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# Chapter 13: Current findings from prophylactic HPV vaccine trials

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**Abstract**

Early data from randomized controlled trials consistently show that prophylactic human papillomavirus virus-like particle (HPV VLP) vaccines are effective in preventing infection and lesions caused by the targeted HPV type(s). Two vaccines, a bivalent HPV-16/18 VLP vaccine and a quadrivalent HPV-6/11/16/18 VLP vaccine, are currently undergoing evaluation in phase III trials with anticipation of receiving regulatory approval for use in immunization programs worldwide. Both vaccines have the potential to substantially reduce HPV-related morbidity and mortality. This review focuses on published data from clinical trials of these two vaccines.


*Keywords:* HPV; Prophylactic vaccines; Prevention; Cervical cancer

## 1. Introduction

The results from four randomized controlled trials [1–7] demonstrate with remarkable consistency that a regimen of three intramuscular injections of HPV virus-like particle (VLP) vaccine provides high-level protection from infection and lesions caused by the targeted HPV type(s). Monovalent (HPV-16), bivalent (HPV-16/18), and quadrivalent (HPV-6/11/16/18) VLP vaccines were evaluated in phase IIb trials (i.e., proof-of-concept trials) that enrolled young women (15–26 years of age) from both developed and developing countries. The bivalent and quadrivalent vaccines are anticipated to receive regulatory approval for use in immunization programs throughout the world. Both vaccines have the potential to substantially reduce HPV-related morbidity and mortality. HPV-16 and HPV-18 cause about 70% of cervical cancers worldwide [8] and HPV-6 and HPV-11 cause at least 80% of genital warts [9,10]. This review focuses on published data from clinical trials of these two vaccines.

## 2. Vaccine formulation

The prophylactic HPV vaccines that have been tested in clinical trials are composed of HPV type-specific L1 proteins that self-assemble into noninfectious, recombinant VLPs. Both vaccines are administered at 0, 1 or 2, and 6 months in a series of three 0.5-mL intramuscular injections. The bivalent HPV-16/18 L1 VLP vaccine (Cervarix®, GlaxoSmithKline Biologicals) is manufactured in an insect-cell system. Each injection includes 20 μg of HPV-16 VLP and 20 μg of HPV-18 VLP in an adjuvant of 500 μg of aluminum hydroxide with 50 μg of 3-deacylated monophosphoryl lipid A (AS04) [2,3]. The quadrivalent HPV-6/11/16/18 L1 VLP vaccine (Gardasil®, Merck and Co., Inc.) is manufactured in a yeast system. Each injection includes 20 μg of HPV-6, 40 μg of HPV-11, 40 μg of HPV-16, and 20 μg of HPV-18 VLP in an adjuvant of 225 μg of aluminum hydroxyphosphate sulfate (alum) [6,7].

### 2.1. Safety

Detailed safety data were collected by daily diary for 7 days and by interview 30 days after each injection (bivalent

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trial) or by daily diary for 14 days after each injection (quadrivalent vaccine). Information on serious adverse events and pregnancy outcomes was collected throughout the duration of each trial. Overall, both vaccines appear to be generally safe and well-tolerated. None of the women in the phase IIb trials experienced a serious adverse event that the on-site physician considered to be vaccine-related. Injection-site adverse events, including pain, redness, or swelling, were reported more often among vaccine recipients than among placebo recipients in the quadrivalent vaccine trial (86% versus 77%) and in the bivalent vaccine trial (94% versus 88%). Systemic adverse events, including headaches, fatigue, and gastrointestinal symptoms, were reported by a similar proportion of vaccine and placebo recipients in both trials: 69% in the quadrivalent vaccine trial and 86% in the bivalent vaccine trial. Most adverse events were recorded as mild or moderate in intensity. Moreover, none of the women in either trial discontinued due to a vaccine-related adverse event [2,6]. Additional data on vaccine safety, including data on pregnancy, fetal, and infant outcomes, are being collected in the on-going phases IIB and III trials, and will continue to be collected in different populations throughout the world after the vaccines are licensed and used in widespread immunization programs.

