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Assessing infection risk and evaluating prevention strategies in the era of HPV-vaccines

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To the pursuit of Science.

In memory of the work carried out by my aunt Patricia Cody who co-founded DES Action in the U.S. and wrote "DES Voices: From Anger to Action". For decades she worked to raise public awareness of the long-term effects of in-utero exposure to diethylstilbestrol and prevent cervical and other gynecological cancers through intensified screening efforts.

This thesis is also dedicated to the memory of my classmate Gretchen Day, whose life ended this year due to cervical cancer. Gretchen died just 10 weeks after the birth of her first child. Behind every mortality statistic there is a face, and a legacy of life left behind.

Abstract

Aim: This thesis aims to provide a multidimensional assessment of infection risks and to evaluate strategies for HPV prevention including vaccination with quadrivalent HPV-vaccines, dose-level vaccine effectiveness and condom use in high STI risk situations.

Methods: Multiple population-based registers and questionnaire responses provided data for this thesis. Various multivariable and univariate regression models were fit.

Findings: Overall, quadrivalent HPV-vaccination was highly effective against genital warts (GW) also referred to as condyloma, which is the first HPV disease endpoint possible to measure. However, effectiveness was contingent upon young age-at-first vaccination, with effectiveness declining steadily the older the age-at-first vaccination. Among women above 20 years of age there was low to immeasurable effectiveness and suggestive evidence vaccinations in this age group tended to reach women at high GW risk. There were marked socioeconomic disparities in the opportunistic (on-demand with co-pay) vaccination strategy evaluated, with women and girls who have parents with the highest education level compared to the lowest having a 15 times greater likelihood to be vaccinated (Study III). Once vaccination was initiated, however, high parental education level was unrelated to vaccination completion. Maximum protection against GW was found among girls vaccinated under the age of 17 who had received three doses of the vaccine. No differences in effectiveness were found for girls who received two-doses between ages 10-16 with that of those who received three-doses between ages 17-19 (Study IV). GW affects more men than women in Sweden as of 2010 with 453 per 100 000 men and 365 per 100 000 women treated. A decline between 25-30% was seen between 2006 and 2010 among women in the age groups with the highest vaccination coverage. No decline was found amongst men and their GW incidence has steadily increased between 2006 and 2010 (Study II). Reported condom use in high risk situations was low among both men and women, with 41% of men and 34% of women reporting always/almost always condom use with temporary partners. STI risk perception was also low, with approximately 10% of sexually active respondents considering themselves at large risk of contracting an STI. There was no association between men's condom use and their STI risk perception but there was an association for women (Study I).

Conclusions: Results suggest that males bear a substantial burden of HPV-related condyloma where incidence has dropped among women. When planning HPV-vaccination among females, efforts should target girls under age 14 for maximum effectiveness. Quadrivalent HPV-vaccination offers most protection against condyloma at three doses. Gross social inequity was found with opportunistic HPV-vaccination. There were large gender differences in factors associated with condom use in high risk situations and STI risk perceptions.

List of Publications

I Leval A, Sundström K, Ploner A, Arnheim-Dahlström L, Widmark C, Sparén P.
Assessing perceived risk and STI prevention behavior: a national population-based study with special reference to HPV
PLoS ONE 6(6):e20624.doi:10.1371/journal.pone.0020624

II Leval A, Herweijer H, Arnheim-Dahlström L, Walum H, Frans E, Sparén P, Fridman Simard J.
Incidence of Genital Warts in Sweden Pre and Post Quadrivalent HPV Vaccine Availability
Journal of Infectious Diseases 2012 Sep;206(6):860-6. Epub 2012 Jul 18

III Leval A, Herweijer E, Ploner A, Eloranta S, Fridman Simard J, Dillner J, Young C, Netterlid E, Sparén P, Arnheim-Dahlström L.
Quadrivalent HPV-vaccine effectiveness on genital warts: population cohort study
(submitted)

IV Leval A, Herweijer E, Ploner A, Eloranta S, Fridman Simard J, Dillner J, Netterlid E, Sparén P, Arnheim-Dahlström L.
Condyloma protection of quadrivalent HPV-vaccine: population cohort analysis of dose effectiveness
(manuscript)

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List of abbreviations

ATC	Anatomical Therapeutical Chemical
CIN	Cervical Intraepithelial Neoplasi
DAG	Directed acyclic graph
FGD	Focus group discussion
GAVI	Global Alliance for Vaccines and Immunisation
GDP	Gross Domestic Product
GW	Genital warts
HBM	Health Belief Model
HIV	Human immunodeficiency virus
HPV	Human papillomavirus
HR	Hazard rate
HSIL	High Grade Squamous Intraepithelial Lesion
IBD	Internet based discussion
IR	Incidence rate
IRR	Incidence rate ratio
IRD	Incidence rate difference
ICD	International classification of diseases
KAP	Knowledge Attitude Practice
LSIL	Low Grade Squamous Intraepithelial Lesion
LISA	Sweden's register containing extensive demographic information
MSM	Men who have sex with men
MMRW	Morbidity and Mortality Weekly Report
OR	Odds ratio
PDR	Sweden's Prescription Drug Register
PIN	Personal Identification Number
PR	Sweden's In and Out Patient Registers
qHPV	Quadrivalent human papillomavirus (vaccine)
RCT	Randomized control trial
SES	Social economic status
STI	Sexually transmitted infection
SVEVAC	Sweden's national vaccination register from 2006-2012
TPR	Total Population Register

Preface: Unfolding epidemiology

Human papillomavirus (HPV) is the most prevalent sexually transmitted infection (STI) in the world with an estimated 80% of sexually active individuals infected during the course of their lifetime[1]. Most HPV infections are transient and will clear without external intervention. Low oncogenic risk types can lead to cases of genital warts so minor as to go undetected while others lead to cases of genital warts so persistent that even after bouts of multiple treatment (including surgery) the infections will not clear. High oncogenic HPV-types can lead to dysplasia, which thanks to screening and early treatment, may never develop into HPV-related cancers. High risk oncongenic HPV-types are a necessary, but not sufficient, cause of many cancers, the most common being cervical cancer. HPV is not the only cancer-causing virus but it is the most common. Roughly fifteen percent of all cancers have been attributed to infectious agents ranging from HPV, Hepatitis B and C, Epstein Barr and Helicobacter pylori [2]. Though cancer-causing viruses are not new discoveries their public health impact and prevention are new. Astrid, one of the women I interviewed to discuss HPV risk and prevention said, "Cancer is nothing I've ever thought about in relation to sex".

My original project plan for this thesis was to conduct qualitative assessments of quantitative analyses using internet-based focus group methodology. The broad intention was to explore how young women and men conceptualized HPV and prevention of HPV-related diseases after the launch of HPV vaccines. Respondents from a large population based survey, "Attitudes toward HPV Vaccination", were to be the sampling frame for this investigation.

To begin this qualitative investigation, I thought it was important to more closely scrutinize respondents' prevention engagement and risk perceptions. I designed the first study in my thesis to examine complex prevention engagement in risk situations: condom use with temporary partners. Though it may not sound excessively complicated I believe condom use is highly complex as it involves continual decision making in various risk situations, with a constant negotiation between individual needs and partner dynamics. I also wanted to examine to what extent perceptions of risk are associated with prevention engagement. Finally, I wanted to determine if there were gender differences in prevention engagement in terms of condom use and STI risk perceptions.

The results from this first study generated more questions for my planned qualitative investigations: why were women engaging in high STI risk sexual intercourse (with temporary partners and without the use of condoms) when they considered themselves to be at risk for contracting an STI? Why was the prevalence of reported condom use with temporary partners higher for men than women? What were men and women doing to avoid risks? What did they think of HPV and their HPV risks? Although my qualitative investigations were not included as papers in my thesis, I will present some preliminary selected results where they pertain to this thesis topic.

What struck me time and time again in the discussions with the almost 100 men and women I interviewed for these qualitative analyses was the gross underestimation of men's HPV risk and burden of HPV-related disease. Some did not understand how men were involved with HPV as they assumed it only infected women. Though our HPV questions mostly centered around HPV-related cancer, study participants expressed concern and had many questions regarding genital warts (GW) and their transmission, cure rates, etc. Many were unaware that GW were caused by HPV. Participants' misunderstandings and underestimations of men's risks reflected the underestimations and uncertainty in the field of HPV-research. While examining the scientific literature I realized there were no population-based estimations for the burden of GW among men in Sweden. A single study from one STI clinic in the 1990s had also reported substantially higher GW incidence among women than men[3]. The natural history of genital HPV infections, their clearance, potential for reinfection – all broached by the participants – was no easy matter to unpack when examining the literature. Participants asked questions to which science is still trying to find answers.

Many women I interviewed expressed feeling like they were shouldering the entire burden of HPV-related disease prevention, which many found unfair considering the other burdens they expressed shouldering for birth control and STI testing. The considerable misunderstanding of men's HPV-related risk and burden of disease that was found convinced me of the need to establish men's burden of HPV-related disease in Sweden. As GW is not one of the reportable STIs in Sweden, establishing accurate estimations was not straightforward. I knew podophyllotoxin was used exclusively in the treatment of GW and that Sweden's relatively new prescription drug register would provide insight into prescription trends. After discussing the matter with various gynecologists around the country who worked in STI clinics, I thought it would be necessary to also examine imoquimod prescriptions. As HPV-vaccines had been launched after the availability of the prescribed drug register, this second study in my thesis allowed for first glimpses into the potential impact of HPV vaccination in Sweden. The short incubation time of GW provided opportunity to measure vaccine effectiveness in the population with an actual HPV-related disease endpoint.

My ambition to establish GW risk estimations for men and women in Sweden put me in the right place at a dynamic time. A researcher in my department was planning to study HPV vaccine effectiveness with a non-ecological study design in collaboration with Merck Sharp and Dohme Corporation. They had originally intended to use podophyllotoxin prescriptions as a proxy for GW and link to individual vaccination status using Sweden's national vaccination register but only in girls ages 13-17. We combined forces and expanded the study to include all girls and women ages 10-44 for the third study in my thesis. Involvement in this vaccine effectiveness study allowed me to move from an ecological to a cohort design, providing a unique opportunity in the context of vaccination effectiveness evaluation.

Traditionally, observational studies are thought to be a necessary but inferior substitute to randomized clinical trials. By design, observational studies are prone to biases that should not be present in well-designed randomized trials. Through the randomization process, different background characteristics which could influence effect estimations should be

evenly distributed throughout the control and treatment groups, allowing for the effect of treatment on the event outcome to emerge clearly. However, in the case of measuring vaccination effectiveness, these observational studies have a unique advantage over clinical trials: real-life situations. Clinical trials create a constrained environment where rigorous inclusion and exclusion criteria are delineated, creating a sub-population which may not be fully generalizable to the more diverse populations in which the treatment, or in this case the vaccinations, will be used. I will continually return to this point throughout this thesis.

Most countries in the world do not have comprehensive population health registers. Those which do are usually limited in their capacity to link individual records between various registers. In another point I will return to throughout this thesis, the Nordic countries, with their extensive population registers and the ability to link to individual-level data, can make unique contributions to a global field in terms of measuring vaccination effectiveness.

With the help of advice from statisticians in my department, the vaccine effectiveness analysis was designed with vaccine dose as a time-dependent exposure using techniques available in survival analysis, also referred to as time-to-event analysis. Many months were spent trying to untangle various effects; we knew the vaccines had to be given prior to HPV exposure, so essentially prior to sexual debut given the prevalence of HPV, to have an effect. We had also learned from our ecological study on men and women's GW risk just how age-sensitive GW occurrence was. Given the relatively short follow-up in our study, less than five years, untangling the effects of age-at-vaccination and attained age was problematic. To complicate matters, we also had the effect of different vaccine dose levels which we could actually account for due to the time-varying exposure design. When we had ascertained just how important age-at-first vaccination was for vaccine effectiveness, it was decided that we would examine dose-level effectiveness in a cohort of younger individuals where we could more precisely ascertain the effects of dose in an age-group where we knew there was high vaccine effectiveness. We also understood we had to more closely probe our cohort for self-selection biases if we were to draw any conclusions on dose-level effectiveness. This dose study became the final study in this thesis, which was conducted independently from Merck Sharp and Dohme Corporation who were in no way involved in financing, design, data collection, analysis, result interpretation or manuscript writing.

In the past years, dose efficacy has emerged as a critical facet of vaccination strategy planning. The two competing HPV-vaccines available on the world markets were both designed to be administrated in a three-dose schedule over the course of six months. Three doses are expensive as is the administration and feasibility of implementing three-doses in the context of public health programs. Clinical trials have recently emerged indicating that one of the vaccines is as protective with a two-dose schedule as a three-dose schedule[4]. This trial has not measured HPV-related disease outcomes, however, just the presence of HPV infection. Another trial has only been able to show data on antibody level responses[5]. Neither of these measures, antibody response and HPV infection, are the disease outcomes which the vaccines are intended to prevent. With the data from the Swedish registers on vaccine exposure status and disease outcomes from the entire

population, complimentary information to the efficacy trials in terms of actual disease-outcome measures related to specific vaccine dose-levels can be provided. In this context, observational epidemiological studies are necessary compliments, and not merely second-best substitutes, to clinical trial findings.

In Journal of Infectious Diseases, Castle and Zhao wrote a commentary: *Population Effectiveness, Not Efficacy, Should Decide Who Gets Vaccinated Against Human Papillomavirus via Publicly Funded Programs* [6]. Here the authors call for observational studies to be used as necessary evidence in planning vaccination strategies. They go so far as to say that clinical trials will not suffice as evidence for designing population-based vaccination strategies as trial populations are not diverse enough to reflect the real-life situations in which vaccines are used. This commentary elucidates a situation where multiple risk perspectives and multiple prevention evaluations are needed to best inform practice. I started my thesis with the intention of examining HPV risk and prevention from multiple perspectives and I find myself ending there as well, except with much different measures of risk and prevention than I originally intended. Science should not lock itself into one design framework nor should practitioners or policy makers draw evidence for practice from one design paradigm. Using observational, reported and interview data, this thesis work aims to assess infection risk and evaluate multiple prevention strategies and in doing so, highlight strategies with the strongest potential for disease reduction in the era of HPV-vaccines.

BACKGROUND

HUMAN PAPILLOMAVIRUS

HPV is the most common STI globally. There are over 200 HPV types, of which roughly 40 are transmitted sexually and a proportion of those are oncogenic. Transmission occurs via epitheliotropic, or skin to skin, contact. HPV is known to be a necessary, but not sufficient, cause of cervical cancer [7]. Besides cervical cancer, high oncongenic risk HPV types are associated with cancers of the vulva, vagina, anus, penis and oropharynx [8]. Low-risk types cause genital warts (condylomata acuminata), which are not fatal but commonly known to recur and as such are difficult to cure completely, contributing to a substantial disease burden among both men and women [9].

Risk of HPV infection among women after their first male sexual partner has been shown to be close to 30% [10]. Most individuals become infected with HPV during the course of a lifetime but 90% of HPV infections are spontaneously cleared within 2 years [11]. Among the relatively small proportion of infections which do persist, most develop into precancerous lesions which either clear spontaneously or with treatment, or develop into invasive cancer [12].

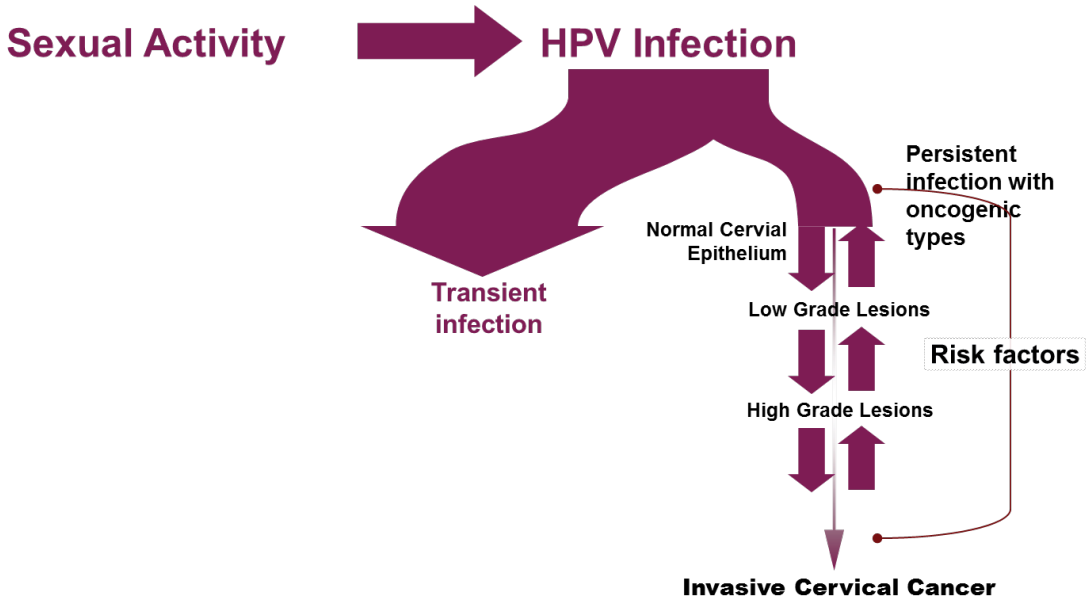

Figure 1. *HPV infection and development of cervical cancer. Potential risk factors for persistent infections include smoking, high parity, long-term oral contraceptive use and infection with other STIs.*

Cervical cancer is the second most common cancer among women globally [8]. Countries with the highest incidences of cervical cancer have the fewest economic resources at their disposal, as the following figure from GapMinder indicates.

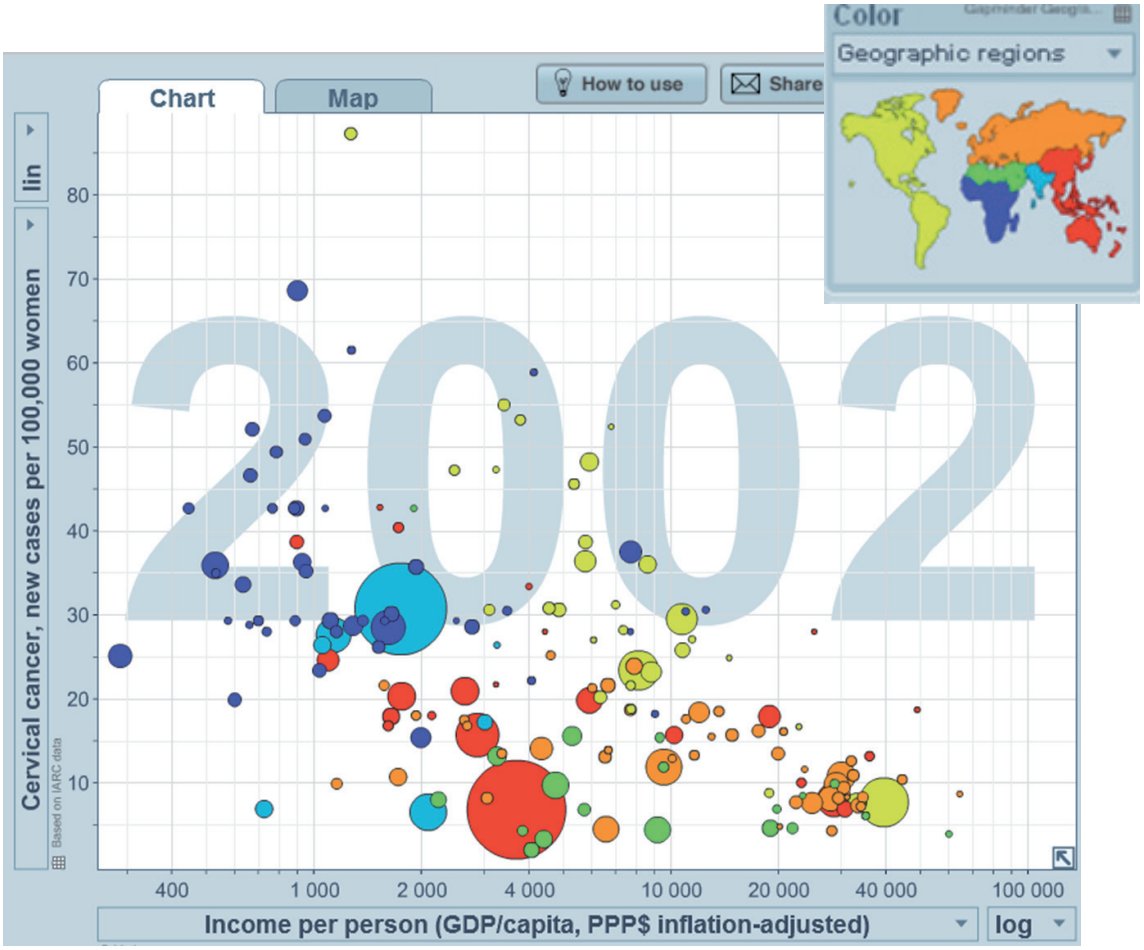

Figure 2. *The relationship between cervical cancer incidence and income per capita. Colors represent geographical areas by continent, bubble size represents country population size. From Gapminder.org.*

Higher-resource countries have been able to implement cervical cancer screening, which has been the driving factor in the decline seen in many countries over the past decades. In Sweden, cervical cancer incidence has declined by 70% over a 40 year period due to organized screening [13]. The 'Pap smear' developed by Papanicolaou in 1943, is still used to screen for cervical cancer with the aim of finding disease in early, non-invasive, asymptomatic stages. Pap screening programs have been shown to reduce mortality and incidence from squamous cell cervical cancer, but such programs are less effective in detecting adenocarcinoma of the cervix. Though Pap screening remains common for cytology analysis, many programs have migrated to liquid based cytology instead. This technology allows for both cytology and HPV-testing. It has been proposed that HPV-testing be combined with cytology as a primary screening tool [14] as HPV tests have higher sensitivity than cytology[15]. However, due to the high prevalence of HPV among young, sexually active adults, HPV testing in the younger age groups would not be as beneficial. Eventual individual or systemic repercussions of detecting HPV positivity have not yet been extensively evaluated. Optimization of cervical cancer screening recommendations in terms of intervals, ages, HPV-testing and cytology combinations is under continual development. The introduction of HPV-vaccines will likely necessitate eventual changes in screening recommendations.

HPV VACCINES

The development and subsequent international launch of prophylactic HPV-vaccines has transformed HPV-related cancer prevention. As these vaccines are prophylactic, they should be given prior to sexual debut to assure maximum protection against HPV. Two HPV-vaccines are currently on the market, a bivalent which protects against infection with HPV-types 16 and 18 (Cervarix®, GlaxoSmithKline) and a quadrivalent (Gardasil®, Merck) which offers additional protection against HPV-types 6 and 11. A nanovalent HPV-type vaccine is currently under development and its launch anticipated in the near future[16]. HPV 16 and 18 are high oncogenic types and found in roughly 70% of invasive cervical cancers [17]. HPV 6 and 11 are considered low oncogenic types and are associated with 90% of GW cases[18]. There is considerable geographic distribution of HPV-type prevalence in HPV-related diseases [19, 20]. For example, HPV 16 contributes to 23% of global HPV infections, but in sub-Saharan Africa it only contributes an estimated 13%; in Southern Asia, it contributes to 32% of HPV infections[20]. Due to this distribution and to the fact that exposure to vaccine HPV-types prior to vaccination would render the vaccines ineffective, cervical screening will still be necessary for women who have been vaccinated[21, 22]. Cross-protection against some non-vaccine HPV-types has been shown but will require further examination [23]. Also unknown are whether competing high oncogenic types will replace 16 and 18 in prevalence, so called type-replacement[24]. The development of other multivalent HPV vaccines is also progressing, indicating future market shifts.

The quadrivalent-HPV (qHPV) vaccine was approved by the Food and Drug Administration in 2006 and became available on the Swedish market in October, 2006. The bivalent vaccine became available in Sweden in the fall of 2007. Starting in May 2007, Sweden began partially subsidizing both vaccines for girls ages 13-17. Substantial out-of-pocket costs of approximately 180 euros were required even with the subsidies, with costs considerably higher for those ineligible for the subsidy [25]. This vaccination program was considered opportunistic as the girls and their parents had to seek information and find a vaccine provider themselves. The National Board of Health and Welfare announced that HPV vaccination for the prevention of cervical cancer should be included in the fully subsidized school-based vaccination program for girls between 10-12 years of age, with a proposed rolled-out in 2010[26]. Tenders were placed by both vaccine companies on the market and bivalent Cervarix® won the initial bid. Merck opposed the tendering processes due to specific legal technicalities and a subsequent bidding process was allowed[27]. In this bidding process, Merck was allowed to include cost-reductions as a result of genital wart protection. Also, the initial choice of a vaccine that did not protect against condyloma was criticized by some gynecologists[28]. Gardasil® won this subsequent tendering process and the school-based vaccination program rolled out in 2012, with a catch-up program for girls 13-18. Each municipality in Sweden is responsible for the procurement and implementation of the program and as this thesis goes to print in 2012 there are substantial discrepancies in proportions vaccinated per municipality.

During the time period when both vaccines were available in the opportunistic vaccination program at partially subsidized costs, 99% of the vaccinations purchased

were Gardasil®. Approximately 30% of 17-year old girls were vaccinated via Sweden's opportunistic vaccination program. Vaccination was approved for men and boys as well, but no subsidies were granted and only a few thousand of the over one hundred thousand vaccinations sold during opportunistic vaccination were inoculated in males.

Dose efficacy has been widely discussed as a fundamental factor in the vaccine strategy decision-making process[4, 29-31]. Dose evaluation studies will be central to the shaping of vaccination strategies. Increased costs and feasibility problems are directly related to an increased number of required doses [4, 31]. Both bivalent and qHPV vaccines follow a three dose schedule over a period of 6 months. There have been discussions regarding the necessity of an eventual booster dose[32, 33]. As invasive cancers take decades to develop, measuring such endpoints would be both unethical and unfeasible given the trials' relatively limited follow-up. HPV-infections, cervical, vulvar and vaginal intraepithelial neoplasias, adenocarcinoma in situ and genital warts are possible to assess to-date. Both vaccines have shown close to 100% efficacy against CIN outcomes in per-protocol populations[34, 35]. However in trials comparing the two HPV-vaccines, the bivalent vaccine has shown a higher immune response rates in vaccinated women[36].

EFFICACY VERSUS EFFECTIVENESS

Besides monitoring safety, randomized controlled clinical vaccine trials provide primary outcome measures of vaccine efficacy. Efficacy is a measure of disease risk difference between the untreated and treated, which in the case of vaccines is the unvaccinated and the vaccinated. Clinical trials provide controlled conditions in which to measure effect. Inclusion criteria for these trials provide measures of the vaccine effect in 'ideal' situations. These ideal situations are the per protocol study populations. Trials also include intention to treat populations, which are less than 'ideal' and are expected to mimic real-life populations more accurately than per protocol populations. However, intention-to-treat populations still adhere to inclusion criteria. In the case of the vaccine trials, common inclusion criteria for per protocol populations included HPV-negativity and specific age limitations, and inclusion criteria for intention-to-treat populations include a limited number of sex partners as well as age limitations[34, 35]. These intention-to-treat populations do not reflect real-life scenarios of individuals who will be exposed to vaccinations. As such, vaccine effectiveness studies are needed to measure the outcome of public health strategies [37]. Vaccine effectiveness is also known as field efficacy and can be measured in the same statistical manner as efficacy, but includes the actual population vaccinated and not only clinical trial participants. The advantages of effectiveness measures are manifold, foremost that they reflect real life scenarios and can capture shifts in herd immunity[6, 37]. Their external validity to broader populations is superior to those of clinical trials[37]. Effectiveness measures provide accurate measures of public health interventions.

Effectiveness is also known as field efficacy, a term meant to reflect the non-controlled environments in which outcomes were assessed[37]. The real-life situations that effectiveness studies measure can capture factors such as vaccine access, distribution and herd immunity. Where a finite number of clinical trials are required to assess efficacy, a

theoretically infinite number of effectiveness studies are warranted to reflect geographic, population, program strategy and economic nuances which will effect disease reduction.

The Nordic registers provide unique data for effectiveness investigations, comparable in some aspects to the data possible to capture in clinical trials in terms of hospitalizations, potential adverse events, long term follow-up, multiple disease outcomes etc. In many countries, access to this individual-level data in an entire population is not possible, hence ecological measures of effectiveness are most feasible. Ecological, or aggregate, measures of incidence are helpful in assessing total disease burden but causality cannot be assessed with individually-based data. Data from registers is potentially biased in a way clinical trial data is not due to the randomization process but aided by linkage of multiple registers, adjustments based on a priori hypotheses of causal pathways can be made to improve quality.

HPV INFECTION PREVENTION

The HPV-vaccines are prophylactic and as such, should be given to HPV-negative individuals for maximum effectiveness. Due to the high prevalence of HPV among sexually active individuals, vaccination prior to sexual debut is recommended [38]. Current HPV-vaccines offer limited protection in terms of HPV-types and will by no means eradicate all HPV infections.

HPV is highly transmittable. This combined with its high prevalence creates a contraction risk with any type of sexual contact including non-penetrative contacts[39]. Transmission from hand to genitals is also possible [39, 40]. Delayed sexual debut will not inhibit infection transmission nor will serial monogamy or monogamy, though the latter should reduce transmission risk [41]. Condoms offer substantial protection if used consistently, reducing a woman's risk of contracting HPV by 70% compared to women whose partners did not use condoms [42]. Male circumcision has also been indicated in HPV transmission reduction and of lower incidence of cervical cancer among female partners [43].

