarna har alla tagit del av Socialstyrelsens regler om jäv och lämnat en förteckning över åtaganden som skulle kunna påverka deras arbete med expertrapporten. Förutom de externa experterna ombads SBU att analysera de hälsoekonomiska förutsättningarna och de var därför adjungerade till gruppen.

I utredningen finns en analys av konsekvenserna med att inkludera vaccination i det allmänna eller riktade barnvaccinationsprogrammen utifrån de kriterier som Socialstyrelsen publicerat. Dessutom analyseras hur användningen skulle kunna organiseras på olika samhällsnivåer. Vidare identifieras de förutsättningar som är grunden för bedömningarna. Vikten av uppföljning av ett HPV-vaccinationsprogram beskrivs, även med syfte att säkerställa kunskap om hur förutsättningarna förändras under programmets gång.

Kunskapsunderlaget är en sammanställning av de vetenskapliga data som finns tillgängliga inom experternas respektive ämnesområden, vilka krävs för ett ställningstagande till vaccination mot HPV inom ramen för det nationella vaccinationsprogrammet. I de fall publicerad information varit otillräcklig har även opublicerad information använts som ett komplement. Dokumentet avslutas med en sammanfattning, inkluderande en analys av vilka kunskaper som idag saknas.

Kunskapsunderlaget har enligt Socialstyrelsens önskan skrivits på engelska för att underlätta jämförelser med liknande utredningar i andra länder. För att följa den internationella utvecklingen har också Socialstyrelsen organiserat ett nordiskt/holländskt möte (inga referat från dessa möten ingår i dokumentet).

Anders Tegnell
Enhetschef

Contents

<i>Förord</i>	3
<i>Summary</i>	8
<i>The disease</i>	14
Background and virology	14
Virology of HPV	14
Disease caused by HPV	16
Invasive cancer	16
Cancer in situ tumours.....	19
Diseases caused by benign genital HPV types	20
The screening program	23
Background.....	23
HPV 16- or 18-related diagnoses, procedures within cervical screening and impact of HPV vaccination.....	25
Cost of the burden of diseases caused by HPV6/11/16/18	27
Costs for cancers.....	27
Costs for condyloma	27
Costs for the screening-program.....	28
Summary.....	29
<i>Legal aspects</i>	31
Background	31
Legal basis for introducing the HPV vaccine in the Swedish vaccination programme	31
Legal basis for follow-up and monitoring	31
Reporting of notifiable diseases.....	32
Registers and processing of data.....	32
Summary.....	35
<i>Vaccines</i>	36
Description	36
Efficacy	36
Clinical studies - Gardasil.....	37
Clinical studies - Cervarix	40
Cross protection	42
Duration of protection, need for booster vaccination	43
Safety and simultaneous administration of other vaccines	44
Gardasil.....	44
Cervarix	45
Pregnancy, lactation, contraceptives.....	45
Concomitant administration of other vaccines	45
Summary	46
<i>Modelling Vaccination Effectiveness</i>	50

Dynamic HPV infection model	50
Estimating sexual activity and HPV incidence for Sweden	50
Target age of a general vaccination program	52
Catch-up program - target age groups and sexes	53
Catch-up program of females	53
Catch-up vaccination of HPV-negative women.....	54
Vaccination of males	54
Conclusions	56
<i>Ecology</i>	57
Type replacement	57
Viral escape mutants	58
Attributable proportion/number of healthy women at risk.....	58
Other conceivable effects	58
Altered age at exposure	58
Reduced attendance rate in cervical screening	58
<i>Logistics</i>.....	60
Logistical aspects of a general HPV-immunisation of school children in Sweden	60
Consideration of the optimal age of general vaccination of girls	60
Estimated costs of a vaccination programme in the schools.....	60
Estimate	60
Logistical aspects of a catch-up vaccination programme for girls 13 to 18 years of age.....	61
Proposed strategy.....	61
<i>Health economics</i>.....	63
Review of the health-economics of vaccination.....	63
Costs	63
Cost-effectiveness analysis.....	63
A general economic estimate for Swedish conditions	65
Discussion.....	67
<i>Attitudes</i>.....	70
Investigations on attitudes	70
Safety concerns due to coincidental diseases.....	72
<i>Ethics</i>	73
<i>Monitoring</i>.....	74
Background	74
Monitoring of a vaccination program.....	74
Epidemiologic surveillance of HPV.....	75
HPV disease surveillance	76
Screening for cervical cancer.....	77
Incidence of cancer, cervical and non-cervical.....	77
Incidence of non-cancer forms of disease caused by HPV	78
Incidence or prevalence of HPV infection.....	78

Surveillance of viral strains	79
HPV immunity surveillance.....	79
Vaccination coverage.....	80
Safety monitoring	81
Safety concerns due to coincidental diseases.....	81
Summary	81
<i>International aspects</i>	83
<i>Medlemmar i expertgruppen</i>	84
Externa experter:.....	84
Socialstyrelsen:.....	84
SBU:.....	84

Summary

The following text comprises brief summaries of different aspects of introducing the HPV vaccine in a vaccination program, as described in the chapters below. Questions on lack-of-knowledge are enclosed after some paragraphs, These questions are adapted from those identified by the ECDC in their evaluation of the HPV vaccine to be relevant to the Swedish situation.

What is the effect of the present preventive screening program?

In Sweden 80% of women in the targeted population participate in the preventive cervical cancer screening program and among them the cervical cancer morbidity is low - about 150 cancer cases and some 30 deaths per year. The rest of the cancers occur among women with inadequate screening participation. It is therefore especially important to gain vaccine coverage in these groups before they get infected.

In view of the effects of the screening program, the prevention of cervical cancer has to be seen as an entity, including both screening and vaccination. General vaccination is a long-term strategy and has to be coordinated with maintenance of current screening procedures, which effectively protects already infected women against all HPV types, including those not included in the vaccines.

Lack of knowledge

The following questions should be answered when the effects of a vaccine-programme are monitored:

- What is the long term impact of HPV vaccines on participation in and outcome of screening programmes?
- What is the cost-effectiveness of cervical cancer prevention programmes that include both vaccination and screening, taking into account observed data on screening compliance after vaccination?
- Could screening programmes be modified once an increasing number of girls/women are vaccinated?
- What is the value of HPV testing as a primary screening tool in vaccinated cohorts?

What is the effect of the vaccine?

Both HPV vaccines available in the market demonstrate high protective efficacy (90-100%) in HPV naïve women against HPV 16/18-related cervical cancer, as measured by the surrogate endpoints CIN 2/3 and other relevant histological endpoints. Vaccine efficacy against CIN 2/3 due to HPV 16/18 in the intention-to-treat population, including women already infected with vaccine HPV types, is substantially lower, 44% after 3 years of follow-up after the first vaccine dose. Based on these data it is evident that vaccination

is of greatest value in females not yet exposed to any of the vaccine HPV types. The value for boys remains to be proven and the added value to vaccinate both sexes will probably be low, if high vaccination coverage among girls is attained.

Serologic studies and mathematic modelling in theory supports that duration of protection will be sustained over many years. However, it is currently not possible to determine the exact duration. Both vaccines are well tolerated in all studied age-groups, with no differences in prepubertal girls as compared to young women, nor did the safety profile for Gardasil differ in prepubertal boys. The vaccines are non-live and it is therefore not likely that any major interference with other childhood vaccines given to the teenagers will be demonstrated.

Lack of knowledge

The following questions remain to be answered if the effects of a vaccine-programme should be analysed further:

- Will exposure to an HPV virus after vaccination act as a natural booster?
- What is the role of cell-mediated immunity in the protection generated by the virus-like particle vaccines?
- What fraction of cancer incidence overall will be prevented by vaccinating against HPVs 16 and 18?
- What benefits might vaccination confer on adults who are already sero-positive to vaccine HPV types?
- Does co-administration of HPV vaccines with other vaccines administered to adolescents result in changed immunogenicity of the vaccines or changed side effect profiles?
- What will be the effect of vaccinating boys?
- If a vaccination-program has the effect that women are infected at an older age to what extent will infections cause cancer?

What is the disease burden?

The major disease caused by HPV is cervical cancer, which is mainly (70%) caused by HPV16 and 18. The disease burden is kept at comparatively low levels by the present screening program. Even so, there are on average 450 cases and 150 deaths from cervical cancer per year and an estimated 290 cases and 110 deaths of those are caused by HPV16 and 18.

HPV16/18 also cause a substantial proportion of other anogenital cancers (vulvar, vaginal, penile and anal) as well as oropharyngeal cancer, estimated at 150 cases and 80 deaths per year.

Altogether HPV16/18 is estimated to cause about 440 cases of cancer and about 190 cases of cancer deaths per year.

HPV16/18 is also a major cause of precursors to cervical cancer, causing about 2,600 cases of high-grade dysplasia and >5,000 cases of low-grade cervical lesions per year.

The major disease caused by HPV6 and 11 is condyloma acuminata (genital warts), which affects about 20,000-40,000 subjects each year.

Lack of knowledge

The following questions remain to be answered if the effects of a vaccine-programme should be analysed further:

- Information on the exact proportion of different types of cancers that are caused by HPV 16 and 18 in Sweden
- Information on the exact proportion of precancerous lesions, in particular of the cervix, that are caused by HPV 6/11/16/18 in Sweden
- Information on the overall burden-of-disease of condylomas and recurrent respiratory papillomatosis and the exact proportion of this burden that is caused by vaccine-types of HPV in Sweden.

Assumed health-economic effect

The published health economic studies indicate, on the assumptions made, that HPV vaccination of 12-year old girls may have a cost effectiveness ratio within a wide range around a couple of hundred thousand SEK per LYS and a slightly lower cost per QALY. However, several assumptions are very uncertain. The sensitivity analyses showed that the results were sensitive to vaccine price, vaccination compliance, protective effect of the vaccine and discounting rate.

In Sweden it can be assumed that after a period of 50 years the combination of vaccination against HPV 16 and 18 and Pap smear screening would result in a total of 980 avoided cases of cervical cancer per year. This means that a further 230 cases of cervical cancer are approximately avoided per year compared with today. A third (77) of these cases is expected to correspond to premature deaths. Calculated as life years saved, 77 avoided deaths correspond to approximately 995 saved life years without discounting.

Health improvements achieved today are assumed to have a higher value for citizens than health improvements far into the future. This means that future health improvements have a lower value than those that can be achieved at present, which is calculated by means of discounting. 995 saved life years are equivalent to 191 saved life years at 3 percent discounting.

Lack of knowledge

The following issues remain to be answered if the effects of a vaccine programme should be analysed further (most of these are related to the effect of a vaccine programme):

- Define common quality-of-life scores, in order to be able to compare studies performed in different settings.
- Include other HPV-related diseases (genital warts, other cancers) in cost-effectiveness evaluation models, in order to fully value the impact of vaccination.
- Expand the use of worst case and best case scenarios, which are useful in order to establish the robustness of the underlying assumptions of the models.

Legal aspects

The legal basis for introducing HPV-vaccination in the Swedish child vaccination programme is found in the Swedish Communicable Diseases Act from 2004 and its ordinance. HPV-vaccination could be included in the child vaccination programme in a binding regulation. In order to ensure an effective implementation, regulation SOSFS 2000:1 concerning handling of pharmaceuticals by the healthcare, should be amended to make it possible for nurses, with a certain level of training, to ordinate vaccination against HPV.

Lack of knowledge

The following issue remains to be answered if the effects of a vaccine-programme should be analysed further:

- The legal aspects of the monitoring needs to be further explored to ensure an effective follow-up.

Which target age group?

Taking into consideration the fact that the vaccine should be given before sexual debut and the fact that it seems possible to add more vaccinations within the school health care, it is evident that the age of 10-12 years is the optimal age group corresponding to grades 5 and 6 in the school. This is also the age-span chosen by other countries in their vaccination programs.

What catch-up should be recommended?

While the best effect is achieved by vaccinating children before the start of sexual activities, there is also a protective effect from vaccination in adolescents and young women, as described in the chapter on modelling vaccine effectiveness. As discussed in the text, the value of vaccination is greatest up to the age of eighteen and then falls rapidly. Since vaccination programs are just starting in countries very little experience of the effects is available.

Lack of knowledge

The following issue remains to be addressed if the effects of a vaccine-programme should be analysed further:

- The effects of and acceptance of different vaccination strategies should be closely monitored

Logistic demands

If immunisation is to be performed in schools, the school health services will have to provide an extra three vaccinations for each girl, in addition to the MMR vaccination that will remain in grade 6 until the school-year of 2013/2014. The total estimated time for carrying out the vaccination programme in a school is between 30 to 45 minutes per pupil. Assuming that a school nurse produces 1,600 active hours per year, this equals a request of one or one and a half school nurses per 3,200 vaccinated pupils.

A catch-up program will have to be performed by an organisation outside the school.

Lack of knowledge

The following questions remain to be answered if the effects of a vaccine-programme should be analysed further:

- Are school-based programmes including 3 doses to each pupil within 12 months organisationally feasible?
- Can catch-up HPV immunisation programmes effectively be integrated into broader health programmes for adolescents?

Attitudes

Information from other countries indicates positive attitudes to the HPV vaccination, which is confirmed by studies carried out in Sweden. Added information from the studies is the great demand for independent information about the vaccines, as expressed by persons taking part in the focus-interviews.

Lack of knowledge

The following questions remain to be answered if the effects of a vaccine-programme should be analysed further

- Can effectiveness of immunisation programmes be enhanced by involving young people in the design of the program and the information materials associated with them?
- What are the determinants for compliance of vaccination and screening?
- Will attitudes and compliance to the cervical screening program change in a vaccinated population?

Ethics

The ethics committee of The National Board of Health and Welfare did not identify any ethical issues that could prevent the introduction of the HPV vaccine. Further ethical discussions in different fora will be necessary.

Lack of knowledge

The following issues remain to be addressed if the effects of a vaccine-programme should be analysed further

- The ethics of diverting funds from other health-issues to this vaccine needs to be discussed

What monitoring needs to be performed?

In addition to the traditional monitoring of a vaccination program, a total surveillance of the complete preventive program for cancer caused by HPV is needed, including regular audits of the screening program, monitoring of viral circulation, and ideally also monitoring of age-specific infection and/or non-cancer forms of HPV-disease. Also, follow-up of the vaccination ef-

fects by registry linkage of national health data and quality registers will be necessary to find answers to effectiveness and safety questions. This is a much more complicated monitoring system than the present systems in use to monitor existing vaccination programs. The screening program and its register provide an important tool to monitor the effects of changes in the prevention program, such as introduction of more general HPV testing and of vaccination, but to be effective there is a need for the coordination of the different monitoring sections in different agencies, the counties and among the professions.

Lack of knowledge

The following issues remain to be addressed if the effects of a vaccine-programme should be analysed further:

- Because the HPV vaccines can affect many diseases, it is important to assess their impact also upon overall mortality, not only disease specific incidence or mortality.
- Much of the research on the current HPV vaccines concentrates on the prevention of cervical cancers. HPV infections are related to a number of other cancers and health outcomes as well, and further information is required from the follow-up studies of the impact of vaccines on these as well.

The disease

Background and virology

The human papilloma virus (HPV) is the most common sexually transmitted infection. Over 100 different types of HPV have been identified and fully sequenced, while over 120 putative types exist that have been partially characterised (1, 2).

All HPV types are epitheliotropic, completing the growth cycle only in differentiating keratinocytes of the skin and the anogenital and oropharyngeal mucosa. Approximately 35 HPV types are known to infect the human genitalia, causing a range of clinical states including asymptomatic infection, genital warts (condyloma acuminata), cytologic abnormalities of the cervix and invasive cervical cancer (1). Most HPV infections are cleared, but some persist. Some of the persistent infections may progress to dysplasias, and it is estimated that ultimately 3-5% of HPV infections progress to invasive cancer.

HPV types are assigned numerical designations once the DNA sequence has been established and comparison to previously known types has been performed. These types can be subdivided into two categories: 'low risk' and 'high risk'. These characteristics refer to the association of the HPV type with cervical cancer. Individuals infected with low-risk viruses have a low risk of developing cervical cancer. The low-risk types such as HPV 6 and HPV 11 are associated with genital warts or condyloma acuminata (3-5). High-risk types such as HPV 16 and 18 cause dysplastic lesions of the cervix, including invasive cancer (6).

The causative relationship between HPV and cervical carcinoma has provided the incentive for the development of prophylactic vaccines, which prevent cancer by protecting uninfected women against infections with the HPV types included in the vaccines (7).

Virology of HPV

HPVs are non-enveloped double-stranded DNA viruses of approximately 55 nm in diameter (8). All of the coding information is contained in one of the two DNA strands. There are seven open reading frames (ORFs), encoding several known viral proteins, some of which are formed by splicing events. The five 'early' proteins are E1, E2, E5, E6, and E7. Transcripts encoding the early proteins are detected in the basal and suprabasal cells in the early portion of the viral replication cycle, and encode proteins required for viral replication and cellular transformation, with the E6 and E7 proteins being the major viral oncogenes.

Expression of the 'late' structural L1 and L2 genes is restricted to the differentiating epithelium where viral assembly occurs (9-12). The L1 ORF encodes the major capsid protein of 55 kDa that makes up the majority of

the virus shell. The L2 ORF encodes a protein of 77 kDa known as the minor capsid protein because it contributes a smaller percentage of the capsid mass than the L1 protein.

The L1 gene is the most conserved gene between individual HPV types and the L1 major capsid protein is the main target of neutralising antibodies. Within individual types are 'subtypes' that vary in DNA sequence to a slight degree, but not enough to be named as a unique type. Subtypes of genital HPVs appear to be immunologically similar, i.e. neutralising antibodies to one HPV subtype will also neutralise other subtypes of the same HPV type with approximately the same efficiency. By contrast, neutralising antibodies against 1 HPV type show little cross-neutralisation against other HPV types (usually about 100 times less).

All prophylactic HPV vaccines that are licensed are based on the L1 protein of HPV. The vaccines protect by inducing neutralising antibodies.

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Disease caused by HPV

Invasive cancer

Cervical cancer

Both the costs and outcome of cervical cancer are strongly dependent on the stage at diagnosis. As stage at diagnosis is strongly dependent on participation in screening programs, cervical cancer at younger ages has a much better prognosis and fewer costs to society than cervical cancer at older ages. In Sweden 80% of the women in the targeted population participate in screening and among them the cervical cancer morbidity is low – a total of about 150 cases and some 30 deaths per year in a population of 9 million. The rest, about 300 cases and some 120 deaths, occur among women with inadequate screening participation (1). The simplest way to accommodate the strongly age-dependent severity of the burden of this disease is to consider it as three different diseases when estimating its effects, namely (1):

- Microinvasive Cervical Cancer (Stage Ia): About 20% of all cases. Occurs in younger ages. Excellent prognosis (about 98% survival rate). Can be treated in most cases with the preservation of fertility.
- Localised Cervical Cancer (Stage Ib): About 40% of all cases. About 85-90% of these can be cured, but treatment is more severe and fertility cannot normally be preserved.
- Advanced Cervical Cancer (Stages II, III and IV): About 40% of all cases. Extensive treatment with radiation and cytostatics. Mortality of >50% within five years.

