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Human papilloma virus vaccination of boys in the Swedish national vaccination programme

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Preface

The Public Health Agency of Sweden has conducted an investigation into whether the national vaccination programme for children against human papilloma virus (HPV), which today is limited to girls, should be extended to also include boys. This report describes the current knowledge, conditions, and assessments that will form the basis for making a decision on whether to extend the HPV vaccination programme to boys.

The Public Health Agency of Sweden should account for 13 factors when proposing changes of the national vaccination programme to the government. This report constitutes the knowledge base for 10 of them. The target groups who will be offered the vaccination (factor 4) is the main question of the investigation and is therefore excluded, the cost-effectiveness of the vaccination and the expenses and savings for the state, municipalities, and county councils (factor 10) is outlined in a separate report, and the medical ethics and humanitarian considerations (factor 13) are analysed and published separately by the Swedish National Council on Medical Ethics.

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

The report was composed by a working group consisting of both analysts from the Public Health Agency of Sweden and external experts (see Appendix 1).

The Public Health Agency of Sweden, Year 2017

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Abbreviations

ADR	Adverse drug reaction
AIDS	Acquired immunodeficiency syndrome
AIN	Anal intra-epithelial neoplasia
CI	Confidence interval
CIN	Cervical intra-epithelial neoplasia
CRPS	Complex regional pain syndrome
DNA	Deoxyribonucleic acid
EGL	External genital lesion
EMA	European Medicines Agency
EVG	Early vaccination group
EPAR	European Public Assessment Report
FIGO	International Federation of Gynecology and Obstetrics
GMT	Geometric mean titre; mean titre calculated on log transformed values and then back transformed in order to achieved normal distribution
HBV	Hepatitis B virus
HIV	Human immunodeficiency virus
HPV	Human papilloma virus
HRA	High resolution anoscopy
IARC	International Agency for Research against Cancer
ICD-10	International Statistical Classification of Diseases and Related Health Problems - Tenth Revision
MAA	Marketing authorisation application
MSM	Men who have sex with men
MPA	Medical Products Agency
NBHW	National Board of Health and Welfare
PCR	Polymerase chain reaction

PIN	Penile/perianal/perineal intra-epithelial neoplasia
POTS	Postural orthostatic tachycardia syndrome
PP	Per-protocol
PPE	Per-protocol efficacy
PPI	Per-protocol immunogenicity
RRP	Recurrent respiratory papillomatosis
SAE	Severe adverse event
SKL	Swedish Association of Local Authorities and Regions
VAIN	Vaginal intra-epithelial neoplasia
VLP	Virus-like particle
VIN	Vulvar intra-epithelial neoplasia
WHO	World Health Organization

Summary

Infections with human papilloma virus (HPV) are considered to be the most prevalent sexually transmitted infections in both men and women. In 2008, it was decided that vaccination against HPV should be included in the Swedish national vaccination programme for all girls aged 10–12. In 2016, the Public Health Agency began an investigation into also including boys in the vaccination programme The investigation has included thirteen factors regulated in the Communicable Diseases Ordinance, of which the knowledge base for ten of them are presented in this report.

HPV infections do not cause symptoms and are usually transient, but may persist and cause a range of clinical states, including precursor lesions of cancer, anogenital warts, and cancer. Over 200 different types of HPV have been identified and numbered, and 13 of these can cause cancer. HPV is considered a necessary but not sufficient cause of cervical cancer, and HPV-types 16 and 18 cause around 70% of all cervical cancer. The other main cancer forms that have been related to HPV are oropharyngeal and anogenital cancers, and are mainly associated with HPV 16. The proportion of these cancers that are estimated to be caused by HPV differ between the different cancer forms and also varies between different geographic regions. Oropharyngeal cancer is one of the most rapidly increasing cancer forms in Sweden, with 384 new cases reported in 2015, of which 71% were males. The incidence of penile cancer in Sweden is relatively stable, with around 100 cases per year. Around 150 patients are diagnosed with anal cancer annually in Sweden, and of these 70% are women. Of note is that the incidence of anal cancer in men who have sex with men (MSM) is much higher than among all men. There are around 500 new cases of cervical cancer detected yearly in Sweden. In 2015, 137 cases of vulvar cancer and 37 cases of vaginal cancer were reported in Sweden.

The incidence of cervical cancer peaks between 35 and 45 years of age, while for the other HPV-related cancers the peak occurs after 60 years of age, which is partly an effect of the Swedish cervical screening programme. The mortality is higher in female genital cancers (cervical, vulvar and vaginal) than other HPV-related cancers, where the 5-year survival exceeds 70%. Treatment of HPV-related cancer is often extensive and often results in long-term side effects and impaired quality of life.

Organized cervical screening has substantially reduced the cervical cancer burden in Sweden since the late 1970s. For anal cancer, trials are ongoing to determine if treatment of screening-detected precancerous lesions also leads to a decrease in invasive anal cancer, but no such programs are implemented yet. For other HPV-

related cancer forms, there are currently no validated methods developed that can be used in screening programmes to detect precancerous lesions.

Extensive follow-up time is needed to show the effects of HPV-vaccination on cancer and mortality. In the ongoing studies, such an effect has not yet been possible to demonstrate due to the limited follow-up time of 10 years. Therefore, epidemiological models based on available data are used to estimate the effects of different vaccination strategies. Such modelling has shown that males are well protected against cancer indirectly through a vaccination programme for girls with a vaccination coverage of 80% (such as in Sweden), but that cancer among both males and females can be further reduced by also vaccinating boys. It has also been shown that cancer among women can be reduced further by also vaccinating boys, but that this effect decreases with increasing vaccination coverage among girls. Furthermore, a vaccination programme for girls is not expected to reduce HPV-related disease among MSM.

The three available HPV vaccines have been approved for the prevention of precancerous anogenital lesions (cervical, vulvar, vaginal, and anal) and cervical and anal cancers causally related to certain HPV types, as well as for genital warts (the quadrivalent and nonavalent vaccines). There are currently no vaccines approved for the prevention of oropharyngeal or penile cancers. During the 10-year follow-up period there has not been any indication of a need for additional booster doses. Studies have shown that the most common adverse events are injection site reactions and headache, and that most reactions are mild to moderate. There is no indication of different safety profiles in males and females. All three vaccines have been approved for use with a 2-dose schedule in boys and girls between 9 and 13 or 14 years of age (depending on the vaccine).

Vaccinations against HPV are offered to girls through the school health care, which would also serve as the platform for vaccination of boys. Each dose is estimated to take 15–20 minutes of work for the school nurses, and extending the programme would almost double the workload related to HPV vaccinations.

Several studies have shown that the majority of parents of boys are positive to HPV vaccination, although the vaccination coverage has been somewhat lower among boys than among girls in countries where a universal vaccination programme has been implemented.

The monitoring and evaluation of a universal vaccination programme can largely be performed in the same way as for the HPV-vaccination programme for girls. The Cancer and Cause of Death registries of the National Board of Health and Welfare provides information about the incidence of relevant cancer forms, and the Swedish National Cervical Screening Registry provides information about the incidence of precancerous lesions of the cervix. Separate studies would have to be

done in order to study the prevalence of HPV infections and distribution of HPV types in the population (in both women and men) for precancerous lesions and cancers. The vaccination coverage could be monitored through the national immunization registry, and vaccine safety could be monitored by the Medical Products Agency's standard routines.

To support the implementation of an extended programme, the national communication should aim to support health care professionals, facilitate children's and guardian's informed decision making, and ensure that information and awareness raising is provided equitably among all target groups, in all school units, and in all parts of the country.

Sammanfattning

HPV-infektion anses vara den vanligaste sexuellt överförbara sjukdomen både bland män och kvinnor. År 2008 beslutades det att HPV vaccination skulle införas i det nationella vaccinationsprogrammet för alla flickor i 10-12 års ålder. År 2016 påbörjade Folkhälsomyndigheten en utredning om att också införa HPV-vaccination för pojkar i Sverige. Utredningen omfattar de 13 faktorer som enligt smittskyddsförordningen (SFS 2004:255, 7 §) ska beaktas vid ändringar i nationella vaccinationsprogram varav tio redovisas i detta kunskapsunderlag.

HPV-infektionen ger i sig inga symtom och läker oftast ut spontant, men den blir ibland kronisk och kan då leda till ett antal kliniska utfall såsom kondylom och olika cancerformer och deras förstadier. Över 200 typer av HPV har identifierats och numrerats, varav 13 typer kan orsaka cancer. HPV anses vara en nödvändig men inte tillräcklig orsak till livmoderhalscancer och HPV-typerna 16 och 18 orsakar omkring 70 procent av all livmoderhalscancer. Annan HPV-relaterad cancer är framförallt anogenital cancer och svalgcancer, och relateras främst till HPV typ 16. Andelen cancer som relateras till HPV varierar mellan dessa cancerformer och även mellan geografiska regioner. Svalgcancer är en av de snabbast ökande cancerformerna i Sverige, med 384 nya fall rapporterade 2015, varav 71 procent var män. Förekomsten av peniscancer är relativt stabil, med omkring 100 nya fall per år. Runt 150 fall av analcancer diagnosticeras varje år, och runt 30 procent av dessa är män. Incidensen av analcancer bland män som har sex med män (MSM) är mycket högre än bland män i allmänhet. I Sverige diagnosticeras runt 500 fall av livmoderhalscancer årligen. År 2015 rapporterades 137 respektive 37 nya fall av cancer i vulva och vagina .

För livmoderhalscancer är incidensen som högst mellan 35 och 45 års ålder men betydligt senare i livet vad gäller annan HPV-relaterad cancer, över 60 års ålder. Den stora åldersskillnaden beror delvis på den höga täckningen av screeningprogrammet för livmoderhalscancer, som bidragit till att minska antalet fall och dödsfall i livmoderhalscancer. Studier pågår för att fastställa om behandling av förstadier till analcancer också leder till en minskning av antalet invasiva fall. För andra HPV-relaterade cancerformer finns det i dagsläget inte några validerade metoder som skulle kunna användas i screeningprogram för att upptäcka förstadier till cancer. Mortaliteten i livmoderhals-, vulva och vaginalcancer är högre än för andra HPV-relaterade cancerformer, där femårsöverlevnaden överstiger 70 procent. Behandlingen av HPV-relaterade cancerformer kan ofta vara komplicerad och resultera i långvariga komplikationer och nedsatt livskvalitet.

MSM löper en hög risk att utveckla HPV-relaterad sjukdom och har också sämre indirekt skydd genom flockeffekt i ett vaccinationsprogram som enbart omfattar

flickor. Vissa länder har därför implementerat vaccinationsprogram för MSM som riskgrupp.

Det krävs en mycket lång uppföljningstid för att visa om HPV-vaccination skyddar mot cancer, och i de studier som pågår har sådan effekt inte kunnat påvisas då uppföljningstiden ännu inte överstiger 10 år. Epidemiologisk modellering används därför för att uppskatta effekten av olika vaccinationsstrategier. Genom sådana modeller har man visat att även om män får ett gott skydd vid vaccination av flickor med en täckningsgrad som den vi har i Sverige (80%), så minskar förekomsten av HPV-relaterad cancer ytterligare bland män när både pojkar och flickor vaccineras. Man har också visat att man genom flockeffekter förebygger ytterligare cancerfall även bland kvinnor, men att denna effekt minskar med ökad vaccinationstäckning bland flickor. Vidare har man visat att vaccination av enbart flickor inte påverkar förekomsten av HPV-relaterad sjukdom bland MSM.

De tre tillgängliga HPV vaccinen är godkända för förebyggande av förstadier till cancer i livmoderhals, vulva, vagina och anus, samt livmoderhals- och analcancer. Inget av vaccinen har förebyggande av svalg- eller peniscancer som indikation. Alla vacciner ger antikroppssvar som vida överstiger det som orsakas av en naturlig HPV-infektion. Hur länge skyddet mot HPV-infektion varar har inte fastställts, men uppföljning under 10 år visar stabilt höga antikroppsnivåer vilket indikerar att antikroppssvaret sannolikt kommer att vara länge. De vanligaste biverkningarna är reaktioner vid injektionsstället (rodnad, smärta eller svullnad) samt huvudvärk. De flesta reaktioner är milda till måttliga. Inget talar för att vaccinerna skulle ha en annorlunda säkerhetsprofil bland pojkar än bland flickor. Alla tre vaccin är godkända för att användas i ett tvådos-schema om de ges före 14 eller 15 års ålder (beroende på vaccin).

Ett vaccinationsprogram mot HPV för pojkar skulle genomföras inom skolan av elevhälsans medicinska insats och uppskattningsvis skulle varje dos ta 15-20 minuter. Denna utvidgning skulle nästan dubblera arbetsinsatsen relaterad till HPV-vaccination inom elevhälsan.

Flera studier har visat att de flesta föräldrar är positiva till HPV-vaccination av pojkar. Täckningsgraden bland pojkar har varit något lägre än bland flickor i länder som implementerat vaccinationsprogram för pojkar. Vaccinationstäckningen bland flickor har varit kring 80 procent sedan det nationella vaccinationsprogrammet startade, vilket är lägre jämfört med andra vaccinationer inom det allmänna programmet som uppnår täckningsgrader på 95 procent och mer.

Uppföljningen av ett vaccinationsprogram mot HPV bland pojkar kan i stor utsträckning samordnas med uppföljningen bland flickor. Cancerregistret och dödsorsaksregistret vid Socialstyrelsen innehåller information om inträffade cancerfall respektive dödsfall i cancer, medan det nationella kvalitetsregistret för

cervixcancerprevention innehåller information om förstadier till livmoderhalscancer. Det behövs riktade studier för uppföljning förekomst av HPV-infektioner totalt och per typ, bland kvinnor och män. Vaccinationstäckningen kan följas genom det nationella vaccinationsregistret och säkerhetsuppföljningen kan genomföras enligt Läkemedelsverkets vanliga rutiner.

För att stödja implementeringen av ett vaccinationsprogram mot HPV för pojkar kommer den nationella kommunikationen fokusera på att stödja hälso- och sjukvårdspersonalen, förenkla beslutsfattandet för barn och föräldrar och säkerställa att information tillhandahålls på lika villkor inom alla målgrupper, i alla skolor och i alla delar av landet.

Background

Human papilloma virus

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

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

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

An estimated 630,000 new cancer cases per year worldwide are attributable to HPV, which corresponds to 4.5% of all cancers (8.6% in women and 0.8% in men). The epidemiology of HPV-associated cancers as well as the number of cases that can be attributed to HPV varies between different geographical regions as well as with economic development status, partly reflecting the presence of preventative health services. More than two thirds of cervical cancers are diagnosed in less developed countries, whereas the highest burden of HPV-attributable oropharyngeal cancer is in North America and Europe (8). The epidemiology and total burden of cervical cancer is also highly dependent on the cervical cancer screening practices of the country (12, 13). For the other HPV-associated cancers, no such screening programmes exist.

