The HPV vaccine

An analysis of the FUTURE II study

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The FUTURE II Study Group. Quadrivalent vaccine against human papillomavirus to prevent high-grade cervical lesions. *N Eng J Med* 2007;356(19):1915-27.

Research question

Does 3-dose administration of quadrivalent vaccine against human papillomavirus (HPV) types 6, 11, 16, and 18 prevent high-grade cervical intraepithelial neoplasia (CIN) and adenocarcinoma in situ?

Type of article and design

Randomized double-blind placebo-controlled trial

Relevance to family physicians

In July 2006, Gardasil—a quadrivalent viruslike particle vaccine for HPV types 6, 11, 16, and 18—was approved in Canada for use in girls and women aged 9 to 26 years of age. Knowledge and understanding of the link between HPV and cervical precancer and cancer remain poor among the general population.[1] Some studies have shown that HPV vaccination is generally appealing to parents and young women[2]; however, they are concerned about safety[3,4] and the potential stigma of vaccinating against a sexually transmitted infection.[5] Physicians will face questions from young women and girls' parents regarding the vaccine's appropriateness and safety, and they will be required to continue counseling about the need for ongoing cervical cancer screening and protection from sexually transmitted infections. Family physician endorsement of the vaccine will likely influence uptake by patients.[2]

Overview of study and outcomes

Women aged 15 to 26 years who were not pregnant, had no history of abnormal Papanicolaou smears, and reported no more than 4 lifetime sex partners were recruited and randomized to receive a 3-dose course of Gardasil or identical aluminum-containing placebo at months 0, 2, and 6.[6] The primary composite outcome was incidence of CIN grades 2 and 3, adenocarcinoma in situ, or invasive carcinoma of the cervix related to HPV types 16 or 18. Secondary outcomes included incidence of each lesion type individually, lesions that contained HPV types 16 or 18, and lesions regardless of HPV type. The outcomes were assessed in women susceptible to HPV types 16 and 18 (ie, women not infected by HPV 16 or 18 through to 1 month after the last dose) who received 3 doses within 1 year (per-protocol susceptible population), in women susceptible to HPV types 16 and 18 at baseline and who had at least 1 dose of vaccine (unrestricted susceptible population), and in all women regardless of HPV or cervical neoplasia status at the start of the study and regardless of adherence to study protocol (intention-to-treat population). Women were followed with gynecologic examination at 1 and 6 months after the third injection and at 24, 36, and 48 months. Women with more than 1 histologic lesion were counted only once in the primary composite end point, as were women with both HPV types 16 and 18. The results are presented as the vaccine efficacy rate, which corresponds to the relative risk reduction. The results were presented after 3 years' follow-up.

Results

More than 12 000 women in 13 countries were randomized, most from Europe. Mean age was approximately 20 years and nearly all women had been sexually active. At baseline, 9% were infected at the cervix with HPV-16 and 4% with HPV-18; 11% had cytologic abnormalities. The average follow-up time was 3 years. In the per-protocol susceptible population, 1 of 5305 women in the vaccine group and 42 of 5260 women in the placebo group developed the composite primary outcome, for a vaccine efficacy of 98% ($P<.001$, 95% confidence interval [CI] 86%-100%). Vaccine efficacy in the susceptible population that did not follow protocol (unrestricted susceptible population) was 95% (95% CI 85%-99%). Efficacy in both susceptible populations was 100% for adenocarcinoma in situ. Vaccine efficacy for the primary composite end point in the full (intention-to-treat) population was 44% (95% CI 26%-58%). Nearly all women (98%) in this full population received at least 1 vaccine and 1 follow-up visit. Further analysis of the intention-to-treat population showed that the vaccine did not alter the course of lesions related to HPV types 16 or 18 that were already present before vaccination. The vaccine was also not efficacious for protecting against CIN grade 3 or adenocarcinoma in situ when considering all HPV types (ie, when including HPV types other than 16 or 18). Although numbers were small and results were not statistically significant, there appeared to be some protection among women with one of HPV types 16 or 18 against lesions containing the other type. In an immunogenicity subgroup, initial

seropositivity was more than 99% for all vaccine types; however, at 24 months more than 90% of women were seropositive for HPV types 6, 11, and 16, and 68% were seropositive for HPV-18. Adverse events were similar in both groups overall; however, in the group of women who became pregnant and whose conception date was estimated to be within 30 days of the last injection date, there was a statistically significant absolute risk increase (5 in the vaccine group versus 0 in the placebo group) in live infants born with a congenital anomaly.

