Original Investigation

Association of Varying Number of Doses of Quadrivalent Human Papillomavirus Vaccine With Incidence of Condyloma

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IMPORTANCE Determining vaccine dose-level protection is essential to minimize program costs and increase mass vaccination program feasibility. Currently, a 3-dose vaccination schedule is recommended for both the quadrivalent and bivalent human papillomavirus (HPV) vaccines. Although the primary goal of HPV vaccination programs is to prevent cervical cancer, condyloma related to HPV types 6 and 11 is also prevented with the quadrivalent vaccine and represents the earliest measurable preventable disease outcome for the HPV vaccine.

OBJECTIVE To examine the association between quadrivalent HPV vaccination and first occurrence of condyloma in relation to vaccine dose in a population-based setting.

DESIGN, SETTING, AND PARTICIPANTS An open cohort of all females aged 10 to 24 years living in Sweden (n = 1 045 165) was followed up between 2006 and 2010 for HPV vaccination and first occurrence of condyloma using the Swedish nationwide population-based health data registers.

MAIN OUTCOMES AND MEASURES Incidence rate ratios (IRRs) and incidence rate differences (IRDs) of condyloma were estimated using Poisson regression with vaccine dose as a time-dependent exposure, adjusting for attained age and parental education, and stratified on age at first vaccination. To account for prevalent infections, models included a buffer period of delayed case counting.

RESULTS A total of 20 383 incident cases of condyloma were identified during follow-up, including 322 cases after receipt of at least 1 dose of the vaccine. For individuals aged 10 to 16 years at first vaccination, receipt of 3 doses was associated with an IRR of 0.18 (95% CI, 0.15-0.22) for condyloma, whereas receipt of 2 doses was associated with an IRR of 0.29 (95% CI, 0.21-0.40). One dose was associated with an IRR of 0.31 (95% CI, 0.20-0.49), which corresponds to an IRD of 384 cases (95% CI, 305-464) per 100 000 person-years, compared with no vaccination. The corresponding IRDs for 2 doses were 400 cases (95% CI, 346-454) and for 3 doses, 459 cases (95% CI, 437-482). The number of prevented cases between 3 and 2 doses was 59 (95% CI, 2-117) per 100 000 person-years.

CONCLUSIONS AND RELEVANCE Although maximum reduction in condyloma risk was seen after receipt of 3 doses of quadrivalent HPV vaccine, receipt of 2 vaccine doses was also associated with a considerable reduction in condyloma risk. The implications of these findings for the relationship between number of vaccine doses and cervical cancer risk require further investigation.

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Human papillomavirus (HPV) types 16 and 18, two HPV types included in the prophylactic HPV vaccines, are implicated in multiple cancer outcomes, including cervical cancer.[1,2] The quadrivalent HPV vaccine also protects against HPV types 6 and 11, which cause about 90% of condylomas, also referred to as genital warts.[3] Condyloma is the first HPV-related disease end point that can be measured after quadrivalent HPV vaccination because of its short incubation time of between 1 and 6 months.[4-6]

Between 2007 and 2011, Sweden had a partially subsidized, opportunistic HPV vaccination program for girls aged 13 to 17 years. Vaccine coverage within this target group was about 25% in 2010.[7] Ninety-nine percent of girls vaccinated received the quadrivalent vaccine. In 2012, a school-based vaccination program was launched for girls aged 10 to 12 years, with a catch-up program for girls aged 13 to 18 years, all free of charge.

Both the bivalent and quadrivalent vaccines currently have a 3-dose schedule, which is associated with increased cost and other program feasibility issues.[8,9] Dose efficacy has been widely discussed as a fundamental factor in decisions regarding vaccination strategies.[8,10,11] The overall protective effects of HPV vaccination programs and requisite efforts appropriate for ensuring complete 3-dose vaccinations are unclear. Small clinical trials have reported measures of vaccine efficacy with less than 3 doses.[8,12,13]

In contrast to vaccine efficacy trials, population-based studies can examine reduction in disease end points and are more likely to reflect the vaccinated population.[14,15] Population-based studies measuring HPV-related diseases provide essential complementary information to studies of vaccine dose efficacy, which primarily assess nondisease end points such as immune response or are designed so that efficacy comparisons cannot be made between multiple dose levels. Registry data in Sweden include unique information on vaccination dose dates for the entire population. The aim of this study was to assess the association between quadrivalent HPV vaccination and condyloma per vaccine dose among young females in a population-based setting.

