Alternatives for Cervical Cancer Screening and Treatment in Low-Resource Settings

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<th>Definition</th>
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<tr>
<td>AGUS</td>
<td>Atypical glandular cells of undetermined significance</td>
</tr>
<tr>
<td>AMREF</td>
<td>African Medical and Research Foundation</td>
</tr>
<tr>
<td>ASCUS</td>
<td>Atypical squamous cells of undetermined significance</td>
</tr>
<tr>
<td>AVI</td>
<td>Aided visual inspection</td>
</tr>
<tr>
<td>BHS</td>
<td>Barangay Health Station, Philippines</td>
</tr>
<tr>
<td>CER</td>
<td>Cost-effectiveness ratio</td>
</tr>
<tr>
<td>CIN</td>
<td>Cervical intraepithelial neoplasia</td>
</tr>
<tr>
<td>CIS</td>
<td>Carcinoma in situ</td>
</tr>
<tr>
<td>CICM</td>
<td>Comprehensive Integrated Cancer Management, Indonesia</td>
</tr>
<tr>
<td>CRHCS</td>
<td>Commonwealth Regional Health Community Secretariat</td>
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<tr>
<td>DALY</td>
<td>Disability-adjusted life year</td>
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<tr>
<td>DOH</td>
<td>Department of Health, Philippines</td>
</tr>
<tr>
<td>DVI</td>
<td>Direct visual inspection</td>
</tr>
<tr>
<td>ECSA</td>
<td>East, Central and Southern Africa</td>
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<tr>
<td>FSU</td>
<td>Former Soviet Union</td>
</tr>
<tr>
<td>HGSIL</td>
<td>High-grade squamous intraepithelial lesion</td>
</tr>
<tr>
<td>HIV</td>
<td>Human immunodeficiency virus</td>
</tr>
<tr>
<td>HPV</td>
<td>Human papillomavirus</td>
</tr>
<tr>
<td>IARC</td>
<td>International Agency for Research on Cancer</td>
</tr>
<tr>
<td>IEC</td>
<td>Information, education and communication</td>
</tr>
<tr>
<td>LEEP</td>
<td>Loop electrosurgical excision procedure</td>
</tr>
<tr>
<td>LGSIL</td>
<td>Low-grade squamous intraepithelial lesion</td>
</tr>
<tr>
<td>LMV</td>
<td>Low-magnification visualization</td>
</tr>
<tr>
<td>LY</td>
<td>Life year</td>
</tr>
<tr>
<td>MCH</td>
<td>Maternal and child health</td>
</tr>
<tr>
<td>MOH</td>
<td>Ministry of Health</td>
</tr>
<tr>
<td>NPV</td>
<td>Negative predictive value</td>
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<tr>
<td>PAISM</td>
<td>Program of Integrated Services for Women, MOH, Brazil</td>
</tr>
</tbody>
</table>
Alternatives for Cervical Cancer Screening and Treatment in Low-Resource Settings

Pap smear  Papanicolaou smear  
PATH  Program for Appropriate Technology in Health  
PCR  Polymerase chain reaction  
PGH  Philippines General Hospital  
PHN  Population, Health and Nutrition  
PID  Pelvic inflammatory disease  
PPV  Positive predictive value  
PROAIS  Program for Integral Health Assistance, Brazil  
RHU  Rural Health Unit, Philippines  
ROC  Receiver operating characteristic  
RTI  Reproductive tract infection  
SIL  Squamous intraepithelial lesion  
SROC  Summary receiver operating characteristic  
STD  Sexually transmitted disease  
US  United States  
VIA  Visual inspection with acetic acid  
WHO  World Health Organization  
YKB  Yayasan Kusuma Buana, Indonesia  
YKI  Indonesian Cancer Foundation  

Abbreviations and Acronyms

**Acetic acid**
A dilute (3–5%) vinegar solution that is applied to cervical tissue to make identification of abnormal tissue easier. The acetic acid interacts with diseased cells, causing epithelial lesions to turn white.

**Aided visual inspection (AVI)**
Visualization of the acetic-acid-washed cervix using a portable, low-power (approximately 4X) magnification device to facilitate cervical cancer screening and, possibly, to guide biopsy and outpatient treatment of pre-invasive lesions.

**Bethesda classification system**
System, proposed in 1988 by the US National Cancer Institute, that relies on only two grades for reporting cervical cancer precursor conditions: low-grade squamous intraepithelial lesion (LGSIL), which includes cellular atypia and CIN I, and high-grade squamous intraepithelial lesion (HGSIL), which includes CIN II, III and CIS.

**Carcinoma in situ (CIS)**
Cellular changes in the stratified squamous epithelium associated with invasive cancer but not extending to adjacent structures. CIS is generally a recognizable precursor of invasive squamous cell cancer.

**Cervical intraepithelial neoplasia (CIN) classification system**
Introduced in the 1960s, the CIN classification system for reporting cytological (Pap smear) results grades the severity of cervical lesions so that mild cervical dysplasia is categorized as CIN I; moderate cervical dysplasia as CIN II; and severe cervical dysplasia as CIN III.

**Cervicography™**
Technique in which a photograph of the cervix is obtained after application of dilute (3–5%) acetic acid using a specifically designed handheld camera (cerviscope™).

**Cervicoscopy**
Naked-eye visualization of the cervix after application of dilute (3–5%) acetic acid (equivalent in this report to VIA).

**“Cold” coagulation**
The use of a thermal probe heated to 100°C to destroy abnormal cervical tissue. It is “cold” only in comparison to traditional cervical hot cautery, which uses a red-hot metal source.
<table>
<thead>
<tr>
<th>Term</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colposcopy</td>
<td>Examination of the vagina and cervix using an endoscopic instrument (colposcope) that provides magnification to allow direct observation and study of vaginal and cervical cells <em>in vivo</em>.</td>
</tr>
<tr>
<td>Cone biopsy</td>
<td>A surgical procedure in which a cone-shaped wedge of cervical tissue is obtained for histopathologic analysis. Such a specimen preserves the tissue’s histological characteristics for review by a pathologist.</td>
</tr>
<tr>
<td>Cryotherapy</td>
<td>A method of outpatient treatment that uses low temperatures (-60° to -90°C) to freeze and destroy abnormal tissue. Most commonly, commercial-grade liquid CO₂ or nitrous oxide is used as the coolant.</td>
</tr>
<tr>
<td>Cytology</td>
<td>The study of the anatomy, physiology and chemistry of the cell, such as those associated with the endo- and ectocervix.</td>
</tr>
<tr>
<td>Dysplasia of the uterine cervix</td>
<td>Epithelial abnormality involving the cervical epithelium. One of several interchangeable terms used to describe this disease process. Other terms include cervical intraepithelial neoplasia (CIN) or squamous intraepithelial lesion (SIL).</td>
</tr>
<tr>
<td>Electrocautery (electrocoagulation)</td>
<td>The process of using an electrically heated (“live”) metal probe reaching very high temperatures to destroy abnormal tissue.</td>
</tr>
<tr>
<td>Gynoscope</td>
<td>A low-power (2.5X) magnification device that may be useful in visual inspection of the cervix (in conjunction with acetic acid) to facilitate cervical cancer screening and, perhaps, to guide biopsy and treatment of invasive disease.</td>
</tr>
<tr>
<td>Laser vaporization</td>
<td>Laser vaporization uses a laser (most commonly a CO₂ device) to vaporize the area of abnormal cells, that is, the lesions(s), and then allows the cervix to heal. Vaporization of the lesion does not allow for any pathologic examination of the specimen; it is vaporized. The laser can also be used to excise a cone-like specimen which can be sent for examination by the pathologist—but this is less commonly performed. Since the advent of LEEP, the laser is much less commonly used for treatment of CIN.</td>
</tr>
<tr>
<td>Loop electrosurgical excision procedure</td>
<td>A method of outpatient excisional biopsy and treatment that is used to remove the entire transformation zone using a thin wire electrode charged with a low-voltage, high-frequency alternating current (600kHz), producing a tissue specimen suitable for histologic analysis in most circumstances.</td>
</tr>
</tbody>
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### Terminology

<table>
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<tr>
<th>Term</th>
<th>Definition</th>
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<tbody>
<tr>
<td><strong>Lugol's stain application</strong></td>
<td>A technique for visualizing the cervix in which the cervix is washed with an iodine-based solution (Lugol's stain). The iodine is absorbed by normal cells, turning them dark brown or black, but abnormal cells do not absorb the stain and are left with a yellow or “unstained” appearance.</td>
</tr>
<tr>
<td><strong>Schiller test</strong></td>
<td>Application of dilute aqueous iodine solution to the cervix to aid in differentiating “mature” normal from “immature” abnormal epithelium.</td>
</tr>
<tr>
<td><strong>Speculoscopy</strong></td>
<td>Aided visual inspection of the acetic-acid-washed cervix using a low-power (5-6X) magnifying device (speculoscope) with illumination provided by a chemiluminescent capsule (Speculite®) which is attached to the upper blade of the speculum.</td>
</tr>
<tr>
<td><strong>Squamocolumnar junction</strong></td>
<td>The point at which columnar cells meet ectocervical squamous cells on the cervix. This junction is located in the center of the transformation zone and is most vulnerable to abnormal changes in cervical cells.</td>
</tr>
<tr>
<td><strong>Transformation zone</strong></td>
<td>Located on the surface of the cervix, the transformation zone is composed of glandular (columnar) epithelium until the onset of puberty, when the glandular epithelium is gradually replaced by squamous epithelium, similar to the lining of the vagina. Cervical cancer generally originates at the edges of the transformation zone.</td>
</tr>
<tr>
<td><strong>Unaided visual inspection</strong></td>
<td>Unaided, unmagnified visual inspection of the cervix without an acetic-acid wash to screen for cervical abnormalities.</td>
</tr>
<tr>
<td><strong>Visual inspection with acetic acid (VIA)</strong></td>
<td>Naked-eye visualization (without magnification) of the acetic-acid-washed cervix (using diluted 3-5% acetic acid) to screen for cervical abnormalities.</td>
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</table>
Introduction

Given the scope of the cervical cancer problem in developing countries, coupled with the difficulties that have been encountered in many of these countries when attempting to implement cytology-based screening programs, this workshop focused on alternative, low-resource screening options—some of which have been available for decades. Major workshop themes included the importance of assessing the cost-effectiveness of currently used cervical cancer screening and treatment methods and finding ways to overcome barriers to implementing successful screening programs in developing countries. Workshop participants were given an opportunity to examine cytology-based screening—the current screening standard worldwide—and consider its clinical effectiveness and programmatic limitations. They also were provided a historical review of research on visual inspection for cervical cancer screening—including updates on recently completed and ongoing studies. This review enhanced the participants' ability to consider the potential role of visual inspection as an alternative to cytology for cervical cancer screening in low-resource settings.

Following a consideration of cervical cancer screening alternatives, cervical cancer treatment options were discussed. This involved a review of the efficacy of loop electrosurgical excision procedure (LEEP) and cryotherapy as well as the feasibility of using these treatment options in low-resource settings.

Several additional themes were also considered that are particularly relevant in many developing countries where resources are scarce. For example, the problem of loss-to-followup (i.e., women not returning for followup diagnostic tests and treatment) is a major barrier to the success of screening and treatment programs in many developing country settings. The “see and treat” approach—in which treatment, if needed, is offered immediately after screening during a single visit—was introduced as a possible solution to this problem. Participants examined this option as it relates to the issue of overtreatment and how this affects healthcare systems and individuals within those systems.

Scope of the Problem

Cervical cancer is the most common cancer and the leading cause of cancer death among women in developing countries. It is estimated that 200,000 to 300,000 women die from cervical cancer every year, mostly in poorer countries (Franco and Monsonego 1997; Parkin, Pisani and Ferlay 1993). Even more sobering are findings from recent studies
which suggest that HIV-positive women are at increased risk for cervical cancer (Judson 1992), and HIV rates are known to be on the increase in many of the same countries in which cervical cancer is a leading cause of cancer deaths. Thus, it is very likely that deaths due to cervical cancer will increase in these countries in the coming years. Death resulting from cervical cancer is particularly tragic because this type of cancer develops slowly and has a detectable precursor condition, carcinoma in situ (CIS), which is treatable.

Primary [and Secondary] Prevention of Cervical Cancer in ECSA

"Cervical cancer is the most common malignancy among women in East, Central and Southern Africa (ECSA). Yet it is a preventable and treatable disease whose primary prevention could be achieved through prevention and treatment of sexually transmitted diseases, and institution of low-cost screening programs (such as visual inspection of the cervix) to detect treatable precancerous conditions of the cervix.

The Commonwealth Regional Health Community Secretariat (CRHCS)-ECSA views cervical cancer as an important public health problem whose prevention should be integrated in all existing primary healthcare and women's health programs in the region."

—Winnie Mpanju-Shumbusho, MD, MPH, MMED; CRHCS, Arusha, Tanzania

Screening

Cost-Effectiveness of Cervical Cancer Screening

A study funded by the World Bank supports the claim that cervical cancer screening is not only of value in terms of lives saved but also that it is a cost-effective public health intervention (Jamison et al 1993). In that study, the cost per disability-adjusted life year (DALY) gained for cervical cancer screening (assuming screening for all women every 5 years) is about $100.2 This compares favorably to other preventive health interventions (e.g., $30 to $250 per DALY for antenatal/delivery care, $15 to $75 for increased condom use, $30 to $150 for IUD services) and is a fraction of the estimated cost ($2,600) for treatment/palliative care for cervical cancer (PATH 1997). It is reasonable to assume that in many settings the cost-effectiveness of cervical cancer screening could be increased even further if there were greater coverage of high-risk women, screened at intervals greater than 5 years, and if less expensive outpatient therapeutic approaches were used to treat cervical lesions.
In 1989, the pathologist Leo Koss observed that “there has been no objective statistical analysis of the optimal performance of [the cervical smear]” (Koss 1989). In fact, the Papanicolaou (“Pap”) smear is one of a unique group of tests that have been widely adopted into standard (western) clinical practice without first being subjected to rigorous, prospective blinded studies to examine their effectiveness (Franco and Monsonego 1997). Regardless, over time, the Pap test has proven to be a clinically useful tool, and both clinicians and researchers alike claim it has played an important role in cancer reduction.

In developed countries, cytology-based services utilizing the Pap smear have been the basis of cervical cancer screening and detection programs for many years. While some data suggest that cervical cancer rates began to decrease before large-scale Pap smear screening programs were introduced (perhaps in association with the reduction in parity which has occurred since World War II), it is generally accepted that the initiation of such national screening programs is largely responsible for, or at least has contributed in a significant manner to, the marked decline in cervical cancer deaths in those countries in the ensuing years. Decreases in the incidence rates of cervical cancer have occurred in Finland, Iceland and Sweden, where national population-based programs have been in operation at least since the early 1970s. In Finland, a 65% reduction in the incidence rates of cervical cancer was observed between 1966–1970 and 1981–1985. By contrast, in Norway, where only 5% of the population was covered by a cervical cancer screening program, the reduction in cervical cancer incidence was only 20% during this same 15-year period. These findings indicate a strong correlation between the extent (coverage) of a screening program and the reduced incidence of invasive cervical cancer (Franco and Monsonego 1997).

In most developing countries, only 5% of women at any point in time have been screened within the past 5 years (WHO 1986). If the burden of disease is high and screening is known to be a cost-effective intervention, why isn’t screening more prevalent in most developing countries? One reason relates to the nature of the Pap smear, the most common form of screening performed worldwide. Cytology-based screening programs are complex and can be costly. Although performing a Pap test may seem relatively simple, from both a clinical and programmatic perspective, a large number of steps are required to take an adequate smear, process and analyze the specimen, and inform patients of the results. If any of these steps are unreliable or logistically burdensome, the entire screening program could break down and, with it, the potential for any public health benefit.
Unfortunately, many, if not all, of these steps can be problematic in many developing countries. For example, whatever cytology screening services that do exist in such resource-limited settings are usually offered only in urban settings by a small private sector or at referral facilities. And, even in these settings, trained cytotechnicians and cytopathologists are scarce and turnaround times for processing and reading specimens are slow. Thus, patients do not receive their results promptly and followup losses (including patients lost to treatment) are high. Given this reality, if screening (and subsequent treatment) is to have a measurable effect on the burden of disease borne by women and the healthcare system, it is apparent that cervical cancer screening based on an approach other than just Pap smears is needed.

**History of Research on Visual Inspection**

Historically, before the advent of Pap smears and programmatic screening, healthcare providers relied on looking at the cervix to detect abnormalities. For example, the Schiller test (i.e., application of dilute aqueous iodine solution to the cervix to aid in differentiating “mature” normal from “immature” abnormal epithelium) has been used for many years.

After the 1950s, when the Pap smear became the standard for cervical cancer screening, increasing numbers of women undergoing this test led to increased utilization of the colposcope (initially developed in the 1930s) to confirm screening findings. Years later, given the expense and inconvenience of colposcopy services, clinicians began to explore whether unmagnified visualization of the cervix (with acetic acid) could be used as an adjunct to cytology so that patients in need of colposcopy could be identified more effectively and efficiently. Few studies were conducted, however, that examined the value of unmagnified inspection of the cervix after the application of acetic acid for purposes of identifying a normal “transformation zone” or detecting precancerous lesions of the cervix (i.e., primary screening).

Then, in 1982, Ottaviano and La Torre published an important study involving 2,400 women who were examined visually and colposcopically after a cervical wash with acetic acid. A key result was that “naked-eye” (unmagnified) inspection detected abnormalities in 98.4% of the cases (i.e., in 307 of 312 patients assessed colposcopically as having an abnormal transformation zone). In addition, (unmagnified) visual inspection with acetic acid (VIA) identified 98.9% of the cases as normal (i.e., in 1,568 of 1,584 women diagnosed as normal by colposcopy). These authors concluded that “colposcopic magnification is not essential in clinical practice for the identification of the cervix ‘at risk’” (Ottaviano and La Torre 1982).
Subsequently, in 1990, Abrams published his experience with the “Gynoscope,” a monocular telescope with a magnifying power of 2.5, which he developed as an adjunct to cytological screening (Abrams 1990). In that study, Abrams reported a high correlation between the (visual) Gynoscope examination and cytology (supplemented by biopsy results in a few cases). His findings suggested that the use of a low-power device could provide excellent results as an adjunct to cytology and “should be considered as a practical adjunct that will encourage better sampling by the clinician . . . [and] alert the pathologist to the presence of a suspicious lesion.”

Two more recent studies also demonstrated that visual inspection of the cervix can be helpful in reducing referrals for colposcopy without compromising quality of care (Frisch, Milner and Ferris 1994; Slawson, Bennett and Herman 1992). For example, Slawson et al found that among women who eventually had an abnormal biopsy, VIA detected disease in approximately 64% of such cases, a very similar rate to what they found for the Pap smear (68%). In addition, as the investigator became more experienced, positive predictive value improved by almost 30%. Thus they concluded that “[VIA] is a safe, simple and effective adjunct to the Papanicolaou smear for cervical cancer screening.” Likewise, Frisch et al discovered that using VIA as an adjunct to cytology improved both the number of dysplastic lesions found as well as the negative predictive value of cytology (that is, if the Pap smear and the visual inspection both were normal, colposcopy and biopsy were also more likely to be normal than if just a Pap smear was performed).

Visual Inspection as an Alternative to Cytology in Low-Resource Settings

“The issue is not to what should we compare visual inspection. We have nothing now that is accessible to the majority of women in our region and visual inspection would at least give us something.”

— Robert J. Leke, Professor, University of Yaoundé, Faculty of Medicine and Biomedical Sciences, Cameroon

Even though all the studies described above contributed to demonstrating the potential value of visual inspection of the cervix as a screening approach, evidence from more rigorous scientific studies was needed before clinicians would accept visual inspection as an alternative to cytology as a primary screening approach—even in settings where Pap smear-based services are not possible (Franco and Monsonego 1997).
To this end, the World Health Organization (WHO) supported a study in India between 1988 and 1991 in which unmagnified visual inspection with acetic acid washing was evaluated as a “downstaging” technique. The results of this study showed VIA to be effective in identifying women with cancer at an earlier, more treatable stage (Singh, Sehgal and Luthra 1992). In 1994 another study was conducted in South Africa involving visual screening and Pap smears, performed in a mobile unit equipped to process smears on site. A gynecologist performed colposcopy to confirm disease in the mobile unit either immediately or within a couple of days after screening. The positive predictive value for VIA was found in this investigation to be similar to that of the Pap smear and the authors thus concluded that “naked-eye visualization of the cervix after application of diluted acetic acid . . . warrants consideration as an alternative to cytologic screening” (Megevand et al 1996). Finally, in a recent 1997 publication, Franco and Monsonego described their experiences with women who had reported to an early cancer detection center in India for opportunistic cervical cytology and agreed to participate in a study to evaluate unaided visual inspection, cervicoscopy and cytology (Franco and Monsonego 1997). Preliminary results of this study indicated that, compared to cytology, VIA was more sensitive in detecting lesions although the difference was not statistically significant. In this study, however, the specificity of cytology was statistically significantly higher than that of VIA.