### 2.2. Immunogenicity

The measurement of anti-HPV antibody titers is specific to the HPV type and the laboratory assay used. Hence, numeric values of specific titers cannot be compared between HPV types, or between the quadrivalent and bivalent vaccines. An ELISA assay was used in the bivalent vaccine trial [2,3] and a competitive radioimmunoassay (cRIA) or competitive Luminex immunoassay (cLIA) in the quadrivalent vaccine trial [6,7]. Current findings based on results from these assays indicate that both vaccine formulations are highly immunogenic, with seroconversion rates to all targeted HPV types of over 98%. Protection is observed among women with a wide range of antibody titers. Peak antibody titers in the phase IIb trials are achieved 1 month after dose three, i.e., at month 7 (Figs. 1 and 2), after which detectable titers decline until about month 18, when the rate of decline decreases considerably and titers appear to stabilize over the next few months at or above titers observed in women with naturally acquired and cleared infections (i.e., those positive for type-specific anti-HPV serum antibodies and negative by PCR-based assay for the same type of HPV-DNA at enrollment) [2,3,5,7]. Additional follow-up of vaccinated cohorts is required to determine whether short-term antibody titers seen in the on-going clinical trials predict long-term protection.

The phase IIb programs of the bivalent and quadrivalent HPV vaccines also included blinded assessment of different formulations of HPV VLPs and adjuvants. In the quadrivalent HPV vaccine program, the following formulations were evaluated: 20/40/40/20 μg of HPV-6, -11, -16, and -18 L1 VLP (including 225 μg of aluminum adjuvant hydroxyphosphate sulfate, AAHS), 40/40/40/40 μg of HPV-6, -11, -16, and -18 L1 VLP (including 225 μg of AAHS), or 80/80/40/80 μg of HPV-6, -11, -16, and -18 L1 VLP (including 395 μg of AAHS) [6,7]. Immunogenicity and safety profiles were similar for all formulations so the lowest dose was chosen for use in the phase III clinical trials. Furthermore, a comparison of HPV-11, -16, and -18 titers generated by monovalent [1,4,11] and quadrivalent vaccine formulations [7] showed that seroconversion rates and antibody levels after dose three were similar for both monovalent and quadrivalent formulations. Thus, there is no indication that, relative to a monovalent

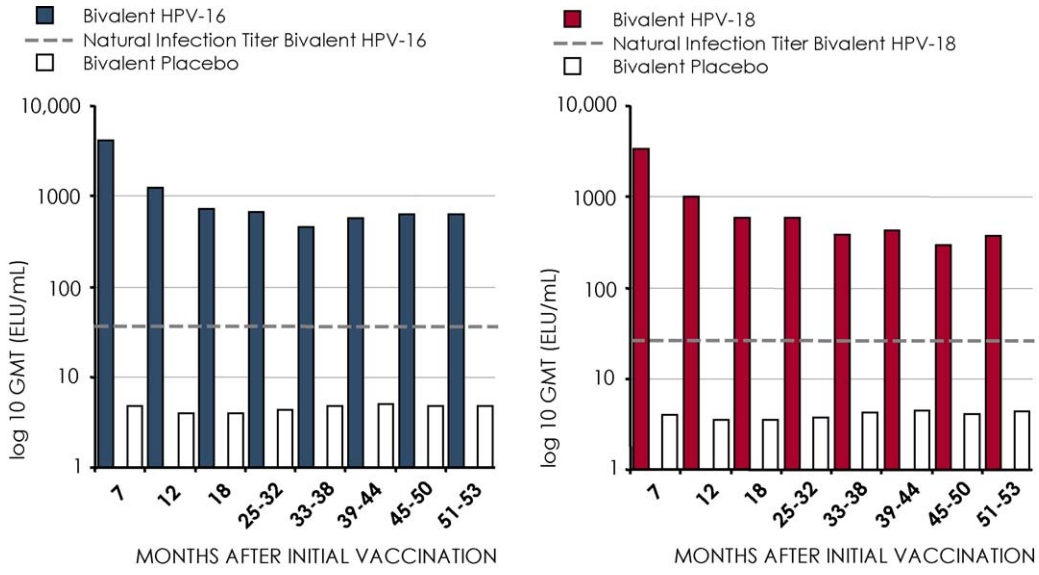


Fig. 1. Type-specific HPV geometric mean antibody titers (GMT) and natural infection titers from the bivalent HPV-16/18 vaccine trials over 54 months for women naïve to vaccine-related HPV types. Natural infection titers are based on data from women who did not receive vaccine or placebo. Data taken from Ref. [3].

