Preventing Cervical Cancer through Early Detection

ISSUE: Cervical cancer is the most preventable women’s cancer, yet it remains a leading cause of death for women worldwide. Women everywhere should have access to routine screening and follow-up care using the most clinically reliable methods.

Cervical cancer is the second most common type of cancer among women worldwide, yet is almost entirely preventable. The WHO estimates that in 2005 there were more than 500,000 new cases of cervical cancer resulting in 260,000 deaths. Because of a lack of screening, many women who develop cervical cancer are either unaware of their disease or are diagnosed late in disease progression. These unfortunate statistics are avoidable because pre-cancerous lesions can be detected and treated early, effectively, and at low cost through systematic screening programs. If the disease is not detected early treatment is much less effective and more costly. The WHO cautions that without urgent action, deaths due to cervical cancer are projected to rise by almost 25% over the next 10 years. Screening for the early stages of cervical cancer and persistent infection with the human papillomavirus (HPV) - the main cause of cervical cancer - are effective public health tools that should be rapidly deployed worldwide.

POSITION: BD supports a comprehensive approach to the elimination of cervical cancer through education, access to routine and high quality screening programs, proper test follow-up, and treatment based on established clinical guidelines. Public policy frameworks to prevent cervical cancer should include the following elements:

1. **Awareness Campaigns and Education for Women and Healthcare Providers**: Campaigns should make women aware of the importance of routine cervical cancer screening and inform healthcare providers of best practices for prevention and management. Women and healthcare providers must be made aware of the burden of cervical cancer on patients and society along with the ability to prevent the disease through screening and follow-up care. Because of the impact of the disease and its preventable nature, cervical cancer awareness and prevention should be a public health priority for policymakers. Low levels of disease awareness and cultural barriers that impede discussions between women and their healthcare providers often limit the effectiveness of screening programs. Pro-active public campaigns to raise awareness of the disease and the availability of screening programs and treatment options contribute to higher screening rates and more lives saved.

2. **Programs Benchmarked Against Goals**: Systematic cervical cancer screening programs should be benchmarked against prevention goals.
   - Screening programs should be measured against goals for broad screening coverage and reduced cervical cancer incidence and mortality over a defined period of time. Progress should be monitored and made publicly available.
• Policymakers should develop guidelines for cervical cancer screening and follow up of abnormalities. Guidelines should include required screening intervals and age ranges plus methodologies relevant to the needs and resources of the health system.

• Timely patient follow-up and access to treatment are required for screening programs to be effective. Registries are a useful tool and should be implemented where resources allow.

• Policies should support equal access across all regions and ethnic and cultural subpopulations. Countries and health systems should build and maintain infrastructure and funding for cervical cancer screening.

• Screening should be included in basic healthcare coverage.

• Policies should enforce high quality lab procedures with an effective quality assurance program.

3. Deployment of High Quality and Effective Diagnostic Technologies: Cytology (Pap) testing is an essential element of effective cervical cancer screening programs. HPV testing can also be an important tool, and when incorporated into screening programs along with Pap testing, may enable longer intervals between screenings and, therefore, fewer procedures and healthcare provider visits for women. Using high quality laboratory tests for accurate detection of early signs of cervical cancer must be the foundation of screening programs. High quality lab tests ensure the highest rates of early detection and provide healthcare systems with the best return on their investment in prevention. Policies should include:

• Pap (cytology) screening. Pap tests detect abnormal cells and provide actionable information regarding treatment or monitoring.

• HPV testing. Incorporating HPV tests into screening programs along with Pap tests may allow for longer intervals between screenings and reduce the number of procedures on women. However, programs should not use HPV tests to fully replace Pap testing. HPV tests detect infection, but do not detect pre-cancerous lesions.

HPV tests detect infection of high-risk oncogenic virus types in women. These high risk types are necessary, but not sufficient, for the development of cervical cancer. There are no treatments available to eliminate HPV infection, and while HPV is a common virus to which most women will be exposed to during their life, very few infections will develop into cervical cancer. Pap testing detects pre-cancerous lesions and diseased cells that may require treatment or monitoring.

• Adequate training of cytologists (interpreters of Pap tests) and health care providers involved in cervical cancer screening.

