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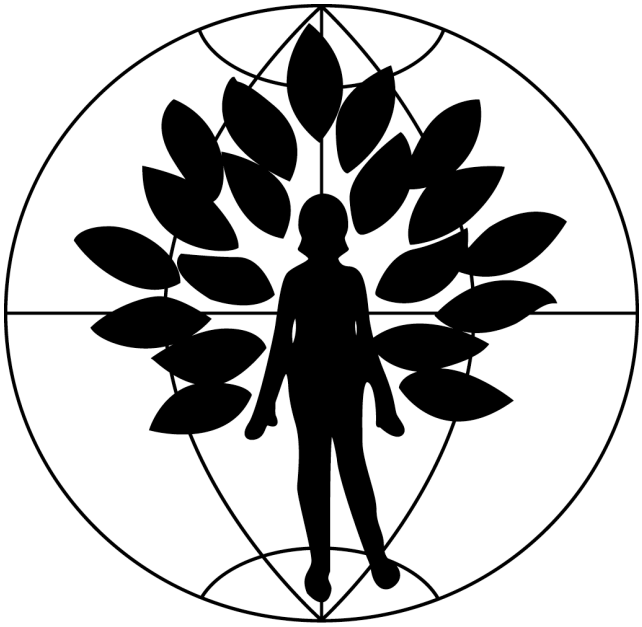

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Overview: *FIGO Comprehensive Guidance*

The International Federation of Gynecology and Obstetrics (FIGO) offers this guidance as a focused update on cervical cancer prevention, screening and treatment strategies. It is intended to be complimentary to the World Health Organization 2006 "Comprehensive Cervical Cancer Control: A Guide to Essential Practice"[1] and bridge the gap with emerging data now available until the next edition, expected out in 2011. It also takes direction from the American College of Obstetrics and Gynecology (ACOG) and Society of Obstetricians and Gynecologists of Canada (SOGC) in these areas.

The information provided is relevant to all settings, with an emphasis on low-resource settings where the disease continues to be the largest cause of cancer death among women. It is intended to provide guidance to clinicians and policy makers and inform current and future planning to prevent and control cervical cancer.

The authors of this guidance for cervical cancer control seek to bring together the most up to date knowledge about options that will provide approaches for diverse settings, that will also encourage cultural sensitivity, resulting in not only control of cervical cancer but improvement in assuring the rights and health of women globally.

Our sincere thanks to the many contributors, writers, editors, reviewers and most of all – the researchers, clinicians and women's health advocates who are making the control of this disease possible.

[1] World Health Organization. Comprehensive cervical cancer control: A guide to essential practice. 2006. Available at: http://www.rho.org/files/WHO_CC_control_2006.pdf

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Cervical Cancer Control: Rights and Ethics

Joanna Cain, MD, and Carla Chibwesha, MD

In this decade, the expanding knowledge of human papillomavirus (HPV) and its relationship to cervical cancer has led to new tools for primary prevention with HPV vaccines and new screening strategies that give clinicians options for every resource setting. The ability to substantially reduce the more than one half million women per year that are diagnosed with cervical cancer, and more importantly the ability to reduce the quarter of a million women per year that die of the disease - particularly in under resourced areas of developing and developed countries - is now in the hands of women's health professionals and governments. There is no longer any justification for NOT addressing the human rights denied to women with cervical cancer diagnoses - the right to the highest attainable standard of health care and the right to quality of life. Controlling cancer not only prevents death and disability but also will create improvement in the health and well being of families by preserving the economic and parental support of women, children, families, and communities.

State of the science: rights and ethics

Fifteen years ago key stakeholders in the human rights and development movements converged in Cairo for the landmark International Conference on Population and Development (ICPD). Sexual and reproductive health was embraced as a basic human right, as well as being critical to economic and social development for all countries.[1,2] As such, educators, politicians, and human rights and legal advocacy groups play a role as pivotal as the role of health professionals in the prevention and treatment of cervical cancer. Protecting health and ensuring access to healthcare is the responsibility of all societies. If women are denied access to health education, quality evidence-based healthcare, and autonomous decision making about the way in which they access that care, their rights are violated.

Contemporary medical ethics provides additional guidance for health practitioners. The principles of beneficence, nonmaleficence, autonomy, and justice form the cornerstone of this ethical framework. Beneficence relates to a provider's obligation to protect patients' interests above all else. The principal of nonmaleficence reminds us to avoid practices that may be harmful. Furthermore, providers are obligated to respect those for whom they care as autonomous individuals. This, in turn, implies that patients be fully educated about health and disease, and when ill, that their treatment options represent current evidence-based standards. Finally, the principal of justice dictates that women are treated fairly; in particular that they benefit equally from scientific advances regardless of their socioeconomic standing or their racial, ethnic, cultural, or religious background.[3] Table 1 highlights examples of these principals as they relate to cervical cancer prevention and treatment.

Barriers to application and gaps in knowledge

Although discourse surrounding women's health has been re-framed to reflect a contemporary human rights paradigm, actions lag far behind.[4] Tragically, the case of cervical cancer is not unlike other preventable illnesses for which the greatest disease burden falls on the poor and those with limited access to health care.

The barriers to prevention and treatment include a broad lack of awareness of cervical cancer and the consequent burdens of bleeding, bowel and bladder dysfunction, fistulas, and pain and suffering that result from advanced disease. This lack of awareness is further complicated by cultural sensitivities that prevent discussion of uniquely women's cancers and the sexual transmission of HPV. The absence of cancer registries and data in many developing countries perpetuates this gap and inhibits the positive influence that "demonstrating improvements in public health can have to enhance the support of and demand for health services."[5]

Other barriers come from limited resources. Sometimes the barrier is resistance to lower level providers providing services and a lack of acceptance of practical technologies for screening where technology such as cytology is not feasible. Treatment options must be tailored to the availability of healthcare funding, trained personnel, health infrastructure and portability of technology, as well as to the accessibility of populations in need. Barriers to primary prevention through vaccination, and secondary prevention through screening and treatment of precancerous lesions, are not dissimilar. Competing healthcare needs may also contribute to under-prioritization of cervical cancer control. Moreover, the fact that women with pre-invasive disease are typically symptom-free may result in delayed presentation to care, particularly in regions of the world where cervical cancer screening has yet to be established.[6]

Finally, human rights violations including poor education, lack of freedom of movement, and gender discrimination in access to healthcare impact the success of initiatives to address this now mostly preventable disease: "A central element that characterizes inequity is that the conditions involved are avoidable."[7]

Recommendations

Achieving successful cervical cancer control requires that all of these barriers, and those that are unique to each culture, be addressed. "Embracing cultural realities can reveal the most effective ways to challenge harmful cultural practices and strengthen positive ones."[8] Only by combining a bundle of options targeted to the unique needs of each region or country and tailored to the local culture will there be progress in controlling cervical cancer.

Women's health professionals must play an integral role in this advocacy. Indeed, the obstetrician-gynaecologist has an ethical and social responsibility to develop and disseminate cost-effective, evidence-based cervical cancer prevention and

treatment modalities that remain locally relevant. Additionally, we are charged with the task of engaging other health professionals, health advocates, policy makers, and political leaders in this global effort to control cervical cancer.

Table 1.

Ethical Principal	**Example**
Beneficence	Ensure that interventions meet the goal of medicine - to prevent cervical cancer, treat the disease, and alleviate suffering – and are accessible to all women.
Nonmaleficence	Discuss HPV and the sexual nature of the infection sensitively. Incomplete information may result in undue anxiety for patients, or worse, put them in danger of physical violence or retaliation from an abusive partner.
Autonomy	Educate women about their health. Seek and respect the choices that women with pre-invasive and invasive disease of the cervix make about their treatment options. See FIGO ethics guidelines (http://www.figo.org/about/guidelines).
Justice	Ensure equitable access to both preventive strategies and cancer therapies, as well as palliative care. Guarantee that scientific gains are accessible to all.

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A Comprehensive Approach to Cervical Cancer:
Improving Impact Today

Sarah Goltz Shelbaya, MPH, MIA, and Debbie Saslow, PhD

This guidance provides evidence-based recommendations for physicians and policymakers to develop a comprehensive cervical cancer programme for a clinic, a community or a country. As clinicians, policy makers, and advocates, we must look to the current tools, resources and knowledge to develop the specific bundle of services that is appropriate for each setting.

Why a comprehensive approach?

Decades of experience, refined by recent research and enhanced by new discoveries, provide a new picture of the necessary elements to impact cervical cancer. Evidence shows that only a comprehensive approach, which effectively embraces diverse tools that meet the needs of distinct populations and environments and expands access to cancer prevention and care within the health system, will have a significant and sustainable impact on this disease. This approach embraces both an expanded and improved "bundle of services" and greater focus on the elements of the public health system necessary to prevent, treat and monitor disease.

Implementing cervical cancer prevention and control programmes is far from simple. Education without screening and treatment will raise hopes among women that we simply do not have the means to support. Screening without treatment would unethically find disease we are unable to treat. Preventive vaccination without screening will impact the youngest generation while failing to provide for women already at risk for the disease. As such, precious resources— women's trust, provider time, clinic infrastructure, and financial resources —should be used toward maximizing the impact on the lives of individual women, their families and communities.

Evidence shows that regardless of resources, health system or geography, <u>all</u> cost-effective comprehensive cervical cancer programmes should include some formulation of the following elements:

- Educated choice by women and girls about disease prevention and care
- Ethical and informed engagement by providers
- Primary prevention, through safe, affordable and accessible vaccination
- Secondary prevention, early diagnosis, and early treatment at the most appropriate point of care
- Health planning and system support that aims for the greatest public health impact and strengthens the national cervical cancer prevention system

including active outreach to eligible women for screening and girls for vaccination, effective monitoring systems that have high coverage and prevent loss to follow up, and strong referral and monitoring systems to ensure that cancer cases are handled and documented appropriately.

- Disease management, palliative care, and end of life care
- A functioning national cancer registry to monitor programme progress and measure impact against national program costs

As evidenced in this guidance, current research has confirmed that there is great variation in tools and strategies that are appropriate and cost-effective in different settings. No one approach will provide the solution. The bundle of services that define a comprehensive approach will likely vary not only between countries, but also within countries. Yet, all elements are essential in order to achieve the greatest public health impact.

The opportunities for new and more effective combinations of strategies for prevention, detection and treatment are many. HPV testing followed by visual inspection methods for test-positive women could be used to cover a greater number of women and focus health worker time on women at risk. As HPV vaccines become increasingly affordable and available, vaccinating young girls can relieve pressure on screening systems, since vaccinated women are likely to need to be screened later and less often than unvaccinated women. There will need to be integration of, and links to other services, including adolescent vaccination programmes, school clinics, family planning and reproductive health services for women.

This guidance reviews current tools and approaches for cervical cancer prevention and treatment in light of several key characteristics to guide decision making.

