Summary of Proceedings

Consultative Forum
on
Cervical Cancer Prevention in Low-Resource Settings

Hosted by Program for Appropriate Technology in Health (PATH)

Baltimore, Maryland
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Table of Contents

Executive Summary 1

Background 2

Summary of Proceedings: Introduction 3

Proceedings: Presentations by ACCP Partners 4

Proceedings: Presentations by Guest Participants 9

Discussions 12

Final Thoughts, Discussion, and Conclusions 16

Appendices
- Conference Agenda
- List of Participants and Contact Information
- Overheads/Slides of Presentations

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EXECUTIVE SUMMARY

Recognizing that cervical cancer is the leading cause of death from cancer among women in the developing world, the Alliance for Cervical Cancer Prevention (ACCP) has been working to develop and implement effective ways to screen for and treat cervical cancer in low-resource settings. The Consultative Forum on Cervical Cancer Prevention in Low-Resource Settings meeting described in this report was convened by the Program for Appropriate Technology in Health (PATH) as a part of the collaborative efforts of the ACCP. The goal of the Consultative Forum was to facilitate discussion about overarching issues key to instituting effective cervical cancer prevention programs. The forum asked participants to address the manner in which programs can work within—or improve upon—a country's current infrastructure, policy efforts, and service delivery systems. The one-day meeting, held in Baltimore, Maryland, was intended to cultivate an exchange of views with a broader community of experts on activities by Alliance organizations and other groups.

The forum brought together thirty researchers, service providers, and advocates from around the world. In the morning, presenters shared country experiences and lessons learned. In the afternoon, discussion groups addressed issues such as identifying key questions for which further research can provide the most helpful information; identifying the social, cultural and economic conditions that contribute to a program's success; and identifying ways in which the Alliance, in the future, can best help programs. In response these questions, participants made a number of recommendations to the ACCP.

In the area of research and evaluation, participants recommended that Alliance members and others working in the area:

- continue to clarify the effectiveness and safety of various screening and treatment approaches;
- document the cost-effectiveness of various cervical cancer prevention strategies and disseminate information on cost-effectiveness to health decision-makers worldwide;
- assess the impact of HIV on screening and treatment effectiveness and the effect of treatment on HIV shedding and HIV transmission;
- ensure that sufficient resources are devoted to human papilloma virus (HPV) vaccine development; and
- advocate for more research on alternative approaches to identify women at risk of cervical cancer, including biomarkers.

In the area of program planning, participants recommended that Alliance members and others working in the area:

- Recognize that different cervical cancer prevention approaches will likely be necessary for different country environments. For example, moderately-developed countries have different needs and program capabilities than lesser-developed countries.
- Ensure that all key components of an effective cervical cancer prevention program are in place before creating demand at the community level. These include effective community education strategies, screening technologies/approaches, treatment capability, follow-up and referral strategies, etc.

- Recognize that effective programs need to ensure demand for services at the community level and from women themselves, as well as support from the "right" allies and opinion leaders.

In the area of advocacy/materials development, participants recommended that:

- advocacy and information dissemination should be designed to build international, national, and grassroots support for cervical cancer prevention activities; and
- standardized training/introduction packages needed for visual inspection with acetic acid (VIA), self-collection of vaginal/cervical samples, cryotherapy, and other newer approaches should be developed, which could then be adapted to country-specific situations.

The support of the Bill & Melinda Gates Foundation for the ACCP has allowed Alliance partners the resources and flexibility to work toward preventing cervical cancer in areas of the world where this goal previously seemed unattainable. The Alliance's early efforts have clarified needs and concerns related to all components of Alliance work and have formed the groundwork for focusing and/or expanding key program activities. Initiatives such as the Consultative Forum on Cervical Cancer Prevention in Low-Resource Settings help to build an expanded network of experts and colleagues who understand Alliance project directions and can provide valuable input and complementary activities in the future.

PATH would like to thank all participants at the Consultative Forum for their valuable insights and contributions.

BACKGROUND

In September 1999, with funding from the Bill & Melinda Gates Foundation, five international organizations with a shared goal of working to prevent cervical cancer in developing countries joined together to form the Alliance on Cervical Prevention (ACCP). Recent data from the International Agency for Research in Cancer (IARC) highlight the importance of the Alliance's work. IARC estimates that the annual number of new cervical cancer cases worldwide reached 466,000 in 2000; annual deaths now top 230,000 (up from 190,000 in 1990). Consistent with previous estimates, at least 80 percent of deaths occur in developing countries, with most occurring in the poorest regions—South Asia, sub-Saharan Africa, and parts of Latin America. What sets cervical cancer apart from most other cancers is that cervical cancer is a preventable disease if pre-cancerous lesions are detected and treated early.

In the first year and a half, the Alliance, made up of EngenderHealth (formerly AVSC International), IARC, JHPIEGO Corporation, Pan American Health Organization (PAHO), and Program for Appropriate Technology in Health (PATH), has been working worldwide to achieve Alliance objectives to:

- assess new cervical cancer **screening and treatment** approaches and technologies appropriate to low-resource settings;
- improve **service delivery** systems;

- ensure that **community perspectives** and needs are incorporated into program design, implementation, and evaluation; and
- heighten **global awareness** and support of cervical cancer and effective prevention strategies.

