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ARTICLE

# Quadrivalent Human Papillomavirus Vaccine Effectiveness: A Swedish National Cohort Study

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**Background** Incidence of condyloma, or genital warts (GW), is the earliest possible disease outcome to measure when assessing the effectiveness of human papillomavirus (HPV) vaccination strategies. Efficacy trials that follow prespecified inclusion and exclusion criteria may not be fully generalizable to real-life HPV vaccination programs, which target a broader segment of the population. We assessed GW incidence after on-demand vaccination with quadrivalent HPV vaccine using individual-level data from the entire Swedish population.

**Methods** An open cohort of girls and women aged 10 to 44 years living in Sweden between 2006 and 2010 (N > 2.2 million) was linked to multiple population registers to identify incident GW in relation to HPV vaccination. For vaccine effectiveness, incidence rate ratios of GW were estimated using time-to-event analyses with adjustment for attained age and parental education level, stratifying on age at first vaccination.

**Results** A total of 124 000 girls and women were vaccinated between 2006 and 2010. Girls and women with at least one university-educated parent were 15 times more likely to be vaccinated before age 20 years than girls and women whose parents did not complete high school (relative risk ratio = 15.45, 95% confidence interval [CI] = 14.65 to 16.30). Among those aged older than 20 years, GW rates declined among the unvaccinated, suggesting that HPV vaccines were preferentially used by women at high risk of GW. Vaccination effectiveness was 76% (95% CI = 73% to 79%) among those who received three doses of the vaccine with their first dose before age 20 years. Vaccine effectiveness was highest in girls vaccinated before age 14 years (effectiveness = 93%, 95% CI = 73% to 98%).

**Conclusions** Young age at first vaccination is imperative for maximizing quadrivalent HPV vaccine effectiveness.

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Prophylactic human papillomavirus (HPV) vaccination programs have been launched around the world with the aim of preventing cervical cancer and other HPV-related cancers. Vaccinated cohorts in Sweden are still too young to assess effectiveness against precancerous lesions or invasive HPV-related cancers. Condyloma acuminata, also referred to as genital warts (GWs), has a shorter incubation time after incident HPV infection and as such is ideal to measure in early evaluations of HPV vaccine effectiveness.

The HPV types 6 and 11 cause about 90% of GW. Although GW is often a transient disease, the treatment, psychosocial, and symptom burdens vary considerably between individuals. In the Nordic countries, 10% of women in the population will have had GW by age 45 years, with similar numbers indicated among men (1,2). Two vaccines offer protection against high oncogenic–risk types HPV16 and HPV18, but only the quadrivalent HPV (qHPV) vaccine also offers protection against HPV6 and HPV11. The qHPV vaccine was approved and became commercially available in 2006. In Sweden, opportunistic vaccination began in October 2006 and has been partially subsidized for girls aged 13 to 17 years since May 2007 (3) (Supplementary Material, available online). As of mid-2011, approximately 130 000 Swedish girls and women were vaccinated with at least one dose, 99% of whom were vaccinated with the qHPV vaccine.

Clinical trials have shown high vaccine efficacy rates for prevention of HPV infection, GW, and precancerous genital lesions in women aged 16 to 26 years (4–7). Among HPV-naive women, the qHPV vaccine has had nearly 100% protection against GW associated with the four HPV vaccine types and an efficacy of about 83% for all GW (regardless of HPV type) (4,6,7). In intention-to-treat analyses, in which young women were vaccinated regardless of their prior HPV exposure but with a maximum of four lifetime sexual partners and no history of abnormal cervical smears, an efficacy against all GW (regardless of HPV type) of 62% was reported (4).

