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Liza Stapleford 7/31/19

A Systematic Review of the Role of HPV Testing in Cervical Cancer Screening in Africa

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An abstract of
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Abstract

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By Liza Stapleford

OBJECTIVE: The purpose of this study was to conduct a systematic review of the effectiveness and implementation feasibility of human papillomavirus (HPV) detection in Africa as part of a solitary, sequential, or combined screening strategy in the context of a screen-and-treat approach.

METHODS: A systematic literature review was performed of studies published between 1/1/2012 and 2/14/2019 that investigated the use of HPV as a screening test for cervical cancer in Africa. For analysis, studies were grouped into topical categories: acceptability and participation, the accuracy of HPV testing, the agreement of self-sampling and clinician-collected sampling, the feasibility of HPV testing, the performance of HPV testing in screen-and-treat approaches, and follow-up.

RESULTS: We included 30 studies in this review, with studies taking place in twelve African countries. Study designs were predominantly cross-sectional (73%), but there were five randomized controlled trials (RCTs) (17%). HPV testing was performed in twenty-six studies (87%), and the sampling methods varied by the study: self-sampling alone (46%), clinician-collected sampling alone (15%), both (35%), randomization to either self-sampling or clinician-collected sampling (4%). Fifteen publications (50%) spanned only one topical category, 14 (47%) covered two or three, and one publication covered four categories. The acceptability and participation category had the most publications (n= 17), while follow-up had the least (n=1).

CONCLUSIONS: Despite considerable heterogeneity in the studies, a few common themes arose: convenience is a critical determinant of women's screening uptake; community-based collection yields higher attendance and participation rates than facility-based collection; self-sampling for HPV testing is generally acceptable to women. Additional implementation research in Africa is needed to test the effectiveness of adopting approaches that have proven efficacious in randomized trials performed in other geographic locations.

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Chapter 1. Introduction

Cervical cancer causes significant morbidity and mortality, with the estimated global burden in 2018 including 569,847 new diagnoses and 311,365 deaths.[1] Over 85% of the deaths from cervical cancer occur in low- and middle-income countries (LMIC), and recent data from the International Association of Cancer Registries (IARC) database shows that the age-standardized mortality rate in LMIC's is more than triple the rate seen in high-income countries.[1, 2] Africa accounted for over 25% of all cervical cancer mortality in 2018, and cervical cancer is the leading cause of cancer death in females in the continent.[1, 3] Africa leads the world in cervical cancer incidence rates, and the incidence in Sub-Saharan Africa is projected to nearly double by 2030.[1, 3]

A study of cervical cancer trends over the past few decades found that age-standardized incidence rates had declined globally, although the incidence rates in the lower-income countries were stable or increased.[4] The decline in cervical cancer incidence in high-income countries was attributed primarily to the introduction of screening, a finding which has been confirmed in various studies.[4, 5] As evidenced by data from the six LMICs participating in the World Health Organization's (WHO) Study on global AGEing and adult health (SAGE), countries without screening guidelines or programs have lower rates of cervical cancer screening as well as higher cancer incidence and mortality rates.[6]. Establishing cervical cancer screening programs in LMIC is challenging, as is reflected in screening rates: in the WHO household surveys from 2001to 2002, the reported screening rates in Sub-Saharan Africa ranged from 2% to 20% in urban areas and from <0.5% to 14% in rural areas.[7, 8] While the implementation methods and benefits of cervical cancer screening may differ between high- and low-resource settings,

economic analyses suggest that screening has the potential to reduce incidence in low-resource settings by 25 to 30%.[9] A detailed study modeling the cost-effectiveness of anti-cancer strategies in Sub-Saharan Africa and South East Asia found cervical cancer screening and treatment to be highly cost-effective.[10]

Cancer was one of the four main diseases targeted at the 2011 United Nations (UN) High-Level Meeting on Noncommunicable Disease (NCD), marking only the second time in history that the UN General Assembly met on a health issue.[11] The summit acknowledged the threat NCDs pose to socio-economic well-being throughout the globe, particularly in LMIC. Screening and treatment of precancerous cervical lesions to prevent cervical cancer was one of the two interventions that the WHO identified as a "best buy" for cancer prevention and control.[12] Building on this platform, in 2016, the UN launched a five-year Joint Global Program on Cervical Cancer Prevention and Control to help address the challenges faced by LMIC in building comprehensive cervical cancer programs.[13]

Comprehensive cervical cancer programs include provisions for prevention via vaccination, screening, diagnosis, and treatment of both pre-cancerous lesions and invasive cancers. Human papillomavirus (HPV) is associated with the development of multiple types of malignancy and is a causative agent of almost all cases of cervical cancer.[14] Much of the global focus for cervical cancer has been on prevention via HPV vaccination; however, vaccination alone is not sufficient for controlling cervical cancer. Vaccination is highly efficacious, but does not cover all HPV types associated with cervical cancer and does not treat pre-existing HPV infections or HPV-associated disease.[15-17] The introduction of vaccination does not immediately translate

to a reduction in the incidence of cancer, as the process of cancer development takes many years.[18] Thus, screening programs are a vital part of cancer control, even with the advent of human papillomavirus (HPV) vaccination.

The WHO recommends introducing HPV vaccination even in the absence of established comprehensive cervical cancer programs, while also advocating for secondary and tertiary prevention with the goal of screening every woman between the ages of 30 and 49 at least once.[19] Traditional cytology-based screening is difficult in resource-limited settings, and alternative techniques like visual inspection with acetic acid (VIA) and HPV testing are better suited to the infrastructure in these settings and can complement vaccination programs.[7] In their 2013 publication titled, "WHO guidelines for screening and treatment of precancerous lesions for cervical cancer prevention," the WHO detailed recommendations for screen-and-treat approaches for premalignant lesions.[20] The guidelines include multiple screen-and-treat algorithms that can be applied based on the accessibility of resources.

While providing a comprehensive overview of the data, the WHO guidelines highlight the multiple knowledge gaps that exist in the development of cervical cancer prevention and screening programs in LMICs, including countries in Africa. A fundamental issue is the lack of data regarding cervical cancer screening rates, disease rates, and treatment outcomes. The IARC collates worldwide cancer statistics in the GLOBOCAN database using mortality data from the WHO and incidence data from population-based cancer registries.[21] Of the 54 Africa countries listed in the 2018 GLOBOCAN, only eight have mortality source data, and 32 have incidence source data.[1] Africa also lags in screening programs, which, as of a 2018 IARC

report, existed in only 31 countries, of whom none had organized screening with recruitment, and only four of whom had accompanying quality assurance programs.[22]

As national cervical cancer screening programs are being prioritized globally, multiple unknowns remain for LMICs regarding the selection of screening tests, target populations, the frequency of testing, and implementation of screening programs. Although extensive research and policy exist in high-resource countries, this knowledge and the accompanying approaches are often less applicable in lower-resource settings. Cytology-based screening is standard in countries like the United States, but its dependency on technical equipment and expertise render the test much less useful in many parts of Africa.[23] Current WHO guideline algorithms for cervical cancer screening allow for a variety of testing options but emphasize the incorporation of HPV testing as either a standalone screening test or in conjunction with VIA or cytology.[24] The authors of the WHO 2013 Guideline acknowledge that the incorporation of HPV testing is primarily based on theory and modeling due to the lack of randomized or other high-quality studies.[20]

The role of HPV testing in cervical cancer screening in Africa is of critical importance as screening is the primary tool available to reduce the burden of cervical cancer until the benefits of HPV vaccination become evident.[25] The purpose of this study is to conduct a systematic review of the effectiveness and implementation feasibility of HPV detection in Africa as part of a solitary, sequential, or combined screening strategy in the context of a screen and treat approach. By focusing on studies published after 2011, this review will address the findings since the

publication of the 2013 WHO guidelines and contribute to the knowledge base until the results of future randomized trials are available.

Chapter 2. Literature Review

I. Cervical Cancer

A. Epidemiology

Cervical cancer is the fourth most incident cancer among females worldwide, trailing only breast, colorectal, and lung cancer.[1] Paradoxically, cervical cancer is a persistent source of morbidity and mortality despite the existence of effective screening and treatment mechanisms. While exact global incidence rates are challenging to quantify, the available evidence demonstrates that for cervical cancer, the divide between the highest and lowest income countries is widening.[4, 26] The disproportionate decline in cervical cancer incidence in high-income countries is largely attributed to the impact of established screening programs.[4, 27] In their 2005 publication reviewing cervical cancer screening, the IARC concluded that high-quality cytology-based screening reduced the incidence of cancer by at least 80%.[27] As of the GLOBOCAN 2018 data, the age-standardized cervical cancer incidence rates per 100,000 were less than ten in North America, Australia, and most of Europe, while the rates were three to four times as high in Southern, Eastern and Western Africa.[28]

Interest in mitigating cervical cancer disparities is growing, likely related to the development of HPV vaccination and advances in HPV screening. The United States Agency for International Development (USAID) recently pledged 12 million dollars to cervical cancer prevention efforts in Mozambique and Malawi, with a focus on HPV screening feasibility.[29] HPV is the most common sexually transmitted infection, and transient infection is highly prevalent in young, sexually active individuals.[14, 18, 30] The development of cervical cancer is related to both the

persistence of HPV infection as well as infection with high-risk HPV genotypes. Of the greater than 40 HPV genotypes associated with genital infections, only 13 have been identified by the IARC as high-risk and types 16 and 18 combined account over 70% of cervical cancer diagnoses.[18, 31]

Longitudinal studies have demonstrated that the majority of HPV infections clear over time, with data showing almost 70% clearance by 12 months and 90% at 24 months.[32] [33] A meta-analysis published in 2008 concluded that HPV persistence was strongly associated with high-grade pre-cancerous lesions and represented a clinical biomarker for the risk of neoplastic transformation.[34] The progression from HPV infection to cervical cancer takes many years and involves the accumulation of multiple genetic alterations and evasion of the host immune system.[14] This appreciation of the role of persistent HPV infection as a driving force in pathogenesis of cervical cancer has galvanized interest in HPV-based screening.

B. Prevention & Screening

Primary Prevention

HPV vaccination has made primary prevention of cervical cancer cases a tangible prospect. There are three Federal Drug Administration (FDA) approved cervical cancer vaccinations that target the high-risk HPV types 16 and 18. In clinical trials, the vaccines have shown high levels of efficacy against both persistent HPV infection and the pre-cancerous cervical lesions associated with HPV16 and 18 in HPV-naive women. [35] The implementation of cervical cancer vaccination has been aided by donor funds from organizations like the Global Vaccine Alliance (Gavi). Gavi predicts that by 2020, around 40 million girls in Gavi-supported countries

will have been vaccinated for HPV.[36] HPV vaccines also have the potential to reduce the incidence of other HPV-related diseases like anogenital warts and anogenital cancers. [37]

The efficacy, safety, and cost-effectiveness of HPV vaccination led the WHO to approve its inclusion in national immunization programs in 2014.[37] The enthusiasm for HPV vaccination may overshadow the need for building screening programs, but continued attention to screening is critical to the success of a comprehensive cervical cancer platform. Vaccination has its limitations: not every female will be vaccinated; vaccines may not cover all HPV types associated with cervical cancer; existing vaccines are preventive but remedial for pre-existing infections or disease.[15-17] In a letter to the editor, a group in Finland recently reported the first evidence that HPV vaccination prevents HPV-associated cancer.[38] As the full benefits and limitations of HPV vaccination will take many years to realize, the WHO, the United States' Centers for Disease Control and Prevention (CDC), and other expert groups continue to recommend screening for cervical cancer.