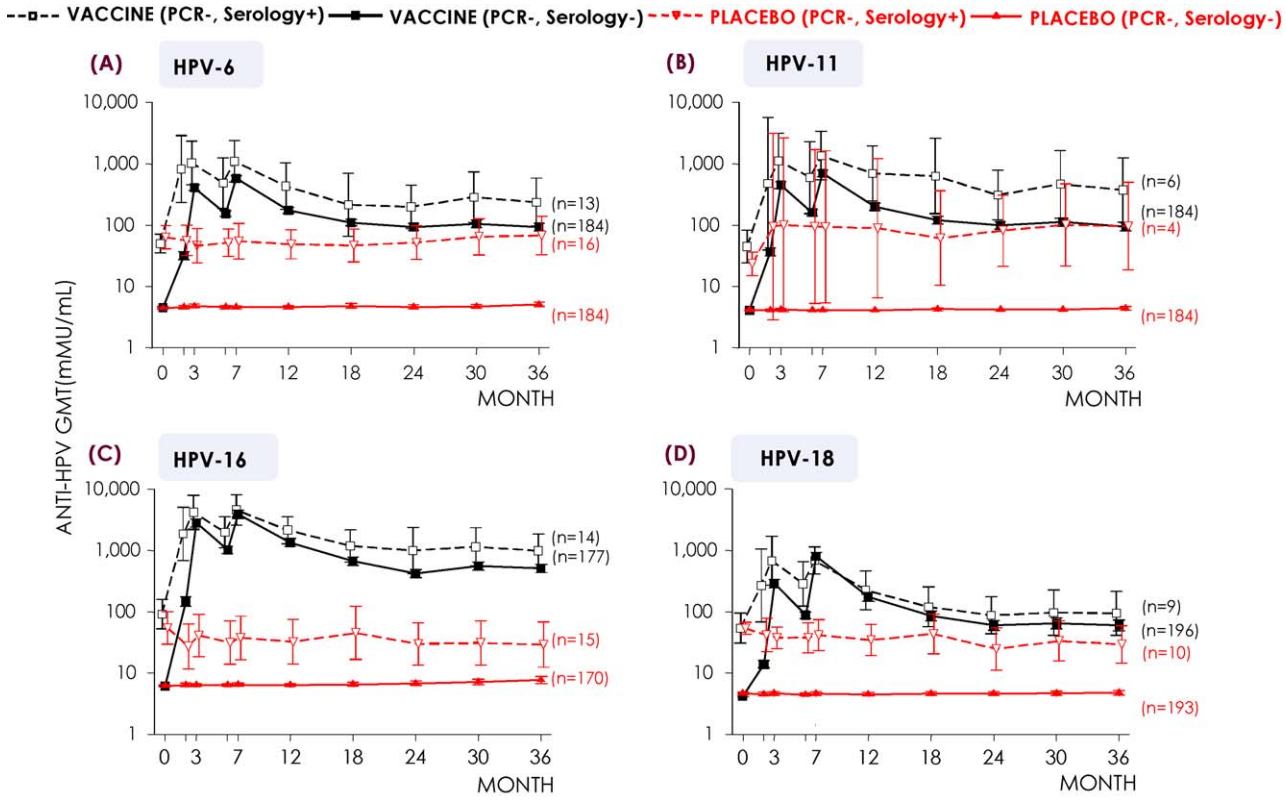


Fig. 2. Anti-HPV geometric mean titers (GMT) with 95% confidence intervals for quadrivalent vaccine and placebo recipients by HPV status (HPV-DNA by PCR and serology according to antibody relevant to HPV type) at recruitment. Longitudinal plots by HPV type for subjects who received all three injections are shown for: (a) HPV-6; (b) HPV-11; (c) HPV-16; (d) HPV-18. Because the titers of the reference sera are not identical, one cannot draw conclusions from the absolute titers with regard to the relative immunogenicity of the four VLP components in the vaccine. *n*: number of subjects contributing to the month-36 time-point. Reprinted from reference [7] with permission from Elsevier.

HPV VLP vaccine, the quadrivalent HPV VLP vaccine is less likely to induce high HPV type-specific antibody titers.