COMMON HPV-RELATED DISEASES AND THEIR TREATMENTS

Cervical cancer is the HPV-related disease with the highest disease burden globally. As cervical cancer can take decades to develop, screening programs have been successful in their early detection and treatment. A recent study from Sweden indicated an actual curative effect of screening, where women who had followed screening recommendations had higher cure proportions of their cancer, not attributable to lead time bias, compared to women who were overdue for screening when their cancer was detected [44]. Treatment for cervical cancer depends on staging at diagnosis, progressing from cervical conisation or hysterectomy without lymphadenectomy in very early stages to radical hysterectomy including pelvic lymphadenectomy with eventual chemoradiotherapy in later stages.

When cervical cytology indicates abnormality, clinical response and treatment will vary between screening programs and between countries. The treatment of precancerous

cervical lesions, referred to in Sweden with nomenclature dysplasia or CIN I-III and in the United States as LSIL and HSIL, will range from 'see and treat' colposcopy, ablative techniques such as cryotherapy or laser ablation and excisional techniques such as large loop excision of the transformation zone and cold knife cone biopsy[45, 46]. "See and treat", or visual inspection with acetic acid and immediate treatment with cryotherapy, is common in countries or with populations where organized screening is not possible [47, 48].

Treatment of other HPV-related anogenital and oropharyngial cancers also involve surgical and chemoradiotherapy combinations. There are no organized screening programs for anal cancers nor FDA approved screening techniques, but some higher risk groups for this cancer type, such as men who have sex with men or HIV positive individuals, are more frequently examined for lesions[49].

Treatment of condyloma

Not all individuals with condyloma (frequently referred to as GW) will seek treatment and of those who do, a proportion will be receive conservative or wait-and-see therapy. Cervical or intra-vaginal warts are treated differently than external genital warts. In cases of non-external GW, patient applied therapies are not recommended and specialist care is required for their management. Either colposcopies and proctoscopies and eventual subsequent biopsies are recommended for internal GW cases, with cryotherapy or electrosurgery as predominant treatment types[50]. First hand treatment for external GW is patient-applied therapy podophyllotoxin or imiquimod [9, 18, 51]. Duration of treatment with podophyllotoxin is estimated at 4-6 weeks with cure rates up to 77%[52]. Phodophyllotoxin is an antimitotic agent which induces local tissue necrosis by hampering cell-division[51]. For imiquimod, treatment duration is 16 weeks with cure rates of up to 54%[53]. Imiquimod is an immune modifier but not an antiviral therapy as it works via the induction of cytokines and interleukins[51]. Recurrence with podophyllotoxin ranges from 4-38% and with imiquimod 13-19% [52]. Podophyllotoxin is not recommended before or during pregnancies while imiquimod may be used with reservation in these situations [51]. Provider applied therapies of tri-chloroacetic acid and podophyllin resin are also used for non-surgical treatment of GW[18]. Non-pharmacological treatments include conservative therapy, laser, and cryotherapy, with surgical excision options for persistent infections that do not respond to pharmacological treatment.

Podophylotoxin is not recommended during pregnancy [51]. Imiquimod has not been properly tested on humans but has been shown safe for pregnancies and fetal development via animal studies. In Sweden, imiquimod is recommended with caution during pregnancy[51].

DEMOGRAPHICS, PRACTICE AND INFECTION TRENDS IN SWEDEN

Income discrepancies in Sweden are relatively small and the country has a high GDP[54]. Health care is provided to all residents through a national health care system.

Sweden has included sexual education in its school curriculum since the 1950s. There is an accepting attitude toward premarital sex for both men and women. Though marriage

is common in Sweden, cohabitation without marriage is equally as common and socially acceptable. Both birth control and abortions are provided under the health care system.

Sweden has seen a noticeable increase in STI trends over the past decades, specifically chlamydia and gonorrhea but also HPV and HPV positive tonsillar squamous cell carcinomas [55-60]. Studies have indicated changes in sexual habits, including an increased number of reported lifetime partners and acceptance of sexual activities outside steady relationships[61, 62].

Sweden has had organized cervical cancer screening since the 1960s, which became national in 1973[63]. It is estimated that approximately three-quarters of the target population attends the screening program, with large regional variation[64]. Approximately 450 women are diagnosed with cervical cancer annually and approximately 150 deaths are attributed to the disease annually accounting for roughly 2% of new cancer cases in Sweden annually [65]. Age standardized incidence rates for cervical cancer are 7/100 000, giving Sweden the second lowest incidence of the disease in the Nordic countries, after Finland with 4/100 000 but lower than Denmark (11/100 000), Norway 9/100 000 and Iceland 8/100 000[63]. Of the over 600,000 cytology tests performed, around 40,000 are diagnosed with some form of cervical dysplasia [46]. One out of ten Swedish women report having had genital warts by age 45 [66]. Cancers of the male genital organs are rarer, accounting for 0.3% of male cancers in Sweden annually and only a proportion of these will be triggered by HPV. Rectum and anal cancers are more common, accounting for approximately 4% of cancers in men and women with an uncertain proportion attributable to HPV[65].

SOCIAL DETERMINANTS OF HEALTH WITH FOCUS ON SES

Socioeconomic status (SES) has been linked to a substantial proportion of health outcomes around the globe and Sweden is no exception[67, 68]. As SES appears to play such a central role in many health outcomes, it is examined in this thesis as it pertains to various health outcomes, from condom use to condyloma, vaccination status and risk perception. What is actually captured by measures of SES is debatable. SES reflects, to some degree, the fiscal and social environment in which individuals live. SES captures some aspects of healthcare access, empowerment, lifestyle, discrimination and culture along with certainly other social and behavioral nuances. When significant for a given outcome, such as cancer, it is usually unclear of the exact mechanism captured by SES variable. What is clear however is that there is some force outside the individual level influencing a health state. Education level is common proxy for SES[67]. A study using longitudinal data on SES in Sweden showed that high education level was related to 'good' occupation, high income and low morbidity[69]. Other SES proxies include composite scores such as income and employment type. The importance of various SES component measures will differ geographically, culturally and periodically (period-effects).

THEORETICAL BACKGROUND

Three theories pertaining to prevention behavior were examined in the context of this thesis: Knowledge Attitude Practice (KAP), Health Belief Model (HBM) and Script theory. The two former are generally supported by public education policy and the latter is more common within sexual behavior research[70-74].

KAP and HBM linearly associate the perceived threat of a disease with the likelihood of taking preventive action[75]. As the acronym KAP implies, knowledge is thought to effect attitudes which in turn effect behavior or practice. This belief that by increasing knowledge about disease severity and shifting attitudes then individuals will take preventive actions if posed with a threat, underlies many public health awareness efforts. KAP and HBM are common undercurrents in sex education curriculums. Though these models are similar with their linear association of perceived risk to likelihood of behavioral change, the HBM is slightly more complex in that it also allows for perceived benefits and perceived barriers to behavioral changes to effect the likelihood of behavioral changes [76]. In medical research there is often an unspoken assumption that by assessing attitudes, predictions on subsequent behavior will be possible[72]. A plethora of studies has emerged around the globe in recent years measuring attitudes toward HPV-vaccination, including one used in this thesis, and questionnaire studies are often designed based on KAP principles [77-81].

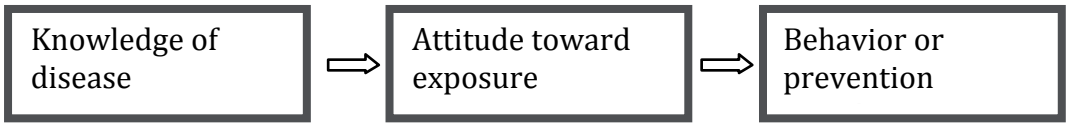

Figure 3. *Knowledge Attitude Behavior/Practice Model (KAP)*

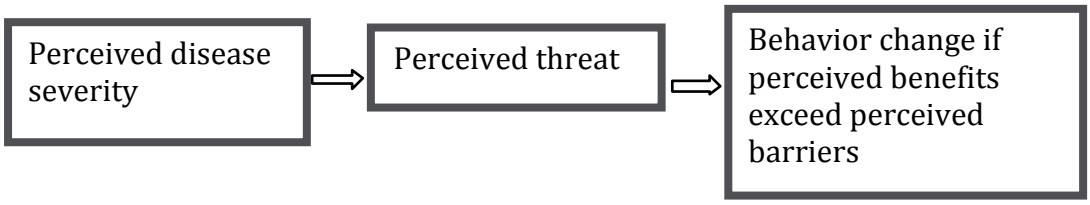

Figure 4. *Simplified Health Belief Model, similar to KAP model*

Sexual behavior, though enacted by individuals, is also determined by relationships and group processes. Simon and Gagnon [82] coined the use of the term 'script' to describe sexual behavior which is regulated by group, gender, and contextual norms. They construe sexuality as scripted on three interrelated levels; a collective, cultural level; an interpersonal level, related to groups and relationships; and an individual intra-psychic level, related to desire management. It has been suggested that existing sexual scripts should be studied as a means to better understand and explain STI trends [74, 83]. Though most studies using sexual script concepts focus on non-disease outcomes related to sexual behavior, studies outside of Sweden have looked at scripts in relation to HIV-prevention and condom use[74, 84].

AIMS

OVERALL AIM

The aim of this thesis is to provide a multidimensional assessment of infection risks and to evaluate strategies for HPV prevention.

Assessment of infection risks includes epidemiological measures of incidence, risk perceptions and risk as described by individuals in situations where infection transmission is high. This thesis aims to evaluate multiple prevention strategies, including vaccination delivery, quadrivalent-HPV dose-level effectiveness and condom use in high STI risk situations.

SPECIFIC AIMS

The primary aim of Study I is to evaluate which factors are associated with utilization of a central STI prevention strategy: condom use with temporary partners. The secondary aim is to investigate factors associated with STI risk perception with the hypothesis that risk perception is indicative of engagement in prevention behavior.

Using internet-based focus groups, the aim is to further investigate how sexually-active young adult women reason about risk for STIs and what strategies they use for prevention, with particular focus on HPV and HPV-related cancers. The secondary aim of these internet-based focus groups is to investigate reasons behind the low prevalence of reported condom use in high risk situations.

Study II aims to establish population estimates of the disease burden of GW in both men and women in order to facilitate understanding the potential public health impact of the quadrivalent-HPV vaccination of girls nationally immediately prior to and following the commercial availability of the quadrivalent vaccine as well as allow for proper discussions of prevention resources and men's risks.

Study III aims to study vaccine effectiveness to assess the actual population impact of opportunistic qHPV vaccination on the incidence of HPV-related disease by assessing GW incidence after complete vaccination in Swedish girls and women using individual-level data from the entire Swedish population. A secondary aim is to assess whether social determinants effected vaccination or risk for GW.

Study IV aims to examine dose-level vaccine effectiveness against GW on a cohort of preadolescent and adolescents using individual level data. A secondary aim is to assess correlates to adherence to the prescribed dosing schedule.

MATERIAL AND METHODS

Study	I	II	III	IV	Qualitative preliminary results
Research questions	What are the factors associated with reported condom use with temporary partners and STI risk perception?	What are the annual incidence proportions of GW among men and women in Sweden immediately prior to and following the availability of qHPV-vaccine?	How effective is complete qHPV vaccination in preventing GW among preadolescent girls and women? Are there social determinants to vaccination or GW?	What is the dose effectiveness of qHPV vaccine against GW in preadolescents and adolescents? Which factors are associated with completing vaccination schedule?	What are the reasons behind the low prevalence of reported condom use in high risk situations? How do individuals prevent transmission of STIs?
Design	Population-based cross-sectional survey	Descriptive population-based ecological	Register-based cohort	Register-based cohort	Group and individual interview study
Study population	8855 young adult women and 1712 men	Men and women aged 10-44 living in Sweden. The study population ranged from 4 167 770 individuals in 2006 to 4 190 658 in 2010.	2 209 263 women ages 10-44	1 045 093 women ages 10-24. Only vaccinations occurring from ages 10-19 were examined for dose effectiveness.	65 young adult women
Data collection method	Questionnaire and LISA register	Prescription Drug and Patient registers	Multiple population-based registers	Multiple population-based registers	Internet-based discussions
Analysis	Multivariable-adjusted logistic regression	Proportions, Poisson regression	Poisson, univariate and multivariate logistic regression	Poisson multivariate regression	Manifest and latent content analysis

MATERIALS – DATA SOURCE

Register data in Sweden

The Nordic region including Sweden is in a unique position globally in terms of ability to perform nationwide observational studies. The reasons for this uniqueness are twofold but first and foremost related to the broad scale usage of personal identification numbers (PIN), assigned to each individual resident[85]. These PIN numbers are used for health care visits, tax purposes, banking, insurance, and education to the point where they are essentially ubiquitous when accessing any publically supported service in the Nordic countries. The PIN contains information on birthdate and sex. The PIN is the key to linking data from multiple registers.

Because of the PIN and Sweden's migration to computer-based records in the 1960s, it is possible to link data from multiple registers and have decades of follow-up time in which to study various exposures and outcomes. Though other countries far surpass the Nordic region in terms of population size, few have the infrastructure capacity for linking data from multiple registers.

In the context of medical research, ethical approval is essential to obtain before registers may be linked. Governmental organizations such as the National Board of Health and Welfare provide linkage services if ethical approval is granted. During the linkage, PIN are removed and replaced with a random serial number. These governmental agencies hold the key identifying the newly assigned serial numbers with their corresponding PIN and usually destroy the keys within a matter of years if another agreement is not made with individual researchers. This handling of data de-identifies the data in accordance with Swedish laws on the public access to information and secrecy (Offtentlighets- och sekretesslag in Swedish) and on personal data (Personuppgiftslagen or PUL in Swedish) and the movement of data which derive from European Union Directive 95/46/EC.

Specific Swedish registers used in the studies in this thesis work will be described here in brief.

Prescription Drug Register (PDR)
In the summer of 2005 Sweden created a national register for prescription drug dispensations. Individual records of all prescriptions dispensed at all pharmacies throughout the country are entered into this register in an automated process. Prescriptions written but not dispensed will not appear in the register. In-patient prescriptions and medical dispensations are not recorded in this register either, nor are school-based vaccinations.

In and Out Patient Registers (PR)
Sweden's in-patient register has had national coverage since 1987, with region-specific and psychiatric in-patient coverage from the 60s and 70s respectively[86]. Day surgery was added in 1997. National out-patient data became part of the PR in 2001 and contains data on non-primary outpatient care, including some but not all private specialists.

Cause of Death Register
The National Board of Health and Welfare in Sweden is responsible for the PR, the PDR and the Cause of Death register among other health registers. The Cause of Death register contains information on underlying causes of death for all residents registered in Sweden starting in 1952, including contributory factors, using ICD-codes. Deaths occurring abroad are also included if the person is a registered in Sweden. It is estimated that 99.5% of deaths among registered residents are recorded [87].

Longitudinal integration database for health insurance and labor market studies (LISA)
Sweden's LISA register contains detailed and extensive demographic information as well as information regarding incomes, subsidies received including social welfare, work history, and education. It was started in 2004 but contains information as early as1990. This database is maintained by Statistics Sweden, along with the Total Population, Education, Multigenerational, and Migration Registers, which are described in more detail below.

Total Population Register (TPR)
Sweden's Total Population Register was formed in 1968 and is the main source for updated demographic information often used to link other registers. The data source comes from the Swedish Tax Authorities, with continual updates on information including address, age, civil status, family information, immigration and emigration status and country of origin, changes in citizenship etc. Statistics Sweden imports this data once annually for its register, the TPR. The TPR generates Statistics Sweden's mid-year population estimates. These estimates provide an estimation of individuals living in Sweden, by age, sex and geographic location. These estimations takes births, deaths and migration information into account provide an average of the population in Sweden at the beginning and end of each calendar year.

Migration register
The Migration register was also formed in 1968 when Sweden's population statistics were computerized. Statistics Sweden creates this register from its TPR, with a focus on emigration and immigration dates.

The Swedish Register of Education
The Education register was started in 1985 but contains information on highest educational status from decades prior as well. Information prior to 1985 was obtained via census and other surveys. The register is updated annually, with education completed outside the country obtained through additional survey information to new immigrants.

Multigeneration Register
A listing of one's familial relations can be found via Sweden's Multigenerational Register. This register was created in 1991 when the Swedish Tax Authorities took over responsibility for address registration from parishes. This register includes family information on all individuals born after 1932 who have had a registered address in Sweden at any point in time from 1961 onward. Information on adoptive or biological parents is also included here.

SVEVAC

A vaccination register, SVEVAC, was initiated locally in 2002 in the region of Östergötland for the purpose of registering child vaccinations and expanded gradually to other regions in the following decade. In 2006 SVEVAC was expanded under the scope of a research project to include all HPV-vaccinations nationally. Coverage of HPV-vaccinations is estimated to be 85%. Unlike the PDR, which de facto includes vaccine registration for all prescription vaccinations dispensed via pharmacies, SVEVAC should also theoretically include vaccination data purchased directly from private vaccination clinics. As this thesis goes to print, discussions are ongoing for a new national vaccination register to be used in lieu of SVEVAC, which will not be used to register girls vaccinated in the school-based HPV program.

Attitudes toward HPV vaccination survey

During January to May 2007, a large-scale questionnaire survey entitled "Attitudes toward HPV vaccination" was conducted. This survey, directed toward 40 000 people in Sweden, included 16 000 young women and 4000 men aged 18-30, as well as 20 000 parents to adolescents between the ages 12-15 years old. More women than men were sampled in order to facilitate longitudinal analysis of women, the original target group for HPV vaccination, in a future follow-up study. The survey aimed at investigating attitudes and knowledge about the new HPV vaccine, with questions on sexual habits, HPV, cervical cancer and cervical cancer screening.

Individuals with a registered address in Sweden were randomly selected from the Swedish Population Register. Invitation to respond to web-based questionnaires was offered to potential participants via a letter and answers were automatically entered into a database. In a first reminder, paper questionnaires were offered to those respondents unable to answer via Internet. The content of paper-based questionnaires was scanned into a database through optical reading. If neither had been completed, a telephone reminder was made and the questionnaire answered via a phone interview and the interviewer entered the answers via web-based questionnaire. As participation was voluntary, respondents provided consent by answering questions in the survey.

Response rates amongst the young women and men were 55% and 43%, respectively, with a total of 8855 women and 1712 men answering. Response rates amongst parents were 70% amongst parents of girls and 69% amongst parents of boys. Survey data was linked with register data from LISA for more complete familial socio-demographic information. This linkage also allowed for a comparison of demographics between non-respondents versus respondents.

METHODS

Epidemiology

The discipline of epidemiology and its inherent applications are as dynamic as the world that it observes. Though health practitioners such as medical doctor John Snow and nurse Florence Nightingale are often cited as pioneers in the discipline's inception[88, 89], modern epidemiologists sometimes don the hats of mathematicians or geneticists. In the field of research, epidemiology has become synonymous with sophisticated observational research and risk prediction and is not only associated with mitigating the spread of communicable diseases as the early pioneers strived to do.

Epidemiology is defined as:

"The study of the occurrence and distribution of **health-related states or events** in specified populations, including the study of the **determinants** influencing such states, and the application of this knowledge to control the health problems. "

- *A Dictionary of Epidemiology*, 5th Edition

This broad definition further delineates **health-related states and events** as: diseases, causes of death, behaviors, reactions to preventive programs or provision and use of health services. **Determinants** are defined as: physical, biological, social, cultural, economic and behavioral factors influencing health[90].

Epidemiological studies can be hypothesis testing (deductive) or hypothesis generating (inductive). As the research question itself should dictate the research method used in investigation and not vice versa, there are a multitude of methods possible to use in the field of epidemiology. This section will provide an overview of the methodologies used in this thesis, which focuses on assessing risks and evaluating prevention from multiple perspectives. Some basic building blocks frequently discussed within the field of epidemiology will be discussed. These building blocks enable the analyses and models defined herein.

Exposure and outcome

An outcome is something we wish to predict or better understand. In epidemiological studies, this is often a disease or death, and in statistics it is known as a dependent variable. Data on outcome and exposures can be collected from clinical observations, medical records, questionnaires, interviews, registers, administrative databases etc.. An outcome variable can be a disease, death, or a belief such as 'vaccine acceptability', which can be measured from questionnaire data where respondents answer numerous questions related to willingness to vaccinate, belief in vaccination safety and effectiveness. Depending upon their answers to these questions, they might receive a score that is meant to represent their level of vaccine acceptability. In randomized control trials (RCT) primary outcomes are often clinical test results such as CD4 count or blood-lipid levels. Secondary outcomes could be side effects or adverse reactions. The May 4th, 2012 issue of the Centers for Disease Control and Prevention's Morbidity and Mortality Weekly Report (MMWR). is entitled "Sexual Experience and Contraceptive Use Among Female Teens – United States 1995, 2002 and 2006-2010". In that issue,

outcome variables were sexual experience levels and types of contraceptive use as the title reveals[91].

Exposure variables are assumed related to the outcome; either causing the outcome or being somehow associated with it and in statistics are known as independent variables. In RCTs exposure variables would be the therapies under investigation. In observational studies exposure variables are correlated with or believed to cause the outcome. In the case of cervical cancer or genital warts (outcomes), HPV would be one possible exposure variable. Another exposure variable could be sexual activity, which might as a proxy measure for HPV exposure. Other exposure variables associated with the outcome cervical cancer are age, oral contraceptive use, screening and vaccination. The study research question, constructed with a priori knowledge, delineates exposures and outcome.

Minimizing biases: Confounding, effect modification and a note on adjustment
Biases are of primary concerns in scientific studies as they undermine result validity. Terms external and internal validity are often used when discussing result biases. External validity is related to the concept of generalizability and whether or not study results are applicable to any other persons or groups of persons (or other objects of measurement) not under investigation. Strict inclusion or exclusion criteria can hinder a study's generalizability to a broader population. Large, population based studies could theoretically enhance result generalizability, as long as the population under study is comparable with other populations. This thesis examines vaccine effectiveness in the entire Swedish female population, making the results generalizable to Sweden or to other countries with similar populations (in terms of baseline HPV risk). However, in the two vaccine effectiveness studies in this thesis, those with a history of GW treatment prior to follow-up were excluded, limiting generalizability to those with no known history of GW.

Self-selection bias of an exposure can also hinder a study's generalizability; in this thesis a question to ponder is whether women who are vaccinated differ in terms of baseline HPV-risk compared to other women who are unvaccinated. This type of bias is sometimes referred to as participation bias. For example, do women in their 20s who choose to get vaccinated have a higher average number of sexual partners than women who do not choose to get vaccinated? If this were the case, then the results found here would be valid to this group of women studied, but not necessarily to Swedish women with different baseline risks.

If studies are poorly designed, internal validity is threatened. Internal validity is an indication of whether or not the association/relationship between the exposure and outcome indicated is accurate. An association could be spurious, or the magnitude or direction of relationship could be inaccurate. The problem with threats to internal validity is that it is not always possible to predict the direction of the bias or know whether it is a true association.

By randomization and proper study design it is possible to assess causation, or effects of exposures on outcomes with reduced biases. This is based on the principle that in the randomization process (with a large enough sample size), only exposure status should

differ significantly between groups of study participants. Distribution of other background characteristics should be non-differential, making participants in essence exchangeable with each other. This quality of exchangeability allows one to draw conclusions about the exposure.

Exchangeability in observational studies is often not plausible. Through some statistical techniques such as adjusting for covariates or potential confounders, it is possible to approach conditional exchangeability. It becomes more plausible if one accounts for covariates, or confounders – variables related to both exposure and outcome. Confounding bias occurs when exposure and outcome have common causes that are unaccounted for. Statistical adjustment for such confounders, one common method used, reduces some of the concern of bias of the exposure-outcome association.

A typical confounder is age. As one ages, one is more likely to succumb to disease or death, two common epidemiological outcomes. Age is also related to eventual exposures, such as alcohol intake, smoking levels, and sexual activity. If one were to examine the effect of alcohol on cancer and not take into account the effect of age on cancer, the results generated would not accurately reflect the effect of alcohol on cancer as they would also include the effect of age on cancer.

When examining the effect of exposure variables on an outcome one must minimize the effects of confounding variables or else estimates will be biased. There are four common ways to reduce confounding bias: adjustment, stratification, matching and restriction. Removing the effects of confounding is also called controlling for confounding variables. When one statistically adjusts what one actually does is hold levels of the confounding variable constant while assessing the relationship. If age were a confounding variable then when assessing the relationship of coffee consumption on cancer one would examine the relationship at each level of age (also referred to as 'holding age constant'). If one would also control for smoking in the above example, one would then assess the hypothetical coffee-cancer relationship by examining it at each level of smoking status. This adjustment can occur in regression modeling or via the process of stratification[92].

When adjusting for a confounder one makes the assumption that association is the same across all levels of a variable. When this assumption does not hold, when an effect or association is assumed to vary across levels of another variable, one has effect modification. When there is known effect modification, stratification can be used to properly assess the effects of exposure on outcome. Stratification examines effect sizes of a variable across variable levels and accounts for effect modification. Effect modification is also called interaction. One can examine the presence of a potential interaction between two variables in a regression model, but the actual effects themselves need to be assessed via stratification procedures or by introducing an interaction term in the regression model[92].

Matching is frequently used in case-control and some cohort studies. Cases, those with the disease or outcome, are matched with controls, or individuals with similar demographic characteristics such as age, sex, ethnicity, SES etc. or other characteristics potentially influencing the outcome such as hospital where care was received or another

pertinent contributory diagnoses. Exposure status is then examined among the cases and among the controls to see if there is a difference in outcome/disease risk. Restriction is another method used to deal with confounding. RCTs use restriction, or study inclusion and exclusion criteria, to avoid results that have biased estimates due to the presence of unmeasured confounders. Restriction can limit generalizability if the study population and the general population in which the treatment (or vaccine etc.) is used differ because of inclusion and exclusion criteria.

Multiple covariate selection procedures

As it is infeasible to examine all health related phenomena via RCTs, not to mention highly unethical (one cannot expose people to factors that may lead to cancer or pre-term death, nor can one withhold treatment that is known to cure), well-designed observational studies are imperative. Multiple confounding variables must be accounted for when designing a study. To do this, there exist a number of approaches investigators use to decide which covariates to include in their analysis. Some use automated stepwise procedures (backward or forward), which relies heavily on p-values. Some look at changes in point estimates following adjustment and consider shifts of more than 10% (or some other cut point that they decide upon) to retain a variable in the model. Using these procedures without careful consideration of underlying mechanisms is not recommended as doing so can introduce bias into estimates[93].

Directed Acyclic Graph (DAG)

In the processes of constructing a model, á priori hypothesis should be clearly specified. DAGs are graphical representations of causal or associative structures. DAGs can be used to specify hypotheses before analyses are performed [94]. They provide an overview of the relationships between variables under investigation. This in turn aids with covariate selection in statistical modeling. DAGs are 'directed' because the causal relationship between two variables is displayed with an arrow as seen in Figure 5 below. DAGs are acyclic as the variables which they display exist in interplay with other variable(s) and are the by definition, not closed structures (cyclic).

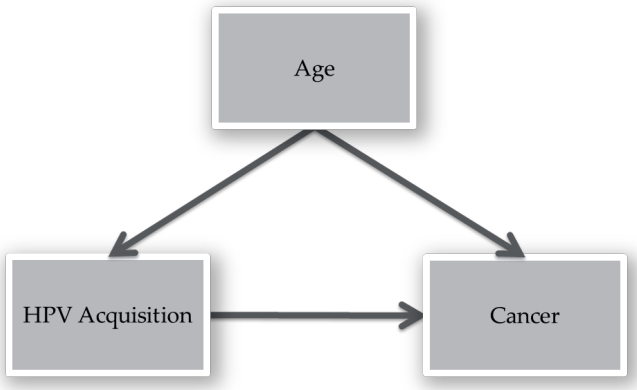

Figure 5. *Simple DAG showing a relationship between age, HPV and cancer*

In Figure 5 HPV acquisition can lead to cancer. In this sketch, one could conceive of HPV as the exposure and cervical cancer as the outcome variable. Age increases risk of cervical cancer development. Age is also related to HPV acquisition. As HPV is sexually

transmitted virus its acquisition will coincide with age of sexual debut and sexual activities. In this DAG, age is a confounder, or a common cause of the exposure and the outcome.

It is possible to oversimplify relationships between variables by drawing incomplete DAGs which lack the presence of unmeasured confounding, or variables relating to either the exposure or outcome but that are unknown or impossible to measure. Though unmeasured confounding cannot be accounted for, it can still be acknowledged. In the case of HPV where HPV is the necessary but not sufficient cause of cancer, a DAG that completely describes all causal pathways is unrealistic as there are many unknown confounders related to the clearance of HPV infections in some individuals and the persistence and development of pre-cancerous lesions in others .