Alliance projects focus on regions in which cervical cancer incidence and mortality are highest: sub-Saharan Africa, Latin America, and South Asia. Alliance-funded research and demonstration projects are underway in a number of countries, including India, Mexico, Peru, Chile, Ecuador, El Salvador, Venezuela, Thailand, Kenya, Ghana, and South Africa.

The process of operating as an alliance ensures that each of the five partner organizations can develop program strategies based on its organizational strengths and resources, at the same time allowing for collaboration and the sharing of information among partners. As part of the Alliance's collaborative efforts, PATH convened the Consultative Forum on Cervical Cancer Prevention in Low-Resources Settings on April 5, 2001, in Baltimore, Maryland. This Forum brought together Alliance partners and outside experts to discuss new insights into the feasibility, effectiveness, and sustainability of various screening and treatment approaches and the challenges that can emerge when introducing them into low-resource settings.

The aims of the Consultative Forum were to (1) present to colleagues working in similar programs the findings and lessons learned from the Alliance's first one and one-half years; (2) to learn from colleagues outside the Alliance about their experiences and challenges in implementing studies and/or establishing cervical cancer prevention programs; (3) to cultivate an exchange of views with a broader community of experts on activities by Alliance organizations and other groups; (4) to explore strategies for working in complementary ways with organizations represented by the invited guests.

The goals that we set out to achieve by hosting the Consultative Forum were to create an expanded network of experts and colleagues who understand Alliance project directions and can provide valuable input, complementary activities, or institutional participation in future Alliance efforts, to gain clarity on what project activities hold promise for the greatest impact, and to develop a stronger workplan for the future work by Alliance and colleague organizations based in part on input gathered at this meeting.

SUMMARY OF PROCEEDINGS: INTRODUCTION

Dr. Jacqueline Sherris of PATH opened the Consultative Forum by welcoming everyone and reviewing the Forum goals, including the discussion of key questions that address how we can most effectively reach the overall goal of reducing cervical cancer deaths. Dr. Sherris began by noting that an effective cervical cancer prevention program implies far more than an effective screening approach of five interlocking pieces. For the program to be effective, it needs:

1. coverage of at least 70 percent of the at-risk population;
2. to have a measurable impact;
3. to have an available, safe, and effective treatment method;

4. to have a screening test with adequate accuracy and reliability; and
5. to have a method of follow-up that keeps loss to follow-up to less than 20 percent.

Forum participants examined several key issues during the day's presentations and discussions:

1. What are the interventions and approaches that show promise for making the greatest long-term health impact?
2. What existing conditions in a country are essential to effective cervical cancer prevention programming and what conditions interfere with such efforts? How can programs best work within current local and national conditions to ensure effective, sustainable programs?
3. How can the Alliance and other institutions best assist developing countries in selecting and/or improving prevention approaches? How should areas of assistance such as training, communication/advocacy, or laboratory support be prioritized to ensure program quality and sustainability?

PROCEEDINGS: PRESENTATIONS BY ACCP PARTNERS

Responding to Service Delivery Challenges in Low-Resource Settings: Cervical Cancer Prevention
Ms. Karen Beattie, EngenderHealth

Karen Beattie presented research being conducted by the partnership of EngenderHealth, Columbia University, and University of Cape Town. The partnership is in its sixth year of collaboration on clinical studies, the last two funded under the auspices of the ACCP.

Ms. Beattie introduced her presentation by noting that technologies are usually developed or introduced in response to a medical problem—a disease needs a cure, a vaccination, some equipment, for example. However, introducing a new technology may often create problems of its own. It may not be practical, feasible, or accessible from a service perspective, or its very nature may make it undesirable for those who can most benefit from it.

In the case of cervical cancer, the Alliance is engaged in a search for appropriate technologies that can be applied in a range of situations and that will help address the limitations of the current technologies. Consider that in sub-Saharan Africa in the 1980s, there were fewer than 100 cancer specialists for a population of 300 million people. In many African countries, there are only a few ob/gyns for the entire country. The technologies chosen, therefore, must be able to be provided in environments where resources for supplies and equipment are constantly under strain. Staff turnover means that a nurse trained today, will, in six months or a year, have moved to another post or another rotation.

In response to these technological challenges, EngenderHealth and its partners have explored the sensitivity and specificity of different screening techniques and the idea of two-stage screening as a means of addressing the lower specificity of some screening options. Its current study is a

randomized, controlled clinical study to assess safety and effectiveness of VIA and immediate treatment with cryotherapy when provided by mid-level clinicians.

