nature medicine

Article

https://doi.org/10.1038/s41591-023-02658-0

Durability of single-dose HPV vaccination in young Kenyan women: randomized controlled trial 3-year results

Received: 28 April 2023

Accepted: 20 October 2023

Published online: 4 December 2023

Check for updates

Ruanne V. Barnabas[1,2,3] ✉, Elizabeth R. Brown[4,5,6], Maricianah A. Onono[7], Elizabeth A. Bukusi[7,8,9], Betty Njoroge[10], Rachel L. Winer[11], Denise A. Galloway[12], Leeya F. Pinder[8,13], Deborah Donnell[4,8], Imelda N. Wakhungu[7], Charlene Biwott[10], Syovata Kimanthi[10], Kate B. Heller[1,8], Diane G. Kanjilal[1], Daniel Pacella[1], Susan Morrison[8], Elena A. Rechkina[8], Stephen L. Cherne[14], Torin T. Schaafsma[8], R. Scott McClelland[8,11,15,16], Connie Celum[8,11,15], Jared M. Baeten[8,15], Nelly R. Mugo[8,10] & the KEN SHE Study Team*

Cervical cancer burden is high where prophylactic vaccination and screening coverage are low. We demonstrated in a multicenter randomized, double-blind, controlled trial that single-dose human papillomavirus (HPV) vaccination had high vaccine efficacy (VE) against persistent infection at 18 months in Kenyan women. Here, we report findings of this trial through 3 years of follow-up. Overall, 2,275 healthy women aged 15–20 years were recruited and randomly assigned to receive bivalent (n = 760), nonavalent (n = 758) or control (n = 757) vaccine. The primary outcome was incident-persistent vaccine type-specific cervical HPV infection. The primary evaluation was superiority analysis in the modified intention-to-treat (mITT) HPV 16/18 and HPV 16/18/31/33/45/52/58 cohorts. The trial met its prespecified end points of vaccine type-specific persistent HPV infection. A total of 75 incident-persistent infections were detected in the HPV 16/18 mITT cohort: 2 in the bivalent group, 1 in the nonavalent group and 72 in the control group. Nonavalent VE was 98.8% (95% CI 91.3–99.8%, P < 0.0001) and bivalent VE was 97.5% (95% CI 90.0–99.4%, P < 0.0001). Overall, 89 persistent infections were detected in the HPV 16/18/31/33/45/52/58 mITT cohort: 5 in the nonavalent group and 84 in the control group; nonavalent VE was 95.5% (95% CI 89.0–98.2%, P < 0.0001). There were no vaccine-related severe adverse events. Three years after vaccination, single-dose HPV vaccination was highly efficacious, safe and conferred durable protection. ClinicalTrials.gov no. NCT03675256.

Cervical cancer burden remains high globally, with more than 600 000 cases and 340 000 deaths in 2020 and incidence and mortality rates in most countries higher than the World Health Organization (WHO) threshold for cervical cancer elimination[1]. Further, there are notable disparities; cervical cancer incidence is three times higher and mortality is six times higher in countries with a United Nations Development Programme-defined low Human Development Index (HDI) than in countries with a very high HDI. Targeted strategies are

A full list of affiliations appears at the end of the paper. ✉e-mail: rbarnabas@mgh.harvard.edu

needed to achieve the WHO goal of cervical cancer elimination and to reduce global cervical cancer disparities.

HPV vaccines prevent more than 90% of persistent oncogenic vaccine type-specific HPV infections, the primary cause of cervical cancer[2,3]. HPV vaccination is foundational in the WHO's Global Cervical Cancer Elimination Strategy as a primary prevention of HPV infection[4]. The strategy aims to vaccinate 90% of girls globally. Four HPV vaccines are licensed to be given as 2–3 intramuscular injections over 2–6 months, all targeting high-risk (oncogenic) HPV types that cause 70–90% of cancers. The bivalent vaccines (Cervarix and Cecolin) prevent HPV 16/18 infection, the quadrivalent vaccine (Gardasil) prevents HPV 16/18/6/11, including the low-risk HPV types 6 and 11 to prevent genital warts, and the nonavalent vaccine (Gardasil-9) prevents HPV 16/18/31/33/45/52/58/6/11 infection, including five additional high-risk HPV types. Vaccinating the current global cohort of women aged 9–18 years would prevent HPV-associated precancerous lesions[5] and 11.6 million cases of cervical cancer over their lifetimes[6]; however, current HPV vaccine coverage remains low. In 2019, only 15% of adolescent girls globally were vaccinated against HPV[7].

Single-dose HPV vaccination would simplify the logistics and reduce costs of scaling up vaccine programs, lowering barriers to reaching high HPV vaccine coverage. The vaccine virus-like-particle (VLP) structure, which self-assembles to mimic the live virus without the replicating DNA, generates strong immunity with a single dose, analogous to highly immunogenic whole-virus vaccines rather than a subunit vaccine, supporting a biological mechanism for single-dose efficacy rather than the prime-boost multi-dose schedule that optimizes subunit vaccine efficacy (VE)[8]. Single-dose HPV vaccine efficacy is comparable to the licensed two- or three-dose regimen in randomized trials and observational studies[9–12]. Thus, in April 2022, the WHO recommended one or two doses of HPV vaccines for children, adolescents and young adults aged 9–20 years; however, a desire for data about longer-term durability of single-dose HPV vaccination persists[13–15] and national guidelines continue to recommend multi-dose strategies. Also, few low-HDI countries have catch-up vaccination programs for persons 15 years and older, although those programs accelerate the impact of vaccination[5].

In Kenya, the age-standardized incidence for cervical cancer is 31.3 per 100,000 person-years; annually, an estimated 5,236 new cases are diagnosed and 3,211 deaths attributable to cervical cancer occur[1]. Kenya's two-dose HPV immunization program was launched in October 2019 to reach 10-year-old girls, in the context of vaccine supply constraints. In 2021, vaccine coverage for the first dose was 77% and 31% for the second dose[16]. With WHO guidance recommending vaccination for the multi-age cohort of 9–14 year olds, the easing of vaccine supply constraints, and the need to deliver immunization services to a larger number of adolescents, evaluating the efficacy of single-dose vaccination would provide evidence to policymakers for immunization scale-up, including multi-age cohorts and catch-up vaccination for those who may have missed vaccination during programmatic scale-up.

This study evaluated zero versus single-dose HPV vaccination and employed a superiority design to support efficacious, feasible, and timely evidence for catch-up vaccination[17,18]. As reported previously, at 18 months, bivalent and nonavalent vaccine efficacy was 97.5% for HPV 16/18 and nonavalent VE was 88.9% for HPV 16/18/31/33/45/52/58[10]. We hypothesized that single-dose HPV VE would be durable over 36 months. Here we report the final single-dose HPV VE 3 years after vaccine administration to evaluate the durability of single-dose HPV vaccination for zero versus single-dose HPV vaccination. As planned, all participants have received HPV vaccination and follow-up continues to evaluate the durability of single-dose efficacy.

Results

Participant disposition and characteristics

Between 20 December 2018 and 15 November 2019, 3,090 participants were screened for study eligibility and 2,275 (74%) were enrolled. Of those ineligible (n = 419), 132 (32%) had a positive pregnancy test, 51 (12%) declined study procedures, 34 (8%) had a positive rapid HIV test and 202 (48%) met other exclusion criteria. Enrolled participants were randomized (Fig. 1): 758 to the nonavalent HPV vaccine group, 760 to the bivalent HPV vaccine group and 757 to the control vaccine group. At enrollment, 57% of participants (n = 1,301) were aged 15 to 17 years and 61% (n = 1,392) had one sexual partner in their lifetime with comparable baseline characteristics between the groups (Extended Data Table 1).

Participants included in the primary analysis tested HPV DNA negative (external genital/lateral vaginal and cervical swabs) at enrollment, by self-collected vaginal swab at month 3, and HPV antibody negative at enrollment in the mITT cohort. For inclusion in the HPV 16/18 mITT cohort, participants were HPV 16/18 naive. Similarly, for the HPV 16/18/31/33/45/52/58 mITT cohort, participants were HPV 16/18/31/33/45/52/58 naive.

For HPV 16/18, participants who tested HPV 16/18 antibody-positive or HPV 16/18 DNA-positive at enrollment or HPV DNA-positive month 3 (n = 661) or had missing antibody results (n = 1) or a missing month 3 swab (n = 155) were excluded. Among the 1,458 participants meeting the criteria for the primary HPV 16/18 mITT analysis, 496 were in the nonavalent group, 489 were in the bivalent group and 473 were in the control group. For HPV 16/18/31/33/45/52/58, participants who tested HPV 16/18/31/33/45/52/58 antibody- or HPV 16/18/31/33/45/52/58 DNA-positive at enrollment or HPV DNA-positive at month 3 (n = 792) or had missing antibody results (n = 1) or a missing month 3 swab (n = 107) were excluded. Of the 615 participants eligible for the primary HPV 16/18/31/33/45/52/58 analysis, 325 were in the nonavalent group and 290 were in the control vaccine group. The median age was 17 years for the HPV 16/18 and HPV 16/18/31/33/45/52/58 mITT cohorts (Table 1) and, overall, the baseline characteristics by study groups were comparable.

One hundred percent of participants received their assigned vaccine and no administration errors were identified. Overall, 19 of 2,275 (0.8%) participants did not contribute follow-up time after enrollment and 5 (0.2%) exited the study during follow-up. Overall, 2,256 of 2,275 (99%) participants contributed a median of 35 months of follow-up time between December 2018 and January 2023. A total of 34% of participants (771 of 2,256) provided a final analysis swab at month 30 and 62% (1,397 of 2,256) at month 36 as participants received cross-over vaccination at their next study visit after regulatory approvals were obtained to allow timely access to the effective intervention. Retention of four or more swabs collected at follow-up for the assessment of primary end points was 96% (2,182 of 2,275) and 91% (2,061 of 2,2,275) for five or more swabs (Extended Data Table 2). Of the end-point swabs, 93% of swabs were cervical and 7% of swabs were self-collected vaginal swabs, which was similar across intention-to-treat (ITT) and mITT cohorts (Extended Data Table 3).

The incidence of persistent non-vaccine HPV types (HPV 26/35/39/40/42/43/44/51/53/54/56/59/61/66/68/69/70/73/82) was comparable between the three study groups: 24.9 of 100 woman-years in the nonavalent group, 25.8 of 100 woman-years in the bivalent group and 22.0 of 100 woman-years in the control group (Extended Data Table 4). The rates of chlamydia and gonorrhea were comparable across the three study groups (Extended Data Table 5).

Primary outcomes

Through month 36, a total of 75 incident-persistent infections were detected in the HPV 16/18 mITT cohort: 1 among the nonavalent vaccine group, 2 among participants assigned to the bivalent vaccine group, and 72 among those assigned to the control vaccine group (Table 2a) (thus, no additional infections in the nonavalent group, one additional infection in the bivalent group and 36 additional infections in the control group compared to month 18). Through month 36, the incidence of persistent HPV 16/18 was 0.08 per 100 woman-years in the nonavalent vaccine group and 0.16 per 100 woman-years in the bivalent group, compared to 6.70 per 100 woman-years in the control vaccine control

