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HPV serostatus pre- and post-vaccination in a randomized phase II preparedness trial among young Western Cape, South African women: The evri trial

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ABSTRACT

Background: HPV antibodies are a marker of past exposure to the virus. Our objective was to assess HPV serostatus pre- and post-vaccination among HIV-negative women.
Methods: Women aged 16–24 years old were randomized in a placebo controlled trial utilizing the 4-valent HPV (4vHPV) vaccine (NCT01489527, clinicaltrials.gov). Participants (n=389) received the 4vHPV vaccine or placebo following a three dose schedule. Sera were collected at Day 1 and Month 7 for assessment of HPV 6, 11, 16, and 18 neutralizing antibody levels using a multiplex competitive Luminex immunoassay (Merck) based on detecting the L1 capsid antigen for each HPV type.
Results: Seroprevalence was 73% for HPV6, 47% for HPV11, 33% for HPV16, and 44% for HPV18. Seroprevalence for any HPV type did not significantly differ by age or lifetime number of partners. The majority of participants (64%) had two or more 4vHPV antibodies present at enrollment and 12% had antibodies to all four. Among women in the vaccine arm, those that were seropositive for HPV16 at enrollment had higher titers at month 7 compared to women that were seronegative for HPV16 at enrollment; this trend holds for the other HPV types as well. Seroconversion among baseline seronegative participants in the placebo group ranged from 5% for HPV16 to 23% for HPV6.
Conclusion: HPV seroprevalence was high in this population, emphasizing the need to vaccinate prior to sexual debut.

1. Introduction

Women and men residing in southern African countries have a high burden of human papillomavirus (HPV) infection and related cancers [1–4]. Age-standardized incidence rate for cervical cancer in Southern Africa is 31.5 per 100,000 women and the age-standardized mortality rate is 17.9 per 100,000 women [3]. Cervical cytology screening can dramatically decrease the incidence of cervical cancer. South Africa has a national policy for cervical cancer screening which has been implemented primarily in the private sector but is lacking in the state sector [5]. A small proportion of South African women are screened for cervical cancer and an even smaller portion return for treatment of lesions [5]. These low trends in cervical screening coupled with the high HIV prevalence likely explain why cervical cancer incidence is high in South Africa.

HPV is a common infection among women worldwide and is the necessary cause of cervical cancer. Once infected with HPV, the majority of individuals will naturally clear the infection through an immune response. A proportion of those individuals that clear the infection will develop a detectable L1 capsid antibody to the specific HPV genotype 9–24 months after infection [6–8]. Antibody titers detectable after a natural infection are significantly lower than the

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Table 1
Baseline characteristics of women seropositive for at least one of the 4vHPV (HPV6/11/16/18) types compared to women that were seronegative for all four HPV types.

	Seronegative (n=47), n (%)	Seropositive (n=342), n (%)	Pvalue*
Age in years			0.68
16 – 18	12 (25.5)	67 (19.6)	
19 – 21	22 (46.8)	172 (50.3)	
22 – 24	13 (27.7)	103 (30.1)	
Survey language			0.08
English	43 (91.5)	331 (96.8)	
Xhosa	2 (4.3)	2 (0.6)	
Afrikaans	2 (4.3)	9 (2.6)	
Marital status			**0.007**
Single/Widowed	41 (87.2)	332 (97.1)	
Married/Living Together	6 (12.8)	10 (2.9)	
Education			0.51
≤ Grade 7	1 (2.1)	19 (5.6)	
Grade 8–12	29 (61.7)	181 (52.9)	
Passed Grade 12	10 (21.3)	70 (20.5)	
me college/tech	7 (14.9)	72 (21.1)	
Ever been pregnant	21 (44.7)	172 (50.3)	0.54
Current birth control use			
Oral Contraceptives	1 (2.1)	13 (3.8)	0.71
IUD/Loop/Coil	1 (2.1)	1 (0.3)	0.24
Depo Provera	11 (23.4)	89 (26.0)	0.73
Condoms	6 (12.8)	88 (25.7)	0.07
Age at first vaginal sex; median (range)[a]	16.5 (14–21)	17.0 (12–21)	0.93
Lifetime no. of male sexual partners[b]			0.87
1	8 (22.2)	48 (18.3)	
2	10 (27.8)	79 (30.3)	
3+	18 (50.0)	134 (51.3)	
Ever received presents/money/drugs for sex	1 (2.1)	11 (3.2)	1.00
Diagnosis of STI through clinical test			
Gonorrhea	5 (10.6)	38 (11.1)	1.00
Chlamydia	10 (21.3)	117 (34.2)	0.10
Herpes Simplex	11 (23.4)	168 (49.1)	**0.001**
Syphilis	2 (4.3)	23 (6.7)	0.57
Cervical Cytology			0.50
Normal	43 (91.5)	300 (87.7)	
Abnormal	4 (8.5)	42 (12.3)	

