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REGISTER-BASED EVALUATION OF HPV VACCINATION PROGRAMS

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ABSTRACT

The studies included in this thesis examined the population-level effect of human Papillomavirus (HPV) vaccination on incidence of HPV-related disease outcomes, and participation to cervical screening following vaccination.

In *study I*, a cohort of young Swedish girls ages 10 to 24 was followed for HPV vaccination and condyloma to investigate the effect of vaccination on condyloma by vaccine dose. The results showed greatest protection against condyloma following administration of three HPV vaccine doses. Considerable protection against condyloma was also seen after vaccination with two doses of the quadrivalent HPV (qHPV) vaccine. Risk reductions of 71% and 82% following vaccination with two and three doses, respectively, were seen when vaccination was initiated prior age 17. Greater protection against condyloma was seen in those younger at vaccination initiation.

In *study II*, a birth cohort of women at cervical screening ages (born between 1977 and 1987) was followed for HPV vaccination, invitation to cervical screening, and attendance to screening. The results showed that, compared to unvaccinated women, women HPV vaccinated through opportunistic vaccination were equally likely, if not more likely to attend organized cervical screening following an invitation letter to cervical screening.

In *study III*, a cohort of young Swedish girls and women at ages 23 to 29 was followed for HPV vaccination and cervical lesions, i.e. cervical intraepithelial neoplasia (CIN) stage 2 or worse (CIN2+) and CIN stage 3 or worse (CIN3+), to investigate the effect of vaccination on incidence of cervical lesions after three-dose vaccination. The results showed reductions in risk for CIN2+ and CIN3+ following vaccination in girls and young women that initiated vaccination up until age 29. Greater reductions in risk for cervical lesions were seen in those younger at vaccination initiation. A maximum reduction of 75% and 84% in risk for CIN2+ and CIN3+, respectively, were seen when vaccination was initiated prior to age 17.

In *study IV*, we assessed the incidence of condyloma following the introduction of qHPV in Sweden. During the study period, girls were mainly vaccinated via opportunistic HPV vaccination, and vaccination coverage remained rather low. Declines in condyloma incidence in girls below age 20 were seen following the introduction of qHPV vaccination in Sweden and confirm anticipated effects. In addition, we observed declines in incidence of condyloma among men and in women age 20 and above indicates possible herd protection.

In conclusion, the results of these studies contribute to the existing evidence on the population level effect of HPV vaccination and the disease monitoring of HPV related disease in an era where opportunistic HPV vaccination was available. The results of study I have also contributed to the discussions on reduced vaccine dosing schedules. Future monitoring of the disease burden over time, as well as observational studies comparing vaccinated and unvaccinated individuals, are necessary to evaluate whether the organized school-based vaccination program has the anticipated effect in the population.

LIST OF SCIENTIFIC PAPERS

I. **Herweijer E**, Leval A, Ploner A, et al. Association of varying number of doses of quadrivalent human papillomavirus vaccine with incidence of condyloma. JAMA. 2014;311(6):597-603. doi:10.1001/jama.2014.95.

II. **Herweijer E**, Feldman AL, Ploner A, et al. The Participation of HPV-Vaccinated Women in a National Cervical Screening Program: Population-Based Cohort Study. PLoS ONE. 2015;10(7):e0134185. doi:10.1371/journal.pone.0134185.

III. **Herweijer E**, Sundström K, Ploner A, Uhnoo I, Sparén P, Arnheim-Dahlström L. Quadrivalent HPV vaccine effectiveness against high-grade cervical lesions by age at vaccination: A population-based study. Int J Cancer. March 2016:n/a - n/a. doi:10.1002/ijc.30035.

IV. **Herweijer E**, Ploner A, Sundström K, Arnheim-Dahlström L, Sparén P. Incidence of genital warts six years after HPV vaccine availability. In manuscript.

RELATED PUBLICATIONS

I. Leval A, **Herweijer E**, Arnheim-Dahlström L, Walum H, Frans E, Sparén P, Simard JF. Incidence of Genital Warts in Sweden Before and After Quadrivalent Human Papillomavirus Vaccine Availability. J Infect Dis 2012;206:860–6.

II. Leval A, **Herweijer E**, Ploner A, Eloranta S, Simard JF, Dillner J, Young C, Netterlid E, Sparén P, Arnheim-Dahlström L. Quadrivalent Human Papillomavirus Vaccine Effectiveness: A Swedish National Cohort Study. J Natl Cancer Inst 2013;105:469–74.

III. Elfstrom K, **Herweijer E**, Sundstrom K, Arnheim-Dahlstrom L. Current cervical cancer prevention strategies including cervical screening and prophylactic human papillomavirus vaccination: a review. Curr Opin Oncol January 2014 2014;26:120–9.

IV. Ploner A, **Herweijer E**, Arnheim-Dahlström L. Number of human papillomavirus vaccine doses and condyloma—reply. JAMA 2014;311:2439–40.

CONTENTS

LIST OF ABBREVIATIONS

9vHPV	9-valent HPV
AAPC	Average Annual Percent Change
APC	Annual Percent Change
ATC	Anatomical Therapeutic Chemical
bHPV	Bivalent HPV
CDR	Causes Of Death Register
CI	Confidence Interval
CIN2 / CIN3	Cervical Intraepithelial Neoplasia Stage 2 / 3
CIN2+ / CIN3+	CIN2 Or Worse / CIN3 Or Worse
EMA	European Medicines Agency
FDA	Food And Drug Administration
HPV	Human Papillomavirus
HR	Hazard Ratio
IARC	International Agency For Research on Cancer
ICD	International Classification Of Diseases
ICD-O/3	International Classification of Diseases For Oncology Version 3
IR	Incidence Rate
IRD	Incidence Rate Difference
IRR	Incidence Rate Ratio
LISA	Longitudinal Integration Database For Health Insurance and Labour Market Studies
LSIL	Low Grade Squamous Intraepithelial Lesions
MGR	Multigeneration Register
NKCx	Swedish National Cervical Screening Registry
NPR	National Patient Register
NVR	National Vaccination Register
PDR	Prescribed Drug Register
PIN	Personal Identity Number
qHPV	Quadrivalent HPV
SCR	Swedish Cancer Register
SKL	Local Authorities and Regions
SMI	Swedish Institute for Communicable Disease Control
SNOMED	Systematized Nomenclature Of Medical Diagnoses

SVEVAC	Swedish HPV Vaccination Register
TPR	Total Population Register
VLP	Virus-Like Particles
WHO	World Health Organization

1 BACKGROUND

The human Papillomavirus (HPV) is found in the large majority of cervical cancer cases and is believed to be a necessary but not sufficient cause of cervical cancer (1–4). HPV DNA was first identified in cervical cancer cases in the early 1980s (3). Not long after this discovery, it was shown that the vast majority of all cervical cancers contain HPV (4,5). Currently, there are over 200 different types of HPV identified (6,7), but not all HPV have the potential to cause malignancies. About 40 types of HPV infect the genital tract and the oncogenic potential of thirteen of these HPV-types (high-risk HPV) has been acknowledged by the International Agency for Research on Cancer (IARC) (8). Genital HPV is transmitted via skin-to-skin contacts, mainly during sexual intercourse. Infection with HPV is common; around 291 million women worldwide are HPV infected (9). The overall prevalence of HPV in women with normal cytology is about 10% and is highest among young sexually active women (9). Though there are differences by regions, there is generally a second peak in HPV prevalence at older ages (9,10). The overall life-time probability for both men and women to acquire an HPV infection before age 45 is estimated to be over 80% (11).

1.1 PROPHYLACTIC HPV VACCINES

The recognition that infection with HPV can lead to cervical cancer has expedited the development of vaccines preventing infection. The HPV vaccines currently available are subunit L1 virus-like particles (VLPs) vaccines and include an adjuvant which is a solution that enhances the immune response. L1 is a capsid protein that can self-assemble to VLPs which trigger an antibody response in the body. In contrast to live-attenuated or weakened virus vaccines there is no risk that vaccination can cause the disease as subunit vaccines do not include infectious viral DNA (12). This is comforting considering the oncogenic potential of HPV.

Three prophylactic HPV vaccines have received marketing authorization by both the Food and Drug Administration (FDA) and European Medicines Agency (EMA). In 2006, the first prophylactic HPV vaccine, the quadrivalent HPV (qHPV) vaccine (Gardasil™; Merck), was approved targeting HPV types 6, 11, 16, and 18 (13,14). The high-risk HPV types 16 and 18 are found in 70% of cervical cancer cases (2,15). The 9-valent HPV (9vHPV) vaccine (Gardasil 9™; Merck) was approved in 2014 by the EMA and in 2015 by the FDA offering protection against five additional high-risk HPV types (HPV types 31, 33, 45, 52, 58) that are estimated to cause about 20% of cervical cancers (16,17). The bivalent HPV (bHPV) vaccine (Cervarix™; GlaxoSmithKline) including HPV types 16 and 18 was licensed in 2007 by the EMA and in 2009 by the FDA (18,19). As of January 2016, 66 countries have introduced HPV vaccination in their national immunization program (20).

The qHPV and 9vHPV vaccines are indicated for use in girls and women to protect against HPV vaccine type related condyloma, and cancer and precursor lesions of the cervix, vulva, and anus. qHPV and 9vHPV vaccination is also approved in boys and men for prevention of condyloma, anal cancer, and its precursor lesions related to HPV types included in the

vaccine (21,22). The bHPV vaccine is indicated for girls and women for prevention of HPV type 16 and 18 related cervical cancer and precursor lesions of cervical cancer (23).

1.1.1 Results from clinical trials

The HPV vaccines have been extensively tested in Phase III trials before market authorization was granted. The vaccines elicit good immune responses. Shortly after vaccination, there is a peak in serum antibody concentration of vaccine HPV-types after which serum antibody concentrations subside until reaching a plateau level (24,25). The antibody responses seen after HPV vaccination were higher than the antibody responses observed after natural HPV infections (25–28). Furthermore, nearly all women that were vaccinated seroconverted (26,29). In contrast, the rate of seroconversion after a natural HPV infection is about 60% following an incident infection with HPV type 16 (30). For qHPV vaccination, about 40% of the women were no longer HPV type 18 seropositive 4 years post-vaccination (31). However, there are no signs of lower efficacy against HPV related disease so far (29,31).

Persistent HPV infections, condyloma, and premalignant disease are the first endpoints that can be studied in the clinical trial data as their incubation times are considerably shorter than the incubation time of cervical cancer. With efficacy rates of up to 100%, vaccine efficacy against HPV vaccine type-related anogenital and cervical disease was high in populations that were both seronegative and DNA negative for HPV vaccine types at vaccination initiation (29,32–36). The vaccine is less effective in intention to treat populations, i.e. a population composed of a mixture of women with past or current HPV exposure or HPV naïve women, most reflective for the real-life population (24,29,32–34,36).

The bHPV and qHPV vaccines do not have an effect on ongoing HPV infections. It was shown that the bHPV vaccine does not influence HPV clearance and no therapeutic effect was observed (37). There is no evidence that the qHPV vaccine has an effect on disease progression to high-grade cervical lesions in women that are HPV infected at the time of vaccination (38). Nevertheless, women previously infected with one or more HPV vaccine types may still benefit from HPV vaccination as the vaccine offers protections against the remaining HPV vaccine types to which the individual has not currently been exposed (39).

