

Conquering Cancer one Poke at a Time: Can the HPV Vaccine Eliminate Cervical Cancer Worldwide?

By Sheri Fink

Cervical cancer is an aggressive and ugly disease that kills more than a quarter of a million women worldwide each year. It is the second leading cause of cancer deaths in women worldwide and the top cause in many developing countries. Virtually all of the women who die share one thing in common—they've been infected with the human papilloma virus, known as HPV. Researchers recently reported that new HPV vaccines from the Merck and GlaxoSmithKline pharmaceutical companies were nearly 100% effective at preventing disease caused by the most dangerous strains of the virus in women who were not currently infected with those types.

Now, a year after the Merck vaccine Gardasil was approved for use in girls and young women in the U.S., it is already being actively sold in 52 countries, with widespread use in North America and Europe (the GSK vaccine, currently under FDA review, has been approved for use as Cervarix in Australia). However in developing countries, where more than 80% of cervical cancer deaths occur, HPV vaccines remain largely unavailable.

On June 4, 2007, the Global Health Program of the Council on Foreign Relations brought together pharmaceutical company representatives, government officials and other health experts to discuss ways to accelerate global access to HPV vaccines. CFR Senior Fellow for Global Health Laurie Garrett, who lost a close friend to cervical cancer last year, moderated the five hour meeting and organized it with Research Associate Kammerle Schneider and CFR Term Members Ella Gudwin of AmeriCares Foundation, Laura Efros of Merck & Co., Inc., and Kiersten Todt-Coon of Business Executives for National Security (BENS). The program was the second installment of a roundtable series developed with the Global Public Health Practice at McKinsey and Company.

A Dream Vaccine

Evidence for Gardasil's efficacy, safety, and cost-effectiveness was so convincing that in 2006 the Advisory Committee on Immunization Practices, the Federal agency responsible for setting U.S. vaccination recommendations, quickly released guidelines calling for routine vaccination of 11 to 12 year old girls. Girls or women up to age 26 who have never been immunized against HPV and ideally have not yet been exposed to HPV through sexual contact are also encouraged to be vaccinated under the ACIP guidelines. The vaccine can be used in girls as young as age 9. Most States have passed legislation aimed at enhancing access to HPV vaccination. "I've never seen a vaccine elicit this much excitement and interest this early," Dr. Mark Kane, former director of the Children's Vaccine Program at the nonprofit global health organization PATH, said.

Many more years of study will be needed to answer important questions about both vaccines, such as whether immunization will confer life-long protection, whether booster shots will be required years after initial immunization, and to what extent the vaccines “cross protect” against other cancer-causing strains of the HPV virus. Women who get vaccinated will still need to undergo Pap testing, which detects precancerous lesions so they can be treated. While both vaccines protect against the forms of HPV that most commonly cause cancer, other strains of the virus exist that are capable of causing cancers, lesions or genital warts.

“We cannot say that cervical cancer will be history,” cautioned Dartmouth’s Dr. Diane Harper, who participated in testing both vaccines. “There will still be women who in the best of circumstances—after vaccination and continued Pap testing—will develop cervical cancer.”

Still, the overall picture is a very rosy one. Research suggests that HPV vaccines have the potential to prevent about 80% of all cervical cancer cases—potentially saving the lives of 224,000 women a year—plus many cases of HPV-related vulvar, vaginal and anal cancer. The vaccines may also prevent some head and neck cancers, and Gardasil is highly protective against genital warts. Preventing infection rather than merely screening for it will avert not only deaths but also costly and unpleasant treatment and monitoring of precancerous lesions. Because men transmit the virus to women, and HPV can cause penile cancer and other cancers and diseases in males, the vaccines are also being tested for their effectiveness in men and boys.

International Challenges

The greatest disease-reducing potential for HPV vaccines lies in the least developed nations. While women in wealthy countries such as the U.S. typically have access to Pap tests and medical procedures that help prevent lesions from progressing into deadly cancers, those services are largely unavailable to women in poor countries. As a result, death rates from cervical cancer in the poorest countries are more than three times that in wealthy nations. Because cervical cancer strikes relatively young women, it is the leading cause of years of life lost to cancer in the developing world, and it claims thousands of mothers every year, increasing the global burden of orphaned children.

