

tend protection to cover additional pathogenic serotypes? Will the economics allow this therapy to reach all who may benefit, such as those in the developing world? Might HPV vaccination be beneficial in preventing other, noncervical HPV-induced cancers (such as HPV-related oropharyngeal cancer³)?

There is no doubt that the findings reported in this issue of the *Journal* open a new field at the interface of basic science, clinical medicine, public health, and public policy. It is important to keep in mind that these new treatments raise many scientific, medical, economic, and sociological questions. We have begun an exciting journey; we need to continue in the right direction.

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HPV Vaccination — More Answers, More Questions

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The availability of a “cancer vaccine” has elicited enormous enthusiasm from the medical community and the public, culminating in advocacy for mandatory vaccination against human papillomavirus (HPV) and a recommendation from the Centers for Disease Control and Prevention (CDC) that 30 million girls and women between the ages of 11 and 26 years in the United States be vaccinated.¹ Previous reports^{2,3} showed a remarkable 100% efficacy of a quadrivalent vaccine targeting HPV types 6, 11, 16, and 18 on outcomes related to vaccine HPV types in women with no evidence of previous exposure to those types. Since HPV types 16 and 18 are implicated in 70% of cervical cancers,⁴ these types are ideal targets for a new vaccine.

In this issue of the *Journal*, reports on two large, ongoing, randomized, placebo-controlled trials show the effect of this vaccine on important clinical outcomes, including rates of adenocarcinoma in situ and cervical intraepithelial neoplasia after an average of 3 years of follow-up.^{5,6} Investigators in these trials have hit their mark soundly: the vaccine showed significant efficacy against anogenital and cervical lesions related to vaccine type in women with no evidence of previous exposure to vaccine-specific types; the vaccine also appeared to be safe. In addition, the

studies report outcomes in all subjects regardless of HPV status at baseline and regardless of whether outcomes were related to HPV types targeted by the vaccine. Policymakers now have more evidence to assess the benefits and risks of widespread vaccination.

Given the rarity of incident cervical cancer, pre-invasive cervical lesions with high invasive potential are used in contemporary studies as surrogate outcomes for cervical cancer. Adenocarcinoma in situ is a rare lesion widely considered to be a precursor of cancer. Cervical intraepithelial neoplasia is graded from 1 to 3 on the basis of histopathological criteria. Grade 1 cervical intraepithelial neoplasia indicates the presence of active HPV infection and is not considered to be precancerous; current guidelines discourage treatment of this condition.^{7,8} Grade 2 cervical intraepithelial neoplasia is treated in most women but is not an irrefutable cancer surrogate, since up to 40% of such lesions regress spontaneously⁹; current guidelines suggest that some young women with such lesions do not need to be treated.^{7,8} Grade 3 cervical intraepithelial neoplasia, on the other hand, has the lowest likelihood of regression and the strongest potential to be invasive. The Food and Drug Administration (FDA) considers grade 2 and 3 cervical intraepithelial neo-

plasia and adenocarcinoma in situ to be acceptable surrogate outcomes for cervical cancer; other observers consider grade 3 cervical intraepithelial neoplasia and adenocarcinoma in situ to be more appropriate surrogates.⁹

In these trials, called Females United to Unilaterally Reduce Endo/Ectocervical Disease (FUTURE) I and II, what is the efficacy of vaccination among all subjects, regardless of causal HPV types? In the FUTURE I trial,⁵ rates of grades 1 to 3 cervical intraepithelial neoplasia or adenocarcinoma in situ per 100 person-years were 4.7 in vaccinated women and 5.9 in unvaccinated women, an efficacy of 20%. Analyses by lesion type indicate that this reduction was largely attributable to a lower rate of grade 1 cervical intraepithelial neoplasia in vaccinated women; no efficacy was demonstrable for higher-grade disease, but the trial may have lacked adequate power to detect a difference. Vaccinated women also had lower rates of external anogenital and vaginal lesions (1.3 vs. 2.1). In the larger FUTURE II trial,⁶ rates of grade 2 or 3 cervical intraepithelial neoplasia or adenocarcinoma in situ were 1.3 in vaccinated women and 1.5 in unvaccinated women, an efficacy of 17%. In analyses by lesion type, the efficacy appears to be significant only for grade 2 cervical intraepithelial neoplasia; no efficacy was demonstrable for grade 3 cervical intraepithelial neoplasia or adenocarcinoma in situ.

