HPV VACCINE RECOMMENDATIONS (www.cdc.gov)
• Females starting at age 11 or 12 (3 doses; day 0, 1 month, 6 months)
  - Catch up vaccination at ages 13 through 26 years
• May be administered to males ages 9 through 26 years

ARTICLE

METHODS
Design: Randomized, double-blind, placebo-controlled trial

Patients: 3819 women, ages 24-45 years (mean age 34) from 38 international study sites
Exclusion criteria:
• Pregnancy
• Previous hysterectomy or cervical surgery
• History of genital warts
• Past or present cervical disease
• Cervical biopsy within the past 5 years
• HIV infection
• Immunocompromised

Intervention: Amorphous aluminum hydroxyphosphate sulfate adjuvanted quadrivalent HPV (types 6, 11, 16, 18) L1 VLP vaccine [Gardisil/Silgard, Merck] or aluminum-containing placebo administered at day 1, and months 2 and 6

Mean follow up time: 2.2 years

Outcomes:
Primary: Composite of infection of at least 6 months’ duration AND cervical and external genital disease related to HPV 6, 11, 16, or 18; and to 16 and 18 alone
Secondary: Combined incidence of infection of 6 months’ or more duration AND cervical and external genital disease related to HPV 6 or 11

Definitions:
Infection of at least 6 months’ duration: Detection of the same HPV type in cervicovaginal or anogenital swabs at 2 or more consecutive visits spaced at least 6 months apart (1 month visit windows); OR presence of cervical or genitai disease associated with the relevant type with type-specific HPV DNA detected on cervicovaginal or anogenital swabs at the visit directly before or after the biopsy was taken
Disease: Tissue sample diagnosed as cervical, vulvar, or vaginal intraepithelial neoplasia; adenocarcinoma in situ; genital warts; or cervical, vulvar, or vaginal cancer with type-specific HPV DNA related to HPV 6, 11, 16, or 18

Disease ascertainment:
• Complete GYN exam (speculum and bimanual)
• External genital inspections with a magnifying glass
• Labial/vulvar/perineal and perianal swabs for HPV multiplex PCR
• ThinPrep Pap testing for cytology
**Statistical analysis:**
- Per-protocol efficacy (PPE) analyses:
  - Seronegative to the relative HPV type at day 1 and PCR negative on day 1 until month 7
  - Received all 3 vaccinations within 1 year
  - One or more follow-up visits after month 7
- Intention-to-treat (ITT) population ($n_{vaccine} = 1886; n_{placebo} = 1883$)
  - All women who received at least 1 dose of the vaccine or placebo
  - One or more follow-up visit after day 1
- Naïve to the relevant type (NRT): modified PPE population
  - Naïve to a vaccine HPV type at day 1
  - Received at least 1 dose of vaccine or placebo
  - One or more follow-up visit after day 1

**VALIDITY**
- Was the assignment of patients to treatments randomized? **Yes**
- Was the follow-up of patients sufficiently long and complete? **Unclear**
- Were all patients analyzed in the groups to which they were randomized? **Yes**
- Were patients and clinicians kept “blind” to treatment? **Yes**
- Were the groups treated equally apart from the experimental treatment? **Yes**
- Were the groups similar at the start of the trial? **Yes**

**RESULTS**

*Baseline demographics:*
- Race/ethnic origin: largest proportion was Hispanic (43.2%)
- 33.2% were HPV-positive (6, 11, 16, or 18) by serology or PCR at study onset
  - 7.9% were positive by PCR alone
  - 90% (3455) were susceptible to 3 or 4 vaccine HPV subtypes
  - 67% (2565) were naive via PCR and serology to all 4 subtypes

<table>
<thead>
<tr>
<th>OUTCOMES</th>
<th>PLACEBO</th>
<th>VACCINE</th>
<th>AT MEAN FOLLOW UP 2.2 YEARS</th>
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<tbody>
<tr>
<td></td>
<td>CER (%)</td>
<td>EER (%)</td>
<td>RRR (%)</td>
</tr>
<tr>
<td>HPV 6/11/16/18</td>
<td>8.1</td>
<td>5.7</td>
<td>30</td>
</tr>
<tr>
<td>HPV 16/18</td>
<td>6.1</td>
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<tr>
<td>HPV 6/11</td>
<td>2.4</td>
<td>1.3</td>
<td>46</td>
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**DISCUSSION**
- Limitations: PPE design, inclusion of HPV-positive women, inclusion of CIN I and II, short follow up
  - GlaxoSmithKline [Cervarix]
  - Women ages 15-25 years, normal cervical cytology, HPV-16/18 seronegative and oncogenic HPV DNA-negative (14 types) at screening