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The time is now to implement HPV testing for primary screening in low resource settings

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Abstract

Unacceptable disparities in cervical cancer between richer and poorer countries persist and serve as reminders of gross disparities in access to and quality of screening services. HPV testing is well-suited to address some of the barriers to implementing adequate screening programs in low resource settings. HPV testing has considerably better sensitivity than cytology providing the same extent of safety with fewer rounds of screening. New robust HPV testing platforms require little to no skill by laboratory workers and some can be used at the point-of-care. This allows for a round of screening to be accomplished in one or two visits, reducing costs and the inevitable attrition that occurs when women need to be recalled to obtain their results. HPV testing is ideal for incorporating into the new "screen-and-treat" approaches designed to overcome limitations of conventional, multi-visit, colposcopy-based approaches to screening. Visual inspection with acetic acid (VIA) is the screening test that has been used most widely in screen-and-treat programs to date but the performance characteristics of this test are poor. HPV-based screen-and-treat is more effective in reducing disease in the population and reduces over-treatment intrinsic to this approach. HPV testing can be adapted or combined with other molecular tests to improve treatment algorithms. Infrastructure established to support VIA-based screen-and-treat can effectively incorporate HPV testing. We are poised at a critical juncture in public health history to implement HPV testing as part of primary screening and thereby improve women's health in low resource settings.

Cervical cancer screening can be held up as a major public health success in high-resource settings but in low-resource settings, screening programs have failed to have a population-level impact.[1] Unacceptable disparities in the incidence of cervical cancer between richer and poorer countries persist and serve as reminders of gross disparities in access to adequate cervical cancer screening services.[1,2] Tota *et al*. outline compelling arguments for introducing molecular HPV testing as primary cervical cancer screening.[3] They pitch their

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argument to audiences in medium to high-resource countries. In these countries, primary HPV screening has the potential not only to make programs more effective but also more efficient. Not discussed in their article, are the potential benefits of introducing HPV testing for primary screening in low resource settings. Here we argue that the benefits of introducing HPV testing in low resource settings are enormous and that the time is now to incorporate HPV testing into screening programs in low resource settings.

It would be naïve to expect a new screening test to overcome all complex and far-reaching weaknesses in health service delivery in low resource settings. However, several characteristics of HPV testing are well-suited to address some of these system weaknesses. Moreover, HPV testing fits well with innovative approaches to cervical cancer screening in low resource settings that have garnered increasing evidence and support over the past 15 years. These innovative approaches, endorsed by the World Health Organization and others, are generally referred to as "screen-and-treat."[1,4]

As Tota *et al.* so clearly point out, HPV testing has considerably better sensitivity than cytology.[35] The poor sensitivity of cytology (Pap) often comes as somewhat of a surprise given the success of cytology-based screening programs in resource-rich countries over the past several decades. Establishing the performance characteristics of a screening test is a challenge as the long natural history of cervical cancer necessitate that imperfect markers have to be used as the gold standard. There are also methodological challenges relating to design, conduct and analysis of clinical studies that need to be taken into account to reduce bias. Despite these challenges, careful review of the data indicates that the sensitivity of cytology to detect cancer precursor lesions is on average 20% to 40% lower than HPV tests.[635]

Why then have cytology-based screening programs had such good impact? The answer is a combination of the natural history of the disease and the practice of repeat screening. A simple arithmetic calculation can demonstrate that after 3 years of annual screening, the sensitivity of cytology-based screening program now exceeds 85%. Given the slow progression of precursor lesions to cancer, finding the lesion 3 years later has little to no effect on the public health benefit of the program. Sensitivity of HPV testing exceeds 90% allowing for lengthening the recommended screening intervals and thereby reducing costs.[7] For screening programs in low resource settings, sensitivity is a key consideration as screening programs generally aim to achieve only a few rounds of screening in a woman's lifetime. Thus a single round of HPV-based screening is worth more than three rounds of cytology-based screening.

One of the reasons why screening programs have been so stymied in low resource settings is the technical obstacle of maintaining good quality cytology laboratories dependent on well-trained technicians. In addition, this relatively sophisticated infrastructure has to be centralized making access to screening for women in more peripheral locations a challenge. Innovative attempts to take cytology into the periphery have been made with some success but have required an extraordinary degree of commitment and have not been successful on a wider scale.[8] While molecular HPV testing may seem at first glance to be beyond the reach of low resource settings, its advantage is its lack of reliance on skilled personnel and its

reproducibility. As methodologies for HPV testing have improved, robust testing platforms that require little to no skill by the laboratory technician have been developed. Molecular HPV testing can thus overcome one of the central health systems weaknesses in low resource settings, namely lack of adequate human resources. Moreover, some of the newer HPV testing platforms have been designed with the capability to be run at the point-of-care and can be easily incorporated into health care programs aimed at the under-served.[9,10] The value of point-of-care testing is avoidance of the costs and inevitable attrition that occurs when women need to be recalled to obtain their results.