* Pvalue calculated from Pearson chi-square or Fisher Exact test and Mann-Whitney tests.
[a] Sample size reduced due to errors in reporting sexual behavior: seronegative (n=36) and seropositive (n=261).
[b] Sample size reduced due to errors in reporting sexual behavior: seronegative (n=36) and seropositive (n=272).

antibody titers achieved following HPV vaccination [9] and titers among the vaccinated remain detectable year post-vaccination [10]. The licensed HPV vaccines are efficacious in preventing HPV infection and pre-malignant anal, cervical, vulvar, and vaginal lesions [10–12]. In countries without adequate cervical cancer screening programs, uptake of the vaccine could have a major public health impact given the high incidence of cervical cancer in those countries.

HPV prevalence is highest in younger women but the age trends differ by country and world region with infection remaining high through older ages in some countries [13,14]. We have previously reported a high cervical HPV prevalence of 71% among HIV-negative 16–24 year olds in Western Cape, South Africa [15]. HPV prevalence was highest in the youngest aged women (83% among age 16–17 years) and decreased with age (60% among 24 year olds) [15]. HPV incidence was also higher among 16–18 year olds compared to 22–24 year olds [16]. HPV antibodies to conformational L1 epitopes are a marker of past HPV exposure to that specific HPV type. Nested within a Phase II vaccine trial, our objective was to assess HPV seroprevalence and seroconversion among HIV-negative women.

2. Methods

The Efficacy of HPV Vaccine to Reduce HIV Infection (EVRI) Trial (NCT01489527, clinicaltrials.gov) preparedness study enrolled women residing in the Western Cape, South Africa from November 2012 to July 2013. A full description of study procedures and conduct of the trial has been published elsewhere [15]. Briefly, women aged 16–24 years that were HIV-negative and non-pregnant were randomized 1:1 in a Phase II controlled trial of Gardasil (4-valent HPV (4vHPV) vaccine) vs. placebo (saline).

This study was conducted in accordance with ethics committee review and approved by the Institutional Review Boards of The University of South Florida and Stellenbosch University. South African policies and ethics approval regarding parental permission for children to take part in research studies were followed.

All staff and study investigators were blinded to participants' vaccine status except the pharmacist dispensing the vaccine (S.K.). Vaccine was administered at enrollment, month 2, and month 6. Study participants were followed for one month after the last vaccine dose (through month 7). At the 7-month visit, individual unblinding occurred, and women randomized to the placebo group were offered the Gardasil vaccine.

At each trial visit after randomization, urine pregnancy tests and rapid HIV tests were performed. Women with positive pregnancy tests were referred to care and excluded from the study. Women with a positive rapid HIV test were retested with two different confirmatory tests. Participants with a confirmed positive HIV test after the enrollment visit were referred to care and remained on trial [17]. At the enrollment and 7-month visits, sexual history, health, and socio-demographic characteristics were assessed by a tablet-based questionnaire using a computer-assisted self-interview.

2.1. Laboratory analyses

Sexually transmitted infection (STI) testing methods for chlamydia, gonorrhea, syphilis, and HSV-2 have previously been reported [15]. For HPV analyses, DNA was extracted from cervical cell specimens using the Qiagen Media Kit and amplified by polymerase chain reaction (PCR) with the PGMY09/11 L1 consensus primer system and AmpliTaq Gold polymerase (Perkin-Elmer) [15,16]. HPV genotyping was conducted on all specimens, regardless of PCR results, using the Linear Array HPV Genotyping Test (Roche Diagnostics), which detects 37 HPV genotypes [18,19].