https://doi.org/10.1038/s41591-023-02658-0

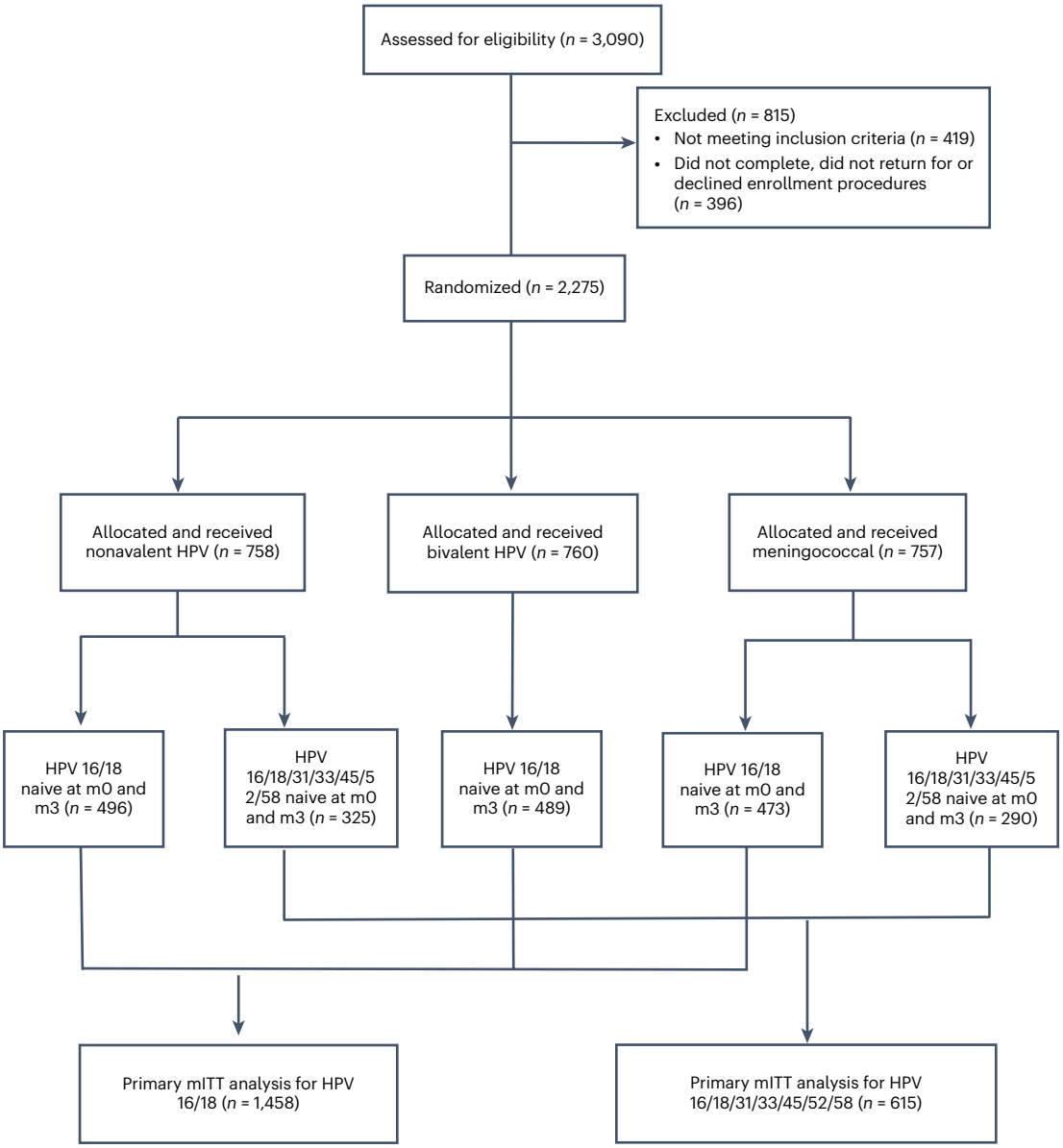

Fig. 1 | Randomized trial profile. CONSORT diagram for the disposition of KEN SHE Study participants, including primary mITT cohort disposition for HPV 16/18 and HPV 16/18/31/33/45/52/58.

group. Nonavalent VE was 98.8% (95% CI 91.3–99.8%, $P < 0.0001$) and bivalent VE was 97.5% (95% CI 90.0–99.4%, $P < 0.0001$) (Fig. 2a).

At month 18, there were 33 incident-persistent infections in the HPV 16/18/31/33/45/52/58 mITT cohort: 4 in the nonavalent group and 29 in the control group. Through month 36, 89 incident-persistent infections were detected in the HPV 16/18/31/33/45/52/58 mITT cohort: 5 in the nonavalent vaccine group and 84 in the control vaccine group (Table 2b) (thus, 1 additional infection in the nonavalent group and 55 additional infections in the control group). Through month 36, the incidence of persistent HPV 16/18/31/33/45/52/58 was 0.61 per 100 woman-years in the nonavalent vaccine group compared to 13.8 per 100 woman-years in the control group. Nonavalent VE for HPV 16/18/31/33/45/52/58 was 95.5% (95% CI 89.0–98.2%, $P < 0.0001$) (Fig. 2b).

Secondary outcomes and efficacy analyses

In the planned secondary sensitivity analysis, including participants with type-specific HPV antibodies detected at enrollment, there were 88 incident-persistent infections in the HPV 16/18 mITT cohort: 1 in the nonavalent vaccine group, 3 among participants assigned to the bivalent group and 84 among those assigned to the control vaccine group (Table 2a). HPV 16/18 incidence was 0.07 per 100 women-years in the nonavalent group, 0.21 per 100 women-years in the bivalent vaccine group and 6.87 per 100 women-years in the control group; nonavalent VE was 99.0% (95% CI 92.5–99.9%, $P < 0.0001$) and bivalent VE was 96.8% (95% CI 90.0–99.0%, $P < 0.0001$; Table 2a). In the sensitivity analysis, there were a total of 124 incident-persistent infections in the HPV 16/18/31/33/45/52/58 mITT cohort: 8 among participants assigned to the nonavalent group and 116 among those assigned to the control group; nonavalent VE was 94.8% (95% CI 89.3–97.4%, $P < 0.0001$; Table 2b).

In the planned secondary extended-sensitivity analysis, excluding participants with HPV DNA detected at month 6, there were a total of 44 incident-persistent infections in the HPV 16/18 mITT cohort: 0 each among participants assigned to the bivalent and nonavalent vaccine groups and 44 among those assigned to the control vaccine group (Table 2a). HPV 16/18 incidence was 0 per 100 women-years in the nonavalent and bivalent vaccine groups and 5.52 per 100 women-years in

https://doi.org/10.1038/s41591-023-02658-0

Table 1 | Baseline characteristics of the mITT cohorts

		HPV 16/18 mITT			HPV 16/18/31/33/45/52/58 mITT	
		Nonavalent HPV	Bivalent HPV	Control	Nonavalent HPV	Control
Characteristic	**Category**					
	Total	**496**	**489**	**473**	**325**	**290**
Age group (years)	15–17	299 (60.3%)	278 (56.9%)	278 (58.8%)	197 (60.6%)	168 (57.9%)
	18–20	197 (39.7%)	211 (43.1%)	195 (41.2%)	128 (39.4%)	122 (42.1%)
Age (years)	Median (IQR)	17 (16, 18)	17 (16, 19)	17 (16, 19)	17 (16, 18)	17 (16, 19)
Marital status	Never married	478 (96.4%)	462 (94.5%)	446 (94.3%)	315 (96.9%)	269 (92.8%)
	Married	14 (2.8%)	24 (4.9%)	20 (4.2%)	7 (2.2%)	15 (5.2%)
	Previously married	3 (0.6%)	3 (0.6%)	7 (1.5%)	2 (0.6%)	6 (2.1%)
	Other	1 (0.2%)	0 (0.0%)	0 (0.0%)	1 (0.3%)	0 (0.0%)
Education (highest level)	No schooling	1 (0.2%)	2 (0.4%)	1 (0.2%)	1 (0.3%)	1 (0.3%)
	Primary school, some or complete	40 (8.1%)	30 (6.1%)	36 (7.6%)	27 (8.3%)	27 (9.3%)
	Secondary school, some or complete	359 (72.4%)	368 (75.3%)	355 (75.1%)	241 (74.2%)	220 (75.9%)
	Post-secondary school	96 (19.4%)	89 (18.2%)	81 (17.1%)	56 (17.2%)	42 (14.5%)
Earns an income of her own	No	437 (88.1%)	417 (85.3%)	417 (88.2%)	284 (87.4%)	248 (85.5%)
	Yes	59 (11.9%)	72 (14.7%)	56 (11.8%)	41 (12.6%)	42 (14.5%)
Has a current main or steady sexual partner	No	144 (29.0%)	152 (31.1%)	145 (30.7%)	98 (30.2%)	95 (32.8%)
	Yes	352 (71.0%)	337 (68.9%)	328 (69.3%)	227 (69.8%)	195 (67.2%)
Age when first had vaginal intercourse (years)	<15	123 (24.8%)	116 (23.7%)	103 (21.8%)	80 (24.6%)	65 (22.4%)
	15–17	265 (53.4%)	274 (56.0%)	282 (59.6%)	185 (56.9%)	173 (59.7%)
	≥18	96 (19.4%)	93 (19.0%)	79 (16.7%)	54 (16.6%)	46 (15.9%)
	Do not remember	12 (2.4%)	6 (1.2%)	9 (1.9%)	6 (1.8%)	6 (2.1%)
Lifetime number of sex partners	1	322 (64.9%)	332 (67.9%)	289 (61.1%)	217 (66.8%)	184 (63.4%)
	2	121 (24.4%)	100 (20.4%)	113 (23.9%)	78 (24.0%)	65 (22.4%)
	≥3	53 (10.7%)	57 (11.7%)	71 (15.0%)	30 (9.2%)	41 (14.1%)
Condom use with last vaginal sex	No	153 (30.8%)	155 (31.7%)	140 (29.6%)	98 (30.2%)	78 (26.9%)
	Yes	237 (47.8%)	235 (48.1%)	238 (50.3%)	156 (48.0%)	144 (49.7%)
	No sex in past year	106 (21.4%)	99 (20.2%)	95 (20.1%)	71 (21.8%)	68 (23.4%)
Syphilis	Negative	496 (100.0%)	489 (100.0%)	471 (99.6%)	325 (100.0%)	289 (99.7%)
	Positive	0	0	1 (0.2%)	0	1 (0.3%)
	Not done	0	0	1 (0.2%)	0	0
Chlamydia trachomatis	Negative	438 (88.3%)	434 (88.8%)	413 (87.3%)	293 (90.2%)	252 (86.9%)
	Positive	58 (11.7%)	55 (11.2%)	60 (12.7%)	32 (9.8%)	38 (13.1%)
Neisseria gonorrhoeae	Negative	488 (98.4%)	480 (98.2%)	466 (98.5%)	322 (99.1%)	285 (98.3%)
	Positive	8 (1.6%)	9 (1.8%)	7 (1.5%)	3 (0.9%)	5 (1.7%)
HSV-2	Negative	407 (82.1%)	387 (79.1%)	375 (79.3%)	264 (81.2%)	226 (77.9%)
	Positive	88 (17.7%)	102 (20.9%)	98 (20.7%)	60 (18.5%)	64 (22.1%)
	Indeterminate	1 (0.2%)	0	0	1 (0.3%)	0
BV[a]	Negative	415 (83.7%)	378 (77.3%)	378 (79.9%)	278 (85.5%)	239 (82.4%)
	Positive	81 (16.3%)	111 (22.7%)	95 (20.1%)	47 (14.5%)	51 (17.6%)
Trichomonas vaginalis	Negative	477 (96.2%)	468 (95.7%)	452 (95.6%)	315 (96.9%)	275 (94.8%)
	Positive	19 (3.8%)	21 (4.3%)	21 (4.4%)	10 (3.1%)	15 (5.2%)

[a]Nugent scores 7–10 were classified as BV positive and Nugent scores 0–6 were classified as BV negative. BV, bacterial vaginosis; IQR, interquartile range; HSV, herpes simplex virus.

the control group; nonavalent VE was 100% ($P < 0.0001$) and bivalent VE was 100% ($P < 0.0001$) (Table 2a). In the extended-sensitivity analysis, there were a total of 51 incident-persistent infections in the HPV 16/18/31/33/45/52/58 mITT cohort: 1 among participants assigned to the nonavalent group and 50 among those assigned to the control group; nonavalent VE was 98.6% (95% CI 90.0–99.8%, $P < 0.0001$) (Table 2b).

https://doi.org/10.1038/s41591-023-02658-0

Table 2 | Incidence of persistent HPV and vaccine efficacy

a

	HPV 16/18									
	Nonavalent HPV		Bivalent HPV		Control		Nonvalent versus control		Bivalent versus control	
	Events/ participants	Incidence of persistent HPV 16/18 per 100 woman-years (95% CI)	Events/ participants	Incidence of persistent HPV 16/18 per 100 woman-years (95% CI)	Events/ participants	Incidence of persistent HPV 16/18 per 100 woman-years (95% CI)	VE (95% CI)	*P* value	VE (95% CI)	*P* value
mITT Primary	1/496	0.08 (0–0.44)	2/489	0.16 (0.02–0.58)	72/473	6.70 (5.24–8.44)	98.8% (91.3–99.8%)	<0.0001	97.5% (90.0–99.4%)	<0.0001
mITT sensitivity	1/569	0.07 (0–0.39)	3/561	0.21 (0.04–0.62)	84/543	6.87 (5.48–8.51)	99.0% (92.5–99.9%)	<0.0001	96.8% (90.0–99.0%)	<0.0001
Extended sensitivity	0/429	0 (0–0.38)	0/404	0 (0–0.40)	44/380	5.52 (4.01–7.42)	100.0%* (NC)	<0.0001	100.0%* (NC)	<0.0001

b

	HPV 16/18/31/33/45/52/58					
	Nonavalent HPV		Control		Nonvalent versus control	
	Events/ participants	Incidence of persistent HPV 16/18/31/33/45/52/58 per 100 woman-years (95% CI)	Events/ participants	Incidence of persistent HPV 16/18/31/33/45/52/58 per 100 woman-years (95% CI)	VE (95% CI)	*P* value
mITT primary	5/325	0.61 (0.20–1.42)	84/290	13.8 (11.0–17.0)	95.5% (89.0–98.2%)	<0.0001
mITT sensitivity	8/437	0.74 (0.32–1.45)	116/392	14.4 (11.9–17.2)	94.8% (89.3–97.4%)	<0.0001
Extended sensitivity	1/264	0.17 (0–0.92)	50/210	12.1 (8.97–15.9)	98.6% (90.0–99.8%)	<0.0001

NC, not calculated. *VE computed as 100×(1−crude incidence rate ratio). Incidence of persistent HPV by randomized vaccine group in the mITT primary, mITT sensitivity cohorts. For the HPV types specified, the mITT primary cohort includes participants who were HPV DNA and antibody negative at enrollment and DNA negative at month 3; the mITT sensitivity cohort includes participants who were HPV DNA negative at enrollment and month 3; and the extended-sensitivity cohort includes participants who were HPV DNA and antibody negative at enrollment, and DNA negative and months 3 and 6. Woman-years of follow-up time is computed from the month 3 swab collection date for the mITT primary and sensitivity cohorts, and from the month 6 swab collection date in the extended-sensitivity cohort. No multiplicity adjustments were performed. **a**, Incidence of persistent HPV 16/18 and VE. For the extended-sensitivity cohort comparisons, VE is reported as 100×(1−crude incidence rate ratio) due to 0 events in the nonavalent and bivalent HPV vaccine arms. Two-sided log-rank *P* values are computed for each comparison using the log-rank test. **b**, Incidence of persistent HPV 16/18/31/33/45/52/58 and VE. Two-sided log-rank *P* values are computed for each comparison using the log-rank test.

