

The Public Health Promise and Potential Pitfalls Of the World's First Cervical Cancer Vaccine

By Cynthia Dailard

After a decade in development, a cervical cancer vaccine appears poised to become available to American women later this year. Given the vaccine's demonstrated high level of effectiveness in preventing transmission of the two strains of human papillomavirus (HPV) responsible for most cases of cervical cancer, researchers believe that widespread vaccination has the potential to reduce cervical cancer deaths around the world by as much as two-thirds. The vaccine, therefore, holds the promise of being an enormous public health advance, both for women in the United States and for women in developing countries, who disproportionately bear the global burden of cervical cancer.

Because HPV is sexually transmitted, experts say the vaccine needs to be administered to as many young adolescent females as possible prior to sexual activity to achieve maximum effectiveness. Adolescents, however, are typically considered to be a difficult population to reach through immunization programs. For the HPV vaccine, moreover, the politics of teen sex are likely to exacerbate many of the practical challenges involved in achieving high vaccination rates—practical challenges that are magnified exponentially in developing countries, where the vaccine is needed most.

What the Science Says

Virtually all cases of cervical cancer are linked to HPV, an extremely common sexually transmitted infection (STI) that is typically asymptomatic and harmless; most people never know they are infected, and most infections typically resolve on

their own. The infection is so common, in fact, that it is considered virtually a "marker" for sexual activity; according to a 1997 *American Journal of Medicine* article, nearly three in four Americans between the ages of 15 and 49 have been infected with HPV at some point in their life.

Of the 30 known types of HPV that are sexually transmitted, more than 13 types have the potential to lead to cervical cancer; two of these types, HPV 16 and 18, are associated with 70% of all cases of cervical cancer. In the United States, notwithstanding the prevalence of HPV infection, cervical cancer is relatively rare. This is largely due to the widespread availability of Pap tests, which can detect cervical cancer in its earliest and most treatable stages, as well as precancerous changes of the cervix, which can be treated before cervical cancer sets in. Nonetheless, the American Cancer Society estimates that in 2006, almost 10,000 cases of invasive cervical cancer will occur to American women, resulting in 3,700 deaths. More than half of all U.S. women diagnosed with cervical cancer have not had a Pap test in the last three years. These women are disproportionately low-income women and women of color who lack access to basic health services.

In resource-poor developing countries, the incidence of cervical cancer is much higher, and the disease is far more lethal. Of the 225,000 annual deaths from cervical cancer globally, 80–85% occur to women in developing countries. Most of these deaths occur in Sub-Saharan Africa, South Asia and Latin America—where the public health infrastructure is extremely poor and basic preventive health services such as Pap smears are largely unavailable. Because women in these

regions typically do not receive care until their disease is well advanced, it is usually fatal (related article, August 2003, page 4).

A cervical cancer vaccine would therefore represent an enormous step forward for women's health. There are actually two currently under development. Merck & Company filed an application for approval of its vaccine, Gardasil, with the federal Food and Drug Administration (FDA) in December; it expects an expedited decision—which is reserved for medications that treat unmet medical needs—from the agency in June. It has also submitted applications to regulatory agencies in Europe, Australia, Mexico, Brazil, Argentina, Taiwan and Singapore. GlaxoSmithKline will be seeking regulatory approval of its vaccine, Cervarix, in Europe in March 2006 and at the end of the year in the United States. Both vaccines target HPV 16 and 18, although

Merck's vaccine also offers protection against two types of HPV that cause

almost all cases of genital warts. A consortium of agencies funded by the Bill & Melinda Gates Foundation, and which includes Harvard University, the International Agency for Research on Cancer, PATH and the World Health Organization, is laying the groundwork for implementation of the vaccine in the developing world, expecting that it may be licensed in selected developing countries as early as 2007.