Results on efficacy of the 9vHPV vaccine in clinical trial settings have recently been published. As the effect of HPV vaccination has been shown previously, it is considered unethical for individuals assigned to the non-intervention group to receive a placebo, instead individuals received the qHPV vaccine (40). Incidence of persistent HPV infections and high grade cervical, vaginal, and vulvar disease due to infection with HPV types 6, 11, 16, and 18 should therefore be comparable after vaccination with qHPV and 9vHPV vaccine. This was confirmed in the trial data (40). Furthermore, the vaccine efficacy against persistent HPV infection and high grade cervical, vaginal, and vulvar disease for the five HPV vaccine types not included in the qHPV vaccine approached 100% in a population seronegative and DNA negative for vaccine HPV types at vaccination initiation (40).

1.1.2 Cross-protective properties of HPV vaccines

The clinical trial data for both bHPV and qHPV vaccine has shown cross-protective properties against non-vaccine type related HPV infection and cervical lesions (24,41–43). At the population level, lower prevalence of non-vaccine HPV types such as 31, 33, and 45 were found advocating cross protection (44,45). Moderate protection against persistent infection with non-high risk HPV types 6, 11, and 74 has been reported after vaccination with the bHPV vaccine (46). After England included the bHPV in the national immunization program a decrease in incidence of condyloma, the result of an infection with non-high risk HPV types 6 or 11, was observed (47).

1.1.3 Vaccination schedules

The HPV vaccines were initially licensed as three-dose vaccination schedules with the qHPV and 9vHPV vaccines given at 0, 2, and 6 months, and the bHPV vaccine given at 0, 1, and 6 months. Immunogenicity results have indicated non-inferiority in antibody response for HPV vaccine types when comparing three versus two dose antibody responses given 6 months apart (48–51). Studies conducted using infection as endpoint have also shown protection against infection with HPV 16 and/or 18 after vaccination with one and two doses of the bHPV vaccine (51–53). A review of the existing data on vaccination with two doses has led to a recommendation of a two-dose schedule by the World Health Organization (WHO). A two-dose schedule, given 6 months apart, may be given to girls at ages 9 to 13 (54).

1.2 VACCINE EFFICACY AND EFFECTIVENESS

Vaccine efficacy cannot be interpreted as vaccine effectiveness which is an estimate of the vaccine's performance when introduced in the target population (55). Vaccine efficacy is measured in a clinical trial setting where optimal conditions regarding to the selection of the study population, controlled and randomized distribution of the vaccine, measurement of the outcome, and vaccination adherence apply. Vaccine efficacy approximates the true effect of the vaccine which can be expected under ideal conditions. Such conditions are not at hand in routine practice. The clinical trials on HPV vaccination included different study populations varying from an ideal study population that approximates a sexually naïve, and thus HPV negative, population to an intention-to-treat population that represents an approximation of a real-life more heterogeneous population of HPV naïve women and women with current and previous HPV exposure. However, women included in the intention-to-treat populations of clinical trials also need to fulfil certain inclusion and exclusion criteria such as: maximum number of previous sexual partners, no prior abnormal pap-smear, and no history of condyloma or a colposcopy (26,36). This makes the study population in clinical trials different from the general population. Vaccine effectiveness is preferable from a public health perspective as it provides information on HPV vaccination programs, strategies, vaccine access, distribution, and direct and indirect effects of vaccination. Randomized clinical trials can effectively control for known and unknown biases, however, in vaccine effectiveness observational studies there is no inherent control for bias and they are therefore susceptible to

confounding (55). Therefore, vaccine effectiveness results at the population level should be interpreted with caution.

1.3 HPV-RELATED DISEASE OUTCOMES

Though HPV has been mainly associated with cervical cancer, its role in the development of precursors and cancers of the vulva, vagina, anus, penis, and oropharynx has been recognized (8). In addition non-high risk HPV types 6 and 11 have been found in the majority of the condyloma cases (56–58). The HPV-related disease outcomes condyloma, precancerous lesions and cancer of the cervix will be discussed in more detail below.

1.3.1 Condyloma

The non-HR HPV types 6 and 11 are found in about 90% of condyloma cases (57). The risk to develop condyloma following an infection with HPV types 6 or 11 is considerable. A previous study estimated that 66% of women with a HPV type 6 or 11 infection develop condyloma within 3 years (58). The infectivity rate, the percentage of individuals that develop condyloma after sexual intercourse with a partner with condyloma, is estimated to be 64% (59). Individuals with condyloma can receive pharmaceutical treatment with podophyllotoxin or imiquimod which can be applied at home. These treatments are considered to be the first-line therapy for the first occurrence of condyloma (60). Other treatments include cryotherapy, application of trichloracetic acid, and surgical treatment (60,61). Condyloma is a benign disease, but the patient can experience considerable anxiety or depression and discomfort (62). Recurrent disease is common and risk for recurrence varies by mode of treatment (61). It is estimated that about 20-30% of the cases recur (60). The median time between infection with HPV and condyloma is typically 1-6 months, although longer periods have also been reported (57–59). Condyloma is common in both men and women; the incidence of condyloma starts to rise sharply from age ~15 to peak in the early to mid-20s for both men and women (63–65). The peak incidence of condyloma is close to 1% (63–65). It is furthermore estimated that 1 out of 10 women will be diagnosed with condyloma before the age of 45 (66).

1.3.2 Cervical abnormalities and cancer of the cervix

The development of cervical cancer after an infection with HPV can take more than a decade (8). Cervical cancer is categorized by its histology and squamous cell cancer and adenocarcinoma of the cervix are the most common types of cervical cancer. Most women that are HPV infected clear the infection within 2 years (67,68). Women that remain persistently HPV infected are at higher risk for developing cervical lesions (69,70) that may develop into invasive cervical cancer (71). The risk for developing a cervical abnormality varies by HPV type and is generally higher for oncogenic HPV types (69,70,72).

The high-risk HPV types 16 and 18 are found in 70% of cervical cancer cases (2,15). These types are also detected in about half of the precursor lesions of cervical cancer and the proportion attributed to types 16 and 18 increases with lesion severity (73). An additional

20% of the cervical cancer cases are positive for HPV types 31, 33, 45, 52, and 58, the types included in the 9vHPV vaccine (2). Yearly, there are over 500,000 women worldwide that are diagnosed with cervical cancer (74). The estimated incidence of cervical cancer standardized by age is 14 per 100,000 individuals worldwide (74). Though there is variation by region: the rate has been estimated to be 27 cases per 100,000 women in Africa whereas it was 11 cases per 100,000 women in Europe (74).

1.4 CERVICAL SCREENING IN SWEDEN

Cervical screening was first introduced in Sweden in the 1960s. Since then the incidence of squamous cell cancer has dropped significantly; the incidence of cervical cancer in Sweden was around 20 cases per 100,000 women in 1968 and has dropped to around 7 cases per 100,000 women since (74,75). Screening does not seem to have as strong an effect on adenocarcinoma; the incidence of adenocarcinoma has not decreased since the introduction of cervical screening (75). Cervical cancer now is the 12th most common female cancer in Sweden, but remains the 4th most common cancer in women worldwide (74,76). The first national screening recommendations were issued in 1985 by the National Board of Health and Welfare. All women between ages 20 and 59 were recommended to attend screening once every 3 years (77). New national guidelines for cervical screening were issued in 1998; the age to start screening was increased to 23, and women between the ages of 51 and 60 years were recommended to attend screening once every 5 years (77). A switch to primary HPV testing has recently been recommended for all women at screening ages except for those 23 to 29 years old, where screening every 3rd year with cytology will continue. Women at ages 30 to 49 years will be screened every 3rd year with HPV testing, and women ages 50 to 64 years will be screened every 7th year with HPV testing. HPV-positive women are followed up with cytology, whereas HPV-testing is used for triage in women with low grade squamous intraepithelial lesions (LSIL) when cytology is the primary test. In addition to the HPV-test, cytological co-testing will be done in women that come in for cervical screening at around age 41 (78).

1.5 HPV VACCINATION IN SWEDEN

HPV vaccination became available in Sweden in the fall of 2006. Girls could get HPV vaccinated with the qHPV vaccine and, as of the fall of 2007, girls also could get HPV vaccinated with the bHPV vaccine. Starting in 2007, both the bHPV and qHPV vaccines were included in the National Pharmaceutical Product insurance program for girls ages 13 to 17. The National Pharmaceutical Product insurance program ensures that individuals do not have to pay more than 1800 SEK for drugs included in the program over a 12 month period (79). Girls that were outside this target age group of ages 13 to 17 were not eligible for reimbursement. From 2006 to 2012, vaccination was opportunistic in Sweden and the vaccination coverage remained rather low (around 25% for girls ages 13 to 17) (80). The National Board of Health and Welfare decided that, as of January 2010, HPV vaccination should be included in the childhood immunization program targeting girls at ages 10 to 12 years. An additional catch-up vaccination program was launched for girls at ages 13 to 18

years. The implementation of the programs experienced a delay due to an extended tendering process. After a renewed tender and three appeals, the qHPV vaccine won the tender in November 2011 and the school-based vaccination program was operative from 2012. The vaccination coverage within the organized school-based program has reached 80%, and is around 60% for girls that were vaccinated in the catch-up HPV vaccination program (81). As of January 2015, the policy was updated and girls ages 9-13 years are now HPV vaccinated based on a two dose schedule. Individuals outside the target age group (9 to 13 years) continue to get vaccinated with a three dose vaccination schedule.

Along with the introduction of HPV vaccination in Sweden, a national epidemiologic surveillance program of HPV vaccination was established. This surveillance work-plan was outlined by the Public Health Agency of Sweden (82). The program concerns the surveillance of HPV-related disease outcomes, seroepidemiology, and vaccination coverage. This information is of importance to confirm findings from clinical trials, but also to monitor the vaccination coverage, and obtain information on possible herd protection, HPV type replacement, and duration protection of the vaccine (82).

2 AIMS

The studies included in this thesis examined the population-level effect of HPV vaccination on incidence of HPV-related disease outcomes, and attendance to cervical screening following vaccination.

The specific study aims were:

Study 1: To examine the association between qHPV vaccination and first occurrence of condyloma in relation to vaccine dose in a population-based setting.

Study 2: To measure attendance to cervical screening after opportunistic HPV-vaccination.

Study 3: To examine the association between qHPV vaccination and first occurrence of cervical intraepithelial neoplasia (CIN) stage 2 or worse (CIN2+) and CIN stage 3 or worse (CIN3+) in a population-based setting.

Study 4: To assess incidence of condyloma following the introduction of qHPV vaccination in Sweden.

3 MATERIAL AND METHODS

3.1 DATA SOURCES AND COLLECTION

Studies I, II, III, IV were part of the long-term evaluation of the effect of HPV vaccination and safety for which ethical approvals were granted by the regional Ethical Review Board in Stockholm. The Swedish national quality and health data registers were used for the data collection for the studies included in this thesis. According to Swedish regulation, informed consent by the study participants is not required for the utilization of register-based data for research purposes (83).

All individuals that are resident in Sweden, for at least one year, have a personal identity number (PIN) (83). The Swedish national health data registers include individual-level data and the PIN is an important variable that can be used for data linkage between the registers. The National Board of Health and Welfare and Statistics Sweden are authorities that perform data linkages. Once a data linkage has been completed, the PIN is replaced by a study ID number. This is done to protect the integrity of personal data included the healthcare registers.

3.1.1 Demographic registers

All individuals that are resident in Sweden are registered with a PIN in the Total Population Register (TPR) which was established in 1968 and is held by Statistics Sweden. It includes basic information such as name, address, place of residence, sex, age, civil status, citizenship, country of birth, place of residence, and family relations between parents or parents and child(ren) (84,85). The Migration Register, including information on domestic moves, immigration, and emigration, and Multigeneration Register (MGR), containing information on an individual's biological and/or adoptive parents, are both extracted from the TPR (86).

