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Human papillomavirus infection and vaccination among young females in rural Uganda

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Abstract

Cervical cancer is the most common cancer in Uganda. In 2015, a national human papillomavirus (HPV) vaccination program was initiated, targeting girls aged 10 years. To provide a pre-vaccination baseline to monitor HPV vaccine effectiveness, first-void urine (FVU) samples were collected from females aged 16–21 years in the General Population Cohort (GPC) in South-East Uganda, between 2019 and 2023. HPV vaccination status was obtained from questionnaires and vaccination cards. FVU samples were tested for 28 HPV types using Allplex HPV28. Among 1009 participants, 28 type prevalence was 33%, and was higher among females reporting sexual intercourse (aPR = 3.7, 95%CI 2.8–4.8) and HIV infection (PR = 1.4, 95%CI 1.1–1.8). HPV16/18 prevalence was 4.8% overall, and lower in 146 vaccinated (1.4%) than 783 unvaccinated (5.6%) females (aPR = 0.4, 95%CI 0.1–1.4). No decrease was observed in other high-risk (aPR = 1.5, 95%CIs 1.0–2.2) or low-risk (aPR = 1.4, 95%CIs 1.0–2.1) types which were more prevalent in vaccinated females. Among vaccinated 16–21 year-olds, 30.8% ($n = 45$) received one, 44.5% ($n = 65$) two, and 14.3% ($n = 21$) three doses. Vaccination status was also obtained from 1121 younger girls aged 10–15 years from the same GPC population, among whom 42.8% ($n = 480$) were vaccinated, 47.1% ($n = 226$) with one, 44.2% ($n = 212$) two, and 6.7% ($n = 32$) three doses. In conclusion, we report high HPV prevalence in young women in Uganda and see first impacts of vaccination on HPV16/18 infection. This population, shown to have suboptimal HPV vaccine coverage and heterogeneity in doses received, can serve as a robust baseline for future evaluations of HPV vaccine effectiveness.

KEYWORDS
cervical cancer, HPV vaccination, human papillomavirus, Uganda

Abbreviations: aPR, adjusted prevalence ratios; CI, confidence intervals; Ct, cycle threshold; FVU, first-void urine; GPC, General Population Cohort; HIV, Human Immunodeficiency Virus; HPV, human papillomavirus; IARC, International Agency for Research on Cancer; PR, prevalence ratios; WHO, World Health Organization.

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What's New?

Uganda's human papillomavirus (HPV) vaccination program for 10-year-old girls, introduced in 2015, marked a decisive step forward in the country's effort to eliminate cervical cancer. The present study assessed the effectiveness of this national HPV vaccination program, using first-void urine (FVU) samples from girls ages 16–21 and information on vaccination status for all girls ages 10–21. Data show that between 2019 and 2023, HPV prevalence was 33 percent among girls 16–21, much higher compared to other countries. Although the vaccination rate and number of doses received were suboptimal for girls ages 10–15, those who received the vaccine benefited from reduced HPV16/18 prevalence.

1 | INTRODUCTION

Cervical cancer, caused by human papillomavirus (HPV) infection, is the most common cancer in Uganda ($n = 6900$),[1] and this burden is expected to more than double by 2045 ($n = 16{,}400$) due to increases in life expectancy.[2] With an estimated age-standardized incidence rate of 54 cases per 100,000 women years,[1] cervical cancer incidence in Uganda is among the highest in the world, and is typical of many southern African countries.

In response to this public health urgency, Uganda implemented an HPV vaccination program, which is a key component of the World Health Organization's recommendations for the elimination of cervical cancer[3] and has been shown to be highly cost-effective for Uganda as elsewhere.[4]

Uganda is divided into 120+ districts. HPV vaccination was initially introduced in two districts in 2008 and 12 districts in 2012 using a 3-dose regimen. HPV vaccination was then rolled out nationally in all districts by the Ugandan Ministry of Health (MOH) in November 2015, under a 2-dose regimen with bivalent HPV16/18 vaccine (Cervarix®) for all girls aged 10 years. The target population was reached by inviting parents and guardians to bring eligible girls to health facilities for vaccination, and by vaccinating girls in grade four of primary schools during biannual Child Health Day campaigns.[5] In 2015, most vaccinations took place at schools.[6] HPV vaccination is covered by a Ugandan law obliging parents to immunize their children and retain their vaccination cards as proof of vaccination.[7]

However, as evidence of HPV vaccination impact on cervical cancer incidence cannot be seen for at least 15 years,[8–11] earlier surrogate evidence of vaccine coverage and effectiveness is needed to monitor and improve programs.