In the planned secondary analyses to assess VE in the prespecified subgroups, as defined at enrollment, for the presence of co-infections (chlamydia, gonorrhea, herpes simplex type 2, trichomoniasis, syphilis and bacterial vaginosis), self-reported condom use, number of self-reported lifetime sex partners (1 versus 2+) and contraceptive method use, there was no difference in VE in predefined subgroups (Extended Data Tables 6 and 7).

Safety

Serious adverse events (SAEs) were experienced by 201 participants, which included 122 participants with pregnancy-related SAEs, 71 with infections or inflammatory conditions (of which 39 were malaria), 7 injuries and 12 mental health illnesses. Overall, the SAE frequency was similar between groups (Table 3). There were five deaths in the study due to unsafe abortion, sepsis, suicide, hepatocellular carcinoma, complications following an emergency cesarean section for fetal distress and one unknown cause with acute symptoms of cough productive of bloody sputum. SAEs were assessed as not related to the study vaccines. Five participants had abnormal cervical cytology at enrollment and were followed until the lesions resolved or the participant received treatment. Social harms were reported by 0.31% of participants ($n = 7$), including partner physical and verbal abuse and lack of social support from friends and family for trial participation.

Exploratory analyses

In exploratory analysis to evaluate cross-protection against related HPV types, bivalent VE against incident-persistent HPV 31/33/45 was 10.1% (95% CI −38.7% to 41.7%) (Extended Data Table 8).

Post hoc analyses

Using only provider-collected end-point cervical swabs and excluding self-collected vaginal swabs, the results for the primary analysis were not different: the VE was 98.7% (95% CI 90.5–99.8%) for the nonavalent vaccine and 97.3% (95% CI 89.0–99.3%) for the bivalent in the HPV 16/18 mITT cohort. Nonavalent VE was 95.3% (95% CI 88.4–98.1%) in the HPV 16/18/31/33/45/52/58 mITT cohort (Table 4).

The absolute reduction in the HPV 16/18 mITT cohort for cumulative incident-persistent HPV 16/18 infection was −16.0% (95% CI −19.5 to −12.5%) for the nonavalent group and −15.8% (95% CI −19.3 to −12.3%) for the bivalent group; an absolute incidence of 0.2% (95% CI 0–0.6%) in the nonavalent vaccine group and 0.4% (95% CI 0–1.0 %) in the bivalent group compared to 16.2% (95% CI 12.7–19.7%) in the control group. For the HPV 16/18/31/33/45/52/58 mITT cohort, the absolute reduction in persistent HPV 16/18/31/33/45/52/58 infection was −30.1% (95% CI −36.1 to −24.2%) for the nonavalent vaccine; an absolute incidence of 1.6% (95% CI 0.2–2.9%) in the nonavalent vaccine group compared to 31.7% (95% CI 25.9–37.4%) in the control group.

Discussion

Three years after vaccine administration, the high efficacy of both single-dose bivalent or nonavalent HPV vaccine was sustained and durable against vaccine-specific oncogenic HPV infection. Protection against type-specific incident-persistent infection was ≥98% for bivalent and nonavalent vaccine protection against HPV 16/18 and >95% for nonavalent vaccine protection against HPV 16/18/31/33/45/52/58, which cause 70% and 90% of cervical cancer cases, respectively. This together with observed high reductions in the absolute cumulative incidence, the potential for public health impact in the context of disparities by HDI in cervical cancer incidence and mortality[1] is substantial. Saliently, there is high certainty of VE of at least 90% against HPV 16/18; the lower confidence interval limit for the bivalent and nonavalent VE.

Taken in context, these data contribute to a suite of studies that provide evidence for single-dose HPV VE. The Costa Rica vaccine trial (CVT)[12] provided the first observational data for bivalent single-dose HPV vaccine effectiveness and recently demonstrated durability over 16 years[19]. The DoRIS study demonstrated that a single-dose nonavalent

https://doi.org/10.1038/s41591-023-02658-0

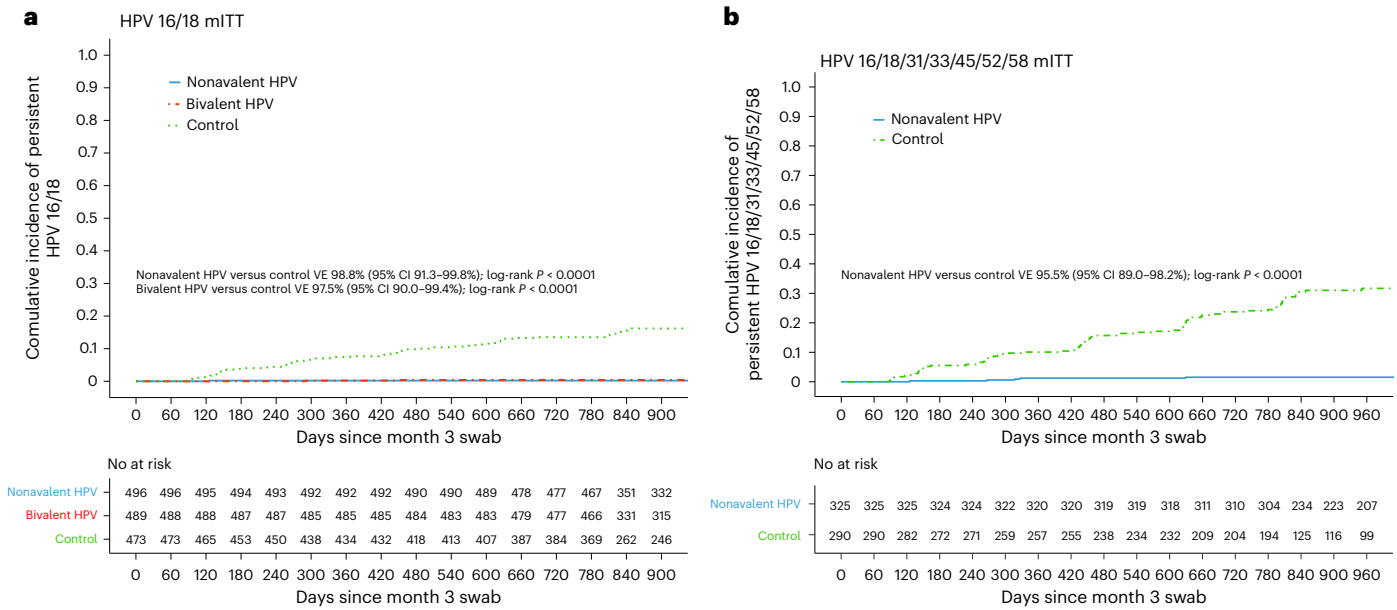

Fig. 2 | Cumulative incidence curves for the incidence of persistent HPV in the modified intention-to-treat primary analyses. Cumulative incidence curves were computed by vaccine group using Kaplan–Meier methods. Two-sided log-rank *P* values were computed for each comparison using the log-rank test. **a**, Cumulative incidence of persistent HPV 16/18 in the HPV 16/18 mITT cohort ($n = 1{,}458$). Four participants in the HPV 16/18 mITT cohort did not contribute a second end-point swab and thus did not contribute time at risk. **b**, Cumulative incidence of persistent HPV 16/18/31/33/45/52/58 in the HPV 16/18/31/33/45/52/58 mITT cohort ($n = 615$). One participant in the HPV 16/18/31/33/45/52/58 mITT cohort did not contribute a second end-point swab and thus did not contribute time at risk.

or bivalent HPV vaccine produced robust immune responses similar to two doses and three doses among 9–14-year-old girls[20]. The IARC-India study reported durability of single-dose quadrivalent HPV vaccine effectiveness over a decade[11]. Thus, consistent evidence on the efficacy and durability of single-dose HPV vaccination supports the WHO guidance for single-dose implementation to increase vaccine coverage. In mathematical modeling analyses of scale-up, implementation of routine single-dose immunization has the potential to avert most cervical cancer cases compared to two doses, with a durability of 20–30 years, in low-HDI settings[21]. Further, single-dose vaccination can increase coverage among girls in the 9–14-year-old group before they age out of vaccine eligibility and provide catch-up vaccination for those who may have missed the immunization due to the COVID-19 pandemic or other reasons.

Of the 11.6 million cases of cervical cancer expected globally among girls born between 2005 and 2014, 75% of the burden will be concentrated in 25 countries largely in Africa and Asia, highlighting the need to focus prevention efforts among recently born girls[5]. Overall, the rate of incident persistent HPV infection in this population of African adolescent girls and young women was high; 13.8 per 100 woman-years in the control group, underscoring the need for effective, scalable vaccine programs that can achieve high coverage and reduce this high incidence of HPV infection and ultimately cervical cancer[22,23]. Catch-up vaccination programs for adolescents and young people aged 15–20 years, who do not qualify for current vaccination programs, have the potential to avert oncogenic persistent infections. Through this head-to-head comparison of bivalent and nonavalent HPV vaccines, sustained VE was demonstrated in the context of high HPV prevalence. Single-dose HPV vaccination could increase vaccine access and coverage and offer a cost-effective strategy for cervical cancer prevention.

The vaccines' underlying immunological mechanism of action could explain the observed VE. The vaccines contain monomers that self-assemble into capsomers and VLPs, a highly immunogenic structure mimicking the ordered, repetitive virus epitope structure and allowing for crosslinking of B cell receptors[8]. This induces high levels of virIon-neutralizing serum antibodies and long-lasting plasma cells, supporting effective and durable VE. We did not see evidence of cross-protection with a single dose of the bivalent vaccine and it may be that two doses are required for cross-protection for the closely related HPV 31/33/45. The confidence interval did not include previous estimates of the multi-dose bivalent strategy of 50% cross-protection for HPV 31/33/45 (ref. 5).

The study has several strengths, including its randomized, double-blind controlled design, high retention rate, use of cervical HPV DNA as the outcome measure, determination of incident persistent HPV DNA, head-to-head comparison of the licensed bivalent and nonavalent HPV vaccines in protection against persistent infection with oncogenic HPV types, and duration of follow-up. Moreover, the trial successfully enrolled individuals exposed to HPV infection and retained them in all randomized groups, facilitating a rapid evaluation of single-dose efficacy. Compared to the 18-month analysis, the final analysis VE estimates are stable through 36 months, with higher point-estimates

Table 3 | Participants experiencing adverse events (ITT)

	Randomized group			
	Nonavalent HPV	Bivalent HPV	Control	All
Enrolled, *n*	758	760	757	2,275
Any SAE, *n* (%)	59 (7.8%)	72 (9.5%)	70 (9.2%)	201 (8.8%)
Any pregnancy-related, *n* (%)	44 (5.8%)	45 (5.9%)	33 (4.4%)	122 (5.4%)
Any infection/inflammation, *n* (%)	13 (1.7%)	26 (3.4%)	32 (4.2%)	71 (3.1%)
Any injury, *n* (%)	0 (0%)	3 (0.4%)	4 (0.5%)	7 (0.3%)
Any mental health, *n* (%)	3 (0.4%)	4 (0.5%)	5 (0.7%)	12 (0.5%)

Participants may have more than one event across categories.

