

## A Long and Winding Road: Getting the HPV Vaccine to Women in the Developing World

By Susan A. Cohen

The development of not one, but two vaccines against human papillomavirus (HPV), which have been shown to be highly effective in preventing infections that cause at least 70% of all cervical cancers, represents a major breakthrough for women's health. In the last year alone, Merck's Gardasil has been approved in 76 countries worldwide, including the United States. GlaxoSmithKline's Cervarix, meanwhile, is poised to receive approval in several European countries imminently and by the U.S. Food and Drug Administration early in 2008. If history is any guide, widespread availability in the near-term future of one or both of these vaccines in most industrialized countries can almost be taken for granted, but most women living in the developing world will have to wait many more years for this lifesaving new technology.

Cervical cancer, although highly treatable with early detection, remains the leading cause of cancer deaths among women in the developing world. Women living in low-resource countries are at highest risk of dying from cervical cancer because, compared with women in industrialized countries, they have far less access to screening and virtually no access to treatment. Achieving broad-based access to the vaccine in the developing world is clearly a matter of public health urgency. It will not be an easy goal to reach, however. Indeed, it will require a major global effort involving cooperation between private and public sectors, partnerships across medical and public health disciplines, creativity and innovation in designing service delivery packages, advocacy at the national and global levels and the political will to make saving women's lives a priority.

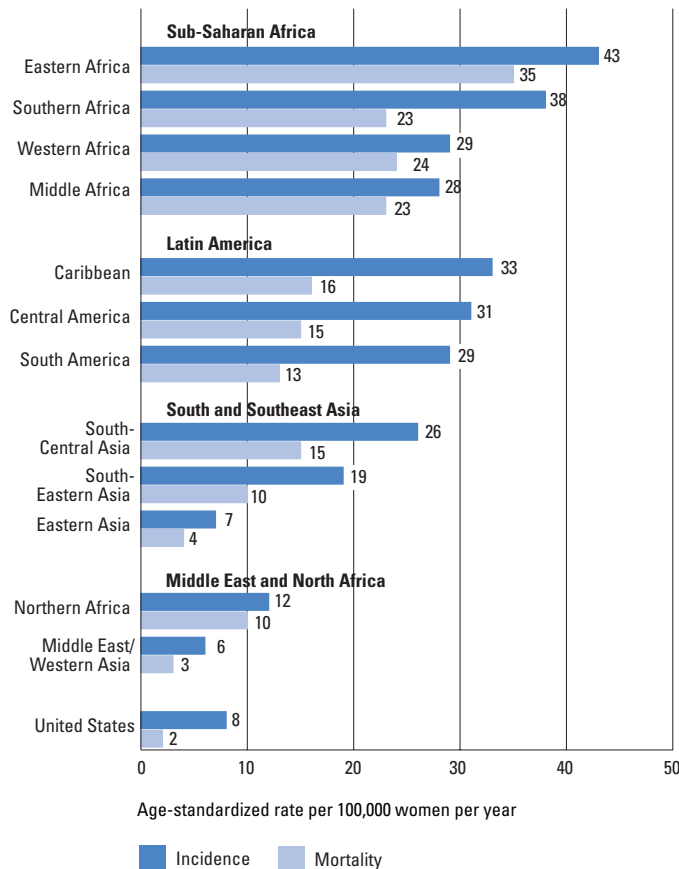
On average, it takes 10–20 years from the time a new vaccine is licensed until it is introduced in the public sector in the world's poorer countries. The HPV vaccine is facing all of the same obstacles that other vaccine introductions face, among them working out an affordable price with the manufacturers, securing sustainable financing to ensure widespread access in the public sector, promoting public education to create demand, and ensuring or establishing a health care infrastructure and providing training for health care workers to deliver the vaccine to the target populations. In addition, the HPV vaccine carries with it extra burdens because it relates to sex, is targeted to females and is aimed at young adolescents—an age-group that while large in number is especially hard to reach with preventive health care.