Secondary Prevention

The goal of cancer screening is not just to detect disease earlier, but to diagnose the disease at a time point when intervention can alter the subsequent course in a manner that reduces morbidity and mortality. Potential treatments must be available and capable of achieving remission or cure, such that the benefits of screening outweigh the risks or harms.[39] In the IARC Handbook of Cancer Prevention, the distinction is made between the efficacy of screening as demonstrated in a clinical trial, and the effectiveness as observed in real life practice.[39] As the IARC notes, effectiveness may vary depending on the population of interest, as populations have different

disease burdens, genetic predispositions, health resources, and cultural priorities.[39] Therefore, screening methods may vary based on population, and population-specific effectiveness research is a logical step for countries to pursue when faced with implementing policy based on clinical trials conducted in other countries and populations.

The three main methods for cervical cancer screening are cytology, visual inspection, and HPV testing. Initially researched by Papanicolaou in the 1920s, cytology consists of the microscopic examination of cells sampled from the cervix.[40] After microscopic examination, specimens are classified on a scale ranging from normal to invasive malignancy (Table 1). Multiple histologic scales and terminology exist, but the goal of all of them is to classify the degree of cervical cellular abnormality to allow for recommendations of treatment or further workup based on the risk of progression to cancer. Cytology is highly specific, although the sensitivity of a single test may be as low as 50%.[26] Although no randomized trials have directly proven the reduction in cervical cancer incidence with screening, the evidence suggests that screening reduces incidence and mortality up to 80%.[27]

The reduction in cervical cancer incidence in many high-resource countries is largely attributed to the implementation of cytology-based screening.[4, 27] Despite this success, cytology may not be the ideal screening method for all countries and populations. Cytology relies on repeat screening to raise its specificity, but this can be challenging in areas where health care resources are scarce. Cytology is resource intensive, requiring a laboratory, trained staff, quality assurance, and more than one visit.[41] Due to these challenges and the low rates of cytology-based screening in many lower-resource countries[42], the WHO and other groups like the American

Society of Clinical Oncology (ASCO) allow for alternative screening techniques like visual inspection or HPV testing.[20, 43]

Visual inspection methods include visual inspection with acetic acid (VIA) and visual inspection with Lugol's iodine (VILI). Neither of these methods requires a laboratory, and both are amenable to a single patient visit approach that allows for immediate treatment of pre-cancerous lesions. The sensitivities of visual approaches are higher than those seen with cytology, but the specificities are lower than those of cytology. VIA is the WHO's recommended visual approach and its reported sensitivity and specificity range from 71-91%[44, 45] and 49-94%[44-48], respectively. [49] VIA is low-cost, requires minimal equipment, and can be performed by non-physician providers.[41] During VIA an acetic acid solution is applied to the cervix, which is then examined for lesions using the naked eye. Randomized control trials from India and South Africa have demonstrated that treating VIA screen-positive women reduced the prevalence or incidence of high-grade cervical precancerous lesions and invasive cancer.[50, 51] In a trial of over 49,000 women in India, one-time screening by trained nurses, followed by subsequent workup or treatment, led to a reduction in mortality in the intervention group, with a hazard ratio of 0.65 (0.47-0.89).[50] One major disadvantage of VIA is its reliance on subjective assessment, which makes the screening process vulnerable to errors if providers are not well trained and consistent.

As a screening method for cervical cancer, HPV testing has advantages over both cytology and VIA. Given its causal role in the pathogenesis of cervical cancer, HPV is a logical biomarker to predict those at the highest risk of developing cervical cancer. Multiple randomized trials have

confirmed that HPV-based testing, alone or in conjunction with cytology, is more sensitive than cytology alone in the early detection of high-grade cervical precancerous lesions, and thus, more efficacious in preventing subsequent invasive cancers.[52-54] Individual patient data from European and North American studies of parallel HPV and cytology testing were summarized in an analysis which concluded that HPV testing had higher sensitivity (96.1% vs 53%) but lower specificity (90.7% vs. 96.3%) than cytology.[55] Additionally, this analysis found that HPV sensitivity levels were consistent across different locations as compared to the variability in results seen with cytology.

Up until recently, widespread application of HPV testing in low-resource settings was not realistic due to cost and requirements for laboratory equipment. However, the introduction of more affordable point-of-care (POC) tests like careHPV, has prompted some experts to advocate for HPV testing as a test of choice in low-resource settings.[56] A significant advantage of HPV testing over VIA or cytology is that HPV specimens can be self-collected. A 2014 meta-analysis found that self-collected samples had lower pooled sensitivity and specificity than clinician-collected ones, but accuracy was comparable when HPV testing was performed with polymerase chain reaction (PCR) based assays.[57] Although further research is needed to determine the exact role of self-collection for HPV testing, its potential for task-shifting and expanding screening capacity is undeniable.

Screening Guidelines for LMIC

Both the WHO and ASCO have published evidence-based cervical cancer screening algorithms appropriate for limited-resource settings.[20, 43] For countries without established cytology-

based screening programs, WHO endorses a screen-and-treat approach where precancerous lesions are treated in the same visit or shortly after. The recommended strategies for the screening program naive countries are HPV testing alone, VIA testing alone, or sequential HPV and VIA testing, with the availability of resources driving the strategy selection. [20] The WHO 2013 guidelines mark a shift from their 2002 report where HPV testing was not recommended for primary screening in low-resource settings, due to lack of effectiveness studies as well as the logistical burdens of changing the established paradigm.[26] In addition to the additional studies reported since the 2002 report, the WHO 2013 guidelines also discussed the shortcomings of cytology in resource-limited settings: issues regarding quality control, high resource requirement, and loss to follow-up due to the delayed nature of cytology results.[20]

The 2016 ASCO guidelines present a resource-stratified set of recommendations that were designed by a multi-disciplinary, international panel of experts. After reviewing existing guidelines, systematic reviews, and cost-effectiveness analyses, the consensus for all resource settings was primary screening with HPV DNA testing. [43] In the lowest-resource settings, ASCO recognized VIA as an alternative primary screening test and as a triage test following a positive HPV-based screening.[43]

C. Staging & Treatment

The International Federation of Gynecology and Obstetrics (FIGO) developed and maintains a universal cervical cancer staging system. Under the FIGO system, cervical cancer is staged from I to IV based on the extent of the primary tumor, the involvement of regional lymphatics, and metastases to distant lymphatics or organs.[58] The treatment for cervical cancer is dependent

on the stage and will frequently include more than one of the three main treatment modalities: surgery, radiation, and chemotherapy. Although cervical cancer is more likely to be diagnosed at a later stage in countries with fewer resources[59, 60], the more advanced stages of cervical cancer can still be treated for a cure, typically with a combination of radiation and chemotherapy.[61] However, access to radiation therapy is severely limited in many regions like the continent of Africa, where only 26 of the 55 countries have radiation therapy centers.[62] Similar disparities exist within Africa as well: almost 60% of the continent's radiation machines are located in either Egypt or South Africa.[62] The growing burden of cancer in Africa is exacerbated by lack of access to treatment, including radiotherapy, chemotherapy, and trained specialists.[61, 63, 64]

Considering the challenges of cancer treatment in many parts of Africa, the WHO has emphasized vaccination as well as the screening and treatment of pre-cancerous cervical lesions. Cervical cancer is very amenable to a screening approach given the typical 10 to 20 year time for progression from pre-cancer to cancer as well as the multiple, efficacious screening tools.[31] Persistent infection of cervical epithelial cells with high-risk HPV can disrupt normal cellular processes, leading to unchecked cell growth and the development of dysplasia.[27, 65] Dysplasia is a pre-malignant stage, and cervical dysplasia is categorized depending on the depth of epithelial involvement as mild, moderate, or severe.[65] These disease states are distinct from carcinoma-in-situ, which refers to full-thickness involvement of the epithelium without penetration through the basement membrane.[65] As seen in Table 1, multiple grading classifications exist for pre-cancerous lesions of the cervix, but the recent WHO guidelines utilize the cervical intraepithelial neoplasia (CIN) classifications for histologic reporting and the

Bethesda system for cytology.[31] In a high-resource setting, an abnormal screening test is followed by further work up including colposcopy with biopsy of visible lesions or endocervical sampling.[66] The histological biopsy results determine the next step: treatment, further work up, or repeat screening at a designated time interval.

Treatment for these pre-cancerous or, precursor lesions of the cervix, is based on their risk of transformation to malignancy and the resources of the screening setting. In a setting with maximum resources, CIN1 confirmed by histology may be followed without treatment.[43, 66] Conservative management is appropriate because CIN1 will often regress over time and has low rates of progression to CIN2 or 3, as low as 12% over two years per one study[67].[66] In settings where resources are limited, the WHO guidelines permit treatment following primary screening with VIA or HPV testing while acknowledging that this may lead to overtreatment.[20] Pre-cancerous cervical lesions can be ablated or excised using a variety of techniques, including cryotherapy, loop electrosurgical excision procedure (LEEP), and cold knife conization (CKC). In the screen-and-treat context, WHO recommends cryotherapy or LEEP over CKC and other ablative techniques.[31]

D. HPV Testing in Screening

HPV testing has been utilized in cervical cancer programs and research in multiple ways, and its role is currently evolving. Some of the most common applications are as a primary screening tool alone, as a co-test in primary screening, as triage following another primary screen test, and as a follow-up test after treatment of pre-cancerous lesions. Multiple varieties of HPV tests are available on the market or in development, and they can be categorized in a variety of ways, such

as by their molecular technique or their targeted HPV types. The cervical screening guidelines from South Africa uses a more practical classification, dividing HPV tests based on whether or not they involve genotyping to detect the presence of one or more specific, individual HPV types.[68] The initial HPV tests were designed to detect the presence of any of thirteen or fourteen HR-HPV types with results expressed as either positive or negative.[69] Over the last fifteen years, the US Federal Drug Administration (FDA) has approved multiple HPV tests that also provide partial genotyping for the HPV types with the highest risk of cervical cancer; usually HPV types 16 and 18.[70] The role of HPV genotyping in cervical cancer screening and follow-up is still developing, but the recent ASCO guidelines list HPV genotyping as a potential triage test following a positive screening test for high-risk HPV.[43] The future role of HPV genotyping in LMIC will likely be dependent on both the results of clinical trials and feasibility as related to the specifics of each test: cost, equipment requirements, need for trained personnel, and processing time.[71]

Primary Screening

Primary screening with HPV testing, as opposed cytology, minimizes the need for repeat screening.[71] A randomized trial from Canada comparing screening with HPV testing versus cytology found that the sensitivity of HPV testing for detecting CIN grade two or higher was 94.6% (95% confidence interval [CI] ,84.2 to 100) versus 55.4% (95% CI, 33.6 to 77.2) for cytology.[72] Several European, population-based randomized trials compared HPV testing with cytology versus cytology alone to determine how the increased sensitivity of HPV testing impacts subsequent screening tests and screening policy.[52-54, 73] These studies all found that initial screening with HPV testing found more high-grade precancerous lesions than cytology,

but this pattern was reversed for subsequent screenings.[52-54] By detecting more lesions at an earlier time point, HPV-based screening allows for longer intervals between screening.