In Sweden the incidence of anal cancer is currently more than three times higher in women than in men (14), and for oropharyngeal cancer it is the opposite situation with almost three times higher incidence in men (15, 16). The incidence of cervical cancer peaks between 35 and 45 years of age, while for the other HPV-associated cancers the peak is generally considerably higher and occurs after 60 years of age

(17). Sweden has had a highly effective cervical screening programme since the 1960s, and a study has shown that in the absence of screening, the Nordic countries would be experiencing incidence rates on par with the high incidence rates in low-income countries (13).

From the screening programme we have learned much about HPV infection and precursor lesions of cervical cancer, cervical intra-epithelial neoplasia (CIN). High-grade lesions (CIN grade 2-3) are typically the result of a persistent HPV infection and can take several years to develop, and invasive cancer is the result of a non-regressive lesion that can take 10 years to develop (6). Similar to the classification of CIN, vulvar intra-epithelial neoplasia (VIN) is classified VIN 1–3, vaginal intra-epithelial neoplasia (VAIN) as VAIN1–3, anal intra-epithelial neoplasia (AIN) as AIN1–3, and penile/perianal/perineal intra-epithelial neoplasia (PIN) as PIN1–3. The natural history, invasive potential, and recurrence rates of these precancerous lesions are not as well described as precursor lesions to cervical cancer (6, 18, 19).

No precursor lesions have been detected in a systematic way for oropharyngeal cancer (20-22), and therefore there are no ways to predict if and when such cancer will develop. It has however been indicated that the time from HPV infection to developing oropharyngeal cancer may also exceed 10 years (23).

Vaccines against HPV

Vaccines against HPV are prophylactic non-live vaccines and contain purified virus-like particles (VLPs) of the recombinant major (L1) capsid protein of different HPV types. Because they do not contain genetic material, neither infection of cells nor viral replication is possible. From an immunologic point of view, the function of the capsid proteins is the same as a live virus, although the antibody concentrations induced by vaccination by far exceed those induced by natural HPV infection (24).

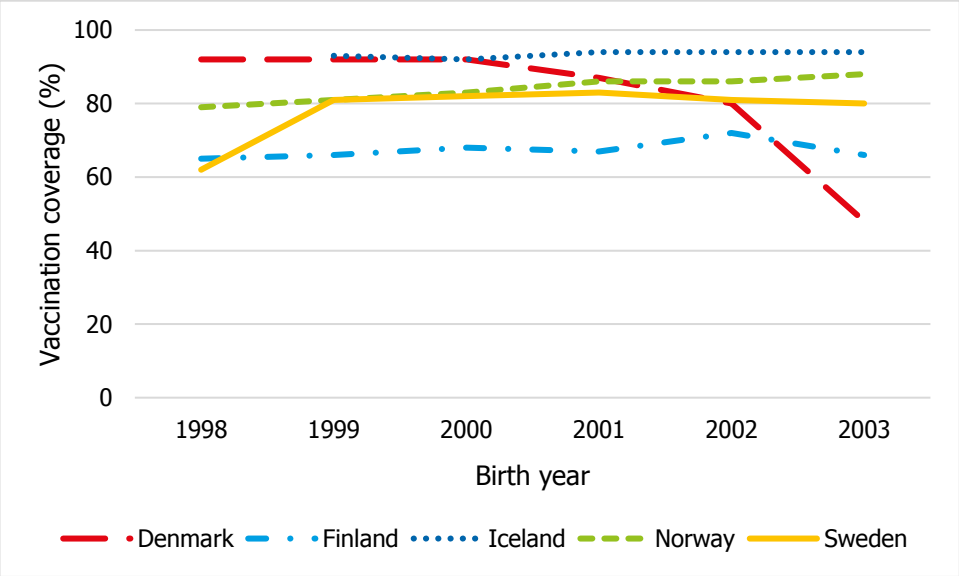
Three different HPV vaccines have been developed so far – a bivalent vaccine containing VLPs of HPV 16 and 18 (Cervarix®), a quadrivalent vaccine containing VLPs of HPV 6, 11, 16, and 18 (Gardasil® also marketed as Silgard®) and a nonavalent vaccine containing VLPs of HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 (Gardasil 9®).

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

Vaccination programmes

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

Figure 1. HPV vaccination coverage in the Nordic countries for females born in 1998–2003.



Vaccination of boys

The NBHW investigation from 2008 supporting the inclusion of vaccination against HPV for girls in the national vaccination programme stated that to also include vaccination of boys was not motivated at the time (27). It was, however, indicated that this position could be reconsidered when knowledge developed further, especially on vaccine effects on male HPV-associated cancer and herd immunity. The benefit of universal vaccination was considered to be limited because very high vaccination coverage among girls could be expected in Sweden.

In 2014, the European Medicines Agency (EMA) approved the first HPV vaccine for use in males, based, among other findings, on demonstrated efficacy of the vaccine against anal intra-epithelial neoplasia grade 2 or worse among MSM and the fact that there were no indications that vaccine protection against anal lesions

related to HPV was sex specific (28). Clear herd immunity effects on boys from vaccinating girls have also been shown (29). There is furthermore a substantial proportion (20%) of unvaccinated Swedish girls (Figure 1) and for whom the herd immunity effects of vaccinating boys would be important. The knowledge of HPV-associated cancers has developed substantially since 2008, and the epidemiology of non-cervical HPV-associated cancers has been changing (8). Most notably, oropharyngeal cancers have increased in incidence rapidly in Sweden and other western countries, and this cancer predominantly occurs among men (30-34).

A few countries have implemented universal vaccination programmes against HPV, including Australia, Argentina, Austria, Barbados, Canada, Israel, USA, Switzerland and Liechtenstein. The UK and Ireland have implemented risk-group vaccination programmes and offer HPV vaccination to MSM in their national programmes (35, 36). Among the Nordic countries, only Norway has decided to include males, and universal vaccination within the national vaccination programme is planned to start in 2018.

Investigation

Legal framework

As of 2013, the national vaccination programmes are regulated by the Communicable Diseases Act (SFS 2004:168). It stipulates that a communicable disease shall be covered by a national vaccination programme if the vaccination against the disease is expected to:

- effectively prevent communicable diseases from spreading among the population
- be socioeconomically cost effective
- be sustainable from an ethical and humanitarian point of view.

The corresponding ordinance (SFS 2004:255) regulates the following 13 factors that the Public Health Agency of Sweden must account for when proposing changes in the national vaccination programme to the Government:

1. The burden of the disease on society, the healthcare sector, and individuals.
2. The expected impact of vaccinations on the burden and epidemiology of the disease.
3. The number of doses that are required to achieve the desired effect.
4. The target groups who will be offered the vaccination.
5. The safety of the vaccine.
6. The effect of vaccinations on the activities of county councils, municipalities, and private healthcare providers.
7. The suitability of combining the vaccine with other vaccines in the national vaccination programme.
8. The general public's ability to accept the vaccine, and the effect of the vaccination on attitudes towards vaccinations in general.
9. Other accessible, preventive measures or treatments that might be alternatives to a national vaccination programme.
10. An assessment of the cost-effectiveness of the vaccination and of the expenses and incomes for the state, municipalities, and county councils.
11. The opportunities to monitor the effect of the vaccination in the ten above-stated factors and the estimated costs for the state for follow-up.

12. The need and cost for information initiatives for the population and healthcare providers.
13. Medical ethics and humanitarian considerations.

The Public Health Agency of Sweden is mandated to define the target groups, number of doses, timing, etc. of vaccinations within national programmes. The vaccination programme for children has been specified through regulations (HSLF-FS 2016:51).

Vaccinations included in national programmes shall be offered by counties or municipalities (depending on the age of the child) free of charge and registered in the national vaccination registry in accordance with the corresponding legal act (SFS 2012:453).

Cause of investigation

When HPV vaccinations were first considered for the national vaccination programme for children in 2008, vaccinating both girls and boys was considered, but it was decided to limit the vaccination programme to girls (37).

In 2015, a group consisting of representatives of government agencies, child and school health care, and medical professional organizations met to discuss and prioritize which changes to the Swedish vaccination programme were the most important to investigate. HPV vaccination of boys was considered a priority because more data had become available concerning disease burden and vaccine effectiveness.

Process

The Public Health Agency started the investigation in 2016. The investigation has been carried out in accordance with the general process for proposing changes to national vaccination programmes (38). A working group (see Appendix 1) consisting of experts in different fields was appointed to describe the factors outlined in the Communicable Diseases Ordinance.

Disease burden, screening programmes and treatment possibilities were described primarily using Swedish registry data and recently updated national treatment programmes for the main disease outcomes. Scientific publications were used to further update and complement this information.

Vaccine safety, efficacy and immunogenicity, number of doses needed, and suitability of simultaneous administration was described using mainly European Public Assessment Reports (EPARs) and summaries of product characteristics.

A structured literature review was conducted to find mathematical models on expected effects of vaccinating males against HPV. Four databases were searched and the resulting articles were assessed for relevance and quality by independent assessors. Attitudes towards HPV vaccination was described by experts in the area, supported by the results of i) a structured literature search in PubMed for scientific articles related to attitudes, perceptions, acceptance or willingness concerning HPV-vaccination among males, parents or health care professionals, ii) a web-based survey among Swedish parents, and iii) a web-based survey among school nurses.[*]

The expected impact on different health care institutions, the function of STI prevention programmes and vaccination programmes, and monitoring and communication activities by Swedish agencies was described by, or following interviews with, representatives familiar with current practises in Sweden.

The working group also convened to identify the ethical and humanitarian considerations that could apply to HPV vaccination of boys. The process followed the steps outlined in the guidance issued by the Swedish Agency for Health Technology Assessment and Assessment of Social Services (SBU) (39). The conclusions of the expert group were sent to the Swedish National Council on Medical Ethics together with the knowledge base for analysis and appraisal. Their analysis and conclusions are published separately.

[*] Details concerning the structured literature searches and assessments are available upon request.

Knowledge base

Burden of HPV-related disease

Oropharyngeal cancer

Head and neck squamous cell carcinoma includes cancers of the oral cavity, the oropharynx, the hypopharynx, the larynx, the sinonasal tract, and the nasopharynx. Of the roughly half a million yearly cases of head and neck cancers worldwide, around 38,000 are considered to be attributable to HPV (8). Oropharyngeal cancer (oropharyngeal squamous cell carcinoma) can be further divided into cancer of the tonsils (ICD-10 code: C09), cancer of the base of the tongue (C01), and cancers in other subsites within the oropharynx (C05, C10) (15). Tonsillar cancer and base of the tongue cancer are the two main subgroups, and in Sweden these add up to about 60% and 30% of the oropharyngeal cancer cases, respectively (15).

Historically, oropharyngeal cancer forms have accounted for roughly 10% of all head and neck squamous cell carcinoma cases (40). Today, oropharyngeal cancer is the second most common head and neck cancer in Sweden with 384 new cases diagnosed in 2015. Seventy-one per cent of patients diagnosed with oropharyngeal cancer are men, and the incidence in Sweden in 2014 was 5.37 cases per 100,000 men and 1.87 cases per 100,000 women. The median age at diagnosis is 63 years for both sexes, which is lower than for most other head and neck cancers (15, 16).

Smoking and alcohol consumption are well known risk factors for head and neck cancers. Over the past three decades, there has been a clear decrease in tobacco use in most Western countries and an associated decline in tobacco-related head and neck cancers. The incidence of HPV-related oropharyngeal cancer, however, has been increasing quite dramatically, which has been shown concurrently in several studies in many Western countries, including Sweden (30-34). Data from the US show that HPV is now being observed in over 70% of the oropharyngeal cancers (41-43), and the incidence of HPV-related oropharyngeal cancer has even been predicted to exceed that of cervical cancer by 2025 (44). In Sweden HPV-virus has been detected in 74-79 percent of oropharyngeal tumours (HPV-related), and oropharyngeal cancer is increasing by 5% per year, which makes it one of the fastest-growing cancer forms in Sweden (16, 32). Even though other subtypes might be involved, HPV 16 is the dominating subtype in oropharyngeal cancer. In 2007 the International Agency for Research against Cancer (IARC) acknowledged HPV 16 as a risk factor for oropharyngeal cancer (45). The reasons behind the documented increase primarily in HPV-positive tonsillar and base of the tongue cancer cases are unknown, but it has been attributed to changes in sexual habits over time (46, 47). Furthermore, it has recently been shown that smoking also increases the risk of incurring also HPV-positive oropharyngeal cancer (48). A

decrease in tonsillectomy has been shown not to explain the increase in HPV-positive oropharyngeal cancer (21, 49).

Despite the fact that more than 75% of patients are diagnosed at an advanced stage (stage III–IV) (16, 50), the prognosis for oropharyngeal cancer is good, with a 5-year relative survival* of 71% for the whole group. One contributing factor to this good relative survival is that HPV-positive oropharyngeal cancer has a better prognosis compared to HPV-negative cancer (42, 51-55).

The treatment of these cancers is, however, extensive with life-long side effects such as dry mouth, taste alterations, swallowing difficulties, trismus, and hearing impairment, all of which have a significantly negative impact on quality of life (56-58).

Penile cancer

The mean age-adjusted incidence of penile cancer (ICD-10 code: C60) in Sweden is 2.1 per 100,000 (59, 60) and has remained relatively unchanged over the past decade. Around 100 men are diagnosed with invasive penile cancer annually, and about 40 with carcinoma in situ (59). Penile cancer is usually diagnosed in older men with a rapidly increasing incidence after 60 years, and the mean age at diagnosis is 66 years. However, 7% of patients in Sweden are under 40 years at diagnosis, and a few are in their 20s (59).

Phimosis (a condition in which the foreskin cannot be retracted to reveal the glans penis) is the most established risk factor for penile cancer. Smoking and local inflammation have also been reported to increase the risk for penile cancer (61-63). However, HPV infection is strongly associated with an increased risk for precancerous lesions and cancer of the penis. HPV 16 and 18 are the dominating subtypes. A systematic review from 2009 showed that the average prevalence of HPV infection in penile cancers was 47% (64), while a study based on Swedish data showed an association with HPV in 83% of cases (65).

The prognosis for patients with penile cancer is generally good with a 5-year relative survival of 73% for patients with invasive cancer (59), but long-term side effects, such as impaired sexual function and lymphedema, have a negative impact on quality of life.

* The 5-year relative survival is the survival of patients with a certain diagnosis (e.g. oropharyngeal cancer) compared to the survival of those of the same age without this diagnosis 5 years after their diagnosis or start of treatment. (National Cancer Institute. NCI Dictionary of Cancer Terms. Available from: https://www.cancer.gov/Widgets/TermDictionaryWidgetEnglish.)