Efficacy trials follow strict protocols containing prespecified inclusion and exclusion criteria and may not be fully generalizable to real-life HPV vaccination programs. Seminal ecologic studies from Australia, Sweden, and the United States have shown

substantial decreases in cases of GW after the introduction of a vaccination program. These observed decreases provide a rapid assessment of potential vaccine impact (8,9). However, the ecologic design of those studies makes ascertaining the cause of the decline in GW impossible (2,8–10). Vaccine effectiveness studies are necessary to assess the actual population impact of HPV vaccination on the incidence of HPV-related diseases so as to best inform emerging prevention programs and assess the actual public health impact of the vaccines on intended outcomes in more diverse populations (10–12). Few countries have the infrastructure capacity to study vaccine effectiveness rates and population impact on a national level because studying this requires individually identifiable information on vaccination status and eventual disease outcomes. This study was conducted to assess GW incidence rates comparing girls and women vaccinated with the qHPV vaccine with those unvaccinated using individual-level data from the entire Swedish population.

## Methods

### Study Population

This study was based on a nationwide open cohort of girls and women aged 10 to 44 years living in Sweden between January 1, 2006, and December 31, 2010. To assess effectiveness against incident GW, all individuals with a GW before individual follow-up (n = 15 656) were excluded from the cohort. Individuals were censored at time of death (n = 3377) or their 45th birthday. We did not have access to data on emigration status after December 31, 2002. Therefore, girls and women who emigrated up to this date were excluded (n = 152 896). Girls and women who received the bivalent HPV vaccine (n = 1381) were censored at vaccination. In total, 2 209 263 girls and women were included in the study. The average follow-up time was 4.4 years (SD ± 1.3 years).

Ethical approval for this study was granted by the Ethical Review Board of Karolinska Institutet, Solna, Sweden. This study is registered at Clinicaltrials.gov (ID number NCT01553994).

### Data Sources

Data were collected using the Swedish population registers. Every resident has a unique personal identification number, which enables individual record linkage from the Total Population Register with multiple registers (13). Data on vaccination exposure status with either the quadrivalent or bivalent vaccine were retrieved by the Prescribed Drug Register (PDR) and from the Swedish vaccination register (SVEVAC), a national HPV vaccination register that started in 2006 (Supplementary Material, available online). The PDR contains all drug prescriptions dispensed at pharmacies in Sweden since July 1, 2005, including subsidized HPV vaccines for girls aged 13 to 17 years. We assumed that almost 100% of the HPV vaccines are registered in the PDR for this group. Data on GW status were obtained from the PDR and the Patient Register (PR) (see "Case Definition"). The PR includes nationwide information on all in- and outpatient hospital visits since 1987 and 2001, respectively. The Cause-of-Death Register was used to obtain information on deaths. Emigration status was derived from the Migration Register, which contains all immigration and emigration dates until December 31, 2002. Mother's and father's highest education level—a proxy for socioeconomic status—was obtained from the Education Register, and the parents themselves were identified from the Multigeneration Register.

### Case Definition

GW cases were defined as the first diagnosis of GW either by the PR and/or a GW treatment prescription identified by the PDR. The International Classification of Diseases, Tenth Revision code A63 was used to identify GW as a main or contributory diagnosis in the PR (14). Reporting for inpatient hospital care in the Swedish Patient Register has been estimated to be valid in 85% to 95% of all cases, depending on the diagnosis (15). For outpatient hospital care, register coverage is estimated to be 85% for somatic care, but no figures on validity of International Classification of Diseases reporting are available. Podophyllotoxin and imiquimod, pharmaceuticals used to treat GW, were identified by the Anatomical Therapeutical Chemical codes D06BB04 and D06BB10, respectively. Podophyllotoxin is used exclusively for the treatment of external GW, whereas imiquimod is also used to treat other skin pathologies that mostly affect older individuals. Age-specific prescription trends for podophyllotoxin and imiquimod were identical in those aged less than 45 years. Imiquimod trends differed in older middle-aged and elderly groups, in whom use of imiquimod as treatment of non-GW skin pathologies is more common, so follow-up was excluded over age 44 years (2). We could not identify cases of GW treated in primary care if no drugs were used.

