



FOCUS ON RESEARCH

Weighing the Benefits and Costs of HPV Vaccination of Young Men

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Related article, p. 401

Sexually transmitted human papillomavirus (HPV) infections contribute to approximately 20,000 cases of invasive cancer in the United States each year; about 50% are cervical cancers, and the rest

involve the vagina, vulva, penis, anus, or oral cavity or oropharynx.¹ Less than 25% of HPV-related cancers occur in men. However, some subgroups, such as men who have sex with men, have markedly higher rates of HPV-related diseases such as anal cancer. Oncogenic types of HPV cause nearly all cases of cervical cancer, 90% of cases of anal cancer, and a smaller proportion of the remaining cancers. The majority of these cancers are attributable to two types, HPV-16 and 18. Nononcogenic types, HPV-6 and 11, cause approximately 340,000 cases of genital

warts in the United States each year.²

Two highly efficacious prophylactic vaccines that target HPV-16 and 18 are available. One of them is a quadrivalent vaccine that also targets HPV-6 and 11. Though the evidence regarding the efficacy of the HPV vaccines to this point has centered on the prevention of HPV infection and diseases in girls and women, the data presented by Giuliano et al. in this issue of the *Journal* (pages 401–411) affirm the potential for HPV vaccines to prevent related disease in boys and men. The investigators report the ef-

ficacy of the quadrivalent HPV vaccine in preventing infections with the HPV types included in the vaccine, as well as external genital lesions, primarily genital warts, in young men 16 to 26 years of age.

These data informed the 2009 approval by the Food and Drug Administration (FDA) of the quadrivalent HPV vaccine for the prevention of genital warts in young men in the United States and the subsequent recommendation from the Advisory Committee on Immunization Practices (ACIP), which advises the Centers for Disease Control and Prevention (CDC), for the permissive use of the vaccine in boys and young men 9 to 26 years of age. The ACIP stopped short of supporting routine HPV vaccination of adolescent boys, even though

routine vaccination of girls between the ages of 11 and 12 years (and as early as 9 years) has been recommended since 2007. However, the committee did recommend financial coverage by the CDC Vaccines for Children program for eligible boys 18 years of age or younger. Since these decisions were made, newer data have shown that the quadrivalent HPV vaccine is effective in preventing anal intraepithelial neoplasia, a precursor to anal cancer, in men, particularly in men who have sex with men.³ On the basis of this new evidence, the FDA recently approved the expanded use of the quadrivalent vaccine to include the prevention of anal lesions and cancer in people of both sexes, a decision that has reignited the debate over routine HPV vaccination of young men.

Arguments for such routine vaccination understandably revolve around the additional health benefits that can be achieved by moving from a sex-specific to a sex-neutral vaccination policy. Not only can vaccination of boys and men bolster and expedite health benefits in girls and women (i.e., by contributing to reduced HPV prevalence among men and therefore reduced transmission to their sexual partners), but there is now clear evidence that boys and men themselves can benefit directly. Other points in favor of routine vaccination of young men include the desirability, from a sex-equity perspective, of distributing the burden of obtaining protection to people of both sexes, since both are responsible for HPV transmission; the concern that a high-risk subgroup, men who have sex with men, could not be targeted at a young age (when the vaccine's potential is expect-

ed to be greatest) and therefore would best be protected by a policy of vaccinating all male adolescents; and the possibility that vaccination of boys and men could actually increase vaccine uptake among girls and women — a desirable outcome given that uptake among adolescent girls in the United States has been low despite guidance from the ACIP and professional organizations such as the American Cancer Society recommending routine vaccination.



Transmission Electron Micrograph of Negatively Stained HPV.

