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Preventing Cervical Cancer: New Resources To Advance the Domestic and Global Fight

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Only a half century ago, cervical cancer killed more women in the United States than any other type of cancer.[1] Today, however, the typical American woman has an extremely good chance of avoiding the disease in her lifetime, despite her high risk of becoming infected with the human papillomavirus (HPV), the most common STI and the cause of almost all cervical cancers. But, women in the developing world are not so lucky: Cervical cancer remains the second leading cause of cancer deaths among women in developing countries.[2]

The major factors contributing to the decline in cervical cancer incidence in developed countries—namely, widespread detection and treatment of precancerous cervical lesions as a part of routine gynecologic care—have not yet been replicated worldwide. Developing countries remain far behind in these basic cancer prevention efforts. Meanwhile, even wealthy nations such as the United States are still grappling with the disease, especially among racial and ethnic minorities who face disparities in access and treatment and, therefore, also in incidence and deaths.

Technological innovations over the last decade hold great promise for advocates and health care providers in developed and developing countries alike to lower the number of new cases of cervical cancer and to help address disparities in access to treatment. Despite these welcome developments, significant barriers remain to cervical cancer prevention.

Evolving Medical Landscape

Scope of the Problem

According to data from the Centers for Disease Control and Prevention (CDC), more than 12,000 new cases of cervical cancer were reported in the United States in 2007, resulting in more than 4,000 deaths.[3] Disaggregation of the data by race and ethnicity reveals stark disparities in how cervical cancer impacts different communities. Hispanic women had the highest rate of cervical cancer, 53% greater than the rate among white women; black women's rate was 36% higher than white women's. However, black women were the most likely to die from the disease: Their mortality rate was twice white women's, while the rate among Hispanics was 36% higher than among whites.

The World Health Organization (WHO) estimates that more than 450,000 new cases of cervical cancer occurred in developing countries in 2008, resulting in 240,000 deaths—or 88% of worldwide mortality from cervical cancer.[2] Already, incidence of and mortality from cervical cancer is considerably higher in developing than developed countries (see chart). In the years to come, the burden of the disease will further shift to countries least equipped to deal with it: By 2030, WHO predicts that virtually all cervical cancer deaths—fully 98%—will occur in developing countries, furthering disparities between richer and poorer countries.[4]

Prevention: Secondary and Primary

Approximately half of all sexually experienced people acquire HPV, which is easily transmitted through skin-to-skin contact.[5] Fortunately, most

HPV infections are eliminated naturally by the immune system before any symptoms develop. If the body is unable to clear the infection, however, HPV can cause cellular changes resulting in precancerous lesions, which, if untreated, may lead to invasive cervical cancer many years later.

The length of time between HPV infection and the presence of invasive cancer makes programs focusing on "secondary prevention"—that is, detection and treatment of precancerous lesions—instrumental in preventing cervical cancer cases and deaths. Until relatively recently, prevention efforts in developed countries such as the United States were focused on regular cytological screenings through Pap smears, followed by more sophisticated diagnostic colposcopy testing to more closely view the cervix if the Pap results were suspicious and, if needed, biopsy to remove a small sample of abnormal tissue for additional testing.

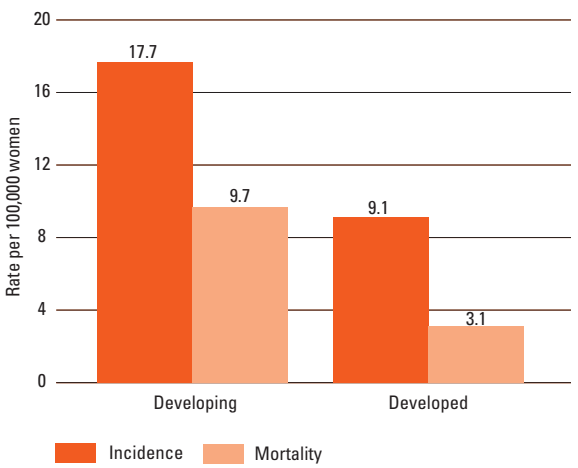
Paps, however, have many limitations. Their low sensitivity to detecting precancerous and cancerous changes can lead to higher rates of false-negatives for this screening method. Consequently, Pap screenings are usually performed yearly or every few years. Moreover, such care requires an extensive health infrastructure, including laboratories and trained personnel, and multiple visits to follow up on abnormalities. Despite these restraints, Pap tests and subsequent treatment efforts have been successful in lowering the incidence of cervical cancer in the United States by 70–80% over the last 50 years.[6]

Meanwhile, scientific advancements have continued to improve secondary prevention methods. For example, a liquid-based Pap test with better detection results became available. Another significant development was the invention of an HPV DNA test to identify high-risk HPV strains in vaginal or cervical samples. The HPV DNA test is more sensitive than cytology-based screenings like the Pap smear and has the potential to become the preferred screening method in wealthy countries; however, because HPV is so prevalent in younger women and usually resolves spontaneously, to avoid unnecessary treatment, the DNA test is only recommended to catch persistent cases among women older than 30.