Sera were collected at Day 1 and Month 7 for assessment of HPV neutralizing antibody levels. Immune response was measured using a multiplex competitive Luminex immunoassay (anti-HPV-6, −11, −16, −18, −31, −33, −45, −52, and −58 cLIA; Merck) at Pharmaceutical Product Development, Inc [20]. This assay simultaneously quantitates neutralizing antibodies to nine HPV types based on the L1 capsid antigen in 50 μL of serum. Antibody levels were reported as milli-Merck units (mMU) per milliliter (mL) serum. Cut points for determination of antibody positivity for HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 were 16, 6, 12, 8, 4, 4, 3, 3, and 4 mMU/mL, respectively.

2.2. Statistical analysis

Demographic and sexual behavior characteristics at enrollment were compared between women that were seropositive for at least one of the 4vHPV types to women that were seronegative to all four types (Table 1) using Pearson chi-square or Fisher Exact test for

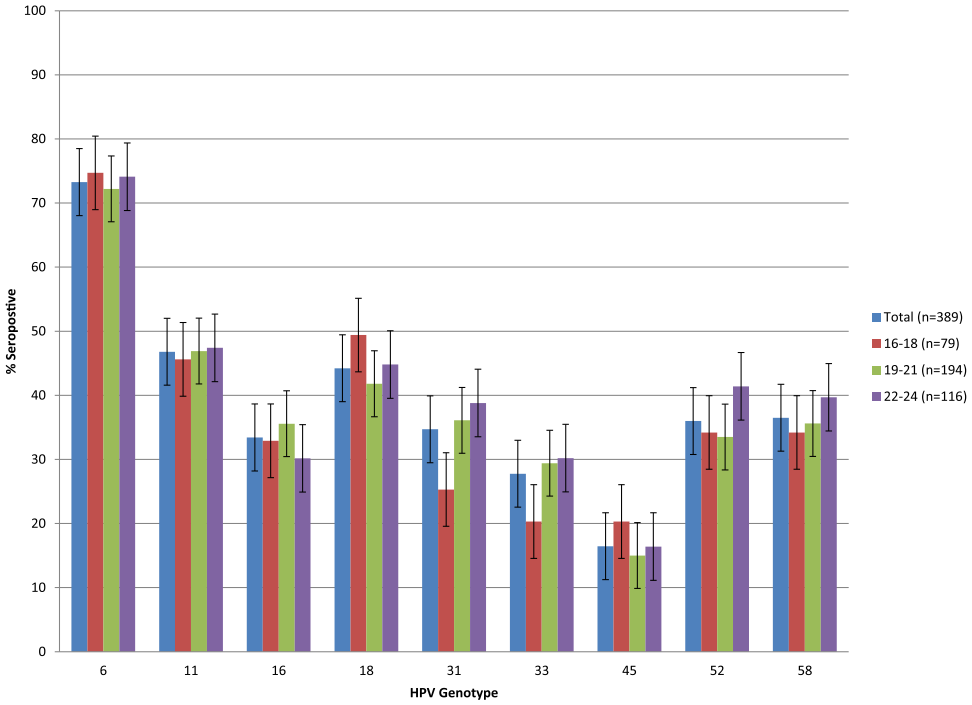


Fig. 1. The proportion of women that were seropositive for HPV at enrollment (n=389) by age category and 95% confidence intervals.

categorical variables and Mann-Whitney for continuous variables. Geometric mean titers (GMTs) and their associated 95% confidence intervals were estimated. Two vaccine populations were evaluated, the intention-to-treat population (ITT) including all women on trial, regardless of HPV DNA and antibody status at enrollment and the per-protocol (PP) immunogenicity population (women who at enrollment were both HPV seronegative and genital HPV DNA-negative for the respective vaccine type).