Although these are important points, other considerations support a more cautious approach. First, less is known about the natural history of (and the effect of the vaccine on) HPV-related cancers in men than about such cancers in women. Second, it is difficult to predict what the uptake of the vaccine would be among young men, let alone how uptake among people of one sex might affect the other. Third, a recent analysis showed that despite the reduced efficacy of the vaccine in people with previous exposure to HPV, vaccinating men who have sex with men at older

ages (up to 26 years), when targeted strategies may be more feasible, would still reduce the incidence of anal cancer and provide good value for the money.⁴ Finally, there is evidence that routine vaccination of young men would be less cost-effective than routine vaccination of young women.

The ACIP elected not to recommend routine vaccination of adolescent boys on the basis of multiple considerations, one of which was the less attractive cost-effectiveness profile. Several cost-effectiveness analyses have indicated that HPV vaccination of both sexes is not cost-effective when compared with the vaccination of girls only, with costs exceeding \$100,000 per quality-adjusted life-year (QALY) gained (and according to one estimate, reaching \$1 million per QALY gained).⁵ However, these analyses also show that the value of including young men in an HPV vaccination program is higher when coverage of young women is low. Since uptake among girls and women has been lower than expected in the United States (as of 2009, according to the CDC, 44.3% of adolescent girls 13 to 17 years of age had received at least one dose and 26.7% had received all three doses of the vaccine), HPV vaccination of boys and men may be cost-effective at this time. However, if uptake among girls and women increases, as it has each year since the recommendations were issued in 2007, we can anticipate that the cost-effectiveness of vaccinating boys and men will diminish over time.

Cost-effectiveness analysis is used to identify interventions that provide the most value for our money. By using cost-effective-

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ness analysis to inform public health policy, we acknowledge that resources are not infinite and that there is an opportunity cost to every dollar spent. By investing in HPV vaccination of boys and men at the current price of nearly \$400 per series (one of the highest prices for any vaccine), we may be missing out on an alternative use of funds that could reap even greater health benefits. Therefore, this use of funds should be compared with that for other interventions for the same disease (e.g., anal cytologic screening and improved treatment), as well as for interventions for other diseases. Future analyses will need to assess the relative costs and benefits of alternative strategies, either alone or in combination with HPV vaccination, to determine the best use of public health dollars for preventing HPV-related diseases.

The report by Giuliano et al. undoubtedly gives us cause to celebrate the extraordinary potential for HPV vaccination to im-

prove health in both women and men. And although enthusiasm for universal vaccination may initially be tempered by uncertainties about the vaccine's safety, efficacy, and duration of protection (as well as its uptake, acceptability, and cost), many of these factors could very well change in the future. For example, the cost-effectiveness profile of routine vaccination of young men will improve if the evidence of efficacy continues to mount, the vaccine price declines, or coverage among girls and women remains low.

To maximize the benefits to the population's health from health services and interventions, we have a responsibility to use resources as efficiently as possible. Indeed, improving the return on our health care investment is a vital imperative for the 21st century, as highlighted by the recent prioritization of comparative effectiveness analysis in the United States. Equally important is our responsibility to revisit policy decisions as influential

new data and new technologies become available, as they undoubtedly will in the case of the prevention and control of HPV-related diseases.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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Harnessing Our Opportunity to Make Primary Care Sustainable

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Despite the heated rhetoric in Congress about repealing and replacing the Affordable Care Act (ACA), there is a dearth of productive ideas for improving on the legislation. As a Democratic U.S. representative from Washington State, I supported the ACA, but I believe that there remain essential areas of concern that must be addressed long before 2014, when 32 million newly insured Americans will join our health care system. Our

foremost task this year must be to develop a strategy to ensure the sustainability of our primary care system.

We have long known that ready access to high-quality primary care permits timely and cost-effective intervention for many health conditions. But access is unreliable for many people in our disordered system. A recent poll conducted by the Kaiser Family Foundation revealed that more than half of

Americans delay obtaining primary care because of its cost.¹ Patients reported splitting or skipping doses of medications, delaying recommended tests, and neglecting mental health care. These practices contribute to our failure to control the world's most expensive yet inefficient health care system: since we lack a strong and accessible primary care infrastructure, people often enter our health care system disadvantaged by chronic disease