The biggest technological game-changer has been the introduction of the HPV vaccine as a primary prevention tool. The U.S. Food and Drug Administration (FDA) has approved two variations—Gardasil in 2006 and Cervarix in 2009—that provide protection against the viral strains that cause the large majority of cervical cancers and have demonstrated other benefits as well. Meanwhile, 37 countries around the world, both developed and developing, offer an HPV vaccine in their national programs or through the public sector, and an additional 24 countries have piloted programs to make the vaccine available (see box, page 10).[7]

MORE CANCER, MORE DEADLY

The incidence of cervical cancer is twice as high in the developing world than in the developed world, and mortality is three times as high.



Source: Reference 2.

Approaches for Lower-Resource Settings

Neither the traditional cytological-based approach nor some of the recent medical developments have been practical for less developed countries that lack adequate infrastructure, skilled health care workers or equipment. In turn, these limitations have spurred low-cost, effective innovations in technology and service delivery for under-resourced settings. For example, studies show that women can easily and effectively collect samples themselves for HPV tests at home.[10–12] (Notably, uptake for home tests was higher than for Pap smears.) This option is espe-

cially important where conventional Pap smears are not logistically or culturally feasible. However, home tests result in more false-positives, which could burden constrained health systems with an increase in referrals and overtreatment. Another development is a new HPV DNA test, called *care*HPV, which is less expensive and requires less infrastructure than either conventional DNA or Pap tests and offers rapid test results. It is expected to come on the market in China and India in 2012.

Among the most important strategies being promoted in developing countries are single-visit or "screen-and-treat" approaches. Women are screened through visual inspection with acetic acid (VIA), which allows observation of precancerous lesions or early cancers, which turn white after the cervix is washed with an acetic acid such as vinegar. If abnormalities are found, women can undergo treatment immediately or soon after, without further testing. Treatment is performed through cryotherapy, which destroys the precancerous areas by freezing them with a metal probe cooled by nitrous oxide or carbon dioxide.

Both VIA and cryotherapy are ideally suited for developing country settings, because they require only basic supplies or equipment that are portable and they can be performed by midlevel health workers who are already part of a primary care system and can be easily trained. Moreover, the results are immediately known, and treatment can be provided during the same visit, so patients are not lost to follow-up care. Such an approach overcomes many of the obstacles to addressing cervical cancer in developing countries. Moreover, VIA's sensitivity is similar to or better than that of a Pap test. Where practicable, HPV testing can be substituted for VIA in the screen-and-treat approach.

The HPV Vaccine: A Primer

More than 100 known strains of HPV exist, some high-risk and others low-risk for causing cancer. Two high-risk strains, HPV 16 and HPV 18, are associated with 70% of all cervical cancer cases. HPV can also cause several other cancers, including vulvar, vaginal, penile, anal and oropharyngeal (throat). Two strains that are low-risk for cancer, HPV 6 and HPV 11, cause 90% of genital warts cases and certain anogenital cancers. Gardasil and Cervarix protect against HPV 16 and HPV 18, and Gardasil also protects against HPV 6 and HPV 11.

Neither Gardasil nor Cervarix clear existing HPV infections. Consequently, vaccination is most effective before any exposure to HPV. Because HPV is easily transmitted through genital contact, including those areas not protected by a condom, and because of its pervasiveness among adults and teens who have had sex, even those who have had only one partner, the HPV vaccine should be administered to individuals before they first have sex. In the United States, the CDC's Advisory Committee on Immunization Practices (ACIP) recommends that the vaccination be given to all females aged 11–12, and "catch-up" vaccinations be administered to those aged 13–26 who were not previously vaccinated. For its part, WHO has advised that HPV vaccines be incorporated into the national immunization programs of less developed countries when certain conditions relating to public health priorities, sufficient infrastructure, sustainable financing and cost-effectiveness are met.[8] Adolescence has also been the standard age for vaccination of females in other countries where the vaccine is offered.