A follow-up pooled analysis of four randomized trials, including the above mentioned three European studies, found that HPV-based screening resulted in a 60-70% reduction in invasive cancer as compared to cytology.[74] Based on the results, authors for this study recommended HPV-based screening every five years, as opposed to the three-year intervals used for cytology-based screening.[74]

Most pertinent for Africa and other LMIC are the randomized trials looking at HPV-based screening in South Africa and India. A cluster-randomized trial in India found that a single round of screening with HPV significantly reduced the incidence of advanced cervical cancers (hazard ratio, 0.47; 95% CI, 0.32 to 0.69) and deaths from cervical cancer (hazard ratio, 0.52; 95% CI, 0.33 to 0.83) when compared with a single round of screening with cytology or VIA.[75] In a South African trial by Denny et al., the screen-and-treat paradigm was evaluated by randomizing over 6,000 women to three arms: HPV testing with cryotherapy for positive results, VIA testing with cryotherapy for positive results, or a control arm where positive results were observed for six months before reassessment.[76] After three years of follow-up, Denny et al. found that HPV-based screen-and-treat reduced the cumulative detection of CIN 2 or worse (CIN2+) over both the control and VIA arms.

A systematic review analyzing the accuracy of HPV screening as compared to either VIA or cytology found that HPV testing had a higher sensitivity and lower specificity when compared to

both VIA and cytology.[77] The authors of the review noted that the large differences in sensitivity would likely impact only 2-5 per 1000 women, while the small differences in specificity would likely lead to hundreds of women per 1000 being overtreated. However, another meta-analysis looking at the population-based screening with cytology versus HPV found a lower false positive rate of HPV testing (101 out of 1000 women) and concluded that this might be balanced out by the higher sensitivity and low rate of false negatives seen with HPV testing.[78]

Secondary Screening (Triage)

Overtreatment of false positives can be reduced by adding a secondary, or triage, test following an initial positive cervical cancer screening test. Triage with HPV following borderline cytology has been tested in the US[79], but for LMIC the focus of WHO[20] and other guidelines[43] have been on triage tests to follow a positive HPV screen. WHO 2013 screening guidelines suggest VIA as a potential triage test following HPV[20], although their 2014 cervical cancer guide briefly mentions the possibility of triage with cytology or a more specific molecular test.[31] The more recently published ASCO guidelines recommend primary screening for HPV with triage using VIA in basic settings and using cytology or HPV genotyping in higher-resource settings.[43]

Regardless of the type of triage test, the goal is to supplement the highly sensitive HPV test by adding a more specific test, which minimizes false positives and unnecessary treatment. This issue is most critical in LMIC where colposcopy is often either unavailable or limited. Colposcopy entails a thorough examination of the cervix using magnification, a light source, and

the application of acetic acid and Lugol's iodine solution. In high resource settings, women with positive or equivocal screening tests typically proceed to colposcopy for visual evaluation and, if indicated, biopsy prior to treatment.[66] Colposcopy-directed biopsy provides the histologic diagnosis, which serves as the basis for treatment, and also assesses for occult carcinoma-in-situ or invasive cancer.[80] Colposcopy is often performed by physicians, as it requires detailed training and a broad understanding of genital tract disease.[80] Given the requirement for highly skilled practitioners as well as access to equipment and pathology services, colposcopy is often not available in limited resource settings and can be challenging in settings with moderate resources.[71]

Screen-and-Treat

Screen-and-treat approaches have emerged as a solution for LMIC where colposcopy is challenging or unavailable, and access to care or travel limits patients' capacities to follow-up for multiple visits. Visual inspection screenings offer the most expedient results, and VIA has been implemented and evaluated in multiple settings as part of a screen-and-treat approach.[65, 81-83] Studies in countries such as Ethiopia[83], Zambia[84], and Ghana[85] have shown that VIA-based screen-and-treat is feasible and acceptable. Randomized trials in both India[50] and South Africa[76] have shown reductions in the incidence of high-grade pre-cancerous lesions, cervical cancer, and cancer mortality. As acknowledged by the WHO, the primary drawback to the screen-and-treat approach is the increase in false positives and overtreatment that result from bypassing the diagnostic testing.[31] The risk-benefit ratio of screen-and-treat approaches varies in different settings based on the population, available resources, and existing treatment

programs, thus making it challenging to create guidelines that are evidence-based yet account for location-specific factors.

With the introduction of HPV-based screening and the emphasis on screen-and-treat approaches, interest has grown in developing point-of-care (POC) HPV assays that are suitable for low-resource settings without sophisticated laboratory support. POC tests that have been tested in clinical settings include the careHPV, Xpert HPV, and the OncoE6 Cervical test.[86, 87] All three of these tests run in 2.5 hours or less, and both the Xpert HPV and careHPV have been accepted on the WHO list of prequalified in vitro diagnostics.[88, 89]

E. Cervical Cancer and HIV

As reflected in the CDC's inclusion of invasive cervical cancer as an acquired immunodeficiency syndrome (AIDS) defining condition, the two diseases share a strong association. Past studies have demonstrated that HPV infections are more prevalent in HIV positive women [90], and HIV positive women are more likely than HIV negative women to have persistent infection with high-risk HPV subtypes.[91] Using pooled data from six studies conducted in Senegal, researchers found that HIV positive women had both higher rates of progression from HPV infections to precancerous lesions and lower rates of regression when compared to their HIV-negative counterparts.[92] A 2014 systematic review of global data observed a 3-times higher incidence of cervical lesions and higher rates of lesion progression in HIV positive women.[93] The rate of transition from HPV infection to precancer appears to correlate inversely with CD4 count.[92-94]

While the evidence supports the need for different cervical cancer screening strategies in HIV positive women, the ideal approach will vary based on a variety of factors, such as HIV prevalence, existing HIV care systems, and the availability of resources. As reflected in existing guidelines, screening for HIV positive women should be more frequent, regardless of the screening modality or the availability of resources.[20, 43, 68, 95] The high prevalence of HIV in Africa, particularly sub-Saharan Africa,[96, 97] compounds the cervical cancer burden and heightens the need to develop evidence-based practices that maintain effectiveness while accounting for the heterogeneity of populations across the continent.

F. Critical Questions Remaining

The 2014 WHO guidelines provide a thorough summary of existing evidence and use this to formulate a series of screening algorithms that exhibit flexibility based on the accessibility of resources and the current status of screening in a particular environment. Since the publication of these guidelines, numerous studies on cervical cancer in Africa have been published, many of which focused on analyzing the effectiveness of various screening tests and paradigms. Another change in the last five to ten years is that the variety and availability of HPV assays have continued to grow, although the level of assay validation varies considerably.[98] As the critical evaluation and modification of screening procedures is an iterative process, interval evaluations of recent literature can be beneficial to supplement the material from formal guidelines.

The 2014 WHO guidelines identify a number of knowledge gaps, some of which have been the subject of research over the past five years. Some of the remaining critical questions pertinent to HPV cancer screening in Africa that will be addressed in this review are:

- What are the collective findings regarding HPV-based screening, either alone or with a triage test, in regard to efficacy and effectiveness?
- Is HPV testing with self-collection acceptable and feasible?
- How accurate is self-collection as compared to clinician-collection?
- Which approaches to HPV-based screening have demonstrated feasibility, and how well can these be translated to other settings?

Chapter 3. Manuscript

Introduction

Over 85% of the deaths from cervical cancer occur in low- and middle-income countries (LMIC), and recent data from the International Association of Cancer Registries (IARC) database shows that the age-standardized mortality rate in LMIC's is more than triple the rate seen in high-income countries.[1, 2] Africa accounted for over 25% of all cervical cancer mortality in 2018, and cervical cancer is the leading cause of cancer death in females in the continent.[1, 3] Africa leads the world in cervical cancer incidence rates, and the incidence in Sub-Saharan Africa is projected to almost double by 2030.[1, 3]

Cancer was one of the four main diseases targeted at the 2011 United Nations (UN) High-Level Meeting on Noncommunicable Disease (NCD), marking only the second time in history that the UN General Assembly met on a health issue.[11] Screening and treatment of precancerous cervical lesions to prevent cervical cancer was one of the two interventions that the WHO identified as a "best buy" for cancer prevention and control.[12] Building on this platform, in 2016, the UN launched a five-year Joint Global Program on Cervical Cancer Prevention and Control to help address the challenges faced by developing countries in building comprehensive cervical cancer programs.[13]

Comprehensive cervical cancer programs include provisions for prevention via vaccination, screening, diagnosis, and treatment of both pre-cancerous lesions and invasive cancers. Human papillomavirus (HPV) is associated with the development of multiple types of malignancy and a causative agent of almost all cases of cervical cancer.[14] Traditional cytology-based screening

is difficult in resource-limited settings, where alternative screening techniques like visual inspection with acetic acid (VIA) and HPV testing are better suited to the infrastructure and can complement vaccination programs.[7] In their 2013 publication titled, "WHO guidelines for screening and treatment of precancerous lesions for cervical cancer prevention," the WHO detailed recommendations for screen-and-treat approaches for premalignant lesions.[20] The guidelines include multiple screen-and-treat algorithms that can be applied based on the level and type of resources available.

While providing a comprehensive overview, the WHO guidelines highlight the multiple knowledge gaps that exist in the process of developing of cervical cancer prevention and screening programs in LMICs, including countries in Africa. A fundamental issue is the lack of data regarding cervical cancer screening rates, disease rates, and treatment outcomes. Africa also lags in screening programs, which, as of a 2018 IARC report, existed in only 31 countries, of whom none had organized screening with recruitment, and only four of whom had accompanying quality assurance programs.[22] As national screening programs are being prioritized globally, multiple unknowns remain for LMICs regarding the selection of screening test, target population, the frequency of testing, and implementation of screening programs.