3. Results

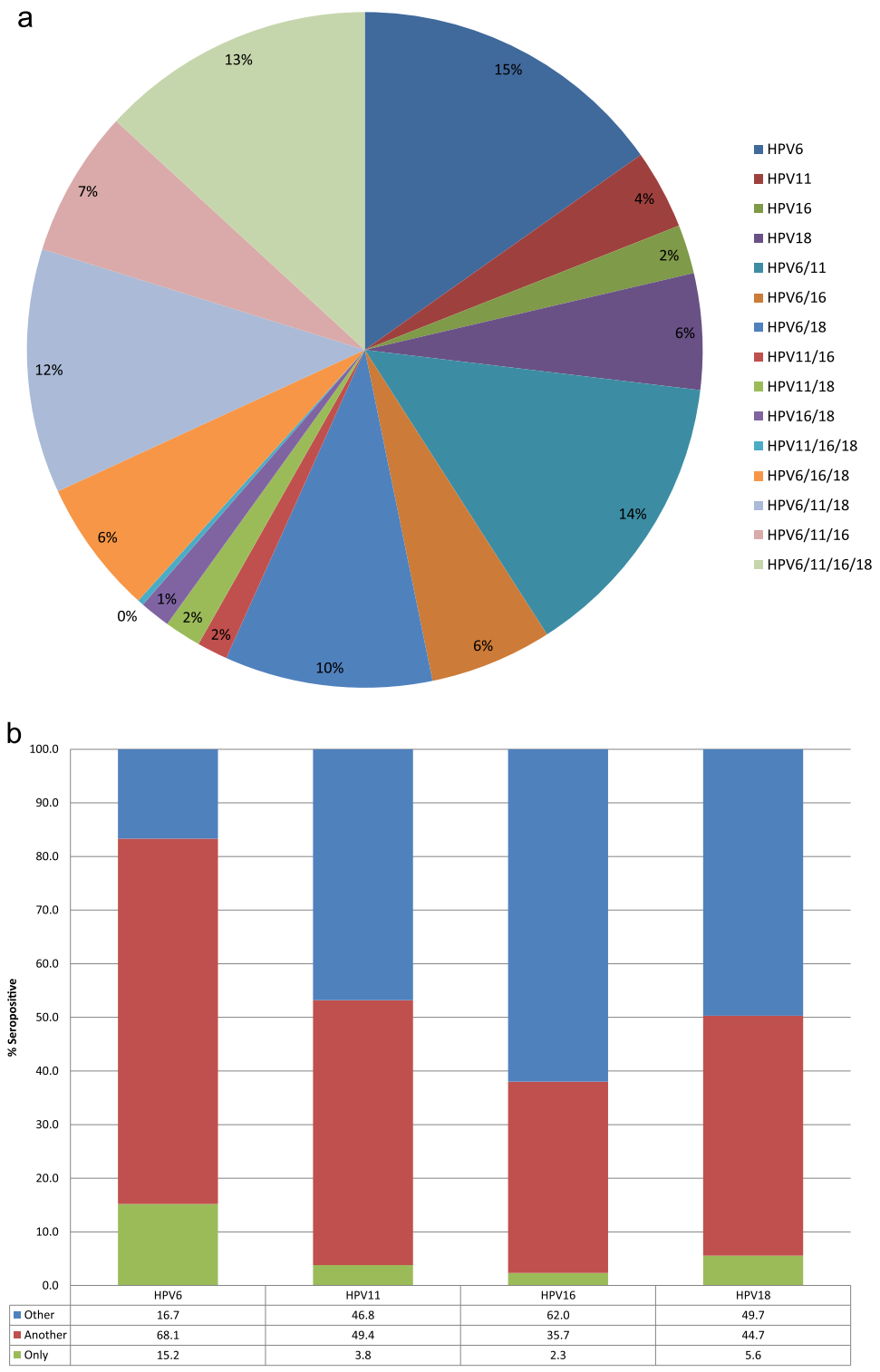
Among the 406 HIV-negative women randomized to receive the placebo or 4vHPV vaccine at enrollment, 389 had 4vHPV antibody results for all four HPV types at enrollment. Baseline demographic characteristics comparing women that were seropositive for at least one of the 4vHPV vaccine types (n=342) were compared to women that were seronegative to all 4vHPV types (n=47) (Table 1). Women that were seropositive to one or more HPV types were significantly more likely to be single/widowed (p=0.007) and seropositive for HSV-2 (p=0.001) compared to women that were seronegative to all 4vHPV types.