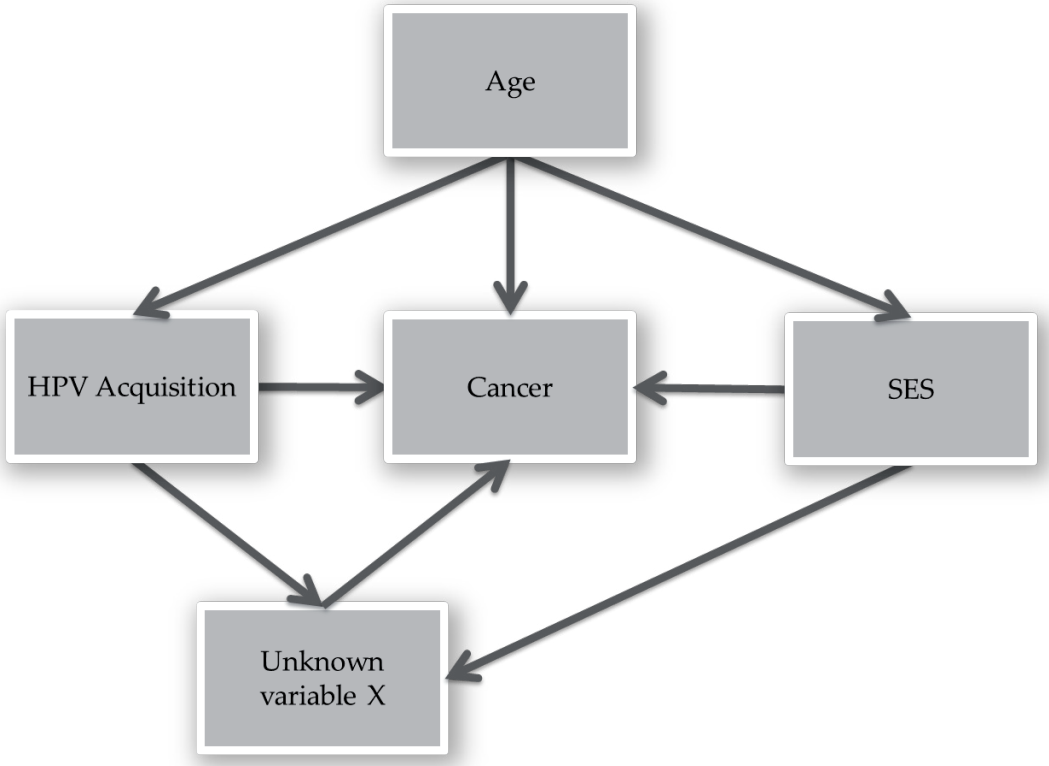

Figure 6. *More complex DAG showing a relationship between age, HPV and cancer and the presence of unmeasured confounders (variable X)*

Incidence versus prevalence

Incident cases of a disease are considered new cases of a disease. Prevalent cases of a disease are not necessarily new and instead indicate the number of cases of a disease in a population at a certain period of time. Incident cancer cases would include new cases of cancer diagnosed while prevalent cancer cases would include all cases of cancer in a population at some specified time, both the newly diagnosed (incident) and those living with the disease for a longer time (disease duration). Simply put, incidence measures risk and prevalence is a function of incidence and disease duration:

$$\textit{Prevalence} = \textit{incidence} \times \textit{disease duration}$$

This relationship holds true if the population has a steady state (in and out migration are stable)[95]. Prevalence is typically greater than incidence as many diseases have a long duration. For non-chronic illnesses such as infections with relatively quick clearance, incidence and prevalence numbers could be similar due to the short duration of the infection. Incidence can be greater than prevalence during epidemic cycles when attack rates are at their highest[95].
Although sometimes referred to as a prevalence rate, prevalence is a proportion. It is the proportion of individuals with a disease at a specific time or during a specific time period and is calculated as:

$$\frac{\textit{Number of cases of disease in the population at a specific time or time period}}{\textit{Number of persons in the population at that specific time or time period}}$$

This proportion can be multiplied by 100,000 to aid interpretation[95]. However then the interpretation would be 648 prevalent cases per 100,000 individuals.

Whether one wishes to measure incidence or prevalence depends on multiple factors including the natural history of the disease under investigation as well as the possibility for obtaining data on disease duration. Incidence and prevalence measure different aspects of disease burden depending on the natural history of the disease and disease duration. Prevalence does provide an important measure of disease burden in a population, such as number of individuals living with cancer, and allows for planning of health services. Incidence measures provide a measure of risk and new case accrual and are necessary when evaluating causality or risk factors, such as the effect of vaccination on disease outcome. In this latter case, prevalence measures are not appropriate as issues of temporality are paramount; exposure by definition must precede disease outcome. In order for this to hold true, the study population must be disease free prior to exposure and followed until disease onset, which would provide an incidence and not prevalence measure.

A measure called cumulative incidence is commonly used and is also referred to as risk or the incidence proportion. When calculating cumulative incidence, all individuals in the population are must be at risk for the outcome of interest. With this assumption, the number who get the disease are a proportion of the total at risk. Closed cohorts, where the number of people in the study either stays the same or decreases, produce measures of cumulative incidence. In open cohorts where individuals enter and exit the study at various points in time depending on pre-specified risk criteria (i.e. from ages 10-44 during the years 2006-2010 as is the case in Study III), then obtaining measured of cumulative incidence is not possible.

When estimating a denominator is difficult or impossible, as in setting of open cohorts, and there is the ability to estimate person-time, incidence rates can be calculated in place of risk (or incidence proportion or cumulative incidence). Person-time refers to the time an individual is at risk for disease and can be measured in days, months, years etc. Person time is measured in cohort studies, both open and closed. Individuals contribute risk time until they contract the outcome, until they are censored or until the end of study follow-up, whichever comes first. If an individual contracts the disease/event in question, the

individual would be considered an event/case. Censoring can occur in the case of death by other cause than the cause under investigation, emigration, or attaining a pre-specified age such as 45 if one were studying disease occurrence in 10-44 year olds as is this case in Study III. If one were measuring risk for uterine cancer by establishing incidence rates, only women (who at risk because they have uteruses) in a population would be followed and typically contribute person time until they get uterine cancer or are no longer at risk for uterine cancer because they got a hysterectomy or moved outside the study area or died from any cause.

If a person were to emigrate during the study follow-up, they would contribute person time until emigration and then be 'right censored'. Right censoring refers to when there is a lack information on an individual pertaining to the end of study follow-up. Conversely, if a person were to not contribute person time from the start of study follow-up due to say living in a geographic area outside the area of investigation but were to move into the study area during the investigation, that person would contribute person time starting from their immigration date and would be considered 'left censored'. Left censoring refers to when there is a lack of information on an individual pertaining to the beginning of or before study follow-up.

Incidence rates are calculated as:

$$\frac{\textit{Number of new cases}}{\textit{Person-time at risk}}$$

Incidence rates are interpreted as for example, 923 GW cases per 100,000 person-years of follow-up.

Measures of risk, absolute and relative

The field of epidemiology lacks verbal precision at times. One of those times is when discussing risk and rates, which can either be absolute and relative measures. The difference and usefulness of absolute versus relative measures of risk is perhaps more a communication limitation than a methodological limitation; but the latter gives rise to the former. For health policy decisions, measures of absolute risk are important to consider when available. Relative measures can easily be misinterpreted in terms of public health risk assessment.

The incidence of a disease in a population is the absolute risk of the disease in that population. Another common measure of absolute risk is risk difference. As the name implies, risk difference is calculated by subtracting the incidence rate among the exposed from the incidence rate of the unexposed. This difference would provide an absolute measure of effect of exposure in the population.

Relative measures of risk compare incidence among exposed and unexposed, but as a ratio instead of as the difference. The incidence of disease among exposed individuals compared to the incidence of disease among unexposed individuals would be the incidence rate ratio (IRR) and looks as follows:

$$\frac{\textit{Incidence among exposed}}{\textit{Incidence among unexposed}}$$

IRR is one relative measure of risk, others include the hazard ratio (HR), and under some circumstances the odds ratio (OR). Technically the OR does not measure risk in the exposed vs. risk in the unexposed but instead measures the odds of getting the disease compared to the odds of not getting the disease. As such, whether the OR is an approximation of a risk ratio will depend on multiple factors based on study design (in the case of case-control studies where it is necessary to use the OR) or whether the disease in question is rare[95].

Effectiveness calculations
Effectiveness and efficacy measures are calculated as follows:

$$1\text{-}IRR \times 100$$

Hazard rate ratios such as those generated from Cox proportional hazards models, or other relative risk measures including odds ratios can also be used to create measures of effectiveness in the same manner as above:

$$1\text{-}OR \times 100$$
$$1\text{-}RR \times 100$$

Effectiveness is also termed field efficacy[37].

Conversely, the number needed to treat (or vaccinate) to avoid one case of the disease is calculated by taking the inverse of the IRD (1/IRD).

Regression modeling
Regression modeling is appropriate when examining the effect of one or more variables (exposures) upon another variable (outcome).

Linear regression is expressed as follows:

$$y = mx+b$$
(for Swedish readers, $y = kx+m$)

Y is the outcome or dependent variable and is a function of the exposure or independent variable x and another constant, b. The m is the slope and the b is the intercept, or the value of y when x is 0.

In regression modeling, the interpretation is that for every unit change in x, the mean of y will change accordingly. The linear regression model, which uses a straight line to describe the relationship between continuous variables and assumes normal distribution of data, can be extended to a multiple regression model to account for multiple predictor variables or other covariates:

$$y=b + mx1+ mx2 + mx3+...mxK$$

Logistic regression
When the outcome variable is not a continuous variable but instead binary (0, 1 or yes disease/no disease), then logistic regression can be used. An odds ratio (OR) is estimated

in logistic regression. A normal distribution is no longer assumed and instead it is assumed data follow the binomial distribution. In multinomial logistic regression the outcome can have more than two categories, such as never, sometimes or always condom use.

Odds are defined as the probability of occurrence divided by the probability of non-occurrence or:

$$\frac{P}{1-P}$$

Instead of modeling the change in mean value of y as a function of x, logistic regression models the log of the odds or the logit ($logit= log\ (p/1-p)$). The logit is used as it extends from negative to positive infinity:

$$Logit\ (y)= mx + b$$

In multivariable logistic regression, or multiple logistic regression as it is sometimes referred to, the equation is:

$$Logit\ (y)= b + mx1+ mx2 + mx3+...mxK$$

Even though the log odds is modeled in this equation, the predictors can be either continuous or categorical and retain the linear function.

Poisson regression

In addition to assessing whether an event, such as cancer, occurred or not, it is also interesting to assess the rate at which it occurred. Poisson regression uses discrete count data such as number of cases and has a Poisson distribution which allows for assessment of the number of events that occur at some rate. Poisson generates incident rate ratios (IRR) and provided absolute incidence measures as opposed to just relative measures as with the Cox proportional hazards model.

Rate data have one element in common: time. In order to calculate time to an event, which underlies rate calculations, data that allows for estimations of person-time is necessary. Time to event analyses estimate incidence rates (IR) and hazard rates (HR) and are referred to as survival analyses in health research – even when death is not the outcome under investigation.

Poisson regression is a type of time to event analysis. The log hazard is modeled as follows:

$$Log\ hazard\ (time) = b(time) + mx1+ mx2 + mx3+...mxK$$

As the intercept here (b) depends on time, the model allows the hazard rate to be time varying [96]. In the above model, the covariates (exposure variables) will not necessarily depend on time but can.

The mean of Poisson distribution is the rate (number of events per time-unit), and the variance is also equal to the rate. Poisson regression allows for the adjustment of multiple

time scales, which is one advantage of using it. The baseline hazard in Poisson does not automatically vary as with Cox regression and instead has to be split at intervals to allow for fluctuations over time.

Interpretive description with qualitative analysis

Though not typically associated with epidemiology, qualitative methodology can be useful in understanding patterns of risk behavior or for investigating feasibility of health promotion strategies. In qualitative research, interviews are commonly the primary unit of analysis. As qualitative research is often inductive – that is to say hypothesis generating and aims to provide a deeper understanding of phenomena under investigation. The primary aim is not to draw conclusions with statistical certainty that can be generalized to a specific population, as is the case with quantitative analysis. Sampling usually occurs until saturation is reached. Saturation is a term used by researchers that denotes a repetition in the patterns of variation constructed from the interviews. Besides expressing depth, qualitative inquiry aims to capture and express the variation in responses.

Though generalizations cannot be made with statistical certainty, results from qualitative analysis can still be used to inform practice [97, 98].

Interpretive description does not prescribe a specific analysis technique (for example content analysis, grounded theory or phenomenology) but instead aims to interpret the clinical or public health issues under investigation in a manner that informs practice or can influence policy decisions. Data collection and analysis occur in tandem to inform one another, as is common in many forms of qualitative research[98]. One interview is conducted and a preliminary analysis made, after which subsequent interviews with other participants are conducted with eventual new questions based on earlier interview preliminary results.

While clear a priori theorizing is recommended in quantitative methods of scientific inquiry, flexibility in a priori theorizing is requested in interpretive description to grant the possibility for an a priori theory to be changed through the evidence of the data. The aim is not merely to generate hypotheses that can be tested in subsequent studies as is sometimes the case with qualitative inquiry, but instead to interpret the data in such a manner that has clinical relevance.

Content analysis

When analyzing text using content analysis, latent or manifest techniques or a combination of the two, are often used[99]. Manifest content analysis places emphasis on what is described outright. Latent content analysis interprets the underlying meaning and relationships in the text. The process of content analysis involves first reading through all text in its entirety. The text is then re-read and coding begins. Coding is a process that assigns a label to portions of the text reflecting specific ideas – these are called condensed meaning units. Meaning units can be assigned multiple codes depending on the richness of the text. Similar codes then form categories. These categories can be presented as results. Often themes are also presented as main results. Themes cover multiple categories and codes and are meant to express the latent content in the text. Themes themselves can be further developed into sub-themes.

Focus group discussions as internet based chat discussions

Focus group discussions (FGD) are often used in health and behavioral research and provide a forum for gaining an in-depth understanding of multiple participants' views while simultaneously generating a group dynamic that can highlight cultural or societal norms related to the issues under investigation[100]. This ability to facilitate understanding of both individual depths and multilevel dynamics such as relationship or societal issues is what makes this method popular.

Traditionally sensitive, deviant or potentially humiliating topics are not broached in face-to-face focus group forums. Developing this method into internet-based discussions allowed for anonymity and the ability to broach sensitive topics, while allowing both normative and non-normative views to emerge.

STUDY I
MATERIAL AND METHODS

A national population-based cross-sectional survey entitled "Attitudes toward HPV vaccination" was sent out in the spring of 2007. This survey was sent to adult men and women between the ages of 18-30 as well as to parents of boys and girl between the ages of 12-15. For this study, only the data from the adults' survey was used as in addition to attitudes, it covered detailed information on prevention utilization and sexual habits.

The adults' survey was sent to 4000 men and 16000 women selected randomly from Sweden's TPR. More women than men were sampled due to a planned follow-up design involving female participants. As women are the vaccination target group, the original intent was to follow trends amongst women over time. The large sample size would allow for anticipated drop-out and a response size still large enough to make statistical inferences.

Invitations to web-based questionnaires were sent via letter. An initial reminder was sent and paper questionnaires were offered to those unable or unwilling to answer via Internet. A second reminder was made via telephone and the possibility of answering questions via a telephone interview was offered. Response rates were 55% for women and 43% for men, with 8855 women and 1712 men participating. Survey data was linked with Statistics Sweden's LISA database to obtain detailed information on socio-economic variables. This also allowed for a comparison of non-responders versus responders.

The outcome variables for this study were derived from two different survey questions. To investigate condom use in high STI risk situations, condom use with temporary partners was examined due to the increased risk for contracting an STI from serial or concurrent partners. Though non-condom use with steady partners can also lead to STI contraction, under monogamous assumptions it is conceivably less of a risk as with temporary sexual partners. Also, factors motivating condom use in steady relationships could primarily relate to birth control as opposed to STI prevention. Respondents to the question: "When you had sex with your temporary partner(s), how often did you use a condom during the past year?" were included in the analysis on condom use (n=2594). Responses were aggregated into the following categories: 1) Always/almost always, 2) Often/sometimes, 3) Seldom/never. Individuals who reported not having sex with temporary partners in the past year were excluded, as were non-respondents and respondents with missing data on this question.

To study STI risk perception, respondents with sexual experience who answered the question: "How large a risk do you think you have of contracting an STI" were included in the analysis (n=9820). Responses were aggregated into the following categories: 1) No/small perceived risk or 2) Somewhat large/large perceived risk. Those who responded "Don't know" (n=534) were categorized as missing. Respondents with no sexual experience, non-respondents and respondents with who did not answer this question were excluded from the analysis.

Covariates from questionnaire and registers considered in the models were age, education, income, employment type, social welfare status, geographic location, birth country, parental birth countries and relationship status, having heard of HPV, belief that men/women can be infected with HPV, knowledge about reasons for and commonness of cervical cancer, knowing cause of genital warts, belief that HPV is sexually transmitted, STI risk perception, severity perception of genital warts, predict more unprotected sex if vaccinated, pap smear screening attendance (women only), willingness to vaccinate against HPV, oral and anal sex habits, types of sexual contact, condom use ever and with temporary and steady partners, age at first intercourse, perception of one's own sex partner number compared to others, temporary sex partner number and sex partner gender.

Hypotheses for potential variable relationships were carefully considered and DAGs were constructed in order to formulate possible associations and causal pathways.

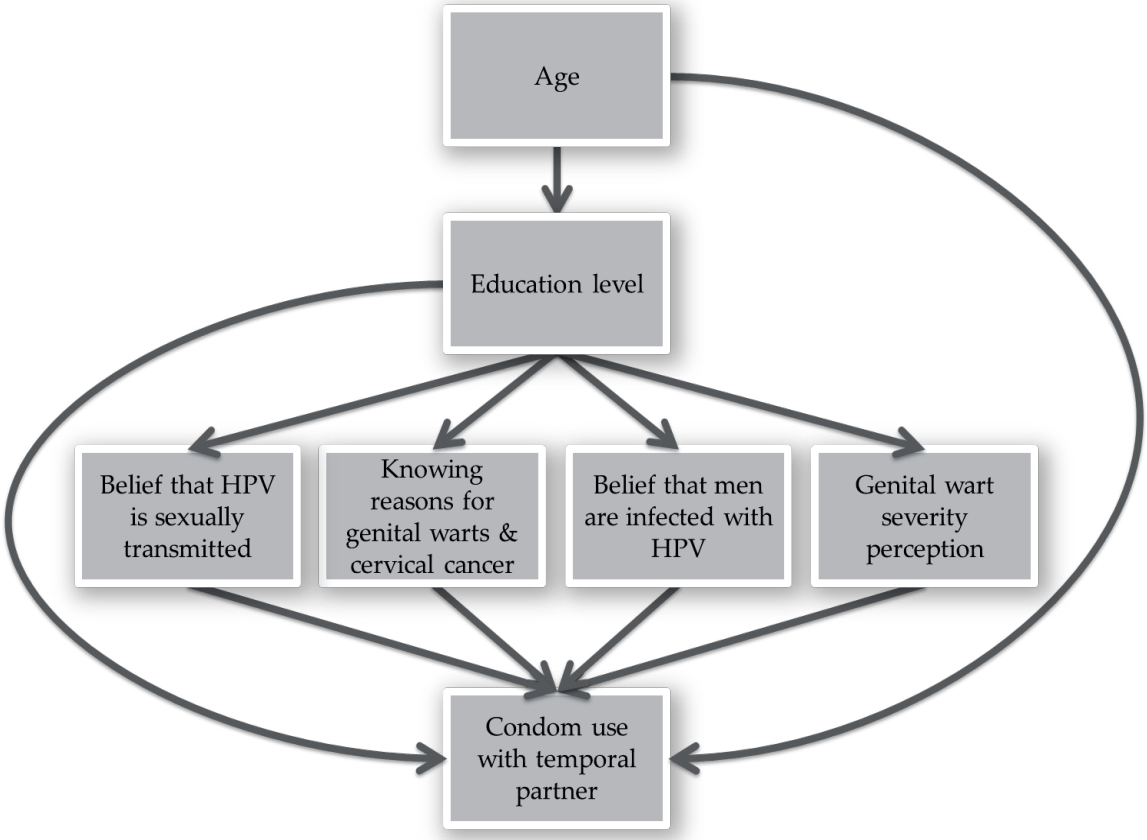

Figure 7. *Example DAG used to delineate hypothesis used in model generation.*

An implicit assumption when constructing the DAGs was that risk perceptions would be indicative of engagement in prevention practice. It was assumed that knowledge would to some degree influence attitudes, which would in turn influence whether or not one engaged in prevention practice. This Knowledge Attitude Practice (KAP) assumption was operationalized via variables pertaining to STI knowledge, attitudes surrounding STI risk and severity perceptions, and condom use with temporary partners as a proxy for safe sex practice. It was also assumed that behaviors would be related to other behaviors so variables pertaining to sexual behavior were assumed related to prevention practices.

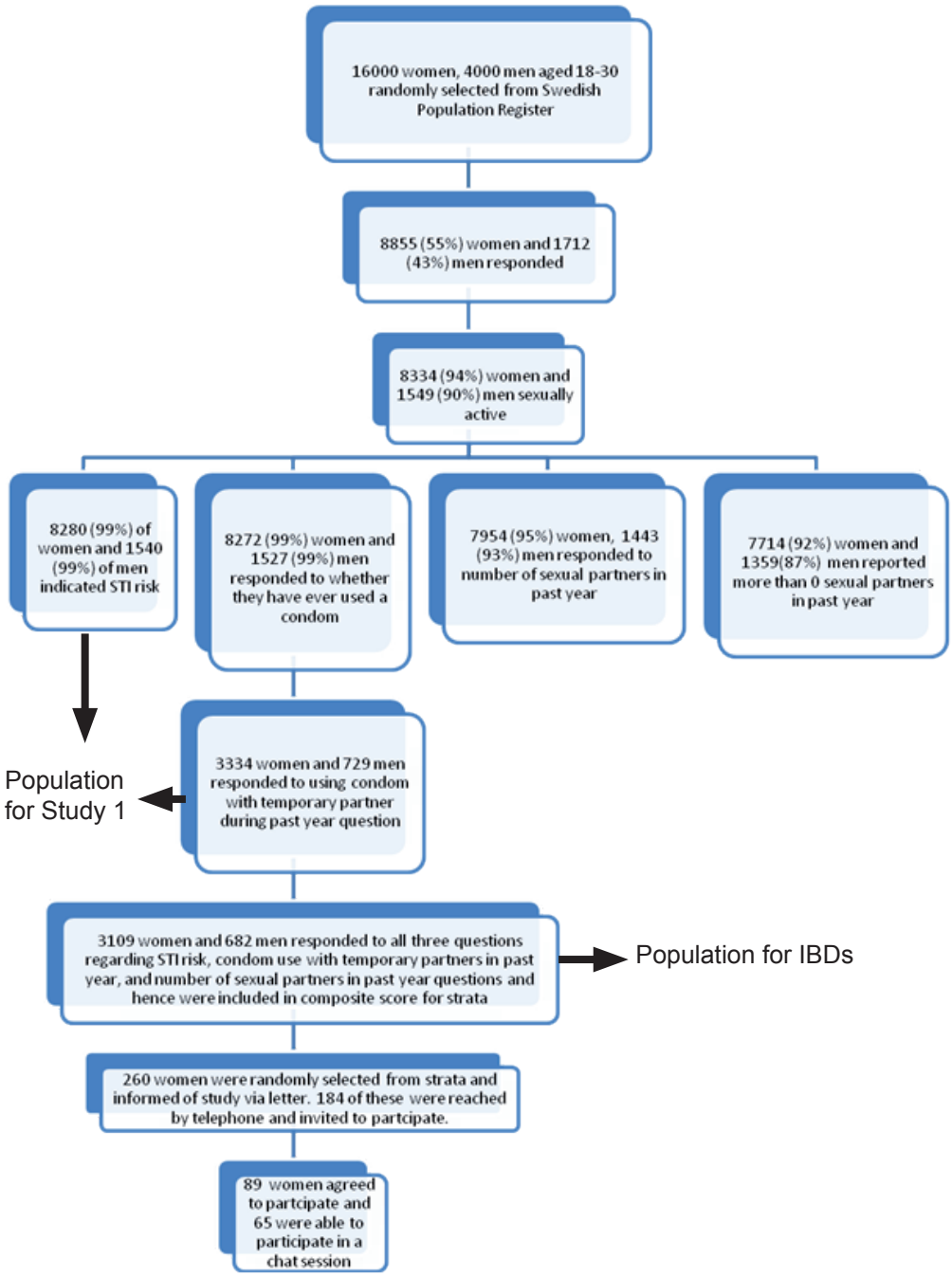

Figure 8: *Study populations for Study I and internet discussions*

Study I data analysis

Statistical analyses were performed using SAS version 9.2. Chi-square tests were performed between the outcome(s) and variables pertaining to knowledge, attitudes, reported behaviors and socio-demographic data. Based on the DAGs, a series of univariate regression models assessed the association between exposure variables and the outcome variables condom use with temporary partner and STI risk perception. Multicollinearity was examined in a correlation matrix for all variables and no serious was found except for use of condoms with steady and temporary partners and number of sexual partners and number of temporary sexual partners. Variables significantly associated with the main outcomes in the univariate analyses were considered for inclusion in the multivariable multinomial model (condom use) and the multivariable

logistic regression model (STI risk).Odds Ratios (OR) and 95% confidence intervals (CI) were generated.

Variables were retained in the models based on statistical significance (p-value less than 0.05), examining confidence intervals, and subject-matter pertinence of the covariates to the outcome(s). Exposures were tested first per categories based on KAP and demographics. Exposures significant per category were added one at a time to the demographic model and all variables excluded were examined separately in a multivariate model to ensure their assumed non-effect held true in various multivariate constellations. Akaike Information Criteria (AIC) and Bayesian Information Criteria (BIC) were also used to examine the fit of the multivariate models.

In the model construction process, significant interaction effects between gender and most covariates were found. Stratification, typically used to obtain accurate estimates in the presence of interaction, was not sufficient as the model predictive for women was not predictive for men. Two separate models were therefore constructed in order to ascertain which variables were predictive for women and men with regard to the study outcome(s).

INTERNET-BASED FOCUS GROUP MATERIAL AND METHODS

To facilitate in-depth investigation on HPV prevention engagement among young adults using focus-group methodology, a web-based platform was developed in collaboration with an internet consultancy company. This platform allowed participants from geographically dispersed areas to attend the same discussion from any computer with internet connection. Study participants were able to use their first name or a pseudonym in the chat room discussions. Discussions ranged from one to two hours.

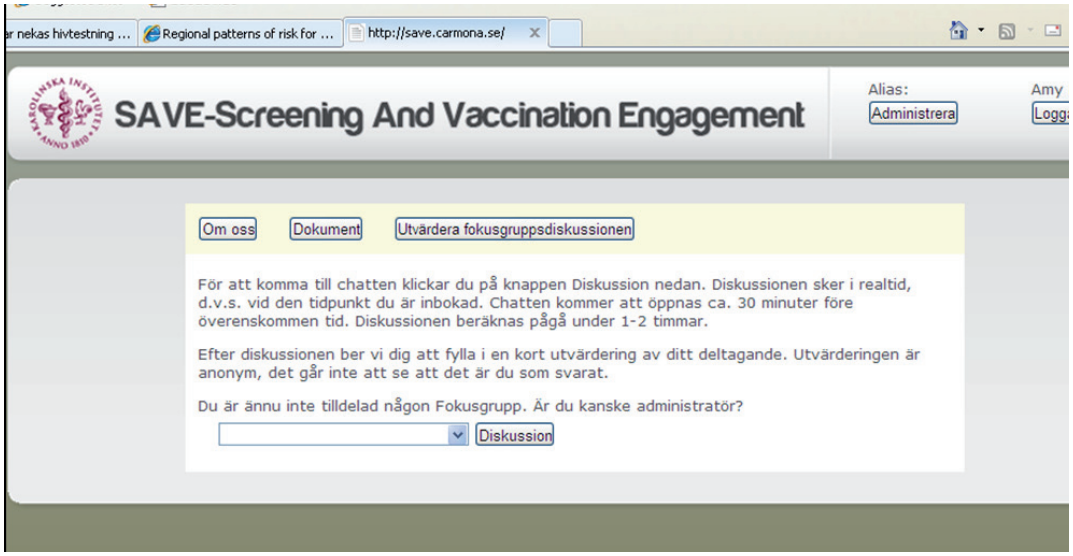

Figure 9. *Web-based platform for qualitative investigation*

Focus group methodology was adapted to explore how women reasoned about risk and prevention, using internet-based discussions (IBD). Four pilot IBDs were first carried out with members of *Kärleksakuten* (the Love Emergency Room), an STI and contraception awareness group working with youth in Sweden. Piloting with this group enabled AL to test and adjust an initial open topic discussion guide which was then continually updated

during the course of the study. The areas to be covered included HPV and cancer, STI risk, condoms, partner responsibility, HPV vaccinations and cervical cancer screening with pap smears. The discussion guide was not structured nor was necessary to use in its entirety in all subsequent IBDs as the aim was for respondent driven discussions on these topics.

Study participants were derived from the national population-based survey, "Attitudes toward HPV vaccination" used in Study I. Women responding to the survey who 1) reported sexual activity in the preceding 12 month period, 2) responded to survey questions on condom use with temporary partners, and 3) specified their perceived risk for contracting an STI, comprised the sampling frame for this study (35% of women survey respondents). As we strove for heterogeneity in our sample in relation to factors that might affect how women reason, recruitment was based on participants' survey responses concerning risk perceptions, risk taking, and prevention-seeking strategies. Women's responses to questions on self-defined as well as researcher-defined STI risk (based on number of reported sex partners during a one-year period and reported condom use with sex partners during this period), were charted into strata. A sum score was constructed where women with high research defined contraction risk had reported three or more sexual partners in the past 12 months and never or seldom condom use with these partners. Women with low contraction risk reported one temporary sexual partner in the past 12 months and reported always or almost always using condoms with this partner. Women with moderate research defined contraction risk had more than one sexual partner in the previous 12 month period and inconsistent condom use with temporary partners. As we wished to investigate risk and prevention reasoning amongst individuals who were at some risk for contracting an STI, we did not include women who reported celibacy in the preceding 12 months nor women who reported being in a steady relationship with no temporary partners in the preceding 12 months.

Table 1. Score matrix for research defined STI contraction risk. Individuals with a total of 2-3 points were defined as low risk, 4 points moderate risk and 5-6 points high risk.