Table 4 | Incidence of persistent HPV and vaccine efficacy using cervical swabs only (mITT primary cohorts)

Randomized group	Enrolled (*n*)	HPV type naive at baseline (mITT) (*n*)	Incident-persistent HPV (*n*)	Woman-years of follow-up	Incidence of persistent HPV per 100 woman-years	95% CI		Statistical comparisons			
						Lower bound	Upper bound	Comparison	VE	95% CI	*P* value (log-rank)
HPV 16/18 mITT cohort											
Nonavalent HPV	758	496	1	1,240.76	0.08	0	0.45	Nonavalent HPV versus control	98.7%	(90.5–99.8%)	<0.0001
Bivalent HPV	760	489	2	1,216.42	0.16	0.02	0.59	Bivalent HPV versus control	97.3%	(89.0–99.3%)	<0.0001
Control	757	473	66	1,057.86	6.24	4.83	7.94				
HPV 16/18/31/33/45/52/58 mITT cohort											
Nonavalent HPV	758	325	5	813.66	0.61	0.20	1.43	Nonavalent HPV versus control	95.3%	(88.3–98.1%)	<0.0001
Control	757	290	79	598.55	13.20	10.45	16.45				

Post hoc analysis used cervical swabs only to ascertain end points; all self-collected swabs after month 3 were excluded. Methods are otherwise the same as described in Table 2. No multiplicity adjustments were performed.

and tighter confidence intervals, as additional follow-up time was accrued beyond the 6–12-month buffer period, during which infections that were prevalent at baseline but not detected at follow-up, and may contribute to a lower estimate of VE[13,14].

We acknowledge that the study has limitations. First, the median duration of follow-up is 35 months and longer-term durability of single-dose VE in a randomized trial would strengthen the evidence as HPV exposure continues through adulthood. Observational data for single-dose HPV vaccination support efficacy over a decade[11]. While participants in the control group have received single-dose HPV vaccination, we are collecting additional data in this cohort to 54 months post-vaccination[24]. The antibody plateau level for single-dose HPV vaccination is reached by 12 months[9], suggesting that we have observed steady state efficacy. Second, 7% of primary end-point swabs were self-collected and 93% were provider-collected. All swabs would ideally be collected with one modality; however, the correlation between self-collected vaginal and provider-collected cervical swabs is high[25] and there was no difference in the results when self-collected swabs were excluded. For the preplanned subgroup analyses by sexually transmitted infection (STI) status, the subgroups were defined at enrollment and may have changed over time; however, the incidence of persistent non-vaccine HPV types was comparable through the study in the three study groups. Finally, while the GST-ELISA multiplex assay used to exclude participants with HPV antibodies at enrollment demonstrated overall agreement of 89% with the gold standard secreted alkaline phosphatase pseudovirion-based neutralization assay[26], misclassification of participants as antibody naive would not be different by study group. Further in sensitivity analysis including participants with HPV antibodies at baseline, overall VE was in keeping with the primary findings (Table 2a,b).

Globally cervical cancer is a leading cause of morbidity and mortality among women in mid-life; it is the second most common cancer and the greatest contributor to cancer-related mortality among women in southern and East Africa carrying a high cost to women, their families and communities[1,27]. Focusing on the cohort of girls and adolescent women who are at risk of developing cervical cancer if not vaccinated, global HPV 16/18 vaccination of women born between 2005 and 2014 would avert 8 million (7.8–8.3) cervical cancer cases and HPV 16/18/31/33/45/52/58 vaccination would avert 10.2 million (10.0–10.6) cases, with 70% of cases averted in low-to-middle HDI countries[6]. Cervical cancer is almost entirely preventable through HPV vaccination. Single-dose HPV vaccination could serve to close the gap between the WHO goal of 90% HPV vaccination coverage by 2030 and the 15% of girls globally currently vaccinated[7], alleviate vaccine supply constraints[27] and provide global policymakers with options to optimally allocate existing HPV vaccine supply. The most recent Cochrane review of the efficacy of single-dose HPV vaccination highlighted that there was moderate evidence on the durability of VE, which we have now provided with robust data over 3 years[13]. Single-dose HPV vaccination could facilitate rapid scale-up of vaccination worldwide.

Over 36 months, single-dose HPV vaccination offered high protection, >95% VE in preventing incident, persistent HPV 16/18/31/33/45/52/58 infection, with the lower bound of the confidence interval at almost 90% (89%) indicating a high minimum level of efficacy. Single-dose HPV vaccination was safe with no vaccine-related SAEs. These data add to the growing suite of evidence to support single-dose HPV vaccination implementation.

Online content

Any methods, additional references, Nature Portfolio reporting summaries, source data, extended data, supplementary information, acknowledgements, peer review information; details of author contributions and competing interests; and statements of data and code availability are available at https://doi.org/10.1038/s41591-023-02658-0.

References

1. Singh, D. et al. Global estimates of incidence and mortality of cervical cancer in 2020: a baseline analysis of the WHO Global Cervical Cancer Elimination Initiative. *Lancet Glob. Health* **11**, e197–e206 (2023).
2. Harper, D. M. & DeMars, L. R. HPV vaccines - a review of the first decade. *Gynecol. Oncol.* **146**, 196–204 (2017).
3. Huh, W. K. et al. Final efficacy, immunogenicity, and safety analyses of a nine-valent human papillomavirus vaccine in women aged 16-26 years: a randomised, double-blind trial. *Lancet* **390**, 2143–2159 (2017).
4. World Health Organization. *A Global Strategy for Elimination of* Cervical Cancer www.who.int/activities/a-global-strategy-for-elimination-of-cervical-cancer (2020).
5. Drolet, M., Benard, E., Perez, N. & Brisson, M., H. P. V. Vaccination Impact Study Group. Population-level impact and herd effects following the introduction of human papillomavirus vaccination programmes: updated systematic review and meta-analysis. *Lancet* **394**, 497–509 (2019).

6. Bonjour, M. et al. Global estimates of expected and preventable cervical cancers among girls born between 2005 and 2014: a birth cohort analysis. *Lancet Public Health* **6**, e510–e521 (2021).
7. Bruni, L. et al. HPV vaccination introduction worldwide and WHO and UNICEF estimates of national HPV immunization coverage 2010-2019. *Prevent. Med.* **144**, 106399 (2021).
8. Lowy, D. R. HPV vaccination to prevent cervical cancer and other HPV-associated disease: from basic science to effective interventions. *J. Clin. Invest.* **126**, 5–11 (2016).
9. Baisley, K. et al. Comparing one dose of HPV vaccine in girls aged 9-14 years in Tanzania (DoRIS) with one dose of HPV vaccine in historical cohorts: an immunobridging analysis of a randomised controlled trial. *Lancet Glob. Health* **10**, e1485–e1493 (2022).
10. Barnabas, R. V. et al. Efficacy of single-dose HPV vaccination among young African women. *NEJM Evid.* **1**, EVIDoa2100056 (2022).
11. Basu, P. et al. Vaccine efficacy against persistent human papillomavirus (HPV) 16/18 infection at 10 years after one, two, and three doses of quadrivalent HPV vaccine in girls in India: a multicentre, prospective, cohort study. *Lancet Oncol.* https://doi.org/10.1016/S1470-2045(21)00453-8 (2021).
12. Kreimer, A. R. et al. Evidence for single-dose protection by the bivalent HPV vaccine: review of the Costa Rica HPV vaccine trial and future research studies. *Vaccine* **36**, 4774–4782 (2018).
13. Henschke, N. et al. *Efficacy, Effectiveness and Immunogenicity of One Dose of HPV Vaccine Compared with No Vaccination, Two Doses, or Three Doses* (Cochrane Response, 2022).
14. Markowitz, L. E. et al. Human papillomavirus vaccine effectiveness by number of doses: updated systematic review of data from national immunization programs. *Vaccine* **40**, 5413–5432 (2022).
15. Whitworth, H. S. et al. Efficacy and immunogenicity of a single dose of human papillomavirus vaccine compared to no vaccination or standard three and two-dose vaccination regimens: a systematic review of evidence from clinical trials. *Vaccine* **38**, 1302–1314 (2020).
16. Umutesi, G. et al. HPV vaccination in Kenya: a study protocol to assess stakeholders' perspectives on implementation drivers of HPV vaccination and the acceptability of the reduced dose strategy among providers. *Front. Health Serv.* **3**, 1233923 (2023).
17. Barnabas, R. V. et al. Single-dose HPV vaccination efficacy among adolescent girls and young women in Kenya (the KEN SHE study): study protocol for a randomized controlled trial. *Trials* **22**, 661 (2021).
18. Shadab, R. et al. Key ethical considerations to guide the adjudication of a single-dose HPV vaccine schedule. *Hum. Vaccines Immunother.* https://doi.org/10.1080/21645515.2021.1917231 (2021).
19. Romero, B. et al. Durability of HPV 16-18 antibodies 16 years after a single dose of the bivalent HPV vaccine: the Costa Rica HPV vaccine trial. in *IPVC 2023* (IPVC, 2023).
20. Watson-Jones, D. et al. Immunogenicity and safety of one-dose human papillomavirus vaccine compared with two or three doses in Tanzanian girls (DoRIS): an open-label, randomised, non-inferiority trial. *Lancet Glob. Health* **10**, e1473–e1484 (2022).
21. Benard, E. et al. Potential population-level effectiveness of one-dose HPV vaccination in low-income and middle-income countries: a mathematical modelling analysis. *Lancet Public Health* **8**, e788–e799 (2023).
22. Harper, D. M. et al. Efficacy of a bivalent L1 virus-like particle vaccine in prevention of infection with human papillomavirus types 16 and 18 in young women: a randomised controlled trial. *Lancet* **364**, 1757–1765 (2004).
23. Joura, E. A. et al. A 9-valent HPV vaccine against infection and intraepithelial neoplasia in women. *New Engl. J. Med.* **372**, 711–723 (2015).
24. Follmann, D. et al. A deferred-vaccination design to assess durability of COVID-19 vaccine effect after the placebo group is vaccinated. *Ann. Intern. Med.* **174**, 1118–1125 (2021).
25. Polman, N. J. et al. Performance of human papillomavirus testing on self-collected versus clinician-collected samples for the detection of cervical intraepithelial neoplasia of grade 2 or worse: a randomised, paired screen-positive, non-inferiority trial. *Lancet Oncol.* **20**, 229–238 (2019).
26. Robbins, H. A. et al. Glutathione-*S*-transferase L1 multiplex serology as a measure of cumulative infection with human papillomavirus. *BMC Infect. Dis.* **14**, 120 (2014).
27. Prem, K. et al. Global impact and cost-effectiveness of one-dose versus two-dose human papillomavirus vaccination schedules: a comparative modelling analysis. *BMC Med.* https://doi.org/10.1186/s12916-023-02988-3 (2023).

