

Quadrivalent HPV vaccine effectiveness against high-grade cervical lesions by age at vaccination: A population-based study

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Human papillomavirus (HPV) types 16/18, included in HPV vaccines, contribute to the majority of cervical cancer, and a substantial proportion of cervical intraepithelial neoplasia (CIN) grades 2/3 or worse (CIN2+/CIN3+) including adenocarcinoma in situ or worse. The aim of this study was to quantify the effect of quadrivalent HPV (qHPV) vaccination on incidence of CIN2+ and CIN3+. A nationwide cohort of girls and young women resident in Sweden 2006–2013 and aged 13–29 ($n = 1,333,691$) was followed for vaccination and histologically confirmed high-grade cervical lesions. Data were collected using the Swedish nationwide healthcare registers. Poisson regression was used to calculate incidence rate ratios (IRRs) and vaccine effectiveness $[(1-IRR) \times 100\%]$ comparing fully vaccinated with unvaccinated individuals. IRRs were adjusted for attained age and parental education, and stratified on vaccination initiation age. Effectiveness against CIN2+ was 75% (IRR = 0.25, 95%CI = 0.18–0.35) for those initiating vaccination before age 17, and 46% (IRR = 0.54, 95%CI = 0.46–0.64) and 22% (IRR = 0.78, 95%CI = 0.65–0.93) for those initiating vaccination at ages 17–19, and at ages 20–29, respectively. Vaccine effectiveness against CIN3+ was similar to vaccine effectiveness against CIN2+. Results were robust for both women participating to the organized screening program and for women at prescreening ages. We show high effectiveness of qHPV vaccination on CIN2+ and CIN3+ lesions, with greater effectiveness observed in girls younger at vaccination initiation. Continued monitoring of impact of HPV vaccination in the population is needed in order to evaluate both long-term vaccine effectiveness and to evaluate whether the vaccination program achieves anticipated effects in prevention of invasive cervical cancer.

Cervical cancer is the fourth most common cancer in women worldwide,¹ but a highly preventable disease.² Human papillomavirus (HPV) types 16/18 account for 70% of the invasive cases^{1,3,4} and is detected in about half of the precursor lesions of this disease,^{3,5} with a larger proportion of these highly oncogenic types detected in lesions in young women (<30 years).^{6,7}

Sweden has a longstanding history of inviting women to organized cervical screening. The recommended screening intervals are 3 years for ages 23–50 and 5 years for ages

51–60. The screening coverage was 80% for women within screening ages in 2014.⁸ Screening that takes place before age 23 is nonorganized, and based on individuals actively seeking healthcare themselves.

There are currently three EMA and FDA approved prophylactic HPV vaccines, all targeting HPV16/18. The quadrivalent HPV (qHPV) vaccine and 9-valent HPV vaccine also target HPV6/11 which are found in the majority of condylo-ma cases.^{9,10} In Sweden, subsidized HPV vaccination was

Key words: HPV vaccination, high-grade cervical lesions, nationwide, vaccine effectiveness

Abbreviations: AIS+: adenocarcinoma in situ or worse; bHPV: bivalent human papillomavirus; 95% CI: 95% confidence interval; CIN2+/CIN3+: cervical intraepithelial neoplasia grade 2/3 or worse; HPV: human papillomavirus; IR: incidence rate; IRR: incidence rate ratio; NKCCx: National Swedish Cervical Screening Registry; PDR: prescribed drug register; qHPV: quadrivalent human papillomavirus; SNOMED: standardized nomenclature of medical diagnoses; VE: vaccine effectiveness

Additional Supporting Information may be found in the online version of this article.

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What's new?

How well does quadrivalent HPV vaccination protect girls from cancer? These authors followed the entire population of Swedish girls ages 13–29 for high-grade cervical lesions and quadrivalent HPV vaccination through a registry-based study. Those receiving the quadrivalent HPV vaccine were less likely to develop of CIN2 and CIN3. In Sweden, the organized cervical screening program begins at age 23. This study showed that the vaccine was more effective against CIN2 and CIN3 if given before age 17 years. Longer follow-up of vaccinated women is needed to determine the long-term effectiveness of Sweden's vaccination program against invasive cervical cancer.

