United Nations Development Fund for Women

UNIFEM

Cervical Cancer Prevention and Treatment: Science, Public Health and Policy Overview

Background Paper 1

Hosted by:

Facilitated by:

Fight against cervical cancer:

challenges and opportunities for women's right to health

27-28 September 2007, Brussels

Cervical Cancer Prevention and Treatment: Science, Public Health and Policy Overview

Miranda S. Balkin, MS-2,
Albert Einstein College of Medicine and Global Health Strategies

Introduction

Until recently, cervical cancer could only be prevented by screening and treating all women for cancers and pre-cancers. Because the disease is often silent ("asymptomatic") until it is quite advanced, and because of broader gaps in women's health services, each year a quarter of a million women die from the disease. Some seek and receive treatment late – others do not receive any treatment, and still others die without ever knowing their diagnosis. Many of these deaths are preventable, as is the physical pain, discomfort and social stigma which often come with advanced disease. This document describes strategies for preventing cervical cancer, including new HPV vaccines and diagnostics, as well as established screening techniques, that could be deployed to have a dramatic impact on this devastating disease. It also explains those technologies, their potential role in disease prevention, and currently unresolved regulatory and safety questions. The document also gives a brief overview of treatments available to women with advanced disease and outlines World Health Organization guidelines for cervical cancer screening.

Cervical cancer: Global disease burden and natural history

Global disease burden

Cancer of the cervix results from persistent infection with specific strains of human papillomavirus (HPV), a large family of viruses, of which other strains cause benign warts.[1] Worldwide, cervical cancer strikes almost half a million women every year, and is fatal in approximately half of these cases. Only breast cancer causes more cancer-related deaths in women worldwide. In less developed countries (LDCs), cervical cancer is the leading cause of cancer-related death.[2] Cervical cancer is a disease of the female reproductive organs, with the burden of it borne disproportionately by women in their perimenopausal years: peak cancer incidence occurs at age 50-54.[3]

Almost 80% of cervical cancer cases and deaths occur in poor countries.[4] The highest rates worldwide are found in sub-Saharan Africa, Latin America and the Caribbean, Melanesia, India and other areas in Asia – but this is not because HPV itself is confined to any particular area.[5] Although different strains of HPV dominate in different geographic areas,[6] HPV overall is considered to be endemic in every region studied.[7] Proven strategies for effective prevention and treatment are well-deployed in industrialized countries, but are sorely lacking in LDCs, where gaps in infrastructure, a dearth of medical providers, insufficient funds, lack of political will and low priority status accorded to women's health hamper effective responses to cervical cancer and many other women's health issues.

1. Walboomers JM, Jacobs MV, Manos MM et al. Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. J Pathol. 1999;189:12–19.
2. Parkin DM, Bray F, Ferlay J et al. Global Cancer Statistics 2002. CA Cancer J for Clin. 2005;55:74–108.
3. Law MR, Morris JK, Wald NJ. The importance of age in screening for cancer. J Med Screen. 1999;6:16-20.
4. Ferlay J, Bray F, Pisani P et al. Globocan 2002 cancer incidence, mortality, and prevalence worldwide. Version 2.0. 2004: Lyon, France, IARC Press. IARC CancerBase No. 5.
5. Parkin DM, Bray F, Ferlay J et al. Global cancer statistics 2002. CA Cancer J Clin. 2005; 55:74–108.
6. Muñoz N, Bosch FX, Castellsagué X et al. Against which human papillomavirus types shall we vaccinate and screen? An international perspective. Int J Cancer. 2004;111:278-285.
7. Baseman, JG and Koutsky LA. The epidemiology of human papillomavirus. J Clin Virol. 2005; 32S1:516–524.

Natural history

Biology
Cervix is the term for the opening of the female uterus. If the uterus is thought of as an upside-down balloon – usually collapsed in on itself, but with the potential to stretch to many times its normal size in the event of pregnancy – then the cervix may be thought of as the neck of the balloon. Its external opening is located at the inner end of the vaginal canal and thus may be easily visualized by a medical provider with the aid of a speculum.

Sexual transmission of HPV
Worldwide, infection with various strains of HPV is highly common among sexually active women. Baseman et al. found that 60% of sexually active women acquired an HPV infection within a five-year period.[8] A woman is most vulnerable to HPV infection while her cervix is still developing (into her early 20's), and most women acquire an HPV infection shortly after their first sexual encounter or "sexual début."[9]

Men can be infected by HPV without symptoms, as is true of most sexually transmitted diseases (STIs), and infect their partners. Because the virus can live on the vulva as well as the vagina, and on the penis plus the pubic area surrounding it, condoms offer significant but incomplete protection.[10]

HPV and cervical cancer
The human immune system can fight HPV and in many women, HPV infection is naturally cleared. However, in some women, the infection persists. The symptoms associated with persistent infection vary depending on the strain or subtype of HPV. There are dozens of subtypes of HPV; some cause external warts, which may be unsightly and painful but are otherwise harmless, while other strains can cause cancer. In a woman with persistent HPV infection, the outermost layers of cells on the cervix will eventually begin to differentiate abnormally. In 90% of cases, these changes will reverse themselves, leaving the woman with a once again normal cervix.[11] Or, they may progress to a precancerous condition, which is classified into progressive stages. Growths beyond a certain stage are considered to be cancer. If not treated, the cancer will continue to grow until it is a very large mass, possibly enveloping other pelvic organs in the process. Advanced cancer can cause severe back pain, fluid retention, shortness of breath and weight loss. The tumor may grow so large that it erodes a hole – known as a fistula – in the woman's bladder, urethra or bowel, which may leak urine and/or feces continually. Metastasis to other parts of the body, unlike in other cancers, is relatively rare.[12]