A	Always/almost always condom use with temporary partner	1
	Often/sometimes condom use with temporary partner	2
	Seldom/never condom use with temporary partner	3
B	Greater than 2 sexual partners in past year	3
	2 sexual partners in past year	2
	Less than two sexual partners in past year (condition that one is defined as temporary)	1
	Total score for STI contraction risk	A + B

To achieve heterogeneity between strata while maintaining a degree of homogeneity within groups, the following matrix was used to define six strata with a total of 3106 women:

Table 2. IBD strata combining self-defined STI risk with measures of risk based on reported sexual behavior (number of partners and condom use with these partners during one year period).

Self-defined STI risk	**Research-defined STI contraction risk**		
	Low	Moderate	High
No to low self-defined STI risk	n=11 (N= 556) Strata 1	n=10 (N=1162) Strata 3	n=13 (N=646) Strata 5
Medium-high self-defined STI risk	n=7 (N=63) Strata 2	n=10 (N=197) Strata 4	n=14 (N=475) Strata 6

Random sampling per strata resulted in 260 study information letters being sent to women for whom there was a listed telephone number. One hundred-eighty four women were reached by telephone and invited to participate, 89 agreed to participate and 64 attended an IBD during the spring of 2010. Eighteen IBDs occurred in groups of 2-6 participants recruited from the same strata, while 12 were one-on-one discussions. One additional woman was interviewed by telephone due to limited computer access, with data from 65 participants underlying this analysis.

Few pre-constructed questions were used and discussions concentrated on sexual risk taking, protection and prevention in regard to STIs; follow-up questions were based on participant responses.

Focus group data analysis

An inductive analysis approach was used in this exploratory study. While interpretive description aided with study design and result interpretation, content analysis procedures were used for data analysis. IBD transcripts were automatically generated from the SAVE platform for content analysis.

Basic content-analysis procedures were used, with the computer program NVIVO 8.0 used to support data coding. Data collection continued until recurring response patterns were seen in the data, which were unchanged by analysis of more IBDs. The IBD transcripts were initially coded into smaller units based on similar substantive data-derived content, i.e. Condom Barriers, Discourse and Disclosure, Health System, Prevention Support and Risk Perceptions. Members of the research team read and discussed the coded data, comparing content both within and between IBDs. The researcher team then formulated categories and theme describing women's prevention seeking strategies.

Quotations presented were selected to typify the IBD discussions; these were translated by AL fluent in both Swedish and English and verified by other bilingual members of the team. Pseudonyms were used for confidentiality.
No differences in IBD content concerning this subject matter based on participant group size could be ascertained. This does not negate possible response differences based on group size, only that no differences were found in the areas examined for this study.

Descriptive statistical analysis and logistic regression was used to compare socio-demographic characteristics of study participants versus survey response participants using SAS 9.0.

STUDY II
MATERIAL AND METHODS

The entire population of men and women living in Sweden aged 10-44 between 2006 and 2010 were included in this study. The study population ranged from 4 167 770 individuals in 2006 to 4 190 658 in 2010. Genital wart episodes were identified using the Prescribed Drug Register (PDR) and the Patient Registers. Population data were obtained from Statistics Sweden on calendar year, age and sex and estimated as the mid-year population to incorporate fluctuations due to death, emigration, and immigration.

For the Patient Registers, International Classification of Disease (ICD)-10 diagnosis code A63 was used to locate cases of GW with both main and contributory discharge diagnoses allowed. For the PDR, prescriptions for topical pharmaceuticals podophyllotoxin and imiquimod were located with ATC codes D06BB04 and D06BB10, respectively.

Prescription trends for podophyllotoxin revealed a distinct age-specific shape that matched with imiquimod trends in the younger age groups. Therefore the study population was restricted to those less than 45 years of age. If an individual had a dispensation for podophyllotoxin or imiquimod within seven days of a diagnosis via the Patient Registers, the pharmaceutical information was used to define the episode, otherwise the sole register that picked up the episode was used. This allowed us to estimate the proportion of GW episodes not receiving prompt treatment via a prescribed pharmaceutical. Non-pharmacological treatment includes conservative therapy, laser, cryotherapy, with surgical excision options for persistent infections that do not respond to pharmacological treatment.

An individual was considered a case during the calendar year if they had either a relevant dispensation from the PDR or a diagnosis from the Patient Registers with no recorded GW episode in the preceding 6 months. Therefore, a 6-month wash-out period was used to remove potentially persistent cases from being counted multiple times. Episodes newly diagnosed and or treated were estimated in this analysis as a measure of annual incident proportions (not first-ever cases exclusively). Only one episode contribution was allowed per person per calendar year as the aim was to estimate the proportion of individuals seeking or receiving treatment for GW during that year. Individuals could contribute with episodes less than 12 months apart, if those episodes were in two different calendar years but more than 6 months apart. Due to aforementioned clinical and diagnostic limitations it was not possible to assess if some of these new episodes were recurring infections or infections with a new HPV-type.

Study II data analysis

SAS 9.2 was used for data analysis. The aim of the analysis was to estimate annual age-standardized incidence proportions for men and women from 2006 through 2010. These were calculated using Swedish mid-year populations as estimates of the underlying time at risk, and then multiplied by 100 000. To assess whether there were significant differences across calendar years, Poisson regression was used to model the incidence as a function of calendar year for ages 15-25, for men and women separately, using 2006 as the reference year. Time trends were also modeled for each age separately, using statistical interaction terms to compare changes in 2007, 2008, 2009 and 2010 with 2006. Seasonal incidence counts were plotted by quarter and month over the 60 month period of this analysis, per age group.

STUDY III
MATERIAL AND METHODS

This study was based on a nationwide open-cohort of all girls and women aged 10-44 living in Sweden between January 1, 2006 and December 31, 2010. To assess effectiveness against incident GW, all individuals with GW prior to individual follow-up (15 656) were excluded from the cohort. Individuals were censored at time of death (n=3405), or their 45th birthday. As it was not possible for us to obtain updated emigration status at the start of follow-up, all women having emigrated up until December 31, 2002 were left censored (n=152 896). Women who received the bivalent vaccine (n=1,384) were censored at vaccination. In total, 2 209 263 women were included in the study contributing 9 640 542 person years. The average follow-up time was 4.4 (SD ± 1.3) years.

Data were collected using the Swedish population registers. Data management was done in SAS version 9. 2. The Total Population Register was used to identify individuals for inclusion in the cohort. Data on vaccination exposure status with either the quadrivalent or bivalent vaccine were retrieved via the Prescribed Drug Register (PDR) and from SVEVAC. The PDR contains all drug prescriptions dispensed at pharmacies in Sweden since July 1, 2005. Data on GW case outcome status were obtained from the PDR and the Patient Registers (PR) in the same manner as with Study II. The Cause-of-Death Register was used to obtain information on deaths. Emigration status was derived from the Migration Register containing all immigration and emigration dates until 2002. As a proxy for socioeconomic status, parents' education levels were obtained from the Education Register and the parents themselves were identified from the Multigeneration Register.

GW cases were defined from first diagnosis of GW either via the PR and/or a GW treatment prescription identified by the PDR. Age-specific prescription trends for podophyllotoxin and imiquimod were identical in the younger age groups. Imiquimod trends differed in the older age groups, likely related to treatment of non-GW ailments, hence follow-up was excluded over age 44 as was case in Study II. History of GW prior to an individual's follow-up in study was defined via GW diagnosis in the PR and/or imiquimod or podophyllotoxin dispensation in the PDR.

Vaccination dates from SVEVAC were primarily used to define vaccination status but because coverage was incomplete, the PDR was also used to identify prescriptions for the quadrivalent and the bivalent vaccines using ATC codes J07BM01 and J07BM02, respectively. If a woman had more than three recorded dates for the qHPV-vaccine, it was assumed that the first three unique dates matched with the first, second and third doses of the vaccine. Nine-hundred-twenty-six women identified via the PDR had more dispensations on file than unique dispensation dates. It was assumed that women with two unique dates and more than three dispensation dates received their first and second dose or their second and third dose at the same date. Women with only one unique date (N=21) listed more than two times were considered to have all three doses on the same date. Vaccination status was assessed as a time-varying exposure with full effectiveness of the vaccine assumed after three doses. Using vaccination status as a time-varying

exposure allowed for the same woman to contribute person-time to all or some of the dose categories (0, 1, 2, 3) depending on whether the woman received all or any vaccine doses during individual follow-up. Age at first-vaccination defined age-at-vaccination. If a woman were to have a case of GW during follow-up and prior to her vaccination, she would be censored at time of GW and only contribute person-time in the unvaccinated group.

Study III data analysis

Statistical analyses were done with Stata version 11.Logistic regression with outcome vaccination status and exposure parental education level was performed to assess if and how socioeconomic status was related to vaccination likelihood SES was also assessed as an independent risk-factor for the outcome GW in a logistic model, adjusting for age. Those with missing SES were retained in a missing category in the analysis. Highest education level of either parent defines variable; if one of them was missing, it was assumed that the one with non-missing education had the highest level.

Kaplan-Meier curves were first constructed to assess proportional hazards. Incidence rates (IR) were calculated from the number of cases per accrued person-time for unvaccinated, partially vaccinated and fully vaccinated women. To study the effect of vaccination on the incidence of GW, incidence rate ratios (IRR) were calculated as the ratio of the incidence rate (IR) in fully vaccinated women divided by the IR in partially and unvaccinated women. As person-time for the unvaccinated women contributed to 97.5% of total person-time it was decided to include the partially vaccinated in the reference group as excluding them did not alter results and would only serve to diminish the cohort. Poisson regression analyses were used to estimate IRRs and 95% confidence intervals (CI) adjusted for attained age (time-scale), age-at-vaccination and SES.

Because younger women were more likely to be vaccinated than older women, individuals were stratified into six different age groups (age 10-13, 14-16, 17-19, 20-22, 23-26, and 27-44) splitting person-time based on attained-age and those who received the vaccine were categorized based on their age-at-first-vaccination. IRR and 95% confidence intervals (CI) were obtained in Poisson regression models adjusting for attained age. Vaccine effectiveness was calculated as (1-IRR)*100%, with corresponding 95% CI.

To assess vaccination self-selection bias, IRs before vaccination availability in Sweden were compared with IRs at the end of follow-up amongst those unvaccinated using Poisson regression stratified by age with the youngest age group as reference.

Population-impact was assessed by calculating GW case vaccine-attributable reduction. Age-stratified incidence rate differences (IRD) were calculated comparing fully-vaccinated and not fully-vaccinated and multiplied by 100,000 to display the number of avoided cases per 100,000 person-years. Age-stratified IRDs were multiplied by person-time amongst the fully-vaccinated under age 20 to calculate the actual reduction in the cohort and divided by mean follow-up time to obtain annual reduction estimates.

STUDY IV
MATERIAL AND METHODS

Girls and women between the ages of 10-24 were followed up between January 1, 2006 and December 31, 2010. Follow-up was individual and based on age. Girls entered the open cohort on their 10th birthday or January 1, 2006, whichever came last. They were followed until their 25th birthdays or December 31, 2010, whichever came first.

To assess dose effectiveness against incident, as opposed to prevalent GW, all individuals with a GW prior to individual follow-up (N=6 792) were excluded from the cohort. Individuals were censored at time of death (N=714). As it was not possible for us to obtain updated emigration status at the start of follow-up, all women having emigrated up until December 31, 2002 were excluded (N=35 953) as their history and follow-up could not be ascertained to the same degree. Women who received the bivalent vaccine (n=1 282) were censored at vaccination. In total, 1 045 093 women were included in the study. The average follow-up time was 3.8 (SD ± 1.6) years.

Data were collected via the population registers in a manner similar to Study III. Data management was done with SAS statistical software version 9.2 (SAS Institute Inc., SAS®). As the database coverage was higher in the PDR than SVEVAC for this age-cohort and as we established that the PDR dispensation dates were an accurate proxy for injection dates, the PDR was solely used to obtain information on vaccination status in this analysis. Vaccination dates for the quadrivalent and the bivalent vaccines were identified in the PDR via ATC codes. If a woman had more than three recorded dates for the qHPV-vaccine, it was assumed that the first three unique dates matched with the first, second and third doses of the vaccine. 1654 women identified via the PDR had more dispensations on file than unique dispensation dates. It was assumed that women with two unique dates and more than three dispensation dates received their first and second dose or their second and third dose at the same date. Women with only one unique date (N=27) listed more than two times were considered to have all three doses on the same date. Unique vaccination dose dates were found for 98.6% of individuals.

Study IV data analysis

Statistical analyses were done with Stata version 11 (StataCorp). Vaccination dose status was used as a time-dependent exposure which allowed for the same woman to contribute person-time to multiple dose categories (0, 1, 2, 3) depending on whether she received none, some or all vaccine doses during individual follow-up . If a woman were to have a case of GW during follow-up and prior to her vaccination, she would only contribute person-time in the unvaccinated group. Those who received the vaccine were categorized based on their age-at-first-vaccination, creating two groups, one vaccinated between 10-16 and the other 17-19. Women who were first vaccinated over the age of 19 were censored at time of vaccination. Dose effectiveness was measured in girls first vaccinated under age 20 compared to the unvaccinated population at the same attained age in order to restrict the population to those who were more likely to have limited HPV-exposure at the age when they were first vaccinated. Attained-age is a term used here to denote individuals' ages during follow-up (time-dependent). Poisson regression was used to estimate incidence rate ratios (IRR) and 95% confidence intervals (CI) of GW by vaccine

dose, adjusting for SES and attained age based on five different attained-age groups (10-13, 14-16, 17-19, 20-21 and 22+), among unvaccinated women and women first vaccinated before age 20 stratified by age-at-first-vaccination. Dose effectiveness was parameterized with the unvaccinated participants as reference group. Using this time-dependent exposure design, the same individual can contribute person time to all dose-level categories (if they complete vaccination and do not contract GW before all three vaccinations are completed). Vaccine dose effectiveness was calculated as (1-IRR)*100%, with corresponding 95% CI. Comparisons between different levels of vaccination (one vs. two doses, two vs. three doses etc.) and age-at-vaccination were based on the corresponding linear contrasts between the base parameters.

To assess for vaccination self-selection bias in the population cohort under study, two-dose effectiveness was recalculated for those who stopped vaccination at two doses, adjusted for age to assess whether these individuals were more likely to get GW at this dose level than those who completed all three doses.

To investigate factors related to three-dose completion, a cohort of individuals who had completed all three doses in the vaccine schedule during the follow-up versus individuals who did not complete vaccination during follow-up and instead stopped at either one or two doses were examined separately. Date of entry into this cohort was date of first vaccination; date of exit was end of study follow-up (December 31, 2010) or third vaccination-dose, whichever came first. Females included in this cohort were vaccinated between 10 and 19 years of age (n=79 441) with no previous history of condyloma and at least six months of available follow-up. Analyses with outcome three- dose vaccination completion were conducted. Vaccine dose was assessed as a time-dependent outcome and GW during follow-up was assessed as a time-varying exposure using multivariable Poisson regression, adjusting for age-at-vaccination and SES.

Population impact was assessed by calculating GW case vaccine-attributable reduction per dose level. Incidence rate differences (IRD) were calculated comparing those vaccinated at ages 10-16 or 17-19 with unvaccinated in the same age group for three vs. zero, two vs. zero and one vs. zero doses and multiplied by 100 000 to display the number of avoided cases per 100 000 person years.

Main findings

The findings on infection risk assessment and prevention strategy evaluation in the era of HPV-vaccines are taken from Studies I-IV and include some data not presented in the papers themselves but which might enhance understanding of the thesis aims. Preliminary results from internet-based focus group discussions with women are also presented here. The findings are presented under two main themes: assessing infection risk and evaluating strategies for prevention.

SUMMARY OF FINDINGS

Overall, quadrivalent HPV-vaccination was highly effective against GW, the first HPV disease endpoint possible to measure. However, effectiveness was contingent upon young age at first vaccination, with effectiveness declining steadily the older the age-at-first vaccination. Low to immeasurable effectiveness was found in women first vaccinated over age 20, with suggestive evidence that vaccinations tended to reach women at high GW risk in this age-group. There were marked socioeconomic disparities in the opportunistic vaccination strategy evaluated, with women and girls who have parents with the highest education level compared to the lowest having a 15 times greater likelihood to be vaccinated. Once vaccination was initiated, low parental education level was unrelated to vaccination completion, however. Maximum protection against GW was found among girls vaccinated under the age of 17 who had received all three doses of the vaccine. However, vaccinating older girls with more than one dose will result in considerable disease reduction as the burden of GW increases with age from the late teens until approximately age 20. No differences in effectiveness were found for girls who received two-doses between ages 10 and16 with that of girls who received three-doses between ages 17 and 19 (p-value 0.631). GW affects more men than women in Sweden as of 2010 with 453 per 100 000 men and 365 per 100 000 women treated. A decline between 25-30% was seen between 2006 and 2010 amongst women the age groups with the highest vaccination coverage. No decline was found among men and their GW incidence has steadily increased between 2006 and 2010. Reported condom use in high risk situations was low among both men and women, with 41% of men and 34% of women reporting always/almost always condom use with temporary partners. STI risk perception was also low, with approximately 10% of sexually active respondents considering themselves at large risk of contracting an STI. There was no association between men's condom use and their STI risk perception but there was an association for women. Women discuss preventing transmission of STIs via partner selection, selective condom use and periodic STI testing. Women describe deferring to men to have condoms in first intercourse situations so as not to jeopardize the potential for a longer-term relationship, as a woman's condom preparedness reveals that sex might be premeditated and suggests a level of sexual experience which women did not feel comfortable expressing to new partners. Women found conceptualizing a sex and cancer connection difficult. Due to HPV's skin-

to-skin transmission, women expressed preventing HPV contraction via sexual behavior changes seemed impossible and outside their control.

ASSESSING INFECTION RISKS

When assessing infection risk, this thesis examines HPV disease burden via GW incidence estimations. Factors associated with excess risk for contracting STIs, including HPV, were also identified. Risk perceptions were of central interest and are presented here, as are results on navigating competing risks.

Disease burden and excess infection risk

Age-stratified incidence proportions of GW were highest for 20-year old women (956 per 100 000 or 1% of women in that age group) while men peaked slightly later at age 24 (1137 per 100 000). In the same year, 2010, incidence declined to 139/100 000 for women aged 44 and 158/100 000 for men aged 44. Crude incidence was marginally higher among men than women during 2006-2007 and appeared to later diverge. Figure 10 shows that among men overall incidence appeared to increase while incidence in women declined between 2008-2010.

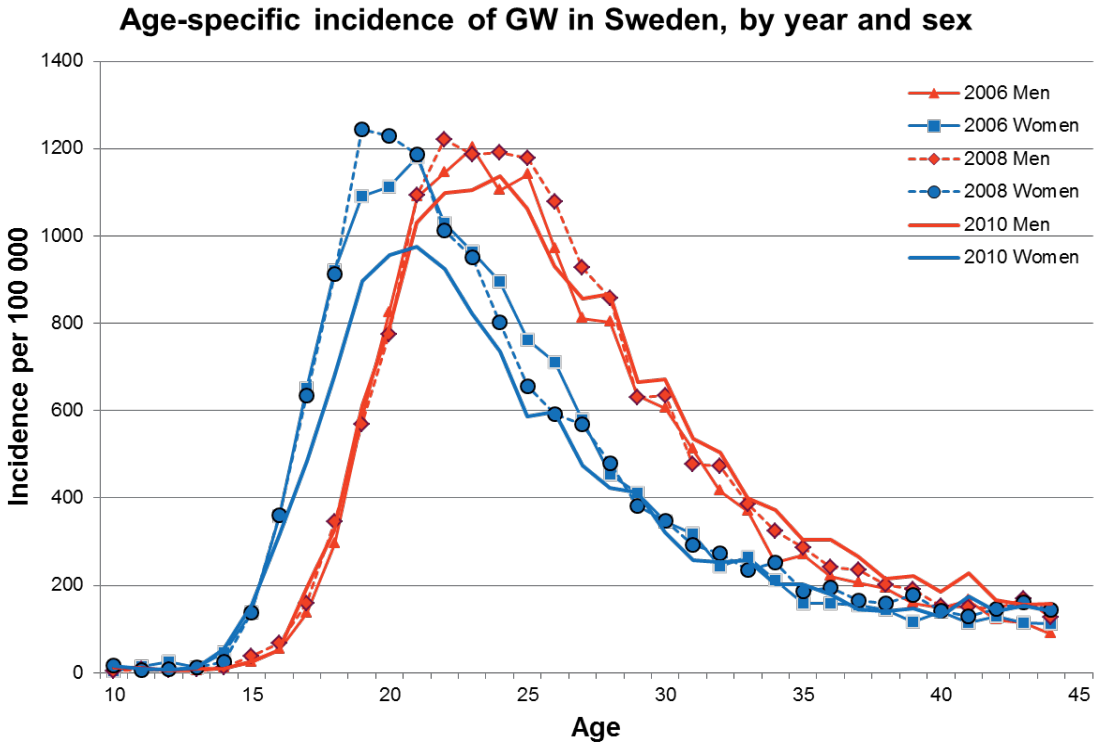

Figure 10. *Age specific incidence proportions per sex and year*

Results from Study III showed that women whose parents had the highest education level compared to the lowest had an increased risk for GW, or seeking treatment for GW which is what was possible to effectively measure (OR 1.33 95% CI 1.28; 1.39) (Table 1). When examining age-stratified rates, a slight protective effect of high parental education status on GW outcome was seen among girls and teenagers but a substantial excess risk was seen among women in their early 20s whose parents had highest education levels.

Table 3. Incidence rate ratio (IRR) from Poisson regression modeling effect of parental education level on outcome GW, adjusting for age. Highest level of attained education defines education level.

	IRR, (95% CI)
Education level of mother	
Missing	0.59 (0.55-0.63)
Less than high school	Ref
High school	1.18 (1.14;1.21)
University studies	1.25 (1.20; 1.29)
Education level of father	
Missing	0.68 (0.65-0.72)
Less than high school	Ref
High school	1.09 (1.06;1.12)
University studies	1.13 (1.10;1.17)
Education level of parents*	
Missing	0.61 (0.56-0.66)
Less than high school	Ref
High school	1.25 (1.20;1.30)
University studies	1.34 (1.28;1.39)

Results from Study III also showed that women with a higher risk for GW were seeking vaccination. This self-selection bias was not seen in younger women.
To assess whether there was a self-selection bias amongst those vaccinated, rates of GW before commercial availability of qHPV were compared with rates in the unvaccinated population at the end-of-follow-up. No significant differences were found in the population with highest vaccine coverage (ages 14-19) (IRR 1.00; 95% CI .98-1.02). Among women over age 20, the GW rates declined in the unvaccinated population compared to the total population before vaccination (IRR 0.96; CI 0.95-0.97) suggesting a self-selection bias with individuals at a higher risk for GW being more likely to seek vaccination.

Regarding excess infection risk, results from Study I indicate that women who report young sexual debut ages were more likely to report seldom or never using condoms with temporary partners later in life (OR 1.95; 95% CI 1.46-2.60). Also at increased risk for reporting seldom or never condom use with temporary partners are women with low education level (OR 1.87; 95% CI 1.30-2.71) and women who come from families who have at some point received social welfare (OR 1.59; 95% CI 1.02-2.46). Women with Swedish born mothers compared to mother's born outside the Nordic region also appear to be at an increased infection risk as they were almost twice as likely to report seldom or never condom use with temporary partners.

Interestingly, preliminary results from the internet-based focus groups indicate that contraction of one infection may potentially reduce risk of subsequent infections in some individuals as there were multiple reports of engaging in safer sex practices due to a previous STI diagnosis. Women diagnosed with viral STIs attributed the diagnoses to an increase in subsequent health seeking behaviors, as the following quote elucidates:

***Anya**: ….I've had cell changes. Before I never thought about the risks…Now I stick it [condom] in front of the guy's nose…(I get) comments like 'Do we have to?' 'Yesssssss' is my answer.*

Infection risk perceptions

Infection risk perception was generally low for young sexually active men and women. Study I showed that over 80% of young, sexually active men and women perceived themselves to be at no or small risk for contracting an STI (83.4% vs. 82.7% respectively). Correlates to STI risk perception differed between men and women even though the prevalence did not. The most notable finding is that men's STI risk perception was not associated with their use of condoms with temporary sexual partners, while women's was strongly correlated. Women who reported seldom or never condom use were three times as likely to perceive themselves to be at high STI risk compared to women who reported always or almost always using condoms with temporary partners (OR 3.1; 95% CI 2.41-4.03).

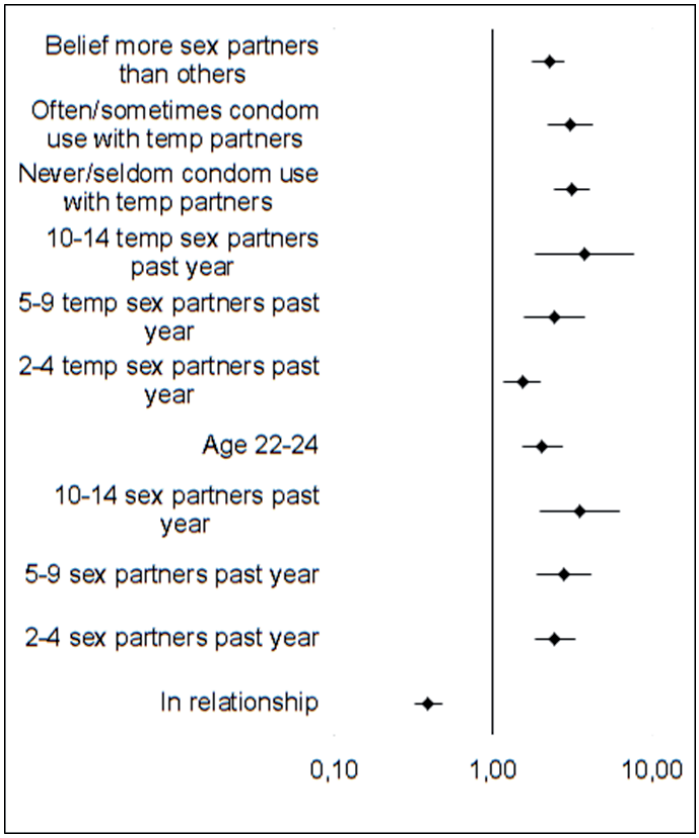

***Figure 11.** Forrest plot of factors significantly associated with women having high STI risk perceptions.*

Many of these factors differ from factors which were significantly correlated for men, shown in the following figure (note only significant correlates are shown in plots, many other factors were examined but no statistically significant correlates were found).

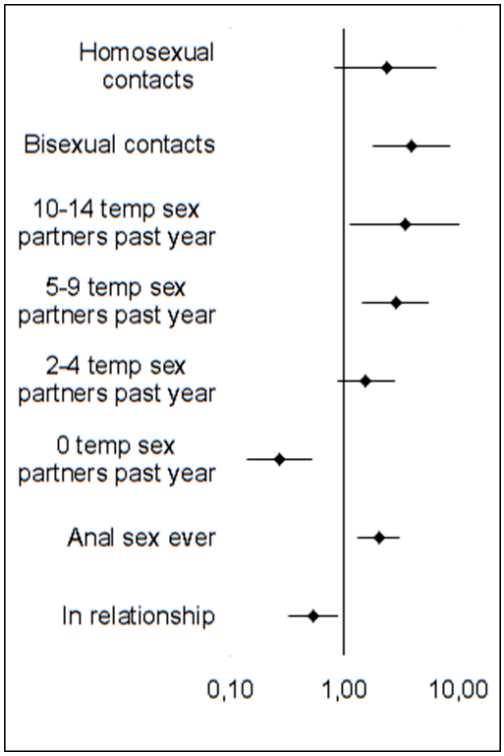

Figure 12. *Forrest plot of factors significantly associated with men having high STI risk perceptions.*

Results from the Attitude survey used in Study I indicate that both men and women are more apt to believe that HPV only infects women. Of those who answered the questions on HPV contraction, 83% believed women could be infected with HPV with 15% reporting they did not know, while only 67% believed that men could be infected with HPV and 26% reported not knowing. 79% believed HPV was sexually transmitted while 17% report not knowing whether it is sexually transmitted or not (with a higher percentage of men than women reporting not knowing).

The following IBD quote also reveals women perceiving a general lack of awareness among men that they can be infected with HPV:

> ***Kate:*** *it seems like the guys don't know they can carry it (HPV)*
> ***Lisa****: I think so too, they don't know*
> ***Anne*****:** *exactly, as if the woman is the only piece in the puzzle*

Navigating HPV risks

Due to HPVs skin-to-skin transmission, women describe preventing HPV contraction via sexual behavior changes as impossible and outside their control. Women found conceptualizing a sex and cancer connection difficult. The relative newness of the awareness that sex and cancer are potentially related is typified in Aili's quote below:

> ***Aili****: before I got vaccinated I didn't know you could get cancer from sex…it was something totally new for me…feels a little like everything in the world is dangerous now…soon there's no point in going outside :P*

She later rationalizes that HPV risk is too overwhelming to seriously consider in sexual encounters:

> ***Aili**: of course you can change your sexual behavior if it will prevent it* [HPV] *but that's not exactly what you're thinking about in those situations…if that were the case you'd have to basically worry about everything*

In response to probing, participants reported that the sexually transmitted nature of HPV was frightening but beyond their control, with the threat of HPV related-cancers too distant in the future to warrant present concern. In contrast to Anya who had been diagnosed with dysplasia, Rebecca reasons about the potential oncogenic effects of HPV as follows: *"you can't take gigantic precautions to protect yourself from something that maybe can develop into cancer"*.

When asked if HPV testing would influence them in any way, most women responded that they would not change their sexual behavior if they discovered they were HPV positive. They motivated this by arguing that it seemed hopeless to protect themselves from HPV transmission, commenting that it would be impossible to "*live in a little box*" (Anya) or "*cover yourself in plastic wrap*" (Melissa).