The Longitudinal Integration Database for Health Insurance and Labour Market Studies (LISA) was first created in 1990. Updates are released annually. LISA is a rich data source containing e.g. information on participation in the labor market, education, and income of all individuals 16 years or older (87). For the studies included in this thesis, data extraction was limited to information on education level and disposable income.

The National Causes of Death Register (CDR) contains information on all deceased individuals that were registered as living in Sweden. The CDR was established in 1952 by Statistics Sweden, and was migrated to the National Board of Health and Welfare in 1994 (88).

3.1.2 National Patient Register (NPR)

The NPR was created in the mid-1960s by the National Board of Health and Welfare, and contained, at that time, only inpatient registration from public hospitals in selected counties. Since 1987 NPR has national coverage for inpatient somatic hospitalizations and from 1997 and onwards outpatient somatic care is included from selected counties. Outpatient care was systematically included starting in 2001 (84). Diagnoses are reported to the NPR using the

International Classification of Diseases (ICD) with the 10th revision of ICD in use since 1997 (89,90). Cases of cervical cancer and cervical lesions can also be identified from the patient register. However, a distinction by histological cell type, i.e. squamous or glandular cells, cannot be made.

3.1.3 Prescribed Drug Register (PDR)

The PDR is an automated register containing information on drug prescriptions dispensed at pharmacies in the entire country and has complete national coverage since its start in July, 2005. The National Board of Health and Welfare is responsible for the PDR. Drugs sold over-the-counter and inpatient prescriptions are not registered in the PDR. Drugs used in ambulatory care but administered at out-patient care are only partially registered. Drug prescriptions, including vaccine prescriptions, are entered in the PDR using Anatomical Therapeutic Chemical (ATC) codes (91,92).

3.1.4 Swedish HPV Vaccination Register (SVEVAC)

SVEVAC is a voluntary reporting system that was initiated by the former Swedish Institute for Communicable Disease Control (SMI), nowadays the Public Health Agency of Sweden. The register initially started in 2002 as a pilot project in three Swedish counties to register childhood vaccinations. Along with the introduction of HPV vaccination in Sweden in 2006, SVEVAC became a nationwide register for registering HPV vaccinations. Early comparisons between the sales figures and the number of vaccine doses registered in SVEVAC have shown register coverage of 85-90% (81). Since 2015 SVEVAC is run by the Swedish Association of Local Authorities and Regions (SKL).

Registration in SVEVAC requires the informed consent of the vaccinated individual or their parent. Vaccinations where informed consent is not obtained will be registered in SVEVAC anonymously. Information on sex, birth year, date of vaccination are still available, but the information cannot be linked to other registers as the PIN is missing. This means that it is not known which information belongs to one or several persons, i.e. whether an individual has multiple vaccine dose registrations or not. In 2012, the rate of anonymous registrations increased in some counties due to changes to the informed consent form made at the municipality level, i.e. a change from opt-out informed consent to opt-in informed consent, and changes to the online data entry form. Subsequently, the informed consent was changed back to an opt-out.

3.1.5 National Vaccination Register (NVR)

From 2013 a Swedish vaccination register for child vaccinations (up to and including age 12) was started by the Public Health Agency of Sweden (93). The NVR is a health data register with mandatory reporting. It includes all childhood vaccinations that are part of the national immunization program. Individuals vaccinated outside the childhood vaccination program, i.e. girls born before 1999 and boys, are registered in SVEVAC. Registration with PIN is

obligatory in the NVR and all HPV vaccinations in the school-based program are included since 2013.

3.1.6 Swedish National Cervical Screening Registry (NKCx)

The Swedish National Cervical Screening Registry, NKCx by its Swedish acronym, is a data quality register and contains information on all cytological and histological samples taken in the country as well as all invitations issued for cervical screening. NKCx has complete national coverage since the mid-1990s though cytology and histology data are available for some counties back to the early 1970s. Data on issued invitations to screening has been recorded since the mid-1990s and has been complete since 2008 (80,94). Results from cytology and histology are entered in NKCx according to the systematized nomenclature of medical diagnoses (SNOMED). This SNOMED coding is translated according to the Swedish standard cytology nomenclature at NKCx (94).

3.1.7 Swedish Cancer Register (SCR)

The National Board of Health and Welfare is responsible for the SCR. All newly detected cancer cases in Sweden have been registered since its start in 1958. It is mandatory for healthcare providers to report all new cases of cancer to the register. Three different types of data are stored in the SCR, namely: patient data, medical data, and follow-up data. The medical data includes detailed information on tumor characteristics such as the tumor site, tumor type, histological type, and staging (95,96). Since 2005, the site and type of the tumor have been characterized using ICD for oncology version 3 (ICD-O/3). However, characterization of the site and type of the tumor using ICD 7th revision and the WHO C24 histopathological code is available for the entire period starting in 1958 (96,97). Based on a comparison with the NPR, the overall underreporting of malignant cancer cases to the cancer register was estimated to be 3.7% in 1998; the rate varies by cancer site and was estimated 3.4% for cancers of the female genital organs (95). For cervix uteri also all cases of CIN3 including cancer in situ are registered.

3.2 EXTRACTION OF VACCINATION EXPOSURE FROM MULTIPLE REGISTERS

There are three data registers that include information on HPV vaccination: PDR, SVEVAC, and the NVR. During the opportunistic vaccination period (2007-2011) vaccinations were registered in SVEVAC. The majority of these vaccinations were also registered in the PDR since reimbursement for the HPV vaccine could only be obtained if vaccine doses were dispensed at the pharmacy. Individuals that directly purchased the vaccine and were subsequently vaccinated at a vaccination center are not registered in the PDR. HPV vaccinations as part of the school-based program (2012 and onwards) have been registered in SVEVAC, and from January 1st, 2013, all childhood vaccinations have been registered in the NVR.

The main exposure for studies I, II, and III is HPV vaccination. SVEVAC was used as the main source to obtain vaccination data. As in SVEVAC, the records in the NVR represent the actual vaccination date, and in study III, data were merged to the vaccination dates obtained from SVEVAC. The completeness of SVEVAC varies over the course of the study and incomplete vaccination records (individuals vaccinated with 1 or 2 doses) were therefore complemented with vaccine dispensation dates from PDR. Vaccine dispensation dates were identified with ATC codes J07BBM01 and J07BBM02 for the qHPV and bHPV vaccines, respectively. This was done using an algorithm where dispensation dates occurring directly after or more than 14 days prior to the vaccination administration date were considered as new doses. Studies I and III only utilize qHPV vaccination data to define vaccination status. As the purpose of study II was to assess screening attendance after HPV vaccination, irrelevant of the vaccine used, both bHPV and qHPV vaccines were included to define HPV vaccination status. Data from the NVR was only utilized in study III as this register only includes HPV vaccinations from 2013 and onwards and study follow-up in study I and II ends in 2010 and 2012, respectively.

3.3 STUDY OUTCOMES

3.3.1 Condyloma

First occurring cases of condyloma were included as the study outcome in study I. For study IV, both first occurring and subsequent cases of condyloma were used to define the study outcome. Cases of condyloma were identified via the NPR by using the 10th revision of the ICD code A63.0 and dispensations of pharmaceuticals podophyllotoxin and imiquimod were taken from the PDR using the corresponding ATC codes D06BB04 and D06BB10. The 10^{th} revision of the ICD code A63.0 is exclusively used to specify a diagnosis of condyloma. Podophyllotoxin is solely used to treat condyloma; however, imiquimod is also used to treat superficial basal cell carcinoma and actinic keratosis which are more likely to occur later in life (98–100). Individuals can have multiple records in the NPR and/or PDR related to one episode of condyloma. Differentiation between subsequent cases of condyloma is not possible. Therefore in study IV, a new subsequent case of condyloma was defined if there were no other condyloma-related hospital visits and no pharmaceuticals were prescribed for treatment of condyloma in the previous 6 months.

3.3.2 Attendance to cervical screening

Attendance to cervical screening was the study outcome in study II. All issued invitations were identified via NKCx. Attendance to cervical screening was defined as the first cytology taken after an invitation was issued. Women eligible for cervical screening, i.e. at ages 23 to 60, receive invitations to attend cervical screening. The first invitation to screening is sent to women at age 23, though some counties send invitations the year a woman turns 23 meaning that these women can receive an invitation and go to screening at age 22. New invitations to screening are issued after three years since the last registered cytology for women ages 23 to 50. For women ages 51 to 60, new invitations are issued five years after the last registered

cytology. Yearly reminders are sent to women that do not attend screening following an invitation.

3.3.3 Cervical lesions

The study outcomes of study III include first occurrence of a histological diagnosis of CIN2+ and CIN3+. Lesions with non-squamous origin, such as adenocarcinoma in situ (AIS) and adenocarcinoma, were also included in the outcomes CIN2+ and CIN3+. Diagnoses were identified via NKCx and the SCR based on the corresponding SNOMED codes and ICD 7th revision, 171 for cervical cancer, respectively. Table 1 shows the SNOMED codes, and their explanations, included in the outcomes CIN2+ and CIN3+.

Table 1. Diagnoses included in the outcomes CIN2+ and CIN3+ as identified from NKCx.

SNOMED	**Explanation**	**Histological diagnosis**	
		CIN2+	CIN3+
M74007	Cervical Intraepithelial Neoplasia grade 2	X	
M80702	Cervical Intraepithelial Neoplasia grade 3	X	X
M80702	Carcinoma in situ	X	X
M81402	Adenocarcinoma in situ	X	X
M85602	Adeno-squamous cancer in situ	X	X
M80703, M81401, M81403, M85601, M85603, M80413	Invasive cancer of any origin (squamous-cell carcinoma, adenocarcinoma, adeno-squamous carcinoma, small cell carcinoma)	X	X

3.4 STUDY DESIGN

3.4.1 Register-based cohort study design

Register-based cohort study designs were used for studies I, II, and III. In studies I and III the effect of vaccination in the population was assessed. A cohort of women ages 10 to 24 years (study I) and ages 10 to 29 years (study III), representing the entire female population resident in Sweden at some point in time during the study period, was followed for HPV vaccination and the disease outcome. As the HPV vaccines are prophylactic, all women that were diagnosed with the outcome prior to study inclusion were excluded. In study II, screening attendance after HPV vaccination was measured. The study base included a birth cohort of women born between 1977 and 1987 years that were invited to organized cervical screening at some point during the study period.

3.4.2 Ecological study design

An ecological study design was used for study IV to examine changes in condyloma incidence prior to and after HPV vaccine availability. Cases of condyloma were collected by calendar year and 5-year age-groups. In contrast to the register-based cohort approach in studies I, II, and III, where individual-level data was used, aggregated data was collected. Within an ecological study design, the exposure status is not linked to the outcome. Furthermore, data are analyzed at the population level rather than the individual level.

3.5 STUDY POPULATIONS

3.5.1 Study I

Data on vaccination, cases of condyloma, education level, and demographic information were merged with the source population comprising all girls and young women ages 10 to 24 years old (Figure 1a). The study period was between January 1, 2006 and December 31, 2010. Individuals were followed from their 10^{th} birthday or start of follow-up until the event of interest or one of the censoring criteria was reached, i.e. bHPV vaccination, death, emigration, age 25, or the end of the study period. Individuals that were diagnosed with condyloma prior to individual start of study follow-up were excluded.

3.5.2 Study II

Figure 1b shows the data that were utilized to construct the study population including women born between 1977 and 1987 that were invited to cervical screening. The study period started on October 1, 2006 and ended on December 31, 2012. The birth cohort was followed from invitation to cervical screening during the study period to attendance or one of the censoring criteria: death, emigration, or the end of the study period.

