

The Risks and Benefits of HPV Vaccination

Charlotte Haug, MD, PhD, MSc

WHEN DO PHYSICIANS KNOW ENOUGH ABOUT THE beneficial effects of a new medical intervention to start recommending or using it? When is the available information about harmful adverse effects sufficient to conclude that the risks outweigh the potential benefits? If in doubt, should physicians err on the side of caution or on the side of hope? These questions are at the core of all medical decision making. It is a complicated process because medical knowledge is typically incomplete and ambiguous. It is especially complex to make decisions about whether to use drugs that may prevent disease in the future, particularly when these drugs are given to otherwise healthy individuals. Vaccines are examples of such drugs, and the human papillomavirus (HPV) vaccine is a case in point.

zur Hausen, winner of the Nobel Prize in Physiology or Medicine in 2008, discovered that oncogenic HPV causes cervical cancer.¹⁻⁴ His discovery led to characterization of the natural history of HPV infection, an understanding of mechanisms of HPV-induced carcinogenesis, and eventually to the development of prophylactic vaccines against HPV infection.

The theory behind the vaccine is sound: If HPV infection can be prevented, cancer will not occur. But in practice the issue is more complex. First, there are more than 100 different types of HPV and at least 15 of them are oncogenic. The current vaccines target only 2 oncogenic strains: HPV-16 and HPV-18. Second, the relationship between infection at a young age and development of cancer 20 to 40 years later is not known. HPV is the most prevalent sexually transmitted infection, with an estimated 79% infection rate over a lifetime.^{5,6} The virus does not appear to be very harmful because almost all HPV infections are cleared by the immune system.^{7,8} In a few women, infection persists and some women may develop precancerous cervical lesions and eventually cervical cancer. It is currently impossible to predict in which women this will occur and why. Likewise, it is impossible to predict exactly what effect vaccination of young girls and women will have on the incidence of cervical cancer 20 to 40 years from now. The true

effect of the vaccine can be determined only through clinical trials and long-term follow-up.

The first HPV vaccine was licensed for use in the United States in June 2006,⁹ and the Advisory Committee on Immunization Practices recommended routine vaccination of girls aged 11 to 12 years later that same month.¹⁰ However, the first phase 3 trials of the HPV vaccine with clinically relevant end points—cervical intraepithelial neoplasias grades 2 and 3 (CIN 2/3)—were not reported until May 2007.¹¹ Previously only reduction in the prevalence of persistent infection and CIN from the 2 virus strains included in the vaccine had been reported. The results were promising, but serious questions regarding the overall effectiveness of the vaccine for protection against cervical cancer remained to be answered, and more long-term studies were called for.¹² However, no longer-term results from such studies have been published since then.

So how should a parent, physician, politician, or anyone else decide whether it is a good thing to give young girls a vaccine that partly prevents infection caused by a sexually transmitted disease (HPV infection), an infection that in a few cases will cause cancer 20 to 40 years from now? Two articles in this issue of *JAMA*^{13,14} present important data that may influence, and probably already have influenced, such decisions about HPV vaccination.

The report by Rothman and Rothman¹³ demonstrates how the vaccine manufacturer funded educational programs sponsored by professional medical associations in the United States. The article illustrates how the Society of Gynecologic Oncology, the American Society for Colposcopy and Cervical Pathology, and American College Health Association helped market the vaccine and influenced decisions about vaccine policy with the help of ready-made presentations, slide sets, e-mails, and letters. It is of course reasonable for professional medical associations to promote medical interventions they believe in. But did these associations provide members with unbiased educational material and balanced recommendations? Did they ensure that marketing strategies did not compromise clinical recommendations? These educational programs strongly promot-

Author Affiliation: *The Journal of the Norwegian Medical Association*, Oslo, Norway.

Corresponding Author: Charlotte Haug, MD, PhD, MSc, *The Journal of the Norwegian Medical Association*, Akersgata 2, Oslo 0107, Norway (charlotte.haug@legeforenningen.no).

See also pp 750 and 781.

ing HPV vaccination began in 2006, more than a year before the trials with clinically important end points were published. How could anyone be so certain about the effect of the vaccine? This matters because the voices of experts such as the professional medical associations are especially important with a complex issue such as this.

In another article, Slade and colleagues¹⁴ from the US Centers for Disease Control and Prevention and the US Food and Drug Administration describe the adverse events that occurred 2.5 years following the receipt of quadrivalent HPV vaccine that were reported through the US Vaccine Adverse Events Reporting System (VAERS). Even though most of the reported adverse events were not serious, there were some reports of hypersensitivity reactions including anaphylaxis, Guillain-Barré syndrome, transverse myelitis, pancreatitis, and venous thromboembolic events. VAERS is a passive, voluntary reporting system, and the authors call attention to its limitations. They point out that only systematic, prospective, controlled studies will be able to distinguish the true harmful effects of the HPV vaccine. These limitations work both ways: it is also difficult to conclude that a serious event is not caused by the vaccine.

Whether a risk is worth taking depends not only on the absolute risk, but on the relationship between the potential risk and the potential benefit. If the potential benefits are substantial, most individuals would be willing to accept the risks. But the net benefit of the HPV vaccine to a woman is uncertain. Even if persistently infected with HPV, a woman most likely will not develop cancer if she is regularly screened.¹⁵ So rationally she should be willing to accept only a small risk of harmful effects from the vaccine.

When weighing evidence about risks and benefits, it is also appropriate to ask who takes the risk, and who gets the benefit. Patients and the public logically expect that only medical and scientific evidence is put on the balance. If other

matters weigh in, such as profit for a company or financial or professional gains for physicians or groups of physicians, the balance is easily skewed. The balance will also tilt if the adverse events are not calculated correctly.

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