When managing multiple risks, such as infection exposure, loss of potential relationship and/or tarnished reputation, avoiding infection exposure was not always prioritized. This point will be further elucidated when results on condom use in high risk situations are presented.

EVALUATING STRATEGIES FOR PREVENTION

Prevention strategies under investigation include opportunistic HPV vaccination, complete vaccination with the qHPV vaccine among girls and women, effectiveness of the qHPV vaccine at various dose levels, reported condom use with temporary partners among men and women, as well as women's own reported strategies for avoiding STI risks.

qHPV-vaccination

Among the 2 209 263 women aged 10-44 followed in the study, over 5% received at least one dose of the qHPV-vaccine. Of all vaccinated women 78% were fully vaccinated. Highest vaccination coverage was seen in women 17-19 (33%) and 14-16 (26%).

Effectiveness was 75% (95% CI 79-72) among those receiving three doses of the vaccine who had received their first dose before age 20. Effectiveness was highest in girls who were vaccinated before age 14 (93%; 95% CI 72-98). Effectiveness was 79% (95% CI 74-83) for those vaccinated between 14 and 16 years old, 70% (95% CI 64-75) for 17-19 years old, and 45% for women vaccinated between 20-22 (95% CI 18-63). No effectiveness was measureable in fully-vaccinated women who received their first dose over the age of 22.

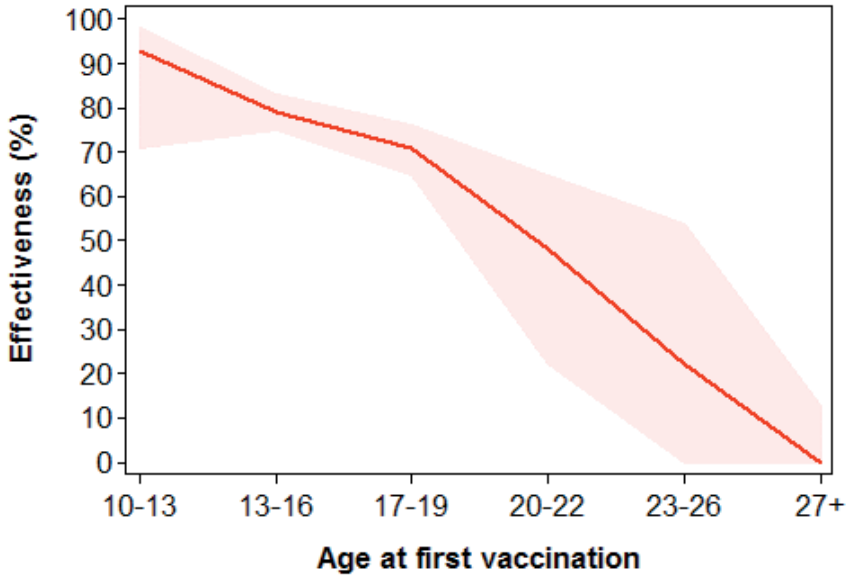

Figure 13. *qHPV-vaccine effectiveness based on incidence of GW by age-at-first vaccination*

Table 4. Incidence rate ratios (IRR) and effectiveness rates comparing fully vaccinated women, with partially and unvaccinated women combined, calculated using Poisson modeling. Stratified by age-at-vaccination and adjusted for attained age and SES. Number of GW cases amongst fully vaccinated women also presented. Absolute incidence rates (IR) among vaccinated and unvaccinated per 100 000 person years shown, along with the incidence rate difference (IRD) and corresponding 95% CI, which translates as the number of estimated reduced cases per 100 000 persons, shown by age strata.

	IRR, (95%CI)	Effectiveness, % (95%CI)	N*	IR vaccinated	IR unvaccinated	Estimated reduced cases (95%CI)
Age at vaccination						
All ages (10-44)	0.27 (0.23;0.30)	73 (70;77)	259	175.92	346.75	170 (152;187)
Under age 20	0.24 (0.21;0.27)	76 (73;79)	217	157.03	539.01	382 (367;394)
10-13	0.07 (0.02;0.29)	93 (71;98)	2	11.97	252.67	240 (211;243)
14-16	0.21 (0.17;0.25)	79 (75;83)	105	126.41	678.35	551 (536;563)
17-19	0.29 (0.24;0.35)	71 (65;76)	110	286.34	935.22	648 (603;685)
20-22	0.52 (0.35;0.78)	48 (22;65)	24	475.15	793.66	318 (97;463)
23-26	0.78 (0.46;1.32)	22 (<0;54)	14	452.45	483.56	31 (0;207)
27+	2.32 (0.87;6.18)	<0 (<0;13)	4	450.44	181.19	0 (0;8)

*n=number of fully vaccinated women with GW

In the previous table, estimated reduced cases was highest for those age 17-19 (648 per 100 000). Total GW case reduction from qHPV-vaccination among women below 20 is estimated as 746 during entire follow-up or approximately 170 cases per year. The total population impact of three-dose vaccination in the cohort of 10-19 year olds vaccinated was a reduction in 516 cases of GW, the population impact for two-doses was a reduction in 249 GW cases and for one dose 104 cases.

However, the partially subsidized on-demand vaccination strategy evaluated in this study showed that having at least one parent with the highest education level compared to the lowest made one 15 times more likely to be vaccinated (OR 15.26 95% CI 14.50;16.07). Mothers' education level had a two-fold higher influence on vaccination status compared to fathers'. Once vaccination was initiated, however, high parental education level had no positive association with vaccine dose schedule completion. Looking only at the vaccinated cohort with at least 6 months of follow-up, those first vaccinated between ages 17 and 19 were less likely to receive all three doses versus girls first vaccinated between ages 10 and 16 (IRR 0.56; 95% CI 0.54-0.57). Contracting GW during follow-up was also associated with being less likely to complete vaccination (IRR 0.58; 95% CI 0.46-0.73).

Results from the ecological Study II show a substantial decline in GW incidence among young women ages 15-25 during the period 2006 through 2010 (test for trend p-value <0.0001). No significant trends over time were observed among men (p=0.71). When analyzing age-specific trends, women ages 17 and 18 years had over a 25% decline in GW rates when comparing 2006 with 2010 (p-value <0.0001), with significant decreases through age 25. While no causal relationship could be established with this type of ecological data, the quadrivalent vaccination program is likely fueling these declines, as we could see in Studies III and IV.

For girls vaccinated between ages 10 and 16, maximum effectiveness was seen with three doses 80% (95% CI 75-83). There was a significant difference between three versus two doses in this younger age group (p-value 0.007), with three doses offering 36% more effectiveness (95% CI 12-54). For individuals vaccinated between ages 17-19, maximum effectiveness (70%, 95% CI 64-76) was also seen with three-doses, offering 26% (95% CI 0-46) more effectiveness than two doses (p-value 0.061), but with borderline significance. No differences in effectiveness were found for girls who received two-doses between ages 10 and 16 with that of individuals who received three-doses between ages 17 and 19 (p-value 0.631).

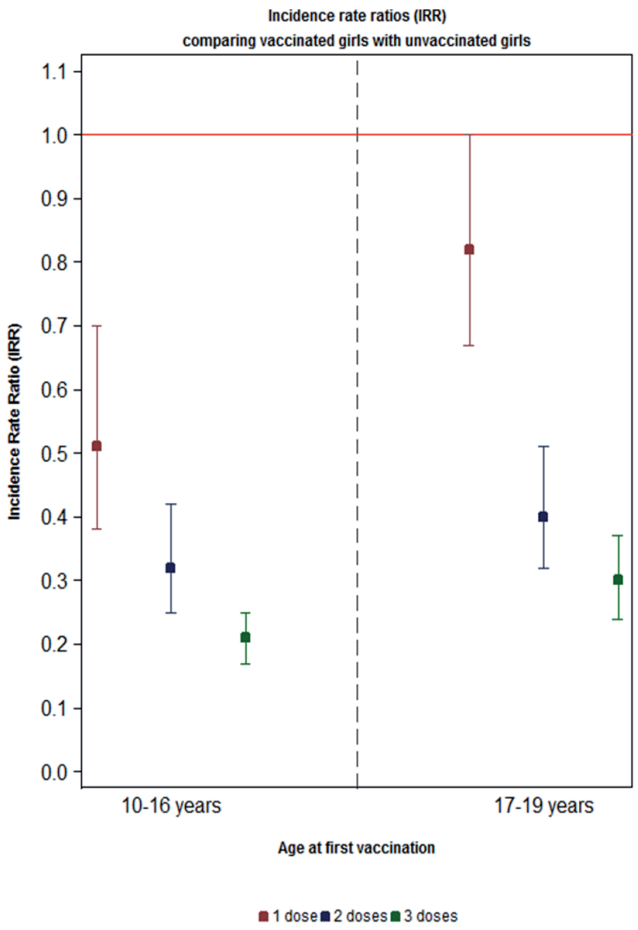

Figure 14. *Dose effectiveness with qHPV by age-at-first vaccination. IRR of GW comparing girls first vaccinated between 10-16 or 17-19 respectively, with unvaccinated girls adjusted for age and parental education.*

Condom use in high STI risk situations

Study I showed that among men, 41% reported always/almost always using condoms with temporary partners while only 34% of women reported the same. 50% of women reported never using condoms with temporary partners; the corresponding number among men was 40%.

There were not correlations between condom use and variables related to HPV-related cancer or GW awareness, knowledge or disease severity perceptions. Variables associated with condom use differed considerably between men and women. The following series of Forest plot figures illustrate these gender differences.

Women were approximately three times as likely to report perceiving a high risk of contracting an STI when they report often/sometimes and seldom/never using condoms compared to those women who report always/almost always using condoms with temporary partners. STI risk perception was not correlated to condom use with temporary partners for men. As mentioned in the previous section on infection risk, younger age at sexual debut was associated with non-condom use later in life for women but not for men. Also associated with non-condom use for women but not for men was coming from a family who had ever received social welfare benefits. Mother's birth country was a factor for condom use for women but not for men.

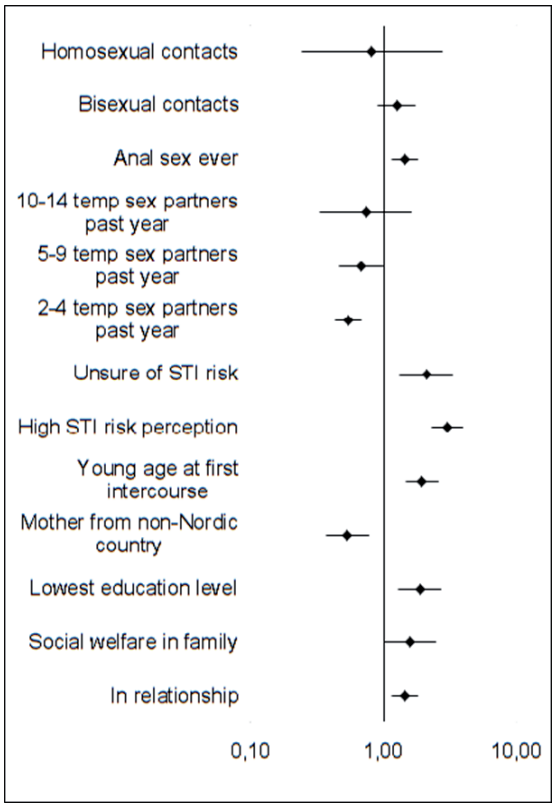

Figure 15. *Correlates to women's never use of condoms with temporary partners compared to always/almost always*

For both men and women, number of temporary partners during the past year was associated with increased odds of inconsistent condom use (often/sometimes vs. always/almost always use). Women were less likely than men to report seldom/never using condoms as their number of partners increased. Inconsistent and non-use of condoms were more commonly reported in both women and men with lower education levels.

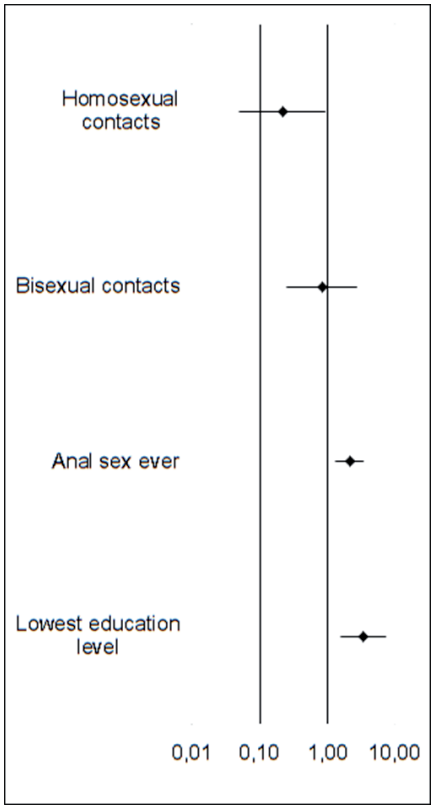

Figure 16. *Correlates to men's never use of condoms with temporary partners compared to always/almost always.*

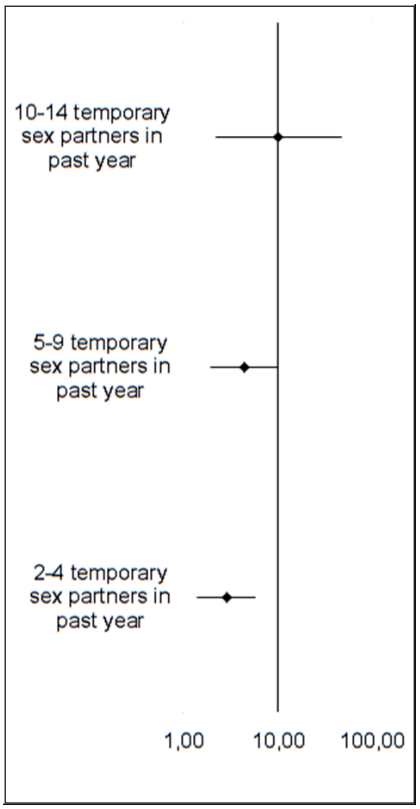

Figure 17. *Correlates to men's sometimes use of condoms with temporary partners compared to always/almost always.*

Women describe exposing themselves to substantial risk for STI contraction in situations where they perceive potential for new longer-term relationships. A primary barrier to using condoms with temporary partner was gender roles. In the internet-based chat discussions, premeditated sexual intentions were described as something that should not be revealed to a new partner. As a woman's preparedness with condoms would reveal that sex might be premeditated, thus suggesting a level of sexual experience, women described instead deferring to the man to have condoms. The participating women described sometimes broaching the subject of condom use immediately prior to penetration, although these women were clear in their preference that men raise the issue of condom use. The following statements from different discussion groups exemplify how women reason about their need to uphold an acceptable facade:

> ***Kathrine:*** *It* [having a condom] *can feel like you're a little too eager and intentional…I think it's so hard to show that I've intended the evening will end with sex. It's better if it just "happens".*

> ***Tara**: You have to act like you didn't know that you were on your way home to have sex until it's really obvious. And then it's supposed to be a little like a surprise, that you absolutely didn't plan for the night to end this way. If you then pull out a condom or ask the person if they've been tested it seems like maybe you're taking everything too seriously.*

The need for covertness appears to be a key element affecting condom use in encounters with 'love potential', or the potential for a continued longer-term relationship. Women describe being covert not only about their sexual desires, but also about their condom preparedness. The implication in the discussions with women is that if a woman is not covert, she risks not only missing this sexual contact and a potential love relationship, but also risks her reputation. Women describe this as one reason why discussions of condom use generally occur immediately prior to penetration. It seems they fear that several negative consequences may ensue if a woman brings up condom use earlier. First, sex will appear premeditated; this is not in line with the script women feel they should act out which involves no sexual intention prior to interaction with this particular man. A second potentially negative consequence is the risk of embarrassment and possible rejection a woman would face by being overt about condom use, before being certain that desire for sexual intercourse is mutual. This segment from one discussion illustrates this:

> ***Kim**: many think it's such a hassle with condoms. Alcohol is involved, no condoms at home, and you don't want to ask…you don't want to ask because you don't know what the answer will be. You maybe want sex and think "if I ask maybe he'll back away"(…) so it's embarrassing if you start talking about condoms right away, easier to just avoid it.*
> ***Kerry**: I agree. If you ask about condoms then it's so obvious that your intentions are to have intercourse, and you're not supposed have those intentions as a girl.*

Men who did address condom use were described as unusual, and this characteristic was said to indicate an 'exceptional man', as illustrated by excerpts from two IBDs:

> ***Anya**: I've met guys who I don't need to tell. They take the condom initiative themselves. Those guys are real men!*
> ***Amanda**: I had a partner who was clear from the beginning that we wouldn't have sex without protection [*condom*]. I thought it was so great and felt safe.*

> ***Astrid**: I like when a guy suggests it* [condom use]. *Feels pretty serious. I would never suggest it myself though.*

Women describe what can be conceptualized as 'symbolic distrust' related to condom use for other reasons than birth control. If condoms were not used at first sexual intercourse and the couple continued to have intercourse, it seems that a praxis was established; condoms were not described as used later in the same relationship, unless motivated by concern about pregnancy. From women's descriptions it appears that they reason that if the potential partner had an STI or thought s/he might be at risk for carrying one, that person would hopefully have informed them. This is particularly notable, given the strong role that covertness played in women's own descriptions of decision-making.

Women's strategies for preventing transmission

One of the aims with the IBDs was to assess how women conceive of HPV and other STI related risks as well as gain understanding of what they do to protect themselves from STIs. Preliminary results show that women describe managing STI risk via partner selection, selective condom use and STI testing. HPV testing specifically and HPV vaccinations were notably outside the scripts for risk navigation narrated by IBD participants. Women discussed HPV only when asked directly by the researchers and did not broach the topic of HPV testing or vaccination spontaneously as they did with the aforementioned results on testing for other STIs, condoms and partner selection. As selective condom use has been presented in the previous section, a brief presentation of how women describe using partner selection and STI testing to prevent transmission will be presented here.

Partner selection

Women described avoiding STI exposure through selection of their sexual partners. They expressed relative confidence in their ability to ascertain whether a potential partner was at high risk for carrying an STI based on multiple cues. Women described conducting an initial partner assessment, influenced by a variety of factors including social cues, nationality of the potential partner, intuition and alcohol intoxication. Individuals who could be at high risk for carrying STIs were described as external to the women's social spheres.

Sexual intercourse was often described by women as one of the first steps in a dating process. In these women's descriptions, intercourse often appears to function as a means of screening for love potential in relationships, rather than as expected only after a relationship was established. The participating women often reasoned that if a man were likely to have an STI, they would have some indication through their intuition or via social cues such as reputation or background; however it is interesting that alcohol and other inebriated states affecting judgment were consistently described as the norm in initial sexual encounters.

> ***Tess:*** *i don't know. It* [condoms] *ruins the moment like, and it's better without. Though I usually only have sex with people I know. Otherwise I would maybe be more careful, I don't know*
> ***Helena:*** *exactly, if someone is known to be a "player" then you're more careful.*
> ***Jennifer:*** *Exactly!*
> ***Carol:*** *I think so too*
> ***Sandra:*** *yes*

Women often appeared to associate the familiar, i.e. Swedish men, with being safer and less risky than the less familiar, in this case non-Swedish men:

> ***Elisabeth****: With the risk of seeming racist, I can imagine that Africans and Eastern Europeans are high up on the list* [of those with high STI risk].
> ***Naomi****:* (…) *South Americans too apparently, I got tested a few weeks ago and they were mentioned as a group* [at STI risk] .

This is in line with the view of the woman in the following quote who perceives less risk for contracting an STI in Sweden than abroad.

> ***Andrea****: I don't know if I feel safer in Sweden. On the other hand there are certain countries where I would not have sex. I lived in Tanzania for a while and lived a celibate life there. Very prejudiced I know, it's just I didn't dare.*

Such risk perceptions were not always in line with the stories told by the participating women. The woman in the quote below reported having contracted genital warts in Sweden earlier in the IBD, yet here expressed feeling less at risk of contracting an STI in Sweden than abroad:

> ***Jill****: If you know the person I think you feel more secure, if you've had sex with the person before. I definitely feel safer in Sweden than abroad…Just the fact that a guy 'offers' to use a condom makes me feel safer, like a sign that he's responsible.*

A central theme that permeated scripts involving potential long-term partners with love potential (as opposed to 'sex buddies') was covertness, i.e. covert sexual premeditations, covert condom preparedness, covert STI history. The participating women generally described it as imperative that these initial covert issues eventually become overt if trust and a steady love relationship were to be established. Intricate timing was said to be involved in a transition from the covert to the overt, as women pointed out that discussions of condom use or STI history were not able to be broached too early without jeopardizing chances of a continued relationship. On the other hand, the participating women maintained that if the existence of current or past STIs remained covert for too long, this covertness would infringe on trust, described as imperative in love relationships. They expressed hope that a man would reveal his current STIs to them as soon as possible but did not expect him to at initial intercourse(s) as elucidated below:

> ***Mikaela****: if you're a couple then you have another [kind of] intimacy and openness. You can maybe even talk about it [STIs]*
> ***Amanda****: are we talking about temporary sex, or sex with your partner? I think that if you're in a relationship you should disclose an eventual STI but with temporary sex then no one wants to know (as long as you've been treated).*

Periodic STI testing

Women described being periodically tested for STIs to assure disease-free status. If intercourse without condom use occurred and the couple did not continue their contact, it was described as likely that the woman would seek STI testing. Women were however uncertain of what they were tested for, appearing to instead leave disease and testing specifics to health care professionals to determine. Chlamydia was an exception in that it was consistently mentioned in conjunction with testing and appears to be the primary STI in focus for these women, and according to them, this focus is shared by the health system. The central role testing plays in women's STI risk navigation could be facilitated by the trust they express in antibiotics to cure STIs, as described in the following quotes from two IBDs:

***Naomi**…Chlamydia is of course most common and I've heard a comment "you just have to take penicillin for 10 days" no problems…*

***Gabriella**…I think most people think about Chlamydia and you can of course cure that.*

Testing allowed for treatment if one was positive for Chlamydia, as the preceding quotes indicate. Women also described that testing results would provide them with the information necessary to avoid having unprotected sex during antibiotic treatment. If testing confirmed a woman to be disease-free, future sex without condoms would not seem overly risk-filled in terms of STIs. Being 'tested' (albeit potentially only for Chlamydia) and obtaining a 'disease-free' status thus seems to act to corroborate the effectiveness of women's previous partner selection strategies for STI avoidance. Participants in the IBDs indicated that they might broach the question 'have you been tested?' with partners, but did not report asking their partners what they had been tested for. The vagueness as reported below characterizes the women's descriptions of testing:

***Kristin**: I remember I asked my boyfriend if he had been tested for any diseases, and he said that he didn't have any, so then we just used birth control pills.*

It appears that testing took place under particular conditions—for example, if neither the man nor woman had been tested recently and had had sex with another partner without using a condom, testing might occur. Testing was described as functioning as a type of relationship rite of passage, from a temporary relationship into one more steady:

***Laura**: If you feel like you are a couple and aren't seeing other people then you hopefully go and get tested* [if you haven't done it before] *and then you maybe don't protect yourself with condoms anymore…*

Women wanting to be tested for HIV described difficulties in convincing health care professionals that this was justified—this may in part relate to the public financing model for health care, with no out-of-pocket costs for this. They reported experiencing a lack of health professional support as shown in this excerpt from one IBD:

***Elisabeth**: And you can't be sure they'll take one* [HIV test] *even if you ask for it!!!!!*
***Naomi**: They ask if you've been travelling, where and which nationalities you've had sex with but then you have to push the issue yourself if you want them to check in any case*
***Juliet**: They'll test you for what there's most risk for, not what you request*
***Naomi**: so the attitude to HIV is pretty lax within Sweden…*

Discussion

METHODOLOGICAL CONSIDERATIONS

"Science is an anti-narcissistic phenomenon. It assumes a profound human tendency to self-deception, employs the scientific method to counteract it, and holds truth higher than any personal desire."

M. Scott Peck, M.D.

Limitations with GW outcome

Studies II-IV in this thesis share one considerable limitation, they all use treatment-seeking behavior as a proxy for HPV-related disease, GW. A proportion of individuals with clinical symptoms will not seek treatment or will self-treat with prescriptions obtained from friends or via internet purchasing. Sub-clinical infections of GW are also missed. As such, these studies will underestimate the actual incidence of GW. Participants in clinical trials are followed rigorously and minor GW cases, perhaps unnoticed by the individuals, will be detected in these trial settings.

Furthermore it is not possible to use the available register data to track non-pharmacological treatment episodes from all private specialist physician settings; only a proportion of private specialist clinicians report into the PR. Any physician visits, including private physician visits and primary care visits, however, resulting in treatment via podophyllotoxin or imiquimod were captured via the PDR. Because these are the primary treatment methods we assume that we capture the vast majority of these visits. It is not possible to estimate proportions not assessed with any reasonable accuracy.

The primary indication for imiquimod is extragenital warts. However imiquimod is sometimes used in practice to treat other skin pathologies such as actinic keratosis, intraepithelial carcinoma, and small basal cell carcinoma. Some misclassification of episodes identified due to imiquimod dispensing is expected. This misclassification should be minimized given the age-restriction imposed after discussing with prescribing professionals and examining age-specific curves. Prescription trends for podophyllotoxin revealed a distinct age-specific shape that matched with imiquimod trends in the younger age groups. Therefore we restricted the study population of interest in Studies II and III to those less than 45 years of age.

For Study II, a six month wash-out period was chosen to distinguish new from persistent episodes. This time-period was based on the estimated incubation time of GW as well as treatment durations[51, 52, 101, 102]. By using this washout period it was possible to remove prevalent episodes from the previous year, which could be considered persistent infections under treatment. Sensitivity analyses were performed with a 12 month wash-out period and annual incidence proportions decreased by roughly 5% for women and 10% for men.

Censoring, right and left

In Studies III and IV many individuals will get GW after the end of study follow-up. This problem of right censoring is not unique to our study. Follow-up time in these studies was similar to that reported from the clinical trials (roughly 5 years). The problem that this right censoring presents is expected to be non-differential in terms of exposure.

As it was not possible for us to obtain updated emigration status at the start of follow-up, all women having emigrated up until December 31, 2002 were excluded from the study population (i.e. left censored) in the event that they had a GW event elsewhere that we could not detect from the available data (n=152 896 in Study III and n=35 953 in Study IV).

As the PDR contains data usable from July 2005 onwards, no data on prescription prior to this time could be obtained. This problem of left censoring will lead to an underestimation of the variable GW history, used in Studies III and IV. As GW incidence peaks at age 20, this misclassification of GW history is expected to be more problematic in the older cohort.

Right censoring of exposure status is present in Study IV. Many of the women in that study will go on to complete vaccination after end of study follow-up and we will not obtain this information nor use it to adjust current estimates. This censoring should be non-informative due to the study's time-dependent exposure design.

Misclassification and potential inaccuracy of exposure

Using two registers to obtain information on vaccine exposure in Study III allowed us to compare differences in coverage between these two registers. The PDR is an automated register for prescription dispensations to an individual whereas SVEVAC provides information on vaccination injection date. Girls under 18 were partially subsidized for the HPV vaccines during the time of the study follow-up, but to receive their subsidies they had to purchase the vaccines at a pharmacy. Otherwise, individuals could pay full out-of-pocket costs if they purchased the vaccines via the vaccination centers and were not reimbursed. All HPV vaccinations are supposed to be registered by the administering clinician in SVEVAC, including those vaccinations obtained outside the pharmacy system. SVEVAC should cover both prescription retrievals, but as registration is not automated and inclusion in the register subject to individual or parental approval, a proportion of cases will not be reported in SVEVAC. When comparing the PDR with SVEVAC, a large variation in SVEVAC coverage was found throughout the country. As SVEVAC is not automated as PDR, its coverage is substantially less. Through the end of 2010 for example, the PDR had approximately 20% more complete vaccination cases than SVEVAC across all age groups, with even higher completion compared to SVEVAC among younger women.

Study III was first carried out using only PDR data. As women vaccinated age 18 and over received no subsidies, it was not necessary for them to purchase via the pharmacy system though most did anyway. There was however some increased coverage in SVEVAC in women vaccinated over age 20 so it was decided d to complement this study with SVEVAC data in order to minimize misclassification of exposure among women vaccinated in their 20s, 30s and 40s.

There were many incomplete or nonexistent dates in SVEVAC in the younger age group compared to the PDR, and as such, PDR was exclusively used in the vaccine dose Study IV. There was also the problem of overlapping dates, or dates for partial vaccination that existed in one but not the other register. By using the PDR exclusively for the dose study we might have missed some vaccinated individuals doing this, thereby underestimating our effectiveness by misclassification of exposure, which would lead to more conservative vaccine effectiveness estimates.

By comparing these two vaccination data sources, it was possible to see that the prescription dispensation date found in the PDR was an accurate proxy for injection date. Comparing those individuals with both SVEVAC records and PDR dispensations showed that the PDR dispensation date was an accurate proxy measure for actual vaccination date as measured in SVEVAC as the PDR coincided within the same week for approximately 90% of vaccinations in SVEVAC.

This became particularly important in Study IV when assessing dose effectiveness as the time between doses one and two is relatively short (per schedule 2 months). Amongst those fully vaccinated during follow-up, there was an average time of 2.2 months (SD±1.2) between doses one and two and an average of 4.2 months (SD±1.6) between doses two and three. These dispensation intervals follow recommended dose scheduling (0, 2, then four months after the second dose at month 6).