All HPV-associated invasive cancers that contain HPV types 16 or 18

The estimated annual number of cases of HPV-associated cancer forms in Sweden is given in Table 1.

For cervical cancer, the data is an average for 1999-2001 and is based on a nationwide audit (Andrae et al) that included a re-review of all diagnostic slides.

For the other HPV-associated cancers the data is an average of the reported cases in Cancer Incidence in Sweden for 2002, 2003 and 2004 (rounded to integers).

For vulvar cancer, vaginal cancer and anal cancer, we assume that Sweden has a similar proportion of HPV16/18-positive cancers to the rest of the world and the world estimates by Parkin et al 2006 are used (2).

These are: vulva and vagina: 32%; penis: 25%; anus: 83%.

For cervical cancer, there is evidence that HPV16 is over-represented in Europe compared to some other parts of the world. European meta-analysis data from Clifford et al 2006 estimated 73% of HPV16/18-positive cases (3). Assuming a relative risk of about 20, this would correspond to an attributable proportion of about 70%.

For oropharyngeal cancers, there is very strong evidence for international heterogeneity in estimates with studies from Europe and North America having substantially higher proportions of HPV-associated cancers. As a

population-based case-control study from Sweden (4) exists, the Swedish estimate of 54% has been used (4).

Table 1. The ICD-codes of cervical, vulvar, vaginal, oropharyngeal, penile and anal cancer, the total number of annual cases and the estimated number of cases attributable to HPV types 16 and 18 in different age groups

ICD-7		All	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84	85+
171	Cervix IA	84	1	9	16	15	15	11	2	3	4	2	2	1	1	0
	16/18	59	1	6	11	11	11	8	1	2	3	1	1	1	1	0
171	Cervix IB	167	1	9	20	19	23	19	19	12	10	6	10	12	4	4
	16/18	117	1	6	14	13	16	13	13	8	7	4	7	8	3	3
171	Cervix II+	159	0	1	5	8	8	11	10	10	14	15	22	21	19	15
	16/18	111	0	1	4	6	6	8	7	7	10	11	15	15	13	11
176.0	Vulva	F 125	0	0	0	1	2	4	8	7	8	9	13	21	26	26
	16/18	40	0	0	0	0	1	1	3	2	3	3	4	7	8	8
176.1	Vagina	F 45	0	0	1	1	2	1	3	2	1	4	4	9	9	8
	16/18	14	0	0	0	0	1	0	1	1	0	1	1	3	3	3
145	Oropharynx	M 103	0	0	0	1	4	9	15	20	20	13	10	6	3	2
	16/18	56	0	0	0	1	2	5	8	11	11	7	5	3	2	1
		F 30	0	0	0	1	3	4	6	6	3	2	3	2	1	1
	16/18	16	0	0	0	1	2	2	3	3	2	1	2	1	1	1
179.0	Penis	M 89	0	0	1	1	3	3	7	12	10	9	12	11	11	9
	16/18	22	0	0	0	0	1	1	2	3	3	2	3	3	3	2
154.1	Anus	M 40	0	0	0	1	2	4	3	7	5	5	3	5	4	2
	16/18	33	0	0	0	1	2	3	2	6	4	4	2	4	3	2
		F 83	0	0	0	2	2	6	7	9	11	7	8	10	12	10
	16/18	68	0	0	0	2	2	5	6	7	9	6	7	8	10	8
Sum 16/18		536	1	13	29	34	41	46	47	51	51	40	48	53	46	38

HPV and cancer: strength of evidence and primary and secondary considerations about vaccination

Primary consideration: cervical, vulvar and vaginal cancers

Evidence for a causal link between HPV and these cancers is strong and well established. For these three cancers, there is evidence that vaccination protects against infection at these sites and also that vaccination protects against the HPV-associated precursor lesions (intraepithelial neoplasias) at these sites.

Secondary consideration: anal, oropharyngeal and penile cancers

Evidence for a causal link between HPV and these cancers is strong and well established.

The effect of vaccination against HPV infection at these bodily sites has so far not been studied. However, it seems reasonable that an intramuscularly administered vaccine that is effective against preventing infection at other bodily sites is likely to prevent infection at these sites as well.

The total health burden of these three cancer forms is also considerable.

Not considered: rare cancers

There is convincing evidence that cancers of the base of the tongue, larynx, conjunctiva, skin cancers of the perineal and perianal area and finger tips are also caused by HPV in a proportion of cases. However, as the total number of cases of these tumours is small, their contribution to the total health burden is small and is therefore not considered here.

There are also rare cancers caused by the so-called benign HPV types 6 and 11 (Buschke-Löwenstein tumours).

Not considered: insufficient evidence

There are also a number of other cancers, e.g. cancers of the mouth (in particular the floor of the mouth) and oesophagus that have also been reported to be HPV-positive to a significant extent. However, the bulk of the literature is smaller and less consistent and the etiology can therefore not be considered to be established in these cases.

There is one exception, namely cancer of the mouth which is included as an established HPV-associated cancer by the IARC (International Agency for Research on Cancer) and is confirmed to be commonly HPV-positive in Sweden as well (4). However, contrary to the other five cancer forms selected for consideration, there are no prospective studies and the mechanism of carcinogenesis is unclear as there does not appear to be expression of E6 and E7 oncogenes in mouth cancers.

Summary: invasive cancer disease caused by HPV type 16 and 18 in relation to vaccination

In summary, the literature on HPV in cervical cancers is currently based on very large numbers of cases. There are a number of other HPV-associated

cancers where the causality is definitely established, but the exact proportion of cases that are caused by HPV16/18 is more uncertain, particularly when it comes to regional data. A number of rare cancers with established HPV etiology have been ignored when considering the health burden. Possible future changes in cancer incidence because of increasing HPV prevalences or improvements in the cervical screening program have not been considered.

The figures in Table 1 therefore represent our best estimate of the cancer preventive impact in Sweden. The figures should not be considered as exact, but as estimates. We estimate that for Sweden about 500 cancer cases could be prevented every year.

Cancer in situ tumours

For cancers of the vulva, vagina, penis and anus, it is well established that there exists HPV-associated precursor lesions (intraepithelial neoplasias). Grade 3 intraepithelial neoplasias are also termed in situ carcinomas and are reported to the cancer registry.

Table 2. Annual number of new cases of 'in situ' cancer for 4 HPV-associated cancer forms, by age at diagnosis. Excerpt from the Swedish Cancer Registry for the following ICD7 codes: Vulva;1760, 1767, 1768 Vagina; 1761 Penis;1790, 1798 Anus; 1541,1548. The table shows average of the annual number of reported cases during 2002-2005.

Men																
Site	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84	85+	Total
Vulva																
Vagina																
Penis	0	1	2	3	2	1	2	2	6	6	4	6	6	4	2	46
Anus	0	0	0	0	0	1	1	0	1	1	1	0	1	1	0	6
Total	0	1	2	3	2	1	3	3	7	7	5	6	7	5	3	52

Women																M+W	
Site	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84	85+	Total	Total
Vulva	3	4	4	6	8	14	18	23	24	14	12	11	12	8	7	166	166
Vagina	0	1	1	1	2	2	3	2	5	2	1	2	1	2	1	24	24
Penis																	46
Anus	0	0	0	1	0	1	1	2	3	2	1	1	1	1	2	16	22
Total	3	5	5	8	10	17	22	27	31	18	14	14	14	11	10	206	258

For oropharynx (ICD7 145), in situ cancers are not well described and there were indeed only about 3 cases/year of oropharyngeal in situ cancer in Sweden (data not shown).

Vulvar and vaginal intraepithelial neoplasias are of particular interest, because they have actually been studied in vaccination trials and there is evidence that HPV vaccination protects against them.

It is described that the vulvar and penile precancers tend to be HPV-positive to a larger extent than the corresponding invasive cancers, particularly when precancers in younger ages are studied. HPV16 is the dominating causative type. Although there is limited data on HPV types in precancers occurring in older ages, it seems likely that the eradication of HPV16/18 should reduce the number of in situ cancers of the vulva/vagina/penis and anus in Sweden by at least 150 cases.

Treatment is through surgery. Vulvar in situ lesions in particular may follow a recurrent course requiring multiple treatments.

Diseases caused by benign genital HPV types

Condyloma Acuminata (Genital warts) is a common sexually transmitted disease, usually caused by HPV6. About 90% of condylomas are estimated to be caused by HPV type 6 (5). Respiratory papillomatosis is a condylomatous disease of the larynx/respiratory tract, which may affect infants (presumably by infection at birth) or young adults. HPV type 11 is a common cause of respiratory papillomatosis in infants for unknown reasons. Respiratory papillomatosis among adults has HPV6 as a dominating cause, similar to condyloma.

There are two common topical drugs taken against condyloma, Podophyllotoxin and Imiquimod, with Podophyllotoxin being the more commonly used drug for first instance condyloma. Podophyllotoxin is only used against condyloma, whereas Imiquimod has condyloma as the leading, but not exclusive, indication.

The total sales of these drugs for the year 2006 are shown below (excerpt from the Swedish Prescription Registry, National Board of Health and Welfare).

Table 3. Use of topical drugs against condyloma

ATC code/Drug	Number of subjects	Number of prescriptions	DDD, 1000	Patients per 1000 inhabitants	DDD per 1000 inhabitants/day
D06BB04 Podofyllotoxin	14039	16427	61,61	1,54	0,02
D06BB10 Imiquimod	2532	4434	15,2	0,28	0

When patients are seeking medical care for condyloma, they can either be treated using topical drugs, surgery or conservative treatment (i.e. no treatment, but a recommendation to come back after half a year or so if the condyloma persists). It is not known how often the different modes of treatment are chosen.

The Swedish Patient Registry registers all visits to hospitals in Sweden, both as in-patient and as out-patient visits. However, the very large proportion of condylomas that are handled in primary care are not registered. The age profile and total number of visits and patients are shown below. The

number of reported cases has been rather similar during 2002-2005 and the average number for these four years is given.

Table 4 Reported cases of A630 Condyloma Acuminata (average annual number of reported cases during 2002-2005)

Age	Visits			Subjects		
	Men	Women	Total	Men	Women	Total
0- 4	3	9	12	3	7	10
05-09	3	3	7	2	2	4
10-14	3	6	9	2	5	7
15-19	87	512	599	74	419	493
20-24	759	990	1,748	641	819	1,460
25-29	791	536	1,326	655	442	1,097
30-34	340	224	564	282	199	482
35-39	184	131	315	151	115	266
40-44	88	78	166	70	68	138
45-49	49	49	98	41	44	85
50-54	30	28	58	24	25	49
55-59	28	23	51	21	20	41
60-64	21	16	36	13	13	26
65-69	15	12	28	9	11	20
70-74	10	7	17	7	7	13
75-79	9	4	12	5	3	8
80-84	3	4	6	2	3	5
85+	0	1	1	0	1	1
Total	2,421	2,630	5,051	2,000	2,203	4,203

A large questionnaire study mailed to a representative sample of >15,000 Swedish women found that 2% of women in the age group 20-25 years reported having had a condyloma during the past year (6). Comparison with the number of reported cases in this age group (819 women, see above) indicates that less than 1/5 of condyloma patients are handled at hospitals. As there are a total number of 4,200 reported patients with condylomas from hospitals, an estimate is that there are at least 20,000 condyloma cases among women each year. Condylomas among men appear to consistently be about 10% fewer, which would amount to approximately 18,000 cases.

As there are about 16,500 subjects who receive prescriptions for topical drugs against condyloma and since these drugs are not always used, an estimate based on the prescription registry data is that there could be about 20,000 cases per year. This estimate is about half of what is estimated from the comparison with the questionnaire survey. A possible explanation could be that subjects commonly make the diagnosis themselves and do not visit health care. In the following, we have assumed that the figure based on prescription data (20,000 cases/year) is more relevant to estimating health care costs.

The clinical course of condyloma is variable, with a minority of lesions being recurrent. Discussions with clinical experts (Drs. A. Wikström & P.

Lidbrink of the Swedish STD Society) have resulted in an approximate estimate of one third recurrences.

The effects of a vaccination program on condylomas will probably manifest itself differently from that on cervical cancers. As the incubation time between exposure and disease is quite short (most estimates range between 3-12 months), the reduced costs would in theory be possible to realise quickly if there is an ambitious 'catch-up' program that efficiently reduces the spread of the virus among the young. If there is only vaccination with relevant serotypes of 10-12-year-olds and no catch-up, it will take about eight years until immunity has reached the most sexually active age groups and large preventive effects against condyloma will be seen.

In scientific literature, respiratory papillomatosis is reported to occur at an incidence of about 0,4/10,000 children. However, the code recommended to be used for reporting to the Swedish Patient Registry (D141- Benign tumour of the larynx) appears to not only cover respiratory papillomatosis. There are annually about 550 cases reported with benign tumour of the larynx, which is a much higher number than the condylomatous diseases of this site and the age peak (35-45 years of age) is not the expected peaks for laryngeal condylomatous disease. Below 10 years of age there is only about 12 cases reported per year (data from the Patient Registry, not shown). Although this disease may be severe and constitute a health burden with associated costs, we have not been able to make any reasonably reliable estimate, because of the paucity of data.

It should also be noted that there are a number of reports that the 'benign' papilloma viruses HPV6/11 may in rare circumstances cause cancer. However, the numbers are small and difficult to estimate with any reliability.

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The screening program

Background

The Swedish cervical cancer screening programme has been working since the end of the 1960s. It is characterized by National recommendations issued by the National Board of Health and Welfare, and Guidelines issued by C-ARG, the working group for cervical cancer prevention of SFOG, the Swedish Society of Obstetricians and Gynaecologists. The latest were issued in 1998 and new guidelines are expected soon, but the 21 counties are autonomous in providing health care and the implementation is therefore regional.

Age limits and intervals for invitation to cervical cancer screening are now almost uniform, every three years from 23-50 years and every five years from 51 to 60 (with exceptions in one or two counties). Invitations are issued by the laboratories except in Stockholm where there is a special screening office covering the metropolitan area.

Invitations are done either by birth cohorts (age 23, 26, 29 etc.) or the time elapsed since last smear taken. Fees for a cytological smear differ between 0 and 200SEK (approx. 20€). In some counties a specific time and place for the test is issued in the invitation, while in others women need to make their own reservations at the Antenatal Centers.

In Sweden routine antenatal care, birth control and smear-taking are generally performed by midwives at Antenatal Centers supervised by gynaecologists. The screening invitation usually gives an appointment to such a clinic, but if the woman prefers to go to a doctor, on her own initiative, that test is registered and the next invitation is postponed. This is what is called integration of opportunistic and organised screening. The doctors who take the smears outside the program are usually private gynaecologists. Coverage is higher in the rural areas where organised screening dominates and personal invitations to screening are the rule (3).

Hitherto the screening has been based on smear-taking and routine testing for presence of HPV has not been implemented within the primary screening. HPV testing is only done in the evaluation of CIN1 and ASCUS. The rationale for replacing cytology with HPV testing in primary screening would be if it could reduce the number of invasive cancer cases below the numbers that are now missed by repeat normal cytology, at present some sixty cases a year. It is a requirement that this change should be done without increasing the number of women that have to be referred to further investigation and preferably also allowing increased screening intervals. HPV testing is not suitable for primary screening below the age of thirty as a very large proportion of the population have transient HPV infection in those ages, and postponing screening above that age would leave many young women, whose fertility is now protected by cytology, at risk. Screening monitoring systems that can handle the combined information of cytology and HPV testing have to be developed before the method of primary screening can be changed

Computer systems linking cytology registers and invitation countywise have been in action since the 1960s. Today there are two different database systems used, and they are implemented with local variations. Terminology

for diagnosing cervical cytology varies between laboratories (today all laboratories uses versions of the SNOMED system). Since 1995 a common terminology with only 14 SNOMED codes is recommended by KVASt (Kvalitets och standardiseringskommittén inom Svensk Förening för Patologi och Klinisk Cytologi). These recommendations were revised in 2007.

Sweden has a National population register and every individual has a national registration number (NRN) used in all contexts of health care from birth throughout life. This makes it possible to collect and compare health data from registers. A National Cancer Registry is in practise since 1958 and it is mandatory for all laboratories and clinicians to report all cases of invasive cancers as well as Cancer in situ/CIN3 by location (T83) and Snomed code. Since 2004 all gynaecological tumours are also classified by FIGO stage (the International Federation of Gynecology and Obstetrics (4).

The Oncologic Centers in some regions have offices for the coordinated supervision of cervical prevention. A nation-wide audit of cervical screening has been performed in connection with the establishment of a National Quality Register for Cervical Screening (Karolinska Institute) in 2007 (6). The register is a tool for evaluating effectiveness in cervical cancer prevention. The screening history of all cervical cancer cases in the years 1999 to 2001 could be related to that of population based controls. The main findings of the audit were that screening is protective in all ages from age 23 and against all types of histopathological lesions. Non-adherence to screening intervals was the main reason explaining incident cervical cancer, especially the advanced cases. The importance of assessment of detected abnormalities has been high-lighted.

Recent development: A network for the coordination of the regional screening programs has been developed in order to optimize the computer systems. The responsibility for long time follow-up after diagnosis and treatment of atypical smears is being transferred from individual clinics to the screening invitation systems, thereby taking advantage of the computerised call and recall systems and of the use of trained midwives to perform the testing. Registers of HPV types can be included in the screening registers to facilitate the integration of HPV tests that are being introduced in some parts of the screening program. In one region a database for comprehensive monitoring and quality assurance has been implemented. Through a web-display doctors can obtain integrated screening, diagnostic and treatment history of individual patients.

In conclusion, the screening program prevents many cancers and must continue. The screening program and its registers are an important part of the infrastructure necessary to monitor the effectiveness of changes in cervical cancer prevention strategies, and to attribute benefits and risks to the different components when HPV testing and vaccination are introduced. However, it has to be better coordinated between counties and the computerized administration has to be updated.

HPV 16- or 18-related diagnoses, procedures within cervical screening and impact of HPV vaccination

A substantial amount of cervical precancers and other lesions requiring medical attention/treatment will be prevented by vaccination. We have searched relevant registries to estimate the public health burden of these lesions in Sweden and how many of those could be prevented by HPV vaccination. We have assumed that the screening intensity will not change in the foreseeable future.

Our analysis is based on data for 2006 from the Regional Cervical Screening Registry for Southern Sweden. This part of Sweden (counties of Skåne, Blekinge, Kronoberg and Halland) has 19.7% of the population of Sweden. An estimate for Sweden is therefore derived by multiplying the figures from Southern Sweden by 5.07.

The data is restricted to *cases occurring in individual women*. For high-grade cervical intraepithelial dysplasia (CIN2/3), the number of specimens with the diagnosis is substantially greater than the number of women with the diagnosis (31% more; 1,728 specimens with CIN2/3 from 1,323 women), which should be considered when comparing our data, with other studies that are based on the total number of CIN2/3 diagnoses.