Methods

Study Population

An open cohort of all girls and young women aged 10 to 24 years and residing in Sweden was followed up from January 1, 2006, to December 31, 2010, for HPV vaccination and first occurrence of condyloma. Girls entered the open cohort on their 10th birthday or at any time after January 1, 2006, whichever came last. They were followed up until the first of the following: their 25th birthday; December 31, 2010; death; vaccination with the bivalent vaccine; or a condyloma diagnosis.

To assess the association between dose level and incident, as opposed to prevalent condyloma, all individuals with condyloma prior to individual follow-up were excluded. As it was not possible for us to obtain updated emigration status at the start of follow-up, all women having emigrated through December 31, 2002, were excluded because their history and

Figure 1. Details on Study Exclusions and Population Analyzed to Study the Association Between Quadrivalent Human Papillomavirus Vaccination and Condyloma per Dose Level
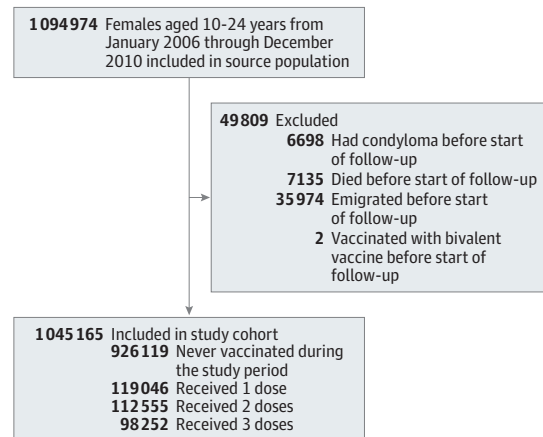
follow-up could not be ascertained. Individuals with a registered date of death before follow-up were excluded, and women who received the bivalent vaccine before follow-up were excluded (**Figure 1**).

Ethical approval for this study was granted by the ethical review board of Karolinska Institutet, Solna, Sweden. Informed consent from study participants was not required.

Data Collection

Data were collected using the Swedish population-based health data registers. Data on vaccination exposure status were retrieved via the Swedish vaccination register and the Prescribed Drug Register. Condyloma status was defined using the Prescribed Drug Register and the Patient Register. The Cause of Death Register provided information on deaths. Emigration status was derived from the Migration Register. As a proxy for socioeconomic status, parents' education levels were obtained from the Education Register and the parents were identified from the Swedish Multigeneration Register.

Condyloma cases were defined as first observed diagnosis of condyloma either via the Patient Register or a condyloma treatment prescription identified by the Prescribed Drug Register. The *International Statistical Classification of Diseases, Tenth Revision* (*ICD-10*) code A63.0 was used to identify condyloma as main or contributory diagnosis in the Patient Register. Prescriptions for the 2 condyloma treatments, podophyllotoxin and imiquimod, were identified with their Anatomical Therapeutic Chemical (ATC) codes D06BB04 and D06BB10, respectively. These treatments are recommended as the primary mode of treatment for condyloma in Sweden. Podophyllotoxin is used exclusively for the treatment of anogenital warts whereas imiquimod is used for treatment of anogenital warts and skin tumors, the latter mostly seen in individuals aged 40 years and older. The health care system in Sweden is publically funded, giving all citizens equal access to health care; however, we acknowledge that equal access may not necessarily result in equal utilization of health care services.