Service challenges for cervical cancer screening and treatments do not differ markedly from those for other health interventions. They include competing health needs; lack of political will; accessibility; under-developed primary health care structures; limited financial, equipment, and human resources; cost; long lines and waits; and missed referrals and follow-up challenges. In response to some of these, the partnership has engaged in advocacy campaigns with policy makers, women's groups, political/tribal leaders, traditional healers, and providers to gain their support. It is difficult to balance the concerns of so many groups, but these potential barriers must be addressed in a constructive way. Through operations research, the EngenderHealth partnership is exploring the issue of integration of services into existing systems, the use of quality management tools to identify and address operating needs; training and supplies procurement; and the development of guidelines and consistent, quality referral, follow-up, and record-keeping mechanisms. In addition, cost-benefit and cost-effectiveness models of alternative screening and treatment regimens are being explored.

At the community level, women and communities are largely uninformed about cervical cancer, often disempowered and poor, and have limited access to services. In addition to thinking about the medical profile of an individual, programs need to take into account the sociocultural and gender influences that shape the woman's life. These include things like the perceived connection between cervical cancer, sexually transmitted infections, and promiscuity, and the resulting stigmatization that can occur with a diagnosis. Other issues include taboos on open discussion of sexual matters, a sense of fatalism or fear of diagnosis, and men as potential barriers to access to screening and treatment services. In response, the EngenderHealth partnership is conducting research to identify specific community needs and to help craft educational and outreach materials for the services.

In collaboration with the other partners of the Alliance for Cervical Cancer Prevention, these research activities are moving towards improving options available to policy makers and program managers to help them design and provide effective services. The work of the EngenderHealth partnership is implemented in the context of equity and cost-effectiveness and to ensure that it can improve the impact of cervical cancer prevention programs in low-resource settings.

Cervical Cancer Prevention Initiatives Being Undertaken in India
Dr. R. Sankaranarayanan, IARC

Dr. R. Sankaranarayanan described in his presentation a number of cervical cancer prevention initiatives being undertaken in India. IARC is active in the evaluation of screening tests, technology assessment, and training, as well as providing global data on cervical cancer incidence and mortality. In a large, cluster-randomized trial in Osmanabad District in India, IARC is comparing the performance of visual inspection using acetic acid (VIA) with cytology, HPV testing, and the "usual care" with health education in reducing cervical cancer incidence and mortality. Using VIA, 17.1 percent of the women were identified as positive with acetowhite lesions. Using cytology, 21.1 percent were identified as positive; and for HPV testing,

11.1 percent of the women were positive. The detection rates of cervical intraepithelial neoplasia (CIN) were 3 percent, 2 percent, and 1 percent with VIA, cytology, and HPV testing respectively.

In a second randomized trial in Dindigal District in Southern India, the effectiveness of VIA in reducing cervical cancer incidence is being evaluated. The VIA screen positive rate in this study is 12.4 percent, and the CIN detection rate is 3.5 percent.

IARC is involved in a third study to evaluate whether an information and education intervention can help decrease the rate of cervical cancer incidence by encouraging women to present earlier for screening. In this study, the women in the intervention group received three rounds of personal health education and one group session. A shift toward early clinical stages of presentation and a non-significant reduction in mortality has been observed in the intervention group in this study.

A cross-sectional study in Kerala assessed the performance of single and sequential tests using VIA, visual inspection with Lugol's iodine (VILI), and cytology. When used sequentially, VIA (with positives defined as any acetowhite lesion) followed by VILI had a sensitivity of 85.9 percent and a specificity of 84.7 percent. VIA (with positives defined as opaque, well-defined acetowhite lesions) followed by VILI had a sensitivity of 79.3 percent and a specificity of 88.9 percent. When VIA was followed with cytology, the sensitivities were much lower (72.6 percent when VIA+ was any acetowhite lesion and 65.9 percent when VIA+ was opaque, well-defined acetowhite lesions) and the specificities were much higher (93.7 percent for VIA+ being any acetowhite lesion and 95.9 percent for VIA being opaque, well-defined acetowhite lesions).

Preventing Cervical Cancer: Early Experiences from Thailand
Dr. Khunying Kobchitt Limpaphayom (Dr. Kobchitt), Royal Thai College of Ob/Gyn

Dr. Kobchitt discussed the development of the test-and-treat strategy for cervical cancer prevention in Thailand. For 40 years, Thailand has had a cytology-based cervical cancer prevention program in place, but has seen little significant improvement in cancer incidence. Among a number of problems with the system, Dr. Kobchitt discussed the lack of training capacity and professional and financial incentives to become a cyto-technician or pathologist, resulting in an insufficient number of trained professionals. Facilities and equipment were inadequate. District hospitals had poor training capabilities and were unable to maintain skills, provide sufficient diagnostic capabilities, or maintain quality assurance. Screening coverage in rural areas was poor, and results were not reported in a timely manner, if at all.