HPV seroprevalence was high in this cohort of young women; 73% for HPV6, 47% for HPV11, 33% for HPV16, and 44% for HPV18 (Fig. 1). Seroprevalence did not significantly differ by age (Fig. 1), age at first vaginal sex, or lifetime number of male sexual partners (data not shown). Among the 389 women, 12% (n=45) were seropositive for all four 4vHPV types, 22% (n=87) were seropositive for three of the 4vHPV types, 30% (n=118) were seropositive for two of the 4vHPV types, 24% (n=92) were seropositive for one of the 4vHPV types, and 12% (n=47) were not seropositive for any of the 4vHPV types. The different combinations of seropositivity for the 4vHPV types among women that were seropositive for at least one of the 4vHPVtypes (n=342) are shown in Fig. 2b. The most common combination of anti-HPV types occurring was HPV 6 and 11 (14%) and all four types (13%) (Fig. 2a). Among the 342 women that were seropositive to one or more of the 4vHPV types, 15% had an antibody to HPV6 only, 68% had an antibody to HPV6 and another HPV type (11, 16, or 18), and 17% did not have an antibody to HPV6 but had antibody to another HPV type (11, 16, or 18) (Fig. 2b). Anti-HPV6 seroprevalence occurred most commonly compared to the other HPV types and was most likely to occur with another anti-HPV type.

Among women in the vaccine arm, the GMTs at month 7 were significantly higher among those that were seropositive to HPV at enrollment compared to those that were seronegative for all four 4vHPV types (Table 2). Seropositivity pre- and post-vaccination by study arm in the ITT population and PP population is presented in Fig. 3 for women that had serology data at enrollment and month 7 (n=337). Seroprevalence in the ITT vaccine and placebo groups increased from enrollment to month 7 for all 4vHPV types (Fig. 3a). As we expected, 100% of the women in the PP vaccine group seroconverted to HPV 6 (n=40), 11 (n=92), 16 (n=107), and 18 (n=86) at month 7 (Fig. 3b). Women in the PP placebo group also seroconverted during the 7 months of follow-up (Fig. 3b). Among the 44 PP placebo women that were DNA negative and seronegative for HPV6 at enrollment, 22.7% (10/44) seroconverted to HPV6 by month 7 (Fig. 3b, Table 3a). Sixteen (16/81, 19.8%) women in the PP placebo group seroconverted to HPV11 and all of those women did not have detectable cervical HPV11 at month 7. Four (4/86, 4.7%) women in the PP placebo group seroconverted to HPV16 and half of those women had detectable cervical HPV16 at month 7 (Table 3b). There were no women at enrollment in the placebo arm that had a prevalent HPV 6 (n=2) and 11 (n=2) infection and were also seronegative to these types (Table 3a). Among the seventeen women in the placebo arm that were HPV16 seronegative and had a prevalent HPV16 infection at enrollment, 24% (4/17) seroconverted to HPV16 at month 7.

4. Discussion

HPV seroprevalence for any of the 4vHPV types was 88%, indicating a very young age at HPV infection and a high prevalence of HPV in



	HPV6	HPV11	HPV16	HPV18
Other	16.7	46.8	62.0	49.7
Another	68.1	49.4	35.7	44.7
Only	15.2	3.8	2.3	5.6

Fig. 2. 4vHPV seroprevalence. a. Combinations of HPV antibodies among women seropositive for at least one 4vHPV type (n=342); b. Among women that were seropositive for one or more of the 4vHPV types (n=342), the proportion of women for each HPV type that were "only" seropositive for that HPV type, or seropositive for that HPV type and seropositive for "another," or not seropositive for that HPV type "other".

the underlying community. The majority of the participants (64%) had two or more 4vHPV antibodies present at enrollment and 12% of participants had antibodies to all four HPV genotypes (6/11/16/18). The latter women had not previously received the HPV vaccine, as confirmed by their relatively low antibody levels (Table 2), which indicates that they acquired this immunity naturally. Within a relatively short period of time, 25% of women who did not receive vaccine seroconverted to at least one of the 4vHPV types during follow-up. Altogether these data suggest the need to vaccinate against HPV at an early age in this population of women at high risk for HPV and HIV in South Africa.