### 2.3. *Efficacy*

Although the basic study design for a double-blinded, randomized controlled trial (RCT) of prophylactic vaccine efficacy is relatively straightforward (Fig. 3), the actual components of trials targeting the same infection(s) are often different. These differences are important to keep in mind when comparing estimates of vaccine efficacy and making inferences as to their generalizability to a broad or more narrowly defined sub-set of the population.

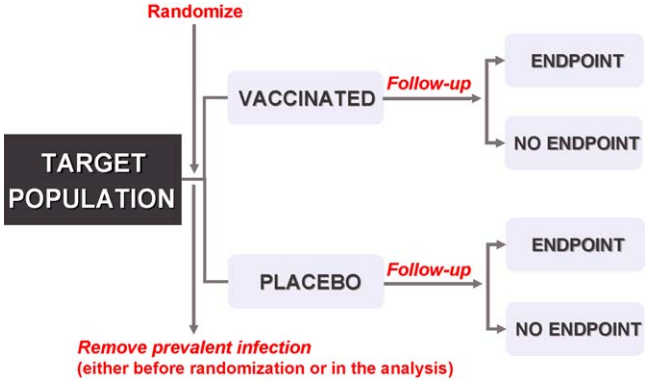


Fig. 3. Diagram of a randomized controlled trial designed to evaluate the efficacy of a prophylactic vaccine.

The target population for both the bivalent and the quadrivalent vaccine trials was healthy young women who were naïve for the HPV types targeted by the vaccine (Table 1). The results presented in this review are from the analysis of the intention-to-treat (ITT) cohort (bivalent vaccine study) and the modified-intention-to-treat (MITT) cohort (quadrivalent vaccine trial). Typically such ITT or MITT analyses are based on data from all women randomized. In both trials however, additional exclusions were made, largely due to pre-existing HPV infections and discontinuations for a variety of reasons. In the bivalent vaccine trial, women with DNA from one or more high-risk (HR) HPV types or an abnormal cytology detected at a screening visit within 90 days before the initial study visit were not enrolled. Women with vaccine-type DNA at the enrollment visit were also excluded from the statistical analyses of efficacy. Although there was no pre-enrollment screening visit for the quadrivalent vaccine trial, women with vaccine-type HPV-DNA or serum antibodies detected at the initial trial visit were excluded from the statistical analyses

Table 1
Comparison of study designs for the phase IIb randomized controlled trials of bivalent HPV-16/18 and quadrivalent HPV-6/11/16/18 L1 VLP vaccines

| | Bivalent vaccine [2,3] | Quadrivalent vaccine [6,7] |
|---|---|---|
| Target population | Healthy women from Brazil, Canada, and the USA, 15–25 years of age, ≤6 sex partners, and no evidence of prior HR HPV infection | Healthy women from Brazil, Europe, and the USA, 16–23 years of age, ≤4 sex partners, and no evidence of prior HPV-6, -11, -16, or -18 infection |
| Prevalent HPV infection: exclusions for defining the intention-to-treat (ITT) or modified-intention-to-treat (MITT) analysis cohorts | ITT: prescreening before randomization to exclude women with an abnormal cytology, HPV-16 or HPV-18 serum antibodies, or HPV-DNA positive by PCR for 14 HR HPV types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68) ≤90 days before study entry | MITT: no pre-screening visit. Excluded from the type(s)-specific analysis if positive for (1) the genotype(s)-specific DNA (i.e., HPV-6, -11, -16, or -18), or (2) genotype(s)-specific antibodies at day 1 |
| ITT or MITT analysis cohorts | ITT: women who received at least one dose of vaccine or placebo, were negative for high-risk HPV-DNA at day 1 (enrollment), and who had any data available for endpoint measurement | MITT: women who had at least one dose of vaccine or placebo and were naïve (i.e., seronegative and DNA negative) to the relevant HPV type at day 1 (enrollment) |
| Randomization | Stratified (age and region) block randomization was centralized with an internet randomization system | Randomization schedules were computer generated using a blocking factor of eight (2:2:2:1:1) |
| Total number randomized | Vaccine 560/placebo 533 | Vaccine 277/placebo 275 |
| Number in ITT or MITT analysis cohorts | Vaccine 560/placebo 533 | Vaccine 276/placebo 275 |
| Vaccine | A 20 μg of HPV-16 L1 VLP, 20 μg of HPV-18 L1 VLP with ASO4 adjuvant containing 500 μg of aluminum hydroxide and 50 μg of 3-deacylated monophosphoryl lipid A (MPL) | A 20 μg of HPV-6 L1 VLP, 40 μg of HPV-11 L1 VLP, 40 μg of HPV-16 L1 VLP, 20 μg of HPV-18 L1 VLP with 225 μg of aluminum hydroxyphosphate sulfate (alum) adjuvant |
| Placebo | A 500 μg of aluminum hydroxide | A 225 or 450 μg of aluminum hydroxyphosphate sulfate (alum) |
| Dose; route of administration; schedule | 0.5 mL; intramuscular injection; day 1, month 1, and month 6 | 0.5 mL; intramuscular injection; day 1, month 2, and month 6 |
| Primary endpoint for ITT/MITT analysis | Incident infection detected after the initial visit defined as: PCR-based evidence of a new cervical infection with HPV-16, HPV-18, or both | Persistent infection detected after 30 days of the initial study visit defined as: (a) cervical, vaginal, and/or external genital samples collected at consecutive visits at least 4 months apart testing positive by PCR-based assay for the same viral genotype (HPV-6, -11, -16, or -18); (b) a biopsy specimen showing an HPV-related lesion and HPV-6, -11, -16, or -18 DNA detected in the same lesion; or (c) positive for HPV-6, -11, -16, or -18 DNA at the last visit before being lost to follow-up |
| Secondary disease endpoints | (1) 6- and 12-month persistent cervical HPV-16 or HPV-18 infection and (2) cytology outcomes (ASCUS, ASC-H, AGC, LSIL, HSIL) associated with HPV-16 or -18 | (1) Persistent HPV-6, -11, -16, or -18 infection and (2) histologically confirmed HPV-6-, -11-, -16-, or -18-related CIN |
| Completed follow-up visits | Vaccine/placebo | Vaccine/placebo |
| Months 33–38 | 304/296 | 239/242 (month 36) |
| Months 39–44 | 384/379 | Not available |
| Months 45–50 | 296/290 | Not available |
| Months 51–53 | 54/50 | Not available |