In response, the Ministry of Health took active steps to address these problems, and began to explore alternative screening options including Thin Prep, HPV testing, and VIA. VIA was chosen because it provides immediate results, has the potential to link screening with immediate case-management decisions, and has the potential to increase coverage. The training period for clinicians is shorter than cytology, and being trained in VIA does not limit one's career in Thailand the way being trained in pathology does. Programmatically, VIA has the advantage of not being dependent on additional resources or infrastructure for its sustainability. After

reviewing the literature, the Royal Thai College of Obstetricians and Gynecologists decided that VIA provided adequate accuracy in cervical cancer screening and that the test-and-treat method (using VIA and immediate treatment of positives with cryotherapy) was a safe and acceptable treatment option. Cryotherapy can be provided in rural facilities where the highest risk, unscreened women can more readily access services. For Thailand's situation, it was decided that the false positives were less important than the false negatives. Dr. Kobchitt closed by stating that, for the situation in Thailand, "Something is better than nothing; something costs less than nothing."

Service Delivery Issues and Preliminary Results from the Pilot Phase. Project TATI: Screening and Immediate Treatment
Dr. Sylvia Robles, PAHO

Dr. Sylvia Robles described their approach to cervical cancer prevention in the San Martin Region of Peru. In Latin America and the Caribbean, Pap screening programs were established through family planning programs in the 1950s and 1960s. However, decades later, cervical cancer incidence remained high and mortality had not decreased significantly.

The San Martin Region is a rural Amazon area with limited infrastructure and significant geographic, economic, and socio-cultural barriers to health care access. About 40 percent of the population lives in jungle areas where distances and lack of adequate transportation make access to health services quite difficult. In San Martin, the Pap program had been in operation for 20 years, yet it has had problems with poor screening and treatment coverage, and inadequate follow-up. Of the women who did receive treatment, the majority of them were treated with hysterectomy, regardless of the lesion's grade. The TATI (a Spanish acronym for test and immediate treatment) demonstration project set out to make use of the already existing services in the region in order to enhance sustainability of the program. In many developing countries, the health systems are ill-equipped for care that requires some follow-up. For this reason Project TATI decided to evaluate screening with immediate treatment. The project is assessing the effectiveness and acceptability of VIA with immediate treatment with cryotherapy. The project will also evaluate the role of visual inspection with acetic acid and magnification (VIAM) in improving accuracy of VIA and will evaluate the feasibility and cost-effectiveness of incorporating VIA and cryotherapy into primary health care services.

Balancing Research Needs and Service Delivery Realities in the Western Kenya Project
Dr. Vivien Tsu, PATH

Dr. Vivien Tsu provided examples from the Western Kenya Cervical Cancer Prevention Project to illustrate some research challenges of implementing demonstration projects. While it is often more efficient to design the demonstration project to help answer multiple research questions, it naturally makes the project and data-collection process more complex. The research process distorts the reality of the service delivery system, introducing tasks like data collection into the routine, and giving extra attention to the project. Often times there is a "start-up effect" where there may be extra enthusiasm among staff, but also many problems that need to be solved for the first time. In addition, there are often local demands for extra inputs that must be balanced

against sustainability concerns. It is important to modify the project model along the way, in response to changing circumstances and lessons learned.

Dr. Tsu highlighted several strategies that can help solve problems that can arise when trying to mesh service delivery with a demonstration project. During the design phase of the project, Dr. Tsu recommended focusing on key questions and talking to policy makers to identify their concerns. By anticipating and documenting changes, their impact can be captured in data collection and in the database. Sub-studies can be set up as needed. At the same time, efforts should be made to minimize research data-collection burden on routine staff. During the analysis and reporting phase, it may be necessary sometimes to yield to the primacy of local sovereignty and patient care, while keeping the goal of the research model in mind. For example, in the Western Kenya project, it was necessary to adjust the model to allow for the one-month follow-up visit to occur at the district hospital where women were accustomed to returning, rather than at the local clinic where staff did not feel prepared to answer the women's questions. Data can be analyzed in subsets to check the effects of changing procedures and personnel before pooling the data. The limitations of the study should be explicitly stated when reporting results. Dr. Tsu concluded that while it is challenging to try to balance research needs with the reality of service delivery, the process is facilitated by recognizing the dilemma of the dual imperatives, remaining creative and flexible, and most importantly, documenting all activities and changes at every step of the way.

Special Report on the WHO Consultation on Cervical Cancer Screening Meeting Held March 27-30, 2001, in Geneva, Switzerland
Dr. Sylvia Robles, PAHO

Dr. Robles reported on the recent World Health Organization (WHO) Consultation on Cervical Cancer Screening. The aims of the meeting were to develop a position paper on implementing cytology screening programs in middle-resource settings; to develop a status report on VIA and HPV screening for cervical cancer; and to identify priority research areas to be addressed by WHO with its partners. The meeting reviewed the strengths and limitations of cytology, VIA, and HPV testing. A written summary of the meeting was made available to Consultative Forum participants in Baltimore. Dr. Robles reported that the goal of the WHO meeting was not to produce a recommendation for any one particular screening method, but rather to provide an overview of what is known to date about the three screening strategies. An official status report from WHO will be made available later this summer.

