

Review Article

Cervical Cancer Screening and Prevention in Low- and Middle-Income Countries: A Perspective from Bangladesh

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Cervical cancer is a major public health concern for women worldwide, particularly in low- and middle-income countries (LMICs). Despite a large number of women (nearly 58 million) are at risk of this preventable cancer, the issue of cervical cancer has not become a public health priority in Bangladesh. The understanding of the challenges and opportunities in Bangladesh about cervical cancer would provide valuable insights for other LMICs also. In this article, we review the epidemiology, risk factors, awareness and treatment of cervical cancer in the context of Bangladesh. Due to lack of awareness and an organized national screening program, the majority of patients are generally diagnosed at the advanced stages of disease, in spite of having a big window of screening opportunity at precancer stage. Most LMICs lack resources for developing a parallel health service system dedicated for cancer prevention and management. In this context, we propose some recommendations including a cost-effective screening strategy by capitalizing available resources of COVID-19 diagnostic and GenXpert labs, and an innovative female-centric primary healthcare workers and high school-based approaches for generating awareness on cervical cancer risk factors, screening and vaccination. Our proposed strategy could also be effective for other similar settings in LMICs.

Keywords: Cervical Cancer, LMICs, HPV, VIA, Colposcopy, Bangladesh, Cancer screening, Cancer prevention

Introduction

Cervical cancer is a major health concern for women worldwide, particularly in developing countries¹. In the past decade, the global incidence and mortality of cervical cancer have sharply increased from 527,624 new cases and 265,672 deaths reported in 2012 to 569,847 new cases and 311,365 deaths in 2018 (8% and 17% increase respectively) [2]. While cervical cancer is the leading cause of cancer-specific mortality in at least 42 countries, this ranks as the fourth most common in the world and second most common in resource-limited countries².

As compared to high-income countries (HICs), females in low-income and middle-income countries (LMICs) are exceedingly more vulnerable (as much as 18 times) in terms of mortality to cervical cancer¹. Also, implementation of high coverage vaccination and screening of target populations may not be effective in case of LMICs, as only 2.7% of females aged 10–20 years received the full course of the HPV vaccine compared to 33.6% in HICs in 2014³. Therefore, understanding of the challenges and opportunities in Bangladesh— one of the most vulnerable countries in the world in regards to cervical cancer— could provide valuable insights into global interventions, particularly for LMICs.

In Bangladesh, more than 55% of the female population falls into the reproductive age group. While life expectancy at birth has increased significantly, a number of challenges still exist on women's health front⁴. According to a recent estimate, cancer

accounts for the highest number of deaths (approximately 24%) of adult females and around 58.7 million women in Bangladesh are at risk of developing cervical cancer^{5,6}. As such, cervical cancer is and will remain as one of the biggest challenges for women's health in Bangladesh in the near future.

Despite ominous prospects, the issue of cervical cancer and other cancers alike is not given due priority in Bangladesh, both at policy and research levels. The fact that there are no national guidelines for the treatment of cervical cancer in Bangladesh reflects the general lack of precedence from the concerning authority. The limited number of cancer care facilities, are mostly located in highly urbanized areas (whereas around 70% of the Bangladeshi population live in rural areas)⁷. Also, there is an absence of national or private health insurance to cover the treatment of cancer in general⁷.

In this review, we aim to shed light on the existing situation of cervical cancer in Bangladesh; while specific recommendations have been proposed to create awareness and enhance the effectiveness of screening strategies in the context of resource-limited countries.

Cervical cancer in Bangladesh

Epidemiology

Due to the nonexistence of a national or population-based cancer registry in Bangladesh, the exact situation (incidence and

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mortality as well as treatment outcome) is mostly unknown. The only hospital-based cancer registry at the National Institute of Cancer Research and Hospital shows that cervical cancer is rising (Figure 1)⁸. According to the World Health Organization (WHO) estimates (extrapolated based on Indian data), 8068 new cervical cancer cases were diagnosed and 5214 deaths were reported in 2018⁶. The crude incidence rate of cervical cancer in Bangladesh per 100,000 women was 9.8 in 2018 while the incidence rates in Southern Asia and in the world were 12.7 and 15.1 respectively. According to 2018 data, the age-standardized incidence rate (ASR) per 100,000 women in Bangladesh, southern Asia, and the world were 10.6, 13, and 13.1 respectively⁶. Unfortunately, most cases of cervical cancer occur in women of middle age in the range of 40 to 64 years when the women are physically active and can contribute to family and society⁶.