What can be inferred from these data about the potential effect of vaccination on populations that include sexually active women? In the FUTURE II trial, 93% of subjects were nonvirgins. With grade 2 or 3 cervical intraepithelial neoplasia or adenocarcinoma in situ as the outcome, the difference in risk so far appears to be modest: 219 of 6087 vaccinated women (3.6%) received this diagnosis over an average of 3 years, as compared with 266 of 6080 unvaccinated women (4.4%). The absolute risk difference of 0.8% indicates that 129 women would need to be vaccinated in order to prevent one case of grade 2 or 3 cervical intraepithelial neoplasia or adenocarcinoma in situ occurring during this period. If grade 3 cervical intraepithelial neoplasia or adenocarcinoma in situ were the most relevant outcome, evidence was insufficient to infer the effectiveness of vaccination.

Why is vaccine efficacy modest in the entire cohort? One factor is the apparent lack of efficacy among subjects with evidence of previous

exposure to HPV types included in the vaccine. The FUTURE II trial showed no effect of vaccination up to month 12, perhaps owing either to preinvasive lesions or to vaccine-type HPV infections that were present at enrollment. Therefore, vaccination before the onset of sexual activity seems to be preferable. In contrast to the CDC's guidelines, the American Cancer Society does not recommend universal vaccination among women between 18 and 26 years of age, citing probable diminished vaccine efficacy as the number of lifetime sexual partners increases.¹⁰ Trial outcomes stratified by risk factors that are strong surrogates for HPV exposure and are readily obtained clinically (e.g., the number of lifetime sexual partners) may prove to be useful in the future development of guidelines.

Another factor explaining the modest efficacy of the vaccine is the role of oncogenic HPV types not included in the vaccine. At least 15 oncogenic HPV types have been identified,⁴ so targeting only 2 types may not have had a great effect on overall rates of preinvasive lesions. Findings from the FUTURE II trial showed that the contribution of nonvaccine HPV types to overall grade 2 or 3 cervical intraepithelial neoplasia or adenocarcinoma in situ was sizable. In contrast to a plateau in the incidence of disease related to HPV types 16 and 18 among vaccinated women, the overall disease incidence regardless of HPV type continued to increase, raising the possibility that other oncogenic HPV types eventually filled the biologic niche left behind after the elimination of HPV types 16 and 18. An interim analysis of vaccine trial data submitted to the FDA¹¹ showed a disproportionate, but not statistically significant, number of cases of grade 2 or 3 cervical intraepithelial neoplasia related to nonvaccine HPV types among vaccinated women. Updated analyses of data from these ongoing trials will be important to determine the effect of vaccination on rates of preinvasive lesions caused by nonvaccine HPV types.

What can be inferred from these data about the potential effect of vaccination among girls 11 and 12 years of age? The FUTURE trials did not enroll subjects in this age group. Within both trials, subgroups of subjects with no evidence of previous exposure to relevant vaccine HPV types were evaluated separately for vaccine efficacy. In these subgroups, efficacy of nearly 100% against all grades of cervical intraepithelial neoplasia and

adenocarcinoma in situ related to vaccine HPV types was reported in both trials. However, it would be important to know the overall rates of grade 2 or 3 cervical intraepithelial neoplasia or adenocarcinoma in situ regardless of HPV types. Without these data, it is difficult to infer both the effectiveness of vaccination and the role of nonvaccine HPV types in overall rates of preinvasive lesions.

What do these results mean for cervical-cancer screening? Screening should continue in all vaccinated women, given the cumulative lifetime risk of exposure to other oncogenic HPV types and the unknown duration of anti-HPV immunity. The effect of vaccination on cervical cytologic findings was not reported in either trial, but if vaccination reduces the rates of abnormal findings, this benefit would be important. Of note, a trial of a monovalent HPV-16 vaccine reported no effect on cytologic abnormalities.¹²

Policymakers, clinicians, and parents have a keen sense of urgency about HPV vaccination. On one hand, the vaccine has high efficacy against certain HPV types that cause life-threatening disease, and it appears to be safe; delaying vaccination may mean that many women will miss an opportunity for long-lasting protection. On the other hand, a cautious approach may be warranted in light of important unanswered questions about overall vaccine effectiveness, duration of protection, and adverse effects that may emerge over time. HPV vaccination has the potential for profound public health benefit if the most optimistic scenario of effectiveness is realized.

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Human Papillomaviruses in Head and Neck Carcinomas

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Each year, almost 650,000 patients worldwide receive the diagnosis of head and neck cancer and some 350,000 die from this disease.¹ Nearly 90% of these cancers are squamous-cell carcinomas. The two main causative factors in approximately 80% of oral, oropharyngeal, and laryngeal carcinomas are smoking and alcohol use. Consumption of vegetables and fruit may modulate the carcinogenic effects of tobacco and alcohol,

whereas low body-mass index increases the risk of oral cancer.² The idea that human papillomavirus (HPV) plays a role in these cancers has been under investigation for at least 20 years.

It is widely accepted that HPV causes cervical cancer.³ HPV has also been associated with several other types of squamous-cell carcinoma and their precursors at different sites — skin, vulva, vagina, penis, esophagus, conjunctiva, paranasal