For cytology, the number of specimens is almost the same as the unique number of women with the diagnosis (data not shown).

There is also a National Quality Registry for Cervical Cancer Screening, but recent national data were not available at the time of this analysis.

Proportion of dysplasias attributable to HPV 16 or 18

To estimate the proportion of cases that today (before introduction of vaccination) are attributable to HPV16/18, we have used the European meta-analysis by Clifford, 2006 (2). This analysis estimates 19% of atypical squamous cells of uncertain significance (ASCUS) and 24% of low-grade cervical intraepithelial dysplasia (CIN1) as HPV16/18-carrying. Assuming that HPV 16/18-positive women have a relative risk of 20 for CIN 2/3, the attributable proportions will be 18% and 23% and this figure has been used as a multiplication factor in Table 5.

For CIN2/3, there exists a Swedish nationwide population-based cohort study (Swedescreen) that has estimated the proportion of CIN2/3 attributable to HPV16/18 to 39% (5) and this figure has been used as a multiplication factor in Table 5.

The European meta-analysis by Clifford et al 2006 (2) estimated that 57% of CIN2/3 were HPV16/18 positive and assuming that HPV 16/18-positive women have a relative risk of 20 for CIN 2/3, this would correspond to an attributable proportion of about 54%. This figure is substantially higher than the 39% estimate from Swedescreen. If 54% had been used instead, we would have estimated that there would be about 1,000 additional annual cases of CIN2/3 prevented by the HPV 16/18 vaccination (3,629 instead of 2,621) and the sensitivity analysis of our estimates may need to consider the effect of this difference in input values.

The reasons for the discrepancy are not quite clear. It could be regional differences or differences in study design (case series versus prospective

cohort study). As Swedescreen is from Sweden and prospective cohort studies are supposed to produce more reliable estimates than case series, the Swedescreen estimate is used in our primary analysis, which is shown in table 5.

Table 5. Number of women in different age groups from the Regional Cervical Screening Registry for Southern Sweden with different degrees of dysplasias during 2006, the estimated number for all of Sweden and the number of these attributable to HPV 16 or 18

		All	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84	85+
Cytology	ASCUS	2,819	16	437	590	377	334	314	240	213	134	91	35	20	14	3	1
	Sweden	14,321	81	2,220	2,997	1,915	1,697	1,595	1,219	1,082	681	462	178	102	71	15	5
	HPV16/18	2,578	15	400	539	345	305	287	219	195	123	83	32	18	13	3	1
Cytology	CIN1	2,341	33	481	574	339	254	210	163	116	79	53	20	14	3	2	0
	Sweden	11,892	168	2,443	2,916	1,722	1,290	1,067	828	589	401	269	102	71	15	10	0
	HPV16/18	2,735	39	562	671	396	297	245	190	136	92	62	23	16	4	2	0
Cytology	CIN2/3 (AIS)	1,243	9	172	281	231	161	141	81	67	43	26	15	8	6	1	1
	Sweden	6,314	46	874	1,427	1,173	818	716	411	340	218	132	76	41	30	5	5
	HPV16/18	2,463	18	341	557	458	319	279	160	133	85	52	30	16	12	2	2
Histopathology	CIN2/3	1,323	8	205	342	250	179	146	82	34	32	22	10	6	2	3	2
	Sweden	6,721	41	1,041	1,737	1,270	909	742	417	173	163	112	51	30	10	15	10
	HPV16/18	2,621	16	406	678	495	355	289	162	67	63	44	20	12	4	6	4

Estimated numbers of treatments due to HPV 16 or 18

In this section we have tried to estimate the burden of procedures initiated by the current screening-program that could be affected by the vaccination against HPV.

Histopathology of CIN2/3: We assume that every woman with a histopathological diagnosis with CIN2/3 will need to be treated with conization and thereafter followed up with additional smears. The follow-up, lasting for ten years, usually consists of biannual check-ups instead of the normal screening every three years. We estimate that two additional smears could be avoided in each one of the women in whom the CIN 2/3 is prevented by vaccination. The annual number of cases that could be prevented by HPV 16/18 vaccination is estimated to 2,621 (39% of total cases; Table 5)

Analysis of the robustness of estimated number of treatments: The data using the screening registry in the table above estimates about 6,721 women with CIN2/3 requiring conizations. In 2005 the Swedish patient registry registered 5,714 conizations performed on 5,704 women, with the number of registered conizations remaining approximately stable since 2002. The extent of underreporting is not known, but variability in reporting from different counties over the years suggests that some underreporting exists.

A survey to all gynaecology clinics in 1995 by the Swedish Association of Obstetrics and Gynaecology (SFOG) found 6,997 treatments (conizations 4,567, cryotherapy 445, and laser vaporisation 1,985) and there was an estimate of about 1,000 additional treatments by private gynaecologists. Estimates using the screening registry, the SFOG survey and the patient registry are therefore essentially consistent.

Cytology with CIN2/3: We assume that all women with CIN2/3 in cytology will need a visit to a gynaecologist that will frequently include a biopsy. This is each year done for >6300 women (Table 5) and we estimate that 2,463 (39%) of these annual cases are preventable by HPV 16/18-vaccination.

Cytology with ASCUS or CIN1: The regional practices of how this is handled vary in Sweden. For this analysis we assume that 50% of cases will (either directly or after an abnormal repeat smear) be referred to a gynaecologist. Out of the 14300 cases of ASCUS and 11900 cases of CIN1, we estimate that each year 2600 ASCUS cases and 2700 CIN1 cases could be prevented by HPV16/18 vaccination. If about half of them are referred, HPV vaccination would annually prevent some 2600 referrals.

Cost of the burden of diseases caused by HPV6/11/16/18

Costs for cancers

Cervical cancer Ia is treated with conization or hysterectomy and is usually completely cured. The cost for treatment is estimated at 20,000 SEK. With 59 cases caused by HPV16/18 this gives 1.2 MSEK

Cervical cancer IB is treated with radical surgery and is cured in about 90% of cases. The cost is estimated at 90,000 SEK. With 117 cases caused by HPV16/18 this gives 10.5 MSEK

Cervical cancer II+ is treated with radiation and cytostatics and then with palliative care. The cost is estimated at 750,000 SEK (300,000 SEK/ year during on average 2-3 years). With 111 cases caused by HPV16/18 this gives 83.2 MSEK. Most of these costs are for cancers occurring in women who have not participated in screening

Specific estimates of the cost of treatment of other HPV-associated cancers (vulvar, vaginal, penile, anal, oropharyngeal) were not available. As a very crude estimate, we have assumed cancer deaths to have the same cost as stage II+ cervical cancer and non-lethal cancers to have the same cost as cervical cancer stage IB. With 150 cases and 80 deaths caused by HPV16/18, this gives 66.3 MSEK.

Costs for condyloma

A crude estimate of condyloma costs to society would be:

Initial visits to health care: 20,000 x 1,000 SEK (Average cost for visit to health care (physician, nurse or midwife) = 20 MSEK

One third recurrences requiring surgery (physician visit): 6,500 x 3,000 SEK = 19.5 MSEK

One third second recurrences requiring surgery: $2,200 \times 3,000 \text{ SEK} = 6.4 \text{ MSEK}$

Small amount of patients with multiple recurrences requiring extensive surgery, is not included in estimate.

- Total treatment and visit costs: 46 MSEK
- Drug costs:
 - Podofyllotoxin: $16,427 \text{ doses} \times 180 \text{ SEK} = 2,956,860 \text{ SEK}$
 - Imiquimod: estimated 3,000 out of 4,400 prescribed doses to be due to condyloma $\times 700 \text{ SEK} = 2,100,000 \text{ SEK}$
- Total drug cost: 5 MSEK
- Total cost estimate: 51 MSEK/year

If 90% of condylomas are caused by HPV6/11/16/18, there would therefore be a potential for cost savings of about 46 MSEK.

Recent data from Sweden (Joakim Dillner, unpublished data) indicates that the proportion of condylomas caused by HPV6/11/16/18 is 82%. We have opted to use published data as the primary estimate. If 82% is used as an alternative measure (sensitivity analysis), the potential for cost savings would be about 42 MSEK.

Costs for the screening-program

Histopathology of CIN2/3: The cost of a conization procedure is estimated at 3,000 SEK and two additional smears are estimated at 300 SEK each. This gives 3,600 SEK/case of CIN2/3 and a total cost of 2,621 HPV16/18-attributable cases $\times 3,600 \text{ SEK} = 9.4 \text{ MSEK}$

Cytology with CIN2/3: A visit to a gynaecologist that will frequently include the taking of biopsies is estimated at an average cost of 1,500 SEK. This gives 2,463 HPV16/18-attributable cases $\times 1,500 \text{ SEK} = 3.7 \text{ MSEK}$.

Cytology with ASCUS or CIN1: With about half of the cases being referred and average cost of referral estimated at 1500 SEK and a repeat smear at 300 SEK, and HPV16/18-attributable cost of 4.8 MSEK is estimated ($2,578 \text{ HPV16/18 ASCUS cases} + 2,735 \text{ HPV16/18 CIN1 cases}$) $\times 0.5 (1,500 + 300) = 4.8 \text{ MSEK}$.

The total health care cost burden caused by HPV6/11/16/18 in Sweden is thus in total estimated to about 225 MSEK/year. Cervical cancer and its precursors are the main health care cost, estimated at about 112 MSEK/year, followed by other HPV-associated cancers at 66 MSEK/year and condyloma at 46 MSEK/year.

It should be emphasized that prevention of HPV6/11/16/18 will lead to savings of health care costs only after a prolonged lag time. The incubation time for development of condyloma after infection is short (below 6 months), but the incubation time for development of cervical cancer is on average about 20 years and for other HPV-associated cancers the mean incubation time is even longer. Thus, even a maximally successful HPV vaccination program will fully realise the health care cost savings only after a life-time has passed. Modelling cost-effectiveness requires elaborate consideration of discounting and timing of disease occurrence and is therefore

the subject of a separate chapter (Chapter 9). The cervical cancer and precursor costs used in Chapter 9 are quite similar to those presented in this chapter, but as they result from an independent estimation they are not identical.

Summary

The major disease caused by HPV is cervical cancer, which is mainly (to about ~70%) related to HPV types 16 and 18. There are about 450 cases and 150 deaths from this cancer per year with associated cancer treatments. If there is population-based HPV 16/18 vaccination, 290 cervical cancer cases and 110 deaths caused by HPV16 or 18 are potentially preventable. Among women who participate in screening, the cervical cancer morbidity is low - about 150 cases and some 30 deaths per year, whereof 105 cases and 20 deaths are attributable to HPV 16 or 18. The rest of the cases occur among women with inadequate screening participation.

HPV16/18 also causes a substantial proportion of other anogenital cancers (vulvar, vaginal, penile and anal) as well as oropharyngeal cancer. The number of cases caused by HPV16/18, and thus potentially preventable by vaccination, is estimated at 150 cases and 80 deaths.

Considering all cancer forms altogether, HPV16/18 is estimated to cause about 440 cases of cancer and 160 cases of cancer deaths per year, with associated treatments.

HPV16/18 is also a major cause of precursors to cervical cancer. Among the 6700 cases of high-grade cervical dysplasia each year, about 2600 cases are potentially preventable by HPV 16/18 vaccination. Among the >26000 cases of low-grade cervical lesions each year, >5000 would be preventable by HPV vaccination.

The major disease caused by HPV6 and 11 is condyloma acuminata (genital warts), which affects about 20,000-40,000 subjects in Sweden each year. About 90% of these are potentially preventable by HPV vaccination

The total health care cost burden caused by HPV6/11/16/18 in Sweden is estimated to about 225 MSEK/year. Cervical cancer and its precursors are the main health care cost, estimated at about 112 MSEK/year, followed by other HPV-associated cancers at 66 MSEK/year and condyloma at 46 MSEK/year.

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Legal aspects

Background

In Sweden the National Board of Health and Welfare issues regulations (mandatory rules), general advice and recommendations for which vaccines should be offered to the public by the health-providers. The legal provisions for the Swedish vaccination-programmes are today found in a regulation giving details on the vaccines offered to all children. Provisions can also be found in some general advice and recommendations mainly dealing with vaccinations offered to risk-groups.

The regulation SOSFS 2006:22 makes it mandatory for the child- and school care systems (county councils and municipalities) to offer all children in Sweden vaccination against eight serious diseases: diphtheria, tetanus, whooping cough, polio, Hib infection (*Haemophilus influenzae* type B), measles, mumps and rubella. Children who are at a high risk of infection are also offered vaccination against hepatitis B, pneumococcal infections and tuberculosis. The childhood vaccination programme is accomplished through several steps between the ages of 3 months and 16 years.

Children who have not been vaccinated in accordance with the child vaccination programme shall – when applicable – be offered such vaccinations up to 18 years (catch-up).

The childhood vaccination program is implemented by county councils and municipalities. Implementation of the programme is normally made by the county councils up to school age of the children (vaccination at child health centres) and thereafter by municipalities (vaccinations in the school health system).

Legal basis for introducing the HPV vaccine in the Swedish vaccination programme

The legal basis for the National Board of Health and Welfare for issuing regulations for vaccinations of children in general vaccination programs and the general advices concerning certain other vaccines is found in the Swedish Communicable Diseases Act from 2004 and its ordinance. Paragraph 12 in the ordinance states that the National Board has the mandate to:

“introduce the regulations necessary to maintain an efficient/appropriate communicable disease protection and to protect individuals.”

Legal basis for follow-up and monitoring

To ensure an effective long-term follow-up it is necessary to compare data from several registers. Existing legislative acts concerning reporting and registers contain the provisions for when data can be collected and in what

situations these data can be analysed or used for research and surveillance purposes

Reporting of notifiable diseases

Today around sixty diseases are classified as notifiable diseases according to the Swedish Communicable Diseases Act. This means that the treating physicians and laboratories must report every suspected or confirmed case to the County Medical Officer and to the Swedish Institute for Infectious Disease Control (SMI). All diseases covered by the childhood vaccination program (SOSFS 2006:22) are subject to mandatory reporting. The reporting includes information concerning name, national registration number and diagnosis. The system also includes a possibility to report source of infection, measures taken to prevent spread of disease and other information of importance to communicable disease control, including vaccination history. The reporting is currently made to the county medical officer and SMI through SmiNet, a web based tool for reporting managed by the SMI.

The ultimate aim of a HPV-vaccination program is to reduce cancer, by means of protecting against infection with the oncogenic HPV-types. To include the oncogenic HPV-viruses in the list of notifiable diseases would ensure that reporting is made when typing is performed. Such a reporting system would make it possible to obtain important information about circulation of the viral types.

Registers and processing of data

Processing personal data

The basis for processing personal data can be found in the Personal Data Act 1998:204 which aims to prevent the violation of personal integrity in the processing¹ of personal data. The act is based on Directive 95/46/EC.

The Personal Data Act lists certain fundamental requirements concerning the processing of personal data and if another act or ordinance contains rules that deviate from the Personal Data Act, those other provisions apply instead.

According to the Act personal data may only be processed for specific, explicitly stated and justified purposes. Personal data may, if these fundamental requirements are satisfied, in principle, only be used if the registered person gives his or her consent. However, there are several exceptions to this rule. Particularly stringent rules apply to the processing of sensitive personal data i.e. concerning health or sex life. Despite the prohibition it is permitted to process sensitive personal data in certain cases.

¹ Processing is any operation or set of operations which is taken as regards personal data, whether or not it occurs by automatic means, for example collection, recording, organisation, storage, adaptation or alteration, retrieval, gathering, use, disclosure by transmission, dissemination or otherwise making information available, alignment or combination, blocking, erasure or destruction.

Sensitive personal data may be processed if the registered person has given his/her explicit consent or in a clear manner publicised the information.

Sensitive personal data may also be processed for health and hospital care purposes, provided that it is necessary for:

- a) preventive medicine and health care,
- b) medical diagnosis,
- c) health care or treatment, or
- d) management of health and hospital care services.

Sensitive personal data may be processed for research and statistics purposes, provided that it is done according to certain preconditions, and provided the interest of society in the research or statistics project within which the processing is included is manifestly greater than the risk of improper violation of the personal integrity of the individual that it may involve. These preconditions are considered to be fulfilled if an ethics committee has approved the processing of data.

The registered person is entitled to information concerning processing of personal data that concerns him/her.

Health care registers

The information that can be found in health care registers (typical information is the patient records) can be processed for the documentation of the care of the patient (Act 1998:544 on Health Care Registers 1998:544) . The information can also be used in the following situations:

- a) compilation of statistics
- b) follow-up, evaluation, guarantee of quality and administration
- c) legislative demands to supply information

Information in the health care registers can only be linked and matched for certain limited purposes. This includes information that is needed for the care of the individual or administrative tasks.

Examples regarding HPV are patient records at regional diagnostic laboratory registers, and Regional Cervical Screening Registry for Southern Sweden, with integrated screening, diagnostic and treatment history of individual patients.

Health data registers

Act (1998:543) states that central public administration for health care can administrate health data registers. The National Board of Health and Welfare is appointed by the Government to manage the specific health data registers (cancer register etc) through governmental regulations. The Centre for Epidemiology (EpC) at the National Board of Health has the national responsibility for national health data registers. According to the Act 1998:543 on health data registers these are only allowed for certain purposes and can not contain more information than necessary to produce statistics, to

monitor, evaluate and ensure quality in health care and for research and epidemiological purposes (section 3 of the Act on health data registers).

Collection of person identified information to the health data registers is permitted (containing for example the unique personal identification number) without acquiring the consent from the individual. This means that all health care providers have to deliver specified health data. The information which can and must be collected is described in detail in special directives attached to the legislation. The National Board of Health and Welfare is given the mandate to issue more detailed regulations concerning the obligation for the healthcare to report information into the registers and what information such reporting should contain.

The information in the health data registers can only be linked and matched for the purposes mentioned in section 3. Information from the registers must always be anonymous. The information can not be used for control or supervision that can have an effect for an individual.

Research projects that requires registry linkage with the health data registers is assessed by the EpC and must be accompanied by an approval from an ethics committee (or an informed consent from the individual).

The Act regulates the following health data registers:

- The Cancer Register makes it compulsory for every health care provider to report newly detected cancer cases to the registry. A report has to be sent for every cancer case diagnosed by clinical, morphological and other laboratory examinations as well as cases diagnosed at autopsy
- The Medical Birth Register with congenital malformation
- The Hospital Patient Register. Includes hospital discharge diagnoses (overnight care) since 1970, and since 2000 also information on outpatient care handled by the hospitals
- The National Prescribed Drug Register contains patient identities for all dispensed prescribed drugs to the entire Swedish population.

The Death Cause Register is another health data base administrated by the National Board of Health and Welfare.

Health quality register

A system of national quality registries has been established in the Swedish health and medical services. These registries contain data on diagnoses, treatments and outcomes for individuals. They make it possible to monitor the effects of treatment on the individual patients and the data can be aggregated to show the effects of a certain type of treatment on entire groups of patients.