Errors in Pap screening are often attributed to improper sample collection and test interpretation. Proper training is necessary to reduce inaccurate reporting: under-reporting of abnormalities puts women at risk of cervical cancer; over-reporting puts women at risk due to unnecessary procedures and wastes healthcare resources.
In extremely resource-limited settings where infrastructure is insufficient in the short-term to implement cytology testing (with or without an HPV testing element), other evidence-based methods, such as visual inspection with acetic acid (VIA), can increase early detection and should be implemented where appropriate. VIA is significantly less effective than Pap testing but it is better than no screening at all.

Other public health tools, such as HPV vaccination are important, but are not designed to replace screening methods for cervical cancer. HPV vaccines do not protect women against all cervical cancers.

4. **Leveraging Technology for Efficient Screening Programs:** Screening programs should prioritize diagnostic and imaging technologies that a) improve sample quality, b) minimize sample collection requirements, c) improve accuracy, and d) maximize efficiency. These technologies include:

- **Liquid Based Cytology (LBC).** LBC minimizes blood, mucous and obscuring material in the sample, which improves interpretation.

- **Automated Imaging.** Automated imaging utilizes computer algorithms to improve cytology interpretation and reduce overall workload in the laboratory. These factors can result in increased disease detection and increase efficiency in the lab.

- **Better sampling devices.** Certain sampling devices have been shown to improve cell collection both in total cells collected and the correct cells collected.

Unlike the conventional Pap test, LBC standardizes sample collection and slide processing, allowing for nearly 100% of the sample to reach the lab. This results in increased sample quality and a reduction in the number of unsatisfactory samples that require costly and time consuming re-testing. LBC also enhances program efficiency. By providing a smaller screening area and removing obstructing material, screening time can be reduced with no loss to disease detection. In some cases, LBC also allows one sample to be used for both Pap and HPV testing.

Using LBC rather than traditional Pap provides an important benefit to programs that utilize Pap and HPV co-testing because it allows for both tests to be processed from the same sample. This minimizes the need to call the patient back to the physician’s office and avoids the costs associated with additional sample collection.

In high HPV-prevalent localities or sub-populations (including culturally, ethnically and linguistically diverse), it is particularly important to utilize Pap screening technologies, such as Liquid-Based Cytology, that provide greater efficiency and sample quality in order to advance the highest rates of early detection and save the lives of more women.

Automated imaging technologies can enhance accurate interpretation of results while increasing cytology interpretation capacity. This can be a critical consideration as countries establish goals for increased population coverage but are limited in their ability to increase screening infrastructure. Automation has increasing value as more and more countries see diminishing numbers of trained cytologists to do the Pap interpretation.
5. **Health Reform Efforts Worldwide Should Prioritize Cervical Cancer Prevention**: Countries and health systems should incorporate long-term cervical cancer screening and treatment goals into reforms to improve healthcare quality and access.

Many regions currently have low rates of screening coverage with insufficient screening infrastructures built around those low rates. Goals to achieve high rates of screening in a sustained manner should be factored into investments in infrastructure.

6. **Build upon Existing Infectious Disease Programs in Resource-limited Settings**: In health system settings that lack routine cervical cancer screening programs, infectious disease program infrastructure (such as HIV, TB, and malaria programs) should be leveraged to provide cervical cancer prevention services to women.

90% of the burden of cervical cancer is in low resource settings, yet it can be prevented and treated effectively at low cost if detected early. The social burden of cervical cancer is especially significant in these areas because the disease affects women in their most productive years when they are working and raising children. This impact of the disease links cervical cancer prevention to broad efforts to improve maternal and child health.

Cervical cancer should also be a top priority in global discussions on combating non-communicable diseases (NCDs) in developing and emerging countries where inadequate laboratory and healthcare infrastructure are hindering the success of screening and follow-up treatment programs.
BACKGROUND: CERVICAL CANCER IS A DEVASTATING DISEASE THAT LEADS TO A PAINFUL DEATH FOR HUNDREDS OF THOUSANDS OF WOMEN WORLDWIDE EACH YEAR WITH TREMENDOUS SOCIETAL AND FINANCIAL COSTS. HOWEVER, WITH EARLY DETECTION THE DISEASE CAN BE LARGELY PREVENTED.