### Vaccination Status

Vaccination dates were primarily derived from SVEVAC, but because not all vaccinations were registered there, the PDR was also used. Prescriptions were identified for the quadrivalent and the bivalent vaccines using Anatomical Therapeutical Chemical codes J07BM01 and J07BM02, respectively. If a woman had more than three recorded dates for the qHPV vaccine, we assumed that the first three unique dates matched with the first, second, and third doses of the vaccine. A total of 926 individuals identified by the PDR had multiple prescription dispensations recorded for the same date. It was assumed that individuals with two unique dates and more than three dispensation dates received their first and second dose or their second and third dose at the same date. Twenty-one women with only one unique date listed three times were considered to have all three doses on the same date. Vaccination status was assessed as a time-varying exposure, with full effectiveness of the vaccine assumed after three doses. Using vaccination status as a time-varying exposure allowed for the same woman to contribute person-time to multiple dose categories (ie, 0, 1, 2, or 3) depending on whether she received some, all, or any vaccine doses during individual follow-up. A woman was considered unvaccinated if she was not vaccinated at all, was considered partially vaccinated if she had one or two doses, and was considered fully vaccinated if she had all three doses. Because person-time for the unvaccinated individuals contributed to 97.5% of total person-time, we decided to include the partially vaccinated girls and women (0.9%) in the reference group because excluding them did not alter the results.

Age at vaccination was defined as the age at first vaccination. Individuals who were diagnosed with GW during follow-up and before first vaccination would only contribute person-time in the unvaccinated group.

### Statistical Analyses

The association between parental education level and vaccine uptake was modeled by multinomial logistic regression with outcomes of no vaccination, first vaccinated before age 20 years, and first vaccinated at age 20 years or older and is reported as the relative risk ratio (RRR). Subjects with missing parental education level were retained in the missing category for the analysis.

Crude incidence rates (IRs) of GW were calculated as the number of cases per accrued person-time for unvaccinated, partially vaccinated, and fully vaccinated individuals. Poisson regression analysis was used to estimate the incidence rate ratio (IRR) between vaccinated and partially vaccinated or unvaccinated individuals, adjusted for attained age (time-scale), age at vaccination, and highest parental education level. Individuals were stratified into six age-at-vaccination groups (aged 10–13, 14–16, 17–19, 20–22, 23–26, and 27–44 years), splitting person-time based on attained age, and those who received the vaccine were categorized based on their age at first vaccination. Cutpoints for age-at-vaccination groups were chosen based on a previous study of underlying age- and sex-specific GW incidence trends. Vaccination was included as a time-varying exposure, so individuals could contribute both vaccinated and unvaccinated risk time to the model. Vaccine effectiveness was calculated as (1 – IRR) × 100%. Both IRR and vaccine effectiveness were reported with 95% confidence intervals (CIs).

Poisson regression stratified by age was also used to assess vaccination self-selection bias in the population cohort under study by comparing IRs before vaccination availability in Sweden with IRs at the end of follow-up among those unvaccinated.

The potential impact of population-wide vaccination programs at different ages was assessed by predicting IRs for the whole study cohort under two assumptions: 1) no vaccination at all and 2) complete vaccination of all girls and women in the age categories defined above. In both cases, the predicted age-specific IRs and the estimated associations with parental education level were averaged over the whole study population.

Data management was done with SAS statistical software version 9.2 (SAS Institute Inc, Cary, NC). Statistical analyses were done with Stata software (version 11; StataCorp, College Station, TX). All statistical tests were two-sided. Statistical significance was defined as $P$ less than .05.

## Results

The population cohort included 2 209 263 girls and women aged 10 to 44 years living in Sweden between 2006 and 2010, contributing 9 640 542 person-years; 33 178 participants had GW during follow-up. More than 5% of the study population received at least one dose of the qHPV vaccine, with 124 000 girls and women vaccinated, 90% of whom were in the subsidized target group. Of all vaccinated girls and women, 78.5% were fully vaccinated. The highest vaccination coverage was among those aged 18 to 19 years (vaccination coverage = 31.9%) and 13 to 17 years (vaccination coverage = 24.7%) (Table 1). Girls and women who had at least one university-educated parent were approximately 15 times more likely to be vaccinated before age 20 years than girls and women whose parents did not complete high school (RRR = 15.45, 95% CI = 14.65 to 16.30) (Table 2). Maternal university education level was more strongly associated with vaccination status outcome than paternal university education level (RRR = 8.58, 95% CI = 8.32 to 8.85; vs RRR = 4.31, 95% CI = 4.22 to 4.41). Similar patterns for associations with education were seen for those vaccinated at age 20 years and older (Table 2).