The legal basis for health quality registers is the Personal Data Act. The Data Inspection Board has made the assessment that the processing of personal data within the frame work of the health quality register is allowed without the informed consent of the registered person. Section 18 of the Act states that sensitive personal data may be processed for health and hospital care purposes, provided it is necessary for preventive medicine and health care, medical diagnosis and health care or treatment.

The National Quality Register for Cervical Screening belongs to this category. It consists of a national linkage of the cytology and pathology registers concerning cytological and histological diagnoses, including invitations to the organised Pap smear screening. All 30 laboratories and one regional oncologic center are reporting to the national register. It is handled by the Department of Medical Epidemiology and Statistics at Karolinska Institute, with support from the National Board of Health and Welfare and the Swedish Association of Local Authorities and Regions.

Vaccination register

There is currently no compulsory register for vaccinations, but the issue was raised within SOU 2007:48 – Patient data and pharmaceuticals, where the status of SVEVAC, a web based information system for vaccinations, was analysed. The information system, that is currently used on a voluntary basis and based on the informed consent of the patient, can be seen as a form of entry in the patient record made by the treating physician. However, there is today no legal possibility to use this register for analysis of effectiveness of vaccines without the informed consent of the individual.

Voluntary reporting to SMI is today done by the county councils and municipalities twice during childhood concerning the cumulated coverage of vaccinations according to SOSFS 2006:22, and from many of the county councils and municipalities also with regard to vaccinations of elderly against influenza according to SOSFS 1997:21. In addition, a SMI project for surveillance of HPV is ongoing that includes vaccination data from any medical service providing HPV vaccinations.

New Patient Data Act

A new Patient Data Act is proposed to enter into force on the 1st of July 2008. The new Act will replace the current Act (1985:562) on patient records and Act (1998:562) on Health care registers. The new legislation contains specific provisions for national and regional quality registers. Such quality registers can gather data from several health care providers in order to allow comparisons on a regional and national level. Personal data can according to the new legislation be collected and processed in order to ensure the quality of the health care, but also with the purpose to compile statistics and for research.

Summary

The legal basis for introducing HPV-vaccination in the Swedish child vaccination programme is found in the Swedish Communicable Diseases Act from 2004 and its ordinance. HPV-vaccination could be included in the child vaccination programme in a binding regulation.

Effective follow-up of a HPV-vaccination program will require comparison of existing registers such as data from national health data and quality registers.

The legal aspects of monitoring of the effect of HPV-vaccination will have to be evaluated more in detail to ensure an effective follow-up.

Vaccines

Description

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. These vaccines therefore consist of viral protein without genetic material and the infection of cells or viral replication is not possible. However, from an immunologic point of view, the function of the capsid proteins are those of a live viral protein, albeit with one major difference, i.e. that the antibody concentrations induced by vaccination are a hundred-fold higher than those induced by natural HPV infection. In animal studies the vaccine-induced antibodies have neutralised challenges with HPV virions, but the human antibody concentrations necessary to protect from infections have not yet been established. At present, two different HPV vaccines have been developed; a bivalent vaccine containing VLPs of HPV types 16 and 18 (Cervarix®) and a tetravalent vaccine containing VLPs of HPV types 6, 11, 16 and 18 (Gardasil®). Both include adjuvants, AS04 and amorphous aluminium hydroxyphosphate sulphate, respectively, and are recommended for use according to a three-dose schedule.

Gardasil was approved in Europe in September 2006 for the prevention of high-grade cervical intraepithelial neoplasia (CIN 2/3), cervical carcinoma, high-grade vulvar intraepithelial neoplasia (VIN 2/3), and external genital warts (condyloma acuminata) causally related to HPV types 6, 11, 16 and 18. The indication is based on the demonstration of efficacy in adult females from 16 to 26 years of age and on the demonstration of immunogenicity in 9- to 15-year old children and adolescents. Protective efficacy has not been evaluated in males.

Cervarix was approved in Europe in September 2007 for the prevention of high-grade cervical intraepithelial neoplasia (CIN 2/3) and cervical cancer causally related to HPV types 16 and 18. The indication is based on the demonstration of efficacy in women aged 15-25 years and on the immunogenicity of the vaccine in girls and women aged 10-25 years.

Efficacy

Human papilloma virus (HPV) infection is currently the most common sexually transmitted disease worldwide. From five years following sexual debut, some 50% of young women will be infected with at least one of the 40 HPV types that preferentially infect the genital mucosa. Over 90% of HPV infections are transient and self-limited. Also dysplastic lesions regress spontaneously and regression rates of 57%, 43% and 32% for CIN 1, CIN 2 and CIN 3, respectively, have been reported (1). Ultimately, only some 3-5% of the HPV infections will progress to invasive cervical cancer. The interval between the acquisition of HPV infection and CIN 1 or CIN 2/3 is

estimated to be from 0 to 1 year or from 0 to 5 years respectively, whereas the interval between HPV infection and cancer development is longer and may exceed 20 years (2).

A WHO meeting in 2003 gathered scientists, regulatory authorities, industry representatives, epidemiologists and government officials to discuss appropriate efficacy endpoint measurements for HPV vaccine clinical trials. The experts stated that ethical and time considerations make it necessary to use a surrogate endpoint – not invasive cancer – to define efficacy of HPV vaccines. A cancer endpoint is not feasible because: i) the median time from acquisition of infection to the development of cancer may exceed 20 years and ii) the standard of care worldwide is to screen women for CIN 2/3 and to excise these lesions prior to the development of cancer. The meeting recommended that the primary endpoint for efficacy should be histological-classified cervical intraepithelial neoplasias of moderate or high-grade as well as cancer. The meeting also noted that persistent HPV infection may represent a useful endpoint in future vaccine efficacy studies, since persistent infection with the same high-risk HPV type is considered a predictor for moderate or high-grade cervical dysplasias (3).

Clinical studies - Gardasil

Efficacy and immunogenicity results available at the time of EU approval (September 2006) (4)

Vaccine efficacy was studied in four placebo-controlled, double-blind and randomised clinical studies including a total of 20,451 women from 16 to 26 years of age in North America, Latin America, Europe, South America and Asia-Pacific regions. Participants with a maximum of four to five lifetime sexual partners were enrolled and vaccinated without pre-screening for the presence of HPV infection. The per protocol efficacy (PPE) analyses included only the women who were seronegative to the relevant HPV type(s) on Day 1, PCR-negative to the relevant HPV type(s) on Day 1 through Month 7 and who received all three doses of the vaccine. Overall 73% of subjects were naïve to all four HPV types at enrolment.

The initial phase II ‘proof-of-concept’ study of a monovalent HPV 16 vaccine demonstrated 100% protection against persistent infection (two PCR-samples with an interval of at least four months) with this viral type, 95% confidence interval (CI) 90-100% (5). In the subsequent phase II dose-ranging study of formulations of the tetravalent HPV 6/11/16/18 vaccine, Gardasil demonstrated 90% protection against persistent infection or genital disease caused by the four vaccine types, CI 71-97% (6)

In one of the two pivotal phase III efficacy trials (FUTURE I) HPV 6/11/16/18-related genital disease outside the cervix (condyloma acuminata, vulvar or vaginal intraepithelial neoplasias of any grade, vulvar cancer or vaginal cancer associated with vaccine-type HPV) was used as one of two primary endpoints, with cervical disease (cervical intraepithelial neoplasias of any grade, adenocarcinoma in situ (AIS) or cervical cancer associated with vaccine-type HPV) as the other. Vaccine efficacy was 100% for each of the two co-primary end points (4). The second efficacy trial (FUTURE II)

evaluated HPV 16- or 18-related CIN 2/3, AIS or cervical cancer related to HPV 16 and/or HPV 18. Vaccine efficacy was 100% (CI 75.8-100.0%) (4).

To increase the precision of vaccine efficacy estimates, a combined analysis of data from all four efficacy trials was pre-planned. The primary results were analysed in the PPE population. In addition, several analyses were performed in different sub-populations according to various possibilities of intention to treat, or modified intention-to-treat (MITT). The MITT-3 population included women who had received at least one vaccination regardless of baseline cytological abnormalities and HPV status on Day 1. This population approximates to a young general female population, with respect to the prevalence of HPV infection and disease at vaccination start.

The primary integrated analysis was based on 53 CIN 2/3 cases in the four efficacy trials and all occurred in the placebo group, giving a vaccine efficacy of 100% in the PPE-population (Table 1). The protective effect against HPV 6/11/16/18/-related high-grade vulvar lesions (VIN 2/3) was also 100% (CI 41-100%), whereas for high-grade vaginal lesions (VaIN 2/3) vaccine efficacy did not reach statistical significance. Altogether there were eight cases of VIN 2/3 and five cases of VaIN 2/3, and all occurred in the placebo group. The efficacy against genital warts caused by the vaccine HPV types was 98.9% (CI 94-100%) in the PPE-population

Vaccine efficacy was much lower in the MITT-3 population, as evident from Table 1.

Table 1: Integrated summary of efficacy in the PPE- and MITT-3 populations

Endpoint	Gardasil	Placebo	Vaccine Efficacy %	95% CI
HPV16/18-related CIN 2/3				
PPE	0	53	100%	92.9, 100.0
MITT-3	122	201	39%	23.3, 51.7
HPV 6/11/16/18-related VIN 2/3				
PPE	0	8	100%	41.1, 100.0
MITT-3	14	28	49.8%	1.5, 75.6
HPV6/11/16/18-related genital warts				
PPE	1	91	98.9%	93.7, 100.0
MITT-3	58	184	68.5%	57.5, 77.0

The protective efficacy against all CIN 2/3 (regardless of HPV-type) was 38.5% among HPV-naïve subjects (CI <0-63.4%) and 12.2 % (<0.0-25.3%) in the MITT-3 population

During the study period, the vaccine did not seem to induce any therapeutic efficacy in females who were already infected with any relevant HPV vaccine type at baseline. However, individuals already infected with one of the vaccine-related types prior to vaccination were protected from clinical disease caused by the other HPV types.

In summary, the studies indicate a very high degree of protection against histological high-grade cervical lesions and condyloma accuminata caused by the vaccine types if the girl/woman is not infected with any of the vac-

cine types at the start of vaccination. However, the value of vaccination decreases with time after sexual debut, and therefore vaccination in a population with unknown HPV-status at the start of vaccination is of reduced value.

There were also immunogenicity studies performed, assessing the tetra-valent vaccine in 12,344 subjects aged 9 to 26 years, also including boys aged 9-15 years. The immunogenicity studies involving children aged 9-15 years were aimed to bridge with the efficacy studies in adult women, since efficacy cannot be evaluated in sexually naïve subjects. Since the minimum anti-HPV levels associated with protection from the acquisition of HPV is not known, the cut-off value of validated assays was used as a surrogate for seropositive level. The type-specific cLIA (competitive Luminex-based immunoassay) method was used. The anti-HPV responses at Month 7 among boys and girls aged 9-15 years were significantly higher than those in 16- to 26-year-old women for whom efficacy was established in phase III trials. In fact, the anti-HPV responses increased as the age at which vaccination was initiated decreased, with the highest responses seen in children aged ≤ 12 years. In view of the non-inferior immune responses, along with the characteristics of the kinetics of the immune response, efficacy bridging from adult women to girls is considered to be justified. Bridging immunogenicity data to males is less obvious since there is no efficacy bridge to adult males, but ongoing efficacy studies in males will address the protection against penile cancer, anal cancer and condyloma.

The observation period in the phase III efficacy trials was limited to two years and to 18 months in immunogenicity trials of adolescents in September 2006 (at the time of approval). Immunogenicity in adult women was further followed for five years in one phase II trial; see duration of protection (below).

Details in the study database used for licensure application can be found in the Swedish monography at the website of the Medical Product Agency (7).

What is noteworthy is the fact that age and gender are not considered in the European indication for Gardasil, whereas in the USA the indication is restricted to females aged 9-26 years. With regard to lesions in the indication, the USA also includes CIN grade 1, cervical adenocarcinoma in situ (AIS), and high-grade vaginal intraepithelial neoplasia (VaIN 2/3), which are not mentioned in the EU SPC (Summary of Products Characteristics) (4).

Efficacy results after approval (May 2007)

Further efficacy results from the FUTURE studies after a longer follow-up period (a mean of three years after the first vaccine dose) have recently been published. In the FUTURE I study, vaccine efficacy in the HPV naïve population remained at 100% for the co-primary endpoint (8). In the FUTURE II study, vaccine efficacy against HPV 16- and/or HPV 18-related CIN 2/3 was 98% (86-100%) in the PPE-population and 44% (26-58%) in the MITT-3 population (9).

In two other publications, a combined efficacy analysis of the four mentioned efficacy trials, was presented with respect to vaccine efficacy against HPV 16- or HPV 18-related CIN 2/3 and AIS (10) and efficacy against high-grade vulvar and vaginal intraepithelial neoplasia (VIN 2/3 and VaIN 2/3) (11).

The integrated analysis for cervical lesions was based on 85 CIN 2/3 cases in the placebo group and one case in the vaccine group, giving a vaccine efficacy of 99% (93-100%) in the HPV naïve population. In the MITT-3 population, the vaccine was 44% (31-55%) effective. When looking at all CIN 2/3 lesions and AIS regardless of causal HPV type, the estimated efficacy was 18% (7-29%). Statistical significance was only reached for CIN 2 when analysed by lesion type.

In the combined analysis of HPV 16- or HPV 18-related VIN 2/3 and VaIN 2/3, the vaccine efficacy was 100% (72-100%) among HPV naïve women. Statistical significance was reached for both VIN 2/3 and for VaIN 2/3 when analysed separately. Vaccine efficacy was 71% (37-88%) among all women (MITT-3 population). If all high-grade vaginal/vulvar lesions were taken into consideration, regardless of causation (HPV or not), vaccine efficacy was 49% (18-69%).

In summary, the longer-term follow-up studies support sustained vaccine efficacy up to three years after the first vaccination.

Clinical studies - Cervarix

The Cervarix vaccine was approved by the EU Commission 20 September 2007 (12). This bivalent vaccine contains HPV 16 and HPV 18 L1 VLPs and a new adjuvant, ASO4, which is a combination of monophosphoryl lipid A (a lipopolysaccharide) adsorbed to aluminium hydroxide. Initial studies revealed higher antibody responses with vaccine formulations containing this adjuvant as compared to the aluminium hydroxide alone (13), allowing for a reduced antigen content of HPV 16.

The efficacy of Cervarix was studied in two placebo-controlled, double-blind and randomised clinical trials including a total of 19,778 women aged 15 to 25 years (14, 15)

An initial placebo-controlled study, enrolled only women who were naïve for 14 oncogenic HPV types (including HPV 16 and HPV 18) and had normal cytology at baseline (n=1113). After a follow-up of up to 27 months 100% (47-100%) protection against HPV 16/18-related persistent infection (two PCR-samples with an interval of at least 6 months) was demonstrated in accordance with the protocol population (ATP) and 95% (64-99%) in the ITT population (14). Thereafter a subset of women (n=776) was recruited into an extension phase with a mean follow-up of 47.7 months (16). Vaccine efficacy against HPV 16/18-related 6-month and 12-month persistent infection was 94% (63-99.9%) and 100% (33-100%), respectively. When efficacy was analysed by HPV type, statistical significance was not reached for HPV 18. In a combined analysis of the initial and follow-up studies, there were five cases of HPV 16-related CIN 2/3 in the placebo group as opposed to none in the vaccine group.

Interim results have been published from a large double-blind phase III trial (PATRICIA) enrolling 18,729 women in four study regions: Asia Pacific, Europe, Latin America and North America (15). The study subjects were randomised to receive either Cervarix or a control hepatitis A vaccine (HAV 360 or HAV 720 depending on age). Participants with a maximum of six lifetime sexual partners were enrolled and vaccinated without pre-screening for the presence of HPV infection.

Vaccine efficacy was evaluated in women who were seronegative and DNA negative to HPV 16 or HPV 18 and who had received at least one dose of the HPV vaccine or control. Women with high-grade or missing cytology (0.5%) were excluded from the efficacy analysis. Overall 74% of subjects were naïve to both vaccine HPV types at study entry. The mean follow-up in the study was limited to 14.8 months after the first vaccination.

Efficacy results are shown below in Table 2. The analysis of all primary and secondary endpoints reached statistical significance for HPV-16. For HPV-18, the difference between the vaccine and control groups was not statistically significant for CIN 2/3 and 12-month persistent infection. However, in a pre-specified analysis in another HPV naïve population that also excluded women with abnormal cytology at study entry, the 12-month persistent infection endpoint for HPV-18 reached statistical significance with a vaccine efficacy of 89.9% (97.9% CI: 11-99.9). In this additional analysis one endpoint case was observed in the vaccine group versus ten cases in the control group.

Table 2: Vaccine efficacy against HPV 16/18-related CIN 2/3 and 12-month persistent infection in HPV DNA negative and seronegative subjects

	Cervarix		Control	Efficacy (97.9% CI)	
	N	n of cases	N	N of cases	
CIN 2/3 (primary endpoint)					
HPV-16 and/or 18	7,788	2	7,838	21	90.4 (53.4; 99.3)
HPV-16	6,701	1*	6,717	15	93.3 (47.0; 99.9)
HPV-18	7,221	1*	7,258	6	83.3 (<0.0; 99.9)
12-month persistent infection (secondary endpoint)					
HPV-16 and/or 18	3,386	11	3,437	46	75.9 (47.7; 90.2)
HPV-16	2,945	7	2,972	35	79.9 (48.3; 93.8)
HPV-18	3,143	4	3,190	12	66.2 (<0.0; 94.0)

* Simultaneous detection of another oncogenic HPV type. HPV 16 and HPV 18 were only found on one occasion, whereas the other oncogenic HPV type was detected in preceding cytology samples.

There was no evidence of protection from disease caused by the HPV types for which subjects were DNA-positive at study entry. However, individuals already infected with one of the vaccine-related HPV types prior to vaccination were protected from clinical disease caused by the other HPV type.

In summary, a very high degree of protection was against HPV 16/18-related high-grade cervical lesions in women naïve to the vaccine HPV types at study entry. However, the follow-up time is as yet very short (~15 months) and longer-term data is needed to evaluate efficacy in the pre-

specified primary efficacy population (ATP (According-to-Protocol) cohort, post-dose 3) and to confirm efficacy against HPV type 18.

The immunogenicity induced by three doses of Cervarix has been evaluated in 5,303 female subjects from 10 to 55 years of age. Studies indicate non-inferior antibody responses in girls aged 10-14 years in comparison with females aged 15-25 years allowing efficacy bridging of data to adolescents. Notably, immune responses were significantly higher in children compared to the young women. In contrast, in older females aged 25-55 years the antibody responses decreased with age, but the concentrations obtained were still high in comparison with natural infection, and with remaining seropositivity throughout the follow-up phase (up to 18 months).

The observation period in the phase III efficacy trial was limited to 15 months and to 18 months in immunogenicity trials of adolescents. Immunogenicity in adult women was further followed for 4.5 years in the phase II efficacy trial, see duration of protection (below).