Etiology and Risk factors

Infection of the cervix with Human papillomavirus (HPV) is the single most important risk factor for developing cervical cancer. Among the high-risk types, HPV 16 and 18 have the most carcinogenic potential and are responsible for over 70% of cervical cancers and pre-cancerous cervical lesions^{6,9,10}. In Bangladesh, a population-based study found HPV16 as the most common high-risk genotype followed by HPV66, HPV18, HPV45, HPV31, and HPV 53; and the overall prevalence of any HPV infection was 7.7% among randomly sampled married women (aged 13 to 64 years) from both urban and rural area. The study result could give a glimpse of the national scenario¹¹.

Around 59% of Bangladeshi girls are married before the legal age of 18 and females are more likely to have children at an early age which further increases the risk of cervical cancer¹². According to the United Nations Fund for Population Activities (UNFPA) report, 78 girls out of 1000 girls aged 15-19 gave birth to their first child from 2006 to 2017¹².

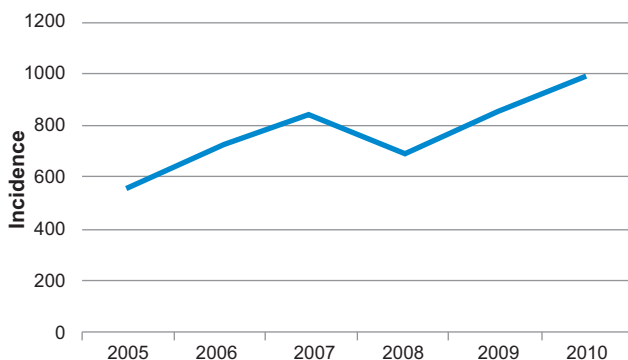


Fig.1: Hospital-based cervical cancer prevalence in Bangladesh

Occupation of urban women could also be a risk factor in Bangladesh, as garments workers and domestic servants were at higher risk of developing HPV infection than women who were housewives. Higher exposure to HPV infection among working

women in urban areas might be the result of an unrestricted increase in sexual engagement and exploitation¹¹.

Awareness and screening

In Bangladesh, knowledge of cervical cancer among females is poor irrespective of educational and socioeconomic status and the key barriers to screening-uptake was found to be lack of awareness and knowledge of cervical cancer rather than cultural and religious factors¹³. Roughly, 40% of study participants who had heard of cervical cancer were unaware of a screening test¹³. Despite little knowledge, the acceptance of the HPV vaccine among rural and urban women in Bangladesh has been reported to be high, which has provided a good basis for its prevention¹⁴.

As per the current strategy, the Bangladesh Ministry of Health with technical support from Bangabandhu Sheikh Mujib Medical University (BSMMU), WHO, and UNFPA has formulated the development of the National Strategy for Cervical Cancer Prevention and Control in Bangladesh spanning over five years from 2017 to 2022¹⁵. This new strategy aimed to implement an organized population-based cancer screening program; and intends to achieve at least 40% coverage of the target population by adopting the visual inspection with acetic acid (VIA) method for primary screening. VIA positive women are evaluated by colposcope/mini-colposcope. Following a “see-and-treat” protocol, colposcopy suspected cervical pre-cancers are treated during the same visit without waiting for histology confirmation. The treatment protocol has included the loop electrosurgical excision procedure (LEEP) and thermal coagulation¹⁵. Currently around 400 VIA centers are operational at primary, secondary, and tertiary level hospitals in Bangladesh. Though more than a million women have been screened so far, the centers were providing opportunistic screening only¹⁵.