Table 1. Parental Education Level and Person-Time Contributing to the Cohort Based on Age at Enrollment

	Age at Enrollment, y					
	10-13	14-16	17-19	20-21	22-24	Total (10-24)
Cohort, No. (%)	451 327 (43.2)	183 820 (17.6)	164 428 (15.7)	99 894 (9.6)	145 696 (13.9)	1 045 165 (100)
Contributing person-time, y	1 698 580	904 588	793 374	387 960	211 128	3 995 631
Highest parental education, No. (%)[a]						
Missing	4585 (1.0)	1576 (0.9)	1590 (1.0)	1324 (1.3)	4570 (3.1)	13 645 (1.3)
Less than high school	21 477 (4.8)	10 466 (5.7)	11 583 (7.0)	8190 (8.2)	13 280 (9.1)	64 996 (6.2)
High school	223 286 (49.5)	93 577 (50.9)	81 061 (49.3)	47 611 (47.7)	67 245 (46.2)	512 780 (49.1)
University studies	201 979 (44.8)	78 201 (42.5)	70 194 (42.7)	42 769 (42.8)	60 601 (41.6)	453 744 (43.4)

[a] Highest parental education was based on the education level of the highest educated parent or the education level of the nonmissing parent.

Vaccination dates for the bivalent and quadrivalent vaccines were identified in the Swedish vaccination register and were complemented with the Prescribed Drug Register (ATC codes J07BM01 and J07BM02) when vaccination data were incomplete. Unique vaccination dose dates were found for 99.6% of vaccinated individuals in the study population.

Statistical Analyses

Vaccination dose was assessed as a time-dependent exposure, which allowed the same woman to contribute person-time to multiple dose categories (0, 1, 2, 3) depending on whether she received none, some, or all vaccine doses during individual follow-up (eFigure 1 in the Supplement). If a woman was diagnosed with condyloma during follow-up and prior to vaccination, she would only contribute person-time in the unvaccinated group with no analysis time included after the case of condyloma. As effect modification with age at vaccination has been shown previously,[7] women who received the vaccine were categorized based on their age at first vaccination, creating 2 groups, one composed of individuals vaccinated when aged 10 through 16 years and the other group composed of individuals vaccinated when aged 17 through 19 years. This categorization reflects the median age at first sexual intercourse in Sweden.[16] A separate analysis was carried out including 3 age-at-first-vaccination strata (ages 10-13, 14-16, and 17-19 years) (eResults 4 and eTable 5 in the Supplement). Women who were first vaccinated when older than 19 years were censored at time of vaccination.

Incidence rates (IRs) per 100 000 person-years were estimated per vaccine dose level based on 5 different attained age groups (10-13, 14-16, 17-19, 20-21, and 22-24 years). Poisson regression was used to estimate incidence rate ratios (IRRs) and 95% confidence intervals of condyloma by vaccine dose, adjusting for parental education and attained age. Incidence rate ratios were calculated independent of and stratifying for age at first vaccination. Incidence rates and incidence rate differences (IRDs) between doses were calculated stratified by age at first vaccination, adjusted for parental education and attained age, and averaged across levels of parental education and attained age in the population.

In organized vaccination programs, testing for prevalent HPV infection at time of vaccination is not performed, and vaccinees' HPV status is therefore unknown. Given that the outcome in this study is condyloma, which has an incubation pe-

riod of 1 to 6 months,[4-6] and the vaccine evaluated here is recommended to be administered at 0, 2, and 6 months, attributing incident condyloma events to the correct vaccine exposure level is complicated. A comparison of the incidence of condyloma after 1, 2, or 3 doses might therefore be biased toward higher incidence of condyloma after dose 1 and 2 unless prevalent infections are considered. Consequently, our Poisson models allow for buffer periods between vaccination and the onset of case counting, where buffer-period risk time is included in previous exposure states (eFigure 2 in the Supplement). Different buffer periods of 0 to 12 months were evaluated as part of a sensitivity analysis (eTable 1 in the Supplement). We also plotted cumulative incidence in a vaccinated cohort over time after dose 1 and compared it with cumulative incidence in an age-matched unvaccinated cohort, to identify a plausible buffer length based on the separation of the incidence curves (eResults 1 in the Supplement).

Additional post hoc analyses were performed to investigate IRRs derived from individuals who completed the 3-dose schedule and those who stopped after receipt of 1 or 2 doses (eResults 3 and eTables 3 and 4 in the Supplement). As a secondary analysis, we calculated IRRs per dose level in individuals who received only 1, 2, or 3 doses. Exposure was fixed over time and defined as the cumulative vaccination status at the end of study follow-up (December 31, 2010) (eResults 5 and eTable 6 in the Supplement).