To this end, a series of cross-sectional surveys were initiated in 2019, nested in the General Population Cohort (GPC) study[12] in rural south-west Uganda. Firstly, a pre-vaccination HPV prevalence survey in first-void urine (FVU) was conducted in females aged 16–21 years. FVU has been validated as a high-quality non-invasive method for HPV detection.[13–15] In addition, we assessed HPV vaccination coverage, both in 16–21-year-olds providing FVU samples, as well as in younger girls aged 10–15 years in the same GPC population, which were the first birth cohorts targeted by Uganda's national program and in whom the effectiveness of the HPV vaccine may be estimated if surveys are repeated when the girls reach age 16–21 years.

2 | MATERIALS AND METHODS

2.1 | Study population

The GPC in rural south-west Uganda, is a long-standing demographic and health surveillance site run by the Medical Research Council/Uganda Virus Research Institute and London School of Hygiene & Tropical Medicine Uganda Research Unit. The GPC comprises a cluster of 25 neighboring villages with approximately 25,000 residents,[12] of which there are approximately 1100 females aged 16–21 years, and approximately 1200 females aged 10–15 years. The GPC was set up in 1989 to study trends in HIV prevalence and incidence, but has since been used to study the epidemiology of other infectious and non-communicable diseases.[12] The GPC conducts annual house-to-house censuses to capture demographic data, alongside biannual health surveys at field research hubs which are temporarily set up within the 25 research villages to collect data using individual questionnaires (including socio-demographic, sexual behavior, and lifestyle information), as well as various types of biological samples.

FVU samples and data for the current study were collected for females aged 16–21 years during the 26th GCR biannual health survey between July 2019 and July 2021 (duration extended due to COVID restrictions), and the 27th survey from February 2022 to March 2023 (Supplemental Figure 1).

Vaccination status was obtained for all females aged 16–21 years, and also for those aged 10–15 years. Specific questions about HPV vaccination status were added to the regular biannual health survey questionnaire and this information was checked for consistency against participant vaccination cards. For the younger girls aged 10–15 years, questionnaires were completed in the presence of a mother or guardian, and they did not provide FVU samples.

2.2 | FVU sampling

Once informed consent was obtained, FVU samples were self-collected from females aged 16–21 years using a 20 mL Colli-Pee device with Urine Conservation Medium (UCM) (Novosanis, Belgium), as reported previously.[13–15] This device is designed to collect the first 13 mL of FVU and transfer it into 7 mL of a UCM to avoid DNA

degradation, and to allow subsequent urine volume to flow out of the device into the toilet. FVU samples were transported to the MRC/UVRI laboratories in Entebbe, Uganda, where they were stored at −80°C and shipped on dry ice for testing.

2.3 | DNA extraction

FVU samples were shipped to the Centre for the Evaluation of Vaccinations, University of Antwerp, Belgium, where they were stored at −80°C (Biobank Antwerpen, Antwerp, Belgium; ID: BE 71030031000). Automated DNA extraction was performed using a previously validated protocol for FVU[16] using the STARMag Universal Cartridge Kit (Seegene Inc., South Korea). In brief, 0.5 mL of FVU was presented to the STARlet device (Seegene Inc., South Korea), of which 0.2 mL was subjected to DNA extraction conducted in accordance with the manufacturer's guidelines, eluting DNA into a final volume of 60 µL.