Medical	• Relevance or contraindications for specific populations or ages • Potential to engage mid-level service providers in delivery • Opportunity to maximize patient visit and reduce loss to follow up
Physical	• Patient access issues • Clinic infrastructure requirements • Health system demands (referral, treatment, palliative care)
Training	• Level of provider training required • Quality assurance mechanisms • Patient education/community mobilization needed
Cost	• Initial and recurring costs associated with materials and delivery • Provider time • Patient time • Cost-effectiveness of approach specific to targeted populations

Educational	• Key information that every woman should know to make an informed choice about her care • Appropriate decision making around integration with other tools
Policy	• Necessary supportive national, regional and international policies focused on task shifting and equitable access to treatment and care • Public financial commitment required • National and regional investment in treatment facilities, cancer registries

FIGO believes that we are at a turning point in the fight against cervical cancer. At no time before have we had the tools and knowledge or even capacity to change the course of this cancer—especially among the most underserved women. As efforts advance, driven by our own vision and that of our partners (other clinicians, public health leaders and champions, such as the World Health Organization, International Pediatric Association, and others), FIGO hopes that the information herein will provide the evidence, guidance and inspiration for a greater, more effective and final assault on cervical cancer.

Overview: Primary Prevention

The focus in this section is on the unparalleled opportunity to prevent cervical cancer through immunity to HPV infection. HPV vaccine programs also provide an important springboard to increase support for cervical cancer prevention among parents, educators and community leaders and reach adolescent girls with important health information. Strategies to deliver vaccines to broad populations of girls will require new collaborations between child health, school health, cancer and reproductive health programmes and clinicians.

HPV Vaccines: Characteristics, Target Population and Safety

Martha Jacob, MBBS, FRCOG, MPH

Background

Cancer of the cervix can be prevented in two ways: (1) preventing initial HPV infection through vaccination and (2) screening for precancerous lesions and providing early treatment to prevent progression to cancer. A comprehensive disease control initiative—a combination of improved screening and treatment with effective HPV vaccination—has the best potential to significantly reduce the burden of cancer of the cervix relatively soon.

Two vaccines have been developed to prevent infection with HPV-16 and -18. Both vaccines use recombinant technology and are prepared from purified L1 capsid proteins that reassemble to form HPV type-specific virus-like particles (VLP). Both vaccines are non-infectious, as they do not contain live biological products or viral DNA. Neither vaccine contains thimerosal or antibiotics. Both vaccines act by inducing humoral and cellular immunity. They are designed for prophylactic use only and do not clear existing HPV infection or treat HPV-related diseases.

Characteristics of the two HPV vaccines

	Quadrivalent vaccine	**Bivalent vaccine**
Manufacturer (trade name)	Merck (Gardasil® also marketed as Silgard®)	GlaxoSmithKline (Cervarix™)
VLPs of HPV genotypes	6, 11, 16, and 18	16 and 18
Substrate	Yeast (*S. cerevisiae*)	Baculovirus expression system
Adjuvant	Proprietary aluminium hydroxyphosphate sulphate, 225 µg (Merck aluminium adjuvant)	Proprietary aluminium hydroxide, 500 µg, plus 50 µg 3-deacylated monophosphoryl lipid A (GSK AS04 adjuvant)
Schedule used in trials - three doses with intervals of:	Two months between doses 1 and 2; six months between doses 1 and 3 (0, 2, 6 schedule)	One month between doses 1 and 2; six months between doses 1 and 3 (0, 1, 6 schedule)

Storage & Transport	Requires a cold chain system, stored and transported at 2^0 C to 8^0 C Should not be frozen	Requires a cold chain system, stored and transported at 2^0 C to 8^0 C Should not be frozen
Approved licenses as of Feb 2009 and WHO prequalification	Licensed in 109 countries WHO prequalified	Licensed in 92 countries WHO prequalified

Immunogenicity

Results from several international, randomized controlled studies with follow up for over five years have shown that nearly all adolescent and young female participants in the studies who were naïve to vaccine-related HPV types 16 and 18 developed type-specific antibody responses to these antigens after three doses. Antibody response peaks after the third dose, declines gradually, and levels off by 24 months. Antibody levels were more than tenfold higher than following natural infection. Both vaccines have been shown to induce immune memory response through higher frequency of memory B cells.[1,2] Both vaccines induce higher antibody levels in females less than 15 years of age.[3,4] The minimum necessary level of antibody response to ensure protection against infection (correlate of protection) is not yet known, as efficacy has been so high that no breakthrough disease has occurred to date.

Vaccine efficacy against persistent infection and precancerous lesions such as CIN 2/3 or adenocarcinoma in situ has been widely accepted as a surrogate marker for protection against cancer. This is necessary as cervical cancer develops slowly and it would require very large, long-term trials (30+ years) to demonstrate impact against invasive disease. In addition, it would be unethical to simply observe women with precancerous lesions when such lesions can be effectively treated. Both vaccines have shown more than 90% efficacy to prevent precancerous lesions in females naïve to vaccine-specific HPV types and who have completed all three doses.[5] Recent data indicate sustained efficacy and immunogenicity of the bivalent vaccine up to 6.4 years.[6]

Recently published studies report that HPV vaccines also induce antibody response to and partial efficacy (around 50%) against HPV types 31 and/or 45. These types are phylogenetically similar to HPV-16 and -18.[7,8]

Age at vaccination

Evidence from clinical studies supports the administration of currently available prophylactic HPV vaccines to young adolescent girls between the ages of 9 or 10 and 13 years prior to initiation of sexual activity. Antibody response is high in this age group and vaccine efficacy is highest in those who are naïve to vaccine-specific oncogenic HPV types. Hence the greatest impact of HPV vaccination on cervical cancer will be through broad participation of young adolescent girls rather than older girls or women. HPV catch-up vaccination in older girls or women can prevent disease due to HPV vaccine type-specific infection in women who are not already infected with these HPV types. However, modelling studies suggest diminishing protection when age of vaccination is increased.

HPV Vaccination in males

Studies show that both vaccines are as immunogenic and safe in young adolescent males as they are in adolescent females. Modelling studies indicate that including boys in vaccination programmes, even if achieving high levels of coverage, conferred little added benefit compared to vaccinating only girls and is not cost-effective.[9,10,11] There are presently no studies indicating that HPV vaccination of males will result in less sexual transmission of vaccine-specific HPV infection from males to females thereby reducing cervical cancer.

Safety

Extensive clinical trials (prelicensure safety data) and post-marketing surveillance continue to show that both HPV vaccines have good safety profiles, with safety similar to other commonly administered vaccines.[5,12 ,13, 14]

The most common adverse event reported is injection site pain, swelling and or erythema. Other reported systemic adverse events were fever, nausea and dizziness, and fatigue, headache and myalgia. Syncope or fainting was reported more following HPV vaccination compared to other vaccines given to teenagers and young women. Fainting after injection is more common among teens than among young children or adults and seems to be related more to the injection process rather than a side effect of the vaccine. In order to prevent injuries due to falls during fainting episodes it is recommended that all vaccinated girls rest and be observed for 15 minutes following HPV vaccination as with other vaccines.

Reported anaphylaxis rates were low (2.6/100,000 doses) similar to other vaccines.[5] Serious adverse events requiring hospitalization or causing disability or other medically important conditions have been reported to be around three events per 100,000 individuals vaccinated.[9] No causal links have been demonstrated

between HPV vaccination and reports of Guillain-Barre syndrome, autoimmune diseases, or to any of the deaths that followed the administration of the HPV vaccine.

Cost/efficacy analysis

Modelling studies consistently show that in developed countries vaccinating adolescent girls is cost effective and the main benefit is from preventing mortality from cervical cancer. Duration of vaccine efficacy is shown to be the most important factor in cost effectiveness.[12] Modelling studies for GAVI-eligible countries show that vaccines against HPV-16 and -18 can be cost effective in reducing cervical precancers and cancers and that HPV vaccine can reduce lifetime risk of cancer by 40-50%.[15] Factors affecting absolute reduction are cervical cancer incidence, population age structure and vaccination coverage (70%). For GAVI-eligible countries, these models suggest that HPV vaccination would be very cost-effective at $2.00/dose or $10 per fully vaccinated girl, including programme costs.

Gaps in knowledge and further areas of research needed

1. Given the known progression of disease from CIN 2/3 to invasive cancer, protection from CIN 2/3 by both vaccines will prevent cervical cancer. Long-term studies (such as those currently underway in Scandinavian countries) will demonstrate the long-term impact of these vaccines.
2. The need for a booster dose to ensure long-term protection is unknown, with no indication of reduced performance at eight years.
3. Further study of immune response to currently available vaccines in HIV-infected and immunocompromised individuals would be helpful.
4. There is lack of data demonstrating that HPV vaccination of males will result in less sexual transmission of vaccine-specific HPV infection from males to females, thereby reducing cervical cancer.
5. Data on co-administration with rubella vaccine and other vaccinations for adolescents and older children is being assessed and has the potential to expand current delivery strategies.
6. The efficacy of alternative dosing schedules and reduced number of doses for both vaccines is needed.
7. Data are awaited on optimal HPV vaccine delivery strategies in different settings.
8. The impact of vaccination on cervical cancer screening behaviour requires further study.

Integration with/or replacement of other prevention approaches

Cervical cancer screening and treatment for precancer should continue as per national guidelines at present, as the currently available vaccine prevents infection

caused primarily by two of the oncogenic HPV types (HPV-16 and HPV-18), potentially missing up to 30% of cancers caused by other oncogenic serotypes. Furthermore, the currently available prophylactic vaccines are not effective for women previously infected.

Consideration for special populations: HIV positive, pregnant women

HPV vaccination is not recommended in pregnancy though adverse events have not been reported in the mother or the foetus for either of the two vaccines in women who were inadvertently administered the vaccine. If the HPV vaccine has been inadvertently administered during pregnancy, further doses should be delayed until after the pregnancy.

There is currently very little data on the antibody response and efficacy of HPV vaccines in HIV-infected and in immunocompromised individuals.

Key points:

1. Both vaccines are prophylactic vaccines preventing HPV-16 and -18 primary infections. They do not clear existing HPV infection or treat HPV-related diseases.
2. Current evidence supports HPV vaccination of young adolescent girls (9 or 10 through 13 years of age) prior to onset of sexual debut to prevent cervical cancer in later life.
3. Both vaccines induce high serum neutralizing antibody levels against HPV 16 and 18 in more than 99% of females who are naïve to specific HPV types. Neutralizing antibodies correlate with vaccine efficacy.
4. Efficacy against surrogate markers such as persistent HPV type-specific infection and precancer lesions such as CIN 2 or higher is more than 90% for both vaccines.
5. Both vaccines continue to show good safety profiles similar to other commonly administered vaccines. Most common statistically significant adverse events reported for both vaccines are injection site pain, swelling or erythema.
6. Several regulatory bodies globally have reviewed the safety and efficacy data for both vaccines and approved the use of the vaccines in over 100 countries.

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Vaccine: Present Delivery Strategies and Results

Scott Wittet, MA, and Suzanne Garland, MD

State of the science

Currently, there are two prophylactic HPV vaccines, one of which is bivalent and the other quadrivalent. Both have been recently licensed in over 100 countries. Registration of these vaccines has been based on immunogenicity, safety and efficacy, as reported in phase 3 trials.[1,2,3] Both vaccines are highly efficacious in preventing infection as well as precursor lesions to cervical cancer (high-grade dysplasia—cervical intraepithelial neoplasias [CIN 2/3+]—a surrogate for cervical cancer), caused by genotypes 16 and 18. Worldwide these make up 70% of cancers, and 50% of CIN 2/3.