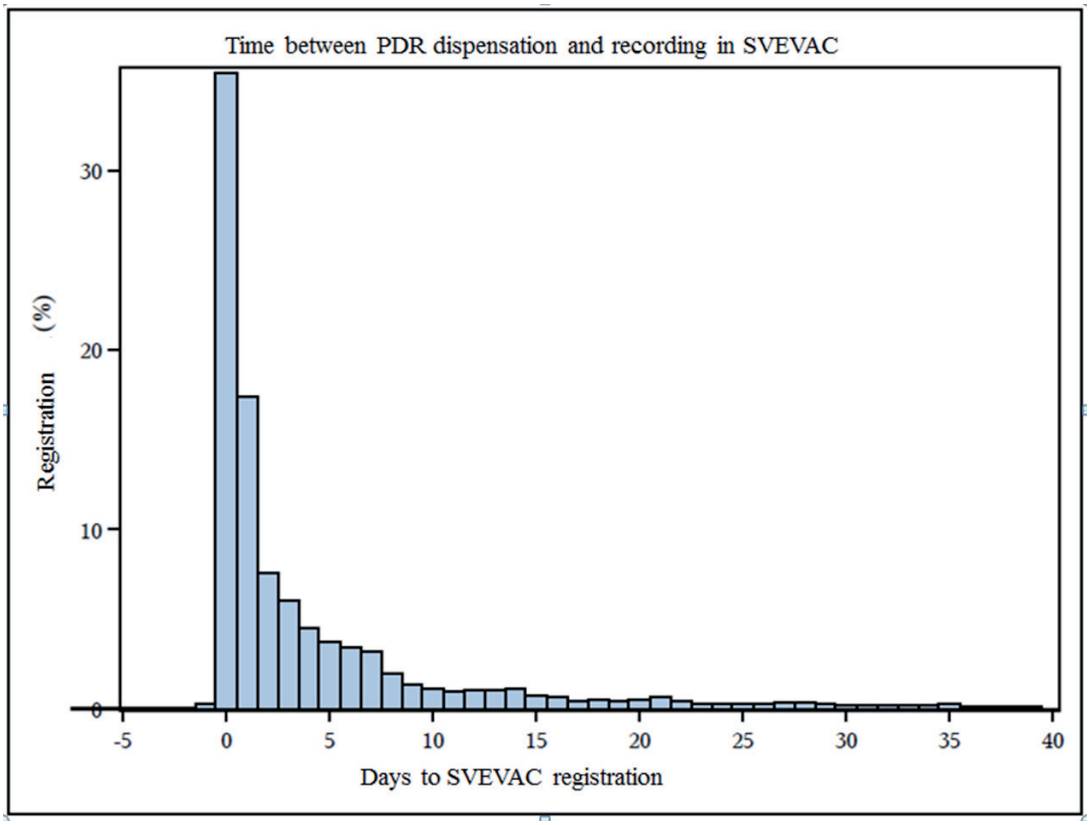

Figure 18. *Number of days from PDR dispensation to injection recording in SVEVAC.*

Selection biases

In the case of the vaccine effectiveness evaluations here, a key concern was vaccination self-selection bias. Were the women and girls getting vaccinated notably different from the general population in terms of HPV-related risk?

To assess for this the following steps were taken. First and foremost, the time-dependent exposure design of Studies III and IV allows individuals to contribute person time to multiple exposure categories thereby minimizing selection bias.

When comparing dose-level effectiveness for example, individuals move through exposure levels and follow-up ceases upon GW diagnosis, even if the individual were to go on and get another vaccine dose. This allows for assessment of two-dose effectiveness even among individuals who would eventually receive three doses. A concern voiced by Merck when they were informed we were going to proceed with a dose-level analysis was that it would be inappropriate to compare dose 'completers' with 'non-completers' as the very fact that an individual did not complete the vaccination schedule indicated a different baseline risk of HPV via behavioral mechanisms. The time-varying Poisson analysis used does not compare completers with non-completers; it compares person-time at each dose level. Many of the individuals who are not followed up after GW diagnosis between shots will go on to complete vaccination.

Second, all women with a known history of GW prior to individual follow-up were removed from the cohort. It was thought that some women sought vaccination in an attempt to treat persistent GW and we wished to exclude these individuals from the analysis as their underlying risk is much different. Thirdly, Poisson regression stratified by age was used to assess vaccination self-selection bias in the population cohort under study by comparing IRs before commercial vaccination availability in Sweden with IRs at the end of follow-up amongst those unvaccinated. No significant differences were found in the population with highest vaccine coverage (ages 14-19) (IRR 1.00; 95% CI 0.98-1.02). Among women over age 20, the GW rates declined over time in the unvaccinated population compared to the total population before vaccination (IRR 0.96; 95% CI 0.95-0.97) suggesting a self-selection bias in which individuals at a higher risk for GW being more likely to seek vaccination. This is one reason dose analysis in Study IV was restricted to those vaccinated under age 20.

In Study III we found that those vaccinated were much less likely to have parents with the lowest levels of education (proxy for SES), indicating a selection bias in exposure. When further examining how SES is related to HPV, it was found that individuals with higher parental SES were more likely to have the outcome GW. Whether this increased risk for GW reflects an actual increased risk or just an increased propensity for treatment once infected, is unknown. As a fourth precaution for self-selection bias, this variable was included in the multivariable Poisson model in Studies III and IV to adjust estimates for some of this bias.

In Study IV two dose effectiveness was recalculated for those who stopped vaccination at two doses, adjusted for age to assess whether these individuals were more likely to get GW at this dose level than those who completed all three doses. There was no significant

difference in GW incidence after two doses in girls vaccinated with two doses who eventually completed their dosing schedule compared to girls vaccinated with two doses who did not complete their dosing schedules (p-value 0.372).

The suggested self-selection bias among older women vaccinated found in Study III likely reveals that women who considered themselves at risk for contracting an STI were more likely to seek vaccination than women who did not consider themselves at risk. HPV-vaccines were on-demand only for women over 18 during our study follow-up and were not covered by pharmacological subsidies so women in these age groups have to pay full out-of-pocket costs themselves. If the entire population of women up to age 45 were offered HPV vaccination, it is possible to speculate that effectiveness would be marginally better than the zero effectiveness against GW we found in women vaccinated over the age of 22. However as qHPV is a prophylactic vaccine, and the prevalence of HPV is estimated at approximately 70% in the population, then the likelihood of being HPV-naïve in an age-group where the majority of women have had multiple sexual partners is small[103]. This study only measured effectiveness against GW, which are primarily caused by HPV-types 6 and 11. Women with exposure to types 6 and 11 but without previous exposure to HPV types 16 and 18 when vaccinated should achieve maximum vaccine protection against lesions caused by types 16 and 18.

SES, missing and otherwise

SES is examined as an exposure in Studies I, III and IV. In all three studies it appears to be a confounder for various outcomes therein. In Study I it was possible to obtain various aspects of SES from Sweden's LISA database including education, disposable income in family and individually, social welfare benefits received in the family, employment type, own and parental immigration status. When these various aspects were examined individually, education and social welfare benefits were most correlated to condom use (though social welfare benefits were only influential for women).

Sweden has a large middle class with little variation in terms of income levels compared to many countries with larger income discrepancies. Manual laborers in Sweden who have never attended university can easily earn just as much, if not more, than their university educated peers. As such, when measuring the influence of SES in Sweden, it may not be recommended to use variables that would be clear indicators in other countries, such as income. SES is clearly an important factor in health outcomes in Sweden even if income discrepancies are minimized [67, 68].

Education level is a good measure for SES in Sweden and is often used as such[67, 69]. There parental education level was used to define SES as many of the girls in Studies III and IV were too young to have obtained their highest level of education and because it was believed to provide some indication of health-seeking behaviors even in older women. The information for parental education level was retrieved from Sweden's Education Register. Individuals who attended Swedish schools will have the data automatically recorded in the register. Individuals who attended schools outside of Sweden will not have information recorded, unless they answered census data on this variable sent to households in 1960, 1970, 1980 and 1990. Due to the ages of the parents examined in Studies III and IV (most well under 70 given the ages of the children), the majority of

individuals with missing information on this education variable will likely be immigrants, or in the case of Studies III and IV, the children of immigrants. As such, the missing status in these two studies is informative. How exactly this would effect estimates however is unclear. These individuals, or their parents, likely belong to all education levels but the very fact that they were not born in Sweden provides another measure of health inequity. Rostila explains in his thesis on social-capital in Sweden that "social capital at individual level seems important in explaining health inequalities especially between groups based on country of birth in Sweden" (p. 7) [104].

Survey biases

Data collected via questionnaires have limitations. Reported behaviors or attitudes in surveys may not reflect real-life behaviors or attitudes of the survey respondent. It is assumed that respondents report 'the truth', or report with as much accuracy to their personal experiences as possible. In the case of our potentially provocative and socially embarrassing questions, this assumption may falter in the context of this survey. There is no way to assess this potential reporting bias.

Interestingly, the *Attitudes toward HPV vaccination* survey data from parents indicated that parents with the highest level of education were less likely to be willing to vaccinate their children against HPV. This attitude did not reflect real-life behavior that we found in Study III. This finding possibly reflects more problems with how attitudes translate into behavior than problems with survey accuracy. It also reflects the problematic nature of some survey questions in being reliable proxies for the intended outcome. It is also a possibility that this finding could reflect a lack of generalizability from the sampled survey respondents to the population at large.

External validity, or generalizability, refers to how well results apply to the target population. Low survey response rate could effect this validity measure. The survey used in this thesis had a population-based sampling frame, which enhances its generalizability in Sweden. With consideration given to the sensitive character of the questions and healthy young population targeted, the 50% participation rate in the survey can be seen as acceptable [78]. A demographic analysis of individuals who did not respond to the survey was carried out using demographic data from Sweden's LISA register. A multivariate analysis of demographic variables and likelihood of non-response showed that men, immigrants, those receiving social welfare, and those with lower education were less likely to respond to the questionnaire. Disposable income was not a predictor of non-response nor was age, living area or population density. There was no indication that only a specific demographic group responded, augmenting the study's generalizability to young Swedish adults.

Because the survey was based on a random selection of the population, this helps to alleviate some of the problem of selection bias, though not all as seen in the demographic analysis of non-responders. There is always the potential for a selection bias, in which those who chose not to participate deviated in regard to the outcome variables under investigation. The possibility of non-response bias in the sexual habits questions cannot be ruled out completely, although the distribution of sexual habits and number of survey respondents whom had not made their sexual debut appeared to be reasonable, reflecting

the relative heterogeneity expected in the population. Furthermore, both men and women proportionally indicated similar risk perception levels. The proportionality of condom use responses did differ based on gender, with men more apt to report consistent use. Therefore, the potential for non-response bias for that variable cannot be ruled out but there was a clear within gender response variation for condom use.

The survey question on STI risk perception might be considered vague, which brings up the issue of construct validity. Is asking participants to estimate their risk for contracting an STI an accurate measure of risk perception? This point could be debated. Asking participants to estimate their risk can provide an estimate of how individuals perceive of their infection likelihood but will provide no indication of how important not contracting an infection would be for them. If someone believes that his/her risk for contracting influenza is high but is not bothered by the thought of coming down with the flu, they may not take any meaningful measures not to contract influenza; this would mean something different in terms of prevention engagement compared to a person who responded that she/he had a high risk for contracting the flu and was greatly afraid of that actually happening. When assessing STI risk perception in the survey, I was under the assumption that most sexually active individuals would be afraid to contract an STI.

Another potential limitation to the survey regarding construct validity is that respondents self-define 'temporary' when asked about condom use with temporary partners in the past year. Respondents were also asked about steady partners, another construct in which it was necessary to rely on self-definition. The term 'one-night stand' in the English version of the survey was not used in the Swedish version as it was thought that Swedes would not recognize their behavior in this type of casual sex but would recognize their situations in terms of having 'temporary' sex partners.

Recall bias is a problem when collecting data retrospectively. To avoid this bias, questions regarding condom use were limited to only asking about sexual relationships in the past year.

Absolute risk

In Studies III and IV, absolute measures of risk were generated in addition to relative measures. From these absolute measures of incidence, we were able to calculate the difference in incidence rates between groups. This absolute calculation was important in our result interpretations for the following reason: despite the difference in magnitude of the relative incidence in terms of disease prevention, the greatest disease reduction was not found in the group with the largest vaccine effectiveness. The reason for this was that the underlying disease rates varied between the strata, with the group with the highest incidence showing the greatest reduction in disease after vaccination even though the vaccine was more effective when administered to those in a younger group, where the underlying disease risk was much lower. This type of information can be important in policy decisions regarding public health interventions.

Qualitative limitations

The preliminary results from the qualitative IBDs presented in this thesis were not designed to make statistical inferences. The study was designed to gain deeper insight

into STI risk perceptions including HPV, as well as gain deeper insight into barriers to prevention utilization. Considerations affecting result trustworthiness are often discussed in qualitative research[105]. Quotes are presented to elucidate result findings so the reader can follow the process of translating the IBD transcripts into findings and assess the accuracy of some of the findings. Validation is an internal process with qualitative research. Researchers met on numerous occasions to read interviews and discuss coding and results.

Researchers influence content of interview questions. How researchers respond (or not) to participants can influence participant response. It is not possible to know what would be revealed if different questions were posed to participants or how another level of openness to sexual unconventionality would influence the IBDs.

Theories applied

Even though KAP and HBM assumptions are supported in research and by public education policy on sexual health, they do not appear predictive of the reported practice of condom use in both sexes. This thesis reveals that efforts primarily aimed to increase STI awareness and/or perceptions of risk will not suffice in influencing this specific prevention behavior. Other recent studies have also tested KAP assumptions as predictive of health or risk avoidant behavior and found knowledge and attitudes uncorrelated with practice[106, 107]. A Swedish report by Herlitz revealed that knowledge and beliefs in condom use being protective against STIs increased between 1987 and 2007 but that those increases did not correlate to an increase in condom use during the same period[70]. Another central report on health in Sweden recently concluded however that the low awareness of HIV risk found amongst Swedish youth would lead to subsequent risk taking behaviors[71]. Risk awareness may not be predictive of prevention behavior for men in terms of condom use, as shown in this thesis, but there was a correlation for women's STI risk awareness and reported prevention practice. Study I closely examined gender differences in the KAP assumption, as well as other potential factors associated with the practice of condom use in high risk situations. A deeper understanding into the actual barriers individuals experience in engaging in prevention behavior, with subsequent strategizing to alleviate these barriers, is necessary in the sphere of public health epidemiology.

Script theory allowed for a more nuanced understanding of barriers to prevention engagement, as well as allowed for an understanding of the contradictions often voiced by participants regarding health promoting behaviors. Examining the IBD data through the lens of sexual scripting allowed for conceptualizing health barriers on multiple levels. As Simon and Gagnon note, "A scripting approach, at best, is not a terminal point but merely a beginning, a way of charting that must remain a complex and changing landscape of uses and meaning" (p. 496 [108]). Gender role barriers inhibit women from overtly expressing their sexual desires and protection needs. These gender barriers represent cultural and interpersonal levels of sexual scripting and are in conflict with women's intrapsychic script. This conflict is evident in the women's contradictory descriptions of believing in shared responsibility for STI protection and not wanting to be ashamed about their sexual desires or safety needs but describing personal situations in which they were themselves covert and in which men were allocated responsibility for condom preparedness and broaching discussions on use. Also, collective or cultural barriers

regarding professional unwillingness to test for HIV perpetuate a systemic dialogue of risk being primarily external.

These findings concerning the difficulties women express in promoting condom use and condom possession are particularly surprising when viewed from a cultural context where Scandinavia is associated with open attitudes towards, and legislation supporting, sexual expression [109]. Despite both efforts and resources, these preliminary results show a substantial negative effect of gender barriers in terms of women's sexual health.

DISCUSSION OF KEY FINDINGS

GW infection risk and STI risk perception in Sweden

The results on GW incidence presented in this thesis are the first published data on GW from registers capturing the entire population of a country. GW incidence estimates to date are not usually calculated on a national level and instead are restricted to various geographic regions within a country or to certain individuals, such as those visiting sexual health clinics or who are covered under an insurance scheme. A German study using an insurance claim register to locate new cases of GW via ICD-10 code A63 estimated crude incidences of 147 cases/100 000 for men and 191 cases/100 000 for women, although the ages of individuals in that study ranged from 10 to 79 years, making comparisons of crude estimations inaccurate [110]. Peak estimations from the German study were considerably lower than estimates reported in this thesis. Not all studies stratify on age and sex, making cross-study comparisons difficult. A report from 2008 in the United Kingdom showed peaks of GW cases, which included new and recurrent cases, among 20–24-year-olds at a similar level as those shown in this thesis[111]. GW estimates from the United States showed a slightly higher burden among men [112]. These U.S. estimates are based on more limited population data sources or on private insurance claims data and were lower than what was found in this thesis, with a range from 162 to 205 cases/100 000 annually.

The first population-based GW incidence proportions for males in Sweden are presented in this thesis. The ages during which peak incidence occur are similar to those reported in 1996 by Persson et al in the only other study in Sweden to-date on men's GW incidence. Persson et al's study comes from one STI clinic in one smaller town and reported a peak incidence of (12 cases/1000 for men aged 20–24 years)[3]. This thesis work also found similar peak trends among women as Persson and colleagues did, however overall rates among men were 30% lower than those among women in his study. This thesis did not find this sex-based discrepancy, instead crude GW incidence among men and women were similar before the vaccine became widely used, although values were slightly higher for men even in this early period. It is possible that men are more likely than women to seek or receive treatment for GW because of anatomical differences that make warts harder to detect in women, despite the equal prevalence of GW.

Estimates presented in this thesis were similar to those from a Nordic study by Kjaer et al that provided country-specific estimates from population-based surveys[66]. There, roughly 1% of women respondents aged 18–45 years self-reported medical attention for GW in the previous year, whereas this thesis shows similar proportions for women aged 18–24

years. The response rate for that survey was 63% in the Swedish sample, with a consistent age distribution among respondents. These similar results among younger women provide some validation for the use of register data in estimating GW episodes. Estimating GW episodes by use of prescription dispensation as a proxy measure alone would provide an underestimation of incidence, but with the patient registers, peak incidence is comparable to clinic and questionnaire data.

Interestingly, higher parental education status was associated with an excess risk of GW. As the GW variable in this thesis is a proxy for treatment seeking behavior, this excess risk of GW among those whose parents are well-educated may reflect treatment seeking behavior as opposed to actual incidence, as families with high educational status may feel more empowered to navigate the healthcare system. It may also be related to differences in sexual habits among these groups, with delayed childbearing and longer periods in the single and dating culture for women from higher educational backgrounds, which they are likely themselves to be if their parents are, with this longer 'dating' exposure period putting them at higher risk for contracting GW[113].

In societies where health risk exposure information is abundant, as is the case today in countries with high GDP per capita such as Sweden or the U.S., few epidemiological studies aim to measure how individuals interpret their risk exposure and whether or how this is in turn associated with prevention behavior. This thesis shows vast gender differences in how STI risk is perceived and correlated with prevention behavior.

This thesis highlights some women's descriptions of risk being external to their social spheres and external to Sweden. The lack of HIV testing support from health practitioners described by some women in the IBDs has also been voiced in mass media [114] and serves to strengthen women's belief of STI risk as irrelevant in Sweden and for themselves. By focusing HIV testing on intercourse with men of particular nationalities, the Swedish health care system may systematically support women in assuming they will avoid STIs in general if they avoid unprotected (non-condom) sex with men with particular characteristics. This risk assessment of HIV risk reflects its epidemiology, as HIV incidence is relatively low in Sweden with over half of the 500 reported cases in 2009 reporting infection in higher-prevalence countries before coming to Sweden [115], and men who have sex with men and intravenous drug users comprised substantial percentages of the remaining infected. However, the praxis of restricted HIV testing described by the women in the internet-based discussions could also exacerbate the notion of STI risk as external and be used to justify unprotected sex with those deemed 'safe'. It is conceivable a message of HIV as a primarily foreign disease (as reported by women in the IBDs) might lead to more unprotected sex domestically. This trend in turn could possibly prove influential to the increase in STI rates at large that have appeared over the last decade [55, 56]

Interestingly, these findings suggest that a positive STI history may function as a protective factor by reducing subsequent sexual risk taking and increasing health promotion. In Hammarlund's Swedish study [116], having contracted condyloma was reported as a 'wake-up call' to disease risk. Another hypothesis generated here is if women who report STI experiences also report more health advocacy in terms of condom use with temporary partners, as a result of these experiences. Further investigation into the potential effects of having received a positive STI diagnosis are warranted.

HPV-vaccine effectiveness

Vaccine effectiveness studies move outside the clinical trial restrictions present in vaccine efficacy studies and instead examine reduction of disease burden in the population at large. Effectiveness results from this thesis will be compared with efficacy trial results as these comparisons prove interesting and are necessary in vaccination program assessments. No other effectiveness studies have been published to-date with individual-level data making effectiveness comparisons impossible. The five-year follow-up in this thesis is comparable with trial follow-up[34, 117-119].

In the age group fully vaccinated with the qHPV-vaccine below 14 years of age, where there is presumably little prior HPV exposure, the effectiveness against GW found in this thesis (93%) was similar to the vaccine-type specific effect reported in HPV-naïve subjects in the clinical trials of the qHPV vaccine (96%; CI 93-98) but was somewhat higher than the any-type GW reported (83%; CI 75-88) in that group[120]. Similarly, the effectiveness among all women under the age of 20 (75%), was similar to the vaccine-type specific GW efficacy (79%; CI 73-84) in the intention-to-treat populations but appeared stronger than the any-type GW efficacy reported there (62%; CI 54-69)[120]. However, women in the trials were older at enrollment (age range 16-26). The trials did not present age-specific results so age-at-vaccination differences could not be ascertained. One could argue that comparisons between efficacy trials and effectiveness studies should be focused on any-type infection as this is the only assumption that can be made with population data (given that HPV-typing of HPV-related disease outcomes is not standard clinical praxis). A possible explanation for effectiveness being higher than the any-type efficacy could be that a relatively high prevalence of GW in Sweden is caused by vaccine-specific types. Another highly plausible explanation would be if HPV 6/11 are preferentially associated with clinically-significant GW and non-vaccine HPVs being preferentially associated with minor GW lesions found in the more intense surveillance in the clinical trials. Considering that vaccinated individuals are known to be almost completely protected against incident HPV infection, indirect protection from herd immunity cannot possibly have contributed to further increasing the effectiveness among the fully vaccinated younger girls found in this thesis[34].

Above the age of 20, the crude estimates of effectiveness are more difficult to interpret, as there was evidence suggesting a self-selection bias with women at high risk preferentially seeking vaccination. However the trials did limit inclusion to those individuals with fewer than four lifetime partners. With this criteria they could have a different risk pattern than the women over age 20 who chose vaccination in Sweden where it has become common among women with increasing numbers of lifetime partners and decreasing trends in condom use with casual partners[121]. Also, circumcision is not common among Swedish men, increasing the likelihood for HPV transmission to women and thereby making comparisons difficult with the efficacy trials regarding baseline HPV risk in countries where circumcision is more common[43]. Nevertheless, failure to find any effectiveness at all for women above 22 years of age suggests that this group of women in Sweden had exposure to HPV prior to vaccination and thus received less benefit from vaccination. It is well known that the vaccine does not alter the course of an already existing HPV-infection, which means that the vaccine will appear less effective if a woman is already infected with one or more of the HPV-types targeted by the vaccine at the time of vaccination [122, 123].

Regarding dose effectiveness for females vaccinated before age 20, disease-specific outcomes after q-HPV vaccination per dose level are presented for the first time in this thesis. The two dose qHPV trial to-date has reported on measures of HPV-antibody responses (Geometric mean antibody titer, or GMT) as an assessment of efficacy[124]. How antibody response translates to disease prevention is currently unknown, though a correlation is assumed[125, 126]. Due to this unknown, it is difficult to compare trial findings on immune response with the findings in this thesis on treatment for the purpose of assessing whether antibody response translates accurately to actual disease protection as this thesis uses observational data with a proxy measure for HPV-infection. Trial data containing both antibody response and eventual disease outcomes are needed to substantiate and provide accuracy to these translation measures. However the most important factor when assessing vaccine effectiveness is actual disease outcomes and not antibody responses as a potential proxy for future outcomes.

Alternative dosing schedules of the qHPV-vaccine have shown good immunogenic responses[127]. The Canadian qHPV dose efficacy trial reported differences in mean anti-HPV type levels[5, 124]. In that trial, one group was vaccinated between 9-13 years of age with a two and three dose schedule while the older group, vaccinated between 16-26 years of age, received all three doses. Only girls and women sero-negative at baseline were included. Results showed no difference in antibody response for HPV 16, while HPV 18 response was better with three doses[5].

A non-inferiority in antibody responses for girls in the two dose schedule compared to the females vaccinated between ages 16-26 with three doses has been reported[124]. Though this conclusion could not be drawn with this thesis data, differences in effectiveness were found depending on age-at-first-vaccination. The trial reported that a three dose schedule in girls was superior to a two dose schedule in girls for HPV-types 6 and 18 (but not 16 and 11)[124]. HPV-type 6 is found in a higher proportion of GW than HPV-type 11[128].

Quadrivalent HPV-vaccine trials have shown that the vaccine elicits a higher antibody response in younger girls fully vaccinated than in older girls and women, all sero-negative at baseline[126, 129]. This initial elevated antibody response could correspond to the higher protection seen in this thesis in girls vaccinated at a younger age versus girls vaccinated at an older age. Another possible explanation would be a higher incidence of baseline HPV-positivity among those first vaccinated between 17-19 year olds, a significant proportion of whom will have had their sexual debut prior to vaccination. With this register data we have no way of controlling for this, but we have excluded women with a history of GW before individual follow-up.

The differences in immune responses based on HPV-types, age and dose shown in trial data further compel the presence of vaccine dose effectiveness studies to demonstrate if and how this response potentially translates into disease protection in real-life situations.

Regarding herd immunity, seminal studies from Australia showed a drastic decrease in GW among younger women and to a lesser but substantial degree even men when comparing ecological trends before and after vaccine program launch [130-132]. While no

causal relationship can be established with this type of ecological data, the quadrivalent vaccination program is likely fueling these declines. Australia's broad school- and community-based vaccination program has over 80% coverage among teenage girls, while Sweden's partially subsidized on-demand program has 25-30% coverage for the same age cohort [130].

The U.K. also has documented declines in GW post vaccination despite using the bivalent vaccine which does not provide coverage for HPV 6&11. Their report suggests some ecological cross-protections and herd immunity among boys [133]. No such herd immunity effects on men in Sweden could be insinuated in this thesis.

Condoms for STI prevention in high risk situations

The rise in multiple STI incidences in Sweden could be related to the relatively low prevalence of condom use with temporary partners shown in this thesis, though by study design this can merely be speculated[56, 59, 60, 134]. A report that came out after this thesis work on condom prevalence was published showed a positive attitude toward condom use but low usage. The same report indicated that young Swedes found not using a condom to signify trust in one's partner[72].

In contrast with Sweden's reputation for gender and sexual equality [109], women from the IBDs describe often deferring to men for condom preparedness and decision-making concerning use. A study from the United States also found that sexually active women described experiences in which they never initiated or negotiated condom use [135]. These findings show discordance with other Swedish research showing that women are positive about condom use and have intentions of using them with new partners [136]. Women in the IBDs expressed a need to be covert about pre-meditated sexual intentions with new sex-partners with love potential; condom preparedness was said to reveal premeditated intentions.

Acting out ideals based on gender stereotypes of sexually active men and sexually passive women was also a theme found in Marston and King's systematic review [137] on factors shaping sexual behavior in young people. In the 268 international qualitative studies they reviewed, common gender stereotypes were found where girls and young women who expressed wanting sex risked a bad reputation which in turn inhibited communications about sex [137]. The preliminary results presented here adds data about women up to ten years older than those in the aforementioned review, suggesting that these gender stereotypes endure into adulthood.

ETHICS IN SCIENCE: WHO GETS A VOICE, WHO GETS A SHOT?

This last section of this thesis discussion will end with questions and not answers. These particular questions have been brought to my attention at various points during my doctoral work and continue to perplex me. I have pondered possible answers throughout the years though satisfactory answers have yet eluded me.

1. **Who gets a voice?** This question is a focal point within qualitative research and in medical research. Nursing science in particular frequently asks this question and attempts to give voices to the often voiceless (i.e. patients, their families or non-medical caregivers). Studies that examine multiple stakeholders' perspectives attempt to make multiple voices heard. Which leads to yet another question in medical research: if multiple voices are heard, who is listening? Are certain voices still so faint as to be overpowered in discussions? Are certain voices selectively tuned-out, and if so, why?

   Through qualitative investigations I was able to ask women and men in STI risk situations how they protected themselves and how they felt about HPV-vaccines. These individuals are some of the voices of HPV risk and prevention but there are many others affected in some way by HPV-vaccinations left unheard.

2. **What voice do people get?** Articles using questionnaire-based research often report on questionnaire validation studies in order to qualify the choice in questionnaire. People will answer questions if asked, but whether or not those questions are salient is another matter. I worked with randomized clinical trials for surgical techniques, where patient post-operative recovery was imperative to track and I was frequently disappointed with how little of what patients experienced in their recovery process was actually assessed using standard questionnaires. Even in this thesis work based on questionnaire data from *Attitudes toward HPV-vaccination* wonders which attitudes experienced by respondents toward HPV-vaccination were even presented to answer in the questionnaire.

   Could some of the decreasing trends in response rates seen in questionnaire studies reflect people's impatience with inappropriate survey questions – inappropriate for their specific circumstances[138]?

3. **Who gets a shot?** Of all the questions listed here, this one makes me most uncomfortable. I wonder who will be held accountable by future generations for the death of millions when it becomes apparent that vaccinations were available but that they never reached many of the people who needed them most. GAVI initiatives are to be credited with attempting to prevent disease and mortality by funding vaccinations in very low-resource settings[139]. The development, testing and distribution of new vaccinations and treatments all require copious financial resources. Will disease prevention measures and treatments ever be more equitably distributed? Will treatments with low potential return on investments even make it to the development phase[140]?