Participants in the WHO meeting in attendance at the Baltimore meeting reported that there was considerable discussion in Geneva of the evidence regarding the effectiveness of VIA. Several of these individuals felt that VIA was discussed more extensively and critically than the other screening methods. In Geneva, participants recognized the lack of longitudinal data available on VIA, and some argued that prior to being able to broadly recommend VIA as a viable screening strategy, more evidence is needed regarding the reduction of cervical cancer incidence and mortality, as well as on the cost implications. It was noted among the Baltimore meeting participants that the field currently is very dynamic and technologies are expected to continue to be developed and improved upon over the next several years.

PROCEEDINGS: PRESENTATIONS BY GUEST PARTICIPANTS

Ethical Considerations in Launching Cervical Cancer Prevention Demonstration Projects
Dr. Laura Koutsky, University of Washington

Dr. Koutsky began the session with a discussion of ethical considerations in demonstration projects and the conflicts that can arise between the desires to conduct good research while at the same time, keeping the individual health of participants as a priority. Dr. Koutsky suggested that when balancing what is research versus standard of care—especially when new procedures are being tested—there often is no right answer. For these reasons, it is a good exercise to prepare a written informed consent form, even if it is not used, to help keep the individual participants health in mind.

Dr. Koutsky reviewed the four principles of ethics in research: equipoise, respect for persons, beneficence, and justice. She concluded by suggesting several important references for participants who were interested in reading more on the subject of ethics: the Belmont Report, the Helsinki Report and an article in *BMJ* entitled "Beyond Helsinki."

Dr. Kobchitt, Royal Thai College of Obstetrics and Gynecology, commented on Dr. Koutsky's presentation, offering her experience in the Thai project. Dr. Kobchitt remarked that there should be no reason to coerce women into doing anything—with proper information and education, women in developing countries do understand the research and procedures being offered.

Cervical Cancer Screening Approaches in Costa Rica
Rolando Herrero, Costa Rica Cancer Institute

Cervical cancer screening in Costa Rica has been available since the 1970s, however, it has had limited impact on incidence and mortality. The Pap screening system, which uses several labs, is not well organized and has no mechanism in place for quality control. There are numerous problems with specimen collection and follow-up. Costa Rica, in the last several years, has invested in a national centralized lab, extensive training of health providers, and new equipment such as cytobrushes, colposcopy and loop electrosurgical excision procedure (LEEP). Still, to perform optimally, the Costa Rican program will need an organized call and recall system, an organized referral and quality control system, and possibly, the introduction of new techniques or combinations of techniques. It was emphasized that many challenges related to implementing a cervical cancer-screening program are not necessarily related to the technique. However, many new technologies are more expensive than cytology and are unproven in developing countries. They often are difficult to implement, and quality is hard to monitor. It was emphasized that introducing new techniques will not necessarily improve an ineffective program, but it can consume a lot of resources.

The Guanacaste project in Costa Rica compares the sensitivity and specificity of conventional cytology, liquid-based cytology, cervicography, and HPV testing. The results from the Guanacaste project showed that combinations of screening methods increase sensitivity, but they also increase the cost of testing and the need for referrals. Therefore, it will be important to find

highly sensitive and specific combinations. Most combinations of the tests increase sensitivity to near 100 percent and some do so without significantly losing specificity. Liquid cytology, read by an expert, and HPV are more sensitive than conventional cytology. Cervicography alone suffers from limited sensitivity in this setting, however, cytology plus cervigram is highly sensitive. Finally, using two cytologies is highly sensitive as well, and the double reading of cytology merits evaluation.

This presentation generated some comment from the audience. It was noted that Rolando Herrero's presentation raises important points. In many developing countries, there is the tendency to "throw the baby out with the bath water" when it comes to evaluating cytology programs. Countries have invested millions in cytology—dollars that have already been spent. It is important now to look at how cytology is performing and find ways to improve it. It is possible to have a big impact from some small investments and, therefore, it may be beneficial to explore how to adapt additional technology to improve cervical screening.

Cost-effectiveness of Cervical Cancer Screening in Rural Thailand
Dr. William Lawrence, Georgetown University

Dr. William Lawrence presented a mathematical model of costs and outcomes of cervical cancer screening in low-resource settings based on data from rural Thailand. The model is designed to evaluate the cost-effectiveness of various screening techniques, including VIA, HPV testing, Pap smears, and combinations of tests, compared to no organized screening. The model assumes that there is a 50 percent dropout rate from the time of referral for a positive screening test. Costs included those associated with providing screening, diagnostic follow-up, therapy for cervical neoplasia, as well as time costs for the women screened. Start-up and infrastructure costs are not included in the model, which will bias the model slightly against VIA and toward cytology.

The model demonstrates that screening can reduce cervical cancer mortality at low cost. While all screening modalities would decrease cervical cancer incidence and mortality under baseline conditions, VIA, followed by immediate cryotherapy if positive (rather than referral), produced the largest gain in life expectancy at reasonable cost. According to the model, the cost-effectiveness of Pap smears would be equal to VIA and immediate treatment if Pap were 80 percent sensitive and there was 100 percent follow-up for positive smears. The cost-effectiveness of HPV DNA testing would be equal to VIA plus immediate treatment if there is 90 percent follow-up and the cost of the HPV tests are less that US$5.00.