Cervical cancer is a devastating disease that afflicts millions of women worldwide. It strikes when women are relatively young and often in their most productive years - including child-rearing years. It can result in death or infertility. As a result, the disease affects not only women, but children and families, economies and society at large.6,7

The primary risk factor for cervical cancer is persistent infection with high-risk types of human papillomavirus (HPV). Persistent infection can lead to pre-cancerous lesions, which can develop into cancer if not detected and treated appropriately. However, the disease progression is relatively slow and progression toward cancer can be prevented with appropriate screening. [See Appendix 1, “The Basics of Cervical Cancer: Disease Progression and Detection.”] If identified early, pre-cancerous cells can be removed through simple surgical procedures before becoming cancerous. At this stage, the disease is highly treatable at relatively low cost. Even when cervical cancer has developed but is detected at an early stage, it can be treated and women have an excellent chance of recovery.8 However, if women are diagnosed in late stages and the disease has spread within the body, treatment is much less effective and has lower cure rates and higher costs.9

The incidence and prevalence of the disease varies regionally and is largely dependent upon access to screening, early detection with proper follow-up and treatment. The highest rates of cervical cancer are among women in developing and emerging economies. However, even in countries and localities with established screening programs, disparities in access to, and uptake of, high-quality clinical diagnostics cause the disease to remain a serious public health concern. Statistics show the severity of the problem across the globe,10,11,12,13,14 Yet the magnitude of the problem is likely far worse because in many locales there is no organized cancer surveillance program and the true rates are not known.

Worldwide Impact of Cervical Cancer

In Europe, 60,000 women develop cervical cancer each year and 30,000 will die from the disease.

In China, 75,000 women will develop cervical cancer and 34,000 will die from the disease.

In Japan, there has seen a sharp rise in cervical cancer in women aged 20 to 39, along with a growing mortality rate. The screening rate in Japan was only 25% in 2007 - less than half of average screening rate for other OECD countries.

In sub-Saharan Africa, when cervical cancer is detected it is usually so advanced that only 21 percent of women survive.

In Latin America and the Caribbean, cervical cancer is the second most common cancer among women.

In addition to the human health and societal costs of cervical cancer, failure to screen for the disease results in heavy financial costs to healthcare systems across the world. Studies from multiple regions have demonstrated that cervical cancer screening programs are highly cost-effective. However, when
the disease is caught in its later stages, medical costs are several times higher and much less effective than early interventions. This is true in both highly developed settings and in localities with less developed healthcare systems.\textsuperscript{15,16,17}

Like many cancers, the frequency and duration of hospitalization and the need for recurrent treatment increase as the stage of disease advances.\textsuperscript{18} However, the survival rate for cervical cancer - when it is detected and treated in its early stages - is among the highest of any form of cancer. Studies have consistently shown that the five-year survival rate for patients diagnosed with localized cervical cancer is 92%, but only 55-60% for locally advanced cancer and 20% for cancer that has spread beyond the cervix.\textsuperscript{19} Ultimately, the incidence, morbidity, and mortality, and costs associated with cervical cancer are largely dependent upon whether women have access to high-quality, routine screening and effective follow-up treatments.

The benefits to patients and to public health of early detection and treatment programs are well-demonstrated. Numerous studies have shown dramatic reductions in both incidence of and mortality due to cervical cancer in countries following the implementation of population-based cervical cancer screening programs.\textsuperscript{20,21} A few examples of these successes are in the table below.

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<tr>
<th>Incidence</th>
<th>Mortality</th>
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<tr>
<td>United States\textsuperscript{22} (1975-2008) - 55%</td>
<td>New Zealand\textsuperscript{23} (1990-2001) -60%</td>
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<tr>
<td>New Zealand\textsuperscript{24} (1991-2002) - 42%</td>
<td>Australia\textsuperscript{25} (1991-2007) -51%</td>
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<tr>
<td>Norway\textsuperscript{26} (1992-2000) -22%</td>
<td>England &amp; Wales\textsuperscript{27} (1987-2002) -47%</td>
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Cytology (Pap) should be an essential element in all screening programs. HPV tests can also be incorporated into screening programs. This may allow for the establishment of evidence-based extension in intervals between screening that are appropriate for sub-populations of women based on age or other risk factors. However, it is important that policies do not rely on HPV testing alone because diagnosis with HPV infection - while a signal for cancer risk - is not a detection of actual diseased cells and there is no treatment available for HPV infection. Moreover, reliance on HPV testing alone could lead to over treatment of women who would self-resolve their HPV infection without any treatment.

Enforcement of quality standards including proper sample handling, appropriate training for cytologists, and accuracy in interpreting results are essential. Poor sample handling can result in samples being rejected and the subsequent need for additional procedures on women. It can also bias results.