Access

Licensure however does not necessarily translate into HPV vaccine provision through public sector programmes, especially in the developing world where HPV vaccines will have the greatest impact. The World Health Organization (WHO) recommends that routine HPV vaccination be included in national immunization programmes when prevention of cervical cancer or other HPV-related diseases, or both, constitutes a public health priority (in that country); vaccine introduction is programmatically feasible; sustainable financing can be secured; and the cost effectiveness of vaccination strategies in the country or region is considered.[4]

Wealthier governments by and large have already begun providing HPV vaccine through public health programmes. For the lowest-resource countries, procurement of vaccine will be possible only with substantial financial support. The GAVI Alliance, which subsidizes vaccines for the 72 poorest countries, is considering including HPV vaccines in the portfolio of vaccines receiving its support.[5] If GAVI support becomes possible, eligible governments will be able to access HPV vaccines at radically lower prices.

Middle-income country governments also are grappling with the challenge of paying for HPV vaccine. Latin American countries may benefit from group purchasing plans such as the Pan American Health Organization's "Revolving Fund" for vaccines. Other countries will need to negotiate lower prices based on the bulk purchasing power of their country alone. Over the past year, HPV vaccine prices have dropped significantly for middle-income country governments—in some cases they are less than one-third of the market price in the United States and Europe. In the coming years, these prices are expected to continue to decline. It is hoped that

HPV vaccine will experience the sort of price reductions seen with other new vaccines. If they enter a price range of less than $10 a dose, low- and middle-income countries may be able to afford to vaccinate most, if not all, vaccine-age girls.

Age

The target age for these prophylactic vaccines is before sexual debut. WHO states that:

> "HPV vaccines are most efficacious in females who are naive to vaccine-related HPV types; therefore, the primary target population should be selected based on data on the age of initiation of sexual activity and the feasibility of reaching young adolescent girls through schools, health-care facilities or community-based settings. The primary target population is likely to be girls within the age range of 9 or 10 years through 13 years."[4]

In addition, the WHO position paper on HPV vaccination notes that extending the age target to older adolescent or young women is recommended *only* "if it does not divert resources from this primary effort or from effective cervical cancer screening." Because HPV vaccines are not therapeutic, they do not benefit women who are or have been infected with the vaccine-related genotypes. While any individual woman may benefit from HPV vaccination (since she may not already have been infected with HPV 16 and/or 18), due to the high prevalence of infection in most communities and the critical need to consider cost-effectiveness, most public health programmes prioritize vaccinating girls at younger ages, where the vaccine is likely to have the greatest impact. Vaccination of boys or men generally is considered to be less cost effective because the burden of disease is much less in males (only about 7% of cancers caused by HPV 16/18 occur in men).[6] Furthermore, computer modelling suggests that vaccinating men to reduce infection in women may not be as cost effective as maximizing immunization coverage among girls.[7]

Strategies for HPV vaccine delivery

Even the poorest countries in the world have Expanded Programmes on Immunization (EPIs), with well-developed delivery systems targeting infants and young children. Hence, should HPV vaccines one day be licensed for use with those groups, it is likely that the vaccine would be integrated into existing EPI programmes, as has been done over the past decade with hepatitis B vaccine. However, most EPI programmes in the developing world do not focus heavily on services for young adolescents and young women, so EPI must be expanded to reach those populations (or the adolescents must be vaccinated using other systems). Hepatitis B vaccine was quickly absorbed into national EPI programs once its price dropped to $0.25 per dose and it became available as an infant vaccine.

Research conducted among programme planners in Peru, India, Uganda and Vietnam found that most respondents endorsed using EPI to deliver HPV vaccine rather than creating parallel systems[8] and expanding beyond infant immunization is a key objective in WHO/UNICEF's "Global Immunization Vision and Strategy" (GIVS).[9]

Schools seem to be promising venues for HPV immunization both in higher- and lower-resource countries. While some girls do not remain in school to the age of vaccination, attendance rates have increased dramatically in the past two decades. Several HPV vaccine demonstration projects in the developing world are assessing schools as vaccination venues, while concurrently developing systems to reach out-of-school youth. Data are being gathered on the relative costs and coverage achieved through school outreach, compared to asking parents to bring their daughters to clinics.[10] Screening programs targeting mothers of adolescent girls are also being studied as a mechanism to create demand for HPV vaccination.

In situations where resources do not permit vaccination of the entire cohort of young adolescent girls, planners may look for a specific high-risk subpopulation. However, the high incidence of HPV across populations does not facilitate such a strategy—as might have been used for other sexually transmitted infections. Instead, the selection of a limited geographic area in which to vaccinate all girls and then to expand the programme in succeeding years may be an appropriate strategy to consider.

Early experience with public or NGO-based HPV vaccination programmes

Public HPV vaccination in high-income countries: Australia

Australia provides an example of a successful vaccination programme in a high resource setting. The quadrivalent vaccine was registered there in June 2007 for both females nine to 26 years of age and boys nine to 15 years of age. From April 2008, a government-funded, school-based vaccination programme was initiated for female adolescents aged 11-12 years with catch-up vaccination up to 26 years of age for females for the subsequent two years. For cost-efficacy reasons, boys are not being vaccinated through the public programme. All these programmes have resulted in relatively high rates of HPV vaccination coverage. For example, HPV vaccine coverage among school aged female adolescents in Australia has been estimated up to 80%.[11] In the second year's school-based cohort of 2008, the figure remains in the high 70 percentiles. This high coverage has already translated into a reduction in genital warts in young women <27 years old and young heterosexual men. The lower rates of warts in heterosexual men suggest the potential for herd immunity.[12]

Similar school-based programmes for all age-eligible female adolescents also have been mounted in the UK and Canada, largely resourced through public funds.[13] In the United States, where HPV vaccines are not actively provided by the government in schools, but provided by clinicians at the expense of individual families or reimbursed by insurance companies, the current vaccine coverage rate is much lower.

Public HPV vaccination in middle- and low-resource countries

HPV vaccination programmes in middle- and low-resource countries are few and tend to be limited in scope. With the exception of Panama, no other developing world government has introduced the HPV vaccine at national scale. Mexico has a significant demonstration project designed to deliver the vaccine to girls in the 125 most disadvantaged municipalities in the country. The majority of HPV vaccine projects in developing countries are being run by national and international NGOs. Many of these are demonstration projects, which aim to develop models for future public sector adoption of the vaccine.

Preliminary findings from demonstration projects in India, Peru, Uganda, Mexico and Vietnam suggest that a school-based approach can achieve coverage rates similar to those found in Australia. Project experience to date also suggests that when efforts are made to educate health care providers and communities about cervical cancer, and when HPV vaccine is introduced as a "vaccine against cervical cancer" (as opposed to using the unfamiliar term "HPV vaccine"), coverage levels of 80-90% are not uncommon, indicating high acceptability.[10]

Selection of vaccine

The key difference between the two vaccines is that the quadrivalent vaccine also protects against two non-oncogenic HPV types that cause the majority of genital warts (types -6 and -11).[14] Programme planners will need to compare the costs of the two vaccines and determine which represents the better value based on available resources and current health priorities. Emerging evidence suggests some level of additional protection with the bivalent vaccine[15] and potential for a two-dose regimen that may be relevant to choice as data matures.

Public debate related to HPV vaccines

Over the past several years, public acceptance of HPV vaccination remains strong in high, middle- and low-income countries, though some issues have inspired debate. In the United States, for example, much of the discussion has focused on efforts to mandate HPV vaccination for middle-school entry. In the UK, the bulk of controversy has focused on the criteria used to select a specific brand of HPV vaccine. Some also worry that limited cervical cancer screening resources could be re-allocated to HPV vaccine programmes.

In both high-resource and low-resource settings, understanding of cervical cancer and HPV vaccines has proven vulnerable to misinformation disseminated by groups who do not understand the evidence, or who are suspicious of allopathic medicine in general and vaccination in particular. Unfortunately these campaigns have proven effective in gaining media attention and raising inappropriate concerns among parents and policymakers.

Regardless of the public debate, current HPV introduction projects are finding very high demand and acceptability for the vaccine among parents, girls and clinicians. As long as the safety record of the vaccine remains positive, it is likely that public support for HPV vaccination will continue to grow as a result of increased education, as vaccine prices drop, and as pilot introduction programme results become available. Furthermore, public acceptance may increase if other health interventions appropriate for older children also are provided along with HPV immunization, such as tetanus, rubella, hepatitis B, measles, and potentially HIV immunization; nutritional supplementation; malaria intermittent preventive treatment; treatment of schistosomiasis, filariasis, and trachoma; deworming; iron and/or iodine supplementation; provision of bed nets and education about hand washing, tobacco, drugs, body awareness, and life-choice decision-making.

Gaps in knowledge and further areas of research needed

More evidence is needed on:

- The most effective models for reaching girls with HPV vaccine, especially in low-resource settings;
- The relative costs of various vaccination strategies;
- Whether alternatives to manufacturer-recommended three-dose vaccination schedules may be more convenient for health systems and may provide similar protection as the standard schedules.

Considerations for special populations – HIV +, pregnant women

While HPV vaccines contain no DNA and consequently are not infectious, they are classified as a pregnancy category B medication. Hence, vaccination is not recommended during pregnancy, as there are still limited data on vaccination and pregnancy to date. However despite the requirement for adequate contraception during phase 3 clinical trials, 17% of vaccinated women became pregnant.[1,2] Follow-up of these pregnancies showed that vaccination did not appear to negatively impact pregnancy outcomes, with no significant differences noted overall for the proportions of pregnancies resulting in live birth, foetal loss, or spontaneous abortion.[16]

Data also are limited relating to use of HPV vaccines in immunocompromised individuals. As the HPV vaccine is not a live virus, the vaccine is safe for HIV positive individuals. What is not well known is the amount of protection conferred when an individual with a compromised immune system is vaccinated. The one research study available shows that immune response and the efficacy of HPV vaccines may be lower—but not insignificant—in HIV positive individuals.[17] Since HIV positive individuals are known to be especially vulnerable to HPV-related diseases, especially cervical cancer, WHO suggests that the benefit to this group remains high. Due to the safety of the vaccine for immunocompromised individuals, WHO does not consider HIV testing to be a pre-requisite of HPV vaccination.[4]

Integration with/or replacement of other prevention approaches

Cervical cancer screening and treatment for precancer should continue as per national guidelines as the currently available vaccine prevents infection caused by HPV 16 and HPV 18 only.

Role of Obstetricians/Gynaecologists, Paediatricians, Nurses and other providers in HPV vaccine education

As with other new health technologies, in many countries access to HPV vaccine through private physicians and clinics is far outpacing public sector programmes. As a result, HPV vaccines are quickly becoming available to girls whose parents have the financial resources to cover the cost.

As girls, parents, teachers, and policymakers seek information on the vaccine, they will turn to obstetrician/gynaecologists, paediatricians, nurses, midwives and community health educators for information. Professional associations and provider networks should find ways to assure that families are getting consistent and accurate information about the vaccine, and to quickly and effectively dispel any misconceptions about its uses, safety and efficacy. Providers also must work with policymakers to ensure that HPV vaccines are directed to communities where they will have the largest impact, especially underserved communities where screening systems continue to be weak.

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Overview: Early Screening and Treatment

Even with a strong vaccination programme, there will be a small percent of the population who are at risk for cancer from uncovered subtypes or those who are already exposed to the virus. In addition, the unvaccinated population will continue to need significant attention to screening and early treatment for decades to come. This will remain a major focus for every cancer control programme. This section reviews screening and treatment strategies for every resource setting.