ASCUS (atypical squamous cells of undetermined significance); ASC-H (atypical squamous cells, cannot exclude high-grade); AGC (atypical glandular cells); LSIL (low-grade squamous cells of undetermined significance); HSIL (high-grade squamous intraepithelial lesions); CIN (cervical intraepithelial lesions).

of efficacy for the specific type(s). Between 12 and 16% of women enrolled and randomized in these trials completed less than three years of follow-up. However, the proportions of women who discontinued were similar for vaccine and placebo groups.

For ethical and scientific reasons, both trials used intermediate endpoints for HPV-16/18-related cervical cancer. Incident HPV-16 or -18 infection, the primary endpoint for the ITT analysis of the bivalent vaccine trial, was defined as PCR-based detection of vaccine-specific HPV-DNA (HPV-16 or -18) in (1) a cervical sample or (2) cervical or cervico-vaginal samples [12] collected after month 7 [2]. Persistent HPV-6, -11, -16, or -18 infection, the primary endpoint for the MITT analysis of the quadrivalent HPV vaccine trial, was a compos-

ite endpoint (detected after day 30) defined by the following criteria: (1) cervical, vaginal, and/or external genital samples collected at consecutive visits at least 4 months apart testing positive by PCR-based assay for the same viral genotype (HPV-6, -11, -16, or -18); (2) a biopsy specimen showing an HPV-related lesion and HPV-6, -11, -16, or -18 DNA detected in the same lesion; or (3) positive for HPV-6, -11, -16, or -18 DNA at the last visit before being lost to follow-up. Secondary endpoints for the bivalent vaccine trial included (1) 6- and 12-month persistent HPV infection, defined as PCR-based detection of vaccine-specific HPV-DNA (HPV-16 or -18) in cervical samples collected during follow-up visits, and (2) cytology outcomes associated with HPV-16 or -18 [3]. Other outcomes evaluated in the bivalent vaccine trial included (1) incident HPV infections related to HR HPV types other than HPV-16 or -18 and (2) histopathology outcomes as defined by a panel of expert pathologists. In the analyses of HPV persistence, women with a single positive DNA result for a vaccine-related HPV type at the last visit of record were classified differently in the two trials: in the quadrivalent vaccine trial they were classified as having an endpoint, whereas in the bivalent vaccine trial they were not.