Targeting Teens

To become widely available in the United States, a vaccine must win the endorsement of the Advisory Committee on Immunization Practices (ACIP) in addition to FDA approval. Organized by the federal Centers for Disease Control and Prevention (CDC), ACIP is a 15-member panel authorized under federal law to recommend who should receive a vaccination, when and how often they should receive it, and the appropriate dosage. In deciding whether to recommend a vaccine, the committee must weigh a host of factors, including efficacy, benefits and risks, and

cost-effectiveness. It also determines whether the vaccine should be available through the federal Vaccines for Children Program, which provides free vaccines to doctors serving eligible low-income children. Although ACIP's recommendations are not binding, they are followed closely by physicians and medical professional organizations, and ACIP's endorsement determines with virtual certainty whether a vaccine becomes the standard of care in this country. ACIP recommendations are also widely relied upon by insurers for setting reimbursement policy and by states for public funding purposes.

Perhaps the single most important decision for ACIP will be the optimal age for administering an HPV vaccine. While the typical American female has intercourse for the first time at age 17, 13% do so prior to age 15, according to the 2002 National Survey of Family Growth. Because HPV

infection is so widespread, most cases of HPV are acquired soon after women

become sexually active, with the peak incidence currently occurring at age 19. Merck's trials, moreover, found that the vaccine produced a stronger immunological response in adolescents aged 10–15 than in women aged 16–23. For these reasons, both Merck and GlaxoSmithKline are recommending that all girls receive their vaccines when they are 10–12 years old.

There are other practical reasons for targeting this age-group. In order to address the historical lack of emphasis on adolescent immunization, ACIP, the American Academy of Pediatrics, the American Association of Family Physicians and the American Medical Association in 1996 jointly identified ages 11–12 as the optimal time for adolescent immunizations. Currently, the federal Childhood and Adolescent Immunization Schedule recommends that every 11–12-year-old receive two vaccines (a new vaccine for bacterial meningitis and a combined booster for tetanus, diphtheria and whooping cough); it also recommends that they be assessed for "catch-up" shots at that time.

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If the vaccine is recommended for preadolescent girls, acceptability among pediatricians and parents will be key to its success. Survey results released in October by researchers from the CDC and the University of California found that most pediatricians would be willing to administer the vaccine to their patients. And, several surveys of parents published in 2005 in the *Journal of Adolescent Health* and elsewhere suggest that parental acceptance of the vaccine will in fact be high. Many of those surveyed who initially expressed reservations about the vaccine changed their minds when educated about HPV and cervical cancer, suggesting the importance of counseling and education targeting parents during an adolescent health visit.

Finally, each state decides for itself whether a particular vaccine will be required in order for children to enroll in school, and they typically rely on ACIP recommendations in making this determination. According to a 2005 report on adolescent vaccination by the National Foundation for Infectious Diseases (NFID),

school-based immunization requirements are by far the most effective means to ensure rapid and widespread use of childhood or adolescent vaccines. Adolescents are typically a hard-to-reach population for vaccine programs, and adding a vaccine to the list of those required for school enrollment boosts vaccination rates considerably—and far more effectively than guidelines recommending the vaccine for certain age-groups or high-risk populations. NFID also notes that timing an adolescent vaccination to middle school entry (ages 11–12) is important given that dropout rates begin to climb at age 13. Along these lines, younger dropouts are at particularly high risk of early sexual activity and poor sexual and reproductive health outcomes, suggesting an even greater imperative for a school-based requirement targeting 11–12-year-olds.