The Single Visit Approach

Neerja Bhatla, MBBS, MD, FICOG

Traditional cervical cancer screening and prevention programmes require the woman to make at least two visits if the test is negative and many more if positive. The cervical smear is taken at the first visit and the woman must wait for a provider response via mail or return to the clinic after a few days. If an abnormality is found, further evaluation may be scheduled depending on availability of personnel and available resources. At that point, diagnostic workup/ treatment will be scheduled as required.

In high-resource settings, in order to prevent loss to follow up, screening programmes have incorporated audits to monitor the efficacy of the programme and devised means to encourage patient compliance. Some countries have introduced incentives for health care workers to encourage screening coverage rates, call-recall systems as a reminder for non- compliant patients, and public education to encourage regular screening. These approaches require resources, patient time, and sophisticated health information systems.

Research by the Alliance for Cervical Cancer Prevention and others indicates that despite decades of effort, the replication of multiple visit-based screening programs has not been successful in reducing cancer rates in low-resource settings. The requirement of multiple visits results in poor patient compliance and loss to follow up. This coupled with a lack of access to treatment at the point of care have all contributed to poor outcomes in low-resource settings. In order to improve outcomes, while working within the technological and logistical limitations of low resource settings, the single visit approach has been developed.

Single visit approach

In the single visit approach, the intent is to have screening and treatment performed at the same visit to minimize the chance of abnormal results going unmanaged. This approach is often referred to synonymously as the “Screen and Treat” or “See and Treat” approach. This unique approach requires that the screening test provide rapid and accurate results and an appropriate, effective, adequate method of treatment is available to women with abnormal tests in the same sitting. Both screening and treatment are performed at the screening site, with no need for transport, delay or reliance on complex infrastructure or specialized care. Sometimes the single visit approach is not feasible because of unexpected findings, or after a rapid screen, a patient decides to think more about options for treatment. However, the goal is to provide both at the same visit.

Over the past several years, a number of screening and treatment options have been considered for use within the single visit approach. Cytology[1] was considered as an

option by placing labs in clinics in order to collapse the time needed to receive test results. These attempts focused on resolving the problem of loss to follow-up, as long as treatment was provided during the same visit. However, this approach did not provide a solution to the associated demands of infrastructure, cost and physician and cytologist time.

HPV testing has also been tried in a screen and treat approach.[2] The use of HPV testing within the single visit approach currently faces two limitations—time and infrastructure required for current HPV tests and a lack of consensus about appropriate follow up for test positives. It is not yet determined if proceeding directly to treatment with cryotherapy after a positive HPV test is the appropriate algorithm for care. If evidence becomes sufficient to recommend treatment directly after a positive HPV test, a fast, simple and affordable HPV test may make HPV testing with the single visit approach feasible within the coming years.[3]

At present, the most accessible modality for the single visit approach is visual inspection with acetic acid (VIA) followed by cryotherapy of positive cases at the same sitting.[4] A randomized trial in South India found a 25% reduction in cervical-cancer incidence and a 35% reduction in mortality compared to controls with VIA followed by cryotherapy.[5] In South Africa, a single-visit approach to cervical cancer prevention combining VIA and cryotherapy was found to be safe, acceptable, and feasible. It was found that this screen and treat method effectively cured CIN in 88% of women, including 70% of women with a baseline diagnosis of CIN 3.[6] Evidence shows that providing a single round of VIA followed by cryotherapy for test positive cases can reduce the lifetime risk of cervical cancer by 30%, if delivered to women between the ages of 35-45 years.[7]

The use of this combined approach has proven to be an effective and viable combination in low-resource settings.

VIA, cytology, HPV and cryotherapy are all reviewed in detail later in this guidance.

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Visual Inspection with Acetic Acid (VIA)

Neerja Bhatla, MBBS, MD, FICOG, and Enriquito Lu, MD

State of the science

In developing countries, cytology based screening has been able to make little impact on cervical cancer. Cytology screening has a relatively high false negative rate but cytology-based screening programmes for cervical cancer compensate for this through frequent, regular screening. These programmes have been successful in developed countries as they are able to ensure compliance, coverage and quality. However, developing countries suffer from major obstacles:

- Lack of infrastructure (laboratories, cytotechnicians), lack of quality control for laboratories and cytology reporting, and poor treatment facilities.
- Poor compliance and lack of follow up. As a result, women with abnormal tests do not receive treatment and costs are incurred without benefits, thereby decreasing cost-effectiveness.

These problems may be addressed in certain settings by visual inspection with acetic acid (VIA) followed by cryotherapy of positive cases at the same sitting (a single visit strategy).

Although not new, this approach has been validated and revitalized by a number of studies between 1996 and 2004, which establish that VIA is an alternative option to screening cervical precancer. These studies demonstrated in Table 1, show the relatively high sensitivity of VIA but a specificity that is slightly lower than cytology.[1,2,3,4,5,6]

VIA uses instrument sets and equipment usually available at healthcare centres. It does not require a laboratory and provides an immediate result, allowing the use of "screen and treat" methodology. Nurses and midwives can be trained, and have demonstrated that they can perform as well as any similarly trained physicians.[7] The ability to utilize mid-level providers is important as it extends accessibility to cervical cancer screening in regions where physician time and resources are scarce.

The procedure involves applying 3-5% freshly prepared acetic acid to the cervix and observing after one minute. Acetic acid dehydrates cells and reversibly coagulates the nuclear proteins. Thus, areas of increased nuclear activity and DNA content exhibit the most dramatic colour change to white. Acetowhite staining is not specific for CIN and may also occur to some extent in areas of squamous metaplasia and inflammation. The VIA results are generally categorized into three subsets: suspicious for cancer, VIA negative and VIA positive. A VIA test positive or positive

cervix is defined by the International Agency for Research on Cancer (IARC) as a raised, thickened, white plaque or acetowhite epithelium at or close to the squamocolumnar junction (SCJ). Additional information on IARC criteria for reporting the results of VIA are available at: http://screening.iarc.fr/viavilichap2.php?lang=1

Adverse reactions to diluted acetic acid are mild and range from a slight warm feeling to an uncomfortable stinging sensation. There are no reports of long-term sequelae or complications.

Barriers to Application

Barrier	**Low and middle resource settings**
Medical	• Resistance from professional medical/specialists to depart from traditional cytologic approach • Lack of referral centres for lesions suspicious for cancer and larger lesions needing additional care • VIA not suitable for post-menopausal women where squamocolumnar has receded into endocervical canal • Combined with cryotherapy, not suitable for women with large lesions, endocervical extension, or suspicion for cancer
Physical	• Absorptive capacity of health centres to meet increased demand for organized screening • [Opportunity: Materials are inexpensive and portable]
Training	• Conducting high quality, competency based, hands-on clinical training
Cost	• Access to cryotherapy equipment and the supply of cryogen • Initial quality assurance supervision for clinicians of 3-6 months. Translating learning into effective screen and treat services requires post training follow-up to support the new provider. Confidence in decision-making, particularly in calling a white lesion significant, and the subsequent application of cryotherapy is strengthened through organized, structured transfer of learning visits in the first 1-3 months post training. Subsequent visits using supportive supervision approaches provide the mechanism to ensure that quality of care is maintained. Implementing this approach requires time, investment in human resources and money. • [Opportunity: Low cost sterilization techniques such as boiling are acceptable for instruments used]

Policy	• National policies that restrict screening and treatment to physicians only • National cervical cancer prevention policies that do not recognize or support the use of VIA.

Cost/efficacy analysis

Goldie et al. compared the cost of different screening approaches in five countries. In 2000, the cost of providing VIA ranged between < US$5 in India to as high as $30 in South Africa. In each country, VIA proved to be the most cost effective screening test.[8]

Gaps in knowledge/further research needed

- VIA as a periodic screen test: VIA has mostly been evaluated as a once-in-a-lifetime screening test. There is a continued need for more information on its performance in periodic screening or consensus on the frequency with which VIA negative women must be re-examined. There is also a need for consensus as to what age to start and stop screening.

- VIA performance detecting recurrent or persistent disease: It is expected that the sensitivity and specificity of visual screening could change when in use in previously screened and treated populations. Large published screening trials have mainly focused on previously unscreened and untreated populations with a high prevalence of lesions. However, the Thailand Safe Study found that among women who were VIA positive and received treatment at the time of screening, about 94.3% were VIA negative one year later.[7] These positive results have been replicated in Ghana, a country with fewer resources.[9]

- Varied results from recent trials created confusion about impact: A recent article on HPV screening in rural Osmanabad, India,[10] reported that a single HPV testing resulted in a 50% reduction in incidence and mortality while VIA and cytology had no effect. Sankaranarayanan in an Alliance for Cervical Cancer Prevention (ACCP) guidance paper[11] noted "the challenges of interpreting the varying results from the two Indian studies in Osmanabad and Dindigul, and observed that the treatment rate among VIA-positive women was much higher in the South Indian trial of Dindigul than the Osmanabad trial, which may be a factor in the different study results." Despite, these contradictory outcomes, VIA has been validated as an effective screening approach and the ACCP and other international bodies continue to support its expansion.

- The advent of a potentially simpler, affordable and sensitive HPV DNA test provides an opportunity to further strengthen single visit programmes based

on visual inspection and cryotherapy. Studies exploring how to deploy this technology in combination with VIA under field conditions will help in the continued development of appropriate, cost effective cervical cancer screening service. Options for combining these tests include using VIA to triage HPV positive women for follow-up treatment or referral. Another option under study is to use VIA only to rule out large lesions and cancer suspects among HPV positive women and to offer treatment regardless of VIA status to all HPV+ women.

- The best screening interval for VIA in populations with high HIV prevalence is not presently well defined.

Recommendations for optimal use

Most VIA screening programmes focus on women between 30- 45 years old. This is the period when cervical pre-cancer lesions start to manifest. It is also the same time period when pre-cancer lesions are still treatable and respond favourably to cryotherapy.

- A three to five year screening interval should be considered for VIA negative women between the ages of 25-49.
- Women under 25 years of age should be screened only if they are at high risk for disease. Women at high risk for cervical abnormalities are those who have had early sexual exposure, multiple partners, previous abnormal screening results or CIN, or are HIV positive.
- VIA is not appropriate for women over 50 years. These women should be screened at five-year intervals using cytology or HPV testing.
- For HIV positive women, annual screening is recommended.
- Annual screening is not recommended at any age for the general population.
- In the single visit approach, VIA-positives are offered cryotherapy at the time of screening to maximize the effectiveness of the cervical cancer prevention programme. Post-cryotherapy, these women are seen in 12 months for a repeat screening.

Integration with, or replacement of other approaches

Thailand, a middle-income country, has demonstrated that the single-visit approach with VIA and cryotherapy is programmatically feasible and sustainable and should be considered in national investments to control cervical cancer.[7] Mid-level providers such as midwives and nurses may be trained for VIA and cryotherapy, and the cervical cancer screening programme can be integrated with existing reproductive health programmes. A referral system may be set up for patients who are high risk, ineligible for cryotherapy or if invasive cancer is suspected. This may be accomplished by providing appropriate training and equipment at the first referral centre.

Considerations for special populations

HIV/AIDS and immune system suppression are associated with more rapid CIN progression and HIV-positive women generally have high recurrence rates of CIN after treatment. Women may also transmit the virus more readily after cryotherapy and, therefore, require counselling regarding abstinence and condom use.