Finally, the findings or preliminary results of four recent or ongoing studies on visual inspection in Indonesia, Kenya, Zimbabwe and South Africa provide supportive additional information. These studies seek to answer the basic research question: “What are the test qualities of visual inspection as a primary screening modality?” Most of these studies also address the more specific question of whether visual inspection is “acceptably” effective in distinguishing diseased from nondiseased persons in a particular healthcare setting by comparing the test qualities of visual inspection with other screening tests (e.g., Pap smears) performed under the same conditions. While it is too early to draw conclusions from ongoing studies, preliminary or final results from the comparative studies suggest that visual inspection with acetic acid performs comparably to the Pap smear and/or other screening tests being investigated in those settings. Once the two ongoing studies are completed, these results should provide the additional evidence needed to support clinicians in their decisions regarding the use of visual inspection as a primary screening approach.
Preface

For cervical cancer screening programs to be effective and ethical, appropriate treatment must be both available and affordable to those who test positive for disease. The treatment options generally suggested for precancerous lesions are cryotherapy and LEEP. A situation analysis report describing the comparative advantages and disadvantages of treatment options noted that the effectiveness of both methods (as revealed in numerous research studies) is acceptably high (Bishop, Sherris and Tsu 1995).

The results of a survey of therapies currently used in developing countries to manage cervical intraepithelial neoplasia (CIN) are also reported in the situation analysis document. The survey revealed that hysterectomy and cone biopsy—both of which involve hospital stays and are associated with significant procedure-related costs and risks—are commonly used methods, despite available scientific evidence that supports both LEEP and cryotherapy as effective outpatient treatment modalities. The use of methods that are more costly and potentially more risky to the patient (e.g., hysterectomy) is due in part to a tendency towards medicalization of healthcare and also to the fact that in some countries screening is not routinely offered at levels of the health system where outpatient treatment such as LEEP and cryotherapy could be made available.

The see and treat approach is based on the principle that screening and treatment can take place during the same visit and, further, that screening and immediate treatment can take place at the lowest possible level of the health system (where the majority of at-risk women will go at least once in their lives). Given that the healthcare provider most often posted to such levels is a nurse or nurse-midwife, the see and treat approach assumes that both screening and treatment can be performed competently by these or similar cadres of health personnel. The see and treat approach offers a potential solution to the problem of loss-to-followup that occurs as a consequence of the need to wait for cytology-based screening results (Pap smear processing and return of results) as well as the need, which often occurs, to go to a different facility for treatment.

Results reported to date pertaining to the specificity of visual inspection from test quality studies suggest that providers might offer treatment to a number of women when, in fact, no disease is clinically detectable. In turn, a significant number of these women might decide to be treated. This “overtreatment” translates into unnecessary costs to the healthcare
Alternatives for Cervical Cancer Screening and Treatment in Low-Resource Settings

system as well as unnecessary discomfort and potential side effects experienced by the women. In a resource-limited environment, however, patients are unlikely ever to receive a diagnosis confirming their "true" disease state. In such settings, treatment for suspicious precancerous lesions might in some cases be "treatment" for subclinical disease likely to exist in women determined to be at high risk for disease. Speculation about some level of preventive effect is based on what is known about the natural history of cervical cancer. Treatment with cryotherapy potentially may reduce the probability of developing cancer or precancerous lesions in women at risk of the disease for at least 5 to 10 years (Lonky et al 1997). If a decision to treat suspicious lesions is made, cryotherapy, cold coagulation or electrocautery are the least expensive and least traumatic procedures. Also, because these methods are noninvasive, unlike LEEP which involves actual removal of tissue, they can be provided at the lowest possible level of the health system by nonphysicians.

Concluding Remarks

Since 1994, JHPIEGO has joined the increasing number of international organizations involved in exploring alternative solutions to detecting and treating cervical cancer in the developing world. This workshop provided an opportunity to share information and lessons learned among a subgroup of these organizations focusing particularly on the potential for visual inspection as a primary screening option linked to appropriate treatment. We hope this workshop report will be a useful resource for healthcare decision-makers and providers as they work to reduce the problem of cervical cancer in low-resource settings throughout the world.

Lynne Gaffikin
Paul D. Blumenthal

December 1997

NOTES

1 "DALYs are a measure of life years gained that combine the number of years of healthy life lost due to both premature morbidity and mortality, using a set of age- and disability-estimated weights" (PATH 1997).

2 In general, the World Bank suggests that any intervention whose cost is less than $100 per DALY gained is worth investing in as a substantially cost-effective public health program (World Bank 1993).

3 The results of this preliminary study—involving 309 sexually active patients using cytology and occasional histology as a gold standard—revealed a sensitivity of 87% and a specificity of 84%. A false negative rate of 12.6% represents a decided improvement over the 15–40% false negative rate that has persisted with cytology alone during the past 10 years. The false positive rate was 16% (Abrams 1990).
4 "Downstaging" is the systematic attempt to find cancer cases at ever lower levels of severity. Using such an approach, over time, the proportion of patients whose disease is discovered when it is still curable should increase and the proportion of incurable cases should, in turn, decrease.

EXECUTIVE SUMMARY

Introduction

Each year since 1994, in conjunction with its annual Board of Trustees meeting, JHPIEGO has convened a workshop that deals with a reproductive health topic in which training plays an important role. This year’s workshop dealt with cancer of the cervix, the same reproductive health topic that JHPIEGO’s first Board of Trustees workshop focused on in 1994 (Blumenthal et al 1994). Whereas the 1994 workshop reviewed the status of cervical cancer screening worldwide and discussed alternative methods of detecting cervical cancer, this year’s presentations discussed screening and treatment options, specifically focusing on alternatives for low-resource settings. Workshop participants included JHPIEGO’s international board members plus a select group of health professionals involved in cervical cancer programs worldwide. (See Appendix A for a complete listing of workshop participants.)

The issue of whether cancer of the cervix is a public health problem meriting attention by national health programs as well as donor and development assistance organizations was not discussed at length in this workshop. Rather, the workshop was dedicated to identifying approaches that could be used to address cervical cancer in settings where this disease has been identified as a public health priority. To accomplish this, participants were first updated on the scientific evidence available that supports various cervical cancer screening and treatment options. These updates were followed by reports on and discussions of country experiences with cervical cancer screening and treatment programs and field perspectives on these types of programs in a number of developing countries.

Workshop Objectives

- Reach consensus on the appropriateness of visual inspection as an alternative cervical cancer screening technique
- Review the usefulness of a see and treat approach for managing pre-invasive cervical disease
- Identify issues related to the introduction of alternative screening and treatment approaches for pre-invasive cervical disease in low-resource settings
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- Identify approaches for integrating competency-based training on the management of pre-invasive cervical disease into reproductive health training

Organization of the Workshop

Jeff Spieler, Chief of the Research Division/Office of Population of the United States Agency for International Development (USAID), opened the workshop with a keynote address: “Objectives, Approaches, Program Priorities and Challenges in Reproductive Health: What About Including the Prevention of Cervical Cancer?” After a discussion of workshop assumptions, concerns and issues, presenters updated the participants on clinical research findings as well as programming issues concerning cervical cancer screening and treatment, and introduced case studies. Specifically, participants reviewed various cervical cancer screening options including the current standard, cytology (i.e., the Pap smear), as well as visual inspection of the cervix—both magnified and unmagnified. Recent or preliminary results from studies—conducted in Indonesia, Kenya, Zimbabwe and South Africa—that included a visual inspection component were shared with workshop participants. Participants then examined potential treatment options including a see and treat protocol. Participants also discussed programming issues including cost, logistics and training. In addition, the seven international Board of Trustees members presented updates on the status of cervical cancer screening programs in their countries, focusing on the potential for an alternative screening approach such as visual inspection. Toward the end of the workshop, small working group sessions were held to formulate strategies for integrating viable screening and treatment combinations into existing health programs in the most efficient way possible. (The complete workshop agenda is included as Appendix B.)

Conclusions and Recommendations

The following recommendations were derived from the various plenary discussions held during the 2-day workshop.

1. If morbidity and mortality due to cancer of the cervix are to be measurably reduced, cervical cancer screening and treatment programs must be implemented for at-risk women on a national or large-scale basis.

2. The test qualities of visual inspection have proven to be reasonably consistent across the various investigative studies to date, including
those for which only preliminary data are currently available. Once ongoing studies are completed, efforts should shift to investigating how visual inspection performs in the field under more routine health delivery (versus field research) conditions, and how the benefits of such visual inspection-based screening programs could outweigh program limitations, including the potential for overtreatment.

3. In addition to documenting further the efficacy and safety of visual inspection under different field conditions, such applied research projects should answer important questions related to the practicality, feasibility and, most important, the acceptability of visual inspection-based screening programs among the target population.
Objectives, Approaches, Program Priorities and Challenges in Reproductive Health: What About Including the Prevention of Cervical Cancer?

*THIS IS AN UNOFFICIAL DOCUMENT*

Objectives of USAID’s Reproductive Health Program

USAID’s reproductive health program is designed to support the overall strategy of the Agency in Population, Health and Nutrition (PHN) and is founded on the following principles and objectives:

- promoting the rights of couples and individuals to determine freely and responsibly the number and spacing of their children;

- improving individual health, with special attention to the reproductive health needs of women and adolescents and the general health needs of infants and children;

- reducing population growth rates to levels consistent with sustainable development;

- making programs responsive and accountable to the end-user.

USAID advocates the following guiding principles as it works to stabilize global population and protect human health:

- No woman should become pregnant if she does not wish to bear a child.

- No family should suffer the death of a child.

- No person should be subject to the risk of disease as a result of responsible sexual activity.

- No woman should be subject to the risk of death or serious illness because of pregnancy.

- No woman should enter adulthood without basic educational skills.
The Approach

USAID's reproductive health program focuses selectively on those interventions that are actionable, are most cost-effective, and can achieve a public health impact. USAID supports interventions that are based on prevention, promote sustainability, and enhance access to and quality of care. In addition, support for these interventions must be in concert with available human and financial resources. USAID maintains that gender considerations, reproductive choice, prevention of adverse cultural practices such as female genital mutilation, and the special needs of adolescents deserve priority attention.

Operationalizing the Approach

The PHN Center approach, in collaboration with USAID missions, generally follows the sequence of:

- Need and/or problem identification
- Program/product development
- Field-testing and validation
- Diffusion and marketing
- Post-diffusion market testing and refinements
- Institutionalization

Establishing New Priorities at the Program Level

The following factors must be considered when determining programmatic direction and focus, including evaluating whether a new activity (e.g., prevention of cervical cancer by means of behavior change, screening and treatment) should be included within the reproductive health program priorities:

1. Establish reproductive health priorities based on:

   - need,
   - available data,
   - actionability,
   - consumer demand,
   - impact on family planning/reproductive health,
   - opportunity costs, and
   - potential for greatest impact.

2. Review the existing portfolio in light of:

   - the Agency priorities,
Alternatives for Cervical Cancer Screening and Treatment in Low-Resource Settings

- comparative advantage,
- available resources, and
- appropriate linkages to the PHN Center.

3. Identify ongoing projects (e.g., operations research, information, education and communication [IEC], policy, training, and service delivery) for expanded reproductive health efforts, focusing on the most promising opportunities for success and impact.

4. Determine technical feasibility and level of investments required.

5. Determine other donor support and potential to leverage resources.

6. Determine if the activity is mandated by Congress or is of special interest to the Congress and the Administration.

Once an activity has been approved:

7. Coordinate its implementation within the Center, with other Bureaus, Missions, Cooperating Agencies, State, etc.

8. Define indicators for reproductive health.

9. Establish a system for monitoring/measuring the activity’s impact.

10. Launch new initiatives.

Program Priorities in Reproductive Health

USAID’s reproductive health programming priorities include the following three components: family planning and related fertility services; safe pregnancy services, including improvement of women’s nutritional status and the promotion of breastfeeding; and the prevention of STDs/HIV/AIDS.¹ These priority programming components are described below.

Family Planning and Related Fertility Services

Family planning services should be available for both child spacing and limiting family size. Family planning program areas that will be addressed include:

- Making available a wide range of contraceptive methods, including the lactational amenorrhea method
- Providing adequate and high-quality supplies
Safe Pregnancy Services, Improvement of Women's Nutritional Status and the Promotion of Breastfeeding

To promote safe pregnancy, improve women's nutritional status and promote breastfeeding, USAID will support:

- Appropriate nutrition education, counseling and supplementation
- Basic prenatal care and early detection and prevention of obstetric complications, including referral
- Safe delivery practices and breastfeeding promotion
- Early detection and treatment of postpartum hemorrhage and infections in the mother
- Postpartum contraception

For the well-being of the newborn, USAID will promote early initiation of exclusive breastfeeding, warming, hygienic care and early detection and rapid treatment of serious infections and asphyxia.

Prevention of STDs/HIV/AIDS

To prevent STDs/HIV/AIDS, USAID will support a variety of primary prevention activities including:

- Policy dialog and general awareness-raising in countries where AIDS is a significant public health problem, or where socioeconomic, cultural and behavioral factors predispose the community to rapid HIV transmission
Alternatives for Cervical Cancer Screening and Treatment in Low-Resource Settings

- Development of strategies and IEC programs that promote behavior change to reduce the risk of STDs and HIV exposure and transmission

- Active promotion of appropriate condom use, and assurance of adequate condom supplies through public- and private-sector channels and evaluation of new technologies for prevention

- Data and information collection to assess the impact of interventions on high-risk behavior, when feasible, to quantify and track STD incidence and prevalence and the progression of the AIDS epidemic

- Identification of people practicing high-risk behaviors, including sexually active women and adolescents

- Establishment of services to detect and treat STDs

Challenges in USAID's Current Reproductive Health Program

Achieving the reproductive health goals set in the Cairo Program of Action for the next two decades will require an extraordinary effort from the world community. In the next decade alone, over 200 million women will enter their reproductive years in developing countries, excluding China. The current unmet need for family planning exceeds 120 million couples in less developed countries. Just to maintain contraceptive prevalence at current levels of modern method use over the next 10 years, family planning programs in developing countries will need to serve almost twice the number of couples currently being served. Over 18 million people in developing countries are infected with HIV and the number could reach 40 million by the year 2000. Close to 600,000 women die annually of avoidable pregnancy-related causes.

Building upon existing programs, USAID will address a number of priority concerns in the immediate years ahead, including:

- Determining the feasibility, costs and effectiveness of reproductive health interventions and packages of services. Without adding prevention of cervical cancer to the list of interventions, critical issues include determining how to:

  - Provide emergency obstetric care at a reasonable cost and enhance the demand and use of safe motherhood services
Alternatives for Cervical Cancer Screening and Treatment in Low-Resource Settings

- Provide integrated sexually transmitted disease/reproductive tract infection (STD/RTI) diagnosis and treatment
- Improve the quality of care and expand contraceptive options in family planning programs
- Provide for the special reproductive health needs of adolescents
- Gaining a better understanding of reproductive health behavior and decision-making, especially health-seeking behavior and appropriate client-focused interventions.
- Continuing to develop strategies for
  - Phasing in new reproductive health services
  - Optimal integration of services
  - Scaling up interventions to achieve measurable and sustainable impact on reducing reproductive morbidity and mortality

Given USAID’s limited resources and the significant amount of work that needs to be done in the current priority areas in reproductive health, it will be a major challenge to determine how to support new activities, like cervical cancer prevention (screening and treatment), without negatively impacting the overall program. As a result of this Workshop, we may be able to provide USAID and other donors with the information about cervical cancer prevention they need so that they can consider adding cervical cancer prevention to the reproductive health services they already support.

- Mobilizing resources for reproductive health and laying the foundations for program sustainability, both through engaging new resources in the public and private sectors of developing countries and through attention to new financing mechanisms, public/private-sector partnerships, and the potential for increased commitments from other bilateral and multilateral donors.

Screening and Treatment to Prevent Cervical Cancer

Cervical Cancer Cervical cancer is a sexually transmitted disease. If precancerous disease/dysplasia is treated early, the cure rates range from 80-95%, depending on the severity of the lesions and the treatment method used. World experts have formally classified human papillomavirus (HPV) types 16 and 18 as carcinogenic. High-risk HPV types 16, 18,
31 and 45 are believed to account for over 80% of all cervical cancer cases. HPV is probably responsible for about 95% of cervical cancer and in the remaining cases there is likely to be either an undefined/novel-type HPV cause or, perhaps, another pathway to the disease. Other cofactors also exist that may increase a woman’s risk of acquiring cervical cancer and which affect the course of progression from mild dysplasia to cancer. In men, HPV is associated with penile cancer, but cases are rare. The virus, transmitted sexually, may also cause oral, vulvar and esophageal cancers.

In April 1996, a National Institute of Health Panel of Experts declared in their Consensus Statement that “virtually all cervical cancer could be prevented by a combination of safe sex and regular screening (Pap smears).” They stated that “More widespread Pap smears, especially among the economically disadvantaged [women] such as minorities, older women, rural residents and the poor could wipe out the disease.” Since the introduction of the Pap test 50 years ago there has been a steep decline in cervical cancer in the US but “there are still 17,500 new cases a year, 6% of all cancers diagnosed and 5,000 American women die each year from cervical cancer.” The Panel added, however, that “half of all women diagnosed with cervical cancer have never had a Pap smear and another 10% have not been tested in the past 5 years.” If even in the United States, where excellent public health systems are in place for cervical cancer screening, we still have a problem reaching all women, then the problems will certainly be magnified many times over in developing countries, even if simpler methods are made available. Nevertheless, it is estimated that deaths due to cervical cancer have declined by approximately 75% in developed countries between the 1940s and 1980s.

Prevalence

In developing countries, cervical cancer is the third most prevalent cancer following stomach and lung cancer and, by far, the most common cancer in women, followed by breast, stomach, mouth/pharynx, colorectal and lung cancers. The highest rates of cervical cancer are found in Latin America, Sub-Saharan Africa and South and Southeast Asia. Age-specific incidence rates generally peak at about 100 per 100,000 women aged 45 to 59, with an overall incidence ranging from 5 to 35 per 100,000 women per year. Globally, it is estimated that about 500,000 new cases are diagnosed each year, predominantly among the economically disadvantaged, in both developing (80% of cases) and industrialized nations. It is estimated that about 200,000 to 300,000 women die of cervical cancer every year.
### Types of Screening

- Cytological (Pap smear)
- Automated reading of Pap smears
- Visual
  - Aided (magnified) visual inspection (AVI), e.g., Gynoscope
  - Unmagnified visual inspection with acetic acid (VIA)
  - Unmagnified visual inspection without acetic acid
- Colposcopy
- Cervicography
- Molecular (HPV/DNA)

### Frequency of Screening, Influenced by Available Resources

- Based on age
  - Incidence peaks at ages 40 to 50 with a minimum of 5 to 10 years lead time
  - Target group is women aged 30 to 50
- Based on risk factors
- Based on prior results of screening

**Note:** Selection of the target population also needs to be based on the number of times a woman will be screened. Cervical cancer progresses slowly and takes from 10 to 20 years to develop (and maybe in some cases 30 years) from the time of infection. The International Agency for Research on Cancer (IARC) estimates from developed countries indicate that screening women aged 35 to 64 once every 5 or 10 years would reduce the cumulative incidence of invasive cervical cancer by 84% and 64%, respectively. In the US, women with CIN I are advised to be screened within 3 to 6 months of initial testing and annually thereafter.

### Risk Factors

As already mentioned, infection with certain types of HPV, a STD, is the primary cause of cervical cancer. Commonly accepted risk factors for cervical cancer include:

- History of early onset of sexual activity
- More than one sexual partner/multiple partners
- Parity
- Smoking
Alternatives for Cervical Cancer Screening and Treatment in Low-Resource Settings

- A partner with more than one sexual partner/multiple partners
- Other risk factors?
  - Some hormonal contraceptives—oral contraceptives and DMPA
  - Male circumcision status
  - Other STDs
  - Immunological differences

<table>
<thead>
<tr>
<th>Treatment Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Cryotherapy</td>
</tr>
<tr>
<td>• LEEP</td>
</tr>
<tr>
<td>• Cold Coagulation</td>
</tr>
<tr>
<td>• Laser Vaporization</td>
</tr>
<tr>
<td>• Electrocautery</td>
</tr>
<tr>
<td>• Cone Biopsy</td>
</tr>
<tr>
<td>• Hysterectomy</td>
</tr>
<tr>
<td>• Radiation</td>
</tr>
</tbody>
</table>

Note: About 60% of LGSIL (cellular atypia, CIN I) regresses spontaneously within about 3 months, or does not progress and treatment is not required. Only about 15% progresses to high-grade lesions (HGSIL, CIN II/III) after about 48 months. About 30–70% of HGSIL (CIN II and III) will progress to cancer within 10 years and thus requires treatment.

- Increased HIV risk?
- Risk of pelvic inflammatory disease (PID)?
- Time and opportunity costs (overtreatment)?

- IEC to prevent/reduce the risk of acquiring HPV
  - Degree of protection provided by condoms needs elucidation—contact with the vulva, introitus and scrotum can lead to HPV transmission. The degree of protection provided by female barrier methods (e.g., diaphragm and cervical cap) and spermicides also needs to be determined.