[1]Division of Infectious Diseases, Department of Medicine, Massachusetts General Hospital, Boston, MA, USA. [2]School of Medicine, Harvard Medical School, Boston, MA, USA. [3]Department of Epidemiology, T. H. Chan Harvard School of Public Health, Boston, MA, USA. [4]Vaccine and Infectious Disease Division, Fred Hutchinson Cancer Center, Seattle, WA, USA. [5]Public Health Sciences, Fred Hutchinson Cancer Center, Seattle, WA, USA. [6]Department of Biostatistics, University of Washington, Seattle, WA, USA. [7]Center for Microbiology Research, Kenya Medical Research Institute, Kisumu, Kenya. [8]Department of Global Health, University of Washington, Seattle, WA, USA. [9]Department of Obstetrics and Gynecology, University of Washington, Seattle, WA, USA. [10]Center for Clinical Research, Kenya Medical Research Institute, Nairobi, Kenya. [11]Department of Epidemiology, University of Washington, Seattle, WA, USA. [12]Human Biology Division, Fred Hutchinson Cancer Center, Seattle, WA, USA. [13]University of Cincinnati, Department of Obstetrics and Gynecology, Cincinnati, OH, USA. [14]Department of Laboratory Medicine and Department of Pathology, University of Washington, Seattle, WA, USA. [15]Division of Allergy and Infectious Diseases, Department of Medicine, University of Washington, Seattle, WA, USA. [16]East Africa STI Laboratory, University of Washington, Mombasa, Kenya. *A list of authors and their affiliations appears at the end of the paper. ✉e-mail: rbarnabas@mgh.harvard.edu

the KEN SHE Study Team

Peter Dull[17], Reena Gulati[17], Sara Vernam[17], Abdul Rawuf Yousufzay[17], Krissa Gunderson[18], Amra Hercinovic[18], Lisa Ondrejcek[18], Gavin Robertson[18], Angela Williams[18], Elizabeth Brown[4,5,6,12], Jody Carter[12], Deborah Donnell[4,8], Denise Galloway[12], Leeya Pinder[8,13], Priya R. Prabhu[12], Robin Smith[12], Marci Wright[12], Stephen O. Abiero[7], Maqline A. Achola[7], Meldah O. Adipo[7], Katherine L. Amukonyi[7], Cynthia Akinyi[7], Teresia O. Akinyi[7], Penina N. Amboka[7], Karl D. Arum[7], Veronica O. Atogo[7], Pius O. Atonga[7], Elizabeth A. Bukusi[7,8,9], Adero J. Cate[7], Daisy Chepkoros[7], Oyamo O. Christopher[7], Imelda N. Imali[7], Mildred Imbayi[7], Lizzie N. Kabete[7], Enericah K. Kanampiu[7], Geoffrey Kebaso[7], Dennis Kegode[7], Timothy Kwena[7], Reina Lenturkana[7], Celestine Lihavi[7], David N. Marwa[7], Patricia Matti[7], Peter O. Mboya[7], Elijah Mbuya[7], Lyna A. Memo[7], Robai M. Mituyi[7], Benard M. Muga[7], David E. Muhoma[7], Elizabeth L. Musi[7], Gilbert C. Mutai[7], Simon M. Muthusi[7], Ivy M. Mutuiri[7], Catherine W. Mwakio[7], Bill Nyongesa[7], Maureen A. Ochieng[7], Vincent R. Ochuka[7], Belder A. Odedo[7], Esther A. Odeny[7], Vincent O. Odera[7], Debora A. Odhiambo[7], Perez O. Odhiambo[7], Janet A. Okeyo[7], Linet A. Okode[7], Nollyne A. Okuku[7], Irene Okumu[7], Lydiah A. Okumu[7], Christine A. Olweny[7], Hellen A. Olweyo[7], George O. Omondi[7], Donnavane A. Ondego[7], Florence A. Ondiek[7], Joan A. Ongere[7], Maricianah Onono[7], Kevin O. Onyango[7], Annette A. Opondo[7], Millicent A. Oronje[7], Beryl A. Osoga[7], Rebecca A. Otieno[7], Job A. Ouma[7], Mildred A. Owenga[7], Samya S. Rashid[7], Vincent K. Salano[7], Moses O. Siaji[7], Roseline Sikolia[7], Imelda N. Wakhungu[7], Nicholas Walukana[7], Nobert B. Walusala[7], Caren A. Wemali[7], Faith Ambiyo[13], Emily Anyango[13], Charlene Biwott[10], Esther K. Charles[10], David Chege[10], Jane Gacheru[10], Anne Gaitho[10], Stephen Gakuo[10], Zachary Gathu[10], Mathew Irungu[10], Vincent Juma[10], Irene Kamau[10], Mary Kibatha[10], Dorcas Kiboi[10], Francis Khaemba[10], Hellen W. Kimani[10], Syovata Kimanthi[10], Catherine Kiptinness[10], Caren Koli[10], Erick Koome[10], Solomon Maina[10], Linet Makena[10], Sarah Mbaire[10], Veronica Muchoki[10], Victor Munene[10], Edwin Mugo[10], Nelly R. Mugo[8,10], Umi W. Mugo[10], Faith Munyaka[10], Paul Mutunga[10], Margaret Mwangi[10], Stanley Mwangi[10], Peter Mwenda[10], Gladys Namboka[10], Grace Ndung'u[10], Rispa Nduuru[10], Esther Neema[10], Sammy Ng'ang'a[10], Josephine Njeri[10], Irene Njeru[10], Alice Njoki[10], Betty Njoroge[10], John Njoroge[10], Sarah Njoroge[10], Peter Nzuve[10], Fridah Nkatha[10], Jemimah Nyakio[10], Edna Nyandiga[10], Jacinta Nyokabi[10], Rose Odera[10], John Okumu[10], Lynda Oluoch[10], Linda Orwa[10], Nina Ouko[10], Matilda Saina[10], Agata Thumi[10], Innes Wambui[10], Victoria Wambui[10], Virginia Wangechi[10], Scholastica Wanjiku[10], Ruanne Barnabas[1,2,3], Francesca Caramazza[1], Kate Heller[1,8], Diane Kanjilal[1], Kyle Kennedy[1], Daniel Pacella[1], Odunayo Kolawole Talabi[1], Rukiya Hassan[16], Emmanuel Kabare[16], R. Scott McClelland[8,11,15,16], Fatma H. Mwidadi[16], Khamis Mwinyikai[16], Salwa Mustafa[16], Juma Shafi[16], Jared M. Baeten[8,15], Connie Celum[8,11,15], Stephen L. Cherne[14], Daphne Hamilton[8], Rachel Johnson[8], John Lin[11], Susan Morrison[8], Justice Quame-Amaglo[8], Elena A. Rechkina[8], Torin T. Schaafsma[8] & Rachel L. Winer[11]

[17]Bill and Melinda Gates Foundation, Seattle, WA, USA. [18]DF/Net Research, Seattle, WA, USA.

Methods

Study design

This randomized, multicenter, double-blind, parallel, three-group controlled, superiority trial tested the efficacy of single-dose bivalent (HPV 16/18) and single-dose nonavalent (HPV 16/18/31/33/45/52/58/6/11) HPV vaccination, as described in the published protocol paper[17] and in the report of the primary results[10]. The study was conducted at three Kenya Medical Research Institute (KEMRI) clinical sites in Kisumu, Thika and Nairobi.

In GAVI-funded countries, including Kenya, multi-dose HPV vaccination is offered to 9–14-year-old girls through the national immunization program. Catch-up vaccination for adolescent girls and young women 15 years of age and older is not provided. Cervical cancer screening is offered to older women instead. We conducted a clinical trial to test the efficacy of single-dose HPV vaccination among young women aged 15-20 years within the context of cytological screening for dysplastic lesions. This was determined to be ethical, as vaccination for this age group in Kenya and many low-HDI countries is not currently supported through national programs or global immunization bodies[18].

Participants

Participants were eligible for the study if they were born female, aged 15–20 years old inclusive, were sexually active with one to five sexual partners reported in their lifetime, and planned to reside in the study area for 37 months. The exclusion criteria were people living with HIV for whom few data on single-dose HPV VE are available, history of previous HPV vaccination, allergies to vaccine components of latex, pregnancy, hysterectomy, history of autoimmune, degenerative or genetic diseases, and investigator discretion regarding participant safety. Sex assigned at birth was assessed through participant self-report at screening. Participants were recruited through community outreach. All participants, and their parents/guardians in the case of minors, provided written informed consent, which included counseling about randomization, risks and benefits of participation, study procedures and their rights as research participants.

Randomization and masking

Meningococcal vaccination was chosen as the control because meningococcal antibodies offer potential clinical benefits and do not impact HPV outcomes. Participants were randomized to (1) nonavalent HPV vaccination (Gardasil-9), (2) bivalent HPV vaccination (Cervarix) or (3) meningococcal (control) vaccination. Following randomization, a single dose of each vaccine was administered.

An unblinded statistical analyst generated the randomization sequence using SAS v.9.4. Randomization was stratified by site, using a fixed block size of 15 and a 1:1:1 allocation. Blinded study assignment was implemented via www.randomize.net. Study staff, participants, investigators, clinic staff, laboratory technicians, the end points adjudication committee members and other study team members did not have access to the randomization codes, except for the unblinded statistical analysts and unblinded pharmacists at each site. At the conclusion of the enrollment visit, an unblinded pharmacist entered the participant identification number (PTID) on randomize.net, obtained the next sequential intervention assignment, recorded the PTID and randomization identifier on an eCRF, drew up the vaccine in a masked syringe and administered the vaccination via the intramuscular route. An independent observer, not on the study team, observed the masked vaccination to assess the success of masking.

Procedures

Potential participants completed eligibility screening with a provider, including a detailed medical history, collection of external genital (labial/vulvar/perineal), lateral vaginal, and cervical swabs for HPV DNA testing, and serum for HPV antibody testing. Participants received cytological screening for cervical cancer screening at enrollment. Sexual and reproductive health services (contraception, STI diagnosis and treatment, HIV testing and HIV pre-exposure prophylaxis) were offered at enrollment and every visit. Participants also received counseling including services for mental health. All questionnaires used electronic case report forms (eCRFs) (DFexplore Software, DF/Net Research).

Participants had study visits at months 3, 6 and then every 6 months for up to 36 months. Providers administered clinical questionnaires and collected a cervical swab at each 6-month visit. Participants self-collected vaginal swabs using validated instructions at month 3; self-collected swabs, which have similar accuracy compared to provider-collected cervical swabs[25], were available at subsequent follow-up visits by participant choice or to comply with COVID-19 research restrictions.

Following dissemination and WHO review of the month 18 primary results, participants were offered vaccination at their next study visit, which was at either month 30 or 36, so as not to delay vaccine receipt. Participants provided a final analysis cervical swab before vaccination. Participants in the meningococcal group received the nonavalent HPV vaccine and those in the HPV vaccine groups received the meningococcal vaccine.

Laboratory methods

HPV DNA genotyping was conducted using the Anyplex II HPV28 assay (Seegene), a multiplexed type-specific real-time PCR-based assay that detects 28 HPV types[28,29] at the University of Washington (UW) East Africa STI Laboratory, Mombasa, Kenya with standard proficiency testing[30]. For HPV-positive samples, a low (+), intermediate (++), or high (+++) positivity was indicated; + or greater was considered positive. The assay runs included negative and positive controls and the housekeeping human gene, β-globin, as an internal control. Runs were performed with CFX96 Real-time PCR System (Bio-Rad).

Serum specimens were shipped to the UW and tested at the Galloway Laboratory, Fred Hutchinson Cancer Research Center. HPV IgG antibodies were detected using a multiplex Luminex assay[31,32]. The mean pre-established fluorescent intensity seropositivity cutoffs for HPV 16/18/31/33/45/52/58 were used[10].

Sexually transmitted infections (*N. gonorrhoeae, C. trachomatis* or *T. vaginalis*) were assessed by nucleic acid amplification testing (APTIMA; Hologic/GenProbe) at the UW East Africa STI Laboratory; HSV-2 was evaluated by the Focus ELISA and BV was evaluated using the Nugent score at the National Quality Control Laboratory, Nairobi, Kenya.

Outcomes

The primary trial end point was incident-persistent cervical vaccine type-specific HPV infection among participants who were vaccine-type HPV naive at enrollment. Persistent HPV infection, a surrogate marker for cervical dysplasia/precancer, was defined as high-risk vaccine-type-specific HPV (HPV 16/18 for the bivalent vaccine and HPV 16/18/31/33/45/52/58 for the nonavalent vaccine) detected at two consecutive visits after the month 3 visit, which were obtained no less than 4 months apart (with the same HPV type at both time points). Cervical swabs were tested for the primary end point; vaginal swabs were substituted if necessary. This analysis included follow-up through month 36 to evaluate the durability of VE.

Secondary analyses assessed VE in the sensitivity cohorts and subgroup analyses. The prespecified subgroups were the presence of co-infections (chlamydia, gonorrhea, HSV-2, trichomoniasis, syphilis and BV), self-reported condom use, number of self-reported lifetime sexual partners (1 versus 2+) and contraception method use.

Safety was assessed through adverse event reporting following Division of Allergy and Infectious Diseases Guidelines[33]. Participants were monitored for adverse events 30 min after vaccination, asked about adverse events at each study visit and reported adverse events

outside of study visits. The study clinical monitor followed SAEs, including permission to access medical records. SAEs were recorded on a CRF. The study Principal Investigator and clinical monitor determined the relatedness of SAEs to vaccination. We followed the KEMRI Scientific Ethics Review Unit's (SERU's) guidance for reporting SAEs.

Statistical analysis

The study was powered for the 18-month analysis, which included follow-up through 18 months and has been previously published[10]. The sample size calculations assumed a combined persistent HPV 16/18/31/33/45/52/58 annual incidence of 5%, single-dose VE of 75%, and loss-to-follow-up of 10% with a fixed follow-up time of 12 months. Sample size calculations assumed that 52% of participants would meet the requirements for inclusion in the 18-month analysis based on the observed prevalence of HPV infection in similar settings[34]. Assuming a proportional hazards model (seqDesign in R) with 80% power to detect 75% efficacy, a sample size of 2,250 participants was planned.