Although extensive research and policy exist in high-resource countries, this knowledge and the accompanying approaches are often less applicable in lower-resource settings. Cytology-based screening is standard in countries like the United States, but its dependency on technical equipment and expertise render the test much less useful in many parts of Africa.[23] Current WHO guideline algorithms for cervical cancer screening allow for a variety of testing options but

emphasize the incorporation of HPV testing as either a standalone screening test or in conjunction with VIA or cytology.[24] The authors of the WHO 2013 Guideline acknowledge that the incorporation of HPV testing is primarily based on theory and modeling due to the lack of randomized or other high-quality studies.[20]

The role of HPV testing in cervical cancer screening in Africa is of critical importance as screening is the primary tool available to reduce the burden of cervical cancer until the benefits of HPV vaccination become evident.[25] The purpose of this study is to conduct a systematic review of the effectiveness and implementation feasibility of HPV detection in Africa as part of a solitary, sequential, or combined screening strategy in the context of a screen-and-treat approach. By focusing on studies published after 2011, this review will address the findings since the publication of the 2013 WHO guidelines and contribute to the knowledge base until the results of future randomized trials are available.

Methods

Search Strategy

Literature searches were conducted in PubMed, Embase, Cochrane Library, and google for studies published between 1/1/2012 and 2/14/2019. The search terms were selected with the assistance of a health sciences librarian and used a combination of Medical Subject Headings (MeSH) and simple keyword search terms. Search terms were created in PubMed and modified according to the database. The full original search terms are:

"(Africa OR African OR Algeria OR Angola OR Benin OR Botswana OR British Indian Ocean Territory OR Burkina Faso OR Burundi OR Cameroon OR Cape Verde OR Central African Republic OR Chad OR Comoros OR Congo OR Djibouti OR Egypt OR Equatorial Guinea OR Eritrea OR Ethiopia OR Gabon OR Gambia OR Ghana OR Guinea OR Guinea-Bissau OR Ivory Coast OR Kenya OR Lesotho OR Liberia OR Libya OR Madagascar OR Malawi OR Mali OR Mauritania OR Mauritius OR Mayotte OR Morocco OR Mozambique OR Namibia OR Niger OR Nigeria OR Reunion OR Rwanda OR Helena OR Ascension OR Cunha OR Sao Tome and Principe OR Senegal OR Seychelles OR Sierra Leone OR Somalia OR South Africa OR South Sudan OR Sudan OR Swaziland OR Tanzania OR Togo OR Tunisia OR Uganda OR Western Sahara OR Zambia OR Zimbabwe) AND ("Cervical Intraepithelial Neoplasia"[Mesh] OR Cervical OR Cervix OR cin OR cin1 OR cin2 OR cin3) AND (Screening OR "Mass Screening"[Mesh]) AND (HPV OR Human Papillomavirus OR Papilloma* OR "Papillomavirus Infections"[Mesh])"

The resulting records from the full search were entered into an EndNote database for screening.

Study Selection Process

In EndNote, all search records were screened for duplicates. After removal of duplicates, the remaining records underwent abstract and title screening using a set of inclusion criteria generated using the PICOTS (Population, Intervention, Comparisons, Outcomes, Time, Studies) framework[99]. (Table 2) A two-step screening process was employed, with initial abstract and title screening using the inclusion criteria, followed by a review of the remaining full-text articles using both the inclusion and exclusion criteria. (Figure 1) Exclusion criteria included: non-

empirical studies (reviews, expert commentaries, and clinical trial protocols), HPV testing done with an intent other than for screening, cost and cost-effectiveness analyses, study population outside Africa or including multiple locations without separate results for African countries, population including only adolescents, studies designed specifically for HIV positive women, studies published in non-English language, studies with duplicate reporting of primary results, and HPV testing other than DNA.

Cost and cost-effectiveness analyses were excluded as results of these may vary significantly based on factors like location, HPV test availability, and testing resources. Thus, cost-effectiveness may be more accurately assessed by evaluating a specific country or a narrow set of HPV screening options. Studies designed to evaluate screening in HIV positive women were excluded given that this population carries a higher risk of HPV infection[90] and cervical lesions[93], and often has access to dedicated HIV clinics and receives routine medical care.

Analysis

All of the full-text articles were transferred to the Rayyan application[100] for filtering and sorting. Excluded articles were labeled with the reason for exclusion, while included articles were labeled by topical categories according to the purpose and domain of the study. The topical categories were acceptability and participation, the accuracy of HPV testing, the agreement of self-sampling and clinician-collected sampling, feasibility of HPV testing, the performance of HPV testing in screen-and-treat approaches, and follow-up. Following the completion of the full-text screening, articles with identical authors were reviewed to ensure that all studies presented unique data without duplication.

The final included articles and their category labels were exported to spreadsheets.
All included articles had basic information extracted: study design, country, number of participants, funding source, reporting of ethical review and consent, study context, screening tests performed, and location of testing analysis. For each topical category, relevant articles were reviewed with key findings documented. If appropriate, articles were included in more than one category.

The topical categories were initially designed after a review of the pertinent literature[101, 102], with an emphasis on the terminology used by the WHO. After analyzing all the included studies, the topical categories were adjusted to provide clarity and ensure a comprehensive examination of the included studies. Given the breadth of the terminology used in cancer screening and public health literature, as well as the variety of interpretations of identical terminology, specific definitions were created for the topical categories used in this review and are listed below. Additionally, attendance is considered a community measure defined by the number of eligible women accessing available screening, while participation is defined on an individual level as the proportion of women enrolled in a study who underwent the designated screening event.

Acceptability and participation: Includes individual acceptability[101] or preference of women for screening, as well as women's attendance and participation in screening events.

Accuracy of HPV testing: Performance of HPV testing as compared to a reference standard test using the standard measures of sensitivity, specificity, positive predictive value, and negative predictive value.

Agreement between self-sampling and clinician-collected sampling:

Concordance of HPV testing results from self-collected samples as compared to HPV testing results from clinician-collected samples using measures of agreement including the kappa statistic

Feasibility of HPV testing: Includes obstacles for translating study design into widespread practice[102], such as logistical barriers, validity issues with tests, or issues with integration or scalability

Performance of HPV testing in screen-and-treat approaches:

Covers both the efficacy and effectiveness of screen-and-treat approaches with and without the use of a triage test; includes both accuracy measures as well as outcome data like the number of women receiving treatment or follow-up

Follow-up:	Contains studies with long-term (> 6 months) follow-up data on patients after HPV screening

Quality Assessment

The Mixed Methods Appraisal Tool (MMAT)[103] was utilized to assess the quality of the articles included in the review. The MMAT is designed to accommodate a variety of study types, including qualitative and quantitative studies, and evaluates each study type using five methodological quality criteria answered with a yes or no response. While no overall quality score is derived from MMAT, the simple design allows for a straightforward comparison between studies.

Results

Search Results

The full search summary is presented in the Transparent Reporting of Systematic Reviews and Meta-analyses (PRISMA)[104] flow diagram shown in Figure 1. A total of 526 records were identified through the search strategy and one record was found while reviewing the studies from the initial search. After removal of duplicates, 507 records remained for eligibility screening. Following the abstract review, 155 full-text articles were screened in using the inclusion criteria. Subsequently, in full-text review, 125 of the 155 articles were screened out by applying the exclusion criteria. A summary of the number of full-text articles and their reasons for exclusion are presented in Figure 1. Over a third of the records were excluded because there was either no HPV screening intervention or the purpose of the study was not to study HPV screening.

Description of Included Studies

After applying the screening criteria, 30 studies were eligible for inclusion in this review (Table 3) and were analyzed according to the seven topical categories previously described. Fifteen publications (50%) spanned only one topical category, 14 (47%) covered two or three, and one publication covered four categories. The acceptability and participation category had the most publications (n= 17), while follow-up had the least (n=1). Study designs were predominantly cross-sectional design (73%), but there were five randomized controlled trials (RCTs) (17%). Studies took place in twelve countries, with Cameroon and Uganda having the most with eight and four, respectively. All studies consented participants and had ethics approval from governing bodies. HPV testing was performed in twenty-six studies (87%), and the sampling methods varied by the study: self-sampling alone (46%), clinician-collected sampling alone (15%), both (35%), randomization to either self-sampling or clinician-collected sampling (4%). Of twenty publications that reported the location of HPV sample analysis, the distribution was evenly split between testing within and outside of the study country.

Acceptability and Participation in HPV Testing

Acceptability of or participation in HPV testing was analyzed in seventeen studies: seven covered both topics, three covered participation only, and seven covered acceptability only. All of the studies covering participation performed HPV testing for all subjects (Table 4), while over two-thirds of the acceptability studies included HPV testing (n=10/14, 71%) (Table 5). When reported, exclusion criteria for the seventeen studies were similar, with the most frequently listed criteria being a history of a hysterectomy (n=10, 58.8%), pregnancy (n=6, 35.4%), or a history of

cervical cancer (n=6, 35.4%). The majority of the study designs were cross-sectional, but four were RCTs.

Details on participation and attendance for the ten reporting studies are found in Table 4. Two studies, Huchko et al.[105] and Swason et al.[106] measured attendance of eligible women at screening events following community outreach. Huchko et al. performed a cluster-randomized trial among women in twelve rural communities comparing self-collection HPV screening uptake via community health campaigns (CHCs) versus government health clinics. The proportion of eligible women accessing screening was higher within the communities randomized to the CHC arm (60%) as compared to the government clinic arm (37%). Swanson et al. used door-to-door solicitation and public outreach strategies to recruit local women to a CHC for HPV testing using self-sampling. They estimated that about a third of eligible women in the community attended the CHC. Both studies used community health workers to estimate the number of eligible women in the community, and both acknowledged the uncertainties inherent in this estimation and, thus, the uncertainties in their assessment of screening uptake at the community level.

As seen in Table 4, participation rates were high when HPV screening was based in the community[106-108], as compared to those based at a clinic[105] or hospital[109, 110]. Three studies compared facility-based versus community-based screening with HPV: Auwa et al.[109], Huchko et al.[105], and Mobdibbo et al. [110] All three found lower rates of participation for facility-based screening, which ranged from 47%[109] to 58%[105], as compared with the participation rates for community-based screening, which ranged from 93%[110] to 99%[105].

In the study by Modibbo et al., the method of specimen collection varied by the location where screening was performed, with 400 women randomized either to self-sampling at home or clinician-collected sampling at a hospital. Self-sampling for HPV was used in both screening settings in the Hucko et al. study, while both self-sampling and clinician-collected sampling were offered to all women in all settings in the Awua et al. study.

In addition to the study by Modibbo et al.[110], the study by Moses et al.[107] also randomized women to two different collection methods. Using local outreach workers to recruit women in their homes or workplace, Moses et al. randomized 500 women to self-collection versus VIA. Women randomized to the self-collection arm were offered immediate specimen collection, while women in the VIA arm received an appointment at the local health center. Both studies found that self-collection outside a facility had higher screening participation rates as compared to facility-based screening using either clinician-collected sampling for HPV (93% vs. 56%, $p<0.001$)[110] or VIA (99% vs. 48%, $p<0.0001$)[107].