A frequently asked question regarding who gets an HPV-shot is ‘what about men’? This came up time and time again in my internet-based discussions with women and comes up frequently at conferences and in public health debates. Will men carry any of the responsibility for HPV prevention? Will men be able to capitalize on any of the benefit of HPV-vaccinations outside of what will eventually come to them via herd immunity? What about MSM who are at high-risk for HPV-related anal cancers?

4. **Who is left out, who gets let in?** In the preface I mentioned one limitation with RCTs: their inclusion and exclusion criteria may not reflect the real-life situations in which treatments or vaccinations are used. Also, their follow-up length is limited by financial constraints, eliciting the question, ‘which outcomes are even possible to assess’? Rarer outcomes or adverse advents that take years to develop will not be possible to assess. Of all the questions here, this is the only one where I have found the start of an answer which provides some satisfaction:

   Nordic population-based registers should be used for continued investigations into possible long-term effects of treatments – not to instill fear with possible risk factors but to do what trials cannot do: investigate long-term follow-up in a more comprehensive population. Effectiveness and safety studies based on observational research provide necessary compliments to RCTs.

5. **If there is a voice, will there be a microphone?** Second to the ‘who gets a shot’ question, this one also makes me very uneasy. Publication bias is known and discussed in scientific literature [141, 142]. The peer-review system for publication is not fool-proof. How often do important negative or contradictory results get silenced? What will the scientific community do to give fiscally detrimental or unpopular science a voice?

Conclusions

Study I revealed that condom use with temporary partners was not associated with STI risk perception for men whereas it was for women, despite a higher percentage of men reporting consistently having used condoms with temporary partners. Correlates to STI risk perception differ substantially between men and women. Awareness and severity perceptions of HPV and HPV-related cancer were not associated with either condom use or risk perception, whereas education level was positively associated with condom use. Women who were youngest at sexual debut also had two-fold increased odds of reporting non-condom use with temporary partners compared to women with later sexual debuts. Also, women with immigrant mothers were almost twice as likely to report using condoms consistently with temporary partners compared to women with Swedish-born mothers. Number of reported temporary partners was the only common factor associated for both men and women with condom use and STI risk perception.

Preliminary results based on analysis of data generated by internet-based discussions with women aged 21-34 years old in Sweden indicate that in situations where women perceive potential for a love relationship, they describe behaving in ways that expose them to substantial risk for STI contraction. The gender roles described subvert these women's own desires and health promotion and thereby act to hinder women's potential condom advocacy. Managing HPV infection risk via behavioral changes was described as virtually impossible. However, these preliminary results suggest that previous diagnosis with a viral STI may function as a protective factor by reducing subsequent sexual risk taking and increasing health-promoting behaviors.

Study II showed that the incidence of GW peaked at a younger age for females and that males accounted for a higher overall proportion of episodes. Podophyllotoxin was the most common first-line treatment for new GW episodes for both sexes, while imiquimod was prescribed to females more often than to males. The incidence of GW peaked at a younger age for females and males accounted for a higher overall proportion of episodes. There was a downward trend of GW incidence among younger females between 2006 and 2010. Among females aged 17–18 years, the GW incidence decreased by more than 25% post HPV-vaccine availability. Such declines were not observed among females over age 25 or under age 16 or among males overall. The burden of GW in Sweden is high, and this study indicates that GW is the second-most-common STI in Sweden after chlamydial infections. This study provides a reasonable estimation of the incidence of GW in the Swedish population by use of register data, with results comparable to those from previous smaller studies.

Study III is the first vaccine effectiveness study of an entire population and showed that qHPV vaccination had high protection against disease among women fully vaccinated under the age of 20, with particularly high effectiveness for girls below 14 years of age. By including more than 2.2 million women ranging from ages 10-44, nuanced effects

of age-at-vaccination could be discerned for the first time in this study. Effectiveness declined as age-at-first-vaccination increased. For women above age 22, there is suggestive evidence that vaccinations tended to reach women already exposed to HPV and there was no measurable effectiveness in these age groups. There is also evidence of inequity in vaccine use, with individuals from families with higher socioeconomic status being 15 times more likely to receive vaccines compared to individuals from families with lower socioeconomic status. It is important to consider that just because this study did not find qHPV-vaccine effective in women vaccinated over age 22, does not mean it is ineffective in all women vaccinated over the age of 22. Also, the outcome in this study is GW, not cervical dysplasia, which is the primary indication for vaccinations.

Study IV revealed maximum protection against GW with three doses, and two-doses is less effective than three doses. No differences in effectiveness were found for girls who received two-doses between ages 10-16 with that of individuals who received three-doses between ages 17-19. This study does not account for HPV-disease outcomes other than GW in measures of dose effectiveness. What is measured is a proxy for GW in terms of treatment-seeking behavior, which in itself is a proxy for HPV infection. More studies with longer follow-up are needed to assess other HPV-related disease outcomes such as CIN.

IMPLICATIONS FOR PRACTICE

Focusing HPV-vaccination efforts on vaccinating girls under age 14 will provide maximum protection. Vaccinating women over 20 will not lead to substantial reductions in GW disease burdens. The results from the dose Study IV should contribute to the HPV vaccine dose discussions but should by no means be solely decisive in regards to effectiveness of less than three qHPV-vaccine doses. Following a three-dose schedule for qHPV provides maximum protection against GW.

Opportunistic or on-demand vaccination programs exacerbate social disparities in negative health outcomes. Social inequities emerge with on-demand vaccination programs, to an extent not anticipated with school-based programs.

With the harmful and sometimes deadly health effects of STIs, proper condom use as a primary prevention measure should remain a top priority for health officials. This thesis concludes, however, that campaigns with a primary aim to increase STI knowledge and awareness with the intention of influencing risk perceptions among those sexually active may not effectively translate into an increase in prevention behaviors. To reach the public health goal of reducing STI prevalence, barriers to engaging in STI prevention need to be addressed. Discourse on detrimental effects of gender-stereotypical behavior should be integrated into sex education curriculums.

Sammanfattning på svenska

Syfte: Att ge en flerdimensionell bedömning av infektionsrisker och utvärdera strategier för HPV-prevention inklusive opportunistisk vaccination med tetravalent HPV-vaccin, effektivitet på dos-nivå och kondomanvändning när det finns hög risk för att överföra en könssjukdom.

Metoder: Flera populationsbaserade register och enkätsvar används som underlag för denna avhandling. Kvinnor som besvarade enkät och som uppgav något mått av riskbeteende i förhållande till könssjukdomar intervjuades vid senare tillfälle via internet-baserad diskussion.

Resultat: Tetravalent HPV-vaccination var mycket effektiv mot kondylom, den första HPV-relaterade sjukdomen efter HPV-exponering som är möjligt att mäta. Effektiviteten var dock knuten till ung ålder vid första vaccination, med en stadig minskning av effektivitet ju äldre åldern var vid första vaccinationen. Bland kvinnor som var över 20 år vid den första vaccinationen hittades det låg till omätlig effektivitet och indikationer på att vaccinationer i denna åldersgrupp tenderade att nå kvinnor som redan exponerats för HPV-typer associerade med kondylom. Stora socioekonomiska skillnader hittades i vem som vaccinerades i det opportunistiska programmet, med 15 gånger större sannolikhet att vaccineras hos kvinnor och flickor som har föräldrar med högsta utbildningsnivå jämfört med den lägsta (Studie III). Maximalt skydd mot kondylom hittades bland flickor som vaccinerades under 17 år som hade fått tre doser av vaccinet. Inga skillnader i effektivitet hittades mellan flickor som fick två doser mellan åldrarna 10-16 och de som fick tre doser mellan åldrarna 17-19 (Studie IV). Kondylom drabbar fler män än kvinnor i Sverige med 453 fall per 100 000 män och 365 fall per 100 000 kvinnor under 2010. En nedgång mellan 25-30% sågs mellan 2006 och 2010 bland kvinnor i åldersgrupperna med den högsta vaccinationstäckningen. Ingen nedgång hittades bland män och deras kondylomincidens har stadigt ökat mellan 2006 och 2010 (Studie II). Redovisad kondomanvändning i högrisksituationer var låg bland både män och kvinnor, där 41% av männen och 34% av kvinnorna rapporterar att de alltid / nästan alltid använder kondom med tillfälliga partners. Infektionsriskuppfattningen var också låg, där cirka 10% av alla sexuellt aktiva respondenter anser sig ha stor risk att smittas av en könssjukdom. Det fanns inget samband mellan mäns kondomanvändning och deras STI-riskuppfattning men det fanns ett samband för kvinnor (Studie I).Kvinnor diskuterade att förhindra överföring av sexuellt överförbara sjukdomar genom val av sexpartner, selektiv kondomanvändning och regelbunden könssjukdomstestning. Kvinnor beskriver dock att männen får ansvara för att ha kondomer vid första samlaget för att inte äventyra möjligheterna till en långsiktig relation. De säger att en kvinnas kondomberedskap visar att de planerat att ha samlag och visar en nivå av sexuell upplevelse som kvinnor inte känner sig bekväma med att uttrycka till en ny partner. Kvinnor tyckte att sambandet mellan sex och cancer var svårt att föreställa sig. På grund av HPVs hud-mot-hud-överföring, uttalade kvinnorna att förebyggande av HPV-spridning genom sexuellta beteendeförändringar verkade omöjligt och utanför deras kontroll (preliminära resultat).

Slutsatser: Resultaten tyder på att män har en betydande incidens av HPV-relaterad kondylom och att incidensen har sjunkit bland kvinnor. Vid planeringen av HPV-vaccination bland kvinnor, bör insatserna inriktas mot flickor under 14 års ålder för maximal effektivitet. Tetravalent HPV-vaccination ger mest skydd mot kondylom vid tre doser. Stora sociala skillnader hittades i den opportunistiska HPV-vaccinationen. Integrering av könsspecifika förebyggande strategier i kursplaner för sexualundervisning, inklusive diskurs om skadliga effekter av könsstereotypiska beteenden för att kunna öka kondomanvändning i höga risksituationer.

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APPENDIX MATERIAL

Questionnaire for men and women in Swedish and English

THE STUDY OF HPV VACCINE'S ACCEPTABILITY IN SWEDEN

QUESTIONNAIRE FOR MALE ADULT AGED 18-30 YEAR OLDS

001 QUESTIONNAIRE IDENTIFICATION NUMBER [_A_|_M_|___|___|___|___]

002 DATE OF FILLING IN QUESTIONNAIRE (mm/dd/yyyy): ____/ ____ / 2006

Section 1: *Background characteristics*

No.	Questions and filters	Coding categories	Skip to
Q101	What is your age?	Age: [__|__]	
Q102	From what country were you born?	Sweden 1 Iceland, Denmark, Finland or Norway 2 Outside the Nordic countries 3	
Q103	What is your current marital status?	Use Swedish version as in CCS study, add registered partner to Married	
Q104	Are you *currently* in a relationship?	Yes 1 No 2	
Q105	Which is your current state of employment? (Please select only one choice)	Full-time employed 1 Part-time employed 2 Un-employed 3 Retired 4 Parental leave 5 Student 6 Other 7 Please specify: …… ……	
Q106	What is your annual income level? (Please select only one choice) Include arbetslöshetsunderstöd, sjukpension, etc. Do *not* include studielån och studiebidrag	Less than 50000 kronor/year 1 50000 – 100000 kronor/year 2 100000 – 150000 kronor/year 3 150000 – 200000 kronor/year 4 200000 – 250000 kronor/year 5 250000 – 300000 kronor/year 6 300000 – 400000 kronor/year 7 400000 – 500000 kronor/year 8 More than 500000 kronor/year 9	
Q107	What is the highest level of school you completed? (Please select only one choice)	Use Swedish version as in CCS study If not going to school then skip to next section	

Q108	How many total years of education have you completed up to now?	# Years completed [__|__]	

Section 2 *Now we would like to ask you some questions about your sexual habits. Your answers are very important in helping us understand how certain diseases can be prevented. All answers will be kept confidential, so please answer each question honestly and accurately.*

No.	Questions and filters	Coding categories	Skip to
Q201	Who have you ever had sex (of any type) with? (Several choices can be given)	A man 1 A woman 2 Never had sex 3	 →**Q301**
Q202	Did you ever have vaginal sex?	Yes 1 No 2 Don't know 998	 →**Q301** →**Q301**
Q203	If you have ever had vaginal sex, how old were you at your first experience?	Years of age [__|__] Don't know 998	
Q204	Have you ever had other types of sex than vaginal sex? (Several choices can be given)	Oral sex 1 Anal sex 2 Other type of sex 3 Only vaginal sex 4 Don't want to reply 999	 →**Q206**
Q205	What age were you when you had any of the above mentioned types of sex for the first time?	Years of age [__|__] Don't know 998	
Q206	How many sexual partners did you have in the last year? (If none, please write 0) Sexual partners include steady partners (wife/girlfriends/registered partner) and one-night stands	Number of sex partners [__|__|__]	
Q207	Among them, how many were one-night stand? (If none, please write 0)	Number of one-night stands [__|__|__]	
Q208	Have you ever used condoms?	Yes 1 No 2 Don't know 998	 →**Q211**

Q209	With regards to sex with your steady partners, with what frequency did you and your steady partner(s) use condoms over the last year? (If you did not have a steady partner, please circle number 9)	Every time (100% of the time) 1 Almost every time (75-99%) 2 Often (50-74%) 3 Sometimes (25-49%) 4 Rarely (1-24%) 5 Never (0%) 6 No steady partner over last year 7 Don't know 998	
Q210	With regards to sex with your one-night stands, with what frequency did you and your one-night stands use condoms over the last year? (If you did not have one-night stand partner, please circle number 9)	Every time (100% of the time) 1 Almost every time (75-99%) 2 Often (50-74%) 3 Sometimes (25-49%) 4 Rarely (1-24%) 5 Never (0%) 6 No one-night stand over last year 7 Don't know 998	
Q211	Compared to other women of your age, do you consider your-self as having had more, fewer, or about the same number of sex partners?	More 1 Fewer 2 About the same 3 Don't know 998	
Q212	What level of risk of sexually transmitted infections do you think you are having?	Not at risk 1 Low risk 2 Medium risk 3 High risk 4 Don't know 998	

Section 3 *Now we would like to ask you some questions about certain health conditions. There is no right or wrong, good or bad answers. Please truly tell us what you know or think.*

No.	Questions and filters	Coding categories	Skip to
Q301	Before you participated in this study, have you ever heard about cancers of the cervix (cervical cancer)?	Yes 1 No 2	→**Q303**
Q302	Do you believe that cervical cancer is a common cancer among women?	Very common 1 Rather common 2 Not so common 3 Very uncommon 4 Don't know 998	

No.	Questions and filters	Coding categories	Skip to
Q303	Have you ever heard about any possible cause(s) of cervical cancer?	Yes 1 No 2	
Q304	Have you ever heard of Condyloma, also called Genital Warts?	Yes 1 No 2	→**Q307**
Q305	Do you believe that Condyloma is a serious disease?	Very serious 1 Rather serious 2 Not so serious 3 Not serious at all 4 Don't know 998	
Q306	Have you ever heard about any possible cause(s) of Condyloma?	Yes 1 No 2	
Q307	Before you participated in this study, have you heard about a virus called Human Papillomavirus (HPV)?	Yes 1 No 2	→**Q401**
Q308	Do you believe that HPV may cause cervical cancer?	Yes 1 No 2 Don't know 998	
Q309	Do you believe that HPV may cause other types of cancer than cervical cancer?	Yes 1 No 2 Don't know 998	
Q310	Do you believe that HPV may cause Condyloma?	Yes 1 No 2 Don't know 998	
Q311	Do you believe that HPV is sexually transmitted?	Yes 1 No 2 Don't know 998	
Q312	Do you believe that women can be infected by HPV?	Yes 1 No 2 Don't know 998	
Q313	Do you believe that men can be infected by HPV?	Yes 1 No 2 Don't know 998	
Q314	Are you aware if there is a vaccine against HPV caused disease?	A vaccine is available 1 A vaccine is being tested 2 There is no such vaccine 3	

	SELECT ONE	Don't know 998	

Section 4 *In this section, we will ask for your general opinions about vaccination. Again, there is no right or wrong answer. Please let us know what you think.*

No.	Questions and filters	Coding categories	Skip to
Q401	In general, do you believe that vaccination is an effective way against diseases? (Please circle one choice only)	Very effective 1 Rather effective 2 Not so effective 3 Not effective at all 4 Don't know 998	
Q402	Do you think that vaccination is a cost-efficient way against diseases?	Very cost-efficient 1 Rather cost-efficient 2 Not so cost-efficient 3 Not cost-efficient at all 4 Don't know 998	
Q403	In your opinion, is vaccination generally a safe way against disease?	Very safe 1 Rather safe 2 Not so safe 3 Not safe at all 4 Don't know 998	
Q404	If there is a vaccine that is coming out that concern you, how would you like to know about it? (Several choices may be given)	Via health workers 1 Educational programs on TV, radios 2 Health education at work/school 3 Booklet, brochure, leaflet 4 Authorized websites 5 Others 6 ……. Don't know 998	
Q405	Which of the above ways would be the *best* way you want to know about a new vaccine? (Please select only one choice)	Via health workers 1 Educational programs on TV, radios 2 Health education at work/school 3 Booklet, brochure, leaflet 4 Authorized websites 5 Others 6 ……. Don't know 998	

Section 5

For your information, an effective three-dose vaccine against HPV has been developed and will soon be ready for use. Please do not go back and "correct" any answer given previously. We would like to ask for your opinion about the usage of this new HPV vaccine.

No.	Questions and filters	Coding categories	Skip to
Q501	If the vaccine is free, would you be willing to vaccinate yourself?	Yes 1 No 2 Don't know 998	→**Q505**
Q502	What if the vaccine is only given at some extra cost, would you still be willing to vaccinate yourself?	Yes 1 No 2 Don't know 998	→**Q504** →**Q504**
Q503	What is the maximum cost that you think you can afford? (Three doses are considered to give full protection) (If you will vaccinate yourself at all cost, please circle number 9)	Price per dose (in SEK) …… Vaccination at any cost 2	
Q504	At what age would you consider vaccinate yourself? (Please circle number 9 if you don't consider vaccinating yourself at any age)	Age to start HPV vaccination [__|__] I don't consider HPV vaccination 9	
Q505	You may have concerns about the new vaccine. If so, please mark what you would like to know more about this new HPV vaccine? (You can select more than one choice if necessary)	If the vaccine is really protective 1 If there are any side effects (safety) 2 If vaccine needs to be repeated with more doses in the future 3 Others 4 Please specify:_____ _____ I have no concerns 5 Don't know 998	→**Q507**
Q506	If it may, what of those concerns could MOST likely make you NOT vaccinate yourself against HPV? (Please circle only ONE choice)	If the vaccine is really protective 1 If there are any side effects (safety) 2 If vaccine needs to be repeated with more doses in the future 3 Others 4 Please specify:_____ _____ I would get vaccinated despite concerns 5 Don't know 998	
Q507	If you are vaccinated, do you think that you would be *fully* protected against condyloma?	Yes 1 No 2 Don't know 9	
Q508	would you consider having more unprotected sex (=not using a	Yes 1 No 2	

	condom) if you get vaccinated?	Don't know 9	

End of the questionnaire

Thank you very much for taking time to answer these questions. We highly appreciate your help!

Karolinska Institutet

UNDERSÖKNING OM INSTÄLLNINGEN TILL ETT NYTT VACCIN
FRÅGEFORMULÄR FÖR MÄN MELLAN 18 OCH 30 ÅR

Fyll i de förtryckta fälten eller kryssa in det alternativ som du anser passar bäst

Del 1. Bakgrund

Nr	Frågor
F101	**Hur gammal är du?** ☐☐
F102	**I vilket land är du född?** **1.** ☐ Sverige **2.** ☐ Danmark, Finland, Island eller Norge **3.** ☐ Annat land
F103	**Vilket är ditt nuvarande civilstånd?** **1.** ☐ Gift/sambo/registrerad partner **- Gå till F105** **3.** ☐ Änkeman **2.** ☐ Ensamstående **999.** ☐ Vill ej svara
F104	**Har du *för närvarande* ett förhållande?** **1.** ☐ Ja **2.** ☐ Nej
F105	**Vilken är din *huvudsakliga* sysselsättning?** ***Välj endast ett alternativ*** **1.** ☐ Heltidsarbetande **3.** ☐ Arbetslös **5.** ☐ Föräldraledighet **2.** ☐ Deltidsarbetande **4.** ☐ Sjukpensionär **6.** ☐ Studerande **7.** ☐ Annat (ange vad) .....
F106	**Vilken är din årliga inkomst före skatt? Inkludera arbetslöshetsunderstöd, sjukpension, etc. Inkludera *inte* studielån och studiebidrag** ***Välj endast ett alternativ*** **1.** ☐ Mindre än 50 000 kr/år **4.** ☐ 150 000–200 000 kr/år **7.** ☐ 300 000–400 000 kr/år **2.** ☐ 50 000–100 000 kr/år **5.** ☐ 200 000–250 000 kr/år **8.** ☐ 400 000–500 000 kr/år **3.** ☐ 100 000–150 000 kr/år **6.** ☐ 250 000–300 000 kr/år **9.** ☐ Mer än 500 000 kr/år **998.** ☐ Vet ej
F107	**Vilken är din högsta avslutade utbildning?** ***Välj endast ett alternativ*** **1.** ☐ Grundskola år 1–9 **5.** ☐ Folkhögskola **2.** ☐ Yrkesskola **6.** ☐ Högskola/universitet upp till 2 år **3.** ☐ Gymnasium **7.** ☐ Högskola/universitet mer än 2 år **4.** ☐ Vuxenutbildning **8.** ☐ Annat .....
F108	**Hur många år har du sammanlagt studerat fram till idag?** Antal (hela) studieår ☐☐ **998.** ☐ Vet ej

Fyll i de förtryckta fälten eller kryssa in det alternativ som du anser passar bäst

Del 2. Nu följer några frågor om sexualvanor. Dina svar kan hjälpa oss att förstå hur vissa sjukdomar kan förhindras. Vi ber dig besvara frågorna så noggrannt som möjligt.

Nr	Frågor
F201	**Med vilka av följande har du någon gång haft någon typ av sexuellt umgänge?** *Flera alternativ kan anges* **1.** ☐ Man **2.** ☐ Kvinna **3.** ☐ Har aldrig haft sexuellt umgänge - **Gå till F301**
F202	**Har du haft vaginalt samlag någon gång?** **1.** ☐ Ja **2.** ☐ Nej - **Gå till F204** **998.** ☐ Vet ej - **Gå till F204**
F203	**Om ja på ovanstående fråga, hur gammal var du första gången du hade vaginalt samlag?** Ålder ☐☐ **998.** ☐ Vet ej
F204	**Har du någonsin haft annan typ av sexuellt umgänge än vaginalt samlag?** *Flera alternativ kan anges* **1.** ☐ Oralsex **2.** ☐ Analsex **3.** ☐ Annan typ av sex **4.** ☐ Endast vaginalt samlag - **Gå till F206** **999.** ☐ Vill ej svara
F205	**Hur gammal var du när du hade någon av ovan nämnda typer av sex första gången?** Ålder ☐☐ **998.** ☐ Vet ej
F206	**Hur många sexpartners har du haft det senaste året? Räkna med fasta partners och tillfälliga förbindelser.** ***(Om ingen, ange 0)*** Antal sexpartners ☐☐☐ **998.** ☐ Vet ej
F207	**Hur många av dina sexpartners det senaste året var tillfälliga förbindelser?** ***(Om ingen, ange 0)*** Antal tillfälliga förbindelser ☐☐☐ **998.** ☐ Vet ej
F208	**Har du någonsin använt kondom?** **1.** ☐ Ja **2.** ☐ Nej - **Gå till F212** **998.** ☐ Vet ej

Fyll i de förtryckta fälten eller kryssa in det alternativ som du anser passar bäst

Nr	Frågor
F209	**När du hade sex med din(a) *fast(a)* partner(s), hur ofta använde ni kondom under det senaste året? (Välj nummer 7 om du inte hade någon fast partner det senaste året?)** **1.** ☐ Varje gång (100% av tillfällena) **2.** ☐ Nästan varje gång (75-99%) **3.** ☐ Ofta (50-74%) **4.** ☐ Ibland (25-49%) **5.** ☐ Sällan (1-24%) **6.** ☐ Aldrig (0%) **7.** ☐ Har inte haft någon fast partner senaste året **998.** ☐ Vet ej
F210	**När du hade sex med din(a) *tillfällig(a)* partner(s), hur ofta använde ni kondom under det senaste året? (Kryssa nummer 7 om du inte hade någon tillfällig partner det senaste året?)** **1.** ☐ Varje gång (100% av tillfällena) **2.** ☐ Nästan varje gång (75-99%) **3.** ☐ Ofta (50-74%) **4.** ☐ Ibland (25-49%) **5.** ☐ Sällan (1-24%) **6.** ☐ Aldrig (0%) **7.** ☐ Har inte haft någon tillfällig partner senaste året **998.** ☐ Vet ej
F211	**Jämfört med andra män i din ålder, tror du att du har haft fler, färre eller ungefär lika många sexpartners (totalt sett)?** **1.** ☐ Fler **2.** ☐ Färre **3.** ☐ Ungefär lika många **998.** ☐ Vet ej
F212	**Hur stor risk att råka ut för sexuellt överförbara sjukdomar tror du att du har?** **1.** ☐ Ingen risk **2.** ☐ Liten risk **3.** ☐ Ganska stor risk **4.** ☐ Stor risk **998.** ☐ Vet ej

Del 3. Nu följer några frågor om hälsoförhållanden. Det finns inga riktiga eller felaktiga svar. Vi ber dig svara uppriktigt vad du vet eller tror.

Nr	Frågor
F301	**Hade du hört talas om livmoderhalscancer innan du deltog i denna studie?** **1.** ☐ Ja **2.** ☐ Nej - **Gå till F304**
F302	**Tror du att livmoderhalscancer är en vanlig cancerform bland kvinnor?** **1.** ☐ Mycket vanlig **3.** ☐ Inte så vanlig **2.** ☐ Ganska vanlig **4.** ☐ Mycket ovanlig **998.** ☐ Vet ej
F303	**Känner du till möjliga orsaker till livmoderhalscancer?** **1.** ☐ Ja **2.** ☐ Nej
F304	**Har du någonsin hört talas om kondylom, även kallade könsvårtor?** **1.** ☐ Ja **2.** ☐ Nej - **Gå till F307**
F305	**Hur allvarligt är kondylom enligt din uppfattning?** **1.** ☐ Mycket allvarligt **3.** ☐ Inte så allvarligt **2.** ☐ Ganska allvarligt **4.** ☐ Inte alls allvarligt **998.** ☐ Vet ej
F306	**Känner du till möjliga orsaker till kondylom?** **1.** ☐ Ja **2.** ☐ Nej
F307	**Hade du hört talas om ett virus kallat humant papillomvirus (HPV) innan du deltog i denna studie?** **1.** ☐ Ja **2.** ☐ Nej - **Gå till F401**
F308	**Tror du att HPV kan orsaka livmoderhalscancer?** **1.** ☐ Ja **2.** ☐ Nej **998.** ☐ Vet ej
F309	**Tror du att HPV kan orsaka annan cancer än livmoderhalscancer?** **1.** ☐ Ja **2.** ☐ Nej **998.** ☐ Vet ej
F310	**Tror du att HPV kan orsaka kondylom?** **1.** ☐ Ja **2.** ☐ Nej **998.** ☐ Vet ej
F311	**Tror du att HPV kan smitta genom sexuellt umgänge?** **1.** ☐ Ja **2.** ☐ Nej **998.** ☐ Vet ej
F312	**Tror du att kvinnor kan smittas av HPV?** **1.** ☐ Ja **2.** ☐ Nej **998.** ☐ Vet ej
F313	**Tror du att män kan smittas av HPV?** **1.** ☐ Ja **2.** ☐ Nej **998.** ☐ Vet ej
F314	**Känner du till om det finns något vaccin mot sjukdom orsakad av HPV?** ***Välj endast ett alternativ*** **1.** ☐ Ett vaccin finns tillgängligt **3.** ☐ Det finns inget vaccin mot HPV **2.** ☐ Ett vaccin testas för närvarande **998.** ☐ Vet ej

Fyll i de förtryckta fälten eller kryssa in det alternativ som du anser passar bäst

Del 4. Nu följer några frågor om din inställning till vaccination.
Återigen finns det inga rätta eller felaktiga svar. Ange bara din åsikt.