3.5.3 Study III

Information on vaccination, diagnoses of cervical lesions, education level, and demographic data were obtained from the Swedish quality and healthcare data registers and were merged to the source population comprising of all girls and young women at ages 13 to 29 (Figure 1c). The study period started on January 1, 2006 and ended on December 31, 2013. Individuals were followed from their 13^{th} birthday or start of follow-up until the event of interest, i.e. CIN2+ or CIN3+, or when one of the censoring criteria was reached, i.e. bHPV vaccination, death, emigration, age 30, or the end of the study period.

Two additional sub-populations consisting of (a) women at pre-screening ages and (b) women at screening ages were defined. Women in the pre-screening population entered the study on their 13^{th} birthday or the start of follow up, in case they were older than 13 years at the start of follow-up, and were followed until the event of interest, or one of the previously defined censoring points, age 23, or first invitation to cervical screening. Women at screening ages entered the study after a normal cytology taken at cervical screening ages or on January 1, 2006, if they have attended cervical screening within 3.5 years prior to study inclusion.

Follow-up ended at the outcome of interest, one of the predefined censoring criteria, an abnormal cytology not confirmed by histology, or 3.5 years after a normal cytology. Individuals diagnosed with the study outcome prior to the start of individual follow-up were excluded.

3.5.4 Study IV

Figure 1d shows the data sources that were utilized to identify new cases of condyloma and the mid-year population estimates of all men and women ages 15 to 44 years in Sweden, i.e. the TPR, NPR and PDR. The study period was between January 1, 2006, and December 31, 2012. Summary statistics on number of cases and mid-year population by year, sex, and age were obtained.

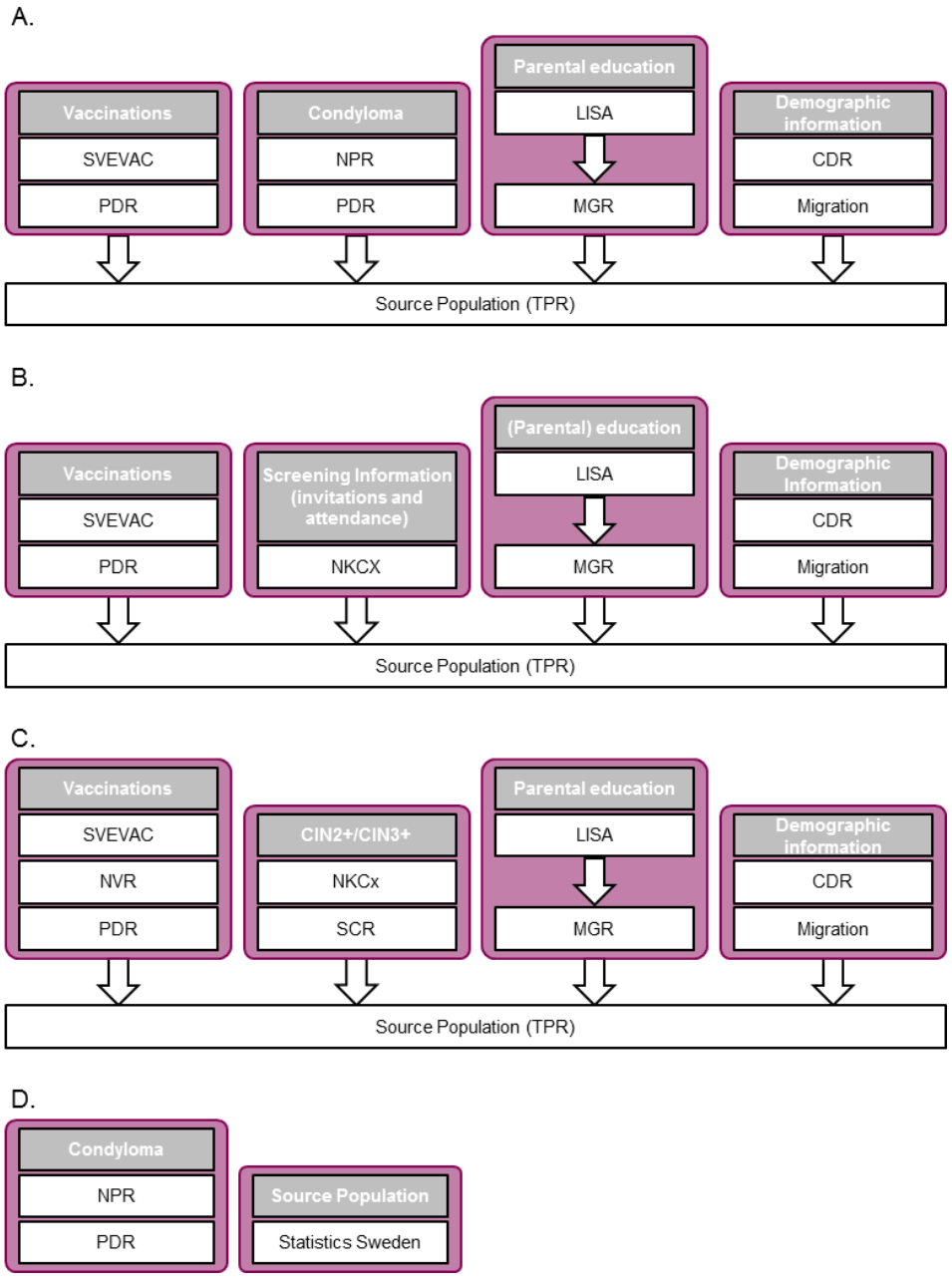

Figure 1. Data used to create the study populations in (A) study I; (B) study II; (C) study III; and (D) study IV.

3.6 STATISTICAL METHODS

3.6.1 Survival analysis

The data in studies I, II, and III are time-to-event data; individuals were followed from study entry to study exit due to either an event or study censoring. The number of cases occurring and person-time in the study were collected and analyzed using survival analysis. The incidence rate (IR) can be calculated as the number of cases divided by the number of person-years. The incidence rate ratio (IRR) can be obtained by dividing the IR among the exposed by the IR among the unexposed.

Rate ratios, adjusted for education level of the parents, comparing the effect of vaccination with non-vaccination on disease incidence, were estimated with survival analyses using a Poisson regression model for studies I and III, and Cox proportional hazards model for study II. The IR and IRR are estimated using a Poisson regression model. The hazard and hazard ratio (HR) can be calculated from a Cox proportional hazards model. The hazard and HR can be interpreted as the IR and IRR. Poisson regression is a parametric model, assuming constant rates over time whereas the Cox model is a semi-parametric model that makes no assumption on the shape of the baseline hazard over time. Both models assume proportional hazards, meaning that the hazards among exposed and unexposed should be proportional over time.

Studies I, II, and III, use attained age as the underlying time-scale. The rate of condyloma, cervical lesions, and screening attendance all depend on age, therefore, attained age was chosen as an underlying time scale. This means that for Poisson regression, different attained age categories were created, i.e. the individual could contribute person-time to several attained age-groups as the individual attains age during follow-up, which is subsequently included in the Poisson regression model. Within each age-category, a constant rate of disease is considered, but the rate can vary between age-categories. The splicing of attained age is automatically done in the Cox proportional hazards model, and does not need to be included in the model. The baseline hazard is not directly estimated from the model.

Some individuals were already vaccinated at the start of individual follow-up, whereas others got vaccinated during follow-up, and others do not get vaccinated during follow-up. The exposure variable HPV vaccination may change over time, therefore it can be considered as a time-varying exposure. In study I, exposure changed after vaccination with dose one, two, and three creating four groups: unvaccinated, partially vaccinated with dose one and dose two, and fully vaccinated (Figure 2), In study II exposure status changed from unvaccinated to vaccinated when an individual got vaccinated with at least one dose (Figure 3). In study III the exposure status changed from unvaccinated to vaccinated if three-dose vaccination was achieved (Figure 4). Depending on the number of doses received, the same individual could contribute person-time to multiple exposure groups (Figures 2-4).

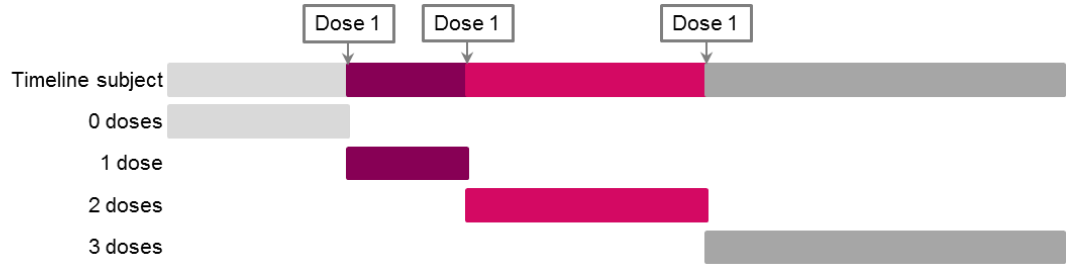

Figure 2. Vaccination per dose level as a time-varying exposure in study I.

Figure 3. Vaccination with at least one dose as time-varying exposure in study II.

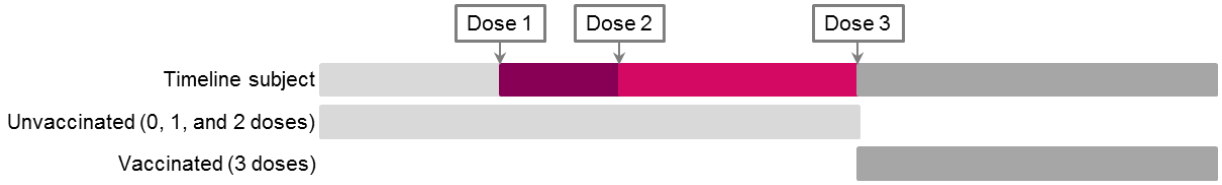

Figure 4. Vaccination with three doses as a time-varying exposure in study III.

3.6.2 Study I

Study I reports crude IR:s with 95% confidence intervals (CI:s) reported per 100,000 person-years by attained age, age at vaccination initiation, and vaccine dose were calculated. Two age at vaccination initiation groups (<17, 17-19 years) were created based on the median age of sexual debut (101). IRR:s, comparing the effect of vaccination per dose level with the unvaccinated, were estimated using a regression model with a Poisson distribution adjusting for parental education level with attained age as the underlying time-scale, and vaccine dose as a time-varying exposure (Figure 2). IRR:s were calculated both stratified on age at vaccination initiation, and for all vaccination initiation ages combined. Based on this Poisson model, incidence rate differences (IRD:s) averaged across the levels of attained age and parental education were estimated between vaccine doses.

To properly evaluate dose effectiveness in a population setting, ideally, only women not HPV-infected at the start of vaccination for which outcome of clinical disease is assessed should be included. However, in a population setting, it is often not feasible to obtain information on HPV infection status at vaccination initiation. As condyloma has an incubation period of 1-6 months (57–59), those who have a prevalent infection at the time of vaccination will be more likely to have their diagnosis shortly after vaccination, i.e. after one or two doses of the vaccine. Estimates of the incidence of condyloma following vaccination with one, two, or three doses may be biased towards a higher incidence of condyloma after vaccination with dose one and two. In study I, prevalent infections were accounted for by

introducing buffer periods of three months following vaccination with dose one, two, and three. The first 3 months following vaccination with a vaccine dose are included in previous exposure-state(s) (Figure 5).