It usually takes decades to progress from persistent infection with an oncogenic (cancer-causing) HPV subtype to advanced cervical cancer, although cancer is occasionally seen in young women. Early screening and detection of precancerous growths can dramatically improve outcomes. Many precancerous growths can be treated in

8. Baseman, JG and Koutsky LA. The epidemiology of human papillomavirus. J Clin Virol. 2005;32S1:516–524.
9. Jamison JH, Kaplan DW, Hamman R et al. Spectrum of genital human papillomavirus infection in a female adolescent population. Sex Transm Dis. 1995;22:236-243.
10. Winer RL, Hughes JP, Feng Q et al. Condom use and the risk of genital human papillomavirus infection in young women. NEJM. 2006;354:2642-2643.
11. Baseman, JG and Koutsky LA. The epidemiology of human papillomavirus. J Clin Virol. 2005;32S1:516–524.
12. World Health Organization (WHO). Comprehensive cervical cancer control: a guide to essential practice. WHO: Geneva, 2005.

outpatient settings. Women who receive this treatment have a promising prognosis: invasive cancer post-treatment occurs in only 56 per 100,000 woman-years (years after treatment that women are monitored).[13] In fact, the earlier the cellular changes are detected, the more likely it is that that a woman will go on to live a normal life.

If cancer has invaded a woman's cervix, she may require more invasive surgery, radiation therapy, and/or chemotherapy, depending on the cancer itself and on what resources are available to her and her doctors. According to one analysis, survival rates among women who have access to these treatments are 61% in industrialized countries and 41% in LDCs.[14] This disparity can be attributed to later age at diagnosis in LDCs as well as lack of access to treatment. Cervical cancer rates peak at around age 50,[15] and these women's illnesses or deaths can prove not only emotionally devastating but also quite economically burdensome to their families and communities.[16]

HPV and genetic variability

There are many different subtypes of HPV, only a relatively small number of which cause cancer or warts. Both of the existing vaccines provide protection against HPV 16 and 18, the strains associated with 70% of cervical cancer cases worldwide. However there are other cancer-causing strains not contained in the vaccines. Therefore, one critical question is whether these vaccines will provide "cross-protection" against strains not contained in the vaccine. There are some data that one of the vaccines, Cervarix®, offers some cross-protection against HPV-31 and 45, the next two most common oncogenic HPV types after 16 and 18 (see section on vaccines below).[17] However, this has not been demonstrated definitively, and more information is needed on this important question.

In the absence of definitive data on cross-protection, it is important to remember that vaccine efficacy data are only for cancers caused by specific strains. Vaccinated girls and women are not protected against the 30% of cancers caused by other strains of HPV. Eliminating even 70% of half a million cancers every year would be a tremendous advancement in public health. However, there is some concern that other oncogenic strains of HPV could conceivably become more common, filling the ecological niche vacated by HPV-16 and 18, so that cervical cancers are not reduced by a full 70%. This concern stems from experiences with other vaccines. Albrich et al. found that as broad coverage was achieved for a 7-valent pneumococcal vaccine, other strains of pneumococcus increased significantly in prevalence.[18] It is expected that future generations of the vaccine will protect against more strains of the virus; the hope is that eventually one or multiple vaccines will be designed to address all oncogenic strains of HPV.

13. Soutter WP, Sasieni P, Panoskaltsis T. Long-term risk of invasive cervical cancer after treatment of squamous cervical intraepithelial neoplasia. Int J Cancer. 2006;118:2048-2055.
14. Parkin DM, Bray F, Ferlay J et al. Global Cancer Statistics, 2002. CA Cancer J Clin. 2005;55:74-108.
15. Pollack AE, Balkin M, Edouard L et al. Ensuring access to HPV vaccines through integrated services: a reproductive health perspective. Bull WHO. 2007;85:57-63.
16. Steinberg M, Johnson S, Schierhout G et al. Hitting home: How households cope with the impact of the HIV/AIDS epidemic. Henry J Kaiser Foundation & Health Systems Trust. 2002. Accessed 8/1/07 at: http://www.kff.org/southafrica/20021125a-index.cfm.
17. Harper DM, Franco EL, Wheeler CM et al. Sustained efficacy up to 4-5 years of a bivalent L1 virus-like particle vaccine against human papillomavirus types 16 and 18: follow-up from a randomised control trial. Lancet. 2006;367:1247-1255.
18. Albrich WC, Baughman W, Schmotzer B et al. Changing characteristics of invasive pneumococcal disease in Metropolitan Atlanta, Georgia after introduction of a 7-valent pneumococcal conjugate vaccine. Clin Infect Dis. 2007;44:1569-1576.