- Screening and treatment of precancerous lesions

Factors that Shape Current Options for Screening and Treatment

- Existing access to healthcare facilities
- Availability of appropriate trained personnel
- Availability of laboratory testing
- Availability of treatment facilities
Ways of Enhancing the Cost-Effectiveness of Cervical Cancer Screening

- Screen frequently
- Target older women and high-risk populations
- Improve the sensitivity and specificity of tests
- Reduce the cost of screening tests
- Use the least expensive treatment strategies with appropriate referral
- Integrate services with other health-related programs

Challenges

The majority of women worldwide do not have access to screening for early-stage cervical changes/cancer. Only about 5% of women in developing countries are screened in a 5-year period compared to 40-50% of women in developed countries. In India, for example, 90,000 new cases of cervical cancer occur annually. According to the best estimates, only 25% of women above 35 years of age in India could be screened by the turn of the century even if the number of cytologists were increased twelvefold. Thus, an alternative strategy for the early detection of precancerous lesions or cervical cancer is clearly needed.

Key Considerations, Especially in Low-Resource Settings

- What types of cervical cancer screening are most appropriate?
- When to initiate screening?
- How often to screen?
- When to recommend treatment and/or followup?
- How to treat?
- Who to treat?
  - Treat only high-grade lesions?
  - Treat only very severe high-grade lesions?
  - Treat low-grade as well as high-grade lesions?

Research Needs

- Collect and analyze recent incidence and prevalence data.
- Further evaluate alternatives for low-cost screening in resource-poor settings.
- Determine the most appropriate treatment strategies for low-resource settings. How many false positives is a program willing to accept?

Note: Screening and treatment options will also be affected by both the prevalence of and current efforts to deal with HIV and other STDs.
Alternatives for Cervical Cancer Screening and Treatment in Low-Resource Settings

- What are the sequelae of treatment? Of overtreatment?

- Determine which other services for women (e.g., family planning, maternal and child health [MCH], postabortion care and/or STD services) are most compatible with cervical cancer prevention.

- Determine provider requirements (level of personnel and training).

- Determine how to target high-risk women for screening: How best to reach women aged 35 to 50? Which services in developing countries, especially services related to family planning and MCH, are most compatible with reaching women aged 35 to 50?

- Determine other factors that influence whether a lesion will progress to cervical cancer so we can increase our understanding of the natural history of the disease.

- Assess provider and client knowledge.

- Evaluate the protective effect of male and female barrier methods in preventing transmission of HPV.

- Develop HPV vaccines for prevention and treatment.

What Is USAID’s Potential Role?

- Can cervical cancer prevention be integrated into STD/RTI prevention, interval sterilization, IUD insertion/removal or other family planning services, or postabortion care services?

- What are the opportunity costs? How difficult is it to integrate training in cervical cancer screening into training in IUD insertion and removal?

- How cost-effective is cervical cancer screening and treatment? Will work in this area be synergistic with current USAID priority areas in reproductive health?

- Are we ready to move into operations research?

- Should USAID just await the results of the several ongoing comprehensive studies before deciding what course of action to take?
NOTES

1 The actual implementation of these program components will vary according to a country’s needs, its human resources, and whether or not an infrastructure capable of delivering services is already in place. In addition, implementation will vary depending upon the financial resources available from USAID, other donors and the host country. USAID’s reproductive health strategy is evolving and program priorities will be refined to reflect experience gained. Operations research will provide a means of testing and evaluating different reproductive health programs and service delivery strategies.

2 Currently, cervical cancer interventions are not covered under the PHN Center’s four strategic objectives.
Why Visual Inspection with Acetic Acid?

Introduction

Based on the criteria that define a good screening test, visual inspection with acetic acid (VIA) can be considered a viable option among various other cervical cancer screening approaches/tests. Although VIA’s effectiveness has been debated in the past, the latest (including some preliminary) research findings are consistent in supporting the conclusion that VIA is effective enough to warrant being included as a screening option in any resource setting. VIA also appears to meet established criteria for an acceptable screening test.

Prescriptive Screening: Principles

When considering the advisability of adopting a screening test for widespread use, it is critical to keep in mind the general principles for initiating any screening program (Mausner and Bahn 1974).

- Is the disease an important public health problem?
- Is there an accepted treatment for recognized disease?
- Are facilities for diagnosis/treatment available and accessible?
- Is there a recognizable latent or early symptomatic stage?
- Is the natural history of the disease understood?
- Is there a consensus on whom to treat?
- Is there an economic balance between case finding and subsequent medical care?
- Is the program sustainable?

Qualities of a Good Screening Test

With respect to the test itself, a good screening test has the following qualities. It is:

- Effective
- Safe
- Practical
- Affordable
- Available
Table 1 summarizes what is known about the basic test qualities of a variety of cervical cancer screening options.

### Table 1. Other Proposed Approaches to Cervical Cancer Prevention in Low-Resource Settings

<table>
<thead>
<tr>
<th></th>
<th>Effective</th>
<th>Safe</th>
<th>Practical</th>
<th>Affordable</th>
<th>Available</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aided Visual Inspection</td>
<td>?</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>(with acetic acid)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visual Inspection with</td>
<td>?</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Acetic Acid (no magnification)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Automated Pap Screening</td>
<td>Yes?</td>
<td>Yes</td>
<td>?</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>HPV Screening</td>
<td>?</td>
<td>Yes</td>
<td>?</td>
<td>?</td>
<td>Yes</td>
</tr>
<tr>
<td>Cervicography</td>
<td>Yes?</td>
<td>Yes</td>
<td>?</td>
<td>?</td>
<td>Yes</td>
</tr>
<tr>
<td>HPV Vaccine</td>
<td>?</td>
<td>?</td>
<td>Yes</td>
<td>?</td>
<td>No</td>
</tr>
</tbody>
</table>

? = no conclusive data available or issue currently under active review


### Why VIA as an Alternative?

In this workshop, we will explore how VIA holds up as a good screening test as well as the potential for incorporating screening by VIA into large-scale programs to detect cervical cancer and its precursors.

VIA is being considered here as an additional screening option because:

- The test is noninvasive, easy to perform and inexpensive.
- It can be performed by almost anyone, in almost any setting.
- Results are apparent immediately; therefore, initial treatment can be provided at the time of the examination.
- System requirements are all available locally.

### NOTE

1 Screening that is directed at “prescribing” action or treatment based on the screening results
Factors Affecting a Screening Test

Introduction

This workshop involved reviewing results or preliminary findings from research studies that have attempted to measure the usefulness and/or effectiveness of visual inspection as a cervical cancer screening option. To be able to assess the value of each study adequately, it was deemed useful to review criteria for a good screening test research study. Having just reviewed what characterizes a good screening test, at this point we went over which factors affect the quality of a screening study and why studies with similar objectives may yield differing results. In addition, methodologic terms that would be referred to throughout the workshop were introduced.

Although different qualities of a screening test can be investigated, two qualities that are commonly measured to allow for comparability among tests are sensitivity and specificity. These measures represent intrinsic qualities of the test, although the specific rate values obtained in a study reflect how the test performs under conditions similar to those characterizing the research investigation. Thus, to maximize the usefulness of study results, research conditions should reflect—as closely as possible—field conditions under which the test will ultimately be used.

Commonly Measured Test Qualities

- **Sensitivity**: Proportion of women testing positive among those who are diseased

- **Specificity**: Proportion of women testing negative among those who are nondiseased

- **Positive predictive value (PPV)**: Proportion of women having disease among those with a positive test result

- **Negative predictive value (NPV)**: Proportion of women having no disease among those with a negative test result (Last 1983)
Table 1 shows how study data are organized to measure the four test qualities described above.

Table 1.

<table>
<thead>
<tr>
<th>Test</th>
<th>Present (+)</th>
<th>Absent (-)</th>
</tr>
</thead>
<tbody>
<tr>
<td>+</td>
<td>a</td>
<td>b</td>
</tr>
<tr>
<td>-</td>
<td>c</td>
<td>d</td>
</tr>
<tr>
<td>a+c</td>
<td>a+b</td>
<td>c+d</td>
</tr>
<tr>
<td>b+d</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Sensitivity = $a/a+c$
Specificity = $d/b+d$
PPV = $a/a+b$
NPV = $d/c+d$

Other Methodological Terms Referred to in the Workshop

- **Accuracy**: degree to which a measurement or estimate represents the true value of the attribute being measured
- **Receiver operating characteristic (ROC)**: A graphic means for assessing the ability of a screening test to discriminate between diseased and nondiseased persons
- **Meta-analysis**: A quantitative approach whereby data from individual (different) research projects measuring the same thing are used collectively as data points in a statistical analysis of that same measure (Last 1983; Vogt 1983)

Factors to be Considered in Comparing Test Qualities

The internal and external validity of research studies is affected by various factors. Below, key factors which could affect the validity and accuracy of screening research findings are listed together with some explanatory points particular to cervical cancer screening studies. Although not exhaustive, this list provided a framework for workshop presenters to refer to when describing their screening research, as well as for other workshop participants to consider when interpreting study findings/conclusions (Fahey, Irwig and Macaskill 1995; Jaeschke, Guyatt, and Sackett 1994).
### Alternatives for Cervical Cancer Screening and Treatment in Low-Resource Settings

<table>
<thead>
<tr>
<th><strong>Threshold of Disease and Definition of Test Positive</strong></th>
<th><strong>Veriﬁcation or Workup Bias</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Terminology used to define disease:</td>
<td>• The results of the test being validated influence the decision to perform the reference or gold standard.</td>
</tr>
<tr>
<td>• Cervical intraepithelial neoplasia (CIN)</td>
<td>• Differing rates (i.e., sampling fractions) are experienced among subjects undergoing the reference test to verify the presence or absence of disease (i.e., test positive versus test negative cases, respectively).</td>
</tr>
<tr>
<td>• Moderate/severe dysplasia</td>
<td>• The proportion of test negatives who go on for each subsequent test (if not 100%) should be randomly selected. (Nonrandom selection can result in major bias and invalid test measures.)</td>
</tr>
<tr>
<td>• Low-grade squamous intraepithelial lesion/high-grade intraepithelial lesion (LGSIL/HGSIL)</td>
<td>• Significant bias of this sort usually results in overestimated sensitivity and underestimated specificity rates.</td>
</tr>
<tr>
<td>• Cutoff point for test positive</td>
<td>• The accuracy of a test may vary according to whether it is being used for screening or followup purposes.</td>
</tr>
<tr>
<td>• Point at which treatment is likely to be most cost-effective programmatically, or</td>
<td>• The best design for establishing the accuracy of a new test is cross-sectional (i.e., across a range of disease).</td>
</tr>
<tr>
<td>• Point which maximizes sensitivity or speciﬁcity</td>
<td>• A test is most valuable when it is studied under conditions which most closely resemble clinical practice (i.e., the clinical conditions under which the test is most likely to be applied).</td>
</tr>
</tbody>
</table>

### Spectrum of Disease

- The accuracy of a test may vary according to whether it is being used for screening or followup purposes.
- The best design for establishing the accuracy of a new test is cross-sectional (i.e., across a range of disease).
- A test is most valuable when it is studied under conditions which most closely resemble clinical practice (i.e., the clinical conditions under which the test is most likely to be applied).

### Independence of Test Assessments

- Interpreters of subsequent tests including the reference test should be unaware of the results of previous tests.
- Otherwise, you are, in effect, measuring the accuracy of joint test results—not a single test.
Reference or Gold Standard

- The reference standard for measuring "true" disease state should be as "gold" as possible. To avoid workup bias, as many study subjects as possible should receive the reference test without causing undue harm.

- The less accurate the reference standard, the less accurate the observed test qualities of the new screening approach under investigation.

Study Sample Size

- The study sample size affects the precision (i.e., width of confidence interval) of measured test quality estimates.

- The study sample size also affects the probability that a difference of the size specified in the study hypothesis could be detected (in a comparative versus single-test study).

NOTE

1 PPV/NPV are affected by the test sensitivity/specificity (respectively) and the prevalence of disease/nondisease in the research population.
Cytology-Based Screening: Technical and Programmatic Considerations

Introduction

The Pap smear (cytologic screening) has played an important role in cervical cancer screening programs over the past 40 years. In fact, in countries where widespread screening is available, cytology is the current cervical cancer screening standard. In many low-resource settings, however, cytology-based services are not practical, affordable or readily available. This reflects the fact that providing cytology-based services involves a number of steps (listed below), each of which is required for the program to screen patients successfully at a steady rate (i.e., rate-limiting steps). Under some conditions, due to the inherent difficulty of successfully carrying out each rate-limiting step, effectiveness rates of Pap smears are considerably lower than those quoted in the general medical literature—approaching those observed in studies to date on visual inspection. The difficulties involved in successfully providing cytology-based services in resource-limited environments—and the fact that cervical cancer screening tests are currently being provided at levels significantly lower than optimal—indicates that attitudes toward acceptable screening effectiveness rates need to be realigned with the reality of screening effectiveness rates under actual (not research and often less than ideal) field conditions.

Rate-Limiting Steps

To assess the logistical realities associated with performing Pap smear screening, it is important to review a number of technical and programmatic considerations that affect the real-world availability of this test. Listed below is a series of steps or requirements which, if not always available, drastically reduce the effectiveness of a cytology-based screening program.

Test-related requirements:

- Slides
- Identification mechanism
- Spatula
- Fixative
Alternatives for Cervical Cancer Screening and Treatment in Low-Resource Settings

- Staining reagents
- Cover slips
- Microscope
- Trained cytotechnician/pathologist

Program-related requirements:

- Light source
- Speculum
- Paper trail (lab slips/log book)
- Transport to laboratory
- Report transmission
- Patient contact
- Referral network
- Accessible center for diagnosis/treatment

Informal surveys among groups of practitioners in a variety of developing world settings have revealed that, in fact, one or more of these steps or requirements are usually not reliably available. This fact underscores the importance of being able to offer a screening method that is not characterized by so many rate-limiting steps.

Concluding Comments

- Cytology-based services are not realistic or practical as a nationally accessible screening option in many developing countries.

- If screening methods are to be reliably available on a large scale in developing countries, these countries must minimize their dependence on imported technology and minimize the amount of technically complex test-related requirements.
SCREENING

Accuracy of Pap Smears: Recent Findings from a Meta-Analysis

Introduction

A recent meta-analysis of the Pap smear (Fahey, Irwig and Macaskill 1995) involved 62 studies conducted between 1984 and 1992. Only studies that met certain criteria were included in the analysis (see inclusion criteria listed below). The authors combined the data from the various independent studies and, using weighted least squares linear regression, developed a summary receiver operating characteristic (SROC) curve to demonstrate the tradeoff between sensitivity and specificity levels at different cutoff points defining “disease.” While it can be argued that meta-analyses have their limitations, this study corroborates other evidence that Pap smear readings in some settings may be missing considerable numbers of precancerous lesions and falsely identifying other cases as abnormal—resulting in unnecessary treatment or referral. Key methodological points and observations/conclusions presented by the meta-analysis authors in their journal article are presented below.

Methods

- Meta-analysis (using weighted least squares linear regression) was used to combine data from a number of independent studies to estimate the accuracy of the Pap test.

- A MEDLINE search was conducted to identify relevant articles published between January 1984 and March 1992.

- The MEDLINE search yielded 500 citations.

- Criteria for inclusion in the meta-analysis included:
  - Written in English
  - Original data
  - Addressed cervical cancer or precursors
  - Included use of Pap smear as the screening test
  - Histology used as the reference standard
  - Sufficient data reported to enable revised estimates of sensitivity/specificity to be calculated
Sixty-two studies met the meta-analysis study inclusion criteria.

The authors used a SROC curve to demonstrate the relationship between sensitivity and specificity as re-estimated from the 62 original study data sets.

Authors’ Observations

- Of the 62 studies, 82% had potential for verification bias.²
- Only 37% of the original study investigators stated that cytology and histology readings were independently assessed.
- Only 3% reported confidence intervals for original sensitivity and specificity estimate(s).
- Original sensitivity estimates from the 62 studies ranged from 11–99%.
- Original specificity estimates ranged from 14–97%.
- Sensitivity and specificity re-estimates were highly negatively correlated.

Results and Conclusions

- The meta-analysis results suggested that the Pap test cannot be characterized by concurrently high sensitivity and specificity values.
- The variation in quality of the 62 studies and thresholds for defining test positive may partially explain the wide variation in the accuracy of reported Pap test estimates.
• One can identify a Pap test specificity rate falling within clinically acceptable levels and read the corresponding sensitivity (or vice versa) from the meta-analysis-computed SROC curve (see Figure 1).

• For example, in the US, false (test) positive rates for the Pap smear are generally quoted at 5–10%. This is equivalent to specificity of 90–95% and corresponds to a sensitivity in the range of 20–35% on the meta-analysis-generated SROC curve (see lower oval in Figure 1). If a 60% level of sensitivity for the Pap test was programmatically acceptable, the corresponding specificity rate according to the meta-analysis-generated SROC curve is 75% (see upper oval in Figure 1).

Figure 1. Sensitivity Plotted Against (1 - specificity) and Unweighted Summary Receiver Operating Characteristic Curve


• Models of screening for cervical cancer use more liberal estimates of the Pap test sensitivity and thus may need to be reformulated.

NOTES

1 See “Cytology-Based Screening: Technical and Programmatic Considerations.”

2 See “Factors Affecting a Screening Test” for definition.
Screening

Implementing Cytology Services: Zimbabwe Cervical Cancer Case Study

Introduction

A large-scale cervical cancer screening study is currently being conducted in Zimbabwe. Before the main study was initiated, a pilot study of 1,000 women was conducted. The cytological results of this pilot study are presented below. The objective of this presentation is to demonstrate both the amount of effort required to ensure quality Pap smear research in countries such as Zimbabwe (which have comparatively good, urban-based cytology programs) and to highlight the difficulties of maintaining quality, large-scale cytology-based cervical cancer screening services in such settings. Although the medical expertise is certainly in place to run a quality screening program, there is an overwhelming volume of cases screened as well as a shortage of continuing medical education for hospital staff, a shortage of supplies, etc.

External Quality Control Procedures

- Pilot Study: All slides reviewed
- Main Study:
  - 10% of all positive slides
  - 10% of all negative slides
  - If possible, cervical biopsies to be reviewed and correlated with Pap smears
Alternatives for Cervical Cancer Screening and Treatment in Low-Resource Settings

Results

Table 1. Comparative Results of Pilot Study: Cytology

<table>
<thead>
<tr>
<th>Zimbabwe</th>
<th>US</th>
<th>Number</th>
<th>%</th>
<th>Cumulative Number</th>
<th>Cumulative %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>Positive</td>
<td>113</td>
<td>12.7</td>
<td>113</td>
<td>12.7</td>
</tr>
<tr>
<td>Positive</td>
<td>Negative</td>
<td>44</td>
<td>5.0</td>
<td>157</td>
<td>17.7</td>
</tr>
<tr>
<td>Negative</td>
<td>Positive</td>
<td>35</td>
<td>3.9</td>
<td>192</td>
<td>21.7</td>
</tr>
<tr>
<td>Negative</td>
<td>Negative</td>
<td>695</td>
<td>78.4</td>
<td>887</td>
<td>100</td>
</tr>
</tbody>
</table>

Positive = Diagnoses of LGSIL or higher
Negative = Diagnoses of normal, inflammation, and atypical squamous cells of undetermined significance (ASCUS)
Atypical glandular cells of undetermined significance (AGUS) were included with ASCUS

Table 2. Comparative Cytology Results (continued)

<table>
<thead>
<tr>
<th>US-Based Pathology Reading</th>
<th>Zimbabwe-Based Pathology Reading</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normal Inflammation</td>
</tr>
<tr>
<td>Normal Inflammation</td>
<td>28</td>
</tr>
<tr>
<td>LGSIL</td>
<td>22</td>
</tr>
<tr>
<td>HGSIL</td>
<td>2</td>
</tr>
<tr>
<td>Cancer</td>
<td>1</td>
</tr>
<tr>
<td>ASCUS</td>
<td>10</td>
</tr>
</tbody>
</table>

Parentheses around numbers in Table 2 signify exact agreement in diagnoses. Blanks in the table signify incomplete data at the time of presentation.

- Overall agreement: 91.1%—whether LGSIL or higher was present.
- In Zimbabwe 5.6% of all final diagnoses rendered were ASCUS, whereas in the US 3.2% of all final diagnoses rendered were ASCUS.
Alternatives for Cervical Cancer Screening and Treatment in Low-Resource Settings

- Acceptable limits for ASCUS diagnoses according to the Bethesda System are:
  - No more than 5% of all Pap smear diagnoses
  - No more than 2.5 times the rate of LGSIL (or higher) diagnoses in the laboratory
- After a "consensus teleconference" there was approximately 80% agreement between the two main (internal and external) study cytopathologists on the Pap smear results.

**Important Statements**

1. Both the Zimbabwe and US pathologists used identical criteria for diagnoses—the Bethesda System.

2. In 25 cases (25/887 or 2.8% of the cases) the US-based pathologist found evidence for a potentially significant lesion, LGSIL or higher, including one cancer. In these cases the diagnostic cells were not identified and marked by the cytotechnologist because of an inflammatory background. These were **not interpretative errors** by the pathologist in Zimbabwe, but rather a function of the atypical cells not being called to the pathologist's attention (i.e., **screening errors**).

3. Both the US and Zimbabwe pathologists had acceptable rates of ASCUS diagnoses (i.e., did not "abuse" the use of this somewhat ambiguous diagnosis).

4. There was a "limited consensus conference" during the site observation. Additionally, a voluntary pathology review in Zimbabwe concurred with the diagnoses rendered by the US pathologist in 80% of the cases with discrepant diagnoses.