2.4 | HPV DNA detection and genotyping

HPV DNA testing was performed at the Centre for the Evaluation of Vaccinations, University of Antwerp, Belgium, using the Allplex HPV28 assay.[16] Allplex HPV28 is an E6/E7/L1-based PCR-based assay, targeting 13 oncogenic HPV genotypes (HPV16, HPV18, HPV31, HPV33, HPV35, HPV39, HPV45, HPV51, HPV52, HPV56, HPV58, HPV59 and HPV68) as well as 15 other HPV genotypes (HPV6, HPV11, HPV26, HPV40, HPV42, HPV43, HPV44, HPV53, HPV54, HPV61, HPV66, HPV69, HPV70, HPV73, and HPV82). The assay generates individual cycle threshold (Ct) values for the 28 distinct genotypes concomitantly. Using 5 µL of extracted DNA, Allplex HPV28 testing was performed using the CFX96 real-time thermocycler (Bio-Rad, USA) following the manufacturer's instructions. To confirm the presence of human cells, the assay targets the human beta-globin gene for internal quality control.

2.5 | Statistical analysis

Age- and type-specific HPV prevalence was estimated according to the protocol established for previous HPV urine surveys conducted by IARC.[15] HPV-DNA prevalence with corresponding 95% confidence intervals (CIs) was assessed assuming a binomial probability distribution. Adjusted prevalence ratios (PR) for HPV positivity, as well as for history of HPV vaccination, were computed with corresponding 95% CI using two binomial regression models with a log link, and adjusted, where appropriate, for age and history of sexual intercourse. Trends in HPV prevalence were assessed by considering categories as continuous variables. High-risk HPV types were defined as the 13 types classified by IARC as Group 1 (HPV16, HPV18, HPV31, HPV33, HPV35, HPV39, HPV45, HPV51, HPV52, HPV56, HPV58, and HPV59) or Group 2A carcinogens (HPV68).[17]

3 | RESULTS

3.1 | FVU survey in girls aged 16–21 years

1057 eligible females signed the informed consent forms and provided FVU samples. After exclusion of 40 participants due to lack of risk factor questionnaires, and 8 with invalid HPV results, data on 1009 participants (median age 18 years; range 16–21 years) were included in final analyses. Our results showed that 335 (33.2%, 95CI 30.3–36.2%) women were positive for any of the 28 HPV types, of which 155 were positive for a single HPV type and 180 with multiple HPV types (Table 1). Specifically, 233 (23.1%; 20.5–25.8%) were positive for high-risk HPV infection and 234 (23.2%; 20.6–25.9%) for low-risk HPV infection. Prevalence of HPV16/18 infection was 4.8% (3.5%–6.3%), and prevalence of HPV16/18/31/33/45/52/58 was 13.7% (11.6%–16.0%). A detailed type-specific distribution of HPV infections is shown in Table 1.

Table 2 shows the relationship between positivity for any of the 28 HPV types and participant characteristics. Variables significantly associated with positivity for any of the 28 types were older age (aPR for 19 versus 16 years = 2.0, 95% CI 1.3–2.9), history of sexual intercourse (aPR = 3.7, 95% CI 2.8–4.8) and HIV infection (aPR for HIV-positive versus HIV-negative = 1.5, 95% CI 1.2–2.0). 146 women reported having received HPV vaccination, but HPV vaccination status was not significantly associated with positivity for any HPV type (aPR = 1.2, 95% CI 0.9–1.4) (Table 2), nor was being eligible for the vaccination program (aPR = 1.2, 95% CI 0.9–1.6).

Participant distribution by age group, and selected characteristics, is shown in Table 3, separately by vaccination history. Vaccinated females were significantly younger (aPR for 19 vs. 16 years = 0.2, 95% CI 0.1–0.5) in comparison to unvaccinated females. Vaccination was much higher (53.3%) (aPR = 9.2; 6.2–13.7) in the 182 females ever eligible for vaccination (age 10 years in 2015 or later), than the 827 never eligible (5.9%).

Figure 1 shows the prevalence and PRs for grouped HPV types by vaccination history. HPV16/18 prevalence (types targeted by the vaccine) was lower in vaccinated (1.4%) than unvaccinated women (5.6%), but this difference was not statistically significant after adjustment for age and history of sexual intercourse (aPR = 0.4; 95% CI: 0.1–1.4). No decrease in vaccinated compared to unvaccinated women was observed for other high-risk HPV types (aPR = 1.5, 95% CIs 1.0–2.2) or low-risk HPV types (aPR = 1.4, 95% CIs 1.0–2.1), for which prevalence actually increased.