HPV and HIV

Any discussion of HPV and cervical cancer would be remiss if it did not also discuss HIV, not only because they are both very common STIs with common constituencies, but also because prior HIV infection and its accompanying reduction in immune function render a woman more susceptible to persistent HPV infection and to developing cervical cancer.[19] According to one study, 77% of HIV-infected women worldwide are also infected with HPV.[20] HPV/cervical cancer treatments appear to be less effective in HIV-infected women,[21] and validated screening protocols for this special population do not yet exist. In total, 17.7 million women were estimated to be living with HIV in 2006.[22] Thus, more than 13 million women are infected with both viruses – yet services for these women are extremely limited, both in terms of finances and in terms of the science available. Some AIDS advocates have already recognized this as a common ground for fighting for HPV services. This is discussed in more detail in the paper "Opportunities for Women's and Girls' Health: Building Support to Prevent Cervical Cancer in Developing Countries". It should be noted that advocates are concerned about both the effectiveness and the safety of HPV vaccines for HIV positive women. However, since the vaccines are not live, there is no evidence to suggest that the vaccine will be unsafe. It is more likely that HIV positive women will have a lower immune response, thereby rendering the vaccines less effective. However if, after data are gathered, it is discovered that either concern is valid for HIV positive women, screening women for HIV before providing the HPV vaccine will merit consideration.

Cervical Cancer Prevention Strategies

A. Screening – Secondary Prevention

There are two kinds of disease prevention, known as primary and secondary. Primary prevention refers to an intervention designed to prevent a person from ever getting sick: for instance, the global administration of smallpox vaccines has completely eliminated the natural transmission of smallpox among humans, by providing immunity to smallpox to everyone who was vaccinated. Secondary prevention refers to a screening test which can detect a disease, or its precursor states, and is routinely used in the absence of symptoms. Examples include colonoscopy, a method of colon cancer screening which is often recommended for all adults over 50 (in settings where it is available), or provider-initiated HIV testing in at-risk populations.

1. Pap smears

There are several technologies available for secondary prevention of cervical cancer. Perhaps the most well-known is the Papanicolau ("Pap") smear. A stiff brush or a small plastic spatula is used to scrape some cells off the surface of the cervix. These cells are mounted on a slide and examined by a pathologist for evidence of cancer or precancerous changes. A Pap smear can be done in one minute as part of a routine pelvic exam, and has, since its introduction more than 50 years ago, become widely-used in industrialized countries.

19. Strickler HD, Burk RD, Fazzari M et al. Natural history and possible reactivation of human papillomavirus in human immunodeficiency virus-positive women. J Natl Cancer Inst. 2005; 97:577-586.
20. Public health, civil society organizations launch global initiative to end cervical cancer. Kaiser Daily Women's Health Policy Report. 11 July 2007. Accessed 8/1/07 at http://www.kaisernetwork.org/daily_reports/rep_women_recent_reports.cfm?dr_cat=2&show=yes&dr_DateTime=11-Jul-07.
21. Massad LS, Fazzari MJ, Anastos K et al. Outcomes after treatment of cervical intraepithelial neoplasia among women with HIV. J Low Genit Tract Dis. 2007;11:90-97.
22. UNAIDS. AIDS epidemic update: special report on HIV/AIDS: December 2006. UNAIDS: Geneva, 2006. Accessed 8/1/07 at: www.unaids.org/en/HIV_data/epi2006/default.asp.

In Scotland, for example, increases in screening programs led to a 30% decline in cervical cancer mortality over the period 1975-1994.[23]

The Pap smear is not without its limitations. It shows a high specificity, meaning that its false positive rates are quite low – but what it detects may be an early abnormality that would regress on its own. Suspicious cells that turn out to be ultimately benign may, in the interim, lead to unnecessary tests and treatment, and anxiety for the patient. The Pap smear's sensitivity, or rate of false negatives, shows better results with the use of newer liquid-based cytology, but overall has been called into question.[24] Less than optimal rates occur partly because its interpretation is not quantitative but is subject to human judgment, which is necessarily fallible, and more often simply because results can be inconclusive.[25] Thus the test must be repeated frequently (in developed countries, different protocols suggest every one to three years) in order to ensure adequate coverage.

Moreover, the Pap smear has many daunting technical requirements. Obtaining an adequate sample of cells from the cervix requires training. A cold chain (constant refrigeration of the sample) must be maintained in transporting the slide from the examining clinician to the lab. A pathologist must have two years of training beyond her degree to be qualified to read a Pap smear.[26] The laboratory facilities and equipment needed to preserve and read the slide are expensive. Finally, in the event of a positive test result, the patient must be called back for a second visit and, depending on institutional protocol, another Pap smear, a colposcopy (microscopic examination of the cervix itself), or an outpatient surgical procedure. The infrastructure, training and multiple clinical visits required make Pap screening expensive and difficult in developing country settings; when it is attempted, it is simply ineffective.[27] In India, as is typical in many parts of the developing world, only 1% of women have ever received a Pap smear.[28]

2. HPV DNA testing

More recently, QIAGEN (formerly Digene) has developed a test for HPV DNA which uses the same cervical sample that is taken for a Pap smear. It tests for 13 oncogenic strains of HPV that together are responsible for over 95% of cervical cancers.[29] Used alone or, where resources permit, in combination with Pap smears, the test is highly effective. False positive and negative rates are quite low with the test.[30] The patient can collect the sample herself with no reduction in efficacy,[31] possibly eliminating the need for what