**Site Observations—Harare, Zimbabwe**

Shortly after the pilot Pap results had been reviewed by both cytopathologists and consensus reached on the majority of findings, the US-based pathologist visited the site to provide update training and technical assistance to the study cytotechnicians. Points of emphasis during this visit included:
• Technical considerations
  
  • Terminology—what classification system is to be used
  
  • Materials—reference texts, marking pens and other supplies needed to provide quality cytology services

• Technologists—The US-based pathologist reviewed Pap smear reading procedures and assessed the competency of the study cytotechnicians using standard testing materials.

• Pathologists—The US-based pathologist reviewed quality control procedures with Harare-based cytopathologists to promote standardization of Pap readings.

Implications for Main Study

The purpose of a technical assistance visit by the external quality control pathologist was to ensure the quality of Pap smear reading during the main study. Although the diagnostic abilities of the Harare-based cytopathologist were unquestionably equal to most US-based cytopathologists, limitations of the existing cytology program (volume of cases screened by cytotechnologists, lack of continuing medical education, periodic shortages of necessary supplies, etc.) were obvious.

This experience underscores the need for alternative cervical cancer screening options, especially in less affluent environments.

At the end of this presentation, workshop participants were challenged to test their quality control skills with the following quote:

"Screening" Bias*

"Finally, to determine that a cytologic diagnosis is false-negative, it is usually compared against the 'gold standard' of histologic diagnosis. However, as we have seen, histologic diagnosis is not error-free. Few studies have examined the 'gold standard' itself when evaluating apparent cytodiagnostics errors. Moreover, there is a body of evidence that even competent pathologists cannot agree with each other—or even themselves—from day-to-day on the classification of cervical tissue biopsies, let alone the Pap smears."

Adapted from: DeMay 1996, p. 146.

*How good a screener are you? There are four spelling errors in the paragraph above.
If you had to reread the quote above to find the spelling errors, you experienced a situation similar to those encountered in research studies in which quality control technicians or pathologists are focusing special attention on study specimens. This “special case” type of re-screening is not sustainable in a routine screening program. This fact suggests that the quality of Pap smear reading experienced in research studies is likely to be higher than what is routinely available under nonresearch conditions—an important point to consider when interpreting and comparing the results of Pap smear findings with other screening tests being validated (e.g., VIA) in research studies.

NOTES

1 See “Zimbabwe Cervical Cancer Screening Study.”

2 Corrected spellings for the four misspelled words are: determine, apparent, moreover, competent.
Visual Inspection of the Cervix as a Screening Option

Introduction

Cervical cancer screening using visual inspection can be performed either *unmagnified* (including visual inspection without acetic acid or visual inspection using acetic acid [VIA], also referred to as direct visual inspection or cervicoscopy) or *with magnification* (referred to as aided, gynoscopy or low-magnification visualization). Although some research on this screening approach has included visual inspection *without* the application of acetic acid, in this workshop we focused on visualization of the cervix after it has first been washed with a dilute (3-5%) solution of acetic acid.

In examining key findings from visual inspection studies conducted in the last 15 years, one notes variations in the findings that are due in part to methodologic differences in the study designs as well as differences in clinical features of the test being studied. Despite such differences, however, there is still remarkable consistency in the findings of visual inspection reports. These findings support the potential of visual inspection as a cervical cancer screening method.

Aided Visual Inspection (AVI) Studies

In the two AVI studies reviewed here, both show that visual inspection compared well to the Pap smear in its ability to differentiate a normal from an abnormal cervix. The 1990 Abrams study demonstrated that gynoscopy (defined here as the use of a 2.5X magnifying device with acetic acid wash) could differentiate a normal from an abnormal cervix and thus could serve as an adjunct to cytology. In the case of speculoscopy, the results (with biopsy as a reference standard) compared quite well with colposcopy. Speculoscopy is defined here as aided visual inspection of the acetic-acid-washed cervix using a low-power (5-6X) magnifying device (speculoscope) with illumination provided by a chemiluminescent capsule attached to the upper blade of the speculum.


*Design Features*

- 309 women selected at discretion of author
- Women with previous history of > moderate dysplasia excluded
Alternatives for Cervical Cancer Screening and Treatment in Low-Resource Settings

- Handheld, monocular device used with 2.5X magnification (gynoscopy)
- Cytologic specimen also obtained
- Biopsies obtained as indicated (for any acetowhite lesions)

Results

Table 1.

<table>
<thead>
<tr>
<th>Gynoscopy</th>
<th>Cytology</th>
<th>Histology*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>Normal</td>
<td>Abnormal</td>
</tr>
<tr>
<td>Normal</td>
<td>200</td>
<td>9</td>
</tr>
<tr>
<td>Abnormal</td>
<td>37</td>
<td>50</td>
</tr>
</tbody>
</table>

* Histology done only on select (n=13) abnormal gynoscopy cases.

b Normal gynoscopy is defined as absence of acetowhite lesions on cervix; reference standard is most severe diagnosis on either cytology or histology.

Prevalence of Dysplasia (71 picked up from cytology or histology (50 + 9 + 12 = 71) / 309) = 23%

Positive Predictive Value (PPV) (50 + 12 = 62 / 100) = 62% (cytology + histology)

Negative Predictive Value (NPV) (200 / 209) = 96% (cytology)


Design Features

- 395 patients scheduled for colposcopy had speculoscopy:
  - Chemiluminescent light (creates cellular reaction which allows "abnormal" cells to be visually apparent)
  - 5X magnification using a loupe
  - Colposcopy performed immediately after speculoscopy
  - Dichotomous outcome measured (normal, abnormal)
**Results**

- When colposcopy results were used as the reference standard, the test qualities of speculoscopy were as follows:
  - Sensitivity 79%
  - Specificity 87%
  - PPV 97%
  - NPV 47%

- When histology results were used as the reference standard, the comparative test qualities were as shown in Table 2.

<table>
<thead>
<tr>
<th></th>
<th>Speculoscopy</th>
<th>Colposcopy</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>82%</td>
<td>97%</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Specificity</td>
<td>49%</td>
<td>25%</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>PPV</td>
<td>72%</td>
<td>67%</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>NPV</td>
<td>63%</td>
<td>83%</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

*P value here indicates the chance probability of finding a difference in the test values of speculoscopy and colposcopy as large as observed in this study.

This table shows that the specificity of the screening test, speculoscopy in this study, was significantly better than the referral (colposcopy). The sensitivity of colposcopy however was higher than that measured for speculoscopy.

Table 3. Proportion of Correctly Identified HGSIL Cases (using histology as the true measure of disease status)

<table>
<thead>
<tr>
<th></th>
<th>CIN II</th>
<th>CIN III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Speculoscopy</td>
<td>90.3%</td>
<td>93.3%</td>
</tr>
<tr>
<td>Colposcopy</td>
<td>98.6%</td>
<td>96.6%</td>
</tr>
</tbody>
</table>

When considering the ability of the two tests to pick up high-grade lesions correctly, visual inspection (speculoscopy) compared favorably to colposcopy.
Unmagnified Visual Inspection Studies

Studies aimed at investigating the test qualities of unmagnified visual inspection date back to the early 1980s. These studies have explored both unmagnified visual inspection as a "stand alone" screening method and as an adjunct to other methods such as cytology. There is a consistent trend across VIA studies indicating—at the very least—that VIA is a useful adjunct to cytology (possibly reducing the need for colposcopy and, at the same time, increasing the detection of diseased cervices). In addition, the implication is quite clear from these studies that in some settings, if providers were given proper training, VIA could be an effective means of offering primary screening on a large scale to needy populations. Five VIA studies are reviewed in this section.

1. Identification of Transformation Zone, Italy 1981 (Ottaviano and La Torre 1982)

   **Design Features**
   - n = 2,400 patients
   - Age: 18 to 65 years
   - VIA and colposcopy performed concurrently
   - VIA results unknown to colposcopist (blinded)
   - Biopsy taken, if clinically indicated

   **Results**

   Table 4. Comparative Findings

<table>
<thead>
<tr>
<th></th>
<th>Colposcopy</th>
<th>VIA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ectopy</td>
<td>5.5%</td>
<td>5.5%</td>
</tr>
<tr>
<td>Physiologic</td>
<td>66% (1,584)</td>
<td>65% (1,568)</td>
</tr>
<tr>
<td>Transformation Zone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Squamo-Columnar (SC)</td>
<td>11 %</td>
<td>11 %</td>
</tr>
<tr>
<td>Junction in the</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endocervix</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&quot;Atypical&quot; Transformation Zone</td>
<td>13% (312)</td>
<td>12.8% (307)</td>
</tr>
<tr>
<td>Other</td>
<td>4.5 %</td>
<td>4.5%</td>
</tr>
</tbody>
</table>

   **Authors' Conclusions**

   "...colposcopic magnification is not essential in clinical practice for the identification of the cervix 'at risk.'"
2. VIA as Adjunct to Cytology, US (1989–1990) (Slawson, Bennett and Herman 1992)

**Design Features**
- 2,827 women
- Cytology and VIA both performed
- Colposcopy performed immediately (i.e., as soon as possible after Pap results available) *if cytology results were positive*
- If only VIA results were positive, but cytology negative, the woman was asked to return 6 months later for colposcopy. (A few patients requested immediate colposcopy—analyzed separately.)

**Results**

<table>
<thead>
<tr>
<th>Total abnormal</th>
<th>358/2,827</th>
<th>13%</th>
<th>VIA, Pap or both</th>
</tr>
</thead>
</table>

PPV (Biopsy as reference)

- Abnormal VIA, immediate colposcopy (n=11) 64%
- Abnormal VIA, colposcopy at 6 months (n=30) 63%

Abnormal Pap + VIA (n=22)* 64%
Abnormal Pap only (n=136) 68%

*These are patients for whom both tests were abnormal at first screening and had "immediate" colposcopy/biopsy.

- Learning Curve
  - PPV of VIA in first 6 months of study—47%
  - PPV after six months—67%

**Authors’ Conclusions**

- 30% improvement in CIN detection using VIA as adjunct to cytology
- VIA reduces unnecessary colposcopy

**Design Features**

- 85 women (referrals from 20 family planning clinics in a US city) with normal Pap smears but positive VIA
- Colposcopy performed with biopsy as indicated
- No clinical training in VIA provided to participants

**Results**

- 13 (15%) were found to have dysplasia on VIA not previously detected by Pap
- 34 (40%) were found to have false positives using VIA (colposcopy = reference standard)

**Authors’ Conclusions**

“[VIA] of the cervix may be useful in settings where cervical screening opportunities are limited, such as third-world countries and other underserved areas. However, further refinements [e.g., training] are necessary to decrease false-positive rates and unnecessary referrals for further evaluation.”

4. VIA as a Primary Screening Method, South Africa, 1994 (Megevand et al 1996)

**Design Features**

- 2,426 women screened in mobile clinic
- Simultaneous performance of Pap, naked-eye inspection with acetic acid (VIA), colposcopy
- Pap smears processed immediately (in the mobile clinic)
- All women with positive smears referred for colposcopy (immediately or within 3 days)
- Women with negative Pap smears not referred for colposcopy
- See and treat approach used as treatment protocol
Results

Table 5. Dichotomous Pap Results Compared to the Reference Standard

<table>
<thead>
<tr>
<th>Histology</th>
<th>Positive</th>
<th>Negative</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pap</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive*</td>
<td>280</td>
<td>35</td>
<td>315</td>
</tr>
<tr>
<td>Negative</td>
<td>0</td>
<td>0</td>
<td>2,111</td>
</tr>
</tbody>
</table>

* Defined in this study as “presence of any squamous intraepithelial lesion(s)"

- PPV of Pap using histology as reference standard—88.9%

Table 6. Dichotomous VIA Results Compared to the Reference Standard

<table>
<thead>
<tr>
<th>Histology</th>
<th>Positive</th>
<th>Negative</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>VIA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive*</td>
<td>55</td>
<td>21</td>
<td>76</td>
</tr>
<tr>
<td>Negative</td>
<td>229&lt;sup&gt;b&lt;/sup&gt;</td>
<td>[2,121]&lt;sup&gt;c&lt;/sup&gt;</td>
<td>2,350</td>
</tr>
</tbody>
</table>

<sup>a</sup> Defined in this study as “presence of acetowhite area(s) on the cervix.”
<sup>b</sup> The 229 patients with negative VIA received colposcopy on the basis of a positive cytology.
<sup>c</sup> Assumes cases with negative cytology would have had negative histology.

- [NPV of VIA—90.3%; assumes cases with negative cytology would have had negative histology]
- PPV of VIA using colposcopy alone as reference standard—85.5%
- PPV of VIA using histology as reference standard—72.4%
If only HGSIL is considered diseased, the study results change as follows:

Table 7.

<table>
<thead>
<tr>
<th>Test</th>
<th>Reference Standard</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Colposcopy</td>
</tr>
<tr>
<td>PPV</td>
<td>VIA</td>
</tr>
<tr>
<td>PPV</td>
<td>Pap</td>
</tr>
<tr>
<td>NPV(^a)</td>
<td>VIA</td>
</tr>
</tbody>
</table>

\(^a\) Assumes no HGSIL among Pap negative.
\(^b\) Assumes cases with negative VIA and negative cytology would have had negative histology.

Authors’ Conclusions

“Naked-eye visualization of the cervix after application of diluted acetic acid can detect more than 60% of high-grade SIL and therefore warrants consideration as an alternative to cytologic screening.”

5. Study Evaluating VIA, Kerala, India (Franco and Monsonego 1997)

Design Features

- 868 women recruited from April to December 1995 for opportunistic cervical cancer screening
- Tests performed: VIA and cytology
- Test positive = acetowhite areas (VIA), dysplasia/cancer (cytology)
- Reference standard = colposcopy/biopsy
Results

Table 8. VIA Test Qualities

<table>
<thead>
<tr>
<th></th>
<th>VIA</th>
<th>Pap</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivitya (positive ≥ LGSIL)</td>
<td>85.2%</td>
<td>69.6%</td>
</tr>
<tr>
<td>Sensitivitya (positive ≥ HGSIL)</td>
<td>91.2%</td>
<td>75%</td>
</tr>
<tr>
<td>Specificityb</td>
<td>89.3%</td>
<td>97.4%</td>
</tr>
<tr>
<td>Detection rate for dysplasia and carcinoma</td>
<td>28.2/1,000</td>
<td>23.0/1,000</td>
</tr>
</tbody>
</table>

Results, unadjusted for verification bias, are based on 868 women recruited for screening of whom 127 qualified for and received colposcopy (positive cervicoscopy or positive Pap smear were eligibility criteria). Of these, 27 had positive colposcopy.

As mentioned above, colposcopy was performed only on women with a positive screening test; however, women with discordant results (positive Pap and negative VIA and vice versa) were eligible for colposcopy. Thus, some women with a negative screening test received colposcopy. As a result of calculations based on these women, the specificity was approximated.

Conclusions

VIA was more sensitive in detecting lesions as compared to cytology, although the difference was not statistically significant. The specificity of cytology was statistically significantly higher than that of VIA.

NOTE

1 See “Factors Affecting a Screening Test.”

Introduction

The study was conducted in Indonesia from 1992 to 1994 with funding from the World Bank. It was performed in two phases with different provider types performing the screening in each phase (Phase I—gynecologists, Phase II—nurse-midwives). Qualitative aspects of the screening test (e.g., client and provider acceptance) were investigated as well as the test qualities (sensitivity and specificity) which are reported on below.

Overall Study Objective

To evaluate whether AVI would be a suitable screening method in settings where cytology services are limited.

Specific Study Objectives

- Estimate the sensitivity and specificity of AVI
  - Phase I—as performed by gynecologists
  - Phase II—as performed by nurse-midwives
- Determine the amount of training needed to enable nurse-midwives to perform AVI
- Determine the acceptability of AVI to providers and clients
- Phase II—estimate sensitivity and specificity of unmagnified visual inspection using acetic acid (VIA) as performed by nurse-midwives

Outcome Measures of Interest

- Sensitivity
- Specificity
- PPV
- Ease of use
- Provider and client acceptability
Design Features

- Inclusion criteria
  - Phase I—women 30 to 50 years attending Indonesian Cancer Foundation (YKI) clinics
  - Phase II—women 30 to 50 years attending Yayasan Kusuma Buana (YKB) clinics or outreach sessions

- Exclusion criteria
  - Had a Pap smear within previous 12 months
  - Had ever been diagnosed with cervical cancer
  - Had been experiencing unusual vaginal bleeding at the time of or immediately prior to their clinic visit

- Cutoff points defining disease
  - Phase I—CIN III or CIS were considered diseased; the rest were nondiseased.
  - Phase II—Results were classified in terms of CIN I, II or III or CIS so that both severe dysplasia and HGSIL could be analyzed as diseased.

- Reference standard as defined in protocol
  - Colposcopy and biopsy (if needed) for all cases positive by Pap or visual inspection and for 10% of negatives
  - Protocol not strictly followed in Phase I, no colposcopy results available for Phase II; Pap smear used as reference standard in these results

- Definition of Test Positive for AVI
  - Categorized as negative, mild, moderate, severe
  - Results were analyzed using varying levels of test positive (see Results below)

- Definition of Test Positive for VIA
  - Categorized as negative, limited, extensive
Alternatives for Cervical Cancer Screening and Treatment in Low-Resource Settings

- Results were analyzed using varying levels of test positive (see Results below)

- Sample size

- Phase I—24 cases of CIN III/CIS
  - Based on estimated sensitivity of 90% with ±10% precision at 95% confidence level

- Phase II—41 cases of HGSIL
  - Based on estimated sensitivity of 80% with ±10% precision at 95% confidence level

Note: All invasive cancers (9 in Phase 1, 8 in Phase II) were detected by visual inspection; they are not included in results since study focus was on dysplasia.

Results

Table 1. Phase I—Distribution of Cases

<table>
<thead>
<tr>
<th>Threshold of Test Positive</th>
<th>Number</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>AVI moderate/severe</td>
<td>17</td>
<td>1.9</td>
</tr>
<tr>
<td>any acetowhite (= mild, moderate, severe)</td>
<td>47</td>
<td>5.2</td>
</tr>
<tr>
<td>Pap CIN III/CIS</td>
<td>15</td>
<td>1.6</td>
</tr>
</tbody>
</table>

Table 2. Phase I—Test Qualities of AVI

<table>
<thead>
<tr>
<th>(n=911)</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>moderate/severe</td>
<td>93.3% (66.0, 99.7)</td>
<td>99.7% (98.9, 99.9)</td>
<td>82.4% (55.8, 95.3)</td>
</tr>
<tr>
<td>any acetowhite (= mild, moderate, severe)</td>
<td>100.0% (74.7, 100.0)</td>
<td>96.4% (94.9, 97.5)</td>
<td>31.9% (19.5, 47.3)</td>
</tr>
</tbody>
</table>

Reference standard = Pap smear
Table 3. Phase II—Distribution of Cases

<table>
<thead>
<tr>
<th>Threshold of Test Positive</th>
<th>Number</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>AVI moderate/severe</td>
<td>148</td>
<td>9.6</td>
</tr>
<tr>
<td>AVI severe</td>
<td>18</td>
<td>1.2</td>
</tr>
<tr>
<td>Pap HGSIL</td>
<td>37</td>
<td>2.4</td>
</tr>
<tr>
<td>Pap CIN III/CIS</td>
<td>12</td>
<td>0.8</td>
</tr>
<tr>
<td>VIA any acetowhite (= limited/extensive)</td>
<td>100</td>
<td>6.5</td>
</tr>
</tbody>
</table>

Reference standard = Pap smear

Table 4. Phase II—Test Qualities of AVI

<table>
<thead>
<tr>
<th>(n = 1,542)</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>moderate/severe</td>
<td>75.7% (58.4, 87.6)</td>
<td>92.0% (90.5, 93.3)</td>
<td>18.9% (13.1, 26.4)</td>
</tr>
<tr>
<td>severe</td>
<td>100.0% (69.9, 100.0)</td>
<td>99.6% (99.1, 99.8)</td>
<td>66.7% (41.2, 85.6)</td>
</tr>
</tbody>
</table>

Reference standard = Pap smear

Table 5. Phase II—Test Qualities of VIA

<table>
<thead>
<tr>
<th>(n = 1,542)</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>any white</td>
<td>75.7% (58.4, 87.6)</td>
<td>95.2% (94.0, 96.2)</td>
<td>28.0% (19.7, 38.0)</td>
</tr>
<tr>
<td>any acetowhite (= limited/extensive)</td>
<td>100.0% (69.9, 100.0)</td>
<td>94.2% (92.9, 95.3)</td>
<td>12.0% (6.6, 20.4)</td>
</tr>
</tbody>
</table>

Reference standard = Pap smear

Conclusion and Remarks

- Based on these small-scale studies, visual inspection shows promise and deserves more comprehensive evaluation.
Lessons Learned

- A rigorous study requires substantial financial and infrastructural resources.

- Performing a screening study in a low-prevalence population is difficult because of constraints in obtaining an adequate sample size.

- To obtain a firm commitment from collaborators to follow the protocol meticulously, it is critical that study procedures are feasible.

- It appears that VIA and AVI (at 2.5X) can achieve similar sensitivity in detecting CIN III, but AVI may have some advantage in specificity.