And although HPV vaccines were originally considered only for females, their use has since broadened. In the United States, the FDA expanded approval of Gardasil for males in 2009. In 2011, ACIP recommended that males aged 11–12 be vaccinated and those aged 13–21 not already vaccinated receive a "catch-up" vaccination. The vaccination of males prior to sexual debut not only protects them against HPV infections that could lead to genital warts and anal cancer, but also protects their future female partners against transmission of the virus. Moreover, new evidence has linked HPV to many cases of oral cancers, which are much more commonly found among men than women.[9] While the HPV vaccine has not been tested for protection against oral cancers, future studies may identify yet more advantages of the vaccine.

The Gold Standard

No matter the setting, the end goal of comprehensive cancer prevention and treatment efforts is universal coverage of the HPV vaccine before exposure to the virus, as primary prevention, accompanied by a parallel track of secondary prevention screening and treatment services as necessary. As the HPV vaccine becomes more widely available and accepted as the first line of defense against cervical cancer, the amount and types of secondary treatment required may change. Frequent screenings may no longer be necessary, as more young people become vaccinated and the incidence of HPV falls. Possibly, women may need only one or two screenings per lifetime with a highly accurate HPV test when they are in their 30s and 40s. Such a shift in gynecologic care could result in considerable cost-savings to health systems both in the United States and abroad.

In the meantime, repetitive screenings continue to be important because of a generation of unvaccinated women over 30, because of the substantial time and effort still necessary to achieve universal vaccine coverage and because women can still be infected from HPV strains that are not covered by the vaccine. Currently, in lower-income settings, an HPV DNA test, where available, or VIA are the preferred methods of screening, followed by treatment through cryotherapy. In developed countries, secondary prevention screening recommendations vary depending on the authority (see box, page 12).

Program Implementation and Policy Advancements

Lessons Learned

The development of the HPV vaccine represented a major public health breakthrough and has raised high hopes for cervical cancer prevention efforts in both rich and poor countries. In the United States, however, six years after initial approval, uptake of the vaccine has been disappointing—only 32% among females 13–17.[14]

This limited acceptance may be partially due to the rocky reception it received from different corners of American society at its introduction. Social conservatives opposed the vaccine, arguing that it would promote teenage promiscuity and undermine abstinence efforts. On the other hand, some communities of color and public health advocates were suspicious of aggressive lobbying efforts to require HPV vaccination for students before entry to school. Indeed, laws to mandate the HPV vaccine into school attendance criteria succeeded in only two locales—Virginia and Washington, DC—which both have parental opt-outs. In hindsight, more public education to slowly build a groundswell of support for the vaccine would have been a more sustainable strategy to promote acceptance, especially before introducing legislation to mandate the vaccine.

In addition to the lack of the HPV vaccine's integration into school-based immunization requirements, other factors may have slowed its uptake. These include its hefty price tag (about $360), multiple dosages and doctor visits (three separate shots over six months), and a relatively older target population compared with other immunizations that are generally administered to infants and toddlers during frequent well visits.

Other countries have had more success in achieving widespread coverage of the vaccine. Australia and the United Kingdom, like the United States, were among the first to approve the vaccine. However, uptake in Australia had reached 71% for all 15-year-olds by 2009—two years after the government funded vaccinations through school programs.[15] Similarly, the United Kingdom had completed vaccinations for 76% of its eligible 12–13-year-old females by the 2009–2010 school year.[16] In contrast to the United States, both countries delivered the vaccines through school-based programs.

Even many lower-income countries with vaccine pilot programs have been able to achieve high vaccine coverage. PATH, a global health nongovernmental organization, has conducted demonstration programs in India, Peru, Uganda and Vietnam to assess different delivery strategies to achieve coverage. High vaccine acceptance was attainable through all three of the delivery strategies it implemented: school-based, health center–based and in combination with other health interventions. For example, in the three countries

where vaccines were delivered through school-based programs, coverage ranged from 83% in Peru to 89% in Uganda to 96% in Vietnam in the demonstration projects. Overall, the highest coverage—at 98%—was attained through a health center–based program in Vietnam.

To lay the groundwork for vaccine delivery in all three delivery strategies, the projects coordinated careful community sensitization and mobilization efforts. One of the most critical and highly effective communications strategies was to focus on cancer prevention as the vaccine's purpose, instead of STI prevention. Keeping this emphasis on an anticancer vaccine rather than HPV infection found more resonance with a population that was unfamiliar with the virus. In turn, participants in the project overwhelmingly identified their reasons for accepting the vaccine as protection against cervical cancer, prevention of disease and their belief that vaccines were good for health. The reasons for refusal were frequently related to program delivery, such as school absenteeism, rather than opposition to the vaccine. In no case did parents cite concerns related to teenage sexuality with respect to this vaccine as a cause for refusal, a distinct difference from the U.S. experience.