We used Cox proportional hazards models stratified by study site to estimate the hazard ratios (HRs) of the interventions versus control for the primary and sensitivity analyses. Models for the sensitivity analyses used crude incidence rate ratios instead of the Cox model when no events were observed in a group. Follow-up was calculated as days since the month 3 visit for the primary analysis and days since month 6 for the extended-sensitivity analysis until the first persistent infection. Participants who did not reach this outcome were censored at the last study visit with HPV testing where they did not meet the criteria for persistent infection. VE was expressed as 1 − HR (or relative risk). The log-rank test stratified by study site was used to calculate the *P* value for each comparison (one degree of freedom). Cumulative incidence curves of time to infection were calculated by intervention group using Kaplan–Meier methods. Efficacy analyses were performed on the month 36 mITT cohorts. In post hoc analysis, we evaluated the absolute difference in cumulative incidence of HPV from the Kaplan–Meier survival estimates at month 36. We calculated the rates of chlamydia and gonorrhea during follow-up by assigned group.

Participants included in the primary analysis tested HPV DNA negative (external genital/lateral vaginal, and cervical swabs) at enrollment and at month 3, by self-collected vaginal swab and HPV antibody negative at enrollment in the mITT cohort. The ITT included all randomized participants. For inclusion in the HPV 16/18 mITT cohort, participants were HPV 16/18 naive. Similarly, for the HPV 16/18/31/33/45/52/58 mITT cohort, participants were HPV 16/18/31/33/45/52/58 naive. Participants without swabs after month 3 did not contribute follow-up time in the primary analysis. Participants in the bivalent vaccine group were excluded from the HPV 16/18/31/33/45/52/58 analysis as the study was not powered to detect cross-protection. Participants who seroconverted to HIV during follow-up are included in analyses.

Sensitivity analyses were planned for the following subsets: participants who tested HPV DNA negative at enrollment and month 3, regardless of antibody status at enrollment (sensitivity cohort) and participants who tested HPV DNA negative at enrollment, month 3, and month 6 and antibody negative at enrollment (extended-sensitivity cohort); the sensitivity cohort was a less conservative definition of an HPV-naive cohort and the extended-sensitivity cohort more closely matched the analysis cohort for HPV vaccine licensure trials. The extended-sensitivity cohort excluded participants who might have had prevalent HPV infection at enrollment that was not detected. Safety was assessed among all participants; the three groups were compared using Fisher's exact test. Exploratory analysis evaluated cross-protection of the bivalent vaccine against HPV 31/33/45. We performed all analyses using SAS software, v.9.4 (SAS Institute) and R (v.4.2.2).

An independent Data Safety and Monitoring Board was constituted to review study progress, participant safety and the primary outcome, and met annually. The trial is registered at ClinicalTrials.gov (NCT03675256).

Ethics and inclusion statement

Data for this study, including from Kenya, were collected via eCRFs in Kenya. Seven colleagues (M.A.O., E.A.B., B.N., I.W., C.B., S.K. and N.R.M.), including the senior author (N.R.M.) are from Kenya, a low-and-middle-income country and one other (R.V.B.) is South African and is now based in a high-income country. We fully endorse and are committed to the Nature Portfolio journals' guidance on low-and-middle-income country authorship and inclusion.

This research is locally relevant to Kenya and other countries that have not achieved the 90% HPV vaccine coverage goal.

The KEMRI SERU (nos. 3745 and 3741) and the Massachusetts General Hospital Institutional Review Board (no. 2022P001178) approved the study. Study participation may have carried stigmatization associated with vaccination. The data collection and analysis techniques employed raised no risks pertaining to incrimination, discrimination, animal welfare, the environment, health, safety, security or other personal risks. All HPV and STI testing was conducted at local laboratories. Serum for specialized HPV antibody testing was shipped to Seattle for testing. No cultural artifacts or associated traditional knowledge has been transferred out of any country. In preparing the manuscript, the authors reviewed relevant studies from Kenya.

Reporting summary

Further information on research design is available in the Nature Portfolio Reporting Summary linked to this article.

Data availability

Data are available subject to controlled access because additional analysis requires regulatory approval. This study was conducted with approval from the KEMRI SERU, which requires that data from studies (including de-identified data) are released only after SERU has provided written approval for additional analyses. To request these data and facilitate submission to SERU for additional analyses, please contact the KEN SHE Scientific Committee at lnakatsuka@partners.org. A complete de-identified dataset and code book sufficient to reproduce the study findings will be made available 1 year after study closeout upon written request after approval from SERU.

Code availability

The custom code and code book sufficient to reproduce the study findings will be made available 1 year after study closeout upon written request after approval from the KEN SHE Scientific Committee. Please contact the KEN SHE Scientific Committee at lnakatsuka@partners.org.

References

28. Jung, S., Lee, B., Lee, K. N., Kim, Y. & Oh, E. J. Clinical validation of Anyplex II HPV HR detection test for cervical cancer screening in Korea. *Arch. Pathol. Lab. Med.* **140**, 276–280 (2016).
29. Hesselink, A. T. et al. Clinical validation of the HPV-risk assay, a novel real-time PCR assay for detection of high-risk human papillomavirus DNA by targeting the E7 region. *J. Clin. Microbiol.* **52**, 890–896 (2014).
30. Eklund, C., Forslund, O., Wallin, K. L. & Dillner, J. Continuing global improvement in human papillomavirus DNA genotyping services: the 2013 and 2014 HPV LabNet international proficiency studies. *J. Clin. Virol.* **101**, 74–85 (2018).
31. Rowhani-Rahbar, A. et al. Antibody responses in oral fluid after administration of prophylactic human papillomavirus vaccines. *J. Infect. Dis.* **200**, 1452–1455 (2009).
32. Waterboer, T. et al. Multiplex human papillomavirus serology based on in situ-purified glutathione s-transferase fusion proteins. *Clin. Chem.* **51**, 1845–1853 (2005).
33. RSC. *DAIDS Adverse Event Grading Tables* rsc.niaid.nih.gov/clinical-research-sites/daids-adverse-event-grading-tables (2018).

34. Watson-Jones, D. et al. High prevalence and incidence of human papillomavirus in a cohort of healthy young African female subjects. *Sex. Transm. Infect.* **89**, 358–365 (2013).

Acknowledgements

We thank the adolescent girls and young women who participated in this study for their motivation and dedication, and the parents of minor participants for their support. We are grateful to the members of the trial's Data and Safety Monitoring Board (H. Weiss (Chair), L. Denny, D. Mbori-Ngacha, S. Kapiga, F. Were and F. Sawe), community advisory boards at each trial location and overseeing ethics review committees for their expertise and guidance. We thank P. Dull and R. Gulati from the Bill & Melinda Gates Foundation for their attentive oversight. We are grateful to the KEN SHE Study Team for their dedication and perseverance. The study is dedicated to K. Ramaswami (Malitha) Ramiah, S. Kanyi Mugo, R. Auma Onono, E. Muga, M. Nduta and all our mothers.
The Bill & Melinda Gates Foundation (INV-010402) and the Francis and Dorothea Reed Endowed Chair in Infectious Diseases (R.V.B.) funded the KEN SHE Study. The content is solely the authors' responsibility and does not necessarily represent the views, decisions or policies of the institutions with which they are affiliated or the KEN SHE Study funders. The funder of the study had no role in study design, data collection, data analysis, data interpretation or writing of the report.

Author contributions

The list of KEN SHE Team members at the end of the paper is in alphabetical order for each institution. R.V.B., D.D., E.R.B., N.R.M. and J.M.B. designed the trial. K.B.H. and T.T.S. performed the data analyses. M.A.O., R.V.B. and N.R.M. oversaw the study operations. All authors (R.V.B., E.R.B., M.A.O., E.A.B., B.N., R.L.W., D.A.G., L.F.P., D.D., I.W., C.B., S.K., K.B.H., D.G.K., D.P., S.M., E.R., S.C., T.T.S., R.S.M., C.C., J.M.B. and N.R.M.) contributed equally to the interpretation of results. R.V.B. wrote the first draft of the manuscript. All authors contributed equally to the execution of the trial and critically reviewed and approved the finalized manuscript.

Competing interests

R.V.B. reports that Regeneron Pharmaceuticals covered the cost of the abstract and manuscript writing, outside the submitted work. She serves on a Gilead Sciences Data Monitoring Committee for which she receives an honorarium, outside the submitted work. J.M.B. reports personal fees from Gilead Sciences, Janssen and Merck, outside the submitted work; and is an employee of Gilead Sciences, outside of the submitted work. C.C. reports personal fees from Gilead Sciences and Merck, outside the submitted work. N.M. reports grant support from Merck Pharmaceuticals, outside the submitted work. D.A.G. reports personal fees from Merck, outside the submitted work. E.A.B. reports personal fees from Gilead Sciences, Merck and ViiV, outside the submitted work. R.S.M. reports personal fees from Lupin Pharmaceuticals and donated testing STI testing supplies from Hologic Corporation, outside of the submitted work. All other coauthors (M.A.O., B.N., R.L.W., D.A.G., L.F.P., D.D., I.W., C.B., S.K., K.B.H., D.G.K., D.P., S.M., E.R., S.C. and T.T.S.) have nothing to disclose.

Additional information

Extended data is available for this paper at https://doi.org/10.1038/s41591-023-02658-0.

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41591-023-02658-0.

Correspondence and requests for materials should be addressed to Ruanne V. Barnabas.

Peer review information *Nature Medicine* thanks Filipe Colaço Mariz, Mohammad Chehrazi, Richard Muwonge, and the other, anonymous, reviewer(s) for their contribution to the peer review of this work. Primary Handling Editor: Ming Yang, in collaboration with the *Nature Medicine* team.

https://doi.org/10.1038/s41591-023-02658-0

Extended Data Table. 1 | Baseline characteristics of the ITT population

Characteristic	Category	Nonavalent HPV (N=758)	Bivalent HPV (N=760)	Control (N=757)	All (N=2275)
Age group (years)	15-17	453 (59.8%)	424 (55.8%)	424 (56.0%)	1301 (57.2%)
	18-20	305 (40.2%)	336 (44.2%)	333 (44.0%)	974 (42.8%)
Age (years)	Median (IQR)	17 (16, 18)	17 (16, 19)	17 (16, 19)	17 (16, 19)
Marital status	Never married	728 (96.0%)	713 (93.8%)	712 (94.1%)	2153 (94.6%)
	Married	25 (3.3%)	39 (5.1%)	32 (4.2%)	96 (4.2%)
	Previously Married	4 (0.5%)	6 (0.8%)	13 (1.7%)	23 (1.0%)
	Other	1 (0.1%)	2 (0.3%)	0 (0.0%)	3 (0.1%)
Education (highest level)	No schooling	1 (0.1%)	3 (0.4%)	3 (0.4%)	7 (0.3%)
	Primary school, some or complete	52 (6.9%)	47 (6.2%)	61 (8.1%)	160 (7.0%)
	Secondary school, some or complete	553 (73.0%)	551 (72.5%)	550 (72.7%)	1654 (72.7%)
	Post-secondary school	152 (20.1%)	159 (20.9%)	143 (18.9%)	454 (20.0%)
Earns an income of her own	No	665 (87.7%)	653 (85.9%)	656 (86.7%)	1974 (86.8%)
	Yes	93 (12.3%)	107 (14.1%)	101 (13.3%)	301 (13.2%)
Has a current main or steady sexual partner	No	209 (27.6%)	222 (29.2%)	211 (27.9%)	642 (28.2%)
	Yes	549 (72.4%)	538 (70.8%)	546 (72.1%)	1633 (71.8%)
Age when first had vaginal intercourse (years)	<15	190 (25.1%)	180 (23.7%)	170 (22.5%)	540 (23.7%)
	15-17	397 (52.4%)	415 (54.6%)	445 (58.8%)	1257 (55.3%)
	>=18	148 (19.5%)	155 (20.4%)	130 (17.2%)	433 (19.0%)
	Don't remember	23 (3.0%)	10 (1.3%)	12 (1.6%)	45 (2.0%)
Number of lifetime sexual partners	1	464 (61.2%)	484 (63.7%)	444 (58.7%)	1392 (61.2%)
	2	195 (25.7%)	176 (23.2%)	194 (25.6%)	565 (24.8%)
	>=3	99 (13.1%)	100 (13.2%)	119 (15.7%)	318 (14.0%)
Condom use with last vaginal sex	No	239 (31.5%)	244 (32.1%)	233 (30.8%)	716 (31.5%)
	Yes	358 (47.2%)	365 (48.0%)	367 (48.5%)	1090 (47.9%)
	No sex in past year	161 (21.2%)	151 (19.9%)	157 (20.7%)	469 (20.6%)
Syphilis	Negative	757 (99.9%)	760 (100.0%)	754 (99.6%)	2271 (99.8%)
	Positive	1 (0.1%)	0	1 (0.1%)	2 (0.1%)
	Not Done	0	0	2 (0.3%)	2 (0.1%)
C. trachomatis	Negative	665 (87.7%)	663 (87.2%)	651 (86.0%)	1979 (87.0%)
	Positive	93 (12.3%)	97 (12.8%)	106 (14.0%)	296 (13.0%)
N. gonorrhoeae	Negative	745 (98.3%)	738 (97.1%)	741 (97.9%)	2224 (97.8%)
	Positive	13 (1.7%)	22 (2.9%)	16 (2.1%)	51 (2.2%)
HSV-2	Negative	616 (81.3%)	597 (78.6%)	584 (77.1%)	1797 (79.0%)
	Positive	141 (18.6%)	162 (21.3%)	173 (22.9%)	476 (20.9%)
	Indeterminate	1 (0.1%)	1 (0.1%)	0	2 (0.1%)
Bacterial vaginosis[a]	Negative	604 (79.7%)	576 (75.8%)	587 (77.5%)	1767 (77.7%)
	Positive	154 (20.3%)	183 (24.1%)	170 (22.5%)	507 (22.3%)
	Not Done	0	1 (0.1%)	0	1 (0.0%)
Trichomonas vaginalis	Negative	723 (95.4%)	728 (95.8%)	722 (95.4%)	2173 (95.5%)
	Positive	35 (4.6%)	32 (4.2%)	35 (4.6%)	102 (4.5%)
HPV DNA 16/18[b]	Positive	112 (14.8%)	124 (16.3%)	131 (17.3%)	367 (16.1%)
HPV DNA 16/18/31/33/45/52/58[b]	Positive	242 (31.9%)	257 (33.8%)	261 (34.5%)	760 (33.4%)
HPV 16/18 Serum Antibodies	Positive	108 (14.3%)	104 (13.7%)	114 (15.1%)	326 (14.3%)
HPV 16/18/31/33/45/52/58 Serum Antibodies	Positive	212 (28.0%)	212 (27.9%)	221 (29.2%)	645 (28.4%)