Although facility-based screening participation rates were generally lower regardless of the type of sampling or screening, there were two studies in which facility-based screening had participation rates of 99% or higher.[111, 112] Broquet et al.[111] recruited 150 women from an urban health care center and 150 women from rural dispensaries for a study involving self-sampling. While specific details on recruitment methods are lacking, the authors reported that all the women who were approached agreed to participate in the study. Obiri-Yeboah et al. [112] offered self-sampling and clinician-collected sampling to a systematic portion of attendees at

general medicine and HIV clinics. Of the 195 eligible women seen in the clinic, all but one consented and participated in the study.

Two similar studies from Synman et al. used school-based vaccination programs to offer self-screening kits to mothers.[113, 114] The initial Vaccine and Cervical Cancer Screen (VACCS) study invited the parents of girls in grades 4-7 to attend information events about cervical cancer and offered self-sampling screening kits for the women.[113] In the VACCS 2 study, female students in grades 4-7 were given printed information and self-screening kits to take home for their female parents. The percent of distributed kits used and returned was 14% [114]when kits were sent home with students and 32%[113] when distributed directly to mothers.

Table 5 provides details on the fourteen studies that reported on women's views on HPV screening, specifically their preferences for self-sampling versus clinician-collected sampling. Overall, most studies concluded that the acceptance of self-collection for HPV testing was high as measured by participation rates and self-reported preference. However, despite these conclusions, women preferred clinician collection in three[109, 115, 116] of the six studies [110, 112, 117] directly soliciting preference (Table 5). Of these six studies reporting preference, all but one [110] of them performed both self-sampling and clinician-collected sampling on all participants or solicited preference only from women who had experienced both. A single study surveyed women about collection preference both before and after screening and found that pre-screen, the majority of women had no preference (89%), while post self-sampling and clinician collection, the majority of women preferred clinician collection (56%).[109] In three studies where women expressed a preference for clinician collection of HPV samples, the reasons for

this preference centered on concerns of reliability and fear of performing the test incorrectly.[109, 115, 116]

Results were mixed regarding the impact of cervical cancer education on acceptance and participation using HPV self-sampling. Two studies concluded that education might positively impact screening acceptance, but one was a qualitative study with purposeful selection of participants[118] while another offered non-standardized education to all participants and surveyed them only post-education.[117] A pair of studies testing the capacity to link cervical cancer screening to school vaccination programs found no difference in participation rates when the educational intervention was removed from the protocol.[113, 114] An RCT study comparing willingness to perform HPV self-sampling in women randomized to self-collection with or without an educational intervention found no differences between the two groups.[119]

Feasibility of HPV Testing

Twelve studies, including two RCTs[105, 107], contained pertinent findings regarding the feasibility of HPV testing in Africa. (Table 6) Regardless of the method of collection or HPV test type, there was a low proportion of HPV samples that were invalid for testing (Table 6). For HPV tests run in the country of sampling, the proportion of invalid HPV samples ranged from zero[107, 108] to 4.7%[106], with four of six studies reporting <1% invalid samples[105, 107, 108, 120]. The study with the highest percent of invalid tests (9.8%) sent samples to Switzerland, and authors attributed the high number of invalid results to delay in the analysis of samples.[121]

Five of the twelve studies reported on HPV test result notification (Table 6), although the studies varied whether the protocol was to notify all women of results or only women with positive test results. Four out of the five studies (80%) had at least 75% of women receiving results. In the two VACCS studies by Synman et al. [113, 114], all women received test results using a combination of school infrastructure and mobile phones. Swanson et al. delivered results to 75% of women using a variety of result notification methods: mobile phones, home visits, and collection from health facilities.[106] While analyzing their result notification findings, they found that women who could not be reached with test results were less likely to have a mobile phone. Ogilvie et al.[108] delivered results via mobile phone and were able to deliver 85% of the positive test results successfully. Contrary to the other studies using mobile phones for result communication, the study by Moses et al.[107] reported that less than 50% of women were successfully reached with test results. However, all but one of the thirty-four women who received test results subsequently attended their follow-up appointment. The low rate of result notification translated to 45 % (33/73) of HPV positive women attending a follow-up appointment, although only 34 of them were aware of their HPV positive status.

The conclusions and limitations of the feasibility studies are presented in Table 7. Eight of these studies also reported on participation, and, given the link between participation and feasibility, these findings are also summarized in Table 7. Most studies concluded that the evaluated screening approach was feasible but may be limited by the cost of HPV kit[122], delays in receiving test results [106, 121], challenges with delivering results[106], and attendance at follow-up or treatment[105-107, 123]. Similar to the findings reported on participation (Table

4), the majority of studies concluded that community-based collection approaches yielded the highest rates of participation and the highest screening uptake rates of for the overall community.

Accuracy of HPV Testing

The accuracy of HPV as a screening test was addressed in seven cross-sectional studies from five countries (Table 8). Four of the studies had a lower age range cutoff of 30 years, while two had a lower age limit of 25 and one had a lower limit at age 18. Out of seven studies, two screened only with self-collection HPV and five screened with multiple tests. Women were typically recruited using screening campaigns promoted through the media and the local community, although one study recruited participants from outpatient HIV and gynecology clinics[124].

Seven different HPV test types were utilized, and two studies included two separate tests (Table 9). As seen in Table 8, three of the seven studies utilized WHO prequalified HPV POC tests. Jeronimo et al.[123] and Umulisa et al.[125] used the careHPV POC assay, while Kunckler et al.[120], used the Xpert HPV assay. For performance assessment, six studies used histology as the reference test while one used cytology[124]. The reference test was generally offered to all screen-positive women (n=5, 71%) with two of those studies[126, 127] (40%) also offering the reference test to a sample of the screen negative patients. The study by Mukanyangezi et al. used cytology as the reference test offered the test to all participants.[124] Mahmud et al. performed colposcopy on all participants upfront with biopsy of all colposcopy positive patients and a portion of those with a negative test.[128] The proportion of the study population without reference test results ranged from a low of 1.1%[120] to a high of 40.8%[123]. The reasons for

missing reference test results included women lost to follow-up, missing test results, or indeterminate results.

HPV test performance varied by study, collection mechanism, the threshold level of reference test, and specific type of HPV test utilized (Table 9). Self- versus clinician-collected samples performed similarly for detecting CIN2+ or HSIL+, although the sensitivity of clinician-collected samples was slightly higher. The specificity of HPV tests was generally higher than the sensitivity (n=5, 71%), but the opposite trend was seen in two studies [126, 127](n=2, 28.6%). The negative predictive values (NPV) of all screening tests were 89% or higher, while the positive predictive values (PPV) ranged from 3.7% for cytology [123] to 57% for VIA[126]. The NPVs for HPV tests were 98% and higher when considering the presence of any HR-HPV genotype as a positive screening test. The PPV's for HPV tests ranged from 10.3%[127] to 36%[126].

Agreement between Self-Sampling and Clinician-Sampling

Seven studies included HPV screening from both self- and clinician-collected samples (Table 10). The majority of the studies were cross-sectional in design (n=6, 85.7%), and one study was a community-based trial where women were randomized to either self- or clinician-collected specimens.[110] Five studies reported a kappa statistic to assess agreement between the two collection methods, with values ranging from 0.47 to 0.89[126, 129]. The study[129] with the lowest reported kappa statistic used genotype agreement as to the measure of agreement, while the others[112, 121, 126, 130] used the presence of any HR-HPV genotype as the measure of agreement. When reported, levels of concordance were generally high (Table 10).

Performance of HPV testing in screen-and-treat approaches

HPV-based screening followed by triage testing was assessed in three cross-sectional studies and one RCT (Table 11). The RCT by Bigoni et al. randomized HPV screen-positive women to either VIA or cytology, while performing cervical biopsy and endocervical curettage (ECC) in both arms.[131] Using histology CIN2+ as the reference test, sensitivity and specificity were higher for cytology (90% and 85%, respectively) as compared to VIA (25% and 74%, respectively). The three cross-sectional studies used histology CIN2+ as a reference test, although biopsies were limited to screen-positive women in two studies[120, 125] and included a sampling of screen negative women in one study[127] (Table 11). The addition of a triage test generally lowered sensitivity and increased specificity. The NPVs were greater than 96% regardless of the use of triage, and the PPVs improved with the addition of a triage test.

With the exception of the study by Kunckler et al.[120], the studies evaluating the addition of a triage test concluded that VIA is not an ideal test. In the Bigoni et al. trial, VIA was inferior to cytology, and the authors recommended exploring alternative triage tests.[131] The study from Rwanda by Umulisa et al. concluded that the greater than 15% loss follow-up that occurred between screening and triage was too high to justify a two-visit strategy. [125] As a one-visit strategy was not achievable, the Rwanda Ministry of Health (MOH) elected to continue screening with VIA only. Tebeu et al. utilized the Abbott RealTime assay with results processed in Switzerland.[127] After analysis in Switzerland, 146 HPV negative and 146 HPV positive women were called back for VIA and biopsy. Overall, 217 of the 292 women (74%) returned for

the follow-up visit and underwent VIA with biopsy. Tebeu et al. found that self-sampling and testing with the HPV test alone had a sensitivity of 100% (95% CI, 79.6 to 100) and specificity of 74.5% (95% CI, 70.6 to 78.1) for the detection of CIN2+ on biopsy. Of the eleven women with CIN2+ on biopsy, all were HPV+, but only four were VIA positive. Thus, the addition of VIA as a triage test dropped sensitivity to almost 30%, although it raised the specificity. The authors concluded that due to its reduction in sensitivity, VIA is not an ideal triage test to follow HPV screening.

Self-collected HPV followed by VIA or VILI to determine eligibility for screen-and-treat was investigated in three studies detailed in Table 12. One study by Kunckler et al.[120] utilized a hybrid approach where women testing positive for HPV 16/18/45 received treatment regardless of their VIA results, while women positive for other HR-HPV types received treatment only if they were VIA or VILI positive. The Kunckler et al. study utilized a same-day treatment paradigm, and 91% (110/121) of women recommended treatment were able to receive it on the same-day as screening, regardless of whether or not a triage test was used to determine treatment. In the cross sectional study by Swanson et al., about 50% of screen-positive women attended follow-up, and 83% of the women attending follow-up received treatment on the same day.[106] The Huchko et al. randomized trial comparing self-collection screening in two settings reported 35.7% of screen-positive women receiving treatment an average of 47 days (IQR, 31-77 days) from screening.[105]

Follow-up

A study of 188 women in Cameroon[132] presented six and twelve-month follow-up testing for HPV-positive women who were originally recruited to a study assessing self-collected HPV in a screen-and-treat paradigm[120]. At the follow-up visits, all women received self- and clinician-collected HPV, cytology, VIA/VILI, and biopsy with ECC for all VIA positive or previously treated women. Out of the 188 women who were HPV positive at baseline, 121 (64.4%) had treatment with thermoablation. With cytology as the reference test and HSIL+ as the threshold, clinician-collected HPV had a higher sensitivity and specificity (100% and 74.3%) than self-collected HPV (88.9% and 66.9%) at six months. At 12 months, self-collection had higher sensitivity but lower specificity. Self-collection had lower specificity among women who were previously treated with thermoablation. The loss to follow-up at 12 months was 30%.