### Public Health Realities

Each year, some 493,000 women worldwide are diagnosed with new cases of cervical cancer. In developing countries, where 90% of cervical cancer cases occur, such a diagnosis is often tantamount to a death sentence (see chart, page 16). Deaths due to cervical cancer are so high in these countries because most affected women do not present themselves for health care—if they do at all—until their cancer is well-advanced. Even if it were detected earlier, treatment is not widely available. And early detection via a Pap test is essentially nonexistent: It is expensive (costing about \$9 in South Africa, for example), requires highly trained personnel and laboratory equipment to analyze the results and necessitates an effective system for following up with women days or weeks after a test indicates precancerous abnormalities.

## CERVICAL CANCER CASES, DEATHS

Limited access to screening and treatment means that cervical cancer is most common in the poorest regions of the world—and most likely to lead to death.



Source: International Agency for Research on Cancer, 2002.

[The Alliance for Cervical Cancer Prevention, a consortium of international health organizations led by the Seattle-based nongovernmental organization PATH, is actively promoting lower-cost, more practical screening technologies. These would likely be tests that assured a reasonable degree of accuracy, while requiring only minimal training of health workers and allowing for a woman to be tested and to receive her results in the same day, possibly even in the same visit to the health center.]

HPV is sexually transmitted and is the cause of 99% of all cervical cancers. While HPV is also virtually ubiquitous, most strains are essentially harmless, causing asymptomatic infections that usually clear by themselves. Since almost everyone will have sex at some point, almost every-

one will be exposed to some form of HPV. Even a woman who abstains until marriage can be exposed to HPV by her husband. In the real world, therefore, a woman's risk of actually contracting cervical cancer hinges less on her sexual behavior than on her access to effective screening, early detection and treatment services. It is persistent infection with specific HPV strains, left undiscovered and untreated, that leads to cancer 20–30 years later.

Both Gardasil and Cervarix have been determined to be highly effective at preventing infection from HPV strains 16 and 18, which account for 70% of all cervical cancers. (Cervarix is also showing promise at protection against three additional HPV strains that cause another 12% of cervical cancers, while Gardasil also protects against strains 6 and 11, which are linked to genital warts.) The key, however, is to reach girls before they become exposed to HPV, which under optimal circumstances means vaccinating them before they begin to have sex. A recent study found that Gardasil is only 44% effective in women already exposed to HPV 16 or 18, while it is 98% effective in women with no prior exposure.

Accordingly, the current target population for HPV vaccination in developing countries is 10–14-year-old girls. The vaccine will not be administered to even younger girls because its safety for this age-group, including possible interactions with other immunizations, is unknown. Moreover, although immunity is known to last for at least five years and possibly longer, research on its duration is ongoing. In addition, more research is needed on the value of administering the vaccine to boys in terms of protecting them against genital warts and rare cancers such as penile or anal cancer. It is also possible that vaccinating boys and men could provide indirect health benefits to girls and women. Doubling the target population would have significant cost implications, however, and cost is clearly a big-ticket issue with this vaccine.

### Cost, Cost-Effectiveness and Disease Burden

The retail price of Gardasil in the United States is about \$360 for the necessary three doses (over a six-month period); Cervarix is likely to be priced

similarly. In countries where total health care spending per capita each year ranges from \$26 in the poorest countries to \$103 in middle-income countries (in contrast to \$3,054 in high-income countries), the industrialized country price is a nonstarter. Although both drug companies have pledged to offer “tiered pricing” to countries according to income, the price will have to be dramatically lower to make it affordable in developing countries. In the end, it is still likely to be many times more expensive than traditional vaccines, such as the combined vaccine for diphtheria, pertussis and tetanus and the vaccine for measles, which are available for pennies a dose. The prospect for a lower price may be expected to improve as consumer demand for the vaccine increases, but of course, the demand (which is not necessarily the same as the need) depends to some degree on the price.

The GAVI Alliance will play a critical role in the vaccine’s affordability in the world’s poorest countries. GAVI was founded in 2000 to support the introduction of new and underused vaccines in the 72 countries around the world that have per capita incomes of \$1,000 or less. GAVI is composed of representatives from developed and developing country governments, the United Nations Children’s Fund (UNICEF), the World Health Organization (WHO), the World Bank, the Bill and Melinda Gates Foundation, nongovernmental organizations, pharmaceutical companies and public health specialists. Later this year, GAVI will make a determination as to the HPV vaccine’s priority among the many important vaccines already in the pipeline.