23. Walker JJ, Brewster D, Gould A et al. Trends in incidence of and mortality from invasive cancer of the uterine cervix in Scotland (1975-1994). Pub Health. 1998;112:373-378.
24. Cervical cancer screening in developing countries: report of a WHO consultation. WHO: Geneva, 2002. Accessed 7/30/07 at whqlibdoc.who.int/publications/2002/9241545720.pdf.
25. Ronco G, Cuzick J, Pierotti P et al. Accuracy of liquid based versus conventional cytology: overall results of new technologies for cervical cancer screening: randomised controlled trial. BMJ. 2007;335:28.
26. Wright TC, Denny L and Pollack A. Strategies for overcoming the barriers to cervical cancer screening in low-resource settings. In: J. Sciarra, ed. (revised edition), Gynecology and Obstetrics vol. 1. Philadelphia: Lippincott William and Wilkin, 2002.
27. Chirenje ZM, Rusakaniko S, Kirumbi L et al. Situation analysis for cervical cancer diagnosis and treatment in East, Central and South African countries. Bull World Health Org. 2001;79:127–132.
28. Bradley J, Barone M, Mahe C et al. Delivering cervical cancer prevention services in low-resource settings. Int J Gynaecol Obstet. 2005;89:S21–S29.
29. Cohen J. High hopes and dilemmas for a cervical cancer vaccine. Science. 2005;308:618-621.
30. Goldie SJ, Kuhn L, Denny L et al. Policy analysis of cervical cancer screening strategies in low-resource settings: clinical benefits and cost-effectiveness. J Amer Med Assoc. 2001;285:3107–3115.
31. Wright T, Denny L, Kuhn L et al. HPV DNA testing of self-collected vaginal samples compared with cytologic screening to detect cervical cancer. JAMA. 2000;283:81-86.

many consider to be an invasive and embarrassing pelvic exam. In its present incarnation it is not as affordable in less developed countries, but a cheaper test is under development through a partnership between QIAGEN, PATH and the Bill & Melinda Gates Foundation. This potentially ground-breaking screening tool should shortly be available commercially. This test offers the possibility of bringing the benefits of DNA screening technology to women in LDCs, providing results more quickly – in just a couple of hours, and it is designed to have undemanding technical requirements that make it less expensive and more feasible for use in low-resource settings.

In most European countries (among other industrialized nations), there is a well-developed network for regularly scheduled Pap smears, with the dramatic results mentioned earlier. Many countries have begun to integrate currently available HPV DNA tests into this process for still more precision in diagnosing cervical cancers and pre-cancers. A model based on data from Thailand showed a 37.6% reduction in cervical cancer mortality could be achieved using only HPV DNA testing every 5 years, or 43.5% mortality reduction using both HPV DNA and Pap testing.[32]

3. Visual inspection

An existing, low-resource screening technology that has shown more promising results for use in LDCs is VIA or VILI (visual inspection with acetic acid or Lugol's iodine). When the cervix is painted with iodine or a weak solution of acetic acid (white vinegar), the diseased areas appear to be a different color than the rest of the cervix. Although interpreting the results of VIA/VILI is not quite as simple as it sounds – clinicians (doctors or mid-level providers) must be trained to determine which results should warrant concern – overall the procedure requires considerably less training than a regimen of Pap smears and DNA tests. The only supplies needed for the screening itself are acetic acid or iodine, a speculum and a bright light. Moreover, this direct visualization allows the clinician to simply excise or freeze the diseased tissue on the spot, eliminating the need for return visits or multiple providers. Thus, VIA/VILI is a realistic option in a setting where women have little money, receive health care infrequently, and cannot be reliably contacted for follow-up. This strategy has been implemented in some regions in developing countries such as Zimbabwe and India with considerable success.[33],[34] A not insignificant downside

is the test's high false positive rate, leading to treatment in perhaps 20% of women screened – although most of them don't need it.[35],[36] The patient could potentially be more vulnerable to HIV infection until this wound heals,[37] raising concerns about whether this particular screen-and-treat approach is appropriate in areas with already high HIV rates. Women in HIV- and HPV-endemic areas need, of course, more comprehensive health care in general, although this goal cannot be quickly achieved. At the very least, it would be prudent to ensure that they are screened with higher specificity, so that women without true persistent HPV infection need not be put at risk of acquiring HIV. QIAGEN's HPV

32. Mandelblatt JS, Lawrence WF, Gaffikin L et al. Costs and Benefits of Different Strategies to Screen for Cervical Cancer in Less-Developed Countries. JNCI. 2002;94:1469-1483.
33. University of Zimbabwe/JHPIEGO Cervical Cancer Project. Visual inspection with acetic acid for cervical-cancer screening: test qualities in a primary-care setting. Lancet. 1999;353:869-873.
34. Sankaranarayanan R, Esmy PO, Rajkumar R et al. Effect of visual screening on cervical cancer incidence and mortality in Tamil Nadu, India: a cluster-randomised trial. Lancet. 2007;370:394-406.
35. Denny L, Kuhn L, Pollack A et al. Direct visual inspection for cervical cancer screening: an analysis of factors influencing test performance. Cancer. 2002;94:1699–1707.
36. Nene BM, Deshpande S, Jayant K et al. Early detection of cervical cancer by visual inspection: A population-based study in rural India. Int J Cancer. 1998;68:770-773.
37. Denny L, Kuhn L, De Souza M et al. Screen-and-treat approaches for cervical cancer prevention in low resource settings. JAMA. 2005;294:2173–2181.

DNA test for low resource settings (see previous section) looks likely to provide just such a higher specificity rate, and other, similar tests may do so as well. Rapidly available test results would mean that it could also be used in a screen-and-treat approach.