Healthcare facility for serving cervical cancer patients

Bangladesh has been confronting a huge challenge to treating cancer patients because of shortage of treatment facilities, oncologists and trained health professionals and poor socioeconomic condition of people. Around 80% cervical cancer patients present with late stage disease in Bangladesh⁸. Unfortunately, Bangladesh has only 6 institutions that are equipped with advance machineries such as linear accelerators, Co-60 teletherapy and brachytherapy needed for treatment. The country needs at least 300 radiotherapy centers as per recommendation by the International Atomic Energy Agency, however, there are only 17 functional radiotherapy centers in the country^{8,16}.

Due to this scarcity, the common treatment algorithm for advanced cervical cancers in Bangladesh is to shrink the cancer with Neoadjuvant chemotherapy (NACT) allowing surgical resection while patients wait for radiotherapy¹⁶. Families of many patients go bankrupt due to overwhelming cost of drugs, treatment procedures and their long stay in the Dhaka city, which is more expensive than many south Asian cities. Unable to bear the cost,

they drop out of treatment. At NICRH only, less than 20% of cancer patients come back for follow up after primary treatment¹⁷.

3. Cervical cancer screening strategies in the context of LMICs

Although HPV vaccination imparts protection against future infection, it cannot eliminate pre-existing HPV infections. Additionally, vaccine coverage in Bangladesh is only 1%¹⁵. In this context, screening becomes the major prevention strategy of controlling cervical cancer in LMICs⁹.

A wide window of screening opportunity

Generally, HPV infections clear up spontaneously within a few months (about 90% resolve within 2 years)¹⁸. Screening of cervical cancer for early diagnosis can substantially reduce the incidence rate, and require less vigorous treatment. However, an effective screening program is expected to screen at least 70% of the target population and reproduce the screening results with high sensitivity and specificity³.

Pros and cons of conventional primary screening tools

Currently, there are several screening tools such as Pap test, HPV DNA testing (molecular tests for the presence of high-risk HPV infection), and the VIA . Though HPV DNA testing has been recommended by the WHO as the best modality for primary screening, due to poor specificity, it often leads to over referral and consequently overtreatment of HPV positive women- as 80% of infected women spontaneously clear the infection within 12 to 30 months and will not develop cancer¹⁹. In absence of HPV DNA testing, VIA has been selected as the second-best screening method in LMICs^{20,21}. Nonetheless, the performance of the VIA test is not satisfactory since the sensitivity and specificity tend

to vary with different setups, personnel performing the tests, and the stages of the infection¹⁹⁻²². For instance, in research settings in Bangladesh, the sensitivity of VIA may range from 56–77% and specificity may range from 64–86%. Moreover, VIA is not recommended for women aged over 50 years (Figure 2).

Alternative but promising protein-based cervical cancer screening tools

As HPV DNA testing alone cannot strongly distinguish between benign or transient infections and persistent ones with the potential risk of cervical intra-epithelial neoplasia (CIN), a considerable number of women with no pathological signs will be referred to colposcopy or further diagnostic tests, constituting an unnecessary treatment burden especially in LMICs¹⁹. Therefore, protein-based screening techniques assessing an individual’s risk in cancer development are getting attention. HPV encoded oncoproteins E6 and E7 proved to be promising as a diagnostic marker in identifying true precancer. Viral early proteins E6 and E7 are produced in an elevated amount in cervical precancers compared to transient infections²³.

Recently, HPV E6/E7 oncoprotein test was used for evaluating its performance as a triage strategy in China¹⁹. In this study, detection of E6/E7 oncoproteins was performed by OncoE6/E7 Test (targeting 8 types-HPV16/18/31/33/35/45/52/58). Strikingly, OncoE6/E7 Test showed superior specificity in detecting high grade lesions (85.9% for CIN3+ and 89.4% for CIN2+) compared to DNA-based test (43.3% for CIN3+ and 46% for CIN2+) and high sensitivity (100%) for detecting only CIN3+ lesions. However, E6 detection test showed poor sensitivity (54.4%) even lower than the DNA test (96.5%) thus, it cannot efficiently rule out or