Data management was done with SAS statistical software version 9.2 (SAS Institute). Statistical analyses were done with Stata version 11 (StataCorp). Statistical significance was defined as $P < .05$; all alternative hypotheses were 2-sided.

Results

The mean (SD) follow-up time was 3.8 (1.6) years. A total of 1596 and 715 women were censored during follow-up because of vaccination with the bivalent vaccine or death, respectively. A total of 1 045 165 individuals in the study cohort contributed 3 995 631 person-years, with 20 383 incident cases of condyloma during follow-up, including 322 cases after receipt of at least 1 dose of the vaccine. Most individuals in the study cohort had a parent who finished high school (49.1%) or university (43.4%), whereas 6.2% had no parent with an education level above high school (**Table 1**). For the 1-dose analysis, 115 197

Table 2. Number of Individuals and Events, Person-Time, and Crude Incidence Rate per Age Group by Dose[a]

	Individuals, No.	Events, No.	Person-Time, y	Crude Incidence Rate (95% CI)[b]
Age 10-13 y				
Unvaccinated	451 319	106	973 880	11 (9-13)
1 dose	11 703	0	1987	
2 doses	8028	0	1918	
3 doses	2978	0	875	
Age 14-16 y				
Unvaccinated	446 724	1460	796 219	183 (174-193)
1 dose	68 505	9	13 784	65 (34-125)
2 doses	63 513	19	21 664	88 (56-137)
3 doses	48 632	23	40 583	57 (38-85)
Age 17-19 y				
Unvaccinated	428 380	7110	780 134	911 (890-933)
1 dose	43 217	58	10 939	530 (410-686)
2 doses	48 247	54	20 037	269 (206-352)
3 doses	61 252	114	69 479	164 (137-197)
Age 20-21 y				
Unvaccinated	366 296	5496	520 363	1056 (1029-1084)
1 dose	1764	9	1028	875 (455-1682)
2 doses	2897	5	1720	291 (121-698)
3 doses	11 667	30	9400	319 (223-456)
Age 22-24 y				
Unvaccinated	398 910	5889	730 701	806 (786-827)
1 dose	109	0	73	
2 doses	192	1	129	773 (109-5487)
3 doses	1172	0	718	
All ages				
Unvaccinated	1 045 157	20 061	3 801 298	528 (520-535)
1 dose	115 197	76	27 810	273 (218-342)
2 doses	107 338	79	45 469	174 (139-217)
3 doses	89 836	167	121 055	138 (119-161)

[a] Numbers of individuals and events and person-time come from the time after a 3-month buffer period through study follow-up.

[b] Per 100 000 person-years.

individuals contributed 27 810 person-years. At 2 doses 107 338 individuals contributed 45 469 person-years, and at 3 doses 89 836 individuals (with 121 055 person-years) were included (**Table 2**). Within the study follow-up time, 77.9% of those vaccinated completed 3-dose vaccination. Mean (SD) time between doses 1 and 2 was 2.35 (1.44) months and 4.35 (1.53) months between doses 2 and 3.

Cumulative incidence curves for women who received at least 1 dose of the vaccine and unvaccinated women were close and parallel until approximately 3 months of follow-up (*t* = 96 days), when the cumulative incidence proportion of condyloma in vaccinated women separated from that among unvaccinated women through the maximum buffer period studied (*t* = 365 days) (**Figure 2**). Therefore, main results are presented using a 3-month buffer period.