Quality Analysis

The results of the quality analysis using the MMAT are presented in Table 13. The one qualitative study by Teng et al.[118] met all the methodological quality criteria. Of the five RCTs, the only study that had a no response to a quality criterion was Huchko et al.[105] for the criteria on baseline group comparability. In the Huchko et al. study, entire communities were randomized to one of two screening strategies, and the two arms were significantly different on a number of baseline characteristics including age, history of prior screening, and HIV status. Only one[131] of the five RCTs clearly stated that assessors were blinded to the participants' randomization designation.

Nineteen studies were evaluated as non-randomized studies, including the majority (18/22, 82%) of the cross-sectional studies. Awua et al.[109] was the only study with a no response to any of

the criteria (Table 13), as in this study, the intervention was not administered as planned for the entire study period. In the original study design, women from the surrounding community were invited to participate in screening at the hospital. However, the initial response rates were low, so the protocol was amended during the study to allow community-based collection. Four[112, 116, 120, 124] of the nineteen studies in this category accounted for confounders either in their design or analysis, while it could not be ascertained if confounders were accounted for in remaining studies.

Of the five studies described as quantitative descriptive studies, only one had a no response to one criterion. In Chamot et al.[133], the study sample was not representative of the target population. Chamot et al. used a survey to assess the screening preferences of women who were attending a visual inspection screening clinic. Given that these women had all chosen to participate in a screening clinic and had all experienced one type of screening, their preferences may not reflect those of the general population who are mostly screen naïve and, thus, have a minimal pre-existing bias towards one type of screening modality.

Discussion

The implementation of HPV vaccination and HPV-based screening have the potential to dramatically alter the approach to cervical cancer prevention in limited-resource settings. However, one of the many challenges in cervical cancer screening is the wide variety of approaches available and the complex algorithmic options detailed in current WHO guidelines.[31] The complexity of the WHO guidelines reflects the challenge of summarizing

and condensing a wide variety of studies conducted in vastly different settings into a set of concise guidelines that are flexible enough to be adapted to the resource level of any country.

This review synthesizes a broad body of research spanning seven years and including thirty studies taking place in twelve countries. The majority of included studies are cross-sectional in design, and thus, lack follow-up to examine the long-term outcomes of HPV-based screening. Given the slow progression from HPV infection to pre-cancerous lesions and invasive cancer, long-term follow-up is critical in the assessment of cervical screening interventions. Despite the lack of follow-up, the existing studies provide insight regarding the integration of HPV testing into screening and highlight the most critical research needs for the future.

Overall, self-collection for HPV testing seems acceptable to the majority of women and produces reasonably high screening participation rates. Available evidence demonstrates that participation rates are improved if the collection is based in a community setting, as opposed to requiring women to return kits to a hospital or travel to a clinic to perform the test.[109] [105] Although community-based strategies are more favorable to women, they may be challenging to accomplish outside of a study setting where funding and resources are available. A unique solution tested in two studies from South Africa was the linking of cervical cancer screening to school vaccination programs by providing mothers and female guardians with self-screening kits.[113, 114] Both studies concluded that this approach is feasible and acceptable, but the disadvantage to this approach was the number of wasted kits. For both studies combined, 413 kits were returned for testing out of 1,920 (21.5%) dispensed.

Self-collection of HPV samples has the potential to increase access to screening, overcome some of the psychosocial barriers that limit testing, and increase screening uptake. Critical questions remain regarding the follow-up of patients who self-collect specimens. Reporting study results to screening participants can be difficult [107], and this contributes to the challenge of linking screening to follow-up and treatment.[106]

Assessing the performance accuracy of HPV-based screening in African studies is difficult given the number of different HPV tests used, the number of missing results, the number of women lost to follow-up, and the frequent lack of reference testing being performed in the screen-negative patients. Similar to a past systematic review [77], this review found that HPV-based screening was typically more sensitive than both VIA testing and cytology. However, in contrast, the specificity of VIA in this review was lower than that of HPV testing in multiple studies.[120, 123, 126] This may reflect underlying differences in the study populations[123] or the subjective nature of VIA which can render it prone to errors. As has been demonstrated in prior studies[134], the level of agreement between self- and clinician-collected HPV specimens varies based on the HPV test type but is overall reasonably good.

Feasibility and participation analysis show that multiple approaches to screening are feasible, but community-based approaches may facilitate attendance and participation for women that do not live close to a health facility or typically attend regular appointments at a health facility (Tables 4 and 7). Regardless of the collection method, for the studies in this review, most of the HPV samples were valid for testing. Delays caused by testing results at a distant location can reduce the yield of valid samples and may increase the loss to follow-up.[121] While some screening

interventions are feasible, cost[122] or resource requirements[113] may render them less effective outside of a study setting.

The risks and benefits of screen-and-treat algorithms versus screen-and-triage ones need to be weighed carefully and, ideally, studied with rigorous methodology. The risk of screen-and-treat is overtreatment due to the lack of diagnostic testing before treatment, while the benefits include improved adherence to treatment and minimization of testing resources. In this review, screen-and-treat was most successfully implemented in a one-day approach, where 91% of women requiring treatment received it on the same day as screening.[120] Outside of the same day paradigm, loss to follow-up increases, and fewer HPV screen-positive women receive treatment.[105, 106] However, screen-and-treat using HPV testing is often not practical due to the logistics of running the analysis. For logistical reasons, the Ministry of Health in Rwanda elected to return to VIA screen-and-treat after reviewing results of a pilot HPV-based screening campaign.[125]

Only one study reported long-term follow-up results after an HPV screen-and-treat strategy.[132] Two important findings from this study were that the loss to follow-up at one year was ~30% and self-collection had lower specificity than clinician-collection among those patients treated with thermocoagulation. Additional follow-up studies are critical to determining how best to screen patients following treatment for pre-cancerous lesions, how best to follow women who are HPV positive but without evidence of cervical lesions, and what is the expected loss to follow-up of treated women over time.

This review is limited by the availability and quality of studies assessing HPV-based screening in Africa. The available literature includes very few RCTs and primarily consists of cross-sectional studies. Therefore, there is a lack of rigorously designed studies with any length of follow-up. The available studies are highly heterogeneous in their design, HPV testing, approach to analysis, and results reporting. Therefore, summarizing and comparing the studies is complicated and reliant on generalizations.

While the burden of cervical cancer in Africa is receiving more attention and research over recent years, continued efforts are needed to prioritize research questions and coordinate efforts to conduct studies. Developing standardized guidelines for study conduct and reporting could be an initial step towards improving coordination. Another step is to develop a central repository for proposed studies, which would allow researchers and funding bodies the opportunity to avoid repetitive studies and to collaborate with others and expand the scope of their proposed studies. Additional implementation research in Africa is needed to test the effectiveness of adopting approaches that have proven efficacious in randomized trials performed in other geographic locations.

Chapter 4. Discussion and Recommendations

HPV testing was initially introduced as a triage test for women with ASCUS or LSIL results on cytology [135], and a 2003 study found HPV testing to be as sensitive as colposcopy for detecting CIN3 and capable of decreasing referrals to colposcopy by half. [136] HPV tests are divided into those that test only for the presence of any high-risk genotype and those that specify the type, particularly those that isolate HPV 16 or 18. HPV cannot be easily replicated in culture using standard techniques, so diagnostic methods typically rely on detecting HPV DNA in an infected cell using molecular techniques.[137, 138] The two main types of molecular assays used are signal amplification and nucleic acid, or target, amplification assays that employ PCR. Many of the available HPV assays are ill-suited for limited-resource settings because of their equipment requirements and cost.[87, 135] Furthermore, the logistical needs of many assays precludes them from being used in a same day screen-and-treat paradigm.[89]

The development of POC HPV assays has renewed interest in HPV-based screen-and-treat paradigms. POC tests that have been tested in clinical settings include the careHPV, Xpert HPV, and the OncoE6 Cervical test. These tests can all be performed in under three hours, and two of them, the Xpert HPV and careHPV, have been accepted on the WHO list of prequalified in vitro diagnostics.[88, 89] Of the seven studies evaluating the accuracy of HPV testing in this review, two utilized the careHPV assay[123, 125] and one utilized the Xpert HPV assay[120] (Table 9). In all three of these studies, the POC HPV tests were processed locally. Both Kamal et al.[126] and Mahmud et al.[128] conducted HPV testing using the Hybrid Capture 2 (HC2) assay, which is FDA approved and commonly used as a reference test for comparing the accuracy of new

HPV tests.[56] The cost and laboratory requirements of the HC2 assay prompted the development of careHPV, which utilizes a similar approach but with a more automated process and shorter run-time. [56, 139]

Out of the three studies that utilized POC testing with careHPV or Xpert HPV, only Kunckler et al.'s study from Cameroon incorporated a screen-and-treat paradigm.[120] In this study, 1012 Cameroonian women performed self-sampling, which was followed by on-site analysis with Xpert HPV assay within one hour of sample collection and immediate communication of results. The Xpert HPV assay simultaneously detects the presence of any of 14 HR-HPV genotypes while also separately distinguishing the presence of HPV16 or HPV18/45. In Kunckler et al., participants testing positive for HPV16/18/45 were treated immediately while those positive for other HR-HPV types were only treated if they tested positive on triage with VIA/VILI. The quick turnaround of test results and screen-and-treat paradigm allowed 91% (110/121) of the eligible women to receive treatment the same day as the screening test (Table 12).

The loss to follow-up in Kunckler et al. was ~1%, as compared to the greater than 15% loss to follow-up seen in a Rwandan pilot study by Umulisa et al., where the triage visit took place on a separate day (Table 11). The loss to follow-up seen in the Rwandan pilot study with HPV testing plus VIA triage prompted the Rwanda Ministry of Health to recommend VIA screen-and-treat as the preferred paradigm.[125] Jeronimo et al. reported results from a multi-country study organized by the Program for Appropriate Technology in Health (PATH) where women were simultaneously screened with three tests (careHPV, VIA, and cytology), with screen-positive women referred for colposcopy.[123] Of the 3,835 screen-positive participants in Uganda, over

40% either had missing results or were lost to follow-up and did not attend the colposcopy visit (Table 9). The study authors concluded that HPV screening with careHPV was more sensitive than VIA or cytology for detecting CIN2+ (Table 9) and that the overall performance of HPV testing was more robust across sites due to the objective nature of results. However, the authors did not address the potential reasons for the high rates of loss to follow-up or the outcomes of participants who were referred for treatment or workup after colposcopy.