The current state of screening technologies for cervical cancer shows a vast gap between industrialized and developing countries. VIA/VILI is the most feasible current solution for LDCs. It is a quick and cheap screening method that folds both screening and treatment into one clinic visit. The HPV DNA test for low resource settings, once it becomes available in the next year or two, has the potential to offer an even better opportunity for providing screening and treatment in a single visit. In settings where women cannot receive regular screening, mathematical models suggest that one or two lifetime visits are best scheduled for a woman in her late 30s, and would be highly cost-effective.[38]

B. Vaccines – Primary Prevention

If it is possible to stop a disease process before it has even begun, the savings to society can be considerable. For girls and young women who receive the HPV vaccine before they have been infected with HPV 16 and 18, the vaccine appears to provide long-term protection against precancerous and cancerous lesions and associated disease. This is a powerful public health tool which could, over many years, lead to dramatic reductions in cervical cancer.

This, however, is a long term goal. The current vaccines work only in females who have not been infected with HPV-16 and 18; given its widespread prevalence among sexually-active women, this means that the vaccines are ideally suited for delivery to girls and young women who have not commenced sexual activity. In spite of this limitation, considerable progress can be made with the recent introduction of HPV vaccines.

Composition and mechanism of action of current HPV vaccines

There are two HPV vaccines available today: Cervarix®, manufactured by GlaxoSmithKline (GSK), protects against HPV-16 and 18, which together are responsible for roughly 70% of cervical cancers worldwide.[39] Gardasil®, manufactured by Merck, protects against these two as well as HPV-6 and 11, which cause 90% of genital warts.[40] Both vaccines consist of so-called virus-like particles (VLPs), which resemble the outer coat, or envelope, of the virus itself. In an actual viral particle, the envelope encloses the viral DNA; however in VLP vaccines, the manufactured proteins only form the viral coat; they are empty inside. In spite of this difference—which renders the vaccines safe and unable to cause disease—the body identifies the particles as HPV and mounts an immune reaction to the vaccine. The immunization therefore "teaches" the body how to fight the actual infectious agent. And a woman who receives the vaccine and later is exposed to infectious HPV (primarily of the subtypes contained in the vaccine) can successfully fight the virus, and prevent persistent infection. Studies have so far shown the vaccines to be very safe overall.[41]

38. Goldie SJ, Kuhn L, Denny L et al. Policy analysis of cervical cancer screening strategies in low-resource settings: clinical benefits and cost-effectiveness. JAMA. 2001; 285:3107–3115.
39. Smith JS, Lindsay L, Hoots B et al. Human papillomavirus type distribution in invasive cervical cancer and high-grade cervical lesions: a meta-analysis update. Int J Cancer. 2007;121:621–632.
40. Greer CE, Wheeler CM, Ladner MB et al. Human papillomavirus (HPV) type distribution and serological response to HPV type 6 virus-like particles in patients with genital warts. J Clin Microbiol. 1995;33:2058--2063.
41. Markowitz LE, Dunne EF, Saraiya M et al. Quadrivalent Human Papillomavirus Vaccine: Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR. 2007;56:1-24.

Each of the vaccines is highly effective, approaching 100% efficacy for at least five years post-vaccination (studies are ongoing with both companies).[42],[43]

Where current vaccines will most likely be available

An HPV vaccine is most effective if administered prior to first sexual intercourse, or "sexual début." In most cultures, this means that it should be given to pre-teens, but the precise age at which it is deemed appropriate will vary by region. In some countries where the vaccines are already approved, slightly older girls and women are also being given "catch-up" vaccinations, because while they may not yet have acquired one or more of the HPV strains covered by the vaccines, they remain vulnerable to infection as long as they are sexually active. Those who have been vaccinated will still require cancer screening as adults, because they could acquire an oncogenic strain not covered by either vaccine, and because if they are vaccinated after sexual début they may already have been infected with HPV at the time of vaccination. There is no evidence to suggest that either vaccine works therapeutically in combating cervical cancer in women already infected with oncogenic HPV. Older women who do not qualify for vaccination will, of course, also need to be screened as usual, according to existing protocols, for the development of cancer.

Current status of licensing and pre-qualification for current vaccines

Merck and GSK are in the process of applying for regulatory approval around the world. The United States Food and Drug Administration (FDA) was the first to license Gardasil® in June 2006, and it has since been approved in more than 80 countries, including licensure by the European Agency for the Evaluation of Medicinal Products (EMEA). In most countries, Gardasil® is sold for more than €300 per three-dose series. Cervarix® is approved for sale in Australia and is pending approval by the EMEA, FDA and other regulatory agencies. Its price is similar to Gardasil's.

Merck has submitted Gardasil to the World Health Organization (WHO) for pre-qualification, an approval process which is similar to FDA or EMEA licensure. GlaxoSmithKline is soon to follow, after receiving licensure for its vaccine in Europe. Pre-qualification also allows for use in the many LDCs which do not have their own developed licensure process and must be achieved before a vaccine can be purchased by UN agencies.

Current status of vaccine pricing

In order for poor women to be vaccinated, the pricing schedule must be radically tiered in less wealthy countries before ministers of health will even consider paying for, or applying for funding for, vaccination. In Tanzania, for example, the annual health budget in 1996 was US$2.18 per capita,[44] and a vaccine that costs 150 times this amount would clearly be out of the question. Tanzania is hardly alone in its budgetary limitations.