Moving Forward

In the United States, health care reform is already helping to strengthen efforts to combat cervical cancer. Under the Affordable Care Act, most private insurance plans are required to cover the HPV vaccine and will soon be required to provide HPV testing, in both cases without cost-sharing.

In the international arena, two recent initiatives should boost global campaigns against cervical cancer. Pink Ribbon Red Ribbon (PRRR) is a public-private partnership among the U.S. State Department, the George W. Bush Institute, Susan G. Komen for the Cure and the Joint United Nations Programme on HIV/AIDS (UNAIDS) to fight breast and cervical cancer in Sub-Saharan Africa and Latin America. The U.S. government's partnering role will be leveraged through its international HIV/AIDS program, the President's Emergency Plan for AIDS Relief (PEPFAR), by using its existing AIDS clinics to screen and treat for cervical cancer. HIV-positive women are 4–5 times more likely to develop cervical cancer.[17] PEPFAR already had been playing a limited role in cervical cancer efforts, but will increase its funding by $10 million, for a total of $30 million over the next five years through PRRR.[18] In total,

A Difference of Medical Opinion

In October 2011, the American Cancer Society and two other prominent cancer groups issued new draft guidelines on cervical cancer screening. Among the changes recommended, the guidelines proposed that women aged 21–29 receive Pap testing every three years instead of annually. For women 30 and older, however, the guidelines identify the preferred strategy as Pap testing plus HPV testing not more than every 3–5 years.

On the same day that the cancer groups released their proposal, the U.S. Preventive Services Task Force (USPSTF), an independent advisory body, also put forth new draft guidelines recommending against simultaneous use of Pap tests and HPV tests.[13] Instead, the task force suggested that women 20–65 years old get a Pap test every three years; they found that there was not enough evidence to recommend HPV testing for those 30 and older. Part of their decision was based on the likelihood that HPV tests produce more false-positives, resulting in unnecessary procedures and treatments.

In contrast, the Institute of Medicine (IOM) has recommended simultaneous HPV testing for women 30 and older as part of women's preventive services under the Affordable Care Act. Accordingly, starting in August 2012, women in private insurance plans will have access to simultaneous HPV testing without cost-sharing. It is unclear, however, whether low-income women under Medicaid will have the same access to simultaneous testing, because Medicaid is not bound to follow any established guidelines, whether those of IOM or USPSTF.

PRRR has secured $75 million over a five-year period to increase access to cancer prevention, screening and treatment, and specifically, to cut cervical cancer deaths by 25% among women screened and treated through the partnership. The alliance has gained commitments from corporate participants to donate supplies and support for vaccines, screening tests, training for health workers and other resources, although it is unclear how much and for how long this private support will be extended.

The second new source of international support for cervical cancer prevention—and perhaps the most important recent policy development in this field—could come later this year when the GAVI Alliance may offer the HPV vaccine to developing countries at highly subsidized prices. GAVI is a partnership of public and private entities—including the United Nations Children's Fund (UNICEF), WHO, the World Bank, the Bill & Melinda Gates Foundation, developing and developed country governments, drug companies, nongovernmental organizations and others—with a mission to support access to vaccines for the world's poorest countries. The vaccine's high cost has been a key obstacle to introducing and improving coverage in poor countries, and GAVI's plan to deliver cervical cancer vaccines to two million females in nine countries by 2015 is contingent upon successful negotiations currently underway with manufacturers to finalize a sustainable price. Aside from costs, GAVI's support means that the vaccine will be available more quickly than the typical 10–20 years it takes after licensing before a new vaccine is available in the public health system of low-income countries.

Despite many advancements, there remain serious challenges to lowering rates of cervical cancer cases and deaths. In the United States, uptake of the HPV vaccine remains slow, and may continue to lag as long as conservative opposition remains steady and the vaccine is not included in organized school-based programs. And screening and treatment efforts may also make little headway unless racial and ethnic disparities are addressed. Worldwide, middle-income countries will continue to face the prohibitive costs of traditional comprehensive prevention and treatment programs, particularly as international support from initiatives such as GAVI are unavailable to them. Finally, the poorest countries will still be struggling to fit in one more health priority among many competing challenges.

Still, the fact remains that cervical cancer is highly preventable and treatable, and many of the medical and technological tools to radically reduce—if not eliminate—cervical cancer as a killer of women are now in place and affordable. What is needed going forward is the leadership and commitment—among developed and developing country policymakers and donor agencies alike—to activate and sustain them. www.guttmacher.org

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