Anal cancer

The incidence of anal cancer (ICD-10 code: C21) differs significantly between men and women with an incidence of 0.62 per 100,000 men and 2.04 per 100,000 women in Sweden (14). Around 150 patients are diagnosed with anal cancer annually in Sweden, and of these 70% are women. The median age at diagnosis is 65 years, but is considerably lower in HIV-positive patients (66).

Around 90% of the tumours are HPV-positive, with HPV 16 and 18 being the dominating types (67, 68). The incidence of anal cancer is increasing worldwide, and it is likely that multiple factors contribute to this increase. Epidemiological studies suggest that anal intercourse, multiple sexual partners, smoking, and immunosuppression, including recipients of organ transplants, are associated with an increased risk of developing anal cancer (66, 69).

Men who have sex with men (MSM) have a significantly higher risk of anal HPV infection. In this group, the incidence of anal cancer is suggested to be as high as 37 per 100,000 (68, 70), and for those who are also HIV-positive this risk is increased even further (71, 72).

The prognosis for anal cancer is quite good with a 5-year overall survival* of around 70% (66, 73). For anal cancer, relative survival data have not been published. However, the relative survival would not be lower than the overall survival. Despite the good survival data, many patients treated for anal cancer suffer from both short and long-term side effects such as impaired bowel function, urinary function, and sexual function.

Cervical cancer

The incidence of cervical cancer decreased dramatically in the first decades of screening in Sweden, but has since levelled off and has remained stable with an age-standardized incidence between 8 and 10 per 100,000 over the past twenty years, resulting in 450 new cases each year and 150 deaths. In Sweden, the incidence peaks between the ages of 35 and 45. An increase in cases has been observed for 2014 and 2015 (559 and 563 cases, respectively) (17), and reasons for this increase have not been fully investigated yet. Squamous cell carcinoma and adenocarcinoma are the two most common histological types of cervical cancer representing 75% and 20% of cases, respectively. Other histological types,

* The 5-year overall survival is the percentage of patients with a certain diagnosis (e.g. anal cancer) who are alive 5 years after their diagnosis or start of treatment. (Ibid.)

including adenosquamous carcinoma, small cell carcinoma, neuroendocrine tumour, and poorly differentiated histological types, are much less common (74).

FIGO (International Federation of Gynecology and Obstetrics) staging is used to classify the extent of tumour invasion in cervical, vaginal, and vulvar cancers and is a significant predictor of curative prognosis (75). In Sweden, about 20% of all cases are micro-invasive (Stage Ia) and occur in younger ages. These cases have an excellent prognosis (98% survival rate). Localized cervical cancer (Stage Ib) represents about 40% of all cases, and about 85%–90% of these can be cured. About 40% of all cases are advanced (Stages II, III, and IV), and these have higher mortality (>50% within 5 years) (75).

Precursor lesions have been identified and classified for squamous cell carcinoma and to a somewhat lesser extent for adenocarcinoma. Low-grade lesions are often considered to be signs of an on-going HPV infection (76). High-grade lesions are typically the result of a persistent HPV infection and can take several years to develop, while invasive cancer is the result of a non-regressive lesion and can take up to 10 years to develop (6).

HPV has been categorized as a necessary but not sufficient cause of cervical cancer, and the majority of cases are caused by HPV 16 and 18 (70%), with some variations between regions (9, 77). Risk factors for cervical cancer are, in essence, the same as risk factors for contracting an HPV infection. Early age at sexual debut, as a proxy for first exposure to HPV, seems to have a particularly strong impact on risk for cervical cancer (78). Other risk factors parallel risk factors for HPV infection and include parity, lifetime number of sexual partners (79), smoking (80, 81), hormonal contraception (82), and infection with other sexually transmitted diseases (83).

Vulvar cancer

Vulvar cancer is rare before 35 years of age, and it increases steadily from age 35 to 80–84 and peaks after 85 years of age in Sweden. Overall numbers of cases have remained stable since the 1980s with some fluctuation. In Sweden in 2015 there were 137 new cases, corresponding to an age-standardized incidence of 1.67 per 100,000, and 52 deaths (17). By stage at diagnosis, the 5-year relative survival is 45% for Stage I, 33% for Stage II, and 18% for Stages III+. Survival differs by age at diagnosis. The relative 5-year survival for women under age 50 diagnosed with Stage I vulvar cancer is 67% compared to 41% for Stage I cancer diagnosed among women over age 50 (calculated using Swedish Cancer Registry data from 2004–2009).

There are two main proposed etiological origins of vulvar cancer – HPV infection and lichen sclerosus* (84, 85). One systematic review from the US showed that approximately 65% of vulvar cancers were positive for high-risk HPV types and were dominated by HPV 16 (50%) and 18 (4%) (86). Data from a meta-analysis completed by IARC show that the proportion of vulvar cancer that is HPV-positive differs by histological type; 69% of warty-basaloid vulvar cancer was HPV-positive whereas only 13% of the keratinized type was (87). The proportion of vulvar cancer that can be attributed to HPV-infection decreases by age (88). Other risk factors include a history of cervical abnormalities, smoking, infection with human immunodeficiency virus (HIV), and acquired immunodeficiency syndrome (AIDS) (71, 89, 90).

Vaginal cancer

Vaginal cancer is relatively rare and mostly a disease found among older women. Incidence increases after 40 years of age and is similar between the ages of 45–49 and 65–69, after which it increases further and peaks at ages 80–84. In total, there were 37 cases of vaginal cancer in 2015 (the age-standardized incidence was 0.52 per 100,000) and 10 deaths. Incidence over time has not changed dramatically, ranging from a high of 0.79 per 100,000 in 1987 (age-standardized) to a low of 0.32 per 100,000 in 2012 (17). Given the small number of cases each year, these fluctuations are likely not reflective of actual changes in underlying disease risk. The relative 5-year survival is 31% for Stage I, 33% for Stage II, and 18% for Stages III+, again with differences by age at diagnosis. Among women diagnosed before the age of 50, the 5-year relative survival is 50%, and among women over the age of 50 it is 30% (calculated using Swedish Cancer Registry data from 2003-2009).

High-risk HPV types have been detected in 73%–78% of vaginal cancers, and HPV 16 (59%) and HPV 18, 31, and 33 (5% each) are the most commonly detected types (86, 91, 92). Aside from HPV infection, risk factors for vaginal cancer include immune system deficiency (71), previous high-grade cervical abnormalities (93), and other factors also associated with cervical cancer such as smoking, life-time number of sexual partners, and age at sexual debut (94).

Condyloma acuminata

Condyloma acuminata (condyloma, genital warts) is a common sexually transmitted disease, usually caused by HPV 6 and 11 (10). A questionnaire study

* Lichen sclerosus is a chronic inflammatory mucocutaneous disease usually affecting the female genitalia.

mailed to a representative sample of over 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 (95). In 2006, before the advent of vaccination, overall incidence of condyloma between the ages of 10 and 44 was estimated to be 399 per 100,000 (males) and 387 per 100,000 (females), with a peak incidence at ages 20–24 (1,070 and 1,038 per 100,000 for males and females, respectively) (96). Further evidence from youth clinics in the greater Stockholm area showed that 38% of condylomas diagnosed were among males, and the peak incidence of condyloma was between the ages of 19 and 23 for males compared to age 20 for females (97).

Data from surveillance of the vaccination impact in Australia show a significant decline in condyloma between the pre- and post-vaccination periods in both males and females aged 25–34 and younger before the advent of male vaccination in Australia. This suggests both a direct effect of vaccination as well as a herd protection effect (98).

Respiratory papillomatosis

Respiratory papillomatosis is a rare condylomatous disease of the larynx/respiratory tract that may affect infants (presumably by infection at birth, vertically transmitted) or young adults. The true incidence of respiratory papillomatosis is difficult to assess, and has in a populations-based study from Norway recently been estimated to occur at an incidence of about 0.17 per 100,000 children, which is in line with other population-based studies (99). HPV 11 is a common cause of respiratory papillomatosis in infants, for unknown reasons. Respiratory papillomatosis among adults is dominated by HPV 6, followed by HPV 11, similar to condyloma (11). There is no up-to-date data on Swedish incidence, and the code recommended to use for reporting the disease to the Swedish Patient Registry is not specific to respiratory papillomatosis. Respiratory papillomatosis can be severe and constitutes a health burden with associated costs because of the need for repeated surgical treatments.

Vaccine efficacy and immunogenicity

Cervarix

The bivalent vaccine Cervarix (bHPV) has demonstrated efficacy against precancerous lesions of the cervix. The efficacy in protection against anal precancerous lesions and anal cancer related to vaccine HPV types, as well as other HPV-related cancers, has not been directly demonstrated. However, by comparing immune responses in males and females, and immune responses of bHPV with the quadrivalent vaccine Gardasil (qHPV), it can be inferred that vaccinating males with bHPV will result in a similar level of protection against anal precancerous lesions as females vaccinated with qHPV or bHPV.

The efficacy relevant for boys and men is described in the European Public Assessment Report (EPAR) for variation II-67 (100). The basis for the approval of protection of anal lesions was the demonstration of non-inferior immune responses of bHPV compared to qHPV (which was already approved for protection against anal lesions related to HPV 16 and 18) in females and by comparing immune responses in males and females.

Studies on immunogenicity of bHPV in females

The immunogenicity of bHPV among females was compared to qHPV in two studies among females 18–45 years of age (3-dose schedule) and 9–14 years of age (2-dose schedule) (studies HPV-010 and HPV-071, see also Table 1.). Non-inferiority to qHPV was demonstrated for both study groups. Because qHPV has demonstrated efficacy against anal lesions, this was considered sufficient to also grant bHPV a license including protection against anal precancerous lesions and anal cancer in females.

Studies on immunogenicity of bHPV in males

Two studies have been performed on the immunogenicity of bHPV in males (studies HPV-011 and HPV-040, see Table 1). Both studies showed that vaccinated individuals became seropositive and developed high geometric mean titres (GMTs). The antibody titres were also shown to be comparable between sexes.

Studies on vaccine efficacy of bHPV among females

In study HPV-010, females 18–45 years old received bHPV in a 3-dose schedule. Their antibody titres remained relatively stable over time after month 12 up to month 60 and superior to 3-dose qHPV regardless of baseline serostatus.

In the HPV-071 study, superiority of the immune response elicited by bHPV was demonstrated when administered to females 9–14 years of age according to the 2-dose schedule (at 0 and 6 months) compared to that of qHPV administered according to the 2-dose (0 and 6 months) and the standard 3-dose (0, 2, and 6

months) schedules for both HPV 16 and HPV 18 up to month 12 regardless of baseline serostatus.

HPV-012 was a pivotal study for the bHPV Marketing Authorisation Application (MAA), and it showed higher immunogenicity in the 10–14-year-old population vs. the 15–25-year-old population in which clinical efficacy was demonstrated (clinical efficacy trials HPV-001 and HPV-008 of the MAA). The study results have been presented in the initial MAA and published in scientific journals (101, 102).

Studies on vaccine efficacy of bHPV among males

In the first study (HPV-011), immunogenicity in healthy male subjects aged 10–18 years old was studied in a phase I/II study in Finland. Subjects were randomly allocated (2:1) to receive either bHPV or a hepatitis B vaccine (Engerix®-B) as control. All subjects were vaccinated according to a 0, 1, 6-month schedule. The duration of the study (including safety follow-up) per subject was approximately 12 months. The primary objective of the study was to evaluate the immune responses to bHPV one month after the third dose (i.e. at month 7). A secondary objective was the evaluation of the immune response one month after the second dose (i.e. at month 2).

After vaccination, all subjects (seropositive and seronegative at baseline) in the bHPV group were seropositive at one month after dose 2 (month 2) and remained seropositive up to one month after dose 3 (month 7) for both HPV 16 and HPV 18. High geometric mean titres (GMTs) were observed in the bHPV group at month 2, with approximately a four-fold increase for HPV 16 and a two-fold increase for HPV 18 between month 2 and month 7. Higher GMTs were observed in the younger age group (10–14 years versus 15–18 years) than in the older age group at month 7. The month 7 results of study HPV-011 have been published (103).

As another secondary objective, the immune responses to bHPV among the 10–18-year-old males were compared to the results in a subset of 15–25-year-old females from study HPV-012 one month after administration of the third vaccine dose (i.e. at month 7). The inter-study inferential analysis between males and females demonstrated comparability of immune responses to bHPV between the sexes, but more importantly non-inferiority of the immune response of three doses of bHPV in males of 10–18 years compared to three doses of bHPV in females of 15–25 years (the population in which efficacy against cervical lesions and cancer was demonstrated). Non-inferiority regarding seroconversion rates was also demonstrated.

In the second study (HPV-040), 12–15-year-old male and female subjects were enrolled in a phase III/IV, community-randomised, partially blinded controlled study in Finland. The objective of this study was to evaluate the effectiveness of

vaccination with bHPV in reducing the prevalence of HPV 16/18 genital infection in females in communities where vaccination had been introduced in girls only compared to communities where vaccination had been introduced in girls and boys. The study included two treatment groups: one received bHPV and the same control vaccine. Subjects in the bHPV treatment groups received three doses of the vaccine according to a 0, 1, 6-month schedule. The study design included three arms:

- Arm A included communities (N = 11) where 90% of male and female adolescents were to be vaccinated with bHPV (vaccination strategy #1).
- Arm B included communities (N = 11) where 90% of the female adolescents were to be vaccinated with bHPV (vaccination strategy #2).
- Arm C included communities (N = 11) where the adolescents were not vaccinated against HPV 16/18 (negative control). These male and female adolescents received the hepatitis B vaccine instead.

For both sexes and for both HPV types included in the vaccine, seroconversion rates of 100% were observed 1 month after administration of the third vaccine dose in subjects that were seronegative at baseline. Furthermore, in a descriptive analysis, GMTs for antibodies to the vaccine HPV types were high in both sexes and comparable between the vaccinated male and the female cohorts.

Table 1. Main studies on bHPV.