Overall HPV seroprevalence to any of the 4vHPV types observed in

Table 2.
Comparison of geometric mean titers (GMT) at Month 7 between women in the 4vHPV vaccine arm that were seronegative[a] and seropositive for anti-HPV 6, 11, 16, and 18 at enrollment.

HPV	Seropositive at enrollment			Seronegative at enrollment		p-value[b]
		Day 1	Month 7		Month 7	
	n	GMT (95% CI)	GMT (95% CI)	n	GMT (95% CI)	
6	128	67.1 (55.4–81.4)	1200.7 (1010.9–1426.1)	41	651.6(506.4–838.5)	< 0.0001
11	78	20.6 (15.9–26.6)	866.1(691.5–1084.6)	95	535.5(454.1–631.4)	0.002
16	52	72.4 (49.6–105.6)	5505.4 (4466.2–6786.2)	123	2541.9(2207.5–2926.9)	0.0006
18	82	34.8 (27.1–44.8)	1045.1 (843.1–1295.4)	92	642.2(520.7–792.1)	0.0004

[a] Cut points for determination of antibody positivity for HPV 6, 11, 16, and 18 were 16, 6, 12, and 8 mMU/mL, respectively.
[b] P-values were calculated using the t-test to compare the antibody titers at month 7 between women that were seronegative and seropositive to HPV at enrollment.

the current study was four-fold higher than observed among women in the licensure trials for Gardasil (19.6%) [21]. A bivalent Cervarix vaccine trial among South Africa HIV-negative women aged 18–25 with six or fewer sexual partners reported an HPV16 seroprevalence of 63.6% and 50.0% for HPV18 [22]. The difference in seroprevalence between the Cervarix trial and our trial may have been impacted by the different serologic assays that were used [8,22,23]. The serologic assay used in Cervarix vaccine trials, which is the ELISA assay for total IgG, results in higher percentage of seropositives than the serologic assay used in Gardasil vaccine trials which only measures the neutralizing component of IgG [23]. In addition to the differences by assay used, differences in cutoff values, and the comparison population will result in differences in seroprevalence estimates across studies [8].

Not only was the seroprevalence high in this cohort of young South African women, but seroconversion in the placebo arm was surprisingly high in the 7-month time period. HPV infection clearance is mediated by cellular immunity and seroconversion to HPV which typically occurs 6–18 months after infection [24]. In our cohort, women that were both seronegative and DNA negative at the cervix for HPV6, 23% seroconverted during the 7-month time period and the majority of those (7/10) did not have HPV 6 detected at the cervix at the 7-month visit. These seven women were likely either in the process of seroconverting at enrollment from an HPV6 infection that they previously cleared or they were infected with HPV6 during the interval between HPV testing, cleared the infection, and seroconverted by month 7. It is also possible that these women may have been infected with HPV at non-cervical sites and seroconverted to HPV based on those infections. The remaining three women that seroconverted to HPV6 had HPV6 detectable at the cervix at the 7-month visit. Several different scenarios may explain how this was possible. Perhaps the HPV infection was new and the antibody produced was not at a high enough level to prevent infection or the infection may have occurred in the period just before antibody was produced. Our study design limits our ability to determine which scenario occurred given that we only assessed HPV antibodies and DNA at two time points and that we only assessed HPV DNA at the cervix when HPV can infect other anatomic sites.

Natural immunity with high antibody titers to HPV has been shown to partially reduce the risk for future HPV infections [25–27] and precancerous cervical lesions [27]. Natural immunity to HPV among this cohort of women may prevent a proportion from acquiring new HPV infections and cervical lesions, but without effective screening in this low-resource setting, we cannot rely on natural immunity to protect these women. After we began our vaccine trial, the South African government initiated a school-based vaccination program for 9 year old girls in 2014 using the Cervarix HPV vaccine [28]. This program should reach half a million school-aged girls and is currently reporting 91% coverage in the first round of vaccination [29].