Both manufacturers have stated their willingness to provide steeply tiered pricing schedules for countries of varying economic means. Industry has expressed its overall commitment to innovation in both vaccines and screening, but the companies have expressed concern about

42. Harper DM, Franco EL, Wheeler CM et al. Sustained efficacy up to 4-5 years of a bivalent L1 virus-like particle vaccine against human papillomavirus types 16 and 18: follow-up from a randomised control trial. Lancet. 2006;367:1247-1255.
43. Villa LL, Costa RL, Petta CA et al. High sustained efficacy of a prophylactic quadrivalent human papillomavirus types 6/11/16/18 L1 virus-like particle vaccine through 5 years of follow-up. Br J Cancer. 2006;95:1459-1466.
44. Bangser M. Reframing policies for gender equality: women's agency, participation and public accountability. Harvard Center for Population and Development Studies Working Paper Series, vol. 10, No. 4. Cambridge, MA: Harvard School of Public Health, 2000.

manufacturing capacity. It can take approximately five years to move from planning stage to a fully operational vaccine manufacturing plant.[45] At present, industry is citing the need for more accurate demand estimates to help determine if and how manufacturing capacity must be expanded. However, developing countries may lack critical data on cervical cancer burden of disease, preferred immunization strategies, availability of long term funding for programmatic implementation (of which vaccine cost is a small fraction), and other variables, which can make it difficult to develop these forecasts. The private market demand in developing countries is likely to be so low as not to affect manufacturing decisions.

High-volume manufacturing could significantly lower the cost of an individual dose, but ramping up to such a volume will require that the demand be assured in the first place. Because even the low end of the pricing scale is likely to be higher than existing vaccines, it will be important to move forward with this cost-saving measure quickly.[46] Some kind of purchasing agreement will be needed: donors must make financial commitments ahead of time, and there must be a mechanism for gathering and disbursing these funds. The GAVI Alliance, which is a model for this kind of agreement is a possible vehicle for funding HPV vaccination. The Alliance requires companies to sell vaccines to them at the lowest price point, ensuring that vaccination is affordable and is the best use of donors' money.

Unanswered questions about current vaccines

Numerous questions remain about the appropriate populations to be vaccinated. There is evidence that Cervarix, at least, is more immunogenic if given to girls age 10-14 than

to 15-25 year olds.[47] Immunogenicity is a measure of the strength of the body's immune responses—in this case, levels or "titers" of antibody against HPV. Information about immunogenicity must be combined with information on duration of protection—how long a girl or woman is protected after being immunized. If a girl has very strong immune responses which wane before she becomes sexually active, then the benefits of the vaccine may not be optimized. Long term studies will be needed to gather additional information on duration of protection and the minimal antibody titer required for protection. Both companies have followed their trial participants for five years, and report that antibody levels plateau and do not appear to decline at the end of this period. However there is no guarantee that this will prove to be the case over the long-term and research is ongoing.[48],[49]

Other questions involve safety in special populations. As noted earlier, HIV-infected women are particularly susceptible to cervical cancer, and the epidemics are often found in the same populations: those with limited or no access to preventive health care. If HIV testing is unavailable, or women do not wish to be tested, should these women be eligible for the vaccine? The question of whether these vaccines are safe and effective

45. Gold D. Ensuring rapid global access to AIDS vaccines. Accessed 8/1/07 at: www.aidsvaccineclearing-house.org/pdf/ensuring_rapid_global_access.pdf.
46. Saxenian H, Hecht R. HPV Vaccines: Cost and Financing. Rockefeller Foundation et al.: New York, 2006. Accessed 8/26/07 at: http://aidsvaccineclearinghouse.org/hpvwatch.htm#meeting.
47. Kaiser Network. GSK HPV vaccine produces stronger immune response in girls ages 10 – 14 than in older women. Kaiser Daily Women's Health Policy Report. 2005 Dec 19. Accessed 7/30/07 at: http://www.kaisernetwork.org/daily_reports/rep_index.cfm?hint=2&DR_ID=34384.
48. Franco EL, Bosch FX, Cuzick J et al. Knowledge gaps and priorities for research on prevention of HPV infection and cervical cancer. Vaccine. 2006;24S3:S242-S249.
49. Hildesheim A, Markowitz L, Hernandez Avila M et al. Research needs following initial licensure of virus-like particle HPV vaccines. Vaccine. 2006;24S3:S227-S232.

in HIV-infected women is an urgent one, although trials are ongoing there are currently no data to answer this question.

Similar questions apply to pregnant women. In resource-poor settings, there may be no access to rapid pregnancy tests, which could ensure that only non-pregnant women are vaccinated. These vaccines are administered in three doses, at zero, one or two, and six months, and are most effective if all three doses are administered. What happens if a woman becomes pregnant shortly after being vaccinated? Is there a risk of birth defects? If she becomes pregnant after one or two doses, should the third be administered as scheduled? Will it be as effective if the last dose is withheld until the pregnancy ends? Research on dose delay is ongoing.

Both questions highlight the importance of vaccinating girls before sexual debut, eliminating concerns about pregnancy and dramatically reducing chances of exposure to HIV.