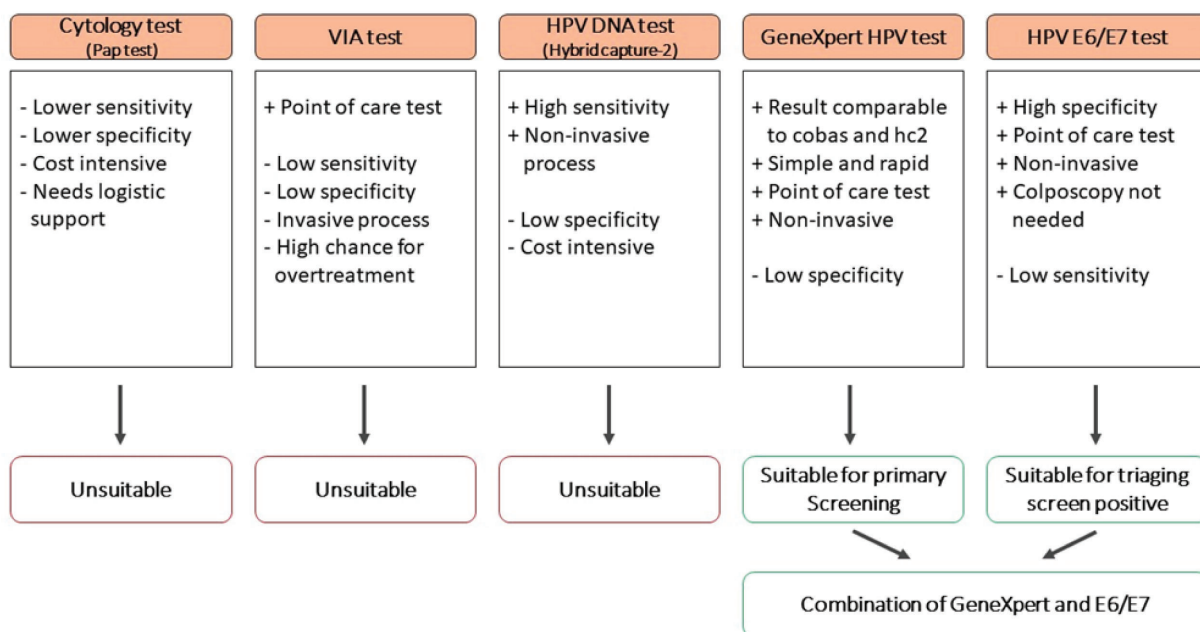


Fig. 2: Pros and cons of different cervical cancer screening strategies in the context of LMICs

detect most HPV infections²⁴. According to study analysis, HPV DNA based tests (high sensitivity but low specificity) and protein-based E6/E7 tests (high specificity but low sensitivity) can be complementary in cervical cancer screening while the former serving for primary screening and the latter as a triage strategy for detection of true precancer and cancer^{19,24,25}.

Future directions

Most developing countries like Bangladesh are confronting the double burden of communicable and non-communicable diseases. Overall healthcare infrastructure in these countries is mostly developed for managing infectious diseases. It is, therefore, very challenging to establish a parallel system to focus on non-communicable diseases like cancers. Capitalizing the underutilized resources that exist in LMICs like Bangladesh could be an effective and sustainable strategy for preventing cervical cancer.

Capitalizing GeneXpert and COVID-19 molecular testing resources for screening cervical cancer in LMICs

Given the limitations of existing screening tools, an HPV DNA test followed by a protein-based point-of-care screening tool (E6/E7) to determine the initiation of cancerous stage would be a cost-effective approach in Bangladesh and other LMICs (Table 1). Importantly, the E6/E7 test could be supplementary or alternative to colposcopy as a triaging technique; and women will be offered treatment at the same visit. This also reduces the number of clinic visits, which poses an extra burden on women

living in villages, and remote places who otherwise would have abandoned the treatment steps. Even where access to colposcopy is not limited, the E6/E7 oncoprotein test can minimize colposcopic referrals to a great extent. Other conveniences of the E6/E7 detection test include simple procedures, the option of self-sampling, and a short time span (~2.5 hours) to get the result¹⁹.