made available for girls ages 13–17 between 2007 and 2011. Girls and women outside this target age range could receive the vaccine but were not eligible for reimbursement. An organized school-based vaccination program using the qHPV vaccine started in 2012 where girls ages 10–12 are vaccinated with 3 doses of the qHPV vaccine through school health services, with catch-up three-dose vaccination offered to girls ages 13–18. In December 2014, Sweden achieved a one-dose vaccination coverage of 82% in the child vaccination program, and close to 60% for catch-up and subsidized vaccinations.¹¹

There is a growing body of evidence showing the effect of HPV vaccination in a population setting against both condyloma and cervical abnormalities.^{12–16} Nationwide population-based studies are important as they give insight into the actual public health impact of vaccination on disease outcomes within a country. It is furthermore important to continue monitoring the vaccine's impact in settings with different vaccine uptake and cervical screening coverage.

It will take a few more years before impact of HPV vaccination against invasive cervical cancer can be determined. High-grade cervical intraepithelial neoplasia (CIN) is a precursor state of cervical cancer that can either regress or progress into cancer and is thereby an important intermediate disease outcome for the evaluation of the population effect of HPV vaccination. Given the unique setting in Sweden where there is both an organized screening program and the ability to track vaccination at an individual level, the aim of this nationwide study was thus to quantify the effect of qHPV vaccination on incidence of high-grade cervical lesions in the Swedish population of girls and young women ages 13–29.

Material and Methods

We used a register-based cohort study design. The study population included all 13 to 30 year old girls and young women that were resident in Sweden at the start of individual follow-up, which was defined as the latest of January 1, 2006, or the 13th birthday of the girl. The study period started on January 1, 2006 and ended on December 31, 2013. Study participants were followed up until the first of the following events: diagnosis of the outcome, their 30th birthday, death, emigration, bivalent HPV (bHPV) vaccination, or December 31, 2013. Women were excluded from the study if one of the following events preceded the start of the study: diagnosis of the outcome, bHPV vaccination, nonresidence in Sweden at start of follow-up, or death (Supporting Information Figs. 1 and 2).

Data collection

Data were collected using Swedish population-based health data registers. Data on qHPV and bHPV vaccination were collected using the Swedish HPV Vaccination register, National Vaccination register, and Prescribed Drug register (PDR). The National Swedish Cervical Screening Registry (NKCx) includes information on all pap-smears taken in Sweden as part of the organized cervical screening program but also all Pap smears taken outside the program. NKCx was used to obtain information on invitation to organized cervical screening, cytological pap-smear results, and histologically confirmed diagnosis of the outcome.⁸ In addition, information on cervical cancer cases and histologically confirmed high-grade cervical lesions was also collected from the Swedish Cancer register.^{17,18} Information on deaths was collected using the Causes of Death register and information on migration was provided by the Migration register. Data on migration was available until 2012. The Multigeneration register provided information on parents to study participants, and was linked to the Education register, from which the education level (attained closest to study entry) of the parents of the study participant was obtained.

Case definition

The study outcomes were first occurrence of a histologically confirmed diagnosis of (1) CIN2 or worse, adenocarcinoma *in situ* (AIS) or worse (CIN2+) or (2) CIN3 or worse, AIS or worse (CIN3+). Diagnoses were obtained from NKCx by using the corresponding standardized nomenclature of medical diagnoses (SNOMED) (Supporting Information Table 1) and the Swedish Cancer register by using the International Classification of Diseases code, 7th revision, 171 for cervical cancer.

Exposure

The Swedish HPV vaccination register, which was launched in parallel with the start of opportunistic HPV vaccination, contains information on vaccine administration dates (both qHPV and bHPV vaccinations), and served as the main source for data on qHPV vaccine exposure. The estimated coverage in the register was 80–85% between 2006 and 2010, and 92% in 2012. Since 2013, childhood qHPV vaccinations have been reported to by the National Vaccination Register which includes all childhood vaccinations that are part of the national immunization program.

The PDR is a 100% complete automated register holding information on vaccine dispensation dates.¹⁹ Data in the vaccination registers were supplemented with vaccine dispensation dates from the PDR. A vaccine dispensation date was considered as a new qHPV vaccine dose if there was >14 days between a vaccine dispensation and an administered vaccine dose. The Anatomic Therapeutic Chemical classification codes J07BBM01 and J07BBM02 were used to identify qHPV and bHPV vaccine prescriptions, respectively.