Tebeu et al.[127] used the Abbott RealTime High-Risk HPV assay, which relies on an automated process that takes 6-8 hours for results, however, requires subjective interpretation of results.[139] The Abbott RealTime assay is currently in the process of evaluation by the WHO for prequalification [140], although it has already been approved in Europe.[89] Although HPV results were analyzed in Switzerland, thus delaying follow-up visits, almost 75% of women returned for follow-up and underwent VIA with biopsy.[127] The sensitivity and specificity of HPV testing alone for detecting CIN2+ on biopsy was high (100% and 95%, respectively). While the addition of VIA as a triage test raised the specificity to 98%, it dropped the sensitivity to almost 30%. This result indicates that the addition of a triage test may lead to more false-negatives screens. Given the logistical burden of adding another step to screening and the concerns of loss to follow-up with a second visit, as yet there is a lack of evidence to persuade LMIC's to recommend routine VIA triage following positive HPV screening tests.

One of the most persuasive arguments for HPV-based screening in limited-resource settings is its accommodation for self-collection of specimens. Self-collection can increase access to screening for women who live far from health facilities or are reluctant to undergo a pelvic examination.

By removing providers from the initial screening process, self-collection is an ultimate form of task-shifting that will give providers and clinics more time and space to address women who have positive screening tests. The main concern with self-collection is the potential for decreased accuracy; however, a meta-analysis published in 2014 analyzed 36 studies and found that while the pooled sensitivity and specificity of self-sampling was lower than clinician-sampling, this difference seemed to resolve with PCR-based assays.[57] A recently published randomized, non-inferiority trial from the Netherlands found that self-sampling was non-inferior to clinician-collected samples when using a PCR-based assay for a clinical endpoint of CIN2+ or CIN3+.[141]

Among the seven studies in this review that evaluated both self- and clinician-collected samples, four used a PCR-based assay alone, two used non-PCR-based assays, and one used both. Jeronimo et al. used the careHPV, a non-PCR assay, and reported slightly lower sensitivity for self-sampling (77% versus 88.5%) but comparable specificity (82% versus 81.8%) (Table 9).[123] From their study of 1,601 women screened in Egypt with self- and clinician-collected samples using the HC2 assay, Kamal et al. concluded that self-sampling HPV performed superiorly to VIA and was as accurate as clinician collection for the diagnostic endpoint of CIN2 or CIN3 on biopsy (Table 9).[126] The current evidence indicates that self-sampling performs as well as clinician-collected sampling when using PCR-based assays and is slightly inferior when using less sensitive, non-PCR assays. Modeling studies suggest that the overall benefits of self-sampling may outweigh the reduction in sensitivity if the self-sampling increases the screening coverage by about 15-20%.[142]

Self-sampling may attract more women to screening by increasing accessibility and removing the embarrassment and discomfort of a pelvic exam. On the surface, acceptability of HPV self-sampling is a straightforward concept; however, the definition of acceptability varied across the 17 studies analyzed in this review. Some studies measured acceptability via attendance and participation rates [107, 113, 114], while other studies[119, 133, 143] did not include HPV testing in the study and simply surveyed women about their willingness to self-collect. Acceptability of self-sampling was assessed using a variety of questions, including participants likeliness to recommend the test to friends, their willingness to perform self-collection in the future, and if they preferred self- or clinician-collected sampling (Table 5). As defined by the number of enrolled women who provided a specimen, participation rates for self-collection were generally quite high (Table 4). Although two studies, Awua et al.[109] and Berner et al.,[115] found that the majority of women preferred clinician collection, at 56% and 62% respectively (Table 5). When study participants were specifically asked if they would repeat self-collection or recommend it to a friend, 97% or more of participants responded positively (Table 5).[106, 111, 119, 144]

A question for future study is which of the following are the most reliable measures of acceptability: attendance and participation rates, self-reported willingness to participate, or willingness to recommend the test to family or friends. Furthermore, if the current goal is to screen women once per lifetime, how valuable is it to assess women's willingness to repeat a test in the future? Questions regarding women's preferences could be modified to explore women's willingness to participate in the screening process if their preferred option is not available. With this modification, the responses may more closely estimate future screening attendance.

The majority of studies did not pre-determine a threshold level of participation or response that would differentiate an acceptable test from a non-acceptable one. Rather than arbitrarily choosing a screening coverage target rate for a study, a more practical approach may be to follow the evaluation method of PATH, which uses past coverage in an area as a baseline for comparing coverage with new screening approaches.[145] This approach may not be feasible in areas where screening has not been available, screening attendance has not been recorded, and or there is no accurate count of screen-eligible women.

Despite the heterogeneity in these 17 studies regarding their design and reporting of acceptability, some common themes arise. Convenience is a critical determinant of screening uptake as evidenced by women's survey responses, but more importantly, as evidenced by screening attendance. The two studies, Huchko et al.[105] and Awua et al.[109], that compared community-based screening versus facility-based found that screening uptake in the community was about 20% higher than in facilities (Table 4). Awua et al. recruited women at home and assigned them to hospital-based or community-based collection. Attendance at the hospital was 38.5% versus 60.4% in the community setting. The initial study design included only hospital collection, but the protocol was modified due to low attendance rates and feedback from women in the community. Using a cluster-randomized design in western Kenya, Huchko et al. randomized twelve communities to facility-based or CHC-based collection. Using estimates of the screen-eligible population in the communities, the proportion of eligible women attending screening was significantly higher in the CHC's (60.0% versus 37.0%, $p<0.0001$). A trial in Uganda randomized 500 women to community-based self-sampling for HPV or VIA at a local

health facility.[107] Over 99% of women in the HPV arm provided samples, while less than 50% of women in the VIA arm attended the screening. Although the HPV arm participation rate was high, over 50% of the HR-HPV positive women could not be reached by phone with their test results. Thus, even though almost all of the women who received results attended a follow-up visit, overall, only 45% of HPV-positive women received and attended a follow-up appointment. These studies highlight the value of community-based screening and the logistical challenges of achieving high follow-up attendance regardless of where the initial testing takes place.

Throughout the studies included in this review, the major obstacles to feasibility were downstream of the actual screening: delays in obtaining test results, difficulties in informing participants of results, low attendance at follow-up for women with positive screening tests. The short processing time and minimal equipment requirements of the POC tests can help address the first two obstacles, depending on the setting where HPV screening occurs. Huchko et al. randomized communities in Kenya to self-collection in either CHC's or health facilities with sample analysis using the careHPV platform.[105] Specimens collected in CHC settings and health facilities were transported to the County Hospital for testing, which was performed within two weeks of collection. For screen-positive women, the mean time from screening to treatment was 47 days (IQR, 31-77days). In comparison, a hospital-based screening study in Cameroon was able to treat over 90% of treatment-eligible women on the same day as screening, using self-collection and the Xpert POC assay.[120]

Employing a same day screen-and-treat paradigm while using HPV-based screening is logistically demanding and requires an efficient system. Even if a triage test is not used, screen-positive women need to be evaluated for treatment eligibility using VIA.[20] Multiple types of treatment can be used for pre-cancerous lesions, but WHO guidelines focus on cryotherapy, LEEP, and CKC.[31] Visual inspection to determine treatment eligibility is used to identify women with either gross lesions requiring further workup or those who are inappropriate candidates for the available therapy. For cryotherapy or other ablative treatment, lesions must be fully visible with no extension into the endocervical canal and covering less than three-quarters of the ectocervix.[31] Theoretically, cryotherapy can be performed in almost any setting, as it does not require anesthesia or extensive equipment; however, providers must be trained in the technique as well as VIA evaluation for eligibility. A systematic review found that cryotherapy is very safe and efficacious with minimal risk of short or long-term complications and an overall cure rate in randomized trials of 89.5% (95% CI, 87.3 to 91.7%).[146] Cryotherapy utilization is limited by the cost, the availability of gas, and maintaining a supply of trained practitioners. [142, 147] LEEP is generally reserved for higher-level facilities like district hospitals as it requires anesthesia and carries a higher risk of postoperative hemorrhage.[31]

Although screen-and-treat paradigms with ablative therapy have acceptable side-effects and minimize loss to follow-up, implementing this approach broadly at the primary health facility level may not be feasible. [142, 147] Furthermore, the high sensitivity of HPV-based testing raises the concern that health systems may become overwhelmed with positive screens.[142] This concern could be mitigated by adding a triage test for HPV screen-positive women, although a triage test often comes at the cost of a second visit and re-introduces the issue of loss

to follow-up. Umulisa et al. showed the impact of adding a second visit for a triage test in their pilot screening study of 764 women in Rwanda.[125] The 177 women who screened positive via careHPV, VIA, or a PCR-based HPV test were invited for a second visit for VIA triage and biopsies. Over 15% (n=29) of women did not return for the follow-up visit, but they were included in an analysis of a hypothetical, one visit, screen-and-treat scenario that was compared to the performed 2-visit approach. While VIA triage improved the specificity of careHPV from 88% (95% CI, 85 to 90) to 98% (95% CI, 97 to 99), this came at a cost of a lowered sensitivity from 71% (95%CI, 44 to 90) for careHPV alone to 35% (95%CI, 14 to 62) for careHPV plus VIA triage (Table 11). After using imputation to estimate the histology results for the 29 women lost to follow-up, the study authors concluded that three cases of HSIL+ were left untreated (10.3%). The authors also note that the number of pre-invasive lesions lost to follow-up is likely underestimated in their study based on higher rates (25-30%) of loss to follow-up seen in other studies.[127, 131, 148, 149] Two of these referenced studies, Tebeu et al. and Bigoni et al., are included in Table 11 and reported triage attendance rates of around 75%.

Of the four studies in this review that evaluated the addition of a triage test following HPV screening, only two directly compared the performance of HPV alone versus HPV plus triage. Tebeu et al. had similar findings to those of Umulisa et al., in that the addition of a triage test improved specificity, but at the cost of reduced sensitivity (Table 11). Tebeu et al. did not estimate the number of cases of CIN2+ missed in the 37 women lost to follow-up, but given the overall rate of CIN2+ in HPV-positive women (10.3%, 11/106), one could estimate a loss of three to four cases of CIN2+. One limitation of all four studies is the potential for verification bias overestimating the sensitivity of HPV screening, as screen-negative women did not

routinely undergo biopsies. In three of the studies[120, 125, 131] none of the screen-negative women were referred for biopsy, although in one study[125] six HPV-negative women inadvertently were referred for a second visit. Tebeu et al. attempted to correct for verification bias by performing biopsies on a random sample of HPV-negative women (n=108) in addition to the HPV-positive women (n=109). Two cases of CIN1 were found among the 102 HPV-negative women with valid histology.

As reflected in the existing guidelines from WHO and other groups, this review finds that considerable questions remain regarding the optimal, evidence-based approaches to cervical cancer screening in limited-resource settings. In their 2016 publication detailing the level of evidence supporting their latest screening recommendations, the WHO conditionally recommended HPV-based screen-and-treat approaches over VIA.[150] The consensus was that the benefits of screen-and-treat outweigh the harms, as compared to no screening, and that HPV-based screening had a larger impact on cancer incidence and death. The strongest evidence supporting this recommendation comes from randomized trials performed in India[75] and South Africa[76]. Over 130,000 women in rural India were randomized to standard of care or screening with HPV using HC2, cytology, and VIA.[75] All screen-positive women were offered colposcopy with biopsy and immediate treatment based on the visual colposcopic examination. As compared with the control group, screening with HPV reduced the incidence of advanced cancers and death, while screening with VIA and cytology did not. The South African study screened all women with VIA and HPV HC2, but randomized women to treatment based on VIA, treatment based on HPV, or no treatment for six months.[76] After 36 months of

follow-up, the HPV screen-and-treat arm had a reduced incidence of CIN2+ cases as compared to both of the other arms.