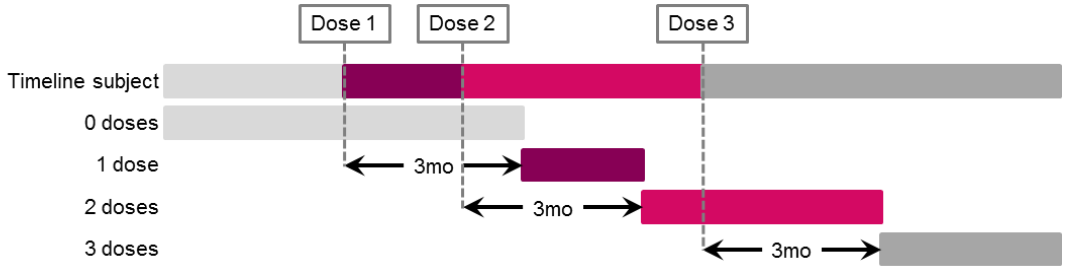

Figure 5. Illustration of buffer-period principle study I.

To estimate a realistic length of the buffer period, the cumulative incidence proportion (1-Survivor function) of condyloma after one dose was calculated. The corresponding cumulative incidence proportion for the unvaccinated based on age during follow-up was calculated and the effect of age was averaged according to the age-at-first-vaccination distribution. This is functionally equivalent to the graphical method for visualizing selection bias suggested in Törner et al. 2011 (102), but using a different scale for the hazard and a non-parametric estimate instead of flexible parametric models.

3.6.3 Study II

In study II, we estimated the cumulative incidence proportion of women attending cervical screening following an invitation to cervical screening in vaccinated and unvaccinated women. Women in this study were considered vaccinated after vaccination with at least one dose of either the bHPV or qHPV vaccine. Data were further analyzed using a Cox proportional hazards model with attained age as the underlying time-scale and vaccination as time-varying exposure. The proportional hazards assumption was tested based on a plot of the Schoenfeld residuals. Model fit was assessed when adjusting for education level and income of the study participant or the parent using the Akaike Information Criterion (103). The model that best fitted the data included adjustments for individual education level and individual income. The model fit including adjustments for other socio-economic variables parental education level and parental income did not result in a better model fit.

The relation between vaccination and attendance to screening was assessed over the entire study period, but was also assessed for the first and second screening round separately to assess whether screening attendance changed over time. Therefore, women were censored after three years of non-attendance in screening round one. Women entered the second screening round at the first invitation to cervical screening following attendance to cervical screening in round one or after three years of non-attendance. Attendance to screening round two was also estimated in only those that attended screening in round one.

3.6.4 Study III

In study III we estimated the effect of three-dose qHPV vaccination on incidence of CIN2+ and CIN3+ in the total population. Crude IR:s with 95%CI:s were reported by attained age, age at vaccination initiation, and vaccination exposure. Adjusted IRR:s with 95%CI:s were estimated using a Poisson regression model adjusting for parental education level with attained age as an underlying time-scale and qHPV vaccination with three doses handled as a time-varying exposure. Cervical lesions are a screen-detected outcome, therefore, the diagnosis can only be made if women attend screening. The same analysis was done in a screened population where lesions detected approximate lesions present. The same analysis was also carried out in the population at pre-screening ages.

There is a diagnostic time lag between the time a cytology was taken and when a colposcopy (histology) takes place. The lesion can progress into a CIN2+ or CIN3+ lesion during this diagnostic time lag, or the CIN2+ or CIN3+ lesion may already be present at the time of the cytology. In both instances, it is likely that the woman is already infected with HPV at the time of cytology. To correct for this diagnostic time lag, a backdating principle was adapted where 6 months was subtracted from the date on which a histologically confirmed CIN2+ or CIN3+ case was diagnosed.

3.6.5 Study IV

Study IV estimated the burden of condyloma following the introduction of qHPV vaccination. Mid-year estimates by age were calculated for year X by multiplying the sum of the population counts within a 5-year age-group for year X and year X-1 with 0.5. The mid-year population counts were taken as a proxy for person-years for the calculation of the IR:s by 5-year age-groups, calendar year, and sex. Mid-year counts of the vaccinated population were calculated as well.

The IR:s with corresponding 95%CI:s were calculated using a Poisson regression model stratifying on sex and age. A Poisson regression model was also used to calculate IR:s with 95%CI:s based on a model with a spline term to adjust for calendar year (natural cubic spline, 3 knots), stratified by age and sex. A broken-line regression model based on the log rates of condyloma was fit to estimate the annual percent change (APC) and 95%CI:s and average APC (AAPC) within a given period (104). Three different periods were created 2006-2007, 2008-2009, 2010-2012 over which the AAPC was calculated. These periods were chosen to represent three periods with increasing levels of HPV vaccination exposure. Only a few individuals were vaccinated during period 2006-2007, and this period was therefore considered to represent a pre-vaccination period. A greater proportion within the target age-group was vaccinated between 2010 and 2012, whereas the vaccination levels were considerably lower during 2008 and 2009, hence different periods were defined.

The underlying transition point that best fitted the data was obtained by using an optimizing method based on a combination of a grid search and golden section search. Where the golden

section search reached a local minimum, the best fitted model obtained via the grid search was selected.

4 MAIN FINDINGS

4.1 STUDY I

In study I, the risk for condyloma after qHPV vaccination per dose level was estimated by including 1,046,165 individuals that contributed 3,995,631 person-years. Of the 115,197 individuals that started qHPV vaccination, 89,836 continued to receive dose 2 and 3 of the qHPV vaccine and thereby completed qHPV vaccination. A total of 20,383 individuals were diagnosed with condyloma during follow-up of which 76, 79, and 167 cases were in individuals vaccinated with 1, 2, and 3 doses of the qHPV vaccine, respectively.

Figure 6 shows the cumulative incidence proportion of condyloma by vaccination status. Initially, no differences were seen in cumulative incidence proportion by vaccination status. At around ~3 months, the cumulative incidence proportion of those vaccinated leveled off compared those unvaccinated.

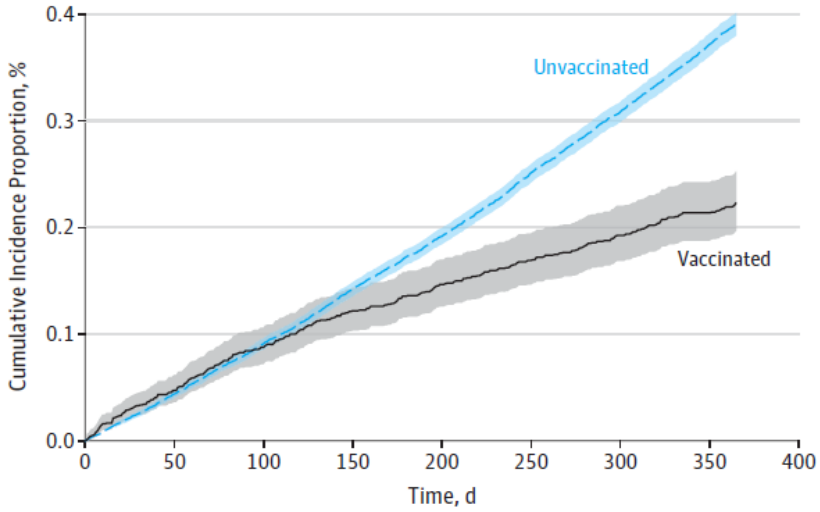

Figure 6. Cumulative incidence proportion of condyloma in vaccinated and unvaccinated individuals (JAMA 2014; Herweijer et al.; Figure 1).

Overall, the highest rates of condyloma were seen amongst those unvaccinated (IR=528, 95%CI=520-535). Vaccination with 1, 2, and 3 doses of the qHPV vaccine resulted in lower rates of condyloma with each additional dose. The corresponding rates were 273 (95%CI=218-342), 174 (95%CI=139-217), and 138 (95%CI=119-161) cases of condyloma per 100,000 person-years. This pattern, where an additional vaccine dose resulted in a lower crude IR, was seen across all attained age categories (Figure 7).

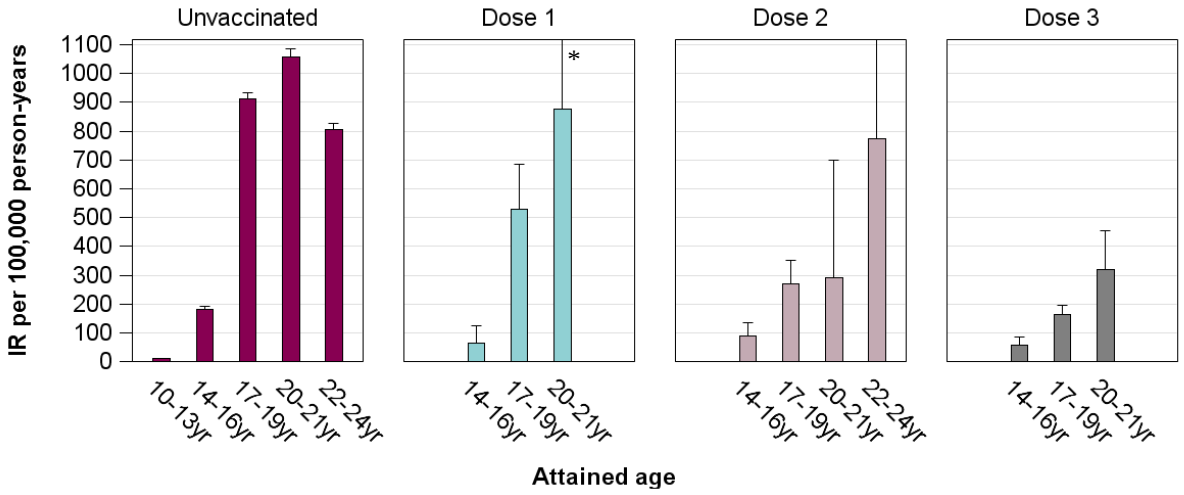

Figure 7. Crude incidence rates of condyloma per attained age-group and dose (JAMA 2014; Herweijer et al.; adapted from Table 2) (* represent truncated upper error bar).

Vaccination with one, two, and three doses was associated with a significant reduction in risk for condyloma. The greatest reduction was seen after three-dose vaccination with observed reductions of 82% (IRR=0.18, 95%CI=0.15 to 0.22) and 77% (IRR=0.23, 95%CI=0.18 to 0.29) in girls initiating vaccination at ages 10-16 years and at ages 17-19 years, respectively. The three versus two-dose comparisons were significant in both girls initiating vaccination at ages 10-16 years and 17-19 years with corresponding reductions of 37% (IRR=0.63, 95%CI=0.43 to 0.93) and 34% (IRR=0.66, 95%CI=0.45 to 0.95). Corresponding differences in number of prevented condyloma cases per 100,000 person-years were 59 (95%CI=2 to 117) and 67 (95%CI=3 to 132) cases.

The current analyses included both individuals that completed their three-dose vaccination, and those that started vaccination but did not continue to receive all three recommended doses of the qHPV vaccine. Individuals who complete three-dose vaccination might differ from those that do not complete three-dose vaccination in terms of risk of acquiring an HPV infection. Therefore, we compared the effect of receipt of two doses of the qHPV vaccine in those that did and did not complete three-dose vaccination and found no difference in risk for condyloma (IRR=0.88, 95%CI=0.53 to 1.44).

4.2 STUDY II

The results in study II showed that vaccinated women were equally likely, if not more likely (HR=1.05, 95%CI=1.02 to 1.08), to attend cervical screening during follow-up. These results were based on a study population comprising 629,703 women that received an invitation to cervical screening during follow-up of which 4,897 (0.8%) women were vaccinated during the study period. The majority of the women were vaccinated after age 19; hence they were opportunistically vaccinated without receiving reimbursement.

