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# Clinical Trial Experience With Prophylactic Human Papillomavirus 6/11/16/18 Vaccine in Young Black Women

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A B S T R A C T

**Purpose:** Human papillomavirus (HPV) is the causative agent of cervical cancer. Black women are disproportionally diagnosed and have higher mortality from cervical cancer in the United States. Here we describe the prophylactic efficacy and safety of a quadrivalent HPV-6/11/16/18 vaccine in black women.
**Methods:** A total of 700 black women from Latin America, Europe, and North America (aged 16–24 years) received the vaccine or placebo in one of two studies. Analyses focused on the efficacy and safety of the vaccine.
**Results:** Baseline rates of *Chlamydia trachomatis* infection and history of past pregnancy were more than twice as high in black women compared with the non-black women who were enrolled in these trials. HPV-6/11/16 or 18 DNA was detected in 18% of black women versus 14.6% in non-black women at day 1. For black women, vaccine efficacy against disease caused by HPV-6/11/16/18 was 100% for cervical intraepithelial neoplasia (0 vs. 15 cases; 95% confidence interval, 64.5%–100%) and 100% for vulvar and vaginal intraepithelial neoplasia and condylomata acuminata (0 vs. 17 cases; 95% confidence interval, 69.3%–100%). There were no serious vaccine-related adverse experiences. A similar proportion of pregnancies resulted in live births (75.8% vaccine; 72.7% placebo) and fetal loss (24.2% vaccine; 27.3% placebo).
**Conclusions:** Prophylactic quadrivalent HPV-6/11/16/18 vaccination of young black women demonstrated high efficacy, safety, and tolerability. HPV vaccination has the potential to reduce cervical cancer-related health disparities both in the United States and around the world.


**IMPLICATIONS AND CONTRIBUTION**

Black women are disproportionally diagnosed with cervical cancer in the United States. A quadrivalent HPV vaccine was highly efficacious among black women. Primary prevention through vaccination offers the long-term prospect of lower overall incidence of cervical cancer and provides additional protection for women who are unable or unwilling to access regular screening.

Cervical cancer remains a significant cause of morbidity and mortality in women, both in the United States and worldwide. Although the majority of cervical cancer mortality occurs in less-developed countries without routine Papanicolaou (Pap) screening programs, there are still approximately 12,000 cases of cervical cancer diagnosed annually in the United States, with about 4,200 deaths anticipated this year [1].

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Persistent infection with certain high-risk (oncogenic) types of human papillomavirus (HPV) is a necessary cause of cervical cancer [2,3]. Most notable of the oncogenic types are HPV-16 and HPV-18, which are responsible for approximately 70% of all cervical cancers, as well as a proportion of cancers of the vagina, vulva, anus, and head and neck [4,5]. Of the low-risk (nononcogenic) types, HPV-6 and HPV-11 are responsible for up to 90% of genital warts (GW) and virtually all cases of recurrent respiratory papillomatosis [6].

To date, there are two prophylactic HPV vaccines that have been approved by the U.S. Food and Drug Administration and European Medicines Agency: a bivalent vaccine targeting HPV-16/18, and a quadrivalent vaccine targeting HPV-6/11/16/18 [7–9]. Both vaccines were highly efficacious in large phase 3 clinical trials.

Although no regional differences have been noted with regard to the safety, efficacy, and immunogenicity of the quadrivalent vaccine [10–14], it is still important to assess whether there are specific racial or ethnic differences related to the safety, immunogenicity, and efficacy of HPV vaccination, as there have been differential responses to antihypertensive therapy [15,16], insulin regimens [17], antidepressants [18,19], and antiretrovirals [20] in black patients. Furthermore, black women, in addition to other racial/ethnic minority women, are disproportionally diagnosed with cervical cancer in the United States. Cervical cancer incidence and death rates are higher in black and Latina women than in white, American Indian/Alaska Native, and Asian/Pacific Islander women [21]. These racial/ethnic differences are believed to be largely owing to unequal access to health care rather than biological differences in susceptibility to HPV infection [21]. Previous published data have reported similar high prophylactic vaccine efficacy and safety in Latin American, Mexican, and Asian women [11,22]. Here we review the safety and prophylactic efficacy of the quadrivalent HPV vaccine in a subset of black women enrolled in two pivotal phase 3 clinical trials.

## Methods

### *Objectives*

The primary objective of this post hoc analysis was to assess the safety and efficacy of a quadrivalent HPV-6/11/16/18 vaccine (Gardasil, Merck Sharp & Dohme, Corp., Whitehouse Station, NJ) in black women who were enrolled in two phase 3 clinical trials.