Until recently, most LMICs lacked resources for molecular diagnosis due to various logistics challenges²⁶. Although the COVID-19 pandemic has tremendously affected human lives in terms of miseries and deaths, the development of capability of molecular diagnostic resources (trained manpower, sampling, transport, result delivery, etc) for detecting COVID-19 is the bright side of this pandemic. For instance, in India, the number of COVID-19 testing labs (RT-PCR) has increased to 1596 from only 14 over a period of five months²⁷. Similarly, Bangladesh also developed 109 such labs while it was only one at the beginning of the pandemic²⁸.

Moreover, GeneXpert, a point-of-care device used for molecular detection of tuberculosis (TB), could effectively be used for HPV DNA screening as recommended by the WHO²⁹. There are over 7000 GeneXpert devices (e.g. 270 in Bangladesh) in LMICs around the world³⁰. These resources could be adapted for detecting HPV DNA screening for ensuring a better preventive strategy against cervical cancer (Figure 3).

Table 1: Molecular tools for cervical cancer screening

| Molecular assay | Sensitivity | Specificity | Sample size | Study site | References |
|------------------------|-------------------------------------|------------------------------------|------------------------------------------------------------------------------|------------|------------|
| GeneXpert HPV Assay | 94.5% for CIN3+ | 93.3% for cancer | 45 women with cervical carcinomas and 187 with premalignant lesions | Norway | [39] |
| | 88% for CIN2+ | 60% for CIN2+ | 200 HIV-infected women | Zambia | [40] |
| | 90.8% for CIN2+ | 42.6% for CIN2+ | 697 colposcopy referred Women | USA | [41] |
| | 92.3% for CIN3+ | 40.0% for CIN3+ | | | |
| OncoE6/E7 Test | 67.7% for CIN2+ 100% for CIN3+ | 89.4% for CIN2+ 85.9% for CIN3+ | 294 HPV positive women | China | [19] |
| OncoE6™ | 52% for CIN2+ | 97% for CIN2+ | 235 colposcopy referred Women | Bangladesh | [42] |
| | 70.3% for CIN3+ 91.7% for cancer | 97.50% | 214 women | Honduras | [43] |
| | 52% for CIN2+ 80% for CIN3+ | 94% for CIN2+ 92% for CIN3+ | 294 HPV positive women | China | [19] |
| | 42% for CIN2+ | 99.2% for CIN2+ | 7421 screen positive women | China | [24] |
| | 54.4% for CIN3+ | 99.1% for CIN3+ | | | |

