Who Should Get the HPV Vaccine? Usage Expands Amid Debate

By Judy Peres

ull-page advertisements inviting parents to immunize their preadolescent boys against human papillomavirus (HPV) have rekindled the debate over who should receive the world’s first cancer vaccine. In the ads for Merck’s Gardasil vaccine (Parade magazine, April 25, 2010), two cherubic faces—one of a mischievous-looking boy in need of a haircut, the other of a tomboyish girl with braces on her teeth—straddle a headline proclaiming, “Your child could be ONE LESS person affected by HPV disease.”

Harald zur Hausen, D.Sc., M.D., the noted virologist who shared the 2008 Nobel Prize in Medicine for discovering that HPVs cause cervical cancer, supports the concept. His finding led to development of the vaccine, the first ever designed explicitly to prevent cancer. Zur Hausen and others think that vaccination should extend to boys and other groups, such as older women. But many in the public health community are less enthusiastic about expanding use of the vaccine.

Gardasil and Cervarix, GlaxoSmithKline’s HPV vaccine, both prevent infection by two HPV types that cause about 70% of cervical cancers and precancers. The U.S. Centers for Disease Control and Prevention (CDC) recommends that they be given routinely to 11- or 12-year-old girls, with “catchup” shots for those aged 13–26 years who have not already been fully immunized. Last fall the agency said that the vaccine given prior to sexual maturity — the patient is initially exposed to HPV, which is transmitted through sexual contact — is more effective when administered before the end of this year whether to grant the company’s application to expand the indications for Gardasil.

Calculating Cost-Effectiveness

The CDC’s Advisory Committee on Immunization Practices voted to permit, but not recommend, routine vaccination of boys, at least partly because of evidence throwing doubt on the vaccines’ cost-effectiveness in boys. One study by researchers at Harvard’s School of Public Health, published in the Oct. 8, 2009, British Medical Journal online, found that giving the vaccine to males was generally not cost-effective.

A health intervention is typically considered to be a good use of resources in the United States if it costs less than $100,000 per quality-adjusted life-year (QALY) gained. Several studies have found that vaccinating 12-year-old girls (assuming they get regular Pap tests as adults) is highly cost-effective, generally less than $50,000 per QALY, compared with the current standard of Pap tests alone. In their comparison of vaccinating only girls versus vaccinating both girls and boys, Harvard researchers Jane Kim, Ph.D., and Sue Goldie, M.D., found that adding boys had cost-effectiveness ratios of more than $100,000 per QALY for nearly all evaluated scenarios.

Both the U.S. Food and Drug Administration and the CDC’s Advisory Committee on Immunization Practices are looking at data from Merck on Gardasil’s ability to prevent anal cancer in 16- to 26-year-old men who have sex with men, a population at elevated risk for the disease.

Both Merck and GlaxoSmithKline are also testing their vaccines for the prevention of cervical cancer and other HPV-related diseases in women beyond their mid-20s. A spokesman for Merck said that the company expects the FDA to decide by the end of this year whether to grant the company’s application to expand the indications for Gardasil.

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In a separate analysis, Kim and Goldie also looked at the cost-effectiveness of adding HPV vaccination to regular cervical cancer screening (Pap tests) for women aged 35–45 years. Their results, published in the Oct. 20, 2009, Annals of Internal Medicine, showed that adding vaccination would cost somewhere between $116,950 and $381,590 per QALY.

According to Allan Hildesheim, Ph.D., chief of the infections and immunopathology branch of the National Cancer Institute, consensus is emerging that giving the vaccine to adults is not cost-effective. That is largely because the vaccine is much more effective when administered before the patient is initially exposed to HPV, which is transmitted through sexual contact. Even zur Hausen, who favors universal vaccination, said that he “prefer[s] to see the vaccine given prior to sexual maturity—that should have a higher priority.”

But less agreement exists on whether to include boys in public vaccination programs. “There are still several unanswered questions regarding the cost-effectiveness of vaccinating males,” said Hildesheim.

The Variables

Several factors could change the cost-effectiveness analysis, starting with the price of the vaccines. The current cost of a three-shot series of either Gardasil or Cervarix is between $300 and $400.

“We expect, as the drug companies recoup their development costs, the price will come down substantially and the case for vaccinating men will be more attractive,” said Jack Cuzick, Ph.D., who runs the Cancer Research UK Centre for Epidemiology, Mathematics, and Statistics at the Wolfson Institute in London.

Other factors that could influence cost-effectiveness include how long the protection lasts (will patients need a booster shot down the line?) and whether the vaccine is
proven to prevent nongenital HPV–related diseases, such as mouth and throat cancers, which affect more than 35,000 men and women each year in the U.S.

Another variable is how many young girls actually get the vaccine. Kim and Goldie’s modeling study assumed high coverage in most of its scenarios. But if fewer girls get vaccinated, then vaccinating boys becomes more useful—i.e., will prevent more HPV infections—and its cost-effectiveness would go up.