NOTE

This study was conducted with support from the Indonesian Cancer Foundation (YKI), the Program for Appropriate Technology in Health (PATH), the World Bank and Yayasan Kusuma Buana (YKB).
RECENT VISUAL INSPECTION STUDIES

Cervical Cancer Screening in Women Attending a Family Planning Clinic in Nairobi, Kenya

Introduction

This study, funded by the Commission of the European Communities (Director General XII), was conducted in 1994-1995 at Ribiero Family Planning Clinic through the Well Women's Clinic in collaboration with the Kenya Medical Women's Association in Nairobi, Kenya. Both aided and direct visual inspection with acetic acid (cervicoscopy) were tested as screening alternatives. Of note is the fact that in this study the number of women who had (or said they had) been previously screened for cervical cancer (53%) was much higher than estimates from the general population (5%) in other low-resource settings (WHO 1986). Measured disease rates however were similar, regardless of previous screening status.

Background

- Carcinoma of the cervix is the most common malignancy in Kenyan women.
- Organized screening programs don’t exist.
- Classic screening programs are difficult to organize.
- Other screening methods could be an alternative.

Study Objectives

- To determine the prevalence of HPV, cervical dysplasia, STD and HIV in this population
- To assess the effectiveness of existing screening methods
- To assess the validity of alternative screening methods

Design Features

- A cross-sectional study of 1,050 women was conducted.
• A random selection of women attending the clinic for routine family planning services were offered screening for STDs including HIV and cervical cancer.

• Clinical “predictors” of dysplasia were noted.

• Visual inspection after application of acetic acid (cervicoscopy) was performed on all study patients.

• Gynoscopy was performed on a subset of 426 patients.

• Only patients with HGSIL were further investigated with colposcopy and biopsy.

• Adequate treatment was given to all patients observed to have cervical lesions.

Demographics of Study Population (n = 1,050)

<table>
<thead>
<tr>
<th>Category</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>mean of 29.7 (minimum 17, maximum 54)</td>
</tr>
<tr>
<td>Marital status</td>
<td>778 (74%) were married</td>
</tr>
<tr>
<td>Education</td>
<td>254 (24%) had primary level education or less</td>
</tr>
<tr>
<td></td>
<td>795 (76%) had secondary level education or higher</td>
</tr>
<tr>
<td>Religion</td>
<td>319 (30%) were Catholic</td>
</tr>
<tr>
<td></td>
<td>718 (68%) were Protestant</td>
</tr>
<tr>
<td></td>
<td>12 (2%) were Muslim</td>
</tr>
<tr>
<td>Employment</td>
<td>785 (75%) were employed</td>
</tr>
</tbody>
</table>

Previous Pap Screening Experience

• Screening rates
  • 246/520 (47%) had never been screened
  • 274/520 (53%) had been screened

• Result of last Pap test (as mentioned by patient)
  • 110/274 (40%) had a normal test
  • 164/274 (60%) had an abnormal test
Results of Current Screening

Results: HPV
- Overall HPV rates (n=863)
  - 171 (19.8%) were HPV positive
  - 692 (80.2%) were HPV negative
- HPV rates by type
  - 11/171 (6.4%) were benign
  - 45/171 (26.3%) could not be typed with certainty
  - 115/171 (67.3%) were oncogenic

Results: Pap and Histology

Table 1. Frequency of Disease Diagnosis

<table>
<thead>
<tr>
<th></th>
<th>Pap Tests (n=1,050)</th>
<th>Histology (n=111)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CINI</td>
<td>57 (5.4%)</td>
<td>67/1,050 (6.4%)</td>
</tr>
<tr>
<td>CIN II</td>
<td>28 (2.7%)</td>
<td>16/1,050 (1.5%)</td>
</tr>
<tr>
<td>CIN III</td>
<td>6 (0.6%)</td>
<td>5/1,050 (0.5%)</td>
</tr>
<tr>
<td>CIS</td>
<td>9 (0.9%)</td>
<td>16/1,050 (1.5%)</td>
</tr>
<tr>
<td>Invasive Cancer</td>
<td>8 (0.8%)</td>
<td>7/1,050 (0.7%)</td>
</tr>
</tbody>
</table>

- Histology findings (Bethesda system equivalent)
  - LGSIL = 6.4%
  - HGSIL (CIN II, CIN III, CIS) = 3.5%
  - Cancer = 0.7%

Results: Screening History by Level of Disease

- Normal/LGSIL
  - 53% had been previously screened
  - Of these, 60% had normal Pap results on past test
- HGSIL/Cancer
  - 52% had been previously screened
  - Of these, 57% had normal Pap results on past test
• Observations

• No apparent relationship between history of screening and current disease status
• No apparent relationship between result of previous screening and current disease status

Table 2. Test Qualities of Cervicoscopy with High-Grade Lesions and Above Defining Disease

<table>
<thead>
<tr>
<th>n = 1,050</th>
<th>Number of Cases</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ectopy</td>
<td>131</td>
<td>18.2%</td>
<td>87.7%</td>
<td>6.1%</td>
<td>96.0%</td>
</tr>
<tr>
<td>Ulcer/mass</td>
<td>122</td>
<td>13.6%</td>
<td>88.4%</td>
<td>4.9%</td>
<td>95.9%</td>
</tr>
<tr>
<td>Friability</td>
<td>276</td>
<td>40.9%</td>
<td>74.3%</td>
<td>6.5%</td>
<td>96.0%</td>
</tr>
<tr>
<td>Abnormal cervix</td>
<td>381</td>
<td>47.7%</td>
<td>64.1%</td>
<td>5.5%</td>
<td>96.5%</td>
</tr>
</tbody>
</table>

Cutoff point defining disease = HGSIL; reference standard = colposcopy, biopsy if colposcopy was positive; test qualities unadjusted for verification bias

Table 3. Test Qualities of Cervicoscopy with Carcinoma in Situ and Above Defining Disease

<table>
<thead>
<tr>
<th>n = 1,050</th>
<th>Number of Cases</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ectopy</td>
<td>131</td>
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<td>3.9%</td>
<td>98.8%</td>
</tr>
</tbody>
</table>

Cutoff point defining disease = CIS; reference standard = colposcopy, biopsy if colposcopy was positive
Table 4. Comparative Test Qualities with High-Grade Lesions and Above Defining Disease

<table>
<thead>
<tr>
<th>Test</th>
<th>Number of Test Positive Cases</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cervicoscopy</td>
<td>129/1,050</td>
<td>25.0%</td>
<td>88.2%</td>
<td>8.5%</td>
<td>96.4%</td>
</tr>
<tr>
<td>Gynoscopy</td>
<td>139/426</td>
<td>40.0%</td>
<td>67.5%</td>
<td>2.9%</td>
<td>97.9%</td>
</tr>
</tbody>
</table>

Cutoff point defining disease = HGSIL; reference standard = colposcopy, biopsy if colposcopy was positive (see above); threshold of test positive = any acetowhite lesion

Table 5. Comparative Test Qualities with Carcinoma In Situ and Above Defining Disease

<table>
<thead>
<tr>
<th>Test</th>
<th>Number of Test Positive Cases</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cervicoscopy</td>
<td>129/1,050</td>
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<td>88.0%</td>
<td>4.6%</td>
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<td>2.1%</td>
<td>99.6%</td>
</tr>
</tbody>
</table>

Cutoff point defining disease = CIS; reference standard = colposcopy, biopsy if colposcopy was positive (see above); threshold of test positive = any acetowhite lesion

Observations and Lessons Learned

- Existing opportunistic screening programs in Kenya are ineffective. A large number of women presenting with HGSIL and/or cancer had been previously screened but not treated. It is unclear whether this is because of false negative results, because of inability to communicate results to patients or because of lack of treatment facilities.

- The results of alternative screening methods in this study were discouraging. Cervicoscopy (VIA) did not prove to be a useful tool for screening because of the observed low sensitivity of the test. Where sensitivity was improved using amplification (gynoscopy), there was a loss of specificity. The sensitivity of the screening test should be at least 70%; a specificity of 70% is acceptable if a see and refer method is applied. With a see and treat approach, the specificity should be at least 90%.
The low PPV is of major concern because it implies considerable overtreatment. If we had applied a see and treat approach in our study, using direct visual inspection (cervicoscopy) for screening, 12 (129/1,050) out of 100 women would have been treated. Of those, 1 (12.3 x .085) would have been correctly treated. The others were false positives. On the other hand, of the 4 women out of 100 with a HGSIL (prevalence of HGSIL by histology = 3.5%), only 1 would have been recognized as such (sensitivity = 25%) and received adequate treatment.

The test qualities (including sensitivity) of aided (AVI) and direct visual inspection (VIA) could possibly be improved through improved training.

NOTE

1 This study was supported by the Commission of the European Communities, Ribiero Family Planning Clinic through the Well Women’s Clinic in collaboration with the Kenya Medical Women’s Association, the University of Ghent and the University of Nairobi.
Zimbabwe Cervical Cancer Screening Study

Introduction

A USAID-funded VIA study was initiated in Zimbabwe in 1995, involving nurses performing screening tests in MCH clinics. This ongoing investigation is designed to compare the effectiveness of VIA to that of Pap smears (the current screening standard in the country/region). The main study was preceded by a 1,000-woman pilot study to determine the feasibility of carrying out the main study as designed. As anticipated, the pilot study yielded important findings which resulted in modifications to the main study protocol, including strengthening the strategy to improve client followup (for diagnostic testing and treatment).

Overall Study Objective

To determine the effectiveness of unmagnified or direct visual inspection as an alternative method of identifying treatable precancerous lesions (i.e., cervical cancer screening) appropriate for developing country settings.

Specific Study Questions

• Is VIA sensitive and specific enough to be a viable alternative to Pap smears in low-resource settings?

• Can VIA be performed in a low-resource setting by nursing staff who provide the majority of women’s health services?

Pilot Study Objectives

• Assess the appropriateness of client recruitment strategies for the main study:
  • Can 80 to 100 clients be screened per day?
  • Which service delivery sites are appropriate?
Alternatives for Cervical Cancer Screening and Treatment in Low-Resource Settings

• Where can colposcopy and cryotherapy services be established in the field?

• Can clients be recalled for further testing or treatment?

• Determine the capabilities of clinical personnel, i.e.:
  • The extent to which nurses are comfortable with speculum exams and visualization
  • The quality of smears taken
  • The accuracy of the study cytotechnicians
  • The degree to which histopathologists’ procedures and reporting are standardized

Research Site: Pilot Study

• Mashonaland, Central Province, Zimbabwe
• 8 MCH service delivery sites

Considerations for selecting this district:

• Rural area within easy access of Harare (to facilitate transport of study investigators and clients)

• A relatively stable and homogenous population

• Well served by primary healthcare facilities (enabling pilot sample size requirements to be met)

Programmatic Lessons Learned

• Nurses are capable of making a screening judgment using VIA.

• Nurses experienced problems differentiating between inflammation and disease (i.e., abnormal or cancerous cervix based on the categories in a visual aid atlas (Blumenthal and Sanghvi 1997).

• VIA is useful for downstaging, (i.e., detecting overt cancer at an earlier, more treatable stage).
Alternatives for Cervical Cancer Screening and Treatment in Low-Resource Settings

- Quality Pap smears are obtainable in Harare but refresher training and continued supplies are necessary. Pap smear reading, however, requires constant attention to quality control.

- Lack of such training and supplies is problematic—which underscores the need for alternatives in low-resource settings.

- Clinic visits can be irregular in such settings, resulting in considerable loss-to-followup, including treatment. This situation underscores the need for a screening test that yields immediate results so that treatment can also be provided on the spot.

Design Features—Main Study

Client Selection Criteria

- Inclusion Criteria
  - Women aged 25 to 55 attending a MCH clinic near Harare

- Exclusion Criteria
  - Women with hysterectomy
  - Menstruating women

Definitional Thresholds

- Cutoff Point: Disease
  - HGSIL or worse

- Cutoff Point: Test Positive
  - VIA—Abnormal or Cancer, according to categories in a visual aid atlas (Blumenthal and Sanghvi 1997)
  - Pap smear—LGSIL or above (excluding ASCUS/AGUS)

Independence of Investigator Assessment

- VIA and Pap smear done concurrently

- Initial colposcopy assessment documented without consideration of VIA and Pap results

- Biopsy readings done without knowledge of VIA or Pap results

Sampling Rates

- Phase I
  - All VIA-positive and Pap smear-positive women referred for colposcopy
  - Sample of VIA-negative and Pap-negative women referred for colposcopy
• All suspicious colposcopies referred for biopsy

• Small proportion of women with normal colposcopy and positive Pap smear referred for biopsy

• Phase II

• VIA, Pap smear and colposcopy carried out concurrently (same day) on all women recruited

• All suspicious colposcopies referred for biopsy (Pap test result not available at time of colposcopy)

Sample Size

• Initially: 24,600 women under the following assumptions:
  - VIA will pick up at least 60% of high-grade lesions (i.e., 60% sensitivity)
  - Confidence level = 95%
  - Power = 80%
  - Precision ± 10%
  - Prevalence of disease = 1.5%

• Modified: 12,000 women under the following revised assumptions:
  - Prevalence of disease = 5.6% (based on pilot Pap test results)
  - Overall, 20% of women testing normal on VIA will go on for colposcopy (one of the study’s reference tests)

Preliminary Results—Main Study

• Distribution of VIA cases (n = 9,660)
  - Normal—30.3%
  - Atypical—48.2%
  - Abnormal—21.3%
  - Cancer—0.2%

• Distribution of Pap smear cases (n = 8,717)
  - Normal—51.7%
  - Inflammation—20.2%
  - ASCUS—10.8%
  - AGUS—0.6
Alternatives for Cervical Cancer Screening and Treatment in Low-Resource Settings

- LGSIL (CIN I)—9.4%
- HGSIL (CIN II, III, CIS)—4.5%
- Squamous Carcinoma—0.2%
- Adenocarcinoma—0.02%

Table 1. Test Qualities: VIA and Pap Smear—Total Clients to Date

<table>
<thead>
<tr>
<th></th>
<th>Number</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>VIA</td>
<td>9,660</td>
<td>.64</td>
<td>.49</td>
<td>.23</td>
<td>.85</td>
</tr>
<tr>
<td></td>
<td>(.59, .68)</td>
<td>(.47, .51)</td>
<td>(.21, .26)</td>
<td>(.83, .87)</td>
<td></td>
</tr>
<tr>
<td>Pap smear&lt;sup&gt;a&lt;/sup&gt;</td>
<td>8,717</td>
<td>.57</td>
<td>.78</td>
<td>.40</td>
<td>.88</td>
</tr>
<tr>
<td></td>
<td>(.52, .62)</td>
<td>(.75, .80)</td>
<td>(.36, .44)</td>
<td>(.86, .89)</td>
<td></td>
</tr>
</tbody>
</table>

Reference standard = colposcopy
<sup>a</sup> Unadjusted for verification bias

Overall to date, the following proportion of women have had colposcopy performed:

- 46% of women testing positive on Pap
- 19% of women testing negative on Pap
- 57% of women testing positive on VIA
- 14% of women testing negative on VIA

Table 2. Test Qualities: VIA—Phase II Only

<table>
<thead>
<tr>
<th></th>
<th>Number</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>VIA</td>
<td>929</td>
<td>.69</td>
<td>.70</td>
<td>.21</td>
<td>.95</td>
</tr>
<tr>
<td></td>
<td>(.58, .77)</td>
<td>(.66, .73)</td>
<td>(.16, .26)</td>
<td>(.93, .97)</td>
<td></td>
</tr>
</tbody>
</table>

Reference standard = colposcopy; adjusted for verification bias; Pap smear results not yet available for Phase II

Since the beginning of Phase II, the following proportion of women have had colposcopy performed:

- 89% of women testing positive on VIA
- 93% of women testing negative on VIA
Summary of Preliminary Findings

- Sensitivity estimates for VIA over all phases of the study (including the pilot) have exceeded the targeted sensitivity established under the study hypothesis (60%).

- Specificity estimates for VIA have varied over the different phases of the study (up to 70% in Phase II).

- Sensitivity estimates for the Pap smear and VIA have been comparable thus far.

- PPV estimates for VIA have remained stable over the study (around 22%).

- NPV estimates for VIA have increased over the different study phases (from 72–95%).

NOTE

1 This study is supported by the Commonwealth Regional Health Community Secretariat (CRHCS); JHPIEGO; the Johns Hopkins University, Bayview Medical Center; the Johns Hopkins University, School of Hygiene and Public Health, Department of Molecular Microbiology and Immunology; and the University of Zimbabwe.
Utility of HPV Testing as an Adjunct to Visual Inspection in Detection of High-Grade Squamous Intraepithelial Lesion (HGSIL) of the Cervix, in Zimbabwe

Introduction

A HPV component was added to the Zimbabwe protocol beginning in Phase II of the study to determine if such testing could improve the usefulness of VIA as a screening alternative, particularly in a see and treat service delivery environment. The HPV specimens had not been analyzed at the time of this workshop and, therefore, only the rationale and study design features are described below.

Background

Cervical Cancer and HPV

- Cervical cancers all over the world are a result of genital tract HPV infections.
- HPV genomes are found, often integrated into the cellular DNAs, in about 95% of invasive cancers.

High-Risk and Low-Risk HPV

- HPV types 16, 18, 31 and 45 account for about 80% of cancers (high-risk HPVs).
- About 10 HPV types account for an additional 15% of cancers (intermediate-risk HPVs).
- About 15 HPV types are found rarely, or never, in invasive cancers (low-risk HPVs).

Pathogenesis of Cervical Cancers

- Although infections with HPV are very common, less than 1% of HPV infections will result in HGSIL or cervical cancer.
- There is a period of 10 to 25 years between HPV infection and invasive cancer.
Rationale for HPV Test in Cervical Cancer Screening

VIA and cervical cytology have been observed to have a sensitivity of at least 60% in detecting HGSIL in the ongoing study in Zimbabwe. The addition of a test for high-risk and intermediate-risk HPVs could increase this sensitivity to 80-90%. This may be important in resource-poor areas with high cervical cancer incidence.

HPV Test in the Zimbabwe Study

The ongoing investigation in Zimbabwe provided an opportunity to incorporate HPV testing in Phase II of the study. Resources for analyzing the HPV test were available as a result of a National Institute of Health grant to the Johns Hopkins University School of Hygiene and Public Health, Department of Molecular Microbiology and Immunology.

Design Features

All recruited women in Phase II had a HPV test. All women had a Pap smear and were examined by VIA and by colposcopy (and biopsy when indicated).

This study design has two major strengths:

- All women are being colposcoped and biopsied, if necessary. A "gold standard" diagnosis is therefore available for all women.
- Since all four procedures are performed within 1 to 2 days, there is no possibility for results of one test to bias the interpretation of another test (i.e., independence of investigator assessment).

HIV Infection

- HIV infection profoundly alters the course of HPV infection. It results in a higher prevalence of HPV infection and of cytological abnormalities, and accelerates progression to cancer.
- Based on other research findings, up to one half of the study subjects in the Zimbabwe study may be HIV-positive. Specimens of oral mucosal transudate are thus also being collected for HIV testing whenever possible. Consequently, we will have HIV antibody data on a sample of the Phase II subjects.

HPV Testing

- Initially, the test for high-risk and intermediate-risk HPVs will be with Hybrid Capture, probe B, in a 96-well format. The test also provides an estimate of viral burden.
• Individual types will then be identified in Hybrid Capture-positive specimens by polymerase chain reaction (PCR).

• Test specimens from HGSIL-positive/HPV-negative subjects will also be done by PCR for a more comprehensive analysis.

Analysis

• Choose HPV result categories which would increase sensitivity of the diagnosis without too much loss of specificity.

• Examine how well HPV testing functions as an adjunct to VIA alone, Pap smear alone, and to VIA and Pap smear combined.

• Results from this analysis should be available in late 1997.
RECENT VISUAL INSPECTION STUDIES

Cape Town Study: South Africa

Introduction

The research currently being conducted in Cape Town, South Africa, is both a screening and treatment study involving VIA (called direct visual inspection), AVI (called low-magnification visualization), Pap smears (conventional and automated), HPV DNA testing (Hybrid capture) and cervicography. A unique design feature of this study is that the gold or reference standard against which the effect of each test is being measured is the results of all the other tests. That is, “no disease” is defined as “no or low levels of high-risk HPV, Pap smears with no lesion, and no lesion by direct visual inspection (DVI), low-magnification visualization (LMV) or cervicography.”

Overall Study Objectives

To evaluate noncytologic screening methods for cervical disease so that screening algorithms for settings with different levels of resources can be developed

Specific Study Objectives

- Determine sensitivity, specificity, PPV, NPV of: Pap smears, HPV DNA testing, DVI, LMV, and cervicography for detecting high-grade disease
- Evaluate reliability of HPV DNA testing in a lesser developed setting
- Determine success rate/complications of LEEP in a lesser developed setting
- Evaluate reliability of LEEP equipment in a lesser developed setting
- Develop an econometric model to perform a cost/benefit analysis of various cervical cancer screening protocols that incorporate HPV DNA testing, DVI, LMV, Paps and LEEP, separately and in combination
Alternatives for Cervical Cancer Screening and Treatment in Low-Resource Settings

Reasons Site Was Selected

- Large unscreened population with high prevalence of disease
- Interest of involved organizations including CANSA, Medical Research Council, South Africa government
- Highly trained collaborators, excellent facilities for referral and research

Tests Being Evaluated

- HPV DNA testing—Hybrid Capture
- Pap smear—conventional and automated
- Direct visual inspection (DVI)
- Low-magnification visualization (LMV)
- Cervicography—National Testing Laboratories

Demographics of Study Population

- Unscreened women 35 to 60 years old
- Living in Khayelitsha, a periurban informal settlement
- Settlement population size is currently about 350,000
- Screening/treatment done at the community level

Design Features

- Initial screen using HPV, DVI, LMV
- Pap smear and cervicogram used as "backup screen"
Figure 1.