Dr. Lawrence's presentation generated much discussion on possible variations to the model including changing the costs of HPV testing, as the costs may be dropping in the future; and changing the model to include the impact of women's age and HIV status on the sensitivity and specificity of the screening techniques. In addition, Dr. Lawrence discussed the cost differences between VIA plus treatment versus VIA plus referral. A major issue that makes VIA followed by immediate treatment more effective than the other screening modalities is the 50 percent dropout rate of women referred for a positive test in the referral scenarios. This dropout rate may even be lower than seen in some low-resource settings. If other screening tests could allow for immediate results and immediate therapy, then effectiveness of screening programs using these tests may increase.

Translating Research into Service Delivery in a Chinese Setting
Dr. Jerome Belinson, The Cleveland Clinic Foundation

Dr. Belinson discussed several key issues to be considered when developing screening programs, based on his experience with cervical cancer screening in China. To develop appropriate programs it is necessary to know the health care infrastructure, both in terms of available human resources and financial resources. Other key determinants of an appropriate program depend upon the sensitivity and specificity of the screening tests being used, the age that the cancer develops, and the prevalence of the disease in the population.

In China, health officials are very interested in using "mainstream" technology. HPV self-testing was chosen as the screening technique for several reasons. It has been shown to have good sensitivity and specificity. The sampling technique has improved and the analysis can be centralized. In addition, it seems to be a good fit for the rural environment in China. Intense competition for health care dollars means that allocative efficiency is extremely important. While initially high, the cost of the HPV test can drop significantly once it is used for thousands of women.

While China has many similarities to other developing countries, such as high rates of cervical cancer, inadequate or no screening, limited financial resources, and large regions that have never been surveyed, there are several important differences as well. China's population and work structure give it unlimited human resources including large numbers of health care workers. In addition, competition from newer health care issues is infrequent, and HIV prevalence is low. In a setting such as this, Dr. Belinson concludes it is possible to provide a tremendous amount of care and make an impact, while still doing good research.

Tips on the Use of Cryotherapy
Dr. Ralph Richart, Columbia University

Dr. Ralph Richart gave an impromptu presentation on the effective use of cryotherapy based on his experiences over the past several decades. The literature from 20 to 30 years ago was all based in developed countries, so Dr. Richart emphasized ways to enhance the performance of cryotherapy in the field in developing countries. First, he emphasized that nitrous oxide gas was better than carbon dioxide gas, unless the CO_2 was medical grade. The NO_2 is a cleaner gas that causes fewer problems with clogging the cryotherapy unit. The best choice in tanks is the 5-foot tank. Though cheaper, the smaller tanks lose pressure faster, which impacts the effectiveness of the treatment. The needle on the pressure gauge is a source of problems, as it is often ineffective. Dr. Richart suggests training people to determine how fast "fast" is so that they can judge when there is insufficient pressure in the tank. For probe tips, Dr. Richart recommends using the biggest size, which gives more depth of freeze. Flat probes can be used for most lesions but probes with a nipple should be used for lesions on a distorted cervix. For the most effective freeze, probes should be applied to cover 4 to 5 mm beyond the edge of the lesion. Some lesions may need multiple applications. To judge the appropriate length of freeze, the probe should be applied until the ice ball stops propagating, then the freeze can be stopped. In response to a question about the evidence behind waiting five minutes between freezes, Dr. Richart replied

that there was no evidence that the five-minute wait or that the single versus double-freeze makes a difference. The key, he recommends, is to freeze the tissue beyond the margins of the lesion.

DISCUSSIONS

<u>Discussion group 1</u>: Karen Beattie (EngenderHealth), Wendy Castro (PATH), Stephen Corber (PAHO), France Donnay (UNFPA), Rolando Herrero (Costa Rica Cancer Institute), Herchel Lawson (CDC), Nina Schwalbe (Soros Foundation)

***Interventions that show promise and questions for future research*.** Participants discussed a broad range of issues. The group identified HPV vaccine development as one of the most important research issues, and felt a successful HPV vaccine was the intervention that would have the greatest long-term, global impact. However, aside from vaccine development, the group emphasized the importance of further research on cost, effectiveness, and acceptability, and felt that providing governments with solid evidence in these three areas would be the most important to help them make informed decisions. Participants recognized how each country needs to choose the intervention with the best fit for the region and that no one approach can be recommended. It is likely that a combination of interventions and approaches will best suit some countries' resources and culture.

The group discussed three issues related to acceptability. It was pointed out that from women's perspectives, pain and fear associated with new techniques could impact acceptability. For providers, acceptability is important in terms of the work and resources needed to adequately screen women. For governments, acceptability is a problem if the country has not identified cervical cancer as a priority.

Factors that help ensure program effectiveness and sustainability. The group discussed whether cervical cancer prevention programs should be integrated into other existing health services or whether they should stand alone as vertical programs. The United Nations perspective is to start service provision with family planning and then add programs as the system gets stronger. However, for cervical cancer prevention, the age ranges of the target groups are different than for family planning and antenatal care services. Many women don't seek health services after their childbearing years; therefore, in some countries, it may be more appropriate to provide cervical cancer screening as a stand-alone program.