The screening attendance three years after invitation to screening, measured as the cumulative incidence proportion, was 86% in vaccinated individuals and 75% in unvaccinated

individuals. This difference in screening attendance among vaccinated and unvaccinated women started shortly after invitation to screening and was present throughout the study period (Figure 8). A temporary small increase in screening attendance was seen in both vaccinated and unvaccinated women at 12 and 24 months (black arrows Figure 8), which most likely represents renewed invitations to attend cervical screening, issued annually to non-attenders.

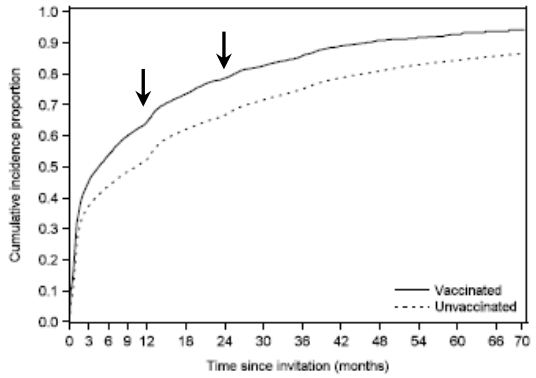

Figure 8. Cumulative incidence proportions of screening attendance since first invitation to screening by vaccination status (PlosOne 2015; Herweijer et al.; Figure 3).

The HR, without adjustments made for income and education level, comparing screening attendance between vaccinated and unvaccinated individuals was 1.28 (95%=CI 1.24 to 1.32). After adjustments were made for income and education level, vaccination status was associated with a higher cervical screening attendance overall and by screening round (HR=1.05, 95%CI=1.02 to 1.08), round 1 (HR=1.09, 95%CI=1.05 to 1.13), and round 2 (HR=1.15, 95%CI=1.10 to 1.20). Screening attendance among those vaccinated and unvaccinated by education level showed that vaccinated women with missing education level, less than high school, high school, and university education were equally or more likely to attend screening as compared to unvaccinated women. Differences in cervical screening attendance among vaccinated and unvaccinated women seem to increase if education level was lower which was seen in both the overall analysis and analyses by screening round.

4.3 STUDY III

In study III, the impact of qHPV vaccination on risk for cervical lesions was estimated by including 1,333,691 girls and young women that contributed 7,252,096 person-years of which 236,372 individuals were vaccinated contributing 604,454 person-years. The majority (88%) of the individuals who had a histological diagnosis of CIN2+ had the diagnosis within 6 months after the abnormal cytology, hence a diagnostic time lag of 6 months was chosen (Figure 9).

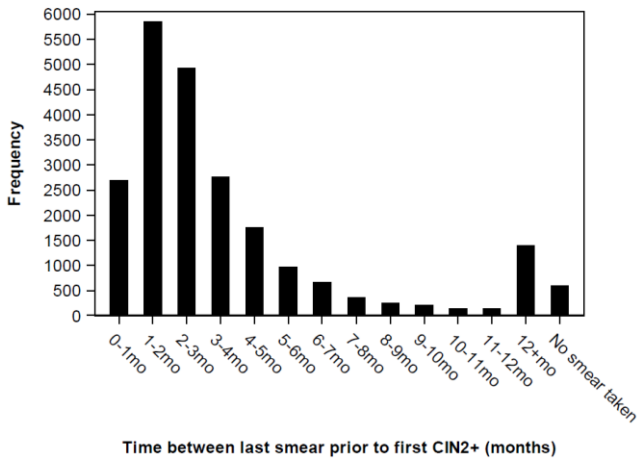

Figure 9. Frequency distribution of time between last smear prior to histologically confirmed diagnosis of CIN2+ (From Herweijer et al., Quadrivalent HPV vaccine effectiveness against high-grade cervical lesions by age at vaccination: A population-based study, Suppl Figure 3, Int J Cancer 2016. Copyright © 2016 by John Wiley Sons, Inc. Reprinted by permission of John Wiley & Sons, Inc.)

Prior to the start of cervical screening, low rates of both CIN2+ and CIN3+ were observed. Peak crude rates of CIN2+ and CIN3+ were seen in women at ages 22-23, which was in accordance with the start of cervical screening. The crude IR per 100,000 person-years of CIN2+ and CIN3+ among vaccinated individuals was lower than the crude IR seen among unvaccinated individuals, with lower rates of CIN2+ and CIN3+ seen in individuals initiating vaccination at a younger age. This observation was seen across all attained age-categories (Figure 10).

The results from the Poisson regression models adjusting for attained age and education level were in line with the observations seen in the crude data. Vaccination was associated with a significant reduction in risk for both CIN2+ and CIN3+ at all vaccination initiation ages. Greatest reductions in CIN2+ and CIN3+ were seen in girls that initiated vaccination <17 years of 75% (IRR=0.25, 95%CI=0.18 to 0.35) and 84% (IRR=0.16, 95%CI=0.08 to 0.32), respectively. The reductions in risk for CIN2+ and CIN3+ decreased with increasing age at vaccination initiation, but the reductions remained significant. Similar results were seen when restricting the analyses by only including screened person-years, i.e. women that recently attended the organized cervical screening program. No cases were observed among women that initiated vaccination prior to age 17. Compared to no vaccination, vaccination was associated with lower rates of CIN2+ of 88% (IRR=0.12, 95%CI=0.02 to 0.85) in individuals 17-19 years at vaccination initiation. For those ages 20-29 at first vaccination, a reduction in risk of CIN2+ of 21% (IRR=0.79, 95%CI=0.56 to 1.12) was observed, but did not reach statistical significance. Similar reductions in risk of CIN3+ of 77% (IRR=0.23, 95%CI=0.03 to 1.64) and 23% (IRR=0.77, 95%CI=0.48 to 1.24) were observed in individuals initiating vaccination at ages 17-19, and 20-29, respectively. These results did not reach statistical significance, most likely due to limited follow-up time. This analysis did not include person-time of individuals that were under-screened, and therefore, lesions detected provide a good estimation of lesions present.

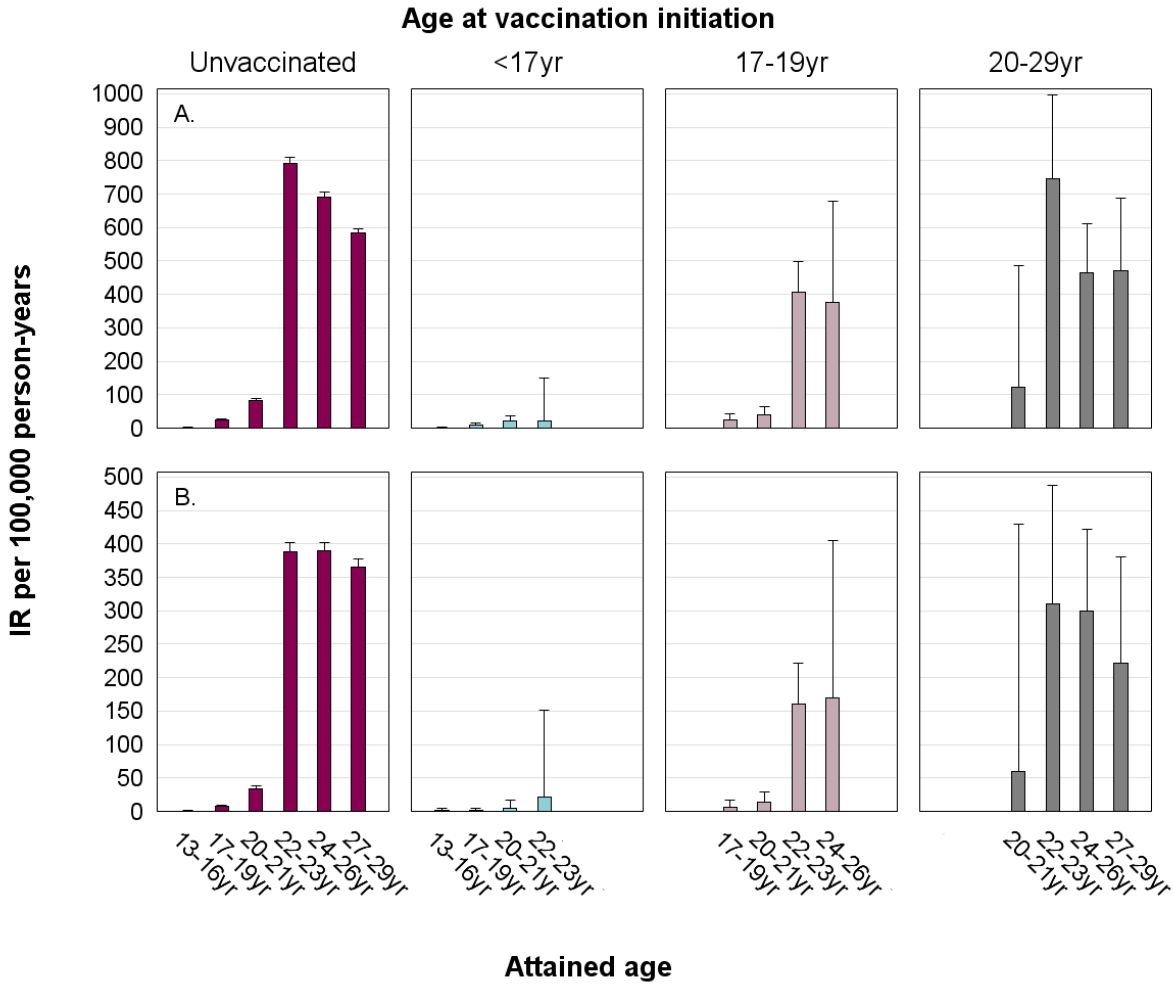

Figure 10. Crude incidence rates of (A.) CIN2+ and (B.) CIN3+ per attained age-group and age at vaccination initiation category (From Herweijer et al., Quadrivalent HPV vaccine effectiveness against high-grade cervical lesions by age at vaccination: A population-based study, adapted from Table 2, Int J Cancer 2016. Copyright © 2016 by John Wiley Sons, Inc. Reprinted by permission of John Wiley & Sons, Inc.)

4.4 STUDY IV

Disease surveillance, both prior to and post vaccine availability, play an important role in the follow-up of both the effect of vaccination on burden of HPV-related disease in vaccinated populations, as well as herd protection in unvaccinated populations. Study IV aimed to monitor condyloma incidence by means of an ecological study design. In this study, vaccinated girls were mainly opportunistically vaccinated at ages 13 to 17 years. During the course of the study, estimated vaccination coverage in girls at ages 15 to 19 years increased to 41.1% in 2012. This is the group where direct effects of vaccination are expected. A change in trend of condyloma incidence was observed at year 2008.6 resulting in an AAPC of -13.1% (95%CI=-14.8 to -11.4) for period 2008-2009 and -18.5% (95%CI=-21.3 to -15.8) for period 2010-2012 (Figure 11). Initially a slight increase in incidence was seen in the corresponding age-group for boys, but after 2009.8 a change in trend occurred, yielding an AAPC of -16.6% (95%CI=-19.9 to -13.2) for the period 2010-2012. As very few boys were

vaccinated, and the decreasing trend in incidence started approximately one year later than that of girls, these observed decreases in incidence of condyloma might suggest herd protection from vaccinated girls in the corresponding age-group (Figure 11). Vaccination coverage was considerably lower (14.1%) in the following age-category of young women ages 20 to 24, which most likely is composed of a mixture of young women vaccinated at ages 20 to 24, and girls that have been vaccinated prior to age 20 and aged into this age category during follow-up. For these women, there was initially no specific trend observed, but rates started to decrease from 2008.5 and onward (2010-2012: AAPC=-11.3%, CI=-12.7 to -9.9) (Figure 11). We saw a similar pattern of declining incidence rates of condyloma, for men ages 20-24 (2010-2012: AAPC=-13.0%, CI=-15.2 to -10.9) which might also point towards herd protection. The incidence of condyloma decreased from 2006-2007 (AAPC= -3.2%, CI=-4.7 to -1.7) to 2010-2012 (AAPC=-5.1%, CI=-6.6 to -3.6) for women ages 25-29, whereas a decrease in AAPC was seen in men for period 2010-2012 (AAPC=-8.8%, CI=-13.2 to -4.3), only. For men and women ages 30 and above, there were no signs of decreasing incidence of condyloma over time.