- Gyn oncologist performing all colposcopies
- Review of all Paps, cervicograms, cervical biopsies
- "No disease" defined as no or low levels of high-risk HPV, Pap with no lesion, no lesion by DVI, LMV or cervicogram (= reference or gold standard)

**Status as of May 1997**

- 2,000 women enrolled
- Data from 1,491 evaluated
- Funded until 10/97—will enroll 3,000
- Hoped to enroll a total of 10,000

**Preliminary Results**

**Table 1. Disease Frequencies**

<table>
<thead>
<tr>
<th>Diagnosis (based on biopsy)</th>
<th>Number (%) (n=1,491)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Within normal limits</td>
<td>1,386 (93%)</td>
</tr>
<tr>
<td>LGSIL</td>
<td>68 (4.6%)</td>
</tr>
<tr>
<td>HGSIL</td>
<td>30 (2.0%)</td>
</tr>
<tr>
<td>Cancer</td>
<td>7 (0.5%)</td>
</tr>
</tbody>
</table>
Table 2. Sensitivity Rates

<table>
<thead>
<tr>
<th>Method</th>
<th>LGSIL</th>
<th>HGSIL</th>
<th>Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytology</td>
<td>60%</td>
<td>77%</td>
<td>100%</td>
</tr>
<tr>
<td>HPV &gt; 10X</td>
<td>40%</td>
<td>53%</td>
<td>43%</td>
</tr>
<tr>
<td>HPV &gt; 1X</td>
<td>56%</td>
<td>70%</td>
<td>86%</td>
</tr>
<tr>
<td>DVI or LMV</td>
<td>62%</td>
<td>83%</td>
<td>71%</td>
</tr>
<tr>
<td>Cervicogram</td>
<td>44%</td>
<td>66%</td>
<td>86%</td>
</tr>
</tbody>
</table>

* Assuming 3 different thresholds defining "disease": 1) LGSIL and above, 2) HGSIL and above, and 3) overt cancer only

Conclusions

- Too few HGSIL cases to date to make any firm conclusions
- Comparative studies using an acceptable gold (reference) standard should be completed before implementing large-scale demonstration projects

NOTE

1 This study is supported by AVSC International, CANSA, Columbia University, Digene Corporation, Medical Research Council, National Testing Laboratories, PATH and the University of Cape Town.
Key Clinical Issues in Treatment of Precancerous Lesions of the Cervix

Introduction

If cervical cancer prevention programs are to be of public health value, screening assessments must be linked to judgments about how the patient will be treated for any precancerous lesions that are detected. Several factors influence the choice of treatment, including the lesion’s extent, size and severity. Treatment choice may also be influenced in the direction of more aggressive forms of therapy in settings where the potential for loss-to-followup is high subsequent to screening. In such situations where followup is expected to be poor, a screening program that is combined with treatment at the same visit—an approach that is called the see and treat approach to managing cervical precancerous disease—is recommended to maximize treatment rates. General issues related to treating cervical lesions as well as issues specific to the see and treat approach are reviewed below.

Factors Affecting Choice of Treatment

- Effectiveness
- Safety and the potential side effects
- Who is allowed to or can legally provide the treatment and what training is required for such persons
- The size and site of the lesion
- Acceptability by clients
- Acceptability by providers
- Equipment and supplies
- Cost

Unlike cancer which peaks in later years, precancerous lesions of the cervix occur most frequently in young women who are still in their childbearing years. This fact must be kept clearly in mind when treatment policy decisions are made. In choosing a treatment modality for younger women with cervical dysplasia, it is also important to recognize and consider the following:
Alternatives for Cervical Cancer Screening and Treatment in Low-Resource Settings

- Effect on fertility
- Safety in pregnancy

What Lesions Need to be Treated?

There is clear consensus that HGSIL must be treated because a majority of these lesions will progress in time to cancer. For LGSIL, in developed countries, the experience had been that the majority of lesions will regress spontaneously and thus do not require treatment. It is not clear, however, whether such patients are at a higher risk of recurrence of the lesion. Therefore, in situations where close followup is not possible, treatment of LGSIL may be advisable, particularly if the treatment is not highly invasive or associated with complications.

Association Between HIV and CIN

Data on the association between HIV and CIN are still equivocal. Two studies, however, from high HIV prevalence areas demonstrate an association between HIV and CIN. For example:

<table>
<thead>
<tr>
<th>Author</th>
<th>Country</th>
<th>Date</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Miotti</td>
<td>Malawi</td>
<td>1996</td>
<td>2.2 (1.10-4.8)</td>
</tr>
<tr>
<td>Maggwa</td>
<td>Kenya</td>
<td>1993</td>
<td>2.69 (1.29-5.49)</td>
</tr>
</tbody>
</table>

The implications of these studies on treatment for CIN are significant. For example:

- Should patients who are known to be HIV positive and who have cervical dysplasia be offered treatment for CIN when resources are limited?

- Will treatment of CIN in HIV-positive patients be as effective; will recurrence rates be greater?

Clearly, more studies on the role of HIV infection as it relates to increased susceptibility to CIN are needed.

See and Treat Approach—Description

- The see and treat approach involves screening followed by immediate treatment if abnormalities are present. This implies that screening results must be available immediately (e.g., by visual inspection of the cervix) so that the decision regarding what
Alternatives for Cervical Cancer Screening and Treatment in Low-Resource Settings

treatment is appropriate can be made and treatment can be carried out on the spot.

- Currently this approach is commonly used when women undergo colposcopy examination for a previous positive Pap test. If colposcopy confirms the result of the Pap smear, many practitioners will proceed to treatment without awaiting histological confirmation.

- There is no experience to date with a see and treat approach in conjunction with screening by visual inspection; however, data from a recent South Africa study on acetic acid visualization of the cervix (Megevand et al 1996) indicate the following:

  - 76 (3.1%) out of 2,426 women screened were positive on visual inspection using acetic acid (i.e., test positive). Of these 76, 61 (80.3%) had squamous intraepithelial lesion (SIL) on Pap smear, 65 (85.5%) had SIL on colposcopy and 55 (72.4%) had SIL on biopsy. In other words, 72% of women who were screened by visual inspection as requiring treatment were indeed confirmed on histology (biopsy), long considered a good "gold" standard.

  - In comparison to this, 315 (12.9%) of 2,426 women had SIL on Pap smears and of these 315 women, 280 (88.9%) had positive SIL on histology, mostly LGSIL.

  - It is notable that of the 31 cases of HGSIL in this study proven by histology, 20 (64.5%) were detected by VIA.

Implications for a See and Treat Strategy

- If treatment had been based on positive VIA test only, 21/2,426 (8.7/1,000) patients would have received treatment even though they had a normal cervix.

Note: Of the 15 cases that were VIA-positive but Pap-negative, 4 (26.7%) were LGSIL on colposcopy and histology.

- If treatment had been based on the Pap test only, 35/2,426 (14.4/1,000) patients would have received treatment for a normal cervix.
• It is noteworthy that in most of the developing world, colposcopy facilities are not available and therefore treatment is often done on the basis of Pap results only.

Given the above, a see and treat strategy in conjunction with visual inspection may be justified when colposcopy facilities are not available or accessible. To support such a strategy, there is an urgent need to conduct a see and treat study in low-resource settings to determine:

See and Treat with Screening by Visual Inspection: Issues That Need Further Study

• What is the safety and efficacy of treating precancerous lesions in primary care settings?

• What is the consequence of treatment in cases of under-diagnosis of overt cancer?

• What is the acceptability of treatment among women being treated and among providers giving treatment?

• What additional infrastructure and logistic support are needed to offer see and treat?

• What counseling and followup care is needed?

• What existing service(s) is most compatible with a see and treat approach to cervical cancer management?
Cervical Cancer Treatment: Options and Experience in Low-Resource Settings

Introduction

Based on findings from a situation analysis of treatment programs for cervical cancer and precancerous lesions of the cervix (Bishop, Sherris and Tsu 1995), there is evidence to support both cryotherapy and LEEP as treatment options for high-grade lesions. In most regions of the world, however, more costly and potentially more risky procedures are the standard of care. Key findings documented in the situation analysis are presented below as well as key questions remaining to be explored. As part of the situation analysis, PATH analyzed treatment survey results from over 100 providers worldwide. Of a total of 110 respondents, the largest proportion were from Africa (37%) followed closely by Asia (32%). (See Figure 1.)

Figure 1. Geographic Distribution of 110 Respondents for Treatment Survey

*FSU = Former Soviet Union

By far the largest proportion (56%) of respondents worked in either a large referral, tertiary care or teaching hospital. The second largest respondent category (29%) included clinicians and women’s health specialists working in some type of nongovernmental health facility such as a private clinic or mission healthcare center. (See Figure 2.)
As indicated in Table 1, the range of effectiveness observed for cryotherapy overlaps with that documented for LEEP. In general, however, LEEP is considered to be more effective than cryotherapy in comparable settings, particularly with larger, more severe lesions. On the other hand, for all of the other characteristics noted, cryotherapy has proven to be more practical as a treatment option for low-resource settings. The implications for acceptability and infection risk associated with the different potential side effects is something that needs to be further investigated.

Table 1. Treatment Options for Dysplasia/CIS

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Cryotherapy</th>
<th>Diathermy Loop Excision (LEEP)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Effectiveness</td>
<td>80–90%</td>
<td>90–95%</td>
</tr>
<tr>
<td>Side effects</td>
<td>watery discharge; infection risk</td>
<td>bleeding</td>
</tr>
<tr>
<td>Anesthesia required</td>
<td>no</td>
<td>yes</td>
</tr>
<tr>
<td>Tissue sample</td>
<td>no</td>
<td>yes</td>
</tr>
<tr>
<td>Power required</td>
<td>no</td>
<td>yes</td>
</tr>
<tr>
<td>Cost</td>
<td>relatively low</td>
<td>relatively high</td>
</tr>
</tbody>
</table>
Table 2 lists the range of effectiveness for cryotherapy in studies which have included, at a minimum, 1 year of patient followup. As indicated, cure rates are consistently lower across all studies when just high-grade lesions are considered. As noted previously, these lesions are likely to be larger, both in area and depth, and therefore more difficult to reach fully with cryotherapy.

Table 2. Cryotherapy for Treatment of CIN: Key Studies with at Least 1 Year of Followup

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Number of Women</th>
<th>Overall Cure Rate (%)</th>
<th>CIN III Cure Rate (%)</th>
<th>Followup in Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Andersen and Husthe</td>
<td>1992</td>
<td>261</td>
<td>83.5</td>
<td>77.8</td>
<td>7 (mean)</td>
</tr>
<tr>
<td>Olatunbosum et al</td>
<td>1992</td>
<td>70</td>
<td>90</td>
<td>80.8</td>
<td>5</td>
</tr>
<tr>
<td>Berget et al</td>
<td>1991</td>
<td>93</td>
<td>96</td>
<td>90.5</td>
<td>2</td>
</tr>
<tr>
<td>Draeby-Kristiansen et al</td>
<td>1991</td>
<td>96</td>
<td>92</td>
<td>86</td>
<td>10</td>
</tr>
<tr>
<td>Wright</td>
<td>1981</td>
<td>152</td>
<td>85.5</td>
<td>75</td>
<td>1 to 3.5</td>
</tr>
<tr>
<td>Hemmingson et al</td>
<td>1981</td>
<td>181</td>
<td>84</td>
<td>82</td>
<td>5 to 8</td>
</tr>
</tbody>
</table>


Table 3 shows the same information for LEEP. Because timing of followup differed between the two sets of studies cited above (1 year versus 6 months), however, the LEEP findings are not fully comparable to the cryotherapy findings.

Table 3. LEEP for Treatment of CIN: Key Studies with at Least 6 Months of Followup

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Number of Women</th>
<th>Overall Cure Rate (%)</th>
<th>CIN III/CIS Cure Rate (%)</th>
<th>Post-op Bleeding (%)</th>
<th>Followup</th>
</tr>
</thead>
<tbody>
<tr>
<td>Keijser et al</td>
<td>1992</td>
<td>395</td>
<td>81</td>
<td>—</td>
<td>8</td>
<td>4.8 years (mean)</td>
</tr>
<tr>
<td>Wright et al</td>
<td>1992</td>
<td>141</td>
<td>94</td>
<td>94</td>
<td>2</td>
<td>6 months</td>
</tr>
<tr>
<td>Gunasekera et al</td>
<td>1990</td>
<td>98</td>
<td>95</td>
<td>94.7</td>
<td>0</td>
<td>6 months</td>
</tr>
<tr>
<td>Luesley et al</td>
<td>1990</td>
<td>557</td>
<td>96.6</td>
<td>95.7</td>
<td>4.3</td>
<td>6 months</td>
</tr>
<tr>
<td>Prendiville et al</td>
<td>1989</td>
<td>102</td>
<td>97</td>
<td>99</td>
<td>4</td>
<td>1.5 years (mean)</td>
</tr>
</tbody>
</table>

As Figure 3 reveals, cone biopsy is a common treatment modality worldwide. Hysterectomy was also noted in the situation analysis to be in common usage for the treatment of CIN in all regions except Latin America. Response to the PATH survey suggests that cryotherapy is more available in Asia and the Caribbean than in Africa and FSU.

Figure 3. Type of CIN Treatment Now Being Used by Region
Respondents report treating all grades of dysplasia—from low- to high-grade lesions—with a smaller proportion of respondents reporting treatment of overt cancer (Figure 4). Equal treatment of all lesions, regardless of severity, with more invasive treatment modalities has potentially serious health implications for women and cost/efficiency implications for programs.

Figure 4. Grade of Dysplasia Treated
Figure 5 reveals how effective the survey respondents feel available treatments are for severe dysplasia. In general, respondents believe that LEEP and cryotherapy are significantly less effective for treating severe dysplasia than hysterectomy and cone biopsy.

**Figure 5. Perceived Effectiveness of Treatment for Severe Dysplasia (CIN III/CIS)**

This survey provides useful insights into the current thinking and perceptions of clinicians and decision-makers in developing countries regarding treatment of cervical cancer and precancerous lesions. The findings point to a number of key questions that still need to be answered:

- Which treatment strategies are most appropriate, cost-effective and acceptable for low-resource settings?
- What kinds of support services such as counseling, followup care, etc. must accompany the use of low-cost treatment in low-resource settings?
- Could aided visual inspection replace colposcopy to facilitate treatment in certain settings?
- What additional infrastructural support will be necessary to introduce low-cost treatment technologies?
Alternatives for Cervical Cancer Screening and Treatment in Low-Resource Settings

- What existing services are most compatible with cervical cancer screening and treatment?
- What types of clinicians can provide treatment?
- What are the best strategies to influence treatment policy?
Cost Considerations of National Cervical Cancer Programs

Introduction

A number of programmatic issues, including costs and logistics, need to be considered when introducing or scaling up to national cervical cancer programs. To aid in the assessment of cost issues, a group at Georgetown University is researching the cost-effectiveness of HPV screening as an adjunct to Pap screening in the United States. A computer-based simulation model provides the basis for assessing cost-effectiveness under various assumptions. A preliminary analysis of the cost-effectiveness of visual inspection of the cervix versus no screening under a specified set of assumptions illustrates how the model could be adapted for use in other countries, once accurate data to measure model parameters/assumptions become available.

Purpose of the Research

- To conduct a preliminary cost-effectiveness analysis of adding HPV screening to Pap screening in older US women
- To explore the appropriateness of applying this model to other screening settings

What is Cost-Effectiveness?

- A measure of economic efficiency: Compared to the next best alternative, are the outcomes expected of a program worth the required investment of resources?
- Incremental cost-effectiveness ratio (CER):

\[
\text{C-E Ratio} = \frac{\text{Cost}_1 - \text{Cost}_2}{\text{Effect}_1 - \text{Effect}_2}
\]

Study Hypothesis

- HPV is a strong risk factor for cervical carcinoma (stronger risk with selected serotypes).
• Hypothesis: Screening for cervical cancer in older (> 45-year-old) US women using both HPV and Pap smears is cost-effective compared to using Pap smears alone.

Methods

• Cost-effectiveness analysis

• Computer simulation modeling
  - Hypothetical cohort of 45-year-old US women
  - Screening options:
    - No screening
    - Pap only
    - Pap and HPV
  - CE-ratio (CER) ≤ $50,000/life year (LY) gained is considered “Cost-effective” (Source: Frame, Frybold and Patterson 1993; Goldman et al 1992.)

Natural History of Disease Model

Figure 1.

In the computer-based simulation model, probabilities would be assigned to each arrow in this natural history of disease model.

Model Parameters/Assumptions

• Screen every 3 years

• Pap smear
Alternatives for Cervical Cancer Screening and Treatment in Low-Resource Settings

- Sensitivity = 70–85%
- Specificity = 95%

- HPV
  - Sensitivity = 61%
  - Specificity = 94%

- Costs for services (1996 dollars)
  - Pap smear = $25
  - HPV testing = $35
  - Office visit = $42
  - Followup colposcopy = $212 to $240
  - Treatment for local invasive cancer = $13,056

Table 1. Results—HPV and Pap Screening

<table>
<thead>
<tr>
<th></th>
<th>Cost ($US)</th>
<th>d(LY)*</th>
<th>Incremental CER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pap versus no screening</td>
<td>$829.87</td>
<td>0.27</td>
<td>$3,069/LY</td>
</tr>
<tr>
<td>HPV and Pap versus Pap alone</td>
<td>$347.72</td>
<td>0.01</td>
<td>$34,181/LY</td>
</tr>
</tbody>
</table>

* Life year gained

Visual Inspection— Preliminary Analysis

- Compare visual inspection to no screening at all (the reality in some countries).

- Vary the accuracy (sensitivity and specificity) of visual inspection according to available research findings.

- Assume:
  - 2 times the US incidence and prevalence of disease (likely to be an underestimate)
  - AVI or VIA does not add to the estimated cost of a screening visit (not considering training-associated costs)
  - Treatment is only considered for HGSIL or worse disease
Table 2. Visual Inspection Versus No Screening—Preliminary Analysis

<table>
<thead>
<tr>
<th>Visual Inspection Accuracy</th>
<th>Cost ($US)</th>
<th>d(LY)*</th>
<th>Incremental CER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low (Megevand)</td>
<td>$1,567</td>
<td>0.54</td>
<td>$2,920/LY</td>
</tr>
<tr>
<td>Intermediate (Abrams)</td>
<td>$1,800</td>
<td>0.67</td>
<td>$2,700/LY</td>
</tr>
<tr>
<td>High (Sjamsuddin)</td>
<td>$1,693</td>
<td>0.74</td>
<td>$2,275/LY</td>
</tr>
</tbody>
</table>

* Life year gained

This very preliminary analysis reveals that, regardless of the assumed level of visual inspection accuracy, the incremental CER for visual inspection versus no screening at all is significantly less (> 20 times) than the cutoff point defining a cost-effective intervention. If the assumptions underlying this particular simulation model were verified, the results would suggest that visual inspection is a cost-effective health intervention at least in countries where, in effect, no screening for cervical cancer currently exists.

Future Work

- Formal meta-analyses on model parameters
- Include adherence rates as a variable: immediate followup and treatment may be important
- Include natural history and treatment protocols of countries other than US

Implications

- In a preliminary analysis, HPV proved to be a cost-effective adjunct screening tool in addition to Pap smear in older US women.
- This simulation model of the natural history of cervical cancer can be extended to include other settings and diagnostic/therapeutic strategies.
Considerations for Designing a Cervical Cancer Control Program

Introduction

A number of programmatic considerations need to be emphasized when designing a large-scale cervical cancer control program. First, it is important to understand the environment within which services will be offered, including client/provider understanding of cervical cancer, barriers to effective service delivery, and the health need for services. For example, results from a study conducted by PATH and the Kenya Medical Women's Association (PATH 1996) illustrate that knowledge and perspectives on cervical cancer and control strategies differ among clients and providers. Selected salient results from this study are provided below.

Table 1. What are the Most Serious Women's Health Problems in the Community?

<table>
<thead>
<tr>
<th></th>
<th>Providers (n=23)</th>
<th>Clients (n=40)</th>
</tr>
</thead>
<tbody>
<tr>
<td>STD/HIV</td>
<td>57%</td>
<td>46%</td>
</tr>
<tr>
<td>Malaria</td>
<td>9%</td>
<td>33%</td>
</tr>
<tr>
<td>Abdominal problems</td>
<td>0%</td>
<td>28%</td>
</tr>
<tr>
<td>Respiratory problems</td>
<td>9%</td>
<td>23%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>13%</td>
<td>10%</td>
</tr>
<tr>
<td>Depression</td>
<td>0%</td>
<td>20%</td>
</tr>
<tr>
<td>Cancer</td>
<td>17%</td>
<td>10%</td>
</tr>
<tr>
<td>Maternal death</td>
<td>17%</td>
<td>0%</td>
</tr>
<tr>
<td>Nonuse of family planning</td>
<td>17%</td>
<td>0%</td>
</tr>
</tbody>
</table>
Table 2. What is the Biggest Cancer Threat in Your Community?