To assess whether there was a self-selection bias among those who were vaccinated, we compared the rate of GW before commercial

**Table 1.** Vaccination status, genital warts cases, and parental education level among all girls and women in Sweden aged 10 to 44 years between January 2006 and December 2010

| | Age at end of follow-up, years | | | | | | |
|---|---|---|---|---|---|---|---|
| **Descriptive variables** | **10–12, No. (%)** | **13–17, No. (%)** | **18–19, No. (%)** | **20–22, No. (%)** | **23–26, No. (%)** | **≥27, No. (%)** | **All ages, No. (%)** |
| Cohort | 133 196 (6.0) | 260 682 (11.8) | 125 831 (5.7) | 179 751 (8.1) | 204 167 (9.2) | 1 305 636 (59.1) | 2 209 263 (100) |
| Unvaccinated | 132 943 (99.8) | 196 388 (75.3) | 85 647 (68.1) | 165 404 (92.0) | 201 022 (98.5) | 1 304 096 (99.9) | 2 085 500 (94.4) |
| Vaccinated | 253 (0.2) | 64 294 (24.7) | 40 184 (31.9) | 14 347 (8.0) | 3145 (1.5) | 1540 (0.1) | 123 763 (5.6) |
| 1× vaccinated | 61 (0.1) | 5428 (2.1) | 2207 (1.8) | 1113 (0.6) | 265 (0.1) | 167 (0.0) | 9241 (0.4) |
| 2× vaccinated | 115 (0.1) | 11 231 (4.3) | 4123 (3.3) | 1542 (0.9) | 253 (0.1) | 124 (0.0) | 17 388 (0.8) |
| 3× vaccinated | 77 (0.1) | 47 635 (18.3) | 33 854 (26.9) | 11 692 (6.5) | 2627 (1.3) | 1249 (0.1) | 97 134 (4.4) |
| % Fully vaccinated of vaccinated | 30.4 | 74.1 | 84.3 | 81.5 | 83.5 | 81.1 | 78.5 |
| Genital warts | 75 (0.1) | 3389 (1.3) | 5647 (4.5) | 8145 (4.5) | 6578 (3.2) | 9344 (0.7) | 33 178 (1.5) |
| Mother's highest education | | | | | | | |
| Missing | 3851 (2.9) | 5619 (2.2) | 2008 (1.6) | 3062 (1.7) | 4576 (2.2) | 174 239 (13.4) | 193 355 (8.8) |
| Less than high school | 15 786 (11.9) | 30 944 (11.9) | 15 917 (12.7) | 25 060 (13.9) | 33 277 (16.3) | 349 490 (26.8) | 470 474 (21.3) |
| High school | 67 175 (50.4) | 138 268 (53.0) | 67 309 (53.5) | 93 683 (52.1) | 100 248 (49.1) | 508 519 (39.0) | 975 202 (44.1) |
| University studies | 46 384 (34.8) | 85 851 (32.9) | 40 597 (32.3) | 57 946 (32.2) | 66 066 (32.4) | 273 388 (20.9) | 570 232 (25.8) |
| Father's highest education | | | | | | | |
| Missing | 3949 (3.0) | 7011 (2.7) | 3229 (2.6) | 5381 (3.0) | 8038 (3.9) | 245 912 (18.8) | 273 520 (12.4) |
| Less than high school | 17 624 (13.2) | 39 435 (15.1) | 22 007 (17.5) | 35 129 (19.5) | 45 598 (22.3) | 382 180 (29.3) | 541 973 (24.5) |
| High school | 69 400 (52.1) | 137 596 (52.8) | 65 442 (52.0) | 89 713 (49.9) | 94 017 (46.1) | 440 073 (33.7) | 896 241 (40.6) |
| University studies | 42 223 (31.7) | 76 640 (29.4) | 35 153 (27.9) | 49 528 (27.6) | 56 514 (27.7) | 237 471 (18.2) | 497 529 (22.5) |