In general VIA is acceptable as a screen for pregnant women if that is the most cost effective method for the region but treatment is generally discouraged during pregnancy.

Key points:

1. A single visit approach to cervical cancer prevention combining VIA and cryotherapy is safe, acceptable, feasible and cost effective for the prevention of cervical cancer in low-resource settings, which minimizes loss to follow up. Once in a lifetime screening with VIA (and appropriate treatment) has the potential to reduce cancer risk by one third.
2. Most studies have evaluated the impact of a single round of screening with VIA in unscreened populations. Health policy modelling studies suggest that it would be best if VIA could be done serially at five-year intervals.
3. Mid-level providers may be trained for VIA and cryotherapy, and the cervical cancer screening programme can be integrated within existing health programmes. Women ineligible for cryotherapy need to be referred for colposcopy, LEEP, or management of invasive cancer, as required.
4. Effective training and quality assurance programmes are essential to ensuring the effectiveness of VIA. This is especially true as VIA is known to have a lower specificity than other methods, thus creating the potential for over treatment if inspection is not carefully and consistently supervised.
5. Cytology or HPV testing are more suitable for screening of post-menopausal women and should be considered in the follow-up of treated women.

Table 1 – VIA test qualities

Study	Country	Number of cases	Detection of HGSIL and cancer	
			Sensitivity	Specificity
Megevand et al (1996)	South Africa	2,426	65%	98%
Sankaranarayanan et al (1998)	India	2,935	90%	92%
University of Zimbabwe/Jhpiego (1999)	Zimbabwe	2,148	77%	64%
Belinson (2001)	China	1,997	71%	74%
Denny et al (2000)	South Africa	2,944	67%	84%
Sankaranarayanan et al (2004)	India	56,939	76.8%	85.5%

Table 2 – Test characteristics and implication on a screen and treat service delivery model

Test characteristics	**Conventional cytology**	**HPV DNA tests***	**VIA**	**VILI**
Sensitivity	**47-62%**	**66-100 %**	**67-79 %**	**78-98 %**
Specificity for HSIL and Invasive Cancer	**60-95 %**	**62-96 %**	**49-86 %**	**73-91 %**
Comments	Assessed over the last fifty years in a wide range of settings in developed and developing countries	Assessed over the last decade in many settings in developed countries and relatively few in developing countries	Assessed in the last ten years in resource poor countries	
Number of visits for screening and treatment	Two or more	Two or more visits	Can be used in a single visit approach / see and treat	Can be used in a single visit approach / see and treat
Sankaranarayanan et al. Int J Obstet Gynaecol, 2005				

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Early Diagnosis of Cervical Neoplasia: Pap Test (Cytology)

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State of the science

Widespread cervical cancer screening in the developed areas of the world has contributed to a decrease in the incidence of cervical cancer, primarily due to cytology screening and treatment of precancerous lesions.[1,2,3] Lack of infrastructure in low resource areas has prevented similar programmes from being successfully implemented.[4]

Many components are needed to establish an effective cytology programme on a wide scale. Governmental/national support and recognition of the need for screening and treatment and the burden of disease per specific area are required to garner appropriate funding.[5] Culturally appropriate education of women and healthcare providers may help ensure compliance with screening recommendations that require more than one cytology exam to increase efficacy. Training personnel such as cytology technicians is necessary to provide follow up for cytology findings. All screening efforts, including cytology, can only be effective if diagnostic and treatment modalities are available and accessible. In low resource settings, particularly developing countries, evidence indicates investments in cytology have not yielded adequate results. For this reason, other screening modalities covered in this guidance should be explored to improve and expand current efforts.

Barriers to application

Medical barriers:
In all environments and resource areas, there are no medical conditions that should exclude patients from receiving appropriate screening, including pregnancy.

Cultural barriers:
Acceptability of cytology screening and pelvic exams varies. In some cultures women do not attend screening programmes after completion of childbearing or cessation of sexual activity. This is particularly important in low- or middle- income areas where screenings are only set in reproductive health clinics. Culturally sensitive education is important to address this barrier.

Physical barriers:
Infrastructure needs for high-quality cytology screening—reliance on laboratories, trained cytologists and information networks have rendered this approach difficult, if not unviable, in many developing country settings.

Two approaches to cytology have slightly different physical demands. The equipment used for *conventional cytology screening* is resilient to temperature

changes, reagents are relatively low cost, usually portable and generally low maintenance. While *liquid based cytology* is temperature resilient, the equipment is large, and therefore requires a relatively large space, reliable electrical source, daily maintenance and is costly. The advantage of the liquid based cytology is the ability to use a computerized screening system. This allows the cytotechnologist/ pathologist to concentrate on the slides most likely to contain abnormalities; therefore more cytological specimens can be screened at a faster rate.[6] Reflex testing for HPV is also facilitated with liquid cytology. However, in a developing country setting, the distance from clinics to a central screening site can be prohibitive.

Training barriers:
A cytology specimen can either be self-collected, promising especially for HPV testing,[7] or collected by medical personnel including trained mid-level personnel. Reading the cytological specimen and performing diagnostic testing with colposcopy is more challenging and requires highly skilled cytologists and health professionals.

Cost barriers:
In low resource areas, the cost of establishing the necessary infrastructure, developing and supervising the required personnel for a cytology-based screening programme has been prohibitive. Even in medium resource areas where screening may exist, there may be limited support for subsequent needed diagnostic testing and treatment or geographic barriers. It is important to note that even in high resource areas, there are pockets of underserved populations with limited access to medical care[8] and consequent failure of a cytology screening structure.

Policy barriers:
In low economic resource areas, policy makers have to evaluate the options to address the need for a sustainable and supported screening programme. In medium or high economic resource areas, ensuring access for all women, particularly beyond the reproductive age, is the challenge. Many of the high economic resource areas also have disparities between insured and uninsured individuals or rural and urban areas.

Cost-benefit analysis

When part of an established programme in high resource settings, with repeated screening at five-year intervals and combined with appropriate diagnosis and treatment, cytology can be cost effective. The majority of the loss to benefit of cytology is the need to have a two or three step process where the patient is screened, needs to follow up for diagnostic testing, and then finally treatment. Multiple visits in poor resource areas lead not only to increased costs but also to higher loss to follow up.

Author	Region	Cytology screen intervals	Reduction in CA (%)	Cost per year of life saved ($)
Kim et al[9]	Hong Kong	3, 4, 5 years	86-90	800-12300
Mandelblatt[10]	Thailand	5 years	13.5	1459
Goldie et al[11]	S. Africa	One time	19	81

Gaps in knowledge and further areas of research needed

Ideal screening models have to be identified per region. Applying the guidelines from developed countries to low resource areas is not cost-effective and could not be sustained. Improvements in cytological testing such as molecular markers for HPV would improve the sensitivity. Ideal screening methodologies are cost effective, rely less on laboratory infrastructure than current cytology methods, and require a one-time visit with high sensitivity and specificity that will yield immediate results, allowing for same day evaluation and treatment.

Recommendations for optimal use

There is no global consensus on age to begin or interval of screening. In developed countries, such as the United States, screening is initiated at age 21 or within three years of sexual activity and continues until the age of 65 or 70.[12] In other countries, such as England, screening is initiated at age 25. It is performed every three years up to the age of 49, and then every five years until age 65 (National Health Screening Programme). In low to middle resource countries, screening is inconsistent, maybe initiated in the mid-30s and then conducted every five years. If only one-time screening is available, then it is usually performed between 35 and 40 years of age usually by visiting groups since no internal systems exist.[13] As with other forms of screening, cytology screening should be provided to both vaccinated and unvaccinated women.

Key points:

1. Well-established screening and treatment programmes have been proven to decrease the incidence of cervical cancer in high resource environments.
2. Components of a comprehensive screening programme should include education, training, screening, diagnostic testing, and treatment.
3. Initiation of cytological screening, where resources are available, should occur between ages 21 and 25. In low to medium resource areas, initiation should be at age 35.
4. Interval of screening should follow accepted regional standards but should not be longer than five years in women under the age of 60.

5. Cytology-based programmes can be cost effective if screening targets the population at highest risk for disease, and the infrastructure is in place.

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HPV Testing: an Adjuvant to Cytology-based Screening and as a Primary Screening Test

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State of the science

There are several diagnostic tests for detection of oncogenic genotypes of human papillomavirus (HPV); some detect HPV-DNA and others target HPV-RNA. Recent research indicates that HPV testing is the most sensitive screening tool available at this time for the detection of CIN 3 and cervical cancer. In 2009, a randomized controlled trial of over 130,000 women in India showed that a single round of HPV testing significantly reduced cervical cancer deaths within the seven years of follow-up.[1]

How to most effectively integrate this new approach into a screening and early treatment regime depends upon the success of current programmes, health infrastructure and resources. Current guidance on the use of HPV testing varies with regards to its use as a stand-alone primary screening test or in combination with cytology or even for follow-up of patients with CIN after completing treatment.

HPV-DNA as primary screening test

The HPV test is highly sensitive, although less specific, in primary screening of precancerous lesions of the cervix (CIN 2 and CIN 3). Global estimates suggest that the overall age-adjusted prevalence of HPV is 10.5%. There is some geographic variation, including a disproportionate prevalence in resource poor regions. This prevalence declines in older women, as most have cleared HPV infection by their early 30s.[2]

Therefore, focusing HPV testing on women over the age of 30 is likely to yield the best results, as positive tests are more likely to pick up persistent infection than among younger women. Meta-analyses of studies have shown that the mean sensitivity of HPV-DNA testing for detection of CIN 2/3 is over 90%[3] although reports from studies performed in developing countries obtained lower sensitivities.[4]

Specificity of HPV-DNA testing for cross-sectional CIN 2/3 ranged from 85-90%.[5] This sub-optimal specificity is one of the limitations of the test since a considerable number of women with positive results may be unnecessarily referred for additional evaluation, usually colposcopy and directed biopsy. This is an especially important consideration in areas where treatment resources are limited and unnecessary follow up treatment presents a worrisome burden to the health system.

One of the advantages of HPV-DNA testing is the high negative predictive value. Recent studies in Europe and the United States demonstrated that the risk of

developing CIN 3 after a negative HPV-DNA test is almost zero within 6 and 10 years respectively.[6,7] This characteristic of HPV-DNA testing could permit longer inter-screening periods and fewer overall screenings during a woman's lifetime.

Several studies have shown that HPV testing of self-collected vaginal samples provide high sensitivity and this may be useful in certain cultures.[8,9,10] If future studies indicate that self-sampling is a viable option for low resource settings, current pressure on clinician time may be relieved. Self-sampling also provides an option for women to access cervical cancer screening, even if they are resistant to a pelvic examination.

HPV-DNA as an ancillary screening test:

- **Triage of patients with cytological abnormalities**

HPV testing does not have a role for triaging women with clear cytological abnormalities (LSIL) since a considerable percentage of these women are HPV infected; adding HPV testing would only add additional cost and delay of treatment.[11] But there is significant benefit in using HPV testing in women with undetermined cytological changes; most of these women will be negative for HPV infection and do not need colposcopy or biopsy. HPV testing women with ASCUS findings reduces the number of referrals to colposcopy, which is especially important in areas where there is a lack of colposcopy and pathology units, where those services are very costly or transportation to such a visit is impractical.