<table>
<thead>
<tr>
<th></th>
<th>Providers (n=23)</th>
<th>Clients (n=40)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast</td>
<td>22%</td>
<td>50%</td>
</tr>
<tr>
<td>Cervical</td>
<td>57%</td>
<td>10%</td>
</tr>
<tr>
<td>Uterus</td>
<td>0%</td>
<td>8%</td>
</tr>
<tr>
<td>Stomach</td>
<td>0%</td>
<td>5%</td>
</tr>
</tbody>
</table>

Table 3. Providers: What Makes it Difficult to Provide Pap Smears? (n=23)

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Lack of facilities/supplies</td>
<td>48%</td>
</tr>
<tr>
<td>Cost</td>
<td>22%</td>
</tr>
<tr>
<td>Client concerns</td>
<td>17%</td>
</tr>
<tr>
<td>Time</td>
<td>13%</td>
</tr>
<tr>
<td>Fear of infection</td>
<td>4%</td>
</tr>
<tr>
<td>Lack of knowledge</td>
<td>4%</td>
</tr>
</tbody>
</table>

Table 4. Clients: What Can Be Done to Prevent Cervical Cancer (n=40)

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Don't know</td>
<td>80%</td>
</tr>
<tr>
<td>Regular medical exams</td>
<td>18%</td>
</tr>
<tr>
<td>Avoid family planning</td>
<td>3%</td>
</tr>
<tr>
<td>Avoid early sex</td>
<td>3%</td>
</tr>
<tr>
<td>Have fewer children</td>
<td>3%</td>
</tr>
<tr>
<td>Pap smears</td>
<td>2%</td>
</tr>
</tbody>
</table>

As these results show, in parts of Kenya, clients are largely unaware of the impact of cervical cancer on women’s health or of strategies to prevent cervical cancer. Providers understand that cervical cancer is an important health problem, but are concerned about logistic and other barriers to offering services.
Clearly, evaluating health need also is important when considering cervical cancer control strategies. Indicators of high health need are listed below.

**Health Need Indicators**

- High cervical cancer incidence
- High prevalence of severe dysplasia
- High prevalence of STD

**Assessing Health Need/Community Demand**

- Is problem big enough to warrant resources?
- Do clients/providers believe cervical cancer is a priority problem?
- Do clients/providers believe benefits of services outweigh disadvantages?

Once the client/provider “demand” for services and the health need have been evaluated, programs can move forward to plan program strategy. Strategies must be designed so that four interlinking goals can be achieved. Otherwise, programs run the risk of developing strategies that will have little or no impact on morbidity and mortality.

**Minimum Cervical Cancer Program Goals**

- **IEC:** Increase awareness of cervical cancer and available health services among women aged 35 to 50.

- **Screening:** Screen women at least once between the ages of 35 and 50.

- **Diagnosis and Treatment:** Treat women with high-grade dysplasia, refer those with invasive disease where possible, and provide palliative care for women with advanced cancer.

- **Monitoring and Evaluation:** Collect service delivery statistics that will facilitate ongoing monitoring and evaluation of program activities and outputs.

The inputs required to achieve these four goals include:
Necessary Inputs

• Increasing Awareness
  • Proven mechanisms for reaching older women
  • Providers trained in counseling/quality services

• Screening
  • Trained providers
  • Adequate supplies and equipment
  • Client followup capability
  • Reliable cytology services
  • Effective resources for diagnosis/treatment

• Diagnosis/Treatment
  • Trained providers
  • Colposcopes/other means of visualizing cervix
  • Adequate supplies/equipment
  • Referral for surgical treatment
  • Palliative care options

• Monitoring and Evaluation
  • Effective local systems for tracking screening/diagnosis results
  • Clinical registry of dysplasia/cancer cases

Once the four goals have been reached, programs can broaden their strategies as indicated below.

Expanding a Program’s Reach

• Increase proportion of highest risk women reached
• Expand target group to older women
• Expand target group to younger women
• Decrease interval between screening

The cost-effectiveness of programs will be influenced by a range of factors as indicated below.
Factors Affecting Cost-Effectiveness of Cervical Cancer Control

- Existing health infrastructure
- Cervical dysplasia/cancer incidence
- Cervical dysplasia/cancer progression rate
- Screening accuracy
- Cost of screening technology
- Screening frequency
- Treatment effectiveness
- Cost of treatment technology
- Availability of nonphysician providers
- Management strategy for invasive cancer
PROGRAMMING

A Regional Approach to Addressing Cervical Cancer in East, Central and Southern Africa

Introduction

Logistical considerations are important in developing or strengthening a cervical cancer control program. Since 1989, the Commonwealth Regional Health Community Secretariat (CRHCS) has identified cervical cancer as a priority women’s health issue, and has worked systematically towards delineating appropriate screening and treatment strategies for the region. The ongoing VIA screening study in Zimbabwe is one example of how CRHCS is supporting regional cervical cancer program development. Another is the situation analysis study described below which is designed to identify factors influencing the provision and use of screening and treatment services in five East, Central and Southern Africa (ECSA) countries. The results of this study will affect both cervical cancer policy and programming in the region.

About the CRHCS-ECSA

- The CRHCS for ECSA was established in 1974 under the auspices of the Global Commonwealth Secretariat in London.

- Since 1980, the CRHCS has operated under the joint full control of the member states’ governments as a permanent facilitating mechanism for promoting health development and standards of health in the region.

- Member countries are Botswana, Kenya, Lesotho, Malawi, Mauritius, Mozambique, Namibia, Seychelles, South Africa, Swaziland, Tanzania, Uganda, Zambia, Zimbabwe.

Mandate of the CRHCS

- Advocacy for health improvement in the region
- Brokerage (resource mobilization for regional health initiatives)
- Catalyst for regional scientific exchange, networking, expertise and information-sharing for health improvement

CRHCS Areas of Focus

- Reproductive health including STDs, HIV/AIDS
- Food and nutrition
Alternatives for Cervical Cancer Screening and Treatment in Low-Resource Settings

- Nursing and allied healthcare
- Health systems management
- Information dissemination

Background: Cervical Cancer Efforts

- 1989: Cervical cancer was listed as a very high priority area during the Reproductive Health Programme needs assessment.

- 1992: CRHCS mobilized an ECSA team of cervical cancer researchers. The initial research proposal on cervical cancer was submitted from Lesotho.

- 1996: 25th Regional Health Ministers Conference resolution: CRHCS to strengthen support towards quantifying the magnitude of cervical cancer in ECSA; to mobilize resources and develop skills required to cope with the disease, especially in rural settings. This resolution also called for incorporating breast cancer screening into cervical cancer screening programs.

- January 1996: The third ECSA cervical cancer investigators’ meeting was held in Victoria Falls, Zimbabwe. At that meeting the investigators:
  - Resolved that a situation analysis of cervical cancer, including existing diagnostic and treatment resources, is vital from the point of view of ECSA countries
  - Expressed the need to link policy implications of the Zimbabwe screening study results with the ECSA situation analysis results
  - Agreed to add a treatment arm and nurse training study to the Zimbabwe VIA screening study

Overall CRHCS Objectives Regarding Cervical Cancer

- To determine the risk factors associated with carcinoma of the cervix in the ECSA region

- To determine factors that impede the early diagnosis and treatment of cancer of the cervix in the region

- To determine the utility of visual inspection of the cervix in a primary care environment in the downstaging of invasive cervical cancer and any role that it might have in an integrated cervical cancer screening and detection program
Alternatives for Cervical Cancer Screening and Treatment in Low-Resource Settings

• To facilitate utilization of the relevant research findings in formulating policies and programs towards cervical cancer control and prevention in ECSA countries

Broad Objectives: Situation Analysis

To establish existing factors influencing early diagnosis and treatment of cervical cancer and identify potential for establishment of integrated cervical cancer screening and detection programs in five ECSA countries

Specific Objectives

• To determine the existing diagnostic facilities and procedures for cervical cancer at the tertiary, secondary and primary levels

• To determine the existing cervical cancer treatment facilities and procedures at the above levels of service delivery

• To determine the human resources available to diagnose and treat cervical cancer at the above levels

• To determine the communication and referral structures available at those levels of service delivery

• To identify requirements for establishment of integrated cervical cancer screening and detection programs in the above countries

Study Sites and Duration

• Study site: selected primary, secondary and tertiary facilities in five countries. This will include both public and private health institutions.

• Study duration: 6 months starting from 1 May 1997

Methodology

• Multicenter cross-sectional study (five countries). Data will be collected via an interview by pre-trained health workers.

• A random selection of tertiary, provincial (regional) hospitals, district hospitals, primary health centers and dispensary facilities will be included in the study.
- Observational visits to these facilities will be conducted and a pre-designed checklist will be used to:
  - Document existing screening and diagnostic facilities and communication resources
  - Determine availability and level of trained staff at a health facility, screening procedures, diagnostic capabilities and information on cervical cancer

Table 1. Sampling Distribution by Country: ECSA Situation Analysis Study

<table>
<thead>
<tr>
<th>Country</th>
<th>Tertiary Hospitals</th>
<th>Regional Hospitals</th>
<th>District Hospitals</th>
<th>Health Centers</th>
<th>Dispensaries</th>
<th>Total Selected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zimbabwe</td>
<td>Existing 4</td>
<td>Existing 8</td>
<td>Existing 52</td>
<td>bSelected 32</td>
<td></td>
<td>47</td>
</tr>
<tr>
<td>Population 11 million</td>
<td>Selected 4</td>
<td>Selected 3</td>
<td>Selected 8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kenya</td>
<td>Existing 1</td>
<td>Existing 7</td>
<td>Existing 60</td>
<td></td>
<td>Selected 28</td>
<td>58</td>
</tr>
<tr>
<td>Population 25 million</td>
<td>Selected 1</td>
<td>Selected 3</td>
<td>Selected 12</td>
<td></td>
<td>Selected 14</td>
<td></td>
</tr>
<tr>
<td>Tanzania</td>
<td>Existing 4</td>
<td>Existing 17</td>
<td>Existing 63</td>
<td>dExisting 103</td>
<td>Selected 32</td>
<td>64</td>
</tr>
<tr>
<td>Population 29 million</td>
<td>Selected 4</td>
<td>Selected 4</td>
<td>Selected 16</td>
<td></td>
<td>Selected 32</td>
<td></td>
</tr>
<tr>
<td>Uganda</td>
<td>Existing 1</td>
<td>Existing 4</td>
<td>Existing 39</td>
<td></td>
<td>dSelected 8</td>
<td>45</td>
</tr>
<tr>
<td>Population 20 million</td>
<td>Selected 1</td>
<td>Selected 4</td>
<td>Selected 12</td>
<td></td>
<td>Selected 20</td>
<td></td>
</tr>
<tr>
<td>Lesotho</td>
<td>Existing 2</td>
<td>cExisting 16</td>
<td>Existing 157</td>
<td></td>
<td></td>
<td>14</td>
</tr>
<tr>
<td>Population 2 million</td>
<td>Selected 2</td>
<td>Selected 10</td>
<td>Selected 2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total Selected</td>
<td>12</td>
<td>24</td>
<td>48</td>
<td>78</td>
<td>66</td>
<td>228</td>
</tr>
</tbody>
</table>

Note: The province/region was used as a catchment area for selecting (randomizing) health facilities for Zimbabwe, Kenya and Uganda; the referral zone was used as a catchment area for selecting (randomizing) health facilities for Tanzania; and the geographical terrain was used as a catchment area for selecting (randomizing) health facilities for Lesotho. For each level of care at least 2 different healthcare workers will be interviewed.
### Alternatives for Cervical Cancer Screening and Treatment in Low-Resource Settings

**Time Frame of Situation Analysis**

<table>
<thead>
<tr>
<th>Month</th>
<th>Activities</th>
</tr>
</thead>
<tbody>
<tr>
<td>March 1997</td>
<td>Completion of study instruments</td>
</tr>
<tr>
<td>May 1997</td>
<td>Commencement of data collection</td>
</tr>
<tr>
<td>September 1997</td>
<td>Preliminary country reports</td>
</tr>
<tr>
<td>October 1997</td>
<td>Multicenter data analysis and report writing workshop</td>
</tr>
<tr>
<td>January 1998</td>
<td>Preliminary regional report</td>
</tr>
<tr>
<td>March 1998</td>
<td>Presentation to Regional Conference on Policy Implications of Reproductive Health Research Findings</td>
</tr>
</tbody>
</table>

**NOTE**

1 See “Zimbabwe Cervical Cancer Screening Study.”
TRAINING

Visual Inspection Training in Indonesia

Providers Trained

- Two groups of providers were trained for this project:
  - 2 gynecologists working at a cancer screening and treatment center were trained in AVI. They used the Gynoscope for their visual inspection procedures.
  - 6 nurse practitioners working at family planning/family health centers were trained in both AVI and VIA. These nurses eventually used both the Gynoscope and their naked eyes for visual inspection procedures.

Training Content

- 2.5 days of training for doctors; 3.5 days of training for nurses

Lecture/Discussion (5 days)

- Background/rationale for visual inspection
  - Etiology and epidemiology of cervical cancer
  - Current screening options
  - Current treatment options

- Appearance of healthy and diseased cervices (slides)
  - How to perform AVI and VIA
  - What to expect
  - Definition of normal and abnormal

Clinical Practice (2–3 days)

- Review of Pap smear technique
  - Speculum examination
  - Obtaining the specimen

- Visual inspection
  - Speculum placement
  - Manipulation of the cervix to obtain satisfactory/complete view of the transformation zone
• Washing the cervix with acetic acid
• Recognition of normal/abnormal cervix

**Assessment**
• Clinical performance assessed by consultant at end of training and focused on:
  • Speculum examination skills
  • Ability to apply acetic acid and manipulate and visualize the cervix

**Training Materials**
• Handouts illustrating the importance of the transformation zone and other key concepts in cervical cancer screening
• Slide set for demonstrating varying appearance of cervix and principles of visual inspection
• Patient population

**Observations/Lessons Learned**
• A reference tool which would provide the doctor/nurse with examples of the cervix with which to compare their own findings would be beneficial.

• An adequate light source is required for both AVI and VIA. Light source should be sufficient to illuminate the cervix and must be placed so that the examiner's head does not block the light. At the same time, the light source should not be so intense or hot that it might burn the patient or the provider.

• Nurses and doctors quickly became confident in their ability to recognize a "normal" cervix.

• High correlation among AVI, VIA and Pap was eventually reported.
Training in Management of Cervical Cancer: Kenya

Objective

To develop training programs to upgrade staff in the management of STDs/RTIs and cervical cancer

Research Setting

- Women's clinic where clinicians are gynecologists

Initial Training: Project Coordinator

- Training in Pap smear-taking using the cervix brush
- Training in cervical smear-taking for HPV DNA PCR
- Introductory lessons in colposcopy
- Advanced training in colposcopy/biopsy-taking and outpatient treatment of precancerous lesions
- Training in the use of the Gynoscope

Colposcopy Training

- Introductory course: 5 days
  - Given by Dr. Renzo Barasso, Paris
  - 9 hours of lectures
  - 5 hours of hands-on exercises on meat specimens (biopsy and loop excision)
  - 20 hours of practical colposcopy on patients
    - 35 colposcopies done
    - 28 biopsies taken
    - 9 loop excisions

- Advanced course: 2 weeks
  - Given by Dr John Sellors, McMaster University
Topics Covered
• Basis of colposcopical examination
• Analysis of basic features observed
  • Without preparation
  • After acetic acid application
  • After Lugol’s stain application
• Concept of normal and abnormal transformation zone
• Biopsy-taking
• Concepts of outpatient treatment
• Official colposcopical classification
• Drawing colposcopical features
• Organization of a colposcopy clinic

Practical Lessons
• Colposcopy features
• Biopsy-taking
• Loop excision/cryosurgery
• Search for atypical vessels

Gynoscopy
• Basic training of the project coordinator by Dr. Rogo (experienced colposcopist and African Medical and Research Foundation [AMREF] site inspector)
• Focused on identification of acetowhite lesions

Subsequent Training
• The project coordinator (a gynecologist) has trained nursing assistants in Pap smear and cervical smear-taking.
• Four other gynecologists have been trained in colposcopy/biopsy-taking and outpatient treatment of precancerous lesions.
• Supervision was coordinated by the project coordinator.

Training Limitations
• High turnover of trained staff
• No followup available
TRAINING

Training for Visual Inspection: Zimbabwe

Providers Trained

- For the Zimbabwe Cervical Cancer Screening Study, 8 mid-career nurses were recruited and provided 5 days of training.
- On Day 1, it became apparent that several of the nurses were not competent in speculum examination. Thus this was included in their training.
- In addition 10 cytotechnicians, attached to the national cytology service, were assessed and trained.

Training Content

- Lectures/discussion
  - Epidemiology and etiology of cervical cancer
  - Precancerous lesions of the cervix
  - Screening methods
  - Treatment
- Exercise to demonstrate qualities of a screening test

Practical Sessions

- Speculum examination, application of acetic acid, taking Pap smears
  - Practice on the ZOE® model
  - Practice on clients
- Recognition of abnormal lesions from photographs and slides
- Clinical demonstration and practice on clients

Assessment

Progress was assessed at mid-course by:
- A multiple-choice knowledge test
- A competency-based assessment for speculum exam
Alternatives for Cervical Cancer Screening and Treatment in Low-Resource Settings

- A test in recognizing the normal and abnormal appearance of the cervix based on unmagnified photographs and slides of cervices

VIA Training Materials

- Unmagnified photographs with descriptive text in a visual aid atlas that illustrates the following types of cervices (Blumenthal and Sanghvi 1997):
  - Normal
  - Atypical
  - Abnormal (precancerous)
  - Cancerous

Length of Training

- Initial training
  - Nurses (5 days)—Nurses were taught to compare visual appearance to a visual aid atlas (Blumenthal and Sanghvi 1997)
  - Cytotechnicians (5 days)
  - Cytopathologists (5 days)

- Followup training (after pilot study)
  - Nurses (2 days)—mainly to reemphasize application of acetic acid and differentiate white lesions from inflammation
  - Cytotechnicians (5 days)
  - Cytopathologists (5 days)

Observations/Lessons Learned

- Nurses—Use of a visual aid atlas (Blumenthal and Sanghvi 1997)
  - All nurses identified at least 7 of 9 photos correctly during initial training.
  - Five out of 8 nurses identified all photos correctly.

- Nurses—Clinical Test (involving 60 clients)
• A high level of agreement was observed between VIA assessment and colposcopy and later with results of Pap tests.

• All cases of high-grade lesions (6) and cancer (2) were correctly identified.

• Nurses reported 7 cases as abnormal that were actually normal or low-grade lesions (false positives).

• Cytotechnicians

• Accuracy and reliability were assessed on a set of 15 slides.

• Skills initially were not at a level required for the study (followup training and technical assistance were provided).

• Only 5 out of 10 showed improvement (as assessed using test slides) following retraining and these were used in the study.

• Colposcopists: both were assessed to be procedurally competent by a Johns Hopkins University colposcopist.

Practical Issues

• If lithotomy tables were not available in the field, nurses were instructed to:

  • Perform the examination at the edge of a couch
  • Use pillows beneath the pelvis
  • Turn the speculum over the urethra
  • Use a Sims’ speculum

• 3–5% solution of acetic acid

  • Apply acetic acid copiously to the cervix and wait 1 minute before observation

• How to manage clients who are in menses?

  • Because VIA involves clearing away all cervical/vaginal discharge with copious amounts of acetic acid, nurses were advised to carry out the examination only if the patient did not object. If the client did object, she was asked to return after menses were over.
• Eyesight: Does it have to be perfect? What about color recognition?
  • Although data on the providers' eyesight were collected, these data have not been analyzed.

• In cases with considerable cervical trauma/large patulous or friable (easily bleeding) cervices
  • Need to maneuver with spatula to bring cervix into view
  • Need to be careful when clearing away any cervical/vaginal discharge
TRAINING

Issues in Training in South Africa

Professionals Trained to Perform Screening

- 2 nurses
  - 1 with 2 years' experience in cervical cancer screening
  - 1 no longer working at clinic
- 1 general practitioner with some experience in colposcopy
- 2 laboratory technicians

Topics Covered

- Clinical staff
  - Inserting specula
  - Technique for taking Pap smears
  - Direct and aided visual inspection
  - Cervicography
- Lab staff
  - HPV testing
- Quality control
  - Carried out in cytology lab
  - No additional training was thought necessary for cytologists

Training Format

- Didactic sessions
- Videos
  - Pap smear technique
  - Cervicography
- ZOE® model practice
- Review of teaching slides
  - Normals and abnormals from direct visualization
- Clinical practice
Length of Training

- Initial training was done over 1 week
- Clinical sessions were 3 afternoons

Training Followup

- Once a week clinical review with gyn-oncologist to review lesions
- A 6-month review of the quality of smears and photos indicated a need for update training to:
  - Review speculum insertion technique
  - Review Pap smear technique
  - Review cervicography technique
  - Review lesions from series of teaching slides from Dr. Wright

Lessons Learned

- Need to have good followup of trainees and ongoing quality control
- Need ongoing mentoring from experts

Future Training: Recommendations

When training is done for large groups:

- Need structured course covering the same content
- Suggest adding a modified colposcopy course for training in direct visualization
- Need to ensure regular followup of trainees and retraining as required
Introduction to International Programming Considerations

When considering the various strategies for promoting large-scale cervical cancer control programs in various countries, it is important first to examine differences in the current status of cervical cancer screening in individual countries. For example:

- In Brazil, providers are currently performing visual inspection at primary healthcare posts in Ceará State.
- In Indonesia, there is political commitment at the national level for a Comprehensive Integrated Cancer Management (CICM) program which is currently being implemented.
- The Philippines is planning a national Pap smear screening program using nurses and midwives, but regulatory issues for treatment and training may be barriers.
- In Thailand, Pap smear screening has been provided by nurse-midwives for 10 years, but human and physical resources are insufficient to achieve national coverage.