That determination, for GAVI and for individual governments, will depend not just on the upfront cost but also on assumptions about the vaccine’s cost-effectiveness. Unlike traditional childhood vaccines, whose impact is measurable in the short term, the HPV vaccine will be administered to young adolescents to prevent illnesses and deaths that could be expected to occur some 30 years later. Moreover, according to WHO, 274,000 women die each year from cervical cancer (90% in developing countries), but 500,000 women die each year from pregnancy-related causes. Malaria kills more than one mil-

lion people per year, and tuberculosis kills almost two million. These realities all will be taken into account as governments consider how to allocate scarce resources, as will the “burden of disease,” a calculation that looks at the toll that various diseases and conditions take in terms of years of life lost to premature death and years of healthy life lost to disability.

Cervical cancers deaths are on the rise, however. WHO projects a 25% increase over the next decade in the absence of widespread intervention. Accordingly, the benefit side of the equation must take into account the long-term advantages to individuals and to society of protecting a very large cohort of young females and preserving their health and lives into their 30s and 40s, their most productive years.

### Girls and Sex

The fact that the HPV vaccine is aimed at a sexually transmitted virus and is targeted mainly to young adolescent girls inevitably raises cultural sensitivities. Even in the United States, many social conservatives initially opposed widespread availability of the vaccine on the grounds that it would amount to a license to have sex and would undermine the abstinence-until-marriage movement (related article, page 9).

If anything, the possibility of resistance in the developing world—whether social, cultural or religious—is likely to be higher. This can be magnified where suspicion of the West—its motives and its medicine—runs deep. As recently as 2003, for example, local opinion leaders in Kano, Nigeria, shut down an effort to immunize children against polio as they perpetrated rumors that the vaccine would result in sterilization or that it contained HIV. Conspiracy theories are of particular concern in the case of the HPV vaccine, because the target population is young adolescent girls. (Some of these fears might be lessened if, in the future, it makes medical and public health sense to administer the vaccine to boys as well.)

Accordingly, public health experts are already discussing the importance of implementing public education campaigns in advance of vaccine intro-

duction to prevent misperceptions from taking hold and to generate in-country demand. This will be challenging in the many parts of the world where communication outlets are limited, illiteracy is common and large numbers of people live in remote areas. Clearly, public awareness of the vaccine and a clear understanding of its benefits, accompanied by an appreciation of the value of cancer screening, will be critical to achieving the ultimate goal of protecting more girls and women from premature death.

### Service Delivery Challenges and Opportunities

Equally important, of course, are workable programs for delivering the vaccine to those most in need. In this respect, even finding the girls will be a challenge. Columbia University's Amy Pollack and her coauthors point out in an article in the *WHO Bulletin* that "young women aged 9–25, and especially unmarried women in that age range, have particular difficulty overcoming social and political barriers to gaining access to reproductive health services" and that "the time between early childhood and sexual debut defines one of the most difficult cohorts to reach for health care." These facts raise the question of what kinds of organizations and which specialties or categories of providers should take the lead programmatically.

Ultimately, the specifics on the ground will vary according to country and local culture. In general, reproductive health and family planning providers, as well as some organizations focusing on HIV prevention, would seem like a logical place to start, because of their experience with adolescents, especially girls, and with outreach programs in remote areas. At the same time, although health professionals in the business of administering immunizations generally deal with infants and young children, their knowledge and experience with transporting, storing and providing vaccines will be extremely important. Furthermore, the expertise of entities and individuals specializing in cancer control and treatment, whose services are mainly oriented toward adults, will be invaluable in advocating for this prevention innovation and leveraging the recognition that cervical cancer is preventable by facilitating education and access to screening.

In addition to the question of *who* should take the lead, there remains the question of *how*. In those countries or areas where adolescent girls are still in school, one widely discussed idea is to hold immunization days. Where large groups of girls have already dropped out of school by this age, one model might be to encourage school children to bring children not in school to the vaccination site. Another might be to encourage women at prenatal, postpartum or family planning clinics to bring in their adolescent daughters or sisters.