**Table 2.** Relative risk ratios (RRRs) from a multinomial logistic model for the effect of parental education on vaccination status*

| Highest attained education level | RRR (95% CI) | | *P*† |
|---|---|---|---|
| | First vaccination before age 20 y | First vaccination age 20 y or older | |
| Of mother | | | |
| Missing | 0.15 (0.13 to 0.17) | 0.52 (0.39 to 0.69) | <.001 |
| Less than high school‡ | 1.00 (referent) | 1.00 (referent) | |
| High school | 4.79 (4.64 to 4.94) | 2.88 (2.52 to 3.30) | <.001 |
| University studies | 8.58 (8.32 to 8.85) | 9.49 (8.34 to 10.80) | .14 |
| Of father | | | |
| Missing | 0.18 (0.17 to 0.20) | 0.50 (0.41 to 0.60) | <.001 |
| Less than high school‡ | 1.00 (referent) | 1.00 (referent) | |
| High school | 2.75 (2.69 to 2.81) | 1.70 (1.54 to 1.88) | <.001 |
| University studies | 4.31 (4.22 to 4.41) | 5.40 (4.91 to 5.94) | <.001 |
| Of parents§ | | | |
| Missing | 0.19 (0.16 to 0.23) | 0.80 (0.56 to 1.14) | <.001 |
| Less than high school‡ | 1.00 (referent) | 1.00 (referent) | |
| High school | 7.48 (7.09 to 7.90) | 3.15 (2.57 to 3.87) | <.001 |
| University studies | 15.45 (14.65 to 16.30) | 12.67 (10.37 to 15.47) | .06 |

* CI = confidence interval.

† Two-sided Wald test of the hypothesis that within the stated education RRR within the same educational level is the same for women first vaccinated before age 20 and for women first vaccinated age 20 or older.

‡ Less than high school indicates a maximum of 9 years in school and high school indicates a maximum of 13 years.

§ Defined as highest education level of either parent or as the education level of the nonmissing parent.

availability of qHPV with rate of GW at the end of follow-up in the unvaccinated population. No statistically significant difference in the rates were found in the age category with highest vaccine coverage (aged 14–19 years) (IRR = 1.00, 95% CI = 0.98 to 1.02). Among women aged 20 years or older, the GW rates declined over time in the unvaccinated population (IRR = 0.96, 95% CI = 0.95 to 0.97), suggesting a self-selection bias in which individuals at a higher risk for GW were more likely to seek vaccination (data not shown).

### Vaccine Effectiveness

Vaccine effectiveness was 76% (95% CI = 73% to 79%) among those who received three doses of the vaccine with their first dose before age 20 years. Vaccine effectiveness was highest in girls vaccinated before age 14 years (effectiveness = 93%, 95% CI = 73% to 98%). Effectiveness was 80% (95% CI = 75% to 83%) for girls vaccinated at ages 14 to 16 years, 71% (95% CI = 65% to 76%) at ages 17 to 19 years, and 48% (95% CI = 22% to 65%) for women vaccinated at ages 20 to 22 years. No effectiveness was measureable in fully vaccinated women who received their first dose when they were aged older than 22 years (Table 3).

When comparing the IR predicted under the assumption of complete vaccination with that predicted under no vaccination, the greatest reduction in IR was for complete vaccination among the earliest age group considered (10–13 years), with a maximum reduction in IR of 332.35 per 100 000. The maximum reduction in IR decreased with each subsequent older age category and was nonexistent for the group aged 27 years or older (Table 3).