[a]Nugent scores 7-10 were classified as BV positive and Nugent score 0-6 were classified as BV negative.

[b]Includes any positive from enrollment cervical or external vaginal swabs.

https://doi.org/10.1038/s41591-023-02658-0

Extended Data Table. 2 | Completeness of end point swab collection

	Swab 1 (Month 6)		Swab 2 (Month 12)		Swab 3 (Month 18)		Swab 4 (Month 24)		Swab 5 (Month 30 or Crossover)		Swab 6 (Month 36 or Crossover)	
	Expected (n)[b]	Completed, n (%)	Expected (n)[b]	Completed, n (%)	Expected (n)[b]	Completed, n (%)	Expected (n)[b]	Completed, n (%)	Expected (n)[b]	Completed, n (%)	Expected (n)[b]	Completed, n (%)
ITT Cohort												
Nonavalent HPV	758	750 (98.9%)	758	747 (98.5%)	758	740 (97.6%)	758	728 (96.0%)	757	679 (89.7%)	418	412 (98.6%)
Bivalent HPV	760	756 (99.5%)	760	751 (98.8%)	760	748 (98.4%)	760	727 (95.7%)	760	691 (90.9%)	428	417 (97.4%)
Control	757	750 (99.1%)	757	748 (98.8%)	757	741 (97.9%)	756	727 (96.2%)	755	691 (91.5%)	413	406 (98.3%)
All	2275	2256 (99.2%)	2275	2246 (98.7%)	2275	2229 (98.0%)	2274	2182 (96.0%)	2272	2061 (90.7%)	1259	1235 (98.1%)
HPV 16/18 mITT Cohort												
Nonavalent HPV	496	496 (100.0%)	496	495 (99.8%)	496	491 (99.0%)	496	487 (98.2%)	496	462 (93.1%)	305	301 (98.7%)
Bivalent HPV	489	489 (100.0%)	489	487 (99.6%)	489	484 (99.0%)	489	479 (98.0%)	489	465 (95.1%)	306	299 (97.7%)
Control	473	473 (100.0%)	473	472 (99.8%)	473	467 (98.7%)	472	459 (97.2%)	471	441 (93.6%)	271	268 (98.9%)
All	1458	1458 (100.0%)	1458	1454 (99.7%)	1458	1442 (98.9%)	1457	1425 (97.8%)	1456	1368 (94.0%)	882	868 (98.4%)
HPV 16/18/31/33/45/52/58 mITT Cohort												
Nonavalent HPV	325	325 (100.0%)	325	325 (100.0%)	325	323 (99.4%)	325	321 (98.8%)	325	306 (94.2%)	217	215 (99.1%)
Control	290	290 (100.0%)	290	289 (99.7%)	290	287 (99.0%)	290	282 (97.2%)	290	273 (94.1%)	169	167 (98.8%)
All	615	615 (100.0%)	615	614 (99.8%)	615	610 (99.2%)	615	603 (98.0%)	615	579 (94.1%)	386	382 (99.0%)

[b]Endpoint swabs defined as post-Month 3 cervical or self-collected vaginal swabs at least 4 months apart. Swabs 1 through 5 are expected for all non-deceased participants. Swab 6 is counted as expected if collected or if a participant with 5 swabs has not yet had a crossover visit and the swab target date has passed.

NOTE: Of the participants in the HPV 16/18 mITT cohort who only provided one endpoint swab (n=4), 0 were positive for HPV 16/18. Of the participants in the HPV 16/18/31/33/45/52/58 mITT cohort who only provided one endpoint swab (n=1), 0 were positive for HPV 16/18/31/33/45/52/58. HPV persistence using two consecutive swabs was evaluable for the remainder of the cohorts.

https://doi.org/10.1038/s41591-023-02658-0

Extended Data Table. 3 | Summary of tested end point swabs and swab collection types

Analysis Cohort	Total Endpoint Swabs (n)	Cervical Swabs (n)	%	Self-Collected Swabs (n)	%
ITT	12208	11369	93.1%	839	6.87%
HPV 16/18 mITT	8013	7523	93.9%	490	6.12%
HPV 16/18/31/33/45/52/58 mITT	3402	3219	94.6%	183	5.38%

NOTE: Endpoint swabs defined as post-Month 3 cervical vaginal or self-collected vaginal swabs at least 4 months apart.

https://doi.org/10.1038/s41591-023-02658-0

Extended Data Table. 4 | Exploratory analysis: incidence of persistent HPV types (combined non-vaccine types, mITT sensitivity cohort)

Randomized Group	Enrolled (n)	HPV non-Vaccine Type-naïve (mITT) (n)	Incident persistent HPV (n)	Woman-years of Follow-up[b]	Incidence of persistent HPV per 100 Woman-years	95% Confidence Interval[a]	
						Lower Bound	Upper Bound
Nonavalent HPV	758	247	110	442.3	24.9	20.4	30.0
Bivalent HPV	760	241	111	429.5	25.8	21.3	31.1
Control	757	250	101	459.3	22.0	17.9	26.7
All	2275	738	322	1331.2	24.2	21.6	27.0

[a]Exact 95% confidence interval for incidence rate computed using the Poisson distribution.

[b]Follow-up time amongst women non-vaccine HPV-type DNA negative at month 0 and month 3 (women are excluded if positive at month 0 or month 3 for any of HPV 26/35/39/40/42/43/44/51/53/54/56/59/61/66/68/69/70/73/82)

https://doi.org/10.1038/s41591-023-02658-0

Extended Data Table. 5 | Summary of follow-up laboratory results by randomized group (mITT cohorts)

		C. trachomatis			N. gonorrhoeae		
Randomized Group	Enrolled (n)	Positive test results for chlamydia (n)[a]	Participants with one or more positive test results for chlamydia (n)	%	Positive test results for gonorrhea (n)[a]	Participants with one or more positive test results for gonorrhea (n)	%
HPV 16/18 mITT Cohort							
Nonavalent HPV	496	185	137	27.6%	55	47	9.5%
Bivalent HPV	489	196	158	32.3%	57	50	10.2%
Control	473	185	134	28.3%	57	49	10.4%
All	1458	566	429	29.4%	169	146	10.0%
HPV 16/18/31/33/45/52/58 mITT Cohort							
Nonavalent HPV	325	128	97	29.8%	35	32	9.8%
Control	290	104	77	26.6%	33	28	9.7%
All	615	232	174	28.3%	68	60	9.8%

[a]Includes testing at six monthly follow-up visits completed within visit window with non-missing HPV DNA swabs.

https://doi.org/10.1038/s41591-023-02658-0

Extended Data Table. 6 | Incidence of persistent HPV 16/18 and vaccine efficacy overall and within subgroups defined by lab results or self-reported behavior at enrollment (mITT cohort)

	Nonavalent HPV			Bivalent HPV			Control			Nonavalent HPV v. Control		Bivalent HPV v. Control	
	HPV 16/18 naïve	N events	Rate[a]	HPV 16/18 naïve	N events	Rate[a]	HPV 16/18 naïve	N events	Rate[a]	VE (95% CI)	p-value	VE (95% CI)	p-value
Overall	496	1	0.08	489	2	0.16	473	72	6.7	98.8% (91.3% - 99.8%)	<0.0001	97.5% (90.0%-99.4%)	<0.0001
Syphilis													
Negative	496	1	0.08	489	2	0.16	471	72	6.73	98.8% (91.2%-99.8%)	<0.0001	97.6% (89.9%-99.4%)	<0.0001
Positive	0	0	NC	0	0	NC	1	0	0	NC	NC	NC	NC
Chlamydia trachomatis													
Negative	438	1	0.09	434	1	0.09	413	58	6.13	98.5% (89.0%-99.8%)	<0.0001	98.5% (88.8%-99.8%)	<0.0001
Positive	58	0	0	55	1	0.71	60	14	10.8	100% (NC)	0.0001	93.5% (48.2%-99.2%)	0.0026
Neisseria gonorrhoeae													
Negative	488	1	0.08	480	2	0.16	466	70	6.6	98.8% (90.8%-99.8%)	<0.0001	97.5% (89.5%-99.4%)	<0.0001
Positive	8	0	0	9	0	0	7	2	13.4	100% (NC)	0.153	100% (NC)	0.128
HSV-2													
Negative	407	0	0	387	1	0.1	375	60	7.11	100% (NC)	<0.0001	98.6% (89.2%-99.8%)	<0.0001
Positive	88	1	0.46	102	1	0.38	98	12	5.2	91.2% (29.6% - 98.9%)	0.0017	92.7% (41.3% - 99.1%)	0.0005
Bacterial vaginosis[b]													
Negative	415	1	0.1	378	2	0.21	378	55	6.38	98.5% (88.8% - 99.8%)	<0.0001	96.7% (86.1% - 99.2%)	<0.0001
Positive	81	0	0	111	0	0	95	17	7.97	100% (NC)	<0.0001	100% (NC)	<0.0001
Trichomonas vaginalis													
Negative	477	1	0.08	468	1	0.08	452	66	6.39	98.7% (90.3%-99.8%)	<0.0001	98.7% (90.1% - 99.8%)	<0.0001
Positive	19	0	0	21	1	1.89	21	6	14.1	100% (NC)	0.0112	86.5% (-16.8% - 98.5%)	0.0603
Number of lifetime partners													
1	322	0	0	332	1	0.12	289	41	6.26	100% (NC)	<0.0001	98.1% (85.6%-99.8%)	<0.0001
2+	174	1	0.23	157	1	0.25	184	31	7.38	96.9% (76.7%-99.6%)	<0.0001	96.6% (74.1%-99.6%)	<0.0001
Condom use with last vaginal sex													
No	153	0	0	155	1	0.26	140	19	6.04	100% (NC)	<0.0001	95.8% (67.1%-99.5%)	<0.0001
Yes, or no sex in past year	343	1	0.12	334	1	0.12	333	53	6.97	98.4% (87.6%-99.8%)	<0.0001	98.3% (87.2%-99.8%)	<0.0001
Hormonal contraceptive use													
None	415	1	0.09	399	1	0.1	383	58	6.7	98.6% (89.3%-99.8%)	<0.0001	98.5% (88.8%-99.8%)	<0.0001
Any hormonal contraceptive method in the past month	81	0	0	90	1	0.43	90	14	6.69	100% (NC)	<0.0001	93.6% (49.6%-99.2%)	0.0002

[a] Per 100 woman-years

[b] Nugent scores 7-10 were classified as BV positive and Nugent score 0-6 were classified as BV negative.