Inadequate training of cytologists can result in errors in the interpretation of Pap test results, including missed detection of pre-cancerous lesions which can put women at risk of not receiving needed early treatment. For example, an evaluation of cervical cytology diagnosis in Mexico revealed that two-thirds of laboratories had greater than 25% false-negative results.\textsuperscript{28} Automation technologies can help reduce
errors in sample handling and evaluation of results, especially in regions with a short supply of well-trained cytologists. They also can be particularly beneficial in enabling programs to reach and sustain long-term goals of high rates of screening coverage.

In order to achieve high rates of screening and reduced incidence and mortality rates of cervical cancer, policymakers should incorporate their long-term goals into healthcare quality improvement and access reforms. This may require investments in laboratory infrastructure and leveraging technologies that enable effective, widespread programs, such as liquid-based cytology and automation. This is particularly important for countries and locales that are actively expanding their healthcare systems.

Unfortunately, some countries and health systems have historically experienced low rates of screening and have a healthcare infrastructure built around those low rates even though official policy in these locales has been to provide screening on a wide basis. For example, in Brazil cervical cancer screening is included as part of universal health care coverage although approximately two-thirds of women do not receive regular screening. In Mexico, while Pap coverage has increased over the years, it is estimated that almost one third of women overall have never received a Pap test. Of those women who did receive a Pap test, approximately one third were unaware of the results. Although concerning, these statistics may actually be worse because of poor record keeping and compliance.\textsuperscript{29}

In some cultures, diseases of the female reproductive tract are viewed as shameful, which prevents some women from discussing symptoms with healthcare providers or seeking treatment. Moreover, some women may fear that a positive screening test means they definitely have cancer and that there is no treatment. These cultural factors and misconceptions must be overcome to advance cervical cancer prevention.\textsuperscript{30} Education and awareness campaigns, sponsored by governments or through public-private partnerships, have proven to be successful tools at combating these concerns when they utilize messaging that is appropriate for the cultural and socio-economic factors in a particular community.

It is recognized that extremely resource-limited settings may have an insufficient infrastructure in the short-term to implement cytology testing or cytology testing in conjunction with HPV testing. Due to the urgency of the problem, other less effective methods for cancer detection should be implemented. For example, in extremely resource limited areas, visual inspection with acetic acid (VIA) allows for later stage detection of cancer which is less than optimal because cervical cancer is far less treatable in later stages. It is, however, better than having no detection effort at all.
Cervical cancer is the second most common cancer among women worldwide, yet it is almost entirely preventable with screening and early intervention.

It is believed that persistent infection with high-risk types of the human papillomavirus (HPV) is necessary, but not sufficient, to cause cervical cancer. Infection with HPV is very common among both males and females during younger years of sexual activity, with four out of five people having the virus at some point in their lives. The vast majority of infections are transient, in which the body clears the virus before it causes harm and there is no need for medical intervention. However, in some cases, the body is not able to clear the virus, leading to persistent HPV infection.

Persistent infection with HPV can lead to pre-cancerous lesions over time. At the pre-cancerous stage, diseased cells are still localized and treatment is highly effective. However, if left undiagnosed and untreated, pre-cancerous lesions can progress to cancer. Once cancer has developed, it will progress from early-stage to late-stage. As the disease progresses over time, the effectiveness of treatment decreases while the cost of treatment increases.

Fortunately, cervical cancer can be prevented through regular intervals of screening for diseased cells. This is referred to as the Papanicolaou, or Pap, test, and it is an essential element in effective screening programs. Since cervical cancer only develops if a woman has a persistent HPV infection, some screening programs also screen for HPV infection. However, HPV testing alone is not good policy. There is no cure for HPV infection, and while diagnosis with persistent HPV infection is a signal for cancer risk, it does not detect cancerous cells. Most people are infected with HPV at some point in their lives, but their immune systems “clear” the virus naturally. Most women who are infected with HPV never develop cervical cancer. Only Pap testing detects diseased and pre-cancerous cells. However, the use of HPV testing, in combination with Pap screening, may allow for an extended interval between Pap tests for those women who test negative for HPV infection.

Vaccines against certain HPV types have also become available. These vaccines are designed to provide protection against two of the highest-risk HPV strains. However, women who are vaccinated still require regular Pap tests. This is because the HPV vaccine does not address all high-risk HPV strains and not all women who are vaccinated develop immunity for the strains that are in the vaccine. In addition, the duration of protection that the vaccine provides against its select HPV strains is not yet known.