### *Study design and population*

Between December 2001 and May 2003, 706 black women aged 16–24 years were enrolled in one of two randomized, double-blind, placebo-controlled trials (FUTURE I and FUTURE II, Females United to Unilaterally Reduce Endo/Ectocervical disease) [8,9]. Of these women, one was randomized but was never vaccinated, and five were randomized to monovalent HPV vaccine as part of an immunogenicity substudy [23] and were thus excluded from the analyses. The studies were conducted in accordance with principles of Good Clinical Practice and were approved by the appropriate institutional review boards and regulatory agencies. Racial/ethnic self-identification was completed as part of a study entry questionnaire. In addition, because these studies were conducted in multiple countries, those who identified as black were not only from the United States but were also from other countries and regions across the globe.

The study designs and the results of the primary hypotheses have been described [8,9]. The trials recruited women who at enrollment (day 1) reported having had 0–4 sexual partners during their lifetime. Neither study included an HPV screening phase; thus, the trials allowed the enrollment of women with active HPV infection or disease.

In both trials, participants were randomly assigned (1:1) to receive intramuscular injections of HPV-6/11/16/18 vaccine or visually indistinguishable placebo on day 1, at month 2, and at month 6. Comprehensive anogenital examinations and ThinPrep cervical cytology (Cytyc, Boxborough, MA) were performed during scheduled visits [8,9]. Cytology specimens were classified using the Bethesda System-2001 [24].

Participants returned to the study sites at month 3 (FUTURE I only), and months 7, 12, 24, 36, and the end of study visit (also at months 18, 30, and 42 for FUTURE I). Comprehensive anogenital examinations were conducted at each scheduled visit, at which time an endo-/ectocervical swab (one specimen) and a combined labial/vulvar/perineal plus a perianal swab (pooled to become a second specimen) were collected. The data reported here include approximately 3.5 years of follow-up on average, with 25th and 75th percentiles of 3.4 and 3.8 years, respectively (maximum follow-up = 4.6 years).

Protocol-specified guidelines were used to triage women with cytologic abnormalities for colposcopy [8,9]. Colposcopists were trained to locate and biopsy all discrete abnormal areas on the cervix and lower genital tract. All biopsies and excisional procedure specimens were tested for the HPV types −6, −11, −16, and −18 using a polymerase chain reaction (PCR)-based assay. Histopathological review of all tissue specimens was performed by the members of a pathology panel who were blinded to the vaccination group and HPV status. A subject was considered to have developed an end point related to HPV-6, −11, −16, and/or −18 (abbreviated as HPV-6/11/16/18-related) if the respective HPV DNA was detected in the same lesion that was diagnosed by the members of the pathology panel as cervical intraepithelial neoplasia (CIN) grade 1 or greater, vulvar intraepithelial neoplasia (VIN) grade 1 or greater, vaginal intraepithelial neoplasia (VaIN) grade 1 or greater, or GW.

### *Safety assessment*

All participants were observed for at least 20 minutes after each injection. In FUTURE I, injection site and systemic adverse events were self-reported in the first 15 days after injections using a vaccination report card. Vaccination report cards were also used in FUTURE II but only in subjects from North America, with general surveillance (querying participants at each visit regarding serious adverse events) used for participants in all other regions. Adverse events determined by the investigator to be possibly, probably, or definitely related to vaccine (or placebo) were classified as vaccine-related events. Adverse events were summarized as frequencies and percentages for the vaccine and placebo groups for the overall safety population, which comprised all enrolled subjects regardless of safety surveillance method.

All participants were required to use birth control during the vaccination phase (day 1 through month 7), and all participants were evaluated for pregnancy before the administration of each dose of HPV-6/11/16/18 vaccine or placebo using a $\beta$-human chorionic gonadotropin assay sensitive to 25 IU [25]. Those with a positive result on pregnancy tests were not vaccinated. For

those who became pregnant before receiving all three doses, vaccination was only resumed after the resolution of the pregnancy (term or preterm delivery, spontaneous pregnancy loss, elective termination, etc.). Participants were eligible to complete the vaccination series, starting at a minimum of 2 weeks after resolution of pregnancy and normalization of $\beta$-human chorionic gonadotropin levels. For participants in whom pregnancy was detected after completion of the vaccine series, study visits and procedures were completed per protocol and at the investigator's discretion.

### *Statistics*

Prophylactic vaccine efficacy was assessed in the per-protocol population, defined as women who had negative results on DNA and serologic testing for HPV-6, −11, −16, or −18 at enrollment, remained DNA-negative for the same HPV type through 1 month after the administration of the third dose of vaccine or placebo (month 7), received all doses within 1 year, and had no protocol violations. Follow-up for case ascertainment for this analysis started 1 month after the administration of the third dose of vaccine or placebo.