- **Combined screening: Cytology and HPV testing**

The combination of HPV testing and cytology has demonstrated a slight increase in sensitivity for detection of CIN 2/3 compared to HPV testing alone, but this benefit will vanish in areas where cervical cytology performance is sub-optimal. Another limitation of combining HPV-DNA testing and cytology is the increased cost, which can be prohibitive in low-resource settings.

- **HPV-DNA for primary screening followed by VIA**

Since access to colposcopy is very limited in low resource areas, especially in rural areas of developing countries, VIA has been proposed as a triage tool for women with a positive HPV result. A study from South Africa showed VIA immediately followed by cryotherapy resulted in a significant reduction in the incidence of CIN 3 at one-year follow-up compared to women triaged with cytology or a control group.[12] It is important to highlight that, in this strategy, VIA is used to identify women who are <u>not</u> eligible for cryotherapy because of a large pre-cancerous lesion or suspicion of invasive cancer; all other women are immediately treated even if no lesion is observed. In high resource countries, HPV testing with triage to cytology has been proposed.

- **A rapid low-resource HPV test**

A rapid, low-cost, portable HPV test designed for rural developing country settings is expected in 2011. This test, the product of a donor funded public-private partnership, is designed to allow for HPV testing within the screen and treat approach as test results are available within hours. A 2008 study conducted among 2,400 women in China found this new test to be 90% accurate at detecting precancerous cells when conducted by a mid-level provider; 84.2% of women without precancerous cells were identified as negative.[13] These encouraging results are now being validated through an expanded demonstration project in several countries. It is hoped that this test can be successfully employed to bring affordable HPV testing to previously unscreened populations.

Barriers to application

- **Medical barriers:** Contraindications - endocervical sampling is not recommended during pregnancy.
- **Physical barriers:** HPV testing requires sophisticated instruments and equipment that are available in developed countries and some urban areas of developing countries. These instruments are difficult to transport and are usually located only in well-implemented laboratories. This barrier may be significantly reduced if a viable, rapid low-resource test becomes available and accessible.
- **Training:** Most HPV tests require well-trained lab technicians.
- **Cost barriers:** Most products for HPV testing require significant investment in laboratories in addition to the cost of each test. Current methods are becoming available through private providers in urban areas in developing countries. Mexico is piloting the use of HPV test in underserved areas of the country. For most countries and underserved communities, these tests are too expensive. In coming years, a low-resource rapid test may be provided at a cost that is within reach of governments and low-income service providers.
- **Policy barriers:** Algorithms for management of patients after an HPV test result are not clearly defined or understood by many professionals. There is a need for medical education on this topic. Also, discounted access to HPV tests to governments, agencies and NGOs will need to be supported by international purchasing mechanisms and donors.

Cost/efficacy analysis

HPV testing is cost effective for screening women at age 30 or older, especially when only a few screening opportunities will be available to a woman in her lifetime.[14] The test is less cost effective in younger women due to the increased prevalence of

transient HPV infections and mild cervical abnormalities. For this age group, HPV testing may be most cost effective as a triage tool for women with suspected cytological abnormalities, pending further targeted research and cost analysis.

Recent reports suggest that performance of VIA or cytology are more cost effective when used for evaluation of HPV infected women.[14]

Gaps in knowledge and further areas of research needed

HPV-DNA testing permits detection of prevalent infection in a given population, but it is still impossible to determine using a single-time test which women will clear the virus and which will become chronically infected and progress to cancer. Additional evaluation is needed to determine patient eligibility for treatment. Guidelines for patient management are needed, especially for areas with limited resources.

Recommendations for optimal use

HPV testing is widely recommended for women above the age of 30 up to 55-65 years of age. In low resource settings, a once or twice in a lifetime screening at age 35 and 45, with triage of HPV positive women to cytology or VIA, may be optimal. In high resource settings, HPV co-testing is recommended (although primary testing with triage to cytology is being studied). The screening interval is currently recommended at 3-5 years but longer intervals are being investigated and early evidence has shown them to be safe and effective.

Integration with or replacement of other prevention approaches

At this time, HPV testing is recommended with existing screening methods or as a triage test. The replacement of current screening approaches with a sole HPV test has not been recommended. This approach may be recommended in the future for certain settings once sufficient evidence is available.

Considerations for special populations (HIV+, pregnancy, etc.)

HPV infection is more prevalent in conditions associated with immune-suppression. HPV prevalence in HIV-infected women is double or triple that of the general population; therefore, a significant percentage of HIV positive women will be referred for additional evaluation after HPV testing. Similarly, natural transient immune suppression occurs during pregnancy when HPV infection is more prevalent, especially during the second and third trimester.

Key points – HPV testing:

1. HPV testing is the most sensitive screening test for detection of CIN 2/3 and cervical cancer.
2. Sub-optimal specificity of HPV testing results in an increased number of women referred for further evaluation. It could be a limitation in settings where colposcopy is not available.

3. HPV testing is cost-effective for primary screening in women 30 years and over, and for triage of abnormal cytology in younger women.
4. The high negative predictive value of HPV testing permits longer inter-screening periods and a reduction in the number of screening visits needed over a lifetime.
5. Introduction of a faster, simpler and more affordable HPV test currently used in demonstration projects will benefit areas with limited resources.

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Colposcopy

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State of the science

Colposcopy was first introduced by Hans Hinselmann in 1925 in Germany. A colposcope allows both magnification and illumination of the cervix, thus facilitating biopsy of the worst area after application of acetic acid and Lugol's iodine. Colposcopy is not a sufficient tool for screening, as alone it has low sensitivity and low positive predictive value. However, it is essential in a cervical cytology screening programme for assessment of abnormal cytology findings to make a diagnosis of pre-invasive or invasive cervical neoplasia. With an abnormal cervical cytology result in a screening programme, guidelines on when to perform colposcopy on minimal abnormalities such as atypical squamous cells of undetermined significance vary among countries. However, for high grade abnormality, colposcopy is indicated.

After 3-5% acetic acid solution is applied to the cervix, the cervix is directly visualized using low- and high-power magnification followed by a green filter inspection. Acetic acid has a temporary dehydrating effect on squamous cells and accentuates their high nuclear-cytoplasmic ratios. To the human eye, the higher the grade of the cervical lesion, the more opaque it appears, as the nuclei impedes light transmission. These lesions are described as "acetowhite." Apart from colour changes, a characteristic microvasculature pattern that includes punctuation and mosaicism may be seen. An experienced colposcopist determines the severity of cervical neoplasia based on such changes. Although benign conditions may cause acetowhite changes on the squamous epithelium, dysplastic lesions are sharply demarcated from adjacent normal epithelium, and are most often located at the squamocolumnar junction. Histological assessment by biopsies taken from the acetowhite lesions is needed to make a definitive diagnosis of lesions causing the abnormal cytology. Colposcopic adequacy is defined by visualization of the entire squamocolumnar junction as well as any acetowhite lesions. Colposcopy is carried out in an out-patient setting. It requires training and assurance of quality and hence accreditation systems are common in many countries.

Barriers to application

The main barrier to colposcopy is lack of resources in acquiring the equipment, which is quite expensive, and the training and retention of skilled medical personnel. A reliable supply of electricity is needed to operate a colposcope. Accreditation and re-accreditation help in maintaining quality of care standards. Other issues include the access to pathology support in processing and interpreting the biopsied samples and the quality assurance of the laboratory. The cost of all of these components may be prohibitive in some settings.

Cost/efficacy analysis

The cost of colposcopy examination contributes to the cost/efficacy analysis of a cytology-based cervical cancer screening programme. Thus, using cytology screening could cost more because of the need for colposcopy for an abnormal cytology. However, the cost for colposcopy examination not only includes the consultation fee, but for the patient, the time and cost for a second or third visit as well as anxiety while waiting for the result. Though see and treat may be an option, over treatment with its related morbidity[1] may not justify the reduction of cost for a second visit. Nevertheless, if an experienced colposcopist identifies a high-grade lesion, see and treat in one visit is acceptable.

Gaps in knowledge and further areas of research needed

Recently, the use of colposcopy/biopsy as the gold standard in detection of cervical lesions following an abnormal cervical cytology was challenged.[2] Four quadrant cervical biopsies from the squamocolumnar junction and endocervical sampling picked up more cervical lesions than colposcopic directed biopsy. More study is needed to confirm this finding.

The role of colposcopy in primary screening with high risk HPV testing needs further study to determine the appropriate follow up.

Recommendation for optimal use

In screening programmes, colposcopy remains the gold standard for making the definitive diagnosis. The indication for colposcopy varies depending on the screening methods used. If cervical cytology is used as the primary screening tool, guidelines should be followed on when colposcopy should be performed. Basically, all high-grade cytology has to be assessed by colposcopy and biopsies within a reasonable length of time such as within four weeks. If high risk HPV testing is used as the primary screening tool, the algorithm is yet to be decided. However, the recent recommendation from ASCCP is to perform colposcopy in women tested to have HPV 16 even in the absence of abnormal cytology. If VIA or VILA is used as the primary screening tool, the role of colposcopy is less certain.

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Cryotherapy

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State of the science

Cryotherapy has been in use for over 40 years as a safe and effective way of destroying (ablating) CIN lesions on the ectocervix by freezing the cervical epithelial tissue. Cells rapidly reduced to -20 degrees C for one or more minutes will undergo cryonecrosis.

After visualization of the cervix using a vaginal speculum, a cryotherapy probe with a circular metal tip of approximately 2 cm diameter is applied to the ectocervix and a refrigerant gas (nitrous oxide or carbon dioxide) is allowed to flow through the instrument cooling the metal tip. Guided by a timer or watch, the affected tissue is frozen for three minutes, allowed to thaw for five minutes and then re-frozen for three minutes.[1]

Cryotherapy is well-suited for low-resource settings. It requires no anaesthetic or electricity, the equipment is portable, the cost of consumables and equipment is less than electrosurgical methods, and with adequate training and supervision, primary health care professionals other than physicians are able to perform the technique. A review of the literature shows a cure rate of 90% at one-year and over 85% of women found the procedure to be safe and highly acceptable. Mild side effects such as fainting during the procedure, vaginal discharge, cramping, and spotting during the first month are common, but do not impact the acceptability or safety of the procedure.[2] Recent studies in developing country settings, with active follow up, show that complications such as cervicitis (1%) and Pelvic Inflammatory Disease (PID) (<1%) are unusual.[3,4] Long term sequelae such as cervical stenosis or infertility are rare.[2] Women are advised to abstain from sexual intercourse for at least one month after treatment or to use condoms. Adequate counselling is very important for better acceptance of side effects and recognition of signs of complication.

Barriers to application

- **Medical contraindications:**
    - Relative: generally not recommended for pregnant women; large lesions more than three cervical quadrants; presence of menstrual bleeding.
    - Absolute: suspicion of invasive cancer; lesion involving the endocervical canal or extending to the vagina; more than 2 mm of lesion margins not covered by the cryoprobe; presence of untreated PID or cervicitis; bleeding diathesis; vaginal wall prolapse causing either inadequate visualization of the cervix or contact of the frozen

probe with vagina; inability to physically or emotionally tolerate the procedure; a woman with a lesion that has not resolved after two cryotherapy sessions should have excisional treatment.