There are several strengths and limitations to the current study that need to be considered in interpreting the results. HPV DNA and HPV antibodies were only assessed at enrollment and at the 7-month visit; therefore it is unknown when a woman acquired the HPV infection compared to receiving each dose of the vaccine. The 4vHPV vaccine is prophylactic and there is no protective effect against clinical endpoints among women who were HPV DNA positive at the initiation of the vaccine series. In this current study where data are only available one month after vaccine completion, we cannot draw conclusions about clinical efficacy to prevent HPV infection, HPV-related disease or HIV. However, in numerous trials among women and men robust clinical efficacy, and long term duration of protection has been repeatedly demonstrated. We encountered comprehension issues in defining sexual activity that led to errors in questionnaire reporting. Therefore, we designed educational posters for participants mid-study, significantly improving the consistency of questionnaire responses. While HPV antibodies to conformational L1 epitopes are a marker of past HPV exposure, current HPV serologic assays underestimate the true lifetime exposure to HPV infection because not all persons that are exposed develop an antibody. Our findings may not be generalizable to all South African women and likely do not represent STI and risk conditions of women in other sub-Saharan countries.

We were successful at implementing this vaccine feasibility placebo-controlled randomized trial in Western Cape, South Africa with high completion rates of the vaccine at 91%. All of the women that received the 4vHPV vaccine seroconverted to all four HPV genotypes. Women in this cohort not only have a high seroprevalence to HPV, but also have a high prevalence of HPV infections at the cervix (71%), other sexual transmitted infections with 33% having a chlamydia infection and 47% seropositive for Herpes Simplex Virus-2, and 12% having abnormal cervical cytology at trial enrollment [15]. HPV vaccines are prophylactic and need to be administered prior to sexual debut to have the greatest effectiveness in preventing disease. Prevention of all STIs and cervical cancer screening needs to continue to be a public health priority in South Africa given that a large proportion of the population is outside of the HPV vaccine age group and will not receive the HPV vaccine.

Funding source

Merck (IISP39582) was the main sponsor of this trial and provided the study product. This work was also supported by the National Cancer Institute at the National Institutes of Health (Cancer Prevention Fellowship R25T CA147832 to S.L.S).

Conflicts of interest

A.R.G. is on the Speaker's Bureau of Merck. M.H.B. is a speaker for Merck, GSK, Roche Diagnostics, and Pfizer. S.L.S. received a grant (IISP53280) from Merck Investigator Initiated Studies Program. M.F.S.v.d.L. received research funding from Sanofi-Pasteur MSD; he is a co-investigator in a Sanofi-Pasteur-MSD HPV vaccine trial; he sat on a vaccine advisory board of GSK; his institution received in-kind contribution for an HPV study from Stichting Pathologie Onderzoek en Ontwikkeling (SPOO); his institution receives research funding from Janssen Infectious Diseases and Vaccines. For the remaining authors, no conflicts of interest were declared.