A point estimate of vaccine efficacy and the 95% confidence interval (CI) were calculated on the basis of the observed case split between vaccine and placebo recipients, adjusted for the accrued person-time in each group. The criterion for statistical significance ($p < .05$) was equivalent to requiring that the lower bound of the 95% CI for vaccine efficacy exclude 0%. An exact conditional procedure was used to evaluate vaccine efficacy under the assumption that the number of cases in the vaccine and placebo groups were independent Poisson random variables [26].

In the efficacy analyses presented, a subject is counted only once for each end point (i.e., once in each row), but a subject may have developed more than one end point during the trial (i.e., a women may appear in more than one row). For example, a subject may have developed two lesions with HPV detected in both an HPV-16-related CIN 2 lesion and an HPV-6-related CIN 1 lesion. Overall, she would be counted as a case once each for (1) HPV-6/11/16/18-related CIN 1 or greater, (2) HPV-6/11/16/18-related CIN 2 or greater, (3) HPV-6/11/16/18-related CIN 1, (4) HPV-6/11/16/18-related CIN 2, (5) HPV-6-related CIN 1 or greater, and (6) HPV-16-related CIN 1 or greater.

## Results

### *Baseline characteristics*

A total of 17,622 women were enrolled in FUTURE I and II, 99.9% of whom received at least one dose of vaccine or placebo (98.4% received two doses and 97.2% received three doses). Of the 700 black women enrolled (4% of total population), the mean age was 20.4 years (range 16–24 years), and the majority of participants (66.3%) were from Latin America. The mean age of first sexual intercourse was 16.4 years, and the median lifetime number of sexual partners was two.

Demographic characteristics were similar between women receiving placebo and women receiving quadrivalent HPV vaccine; however, a higher proportion of vaccine recipients (52.4%) than placebo recipients (41.5%) had experienced a past pregnancy and a slightly higher proportion of placebo recipients (19.3%) than vaccine recipients (14.0%) were current smokers. Among the black women enrolled in the trials, a history of having had at least one past pregnancy was twice that of the non-black women [27]. Baseline prevalence of non-HPV-related cervicovaginal infections or sexually transmitted diseases was 11.4% (13.0% vaccine; 10.2% placebo). Chlamydia infection among the black women enrolled in the trials (9.7%) was more than twice that of the non-black women (4.0%). Of the black women with chlamydia infection, 73% were from Latin America, 25% were from North America, and 1% were from Europe. Roughly 14% (15.9% vaccine; 11.9% placebo) of women with a satisfactory cytology test result at enrollment had ASC-US (atypical cells of undetermined significance) or greater, which was slightly higher than the non-black women (11.3%) [27]. Only one participant (vaccine arm) had HSIL (high-grade squamous intraepithelial lesion) at enrollment.

Infection with HPV-6, −11, −16, or −18 detected by PCR was similar between vaccine (17.6%) and placebo (18.3%) recipients, although a nominally higher proportion of placebo recipients (6.4%) than vaccine recipients (3.6%) were infected with HPV-6. Infection with HPV-6, −11, −16, or −18 detected by serology was similar between vaccine and placebo recipients in total (33.2% vaccine; 29.3% placebo) and for the individual HPV types (Table 1). Infection with HPV-6, −11, −16, or −18 detected by PCR was higher than the overall study population (14.8%), as was infection with HPV-6, −11, −16, or −18 detected by serology (19.8%) [27].

### *Vaccine efficacy*

After a median follow-up of 3.6 years, vaccine efficacy in the per-protocol population was 100% for HPV-6/11/16/18-related CIN 1 or greater (0 vs. 15 cases; 95% CI: 64.5%–100%) (Table 2 [by lesion type]). Of the 15 women in the placebo arm who developed CIN, 12 were diagnosed with CIN 1 (with or without an additional diagnosis of CIN 2, CIN 3, or adenocarcinoma in situ), and six were diagnosed with CIN 3 (with or without an additional diagnosis of CIN 1, CIN 2, or adenocarcinoma in situ). HPV-6, −11, −16, and −18 were detected in the cervical lesions of 6, 0, 4, and 6 women, respectively (Table 2 [by HPV type]). There were no cases of cervical cancer. Vaccine efficacy for HPV-6/11/16/18-related condylomata, VIN, or VaIN was also 100% (0 vs. 17 cases; 95% CI: 69.3%–100%) (Table 2 [by lesion type]). The majority of these cases were diagnosed as condyloma (diagnosed in 13 women). There were three women with high-grade vulvar or vaginal disease (VIN 2/3 or VaIN 2/3) (one case with HPV-16 DNA detected in the lesion, one with both HPV-6 and HPV-16 detected in the lesion, and one with HPV-11 detected in the lesion) and no cases of vulvar or vaginal cancer. For most of the individual end points, statistical significance was not reached because of the overall small number of cases observed.