3.2 | Vaccine coverage survey in girls aged 10–15 years

A total of 1121 females aged 10–15 years old were included in the survey on vaccination status (no urine samples were taken). Our results showed that 480 (42.8%) were vaccinated,

TABLE 1 Prevalence of 28 HPV types among 1009 girls aged 16–21 years in Uganda, 2019–2023.

	HPV positivity			
HPV type	Single	Multiple	Total % (95 CI)	
HPV−	-	-	674	66.8 (63.8–69.7)
HPV+	155	180	335	33.2 (30.3–36.2)
High-risk				
16	10	22	32	3.2 (2.2–4.4)
18	5	12	17	1.7 (1.0–2.7)
31	2	13	15	1.5 (0.8–2.4)
33	2	7	9	0.9 (0.4–1.7)
35	3	22	25	2.5 (1.6–3.6)
39	8	22	30	3.0 (2.0–4.2)
45	0	7	7	0.7 (0.3–1.4)
51	8	33	41	4.1 (2.9–5.5)
52	12	40	52	5.2 (3.9–6.7)
56	7	24	31	3.1 (2.1–4.3)
58	7	33	40	4.0 (2.8–5.4)
59	5	21	26	2.6 (1.7–3.8)
68	11	23	34	3.4 (2.3–4.7)
Any	80	153	233	23.1 (20.5–25.8)
Low-risk				
6	5	22	27	2.7 (1.8–3.9)
11	2	5	7	0.7 (0.3–1.4)
26	0	1	1	0.1 (0.0–0.6)
40	4	27	31	3.1 (2.1–4.3)
42	9	42	51	5.1 (3.8–6.6)
43	6	21	27	2.7 (1.8–3.9)
44	4	7	11	1.1 (0.5–1.9)
53	7	27	34	3.4 (2.3–4.7)
54	11	28	39	3.9 (2.8–5.2)
61	10	40	50	5 (3.7–6.5)
66	9	38	47	4.7 (3.4–6.1)
69	0	6	6	0.6 (0.2–1.3)
70	3	15	18	1.8 (1.1–2.8)
73	1	14	15	1.5 (0.8–2.4)
82	4	11	15	1.5 (0.8–2.4)
Any	75	159	234	23.2 (20.6–25.9)
16/18	15	33	48	4.8 (3.5–6.3)
16/18/31/33/45/52/58	38	100	138	13.7 (11.6–16.0)

Abbreviations: CI, confidence interval; HPV, human papillomavirus.

599 (53.4%) were unvaccinated, and 42 (3.8%) were unsure of their vaccination status (Table 4). Of the 480 vaccinated girls, 226 (47.1%) reported having received only one dose, 212 (44.2%) two doses, and 32 (6.7%) three doses (Table 4). Most (68.3%) vaccinated girls reported being vaccinated at ages 10–12 years, with smaller proportions reporting being vaccinated at <10 years (9.8%) and >12 years (12.1%) (Table 4). Attendance in primary school was reported among 99% of girls aged 10–15 years. The relationship between age and HPV vaccination status is shown in Supplementary Table 1.

4 | DISCUSSION

We report on type-specific HPV infection in a representative sample of young females in rural Uganda, based on HPV testing and genotyping from FVU samples, soon after the country initiated a national program for HPV vaccination. Our HPV prevalence estimates can be compared with other urine surveys in young women conducted in other countries according to similar protocols. For example, Uganda's HPV prevalence of 33% in females aged 16–21 years can be compared to the 20% in females of similar ages in neighboring Rwanda,[15] but also globally to the 14% in Bhutan[15] and the 4.6% in Armenia,[14] highlighting rural Uganda's particularly high HPV prevalence in young women in comparison to other global settings. Whilst high HPV prevalences have been reported (60%–70%) in similarly sized samples of young women in Uganda using cervical swab samples,[18,19] these studies have focused on sub-groups of sexually active women only. Indeed, our report of a significantly higher HPV prevalence in FVU of sexually active compared to non-sexually active females, highlights the potential for application of FVU for HPV detection in representative samples of young females, including those who are not sexually active, and must be accounted for when interpreting and comparing HPV prevalence estimates across different studies in Uganda[20] and elsewhere, which may focus on cervical cells from sexually active females only. HIV infection was 2.2% in females aged 16–21 years in this rural Ugandan population and was confirmed to be a significant risk factor for HPV infection.