The Politics of Teen Sex

No sooner had Merck publicly announced the results of its long-term clinical trials in October 2005 than conservative activists began suggesting that inoculating young adolescents against HPV would encourage teenage sexual promiscuity. The heads of various “family values” groups publicly declared that they would not vaccinate their own children. Vaccination “sends the wrong message,” asserted Tony Perkins of the Family Research Council (FRC). “Our concern is that this vaccine will be marketed to a segment of the population that should be getting a message about abstinence.” This shot across the bow signaled that the cervical cancer vaccine could become the next battlefield in the social conservatives’ crusade to advance an abstinence-only-unless-married agenda, and that leading activists would be working to ensure that it would meet

Key Scientific, Logistical and Policy Questions About the Cervical Cancer Vaccine

- *Should older women who are already sexually active receive “catch-up” vaccines at the start of any vaccination effort?*
- *Should males be vaccinated, both to prevent HPV transmission to women and to protect against HPV-related genital and anal cancers, as well as genital warts, in men?*
- *Could a therapeutic vaccine be developed to help those who are already infected with HPV or have a persistent infection?*
- *Could a vaccine be developed that targets additional cancer-causing types of HPV?*
- *Could the HPV vaccine be combined with other vaccinations for ease of administration, and would that help to institutionalize the adolescent health visit?*
- *Will uptake of the vaccine prompt professional medical organizations and public health entities to change their recommendations for Pap smears, and what might longer recommended intervals between Pap smears mean for women’s health and health care-seeking behavior?*
- *Will the uninsured, the underinsured and those who rely on public programs for their care be able to access this relatively expensive vaccine, or will the vaccine simply widen the cervical cancer disparities that already exist?*

the same regulatory fate as efforts to bring emergency contraception over the counter.

Yet, these same groups now appear to be softening their stance. A statement on the FRC website now says that “media reports suggesting that the Family Research Council opposes all development or distribution of such vaccines are false” and that it “welcomes the news that vaccines are in development.” At the same time, the statement warns, “we will seek to ensure that there is full disclosure to the public of what these vaccines can and cannot achieve, their efficacy, and their risks (including side effects) and benefits. We believe that adults must be provided with sufficient information to make an informed, free choice whether to vaccinate either themselves or their children for HPV.”

Whether the new FRC statement heralds a genuine change in posture on the part of social conservatives remains to be seen. A more likely scenario, perhaps, is that leaders of that movement have made a tactical decision not to oppose federal approval of the cervical cancer vaccine outright but, rather, to hold their fire for 50 state battles over whether the vaccine will be mandatory for middle and high school students. The public health ramifications of such a decision could still be significant. Because universal uptake of the vaccine will have the most impact on cervical cancer rates, efforts designed to prevent mandatory vaccination programs in the name of “parental control” may ultimately hinder the eradication of cervical cancer in the United States.

Beyond Politics

Beyond these political challenges, the impending roll-out of a cervical cancer vaccine raises some very serious practical challenges, as well as a range of longer-term scientific, logistical and policy questions that must be confronted over time (see box). One immediate challenge, for example, is successfully providing the vaccine’s

three required doses over a six-month period to adolescents, who, unlike infants and toddlers, do not typically make frequent, successive visits to a doctor’s office or health care clinic. Moreover, the three-shot regimen is likely to be relatively expensive—somewhere in the vicinity of \$100–150 per shot, according to newspaper reports. And since ongoing clinical trials to date have only demonstrated the vaccine’s effectiveness for four years, it may be that booster shots will be needed—either later in adolescence or during adulthood.

If anything, the challenges in developing countries are more acute, and overcoming them may be far more difficult. These include raising awareness of the need for a vaccine where knowledge of HPV is very low; ensuring acceptability among parents, providers and policymakers in cultural and political contexts that are particularly sensitive to teenage sexuality; delivering a series of three injections to a population that often has

minimal contact with health care facilities or providers; and ensuring that the vac-

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cines are affordable in extremely-low-resource settings. While some global health experts, as in the United States, note the appeal of school-based vaccination programs as a means for reaching large numbers of adolescents, sizeable proportions particularly of female adolescents in many developing countries do not enroll in school or leave school prior to the recommended age of vaccination.

Despite these considerable challenges, one thing is certain: widespread vaccination against HPV in order to prevent cervical cancer would bring an enormous payoff to women, both in the United States and abroad. It can only be hoped that the politics will not be allowed to sabotage the promise first. • www.gutmacher.org