The availability of effective screening tools allows cervical cancer to be almost entirely preventable. Programs, policies and funding must be in place and available to ensure that women benefit from these interventions.
## Types and Roles of Cervical Cancer Preventative Services

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<th>Preventative Service</th>
<th>Role in Cervical Cancer Prevention</th>
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<tr>
<td><strong>Pap test</strong></td>
<td>Detects abnormal, precancerous, or cancerous cells. Women can then be referred for treatment or further investigation. There are different methods available for Pap testing, described below.</td>
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<tr>
<td><strong>Conventional</strong></td>
<td>Cells are scraped from a woman’s cervix and smeared on a glass slide. The cells are fixed at the time of collection with a spray fixative and the slide is then sent to a laboratory to be stained, coverslipped, and inspected by a trained cytologist.</td>
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<td><strong>Liquid based cytology (LBC)</strong></td>
<td>An improvement over conventional testing, in which cells are collected and preserved in a liquid medium. A slide is then prepared at the lab under standardized and often automated conditions. Obstructing material is removed, resulting in a cleaner and clearer presentation of cells at the time of review.</td>
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<td><strong>LBC provides significant benefits in quality and efficiency compared to conventional Pap testing, including:</strong></td>
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<td>- increased sample quality with a reduction in the number of unsatisfactory samples that require costly and time consuming re-testing</td>
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<td>- screening time can be reduced with no loss to disease detection due to the smaller screening area and removal of obstructing material</td>
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<td>- allows one sample to be used for both Pap and HPV testing</td>
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<td><strong>Automated imaging</strong></td>
<td>Assists cytologists in the review of Pap slides (both conventionally prepared and LBC) by directing them to the cells that are most likely to be abnormal. Automated imaging can also reduce the number of Pap slides that require interpretation by cytologists. This technology has been demonstrated to increase disease detection and improve lab efficiency.</td>
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<td><strong>Automated imaging technologies can enhance the accuracy of interpretation. By reducing the overall cytology screening time, automated imaging can be a critical consideration as countries, regions and health systems establish goals for increased coverage and strive for sustainable high-quality and efficient large-scale screening programs.</strong></td>
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<td><strong>These benefits are especially important in regions where there is a shortage of adequately trained cytologists - an increasing problem in many localities.</strong></td>
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| **Human Papillomavirus (HPV) test** | Determines the presence of one or more high-risk HPV types, but does not detect diseased cells. Evidence shows that infection with high risk HPV is necessary, but not sufficient, for cervical cancer to develop.  

*Infection with a high-risk HPV type is a signal for cancer risk (there are 14 known high-risk oncogenic types). However, there is no treatment for HPV infection and it is very common among both males and females during younger years of sexual activity. The body’s immune system clears the virus in most cases and few women will develop cervical cancer from the infection.*

*Incorporating HPV tests into screening programs along with Pap tests may allow for longer intervals between screening and a reduced number of procedures on women.*  

*Programs should not use HPV tests to fully replace the Pap test.* |
| **HPV Genotyping** | Determines the specific type of HPV infection. Among the 14 high-risk HPV types, certain types are more likely to be associated with rapidly developing cervical cancer than others. Also, different high risk types have a higher correlation with cervical cancer depending on the type of cancer (e.g., type 18 is glandular carcinoma) and the region of the world (e.g., type 52 is highly correlated to some Asian countries).  

*Since it is persistence of a specific high-risk HPV type infection that causes cervical cancer, it may be important to track HPV infection types in a woman. Testing for specific types may give a better indication of risk and necessary follow up.* |
| **HPV vaccine** | Currently available vaccines immunize against the two types of HPV that are responsible for most cases of cervical cancer (up to 70%).  

*Vaccines are a valuable public health tool, but they do not address all 14 types of HPV responsible for cervical cancer and they do not provide protection against HPV infections that occurred prior to vaccination.*

| **Visual Inspection with Acetic acid (VIA)** | A sub-optimal technique that is typically used in extremely resource-limited areas.  

*VIA allows the possibility of screening and treatment in one visit. The cervix is inspected with the naked eye using a speculum and a bright halogen focus lamp for one minute after application of 5% acetic acid. Immediate treatment may be carried out if certain visible conditions exist on the cervix during inspection.* |
References:


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