In an ongoing community-based trial in Costa Rica, the effect of Cervarix on viral clearance was evaluated among 2,189 women aged 18 to 25 years infected with HPV 16/18 at the time of vaccination (17). Among women positive for HPV 16 or HPV 18 at baseline, vaccine efficacy for preventing persistent infection with HPV 16/18 at 12 months was -2.0% (95% CI: -24.3-16.3%). The results demonstrating no vaccine effect on viral clearance of HPV 16 and HPV 18 indicate that no therapeutic benefit of the vaccine is to be expected among women already infected at baseline.

Cross protection

The HPV types are organised into different species based on L1 (major capsid protein) gene homology. HPV 16 and HPV 18 belong to different species and share varying degrees of homology with respective species members. There is a high degree of L1 amino acid homology between HPV types 45 and 18 and between HPV types 31 and 16. However, the serologic cross-reactivity is low, with almost a 2-log difference in antibody responses. It is therefore not expected that any substantial cross-protection against types 45 or 31 will follow from immunisation against types 18 or 16. Also, low antibody concentrations are likely to wane earlier and persistence of cross-protection can therefore not be assumed a priori, i.e. without long-term follow-up.

Despite this assumption, one ongoing long-term efficacy follow-up study of Cervarix suggests that there might be some cross-protection against related non-vaccine HPV types. According to preliminary results, somewhat fewer than expected cases of incident infections with HPV 45 and 31 were observed (1 and 14 cases respectively in the vaccine group, whereas the corresponding figures in the placebo group were 17 and 30) (16). However, data on cross-protection against the more valid endpoint, CIN 2/3, are awaited. For Gardasil preliminary results were recently presented suggesting certain vaccine efficacy against HPV 31/45-related CIN 2/3 in the HPV naïve population (18).

Duration of protection, need for booster vaccination

Antibodies against intact L1 VLPs are essentially HPV type-specific, although there is strong cross-reactivity between HPV types 6 and 11. Detectable antibodies against HPV in a non-vaccinated person constitute a marker of the cumulative HPV exposure, and can predict such an exposure with about 50% sensitivity. In population studies, there is a correlation between seropositivity and the number of lifetime sexual partners, but not with respect to the number of recent partners (19). The detection of HPV-DNA and IgA against HPV in cervical secretion is, however, correlated to the number of recent partners (19). Serum antibody concentrations in naturally infected subjects usually persist for many years after the clearance of an infection. However, waning antibody responses have been demonstrated particularly when there has only been transient PCR-positivity for HPV.

Comparisons of antibody concentrations obtained by ELISA techniques at different laboratories are at present hampered by the lack of an international reference serum. Such a standardisation tool would enable the presentation of follow-up results in international units. Current methods for analysis of neutralising antibodies demonstrate good interlaboratory correlations, and also the correlations between neutralising antibodies and binding antibodies are good (20). While waiting for international comparisons by use of standardised methodology, the antibody analyses in long-term serologic follow-up studies are carried out in-house at the laboratories of the two vaccine manufacturers.

For Gardasil, there is one published five-year efficacy/immunogenicity follow-up of one of the phase II trials, see table below (21).

Table 3. Efficacy of Gardasil over 5-year follow-up for per protocol participants (Adapted from Villa LL, Costa RLR, Petta CA et al)

Endpoint	Vaccinated N	Vaccinated Cases	Placebo N	Placebo Cases	Efficacy (95% CI)
Infection or disease	235	2	233	46	96% (84-100%)
Infection	235	2	233	45	96% (83-100%)
Disease	235	0	233	6	100% (12-100%)
CIN 1-3	235	0	233	3	100% (<0-100%)
Condyloma	235	0	233	3	100% (<0-100%)
Endpoints by HPV type					
HPV 6	214	0	209	17	100% (76-100%)
HPV 11	214	0	209	3	100% (<0-100%)
HPV 16	199	1*	198	28	97% (79-100%)
HPV 18	224	1**	224	11	91% (36-100%)

Two vaccine cases:

*HPV 16(+) at the last visit on record (month 36) without confirmed persistence

**HPV 18 infection at months 12 and 18, subsequent time points tested HPV DNA-negative

The geometric antibody titres peaked at Month 7 and then declined to Month 24, after which they were stabilised until Month 60. After five years the immune response was equal to or greater than that observed during natural HPV infection. Overall 90-99% of subjects remained seropositive at Month 60, except with respect to HPV 18, for which only 63% were still seropositive. There was no evidence that the rate of seropositivity was associated with loss of protective efficacy (Table 3).

A subset of vaccinated individuals who received a challenge dose of Gardasil 5 years after the primary series exhibited a rapid and strong anamnestic response to all vaccine HPV types that exceeded the antibody titres observed after the primary immunisation. For HPV 18, the geometric mean titres increased 23-fold and seropositivity rate was 99%. These data demonstrate evidence of a vaccine-induced memory. However, it is not known at present whether an immune memory would be sufficient to protect against disease at the genital mucosal level. Evidence of an anamnestic response was also seen in vaccinated individuals, who were seropositive to relevant vaccine HPV types prior to vaccination.

For Cervarix, the long-term follow-up of the initial study in young women aged 15-26 years indicates persisting high antibody concentrations for up to 4.5 years. At this time-point the concentrations were about 17-20 times higher than those obtained after natural infection, and the protection against persistent infection remained at 94% (63-100%) (16).

An immunological correlate of protection for HPV vaccines has not been established. Therefore, only the ongoing long-term surveillance of immunogenicity/effectiveness of the HPV vaccines will give data on the duration of protection and the possible need and timing for booster doses.

Safety and simultaneous administration of other vaccines

Gardasil

The proportion of subjects reporting an adverse experience in the injection site was significantly higher in patients receiving the vaccine (83%) compared with subjects receiving the aluminium-containing placebo (77%) or the non-aluminium containing placebo (50%). Any grade/size of pain, erythema and swelling at the injection site were very common in all groups, and severe local reactions (swelling or redness >5 cm or incapacitating with inability to work or do usual activity) were observed in 5% of vaccine recipients compared with 2% of placebo recipients. Headache, nausea and other systemic reactions were commonly occurring in around 60% of vaccine and placebo recipients. Pyrexia was recorded in 10-11% in both groups, and high fever above 39.9°C in 0.1-0.2%. The seven overall serious systemic adverse events (<1%) were assessed as not related to the study vaccines by the investigators. The safety profiles of the different age groups and sex were similar.

Cervarix

The Cervarix studies also indicate that local pain/tenderness occur in significantly higher frequencies among vaccine recipients (78%) compared with the aluminium-containing (ALU) placebo recipients (53%) and the control vaccine recipients (41% and 59%) (two different doses of hepatitis A vaccine). Severe local reactions were reported in 6% of vaccinees compared with 0.8-3.4% of control subjects. The frequency of systemic adverse events was comparable in the HPV (67%) and control vaccine (73%) groups, but lower in the ALU group (55%). The incidences of arthralgia and myalgia were somewhat higher in the HPV group in comparison with the control vaccine group (10.2% vs. 8.6% and 28% vs. 26.5%, respectively). Severe myalgia was more common in the HPV vaccine group compared with the control groups (1.4% vs. 0.2-0.5%). Most adverse reactions were mild to moderate in intensity, of short duration and resolved without sequel. Few subjects (0.2%) were withdrawn from the study for safety reasons.

Overall, fatigue, muscle pain or headache were very common (reported by $\geq 1/10$), while fever ($>38^{\circ}\text{C}$), arthralgia, gastro-intestinal symptoms itching or exanthemas were common (reported by $\geq 1/100$). Of the vaccine recipients 2.8% reported serious systemic adverse events compared with 2.2-3.8% of the control groups. In the vaccine group 11 serious adverse events were considered to be possibly related to vaccination compared with 13 events in the control groups. Seven cases of neurological disorders (five in the HPV vaccine group and 2 in the control group) were reported. The relation of these events to vaccination was unclear and there was no cluster in terms of time or number of doses. These cases were not considered indicating an increased risk of demyelinating disease or nerve disorders (12).

Pregnancy, lactation, contraceptives

Pregnancies occurred in 1,115 vaccinees during the Gardasil clinical study program and in 870 women who had received Cervarix. There was no evidence that the vaccine had an impact on fertility, the outcome of pregnancy, foetal deaths or congenital anomalies. Overall, the data on vaccine administration during pregnancy did not indicate any safety signal. However, the data are insufficient to recommend the use of HPV vaccines during pregnancy. Vaccination should, therefore, be postponed until after the completion of pregnancy.

A total of 995 breastfeeding mothers were given Gardasil or placebo during the vaccination period of the clinical trials. The rates of adverse reactions in the mother and the breastfed infant were comparable between the vaccination and the placebo groups, as was the immune response. Administration to a breastfeeding mother is therefore considered safe for both the mother and the infant. The effect on breast-fed infants of the administration of Cervarix to their mothers has not been evaluated in clinical studies.

Concomitant administration of other vaccines

Studies of concomitant administration of HPV vaccines and other vaccines are as yet scarce. There is, however, documentation on concomitant admini-

stration of HBVAXPRO (hepatitis B vaccine) and Gardasil. There were no increases in adverse reaction rate, and no differences in HPV antibody responses as compared to separate injection visits. However, the geometric mean concentrations of anti-HBs antibodies were somewhat lower in the group receiving both vaccines at the same time as compared to separate injections, but there were no differences in seroprotection rates (anti-HBs ≥ 10 IU/ml).

Summary

Gardasil and Cervarix demonstrate high protective efficacy (90-100%) in HPV naïve women against HPV 16/18-related cervical cancer, as measured by the surrogate endpoints CIN 2/3 and other relevant histological endpoints. For Cervarix only data on short-term efficacy is at present available. Gardasil has also been evaluated for external genital lesions and high vaccine efficacy has been shown against HPV 16/18-related pre-cancerous vulvar and vaginal lesions (VIN 2/3 and VaIN 2/3) as well as against HPV 6/11-related genital warts.

Vaccine efficacy against CIN 2/3 due to HPV 16/18 in the intention-to-treat population, including women already infected with vaccine HPV types, is substantially lower; 44% for Gardasil after three years of follow-up. Similar data are not available for Cervarix.

Efficacy of Gardasil against all cervical lesions (any grade) regardless of causal HPV types in the intention-to-treat population varied between 17 to 20% in the phase III trials. A significant effect was only demonstrated for CIN 2 lesions in one of the trials, whereas statistical significance was not reached for CIN 3.

Based on these data it is evident that vaccination is of greatest value in females not yet exposed to any of the vaccine HPV types. The degree of vaccine protection will be reduced in sexually active women depending of the number of sexual partners before the start of the vaccination series. There is, however, a substantial uncertainty in the estimates of median age of infection, and it is also likely that individual variation may be considerable.

Protection remains high up to 4-5 years after vaccination in the follow-up studies performed so far. Serologic studies and mathematic modelling support the theory that protection will be sustained over many years. However, it is currently not possible to determine the exact duration of the protection, and there is therefore no information on whether or when booster(s) will be needed.

There are no indications of a therapeutic effect in women who are HPV-positive to relevant vaccine types, but it is as yet unclear whether or not vaccination of women who have already had (and cleared) an HPV-infection is of value or not. Further studies of vaccination in older age-groups need to address the issue of pre-screening for HPV status in order to select individuals who are most likely to benefit from vaccination.

Both vaccines are well tolerated in all studied age-groups, with no differences between prepubertal girls and young women, nor did the safety profile

for Gardasil differ in prepubertal boys. It is noteworthy that substantially higher antibody responses were obtained in the youngest age-groups, i.e. prepubertal girls and boys. Extended follow-up of immunised subjects is needed to identify any long-term adverse effect associated with the HPV vaccines. The safety of the vaccine has not been studied in subjects younger than 9 years old and its use should be avoided in this age group.

The vaccines are non-live and it is therefore not likely that any major interference with other childhood vaccines of teenagers will be demonstrated. However, until studies are conducted some antibody interference cannot be excluded.

There is insufficient safety data in pregnant women and vaccination during pregnancy should therefore be postponed until after the completion of pregnancy.

Ongoing studies are addressing the protective value against other types of anogenital HPV-related cancers and dysplasias in men, and there are also studies ongoing in mid-aged women.

There are at present no studies on reduced vaccination schedules, such as two doses with a 6 month interval. Considering the high immunogenicity, especially in prepubertal girls and boys, studies of two doses with a 6 month interval seem warranted.

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Modelling Vaccination Effectiveness

Dynamic HPV infection model

Considerations on immunisation strategies should as far as possible be based on scientifically founded predictions of effect. For prediction of how different vaccination strategies impact on the circulation of HPV infections, the dynamic effects should be taken into account. As protected subjects do not transmit the infection, the protective effect of programs targeting substantial proportions of entire populations is greater than the sum of the protective effect on vaccinated individuals.

We used the published and well characterised dynamic model of HPV infection by French et al, 2007, which requires the following input data: 1) the proportion of sexually active individuals in the age strata of the population that are considered to be targeted for vaccination and 2) the HPV seroprevalence in the age groups to be targeted for vaccination.

To increase the transparency of the model as far as possible, we restricted the model to HPV infection as the outcome. Models that use cervical cancer or other HPV-associated diseases as the outcome are dependent on a number of critical input values (such as progression and regression rates, screening attendance rates) that have substantial uncertainty and result in complex models with limited transparency. By contrast, the total age-specific health burden of HPV-associated diseases can be estimated in a transparent manner (see section 1).

Estimating sexual activity and HPV incidence for Sweden

The original modelling paper that estimated optimal target groups for vaccination (French et al, 2007) used input data from Finland (below).

Table I Percentage of each age that is sexually active in the model

Age	12	13	14	15	16	17	18	19	20+
Sexually active (%)	0.6	1.7	4.4	10.6	30.0	50.0	65.0	80.0	99–100

The percentage of subjects in each age group that is sexually active in Sweden was last estimated in 1997 in the ‘Sex in Sweden’ investigation by the Public Health Institute of Sweden. The detailed data for the age strata of interest was obtained from the main author of Sex in Sweden (Bo Lewin) and is shown below.

Table 2 Percentage of subjects in each age group that is sexually active in Sweden

	Age	Women	Cumulative	Men	Cumulative
First experience of sexual intercourse (among those with experience of sexual intercourse)	13 or younger	0.05	0.05	0.05	0.05
	14-15	0.33	0.38	0.29	0.34
	16-17	0.35	0.73	0.33	0.67
	18-19	0.19	0.92	0.21	0.88
	20-24	0.08	1	0.12	1

Sex in Sweden had a meagre response rate to the population-based inquiries, which may have biased estimates and was performed ten years ago. To investigate whether sexual behaviour has been changing over the last decade, detailed data on reported cases of Chlamydia Trachomatis infections was obtained from the Swedish Institute for Infectious Disease Control and is shown below.

Table 3 Data on reported cases of Chlamydia Trachomatis infections in Sweden.

Age	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006
9	1	1		1						
10			2		1					
11				1						
12		1	1	1	3	8	1	1	3	2
13	5	8	12	13	15	25	27	28	26	14
14	55	59	58	89	112	124	136	191	155	162
15	200	202	239	227	353	399	514	682	576	509
16	506	470	533	578	750	903	1069	1367	1704	1261
17	741	822	894	927	1159	1372	1559	2161	1683	2086
18	981	1253	1269	1460	1683	1950	2240	2873	2831	2645
19	1152	1323	1493	1720	2113	2170	2447	3073	3109	3011
20	1337	1442	1584	1926	2242	2357	2548	3112	3860	3252
9-20 years	4978	5581	6085	6944	8431	9308	10541	13490	13947	12942
Total	13905	15199	16710	19284	22267	24691	26803	32281	33060	32518

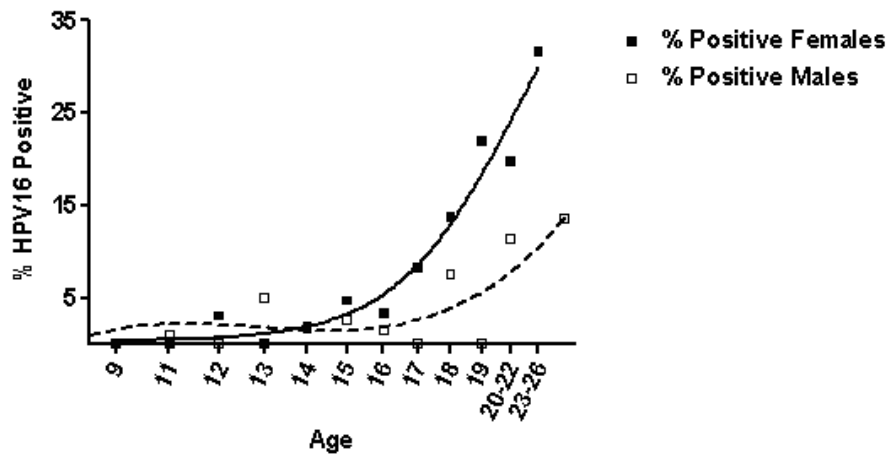
The data suggests that there has been a change over time in behaviour resulting in increased spread of sexually transmitted infections (STI) and a tendency for STI in lower age groups. It should be noted that the risk for chlamydia keeps increasing with every year between 12 and 20 years of age.

For estimating HPV seroprevalence, we used the Swedish Institute for Infectious Disease Control's nationwide survey of immunity from 1997. The survey had not sampled all ages that were of interest in the potential target age groups and the nationwide survey was therefore combined with samples from a regional biobank in Southern Sweden (Malmö Microbiology Biobank). Overall, 3,300 subjects were sampled, with at least 100 in each age

group. Seroprevalence for HPV16 was then assessed by use of the conventional virus-like particle ELISA.

The resulting estimate of cumulative incidence of HPV16 infection in Sweden is shown below.

Figure 1. Total HPV16 seroprevalence among females and males aged 9-26. Estimate of infection.

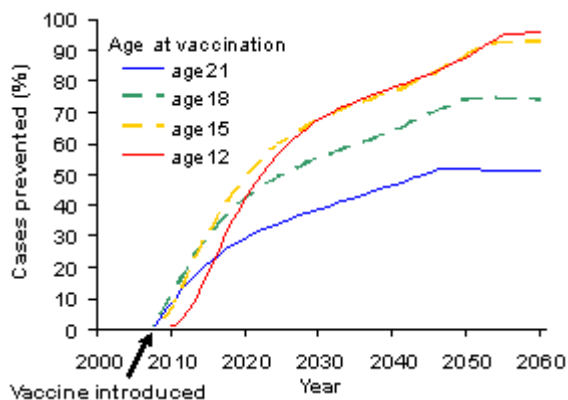


The age-specific seroprevalence curve shows a strikingly similar shape to the age-specific reporting of chlamydia cases, with a rapidly increasing incidence between 17 and 22 years of age.

Target age of a general vaccination program

The proportion of HPV16 infections prevented by different ages at vaccination is shown below for a program vaccinating only females and having 90% population coverage.

Figure 2. Graph showing percentage of cases being prevented by targeting different age groups of girls.



