A quadrivalent vaccine against human papillomavirus prevented anogenital diseases in young women

Garland SM, Hernandez-Avila M, Wheeler CM, et al. **Quadrivalent vaccine against human papillomavirus to prevent anogenital diseases.** N Engl J Med. 2007;356:1928-43.

Clinical impact ratings: GIM/FP/GP ★★★★★★☆ Infectious Disease ★★★★★★☆ Oncology ★★★★★☆☆ Public Health ★★★★★☆☆

QUESTION

Does a quadrivalent vaccine against human papillomavirus (HPV) prevent anogenital diseases in young women?

METHODS

Design: Randomized, placebo-controlled trial (Females United to Unilaterally Reduce Endo/Ectocervical Disease [FUTURE] I study).

Allocation: Concealed.*

Blinding: Blinded (participants, clinicians, outcome assessors, adjudication committee, {data analysts, and data safety and monitoring committee}†).*

Follow-up period: Mean 3 years (maximum 4 y). Follow-up started on day 1 in the intention-to-treat and susceptible populations and 1 month after the third dose of vaccine in the per-protocol population.

Setting: 62 sites in 16 countries worldwide.

Participants: 5455 healthy, nonpregnant women 16 to 24 years of age (mean 20 y) with no history of genital warts or abnormal results on cervical cytologic testing. Women with > 4 lifetime sex partners were excluded.

Intervention: Quadrivalent HPV-6/11/16/18 L1 viruslike-particle vaccine (n = 2723) or placebo (n = 2732) in 3 doses injected on day 1, month 2, and month 6.

Outcomes: 2 primary composite endpoints: external anogenital and vaginal lesions (anogenital warts or vulvar or vaginal intraepithelial neoplasia grades 1 to 3 or cancer associated with vaccine-type HPV) and cervical lesions (cervical intraepithelial neoplasia [CIN] grades 1 to 3, adenocarcinoma in situ, or cancer associated with vaccine-type HPV).

Patient follow-up: 100% in the intention-to-treat population (all randomized women); 98% in the susceptible population (women who were negative for HPV type 6, 11, 16, or 18 on day 1); and 83% in the per-protocol population (women who received all 3 doses of vaccine, had no major protocol violation, and were negative for HPV type 6, 11, 16, or 18 on day 1 and through 1 mo after the third dose).

MAIN RESULTS

In the intention-to-treat population, vaccine efficacy was 73% for external anogenital and vaginal lesions and 55% for cervical lesions associated with vaccine-type HPV (Table). Results for the susceptible and per-protocol populations are shown in the Table. Adverse events at the injection site and fever were more frequent in the vaccine group than in the placebo group.

CONCLUSION

A quadrivalent vaccine against human papillomavirus (HPV) in young women prevented anogenital warts, intraepithelial neoplasia, and adenocarcinoma in situ of the vulva, vagina, and cervix associated with HPV types 6, 11, 16, and 18.

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*See Glossary.

†Information provided by author.

Quadrivalent vaccine against human papillomavirus (HPV) types 6, 11, 16, and 18 vs placebo to prevent vaccine-type HPV-associated anogenital diseases in young women at mean 3 years‡

Populations (n)	Outcomes	Rate/100 woman-y		Vaccine efficacy (95% CI)
		Vaccine	Placebo	
Intention-to-treat (5455)	External and vaginal lesions	0.4	1.3	73% (58 to 83)
	Cervical lesions	0.9	2.1	55% (40 to 66)
Susceptible (5351)	External and vaginal lesions	0.1	1.1	95% (87 to 99)
	Cervical lesions	< 0.1	1.2	98% (92 to 100)
Per-protocol (4540)	External and vaginal lesions	0	1.1	100% (94 to 100)
	Cervical lesions	0	1.2	100% (94 to 100)

‡CI defined in Glossary.

COMMENTARY

The FUTURE I study by Garland and colleagues provides evidence for the efficacy and safety of the quadrivalent HPV vaccine. The vaccine was shown to have considerable efficacy against the surrogate outcomes of anogenital and cervical lesions related to vaccine HPV types in women with no evidence of previous exposure to these types. The vaccine also seemed to be safe. The study was somewhat limited by length of follow-up; longer follow-up will be required to establish the benefit for cancer outcomes, the durability of immunization, and the need for booster immunization.

Although relying on surrogate endpoints is not optimal, the study endpoints were feasible and appropriate given the study duration and sample size. CIN grade 2 or 3 is preferred as a surrogate marker for cancer, whereas CIN 1 is more likely to be a morphologic marker of acute HPV infection than of risk for progression. Up to 90% of women who test positive for HPV will become HPV negative on the same tests within 6 to 24 months because of an effective immune response to HPV. 10% to 20% of women with HPV lesions will have persistent cervical dysplasia. The duration between acquisition of HPV and diagnosis of cancer is measured in years to decades. Furthermore, the age-adjusted incidence of cervical cancer in the United States is only 8.7 per 100 000 women per year (1).

In the study by Garland and colleagues, the age range (16 to 24 y) was narrower than the current guidance for vaccination in the United States (9 to 26 y). However, the results of the study provide indirect evidence to support use of the vaccine in young girls (9 to 13 y) because the vaccine had 100% efficacy in the subgroup that was HPV naive. The vaccine did not seem to be efficacious among women with previous exposure to quadrivalent subtypes, supporting early administration of the vaccine before sexual activity begins.

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Reference

1. **National Cancer Institute.** Surveillance Epidemiology and End Results. Fast stats: cervix uteri cancer. seer.cancer.gov/faststats/sites.php?site=Cervix+Uteri+Cancer&stat=Incidence (accessed 24 August 2007).