In the period under study, three-dose vaccination was recommended by the National Board of Health and Welfare in both the school-based and catch-up immunization program.

Screening in Sweden

To have Pap smears prior to the start of organized screening is rather uncommon in Sweden (around 13% of women had a Pap smear before the age of 23, while this figure increased to 58% once they reached age 23). Pap smears before the age of 23 are taken on women who are already sexually active and they thus represent a different risk group for already prevalent infections than women starting screening at age 23 or later. We therefore carefully designed two strategies for considering women screened at preorganized program ages 13–22, and women screened at program ages 23–29, to account for possible differences in underlying risk for disease.

Women at screening ages

The cohort of women at screening ages (23–29) included those that have reached the cervical screening age 23, and that had recently been screened in the organized program. Follow-up started at the time the Pap-smear was taken within the organized screening program during the study period or alternatively from the start of the study period if they had the cytology taken no more than 3.5 years prior to study start. Follow-up continued until an abnormal cytology not linked to histological high-grade cervical lesions (see Supporting Information Table 1), 3.5 years after the last normal cytology, or one of the other previously defined study exit criteria. The cut-off of 3.5 years was chosen to only include person-time of recently screened individuals.

Girls/young women at prescreening ages

Girls/young women at prescreening ages (13–22) included everyone that had not reached screening eligible age (*i.e.*, age 23). These individuals were followed from entry to study until they reached age 23 or one of the previously defined study exit criteria. Screening age was reached when a woman received her first invitation to screening or at age 23, whichever came first.

Statistical analysis

We used Poisson regression to estimate incidence rate ratios (IRR) with corresponding 95% confidence intervals (CI) comparing the incidence of high-grade cervical lesions in unvaccinated/partially vaccinated women with that in fully vaccinated

women (registration of 3 doses). Vaccination effectiveness (VE) was calculated as $(1-IRR) \times 100\%$. Attained age was handled as an underlying time scale (attained age categories 13–16, 17–19, 20–21, 22–23, 24–26 and 27–29 years) where individuals could contribute person-time to multiple categories. Three-dose vaccination was assessed as a time varying exposure. Partially vaccinated women (vaccinated with one or two doses) were classified as unvaccinated until they received their third dose. Analyses were adjusted for attained age, and parental highest education (categories: <high school, high school, university studies, missing information). Analyses were stratified on age at vaccination initiation (categories: ages ≤ 16 , 17–19, and 20–29) as the probability of previous HPV exposure in those vaccinated increases with increasing age.²⁰

In order to correct for the diagnostic time lag between an abnormal cytology and histology, we back-dated the histological diagnosis date of high-grade cervical lesions cases with 6 months to provide a more accurate estimate of when disease was first present. Consequently, individuals with histological diagnosis of high-grade cervical lesions who were vaccinated within 6 months prior to histological diagnosis were considered unvaccinated as disease presentation occurred prior to vaccination. We explored the length of the diagnostic time lag by calculating the frequency and cumulative incidence proportion of the time between an abnormal cytology (closest to histology) and histology, and 6 months appeared to be appropriate (Supporting Information Fig. 3).

Data management and statistical analyses were done with SAS statistical software version 9.4 (SAS Institute) and Stata version 13 (StataCorp). All statistical tests were two-sided. Ethical approval was granted by the Regional Ethical Board in Stockholm, Sweden, which determined that informed consent from the participants, was not required.

Results

For the analysis with outcome CIN2+, we included 1,333,691 individuals contributing 7,252,096 person-years. Mean follow-up time was 5.1 years (SD = 2.7) for unvaccinated and 2.6 years (SD = 1.8) for vaccinated individuals. A total of 236,372 (17.7%) individuals were vaccinated of which 182,861 (77.4%) individuals initiated vaccination before age 17. The proportion of individuals with a parent holding a university degree prior to study start was 40.6% for those unvaccinated, and 58.3%, 54.9%, and 68.5% for individuals initiating vaccination before age 17, ages 17–19 and ages 20–29, respectively (Table 1).

A total of 21,049 (93.1%) women with CIN2+ had an abnormal cytology prior to diagnosis; 88.8% of these cases had their CIN2+ confirmed within 6 months after the abnormal cytology (Supporting Information Fig.3).