Our HPV prevalence data are predominantly representative of female birth cohorts untargeted by the vaccine program, and can serve as an epidemiological baseline for comparison with future surveys in fully vaccinated cohorts when they reach the same age. Unexpectedly, due to delays in recruitment imposed by the COVID-19 pandemic, some of the younger females recruited toward the end of this urine survey had become eligible for HPV vaccination. This enabled a first ad hoc evaluation of vaccination impact in this Uganda population and we were able to observe a reduction in vaccine-targeted HPV16/18 in the participants who had been vaccinated. Whilst this ad hoc analysis was not an initial objective of the study, and hence vaccinated and unvaccinated females were unbalanced with respect to age and history of sexual intercourse, there was evidence of impact (albeit non-significant) after adjustment for these factors. Further plausibility for the vaccine-driven reduction in HPV16/18, was that no significant difference was observed between vaccination status and the prevalence of HPV types not targeted by the vaccine (which actually increased).

Whilst HPV16/18 infections accounted for about 14% of all HPV infections with the 28 types, and about 20% of all high-risk HPV infections in these young women, these two high-risk HPV types are by far the most carcinogenic HPV types and have together been

TABLE 2 Prevalence ratios (PRs) for human papillomavirus (HPV) positivity and corresponding 95% confidence intervals (CIs) according to selected characteristics among 1009 young females, Uganda, 2019–2023.

	Any HPV[a] prevalence			
Characteristic	***N***	**HPV-positive *n* (%)**	**Crude PR (95% IC)**	**Adjusted[b] PR (95% IC)**
All	1009	335 (33.2)		
Age-group (years)				
16	169	23 (13.6)	1	1
17	234	54 (23.1)	1.7 (1.1–2.6)	1.4 (0.9–2.2)
18	187	68 (36.4)	2.7 (1.7–4.1)	1.8 (1.2–2.7)
19	128	64 (50.0)	3.7 (2.4–5.6)	2.0 (1.3–2.9)
20	153	64 (41.8)	3.1 (2.0–4.7)	1.6 (1.0–2.4)
21	138	62 (44.9)	3.3 (2.2–5.0)	1.5 (1.0–2.2)
χ^2_5 for trend			p <.001	$p = .331$
Highest education level[c]				
Primary school and less	163	50 (30.7)	1	1
Secondary school and more	578	151 (26.1)	0.85 (0.65–1.11)	1.06 (0.84–1.34)
History of sexual intercourse				
Never	483	61 (12.6)	1	1
Ever	526	274 (52.1)	4.1 (3.2–5.3)	3.7 (2.8–4.8)
HIV status				
Negative	984	319 (32.4)	1	1
Positive	25	16 (64.0)	2.0 (1.4–2.7)	1.5 (1.2–2.0)
HPV vaccination status				
No	783	274 (35.0)	1	1
Yes	146	48 (32.9)	0.9 (0.7–1.2)	1.2 (0.9–1.4)
Not sure	80	13 (16.3)	0.5 (0.3–0.8)	0.6 (0.4–1.0)
Eligibility for vaccination				
Age 10 <2015	827	293 (35.4)	1	1
Age 10 in 2015 or later	182	42 (23.1)	0.6 (0.5–0.9)	1.2 (0.9–1.6)

Abbreviation: HIV, human immunodeficiency virus.
[a]Of 28 HPV types.
[b]Adjusted for age and history of sexual intercourse, as appropriate.
[c]Does not add up to the total due to missing values.