### *Safety*

Among all subjects with safety follow-up, 35.8% of vaccine recipients and 29.1% of placebo recipients reported one or more systemic adverse experiences (AEs) (Table 3). Of these, 23.8% and 18.2% were considered vaccine related. Few serious AEs were reported (1.7% vaccine; 1.6% placebo) of which none were considered vaccine related. Two subjects in the vaccine arm discontinued because of a vaccine-related AE (one owing to hive and one owing to rash). There were no deaths. Injection-site AEs were more frequent in vaccine (49.0%) than placebo (41.0%) recipients.

**Table 1**
Baseline characteristics of the black women enrolled in the phase 3 trials of the quadrivalent vaccine[a]

| Characteristic | Vaccine (N = 307) | Placebo (N = 393) |
|---|---|---|
| Mean age, years (SD) | 20.3 (1.9) | 20.4 (2.0) |
| Region, n (%) | | |
| Europe | 3 (1.0) | 12 (3.1) |
| Latin America | 204 (66.4) | 260 (66.2) |
| North America | 100 (32.6) | 121 (30.8) |
| Body mass index, mean (SD) | 25.2 (7.1) | 24.7 (5.8) |
| Smoking status, n (%) | | |
| Current smoker | 43 (14.0) | 76 (19.3) |
| Exsmoker | 16 (5.2) | 18 (4.6) |
| Never smoked | 248 (80.8) | 299 (76.1) |
| Mean age at first sexual intercourse among nonvirgins, years (SD) | 16.3 (1.9) | 16.4 (2.1) |
| Lifetime number of sexual partners at enrollment among nonvirgins, n (%) | | |
| Unknown | 0 (0.0) | 1 (0.3) |
| 1 | 96 (32.2) | 119 (31.3) |
| 2 | 102 (34.2) | 123 (32.4) |
| 3 | 56 (18.8) | 88 (23.2) |
| 4 | 44 (14.8) | 49 (12.9) |
| Median | 2 | 2 |
| Past pregnancy, n (%) | | |
| Yes | 161 (52.4) | 163 (41.5) |
| No | 146 (47.6) | 230 (58.5) |
| Spontaneous abortion, n (%) | | |
| Yes | 23 (7.5) | 21 (5.3) |
| No | 136 (44.3) | 141 (35.9) |
| Unknown | 2 (0.7) | 1 (0.3) |
| Elective abortions, n (%) | | |
| Yes | 29 (9.4) | 24 (6.1) |
| No | 132 (43.0) | 135 (34.4) |
| Unknown | 0 (0.0) | 4 (1.0) |
| Non-HPV cervicovaginal infections or sexually transmitted diseases, n (%) | 40 (13.0) | 40 (10.2) |
| Chlamydia[b] | 32/303 (10.6) | 35/388 (9.0) |
| Gonorrhea[b] | 5/303 (1.7) | 5/387 (1.3) |
| Bacterial vaginosis[c] | 2/307 (0.7) | 1/393 (0.3) |
| Hepatitis B[c] | 2/307 (0.7) | 1/393 (0.3) |
| Cytology, n (%) | | |
| Number with a satisfactory cytology test result[d] | 296 (97.7) | 377 (96.9) |
| SIL present | 47 (15.9) | 45 (11.9) |
| ASC-US | 19 (6.4) | 13 (3.4) |
| ASC-H | 4 (1.4) | 3 (0.8) |
| LSIL | 23 (7.8) | 29 (7.7) |
| HSIL | 1 (0.3) | 0 (0.0) |
| PCR positive for HPV-6, −11, −16, and/or −18 | 54 (17.6) | 72 (18.3) |
| HPV-6 | 11 (3.6) | 25 (6.4) |
| HPV-11 | 1 (0.3) | 4 (1.0) |
| HPV-16 | 36 (11.7) | 33 (8.4) |
| HPV-18 | 9 (2.9) | 21 (5.3) |
| Seropositive for HPV-6, −11, −16, and/or −18 | 102 (33.2) | 115 (29.3) |
| HPV-6 | 45 (14.7) | 61 (15.5) |
| HPV-11 | 10 (3.3) | 15 (3.8) |
| HPV-16 | 55 (17.9) | 68 (17.3) |
| HPV-18 | 27 (8.8) | 30 (7.6) |

HPV = human papillomavirus; PCR = polymerase chain reaction; SD = standard deviation; ASC-US = atypical squamous cells of undetermined significance; ASC-H = atypical squamous cells, cannot rule out high-grade squamous intraepithelial; HSIL = high-grade squamous intraepithelial lesion; LSIL = low-grade squamous intraepithelial lesion.