Group members discussed the concept of women's agency and identified many barriers that prevent women from seeking services. Often, women need to feel that they can look after themselves and should be encouraged to seek services. Pain, fear, rude service providers, and previous bad experiences may keep women from seeking services. There needs to be a demand for services at the community level and from women themselves. Participants recognized that intensive advocacy and health-education efforts are necessary to make this happen.

Successful programs must have the support of opinion leaders, either from the government, medical societies, or other involved organizations. Services should be in place before creating

demand at the community grassroots level to ensure that service providers do not get overwhelmed. The group identified the need for available resources and infrastructure at the appropriate level—in essence, an "effective organization of services."

***Ways in which the Alliance can best assist in selecting or improving prevention approaches*.** Participants felt that the Alliance could best assist other institutions and developing countries by continuing their work on cost, screening and treatment effectiveness, and acceptability. Advocacy and information dissemination were identified as important components of the Alliance's work, and it was mentioned that other institutions look to the Alliance for assistance and resources.

Participants discussed the Alliance's role in lobbying governments to make cervical cancer prevention a health priority. The assumption that cervical cancer has a high burden of disease is not necessarily true for all countries, especially when compared to other competing health needs. Therefore, information and data are important to help governments understand that cervical cancer is an issue that they can do something about. Cervical cancer represents a great public health issue for governments to work on, in that it has preventable mortality. Participants felt that the dynamic nature of the issue was an attractive feature for governments and practitioners. Since no one method of prevention can be recommended, decision-makers have many options. Participants suggested that the Alliance's advocacy role should also include the training of physicians. A lot of time and resources are spent on pilot projects, and it was proposed that it would be beneficial if the Alliance could address ways to help countries scale- up their programs.

<u>Discussion group 2</u>: Jerome Belinson (The Cleveland Clinic Foundation), Jack Cuzick (Imperial Cancer Research Fund), Catterina Ferreccio (PAHO), Khunying Kobchitt Limpaphayom (Royal Thai College of Ob/Gyn), William Lawrence (Georgetown University), Ralph Richart (Columbia University), Vivien Tsu (PATH)

***Interventions that show promise and questions for future research*.** Group members discussed the distinction between the needs of developing countries that have moderately developed health-sector resources and economies and those developing countries that have very low resources. In countries with moderately-developed health sectors that have established Pap smear screening, it may be appropriate to keep the system in place if improvements can be made to increase quality and effectiveness. If improvements cannot be made, supporting cytology programs will be a waste of resources. Both Chile and Costa Rica have upgraded their Pap smear screening system, but research is needed to determine the most cost-efficient strategies. The group noted that program effectiveness was a very important part of an evaluation and that loss to follow-up affects costs dramatically.

The group agreed that role of Pap smear screening in successful screening programs is limited and will diminish in the future. The group identified instead the need for more information on program effectiveness and on integrating new technologies into existing programs. Research is also needed on effective follow-up mechanisms in terms of cost and the infrastructure necessary to organize the system. There was consensus in the group for more support for information on quality control procedures for VIA. The quality of light, the health of the population, and the inflammation rate can all impact the quality of the screening. Suggested solutions included using

digital cameras and a system of centralized review. Participants also identified the need for a common set of teaching materials and methods to reduce the variability in VIA screening.

The group also discussed what levels of evidence were necessary when evaluating the impact of screening and treatment programs. It was suggested that mortality and cervical cancer do not need to be used as endpoints. It is enough to use data from either developed or developing countries with high-grade squamous intraepithelial lesions (HSIL) or CIN III as endpoints. There is historical data that show detection and successful treatment prevents cervical cancer. Future efforts and funding, therefore, do not need to be put into cancer registries.

***Ways in which the Alliance can best assist in selecting or improving prevention approaches*.** The groups made several suggestions for ways that ACCP can further support future work on cervical cancer prevention. These included developing standardized training packages for methods like VIA, self-testing, and cryotherapy. The group also identified a need for a package of advocacy tools that could be adapted and used in various countries. Finally, the group concluded that further ACCP efforts do not need to focus on providing laboratory support, unless it is for HPV testing or other new tests being developed such as biomarkers. While VIA may be the most generalized strategy for ACCP to invest in, ACCP projects should be prepared to incorporate new technologies into their evaluations.

<u>Discussion group 3</u>: Mark Barone (EngenderHealth), Amie Bishop (PATH), Jose Jeronimo (Instituto de Enfermedades Neoplasicas), Laura Koutsky (University of Washington), Mark Schiffman (National Cancer Institute), Edward Trimble (National Cancer Institute), Patti Ringers (JHPIEGO)

***Interventions that show promise and questions for future research*.** Group members reported that it was not possible at this time to rule out or prioritize screening technologies. Each country needs to consider a variety of factors when deciding what type of screening technology will be best suited for their population. Factors such as the age of the target population and the HIV prevalence may affect some test's sensitivity and specificity. Combinations of strategies may be appropriate, and varying screening intervals may need to be considered. Other important considerations include the acceptability of the approach for women, treatment methods available, and whether services will be centralized or decentralized. Decisions should be made whether to assess mortality prevention or morbidity prevention.