As of yet, neither vaccine has been formulated to allow maximum efficacy with only one or two doses. Fewer doses would make effective administration much easier in LDCs. A more flexible dosing schedule is desirable in any setting where return visits are not easily scheduled, where women and girls have more pressing obligations or where their healthcare is simply a low priority for society at large. Research is ongoing to determine whether fewer doses are feasible, and whether the vaccines can be equally efficacious on a different schedule.[50]

Finally, there is the question of whether to vaccinate boys and men. At present there are no data showing efficacy in men, although studies are underway. There are several arguments in favor of vaccinating them too. First, Gardasil protects against the two most common genital wart-causing strains of HPV. Genital warts can cause discomfort and emotional distress. In addition, although genital warts are in and of themselves benign, studies suggest that any irritation in the genital area increases vulnerability to HIV infection.[51],[52] Second, vaccinating men against oncogenic strains of HPV would presumably protect their female partners from cervical cancer, although a modeling study by Barnabas et al. showed that this "herd effect" would only modestly improve women's cancer rates in a population that already had good female coverage.[53] Third, the same strains of HPV that cause cervical cancer have also been shown to cause anal cancer in men who have (receptive) sex with men (MSM).[54] The vaccine could therefore help to prevent some cases of anal cancer in men and women. This indication will require frank discussions about anal sex between men and in heterosexual couples. At present, no country has made a recommendation to vaccinate men with Cervarix or Gardasil. While supplies remain limited, it may be more important to vaccinate women, who are the most vulnerable population, but as production is increased it will become critical to have data on hand about safety and efficacy in men in regards to preventing disease both in men and in their partners.

50. Franco EL, Bosch FX, Cuzick J et al. Knowledge gaps and priorities for research on prevention of HPV infection and cervical cancer. Vaccine. 2006;24:S242-S249.
51. Kjetland EF, Ndhlovu PD, Gomo E et al. Association between genital schistosomiasis and HIV in rural Zimbabwean women. AIDS. 2006; 20:593-600.
52. Celum C, Levine R, Weaver M et al. Genital herpes and human immunodeficiency virus: double trouble. Bull World Health Org. 2004; 82:447-453.
53. Barnabas RV, Laukkanen P, Koskela P et al. Epidemiology of HPV 16 and Cervical Cancer in Finland and the Potential Impacct of Vaccination: Mathematical Modelling Analyses. PLoS Med. 2006; 3:138.
54. Daling JR, Madeleine MM, Johnson LG et al. Human papillomavirus, smoking, and sexual practices in the etiology of anal cancer. Cancer. 2004; 101:270–280.

What needs to happen for current vaccines to become widely available?
In order young women and girls in any low-income country to access HPV vaccine, the following steps must be taken:

- Vaccine prequalification by the WHO
- In-country licensure
- Funding commitment from donor agencies
- Support and commitment of in-country health officials
- Developing country pricing and supply commitment from industry
- Platform chosen or developed for vaccine delivery
- Personnel designated to provide vaccinations
- Vaccines made available on the ground
- Public education campaign (national, regional or local) about HPV vaccines
- Outreach to target population, possibly including securing parental permission
- Follow up to ensure second and third doses are delivered

With the development of HPV vaccines and screening tests, there is some optimism about the future of cervical cancer prevention. But decisive action is needed if we are to avoid past failures, such as the unconscionable delay in introduction of hepatitis B vaccine. This vaccine became widely available in the developing countries 10 to 15 years after its licensure in industrialized countries, and it has yet to achieve global distribution.[55] The hepatitis B vaccine has some important similarities to HPV vaccine. It prevents

a relatively common infection that is (at least sometimes) sexually transmitted; it is recommended that it be administered to children before they are old enough to be exposed; and it prevents the eventual development of a deadly cancer – in this case, of the liver. Without concerted action from many stakeholders, the very women who stand to gain the most from vaccination—those that lack access to preventive screening and care—will be the hardest to reach. A combination of screening and vaccination for all women must be actively and aggressively pursued in order to begin saving lives as soon as possible.

Cervical cancer: Treatment strategies
As with most cancers, treatment of cervical cancer can be physically, emotionally and financially taxing. The more advanced the cancer, the more true this becomes; hence the importance of both prevention and screening, especially in a cancer which is so slow to grow, and so seldom fatal if caught early.

Depending on the size of the cancer, it may be possible to excise the whole tumor. A small cancer can be removed with cryotherapy, which freezes the cancer with a cold metal instrument,[56] or with a procedure known as LEEP, Loop Electricosurgical Excision Procedure. A loop of wire is placed on the cervix over the cancer and an electrical current is run through it; the cancerous tissue is essentially cauterized.[57] Larger cancers require more elaborate surgeries. Chemotherapy and radiation therapy may be used either instead of or in addition to surgery. Facilities for this kind of treatment vary

55. Zuckerman JN. Vaccination against hepatitis A and B: developments, deployments and delusions. Curr Opin Inf Dis. 2006;19:456-459.
56. Castro W, Gage J, Gaffikin L et al. Effectiveness, safety, and acceptability of cryotherapy: a systematic literature review. Cervical Cancer Prevention Issues in Depth, No. 1. Seattle: PATH, 2003. Accessed 7/30/07 at: http://www.path.org/publications/pub.php?id=687.
57. World Health Organization (WHO). Comprehensive cervical cancer control: a guide to essential practice. WHO: Geneva, 2005.

tremendously from country to country. Advanced cervical cancer needs to be treated at a tertiary care facility, of which there are few in LDCs. For instance, Ethiopia has just one radiotherapy machine, staffed by one radiation oncologist, for the entire country – and this must serve all cancer patients, not just women with cervical cancer.[58]

Current WHO guidelines

The WHO has provided guidelines for creating and/or updating cervical cancer screening programs in all settings.[59] Because neither HPV vaccine has achieved WHO pre-qualification, there are as of yet no WHO guidelines for vaccine administration.