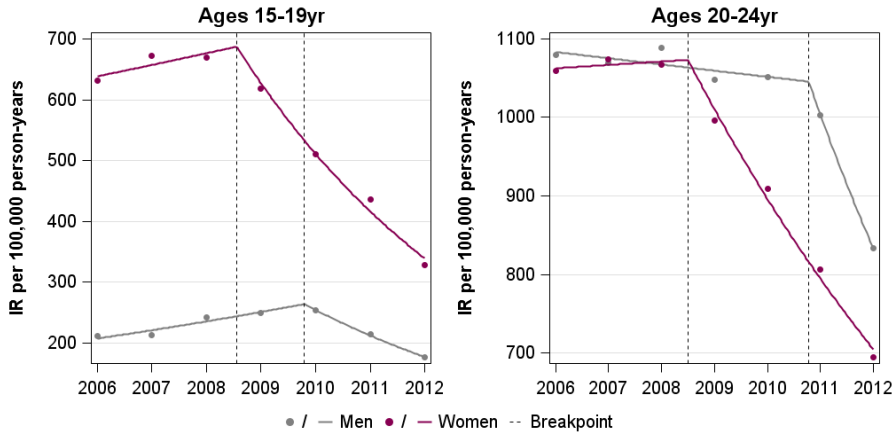

Figure 11. Fitted broken-line regression of incidence of condyloma by, calendar time, sex, and age.

5 METHODOLOGICAL CONSIDERATIONS

The following section will discuss methodological considerations underlying studies I-IV in more detail and how these concerns were addressed.

5.1 VACCINE UPTAKE AND SELF-SELECTION BIAS

Most of the girls that were vaccinated during study follow-up in studies I, II, and III were opportunistically vaccinated. Girls at ages 13 to 17 were eligible for subsidized vaccination, whereas those not eligible for subsidized vaccination could only get HPV-vaccinated at their own expense. Individuals vaccinated within this period might therefore represent a selected group as they actively chose to get HPV-vaccinated and were willing to pay for the vaccine. Likewise, socio-economic mechanisms might have played a role. It has previously been shown that a parent's education level is positively associated with vaccination status of their daughter(s) (105). Subsequently, the model in study I, II, and III was adjusted for level of education to account for such bias.

Furthermore, individuals that actively chose to vaccinate might have been more health-conscious in terms of healthcare seeking behavior. With regard to study I, differences in healthcare seeking behavior is expected to be non-differential by dose. In addition, a previous study tested the presence of self-selection bias, i.e. individuals that were at higher risk for development of condyloma were also more likely to be vaccinated, by comparing the rate of condyloma in the unvaccinated population before and after the qHPV vaccine was available. There was no indication that girls below the age of 20 vaccinated via the opportunistic vaccination program were self-selected, however, rates of vaccination in the unvaccinated population over age 20 declined over time which could indicate that women vaccinated over age 20 were self-selected, i.e. vaccinated women were at higher risk for condyloma (105).

In study I, fully vaccinated girls might have been different from girls that were partially vaccinated with one or two doses of the qHPV vaccine in terms of life-style factors and might therefore be at greater risk for condyloma. There is no information on life-style factors, such as HPV status and the number of sexual partners, available in the national healthcare data registers. However, we did exclude women previously diagnosed with condyloma as a proxy for HPV status. Furthermore, we compared the effect of qHPV vaccination after two doses in girls that did complete three-dose vaccination with girls that did not complete three-dose vaccination and found no evidence of the presence of such a bias.

If HPV-vaccinated women are also more likely to attend cervical screening, a higher screening attendance in vaccinated women will lead to a greater likelihood to detect cervical lesions as compared to women that were not vaccinated thereby rendering the vaccine less effective. Study II showed that the level of education explained part, but not all, of the increased likelihood of attending cervical screening after vaccination. With regard to study III, we performed an additional analysis in recently screened women accounting for under-screening. Results were in line with the results on vaccination effectiveness observed in the total population. For the assessment of cervical screening attendance after HPV vaccination,

we have only included women that were invited to the cervical screening program. Women that attend cervical screening with an interval of less than three years, which might be even more health conscious, were not captured as invitations to cervical screening are issued three years after the last attendance to screening for women with a normal test result. The invitation system integrates these opportunistic screening tests, delaying the next invitation to organized screening until the age-specific interval has passed (94).

5.2 PREVALENT INFECTIONS VERSUS INCIDENT INFECTIONS

The HPV vaccines are prophylactic and have no effect on the clearance of an infection or progression into a lesion (37,38). The study participants in the clinical trials were tested for HPV DNA, and information was available on whether participants were seropositive for one or more HPV types. Such data is usually not available in a population-based setting where little is known about prevalent HPV infections at the time of vaccination. It can be argued whether observed "vaccine failures" truly represent a vaccine failure or are the result of infections acquired prior to vaccination.

For the studies presented in this thesis, it was not possible to obtain information on HPV status at the time of vaccination. The true effect of vaccination on condyloma incidence might therefore be underestimated in study I. We tried to correct for prevalent infections by introducing buffer-periods where case counting started three months after receipt of a vaccine dose in study I. A diagnostic time lag between abnormal cytology and confirmation of disease via histology was introduced in study III. Furthermore, vaccine effectiveness in study III was measured after three-dose vaccination, which means that there was approximately six months of partially vaccinated person-time that were included in the unvaccinated group. Cases occurring in that time-window, between vaccination initiation and completion, were most likely due to prevalent infections prior to start of vaccination.

5.3 MISCLASSIFICATION OF CASES

Pharmaceutical treatment with podophyllotoxin and imiquimod was used as a proxy for condyloma. Imiquimod can be prescribed to treat condyloma, but can also be prescribed to treat other skin modalities. The other treatment indications of imiquimod might have falsely attributed cases of condyloma to individuals that were treated with imiquimod. We have done a descriptive analysis on prescription patterns of imiquimod and podophyllotoxin for the period 2006-2012 by age. The podophyllotoxin prescriptions increase sharply at ages where condyloma incidence peaks after which the number of prescriptions sharply decreased. A similar, but lower, peak around age 20 is seen for the number of imiquimod prescriptions with a higher peak seen at older ages (Figure 12.).

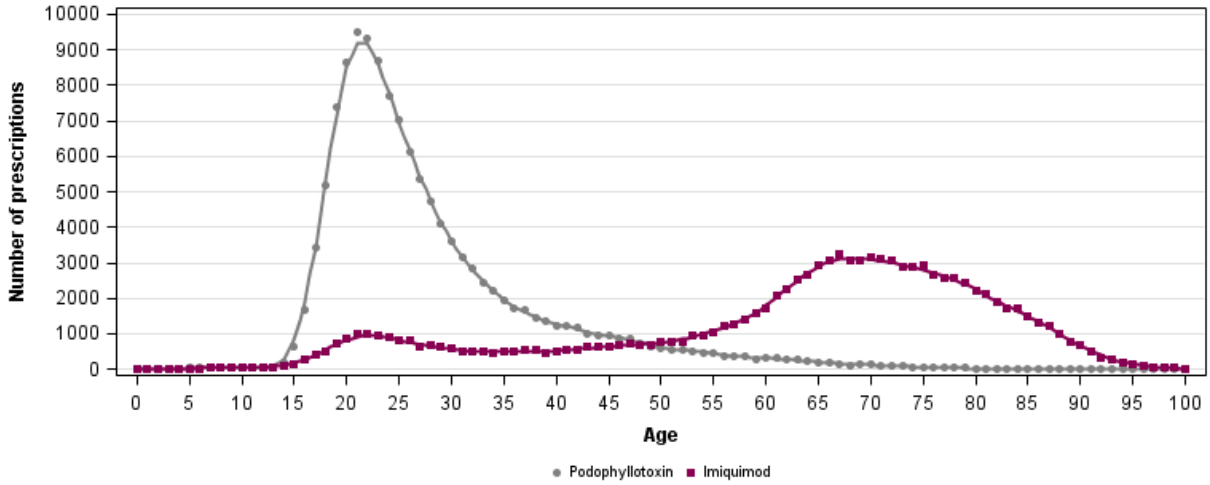

Figure 12. Number of prescriptions and loess smoothing line for pharmaceuticals imiquimod and podophyllotoxin registered to the PDR between 2006 and 2012 by age.

The dispensations of pharmaceutical imiquimod as a proportion of the total expenditure of pharmaceuticals used for treatment of condyloma, i.e. podophyllotoxin and imiquimod, for period 2006-2012 as registered in the PDR is shown in Figure 13. The share of imiquimod prescriptions increases from age 20 to about age 65 from ~10% to almost 100%. This most likely reflects the increasing use of imiquimod to treat other skin abnormalities.

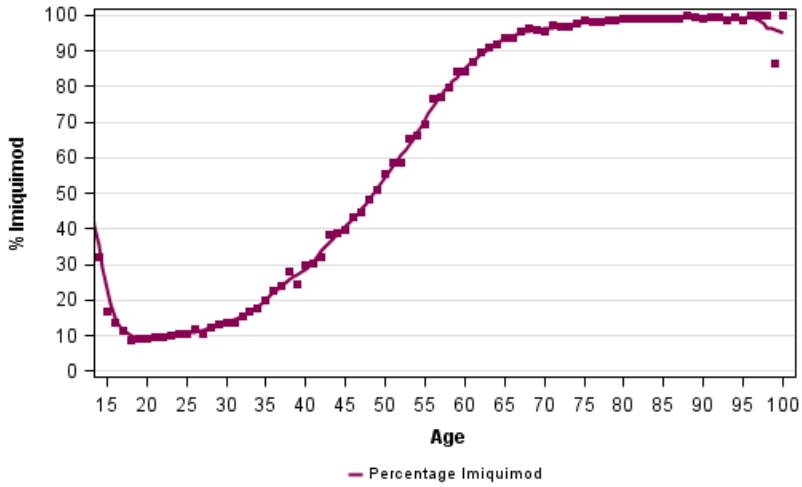

Figure 13. Share (%) and loess smoothing line of dispensations of pharmaceutical imiquimod to total expenditure of pharmaceuticals used for treatment of condyloma (podophyllotoxin and imiquimod) for period 2006-2012 as registered in the PDR.

The misclassification of falsely attributing condyloma cases to individuals treated with imiquimod was not considered an issue in study I, due to low upper age limit of the study population. However, in study IV, it might be considered an issue. Therefore, the upper age limit was set to 44 to minimize misclassification. Furthermore, not all cases of condyloma were captured in the registers; diagnoses made in private care settings that did not receive pharmaceutical treatment might have falsely misclassified individuals as healthy. Study IV includes both first occurring and subsequent cases of condyloma.

The outcome in study III was histologically confirmed diagnosis of CIN2+ or CIN3+. This diagnosis is, as mentioned earlier in this thesis, mainly detected via cervical screening. Those individuals with CIN2+ or CIN3+ that do not go to cervical screening or do not take opportunistic Pap-smears, will not be diagnosed and are misclassified as being healthy. This would not be a problem if this misclassification is non-differential by vaccination status with regards to vaccine effectiveness results as analyzed in the total population. We have performed an additional analysis including recently screened women only, i.e. lesions detected approximate lesions present, and the results on vaccine effectiveness seen in the screened population were comparable to those seen in the total population. These results indicated that the misclassification of women with CIN2+ or CIN3+ as healthy is non-differential by vaccination status.