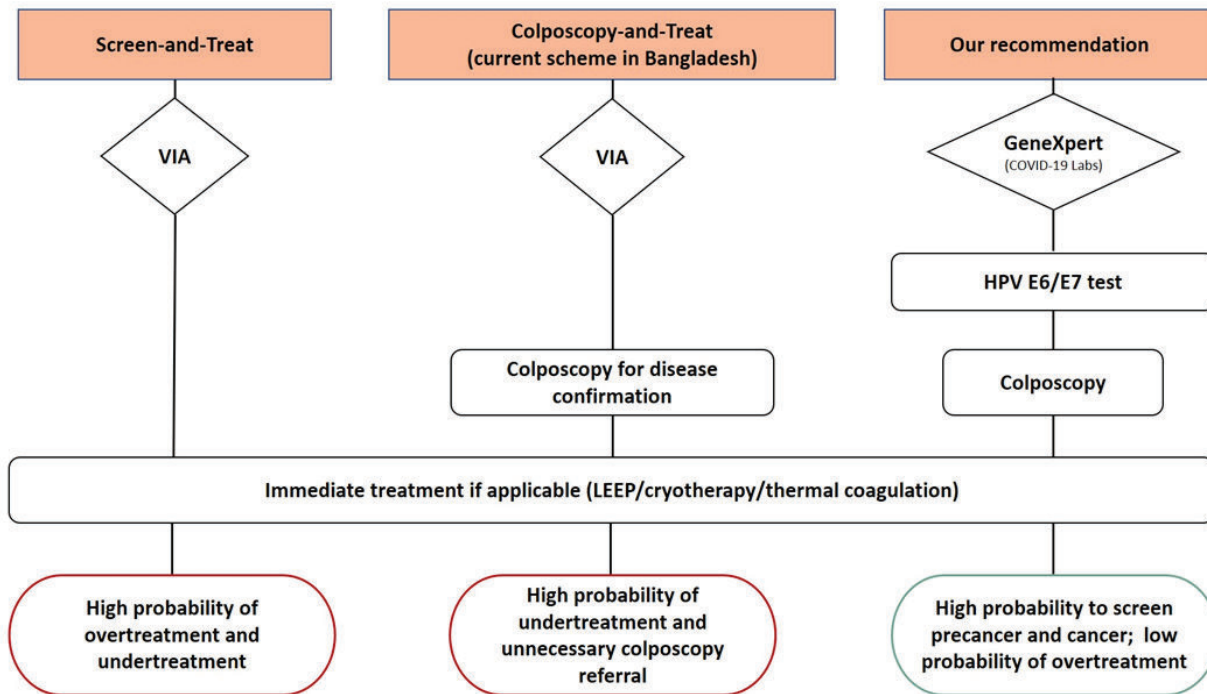


Fig. 3: Recommendation of effective cervical cancer screening strategy for Bangladesh and other LMICs

School curriculum-based awareness of cervical cancer

Over 50 million women are at risk of developing cervical cancer in Bangladesh. Despite a big window of screening opportunity (as it takes 10-20 years for developing cervical cancer from the pre-cancerous stage), most women are generally unaware of the danger irrespective of their education and socioeconomic status. A prior study has shown that the rate of cervical cancer screening uptake was less than 10% in Bangladesh and the key barrier of screening was lack of knowledge, rather than cultural and religious factors¹³. The success of screening program depends on high participation. In recent years, Bangladesh has given the highest priority for educating women by providing a special stipend and tuition fee waiver. Consequently, the majority of girls (enrollment increased from 39% in 1998 to 67% in 2017) get an opportunity for high school level education in Bangladesh³¹. Therefore, a high school-based (particularly, grade IX and X) curriculum focusing on cervical cancer is likely to be effective to raise awareness about screening, and vaccination program of this preventable cancer.

Female-centric community-based healthcare workers for awareness of screening

Women in Bangladesh are often hesitant and reluctant to discuss about sex-oriented problems and sexually transmitted diseases, particularly in front of male health professionals. As such, the existing female-oriented and community-based primary healthcare infrastructure in Bangladesh could be highly effective for spearheading the cervical cancer awareness and screening campaign. Bangladesh has developed a primary healthcare system over the years where community-based female healthcare workers recruited from their communities play a pivotal role. These female

healthcare workers frequently visit households in the community³²⁻³³. Because of this endeavor, childhood and maternal mortality have significantly reduced in Bangladesh and hence it was lauded as a model for other resource-limited countries³⁴. There are over 200,000 female community health workers in Bangladesh, a major proportion of whom are supported by a non-governmental organization, BRAC. This countrywide female-centric network could be instrumental for preventing cervical cancer in Bangladesh.

Engaging religious leaders at the community level

In Bangladesh, religion plays a central role in the day-to-day lives. Religious leaders (called imam) are highly respected in the community and they have a strong influence on various societal norms and attitudes. Apart from leading five times daily and weekly congregational prayers in the mosque, they engage in communal decision-making and serve as the gatekeepers for many social and cultural issues³⁵. Therefore, several studies recommended engaging them for health promotion including breast and cervical cancer screening³⁶⁻³⁷. In this perspective, religious leaders could contribute significantly by encouraging and engaging male members of the family for screening. A recent in-depth study has highlighted this underutilized resource for community development³⁵.

Special healthcare insurance coverage for the poor

Treatment dropout is a major problem for cervical cancer, especially in rural settings. A study from India found that only one third (~35%) of HPV positive women returned for colposcopy³⁸. To minimize such losses, the national strategy

should establish regional programs to offer services and digital information systems to track women who are due to follow up. A national health insurance plan should also be formulated providing coverage for at least those who are extremely poor or unable to bear the minimum cost of cancer treatment.

Conclusion

Choosing the appropriate screening modality among the limited options and utilizing the underutilized resources from the community can rapidly improve the effectiveness of cervical prevention program in LIMCs.

Conflict of interest

Authors declare that they do not have competing interest.

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