However, the populations that could benefit the most from new medical technologies often must wait a long time to access them. “Historically new vaccines have reached those in developing countries ten to fifteen years after they’re available in developed countries,” said Dr. Mark Feinberg, Vice President of Medical Affairs and Policy at Merck. He said that HPV vaccines are a chance to prove that the world could do better.

That effort, though, faces significant challenges. At \$96.75 per dose in the U.S. (\$120.50 per dose for the private sector), Gardasil is the most expensive pediatric vaccine on the price list of the Centers for Disease Control and Prevention (CDC)—and immunization requires three doses. Rear Admiral Dr. Anne Schuchat, Director of the National Center

for Immunization and Respiratory Diseases at the CDC, said the high price tag has presented an obstacle to introduction even in the U.S.

In Mexico, according to Dr. Roberto Tapia-Conyer, the country's former Vice Secretary of Health, only people who can afford to pay around \$240 in the private sector can obtain Gardasil. Although Mexico makes a higher public investment in vaccines than most countries, each dose of Gardasil would cost the country more than it invests in the entire panel of vaccines for a children under five.

Representatives of both Merck and GlaxoSmithKline have committed to offering their new products on a sliding scale to countries based on income. Merck's commitment includes offering its new vaccines, including Gardasil, at dramatically lower prices at which the company will not profit in the lowest income countries.

However, neither company has yet revealed its price plan for different countries. Deborah Myers, director of External and Government Affairs and Public Partnerships for GlaxoSmithKline Biologicals, said her company first needs to know the extent of demand. "You can't expect to get the same price for a million doses as you get for 100 million doses," she said. "Unfortunately the economics in terms of production doesn't work that way."

Of course, that calculus also flows in the opposite direction—price is one of the top determinants of vaccine demand. No single global agency is responsible for ensuring equitable, worldwide access to new vaccines, and securing financing for vaccines meant for children over five years of age is particularly problematic. Thus far the GAVI Alliance, a partnership of public and private sector organizations that work to increase vaccination in poor countries, has yet to begin supporting HPV immunization efforts. That may be due in part to a recent surge in vaccine breakthroughs. Several significant products have hit the market within a short time span, including vaccines that protect against pneumococcal pneumonia and rotavirus infection, a major cause of diarrheal disease in young children.

"In a real sense these vaccines are competing with each other for scarce resources," said Mark Kane. PATH is leading an effort to develop a strong "investment case" for HPV vaccines, and GAVI officials have expressed an interest in reviewing the case for financing. However, even if measures such as GAVI support and significant manufacturer price reductions made the HPV vaccines affordable for girls in developing countries, there's no guarantee the vaccines would be accessible. Poor health infrastructure, low per-capita health expenditures and a high burden of other diseases mean that other health priorities may well trump delivery of HPV vaccines. Most adolescent girls have little contact with health personnel that could administer the necessary three doses of the vaccine. In some countries where women have a lower social status, their health needs are not prioritized, and in places where women are already commonly blamed for sexually transmitted diseases, administering a vaccine exclusively to females could exacerbate their stigmatization. Some religious and political leaders might oppose the vaccine as, in recent years, they have blocked polio

immunization campaigns, claiming that the vaccines contained poisons that would sterilize girls.

The Way Forward

Still, participants in the CFR meeting were optimistic about overcoming these obstacles to HPV vaccination in low and middle income countries. Moreover, they viewed HPV vaccination as a promising means to reach pre-teen females for a range of previously overlooked health and education interventions.

In recent years, donors, government agencies and nonprofit health organizations have partnered with for-profit pharmaceutical companies, creating incentives for them to promote the diffusion of lifesaving new technologies in the developing world. According to Feinberg, Merck recently sought WHO prequalification for Gardasil—an important step toward expanding access; Merck is also collaborating with the nonprofit organization PATH in India, Peru and Vietnam to evaluate the effectiveness of different vaccination strategies and alternative dosing schedules. Likewise, GSK is working with PATH in Uganda and India on pilot HPV vaccine introduction and is testing alternate financing and delivery channels for its vaccine in the Philippines.

