EDITORIALS

Human Papillomavirus Vaccine — Opportunity and Challenge

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In this issue of the *Journal*, we publish three Original Articles,[1-3] two Perspective articles,[4,5] two editorials,[6,7] a letter to the editor,[8] and an audio interview[9] on the subject of human papillomavirus (HPV). We bring together this unique body of information in response to the enormity of the health problems that stem from HPV and the broad interest that has been kindled by the possibility of preventing HPV-related cervical cancer and other anogenital conditions through vaccination.

The HPV vaccine is the first vaccine explicitly designed to prevent cancer induced by a virus. (The hepatitis B vaccine was not primarily designed to prevent cancer.) As noted in the Perspective article by Agosti and Goldie,[5] the consequences of HPV infection are a global health concern that disproportionately affects those in developing countries. The potential ability to reduce the burden of HPV-related disease by vaccination against certain disease-inducing strains of the virus has created a volatile intersection between the community's interest in limiting the transmission of infectious diseases and promoting health on the one hand and social mores on the other, as discussed by Charo in her Perspective article[4] and related audio interview (podcast available at www.nejm.org).[9] However, this volatility should not keep us from recognizing the enormous potential for medical progress and from addressing the numerous unanswered questions that remain.

The finding that infection with HPV is a critical factor in the majority of cases of cervical cancer allowed the development of strategies to prevent this form of oncogenesis. It is important to note that several other cancers are also associated with HPV infection, including head and neck cancers, as demonstrated by D'Souza and colleagues.[3] Although there are many HPV serotypes, two of them — 16 and 18 — account for the lion's share of the oncogenesis. The data that are presented in reports on the vaccine efficacy trials in this issue of the *Journal*[1,2] confirm the success in reducing the incidence of precancerous cervical lesions with vaccine directed against the HPV-16 and HPV-18 serotypes.

Although this is a remarkable achievement, the efficacy of the vaccine is limited by at least these two factors. First, not all cervical cancer is caused by HPV-16 or HPV-18, and second, it appears necessary to vaccinate young women before they are infected with these two serotypes. Also, whether this approach will extend the paradigm of vaccination to the prevention of death and disability from cervical cancer is an unanswered question.

It is difficult to show that an intervention prevents cancer, given the relatively long induction phase between exposure to an inducing agent and development of disease. Thus, key surrogate markers, in this case cervical intraepithelial neoplasia grades 2 and 3, were used so that data could be gathered in a timely fashion. However, correlation with the ultimate outcome — cancer prevention — will require the long-term observation of a large number of treated women. We must also carefully monitor for unintended adverse consequences of vaccination. For example, when selective immunologic pressure is applied with vaccination, the potential exists for nonvaccine-related strains to emerge as important oncogenic serotypes. These critical points are clarified in the editorial by Sawaya and Smith-McCune.[6]

Many other questions are raised by these remarkable data. Should young men be vaccinated? What is the durability of immune protection? Could fewer than three vaccinations provide adequate protection? Will future HPV vaccines ex-

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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 cancer[3])?

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.

1. The FUTURE II Study Group. Quadrivalent vaccine against human papillomavirus to prevent high-grade cervical lesions. N Engl J Med 2007;356:1915-27.
2. Garland SM, Hernandez-Avila M, Wheeler CM, et al. Quadrivalent vaccine against the human papillovmavirus to prevent anogenital diseases. N Engl J Med 2007;356:1928-43.
3. D'Souza G, Kreimer AR, Viscidi R, et al. Case–control study of human papillomavirus and oropharyngeal cancer. N Engl J Med 2007;356:1944-56.
4. Charo RA. Politics, parents, and prophylaxis — mandating HPV vaccination in the United States. N Engl J Med 2007;356:1905-8.
5. Agosti JM, Goldie SJ. Introducing HPV vaccine in developing countries — key challenges and issues. N Engl J Med 2007;356:1908-10.
6. Sawaya GF, Smith-McCune K. HPV vaccination — more answers, more questions. N Engl J Med 2007;356:1991-3.
7. Syrjanen S. Human papillovmaviruses in head and neck carcinomas. N Engl J Med 2007;356:1993-5.
8. Stewart S. Mandating HPV vaccination — private rights, public good. N Engl J Med 2007;356:1998-9.
9. Interview with R. Alta Charo. (Available at www.nejm.org.)

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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, preinvasive 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 spontaneously[9]; 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-

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