Study	HPV-010	HPV-012	HPV-071	HPV-011	HPV-040
Target group	Females, 18–45 years old	Females, 10–14 and 15–25 years old	Females, 9–14 years old	Males, 10–12, 13–15, and 16–18 years old	Males and females, 12–15 years old
Intervention	3-dose bHPV	3-dose bHPV	2-dose bHPV	3-dose bHPV	3-dose bHPV
Outcome measure	Immunogenicity	Immunogenicity	Immunogenicity	Immunogenicity	Seroconversion, seropositivity
Comparison vaccine	3-dose qHPV	None	2- and 3-dose qHPV	Hepatitis B vaccine	Hepatitis B vaccine
Follow-up period	60 months	48 months	12 months	12 months	N/A
Selected results	Non-inferior immunogenicity of bHPV compared to qHPV	Higher immunogenicity in the 10–14 year-olds vs. the 15–25 year-olds	Non-inferior immunogenicity of 2-dose bHPV compared to both 2- and 3-dose qHPV	Non-inferiority of the immune response of 3 doses of bHPV in males 10-18 years as compared to 3 doses of bHPV in females 15–25 years	100% seroconversion rates in both sexes 1 month after dose 3.

bHPV – bivalent HPV vaccine. qHPV – quadrivalent HPV vaccine. N/A – Not available

Gardasil

The quadrivalent HPV vaccine Gardasil (qHPV) is expected to protect against anal precancerous lesions and anal cancer as well as genital warts related to HPV vaccine types in males and females based on the following:

- Demonstrated efficacy against anal intra-epithelial neoplasia grade 2 or worse among MSM
- Demonstrated efficacy against genital warts related to HPV 6 and 11 in males and females
- Demonstrated efficacy against cervical lesions in women, and the similarity in histology, natural history, and pathogenesis between cervical and anal HPV-related lesions
- No indication that vaccine protection against anal lesions or genital warts related to HPV is sex specific
- Demonstration of immune responses in boys and girls (9–15 years) that are superior compared to those of women and men (16–26 years) in which efficacy studies have been performed

The use of qHPV in males was approved following a variation application (i.e. a regulatory change in the product information) in 2014 (28).

Studies on immunogenicity in males

The pivotal study in males was Protocol 020 (P020). This was a randomized, double-blind, placebo-controlled, multicentre safety, efficacy, and immunogenicity study. The study included 4,055 males of whom 3,463 subjects (85%) were heterosexual males aged 16–23 years and 602 subjects (15%) were MSM aged 16–26 years. The study subjects were randomized in a 1:1 ratio and vaccinated with either qHPV (N = 2,025) or placebo (N = 2,030). The primary objective of P020 was to determine whether administration of a 3-dose regimen of qHPV to men who were naïve to HPV 6, 11, 16, and/or HPV 18 at baseline would reduce their risk of external genital lesions (EGLs), PIN, penile/perianal/perineal cancer, and genital warts caused by vaccine-matched HPV types. In the MSM substudy, which was embedded within P020, the efficacy of three doses of qHPV against HPV 6/11/16/18-related AIN and anal cancer was assessed in MSM who were naïve to these HPV types at baseline.

In an extension of the study (study 020-10), vaccination was offered to all subjects worldwide who had received placebo or an incomplete series of vaccinations in the base study. A total of 1,098 subjects who had originally received placebo thereby received one or more doses of qHPV.

In addition, a long-term follow-up study of P020 was performed (study 020-21). This was a long-term effectiveness, immunogenicity, and safety study of qHPV in young men with a 6-year follow-up period. Time points through month 36 were part of the base study. The early vaccination group consisted of 936 subjects, and the catch-up vaccination group consisted of 867 subjects.

Efficacy against HPV 6/11/16/18-related external genital lesions

Vaccine efficacy against HPV 6/11/16/18-related EGL in the per-protocol efficacy population was 90.6%. There were a total of three EGL cases in the vaccine group and 32 cases in the placebo group. All of the cases in the vaccine group and the majority of the cases in the placebo group had positive PCR results for HPV 6 and/or 11 and were from diagnosed condyloma. Of the 32 cases in the placebo group, 4 were diagnosed PIN1 or worse, with 2 cases of PIN2/3 identified. No cases of cancer were detected during the study.

Two of the vaccine subjects had HPV 6-related EGLs. Both had anti-HPV 6 titres at month 7 that were comparable to the GMTs among per-protocol subjects who received qHPV and were naïve to HPV 6 during the vaccination period. The third vaccine subject diagnosed with an EGL related to HPV 6 and 11 had anti-HPV 6 and 11 titres at month 7 that were considerably above the levels observed among per-protocol HPV-naïve recipients as well as those who had evidence of prior infection of HPV 6 or 11 at day 1. The explanation for this is unknown, but these results do not suggest a failure of efficacy related to low antibody titres.

Efficacy against HPV 6/11/16/18-related AIN and anal cancer (MSM per-protocol efficacy population)

The MSM per-protocol efficacy population included a total of 402 subjects. Vaccine efficacy against HPV 6/11/16/18-related AIN was 77.5% (95% confidence interval (CI): 39.6, 93.3). There were a total of 5 AIN cases in the vaccine group and 24 cases in the placebo group. All of the cases in the vaccine group and the majority of the cases in the placebo group had positive PCR results for HPV 6 and/or 16.

The vaccine efficacy estimate for HPV 6/11/16/18-related AIN2 or worse was 74.9% (95% CI: 8.8, 96.4). Of the 24 cases in the placebo group, 13 were identified with diagnoses of AIN 2 or worse. In the vaccine group, 3 out of 5 cases had AIN 2 or worse. There were a total of 9 cases of AIN 2 or worse related to HPV 16/18. Of these, 1 case was in the vaccine group and 8 were in the placebo group. No cases of cancer were detected during the study.

Long-term effectiveness (per-protocol population)

Three cases of HPV 6/11-related genital warts were observed in the EVG per-protocol population during the base study. In follow-up visits before 1 June 2012,

no additional cases of this endpoint had occurred. There were five cases of HPV 6/11/16/18-related AIN in the EVG MSM per-protocol population during the base study. In the follow-up visits, no additional cases of this endpoint were diagnosed. Incidence of this endpoint remained low during the extension period.

Persistence of Antibody Response in the Per-Protocol Immunogenicity Analysis Population

The GMTs observed at month 48 through month 72 of subjects in the per-protocol immunogenicity population, EVG, were comparable to those at month 36, indicating no further reduction of titres in the extension period. The small group of subjects who commenced their long-term follow-up in time for a month 48 visit were all MSM subjects. As noted in the base study, MSM subjects demonstrated lower titres than heterosexual male subjects. Titres observed at follow-up visits (month 48, month 60, and month 72) within the early vaccination group in this population were comparable to those at month 36, indicating no further reduction of seroprotection in the extension period. As noted in previous studies, and in the base study Protocol 020, the proportion of subjects seropositive to HPV 18 declined over time. However, no cases of HPV 18-related disease were observed in the EVG per-protocol efficacy population during the base study or during follow-up (as of 1 June 2012).

Gardasil 9

The protection of the nonavalent HPV vaccine (nHPV) Gardasil 9 against HPV disease related to the four common HPV types (6, 11, 16, and 18) is expected to be the same as that of qHPV based on demonstrating equal immunogenicity of the immune response in females and males 9–26 years of age. Non-inferiority of the GMTs has been shown following vaccination with the nonavalent vaccine compared to the quadrivalent vaccine, and the rates of seroconversion have been similar (104). The efficacy of nHPV against a combined endpoint of CIN2/3, adenocarcinoma in situ, cervical cancer, VIN2/3, VAIN 2/3, vulvar cancer, and vaginal cancer was 97.4% in women 16–26 years of age. The efficacy of nHPV in males is expected to be at least the same as qHPV, with the additional protection against HPV 31, 33, 45, 52, and 58. nHPV has also shown high efficacy against persistent infections (at 6 and 12 months) and CIN1, CIN2 and CIN2+ related to HPV types 31, 33, 45, 52, and 58 (104).

A detailed description of the available data at the time of approval is available in the EPAR (105).

Number of doses needed

All three vaccines have been approved for use with a 2-dose schedule and a dose interval of 6 months in boys and girls 9–13 (qHPV) or 9–14 years of age (nHPV and bHPV). The protection of two doses is expected to be the same as that of three doses in this age group. This is based on the observation that immune responses in 9–14-year-old boys and girls are non-inferior or superior to those of women 16–26 years old (where efficacy has been demonstrated). It is assumed that there are no sex differences in the number of doses needed because there are no known sex differences in immune responses that are considered clinically relevant.

The duration of the protective effect of the vaccines and the need for additional booster doses have not yet been established, but stable and high antibody levels over 10 years of follow up together with effectiveness data indicate that antibodies and protective effects are likely to last long term (104). There is also a discussion on the possibility of a 1-dose regimen, but data on whether this would give adequate protection is still contradictory (104).

Safety of HPV vaccines

All three licensed HPV vaccines are approved for use in a male population. The safety profiles of the three available HPV vaccines have been determined in clinical studies as well as from global post-marketing experience. The adverse events that have been reported in clinical trials and spontaneously reported from patients and health care providers are described in the product information for each vaccine (106-108). The most common adverse reactions are injection site reactions and headache, and most reactions are mild to moderate. There is no indication of a different safety profile in males compared to females based on the available safety data (see below). There is no biological reason to expect major differences in safety profile between genders for a vaccine, and there is currently no vaccine that is restricted to either sex for safety reasons. A summary of the safety data in males for each vaccine is given below as well as a brief summary of the available data in females.

Cervarix

Since registration in 2007 and up until 17 Nov 2016, almost 65 million doses had been distributed (the Medical Products Agency, June 2017). The safety data in males receiving this vaccine are described in detail in the European Public Assessment Report for Type II variation 67 (100).

In clinical studies that enrolled girls and women aged 10–72 years (of which 79.2% were aged 10–25 years at the time of enrolment), bHPV was administered to 16,142 females, and 13,811 females received control vaccine. These subjects were followed for serious adverse events over the entire study period, up to 8.9 years. In a pre-defined subset of subjects (bHPV = 8,130 versus control = 5,786), all adverse events were followed for 30 days after each injection.

In two clinical studies that enrolled males aged 10–18 years (HPV-011 and HPV-040), 2,617 males received bHPV and were followed with active safety surveillance. The studies that included both males and females, used the hepatitis vaccine Engerix®-B as the control vaccine and are further described below.

Within the 10–18 year age group (study HPV-011), and in line with previous observations in other studies conducted in females, the safety and reactogenicity* profile of bHPV seemed comparable to that of the control vaccine, with the exception of local solicited symptoms and myalgia that seemed to be more frequent in the bHPV group. The apparently higher rate of solicited symptoms did not

* Reactogenicity is the property of a vaccine being able to produce common, "expected" adverse reactions, especially excessive immunological responses and associated signs and symptoms—fever, sore arm at injection site, etc.

negatively impact the acceptance of the vaccination, as 97% of both study groups completed the 3-dose vaccination schedule. Together with the overall low percentage of grade 3 symptoms* (solicited and unsolicited) during the 30 days post-vaccination, which seemed comparable between the two treatment groups (i.e. bHPV and the control vaccine), these data indicate that bHPV is generally well tolerated in males. In the larger population among the 12–15 year age group (2,440 males; HPV-040), the same conclusion can be drawn. Whereas the results suggested a higher frequency of local solicited symptoms (e.g. pain) in the bHPV group compared to the control group, reported as part of the active surveillance, the frequency of solicited general symptoms was lower compared to the local symptoms, and the potential difference between the treatment groups was less pronounced. The most frequently reported general symptoms were fatigue, headache, and myalgia, which were already mentioned in the current label of the vaccine as very common symptoms.

For the administration of the vaccine in males, the severe adverse event (SAE) rate was within the rate observed for the female population, for which the vaccine was already approved. Also, no differences in the nature of new-onset autoimmune diseases (i.e. autoimmune diseases debuting during the study period) were observed between males and females. In addition, the overall SAE reporting rate was similar between bHPV and the hepatitis B vaccine.

Gardasil

Since registration and up until 31 May 2016, more than 216 million doses had been distributed (the Medical Products Agency, June 2017). The use of qHPV in males was mainly assessed in a regulatory change of the product information to include prevention of anal cancer and anal precancerous lesions in the indication (28).

In seven clinical trials (six placebo-controlled), individuals (both females and males) were administered qHPV or placebo on the day of enrolment and approximately 2 and 6 months thereafter. Few individuals (0.2%) discontinued due to adverse reactions. Safety was evaluated in either the entire study population (six studies) or in a predefined subset (one study) using vaccination report card-aided surveillance for 14 days after each injection of qHPV or placebo. The individuals who were monitored using vaccine report card-aided surveillance included 10,088 individuals (6,995 females 9–45 years of age and 3,093 males 9–26 years of age at enrolment) who received qHPV and 7,995 individuals (5,692 females and 2,303 males) who received placebo. The most common adverse reactions observed were

* Grade 3 symptoms include severe symptoms involving markedly reduced daily activities usually requiring some assistance, medical intervention/therapy, and possibly hospitalisation or hospice care.

injection-site adverse reactions (77.1% of vaccinees within 5 days following any vaccination visit) and headache (16.6% of the vaccinees). These adverse reactions were usually mild or moderate in intensity. The safety profile in male subjects was not found to differ from that of female subjects.

A large post-marketing observational safety follow-up of males vaccinated with qHPV is ongoing in the US, and results are expected late in 2017 or early 2018. The study target inclusion is 44,000 male subjects receiving three doses.

A register-based cohort study performed in Denmark and Sweden found no evidence supporting associations between exposure of girls to qHPV vaccine and autoimmune, neurological, or venous thromboembolic adverse events (109).

Gardasil 9

Since registration and up until 9 Dec 2016, more than 18 million doses had been distributed (the Medical Products Agency, June 2017).

In seven clinical trials, individuals (males and females) were administered nHPV on the day of enrolment and approximately 2 and 6 months thereafter. Control vaccine was either qHPV or placebo. Safety was evaluated using vaccination report card-aided surveillance for 14 days after each injection. A total of 15,776 individuals (10,495 subjects 16–26 years of age and 5,281 adolescents 9–15 years of age at enrolment) received nHPV. Few individuals (0.1%) discontinued due to adverse experiences. The most common adverse reactions observed were injection-site adverse reactions (84.8% of the vaccinees within 5 days following any vaccination visit) and headache (13.2% of the vaccinees within 15 days following any vaccination visit). These adverse reactions usually were mild or moderate in intensity.

Detected safety signals for HPV vaccines

A number of safety signals have been detected over the years for all three HPV vaccines, and they have either resulted in a change in the product information for the vaccine or a conclusion that no change is necessary. Recently the evaluation of a suspected causal relationship between HPV vaccines and postural orthostatic tachycardia syndrome (POTS) and complex regional pain syndrome (CRPS) attracted media and public attention. However, it was concluded by the EMA that the evidence did not support a causal link between vaccination with HPV vaccines and these syndromes (110).

All safety signals since September 2012 that have been discussed at the EMA's committee for safety of medicinal products, the Pharmacovigilance Risk Assessment Committee, are listed on the EMA's website (111).

Suitability of simultaneous administration

A systematic review of nine studies looking at safety and immunogenicity of HPV vaccines co-administered with other vaccines concluded that the safety profile was acceptable and that the antibody responses to HPV vaccines met non-inferiority criteria (112). Furthermore, the authors concluded that the available data suggest that HPV vaccines are safe and effective when administered with other vaccines. Even though there are no data on the simultaneous administration of HPV vaccines with other vaccines beyond the ones listed below, the WHO recently stated that they can be co-administered with other non-live and live vaccines (104).

There is no expected sex difference in suitability of simultaneous administration of vaccines. No specific issues regarding the use of HPV vaccines in boys are foreseen.