Many developing countries have extensive experience in carrying out mass vaccination campaigns, which has led to considerable progress toward eradicating polio and reducing measles mortality in recent years. The relatively new hepatitis B vaccine has been successfully introduced for routine use in many poor countries, offering lessons and a potential model for the introduction of HPV vaccines. Furthermore, promoting HPV vaccination would logically fall within the purview of advocacy communities working in the areas of reproductive health, adolescent health, women's rights, cancer prevention, and HIV prevention (people living with HIV are prone to more severe disease caused by HPV). Several roundtable participants felt that the President's Emergency Plan for AIDS Relief, or PEPFAR, ought to fund HPV vaccination in the countries it targets, particularly in light of recent White House requests for a doubling of the PEPFAR budget, and expanded emphasis on youth infection prevention efforts.

Meeting participants also suggested that the vaccines be marketed in the least controversial way possible, emphasizing cancer prevention. Immunizing boys in addition to girls could increase acceptability, as could the establishment of several high profile demonstration projects. So, too, could approving the vaccines for use in older women, particularly if ongoing research confirms a trend suggesting that immunization protects women who have been exposed to (but are not currently infected with) the most dangerous strains of HPV.

A graduated pricing scale within countries could also promote access, according to GSK's Myers. "We believe that every country no matter what income segment they're in has a private market, a group of people that has disposable income and an ability to pay,"

Myers said. “You have a price for the private market, a price for the public market, and a price in between.”

Mexico’s Tapia-Conyer said that countries should not wait until they can afford to provide HPV vaccines to their entire populations before beginning to purchase the products. Instead, countries should adopt a “tiered approach,” targeting their highest risk or most socially vulnerable populations first, such as female members of Mexico’s indigenous populations. He argued that individuals have a social right to vaccination that should be guaranteed by governments—which can and should invest more in healthcare. Mexico raised the percentage of its health budget devoted to public health activities like disease surveillance, health education, and vaccinations from 4% in 2000 to 32% at the end of last year. “There’s room for governments to ... invest more in vaccines,” Tapia-Conyer said. He also stressed that developing countries are not monolithic, and distinct vaccine promotion strategies should be developed, financed and promoted for different world regions, led by interested multi-lateral agencies or foundations.

Leveraging HPV Vaccination

Developing the infrastructure needed to reach adolescents will be critical not only for the current immunization effort, but also for the introduction of future products, particularly a hoped-for AIDS vaccine. Experts with the International AIDS Vaccine Initiative (IAVI) have experience analyzing vaccine-related policy issues and conducting advocacy. The group is now partnering with PATH to explore potential HPV vaccine delivery options, including school-based programs, child health days and coordination with existing AIDS programs.

“We feel we can learn from HPV vaccines and disseminate those lessons because there’s a lot in common (with AIDS vaccines),” said Dr. Robert Hecht, senior vice president of public policy at IAVI. “Sexuality and stigma are major factors for both infections and vaccines.”

Judith Bruce, senior associate in the poverty, gender and youth program at the Population Council, said that multipurpose girls’ clubs should be established to help capture socially isolated groups, such as out of school and married girls, who are at high risk of infection with HPV and other sexually transmitted diseases. Platforms like this could be used to offer not only the HPV vaccine, but also other adolescent services, from AIDS prevention information to issuance of national ID cards and savings accounts. Many meeting participants felt that campaigns that increase awareness of cervical cancer should also be leveraged to enhance cervical cancer screening programs in developing countries.

Ultimately, HPV vaccines represent a major test for the global health field. “We view HPV vaccines as a tremendous opportunity, but one we can not take for granted,” said IAVI’s Hecht. “We could also blow it here. We need to make sure that doesn’t happen.” If governments, industry, advocates and charitable organizations succeed in promoting access to HPV vaccines among the world’s poor, that could catalyze a range of health and social interventions for adolescents. However failure would cast doubt on future

initiatives to bring lifesaving new technologies to the developing world. It would signal the pharmaceutical industry that medicines and vaccines will not be taken up readily in poorer countries. Likewise, it would send a message to developing countries that equitable access to medical breakthroughs is not a serious goal for the now multi-billion dollar global health enterprise.