- **Physical barriers**: After use the metal tip of the cryoprobe needs to be adequately decontaminated as recommended by the manufacturer (10% bleach solution or 70% ethyl alcohol), scrubbed with detergent and water by personnel wearing rubber gloves and processed by either sterilization or high level disinfective before reuse to prevent spread of infection from one patient to another. The equipment is simple to store (preferably covered) and ease of repair varies with the type of equipment and availability of service and spare parts.

- **Training:** Cryotherapy is technically simpler than other treatment methods and training requires a few days for most primary health care providers with the requisite skills and knowledge. Ongoing monitoring and supervision is necessary to maintain provider skills.[5]

- **Cost barriers:** In addition to direct costs for the facility, personnel for treatment and two follow up visits (at 1-2 months and test of cure at one year), treatment cost depends on the refrigerant used and size of tank (larger tanks generally cost less per treatment). Industrial grade carbon dioxide is approximately 3-5 times cheaper than nitrous oxide. The cost of a cryotherapy unit varies from about $400 for reliable units made in less developed countries to over $1200 for North American or European units. Due to the high rates of cervicitis in many developing country settings, presumptive treatment with a short course of antibiotics may be prescribed immediately after cryotherapy (e.g., combination of metronidazole 400 mg TID and doxycycline 100 mg BID x 5 days).

- **Policy barriers**: Cryotherapy is recommended as cost-effective, safe and acceptable and currently is permitted in most developed and developing countries. It was common in the industrialized world until other techniques, such as LEEP, were adopted in its place. Since many countries allow trained and supervised nurses and paramedical staff to perform cryotherapy, this addresses the barrier of limiting the procedure to physicians.

Cost/efficacy analysis

Based on a review of published evidence in both developed and developing countries, cure rates at one year are 90% overall, 83-100% for CIN 1, 65-95% for CIN 2, and 55-92% for CIN 3.[2] Modelling has shown that, in low-resource settings where screening is limited to once or twice in a lifetime, cryotherapy is very cost-effective relative to other treatment methods.

Gaps in knowledge and further areas of research needed

Experience has shown that in some low-resource settings, blockage (or clogging of the gas flow within the passages of the cryo unit) may occur during the procedure. An interagency collaboration is addressing technical issues such as how to prevent blockage and equipment failure by developing specifications for procedures, equipment, refrigerant gas, and accessories. The degree of risk of STI or HIV transmission or acquisition during the healing phase after cryotherapy needs further research.[6,7] The effectiveness of cryotherapy in women with HIV in relation to their CD4 count should also be explored.

Recommendations for optimal use

Cryotherapy may be used in a wide variety of settings, including low-resource settings, where there are adequate quality assurance mechanisms in place such as clinical monitoring and supervision. Use of cryotherapy in a single visit approach optimizes programme effectiveness. The equipment is portable and the treatment method is simple enough that it can be used in a mobile outreach cervical cancer prevention programme.

Integration with or replacement of other prevention approaches

In low-resource settings cryotherapy is recommended as the main treatment method in suitable patients. In those with contraindications to cryotherapy other treatments should be considered such as LEEP or conization.

Considerations for special populations (HIV+, pregnancy, etc.)

Previously mentioned in subhead dealing with Barriers and Gaps in knowledge.

Key points – Cryotherapy:

1. Cryotherapy is an acceptable, affordable, safe and effective treatment of ectocervical CIN in both low- and high-resource settings.
2. Compared to the equipment and supplies required for LEEP, cryotherapy costs much less and does not require electricity.
3. Accessibility to treatment is increased since primary health care personnel other than physicians can be trained to perform cryotherapy under monitoring and supervision.
4. In suitable patients cryotherapy cures 90% of CIN overall but is not recommended for lesions involving the endocervix or vagina.
5. Pending answers to questions on the risk of transmission and acquisition of STI's and HIV during the post-cryotherapy healing period, patients are advised to avoid intercourse or to use condoms for at least one month.

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LEEP/ Cervical Cone

Katina Robison, MD

State of the science

Cervical cancer and cervical dysplasia remain substantial health burdens worldwide. Cervical conization is widely accepted as the preferred management of cervical intraepithelial neoplasia (CIN).[1,2,3,4] Cervical cone techniques currently used include cold knife cone (CKC), loop electrosurgical excision procedures (LEEP and LLETZ), and laser conization. All three techniques are effective in the treatment of CIN and studies have found no difference in the sample adequacy between the techniques.[1,2,5,6] Cervical cone procedures have been shown to be safe in most settings. Bleeding, infection and anaesthesia reactions are the most common complications, but the rates of complications remain low.[4,5]

The cervical conization technique chosen is based on multiple factors, including histologic diagnosis, location of the lesion, and available anaesthetic and procedural resources. For example, in low resource settings a loop excision is preferred because it is more cost effective and safer than a CKC. In addition, the availability of resources may influence the management decision. Conventionally, a cervical cone procedure is performed after colposcopy and biopsies. However, a cervical cone procedure may also be done in a single-visit "see-and-treat" approach in which evaluation and treatment are performed at the same time.[1] The approach to cervical dysplasia can be tailored based on resource availability and disease status.[7,8,9,10]

Barriers to cervical cone procedure

Barriers	**Low resource settings**	**High resource settings**
Medical	• Anatomical: cervix flush with vagina • Infection	• Anatomical: cervix flush with vagina • Infection
Physical	• Voltage mismatch/irregularities • Inadequate haemostatic equipment • Lack of clean water • Hazardous waste disposal • Equipment • Operating room/clinic space • Pathology Services • Travel to central treatment facility • Availability of anaesthesia	• Travel to central treatment facility

Training	• Requires trained medical practitioner • On-site training (at least four weeks) and retraining	• Requires trained medical practitioner • Training during residency/fellowship
Cost	• Equipment • Laboratory • Pathology services • Delivery of supplies	• Insurance scheme/coverage dependent
Policy	• Follow-up limited • Requires support of local providers	• Insurance scheme/coverage dependent

Adapted from Holschneider CH, Ghosh K, Montz FJ.

Cost/efficacy analysis

There are multiple management options for cervical dysplasia. Cold-knife cone and loop excision have been shown to be equally effective for the treatment of cervical dysplasia. However, there is some evidence that CKC is better at evaluating endocervical extension. In addition, when CKC is immediately available it may be preferred for larger lesions as it has been shown to remove more tissue than loop excision.[1,2,4,6]

Conventional management of cervical dysplasia in high resource settings consists of colposcopy with directed biopsies. If necessary, a cervical conization is performed based upon histologic findings. In low resource settings, the "see-and-treat" strategy has been shown to be a cost-effective alternative. Holschnieder et al. found a 41% cost reduction compared to conventional management.[8]

Recommendations for use

<u>Low resource settings</u>

Cold knife cone: Use is limited because it requires general anaesthesia and an operating room. It may be performed as a treatment option in early stage cervical cancer when future fertility is desired.

LEEP/LLETZ: Trained medical practitioners may use these procedures in single visit/ "see-and-treat" approach. Visual inspection with acetic acid may be performed at the same visit as loop excision or prior with a trained nurse and referred for treatment when appropriate. Women with high-grade squamous intraepithelial lesion (HGSIL) cytology, large lesions (>3 quadrants) and/or high grade appearing lesions on visualization should receive a LEEP.[10]

High resource/high access settings

Cold knife cone: A gynaecologist or gynaecologic oncologist should perform in an operating room. After colposcopy, women with biopsy proven adenocarcinoma-in-situ, microscopic invasive squamous cell carcinoma or microscopic adenocarcinoma should have a CKC. CKC is also recommended with high-grade dysplasia on endocervical curettage (ECC).

LEEP/LLETZ: Trained medical practitioners should use these procedures in the office or operating room after colposcopy and cervical biopsies have been performed. Loop excisions are preferred when invasive cancer cannot be ruled out and the risk is high. This includes women with unsatisfactory colposcopic examinations, positive endocervical curettage, large lesions with high-grade colposcopic impression and post-treatment recurrence of CIN 2 and 3. Loop excision may also be considered as part of a "see-and-treat" approach for women referred for a high-grade squamous intraepithelial lesion on cytology, regardless of colposcopic findings.[1]

Gaps in knowledge

There is strong evidence supporting the use of the "see-and-treat" approach in low resource settings. However, the definition of low resource is broad and can include rural areas in developed countries, uninsured individuals with limited access and women that do not routinely participate in screening. It is less clear if this approach should be offered in these settings where national guidelines may already exist and this approach deviates from these guidelines. In some of these settings, there may only be the opportunity for one visit and the "see-and-treat" approach may be the most effective. However, there are limited studies comparing this approach to the conventional approach in such settings.

Integration with/or replacement of other approaches

Loop excision should be used in conjunction with either cytology followed by colposcopy or VIA based on the resource setting where it is performed. Loop excision has widely replaced CKC in low resource settings and may be used in place of CKC in high resource settings as discussed in the "recommendations for use" section. Alternatives to loop excision include CKC and cryotherapy.

Considerations for special populations

Pregnancy

Treatment of CIN should be avoided during pregnancy, as it is associated with a high rate of complications, including severe haemorrhage.[11] Additionally, when excision is performed during pregnancy there is a high rate of incomplete excision and recurrence. The only indication for excision is diagnosis of invasive cancer.

However, early-stage cervical cancer may be followed during pregnancy and treatment delayed until delivery.

Adolescents

The risk of invasive cancer is low in adolescents and there is a high rate of spontaneous regression of squamous intraepithelial lesions among this group. Cervical cone procedures have been associated with increased risk of preterm delivery. Kyrgiou et al, performed a meta-analysis and found CKC and LLETZ are associated with preterm delivery (<37 weeks).[12] A recent case-control study reported a short conization-to-pregnancy period (conception within 2 to 3 months) was associated with an increased risk of preterm delivery, but not cervical conization alone.[12,13] Performing cervical cone procedures on adolescents would increase the risk of future pregnancy complications and potentially be unnecessary.

HIV-infected women

HPV is more prevalent among HIV infected women and HIV-infected women have more rapid progression rates of CIN to cervical cancer.[10] Therefore, routine screening is preferred in all resource settings. However, indications for cervical conization are the same for HIV-infected women and non-HIV-infected women. The "see-and-treat" approach has been implemented in low resource settings for HIV-infected women and appears to be feasible.

Key points: LEEP/Cervical Cone

1. Cervical conization is safe and effective in the management of CIN 2/3
2. Cold knife cone and loop electrosurgical excision procedures appear to be equally effective in the treatment of cervical dysplasia.
3. Follow up after cervical conization should be based on pathology results and the resource setting.
4. The "see-and-treat" approach is cost-effective in low resource settings.
5. Cervical conization should be avoided in pregnancy unless there is invasive cancer.

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Overview: Cervical Cancer Treatment

The best strategy for cervical cancer control is primary prevention, screening and treatment of pre-invasive disease. Of necessity, cervical cancer treatment requires focused expertise and availability of operating theatres, chemotherapy and radiotherapy, all of which carry high price tags. In resource poor countries, concentration of these expensive resources in one central facility helps to limit costs but requires adequate transportation and support mechanisms for women and families to use when such care is needed. Regardless of the efficacy of prevention, screening and early treatment of preinvasive disease, there will still be cases of invasive cancer. This requires each programme to have a plan in place for women with cervical disease. In addition, a strategy for end of life treatment including adequate pain control is a critical part of the creation of the unique bundle of services for cervical cancer control in each setting.