The product information regarding co-administration of each HPV vaccine with other vaccines is reproduced below (106-108).

Cervarix

The bivalent vaccine may be administered concomitantly with a combined booster vaccine containing diphtheria (d), tetanus (T), and pertussis [acellular] (pa) with or without inactivated poliomyelitis (IPV) (dTpa or dTpa-IPV vaccines) with no clinically relevant interference with antibody response to any of the components of either vaccine. The sequential administration of combined dTpa-IPV followed by bHPV one month later tended to elicit lower anti-HPV 16 and anti-HPV 18 GMTs as compared to bHPV alone. The clinical relevance of this observation is not known.

This vaccine may also be administered concomitantly with a combined vaccine against hepatitis A (inactivated) and hepatitis B (recombinant DNA (rDNA)) or with a hepatitis B (rDNA) vaccine.

Administration of bHPV at the same time as a combined vaccine against hepatitis A and B has shown no clinically relevant interference in the antibody response to the HPV and hepatitis A antigens. Anti-HBs geometric mean antibody concentrations were significantly lower on co-administration, but the clinical relevance of this observation is not known because the seroprotection rates remain unaffected. The proportion of subjects reaching anti-HBs $\geq$ 10 mIU/ml was 98.3% for concomitant vaccination and 100% for the hepatitis vaccine given alone. Similar results were observed when bHPV was given concomitantly with the vaccine against hepatitis B.

Gardasil

The quadrivalent vaccine may be administered concomitantly with combined booster vaccines against diphtheria, tetanus, pertussis, and poliomyelitis (dTap, dT-IPV, and dTap-IPV vaccines) with no significant interference with antibody response to any of the components of either vaccine. However, a trend of lower anti-HPV GMTs was observed in the concomitant group. The clinical significance of this observation is not known. This is based on the results from a clinical trial in which a combined dTap-IPV vaccine was administered concomitantly with the first dose of qHPV.

Administration of qHPV at the same time as hepatitis B (rDNA) vaccine did not interfere with the immune response to the HPV types, and the seroprotection rates were unaffected. The geometric mean titres of antibodies against one hepatitis B-antigen (anti-HBs) were lower on co-administration, but the clinical significance of this observation is not known.

The concomitant administration of qHPV with vaccines other than the ones above has not been studied.

Gardasil 9

The nonavalent vaccine may be administered concomitantly with combined booster vaccines against diphtheria, tetanus, pertussis, and poliomyelitis (dTap, dT-IPV, or dTap-IPV vaccines) with no significant interference with antibody response to any of the components of either vaccine. This is based on the results from a clinical trial in which a combined dTap-IPV vaccine was administered concomitantly with the first dose of nHPV.

Expected impact of vaccinations on burden of disease and HPV epidemiology

Long-term follow-up studies are needed to demonstrate if there is an effect of HPV vaccination on cancer-related mortality and cancer prevalence for HPV-associated cancers. In the absence of substantial real-life data on the population impact of male vaccination, models provide us with a chance to estimate the predicted effects of vaccination on a range of disease outcomes. Models allow us to make inferences about the future based on available data and give us an opportunity to simulate potential interventions and their impact on health outcomes. Considerations on immunization strategies should be, as far as possible, based on scientifically founded predictions of effect.

Mathematical models are equational representations of complex occurrences that facilitate the study of systems. Infectious disease modelling seeks to represent the dynamics of an infectious agent as well as the spread of it in the population (the transmission between individuals). It can be further extended to investigate control measures, such as vaccination (113). Substantial modelling work is currently being done on HPV and HPV-related diseases since the advent of HPV vaccination programmes with the aim to further evaluate prevention strategies and related costs. Models typically differ quite significantly, not only in the modelling approach but also with regard to how the input data are defined and which assumptions are made – e.g. duration of vaccine-induced immunity, vaccine cross-protection, and sexual assortative behaviour as well as estimates of disease incidence, vaccine efficacy, coverage, and implementation strategy (114, 115). The ability of a model to represent reality is influenced by the quality and detail of existing data sources and assumptions about uncertainties in the natural history and spread of the disease.

For prediction of how different vaccination strategies impact the circulation of HPV infections, the dynamic effects should be taken into account. Because 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. For this section, a systematic review of the literature was completed to summarize current evidence in the field on models evaluating HPV vaccination. Studies were selected for inclusion based on whether the title and abstract included the impact of vaccination on HPV infection or HPV-related diseases and cancers and whether the study used a mathematical, statistical, or theoretical modelling analysis. Models that only examined vaccination of females or estimated HPV-related outcomes only among females were excluded. Cost-effectiveness models were not of interest *per se* unless they also provided model-generated disease estimates as an outcome. The results of this review are summarized below.

Review of effect by outcomes

HPV vaccination modelling studies that evaluate impact on infection have examined varying strategies with regard to age, coverage level, dosing, and more recently, sex. Models are typically country-specific with regard to influence of input data on baseline disease outcomes and transmission dynamics. Estimates of the added benefit of vaccinated males on HPV infection control are largely driven by vaccination coverage and duration of protection offered by the vaccine. With 80% coverage of females only and with an assumption of life-long duration of the vaccine, elimination of the vaccine HPV types is shown in a heterosexual transmission model from the UK (116). In a model examining a scenario with 90% coverage and assuming a 75% efficacious vaccine, HPV prevalence among women is reduced by 44% if both males and females are vaccinated, but it is reduced by only 30% if just females are vaccinated (117). However, evidence from modelling work on Italian data suggests that increasing coverage among females is the most effective approach to reducing vaccine-type prevalence in females, unless this is not feasible, in which case male vaccination could be a strategy where vaccine pricing allows (118). Early modelling work from Australia, where the impact of male vaccination on female infection levels was examined, suggests that 80% coverage in males and females would result in a reduction in HPV 16 prevalence of 74%–100% in vaccinated and 86%–96% in unvaccinated females (119). In the Netherlands, modelling results examining the effects of different vaccination coverage levels suggests that coverage of females would need to be over 80% in order to outweigh including males with 60% coverage (120). Put another way, the Australian modelling results suggest that the additional contribution of vaccinating males will be low when vaccination coverage of females is high (121).

Condyloma is the first disease outcome beyond infection to be measureable after the implementation of a vaccination programme. In Australia, modelling work predicts a near elimination of condyloma in males and females with the extension of vaccination of males (122). Assuming that the duration of vaccine protection is 10 years (a conservative estimate), a 2-dose vaccination schedule for males and females compared to a 2-dose schedule among females only would result in an additional 9% reduction in condyloma consultations (and an additional 3% reduction in HPV-related cancer cases) in Canada (123). Results from modelling work comparing adult catch-up vaccination strategies in the Netherlands show that there is a greater impact on condyloma incidence reduction if adult males are targeted compared to adult females (124). In a UK modelling exercise, male vaccination gave an added benefit for prevention of genital warts, but this effect was influenced by the duration of vaccine-induced immunity and vaccination coverage levels (116). Taken together, male vaccination enhances the impact on condyloma among both males and females across different ages at vaccination when using conservative estimates of vaccine duration.

Models examining the impact of universal vaccination programmes on other HPV-related disease outcomes without focusing on the cost-effectiveness aspects of vaccination have, in many instances, focused on cervical cancer outcomes. We found four main analyses that investigated the impact of male vaccination on male HPV-related disease outcomes. Bogaards et al studied cancers of the penis, anus, and anal canal as well as squamous cell carcinoma of the oropharynx in men and the incremental benefit of vaccinating males along with females (125). The results are presented as the number of males needed to be vaccinated in order to prevent one cancer case under varying levels of vaccination coverage among females and as the number of QALYs gained through adding vaccination of males to varying levels of vaccination coverage among females. They conclude that female vaccination has a strong effect on incidence of oropharyngeal cancer but not on anal cancer because anal cancer is more common among MSM who do not benefit from a herd effect of female vaccination (125). A model run on Austrian data compared the preventive effect of the quadrivalent and nonavalent vaccines in a scenario where 9-year-old females and males were vaccinated with 60% and 40% coverage, respectively (126). Compared to no vaccination, universal vaccination with the quadrivalent vaccine resulted in reductions of 76% for anal cancer incidence, 79% for condyloma, 54% for penile cancer, and 77% for head and neck cancers among males (126). Using the HPV-ADVISE model, different vaccination strategies (females only and universal vaccination) for the quadrivalent and nonavalent vaccines in the US context were compared (127). Observed 3-dose vaccination coverage for females and males was used (coverage was assumed to be 46% and 25% among females and males, respectively, for 13–17 year olds, reaching 62% and 38% by age 17). In the base-case universal scenario in which females and males were vaccinated with the quadrivalent vaccine, incidence of HPV-attributable cancers and condyloma would be reduced by 76 and 80 percentage points, respectively, in females and males (127). Elbasha et al have explored the mean reduction in cases of HPV-related disease in females and males at different time points after a scenario in which male vaccination was introduced. Substantial reductions in condyloma, and later, incidence of anal, penile, and head and neck cancers were seen, but the relative magnitudes of these reductions were not given, thus making the results somewhat difficult to interpret (128).

These models show reductions in HPV-related disease among males when implementing male vaccination alongside female vaccination. The magnitude of these reductions is dependent on the distribution of disease in the male population (125) and is somewhat difficult to evaluate compared to other strategies (female-only vaccination) given that these models compare impact between vaccines (126, 127) and include various endpoints (128). A key point is made, however, by the Dutch study in which female-only vaccination does not appear to have a large impact on anal cancer incidence among males (125).

To our knowledge, the only transmission model run on Swedish data where universal vaccination was explored showed that with inclusion of males in routine vaccination, vaccine effectiveness among females was similar to that of including an extended catch-up of females (129). Vaccinating males in addition to females would also accelerate the reduction of HPV prevalence among women (129), which could further reduce HPV-related outcomes detected in screening among women.

The vaccination programme's resilience, or the ability of the programme to maintain effectiveness despite threats to coverage levels, was also explored in this model. This was examined by halving the assumed coverage for a period of 5 years and comparing the HPV-prevalence reduction attributable to vaccination among females. If only females were vaccinated, the effectiveness decreased up to 3.1%, whereas if males were included in the vaccination programme, either as routine vaccination or as routine vaccination with an extended catch-up, the decrease in effectiveness was negligible (peak reduction was 0.43%) (129). Given recent examples of programs where coverage has decreased dramatically (Colombia, Denmark, and Japan), ensuring the robustness of the vaccination programme is an important consideration and benefit of male vaccination.

Finally, recent data suggest that cross protection is enhanced by universal vaccination. Additional analyses of the community-randomized trials of vaccine effectiveness and vaccination strategies in Finland show that in a scenario with low to moderate universal vaccination coverage with the bivalent vaccine, a herd effect is seen even for cross-protection types (M. Lehtinen, presentation at EUROGIN 2016, slides obtained from the presenter).

Impact of vaccinations on health care providers

This section describes the direct impact on health care providers of implementing a universal HPV vaccination programme. The impact related to reduced burden from HPV-related disease as a result of a vaccination programme for boys has been quantified within the health economic evaluation (130). No imminent changes to the national cervical screening programme are foreseen due to also including boys in the national HPV vaccination programme, although recommendations may need to be further adjusted to ensure performance of the screening tests used and to optimize the balance of prevention strategies as the number of screening-positive women decreases.

Impact on school health care

HPV vaccination of girls is predominantly carried out by school nurses within the school health organization. In 2014, there were 2,344 school nurses working within the municipal schools according to the Swedish Association of Local Authorities and Regions (SKL) (131). Only part of these school nurses work with children in grades 5 and 6. Data for the number of students per school nurse are lacking, but the variations are large in the country. Fifteen per cent of the students go to independent schools (i.e. run by private enterprises and not the municipalities) (132). The number of school nurses working in independent elementary schools is not available, but these schools have the same obligation to provide access to school health care as municipal schools.

A nurse with specialist competence either as a district nurse or within child and youth medicine may prescribe drugs for vaccination of children in line with the general vaccination programme for children (133). Nurses without specialist competence need to have the vaccinations prescribed by a nurse specialist or medical doctor.

The possibility of vaccinating in either grade 5 or 6 gives the health-care provider and school nurse more flexibility to take into account school activities when planning vaccinations. The 2-dose regimen of HPV vaccination is easier to administer than the 3-dose regimen, but the 2-dose regimen applies only for children up to 13 or 14 years of age (depending on what vaccine is used). For older children and immunosuppressed children, a 3-dose regimen applies (134). Guardians sometimes choose to postpone the HPV vaccination, which might lead to three doses being required.

Time needed to vaccinate both girls and boys

The vaccination procedure can be divided into the following steps:

Preparations

- Order the vaccine and emergency drugs for treatment of allergic reactions.
- Prescribe the vaccine after a review of the child's previous vaccinations.
- Contact the guardians and/or school doctor in case of doubt concerning the vaccination status.
- Provide information to students in the classroom concerning the reason for the immunization, the vaccination procedure, the procedure for getting informed consent, and how to manage pain and anxiety before and during vaccination.[*]
- Obtain informed consent from the guardians. Written information with a consent form is given to the guardians who return the signed consent form to the school nurse. The consent form must be designed so that both guardians clearly have the opportunity to decide and confirm the decision with their signatures (135). If the guardians disagree, the child cannot be vaccinated.[*]
- Plan vaccination of each class in coordination with the teachers.
- Have separate contact with guardians and children with questions, special demands, or needs.

The vaccination procedure [†]

- Vaccination and distraction.
- Observation of the child after the vaccination.

Follow-up

- Follow-up and separate vaccination of children dropping out from the scheduled time.

Documentation

- Document all vaccines given in the child´s medical record and report all vaccines given to the national vaccination registry in line with the respective regulations (136, 137). Some health care providers have an automatic transmission from the digital medical record to the vaccination registry. Otherwise, and for children without permanent residence permits, the

[*] Providing information in the classrooms and obtaining consent from the parents is only required before the first dose.

[†] Two school nurses usually work together when performing the vaccination in order to maintain a high level of patient safety and quality. The municipalities and independent schools determine what vaccination routines should apply in their district or school.

registration must be conducted on paper or via the national vaccination registry website.

- Inform the guardians after vaccination.

Survey among school nurses

A survey was conducted in January-February 2017 to determine the impact on the school health care regarding extra time needed for HPV vaccination of boys. School nurses in 15 municipalities and some independent schools were asked about their estimated time for the different parts of the vaccination procedure listed above with regards to HPV vaccination of girls. Around 235 school nurses responded to the questionnaire.

Some parts of the vaccination procedure, e.g. ordering vaccine, providing information in the classroom, and planning for the vaccination with the teacher, are independent of whether boys are also offered vaccinations. These steps together are estimated to take an average of 30 minutes for each round of vaccinations. The operations carried out on an individual level, however, would require more time if boys are also included in the vaccination programme, estimated as an average of 15–20 minutes per child and dose.