Guidelines for screening are specific to a country's financial resources. Currently, the WHO considers cytology (Pap smears) to be the gold standard for cervical cancer screening.

However, it acknowledges that the physical plant, finances and appropriate training necessary to implement cytology are not possible in all countries. In fact, the organization takes pains to point out that in any screening program, the following criteria must be met: high levels of coverage (at least 80% of women aged 35-39 receiving at least one screening visit), high-quality care following informed consent, and adequate referral and follow-up systems. It recommends cytology for use in all developed countries, and in middle-income countries where possible. The WHO points out that cytology has only succeeded in countries where the screening is routine for all women in a certain age range. This has been primarily in developed countries. In countries that have previously lacked cytology programs, the WHO currently recommends VIA, which has been shown to be effective in reducing cancer in low-resource settings, and looks optimistically at the future roll-out of HPV DNA testing which shows "sufficient evidence that … as the primary screening modality can reduce cervical cancer incidence and mortality rates."[60],[61] Throughout the organization's recommendations, there is an emphasis on choosing the technology or combination of technologies that is culturally, infrastructurally and financially appropriate for each setting.

The key parameter for choosing a target population, according to the WHO, is age. The WHO stresses culturally appropriate outreach and education for whichever women that country would like to screen. It notes that any successful screening program must be integrated into either existing or developing infrastructure to assure long-term success, but should not be included within existing maternal and child health (MCH) programs, because this too often reached the wrong population: most women receiving treatment in MCH programs are in their twenties, and as noted earlier, the ideal time for a single lifetime screening is when a woman is in her late thirties. A strong program must eventually be funded by the government – it considers long-term funding from outside donors to be an unrealistic goal in the absence of political will from within.

58. International Atomic Energy Agency. Millions of cancer victims in developing countries lack access to life-saving radiotherapy. Press release. 26 June, 2003:2003(11). Accessed 7/31/07 at: http://www.iaea.org/NewsCenter/PressReleases/2003/prn200311.html.
59. Cervical Cancer Screening in Developing Countries: Report of a WHO Consultation. WHO: Geneva, 2002. Accessed 8/2/07 at: whqlibdoc.who.int/publications/2002/9241545720.pdf.
60. Rengaswamy Sankaranarayanan, Pulikkottil Okkuru Esmy, Rajamanickam Rajkumar, et al. Effect of visual screening on cervical cancer incidence and mortality in Tamil Nadu, India: a cluster-randomised trial. Lancet 2007. 370:398-406.
61. IARC/WHO, "IARC Handbook of Cancer Prevention," 2005

The Global Reproductive Health Strategy of the WHO lists five priority areas, of which STIs are one, and specifically addresses cervical cancer.[62] National governments and multilateral donors take their cues for prioritizing funding from the WHO. The WHO document "Cervical Cancer Screening in Developing Countries" can provide a strong argument for funding certain programs and for de-funding, or declining to fund, certain others. Whether the WHO chooses to add HPV vaccines to the EPI schedule, once they have been pre-qualified for UN agency purchase, will thus mean the difference between being vaccinated or not for millions of girls worldwide. This would raise a host of logistical issues: since most EPI vaccines are given to small children. In other words, this vaccine is currently being administered to a new target group, so lessons learned in the past about wide-scale vaccination must be applied with caution. Public health advocates will need to develop new strategies for how to educate the target group of vaccinees, as well as their parents; decide whether girls and their parents should be educated together or separately; ascertain the best venue for administering vaccines (e.g., school, primary care clinic, etc.), which will vary based on local sociocultural and economic issues; and identify a sustainable funding stream. Vaccinating pre-teen girls raises the question of when and how much to talk to these girls about sexual and reproductive health (SRH). Answering this question may pose a challenge, but it also opens the door for future SRH education, either directly related to health interventions or more general. The WHO has been extraordinarily pro-active on this issue, convening multiple meetings on HPV vaccines in 2006, which were planned even before any country had licensed one of the vaccines.

Conclusion

Cervical cancer is a deadly disease and unlike many other infectious epidemics, we already know how to prevent the disease. Young girls can and should be vaccinated today to prevent many cases of cervical cancer from ever developing. Older generations of women must have access to economically appropriate screening for cervical cancers and pre-cancers; while wealthy countries use both Pap smears and HPV DNA tests, LDCs can rely on new, less expensive HPV DNA tests that are almost ready for the market, as well as existing cheap, efficacious direct visualization methods. Protocols already exist for prevention and treatment, but millions of women in LDCs languish neglected for want of the necessary programs. Although there is no single solution to eradicating cervical cancer around the world, a combination of vaccination, regionally appropriate screening programs, and access to treatment can drastically reduce its morbidity and mortality. A comprehensive effort from all involved stakeholders will be needed to evaluate the potential of each of these components in regards to the best array of options for different settings, how best to deliver this care, and how to ensure access for all girls and women.

62. Reproductive health strategy to accelerate progress towards the attainment of international development goals and targets. WHO: Geneva, 2004. Accessed 7/30/07 at: www.who.int/reproductive-health/strategy.htm.