estimated to account for 72% of cervical cancers in Africa,[21] including in Uganda.[22,23] With respect to non-HPV16/18 types, HPV45 (9%) and HPV35 (4%) cause a greater proportion of invasive cervical cancer in Africa than in other world regions.[21]

Less than half of the girls aged 10–15 years included in our survey reported being vaccinated despite being eligible for vaccination under Uganda's national program. These data are consistent with the sub-optimal coverage (22%–36%) reported in a number of smaller HPV vaccine coverage surveys undertaken in other parts of Uganda for these same birth cohorts,[24–28] including females living with HIV.[29,30]

WHO yearly estimates of two-dose HPV vaccine coverage in Uganda for females aged 9–14 years, range from 30% in 2016 up to 68% in 2022, but with dips of 31% and 45% observed in 2020 and 2021, respectively.[31] The dips are likely due to the impact of the COVID-19 pandemic on the vaccination program, and occurred in the years most comparable with our survey. A 22% two-dose national coverage in 2016 was also reported from other sources based on the Uganda Demographic and Health Survey[5,32,33]: this includes coverage in 14 districts where HPV vaccine was initiated prior to 2015, and for which specific coverage estimates have also been reported.[34–36]

We observed that approximately half of vaccinated females aged 10–15 years (as well as approximately one third of vaccinated females aged 16–21 years), had received only one dose of HPV vaccine, despite being eligible for a two-dose regimen. Much higher coverage with a single rather than two doses is consistent with previous small surveys in similar birth cohorts, in other parts of Uganda.[25,26,30] National single-dose coverage rates reported by the Ministry of Health of Uganda of 83% in 2017[5] and 96% in 2020,[37] were both much higher than two-dose coverages in those years (22% and 57%, respectively). Importantly, there is substantial and growing evidence

TABLE 3 Comparison of HPV-vaccinated and unvaccinated females according to selected characteristics among 1009 young females, Uganda, 2019–2023.

	All *N*	Vaccinated *N* (%)	Unvaccinated *N* (%)	Not sure *N* (%)	Vaccination ratio	
					Crude (95% CI)	Adjusted[a] (95% CI)
All	1009	146 (14.5)	783 (77.6)	80 (7.9)		
Age group (years)						
16	169	37 (21.9)	113 (66.9)	19 (11.2)	1	1
17	234	56 (23.9)	159 (68.0)	19 (8.1)	1.1 (0.7–1.5)	1.1 (0.7–1.5)
18	187	29 (15.5)	140 (74.9)	18 (9.6)	0.7 (0.4–1.1)	0.7 (0.5–1.1)
19	128	7 (5.5)	113 (88.3)	8 (6.3)	0.2 (0.1–0.5)	0.2 (0.1–0.5)
20	153	9 (5.9)	134 (87.6)	10 (6.5)	0.3 (0.1–0.5)	0.3 (0.1–0.6)
21	138	8 (5.8)	124 (89.9)	6 (4.4)	0.2 (0.1–0.5)	0.3 (0.1–0.6)
Highest education level[b]						
Primary School and less	163	39 (23.9)	101 (62.0)	23 (14.1)	1	1
Secondary school and more	578	106 (18.3)	424 (73.4)	48 (8.3)	0.72 (0.52–0.98)	0.74 (0.54–1.02)
Current education level[b]						
Primary School or less	163	39 (23.9)	101 (62.0)	23 (14.1)	1	1
Secondary school	516	103 (20.0)	369 (71.5)	44 (8.5)	0.78 (0.57–1.07)	0.80 (0.58–1.10)
Higher education	32	0 (0.0)	28 (87.5|)	4 (12.50)	-	-
Vocational college	30	3 (10.0)	27 (90.0)	0 (0.0)	0.36 (0.12–1.08)	0.39 (0.13–1.18)
Eligibility for vaccination						
Age 10 <2015	827	49 (5.9)	707 (85.5)	71 (8.6)	1	1
Age 10 in 2015 or later	182	97 (53.3)	76 (41.8)	9 (5.0)	8.6 (6.4–11.7)	9.2 (6.2–13.7)
History of sexual intercourse						
Never	483	90 (18.6)	343 (71.0)	50 (10.4)	1	1
Ever	526	56 (10.7)	440 (83.7)	30 (5.7)	0.5 (0.4–0.7)	0.9 (0.7–1.5)
Age at first sexual intercourse[c]						
≤15	89	13 (14.6)	74 (83.2)	2 (2.3)	1	1
16	125	24 (19.2)	94 (75.2)	7 (5.6)	1.4 (0.7–2.5)	1.4 (0.8–2.7)
17	122	11 (9.0)	101 (82.8)	10 (8.2)	0.7 (0.3–1.4)	0.9 (0.4–1.9)
18	117	6 (5.1)	105 (89.7)	6 (5.1)	0.4 (0.1–0.9)	0.7 (0.2–2.0)
≥19	61	2 (3.3)	57 (93.4)	2 (3.3)	0.2 (0.1–1.0)	0.5 (0.1–2.3)
Do not recall	12	0 (0.0)	9 (75.0)	3 (25.0)	-	-
HIV status						
Negative	984	144 (14.6)	761 (77.3)	79 (8.0)	1	1
Positive	25	2 (8.0)	22 (88.0)	1 (4.0)	0.5 (0.1–2.0)	0.6 (0.2–2.4)
			Column %[2]			
Number of HPV vaccine doses received[d]						
1		45	(30.8)			
2		65	(44.5)			
3		21	(14.3)			
Do not recall		15	(10.3)			
Age when received first dose[d] (years)						
10–12		36	(24.7)			
13		31	(21.2)			
14		37	(2.34)			
15–20		24	(16.4)			
Do not recall		18	(12.3)			