Among those first vaccinated at ages 10 to 13 years, receipt of 3 doses was associated with an IRR of 0.08 (95% CI, 0.02-0.30) (eTable 5 in the Supplement). No condyloma cases were identified after receipt of 1 or 2 doses of vaccine, and therefore main results will be presented for the collapsed age-at-first-vaccination group of 10 to 16 years.
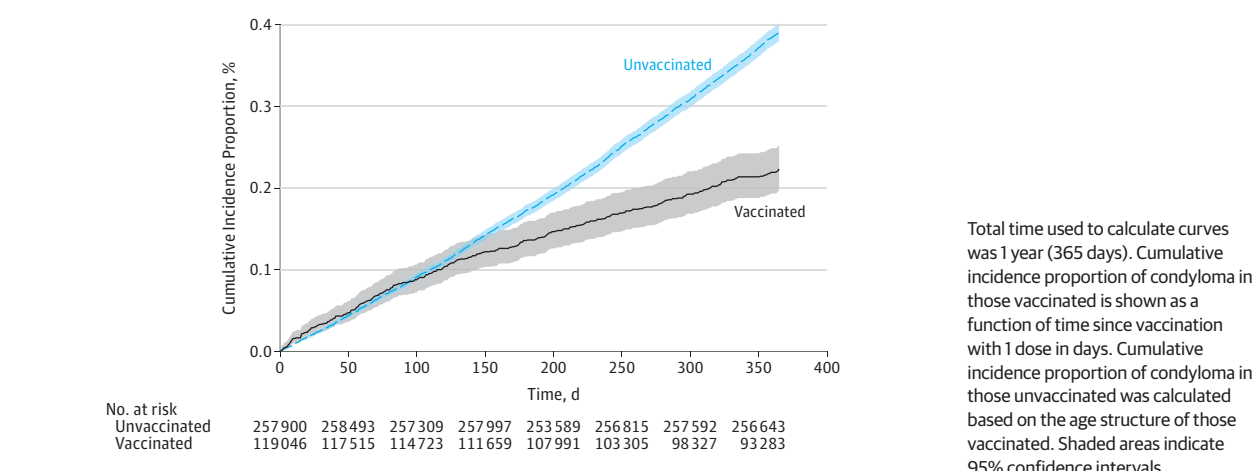
Comparing women first vaccinated at ages 10 to 16 years with those unvaccinated, 3 doses were associated with an

IRR for condyloma of 0.18 (95% CI, 0.15-0.22), which corresponds to an IRD of 459 cases (95% CI, 437-482) per 100 000 person-years. Two doses were associated with an IRR of 0.29 (95% CI, 0.21-0.40; IRD, 400; 95% CI, 346-454), and 1 dose was associated with an IRR of 0.31 (95% CI, 0.20-0.49; IRD, 384; 95% CI, 305-464). Receipt of 3 vs 2 doses was associated with an IRR of 0.63 (95% CI, 0.43-0.93). The IR for 3 doses was 101 cases (95% CI, 80-122) per 100 000 person-years vs 160 cases (95% CI, 107-214) for 2 doses, which corresponds to an IRD of 59 cases (95% CI, 2-117) per 100 000 person-years (**Table 3**).

Comparing women first vaccinated at ages 17 to 19 years with those unvaccinated, 3 doses were associated with an IRR of 0.23 (95% CI, 0.18-0.29; IRD, 433; 95% CI, 403-462), 2 doses were associated with an IRR of 0.35 (95% CI, 0.26-0.47; IRD, 365; 95% CI, 307-424), and 1 dose, an IRR of 0.71 (95% CI, 0.55-0.92; IRD, 162; 95% CI, 58-266). The IR for 3 doses was 128 cases (95% CI, 99-156) per 100 000 person-years vs 195 cases (95% CI, 137-253) for 2 doses, which corresponds to an IRD of 67 cases (95% CI, 3-132) per 100 000 person-years (Table 3).

The lower IRR after 1 dose for those first vaccinated at age 10 to 16 years compared with those aged 17 to 19 years was not

Figure 2. Cumulative Incidence Proportion of Condyloma in Vaccinated and Unvaccinated Individuals

No. at risk								
Unvaccinated	257900	258493	257309	257997	253589	256815	257592	256643
Vaccinated	119046	117515	114723	111659	107991	103305	98327	93283

Total time used to calculate curves was 1 year (365 days). Cumulative incidence proportion of condyloma in those vaccinated is shown as a function of time since vaccination with 1 dose in days. Cumulative incidence proportion of condyloma in those unvaccinated was calculated based on the age structure of those vaccinated. Shaded areas indicate 95% confidence intervals.