The presentations that follow provide an international perspective on many of the cervical cancer issues discussed during the workshop. Four of JHPIEGO’s Board of Trustees members considered the following key issues as they apply to their countries (Brazil, Indonesia, the Philippines and Thailand):

- What is the status of their cervical cancer control program including the extent of screening coverage, feasibility of a nationwide (or statewide) Pap smear screening program, and any targeted interventions implemented to strengthen/extend cervical cancer screening and treatment?
- What is the standard of care for treating pre-invasive cervical lesions (e.g., conization, LEEP, cryotherapy) at different levels of the health system (capital city, urban areas, district and sub-district facilities)?
Alternatives for Cervical Cancer Screening and Treatment in Low-Resource Settings

- What mechanisms/strategies can be used to introduce alternative approaches for managing pre-invasive cervical disease considering the following:

- At which health facility level(s) would it be appropriate to introduce visual screening? What proportion of all women in the country currently have access to this level of health facility?

- Into which health services currently being (or planned to be) offered would it be most appropriate to integrate visual screening (e.g., family planning, STD, etc.)?
INTERNATIONAL PERSPECTIVES

Country Programming Experience: Cervical Cancer Screening in Brazil

Update on the National Cervical Cancer Screening Program

- Extent of coverage at present
  - Cervical cancer incidence among the highest in the world
  - Detection at advanced stages only (77% women at Stage II or greater) (1994, Hosp. do Cancer, Rio de Janeiro)

- Feasibility of nationwide Pap smear screening program: low
  - Infrastructure at public health posts poor
  - Pap smear screening non-existent/low quality

Treatment of Pre-Invasive Cervical Lesions in Brazil

- Standard of care (conization, LEEP, cryotherapy) in the health system
  - Secondary: conization
  - Tertiary: surgery/radiotherapy

Introducing Alternative Approaches for Managing Pre-Invasive Cervical Disease

- Targeted interventions:
  - Ceará State implementing visual inspection screening program through PROAIS (Program for Integral Health Assistance)
  - Primary Health Unit Level
    - Auxiliary nurses/trained traditional birth attendants do visual inspection screening
    - Referral to nurse for Schiller test (available on a weekly basis)
    - Biopsy/treatment with cautery by physician (available on a monthly basis)
Alternatives for Cervical Cancer Screening and Treatment in Low-Resource Settings

- Results:
  - 7 positive cases identified in 1,000 examined women
  - Same results as physician-based screening at the University Hospital

Figure 1. Percentage of Positive Cases (Micro to Invasive Cancer) Detected at University Hospital Maternity Outpatient Service, Ceará, Brazil, 1987-1996

Summary Points

- Visual inspection screening
  - Proven to be feasible (at primary health post) in Ceará State; Referral for treatment at next higher level also successful
  - Could be implemented through PAISM (Program of Integrated Services for Women, Ministry of Health [MOH]) with National Cancer Institute
  - Screen ages 20 to 70 but should be emphasized at ages 40 and above where mortality greatly increases

- Treatment
  - Electricity common at primary health post so that cautery is more likely to be available and is cheaper
INTERNATIONAL PERSPECTIVES

Country Programming Experience: Cervical Cancer Screening in Indonesia

Update on the National Cervical Cancer Screening Program

- Extent of coverage at present
  - 190,000 new cancers annually with gynecologic cancers at top
  - Faculty of Medicine, Department of Ob/Gyn in Jakarta: more than 60% of cervical cancer cases at advanced stage
  - MOH committed to CICM

- Feasibility of nationwide Pap smear screening program: low
  - Non-existent because cancer not a priority
  - No organized, regular screening strategy

- Proportion of women currently having access is extremely low: estimated at 5% of women having a Pap smear (usually at family planning clinic, so skewed to women under 35 years old)

- Targeted interventions:
  - Phases of MOH cancer management program (CICM)
    - First 5-year phase: six provinces of Java/Bali (meet criteria for sites for CICM). Begin at four provinces outside Java/Bali to develop Class B hospitals
    - Second 5-year phase: provinces in Sumatra/Kalimantan
    - Third 5-year phase: all provinces
  - Studies on VIA and AVI (with Gynoscope)

Treatment of Pre-Invasive Cervical Lesions in Indonesia

- Standard of care (conization, LEEP, cryotherapy) in the health system
  - No standardization—variable
Alternatives for Cervical Cancer Screening and Treatment in Low-Resource Settings

- Conization, LEEP, cryotherapy at Class C hospitals (Jakarta, provincial hospitals, some district hospitals)
- Theoretically, cryotherapy acceptable at health center (sub-district and below) but limited resources
  - Limited availability of coolant (CO₂ or nitrous oxide)
  - No experienced provider

Introducing Alternative Approaches for Managing Pre-Invasive Cervical Disease

- Appropriate health facility level(s) for introducing visual screening:
  - Health center because more than 60% of women have access to this level
  - Family planning clinic (but skewed to screening younger women)

- Cryotherapy—Implementation
  - Theoretically feasible at health center level
  - Can cryotherapy be performed based on VIA/AVI results (i.e., not waiting for Pap smear reading)?

Summary Points

- MOH committed to CICM
  - Focusing on upgrading facilities
  - Training providers
- Cancer not seen as a priority by many
- No national screening program available yet: sporadic and unorganized
- More than 60% of women have access to health centers where cryotherapy would be feasible
INTERNATIONAL PERSPECTIVES

Country Programming Experience: Cervical Cancer Screening in the Philippines

Update on the National Cervical Cancer Screening Program

- Extent of coverage at present
  - Second most important cancer among women in Philippines
  - 557 cases of 4,897 patients seen at Philippines General Hospital (PGH) in 1995
  - Ongoing project in women’s health related to cancer of the cervix
    - Started in 1995 in 10 regions
    - Ends in 2000

- Feasibility of nationwide Pap smear screening program considered low
  - Doctors: speculum/pelvic exam, Pap smear, colposcopy and punch biopsy and interpret results
  - Only nurses on a selective basis trained to do Pap smears and pelvic exam

- Targeted interventions:
  - Nationwide Pap smear screening program to involve midwives at the community level
  - At PGH, all gynecological patients have Pap smears at first visit
  - High-risk women required to have a Pap smear annually

- Proportion of women currently having access
  - No data (70% of population do not see a physician for consultation)
  - Approximately 1–2% of patients with gynecologic concerns approach a physician. These are almost always cases of invasive cancer.
Treatment of Pre-Invasive Cervical Lesions in the Philippines

- Standard of care in the health system
- Capital city/provincial hospitals
  - Gynecologists perform colposcopy first and Pap smears followed by conization
  - If results of previous two are questionable, then cryotherapy is done (only in capital cities of Metro Manila)
  - LEEP not done in the Philippines
- District and subdistrict facilities: no treatment available

Introducing Alternative Approaches for Managing Pre-Invasive Cervical Disease

- Appropriate health facility level(s) for introducing visual screening
- Primary healthcare settings
  - Barangay Health Station (BHS) by nurses/midwives
  - Rural Health Units (RHU) (lowest level for physicians)
- Proportion of women currently having access to the BHS
  - 68% of population is rural so at least this many women have access to BHS

Mechanisms/Strategies for Managing Pre-Invasive Cervical Disease

- Health services for integrating visual screening: family planning, STD, Women’s Health and Safe Womanhood Services, Adolescence Clinic
- Continuing education programs for medical and nursing practitioners
- Wet clinics for actual performance of procedures (colposcopy, Pap smear and conization, etc.)

Feasibility of a Nationwide Screening and Treatment Program

- Cryotherapy—Implementation
  - Currently done by physicians only
• Nurses need special training with certification; not possible until the Professional Regulation Commission Board of Nursing credentialing committee is fully operational

• Budgetary constraints for cryotherapy as a treatment option:
  • Nitrous oxide for cryotherapy costs around US$300
  • Can only be used for treating 6 to 7 patients (US$40/patient)
  • PGH charges US$10 per patient per therapy; hospital loses money

Summary Points

• Commitment from Department of Health (DOH): plan, organize and implement the Philippine cancer control program targeted toward the reduction of cancer morbidity and mortality and the improvement of survival rates and quality of life of cancer victims

• DOH gives final approval to all government and private institutions
  • New clinical techniques always welcome
  • Most Philippine studies are replications

• Limited capacity to screen if only selected nurses can do a pelvic exam

• Budget limitations for cryotherapy treatment costs at all health services levels
International Perspectives

Country Programming Experience: Cervical Cancer Screening in Thailand

Update on the National Cervical Cancer Screening Program

- Medical school curriculum: training in Pap smears since 1960s
- Family Health Division/MOH: nationwide Pap smear screening program
  - Started 10 years ago: training of nurse-midwives (who insert IUDs)
  - 30.8% married women of reproductive age (15 to 44) screened with Pap smear
- National Cancer Institute—screening program targets
  - Standard: every woman 35 years and older screened once every 5 years
  - Targets:
    - 1996: 60%
    - 2000: 80%
  - Present: 15% actually screened (women aged 35 to 59)
- Population of women of reproductive age (15 to 44) = 9 million
  - If 30.8% screened already, should have read 3 million smears
  - Family Health Division has screened only about 500,000 (1 of 6 women)
- National screening program
  - Available: spatulas, slides, specula, trained providers
  - Not available:
    - Fixative (district level and below)
    - Cytologists (only 200 in the country, in urban centers)
Alternatives for Cervical Cancer Screening and Treatment in Low-Resource Settings

Timely return of results outside major cities (takes 1 to 3 months to return)

Treatment of Pre-Invasive Cervical Lesions in Thailand

Standard of care in the health system:

- Medical school hospital/Bangkok: LEEP
- Capital city/large cities:
  - Conization
  - Cryotherapy available but is not popular
    - Not enough logistics
    - Women don’t like the post-treatment discharge
- District and subdistrict facilities: None
  - Refer to one of the 18 large hospitals in country

Introducing Alternative Approaches for Managing Pre-Invasive Cervical Disease

- Appropriate health facility level(s) for introducing visual screening
  - Primary healthcare center: nurse who can insert IUD is here
  - Health center/district hospital: Gyn clinic, family planning clinic, STD clinic

Summary Points

- Commitment from government for Pap smear screening for over a decade
- Implementation of the program still has limitations
  - Lack of logistics at peripheral levels
  - Limited number of cytologists in the country
- Screening targets not being reached even with government commitment
- Visual inspection is an appropriate screening alternative
In Cameroon, Haiti and Côte d'Ivoire, significant barriers impede the implementation of a national cancer screening program. Three Trustees, Drs. Welfens-Ekra, Leke and Brutus, fielded questions from the facilitator and the audience on the status of cervical cancer screening and treatment in their countries. The issues, questions and responses are summarized below by key topic area.

- **Availability of cervical cancer screening services: extent of coverage at present**

  If screening is available at all, it is usually available only in the capital city and in larger cities in these countries. Screening is through Pap smear and annual coverage is very low.

- **Availability of cervical cancer screening services: feasibility of a nationwide Pap smear screening program**

  Pap smear screening is available in capital cities where cytopathology is centralized. Political will for national screening is lacking in Cameroon and Haiti whether resources are available (Cameroon) or not (Haiti).

- **Treatment of pre-invasive cervical lesions at different levels of the health system**

  In Cameroon, treatment is given at the tertiary level with conization and gynecologic surgery available at the provincial level. In Haiti and Côte d'Ivoire, conization and LEEP are available only in the capital city.

- **Barriers hindering implementation of a national cervical cancer screening and treatment program**

  Cultural barriers hindering program implementation in Cameroon are exemplified by the fact that none of the 250 dialects has a word for “cancer.” Resource problems (e.g., limited funds, health
infrastructure inadequacies, communication problems in rural areas, and inadequate numbers of cytopathologists and technicians) are exacerbated by the fact that healthcare providers have little to no exposure to cervical cancer screening and treatment during basic training. In Haiti, for example, nurses do not even learn to do a pelvic examination during their basic training. In Côte d'Ivoire, caring for HIV-infected women who have cervical dysplasia is an issue.

• Commitment

A small group of obstetrician-gynecologists in Haiti are organizing themselves to assess the problem more effectively, develop a strategy and lobby the government. In Côte d'Ivoire, a multidisciplinary group was created in September 1996 by the National Society of Gynecology and Obstetrics to develop a cervical cancer screening program. In Cameroon, there is almost no governmental commitment, although key professional community members are committed.

Summary

Some professionals or groups within these countries are interested in developing cervical cancer control programs including training interventions. A mechanism for translating political commitment into action/implementation is needed, however. In addition, working with key providers to determine the appropriateness of various screening and treatment modalities for various health facility levels must be supported with appropriate awareness campaigns for informing the public about cancer.
The following recommendations were derived from the various plenary discussions held during the 2-day workshop.

1. If morbidity and mortality due to cancer of the cervix are to be measurably reduced, cervical cancer screening and treatment programs must be implemented for at-risk women on a national or large-scale basis.

2. The test qualities of visual inspection have proven to be reasonably consistent across the various investigative studies to date, including those for which only preliminary data are currently available. Once ongoing studies are completed, efforts should shift to investigating how visual inspection performs in the field under more routine health delivery (versus field research) conditions, and how the benefits of such visual inspection-based screening programs could outweigh program limitations, including the potential for overtreatment.

3. In addition to documenting further the efficacy and safety of visual inspection under different field conditions, such applied research projects should answer important questions related to the practicality, feasibility and, most important, the acceptability of visual inspection-based screening programs among the target population.

Large-scale visual inspection-based screening programs should have the following characteristics:

- As a primary means of screening, the use of visual inspection should enable the largest proportion of at-risk women to be screened at least once during their lives, preferably more frequently, if feasible.

- In countries where cytology programs are well established and functioning in at least part of the public sector, visual inspection could be used as an adjunct to cytology or as the primary means of screening, if desired, to reduce program-related costs. Confirmation of disease as well as treatment should take place at whichever level of the health system supports the least loss-to-followup, balanced by appropriate treatment.
• In countries where cytology programs exist only in the private sector, visual inspection could be considered the primary screening method in the public sector—with referral for diagnostic testing, if practical, or treatment on the spot if significant loss-to-followup is likely.

• In countries where, in effect, no screening exists, visual inspection may be the only feasible option for screening for precancerous lesions. Practical ways to increase sensitivity and specificity of this test need to be investigated. This could include, for example, repeat testing over time or treatment protocols that target women most likely to be diseased, given a positive screening test (e.g., women with higher parity and/or women over age 30). In such settings, treatment would need to be on-the-spot or close enough in time and proximity to limit loss-to-followup.

Working Group Recommendations

Specific recommendations in the areas of screening, treatment and programming were developed by small working groups during the afternoon of Day 2. Key points from those groups, presented in the final plenary meeting, are summarized below.

Screening

• The gold standard in any studies to document further the test qualities of visual inspection should be colposcopy at a minimum, biopsy wherever possible.

• Standardization of what constitutes visual inspection “test positive” is critical. At a minimum, the threshold of test positive should be acetowhite change. More exact definitions and teaching aids will improve or maintain acceptable test qualities in the field.

• The threshold defining who is “diseased” (e.g., high- or low-grade lesions) and thus who should be treated should reflect the epidemiology of disease in that country. In unscreened populations, diseased women constitute prevalent cases. In such settings, treating all cases of precancerous lesions might result in a greater immediate programmatic impact. On the other hand, in screened populations—where diseased cases are new (incident) ones—treatment should be targeted at high-grade lesions most likely to progress.

• A test with 60% sensitivity or above should be considered a viable screening option for picking up cases of disease in settings where
the current screening option has comparable or similar sensitivity, or no screening option exists.

- A screening test should have a specificity of 70% or above to be considered a viable option for correctly identifying those without disease if cryotherapy is used as the treatment modality. Higher specificity is recommended for situations in which LEEP is used to treat precancerous lesions.

**Treatment**

- Additional research is needed on the natural history of disease or disease progression in the presence of various cofactors (in particular HIV).

- Further studies (including examination of treatment failure rates among HIV-positive women) need to be conducted to determine the most appropriate treatment modality in countries where HIV prevalence is high.

- The role of cold coagulation and electrocautery as treatment options should be further investigated.

- Appropriate counseling is critical as a means of informing women about their screening results and of assisting them in deciding what further action—including treatment—they should take.

- Based on the results of what is likely to be an imperfect screening test, the woman, together with her provider, should decide whether or not to treat. This decision should be consistent with national policy, which dictates how public healthcare funds are spent.

- The projected cost to the health system of potentially overtreating some women should be balanced against costs currently incurred by the system in treating women with more advanced disease (which requires more expensive treatment modalities).

- The projected "cost" to a woman (and her family) of potentially overtreating her when no disease is present should be balanced against the potential benefit a woman might perceive she has gained from being protected from advanced (clinical) disease for at least 5 to 10 years.

**Programming**

- A priority for cervical cancer programs should include primary prevention aimed at reducing the risk of acquiring HPV and developing precancerous lesions (e.g., reduced parity through
family planning, safer sexual practices to reduce STDs through IEC and condom promotion).

- Health policy- and decision-makers and providers need to be sensitized about the new data regarding screening and treatment options and encouraged to develop context-specific plans to integrate these options into existing cervical cancer programs.

- Health delivery settings—in which offering cervical cancer screening and treatment would be most advantageous to women and the health program as a whole—need to be identified.

- Ways of integrating cervical cancer screening and treatment services into existing women’s health services are critical in resource-limited environments.
REFERENCES


APPENDIX A

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APPENDIX B

Workshop Agenda
Alternatives for Cervical Cancer Screening and Treatment
in Low-Resource Settings
21–22 May 1997

DAY 1

8:00–8:30  Continental Breakfast

8:30–9:30  Opening

Welcome and introduction  Paul Blumenthal
Keynote address  Jeff Spieler
Workshop objectives and organization of workshop  Paul Blumenthal
Facilitated Discussion  Lynne Gaffikin

9:30–12:15  Screening

Currently available screening tests: Cytology

• Why visual inspection with acetic acid?  Paul Blumenthal
• Factors affecting a screening test  Lynne Gaffikin
• Cytology-based screening: Technical and programmatic considerations  Paul Blumenthal
• Accuracy of Pap smears: Recent findings from a meta-analysis  Lynne Gaffikin
• Implementing cytology services: Zimbabwe cervical cancer case study  Richard Szumel
• Facilitated discussion  Paul Blumenthal

Break

Currently available screening tests: Visualization

• Introduction—Method characteristics  Paul Blumenthal
• Visual inspection studies
  • Visual inspection of the cervix as a screening option
  • Cape Town Study: South Africa
  • Cervical cancer screening in women attending a family planning clinic in Nairobi, Kenya

12:15–12:45 Lunch

12:45–2:15 Screening (continued)
  Vivien Tsu
Zimbabwe Cervical Cancer Screening Study
  • Background
  • Methods and results
  • Utility of HPV testing as an adjunct to visual inspection in detection of high-grade squamous intraepithelial lesion (HGSIL) of the cervix, in Zimbabwe
  • Facilitated discussion

2:15–3:30 Treatment
Key clinical issues in treatment of precancerous lesions of the cervix
  Harshad Sanghvi
Cervical cancer treatment: Options and experience in low-resource settings
  Jacqueline Sherris
Facilitated discussion
Break
### Alternatives for Cervical Cancer Screening and Treatment in Low-Resource Settings

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<td>Cost considerations of national cervical cancer programs</td>
<td>William Lawrence</td>
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<td>Cost considerations for treating HGSIL</td>
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<td>A regional approach to addressing cervical cancer in East, Central and Southern Africa</td>
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<td>9:30–11:15</td>
<td><strong>Country Programming Experience</strong></td>
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<td>Introduction to international programming considerations</td>
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<td>Country programming experience: Cervical cancer screening in Brazil</td>
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<td>Country programming experience: Cervical cancer screening in Indonesia</td>
<td>Abdul Bari Saifuddin</td>
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### 11:15–12:15 Training Issues

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### 11:15–12:15 Panel Discussion: The Introduction of National Cervical Cancer Screening Programs

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<td>Robert Leke</td>
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<td>Côte d’Ivoire</td>
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### 12:15–12:45 Lunch

### 12:45–1:45 Programming Strategies

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<td>Group work</td>
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### 4:30–5:30 Wrap-up/Next Steps

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