Quadrivalent HPV vaccine prevented cervical neoplasia caused by HPV-16 and HPV-18

The Future II Study Group. **Quadrivalent vaccine against human papillomavirus to prevent high-grade cervical lesions.** N Engl J Med. 2007;356:1915-27.

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

QUESTION

How effective was a quadrivalent vaccine against human papillomavirus (HPV) types 6, 11, 16, and 18 in preventing cervical neoplasia grade 2 or 3 or adenocarcinoma in situ caused by HPV-16 or HPV-18 in healthy young women?

METHODS

Design: Randomized placebo-controlled trial (Females United to Unilaterally Reduce Endo/Ectocervical Disease [FUTURE II]).
Allocation: Concealed.
Blinding: Blinded (outcome assessors).
Follow-up period: Up to 4 years (mean follow-up 3 y).
Setting: 90 study sites in 13 countries in Asia, North America, Latin America, and Europe.
Patients: 12 167 women 15 to 26 years of age (mean age 20 y). Exclusion criteria included pregnancy, abnormal results on a Papanicolaou smear, and > 4 sex partners over lifetime.
Intervention: 3 doses of quadrivalent HPV 6/11/16/18 viruslike-particle vaccine with amorphous aluminium hydroxyphosphate sulphate adjuvant (n = 6087) or placebo (n = 6080) at day 1, month 2, and month 6.
Outcomes: Cervical intraepithelial neoplasia (CIN) grade 2 or 3, adenocarcinoma in situ, or invasive carcinoma of the cervix with detection of DNA from HPV-16, and/or HPV-18 in 1 of the lesions for women who were negative for HPV-16 or HPV-18 through to 1 month after the third dose and completed the study (primary outcome) or for all women (intention-to-treat analysis).
Patient follow-up: 87% completed the study (100% were included in the intention-to-treat analysis).

MAIN RESULTS

In women who completed the study and were negative for HPV-16 and HPV-18 until 1 month after the third dose, the quadrivalent vaccine was 98% effective (95% CI 86 to 100) in preventing high-grade cervical lesions. Overall, fewer women in the vaccine group than in the placebo group had any lesion, cervical neoplasia grade 2, or cervical neoplasia grade 3; groups did not differ for adenocarcinoma in situ (Table).

CONCLUSION

A quadrivalent vaccine against HPV types 6, 11, 16, and 18 was effective in preventing cervical neoplasia caused by HPV-16 or HPV-18 in healthy young women.

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* See Glossary.

Human papillomavirus (HPV) vaccine against types 6, 11, 16, and 18 vs placebo for preventing high-grade cervical lesions caused by HPV-16 and HPV-18†

Outcomes at mean 3 y	Vaccine	Placebo	RRR (95% CI)	NNT (CI)
All lesions	1.4%	2.4%	44% (27 to 57)	94 (64 to 170)
Cervical neoplasia grade 2	0.7%	1.6%	57% (39 to 70)	111 (78 to 186)
Cervical neoplasia grade 3	0.9%	1.7%	45% (25 to 60)	130 (84 to 269)
Adenocarcinoma in situ	0.08%	0.1%	29% (–112 to 76)	Not significant

†Abbreviations defined in Glossary. RRR, NNT, and CI calculated from data in article.

COMMENTARY

The purpose of the HPV vaccine is to reduce the incidence of cervical cancer among all women. The FUTURE II study documents the benefits of the quadrivalent HPV vaccine.

The vaccine has some limitations. First, it takes an extended time to see disease reduction. Initial phase III trial data from FUTURE II showed vaccine efficacy of 12% for all CIN grade 2 or 3 lesions and adenocarcinoma in situ in all women 15 to 26 years of age 2 years after vaccination (Gardasil product insert). One year later (3 years after vaccination), the vaccine efficacy increased to 17%: a slow gain. It will take 20 to 30 years to see the number of women with cervical cancer caused by HPV-16 and -18 in the United States decrease by half with vaccination (1), in part because the time from HPV infection to cancer development can be decades. Second, new cases of cervical cancer will continue to occur. Even with the quadrivalent vaccine, its boosters as they become necessary, and routine repeated Pap screenings, some women will still develop cervical cancer caused by other types of high-risk HPV. Third, diagnostic workup and therapy for CIN will still be necessary. After decades of vaccination, assuming 70% population coverage, the quadrivalent vaccine will reduce the colposcopy clinic burden of cervical disease by approximately one third, when all levels of abnormal cervical cytology and histology are considered. The remaining health care burden of vaccinated women who continue to have abnormal Pap tests and CIN lesions will remain substantial.

The Web supplements of the FUTURE II trial, though, present the most important clinical data for public health. A small number of women with past exposure to HPV-16 or -18 who were not infected with HPV-16 or -18 at the time of vaccination enjoyed a 100% vaccine efficacy for HPV-16/18–related CIN grade 2 or 3 lesions and adenocarcinoma in situ. To maintain public health support of HPV vaccinations, cervical disease reduction must occur as soon as possible. To accelerate this disease reduction, public health emphasis must be on vaccinating all women regardless of past HPV exposure, not just 12-year-olds.

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Reference

1. **Elbasha EH, Dasbach EJ, Insinga RP.** Model for assessing human papillomavirus vaccination strategies. Emerg Infect Dis. 2007;13:28-41.