There were 22,616 events of CIN2+ during follow-up, 296 cases of which were in vaccinated women, while the number of CIN3+ events was 12,645 and 126, respectively (Table 1). Table 2 shows the unadjusted IRs for CIN2+ and CIN3+. Focusing on the overlapping age range 20–23, we

Table 1. Information on vaccination status, CIN2+, CIN3+, and parental education level among girls and women aged 13–29 years between January 1, 2006 and December 31, 2013

Descriptive variables	Unvaccinated, No. %	Age at vaccination initiation		
		≤16 y, No. %	17–19 y, No. %	20–29 y, No. %
Cohort size ¹	1,097,319 (82.3)	182,861 (13.7)	44,284 (3.3)	9,227 (0.7)
CIN2+	22,320 (98.7)	33 (0.2)	139 (0.6)	124 (0.6)
CIN3+	12,519 (99.0)	8 (0.1)	52 (0.4)	66 (0.5)
Parental education level ^{1,2}				
Missing education	57,128 (5.2)	624 (0.3)	88 (0.2)	60 (0.7)
Less than high school	89,661 (8.2)	4,992 (2.7)	1,302 (2.9)	217 (2.4)
High school	504,879 (46.0)	70,660 (38.6)	18,598 (42.0)	2,630 (28.5)
University studies	445,651 (40.6)	106,585 (58.3)	24,296 (54.9)	6,320 (68.5)

¹Distribution of women across age at vaccination initiation categories shown for cohort with CIN2+ as the outcome.

²*p* values <0.001 for χ^2 test between parental education level and age at vaccination initiation.

find that the unadjusted IR for unvaccinated individuals increased sharply from 82 (95% CI = 76–88) at ages 20–21 to 791 (95% CI = 772–810) cases per 100,000 person-years at ages 22–23 where after the rates slightly decreased. The observed IRs at age 20–21 were 21 (95% CI = 11–38), 41 (95% CI = 27–63), and 121 (95% CI = 30–485) per 100,000 person-years when vaccination was initiated before age 17, ages 17–19, or ages 20–29, respectively. The observed IRs for CIN2+ at ages 22–23 were 21 (95% CI = 3–151), 406 (95% CI = 330–498), and 745 (95% CI = 556–998) cases per 100,000 person-years, for age at vaccination initiation categories before age 17, ages 17–19, or ages 20–29, respectively (Table 2).

The unadjusted IR of CIN3+ in unvaccinated individuals increased sharply from ages 20–21 (IR = 34 per 100,000 person-years, 95% CI = 30–38) to ages 22–23 (IR = 388, 95% CI = 375–402). IRs remained stable in the subsequent age-groups (ages 24–26: IR = 390, 95% CI = 379–402; ages 27–29: IR = 366, 95% CI = 356–378). For individuals initiating vaccination before age 17, ages 17–19, or ages 20–29, observed IRs at ages 20–21 were 4 (95% CI = 1–17), 14 (95% CI = 7–29), and 60 (95% CI = 9–429) cases per 100,000 person-years, respectively. The corresponding IRs at ages 22–23 were 21 (95% CI = 3–151), 160 (95% CI = 115–222), and 311 (95% CI = 199–488) cases per 100,000 person-years, respectively (Table 2).

Vaccine effectiveness against CIN2+ was estimated at 75% (IRR = 0.25, 95% CI = 0.18–0.35), 46% (IRR = 0.54, 95% CI = 0.46–0.64), and 22% (IRR = 0.78, 95% CI = 0.65–0.93), when vaccination was initiated before age 17, ages 17–19 or ages 20–29, respectively. Similar vaccine effectiveness against CIN3+ was observed for individuals initiating vaccination before age 17 (VE = 84%; IRR = 0.16, 95% CI = 0.08–0.32), between ages 17–19 (VE = 57%; IRR = 0.43, 95% CI = 0.33–0.57), and at ages 20–29 (VE = 25%; IRR = 0.75, 95% CI = 0.59–0.96) (Table 3).

When restricting the study population to women screened as part of the organized screening program, individuals initiating vaccination before age 17 contributed little person time and no cases of CIN2+ (no IRR reported). The IRR of

vaccination was 0.12 (95% CI = 0.02–0.85) in women initiating vaccination at ages 17–19, compared to unvaccinated women. No statistically significant effectiveness was found when vaccination was initiated at ages 20–29 (IRR = 0.79, 95% CI = 0.56–1.12) (Table 4). IRRs for CIN3+ were similar but did not reach statistical significance (Supporting Information Table 3).