Similar to the published model that used Finnish input data and used cervical cancer as the outcome, we see little difference in the ultimate outcome when completing the vaccination series at 12 or at 15 years of age, apart

from the expected delay that the effect will come three years later when vaccinating 12 year olds. Logistic and safety reasons argue in favour of the 12-year-old scenario.

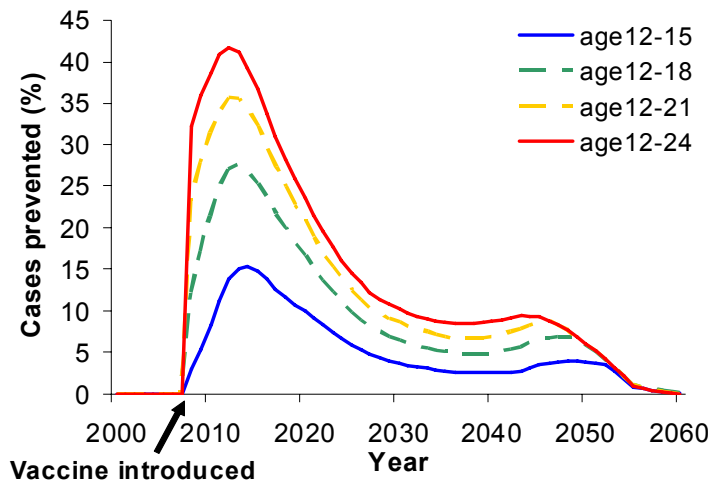
Catch-up program - target age groups and sexes

The effect of the infection on different catch-up strategies is shown below, assuming a basic program vaccinating all females at 12 years of age. In the absence of a catch-up program, there will be an excess of HPV16 infections that will not disappear until 2060.

Catch-up program of females

There are several alternatives in a catch-up strategy, of which the most commonly considered is catch-up of females up to certain ages.

Figure 3. Graph showing percentage of cases being prevented by targeting different age groups of girls



The same data as in the figure above is shown in table 4 below.

Table 4 .Effects of catch-up in different age-groups

By 2055	Cumulative infections prevented (millions)	Added benefit	
		Cumulative	1 more year
No catch-up	5.8	-	-
13 years of age	6.0	+3.4%	+3.4%
14 years of age	6.2	+6.7%	+3.3%
15 years of age	6.3	+9.9%	+3.2%
16 years of age	6.5	+13.0%	+3.1%
17 years of age	6.7	+15.8%	+2.8%
18 years of age	6.8	+18.3%	+2.4%
19 years of age	6.9	+20.4%	+2.2%
20 years of age	7.1	+22.3%	+1.9%
21 years of age	7.1	+24.0%	+1.6%
22 years of age	7.2	+25.4%	+1.5%
23 years of age	7.3	+26.8%	+1.3%
24 years of age	7.4	+28.0%	+1.2%

As can be seen from the table, there are substantial gains to be made with catch-up programs reaching up to 18 years of age. Diminishing, but measurable, gains are also seen when performing catch-up to the age of 24.

Catch-up vaccination of HPV-negative women

The high protective efficacy of the vaccines is in all trials confined to a population that is naïve for the HPV types in the vaccine, as determined by pre-testing for HPV DNA and HPV antibodies. When there is vaccination of girls before their sexual debut, virtually all of them are negative and pre-testing is clearly unnecessary – this population approximates the per-protocol population in the HPV vaccination trials.

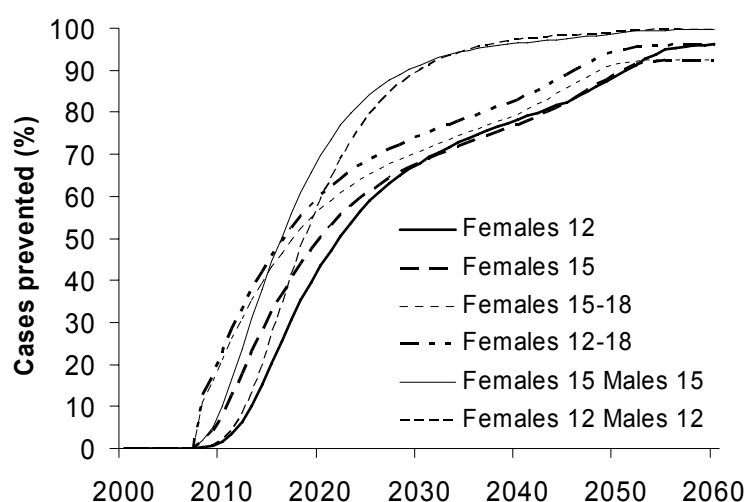
In catch-up vaccination of women after their sexual debut, there is a substantial risk that women are previously infected. Efficacy without pretesting in such populations is considerably lower in the HPV vaccination trials, and the mathematical models used have assumed vaccination without pre-testing in catch-up programs. Dynamic mathematical models – that include the effect of spread of infection between subjects (“herd immunity”) – tend to favour catch-up programs targeting the age groups that are most active in spreading the infection.

The present report is focused on vaccinating targeting age groups where substantial health benefits for society are expected, and in the age groups under consideration, prior HPV exposure is still limited, making pretesting less relevant.

Vaccination of males

Other catch-up strategies include vaccination of males, in addition to female-only vaccination programs (with or without catch-up of the females). We evaluated strategies including combinations of female and male vaccination at defined ages, but without catch-up of females beyond the vaccination age.

Fig 4 Proportion of infections prevented with different strategies



In terms of the number of infections prevented the strategies are compared below:

Table 5 Number of infections prevented with different strategies .

Vaccination Strategy	HPV 16/18-related cervical cancer cases prevented in 2055	Prevented cases per 100 vaccinations given	Cumulative cases prevented by 2055 (millions)
Females 12	95.0%	20.2	5.8
Females 15	92.3%	21.7	6.0
Females 15-18	92.5%	21.8	6.5
Females 12-18	95.5%	21.0	6.8
Females 15 + Males 15	99.5%	13.9	7.5
Females 12 + Males 12	99.8%	12.7	7.1

The strategies including the vaccination of males reach almost 100% protection – in spite of the fact that the model is based on four sexual activity classes with assortative mixing; a scenario that models difficult circumstances for the eradication of disease.

The program with basic vaccination of females at 10-12 years of age and catch-up vaccination of females for ages 13-18 compares favourably with basic vaccination of females plus vaccination of males in the number of cases prevented per vaccination dose given. In terms of the number of doses required for effect, the programs that include males are hence less effective as almost twice as many doses are required and result in only rather limited gains. All calculations assume 90% coverage for all groups vaccinated.

A major weakness of the model is that it includes only heterosexual transmission of HPV. Anal cancer is one of the more important health burdens of HPV and, although no specific modelling studies on the issue exist, there is reason to believe that strategies targeting females may only have limited effect on the spread of HPV among men having sex with men

(MSM) resulting in a less than optimal health effect in terms of prevention of anal cancer and other HPV-associated diseases in MSM. As HPV spreads very rapidly even among girls (risk for HPV16 infection is estimated at about 8% for each partner change among women) vaccination strategies specifically targeting MSM may risk mainly reaching subjects who have already been exposed. General vaccination of MSM is therefore not recommended. Whether strategies aimed at reaching as yet unexposed MSM are possible to perform in other ways than by vaccinating all boys is debatable.

Vaccination strategies specifically targeting heterosexual high risk-taking groups are not recommended, as most subjects will already have been exposed.

Conclusions

There is little extra effect on incidence of HPV 16 in girls to gain from catch-up programs targeting males.

Programs targeting both males and females in the basic vaccination at age 12 appear to give substantial health gains and almost reach the extinction of HPV, at least under the assumption of 90% vaccination coverage and substantial sexual activity heterogeneity in the population. Vaccination coverage among females that exceed 90% would diminish any additional gains from vaccinating males. As programs that include vaccinating males will have a lower effect per dose given and would involve substantial extra effort, it seems reasonable to postpone consideration of vaccinating males until the success (population coverage and resulting decline in HPV prevalence) of vaccinating females is known and the real data on the coverage can be used for estimating the benefit of vaccinating males.

Given the current data, a basic program vaccinating females only at 12 years of age and an ambitious catch-up program targeting women aged 13-18 years appears to be the optimal strategy for HPV control.

Ecology

Type replacement

There is a theoretical concern that the eradication of some HPV types will cause post-vaccination emergence of disease caused by types not included in the vaccine. This is known as ‘type replacement’.

Type replacement is a viral population dynamics phenomenon and is defined as the elimination of some types causing an increase in the incidence of other types. This effect can only occur if two conditions apply: 1) if there exists partial competition of different types during natural infection and 2) the vaccine does not afford cross-protection against incident infection against types naturally competed against (1).

Several epidemiological studies have addressed the question of possible competition between infections with different HPV types. The presence of type-specific antibodies (a marker of past or present infection) for one HPV type is associated with a strongly *increased* risk for being seropositive for other HPV types as well; also when adjusted for determinants of sexual behaviour. For example, the OR for being seropositive for HPV16/18/33 is 2.9 (95% CI: 1.6-5.3) if a woman is seropositive for HPV6/11, even when the risk is adjusted for sexual behaviour and other sexually transmitted infections (2). This is the opposite tendency to the expected finding if there had been competition.

Furthermore, studies of multiple positivities of HPV DNA in the same samples have, in general, not found clear examples of types of HPV DNA that do not go together, as would have been expected if there had been competition (3). If anything, past infection with HPV appears to increase the likelihood of acquiring a new infection. For example, Mendez et al 2005 reported on a cohort study where baseline HPV6/11 DNA positivity was associated with a 14.1-fold (95% CI 2.1-95.4) increased risk for incident infection with HPV18 at subsequent visits, where baseline HPV16/18 DNA was associated with a 5.7-fold (95% CI: 2.2-15.1) risk for HPV58 acquisition and no statistically significant decreased HPV incidences. Viral dynamics could also be affected if the duration of infectivity is affected, i.e. if prior infection with one HPV type would affect the time it takes to clear infection with another HPV type. In a population-based cohort study of >6,000 women, baseline HPV seropositivity did not affect the clearance rate of other HPV types (4).

It would therefore seem that the first prerequisite for type replacement, natural competition, does not apply and that type replacement therefore is unlikely. However, it should be pointed out that most of the studies that have investigated viral type competition effects on incidence and/or clearance have had limited statistical power to detect small effects, particularly for rare HPV types.

Although it is not yet clear if there will be any cross-protection of the VLP vaccines, there is preliminary data from a trial vaccinating with an HPV16/18 VLP vaccine, where some cross-protection against incident infection with related HPV types was seen (data in chapter on Vaccines, reference 16) further decreasing the likelihood for replacement phenomena.

Viral escape mutants

Apart from the risk of changes in population dynamics of already existing types, there is a possibility that viral escape mutants forming new serotypes could occur. However, the fact that HPV replicates using the cellular DNA polymerases and therefore has a very slow mutation rate suggests that this risk is low. This is also indicated by the fact that so far all different viral strains and variants of HPV16 from all over the world have been found to constitute a single serotype (5).

Attributable proportion/number of healthy women at risk

Because many women will be saved from cervical cancer caused by HPV16/18 by vaccination, the amount of healthy women who will be at risk for cervical cancer caused by other HPV types will increase. The proportion of cases prevented if an HPV type is eliminated is therefore not exactly the same as the proportion of positive cases, but is given by $S \cdot 1/1-RR$, where S is the proportion of positive cases and RR is the relative risk. As the HPV-related relative risks for cancer are very high, this effect is rather small.

Other conceivable effects

Altered age at exposure

When the spread of infection is reduced, the likelihood of becoming infected ('force of infection') will decrease resulting in the age peak of prevalence of infection peaks shifting towards a later age. There is a substantial amount of literature suggesting that early age of exposure may increase the risk of cervical cancer. An explanation that has been offered is that the immature cervix would be more susceptible, perhaps by exposing more of the transformation zone. However, it is difficult to separate the effect of early coitarche from sexual behaviour later in life in epidemiological studies. In any case, there are no indications that delaying the age of exposure will have detrimental effects.

Reduced attendance rate in cervical screening

Cancer incidence may increase if vaccination is perceived as a replacement to screening by the public, or if funding is transferred from screening to vaccination by politicians.

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Logistics

Logistical aspects of a general HPV-immunisation of school children in Sweden

Consideration of the optimal age of general vaccination of girls

The age of 12 years is not so far from, but prior to, the ages where sexual relationships are normally established. It is also a convenient age for performing the immunisation in school. At this age pupils attend the last year of middle school (grade six). They still have their own classrooms and are not split up into different subgroups during the school day. This enhances the coverage of the vaccination as it is carried out for all girls in an entire class at a time. To ensure that all can be vaccinated before they leave middle school it will in some instances be preferable to start already in the fifth grade. This means that an age-span where vaccination can take place between 10-12 years will be needed.

Estimated costs of a vaccination programme in the schools

Prerequisites

- General vaccination of girls by 10-12 years of age.
- The compliance is high, about 95%.
- The vaccination is carried out by school nurses, working in pairs.
- There is no spare time available in the daily work.
- Full immunisation requires three injections.

Estimate

Time required for the vaccination procedure

Two nurses usually work together, either as parallel vaccinators or one nurse performing the vaccination while the other is documenting. The experience from other vaccination programs is that ten pupils can normally be vaccinated per hour per nurse independent of the method chosen. That means that the time required for the vaccination procedure can be calculated to about five minutes per pupil and shot. For three injections the estimated time will be 15 minutes per pupil.

Time required for preparations and follow-up

The preparations and the follow-up include

- Information in the class by the nurse, concerning both the reason for the immunisation, the vaccination procedure, possible adverse effects and the procedure for getting informed consent.

- Obtaining informed consent from the parents. Written information is given to the parents by each pupil, who will then return the signed consent form to the school.
- Planning for the immunisation of each class carried out in coordination with the teachers.
- Follow-up of and separate vaccinations of pupils dropping out from the scheduled time.
- Separate contact with parents and pupils with special questions or demands.

The required time for this depends on many factors: for example how well informed parents already are through media information; the structure and size of the school and whether it is located in remote or urban areas. Interviews with experienced school nurses showed that the general estimated time for preparations and follow-up is calculated at between 15 to 30 minutes per pupil, covering all three injections.

Total time

The total estimated time for carrying out the vaccination program in school is between 30 to 45 minutes per pupil. Assuming that one school nurse produces 1,600 active hours per year this equals a request of one or one and a half school nurses per 3,200 vaccinated pupils. The yearly total cost for a Swedish school nurse is 450,000 SEK. This equals a cost of between 125 to 190 SEK per vaccinated pupil. The cost of the vaccine is not included in this estimate.

Logistical aspects of a catch-up vaccination programme for girls 13 to 18 years of age

A catch-up programme could according to previous chapters be considered for girls between 13 and 18 years. It would mean a considerable burden to the part of the health-sector and any catch-up vaccination will have to be carried out outside the school health care system. The main reason for this is that it otherwise may seriously disturb the introduction in school of the general vaccination program for 10-12-year-old girls.

Proposed strategy

The vaccination is most easily administered by nurses at the Primary Care Centres.

Written information concerning the vaccine is sent to all parents of girls who are 13-18 years of age, with a recommendation to contact the local primary care centre for further assistance.

At the primary care centres the vaccination procedure can be organised as in school, with two nurses working in pairs. The estimated time for the procedure and the preparation time ought to equal those in school. That means

that the estimated costs for the catch-up vaccination also range from 125 to 190 SEK per girl for three shots.

An alternative provider could be the Youth Clinics (Ungdomsmottagnin-gar) run by the local communities, staffed by midwives supervised by GPs or gynecologists. One of their most important tasks is serving adolescents, mostly, girls with information, advice and diagnosis on STI and sexology. Young women have confidence in them and they would be natural providers of catch-up vaccination to adolescents who have not come to the Primary Care Centers. The vaccinations can also function as an entry point to this type of services where information on preventive measures can be given in the meantime. The estimated cost in this setting would be similar to the cost in school.

Health economics

The following section is taken from the SBU report “ SBU Alert-rapport nr 2008-01: Allmän barnvaccination mot HPV 16 och 18 i syfte att förebygga livmoderhalscancer. www.sbu.se <<http://www.sbu.se/>>”

Review of the health-economics of vaccination

The literature search included studies and health technology reports on vaccination against HPV 16 and 18 to prevent cervical cancer, published until August 2007. Thus, studies including other diseases related to HPV 16 and 18 or other HPV's were excluded.

Costs

The cost per vaccine dose is approximately SEK 1,100 for both vaccines. A general vaccination against HPV16 and 18 in a cohort of girls in Sweden (n = 60,000 is assumed) is estimated to incur an annual cost of around SEK 197 million in an extended programme that has been running for several years. In this calculation the cost of personnel is assumed to be SEK 50 per vaccination with 95 percent compliance, i.e. $\text{SEK } (60,000 \times 0.95) \times (1,100 + 50) \times 3 = 196,650,000$. A booster dose is estimated to cost around SEK 65.5 million per annum, which gives a total cost of approx. SEK 262 million per annum. To be added to this are the costs of following up a vaccination programme, which are probably considerable, but are difficult to estimate. If boys were also to be vaccinated, this would double the above cost.

Cost-effectiveness analysis

The published health-economic model studies for vaccination against HPV 16 and 18 were based on epidemiology and cost data from the respective countries [1-4]. This may mean that infection frequency and costs may differ from Swedish conditions. Table 5 presents the six health economic model studies in which general vaccination against HPV 16 and 18 were evaluated [5-10]. Three different alternatives were analysed in the studies: gynaecological cell sample tests, vaccination, or a combination of both these methods. Four studies only include direct medical care costs, i.e. they have a medical care perspective. The health economic evaluations from Denmark [9] and Norway [7] also include indirect costs, i.e. they have a societal perspective. With the generally low vaccination compliance in Denmark, 70 percent compliance was assumed for the basic calculation. Sanders and Taira also assumed 70 percent compliance, the Norwegian study 90 percent, whilst Goldie and Kulasingam assumed 100 percent compliance. Three of the studies, including the Norwegian and Danish, also included effects of herd immunity in the calculations.

The estimated cost effect quotient in the model studies for vaccination against HPV 16 and 18 varies from less than SEK 100,000 to well over SEK 458,000 per life year saved (LYS), assuming general vaccination of girls aged 12 (see Table 5 for other assumptions). In the Danish study the cost was estimated at SEK 125,900 per LYS with 70 percent compliance, and SEK 171,200 per LYS with 85 percent compliance with the vaccination programme (at the exchange rate of 1 DKK = 1.24 SEK). The Danish analysis also included vaccination of girls up to the age of 19 (so-called catch-up), but no booster dose of the vaccine. The Norwegian analysis also used quality-adjusted life years (QALY) as an outcome measure based on information from the USA. In the Norwegian calculation the direct medical care cost was estimated at SEK 458,850 per QALY (at an exchange rate of 1 NOK = 1.15 SEK). When the costs of avoided production loss were included in the calculation (so-called indirect costs or social perspective), the cost decreased to SEK 135,700 per QALY. A ten percent decreased compliance with vaccination increased the direct cost by SEK 86,250 to SEK 545,100 per QALY. If the effect of the vaccine was also assumed to drop by 5 percent, the direct cost increased to SEK 584,200 per QALY.