The use of sensitive and specific methods for endpoint determination is critical to the validity and generalizability of trial results. HPV is well established as a necessary cause of cervical cancer (see Chapter 1). Reliable methods for HPV-DNA type identification in cellular and tissue samples have been developed and used in multiple laboratories (see Chapter 10). In both trials, vaccine-specific HPV types were detected by PCR-based assay of cellular and tissue specimens that were collected at multiple time-points throughout follow-up. In the long-term follow-up bivalent vaccine trial, cellular samples for HPV detection were obtained by clinician sampling directly at the cervix. In the quadrivalent vaccine trial, samples were obtained by a clinician from the cervix, vagina, and external genitalia.

The $SPF_{10}$ broad-spectrum primers with the line probe assay (LiPA) followed by HPV-16 and -18 type-specific PCR was used for detection of HPV-16 and -18 infection in the bivalent vaccine trial [13]. A multiplex PCR-based assay using HPV type-specific and gene-specific (L1, E6, and E7) primers and probes was used for detection of HPV-6, -11, -16, and -18 infection in the quadrivalent vaccine trial [1,5].

Liquid-based cervical cytology samples were collected every 6 months in both trials. The algorithm used for colposcopy referral after an abnormal cytology was different for the two trials, however: referral to colposcopy in the bivalent vaccine trial required two repeated cytologies showing (a) atypical squamous cells of undetermined significance (ASCUS) with a positive Hybrid Capture 2® test (Digene, Gaithersburg, MD) for HR HPV-DNA, (b) low-grade squamous intraepithelial lesions (LSIL), or (c) a single cytology showing atypical squamous cells, cannot rule out high-grade lesion (ASC-H), high-grade SIL, atypical glandular cells (AGC), or worse. Women in the quadrivalent vaccine trial were referred for colposcopy after a single abnormal cytology or a single clinical observation of a cervical lesion, and routinely for all women at the month-36 visit. Biopsy samples of external genital lesions were also obtained in the quadrivalent trial.

Histologic changes indicative of HPV-related precancerous lesions of the cervix are classified as cervical intraepithelial neoplasia (CIN) grade 2 or 3 (CIN-2/3) [14], which includes carcinoma *in situ*, and adenocarcinoma *in situ* (AIS). CIN-1, a histological manifestation of acute cervical HPV infection, usually resolves without treatment [15,16]. Other HPV-related lesions of the female genital tract are classified as vulvar intraepithelial neoplasia (VIN) grades 1–3, vaginal intraepithelial neoplasia (VAIN) grades 1–3, and condyloma acuminatum, which is genial wart. To minimize the well-recognized problem of variability between pathologists in the histological classification of the same lesion [17–20], both vaccine trials relied on a masked panel of expert gynecological pathologists to reach a diagnosis for the histologically defined endpoints.

Both trials showed efficacy for prevention of the prespecified primary endpoint. In the ITT analysis of the bivalent trial, the vaccine was 89% (95% CI: 77–95) effective in preventing incident cervical HPV-16 or -18 infection and in the MITT analysis of the quadrivalent trial, the vaccine was 89% (95% CI: 73–96) effective in preventing persistent HPV-6/11/16/18 infection (Table 2). With respect to secondary endpoints in the ITT analysis, the bivalent vaccine was 94% (95% CI: 61–100) effective in preventing 12-month persistent HPV-16 or -18 infection of the cervix, and 96% (95% CI: 84–100) effective in preventing HPV-16/18-associated abnormal cytology. In addition, there was 100% (95% CI: 42–100) vaccine efficacy against CIN due to HPV-16 or -18 (Table 2). The quadrivalent vaccine was 100% (95% CI: 32–100) effective in preventing CIN due to HPV-6, -11, -16, or -18. Results based on the MITT analysis of a large phase IIb trial of monovalent HPV-16 vaccine ($n = 2391$) with 48 months of follow-up showed 100% (95% CI: 74–100) protection from HPV-16-related CIN-2/3 [5].

Women who received at least one dose of the bivalent vaccine were less likely than those who received placebo to become infected with HPV types 45 and 31 throughout the entire 4.5 years of the trial [3]. The vaccine was as effective protecting against incident infections with HPV-45 (94%), which is HPV18-related, as it was against HPV-18 (90%). Protection against HPV-31, which is HPV16-related, was partial (55%). Protection against HPV-33, -52, and -58, which are also HPV-16-related high-risk types was not observed. The current findings suggest that vaccine-related protection might be HPV type-restricted, although not entirely HPV type specific. The extent of sustained cross-protection against persistent infections, abnormal cytology and precancerous lesions remains to be determined.