5.4 MISCLASSIFICATION OF VACCINATION EXPOSURE

There has been some underreporting of HPV vaccinations to SVEVAC which might have resulted in misclassification of the exposure, i.e. HPV-vaccinated women were considered falsely unvaccinated. However, the individuals that could be reimbursed for the HPV vaccine could only receive the reimbursement if vaccine doses were dispensed at the pharmacy. Vaccine dispensations were subsequently registered in the PDR. Since both PDR and SVEVAC were used, misclassification of exposure was minimized during the opportunistic vaccination period.

5.5 AGE AT VACCINATION INITIATION

The effect of HPV vaccination on incidence of condyloma has been shown to vary across different levels of age at first vaccination (105,106), where the effect of vaccination increases with decreasing age at vaccination initiation. Age at vaccination is thereby considered an effect modifier. In study I and III, effect modification by age at vaccination initiation was corrected for by stratifying on age at first vaccination which was based on individuals' vaccination status (vaccinated or not vaccinated) and if vaccinated, the age of vaccination initiation.

5.6 ATTAINED AGE

Age at vaccination initiation is not equivalent to attained age. The age an individual starts vaccination cannot change over time once vaccination is initiated. In contrast, individuals attain age during follow up. The incidence of condyloma (study I) and cervical lesions (study III) highly depend on attained age. Attained age is considered a confounder as the rate of condyloma (study I) and cervical lesions (study III) change with age. Furthermore, efforts made to vaccinate girls and young women were mainly directed towards girls' ages 13 to 17 years in the opportunistic vaccination period, and to girls ages 10 to 18 afterwards. The likelihood of getting vaccinated therefore depends on age. Attained age was subsequently adjusted for by including attained age as an underlying time-scale in the analyses.

6 DISCUSSION, IMPLICATIONS, CONCLUSIONS

Individuals that were HPV-vaccinated in Sweden during the opportunistic vaccination period have been vaccinated with either the bHPV or qHPV vaccine. Both vaccines include protection against HPV types 16 and 18 that are found in about 70% of the cervical cancer cases. This means that vaccinated individuals are still at risk of developing cervical lesions which can develop into cervical cancer as a result of non-vaccine types. To optimally benefit from cervical cancer prevention programs, vaccinated women will need to continue cervical screening. Study II showed that individuals, opportunistically vaccinated, were equally likely, if not more likely to attend cervical screening. Since screening attendance in this study was based on a cohort of opportunistically vaccinated women, it remains unclear how these results translate to cohorts vaccinated via organized HPV vaccination programs. The girls that get HPV-vaccinated free-of-cost via organized vaccination programs today might have different attitudes towards cervical screening compared to cervical screening behaviors of women that actively choose to get vaccinated out-of-pocket. Therefore, to optimize cervical cancer prevention efforts, continued monitoring of screening attendance in populations vaccinated via organized HPV vaccination programs, and unvaccinated populations, will be needed to anticipate changes in attendance that might compromise the effectiveness of the cervical screening programs. If 80% of women are vaccinated, the cervical screening program will require changes, ex. the cytology test for young women could be replaced by primary HPV testing. While study II has showed that there are no indications so far that cervical screening rates drop over time in women opportunistically vaccinated, we need to ensure that women opportunistically vaccinated keep going to cervical screening.

Studies I and III assessed the impact of vaccination on HPV-related disease in the population. As it will take several years before the impact on cervical cancer can be assessed, condyloma and cervical lesions, CIN2+ and CIN3+, were used as outcomes and surrogate markers for vaccination impact on cervical cancer incidence. Population level effect of three-dose vaccination against condyloma has been shown previously in various countries, including Sweden (105–107). Study III estimated the impact of HPV vaccination on incidence of cervical lesions. Greatest reductions in risk for cervical lesions were seen if vaccination was initiated at a young age, highlighting the importance of early vaccine administration in young girls. In addition, cervical lesions diagnosed in younger girls are more often positive for HPV types 16 and/or 18 (108–110), and in theory, greater impact of HPV vaccination against cervical lesions can be expected in young girls. The results found in study III support these findings; the observed vaccine effectiveness against CIN2+ and CIN3+ in study III was high, especially in those younger at vaccination with risk reductions of 75% and 84% for CIN2+ and CIN3+, respectively. Furthermore, the results found in study III were in line with results from population-based studies conducted in countries other than Sweden (111–115).

Study I was the first study to report on the effect of vaccination with less than three doses of the qHPV vaccine on incidence of HPV-related disease in the population. The results showed greatest protection against condyloma after vaccination with three doses of the qHPV

vaccine, though receipt of two doses of the qHPV vaccine also resulted in considerable reduction in risk for condyloma. One more population-based study has now reported on dose effectiveness against condyloma and showed similar results: lower incidence of condyloma with each additional dose (116). In addition, this study showed that the effect of two-dose vaccination on condyloma incidence approached that of three-dose vaccination when two doses were received with more time between dose one and two (116). Furthermore, other studies have reported on impact of vaccination on cervical lesions per dose level (112,113), and found a lower incidence of cervical lesions with each additional dose. However, the effect of vaccination on cervical lesions per dose level in the Swedish population, including timing between dose one and two, has not been published yet.

Estimates of vaccine effectiveness can easily be biased. For example, if vaccination coverage is high enough, it is expected that unvaccinated individuals will benefit via herd protection. Comparing disease incidence in vaccinated individuals with unvaccinated and partially vaccinated individuals will, in that case, be biased towards an underestimation of vaccine effectiveness. The vaccination coverage remained low during the opportunistic vaccination period, and it was not likely that such bias was present in studies I and III. However, with the introduction of organized vaccination programs, vaccination coverage has increased and both direct and indirect effects of vaccination are anticipated. Future studies on vaccination effectiveness should therefore consider such bias when assessing vaccination effectiveness.

Population level impact of HPV vaccination on prevalence of HPV vaccine types has been reported in several countries (44,45,117,118). In Sweden, reduction of HPV types 6, 11, and 16 have been observed with decreases in prevalence of 40%, 41.6%, and 45.6%, respectively, in girls ages 14 to 22 (117). With an incubation time of typically 1 to 6 months (57,58), condyloma is the first HPV-related disease outcome that can be used to assess the effect of vaccination and its effect on disease reduction in the population. Direct effects of vaccination are expected in birth cohorts with higher HPV vaccination coverage, whereas indirect effects of vaccination, through reduced transmission rates of the virus from cohorts with higher vaccination coverage, are expected in men and birth cohorts of women with low vaccination coverage. The expected effects of vaccination in the population depend on various factors such as the implementation of HPV vaccination programs, type of program, i.e. opportunistic or organized, and the achieved vaccination coverage. It has been shown that vaccination coverage is related to reductions of condyloma cases and HPV type 16 and 18 infections (45). These parameters vary across countries and results cannot directly be extrapolated across other countries. In study IV, an ecological study design was used to monitor trends in burden of condyloma over time shortly after qHPV vaccine introduction. Condyloma cases were not linked to HPV vaccination status, but instead, summary estimates were used to provide information on population trends. Reductions in incidence of condyloma were seen in both men and women. The greatest reductions were seen in girls at those ages where vaccination coverage was highest. Reductions were also seen in the corresponding age-groups of boys, but the point in time where incidence started to decrease occurred slightly later, which could be interpreted as herd protection.

CONCLUSIONS

Women that have been HPV vaccinated through opportunistic HPV vaccination were equally likely, if not more likely to attend organized cervical screening following an invitation letter to cervical screening. Maximum reductions in risk for CIN2+ and CIN3+ were seen following three-dose vaccination in girls and young women that initiated vaccination up until age 29. Greater reduction in risk for CIN2+ and CIN3+ were seen in those younger at vaccination initiation; maximum reductions of 75% and 84% in risk for CIN2+ and CIN3+ were seen in those who initiated vaccination prior to age 17.

Maximum reduction in risk for condyloma was observed after vaccination with 3 doses of the qHPV vaccine. Vaccination with two doses of the qHPV vaccine was also associated with a considerable reduction in risk for condyloma. Though risk for condyloma was reduced for all girls and young women under study, greater risk reductions were seen in those younger at vaccination initiation with a maximum reduction in risk for condyloma of 82% seen after three-dose vaccination in those under age 17 at vaccination initiation.

Declines in condyloma incidence in girls below age 20 were seen following the introduction of qHPV vaccination in Sweden and confirm anticipated effects. The observed decline among men and in women age 20 and above indicates possible herd protection.

Future monitoring of the disease burden over time, as well as observational studies comparing vaccinated and unvaccinated individuals, are necessary to evaluate whether the organized school-based vaccination program has the anticipated effect in the population.

7 FUTURE DIRECTIONS

The HPV vaccines' protective properties against vaccine HPV type related and non-vaccine HPV type related infections, condyloma, precursor lesions of cervical cancer, and other precursor lesions of HPV-related cancers have been shown in both clinical trial and population-based settings. How these results translate in terms of protection against cervical cancer has yet to be determined. However, based on results of the effect of vaccination on risk for cervical lesions, which is an appropriate intermediate disease outcome between an HPV infection and cervical cancer, a protective effect of HPV vaccination on invasive cervical cancer can be anticipated (34).

The bHPV and qHPV vaccines have been on the market for almost a decade. Population-based studies have extrapolated findings from clinical trials. However, some questions remain unanswered. Though long-term protection is assumed, the duration of protection after HPV vaccination against HPV infection and HPV-related disease remains unclear for both the initially recommended three-dose schedule and the new two-dose recommendations. Furthermore, the protective properties of HPV vaccination against infections and lesions caused by non-vaccine HPV types have been shown. Kemp et al. has shown that, following vaccination, neutralizing antibodies of HPV types 31 and 45 were about 100 times lower than levels observed for HPV types 16 and 18 (119). It remains unclear whether there are differences in the duration of protection between vaccine and non-vaccine HPV types (42,43,119). This information will be of particular value for policy makers and serve as input for cost-effectiveness models.

Now that organized HPV vaccination programs are in place in Sweden and vaccination coverage has reached higher levels of 60% in catchup programs and 80% in organized school-based programs (81), the incidence of condyloma and other HPV-related diseases are expected to go down. It will be important to monitor and maintain subsequent vaccination coverage to anticipate changes in vaccine uptake. But also close monitoring of circulating HPV types will be required to investigate the cross-reactive properties of the HPV vaccines and determine possible HPV type replacement (82). Disease surveillance using an ecological design does not provide information on type replacement, or waning immunity resulting in increases in disease incidence. Typing of HPV-related lesions in a subset of the population and vaccination effectiveness studies can provide information on these issues.

Soon there will be a mixture of opportunistically vaccinated cohorts from when there were no organized programs in place or as part of the catchup vaccination program, and birth cohorts that have been vaccinated with either two or three doses of the qHPV vaccine within the school-based vaccination program. In the future, there will also be birth cohorts that will be vaccinated with next-generation vaccines. Now that the 9vHPV vaccine has been recommended by the EMA for commercial use, countries have the opportunity to include the 9vHPV vaccine in the national HPV vaccination programs thereby maximizing prevention efforts of HPV related disease. This needs to be done in a systematic manner. However, these birth cohorts all remain at risk for cervical cancer and will need to go to screening, but

with different prerequisites. The cervical screening guidelines require adaptation to optimize cervical cancer prevention efforts while achieving cost-effectiveness.

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