According to Cuzick, only 20%–30% of eligible girls are vaccinated in the U.S., compared with more than 80% in Australia and the United Kingdom, where the government pays for (but does not mandate) the vaccine and school-based programs administer it. Various factors keep down the proportion of American girls who get the vaccine, in addition to the high cost and some parents’ fear of appearing to condone premarital sex. One is the structure of the U.S. health care system. “The current piecemeal approach of asking patients to go to their doctor [for a series of shots] and relying on insurance companies to pay is not a very effective approach for achieving high coverage,” said Cuzick.

Ironically, another factor working against the HPV vaccine in the U.S. is the fact that screening for cervical cancer is so widespread that most cases can be detected early and treated effectively. “If we didn’t have an effective way to screen,” said Ranit Mishori, M.D., a family physician and assistant professor at
Georgetown University School of Medicine, “it would be a no-brainer. The problem is that the vaccine covers most, but not all, types of HPV. Women who get the vaccine still need to get periodic Pap smears. So a woman might ask, ‘Why should I subject my daughter to three painful shots?’”

If vaccination rates increase, screening practices may also have to change to avoid overscreening and overtreatment of clinically insignificant disease. “As you vaccinate more and more of the younger population, you’re reducing their risk of a serious abnormality by over 50%,” said Diane Solomon, M.D., senior investigator at the NCI’s Division of Cancer Prevention. “So now you might want to wait until they’re older to start screening or increase the interval between screening tests. That’s what we’ll be evaluating in the future.”

**Arguing for Wider Use**

Part of the argument for vaccinating males is that doing so would indirectly reduce the burden of cervical cancer, because women are infected by their male sexual partners. Zur Hausen, former director and now professor emeritus at the German Cancer Research Center in Heidelberg, calls that “gender solidarity.”

Another argument is that men stand to benefit directly from the vaccine, not only because it prevents genital warts but also because it reduces their risk for anal, penile, and perhaps other cancers. Zur Hausen said that the direct benefit to men would include “a drastic reduction in anal cancer and a one-third reduction in oropharyngeal cancer incidence.”

According to a review last year in the *New England Journal of Medicine* by Jessica Kahn, M.D., of the University of Cincinnati College of Medicine, infection with high-risk HPV types causes virtually all cervical cancers; approximately 90% of anal cancers; 50% of vulvar, vaginal, and penile cancers; and 12% of oropharyngeal (mouth and throat) cancers. However, men are more than twice as likely as women to develop oropharyngeal cancers.

Merck’s latest data, presented in February at a conference of the European Research Organization on Genital Infection and Neoplasia, showed that its quadrivalent Gardasil was 77.5% efficacious against anal intraepithelial neoplasia, a precursor of anal cancer, associated with the virus types covered by the vaccine. That figure, however, applied to study participants not already infected with one of the virus types that the vaccine covered. One could expect the efficacy rate to drop sharply in a population already exposed to the virus.

Since it’s impossible to know which preadolescent boys will grow up to become men who have sex with men, it would not be feasible to target the vaccine to that subgroup of males, in which the cost-effectiveness would be greatest. That’s one argument for offering the vaccine to all boys.

But Solomon is concerned that this approach might not be a “rational use [of resources] in terms of public health benefit.”

“Sometimes people justify vaccinating an entire group because we can’t target the subgroup with the biggest risk,” said Solomon. “You can’t use the risk profile of a select group to justify vaccinating the whole group if it is not cost-effective.”

But then there’s the philosophical, or individual-oriented, argument.

“To have a vaccine that prevents cancer and not use it would be one of the greatest tragedies,” said Bradley Monk, M.D., director of research in the division of gynecologic oncology at the University of California, Irvine, who supports universal vaccination.

Zur Hausen agrees. “One of the major reasons for vaccinating boys,” he said, “is that we have a chance to eradicate these infections if we can apply it to both sexes as quickly as possible. That would be a real blow to the virus spreading.”

Some physicians are giving the vaccine both to midadult women and to gay men. Mishori said that she offers the vaccine to all her female patients aged 11–26 years and has administered it to older women and to men who have sex with men “as long as they understand the benefit for them is smaller.”

Others say that Gardasil’s ability to prevent infection with two HPV strains that cause about 90% of genital warts is reason enough to promote its acceptance for preadolescents of both sexes. According to Yvonne Collins, M.D., a gynecologic oncologist with Advocate Medical Group in Oak Lawn, Ill., the economic burden of treating genital warts, a condition that can be extremely persistent, is $200 million per year.

“It’s not cancer,” said Collins, “but there will be substantial economic benefit if we can eliminate that disease—and also psychological benefit. I say it’s worth it for that alone.” But Collins believes that vaccinating boys will become even more compelling if the data prove that the vaccine protects against anal and penile cancers.

“As the mother of a boy,” she said, “I’d hate to know I had the opportunity to prevent disease, not only for my son but also for my daughter-in-law, and I didn’t do it.”