The time required for the documentation of vaccination is influenced by various factors. Documentation in digital medical records with access to templates requires less time than the documentation in paper-based records. Caregivers with digital records have the option of transferring vaccination data from the medical records, directly or via Svevac, to the national immunization registry. Manual online reporting to the vaccination register must be carried out by caregivers with paper-based records, caregivers without automatic transfer, and when registering vaccinations of children without a permanent residence permit, which increases the time required.

It is also important to note that the different parts of the vaccination procedure are spread out over a period of time that can range from a few to several weeks or months. Obtaining consent is a time-consuming process both in terms of minutes per child and regarding the period of time from handing out the forms to getting all of them back.

Impact of extending the programme to boys

Sweden has roughly 100,000 children per cohort, and around 50,000 of them are boys. Extending the vaccination programme to also include boys, assuming a 2-dose schedule and a vaccination coverage of 100%, but not taking into account the practise of two nurses vaccinating together, would require an additional:

- 25,000–33,000 working hours per cohort
- 250–330 working hours for the school nurses in a municipality with a cohort of 1,000 children of which 500 are boys
- 12–17 hours for one nurse working with two classes of 25 students each.

Even though some parts of the vaccination procedure are the same for girls and boys, the individual vaccinations are the part of the process that are most time demanding. Therefore, the inclusion of boys in a national programme would almost double the workload for HPV vaccinations. The survey among school nurses also clearly showed that the time required to vaccinate is what school nurses consider the biggest practical challenge if HPV vaccination is extended to boys.

The circumstances for the school nurses can differ between various municipalities and independent elementary schools but also between schools within the same municipality or independent school group. There are differences concerning the number of pupils and schools per school nurse, routines, leadership, access to school doctors, etc. In recent years, the school nurse's tasks and working conditions have partially changed, including:

- receiving the right to prescribe vaccinations for children who have not followed the vaccination schedule (which was previously the task of the school doctor)
- receiving the responsibility for providing missing vaccinations to immigrant children according to the Swedish national vaccination programme (which was previously the task of primary health care)
- increased teamwork with the other health professionals within the school health care organisation
- increased number of immigrant children with different needs of healthcare (not restricted to vaccinations)
- increased frequency of mental health issues among schoolchildren

The school health services have been compensated to varying degrees. There are, however, many municipalities and independent elementary schools where none of the school nurses' services have been extended. This means that the capacity for imposing additional duties on the school nurses differ within the country. More statutory tasks risk pushing aside non-statutory work, such as open reception for students, health education, etc.

Impact on youth health clinics

According to representatives from youth health clinics, vaccinations are rarely performed in these institutions, partly because vaccination of younger children, who might come unaccompanied, still require the guardians' approval, and partly because physicians or nurses with specialist competence need to be available to prescribe the vaccine (personal communication, Marianne Wiksten-Almströmer, Stockholms skolors ungdomsmottagning, 2017-04-05). Therefore, the extension of the vaccination programme against HPV to include boys would have little impact on the youth health clinics.

Impact on primary care providers

Since the introduction of HPV vaccines in Sweden, males have had the opportunity to be vaccinated at their primary care centre or at vaccination centres. The health care providers have been urged to document the given doses in an electronic system for vaccinations (Svevac).

During the period 2006–2015, about 2,600 doses of HPV vaccine were registered in Svevac as having been given to boys and men (personal communication, Pär Sparén, 2016-12-15). Almost 60% of the doses had been given to boys 10–17 years old. If it is assumed that the doses have been evenly distributed over the country and the years, vaccination of boys against HPV within a national vaccination programme will probably have little impact on the primary health care system.

Attitudes towards HPV vaccinations

Several factors are important for the acceptance of, and attitudes to, HPV vaccination in high-income countries, including parental beliefs, previous acceptance of childhood vaccinations, cultural norms and values related to sexual activity, health care professionals' recommendations, trust in the vaccine, and trust in government recommendations (138-140).

Healthcare professionals are important for the success of vaccination programmes. They have a vital role for communication and information and addressing parents' vaccine hesitancy (141-145). It is important that they are adequately trained and informed in addressing emotions, doubts, and misconceptions related to vaccinations (146, 147). The intention of health care professionals to encourage parents' willingness to vaccinate against HPV and their intentions to recommend the vaccine are predictors for high HPV vaccination uptake (148). Furthermore, their recommendations have been shown to be a major factor in families' decisions to vaccinate their children (149).

In countries with school-based vaccination such as the UK, Australia, and Canada, school nurses play a key role for the success of HPV vaccination programmes. School nurses are advocates of children's health and are often a primary source of information about HPV (150-154). A firm understanding and knowledge of HPV vaccination among school nurses is therefore important (155, 156).

Parental acceptance and attitudes to HPV vaccination of girls

According to a register study conducted in Norway, HPV vaccine initiation was associated with parental age, income, education, maternal employment status, and parental country of birth, but there was no association with marital status. Lower vaccine initiation was found among girls of older mothers (above age 50), mothers in the lowest income level, and unemployed mothers. In addition, highly educated Norwegian mothers had a lower likelihood of initiation of HPV vaccine. In contrast, a higher completion rate was observed among girls with mothers in the highest income level. A lower likelihood of HPV vaccine completion was also found among girls who had not received previous childhood vaccinations against MMR (157).

Differences in vaccine initiation and completion depending on maternal education and income have also been shown in Denmark (158). Low maternal education and disposable income were associated with lower vaccine initiation. In addition, differences in vaccine initiation also depended on maternal employment and marital status. Lower vaccine initiation was observed among girls of unemployed mothers and divorced or unmarried mothers (158).

Early results of opportunistic vaccination in Sweden showed that parents' education is associated with the likelihood of their daughters being vaccinated (159). A population-based survey examined parents' attitudes to implementation of the national HPV vaccination programme in Sweden (160) and demonstrated that parents born outside of Europe and parents with a higher education were less willing to vaccinate their children if the vaccine was not free compared to those born in Sweden and parents with lower education. This is in contrast to a Swedish register-based cohort study among girls and women in 2006–2010 where girls under the age of 20 were more likely to be vaccinated against HPV if at least one parent had a university degree compared to girls and women with parents who had not completed high school (161).

A pilot study regarding parental attitudes to HPV vaccination in relation to socioeconomic factors and behaviour conducted after the implementation of the national HPV vaccination programme in Sweden (162) found no differences between parents accepting and declining the HPV vaccine in relation to socioeconomic factors. Parents that had not agreed to previous childhood vaccinations were, however, less likely to have accepted HPV vaccination for their daughters. The study has some limitations, mainly due to the small sample size and that few of the included parents had declined the vaccine. The findings are, however, in accordance with studies among Canadian and Australian parents and a Norwegian register study (139, 140, 157, 163). In addition, parents in the recent Swedish study declining HPV vaccine were more likely to have declined the influenza vaccine against AH1N1 (the so-called swine flu) in 2009–2010 (162). This is in line with previous findings in Swedish qualitative studies among parents both accepting and declining HPV vaccine for their daughters within the school-based vaccination programme (153, 154). All participating parents except one brought up the vaccine against AH1N1 during the interviews and drew a parallel between the two vaccinations (153, 154). Fear of similar side effects, especially narcolepsy, was a commonly cited reason for declining HPV vaccine and for not trusting the governments' recommendations for HPV vaccination.

In a qualitative study among immigrant women in Sweden, participants were positive to the prevention of cervical cancer and perceived the benefits of cervical cancer screening programmes. They expressed the importance of attending regular check-ups and would accept HPV vaccination for their daughters. Regardless of this, several barriers were identified, such as limited awareness and knowledge about HPV and cervical cancer, cultural barriers, and difficulties in communication with health care professionals due to language problems (164).

Acceptance, attitudes, and knowledge of HPV vaccination of boys among parents

According to recent surveys among European parents, most seem to be in favour of HPV vaccination of their sons (165, 166). Although parental beliefs and attitudes have been shown to be important predictors of HPV vaccination in the US (167, 168), there may be a significant discrepancy between parents´ general support of male HPV vaccination and their intention to have their son vaccinated (169). The main reasons for accepting HPV vaccine have been stated to be concerns for the son's health and the wish to protect the son against HPV-related diseases (165, 166, 170-172) and low concerns about negative side effects (171). On the other hand, scepticism about the HPV vaccine and fear of side effects, as well as a lack of knowledge and low awareness of HPV and HPV vaccination were barriers for vaccine acceptance (165, 171, 173). Studies from the US, Canada, and Italy found limited knowledge about HPV and HPV vaccine among parents of boys (170-175).

In a recent Swedish qualitative study exploring parents' views of extending the national vaccination programme to also include boys, parents had low knowledge and awareness about possible health benefits of male HPV vaccination and perceived the risk for boys acquiring an HPV-related disease to be low. Still, these parents preferred sex-neutral vaccination. However, some parents could not see any reason for vaccinating boys. Also, some of the parents who had not accepted HPV vaccination for their daughter expressed that they would be willing to accept vaccination for their son if it was offered (176).

In a survey conducted early in 2017, Swedish parents participating in the web-based project Hälsorapport were asked about HPV vaccination of boys. Of the 911 parents who responded to the survey, the majority (89%) considered diseases caused by HPV to be severe or very severe for boys, 76% found it necessary to vaccinate children against HPV, and 18% found it partly or completely unnecessary. However, 96% of the parents of boys would want to vaccinate their child if the vaccine was offered free of charge and officially recommended (Folkhälsomyndigheten, unpublished results). Even though sampled to represent the Swedish population, the web-based panel of participating parents had, for instance, a higher than average education, and therefore the results might not be completely generalizable to the entire Swedish parental population.

The vaccination coverage in universal school-based vaccine delivery programmes in Australia and in one Canadian province was higher among girls than among boys, and girls also had better completion, receiving all recommended doses to a greater extent than boys (177, 178).

Boys' knowledge of and attitudes to HPV vaccination for boys

Studies conducted in the US, Europe, and Sweden indicate low knowledge about HPV among adolescents (179-182). According to a recent systematic review, there are also sex differences, and boys have lower knowledge about HPV and HPV vaccines compared to girls (183).

The findings worldwide indicate that there is a lack of education of boys about HPV (what HPV is, what it can cause, and how the virus can be prevented) (182, 184-187). School-based education of adolescents in Hungary and in Sweden increased knowledge about HPV and contributed to greater awareness of HPV and HPV vaccines (180, 185, 188). The educational interventions also improved favourable attitudes towards HPV prevention among boys (180, 185).

Few studies have been conducted looking at adolescent boys' attitudes to HPV vaccinations, and most studies have been performed with MSM and male college students (189-191). The findings in a qualitative study among adolescents in Scotland indicated low knowledge and awareness about HPV vaccination, and the boys commonly believed that HPV only affected girls and there was confusion regarding the association between HPV and cancer (186).

Healthcare professionals' attitudes to HPV vaccination of boys

Studies have been conducted in Sweden to examine school nurses' knowledge, attitudes, and experiences of the vaccination programme (192-194). In a population-based survey among school nurses vaccinating against HPV in 2013, at the start of the vaccination programme 41% of the participating school nurses strongly agreed and 40% partially agreed that boys should also be offered the HPV vaccine in the school-based vaccination programme (192). A follow-up study performed in 2016 showed a significant increase; over half of the school nurses (56%) now strongly agreed and more than one third (32%) partially agreed to the statement that boys should also be offered the HPV vaccine (194).

In a UK survey among health care professionals working at sexual health clinics, 84% of the participants were in favour of universal vaccinations and supported HPV vaccination for all men regardless of sexual orientation (195).

The effect of vaccinating boys against HPV on other vaccinations within the vaccination programme

In general, Swedish parents have had a positive attitude to childhood vaccinations offered within the vaccination programme. This has been reflected in the consistently high coverage of about 96%–98% for all vaccinations – except for HPV vaccination. The coverage among girls for HPV dose 1 has been stable around 80% since vaccination started in schools, and lower for completing the full

series (three doses until 2014, and thereafter two doses) (196). The introduction of the HPV vaccine has, however, so far not caused any decline in the coverage of other vaccinations. In discussions within the Public Health Agency's reference group for national vaccination programmes, it is acknowledged that extending HPV vaccination to also include boys could have a negative impact on other vaccinations, although it is not expected. On the contrary, it has been suggested that the vaccination coverage among girls could instead increase if the vaccination programme against HPV became universal because the vaccination messaging thereby could be simplified and become more focused on prevention of cancer rather than on girls' sexual activity or debut.

Other preventive measures or treatments

In addition to universal HPV vaccination, there are different preventive measures and treatments that might contribute to preventing and reducing the burden of HPV infection and HPV-related disease. This section discusses whether sexually transmitted infection (STI) prevention, raising HPV-vaccination coverage among girls and screening programmes, as well as risk-group vaccination and cancer treatment, may contribute to reducing the HPV-related disease burden and to what extent they might constitute an alternative to universal HPV vaccination within the Swedish national vaccination programme.

STI prevention programmes

Unlike other STIs that are transmitted through bodily fluids, HPV is transmitted by skin-to-skin contact. Therefore, condoms can reduce the risk of transmission but do not fully prevent transmission (197).

Some studies have examined a potential preventive role of male circumcision, but the evidence on circumcision as a preventative measure is not conclusive (198, 199). A case-control study from the US showed that while circumcision status was associated with a reduced risk for penile cancer, the proportion of cancers that were HPV positive did not differ by circumcision status, thus confirming HPV as a strong risk factor for penile cancer independent of circumcision status (61).

More recent studies examining the oral prevalence of HPV suggest that HPV can be transmitted through oral-oral as well as oral-genital routes (200). Although rare, HPV can also be vertically transmitted from mother to child, with vaginal delivery being more risky than caesarean section (201). Risk factors for HPV infection are number of sexual partners, age at first intercourse, oral contraceptive use (women), infection with other STIs, immunosuppressive conditions (e.g. HIV), and smoking (202-205). Studies on prospectively intervening on these risk factors to prevent HPV are lacking. In sum, STI prevention is not a viable alternative to introducing HPV vaccination for boys.

Screening programmes

There are no validated methods that currently can be used in screening programs to detect precursor stages for cancer of the penis, vagina, or vulva.

Oropharyngeal cancer screening

In studies of HPV in mouthwash samples, oral HPV varies roughly around 1%–10% (206, 207). In the US, studies have shown that the highest oral prevalence is found in middle-aged men (around 6.9%) and that oral HPV prevalence in general is lower in women (207).

In one study, 76% of the patients with HPV-positive tonsillar cancer exhibited HPV 16 in their mouthwash samples, and the levels of virus were, in general, higher than in healthy youth (22). Still, the risk of cancer associated with one-time detection of HPV in the oral cavity is not known, but the importance of HPV in the oral cavity and its possible use in predicting the development of cancer is being studied (46, 207, 208). The natural history of a disease must be known, and early intervention must lead to better survival in order for screening to be useful. For oropharyngeal cancer, the time from infection to developing cancer is not known. Additionally, in contrast to the genital tract, where secretion is minimal, around 0.5–1.5 litres of saliva is produced in the oral tract per day, thus diluting any HPV signal and increasing the likelihood of a false HPV-negative result. While mouthwash analysis may allow for the detection of HPV in the oral cavity, the clinical meaning of an HPV-positive test result is not known, and evidence-based triage strategies do not exist.