## Discussion

This first effectiveness study of the qHPV vaccine in an entire population showed that vaccination offered high protection against GW among girls and women who were fully vaccinated before age 20 years. By including more than 2.2 million girls and women ranging in age from 10 to 44 years, we could, for the first time, discern nuanced effects of age at vaccination. Effectiveness declined as the age at first vaccination increased. In the age group vaccinated before age 14 years, in which there is presumably little prior HPV exposure, the effectiveness against GW seen in this study (93%) was higher than efficacy among HPV-naive subjects reported in the qHPV vaccine clinical trials (83%) (4). Similarly, the effectiveness among all girls and women aged younger than 20 years (76%) appeared higher than the any-type GW efficacy reported in intention-to-treat clinical trial populations (62%) (4). However, women in the trials were older at enrollment (age range = 16–26 years) than individuals included in our study. Also, because the trials did not present age-specific results, age-at-vaccination differences could not be ascertained. A plausible explanation for effectiveness being higher than efficacy would be if HPV6 or HPV11 is preferentially associated with clinically significant GW and nonvaccine HPV types are preferentially associated with minor GW lesions that were found because of the more intense surveillance in the clinical trials. Considering that vaccinated individuals are known to be almost completely protected against incident vaccine-specific HPV infection, indirect protection from herd immunity cannot possibly have contributed to further increasing the effectiveness among the vaccinated women because the vaccine coverage was not high enough. Effectiveness studies extend beyond clinical trial restrictions present in efficacy studies and instead examine reduction of disease burden in the population at large. We compared our results with efficacy in trials because these comparisons are interesting and are advisable in vaccination program assessments. The 5-year follow-up in this study is comparable with that in other HPV vaccine studies investigating efficacy or effectiveness (4–7,16,17).

Interpreting the crude estimates of effectiveness for those aged 20 years or older at first vaccination is difficult because we found

**Table 3.** Observed incidence, estimated incidence rate ratios (IRRs) and effectiveness rates, and predicted incidence rates (IRs) per 100 000 person years for different vaccination scenarios*

| Age at vaccination, y | Observed number of cases | | Estimated IRR (95% CI) | Estimated effectiveness, % (95% CI) | Predicted IR | | |
|---|---|---|---|---|---|---|---|
| | Vaccinated | Not fully vaccinated | | | Vaccinated† | Not fully vaccinated‡ | Maximum reduction§ |
| <20 | 217 | 20 795 | 0.24 (0.21 to 0.27) | 76 (73 to 79) | 85.23 | 358.65 | 273.41 |
| 10–44 | 259 | 32 918 | 0.27 (0.24 to 0.30) | 73 (70 to 76) | 89.47 | 336.76 | 247.29 |
| 10–13 | 2 | 5733 | 0.07 (0.02 to 0.27) | 93 (73 to 98) | 24.35 | 356.70 | 332.35 |
| 14–16 | 105 | 14 392 | 0.20 (0.17 to 0.25) | 80 (75 to 83) | 73.62 | 357.36 | 283.74 |
| 17–19 | 110 | 19 162 | 0.29 (0.24 to 0.35) | 71 (65 to 76) | 115.15 | 356.39 | 241.24 |
| 20–22 | 24 | 15 692 | 0.52 (0.35 to 0.78) | 48 (22 to 65) | 225.77 | 349.59 | 123.82 |
| 23–26 | 14 | 10 714 | 0.79 (0.47 to 1.33) | 21 (<0 to 53) | 305.90 | 342.07 | 36.17 |
| ≥27 | 4 | 9336 | 2.32 (0.87 to 6.18) | <0 (<0 to 13) | 444.81 | 317.70 | ‖ |

* We compared fully vaccinated girls and women with not fully vaccinated girls and women, combining both unvaccinated and partially vaccinated girls and women. Estimates and predictions are based on Poisson regressions stratified by age-at-vaccination and adjusted for attained age and parental education level as a proxy for socioeconomic status. Predicted IRs are for the whole study population, under the assumption of either no vaccination at all or complete vaccination of the whole population in the indicated age category. CI = confidence interval.