FIGO Cancer Committee Guidelines for Early Invasive Cervical Cancer Management

Hextan Y.S. Ngan, MBBS, MD, FRCOG

State of the science

Stage	Standard treatment	Special consideration
Stage IA1	Simple hysterectomy	Conservative – cone with clear margin
Stage IA2	Simple or radical hysterectomy and bilateral pelvic lymphadenectomy depending on local or regional guidelines	Conservative – large cone or trachelectomy and bilateral pelvic lymphadenectomy depending on local or regional guidelines
Stage IB1	Radical hysterectomy and bilateral pelvic lymphadenectomy or radiotherapy	Conservative for small lesion - trachelectomy and bilateral pelvic lymphadenectomy
Stage IB2	Chemoradiation or radical hysterectomy and bilateral pelvic lymphadenectomy +/- adjuvant radiotherapy or chemoradiation	Neoadjuvant chemotherapy then surgery in selected patients
Stage IIA 1 or 2	Chemoradiation or radical hysterectomy and bilateral pelvic lymphadenectomy in selected patients +/- adjuvant radiotherapy or chemoradiation	Neoadjuvant chemotherapy then surgery in selected patients
Stage IIB	Chemoradiation or radical hysterectomy and bilateral pelvic lymphadenectomy in selected patients +/-	Neoadjuvant chemotherapy then surgery in selected patients

	adjuvant radiotherapy or chemoradiation	
Stage III A	Chemoradiation or radiotherapy	
Stage III B	Chemoradiation or radiotherapy	
Stage IV A	Chemoradiation or radiotherapy	Pelvic exenteration
Stage IV B	Palliative radiotherapy or chemotherapy	End of life care especially adequate pain control and use of morphine

Barriers to treatment

Treatment of invasive cervical cancer requires multidisciplinary contributions from gynaecological oncologists, radiation oncologists, radiation oncology specialists, medical oncologists, radiologists and nurse specialists. Establishment of a regional treatment centre with appropriately trained specialists could be a problem in low resource settings. In the case of radiation therapy, there is a need for both an external radiotherapy machines as well as a brachytherapy system. Apart from the facilities, appropriately trained support staff and radiotherapists may not be available in low resource settings. Other barriers include lack of knowledge of detection and cure of cervical cancer and cultural barriers of what is perceived as foreign. Physical access to a cancer treatment centre (transportation and ability to live nearby while receiving treatment) could be a barrier in some countries.

Cost/efficacy analysis

In order to reduce the cost and increase efficacy, early detection and prompt treatment can increase chances of survival and reduce cost of palliative care. The cost of radiotherapy treatment versus surgical treatment varies between countries. Thus, the choice of treatment may also vary depending on expertise and facilities available on-site.

Gaps in knowledge and further areas of research needed

The optimal types and number of courses of chemotherapy concurrent with radiation need to be better defined. The role of adjuvant chemotherapy after chemoradiation for advanced disease and the role and choice of chemotherapy regimen in neoadjuvant chemotherapy before surgery in advanced disease are

undergoing study. The role of new radiotherapy technology such as intensity-modulated radiotherapy in decreasing side-effects of radiotherapy need further study.

Recommendations for optimal use

Women with cervical cancer should preferably be treated by gynaecological oncologists or radiotherapists in a centre with adequate facilities. These centres should be established with easy access and affordability so as not to deprive women with cervical cancer the chance of a cure. The choice of optimal treatment of cervical cancer depends not only on the stage of the disease but also on the availability of expertise, facilities, patient's wishes and accessibility. A good pre-treatment assessment, appropriate treatment, post-treatment monitoring and psychosocial support are important. Palliative care, including the legal use of morphine, should be made available for those with no hope of being cured. In order to have a better understanding of the burden and outcome of women with cervical cancer, a cancer registry should be established in each locality.

The World Health Organization's "Comprehensive cervical cancer control: a guide to essential practice" has a useful chapter on palliative care.

Resource –based Approaches to Cervical Cancer Control

Potential "Bundles of Services"

Cancer registry for ALL	***Limited visits (One to few)***	***Unlimited follow-up***
Highly Limited Resources Prevention Screening / Treatment Dysplasia Cancer	HPV Vaccine Single Visit Approach • VIA* *or* • Single lifetime HPV screen-and-treat • Cryotherapy or LEEP *Referral system to appropriate central treatment*	HPV Vaccine Single Visit Approach ** • VIA* *or* • Single lifetime HPV screen-and-treat • Cryotherapy or LEEP *Referral system to appropriate central treatment*
Moderately Limited Resources Prevention Screening Treatment Dysplasia Cancer	HPV Vaccine VIA* *or* HPV Testing • If +, VIA or Colposcopy Single Visit Approach • Cryotherapy or LEEP *Referral system to appropriate central treatment*	HPV Vaccine Cytology *and*/*or* HPV Testing • If +, VIA *or* Colposcopy +/- biopsies Cryotherapy or LEEP *Referral system to appropriate central treatment*
Resource Rich Prevention Screening	HPV Vaccine Cytology and HPV Testing • Colposcopy as needed	HPV Vaccine Cytology and HPV Testing

Treatment	Cryotherapy or LEEP	
Dysplasia		Cryotherapy or LEEP
Cancer	*Referral to Gynaecologic Oncologist*	*Referral to Gynaecologic Oncologist*

*Rapid HPV test availability may change recommendations

**Preferable do to limitations to unlimited follow-up in highly limited resource areas

Useful Website and Resources*

Websites

RHO Cervical Cancer
www.rho.org

PATH cervical cancer prevention
www.path.org/cervical-cancer.php

Alliance for Cervical Cancer Prevention (ACCP)
www.alliance-cxca.org

International Agency for Research on Cancer (IARC) Screening Group
www.iarc.fr/cervicalindex.php

World Health Organization— cancers of the reproductive system
www.who.int/reproductive-health/publications/cancers.html

Two websites on HPV vaccine safety:

Medicines and Healthcare Products Regulatory Agency (MHRA) —currently monitoring the safety of GlaxoSmithKline's Cervarix® HPV vaccine. Cervarix® is currently being introduced through the UK National Health System (NHS)
http://www.mhra.gov.uk/Safetyinformation/Generalsafetyinformationandadvice/Product-specificinformationandadvice/HumanpapillomavirusHPVvaccine/CON023340

The U.S. Food and Drug Association (FDA) and the Centers for Disease Control and Prevention (CDC) — currently monitoring the introduction and safety of Merck's Gardasil®, the only vaccine registered at present in the United States
http://www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/VaccineSafety/ucm179549.htm

Reference Materials and Training Manuals:

World Health Organization. Comprehensive cervical cancer control: A guide to essential practice (2006)
The guide aims to compile what is known about cervical cancer and related morbidity and mortality. It is designed as a comprehensive and easy-to-use resource for health care providers at the primary and secondary levels (primarily in limited-resource settings) on how to prevent, detect and treat cervical cancer. Evidence-based recommendations cover the full continuum of care. *Accessible at:*
http://www.rho.org/files/WHO_CC_control_2006.pdf

EngenderHealth. COPE® for cervical cancer prevention services: A toolbook to accompany the COPE® handbook (2004) COPE (client-oriented, provider-efficient services) is a process that involves facility staff and supervisors to jointly assess services in order to improve quality. This toolbook includes guides, checklists and forms to help those in settings where resources are highly restricted to integrate the various elements of service provision into a comprehensive and quality whole. *Accessible at:*
http://www.rho.org/files/EngenderHealth_COPE_toolbook_2004.pdf

ACCP. 10 key findings and recommendations for effective cervical cancer screening and treatment programs (2007 Apr)
ACCP partners met in early 2007 to assess the results of key studies in four countries from across regions: India, South Africa, Peru, and Thailand. These ten key findings and recommendations are the result of this fresh data and are intended to shape policy and practice related to cervical cancer screening and treatment in low-resource settings. *Accessible at:*
http://www.guttmacher.org/archive/IFPP.jsp

World Health Organization. WER 2009 index. WHO Position Paper on HPV *Vaccines* 10 Apr 2009;84(15):117-32.
This paper on HPV vaccines, provided in both English and French, is part of a series that predominantly focused on large-scale immunization programmes. It has been reviewed by WHO and outside experts and has been endorsed by WHO's Strategic Advisory Group of Experts on vaccines and immunization. It is mainly intended for use by national public health officials and immunization programme managers, but may also be relevant to international funding agencies, vaccine manufacturers and the medical community at large. *Accessible at*:
http://www.rho.org/files/WHO_WER_HPV_vaccine_position_paper_2009.pdf

World Health Organization (WHO), PATH, United Nations Population Fund (UNFPA). Cervical cancer, human papillomavirus (HPV), and HPV vaccines: Key points for policy-makers and health professionals. WHO publications 2007.
This booklet summarizes and updates previous WHO and WHO/UNFPA publications (WHO's, "Human papillomavirus and HPV vaccine: Technical information for policy-makers and health professionals" and the WHO/UNFPA guidance note, "Preparing for the introduction of HPV vaccine: Policy and programme guidance for countries"). This document provides information on HPV, the link between HPV and cervical cancer, as well as safety, efficacy and delivery strategies for the HPV vaccine (including cost-effectiveness, financing and communications strategies). *Accessible at*: http://www.rho.org/files/WHO_PATH_UNFPA_cxca_key_points.pdf

Prevention of cervical cancer: Progress and challenges on HPV vaccination and screening. Bosch FX, Wright TC, Ferrer E, Munoz N, Franco EL, R Herrero R, Bruni L, Garland SM, Cuzick J, Louie KS, Stanley M, eds. *Vaccine* 19 Aug 2008;26(Supplement 10):K1-94.

An extensive compilation covering HPV epidemiology, screening technologies, and vaccines (developed and developing country introduction). *Accessible at:* http://www.sciencedirect.com/science?_ob=PublicationURL&_tockey=%23TOC%235188%232008%23999739999.8989%23697474%23FLA%23&_cdi=5188&_pubType=J&_auth=y&_version=1&_urlVersion=0&_userid=10&md5=3cc9a1872973aadf4dff06fdb14c5b29

RHO Cervical Cancer. Shaping strategies to introduce HPV vaccines: formative research results from India, Peru, Uganda, and Vietnam (2009) These overviews present results from PATH's formative research on HPV and the HPV vaccine in India, Peru, Uganda, and Vietnam. The research examines health systems and the policy context that will affect vaccine introduction, as well as beliefs, values, attitudes, knowledge, and behaviors related to HPV, cervical cancer, and vaccination. Includes vaccine delivery, communications and advocacy strategies. *Accessible at*: http://www.rho.org/formative-res-reports.htm

EngenderHealth, PATH. **Palliative care for women with cervical cancer: A field manual** (2003)
A manual designed to be used as a resource for health care providers such as community nurses and medical doctors who care for women who are dying of advanced cervical cancer in most low-resource settings. Includes chapters on symptoms management, pain relief, nutrition, social and spiritual issues. A Kenyan field manual is available from PATH, designed for visiting nurses or health facility-based nurses and physicians. *Accessible at*:
http://www.path.org/files/RH_palliative_care_guide.pdf

Planning and Implementing Cervical Cancer Prevention and Control Programs: A Manual for Managers (2004) PATH and ACCP This publication provides thorough background information on cervical cancer and extensive detail on screening.
http://www.rho.org/files/ACCP_mfm.pdf

* Courtesy of PATH