Vaccine-induced protection was robust, and even women with relatively low levels of antibodies after vaccination appeared to be protected. Rare instances of possible breakthrough infections did not appear to be correlated with low

Table 2
Results from the phase IIb ITT analysis of the bivalent HPV-16/18 and the phase IIb MITT analysis of the quadrivalent HPV-6/11/16/18 L1 VLP vaccines

| | Intention-to-treat (ITT) analysis of bivalent vaccine [3]; vaccine efficacy (95% CI) | Modified-intention-to-treat (MITT) analysis of quadrivalent vaccine [6,7]; vaccine efficacy (95% CI) |
|---|---|---|
| Primary objectives (ITT analysis) | | |
| Determine vaccine efficacy for prevention of incident infection defined as PCR-based evidence of a new cervical infection | HPV-16 cervix: 88% (74–95); vaccine/placebo events: 7/55<br>HPV-18 cervix: 90% (68–98); vaccine/placebo events: 3/29<br>HPV-16/18 cervix: 89% (77–95); vaccine/placebo events: 9/73 | |
| Primary objective (MITT analysis) | | |
| Determine vaccine efficacy for prevention of persistent infection (composite endpoint), defined as: (a) cervical, vaginal, or external genital samples collected at consecutive visits at least 4 months apart testing positive by PCR-based assay for the same viral genotype (HPV-6, -11, -16, or HPV-18); (b) a biopsy specimen showing an HPV-related lesion and HPV-6, -11, -16, or -18 DNA detected in the same lesion; or (c) first positive for HPV-6, -11, -16, or -18 DNA at the last follow-up visit | | Persistent HPV-6/11/16/18 infection (composite infection and lesion endpoint): 89% (73–96); vaccine/placebo events: 6/48 |
| Secondary objectives (ITT analysis) | | |
| Determine efficacy for preventing (1) 6- and (2) 12-month HPV-16/18 persistent infections; (3) determine efficacy for preventing abnormal cytology associated with HPV-16 or -18 (ASCUS, ASC-H, AGC, LSIL, HSIL) | (1) 6-month persistent cervical HPV-16/18 infection: 94% (78–99); vaccine/placebo events: 2/34. (2) 12-month persistent cervical HPV-16/18 infection: 94% (61–100); vaccine/placebo events: 1/16. (3) HPV-16/18 associated abnormal cytology: 96% (84–100); vaccine/placebo events: 2/44 | |
| Secondary objectives (MITT analysis) | | |
| Determine efficacy for preventing persistent infection or CIN defined as: (1) cervical, vaginal, or external genital samples collected at consecutive visits at least 4 months apart testing positive by PCR-based assay for the same viral genotype (HPV-6, -11, -16, or -18), or first positive for HPV-6, -11, -16, or -18 DNA at the last follow-up visit; (2) a cervical biopsy specimen showing CIN and HPV-6, -11, -16, or -18 DNA detected in the same tissue | | (1) Persistent HPV-6/11/16/18 infection: 88% (72–96); vaccine/placebo events: 6/47. (2) HPV-6/11/16/18 CIN: 100% (32–100); vaccine/placebo events: 0/7 |

ASCUS (atypical squamous cells of undetermined significance); ASC-H (atypical squamous cells, cannot exclude high-grade); AGC (atypical glandular cells); LSIL (low-grade intraepithelial lesions); HSIL (high-grade intraepithelial lesions); CIN (cervical intraepithelial lesions)

antibody titers. A portion of women enrolled in the trials did not receive all three doses of vaccine within 6 months of the first dose, which suggests that there might be flexibility around the timing of vaccine administration. However, efficacy for less than three doses cannot be inferred as an insufficient number of women received only one or two doses to determine efficacy for less than three doses. Analyses of the smaller and more restrictive per- or according-to-protocol cohorts of women who received all three doses of vaccine showed somewhat higher levels of protection, but overall the results were similar to those of the ITT or MITT analyses presented in Table 2.