Thus, there is as of yet no method developed that can detect risk for developing oropharyngeal cancer by screening.

Cervical cancer screening

Organized cervical screening began in the 1960s in Sweden and was nationwide by the late 1970s (209). National screening recommendations and guidelines define the programme and processes, but because health care is provided autonomously by the 21 counties, screening is regionally implemented. Therefore, screening practice has differed somewhat across the country. Cervical screening has been based on smear-taking and cytological analysis of samples, and until recently, testing for HPV was mainly reserved for reflex testing of abnormal cytological samples.

In 2015, the recommendations were updated by the National Board of Health and Welfare (NBHW) to include new test methods and screening intervals (210). Cytology is now only recommended as the primary test for women ages 23–29, while HPV testing is recommended as the primary screening test for women ages 30–64. Evidence from a pooled analysis of the European HPV-based screening trials demonstrated a reduced incidence of invasive cancer among women screened with HPV testing compared to cytology (211). These results, along with a mounting body of evidence suggesting better performance (sensitivity and negative protective effect) of HPV-based screening (212), influenced the decision to recommend using HPV as the primary screening test among women over age 30. Given that a significant proportion of the population under age 30 have transient HPV infections, cytology will remain the primary test for this age group to avoid unnecessary referrals.

Furthermore, 3-year intervals are now recommended for women up to age 50 and 7-year intervals are recommended thereafter. The new recommendations will not reduce the number of screening tests over a lifetime. Instead, by switching to a more sensitive test above age 30 and extending the upper age limit (previously age 60) the aim is to strengthen the screening programme's effect and further reduce the incidence of invasive cancer.

New guidelines for the implementation of these recommendations were adopted by the association of Regional Cancer Centres in January 2017 (213). In addition to the updates on tests and screening intervals, these guidelines also include a review and revision of issues related to education and information, quality assurance, organization, logistics, triage, and treatment. Rollout of the new recommendations and guidelines is on-going at the time of writing (May 2017).

As the proportion of women being vaccinated increases and women vaccinated in the school-based programme enter screening, recommendations may need to be further adjusted to ensure performance of the screening tests that are used. The screening programme and its registers are important parts 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. In 2015, 18%–34% of women invited to screening for the first time were vaccinated (1992 birth cohort, coverage varied by county), and in 2016 closer to 56% of those first invited to screening were vaccinated (1993 birth cohort). By switching to HPV-based screening, the aim is to increase the sensitivity of screening. Cytological cervical screening has been shown to be more effective for the prevention of squamous cell carcinoma than adenocarcinoma, perhaps as a result of greater ease in sampling the squamocolumnar junction (214). The incidence of precancerous cervical lesions is increasing in the population, especially among young women (215).

Anal cancer screening

The issue of anal screening is a matter of significant research focus given the increasing incidence of the disease in the general population and the particularly high risk for anal cancer among MSM and individuals with HIV. Detection and treatment of anal lesions has been done in the context of studies and in high-risk populations. It is recommended by some expert groups, but no official policies exist for anal screening yet. This is due to the high rate of recurrence following treatment of AIN and the lack of conclusive evidence for the effect of screening on the incidence of cancer (216, 217).

Methods have been adapted from cervical screening, and the main approaches consist of anal cytology and high resolution anoscopy (HRA) (where lesions are

visualized with acetic acid and biopsied, similar to colposcopy). The sensitivity of anal cytology is limited compared to HRA, and the sensitivity has been shown to be differential by HIV status (218, 219). While HRA is considered to be the gold standard for detection of AIN, the procedure is costly and requires specialized training, which limits its applicability as a broad screening test (216). In settings where HRA expertise is lacking, an annual digital anorectal examination for high-risk populations may be used (216, 220). AIN lesions are often multifocal, which complicates treatment, and recurrence rates after ablative treatment are high, according to a medical chart review study (216, 221). Using HPV testing to screen for anal cancer is currently not expected to improve outcomes because treatment of AIN is not optimized (216).

Several randomized controlled trials of anal cancer prevention designed to provide evidence to support a decrease in invasive anal cancer as a result of treating screening-detected lesions are currently running (The US-based Anal Cancer HSIL Outcomes Research (ANCHOR) study; the Study of the Prevention of Anal Cancer (SPANC) in Australia; and the ANALOGY study in England that focuses on high-risk groups.

Increasing vaccination coverage among females

Increasing the vaccination coverage among girls would provide the vaccinated girls with direct protection against HPV-infection, and the unvaccinated females and males with increased protection through herd immunity (127). However, MSM would not benefit from a herd effect following female vaccination (125), and boys would not have the opportunity of direct protection from vaccination.

Modelling work from Australia including only heterosexual transmission shows that female-only vaccination can provide three quarters of the maximum benefit that male and female vaccination could confer (222). Models from high-income countries on heterosexual transmission also show that raising vaccination coverage up to 80% in a female-only vaccination programme effectively prevents infection with HPV types 16 and 18 among males, after which increasing coverage further had marginal effects (127). This is important because there might be a point of diminishing returns in attempting to increase vaccination coverage among females in settings where coverage is already high. It might be more effective to focus on quickly achieving moderate coverage among males. The stable vaccination coverage among girls in Sweden and other Nordic countries (Figure 1) indicates that increasing the vaccination coverage might also be challenging.

Risk group vaccination

Some individuals are at higher risk of HPV infection and associated cancers, such as MSM, transplant recipients, and immunocompromised groups, especially those with HIV (70, 223). In HIV-positive individuals, the HPV vaccine appears safe and immunogenic (224). For some groups of transplant recipients, the immunogenicity of HPV vaccines is not optimal, and further studies on immunogenicity and vaccination strategies are needed (225-227).

MSM have a high lifetime risk of HPV-associated disease (70). MSM also benefit less from herd protection than heterosexual males in settings with female-only HPV vaccination, which has been confirmed by post-implementation female vaccination data from Australia (228, 229). Therefore, some countries (e.g. the UK and Ireland) are considering or implementing risk-group vaccination of MSM in addition to vaccinating all girls (35, 36).

In MSM, HPV vaccination has been shown to reduce AIN (230). It has also been shown through modelling that vaccinating HIV-positive MSM aged over 27 years against HPV after high-grade AIN treatment can decrease the lifetime risk of anal cancer (231).

In health economic analyses in the US and UK, risk-group vaccination of MSM with HPV vaccine has been modelled to be a cost-effective intervention for the prevention of genital warts and anal cancer. The cost-effectiveness ratio was best when vaccinating at 12 years of age in unexposed children, but was still considered cost-effective up to 40 years of age (232, 233).

Because HPV spreads very rapidly in most populations and infection typically occurs shortly after sexual debut, vaccination strategies specifically targeting MSM may risk mainly reaching subjects who have already been exposed. It is also problematic to require school-aged males to self-identify as MSM to receive a health benefit, and this may pose problems of stigmatisation as well as complicate programme delivery (234).

Targeted vaccination programmes directed at either MSM or heterosexual high risk-taking groups as alternatives to a universal national vaccination does not appear to be optimal from a prevention standpoint.

Treatment of HPV-related disease

Oropharyngeal cancer treatment

Oropharyngeal cancer is treated with high-dose radiotherapy, and the treatment takes 6–7 weeks to complete. Many patients with advanced stage (III-IV) cancers also have chemotherapy depending on tumour burden and whether they are medically fit. The treatment is demanding, with acute side effects such as pain,

swelling, and eating difficulties caused by radiation-induced mucositis, nausea, local and/or systemic infections, and fatigue. Surviving patients also suffer from late side effects such as xerostomia, taste alterations, swallowing difficulties, trismus, and hearing impairment (56-58). Late side effects from both radiotherapy and chemotherapy are often life-long and can worsen with time.

Patients who have remaining lymph node metastases after completing radiotherapy have to further complete their treatment with modified neck node surgery. This often gives additional side effects such as increased fibrosis and stiffness of the neck, impaired shoulder mobility, and sometimes a worsening of the swallowing difficulties caused by radiotherapy.

Patients with recurrent disease can sometimes be treated with salvage surgery or re-irradiation with or without chemotherapy. When no curative treatment is possible, chemotherapy or biological therapies can be given with palliative intent (15).

Penile cancer treatment

Non-invasive and early-stage invasive (T1a) penile cancer is treated with local surgical resection. Medium-stage invasive tumours (T1b and selected T2-T3) can be treated with organ-sparing surgery, often glansectomy, with simultaneous reconstructive surgery. More advanced T2-T3 tumours are treated with partial or total penile amputation with or without reconstruction, while the most advanced T4 tumours are treated with neo-adjuvant chemotherapy followed by amputation. More advanced cancers also have an increased risk of regional lymph node metastases. Patients who are diagnosed with lymph node metastases undergo additional radical inguinal lymph node dissection, and in the most advanced cases also pelvic lymph node dissection. If viable cancer is present in the resected cancer or lymph nodes, post-operative radiotherapy, sometimes with the addition of chemotherapy, is recommended.

Common side effects after penile surgery is impact on urination and sexual function, where the severity of the side effects is dependent on the extent of the surgery. After lymph node dissection, 20%–25% of patients suffer from lymphedema in the lower extremities.

Patients with recurrent local and/or regional disease should be considered for another surgery with curative intent. In palliative situations, chemotherapy and/or radiotherapy can be of value (59).

Anal cancer treatment

Anal cancer is in the majority of cases treated with radiotherapy in combination with chemotherapy over a treatment period of 4–6 weeks. The total radiation dose

and the number of cycles of chemotherapy depend on tumour size and the extent of lymph node metastases. Common acute side effects are bacterial infections and febrile neutropenia, nausea, local dermatitis, diarrhoea caused by radiation-induced enteritis, and fatigue. The majority of patients also suffers from late side effects after treatment, including bowel dysfunction, sexual dysfunction in both men and women, infertility, hormonal dysfunction, urinary dysfunction, increased risk of pelvic fractures, and lymphedema in the pelvis and lower extremities (66). These side effects can impair the quality of life and restrict the patient`s social life (235, 236).

Of patients who have curative treatment with chemo-radiotherapy, 25%–30% have residual tumours or a local recurrence (66). The majority of these patients are candidates for salvage surgery, which in most cases is extensive and the risk for complications is high.

For patients with limited metastatic disease to the lung or liver, surgery of the metastases can be a treatment option. Patients who develop more extensive metastatic disease can be treated with palliative chemotherapy (66).

Cervical cancer treatment

New guidelines for diagnosing and treating cervical and vaginal cancer are under review. Micro-invasive (Stage IA1) cervical cancer without lymph node involvement can be treated with conisation, similar to CIN3 (carcinoma *in situ*) or hysterectomy if fertility preservation is not desired. With lymph node involvement, lymph node dissection and trachelectomy (to preserve fertility) or hysterectomy are recommended. Treatment for advanced stages is more severe; fertility cannot normally be preserved, and treatment includes extensive radiation therapy and chemotherapy (for Stages IB2-IVA). For Stages IA2, IB1, and IIA1, radical hysterectomy with or without a salpingo-oophorectomy and pelvic lymph node dissection are recommended. A radical trachelectomy can be done in some instances (dependent on tumour size) to preserve fertility. Separate guidelines are written for women diagnosed with cervical cancer during pregnancy. (237)

Morbidity as a result of surgery includes damage to the urinary tract, intestines, and pelvic nerves. Surgery for cervical cancer has a lasting effect on sexual well-being because vaginal length and hormone and lubrication production are impacted. Radiation therapy can affect the mucosal membranes, causing them to be dry and painful.

Vulvar cancer treatment

Vulvar cancer is primarily treated surgically (238) with or without lymph node removal. Surgical depth is determined by the tumour in order to reduce surgery-

related morbidity. In Stage IAI, lymph node removal is often deemed unnecessary because the risk of metastasis is low. Radiation therapy and radiation in conjunction with chemotherapy are used when the cancer is inoperable for medical reasons or because of the size and location of the tumour (Stage IV cancers and some Stage III), or in special cases where surgery is not recommended. After more radical surgery, reconstructive surgery (various approaches) may be used to improve quality of life and assist in the healing process (238).

According to a longitudinal, mixed methods study of women diagnosed with different stages of vulvar cancer, side effects of treatment can be long-lasting and impact both physical and mental quality of life (239). Morbidity related to treatment is dependent on stage at diagnosis, with women who had a later stage at diagnosis reporting worse mental health scores post-treatment than women with an earlier stage cancer (239). Morbidity related to lymphedema and sexual function is commonly reported (239).

Vaginal cancer treatment

While surgical treatment can be used for Stage I vaginal cancer and some advanced stages of cancers, radiation therapy is the main form of treatment for primary vaginal cancer given the proximity to the urethra, bladder, and intestines. Chemotherapy is indicated for palliative care. Similar to vulvar and cervical cancer, treatment for vaginal cancer is dependent on age, stage, localization, and tumour size.

Radiation treatment can affect the bladder and cause skin discomfort. Long-lasting side effects are similar to those in cervical cancer patients, including lymphedema, early menopause, lack of hormone production, and changes to sexual well-being.

Condyloma treatment

In Sweden, there are two common topical drugs used for treating condyloma – podophyllotoxin and imiquimod. Podophyllotoxin is 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 (240). The clinical course of condyloma is variable, and the proportion of cases that recur varies by treatment (4%–38% with podophyllotoxin and 13%–19% with imiquimod) (241).

When patients seek medical care for condyloma, they can either be treated using topical drugs or surgery, or be given a recommendation to return if the condyloma persists (also known as conservative treatment). 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 inpatient and as outpatient visits. However, a

large proportion of condyloma cases are handled in primary care, and thus not registered.

Recurrent respiratory papillomatosis treatment

Consensus on optimal treatment methods of recurrent respiratory papillomatosis (RRP) is lacking. Treatment usually consists of excision of papillomas in the larynx, often by laser with anaesthesia, and repeated as necessary to address symptoms (1–4 times per year). There is currently no curative treatment available (242). Adjuvant treatment with antiviral agents has been used in studies, but a Cochrane review from 2010 concluded that there was insufficient evidence to recommend such treatment for RRP in adults and children (243). Some evidence from a chart review of patients with RRP suggests that vaccination with the quadrivalent HPV vaccine may modulate the course of RRP by increasing the time between surgeries or inducing remission (the effect was greater among males than among females) (244).