[a] Percentages computed as 100 [a](n/N), unless otherwise indicated.

[b] Mandatory test at enrollment.

[c] Nonmandatory test at enrollment—performed at the discretion of the investigator if subject showed symptoms of sexually transmitted disease.

[d] Percentages computed as 100 [a](n/number with satisfactory cytology test result).

The most common injection site AEs were pain (48.0% vaccine; 40.0% placebo) and swelling (12.9% vaccine; 10.9% placebo).

As shown in Table 4, 25.4% (78/307) of the women in the vaccine group and 24.9% (98/393) of those in the placebo group reported at least one pregnancy during the studies. This rate is higher than the population of non-black women enrolled in the trial, in which 1,518/8,492 (18%) vaccine and 1,517/8,407 (18%) of placebo recipients reported at least one pregnancy. The total number of fetuses and/or neonates with known outcomes was 95 and 110 in the vaccine and placebo groups, respectively. Among live births, the percentage of infants with normal characteristics was 95.8% in the vaccine group and 93.7% in the placebo group. Two infants (one born to a vaccine recipient; one born to a placebo recipient) were diagnosed with a congenital anomaly. The estimated dates of conception for these infants were 696 (vaccine group) and 214 (placebo group) days after the last dose of vaccine or placebo, respectively. Overall, rates of fetal loss were similar between vaccine (24.2%; 23/95) and placebo recipients (27.3%; 30/110); however, of the pregnancies that resulted in fetal loss, the rate of spontaneous abortion was nominally higher among vaccine (82.6%; 19/23) than placebo (23.3%; 7/30) recipients, whereas the rate of elective abortion was nominally lower among vaccine (17.4%; 4/23) than placebo recipients (66.6%; 20/30). In the vaccine group, the 19 spontaneous abortions were among 15 women; two women each had two spontaneous abortions in separate gestations, and one woman had three spontaneous abortions in separate gestations. In the placebo group, the seven spontaneous abortions were among seven women. In the vaccine group, the four elective abortions were among four women, and in the placebo group, the 20 elective abortions were among 18 women; two women each had two elective abortions (all different pregnancies). There were three late fetal deaths, all in the placebo arm (among three women). There were no late fetal deaths in the vaccine arm. As shown in Figure 1, the pregnancies that resulted in fetal loss were distributed across the entire study period in both the vaccine and placebo arms, with no apparent clustering with respect to the timing of vaccine exposure relative to the pregnancy outcome. As shown in Figure 1, 16/19 (84%) and 7/10 (70%) of the spontaneous abortions and late fetal deaths, respectively, in the vaccine and placebo groups occurred at least 12 months after vaccination.

## Discussion

In FUTURE I and II, prophylactic vaccination was highly effective in preventing precancerous lesions of the cervix, vagina, and vulva, as well as GWs. Similar high prophylactic vaccine efficacy was observed among the population of black women who were enrolled in these studies. Vaccination was generally well tolerated, and safety-related outcomes were similar for vaccine and placebo recipients. In addition, there were no substantial differences in safety outcomes among these black women when compared with the larger FUTURE I and II study populations [8,9].

A previous study examined the impact of race on the immune response to quadrivalent vaccine [14]. Although small numeric differences in titers were observed 1 month after the third dose of vaccine among subpopulations defined by race and ethnicity, no consistent pattern was demonstrated across all vaccine types. For example, Hispanic women had numerically higher titers for HPV-6 than white, black, and Asian women, and black women had numerically higher HPV-16 responses than white, Asian, and Hispanic women. Because of the lack of disease breakthrough to