### *2.4. Most recent results and status of the licensing process in July 2006*

Recent results from pre-specified interim analyses of the phase III quadrivalent HPV6/11/16/18 vaccine trials (submitted for publication) showed high level efficacy for prevention of HPV16- and HPV18-related CIN2-3 or worse, and pre-

vention of HPV-6-, -11-, -16-, and -18-related CIN, VAIN, VIN, and condyloma acuminatum. Based on these results and findings from trials of immunogenicity and safety in children (discussed below), regulatory agencies in Australia, Canada, Mexico, New Zealand, Togo, and the United States have approved the use of this vaccine. Regulatory authorities in several other countries are also considering its approval.

In the United States, the Centers for Disease Control and Prevention (CDC) Advisory Committee for Immunization Practices (ACIP) recommended that the approved vaccine be routinely administered to girls when they are 11 to 12 years old. The ACIP recommendation also allows for vaccination of girls as young as nine years of age as well as vaccination of girls and young women 13 to 26 years of age [http://www.cdc.gov/nip/vaccine/hpv/default.htm]. Australia approved the same HPV vaccine for girls and young women 9 to 26 years of age and for boys 9 to 15 years of age. A positive opinion for the quadrivalent vaccine has been received from the CHMP (Committee for Medicinal Products for Human Use) of the EMEA (European Agency for the Evaluation of Medicinal Products) and licensing is imminent in the European Union. The licensing dossier for the bivalent vaccine has been submitted and is under consideration at the EMEA.

## 3. Discussion

Although there are differences in the overall design of the phase IIb prophylactic HPV vaccine trials, published data from the trials are consistent and indicate that a three-dose regime of either bivalent or quadrivalent vaccine is generally safe and highly effective in preventing HPV-16 and -18 infections and related cervical lesions. In the quadrivalent vaccine trial prevention of HPV-6/11 infections and HPV-6/11/16/18-related lesions was also observed. Both vaccines were developed relatively recently and thus published information on the durability of protection is limited to 36 months for the quadrivalent vaccine and 53 months for the bivalent vaccine. Continued follow-up of women participating in the phase IIb trials and of women participating in the ongoing phase III trials will provide more precise estimates of longer term efficacy. Results from large (5000+ and 10,000+) phase III trials of efficacy will be published shortly. Primary endpoints for the phase III bivalent vaccine trials include 12-month persistent HPV-16 and -18 infection and HPV-16- or -18-related CIN, including CIN-2/3 or worse. Primary endpoints for the phase III quadrivalent vaccine trials include HPV-16- or -18-related CIN-2/3 or worse, and HPV-6-, -11-, -16-, or -18-related CIN, VAIN, VIN, or condyloma acuminatum.

Additional on-going trials are addressing issues of vaccine safety, immunogenicity, and efficacy in populations other than those comprised of young women. Safety and immunogenicity have been evaluated in 9–15-year-old boys and girls (quadrivalent vaccine) or 10–14-year-old girls (bivalent vaccine). Abstract data presented at scientific meetings indicate that both vaccines are generally safe and highly immunogenic in children. Trials of women over 26 years of age (both bivalent and quadrivalent vaccines) and of young men (quadrivalent vaccine) are on-going. Other populations to be studied include infants and immunocompromised children and young adults (e.g. those with HIV/AIDS, transplants, chronic immunosuppression, or autoimmune diseases). However, it is likely that one or both of these vaccines will be approved and available for widespread use before results from trials of infants, children, and adults older than 26 are published.

Preliminary results from a monovalent HPV-16 vaccine trial [21] and from the phase IIb quadrivalent vaccine trial (Fig. 2) suggest that HPV L1 VLP vaccines induce anamnestic responses. Compared to women who are negative for vaccine-type antibodies and DNA at enrollment, those with detectable vaccine-type antibodies usually respond with antibody titers that rise faster, peak higher, and remain at higher levels following administration of the vaccine. Such responses indicate the possibility of long-term vaccine-induced protection, either following a primary series or with a booster injection(s).

In summary, despite differences in how the bivalent and quadrivalent HPV vaccines are formulated and how the phase IIb clinical trials were designed and analyzed, published results are consistent and indicate that a three-dose regimen of either vaccine is generally safe and highly effective in preventing infections and lesions caused by the targeted HPV types.

## Disclosed potential conflicts of Interest

LAK: Research Grants (Merck and Co., Inc.

DMH: Consultant/Research Grants (GlaxoSmithKline, Merck and Co., Inc.)

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