Taira et alia also calculated the cost effectiveness assuming vaccination of both girls and boys aged 12 [18]. This resulted in an increase in cost from SEK 94,350 per QALY (girls only) to SEK 2,860,000 per QALY (both girls and boys) (at the exchange rate of 1 USD = 6.47 SEK).

The American studies are based on cost data and incidence that may differ from Swedish conditions, but there are also differences between the Nordic countries. Compared with Sweden, Denmark has a 60 percent higher incidence of cervical cancer, 16 compared to 10 per 10,000 inhabitants. Compliance analyses showed that the results in the Danish and Norwegian studies were sensitive to vaccine price, compliance with the vaccination programme, the protective effect of the vaccine and level of the discounting rate.

Table 1 Health economic model studies of vaccination against HPV 16 and HPV 18.

	Denmark 2007	Norway 2007	Goldie et al, 2004*	Kulasingam et al, 2003*	Sanders et al, 2003	Taira et al, 2004
	[9]	[7]	[6]	[5]	[8]	[10]
Target group	Girls of 12 Catch-up	Girls of 12	Girls of 12	Girls of 12	Girls of 12	Girls of 12 Boys of 12
Perspective	Medical care, partially societal	Societal	Medical care, partially societal	Medical care	Medical care	Medical care
Model	Dynamic, herd immuni- ty	Dynamic, herd immunity	Cohort, Markov	Cohort, Mar- kov	Cohort, Markov	Hybrid, i.e. cohort + herd immunity
Economic analysis	CEA	CEA and CUA	CUA	CEA	CUA	CUA
Time frame	62 years (up to the age of 75)	52 years (up to the age of 65)	Whole life	70 years	70 years	70 years
Proportion of HPV 16/18- related cancer cases	70%	70%	70%	70%	70%	70%

Screening programme continues (participation)	Yes (70%)	Yes (Present position)	Yes (84–97% Different assumptions)	Yes (100%)	Yes (71%)	Yes
Protective effect	90%	90%	90%	90%	75%	90%
Vaccination compliance	70%	90%	100%	100%	70%	70%
Persistence of the vaccine	Whole life	10 years, then booster	Whole life	10 years, then booster	10 years, then booster	10 years, then booster
Cost of vaccine per dose	868 DKK (1,076 SEK)	1,259 NOK (1,448 SEK)	377 USD (2,639 SEK)	200 USD (1,400 SEK)	300 USD (2,100 SEK)	300 USD (2,100 SEK)
Discounting	3%	4%	3%	3%	3%	3%
Increased survival, days					2.8 days all, quality adjusted 4 days	5 days all, quality adjusted 6.1 days
NNT					1 484	
The basic model, cost per QALY and LYS	101,526 DKK per LYS direct costs, 11,396 DKK per LYS direct +	399,000 NOK/QALY direct costs, 118,000 NOK/QALY direct +	20,600 USD/QALY	44,899 USD/LYS	22,755 USD/QALY	14,583 USD/QALY, Including boys 442,039 USD/QALY

* The studies were conducted with the financial support of the vaccine producing drug companies. Booster = Booster dose; Catch-up = Vaccination of older age groups; CEA = Cost effectiveness analysis; CUA = Cost utility analysis; LYS = Life Years Saved; NNT = Number needed to treat; QALY = Quality adjusted life years.

A general economic estimate for Swedish conditions

What costs and effects may be expected in the long term if a general child vaccination against HPV 16 and 18 is introduced in Sweden? The calculations below are highly simplified and are based on the assumption that costs and effects are distributed proportionally with the volume of activity. Today the Pap smear screening is estimated to incur medical care costs of approximately SEK 202 million per annum (based on 690,000 screening Pap smears at a cost of SEK 250 and 20,000 secondary Pap smears at a cost of SEK 1,500). This cost is not expected to decrease if a general child vaccination against HPV 16 and 18 is introduced. On the other hand, a reduction in the treatment costs for CIN 2/3 and cervical cancer, costs which currently amount to approximately SEK 120 million per annum².

The number of cases of cervical cancer is currently approximately 450 per annum. Without Pap smear screening the incidence of invasive cervical cancer would be higher and is here assumed to be 1,200 cases per annum. [40]. Based on this assumption the Pap smear screening would today result in 750 avoided cases of cervical cancer per annum (1,200-450=750).

² Cost estimates according to the working group of the Swedish National Board of Health and Welfare. Diagnosis and treatment costs per annum: Mild dysplasia = SEK 2,500 (n = 2,500); moderately severe dysplasia = SEK 5,500 (n = 10,000); micro invasive cancer = SEK 20,000 (n = 84); localised cancer = SEK 93,000 (n = 167); advanced cancer = SEK 263,000 (n = 159).

Table 2 Summary of costs for prevention of cervical cancer

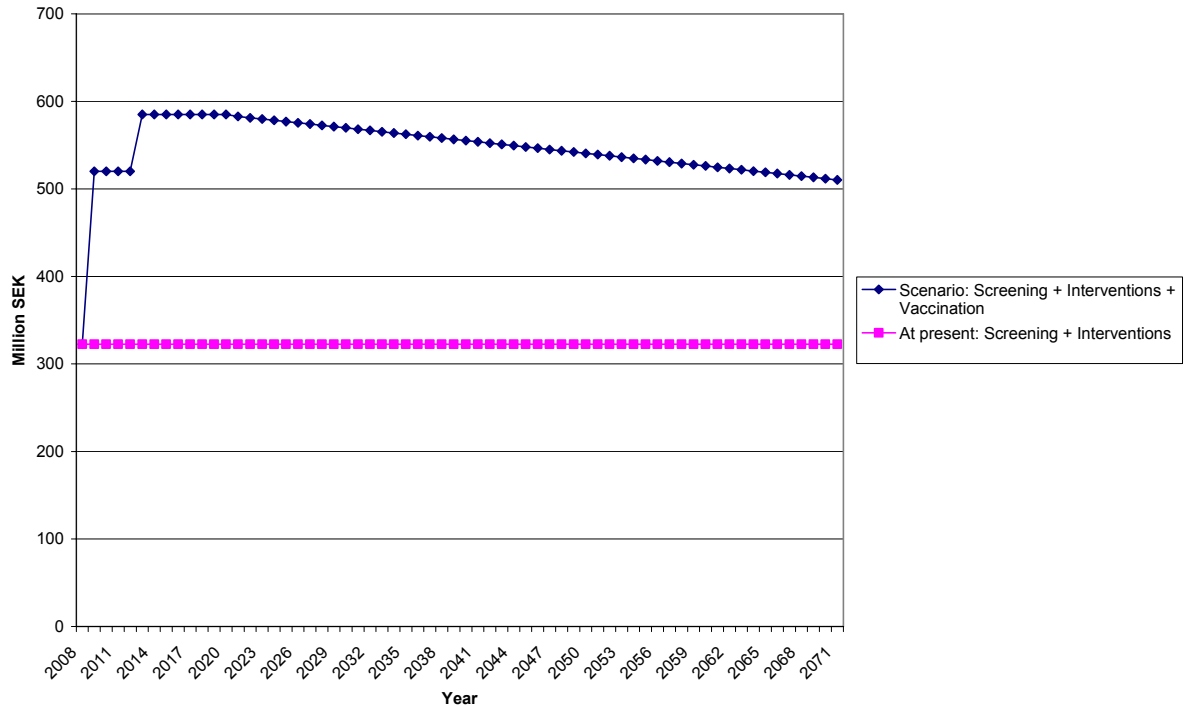
Alternatives	Number of avoided cases of cervical cancer	Cost per annum (SEK million)
Present position		
-Pap smear screening	750	202
-treatment		120
Total	750	322
Future (the situation after 50 years)		
-vaccination against HPV 16/18 and gynaecological cell sample tests	980	398
-treatment		85
Total	980	483

We also assume that a general vaccination against HPV 16 and 18 of girls will be introduced and that the programme for Pap smear screening will continue. Here a constant population is assumed, which is why we are calculating on the basis of 60,000 girls, a vaccination compliance of 95 percent and that HPV 16 and 18 would account for 70 percent of the cases of cervical cancer. After 50 years the combination of vaccination against HPV 16 and 18 and Pap smear screening would result in a total of 980 avoided cases of cervical cancer per annum. This means that a further 230 cases of cervical cancer approximately are avoided per annum compared with today of which a third (77) of these cases is expected to correspond to premature deaths. Calculated as life years saved, 77 avoided deaths correspond to approximately 995 saved life years without discounting.

Health improvements achieved today are assumed to have a higher value for citizens than health improvements far into the future. This means that future health improvements have a lower value than those that can be achieved at present, which is calculated by means of discounting. 995 saved life years are equivalent to 191 saved life years at 3 percent discounting.

An overview of the executed annual cost of Pap smear screening and general child vaccination against HPV 16 and 18 for a period of 63 years is presented in Figure 7. The reduced morbidity is assumed to result in reduced treatment costs, from approximately SEK 120 to 85 million per annum. If a booster dose is required, the vaccination cost increases by SEK 65 million per annum.

Figure 1. Expected annual cost of screening and vaccination for a period of 63 years (i.e. up to the age of 75 for those first vaccinated, assuming vaccination at the age of 12). The calculations presuppose a constant population and unchanged prices.



Discussion

Health economic analyses of cost effectiveness are aimed at providing a basis for prioritisation. The clinical data currently available for present HPV vaccines are relatively limited. Published studies have evaluated different surrogate measurements such as antibody levels against vaccine-specific HPV types and high-grade precancerous lesions (CIN 2/3) caused by HPV 16 and 18. There are no follow-ups longer than five years. The requirement for possible booster doses has not been established and there is insufficient data on the frequency of HPV 16 and 18 in the Swedish female population. This means that the possible effect of the vaccines on future contraction of cervical cancer can only be estimated in model analyses for the time being.

The published health economic studies indicate, based on the assumptions made, that HPV vaccination of 10-12-year old girls may have a cost effectiveness ratio within a wide range around a couple of hundred thousand SEK per LYS and a slightly lower cost per QALY (Table 1). However, several assumptions are very uncertain. An effect of herd immunity may be considered both uncertain and hypothetical. The sensitivity analyses showed that the results were sensitive to vaccine price, vaccination compliance, protective effect of the vaccine and discounting rate. However, the assumption regarding the proportion of cancer cases that can be prevented with a vaccination against HPV 16 and 18 does not change in any of the studies. In all

the studies 70 percent of the cases of cervical cancer are assumed to be associated with HPV 16 and 18. Epidemiological studies from Iceland and Sweden show that between 55 and 60 percent of cervical cancer cases may be associated with HPV 16 and 18. If the proportion of cervical cancer cases that can be influenced by a vaccination against HPV 16 and 18 is lower than the 70 percent assumed in the model analyses, the effect of a general vaccination has generally been overestimated in the analyses. The sensitivity analyses also showed that the results were largely sensitive to the price of the vaccine. In a competitive situation, and when a general vaccination programme is introduced, the conditions may change. A halving of the price would reduce the cost per life year saved considerably. At a lower price the likelihood that a vaccination would be considered cost effective in relation to an alternative use of the resources in health and medical care increases.

In the health economic models various assumptions were made regarding participation in the Pap smear screening. We do not yet know whether a general child vaccination against HPV 16 and 18 will influence the willingness of the vaccinated girls/women to participate in the cervical cancer screening programme. Theoretically there is a risk that they will have a false sense of security, for example that they will believe that they are protected against all HPV types that can cause cervical cancer. Reduced participation in the screening programme would also substantially alter the estimated cost effect quotients. The studies examined did not include sensitivity analyses in this regard.

Cost effectiveness analyses are to a large extent determined by the conditions prevailing in the respective countries. A decision on the introduction of vaccination against HPV 16 and 18 in Sweden should preferably be based on a model analysis with Swedish data on epidemiology and costs. We now have access to health economic analyses from Denmark and Norway. The Norwegian study is based on epidemiological data that correspond fairly closely to Swedish conditions and could therefore be relevant to Swedish health and medical care. However, this model is limited by the fact that it is calculated on the basis of an assumed follow-up over a period of 52 years until those vaccinated reach the age of 65, thus ignoring the majority of the cases of cervical cancer that arise in older age groups.

The above discussion indicates that any introduction of HPV vaccine in the Swedish child vaccination programme requires close monitoring and evaluation of the possibility of revising the decision as new knowledge is generated. The scientific basis relating to cost effectiveness for general child vaccination in Sweden is uncertain and is still regarded as insufficient.

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Attitudes

The attitudes to vaccines in general and to the new HPV vaccines among parents, children and health-staff are important for the success of a new HPV vaccination program. Studies published from other countries are not necessarily applicable to Sweden, since attitudes do change over time and by geographical locations. In general, attitudes to vaccination are positive in Sweden, but specific information about the HPV vaccine was important to collect.

Investigations on attitudes

The Swedish National Board of Health and Welfare (Socialstyrelsen), therefore commissioned Kommunikera AB, a research company, to conduct a qualitative research study with the objective to gain information about what parents, youth and school nurses know about HPV and HPV vaccination, as well as their attitudes towards such a vaccine and the possibility of this vaccine being offered in the childhood vaccination program. The results of the study were intended to be used to understand the impact, benefits and disadvantages such a vaccine would have among school nurses, youth and their parents and also to gain knowledge about the best way to communicate such an introduction in the scope of the childhood vaccination program.

The methodology used in this research study was individual in-depth interviews, moderated by psychologists. In connection with the interviews, the respondents were given a short introduction brochure about cervix cancer and HPV infection developed by the Swedish Cancer Society in collaboration with the Centre for Epidemiology.

The study population consisted of the following three sub-groups:

- 10 parents to girls and boys aged 11 to 18 years
- 10 youths of both sexes aged 16 to 18 years
- 6 school nurses in junior high and high schools

All interviews were conducted among people of varying socioeconomic status living in the greater Stockholm area.

In Sweden vaccines included in the childhood vaccination program are considered “a must” by all parents and school nurses. Parents report that they are also prone to have their children vaccinated against various infectious diseases outside the childhood vaccination program – commonly hepatitis A and B, but also vaccines against pneumococcal diseases (various infections of the respiratory airways), and TBE (Tic-borne Encephalitis). In other words; vaccination is perceived as a modern, reliable, and trustworthy way of prevention. The efficacy and degree of immunization is believed to be close to 100 per cent, according to parents.

In this study, the knowledge about HPV infection was low among all respondents although school nurses were more knowledgeable than parents.

At the same time, youths and parents have lately become aware of HPV vaccination through advertisements for Gardasil and Cervarix in magazines directed towards youths and women. Some parents had even decided to vaccinate their daughters with the available HPV vaccine on the Swedish market, a decision based on the information given during the initial recruitment call, discussions with other parents and by information available on the internet.

Among youth and parents, it was unknown what the abbreviation HPV stands for, what the symptoms are and its consequences. That viral infections are associated with cancer was a fact that surprised most respondents in the youth and parent's sample. Among all respondents there was an uncertainty if HPV and condyloma infections were the same. The interviewed parents took great interest in the subject of HPV vaccine and expressed mainly positive reactions towards the vaccine being added to the childhood vaccination program. The youth was also in favour, although expressed with less enthusiasm and conviction than parents – showing more concern for STDs than a possible future cancer illness.

School nurses were also positive, although much more rational, taking cost-benefit into consideration on both the individual and the societal level. They also expressed some hesitation due to the fact that the vaccines are currently becoming available on the market and that they themselves had no personal experience, and the lack of longitudinal studies of long-term consequences.

The fact that not all strains of HPV are included in the vaccine came as a surprise to all respondents and resulted in a few respondents being more hesitant towards the vaccine and its efficacy.

Several but not all respondents in all sample groups expressed a notion that not only girls should be vaccinated. It was to some extent a gender equality issue, but also based on the fact that boys also contract the infection as well as transmit it to girls.

The ideal age for the beginning of an HPV immunisation in the childhood vaccination program was said to be around 12 years. At that time it is safe to assume that girls are uninfected with HPV, and there is reasonable time to complete the immunisation. School nurses also said that this is a time when the children themselves ask fewer questions about the purpose of the vaccination and there is less risk for parents of moral conservative family values opposing the vaccination against sexually transmitted diseases.

To include a HPV vaccine in the childhood vaccination program will have a crucial effect on the shaping of HPV vaccine information to the public. It was clear from the interviews that there is very limited knowledge about the vaccine and the disease among the public and that most respondents had many unanswered questions. If a HPV vaccine is included, a major information program will be needed, with focus on “post-immunisation-information”. Suggested channels for information could be the internet (blogs, communities), women's magazines, alongside with civic information by post or via TV.

If the HPV vaccine is not included, the focus needs to be put on reaching out to parents of youths at an early stage presenting pro's and con's in a trustworthy manner from a reliable sender; such as the National Board of

Health and Welfare and the School Health Service or Guidance Centres for Young People.

In addition, a larger study investigating attitudes to the HPV vaccine among parents and adolescents has been carried out at the Karolinska Institute. Preliminary information from that study indicates very similar results on the attitudes to the vaccine.

Safety concerns due to coincidental diseases

Concerns about supposed adverse effects of vaccines seem to occur regularly. Single case reports cause "suspicion" but usually the suspected adverse reaction is simply coincident in time with administration of the drug or vaccine.

A recent example is the large-scale vaccination in France with hepatitis B vaccine given to 20 million individuals, mostly adolescents and young adults. Reports of temporal association between that immunization and onset of MS made the public lose confidence in the programme after a few years. Similarly fifteen cases of Guillain-Barré syndrome within six weeks after vaccination with a new meningococcal vaccine forced the US authorities to launch an alert. Later studies have not been able to confirm any cause-relationship between the vaccines and these autoimmune diseases.

Large-scale implementation of HPV vaccines may reactivate the vaccine-safety debate where vaccination is linked to autoimmune diseases.

Prior use of population-based data allows for identification of issues of potential concern. Data from The Hospital Patient register will give us the possibility to rapidly address such safety issues. We have seen a dramatic increase in incidence of diabetes type 1 over the last ten years, especially among young children. The reason for that is not known, but lifestyle and genetic factors may be important. Epidemiological studies have excluded recently introduced vaccines (acellular pertussis vaccine and vaccine against *Haemophilus influenzae* type b) as the cause.

Ethics

The issue of using the HPV vaccine in the national vaccine program in Sweden was presented to the ethics committee by the National Board of Health and Welfare in June 2007, who made the following statement.

Offering a medical intervention to a large group of individuals always implies that some individuals in this group will be at some kind of risk. When the target group is healthy and the risk for infection at the individual level is very small, the balance between benefit and risk is very difficult to evaluate. The individual with an unexpected adverse event following vaccination is not necessarily a person who would have fallen ill, if left unvaccinated. Also when the risk of infection is very high – such as the lifetime risk for a young girl to become infected with HPV – it is still a difficult issue since only few infections progress to cervical dysplasia and ultimately to cervical cancer. On the other hand, not using available tools to protect children from later events of life-threatening disease is also a difficult ethical question.