When restricting the study population to individuals at prescreening ages only, the effect of vaccination on CIN2+ incidence among those initiating vaccination before age 17 and at ages 17–19 remained stable (IRR = 0.27, 95% CI = 0.19–0.38 and IRR = 0.51, 95% CI = 0.41–0.63, respectively). No vaccination effect on incidence of CIN2+ was found among women initiating vaccination after age 19 but before reaching screening ages and who were opportunistically screened (IRR = 0.96, 95% CI = 0.59–1.58) (Table 5). IRRs for CIN3+ were robust also in this group (Supporting Information Table 2).

Discussion

In this nationwide study, we provide estimates on impact of qHPV vaccination on high-grade cervical abnormalities eight years after qHPV vaccine introduction. We found lower incidence rates of CIN2+ and CIN3+ lesions following three-dose qHPV vaccination, most evidently so in girls and young women initiating vaccination before age 17. The estimated effectiveness of qHPV vaccination on incidence of CIN2+ and CIN3+ increased with decreasing age at vaccination initiation.

We were able to measure information on cervical abnormalities after vaccination exposure in the total population of women attending organized screening (either according to guidelines or sporadically) as well as in women below screening ages. Furthermore, we were able to give an estimate on the effect of qHPV vaccination on incidence of high-grade lesions as detected in the total population. This provides an estimate of the actual public health impact of qHPV

Table 2. Information on individuals included, number of events, person-time, and crude IRs for CIN2+ and CIN3+ by attained age and age at vaccination initiation

Attained ages	CIN2+				CIN3+			
	Individuals, No.	Events, No.	Person years	IR, (95% CI) ¹	Individuals, No.	Events, No.	Person years	IR, (95% CI) ¹
<i>Unvaccinated</i>								
13–16 y	62,5890	20	1,544,899	1 (1;2)	625,891	5	1,544,911	0 (0;1)
17–19 y	551,057	283	1,139,915	25 (22;28)	551,104	83	1,140,161	7 (6;9)
20–21 y	497,203	666	812,351	82 (76;88)	497,494	278	813,084	34 (30;38)
22–23 y	515,208	6,507	822,804	791 (772;810)	516,200	3,209	827,062	388 (375;402)
24–26 y	559,553	8,153	1,179,713	691 (676;706)	564,915	4,662	1,194,745	390 (379;402)
27–29 y	540,008	6,691	1,147,960	583 (569;597)	548,541	4,282	1,168,652	366 (356;378)
Total	1,307,091	22,320	6,647,642	336 (331;340)	1,311,463	12,519	6,688,615	187 (184;190)
<i>Vaccination initiation ≤16 y</i>								
13–16 y	161,690	1	186,563	1 (0;4)	161,691	1	186,564	1 (0;4)
17–19 y	98,519	21	201,754	10 (7;16)	98,519	4	201,767	2 (1;5)
20–21 y	41,145	10	48,290	21 (11;38)	41,159	2	48,315	4 (1;17)
22–23 y	8,333	1	4,707	21 (3;151)	8,338	1	4,709	21 (3;151)
Total	182,861	33	441,315	7 (5;11)	182,862	8	441,355	2 (1;4)
<i>Vaccination initiation 17–19 y</i>								
17–19 y	42,733	16	62,567	26 (16;42)	42,744	4	62,591	6 (2;17)
20–21 y	32,817	21	51,031	41 (27;63)	32,840	7	51,082	14 (7;29)
22–23 y	19,167	91	22,436	406 (330;498)	19,192	36	22,518	160 (115;222)
24–26 y	3,727	11	2,927	376 (208;679)	3,764	5	2,965	169 (70;405)
Total	44,284	139	138,960	100 (85;118)	44,298	52	139,156	37 (28;49)
<i>Vaccination initiation 20–29 y</i>								
20–21 y	2,358	2	1,650	121 (30;485)	2,367	1	1,655	60 (9;429)
22–23 y	4,867	45	6,040	745 (556;998)	4,909	19	6,100	311 (199;488)
24–26 y	6,978	50	10,769	464 (352;613)	7,144	33	10,996	300 (213;422)
27–29 y	3,651	27	5,721	472 (324;688)	3,768	13	5,893	221 (128;380)
Total	9,227	124	24,179	513 (430;612)	9,422	66	24,644	268 (210;341)

¹IRs reported per 100,000 person-years.