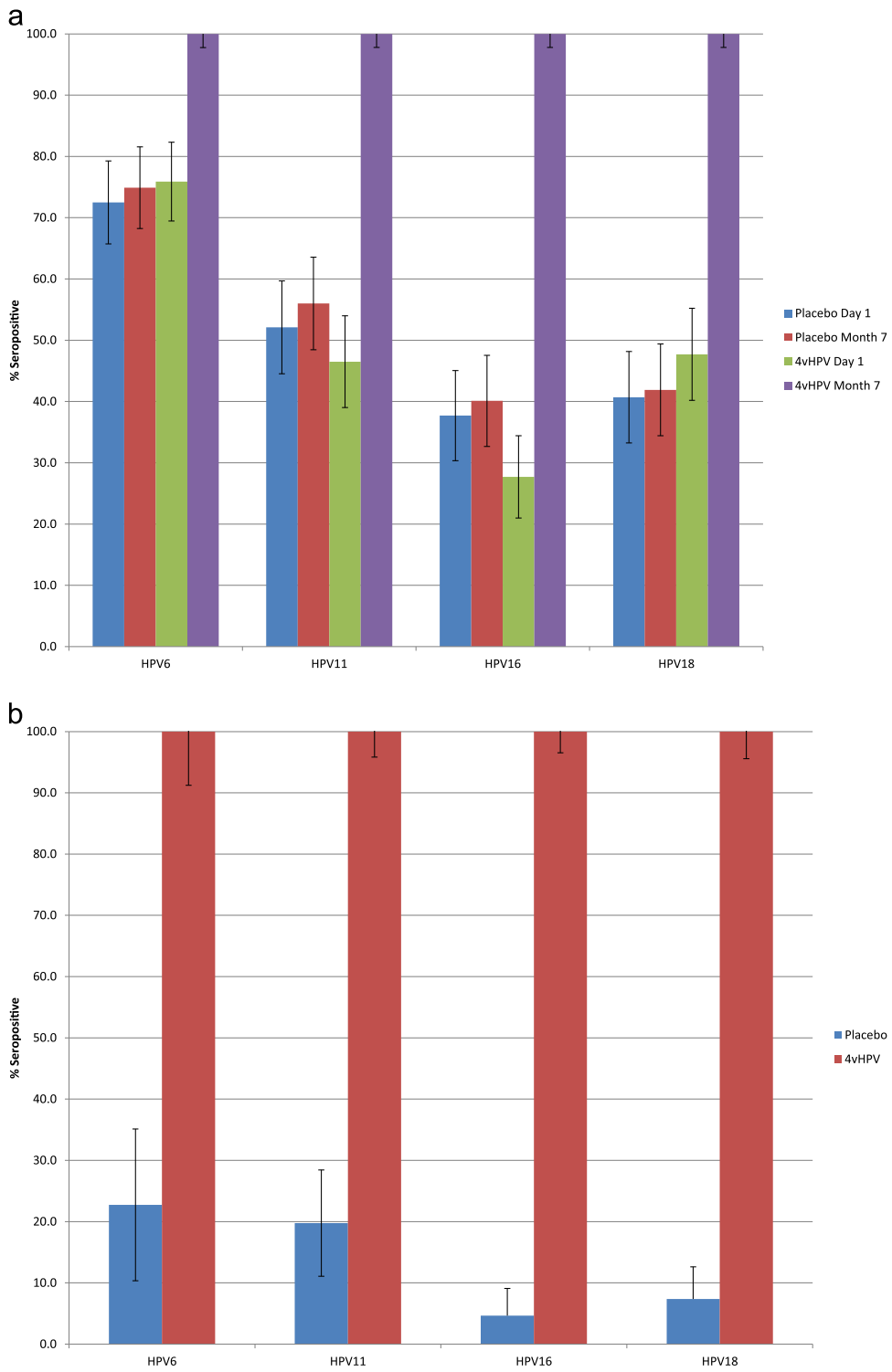


Fig. 3. Serostatus among the "Intention-to-treat" and "Per-protocol" Populations. a. Intention-to-treat: Proportion of participants that were seropositive to HPV at enrollment and month 7 regardless of genital HPV infection and serostatus at enrollment and 95% confidence intervals; b. Per-protocol: Among women that were HPV DNA negative and HPV seronegative at enrollment, the proportion of participants that were seropositive to HPV at month 7 and 95% confidence intervals.

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Table 3a.
Among women that were seronegative for each HPV genotype in the placebo group, the proportion of women that seroconverted with and without the HPV being prevalent at enrollment.

	Prevalent genital HPV infection and seronegative at enrollment		Negative for genital HPV infection and seronegative at enrollment	
HPV	**n**	**Seroconverted by 7 month visit, n (%)**	**n**	**Seroconverted by 7 month visit, n (%)**
6	0	0 (0.0)	44	10 (22.7)
11	0	0 (0.0)	81	16 (19.8)
16	17	4 (23.5)	86	4 (4.7)
18	2	1 (50.0)	95	7 (7.4)

Table 3b.
Extension of Table 3a, among the women that were negative for genital HPV infection and seronegative at enrollment in the placebo group, the proportion of women at month 7 that had a genital HPV infection.

HPV	N	Seroconverted at month 7		Remained Seronegative at month 7	
		HPV+	HPV-	HPV+	HPV-
6	44	3(30.0)	7(70.0)	1(2.9)	33(97.1)
11	81	0 (0.0)	16(100.0)	3(4.6)	62(95.4)
16	86	2(50.0)	2(50.0)	4(4.9)	77(95.1)
18	95	1(14.3)	6(85.7)	4(4.6)	83(95.4)

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