Analysis of methodology

This study was a phase 3 trial conducted mainly in non–North American settings, among women aged 15 to 26 years. Randomization was performed centrally using an interactive voice response system. Histology outcome assessment was centralized and blinded, and the endpoint determination was made by a panel of 4 pathologists. The study was designed to follow women for 4 years after vaccination; however, the average follow-up was 3 years.

The authors report the primary hypothesis as vaccine reduction of outcomes in the per-protocol susceptible population and that the primary efficacy analysis was conducted in this group. There were 1602 (13%) postrandomization exclusions to formulate this group. Reintroduction of these subjects in the intention-to-treat analysis supported the conclusion that the vaccine substantially decreased the occurrence of precancer lesions associated with HPV types 16 or 18.

A number of subgroup analyses were performed, which also showed substantial reduction of outcomes related to HPV types 16 or 18. These analyses met most of the subgroup analysis validity criteria of Oxman and Guyatt[7]: the analyses were specified a priori; the difference was clinically and statistically significant; and there was indirect previous evidence[8] as well as biologically plausibility that the vaccine would be efficacious in these subgroups. The α levels in statistical comparisons were adjusted to account for the interim analysis, but not for multiple comparisons of outcomes and adverse events.

Loss to follow-up is difficult to ascertain but appears to be only 239 (2%) subjects in the intention-to-treat population (ie, subjects who did not receive at least 1 vaccine dose and who did not have at least 1 follow-up visit after the last dose).

Application to clinical practice

This study shows that the Gardasil vaccine has high efficacy for preventing HPV types 16 or 18, high-grade CIN, and cervical cancer among sexually active women aged 15 to 26 years with no prior infection with these types and moderate efficacy among a general population of women. The vaccine covers 2 of the most common carcinogenic HPV types, which cause approximately 70% of all cervical cancers[9]; therefore, there will continue to be a need for Pap smear screening.

The study follow-up time was 3 years, and the extent of long-term protection is currently unknown, although the authors note there is a 15-year follow-up study under way. There could be waning immunity, as has been suggested with the varicella vaccine.[10] Cervical cancer often takes many years to develop after HPV infection; however, CIN grades 2 and 3 often occur within 2 years of infection, particularly those associated with HPV types 16 or 18,[11] and 25% of CIN grade-2 lesions progress to CIN grade 3 or worse in 2 years.[12]

The average age at first intercourse among participants in this study was nearly 17 years of age. A Canadian study in 2002 found that 19% of females in grade 9 (approximately 14 to 15 years of age) reported having vaginal intercourse at least once.[13] The vaccine will likely be most beneficial when administered before sexual activity. In the intention-to-treat population, most of whom were sexually active, the vaccine was only efficacious for preventing lesions associated with HPV types 16 and 18, but it was not efficacious for preventing high-grade cervical disease when considering all HPV types.

BOTTOM LINE

- There is good evidence for vaccination of girls and women who are susceptible to HPV types 16 and 18 for the prevention of high-grade cervical lesions and cancer.
- The only way to ensure results similar to the study in women who are susceptible to HPV types 16 and 18 is to vaccinate before the onset of sexual activity. Even among women vaccinated before onset of sexual activity, cervical screening will continue to be necessary.
- Patients or their parents should be aware of the current limitations in knowledge regarding duration of protection.

POINTS SAILLANTS

- De bonnes données scientifiques corroborent le bien-fondé de la vaccination des filles et des femmes susceptibles au papillomavirus de types 16 et 18 pour la prévention de lésions cervicales graves et du cancer du col de l'utérus.
- La seule façon d'assurer des résultats semblables à ceux de l'étude chez des femmes vulnérables au papillomavirus de types 16 et 18 est de les vacciner avant qu'elles ne commencent à avoir une activité sexuelle. Même les femmes vaccinées avant le début de leur activité sexuelle doivent continuer à avoir des tests de dépistage du cancer du col.
- Les patientes ou leurs parents doivent être au courant des limites actuelles des connaissances concernant la durée de la protection.

Public funding of the vaccine in Canada has begun. In the province of Ontario, the vaccine is covered for girls in grade 8. The complete course costs $405 in Canada. The vaccine is already free in some countries, such as Australia, for girls and women aged 12 to 26 years until June 2009, after which time girls aged 12 and 13 will be targeted. The vaccine is approved for use in girls and women aged 9 to 26 in Canada. The optimal age for vaccination remains uncertain, as studies of efficacy have not been done in girls younger than 15; however, it seems reasonable to vaccinate at a slightly younger age to increase the chances of vaccinating while susceptible.

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Competing interests

Dr Lytwyn *has received grants from Merck Canada.*

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