Table 3. IRRs comparing fully vaccinated individuals with unvaccinated individuals by age at vaccination initiation in the total population for CIN2+ and CIN3+

	CIN2+				CIN3+			
	Person-years	IR (95% CI) ¹	IRR (95% CI) ²	<i>p</i> values	Person-years	IR (95% CI) ¹	IRR (95% CI) ²	<i>p</i> values
Unvaccinated	6,647,642	336 (331;340)	Reference		6,688,615	187 (184;190)	Reference	
Age at vaccination initiation								
≤16y	441,315	7 (5;11)	0.25 (0.18;0.35)	<0.001	441,355	2 (1;4)	0.16 (0.08;0.32)	<0.001
17–19y	138,960	100 (85;118)	0.54 (0.46;0.64)	<0.001	139,156	37 (28;49)	0.43 (0.33;0.57)	<0.001
20–29y	24,179	513 (430;612)	0.78 (0.65;0.93)	0.006	24,644	268 (210;341)	0.75 (0.59;0.95)	0.019

¹Crude IRs reported per 100,000 person-years.²IRRs reported were stratified on age at vaccination initiation, and adjusted for attained age, and parental education.**Table 4.** IRRs comparing fully vaccinated individuals with unvaccinated individuals by age at vaccination initiation in the screened population ages 23–29 years old

	Individuals, No.	CIN2+, No.	Person-years	IR (95% CI) ¹	IRR (95% CI) ²	<i>p</i> values
Unvaccinated	602,882	4,765	1,623,109	294 (285;302)	Reference	Reference
Age at vaccination initiation						
≤16y	298	0	93	–	–	–
17–19y	5,227	1	4,669	21 (3;152)	0.12 (0.02;0.85)	0.033
20–29y	6,665	32	13,221	242 (171;342)	0.79 (0.56;1.12)	0.183

¹Crude IRs reported per 100,000 person-years.²IRRs reported were stratified on age at vaccination initiation, and adjusted for attained age, and parental education.**Table 5.** IRRs comparing fully vaccinated individuals with unvaccinated individuals by age at vaccination initiation in a population at pre-screening ages (ages 13–22)

	Individuals, No.	CIN2+, No.	Person-years	IR (95% CI) ¹	IRR (95% CI) ²	<i>p</i> values
Unvaccinated	935,647	3,352	3,851,513	87 (84;90)	Reference	Reference
Age at vaccination initiation						
≤16y	182,860	33	440,963	7 (5;11)	0.27 (0.19;0.38)	<0.001
17–19 y	44,274	79	128,366	62 (49;77)	0.51 (0.41;0.63)	<0.001
20–22 y	3,606	16	3,971	403 (247;658)	0.96 (0.59;1.58)	0.885

¹Crude IRs reported per 100,000 person-years.²IRRs reported were stratified on age at vaccination initiation, and adjusted for attained age, and parental education.

vaccination on incidence of cervical lesions in a well-defined Western population.

Other register-based studies utilizing individual level data of the total population have investigated vaccine effectiveness against cervical abnormalities in a population setting. In Denmark, risk for CIN2/3 following qHPV vaccination was reduced by up to 80% in the youngest birth cohorts born 1993–1994¹² and in Canada, Mahmud *et al.* observed 53% vaccine effectiveness against detection of high-grade lesions in girls ages 15–17.¹⁴ Although those results were based on vaccination with at least one dose, and vaccination programs in Canada and Denmark are different from Sweden in terms of coverage and vaccination initiation ages, theirs and our findings are well in agreement for girls below age 20 at vaccination initiation. In studies including screened populations

only, reductions of cervical abnormalities following vaccination have also been observed. Gertig *et al.* investigated vaccine effectiveness against cervical abnormalities in girls qHPV vaccinated in Australia's school-based cohorts and found an overall vaccine effectiveness against high-grade lesions of 39%.¹³ As part of Australia's (school- and community-based) catch-up program, Crowe *et al.* estimated the effect of qHPV vaccination against high-grade lesions in women and found an overall risk reduction for high-grade lesions of 46% in women ages 11–27.¹⁶ We extend these findings to include demonstrated, statistically significant, effectiveness also in older age groups, estimates for CIN3+, that is, including lesions of the worst severity, and a structured assessment of effectiveness in the total population, pre-screening and screening populations, respectively.