**Table 2**
Vaccine efficacy in preventing HPV-6/11/16/18-related lesions

| Endpoint | Vaccine (N = 307) | | | Placebo (N = 393) | | | Efficacy (%) | 95% CI |
|---|---|---|---|---|---|---|---|---|
| | n | No. of women with a lesion | Rate[a] | n | No. of women with a lesion | Rate[a] | | |
| By Lesion type[b] | | | | | | | | |
| CIN 1 or greater | 256 | 0 | 0.0 | 332 | 15 | 1.6 | 100 | 64.5, 100 |
| CIN 1 | 256 | 0 | 0.0 | 332 | 12 | 1.3 | 100 | 54.2, 100 |
| CIN 2 or greater | 256 | 0 | 0.0 | 332 | 6 | 0.6 | 100 | −9.0, 100 |
| CIN 2 | 256 | 0 | 0.0 | 332 | 1 | 0.1 | 100 | −4,904.9, 100 |
| CIN 3 | 256 | 0 | 0.0 | 332 | 6 | 0.6 | 100 | −9.0, 100 |
| AIS | 256 | 0 | 0.0 | 332 | 1 | 0.1 | 100 | −4,904.5, 100 |
| Condylomata, VIN or VaIN | 256 | 0 | 0.0 | 333 | 17 | 1.8 | 100 | 69.3, 100 |
| Condylomata | 256 | 0 | 0.0 | 333 | 13 | 1.4 | 100 | 58.3, 100 |
| VIN1/VaIN 1 or greater | 256 | 0 | 0.0 | 333 | 4 | 0.4 | 100 | −95.5, 100 |
| VIN 1 or VaIN 1 | 256 | 0 | 0.0 | 333 | 2 | 0.2 | 100 | −587.9, 100 |
| VIN 2/3 or VaIN 2/3 | 256 | 0 | 0.0 | 333 | 3 | 0.3 | 100 | −212.3, 100 |
| By HPV type[b] | | | | | | | | |
| CIN 1 or greater | | | | | | | | |
| HPV-6 | 215 | 0 | 0.0 | 264 | 6 | 0.8 | 100 | −2.4, 100 |
| HPV-11 | 215 | 0 | 0.0 | 264 | 0 | 0.0 | NA | NA |
| HPV-16 | 197 | 0 | 0.0 | 260 | 4 | 0.5 | 100 | −100.1, 100 |
| HPV-18 | 226 | 0 | 0.0 | 301 | 6 | 0.7 | 100 | −10.3, 100 |
| Condylomata, VIN, or VaIN | | | | | | | | |
| HPV-6 | 215 | 0 | 0.0 | 264 | 12 | 1.6 | 100 | 56.8, 100 |
| HPV-11 | 215 | 0 | 0.0 | 264 | 4 | 0.5 | 100 | −84.9, 100 |
| HPV-16 | 196 | 0 | 0.0 | 261 | 5 | 0.7 | 100 | −44.8, 100 |
| HPV-18 | 226 | 0 | 0.0 | 302 | 0 | 0.0 | NA | NA |

AIS = adenocarcinoma in situ; CI = confidence interval; CIN = cervical intraepithelial neoplasia; VaIN = vaginal intraepithelial neoplasia; VIN = vulvar intraepithelial neoplasia.
[a] Cases at risk per 100 person-years.
[b] Participants are counted only once in a given row regardless of their number of lesions, but they may appear in multiple rows.

date with HPV vaccines, it has not been possible to establish a minimum level of antibodies needed to protect against HPV-related disease.

The study had some limitations. First, black women were underrepresented in the phase 3 studies. This can, in part, be explained by the fact that the bigger phase 3 study (FUTURE II) enrolled a large number of participants from northern Europe, which has a lower proportion of blacks than the United States. However, even the proportion of black participants enrolled from North America (n = 221; 8.8% of those enrolled from North America) is lower than might be expected when referring to the 2000 U.S. Census data for 15–24-year-old females, in which 11% of the population is black [28]. It has been previously shown that enrollment of black participants in clinical trials in the United States is generally lower than their representation in the population, [29–32], and several studies have shown that black people hold more distrust and fear about participating in clinical research than do white people [33–35]. This can be more pronounced when this research involves young women of childbearing age [34] and adolescents aged less than 18 years. [35–37].

**Table 3**
Adverse experiences (AE) summary

| Adverse event | Vaccine N = 307 | Placebo N = 393 |
|---|---|---|
| No. with follow-up | 302 | 385 |
| No. (%) with: | | |
| One or more injection-site AE[a] | 148 (49.0) | 158 (41.0) |
| One or more systemic AE | 108 (35.8) | 112 (29.1) |
| Vaccine-related systemic AE | 72 (23.8) | 70 (18.2) |
| Serious AE | 5 (1.7) | 6 (1.6) |
| Serious vaccine-related AE | 0 (0.0) | 0 (0.0) |
| No. (%) who | | |
| Discontinued owing to an AE | 2 (0.7) | 0 (0.0) |
| Discontinued owing to a vaccine-related AE | 2 (0.7) | 0 (0.0) |

[a] By definition, all injection site AEs are determined by the investigator to be possibly, probably, or definitely vaccine related.