Table 3. Incidence Rate Ratios and Incidence Rate Differences per 100 000 Person-Years Comparing Vaccinated Individuals With Those Unvaccinated[a]

Age at First Vaccination, y	IRR (95% CI)[b]	P Value	IR Dose Comparisons (95% CI)[c]	IRD (95% CI)[c]	P Value
10-16 y: No. of doses					
3 vs 0	0.18 (0.15-0.22)	<.001	101 (80-122) vs 561 (553-568)	459 (437 to 482)	<.001
2 vs 0	0.29 (0.21-0.40)	<.001	160 (107-214) vs 561 (553-568)	400 (346 to 454)	<.001
1 vs 0	0.31 (0.20-0.49)	<.001	176 (97-255) vs 561 (553-568)	384 (305 to 464)	<.001
3 vs 2	0.63 (0.43-0.93)	.02	101 (80-122) vs 160 (107-214)	59 (2 to 117)	.04
3 vs 1	0.57 (0.35-0.94)	.03	101 (80-122) vs 176 (97-255)	75 (−7 to 157)	.07
2 vs 1	0.91 (0.52-1.59)	.74	160 (107-214) vs 176 (97-255)	16 (−80 to 111)	.75
17-19 y: No. of doses					
3 vs 0	0.23 (0.18-0.29)	<.001	128 (99-156) vs 561 (553-568)	433 (403 to 462)	<.001
2 vs 0	0.35 (0.26-0.47)	<.001	195 (137-253) vs 561 (553-568)	365 (307 to 424)	<.001
1 vs 0	0.71 (0.55-0.92)	.01	399 (295-502) vs 561 (553-568)	162 (58 to 266)	.002
3 vs 2	0.66 (0.45-0.95)	.03	128 (99-156) vs 195 (137-253)	67 (3 to 132)	.04
3 vs 1	0.32 (0.23-0.45)	<.001	128 (99-156) vs 399 (295-502)	271 (163 to 378)	<.001
2 vs 1	0.49 (0.33-0.73)	<.001	195 (137-253) vs 399 (295-502)	204 (85 to 322)	.001
10-19 y: No. of doses					
3 vs 0	0.20 (0.17-0.23)	<.001	112 (95-129) vs 561 (553-568)	449 (430 to 467)	<.001
2 vs 0	0.32 (0.26-0.40)	<.001	178 (139-218) vs 561 (553-568)	382 (342 to 423)	<.001
1 vs 0	0.54 (0.43-0.68)	<.001	303 (235-372) vs 561 (553-568)	257 (189 to 326)	<.001
3 vs 2	0.63 (0.48-0.82)	.001	112 (95-129) vs 178 (139-218)	66 (23 to 109)	.002
3 vs 1	0.37 (0.28-0.48)	<.001	112 (95-129) vs 303 (235-372)	191 (121 to 262)	<.001
2 vs 1	0.59 (0.43-0.81)	.001	178 (139-218) vs 303 (235-372)	125 (46 to 204)	.002

Abbreviations: IR, incidence rate; IRD, incidence rate difference; IRR, incidence rate ratio.

[a] Numbers of individuals and events and person-time come from the time after a 3-month buffer period through study follow-up.

[b] Adjusted for age and parental education level.

[c] Per 100 000 person-years; based on Poisson regression adjusted for parental education and attained age and averaged across parental education and attained age in the cohort. Because of case rounding, the differences between IRs do not always sum to the IRDs reported.

affected by use of different buffer period lengths of 0 to 12 months (eTable 1 in the Supplement). However, the IRR for 3 vs 2 doses was affected by the buffer period lengths so that buffer periods of 4 months or less generally gave a statistically significant lower IRR for 3 compared with 2 doses, while buffer periods longer than 4 months did not. This pattern was virtually the same irrespective of age at first vaccination.

The association of 2 doses (IRR, 0.27; 95% CI, 0.15-0.51) and 3 doses (IRR, 0.18; 95% CI, 0.14-0.22) with incident condyloma remained unchanged when vaccination was measured as a fixed exposure at the end of follow-up (eTable 6 in the Supplement). However, the IRR after 1 dose was 0.44 (95% CI, 0.22-0.88), which was higher than in the main analysis.

Discussion

To our knowledge, this is the first study to report an association between quadrivalent HPV vaccination and condyloma by vaccine dose level. Maximum risk reductions were found after 3 doses. Receipt of 2 doses was associated with considerable risk reduction. The number of condyloma cases prevented by 3 doses vs 2 doses was 59 cases per 100 000 person-years, which is a small difference.