Monitoring the impact of vaccinations

The main purpose of monitoring vaccination programmes is to verify that they achieve the stated goals and expectations on effectiveness and safety as well as implementation, both in the short and the long term. The monitoring provides a basis for long-term prognoses and for making evidence-based decisions regarding the vaccination programme. The results can indicate if single vaccinations in the programme need to be altered (e.g. timing and intervals) or if the programme as a whole needs to be revised to achieve the stated goals (245).

The monitoring of the effects of vaccinations in the national vaccination programme for children includes the following cornerstones:

- Disease surveillance
- Microbiological surveillance
- Monitoring of vaccination coverage
- Immunosurveillance (seroepidemiological investigations of immunity in the population)
- Safety monitoring

In addition, monitoring of other public health interventions and behavioural patterns can also provide insights for changing existing vaccination programmes.

The Swedish Institute for Communicable Disease Control (Smittskyddsinstitutet, SMI) published a work plan in 2012 for monitoring the impact of introducing HPV vaccination of girls (246). The work plan was based on the same cornerstones as for other illnesses of the national vaccination programme, but modified due to the special characteristics of HPV and HPV-related diseases. The plan included registry studies, clinical studies, and laboratory-based surveillance.

Some structural changes of importance for the capacity to monitor vaccination programs have taken place since the introduction of HPV vaccinations in the national vaccination programme in 2012, one of which was the establishment of a national immunization registry in 2013 through a government ordinance (SFS 2012:453). Thereby all vaccination doses given within national vaccination programmes should be registered, and this will provide new and better possibilities to monitor vaccination coverage. Another change is that SMI has been replaced by the Public Health Agency of Sweden, and the responsibility for introducing and monitoring vaccination programmes has been transferred to the Public Health Agency from the NBHW. Also, in 2014 Svevac was transferred to SKL and Inera. Furthermore, a number of research projects have been completed.

Monitoring HPV vaccination of boys

If boys are to be offered vaccinations against HPV through the national vaccination programme, the monitoring of effects will be based on the above-mentioned cornerstones and work plan, but adapted and updated to reflect new circumstances. In general, the monitoring will strive to use the same methods regardless of sex. If vaccination for boys is included in the programme, the vaccination programme can be monitored as described below.

Disease surveillance

Unlike the other infections covered by the national immunization programme for children, HPV infections are not notifiable according to the Communicable Diseases Act. However, because HPV infections are usually asymptomatic and most often transient and control measures are not required (as regulated in the Communicable Diseases Act), such a regulation and surveillance is not relevant.

The work plan published by SMI included monitoring the incidence and mortality of several HPV-related cancer forms, including cervical, vulvar, vaginal, anal, and tonsillar cancers. Since then, the link to HPV as a causative agent of oropharyngeal cancer has become stronger. Therefore, if vaccination of boys is included in the vaccination programme, the list of cancer forms under surveillance should be extended to also include penile and oropharyngeal cancers. This would increase the amount of work needed to manage and analyse the data, although the method and frequency of analysis could remain the same. Data from the Cancer and Cause of Death registries of the NBHW should preferably be analysed yearly, starting at least 10–15 years after the introduction of a vaccination programme.

Because the time from becoming infected with HPV to developing cancer is long, often several decades depending on type of cancer, it is necessary to have other, earlier markers of disease to monitor the effects of the vaccination programme. For effects among girls and women, the occurrence of precancerous lesions of the cervix can be monitored through the cervical screening programme and the Swedish National Cervical Screening Registry. Screening programmes for other relevant cancer forms are not in place (see Screening programmes). Prevalence of precancerous lesions in women will be of continued importance in a universal vaccination programme, and may, due to herd immunity effects, also provide indirect information for vaccine impact among men.

The prevalence of condyloma among youths of both sexes could also be used as an early marker of vaccine and herd effects if the vaccine offered contains antigens for HPV 6 and 11. Given the short incubation time (3–12 months), condyloma is one of the first relevant vaccination impact outcomes available for vaccines containing antigens for HPV 6 and 11 and has therefore been studied extensively in Sweden

since the implementation of HPV vaccination (96, 161, 247). New methods for identifying condyloma cases nationally have been developed that rely on the Prescribed Drug Register to find prescriptions for the two common topical drugs used for treating condyloma (96).

Microbiological surveillance

Not all HPV types are covered by the available vaccines, and it will be important to monitor the prevalence of specific HPV types in different samples in order to provide data on which HPV types cause cancer in Sweden and what proportion of cancer cases are caused by the different HPV types. This knowledge is important to guide the use of multivalent vaccines based on expected health benefits. Therefore, HPV typing of cervical cancers, but also other cancer forms and precancerous lesions of the cervix, will be needed to collect the necessary information.

HPV typing of cervical cancers is currently not performed regularly but has been performed in the context of the national audit of cervical cancer cases through a research project coordinated by teams at Karolinska Institutet. Cervical cancer cases from 2002–2011 were reviewed, and HPV was tested and typed. The results of this audit will be published in a series of scientific papers.

HPV typing of other cancer forms is not currently systematically performed. HPV testing and typing of other HPV-related cancers would require collection and processing of tumour blocks, the development of standard operating procedures, and delegation of this work to accredited laboratories. Coordination between labs and biobanks would need to be strengthened, and permissions would need to be granted to perform testing within routine care.

Through the new recommendations for cervical cancer screening, information will become available on the HPV prevalence in routinely screened women above age 30 (210). HPV typing of condylomas and prevalence studies in the youth population through specific studies could also be considered. These studies would provide data directly related to vaccine effect among males.

Vaccination coverage

The national immunization registry can be used to calculate vaccination coverage per birth cohort, county, and sex. By merging individual vaccination data with data from SCB on the families' level of education, income, origin, etc., it will be possible to identify determinants of vaccination coverage. The analysis of vaccination coverage through the national immunization registry is currently done yearly by the PHA. This would require small changes in method, frequency, and work load to also include the coverage among boys in the analysis.

Studies to quantify the impact of vaccination programmes

In order to attribute changes in disease burden or HPV prevalence to the vaccination programme, it is necessary to perform studies where information about disease or HPV status and vaccination status is analysed together at the individual level. These studies should preferably also adjust for demographic factors to provide a more detailed picture. The cervical screening programme 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. Studies on the impact of the vaccination programme for girls have been planned. Because these studies are usually registry based and the analysis is done with the help of statistical software, additional costs to study the effects of a universal vaccination programme would be negligible.

Immunosurveillance

Immunosurveillance will for several reasons not be part of the basic monitoring of HPV vaccinations – HPV infections are very common, HPV infections only give detectable serologic antibody responses in around 50%–60% of infections (248, 249), and the lowest antibody concentrations necessary to protect humans from infections have not yet been established (250). A serosurvey would therefore not be able to give reliable information about what proportion of the population has protective immunity against the HPV-associated with cancer.

Safety monitoring

The safety monitoring is product oriented, i.e. it is dependent on which safety profile each vaccine has, and it is carried out by several parties. The producer of the vaccine has the main responsibility for the product, including safety monitoring. The Swedish Medical Products Agency (MPA) together with agencies in other EU countries, the EU commission, and the European Medicines Agency (EMA) are responsible for approval, safety monitoring, and supervision of medical drugs, including vaccines, in Europe (251).

The MPA’s routine monitoring of vaccine safety is based on data from adverse event reports and other safety information (e.g. the mandatory periodic safety reports from the companies), and includes data from scientific literature studies as well as from epidemiological and other studies.

The EMA’s main responsibilities in the safety monitoring of medicines include the coordination of the European pharmacovigilance system, the provision of information on the safe and effective use of medicines, and the operation and maintenance of the EudraVigilance system (252). The EudraVigilance database is

an important source of information on suspected adverse reactions and safety signals and is publicly available at: http://www.adrreports.eu. Both the EMA and the medicines regulatory authorities in EU Member States are required by legislation to continuously monitor the adverse drug reaction data reported to EudraVigilance to determine whether there are new or known risks and whether those risks have an impact on the overall benefit-risk balance of a medicine.

A safety signal is information on a new or known adverse event that may be caused by a medicine and requires further investigation. The EMA, together with the regulatory authorities in the EU Member States and marketing authorization holders are responsible for detecting and managing safety signals. Safety signals can be detected from a wide range of sources, such as spontaneous reports, clinical studies, and scientific literature. The presence of a safety signal does not mean that a medicine has directly caused the reported adverse event. An illness or another medicine taken by the patient could also be the cause. The assessment of safety signals establishes whether or not there is a causal relationship between the medicine and the reported adverse event. The evaluation of safety signals is part of routine pharmacovigilance and is essential to ensuring that regulatory authorities have the most up-to-date information on a medicine's benefits and risks (253).

Considering that HPV vaccination is already established in girls and no sex differences are expected regarding adverse reactions (see Safety of HPV vaccines), and that HPV vaccines are extensively used globally, the MPA does not foresee a need to specifically follow safety in boys in Sweden following a change in the national vaccination programme. The safety of the three available HPV vaccines is monitored regularly in periodic safety update reports where all available safety data are considered, including spontaneous reports, clinical studies, literature reports, and signal detection in the available global safety databases.

Associated costs

The current monitoring of the vaccination programme against HPV is estimated to cost the PHA circa 160,000 SEK yearly. The cost is heavily influenced by the amount of registry studies planned for each year, as these are labour intense and require purchase of data from other agencies (such as the NBHW and Statistics Sweden). If boys would be offered vaccinations within the programme, the costs are estimated to increase by 30%, totalling circa 200,000 yearly. It is important to note that the monitoring of a vaccination programme targeting boys, and associated costs, depend on the existing monitoring activities.

The inclusion of boys in the vaccination programme against HPV is not expected to incur extra costs in relation to safety monitoring by the MPA.

Necessary communication activities

In relation to the public and health care providers, and associated costs.

Communication activities to support the implementation of a national universal HPV vaccination programme are related to a large number of aspects, for example, the knowledge level and attitudes among school health personnel, children, and parents. The communication should mainly support action, such as parents' and children's informed decision making and nurses' administering and registering of the vaccinations. As described in earlier sections about attitudes and impact on health care, knowledge about HPV and related cancer forms is assumed to be relatively low among boys and their parents. Considering the important role of the school nurses in communicating with parents and children, the planned national communication activities would aim at supporting nurses with facts, hands-on tools for dialogue in the school setting, and guidance for registering the vaccinations. Additionally, national activities would seek to clear up misunderstandings and lack of knowledge that could hinder parents' and children's individual and informed decision making. A shift to universal vaccination of both boys and girls would also enable a reframing of the problem – the risk of cancer related to HPV – which could possibly benefit the vaccination programme as a whole.

Objectives

During the introduction and further on, the communication activities would aim at

- empowering health care professionals and relevant key actors in their task of offering and administering the vaccination
- facilitating children's and guardians' informed decision making
- supporting equivalent communication and awareness in all school units in all parts of the country.

Methods and activities

Several actors are involved in supporting a successful national vaccination programme through their communication. The most effective face-to-face communication will take place in, or in relation to, the local school setting. This will be supported by national communication activities mainly through broader, non-personal communication channels and the various channels of the health care sector, such as 1177 Vårdguiden.

The Public Health Agency will provide key actors with overall messages and basic information material. The agency will also collaborate with 1177 Vårdguiden and other digital communication channels such as UMO and YOUMO to coordinate the dissemination of information to the public.

Content, such as Questions and Answers, will be available on national websites, as well as relevant texts, films, and graphic material. The national resources will aim at filling the gaps related to varying resources and at offering a variety of tools for communication. Web-based education and webinars as well as communication through social media will allow needs to be identified and information to be disseminated. The extension of the programme will also be an opportunity to strengthen the national communication supporting registration of administrated doses in the national vaccination registry. County councils, municipalities, and school health care units can build on the national material to develop their own activities that are tailored and supplemented according to the needs of the local target groups.

To support communication in the local setting, national print material to hand out to parents and children, and material to support dialogue and reflection, would be a priority. When needed, timely support and updates through established networks would aim at preventing rumours and misunderstandings that might prevent parents from accepting the vaccination. Because scares and rumours (often facilitated by media and social media) might occasionally affect public views of a vaccination, clear and timely support for communication by the well-trusted school health care system aimed at maintaining confidence in the vaccination programme is important.

Time is a scarce resource already in school health care. This was shown in the previously mentioned survey among school nurses (see Impact of vaccinations on health care providers). If issues with time negatively affect the nurses' ability to acquire knowledge and to communicate and have an active dialogue with parents and children, this can become a problem for the extension of the vaccination programme. This cannot be solved by national communication, but has to be planned for in the local school setting.

Estimated costs for communication activities

The cost for communication activities for the first year following the introduction is estimated to be 1,620,000 SEK.

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Appendix 1. Contributing experts

The knowledge base has been developed by the following working group:

- Charlotta Bergquist, assessor, Medical Products Agency
- Andreas Börjesson, assessor, Medical Products Agency
- Tina Dalianis, professor of tumour virology, Department of Oncology-pathology, Karolinska Institutet
- Madelene Danielsson, analyst (communicator), Unit for Corporate Communication, The Public Health Agency of Sweden
- Miriam Elfström, epidemiologist at the Department of Laboratory Medicine, Karolinska Institutet and operations developer for cancer prevention at the Regional Cancer Center of Stockholm-Gotland
- Hélène Englund, analyst (epidemiologist), Unit for Vaccination Programmes, The Public Health Agency of Sweden
- Agnetha Fredin, Head of School Health Care, City of Malmö, and Chairman of the board, Swedish association of school nurses
- Hedda Haugen Cange, Senior consultant, Department of Oncology, Sahlgrenska University Hospital
- Marie Johannesson, Senior consultant, Head of school health Stockholm City
- Adam Roth, analyst (medical doctor), Unit for Vaccination Programmes, The Public Health Agency of Sweden
- Pär Sparén, professor of medical epidemiology, Department of Medical Epidemiology and Biostatistics, Karolinska Institutet
- Ellen Wolff, analyst (health economist), Unit for Epidemiology and Health Economics, The Public Health Agency of Sweden

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

- Christina Stenhammar, Head of school health , Uppsala, Sweden, *(attitudes to vaccination)*
- Maria Grandahl, Senior lecturer, Department of Public Health and Caring Sciences, Uppsala University *(Attitudes to vaccination)*
- Marie-Louise Lydrup, Senior Consultant, Department of surgery, Skåne University Hospital *(anal cancer)*
- Peter Kirrander, Senior Consultant, Urologic Department, Örebro University hospital *(penis cancer)*

This report describes the current knowledge, conditions and assessments that, together with information about the cost-effectiveness of the vaccination and medical ethics and humanitarian considerations, will form the basis for making a decision on whether to extend the HPV-vaccination programme to boys.

The main target group for this publication is the Ministry of Health and Social Affairs within the government of Sweden. It could also be of interest for public health institutions in other countries that are considering universal vaccination programmes against HPV.

The Public Health Agency of Sweden is an expert authority with responsibility for public health issues at a national level. The Agency develops and supports activities to promote health, prevent illness and improve preparedness for health threats.

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