The conclusion was as follows:

“Even if the principle of caution often should be adhered to, the committee could not find any strong ethical reasons to refrain from vaccination on a large scale. The present knowledge supports targeted vaccinations of females and the known medical risks to the individual is estimated to be minor. Other potential risks include changes with respect to sexual behaviour and attendance to the screening program. These risks were judged as small. It is important that vaccination takes place before the sexual debut. The issue of a concurrent catch-up program warrant further discussion.

In published health economic evaluations only vaccination in combination with screening has proved to be cost effective. There is a lack of data regarding the effects of also vaccinating boys. When more knowledge on this issue has been gained, the program may also include boys. There are also as of today no studies indicating whether or not reduced vaccination schedules could be used in the youngest age-groups, which would facilitate implementation within school health care, and reduce costs. The use of the vaccine in developing countries should be considered”.

A further discussion on the ethics can be found in the evaluation from SBU.

Monitoring

Background

All national vaccination programs are implemented based on detailed evaluations including whether or not it is possible to obtain containment, elimination, or eradication of the disease. Containment means that there is still an endemic transmission of infection, but that morbidity is reduced to an 'acceptably' low level, which inevitably is a concept that may change over time. Disease elimination requires that there are only sporadic cases due to importations from outside, with limited spread so that endemic transmission is not re-established. Eradication requires the global elimination of the pathogen and may be possible if there is no animal reservoir of the pathogen, provided that the vaccine is effective in preventing transmission.

Before a vaccination policy can be determined, the aim in terms of disease control must be clearly defined. The establishment of a surveillance system that can monitor progress towards the target outcome is also essential. In fact, a key requirement for achieving a successful immunisation program is to have a surveillance strategy in place that can measure both the process (i.e. vaccine uptake) and the outcome (i.e. the epidemiological impact when compared with the pre-vaccination period)(1).

Monitoring of a vaccination program

Traditionally, the surveillance of national vaccination programs is based on four cornerstones: disease surveillance, immunosurveillance (seroepidemiology), vaccination coverage and the surveillance of adverse events. Information on the age-specific incidence of disease and on the age-specific distribution of immunity, before and after the introduction of the immunisation program, is essential in order to follow both direct protective effects on those vaccinated and indirect effects exerted on the unvaccinated through herd immunity. Surveillance of vaccine safety must also be established in order to assess the overall risk-benefit of the immunisation program. In addition, there is also a need to monitor microbiological epidemiology, i.e. to detect changes in the bacterial or viral population in relation to vaccines used. Furthermore, effects of introducing the vaccine on other public health interventions might be needed to be monitored as well as effects on behavioural patterns. The aims of each of the surveillance/monitoring systems, and therefore also the detailed methodology, will vary according to the stage of the vaccination program.

Surveillance of the impact on disease incidence can involve a number of different data sources, including death notifications, clinical reporting schemes, and laboratory-based reporting. Reliance on sentinel reporting derived from representative subsets of the population rather than nationally

based reporting may be adequate when disease incidence is relatively high in the early stages of a new immunisation program, but it is not sufficient if elimination policies are being pursued. Laboratory confirmation of suspected cases becomes increasingly important as disease incidence declines. This is because the positive predictive value of a clinical case definition (i.e. the proportion of clinically suspected cases that are correctly diagnosed) will progressively decrease, becoming zero when the disease is eliminated. In addition, microbiological surveillance is required afterwards if the bacterial/viral population changes, i.e. shifts in type distribution. Once a disease is fairly well controlled, the monitoring systems will change to focus on pockets-of-susceptibles, on maintaining high coverage, and on the detection of late adverse events. It is also essential to continue the monitoring of the pathogen and to monitor signs of waning immunity/protection, which may occur in a non-foreseeable manner due to loss of natural boosting (1).

There are differences between different infectious diseases and also between different vaccines. The surveillance of a vaccination program will therefore vary depending on the biological properties of the organism, the epidemiology of the disease and the mechanism of action of the vaccine(s). In addition, national surveillance will vary with national/regional availability of monitoring systems.

Epidemiologic surveillance of HPV

The primary goal of an HPV program, based on current knowledge of the disease and the vaccine, will be to reduce high-grade cervical dysplasias and cancer. The surveillance of HPV disease will pose significant challenges because of the exceptionally long incubation period, which may amount to decades from the HPV infection to HPV-related dysplasias or cancers. The least ambitious of the aims of control (disease reduction to an acceptable level) will not be reached until a long time after the introduction of the vaccination. There is hence a need to establish surrogate markers for monitoring of effect during the decades until reduction in the morbidity is achieved. Furthermore, the long-term follow-up of the effects of vaccination against HPV-related disease will require close collaboration between the vaccination program and the gynaecological screening program, which has already reduced HPV-related cervical morbidity to lower levels in Sweden than in many European countries, and with other long-term population-based surveillance systems. In addition, the monitoring of circulating strains is essential, since only a few viral types cause cancer. To be able to assess the effect of HPV vaccines on the incidence of cervical cancer and dysplasias, and on the possibility of type replacement, a registry of those vaccinated should be established. Altogether several issues need long-term surveillance:

- Vaccination effectiveness in reducing the incidence of cervical dysplasias and cervical cancer
- Vaccination effectiveness in reducing the incidence of other forms of HPV-related disease
- Duration of vaccine-induced protection against HPV-related disease

- Incidence of vaccine failure (disease breakthrough in a vaccinated individual)
- Occurrence of rare or late adverse events
- Changes in circulating HPV types (type replacement)
- Implementation of vaccination (vaccination coverage)
- Vaccination effects on participation in gynaecological cytology screening program.

This means that several variables need to be monitored both to measure whether the expected positive effects of the program occur as well as to make an early recognition of possible negative effects. Several government authorities will need to participate in the monitoring program, and the counties will need both to coordinate the different parts of the HPV prevention program, i.e. the cytology screening and the vaccination programs, and also to collect the surveillance data.

In Sweden, national health data and quality registers, regional treatment data registers and the development of a national vaccination register, offer good opportunities through registry-linkage to find answers to the effectiveness and safety questions above in a large population group. Large biobanks of biological samples also offer the opportunity to perform additional biological analyses as and where appropriate.

During autumn 2006 a long-term surveillance program of population-based epidemiological studies was initiated by the Swedish Institute for Infectious Disease Control (SMI) in collaboration with the Department of Epidemiology at Karolinska Institute in Solna and the WHO reference laboratory for HPV in Malmö. The project, which is approved by the ethics committee, will compare vaccinated and unvaccinated subjects through registry linkage of vaccination data and data from national health and quality registers. Vaccinated individuals will be searched for by NRN in several national and regional registers, including biobanks. Controls (unvaccinated people) will be identified in Swedish population registers (Statistics Sweden) and searched in the same databases as vaccinated people. Only de-identified data will be compiled and reported. The transferral of this surveillance project from its implementation to routine surveillance will require further definitions of who is doing what among the long-term players in the arena of HPV surveillance, including collaborative efforts in long-term funding.

HPV disease surveillance

The aim of a targeted HPV vaccination program will be containment, i.e. to reduce morbidity and mortality caused by vaccine-types of HPV to an 'acceptably' low level in women, in addition to the reduction of high-grade dysplasias and cancers that is already achieved within the gynaecological cytology screening program. Vaccination will provide direct protection of adolescent women against infection with the HPV types 16 or 18, and therefore also protect against dysplasias/cancer from these viral types several decades later. The screening program will remain unchanged, in order to

maintain the reduction of cervical disease in non-vaccinated women. Also protected women will still need to participate in the screening for the detection of cervical disease caused by non-vaccine types of HPV. Indirect effects, i.e. of reduced transmission of HPV, are likely to account for the reduced incidence of non-cervical forms of HPV disease, in women and men.

Screening for cervical cancer

Existing system

There is currently a register aimed at controlling the quality of the system run by volunteers from the profession (the National Quality Register for Cervical Screening, Karolinska Institute). The Epidemiological Centre at the National Board of Health and Welfare (EpC) collects data on polyclinical procedures, which contain some of the data needed, but this system is not complete.

Future system

If the vaccine is being used extensively, such as it would be in a general vaccination program, it will be very important to follow up how well the screening program is maintained and ensure that it remains effective. There will be a need for frequent analysis of the data in the system to find negative trends at an early stage. The first positive changes caused by the vaccine should also be noticed in this reporting process. The screening program and its registers provides the infrastructure necessary to monitor the effectiveness of changes in cervical cancer, and to attribute benefits and risks to the different components such as introduction of more general HPV testing and vaccination. There is hence a need for regular audits of cervical cancer morbidity regarding age, stage in different ages and related to screening history and vaccination. However, the coordination between counties needs to be improved and the computerized administration has to be updated. A more complete system at EpC, including both screening results and hospital/polyclinical procedures, could be an alternative to the current organisation with separate locations of data sources.

Incidence of cancer, cervical and non-cervical

Existing system

The Cancer Register (EpC, National Board of Health and Welfare) follows the incidence of all cancers including cervical and other anogenital cancers, oropharyngeal and other cancers and regardless of HPV type. The quality of data is high and the system has complete coverage, although with varying routines for testing of histological samples for HPV viral types.

Future system

This cancer register combined with registers of vaccinations and screening will be the main tool to evaluate the program in the distant future. There are also other registers with relevance for the issue of surveilling HPV-related diseases, such as the Hospital Patient Register (EpC), the Death Cause Reg-

ister (EpC), the Medical Birth Register (EpC) and the Swedish Population Registers (Statistics Sweden). An overall analysis of vaccination data together with data from these systems will make it possible to adapt the vaccination program as needed.

Incidence of non-cancer forms of disease caused by HPV

Existing system

It is well-known that HPV also causes tumours such as respiratory papillomatosis and anogenital warts. There is at present no registry to follow these tumour forms, although cases of respiratory papillomatosis and genital warts treated at hospitals would be registered in the Hospital Patient Register.

Future system

Reduction of these tumour forms is not included in the primary or secondary considerations of the present vaccination program, and follow-up of changes will therefore remain within the possibilities of the present registries and research-oriented projects. Benign warts can to a large extent be followed by yearly extraction from the register of prescriptions of pharmaceuticals. A reduction in the frequency of benign warts could be an early sign of changing epidemiology due to vaccination with the quadrivalent HPV vaccine.

Incidence or prevalence of HPV infection

Existing system

There is no present surveillance system to monitor infections caused by HPV, except for serosurveillance (see 'Immunity surveillance' below). Viral testing within gynaecological practice is restricted to women with dysplasias or clinical signs rather than healthy women without dysplasias.

Future system

It would be desirable to monitor the age-specific incidence of HPV infections before and after the introduction of general vaccination, but the infections caused by HPV are non-symptomatic and it is therefore not possible to establish any surveillance system based on clinical reporting schemes. Routine viral testing of the whole population is impossible for practical, as well as ethical reasons. Viral testing within gynaecological practice may increase, but is unlikely to include the whole population of healthy women without dysplasias. The incidence of HPV infections before and after the introduction of vaccination will therefore have to be estimated based on viral and immunologic studies of representative subsets of the population, with the addition of the information obtained from national serosurveillance studies.

Surveillance of viral strains

Existing system

Today there are only small research-oriented studies that provide information on the circulation of different viral types of HPV and there is no continuous collection of data on which viral strains are circulating. Relatively few women are currently tested for viruses, although there is accumulating evidence that HPV testing may be useful in some indications within the cervical screening program.

Future system

The vaccine protects against the two most common cancer-causing types of viruses. Early detection of changes in the circulation of viral types (type replacement) is essential. There is a need for a system that continuously collects strains, with systematic typing of a representative number of strains to provide information on the occurrence of different types and changes over time. Ideally, age-stratified sample tests from young people should be collected. It is also essential to establish routine viral typing for all cases of cancer and other serious diseases that could be caused by HPV. The vaccination status needs to be checked for each individual that turns out to be positive for vaccine-preventable viral types. The cervical screening registries collect information on all screening tests performed, which are likely to also include HPV tests in the future. Viral strains will be collected and typed for a number of different reasons and it could be considered whether it should be mandatory to report laboratory-diagnosed HPV infections to a national surveillance system.

HPV immunity surveillance

The age-specific immunity in the population is not known, and cannot be measured by antibody analyses at present because there are no established serologic correlates of protection. It is known that neutralising antibodies against HPV confer protection, but the concentration needed is not as yet established, and it is therefore not possible to estimate the population immunity by estimating the proportion with antibodies above a certain level.

However, antibody levels in the population provide information on the cumulative exposure to HPV in different age-groups (see section “Modelling Vaccination Effectiveness”) and it is therefore important to follow the seroepidemiologic changes over time, with due respect to vaccination-induced increases in antibody levels.

Existing system

SMI conducts cross-sectional national sero-surveys about every ten years, to monitor the population immunity against the vaccine-preventable diseases included in the national vaccination program. At present, serum samples to be included in the 2007 survey are collected, with measurement of antibodies against HPV included as optional in the study protocol.

Future system

Repeated sero-surveys in defined age-groups will provide information on the dynamics of seroepidemiology, and help in evaluating whether or not there is a need for late booster(s). It is not unlikely that serologic correlates of protection will be established, and if so estimates of population immunity can be made, including predictions of duration of protection. Information on the duration of vaccine-induced immunity will to some extent be provided by the manufacturers within their pharmacovigilance commitments, see safety monitoring below. It is not known how this long-term data can be translated to the general population.

Vaccination coverage

If the vaccination would be a part of the school vaccination program, the issues regarding reporting of coverage would utilise the same system as for the other vaccines given by the schools.

Existing system

At present, the County Medical Officers for Communicable Disease Control are responsible for collecting immunisation reports from the Swedish schools regarding immunisation status among pupils. The school health nurses provide the number of pupils enlisted in grade 6 and the number of these who have received the recommended number of doses, up to the date of the report. A summary by county is then sent to SMI for national reporting. The data represents more than 90% of all the 6th grade students.

Future system

The choice of grade for the school reporting system may need to change, but with this exception the method of data collection is likely to be maintained until a vaccination registry project is nationally implemented, which means that coverage at a certain age can be estimated, but that there are no individual vaccination data recorded. This is a critical issue in long-term comparisons of HPV disease in relation to vaccination data.

A web-based system to report vaccines (Svevac) has been tested in some child health districts, some schools and some counties while waiting for the ongoing national evaluation of computerised medical records and the legislative basis for establishing a nationwide vaccination register. If implemented, this system would provide the individual vaccination data necessary for long-term follow-up

The SMI project for surveillance of HPV already today includes vaccination data from any medical service providing HPV vaccinations, and this project could be extended to include vaccinations in school. It will represent an important basis of information on vaccine use until a more permanent reporting system is established. The project includes co-processing with the Prescribed Drug Register (EpC) to evaluate the coverage of vaccination registration.

Safety monitoring

Existing systems

When a medical product is granted marketing authorisation by the European Medicines Agency (EMA), there are regulatory requirements drawn up for long-term follow-up programs for the product. For vaccines, these programs include both duration of immunity at individual level, safety follow-up and other relevant issues such as outcome in the event of accidental vaccination during pregnancy. The HPV manufacturers will therefore have a continued responsibility to follow up the safety of their vaccines, including regular reporting to EMA by Periodic Safety Update reports. This also includes close monitoring of new medical events in the vaccinated population, such as autoimmune disorders. At a national level, the Medical Products Agency (MPA) has the responsibility to monitor suspected side-effects for all kinds of pharmaceuticals, which are further reported to the global safety database of the marketing authorisation holder. The present reporting system is based on spontaneous reports from medical care (doctors and nurses as well as consumers), and serves mainly to recognise warning signals if unusual side-effects occur. Analyses of causal relationship, frequency, etc., require targeted studies. The HPV vaccination in Sweden is followed in a specific registry. There is currently no ongoing analysis of correlation of the incidence of chronic diseases and vaccines at population level.

Safety concerns due to coincidental diseases

Concerns about supposed adverse effects of vaccines seem to occur regularly. Single case reports cause "suspicion", but usually the suspected adverse reaction is simply coincident in time with administration of the drug or vaccine. Large-scale implementation of HPV vaccines may reactivate the vaccine-safety debate where vaccination is linked to chronic diseases such as autoimmune disorders. Prior use of population-based data allows for identification of issues of potential concern. Data from The Hospital Patient Register will give us the possibility to rapidly address such safety issues.

Future systems

There will be a need for an intensified analysis of reports of side-effects in the present Swedish adverse event reporting system. Within the SMI project there is a preparedness to run studies of correlations between HPV vaccinations and the incidence of chronic diseases using existing registers. Immunity at individual level will be followed by the manufacturers within their pharmacovigilance commitments, for validation of the current estimates of the long-term duration of protection by the vaccines.

Summary

To follow the effect of an HPV vaccine program, a total surveillance of the complete preventive program for cancer caused by HPV will be executed, including regular audits of the screening program, monitoring of viral circu-

lation, and ideally also monitoring of age-specific infection and/or non-cancer forms of HPV disease. This is a much more complicated system than the ones in place to monitor existing vaccination programs. The screening program and its register provide an important tool to monitor the effects of changes in the prevention program, such as introduction of more general HPV testing and of vaccination, but to be effective there is a need for coordination of the different monitoring parts in different agencies, the counties and among the professions.

References:

1. Miller E. Potential and existing impact of vaccines on disease epidemiology. In: *The Vaccine Book*, Eds: Bloom BR, Lambert PH, pp 37-50. Elsevier Science 2003, San Diego, CA, USA

International aspects

The HPV vaccine has attracted attention not only in Sweden but all over the world and a number of countries and international organisations are considering how to use it within their systems. This has generated a considerable activity in the form of working-groups, international meetings and publications. Experiences of the national proceedings have been shared in many different formats and constitute an important basis for this document. A detailed account will not be provided here, but some events will be noted.

During the development of this document Sweden invited all Nordic countries and the Netherlands to a meeting to share experiences in evaluating the vaccine for use in national programs. It was considered a valuable meeting for all countries in the understanding how the process works and all the different aspects that need to be taken into account when deciding when and if to include the vaccine into a national program.

Both the European Commission (EC) and the European Regional office of the WHO have hosted meeting for experts working with the evaluation of the vaccine. The WHO meeting focused on the prevention of cervical carcinoma and how the vaccine could complement what is already being done in the member states. This differs considerably between countries due to differences in economical resources. The EC meeting focused on possible areas of collaboration between the member states and among other things discussed the possibility of common procurement of the vaccine. No agreement could be reached on this issue. Possibilities to share the written evaluations of different countries were also discussed and since then a number of reports have been published including a recent report from an expert-group working for the ECDC.

The HPV vaccine has also been discussed in a great number of scientific meetings during the last years.

It has proven very difficult to follow the evaluation of the vaccine in the EU countries since the process to implement a vaccination programme differs considerably. Many lists have been published claiming that a majority of countries have decided to use the vaccine, but in reality only a few have actually come as far as implementing the programme. In a recent survey by an EU project in October 2007, seven countries had taken final decision to implement a vaccination program, while a further seven had published an official recommendation. In a follow-up in January 2008 three additional countries had taken a final decision.

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