An advantage of population-based studies such as this is that they examine associations, or vaccine effectiveness, without imposing exclusion criteria, making the results generalizable to the more diverse populations actually vaccinated.[14] In phase 3 clinical trials of the HPV vaccine, women were randomized to receive full 3-dose schedules or the placebo/hepatitis vaccine,[17,18] with data on effect of incomplete vaccination lacking. Previous national studies have examined the effect of HPV vaccination; however, none to date have examined associations by vaccine dose level,[7,19-24] which is important because actual vaccination programs include substantial numbers of women who do not complete the full vaccination schedule.[25,26]

In terms of immunogenicity, the Canadian immunogenicity trial showed noninferiority for HPV types 6, 11, 16, and 18 at month 7 after vaccination in girls aged 9 to 13 years comparing a 2- vs 3-dose schedule. At 24 and 36 months after vaccination, noninferiority disappeared for HPV types 18 and 6, respectively.[12]

How antibody response translates to disease prevention is currently unknown, although a correlation is assumed.[27,28] Available literature shows that titer responses to HPV types 6 and 11 move in parallel to HPV-18 and decrease slightly faster than HPV-16.[29,30] Although decreasing over time, antibody titer responses were sufficient to protect against disease caused by any of these HPV types.[30] However, the most important factor when assessing the effect of the vaccine is actual disease outcomes.

The Costa Rican bivalent vaccine trial has reported on dose efficacy against incident and persistent HPV-16 and -18 infection in seronegative women vaccinated between the ages of 18 and 25 years. A 2-dose schedule was as protective as a 3-dose schedule.[8]

Incorporating a buffer period in our analyses allowed for the influence of prevalent HPV infections. Although the chosen value of 3 months reported in the Results section falls well within the range of incubation periods for condyloma reported previously,[4-6] our buffer period is not necessarily equivalent to an incubation period. Our estimate for the buffer period may represent just a lower bound for the actual incubation period. With a buffer period of 5 months or longer, no statistically significant difference in the risk of condyloma between 2 and 3 doses could be ascertained.

Previous studies have suggested an indirect protection of HPV vaccination against infection in unvaccinated men and women.[19,31] However, in our population, vaccination uptake of 25% is probably too low for unvaccinated women to benefit from herd immunity, and therefore, we do not believe this effect to be applicable in the current study.[7]

Selection bias can be problematic in observational studies such as ours. We have performed several post hoc analyses for selection bias and found no such biases present (eResults 3 in the Supplement).

Limitations of the study include the possibility that registry data underestimate the true number of condyloma cases,[7] although we expect this underestimation to be nondifferential with regards to vaccination exposure. A proportion of individuals with condyloma will not seek medical care, perhaps because they experience less severe symptoms or are unable to fully use health services. Vaccinated women have been shown more likely to access health care, but we expect this to be nondifferential by dose. Also, patients who receive nonpharmaceutical treatment, eg, laser therapy and cryotherapy, in some private care settings are not captured by registry data, although this group should be small. We were able to exclude women with a history of condyloma before individual follow-up as a proxy for HPV status. In addition, we introduced buffer periods after vaccination to account for prevalent HPV infections in girls already sexually active at the time of vaccination. In the current study, it was not possible to estimate associations per dose level separately in girls first vaccinated between ages 10 and 13 years, and hence most likely HPV naive, because of limited follow-up time (eTable 5 in the Supplement). Further, limited vaccinated follow-up time resulted in wide confidence intervals, particularly in comparisons involving just 1 vaccine dose.

This study does not account for HPV disease outcomes other than condyloma. More studies with longer follow-up are needed to assess if these observed reductions in condyloma risk by vaccine dose apply for other HPV-related disease outcomes such as cervical intraepithelial neoplasia and cervical cancer.

Conclusions

Although maximum reduction in condyloma risk was seen after receipt of 3 doses of the quadrivalent HPV vaccine, receipt of 2 vaccine doses was also associated with a considerable reduction in condyloma risk, particularly among women who were younger than 17 years at first vaccination. The implications of these findings for the relationship between number of vaccine doses and cervical cancer risk requires further investigation.

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