Abbreviation: HPV, human papillomavirus.

[a]Adjusted for age and history of sexual intercourse, as appropriate.

[b]Does not add up to the total due to missing values.

[c]Among 531 sexually active young females.

[d]Among 146 vaccinated young females.

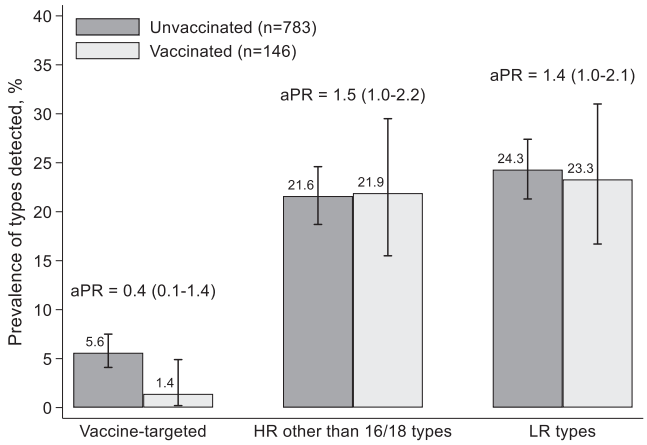

FIGURE 1 Human papillomavirus (HPV) positivity according to vaccination status and HPV type among 1009 girls, Uganda, 2019–2023. aPR, adjusted prevalence ratio; HR, high-risk; LR, low-risk.

TABLE 4 Human papillomavirus (HPV) vaccination status for girls aged 10–15 years, Uganda, 2019–2023.

Vaccination status	Frequency	Percent (%)
Total	1121	100
Unvaccinated	599	53.4
Vaccinated	480	42.8
By dose[a]		
1 dose	226	20.2 (47.1% of vaccinated)
2 doses	212	18.9 (44.2% of vaccinated)
3 doses	32	2.9 (6.7% of vaccinated)
By age at vaccination[b]		
<10 years	47	9.8
10 years	134	27.9
11 years	100	20.8
12 years	94	19.6
>13 years	58	12.1
Not sure	42	3.8

[a]$n = 10$ who could not remember the number of doses received.
[b]$n = 47$ who could not remember their age at vaccination.

that a single dose of HPV vaccine offers similar direct protection to that of two or three doses,[38,39] including for bivalent vaccines.[40–42]