It has been demonstrated in randomized clinical trials that HPV vaccination does not alter the course of an ongoing HPV infection.^{21,22} In population-based studies such as ours, it is not possible to obtain information on what an individual's HPV status was at the time of vaccination. Asymptomatic prevalent infections with (non)vaccine types, or cervical lesions caused by such types, may have been present already at the time of vaccination. This could have significant impact on vaccine effectiveness, especially when outcomes are measured in close proximity after vaccination. A recent study compared incidence of HPV16/18-attributable CIN2+ with incidence of lesions attributable to other HPV-types by qHPV vaccination status. It showed significant reductions in HPV16/18-related CIN2+ in women that were vaccinated at least 24 months prior to their diagnosis, but no effect of vaccination in women that were vaccinated <24 months prior to their diagnosis.²³ This was also apparent in our results for women at prescreening age showing that those initiating vaccination at age 20–22, where follow-up ended prior to age 23 (*i.e.*, within 3 years following vaccination) had no benefit of HPV vaccination (IRR = 0.96, 95% CI = 0.59–1.58, Table 5).

It has been shown that acquisition of HPV following sexual debut is high.^{24,25} Given that 16 is the median age for girls to start sexual activity in Sweden,²⁶ we expect that our results in girls initiating vaccination before age 17 should, therefore, provide information on vaccine effectiveness in a group where influence of infections present already at the time of vaccination would be relatively small. These results should therefore be the most representative ones for vaccine effectiveness expected following vaccination in a school-based vaccination program targeting young girls.

The strengths of this study include that this is a nationwide study including the entire Swedish female population ages 13–29. By using high quality national register-based data, we were able to link vaccination status to disease outcome at the individual level. NKCx has been 100% complete since 1995 and has complete ascertainment of all histologies and cytologies taken as part of the organized cervical screening program, and also includes all opportunistic smears taken outside the organized program.

A limitation of this study is that the Swedish HPV Vaccination register is not totally complete and thus a small proportion of vaccinated individuals might have been misclassified as unvaccinated – potentially resulting in underestimation of vaccine effectiveness. However, the younger participants in our study who were vaccinated and were eligible to receive a subsidy will to a very large part have been captured in the PDR. It has also previously been shown that, within this opportunistic HPV vaccination period, differences in socioeconomic status led

to unequal uptake of the vaccine.²⁰ We therefore made adjustments for parental education as a marker for socioeconomic status. We have also found in a previous study that women vaccinated in the opportunistic HPV-vaccination program were equally, if not more likely, to attend the cervical screening program in Sweden at age 23 and onwards.²⁷ Thus, higher cervical screening attendance among vaccinated women could result in a detection bias of relatively more cervical lesions in vaccinated compared to unvaccinated women and could result in underestimation of the impact of vaccination on high-grade cervical lesions.

Furthermore, the age distribution differed between vaccinated and unvaccinated subjects, leading to different median follow-up time and greater screening opportunity for vaccinated girls and women. This in turn could have increased their chance of detecting cervical lesions, and lead to inflated crude estimates of vaccination impact. However, this bias was addressed in our statistical model, which corrects for attained age. We have also analysed our data conditional on attendance to the organized cervical screening program, where only person time of recently screened women was included—women not attending screening were excluded, and women not attending regularly were censored when they were no longer protected by a negative Pap-smear result. In this way, we can account for under-screening in both vaccinated and unvaccinated women. The results in this screened population agreed well with the results obtained in the total population.

In addition, due to our register-based study design, we did not have information on lifestyle factors, sexual behavior, or HPV status at time of vaccination. Due to limited precision, we could not assess vaccine effectiveness by number of doses in this study.

In conclusion, we show effectiveness of opportunistic qHPV vaccination for preventing CIN2+ and CIN3+ lesions, with greater effectiveness observed in girls younger at vaccination initiation. In future studies we will continue to follow these girls, but also girls that have been vaccinated as part of the organized HPV vaccination program, to evaluate long-term vaccine effectiveness and to evaluate whether the vaccination programs are reaching anticipated effects, including protection against invasive cervical cancer.

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