The group developed a list of important questions for which research can provide key information. The list included a need for more research on cost-effectiveness of strategies, and a growing need to examine the effect of treatment on HIV shedding and HIV transmission. Other important issues for future research include evaluating community-based recruitment strategies and exploring what women know and understand about cervical cancer prevention.

***Factors that help ensure program effectiveness and sustainability*.** The group discussed the need for enlisting the support of the "right" allies and opinion leaders. Building awareness of the problem of cervical cancer will facilitate program success. Also important, however, are issues of infrastructure capabilities. The group identified a need for a country to have treatment

capabilities and a viable health system in place in order to ensure effective and sustainable program efforts.

***Ways in which the Alliance can best assist in selecting or improving prevention approaches*.** Participants suggested that the Alliance could help strengthen prevention efforts through its advocacy work by assisting in building national-level approval for cervical cancer prevention. It was suggested that building support from the grassroots level rather than from the top down also would be an important area in which the Alliance could offer assistance. In addition, participants suggested that the Alliance should focus on the issue of quality control.

Discussion group 4: Lynne Gaffikin (JHPIEGO), Francisco Garcia (University of Arizona), Nancy Kiviat (University of Washington), Karen Levin (EngenderHealth), Sylvia Robles (PAHO), R. Sankaranarayanan (IARC), John Sellors (PATH)

***Interventions that show promise and questions for future research*.** Discussion group participants covered a wide range of issues. The group identified several approaches that would have a large impact in the long-term, medium-term, and short-term. Long-term, it was agreed that research on a prophylactic HPV vaccine and on biomarkers for disease have the potential to make the biggest impact. Further research on self-sampling techniques, including urine-based sampling, would be the most beneficial for the medium-term. For the short-term, the group concluded that approaches are very much resource- and site-specific. There is no "one-size-fits-all" approach that will have a big impact in the short-term.

The group agreed that further research on how HIV rates and age distributions affect screening techniques would be beneficial. Participants identified several additional research needs including continued research on selective screening approaches that would improve the positive predictive value of a test by increasing the apparent prevalence of CIN in the population, and further exploration of appropriate screening intervals.

***Factors that help ensure program effectiveness and sustainability*.** For programs to have maximum effectiveness and sustainability in the context of national and local conditions, programs should have the ability to recall women for test results and treatment and to follow-up women post-treatment. There should be a mechanism in place for recruiting women and for case management prior to the implementation of the program.

***Ways in which the Alliance can best assist in selecting or improving prevention approaches*.** Participants felt the Alliance could offer the best assistance by challenging itself to "think outside of the box." There also are specific needs for evaluation of ongoing programs, looking at program factors, datasets, and specimens. It was felt that it would be beneficial if the Alliance helped advocate for more research on biomarkers. The Alliance should continue to give attention to health education, and to do further research on light sources, cryotherapy equipment, training, and quality assurance.

FINAL THOUGHTS, DISCUSSION, AND CONCLUSIONS

The day's presentations and discussions brought out a number of common issues to be addressed in the coming years. Participants agreed that there is no quick fix, or one-size-fits-all approach to preventing cervical cancer among women in the poorest countries. Clearly, the acceptability of current and new screening approaches will be based on each country's culture, political situation and resources. In the age of the ballooning HIV epidemic, there is an urgent need to have more research on the impact of HIV on screening test performance and on the transmission of the virus after treatment for cervical lesions. Cultural norms, training, and shortages of practitioners make self-sampling techniques another research priority for the near future.

Any cervical cancer prevention program, regardless of the screening technique being used, needs the ability to do quality control. For a program to be able to implement and sustain adequate quality control, it is imperative that an infrastructure be in place. The health system should be able to provide treatment to women identified with precancerous lesions, prior to the implementation of any screening program. Successful and effective cervical cancer prevention programs need to include efforts to keep women informed and instill a sense of women's agency.

To better assist countries in making difficult decisions regarding cervical cancer screening, participants recommended the Alliance invest its efforts in providing countries and programs with standardized training, guidelines, and procedures for VIA, HPV testing, and cryotherapy treatment. Participants recognized that the strength of the Alliance stems from its diverse work, breadth of knowledge, and visibility that comes from the collaboration between the five international agencies. In this respect, the Alliance is well situated to assist countries with advocacy efforts at the grassroots and national policy level. The voice of the Alliance can also be used to accelerate work on using biomarkers for cervical cancer screening, and to help place HPV vaccine development on the international research community's agenda. The discussions and recommendations from the meeting of the Consultative Forum on Cervical Cancer Prevention in Low-Resource Settings will help shape the future goals of the Alliance and strengthen its collaborative efforts both within and outside of the five Alliance member agencies.

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