Subgroups are defined by lab results or self-reported behavior at the enrollment visit. No adjustments for multiplicity were done. Two-sided log-rank p-values are computed for each comparison using the log-rank test.

https://doi.org/10.1038/s41591-023-02658-0

Extended Data Table. 7 | Incidence of persistent HPV 16/18/31/33/45/52/58 and vaccine efficacy overall and within subgroups defined by lab results or self-reported behavior at enrollment (mITT cohort)

	Nonavalent HPV			Control			Nonavalent HPV v. Control	
	HPV 16/18/31/33/45/52/58 naïve	N events	Rate[a]	HPV 16/18/31/33/45/52/58 naïve	N events	Rate[a]	VE (95% CI)	p-value
Overall	325	5	0.61	290	84	13.8	95.5% (89.0%-98.2%)	<0.0001
Syphilis								
Negative	325	5	0.61	289	84	13.8	95.6% (89.0%-98.3%)	<0.0001
Positive	0	0	NC	1	0	0	NC	NC
Chlamydia trachomatis								
Negative	293	4	0.54	252	71	13.2	95.9% (88.7%-98.5%)	<0.0001
Positive	32	1	1.27	38	13	17.9	92.7% (43.9%-99.0%)	0.0009
Neisseria gonorrhoeae								
Negative	322	5	0.61	285	82	13.7	95.5% (88.7%-98.2%)	<0.0001
Positive	3	0	0	5	2	18.8	100% (NC)	0.445
HSV-2								
Negative	264	3	0.45	226	66	14	96.7% (89.6%-99.0%)	<0.0001
Positive	60	2	1.34	64	18	12.9	89.7% (55.3%-97.6%)	0.0002
Bacterial vaginosis[b]								
Negative	278	4	0.57	239	70	13.9	95.9% (88.8% - 98.5%)	<0.0001
Positive	47	1	0.83	51	14	13	93.5% (50.2% - 99.1%)	0.0003
Trichomonas vaginalis								
Negative	315	5	0.63	275	78	13.4	95.3% (88.2%-98.1%)	<0.0001
Positive	10	0	0	15	6	20.1	100% (NC)	0.0289
Number of lifetime partners								
1	217	1	0.18	184	51	13.2	98.6% (89.8% - 99.8%)	<0.0001
2+	108	4	1.49	106	33	14.8	89.9% (71.5% - 96.4%)	<0.0001
Condom use with last vaginal sex								
No	98	2	0.81	78	20	12.2	93.3% (71.3%-98.4%)	<0.0001
Yes, or no sex in past year	227	3	0.52	212	64	14.3	96.3% (88.3%-99.0%)	<0.0001
Hormonal contraceptive use								
None	273	3	0.43	229	68	14.2	96.9% (90.1%-99.0%)	<0.0001
Any hormonal contraceptive method in the past month	52	2	1.51	61	16	12	88.3% (48.5%-97.3%)	0.0003

[a] Per 100 woman-years

[b] Nugent scores 7-10 were classified as BV positive and Nugent score 0-6 were classified as BV negative.

Subgroups are defined by lab results or self-reported behavior at the enrollment visit. No adjustments for multiplicity were done. Two-sided log-rank p-values are computed for each comparison using the log-rank test.

https://doi.org/10.1038/s41591-023-02658-0

Extended Data Table. 8 | Exploratory analysis: Incidence of persistent HPV 31/33/45 (HPV 31/33/45 mITT cohort)

Randomized Group	Enrolled (n)	HPV 31/33/45 naive (mITT) (n)	Incident persistent HPV 31/33/45 (n)	Woman-years of Follow-up[b]	Incidence of persistent HPV 31/33/45 per 100 Woman-years	95% Confidence Interval[a]		Statistical Comparisons[c]			
						Lower Bound	Upper Bound	Comparison	Vaccine Efficacy	95% CI	P-value (Log-rank)
Nonavalent HPV	758	530	4	1333.5	0.3	0.08	0.77	Nonavalent v. Control	91.48%	(76.29% , 96.94%)	<.0001
Bivalent HPV	760	516	39	1240.4	3.14	2.24	4.3	Bivalent v. Control	10.11%	(-38.67%, 41.74%)	0.6338
Control	757	506	43	1212.4	3.55	2.57	4.78				
All	2275	1552	86	3786.4	2.27	1.82	2.81				

[a]Exact 95% confidence interval for incidence rate computed using the Poisson distribution.

[b]Follow-up time amongst women HPV 31/33/45 DNA-naive at month 0 and month 3, and antibody-naive at month 0.

Two-sided log-rank p-values are computed for each comparison using the log-rank test. No adjustments for multiplicity were done.

nature portfolio

Corresponding author(s): Dr. Ruanne Barnabas

Last updated by author(s): Apr 27, 2023

Reporting Summary

Nature Portfolio wishes to improve the reproducibility of the work that we publish. This form provides structure for consistency and transparency in reporting. For further information on Nature Portfolio policies, see our Editorial Policies and the Editorial Policy Checklist.

Statistics

For all statistical analyses, confirm that the following items are present in the figure legend, table legend, main text, or Methods section.

n/a	Confirmed	
☐	☒	The exact sample size (*n*) for each experimental group/condition, given as a discrete number and unit of measurement
☐	☒	A statement on whether measurements were taken from distinct samples or whether the same sample was measured repeatedly
☐	☒	The statistical test(s) used AND whether they are one- or two-sided *Only common tests should be described solely by name; describe more complex techniques in the Methods section.*
☐	☒	A description of all covariates tested
☐	☒	A description of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons
☐	☒	A full description of the statistical parameters including central tendency (e.g. means) or other basic estimates (e.g. regression coefficient) AND variation (e.g. standard deviation) or associated estimates of uncertainty (e.g. confidence intervals)
☐	☒	For null hypothesis testing, the test statistic (e.g. *F*, *t*, *r*) with confidence intervals, effect sizes, degrees of freedom and *P* value noted *Give P values as exact values whenever suitable.*
☒	☐	For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings
☒	☐	For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes
☐	☒	Estimates of effect sizes (e.g. Cohen's *d*, Pearson's *r*), indicating how they were calculated

Our web collection on statistics for biologists contains articles on many of the points above.

Software and code

Policy information about availability of computer code

Data collection	Electronic case report forms (eCRFs) in DFExplore (DF/Net Research, Inc. ©, Seattle, WA, US)
Data analysis	SAS software, version 9.4 (SAS Institute, North Carolina, US) and R (version 4.2.2)

For manuscripts utilizing custom algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors and reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Portfolio guidelines for submitting code & software for further information.

Data

Policy information about availability of data

All manuscripts must include a data availability statement. This statement should provide the following information, where applicable:

- Accession codes, unique identifiers, or web links for publicly available datasets
- A description of any restrictions on data availability
- For clinical datasets or third party data, please ensure that the statement adheres to our policy

Data availability: Data is available subject to controlled access because additional analyses requires regulatory approval. This study was conducted with approval from the Kenya Medical Research Institute (KEMRI) Scientific and Ethics Review Unit (SERU), which requires that data from studies (including de-identified data) are released only after SERU has provided written approval for additional analyses. To request these data and facilitate submission to SERU for additional analyses, please contact the KEN SHE Scientific Committee at lnakatsuka@partners.org.

Code availability: A complete de-identified dataset and code book sufficient to reproduce the study findings will be made available one year after study closeout upon written request after approval from SERU. The custom code and code book sufficient to reproduce the study findings will be made available one year after study closeout upone written request after approval from the KEN SHE Scientific Committee. Please contact the KEN SHE Scientific Committee at lnakatsuka@partners.org.

Research involving human participants, their data, or biological material

Policy information about studies with human participants or human data. See also policy information about sex, gender (identity/presentation), and sexual orientation and race, ethnicity and racism.

Reporting on sex and gender	Self-reported female sex at birth was an inclusion criterion for KEN SHE study enrollment. The KEN SHE study findings pertain to individuals with female sex at birth only.
Reporting on race, ethnicity, or other socially relevant groupings	The KEN SHE study did not collect data on race, ethnicity, or other social groupings. In this manuscript, minimal self-reported socioeconomic data (highest level of schooling and whether a participant earns an income on her own) is used to demonstrate successful randomization and balance of the randomized groups.
Population characteristics	KEN SHE participants are young women, age 15-20, living in proximity to one of the three KEN SHE study sites in Thika, Nairobi, or Kisumu, Kenya. At the time of enrollment, participants had 1 to 5 lifetime sexual partners (inclusive), no history of previous HPV vaccination, and negative pregnancy and HIV rapid test results.
Recruitment	Participants were recruited through community outreach programs, which limits bias associated with facility-based recruitment but this is not a formal general population sample.
Ethics oversight	The Kenya Medical Research Institute (KEMRI) Scientific Ethics Review Unit (SERU) and Massachusetts General Hospital Institutional Review Board (MGH IRB) reviewed and approved the study protocol.

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Field-specific reporting

Please select the one below that is the best fit for your research. If you are not sure, read the appropriate sections before making your selection.

☒ Life sciences ☐ Behavioural & social sciences ☐ Ecological, evolutionary & environmental sciences

For a reference copy of the document with all sections, see nature.com/documents/nr-reporting-summary-flat.pdf

Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size	The sample size calculations also assumed a combined persistent HPV 16/18/31/33/45/52/58 annual incidence of 5%, single-dose vaccine efficacy of 75%, and loss-to-follow-up of 10% with a fixed follow-up time of 12 months. Sample size calculations assumed that 52% of participants would meet the requirements for inclusion in the primary analysis based on the observed prevalence of HPV infection in similar settings. Assuming a proportional hazards model (seqDesign in R) with 80% power to detect 75% efficacy, a sample size of 2,250 participants was planned.
Data exclusions	As pre-established in the statistical analysis plan, the primary analysis is conducted within the mITT cohorts for HPV 16/18 and HPV 16/18/31/33/45/52/58, which respectively exclude participants DNA- or antibody-positive at enrollment, or DNA-positive at month 3 for the HPV DNA types 16/18 or 16/18/31/33/45/52/58.
Replication	Analysis cohorts (n participants), persistent HPV (n events), incidence rates (n events/100 woman-years), vaccine efficacy (1-HR), and corresponding confidence intervals and p-values were coded independently by two analysts. All findings were replicated.
Randomization	An unblinded statistical analyst generated the randomization sequence using SAS v9.4. Randomization was stratified by site, using a fixed block size of 15 and a 1:1:1 allocation. Blinded study assignment was implemented via http://www.randomize.net (Ottawa, ON, Canada).
Blinding	Study staff, participants, investigators, clinic staff, lab technicians, the endpoints adjudication committee members, and other study team members did not have access to the randomization codes, except for the unblinded statistical analysts and unblinded pharmacists at each site. An unblinded pharmacist entered the participant identification number (PTID) on randomize.net, obtained the next sequential intervention assignment, recorded the PTID and randomization identifier on an eCRF, drew up the vaccine in a masked syringe, and administered the vaccination via the intramuscular route. An independent observer, not on the study team, observed the masked vaccination to assess the success of masking.

Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

Materials & experimental systems

n/a	Involved in the study
☒	☐ Antibodies
☒	☐ Eukaryotic cell lines
☒	☐ Palaeontology and archaeology
☒	☐ Animals and other organisms
☐	☒ Clinical data
☒	☐ Dual use research of concern
☒	☐ Plants

Methods

n/a	Involved in the study
☒	☐ ChIP-seq
☒	☐ Flow cytometry
☒	☐ MRI-based neuroimaging

Clinical data

Policy information about clinical studies

All manuscripts should comply with the ICMJE guidelines for publication of clinical research and a completed CONSORT checklist must be included with all submissions.

Clinical trial registration	NCT03675256
Study protocol	The trial protocol paper has been published and the full protocol is available upon request lnakatsuka@partners.org.
Data collection	Study recruitment and enrollment occurred between December 20, 2018 and November 15, 2019, at three study sites in Thika, Nairobi, and Kisumu, Kenya. Data collected between December 20, 2018 and January 9, 2023 are reported in this manuscript. The study was conducted at three Kenya Medical Research Institute (KEMRI) clinical sites in Kisumu, Thika, and Nairobi.
Outcomes	The primary trial endpoint was incident persistent vaccine type-specific HPV infection in cervical and self-collected (when necessary) swabs collected at least four months apart. HPV DNA genotyping was conducted using the Anyplex II HPV28 assay (Seegene, Seoul, South Korea). Secondary analyses assessed vaccine efficacy in the sensitivity cohorts and subgroup analyses. The pre-specified subgroups were the presence of co-infections (chlamydia, gonorrhea, herpes simplex type 2, trichomoniasis, syphilis, and bacterial vaginosis), self-reported condom use, number of self-reported sex partners in the last three months (0-1 vs. 2+), and contraception method use.