Human Papillomavirus Vaccination — Reasons for Caution

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Despite great expectations and promising results of clinical trials, we still lack sufficient evidence of an effective vaccine against cervical cancer. Several strains of human papillomavirus (HPV) can cause cervical cancer, and two vaccines directed against the currently most important oncogenic strains (i.e., the HPV-16 and HPV-18 serotypes) have been developed. That is the good news. The bad news is that the overall effect of the vaccines on cervical cancer remains unknown. As Kim and Goldie[1] point out in this issue of the *Journal*, the real impact of HPV vaccination on cervical cancer will not be observable for decades.

Although it was licensed for use in the United States in June 2006, the first phase 3 trials of the HPV vaccine with clinically relevant end points — cervical intraepithelial neoplasia grades 2 and 3 (CIN 2/3) — were not reported until May 2007, first in the *Journal*[2] and 1 month later in the *Lancet*.[3,4] The vaccine was highly successful in reducing the incidence of precancerous cervical lesions caused by HPV-16 and HPV-18, but a number of critical questions remained unanswered.[5,6] For instance, will the vaccine ultimately prevent not only cervical lesions, but also cervical cancer and death? How long will protection conferred by the vaccine last? Since most HPV infections are easily cleared by the immune system, how will vaccination affect natural immunity against HPV, and with what implications? How will the vaccine affect preadolescent girls, given that the only trials conducted in this cohort have been on the immune response? The studies with clinical end points (i.e., CIN 2/3) involved 16- to 24-year-old women. How will vaccination affect screening practices? Since the vaccines protect against only two of the oncogenic strains of HPV, women must continue to be screened for cervical lesions. Vaccinated women may feel protected from cervical cancer and may be less likely than unvaccinated women to pursue screening. How will the vaccine affect other oncogenic strains of HPV? If HPV-16 and HPV-18 are effectively suppressed, will there be selective pressure on the remaining strains of HPV? Other strains may emerge as significant oncogenic serotypes.

Resolving the first essential questions will require decades of observation of large numbers of women. The last question may be answered sooner. Published reports of trials show an increasing trend of precancerous cervical lesions caused by HPV serotypes other than HPV-16 and HPV-18.[2,4,6] The results were not statistically significant, however, possibly because there were too few clinically relevant end points in the observation periods reported. If randomized, controlled trials involving vaccinated and unvaccinated women continue for a few more years, we will most likely be able to tell whether this is a true trend. If so, there is reason for serious concern.

By the summer of 2007, there were definitely promising results with regard to the effectiveness of the HPV vaccine in the prevention of precancerous lesions (i.e., CIN 2/3) caused by the HPV-16 and HPV-18 serotypes. However, serious questions regarding the overall effectiveness of the vaccine in the protection against cervical cancer remained to be answered, and more long-term studies were called for before large-scale vaccination programs could be recommended.[5,6] Unfortunately, no longer-term results from such studies have been published since then.

In the meantime, there has been pressure on policymakers worldwide to introduce the HPV vaccine in national or statewide vaccination programs. How can policymakers make rational choices about the introduction of medical interventions that might do good in the future, but for which evidence is insufficient, especially since we will not know for many years whether the intervention will work or — in the worst case — do harm? One way to provide decision support is to develop mathematical models of the natural history of the disease in question, introduce various intervention strategies, and use cost-effectiveness analysis to estimate the costs and health benefits associated with each clinical intervention. The results are typically expressed in terms of the amount we will have to pay for the extra health benefit of the treatment — that is, in dollars per life-year or quality-adjusted life-year (QALY) saved. Cost-effectiveness analyses are tools for decision

making under conditions of uncertainty. These analyses do not in themselves provide evidence that medical interventions are effective. In this issue of the *Journal,* Kim and Goldie present a model of HPV vaccination, and they use a cost-effectiveness analysis to make projections of the possible health and economic implications of the use of the vaccine.[1]

To evaluate the quality of a cost-effectiveness analysis, it is essential to appraise the model's input variables, the uncertainties, and the choices the researchers have made. To set up such an analysis of a preventive medical intervention — in this case, a vaccine given to healthy 12-year-old girls — that might have an effect on the incidence of cervical cancer decades from now is extremely complex. The analysis has to model the natural history of HPV infection in this cohort of girls over their lifetime, the effect of the vaccine over all those years (whether it is the same effect or one that is waning), the effect on other HPV strains, the effect of the vaccine on the natural immunity against HPV infections, the sexual behavior of the girls and women and their partners, and finally, women's cervical-cancer screening practices.

The model presented by Kim and Goldie is well done and ambitious, and it includes most of these factors. They conclude that under certain assumptions, vaccinating 12-year-old girls is associated with an incremental cost-effectiveness ratio of $43,600 per QALY gained, whereas adding a catch-up program for older girls and women is not cost-effective. However, their base-case assumptions are quite optimistic. They presume lifelong protection of the vaccine (i.e., no need for a booster dose), that the vaccine has the same effect on preadolescent girls as on older women, that no replacement with other oncogenic strains of HPV takes place, that vaccinated women continue to attend screening programs, and that natural immunity against HPV is unaffected. Whether these assumptions are reasonable is exactly what needs to be tested in trials and follow-up studies. If the authors' baseline assumptions are not correct, vaccination becomes less favorable and even less effective than screening alone. For example, as shown in the article, if the protection of the vaccine wanes after 10 years, vaccination is much less cost-effective and screening is more effective than catch-up programs.

With so many essential questions still unanswered, there is good reason to be cautious about introducing large-scale vaccination programs. Instead, we should concentrate on finding more solid answers through research rather than base consequential and costly decisions on yet unproven assumptions.

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