† IR was estimated under the assumption that all girls and women within the specific age-at-vaccination group were fully vaccinated.

‡ IR was estimated under the assumption that girls and women within the specific age-at-vaccination group were partially vaccinated (1 or 2 doses) or had 0 doses.

§ Maximum reduction in IR was denoted as the difference between $IR_{\text{fully vaccinated}}$ and $IR_{\text{partially and nonvaccinated}}$.

‖ The value was negative.

evidence suggesting a self-selection bias with women at high risk preferentially seeking vaccination. Nevertheless, our failure to find any effectiveness at all for women aged older than 22 years suggests that this group had exposure to HPV before vaccination and therefore the impact of vaccination was lower. It is well known that the vaccine does not alter the course of an already existing HPV infection, which means that the vaccine will appear less effective if a woman is already infected with one or more of the HPV types targeted by the vaccine at the time of vaccination (6). Individuals with GW history before individual follow-up were excluded, but because the PDR was not available before 2005, misclassification is likely, especially among older individuals, leading to underestimation of the effectiveness for this group.

Previous studies (18,19) have examined parental attitudes toward HPV vaccinations and the influence of parental education level on these attitudes, but this is the first study examining the relationship between parental education level and actual vaccination status of children on a national, population-based level. One Swedish study showed that a higher parental education level was associated with a decreased willingness to vaccinate daughters, an attitude which is in contrast to the real-life results in this study (20). That parents' education influences vaccine uptake when out-of-pocket costs are involved may be anticipated, but the magnitude of the relative effect found in this study was surprising.

A potential limitation related to vaccine exposure is that vaccine dispensation dates from the PDR were used as a proxy measure to classify a woman's vaccination date when there was no information available from SVEVAC. This will slightly overestimate the actual vaccination dose status because individuals with multiple identical dates were considered fully vaccinated at the earliest date. However, given that unique vaccination dose dates were found for more than 99% of individuals, multiple identical dates is expected to be a minor issue. There are also limitations in using treatment-seeking behaviors as an outcome variable. Some individuals with clinical symptoms will not seek treatment, leading to an underestimation of the total number of GW cases. Also, regardless of how disease-specific a treatment is, using prescriptions as proxy for actual disease is not as precise as clinical diagnostics. Furthermore, individuals who visit nonhospital care for GW but who do not receive any pharmacological treatment are not included in the registers. Although this register limitation will result in an underestimation of the total number of GW cases, we expect it to be nondifferential with regard to vaccination exposure, which would tend to dilute our effectiveness estimates. We did not have adequate statistical power to assess vaccination effectiveness on recurrent GW among those with known GW history.

To our knowledge, this is the first population-based study investigating effectiveness of the qHPV vaccine that used nationwide linkage of individual vaccination status to GW care and treatment for all girls and women aged 10 to 44 years. Given that the time between HPV infection and diagnosis of GW is shorter than the time between HPV16 and/or HPV18 infection and the development of related precancerous lesions and cancer, the study of vaccination effectiveness against GW can provide an early feedback about whether there has been an adequate use of the HPV vaccines. For example, the HPV vaccine was licensed and made commercially available for individuals outside the recommended target group of girls aged 13 to 17 years. Although individuals needed to pay the entire vaccine cost themselves, there was still a large number vaccinated outside the target age. We found that among women first vaccinated at age 20 years or older there was low to immeasurable effectiveness and suggestive evidence that vaccinations tended to reach women at high GW risk. This suggests that vaccinations in this age group were not adequate for achieving the intended health benefit. However, the effectiveness for other outcomes, such as cervical intraepithelial neoplasia 1 and 2, might be different from that of GW.

In conclusion, this study shows that opportunistic qHPV vaccinations in Sweden have led to a substantial reduction in GW among girls and women vaccinated before age 20 years. However, the program had severe limitations because it preferentially reached individuals from families with higher socioeconomic status.

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## Notes

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