Screening tests inevitably involve trade-offs: cytology is blessed with moderately good specificity to counter-act its poor sensitivity. HPV testing presents us with the opposite problem: excellent sensitivity and could-be-better specificity. HPV testing for primary screening has been resisted in some quarters because of concerns about the potential "harm" of referring more women to colposcopy. Sensitivity of a screening test tells us about the potential benefits of the program i.e. correct identification of those women who need treatment to prevent the development of invasive cancer. Specificity tells us about the potential harms i.e. incorrect identification of women who will not go on to develop invasive cancer and who will have to suffer a needless treatment procedure. Treatment procedures in widespread use are generally considered safe and have minor discomforts and rare serious side effects. However, in recent years, epidemiological data have suggested that some of these treatment procedures may lead to a marginally-increased risk of preterm birth.[11] Given current social norms in many richer countries, child bearing is often delayed to older ages and hence the child-bearing population and the cervical cancer screening population overlap to a modest extent.

While the seriousness of preterm birth is not to be under-estimated, it is curious to count colposcopy referral as a marker of harm. Theoretically in the conventional model of screening, colposcopy/biopsy is the gold standard diagnostic test. In other words, colposcopy/biopsy is the step in the screening cascade that if perfectly implemented should lead to no overtreatment. Unfortunately, colposcopy/biopsy is an alloyed gold standard and counting it as a marker of harm is a tacit acknowledgement of this. Colposcopy is subjective and dependent on the skill of the practitioner. In many clinical scenarios it is requiring of the practitioner to do the impossible. It has taken up this haloed role because to date it has been the best there is. In recent years, molecular testing technologies have blossomed paving a way for more precise diagnostics for many diseases, particularly cancer.

Alongside the shift to using HPV tests for primary screening have been shifts in the approach to decide which women with positive screening tests require treatment. Molecular tests play a key role here – including refinements in HPV testing to provide specific information about the genotypes present or the quantity of virus detected and inclusion of additional cancer biomarkers, such as p16.[12,13] It has also included new developments in technologies that can improve colposcopy such as high resolution microendoscopy.[14] The plethora of possible triage options may lead the average clinician to throw up their hands in despair at the complexity! Nevertheless if we are prepared to patiently trace through the complex algorithms (and the second article by Tota *et al.*[15] give us a great deal of assistance

in this regard), we see a net result that improves the accuracy of the screening cascade considerably – leading to both greater population impact and less societal harm.

For those middle income settings able to establish at least some level of coverage with cytology screening, referral to colposcopy has long been the next major stumbling block. First there is a shortage of clinicians able to undertake colposcopy and lack of capacity of ensure quality control. Next there are complex systems challenges to locate the women with abnormal screening test results and ensure that they are referred to and attend a colposcopy clinic. Loss to follow-up at this stage is substantial seriously undermining the public health benefit of establishing the initial screening in the first place. Given the almost complete absence of gynecologic pathology services and the additional attrition if yet another follow-up visit is required, most programs that have attempted this model have opted for treatment on the basis of colposcopic diagnosis. However, for most low resource settings colposcopy is simply not an option.

In the past decade, there has been global recognition of the failure of this multi-step process to cervical cancer screening to achieve its intended objective of improving women's health.[4] There has also been increasing recognition of the unacceptability of this failure. Advocacy and policy groups, combined with researchers who undertook clinical trials and demonstration projects helped shape an innovative approach to cervical cancer screening in low resource settings – generally referred to as screen-and-treat.[1,16,17] This approach simplifies the screening cascade and eliminates the requirement for colposcopy aiming to provide screening and treatment in one or two visits. This approach has been extensively evaluated in both clinical trials and implementation projects.[1,16,17] HPV-based screen-and-treat is particularly effective even in HIV-infected women.[18] The success of HPV-based screen-and-treat for HIV-infected women is important as for most of sub-Saharan Africa, especially in the southern parts, the prevalence of HIV among women is at shockingly high levels.

There are various variations on this model but the one that has been most successful is based on visual inspection with acetic acid (VIA). VIA is appealing for many reasons, not the least of which is its capacity to yield an immediate on-site result so that screening and treating can occur at a single visit. VIA has also captured the imagination of advocates of women's health with many spill-over benefits. Large new programs have been established in places where there was little interest or capacity before.[19] Intrinsic to screen-and-treat is over-treatment as in this approach the colposcopy/biopsy step is eliminated from the screening cascade. Unfortunately performance characteristics of VIA as a screening test are poor – with sensitivity slipping below cytology's low benchmark and specificity slipping below that of HPV testing.

Nevertheless, the impetus and infrastructure built to support VIA-based screen-and-treat is ideally positioned to now incorporate the better screening test – namely HPV testing. Almost all of the necessary struts to support HPV-based screen-and-treat are already in place. Moreover, we have recently completed a study in South Africa investigating whether improvements could be made to a HPV-based screen-and-treat algorithm to reduce over-treatment. We demonstrated that restricting to specific HPV types and tolerating less

stringent cut-offs for detecting HPV can lead to substantial improvements in specificity while maintaining adequate sensitivity.[20] These improvements in specificity could even be attained in HIV-positive women – a group known to have very high prevalences of HPV infection.[20]

We are now poised at a critical juncture in public health history where the opportunity exists to implement HPV testing as part of primary screening. This new technology has the potential to make a major impact to improve women's health in low resource settings.

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