Nr	Frågor
F401	**Tror du att vaccination kan vara ett effektivt sätt att förebygga sjukdomar?** ***Välj endast ett alternativ*** **1.** ☐ Mycket effektivt **3.** ☐ Inte så effektivt **2.** ☐ Ganska effektivt **4.** ☐ Inte alls effektivt **998.** ☐ Vet ej
F402	**Tror du att vaccination kan vara ett kostnadseffektivt sätt att förebygga sjukdomar?** ***Välj endast ett alternativ*** **1.** ☐ Mycket kostnadseffektivt **3.** ☐ Inte så kostnadseffektivt **2.** ☐ Ganska kostnadseffektivt **4.** ☐ Inte alls kostnadseffektivt **998.** ☐ Vet ej
F403	**Tror du att vaccination är en säker metod att förebygga sjukdomar?** ***Välj endast ett alternativ*** **1.** ☐ Mycket säker **3.** ☐ Inte så säker **2.** ☐ Ganska säker **4.** ☐ Inte alls säker **998.** ☐ Vet ej
F404	**Om det lanseras ett vaccin som du skulle kunna ha nytta av, hur skulle du helst vilja få reda på det?** ***Flera alternativ kan anges*** **1.** ☐ Via sjukvårdspersonal **5.** ☐ Via Internet **2.** ☐ Utbildningsprogram på TV eller radio **6.** ☐ Annat sätt (Ange vad) ..... **3.** ☐ Hälsoundervisning på arbete/skola **4.** ☐ Informationsfolder, broschyr, häfte ..... **998.** ☐ Vet ej - **Gå till F501**
F405	**Vilket av ovanstående sätt skulle vara det bästa för dig att få information om ett nytt vaccin?** ***Välj endast ett alternativ*** **1.** ☐ Via sjukvårdspersonal **5.** ☐ Via Internet **2.** ☐ Utbildningsprogram på TV eller radio **6.** ☐ Annat sätt (Ange vad) ..... **3.** ☐ Hälsoundervisning på arbete/skola **4.** ☐ Informationsfolder, broschyr, häfte ..... **998.** ☐ Vet ej

Fyll i de förtryckta fälten eller kryssa in det alternativ som du anser passar bäst

Del 5. **Vi vill informera dig om att HPV är ett sexuellt överförbart virus som kan orsaka kondylom hos män och kvinnor och livmoderhalscancer hos kvinnor. Ett effektivt HPV-vaccin har utvecklats och är klart för användning.** ***Vi ber dig att inte gå tillbaka och ändra något av de tidigare avgivna svaren.***
Nu vill vi fråga om din åsikt angående användning av det nya HPV-vaccinet.

F501 **Skulle du vilja vaccinera dig mot HPV om vaccinet är gratis?**

1. ☐ Ja 2. ☐ Nej - **Gå till F505** 998. ☐ Vet ej

F502 **Skulle du vilja vaccinera dig mot HPV om vaccinet kostar pengar?**

1. ☐ Ja 2. ☐ Nej - **Gå till F504** 998. ☐ Vet ej - **Gå till F504**

F503 **Vilken är den högsta kostnad du kan tänka dig att betala för att vaccinera dig mot HPV? (Tre doser anses ge ett fullgott skydd).**

Pris för vaccination per dos (i kr) ..... **2.** ☐ Vaccination oavsett kostnad

F504 **Vid vilken ålder anser du att man ska vaccinera mot HPV?**

Ålder för att påbörja HPV-vaccination ☐☐ **9.** ☐ Jag överväger inte HPV-vaccination

F505 **Vilken information skulle du vilja ha om det nya vaccinet?** ***Flera alternativ kan anges***

1. ☐ Om vaccinet verkligen skyddar
2. ☐ Om vaccinet har biverkningar
3. ☐ Om vaccinationen behöver upprepas
4. ☐ Annat (Ange vad) .....

.....

5. ☐ Jag har inga frågor - **Gå till F507**
998. ☐ Vet ej

F506 **Skulle någon av ovanstående frågor kunna få dig att avstå från att vaccinera dig mot HPV?** ***Välj endast ett alternativ***

1. ☐ Om vaccinet verkligen skyddar
2. ☐ Om vaccinet har biverkningar
3. ☐ Om vaccinationen behöver upprepas
4. ☐ Annat (Ange vad) .....

.....

5. ☐ Jag skulle vaccinera mig oavsett frågor
998. ☐ Vet ej

Fyll i de förtryckta fälten eller kryssa in det alternativ som du anser passar bäst

Nr	Frågor
F507	Tror du att du skulle vara fullständigt skyddad mot kondylom om du vaccinerade dig mot HPV? 1. ☐ Ja 2. ☐ Nej 998. ☐ Vet ej
F508	Skulle du kunna tänka dig att ha mer oskyddat sex än idag (=utan att använda kondom) om du vaccinerar dig mot HPV? 1. ☐ Ja 2. ☐ Nej 998. ☐ Vet ej

Slut på frågeformuläret

Ett stort tack för att Du tog dig tid att svara på dessa frågor. Vi uppskattar verkligen din hjälp!

THE STUDY OF HPV VACCINE'S ACCEPTABILITY IN SWEDEN

QUESTIONNAIRE FOR FEMALE ADULT AGED 18-30 YEAR OLDS

001 QUESTIONNAIRE IDENTIFICATION NUMBER [_A_|_M_|___|___|___|___]

002 DATE OF FILLING IN QUESTIONNAIRE (mm/dd/yyyy): ____/ ____ / 2006

Section 1: *Background characteristics*

No.	Questions and filters	Coding categories	Skip to
Q101	What is your age?	Age: [__|__]	
Q102	From what country were you born?	Sweden 1 Iceland, Denmark, Finland or Norway 2 Outside the Nordic countries 3	
Q103	What is your current marital status?	Use Swedish version as in CCS study, add registered partner to Married	
Q104	Are you *currently* in a relationship?	Yes 1 No 2	
Q105	Which is your current state of employment? (Please select only one choice)	Full-time employed 1 Part-time employed 2 Un-employed 3 Retired 4 Parental leave 5 Student 6 Other 7 Please specify: …… ……	
Q106	What is your annual income level? (Please select only one choice) Include arbetslöshetsunderstöd, sjukpension, etc. Do *not* include studielån och studiebidrag	Less than 50000 kronor/year 1 50000 – 100000 kronor/year 2 100000 – 150000 kronor/year 3 150000 – 200000 kronor/year 4 200000 – 250000 kronor/year 5 250000 – 300000 kronor/year 6 300000 – 400000 kronor/year 7 400000 – 500000 kronor/year 8 More than 500000 kronor/year 9	
Q107	What is the highest level of school you completed? (Please select only one choice)	Use Swedish version as in CCS study If not going to school then skip to next section	

Q108	How many total years of education have you completed up to now?	# Years completed [__|__]	

Section 2 *Now we would like to ask you some questions about your sexual habits. Your answers are very important in helping us understand how certain diseases can be prevented. All answers will be kept confidential, so please answer each question honestly and accurately.*

No.	Questions and filters	Coding categories	Skip to
Q201	Who have you ever had sex (of any type) with? (Several choices can be given)	A man 1 A woman 2 Never had sex 3	 →**Q301**
Q202	Did you ever have vaginal sex?	Yes 1 No 2 Don't know 998	 →**Q301** →**Q301**
Q203	If you have ever had vaginal sex, how old were you at your first experience?	Years of age [__|__] Don't know 998	
Q204	Have you ever had other types of sex than vaginal sex? (Several choices can be given)	Oral sex 1 Anal sex 2 Other type of sex 3 Only vaginal sex 4 Don't want to reply 999	 →**Q206**
Q205	What age were you when you had any of the above mentioned types of sex for the first time?	Years of age [__|__] Don't know 998	
Q206	How many sexual partners did you have in the last year? (If none, please write 0) Sexual partners include steady partners (wife/girlfriends/registered partner) and one-night stands	Number of sex partners [__|__|__]	
Q207	Among them, how many were one-night stand? (If none, please write 0)	Number of one-night stands [__|__|__]	
Q208	Have you ever used condoms?	Yes 1 No 2 Don't know 998	 →**Q211**

Q209	With regards to sex with your steady partners, with what frequency did you and your steady partner(s) use condoms over the last year? (If you did not have a steady partner, please circle number 9)	Every time (100% of the time) 1 Almost every time (75-99%) 2 Often (50-74%) 3 Sometimes (25-49%) 4 Rarely (1-24%) 5 Never (0%) 6 No steady partner over last year 7 Don't know 998	
Q210	With regards to sex with your one-night stands, with what frequency did you and your one-night stands use condoms over the last year? (If you did not have one-night stand partner, please circle number 9)	Every time (100% of the time) 1 Almost every time (75-99%) 2 Often (50-74%) 3 Sometimes (25-49%) 4 Rarely (1-24%) 5 Never (0%) 6 No one-night stand over last year 7 Don't know 998	
Q211	Compared to other women of your age, do you consider your-self as having had more, fewer, or about the same number of sex partners?	More 1 Fewer 2 About the same 3 Don't know 998	
Q212	What level of risk of sexually transmitted infections do you think you are having?	Not at risk 1 Low risk 2 Medium risk 3 High risk 4 Don't know 998	

Section 3 *Now we would like to ask you some questions about certain health conditions. There is no right or wrong, good or bad answers. Please truly tell us what you know or think.*

No.	Questions and filters	Coding categories	Skip to
Q301	Before you participated in this study, have you ever heard about cancers of the cervix (cervical cancer)?	Yes 1 No 2	→**Q304**
Q302	Do you believe that cervical cancer is a common cancer among women?	Very common 1 Rather common 2 Not so common 3 Very uncommon 4 Don't know 998	

No.	Questions and filters	Coding categories	Skip to
Q303	Have you ever heard about any possible cause(s) of cervical cancer?	Yes 1 No 2	
Q304	Have you ever heard of Condyloma, also called Genital Warts?	Yes 1 No 2	→**Q307**
Q305	Do you believe that Condyloma is a serious disease?	Very serious 1 Rather serious 2 Not so serious 3 Not serious at all 4 Don't know 998	
Q306	Have you ever heard about any possible cause(s) of Condyloma?	Yes 1 No 2	
Q307	Before you participated in this study, have you heard about a virus called Human Papillomavirus (HPV)?	Yes 1 No 2	→**Q401**
Q308	Do you believe that HPV may cause cervical cancer?	Yes 1 No 2 Don't know 998	
Q309	Do you believe that HPV may cause other types of cancer than cervical cancer?	Yes 1 No 2 Don't know 998	
Q310	Do you believe that HPV may cause Condyloma?	Yes 1 No 2 Don't know 998	
Q311	Do you believe that HPV is sexually transmitted?	Yes 1 No 2 Don't know 998	
Q312	Do you believe that women can be infected by HPV?	Yes 1 No 2 Don't know 998	
Q313	Do you believe that men can be infected by HPV?	Yes 1 No 2 Don't know 998	
Q314	Are you aware if there is a vaccine against HPV caused disease?	A vaccine is available 1 A vaccine is being tested 2 There is no such vaccine 3	

	SELECT ONE	Don't know 998	

Section 4 *In this section, we will ask for your general opinions about vaccination. Again, there is no right or wrong answer. Please let us know what you think.*

No.	Questions and filters	Coding categories	Skip to
Q401	In general, do you believe that vaccination is an effective way against diseases? (Please circle one choice only)	Very effective 1 Rather effective 2 Not so effective 3 Not effective at all 4 Don't know 998	
Q402	Do you think that vaccination is a cost-efficient way against diseases?	Very cost-efficient 1 Rather cost-efficient 2 Not so cost-efficient 3 Not cost-efficient at all 4 Don't know 998	
Q403	In your opinion, is vaccination generally a safe way against disease?	Very safe 1 Rather safe 2 Not so safe 3 Not safe at all 4 Don't know 998	
Q404	If there is a vaccine that is coming out that concern you, how would you like to know about it? (Several choices may be given)	Via health workers 1 Educational programs on TV, radios 2 Health education at work/school 3 Booklet, brochure, leaflet 4 Authorized websites 5 Others 6 ……. Don't know 998	
Q405	Which of the above ways would be the *best* way you want to know about a new vaccine? (Please select only one choice)	Via health workers 1 Educational programs on TV, radios 2 Health education at work/school 3 Booklet, brochure, leaflet 4 Authorized websites 5 Others 6 ……. Don't know 998	

Section 5

For your information, an effective three-dose vaccine against HPV has been developed and will soon be ready for use. Please do not go back and "correct" any answer given previously. We would like to ask for your opinion about the usage of this new HPV vaccine.

No.	Questions and filters	Coding categories	Skip to
Q501	If the vaccine is free, would you be willing to vaccinate yourself?	Yes 1 No 2 Don't know 998	→**Q505**
Q502	What if the vaccine is only given at some extra cost, would you still be willing to vaccinate yourself?	Yes 1 No 2 Don't know 998	→**Q504** →**Q504**
Q503	What is the maximum cost that you think you can afford? (Three doses are considered to give full protection) (If you will vaccinate yourself at all cost, please circle number 2)	Price per dose (in SEK) …… Vaccination at any cost 2	
Q504	At what age would you consider vaccinate yourself? (Please circle number 9 if you don't consider vaccinating yourself at any age)	Age to start HPV vaccination [__|__] I don't consider HPV vaccination 9	
Q505	You may have concerns about the new vaccine. If so, please mark what you would like to know more about this new HPV vaccine? (You can select more than one choice if necessary)	If the vaccine is really protective 1 If there are any side effects (safety) 2 If vaccine needs to be repeated with more doses in the future 3 Others 4 Please specify:_____ _____ I have no concerns 5 Don't know 998	→**Q507**
Q506	If it may, what of those concerns could MOST likely make you NOT vaccinate yourself against HPV? (Please circle only ONE choice)	If the vaccine is really protective 1 If there are any side effects (safety) 2 If vaccine needs to be repeated with more doses in the future 3 Others 4 Please specify:_____ _____ I would get vaccinated despite concerns 5 Don't know 998	
Q507	Do you think that you would be fully protected against cervical cancer if you get vaccinated?	Yes 1 No 2 Don't know 998	
Q508	Do you think that you would be fully protected against condyloma if you	Yes 1 No 2	

	get vaccinated?	Don't know 998	
Q509	Would you consider having more unprotected sex (=not using a condom) if you get vaccinated?	Yes 1 No 2 Don't know 998	

Section 6 *Cervical cancer screening program*

No.	Questions and filters	Coding categories	Skip to
Q601	Have you ever heard about the cervical cancer screening program?	Yes 1 No 2	 **→Q604**
Q602	Have you ever participated in a cervical cancer screening program?	Yes 1 No 2 Don't know 998	 **→Q604** **→Q604**
Q603	How would your behavior regarding cervical cancer screening be affected if you get vaccinated against HPV?	I would stop having Pap smears 1 I would have Pap smears less frequently than today 2 I would have Pap smears as usual 3 Don't know 998	
Q604	If the answers is No or Don't know in Q601 or Q602, do you think you will participate in a cervical cancer screening program in the future, even if you are vaccinated against HPV?	Yes I will 1 No I will not 2 I don't know 998	

End of the questionnaire

Thank you very much for taking time to answer these questions. We highly appreciate your help!

Karolinska Institutet

UNDERSÖKNING OM INSTÄLLNINGEN TILL ETT NYTT VACCIN
FRÅGEFORMULÄR FÖR KVINNOR MELLAN 18 OCH 30 ÅR

Fyll i de förtryckta fälten eller kryssa in det alternativ som du anser passar bäst

Del 1. Bakgrund

Nr	Frågor
F101	**Hur gammal är du?** ☐☐
F102	**I vilket land är du född?** **1.** ☐ Sverige **2.** ☐ Danmark, Finland, Island eller Norge **3.** ☐ Annat land
F103	**Vilket är ditt nuvarande civilstånd?** **1.** ☐ Gift/sambo/registrerad partner **- Gå till F105** **3.** ☐ Änka **2.** ☐ Ensamstående **999.** ☐ Vill ej svara
F104	**Har du *för närvarande* ett förhållande?** **1.** ☐ Ja **2.** ☐ Nej
F105	**Vilken är din *huvudsakliga* sysselsättning?** ***Välj endast ett alternativ*** **1.** ☐ Heltidsarbetande **3.** ☐ Arbetslös **5.** ☐ Föräldraledighet **2.** ☐ Deltidsarbetande **4.** ☐ Sjukpensionär **6.** ☐ Studerande **7.** ☐ Annat (ange vad) .....
F106	**Vilken är din årliga inkomst före skatt? Inkludera arbetslöshetsunderstöd, sjukpension, etc. Inkludera *inte* studielån och studiebidrag** ***Välj endast ett alternativ*** **1.** ☐ Mindre än 50 000 kr/år **4.** ☐ 150 000–200 000 kr/år **7.** ☐ 300 000–400 000 kr/år **2.** ☐ 50 000–100 000 kr/år **5.** ☐ 200 000–250 000 kr/år **8.** ☐ 400 000–500 000 kr/år **3.** ☐ 100 000–150 000 kr/år **6.** ☐ 250 000–300 000 kr/år **9.** ☐ Mer än 500 000 kr/år **998.** ☐ Vet ej
F107	**Vilken är din högsta avslutade utbildning?** ***Välj endast ett alternativ*** **1.** ☐ Grundskola år 1–9 **5.** ☐ Folkhögskola **2.** ☐ Yrkesskola **6.** ☐ Högskola/universitet upp till 2 år **3.** ☐ Gymnasium **7.** ☐ Högskola/universitet mer än 2 år **4.** ☐ Vuxenutbildning **8.** ☐ Annat .....
F108	**Hur många år har du sammanlagt studerat fram till idag?** Antal (hela) studieår ☐☐ **998.** ☐ Vet ej

Fyll i de förtryckta fälten eller kryssa in det alternativ som du anser passar bäst

Del 2. Nu följer några frågor om sexualvanor. Dina svar kan hjälpa oss att förstå hur vissa sjukdomar kan förhindras. Vi ber dig besvara frågorna så noggrannt som möjligt.

Nr	Frågor
F201	**Med vilka av följande har du någon gång haft någon typ av sexuellt umgänge?** *Flera alternativ kan anges* **1.** ☐ Man **2.** ☐ Kvinna **3.** ☐ Har aldrig haft sexuellt umgänge - **Gå till F301**
F202	**Har du haft vaginalt samlag någon gång?** **1.** ☐ Ja **2.** ☐ Nej - **Gå till F204** **998.** ☐ Vet ej - **Gå till F204**
F203	**Om ja på ovanstående fråga, hur gammal var du första gången du hade vaginalt samlag?** Ålder ☐☐ **998.** ☐ Vet ej
F204	**Har du någonsin haft annan typ av sexuellt umgänge än vaginalt samlag?** *Flera alternativ kan anges* **1.** ☐ Oralsex **2.** ☐ Analsex **3.** ☐ Annan typ av sex **4.** ☐ Endast vaginalt samlag - **Gå till F206** **999.** ☐ Vill ej svara
F205	**Hur gammal var du när du hade någon av ovan nämnda typer av sex första gången?** Ålder ☐☐ **998.** ☐ Vet ej
F206	**Hur många sexpartners har du haft det senaste året? Räkna med fasta partners och tillfälliga förbindelser.** ***(Om ingen, ange 0)*** Antal sexpartners ☐☐☐ **998.** ☐ Vet ej
F207	**Hur många av dina sexpartners det senaste året var tillfälliga förbindelser?** ***(Om ingen, ange 0)*** Antal tillfälliga förbindelser ☐☐☐ **998.** ☐ Vet ej
F208	**Har du någonsin använt kondom?** **1.** ☐ Ja **2.** ☐ Nej - **Gå till F212** **998.** ☐ Vet ej

Fyll i de förtryckta fälten eller kryssa in det alternativ som du anser passar bäst

Nr	Frågor
F209	**När du hade sex med din(a) *fast(a)* partner(s), hur ofta använde ni kondom under det senaste året? (Välj nummer 7 om du inte hade någon fast partner det senaste året?)** **1.** ☐ Varje gång (100% av tillfällena) **2.** ☐ Nästan varje gång (75-99%) **3.** ☐ Ofta (50-74%) **4.** ☐ Ibland (25-49%) **5.** ☐ Sällan (1-24%) **6.** ☐ Aldrig (0%) **7.** ☐ Har inte haft någon fast partner senaste året **998.** ☐ Vet ej
F210	**När du hade sex med din(a) *tillfällig(a)* partner(s), hur ofta använde ni kondom under det senaste året? (Kryssa nummer 7 om du inte hade någon tillfällig partner det senaste året?)** **1.** ☐ Varje gång (100% av tillfällena) **2.** ☐ Nästan varje gång (75-99%) **3.** ☐ Ofta (50-74%) **4.** ☐ Ibland (25-49%) **5.** ☐ Sällan (1-24%) **6.** ☐ Aldrig (0%) **7.** ☐ Har inte haft någon tillfällig partner senaste året **998.** ☐ Vet ej
F211	**Jämfört med andra kvinnor i din ålder, tror du att du har haft fler, färre eller ungefär lika många sexpartners (totalt sett)?** **1.** ☐ Fler **2.** ☐ Färre **3.** ☐ Ungefär lika många **998.** ☐ Vet ej
F212	**Hur stor risk att råka ut för sexuellt överförbara sjukdomar tror du att du har?** **1.** ☐ Ingen risk **2.** ☐ Liten risk **3.** ☐ Ganska stor risk **4.** ☐ Stor risk **998.** ☐ Vet ej

Del 3. Nu följer några frågor om hälsoförhållanden. Det finns inga riktiga eller felaktiga svar. Vi ber dig svara uppriktigt vad du vet eller tror.

Nr	Frågor
F301	**Hade du hört talas om livmoderhalscancer innan du deltog i denna studie?** **1.** ☐ Ja **2.** ☐ Nej - **Gå till F304**
F302	**Tror du att livmoderhalscancer är en vanlig cancerform bland kvinnor?** **1.** ☐ Mycket vanlig **3.** ☐ Inte så vanlig **2.** ☐ Ganska vanlig **4.** ☐ Mycket ovanlig **998.** ☐ Vet ej
F303	**Känner du till möjliga orsaker till livmoderhalscancer?** **1.** ☐ Ja **2.** ☐ Nej
F304	**Har du någonsin hört talas om kondylom, även kallade könsvårtor?** **1.** ☐ Ja **2.** ☐ Nej - **Gå till F307**
F305	**Hur allvarligt är kondylom enligt din uppfattning?** **1.** ☐ Mycket allvarligt **3.** ☐ Inte så allvarligt **2.** ☐ Ganska allvarligt **4.** ☐ Inte alls allvarligt **998.** ☐ Vet ej
F306	**Känner du till möjliga orsaker till kondylom?** **1.** ☐ Ja **2.** ☐ Nej
F307	**Hade du hört talas om ett virus kallat humant papillomvirus (HPV) innan du deltog i denna studie?** **1.** ☐ Ja **2.** ☐ Nej - **Gå till F401**
F308	**Tror du att HPV kan orsaka livmoderhalscancer?** **1.** ☐ Ja **2.** ☐ Nej **998.** ☐ Vet ej
F309	**Tror du att HPV kan orsaka annan cancer än livmoderhalscancer?** **1.** ☐ Ja **2.** ☐ Nej **998.** ☐ Vet ej
F310	**Tror du att HPV kan orsaka kondylom?** **1.** ☐ Ja **2.** ☐ Nej **998.** ☐ Vet ej
F311	**Tror du att HPV kan smitta genom sexuellt umgänge?** **1.** ☐ Ja **2.** ☐ Nej **998.** ☐ Vet ej
F312	**Tror du att kvinnor kan smittas av HPV?** **1.** ☐ Ja **2.** ☐ Nej **998.** ☐ Vet ej
F313	**Tror du att män kan smittas av HPV?** **1.** ☐ Ja **2.** ☐ Nej **998.** ☐ Vet ej
F314	**Känner du till om det finns något vaccin mot sjukdom orsakad av HPV?** ***Välj endast ett alternativ*** **1.** ☐ Ett vaccin finns tillgängligt **3.** ☐ Det finns inget vaccin mot HPV **2.** ☐ Ett vaccin testas för närvarande **998.** ☐ Vet ej

Fyll i de förtryckta fälten eller kryssa in det alternativ som du anser passar bäst

Del 4. Nu följer några frågor om din inställning till vaccination.
Återigen finns det inga rätta eller felaktiga svar. Ange bara din åsikt.

Nr	Frågor
F401	**Tror du att vaccination kan vara ett effektivt sätt att förebygga sjukdomar?** ***Välj endast ett alternativ*** **1.** ☐ Mycket effektivt **3.** ☐ Inte så effektivt **2.** ☐ Ganska effektivt **4.** ☐ Inte alls effektivt **998.** ☐ Vet ej
F402	**Tror du att vaccination kan vara ett kostnadseffektivt sätt att förebygga sjukdomar?** ***Välj endast ett alternativ*** **1.** ☐ Mycket kostnadseffektivt **3.** ☐ Inte så kostnadseffektivt **2.** ☐ Ganska kostnadseffektivt **4.** ☐ Inte alls kostnadseffektivt **998.** ☐ Vet ej
F403	**Tror du att vaccination är en säker metod att förebygga sjukdomar?** ***Välj endast ett alternativ*** **1.** ☐ Mycket säker **3.** ☐ Inte så säker **2.** ☐ Ganska säker **4.** ☐ Inte alls säker **998.** ☐ Vet ej
F404	**Om det lanseras ett vaccin som du skulle kunna ha nytta av, hur skulle du helst vilja få reda på det?** ***Flera alternativ kan anges*** **1.** ☐ Via sjukvårdspersonal **5.** ☐ Via Internet **2.** ☐ Utbildningsprogram på TV eller radio **6.** ☐ Annat sätt (Ange vad) ..... **3.** ☐ Hälsoundervisning på arbete/skola **4.** ☐ Informationsfolder, broschyr, häfte ..... **998.** ☐ Vet ej - **Gå till F501**
F405	**Vilket av ovanstående sätt skulle vara det bästa för dig att få information om ett nytt vaccin?** ***Välj endast ett alternativ*** **1.** ☐ Via sjukvårdspersonal **5.** ☐ Via Internet **2.** ☐ Utbildningsprogram på TV eller radio **6.** ☐ Annat sätt (Ange vad) ..... **3.** ☐ Hälsoundervisning på arbete/skola **4.** ☐ Informationsfolder, broschyr, häfte ..... **998.** ☐ Vet ej

Fyll i de förtryckta fälten eller kryssa in det alternativ som du anser passar bäst

Del 5. **Vi vill informera dig om att HPV är ett sexuellt överförbart virus som kan orsaka kondylom hos män och kvinnor och livmoderhalscancer hos kvinnor. Ett effektivt HPV-vaccin har utvecklats och är klart för användning.** ***Vi ber dig att inte gå tillbaka och ändra något av de tidigare avgivna svaren.***
Nu vill vi fråga om din åsikt angående användning av det nya HPV-vaccinet.

Nr	Frågor
F501	**Skulle du vilja vaccinera dig mot HPV om vaccinet är gratis?** **1.** ☐ Ja **2.** ☐ Nej - **Gå till F505** **998.** ☐ Vet ej
F502	**Skulle du vilja vaccinera dig mot HPV om vaccinet kostar pengar?** **1.** ☐ Ja **2.** ☐ Nej - **Gå till F504** **998.** ☐ Vet ej - **Gå till F504**
F503	**Vilken är den högsta kostnad du kan tänka dig att betala för att vaccinera dig mot HPV? (Tre doser anses ge ett fullgott skydd).** Pris för vaccination per dos (i kr) ..... **2.** ☐ Vaccination oavsett kostnad
F504	**Vid vilken ålder anser du att man ska vaccinera mot HPV?** Ålder för att påbörja HPV-vaccination ☐☐ **9.** ☐ Jag överväger inte HPV-vaccination
F505	**Vilken information skulle du vilja ha om det nya vaccinet?** ***Flera alternativ kan anges*** **1.** ☐ Om vaccinet verkligen skyddar **5.** ☐ Jag har inga frågor - **Gå till F507** **2.** ☐ Om vaccinet har biverkningar **998.** ☐ Vet ej **3.** ☐ Om vaccinationen behöver upprepas **4.** ☐ Annat (Ange vad) ....
F506	**Skulle någon av ovanstående frågor kunna få dig att avstå från att vaccinera dig mot HPV?** ***Välj endast ett alternativ*** **1.** ☐ Om vaccinet verkligen skyddar **5.** ☐ Jag skulle vaccinera mig oavsett frågor **2.** ☐ Om vaccinet har biverkningar **998.** ☐ Vet ej **3.** ☐ Om vaccinationen behöver upprepas **4.** ☐ Annat (Ange vad) ....

Fyll i de förtryckta fälten eller kryssa in det alternativ som du anser passar bäst

Nr	Frågor
F507	**Tror du att du skulle vara fullständigt skyddad mot livmoderhalscancer om du vaccinerade dig mot HPV?** **1.** ☐ Ja **2.** ☐ Nej **998.** ☐ Vet ej
F508	**Tror du att du skulle vara fullständigt skyddad mot kondylom om du vaccinerade dig mot HPV?** **1.** ☐ Ja **2.** ☐ Nej **998.** ☐ Vet ej
F509	**Skulle du kunna tänka dig att ha mer oskyddat sex än idag (=utan att använda kondom) om du vaccinerar dig mot HPV?.** **1.** ☐ Ja **2.** ☐ Nej **998.** ☐ Vet ej

Del 6 Nedan följer några frågor om deltagande i gynekologisk cellprovskontroll.

Nr	Frågor
F601	**Har du någonsin hört talas om gynekologisk cellprovskontroll för att förebygga livmoderhalscancer?** **1.** ☐ Ja **2.** ☐ Nej - **Gå till F604**
F602	**Har du någonsin tagit ett gynekologiskt cellprov?** **1.** ☐ Ja **2.** ☐ Nej - **Gå till F604** **998.** ☐ Vet ej - **Gå till F604**
F603	**Hur skulle ditt beteende beträffande gynekologisk cellprovskontroll påverkas om du vaccinerar dig mot HPV?** **1.** ☐ Jag skulle helt sluta ta cellprov **3.** ☐ Jag skulle forsätta ta cellprov som tidigare **2.** ☐ Jag skulle ta cellprov mer sällan än idag **998.** ☐ Vet ej
F604	*Denna fråga gäller endast dig som svarade nej eller vet ej i någon av frågorna F601 eller F602* **Om du vaccinerar dig mot HPV, tror du att du kommer att ta gynekologiska cellprov i framtiden?** **1.** ☐ Ja **2.** ☐ Nej **998.** ☐ Vet ej

Slut på frågeformuläret

Ett stort tack för att Du tog dig tid att svara på dessa frågor. Vi uppskattar verkligen din hjälp!