Quadrivalent HPV Vaccine Moderately Efficacious in Preventing HPV Infection and Related Disease in Women Aged 24 to 45 Years

Munoz N, Manalastas R, Pitisuttithum P, et al. Safety, immunogenicity, and efficacy of quadrivalent human papillomavirus (types 6, 11, 16, 18) recombinant vaccine in women aged 24–45 years: a randomized, double-blind trial. Lancet 2009; 373:1949–57.

Study Overview

Objective. To determine if the quadrivalent human papillomavirus (HPV) vaccine (types 6, 11, 16, 18) is efficacious in preventing HPV infection or related disease in women aged 24 to 45 years.

Design. Randomized, double-blind, placebo-controlled phase III trial.

Setting and participants. Women were recruited through health centers and primary care providers in 7 countries: Colombia, France, Germany, Philippines, Spain, Thailand, and the United States. Women were excluded if they were pregnant, had a history of genital warts or cervical disease, had prior surgery on the cervix, had a cervical biopsy within the last 5 years, or had HIV or were immunocompromised. Randomization was done separately for patients < 35 years old and those ≥ 35 years old. 1910 were assigned to the vaccine arm and 1908 to the placebo arm. Subjects were screened for immunity to the HPV serotypes through serum analysis at baseline. Infection with HPV was determined through Pap testing and HPV PCR (polymerase chain reaction) conducted on labial, vulvar, perineal, perianal, endocervical and ectocervial swabs at baseline and every 6 months following. Complete gynecologic exams were done at baseline, 7 months, 12 months, and yearly thereafter and external genital exams were conducted every 6 months.

The determination of efficacy was made using per-protocol efficacy (PPE) analyses, a population naive to relevant type (NRT) analysis, and intention-to-treat (ITT) assessment, with the PPE results reported as the primary efficacy results. Subjects were included in the PPE group if they were seronegative to the relevant HPV type at baseline, had no evidence of HPV infection on PCR or biopsy samples from baseline to month 7, had all 3 vaccine or placebo injections during 1 year and had at least 2 follow-up visits after month 7. NRT subjects were those who were seronegative and PCR-negative to the relevant HPV type at baseline, had at least 1 vaccine or placebo injection, and had 1 or more visits after the baseline visit. ITT subjects included all women who had at least 1 injection and 1 or more follow-up visits.

Main outcome measures. The combined incidence of HPV infection for 6 months or more and HPV-associated disease (cervical, vulvar, or vaginal intraepithelial neoplasia; adenocarcinoma in situ; cervical, vulvar, or vaginal cancer; or genital warts) related to HPV 6, 11, 16, or 18 and to HPV 16 or 18 alone. The secondary endpoint included the combined incidence of infection related to HPV 6 or 11 for 6 months or more and cervical or external genital disease. Infection was defined as (1) the isolation of the same HPV type on 2 occasions at least 6 months apart or (2) HPV-associated disease found on biopsy with positive HPV testing in the visit before or after the biopsy was taken. Disease was defined as a tissue sample with 1 of the identified disease states. The intended duration of the study is 4 years.

Main results. These results represent interim results after a mean of 2.2 years of follow-up. Mean age of participants was 34.3 years. Hispanics comprised 43.2% of the sample while 31.2% were Asian and 20.6% were white. Baseline characteristics were similar in the vaccine and placebo groups. 33.5% and 32.8% were either immune to or had an active infection with at least 1 HPV serotype at baseline. Less than 2% were immune to or infected with more than 1 serotype. In the PPE group, vaccine efficacy for the primary endpoint (HPV infection and related disease from any serotype) was 90.5% (95% confidence interval [CI], 73.7%–97.5%; 4 cases in vaccine group, 41 in placebo). Efficacy against the second primary endpoint (HPV 16 or 18 infection and disease) was 83.1% (95% CI, 50.6%–95.8%; 4 cases in vaccine group, 23 in placebo) while efficacy against the secondary endpoint (HPV 6 or 11 infection and disease) was 100% (95% CI, 79%–100%; 0 cases in vaccine group, 19 in placebo). In the NRT and ITT analyses, vaccine efficacy was 74.6% (95% CI, 58.1%–85.3%; 20 cases in vaccine group, 77 in placebo) and 30.9% (95% CI, 11.1%–46.5%; 108 cases in vaccine group, 154 in placebo) for the primary endpoint. Safety was comparable between the groups with serious adverse events reported in 3 of the vaccine subjects and 7 of the placebo subjects.

Conclusion. HPV quadrivalent vaccine is moderately effective in preventing HPV infection and related disease among women aged 24 to 45.

Commentary

The quadrivalent HPV vaccine is currently recommended by the CDC's Advisory Committee on Immunization Practices (ACIP) as part of the routine vaccination schedule for girls aged 11 to 12 years with catch-up vaccinations for girls and women up to age 26 years [1]. The recommendations arose from published data on the efficacy of the vaccine in preventing cervical and anogenital diseases among women under age 26 [2,3]. The vaccine was tested first in this younger age-group because most HPV infection is acquired by young women soon after becoming sexually active [4–6]. Initial data also demonstrated that the vaccine's efficacy was primarily achieved for women who were not exposed to HPV before vaccination [1–3], thus compelling the ACIP to recommend vaccination very early in life.

However, the cumulative, 5-year incidence of high-risk HPV infection in women between 30 and 44 years of age is still high—18.2% in one cohort of 1610 Colombian women [6]. A recent meta-analysis found evidence of a 2nd peak in prevalence of HPV infection after the age of 44 [7]. As a result, the manufacturer of the quadrivalent HPV vaccine, Merck, funded this study to determine whether efficacy extended to women older than the age-group for which the vaccine is currently approved.

The trial was well-conducted with very little loss to follow-up. The efficacy of the vaccine in preventing HPV infection and related disease appears to be strong, with 90.5% efficacy in the per-protocol analysis. Further data in this study show that immune responses to the vaccine were strong in this older population although slightly lower for HPV serotypes 6, 11, and 18 compared with younger populations.

Based on these results, which were most robust in the PPE group, a targeted vaccination strategy for those women known to be HPV-naive at baseline would seem logical. However, the clinical application of this study is significantly attenuated by the small absolute differences in endpoints between the intervention and placebo groups and the diminished efficacy in the intention-to-treat analysis, the group that most directly resembles the population encountered in practice. HPV testing is not considered part of routine cervical cancer screening except as a means to prevent unnecessary biopsies (reflex HPV testing for atypical cells of undetermined significance results) or to prolong the interval for Pap testing among women in monogamous relationships [8]. Mass vaccination of older populations does not appear to be supported by this study, and targeted vaccinations of HPV-naive populations would require proof of the clinical effectiveness and cost-effectiveness of HPV screening first.

Applications for Clinical Practice

The HPV vaccine is efficacious in preventing HPV-related diseases among women aged 24 to 45, especially if women are HPV-negative at baseline. The absolute reduction in disease is small, and further research must determine whether HPV vaccination is cost-effective, either as a mass vaccination strategy or as a targeted strategy for those who are HPV-negative at baseline.

—Review by Jason P. Block, MD, MPH

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