**Table 4**
Overall pregnancy outcome summary

| Pregnancy outcome | Vaccine (N = 307) | Placebo (N = 393) |
|---|---|---|
| Total number of subjects who became pregnant | 78 (25.4) | 98 (24.9) |
| Total number of pregnancies | 97 | 114 |
| Total number of fetuses/neonates with known outcome | 95 | 110 |
| Live births | | |
| Number of live births/number of fetuses/neonates with known outcome | 72/95 (75.8) | 80/110 (72.7) |
| Normal | 69/72 (95.8) | 75/80 (93.7) |
| Abnormal | 3/72 (4.2) | 5/80 (6.3) |
| Congenital or other anomaly | 1/72 (1.4) | 1/80 (1.3) |
| Other medical condition | 2/72 (2.8) | 4/80 (5.0) |
| Method of delivery | | |
| C-section | 19/72 (26.4) | 26/80 (32.5) |
| Vaginal | 53/72 (73.6) | 54/80 (67.5) |
| Fetal loss | | |
| Number of fetal losses/number of fetuses/neonates with known outcome | 23/95 (24.2) | 30/110 (27.3) |
| Type of loss | | |
| Spontaneous abortion | 19/23 (82.6) | 7/30 (23.3) |
| Late fetal death | 0/23 (0) | 3/30 (10.0) |
| Elective abortion | 4/23 (17.4) | 20/30 (66.6) |

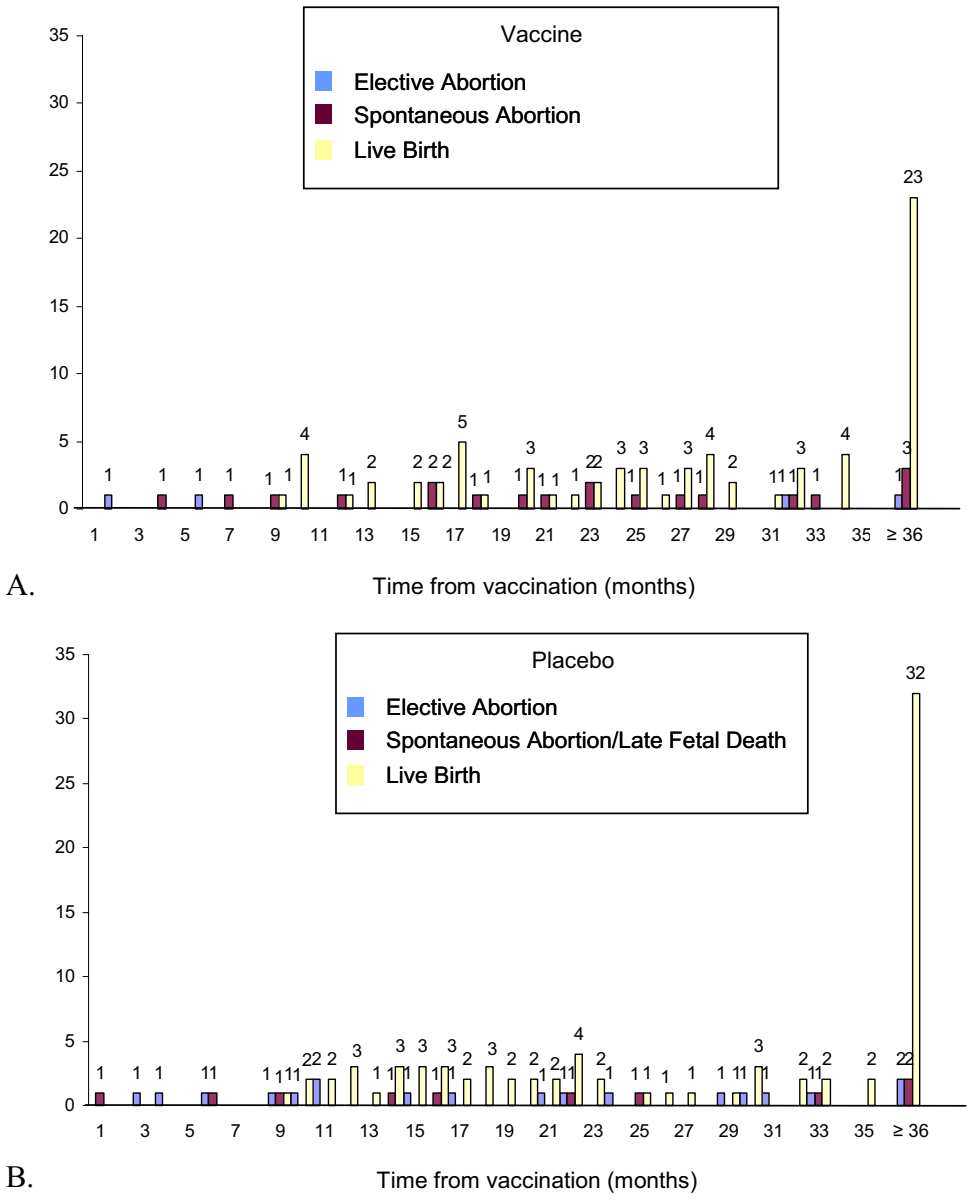


**Figure 1.** (A) Pregnancy outcomes (live births, spontaneous abortion, or elective abortion) relative to HPV-6/11/16/18 vaccine exposure. (B) Pregnancy outcomes (live births, spontaneous abortion/late fetal death, or elective abortion) relative to placebo exposure.