These are only some of the possibilities, but it is already becoming apparent that finding creative ways to deliver the HPV vaccine could have important collateral benefits both for individuals and for health care delivery systems in resource-poor countries. As Mark Kane, former director of PATH's children's vaccine program, and his colleagues write in *Vaccine*, the delivery of the vaccine could serve as an entry point for providing other vaccine boosters to this difficult-to-reach age-group as well as other health-promoting interventions such as nutritional supplements and comprehensive sex education. Indeed, Kane observes that WHO and UNICEF strongly support "integration of vaccination as part of strengthening school and adolescent health services" and writes that the "HPV vaccine is seen by some as providing a new incentive both for the expansion of adolescent health services and for their uptake by young persons in a wide range of settings."

At the same time, as Kane and his colleagues suggest, the advent of the HPV vaccine can help clinic-based providers of sexual and reproductive health services become core partners in promoting a comprehensive societal approach to cervical cancer prevention. In addition to potentially becoming an entry point for the delivery of the vaccine itself, they also can and should educate the women they see about the importance of cervical care screening for themselves and vaccinations for their daughters and younger sisters. This will be important to generating increased demand for the vaccine, which in turn would allow manufacturers to increase production and make it easier to lower the price.

Finally, the HIV/AIDS community is looking to the rollout of the HPV vaccine as a potential model for an eventual HIV vaccine. The target age-group would likely be similar, as would some of the programmatic and cultural challenges. Indeed, the link between HIV and cervical cancer already exists in that HIV-positive women are about four times more likely than those who are HIV-negative to develop precancerous lesions.

In an effort to experiment with different approaches and delivery system models, PATH is preparing to undertake HPV vaccine demonstration projects starting early next year in India, Peru, Uganda and Vietnam. Working closely with key partners and stakeholders at the local, national and global levels, PATH will be examining social and cultural barriers to the vaccine's acceptance; the most effective ways to reach adolescent girls; how to integrate vaccine delivery into the existing health system; cost and financing issues; and what combination of primary prevention (vaccine), secondary prevention (screening) and treatment interventions might be most effective in driving down cervical cancer rates. PATH's findings, expected in 2008, will be extremely important in informing policymakers, manufacturers, program specialists and activists about how to get the vaccine to developing countries as soon as possible.

### Doing It Right, Doing It Soon

Pollack and her coauthors aptly summarize the situation noting that "cervical cancer is a unique public health challenge." They observe that "it is gender specific, caused by a sexually transmitted virus, and primary and secondary prevention target opposite ends of a wide age spectrum."

In response to this unique challenge, a broad-based coalition including the WorldYWCA, the International Federation of Gynecology and Obstetrics, the Rockefeller Foundation, American Cancer Society, International AIDS Vaccine Initiative and International Planned Parenthood Federation launched The Global Call to Stop Cervical Cancer in Nairobi in early July. The Call is seen as an organizing tool to raise global

awareness about cervical cancer and to demonstrate to policymakers at all levels broad-based support for getting lifesaving technologies—including the vaccine, screening and treatment—to women and girls in poor countries as soon as possible. It advocates that:

- Governments make cervical cancer a priority in their national health plans;
- United Nations and other multilateral agencies provide leadership and help to expedite the necessary approvals and availability of the vaccine, as well as screening and treatment technologies;
- International donors commit the resources to getting these technologies to the people who need them most as soon as possible;
- Medical professionals become educated and inform their patients about the availability of these lifesaving innovations;
- Manufacturers ensure adequate supplies of these technologies in a tiered pricing structure that allows poor countries to provide access in the public sector; and
- Civil society groups coalesce and catalyze global action.

Such a wide-ranging coalition is entirely appropriate. Because preventing cervical cancer can be considered a sexual and reproductive health issue, involves immunization and is also a matter of cancer control, it belongs to everyone and to no one in particular. At the same time, however, cervical cancer clearly—if tragically—is the property of women. Accordingly, women and women's rights organizations will play a central role in its reduction and eventual eradication. In the short term, at least in some countries, the fact that cervical cancer is a disease that affects only women will make it more difficult to ensure that initiating and maintaining a program to stop it ranks as a top health priority. But as they have demonstrated before, with good education and information, access to high-quality services and broad-based support across many social, business, scientific and health sectors, women can become their own best advocates.

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