Reasons for initial slow national uptake have been cited as shortfalls in planning with respect to other vaccines, as well as a mismatch between the final vaccination launch date and the school calendar, and delayed rollout in several districts due to late receipt of vaccines.[32] Both individual and community factors have been associated with the lack of HPV vaccination in Uganda, including living in rural versus peri-urban areas,[26] low socio-economic status and non-attendance at school,[33] as well as important variations by tribe.[33] The vaccination program was further disrupted in 2020 and 2021 due to COVID-19.[43] Since then, a number of adjustments have been made by Uganda's National Immunization Programme to improve vaccination coverage.[43] In 2023, Uganda reported 98% coverage with a single-dose regimen,[31] following the decision by the Ministry of Health of Uganda to switch from a two to single dose program, and a transition from a bivalent vaccine to the Gardasil quadrivalent vaccine.

This study has a number of strengths. As our surveys were conducted as part of the routine health surveys of the GPC, and because FVU collection was highly acceptable to the eligible population irrespective of sexual activity, our results are expected to be highly representative of the local population, without self-selection of study participants based on their sexual behavior. In addition to high representativeness and acceptability, we also used a protocol for FVU collection that has been widely validated in previous similar surveys,[13–15] and a protocol for DNA extraction and HPV genotyping (Allplex HPV28) that is optimized and validated for HPV testing from FVU.[16] Obtaining HPV vaccination coverage concomitantly in younger birth cohorts from the same population is also a strong advantage, as these first girls who were eligible for HPV vaccination in the early years of the program will be aged 16–21 years in 2026, at which time HPV vaccine impact can be robustly assessed from repeat urine surveys (Supplementary Figure 1).

The main limitation of the study was its extended duration of recruitment, driven by lockdowns during the COVID pandemic, meaning that a larger number of birth cohorts were included than originally planned. Whilst this enabled an unplanned ad hoc assessment of HPV vaccine impact after controlling for age and sexual activity, we did not have the appropriate statistical power to answer key questions about HPV vaccination according to the number of doses, nor for questions about cross-protection against HPV types that are not targeted by the vaccine. Also, we relied on self-reported vaccination status (or parent/guardian-reported vaccination status for girls aged 10–15 years).

In conclusion, we provide evidence of high HPV infection levels in young women in Uganda and see early signs that the HPV vaccine is reducing HPV16/18 prevalence. However, HPV vaccination coverage remains suboptimal and heterogeneous in the number of doses received. These data will serve as a robust baseline for future evaluations and predictions of HPV vaccination program effectiveness to inform future cervical cancer control strategies in Uganda and globally.

AUTHOR CONTRIBUTIONS

Rob Newton: Conceptualization; funding acquisition; methodology; supervision; writing – review and editing. **Vanessa Tenet:** Data curation; formal analysis; software; writing – review and editing; visualization; validation. **Joseph Mugisha:** Writing – review and editing; project administration; resources. **Beatrice Kimono:** Writing – review and editing; resources; project administration. **Alex Vorsters:** Data curation; methodology; investigation; resources; writing – review and editing; validation. **Margo Bell:** Data curation; investigation; validation; writing – review and editing. **Gary M. Clifford:** Conceptualization; formal analysis; funding acquisition; methodology; supervision; writing – review and editing; writing – original draft.

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CONFLICT OF INTEREST STATEMENT

AV is a co-founder and former board member of Novosanis (subsidiary of OraSure Technologies Inc., Wijnegem, Belgium), a spin-off company of the University of Antwerp, and was a minority shareholder until January 2019. The University of Antwerp received a project grant and honoraria fee for lectures, presentations, and speaker bureaus from Merck. The University of Antwerp received funding from Novosanis and Seegene. The other authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

Ethical approvals were obtained from the Uganda National Council for Science and Technology (Reference SS4981), the Uganda Virus Research Institute (Ref: GC/127/19/10/710), and the IARC Ethics Committee (Project No IEC 19−27). Written informed consent for participation in the urine survey was obtained from all participants aged 16–21 years. Written informed consent was obtained from both the participant and the parent or guardian for the participants aged 16–17 years. This study adhered to the Declaration of Helsinki for studies involving human participants.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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