The studies were also neither designed nor powered to estimate vaccine efficacy or safety among the subgroup of black women. Although efficacy was 100% for each end point, statistical significance was not reached because of the small number of cases. However, all previous studies of the quadrivalent vaccine among North American, Latin American, European, and Asian women have shown similar high vaccine efficacy, suggesting that in a larger population of black women, vaccine efficacy would remain high. The studies also did not randomize patients based on race. As shown in Table 1, there were more black women enrolled in the placebo arm (n = 393) than in the vaccine arm (n = 307). It is not known if this resulted in some of the observed imbalances for pregnancy outcomes, such as the difference in the rate of spontaneous and elective abortions between vaccine and placebo recipients. Ultimately, long-term surveillance in vaccinated populations will determine the long-term safety and effectiveness of HPV vaccines. Several systems are in place or are being established for post-licensure monitoring of the safety (including pregnancy outcomes) and efficacy of HPV vaccines in the United States and other countries [38,39].

Prophylactic HPV vaccines do not have a therapeutic effect, and vaccination, therefore, should ideally be initiated before sexual debut. The prevalence of HPV types 6, 11, 16, and 18 was high in our relatively low-risk study population with four or fewer lifetime sex partners (17.6%–18.3% by PCR and 29.3%–33.2% by serology). However, few subjects were seropositive and/or PCR positive for more than two vaccine-related HPV types (3.6%, data not shown), and a previous study has shown that women infected with one or more vaccine HPV types will derive residual benefit from the vaccine's prevention of infec-

tion and disease due to HPV type(s) to which the woman has not yet been exposed [27]. Thus, on an individual level, vaccination of black women with past or existing HPV-related disease may be warranted.

In the United States, data stratified by race show a later age for peak incidence of invasive cervical cancer in Hispanic, American Indian, and Native Alaskan women compared with white women, and among black women, cervical cancer rates increase steadily throughout adulthood to peak at 75–79 years of age [40]. Given the availability of prophylactic HPV vaccines, there are now two complementary strategies for the prevention of cervical and other HPV-related cancers among black women. First, continued efforts to address disparities in access to cervical cancer screening are needed. Although cancer deaths have declined for both white and black women living in the United States, black women continue to suffer the greatest burden for each of the most common types of cancer (i.e., breast) [21]. Black women have the highest death rate for cervical cancer, which reflects both a higher incidence and a later stage of disease at diagnosis [21]. The reasons for this disparity are complex, but the most evident factors include lack of health care coverage and low socioeconomic status [21].

Given the challenges involved in addressing these barriers, primary prevention through vaccination offers the long-term prospect of lower overall incidence of cervical cancer and provides additional protection for women who are unable or unwilling to access regular screening. The National Cancer Institute notes that HPV vaccines have the potential to reduce cervical cancer-related health disparities both in the United States and around the world [21]. Although data are limited, our study provides important information on the safety and efficacy of the quadrivalent vaccine in black women.

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All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author), and they declare that E.M. has received consulting fees or honorarium, support for travel to meetings for the study or other purposes, fees for participation in review activities, such as data monitoring boards, statistical analysis, end point committees, and the like, and consultancy fees from Merck; consultancy fees and grants/grants pending from GlaxoSmithKline; and grants/grants pending from Gen-Probe. W.H. has received consultancy fees, grants/grants pending, and payment for lectures including service on speakers bureaus for Merck and consultancy fees, grants/grants pending, and payment for lectures including service on speakers bureaus from GlaxoSmithKline. E.J. has received grants, consulting fees or honorarium, support for travel to meetings for the study or other purposes, board membership, grants/grants pending, payment for lectures including service on speakers bureaus and travel/accommodations/meeting expenses from Merck; has grants/grants pending, payment for lectures including service on speakers bureaus and travel/accommodations/meeting expenses from GlaxoSmithKline; and travel/accommodations/meeting expenses from Roche. J.P. reports receiving grant support from Merck. G.P. has received lecture fees from Merck and is now an employee of Merck. L.C., M.J., H.S., R.H., A.S., and E.G. are current or former employees of the sponsor and hold stock/stock options.

Studies were conducted in conformity with country or local requirements regarding ethics committee review, informed consent, and other statutes or regulations regarding the rights and welfare of human subjects participating in biomedical research.

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