Concerning the issue of triage tests, the WHO panel recommended either HPV screen-and-treat or HPV screen plus VIA triage to determine treatment.[150] As discussed in the supplementary material to the WHO 2016 publication, the level of evidence supporting the superiority of either of these strategies is minimal due to the lack of randomized trials with direct comparisons. This review did not include any randomized trials that addressed the role of triage. The most relevant study on triage was the Cameroon study from Tebeu et al., which screened women with the Abbott RealTime HPV assay and evaluated an equal number of HPV positive and HPV negative women with VIA and biopsy.[127] Although VIA triage decreased false positives by ~50%, the authors concluded that VIA triage was unacceptable in a screening paradigm due to its low sensitivity (Table 11).

As noted in the discussion section of the WHO's 2016 publication on screen-and-treat strategies, randomized trials comparing HPV alone screen-and-treat versus HPV plus triage screen-and-treat are needed.[150] Furthermore, given the challenges of performing cytology in limited-resource settings and the lowered sensitivity as well as the subjective nature of VIA, the option of molecular-based triage tests is appealing. Other triage options worthy of exploring in trials include coupling visual inspection methods with digital cervicography[151] or portable magnifying devices[152]. Results of randomized trials and studies with longer-term follow-up can be utilized in conjunction with modeling and cost-effectiveness analyses to more clearly identify the costs and benefits of various approaches.[142] Specific information on the monetary

cost, health system requirements, anticipated utilization, and expected outcomes will help ministries of health determine if and how a cervical cancer screening program fits into their budget and overall health system.

The decision to implement a cervical cancer screening program requires a thorough review of the evidence to ensure that screening in a particular setting will be effective and maintain consistent support from the health system and the public.[39] A successful screening system requires infrastructure and personnel but also relies on the availability of quality surveillance data to monitor cancer incidence and mortality, the outcomes of screening, and the number of individuals screened.[39] In the case of cervical cancer, health systems and governments with limited resources also need to weigh the benefits of primary prevention with vaccination versus secondary prevention with screening. While vaccination and screening are complimentary, screening requires more downstream resources as women with positive screening tests require further workup or treatment. Strengthening the overall infrastructure of the health systems in Africa will benefit not only future cervical cancer screening efforts, but also address the burden of other cancers and chronic diseases. Some of the basic infrastructure needs include expanding the availability of pathology, implementing electronic databases for both health facilities and ministries of health, and expanding the use of community health workers. While these overarching goals may not impact cervical cancer screening rates in the short-term, these efforts are critical for the long-term sustenance of a cancer control program.

Table 1. Classification Systems for Grading Preinvasive Cervical Lesions [27, 31, 153]

Histologic Classification (Diagnostic)		**Cytologic Classification (Screening)**
WHO descriptive classifications	**Cervical Intraepithelial neoplasia (CIN)**	**Bethesda system**
Atypia	Atypia	ASCUS, ASC-H
Mild dysplasia	CIN 1	LSIL
Moderate dysplasia	CIN 2	HSIL
Severe dysplasia	CIN 3	HSIL
Carcinoma *in situ*	CIN 3	HSIL
Invasive carcinoma	Invasive carcinoma	Invasive carcinoma

ASCUS: atypical squamous cells of undetermined significance; ASC-H: atypical squamous cells, cannot exclude a high-grade squamous intraepithelial lesion; LSIL: Low-grade squamous intraepithelial lesion; HSIL: High-grade squamous intraepithelial lesion.

Table 2. Eligibility Criteria
PICOTS (Population, Intervention, Comparisons, Outcomes, Time, Studies)

Population	African women with no history of cervical cancer or current symptoms suggestive of cervical cancer
Intervention	Cervical HPV DNA testing for screening (alone or in combination)
Comparisons	Other screening techniques (VILI, VIA, Cytology)
Outcomes	Effectiveness and efficacy of HPV screening interventions
Time	1/1/2012-2/14/19
Studies	RCT, Cohort, Quasi-Experimental Designs, Qualitative, Case-Control, Cross-Sectional, Intervention Series, Case Series, Case Reports, Before-after Study
Other	Full-text publications in English language

Figure 1. PRISMA Flow Diagram[104]

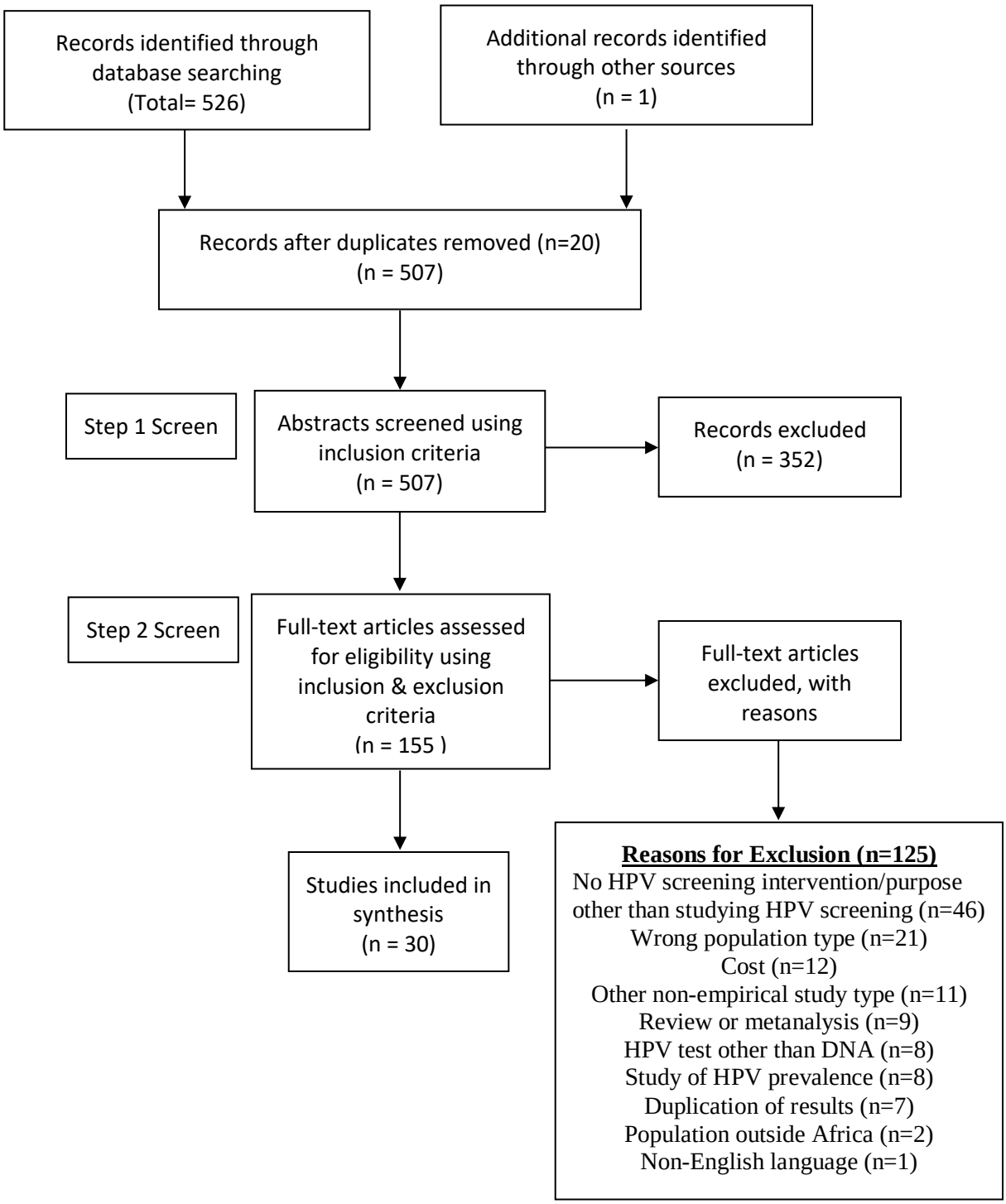

Table 3. Complete Listing of Studies Included in the Review

Author	Year	Citation	Design	N	Country
Ajenifuja	2018	Ajenifuja, O.K., et al., Comparison between self sampling and provider collected samples for Human Papillomavirus (HPV) Deoxyribonucleic acid (DNA) testing in a Nigerian facility. Pan Afr Med J, 2018. 30: p. 110.	Cross-Sectional	194	Nigeria
Awua	2017	Awua, A.K., et al., A tailored within-community specimen collection strategy increased uptake of cervical cancer screening in a cross-sectional study in Ghana. BMC Public Health, 2017. 18(1): p. 80.	Cross-Sectional	377	Ghana
Berner	2013	Berner, A., et al., Human papillomavirus self-sampling in Cameroon: women's uncertainties over the reliability of the method are barriers to acceptance. J Low Genit Tract Dis, 2013. 17(3): p. 235-41.	Cross-Sectional	243	Cameroon
Bigoni	2015	Bigoni, J., et al., Cervical cancer screening in sub-Saharan Africa: a randomized trial of VIA versus cytology for triage of HPV-positive women. Int J Cancer, 2015. 137(1): p. 127-34.	Randomized Controlled Trial	846	Cameroon
Broquet	2015	Broquet, C., et al., Acceptability of self-collected vaginal samples for HPV testing in an urban and rural population of Madagascar. Afr Health Sci, 2015. 15(3): p. 755-61.	Cross-Sectional	300	Madagascar
Chamot	2015	Chamot, E., et al., Preference for human papillomavirus-based cervical cancer screening: results of a choice-based conjoint study in Zambia. J Low Genit Tract Dis, 2015. 19(2): p. 119-23.	Choice-Based Conjoint Survey	238	Zambia
Crofts	2015	Crofts, V., et al., Education efforts may contribute to wider acceptance of human papillomavirus self-sampling. Int J Womens Health, 2015. 7: p. 149-54.	Cross-Sectional	540	Cameroon
Cubie	2017	Cubie, H.A., et al., HPV prevalence in women attending cervical screening in rural Malawi using the cartridge-based Xpert((R)) HPV assay. J Clin Virol, 2017. 87: p. 1-4.	Cross-Sectional	763	Malawi
Esber	2017	Esber, A., et al., Factors influencing Malawian women's willingness to self-collect samples for human papillomavirus testing. J Fam Plann Reprod Health Care, 2017. 43(2): p. 135-141.	Cross-sectional	824	Malawi

Table 3. Continued

Author	Year	Citation	Design	N	Country
Huchko	2018	Huchko, M.J., et al., Cervical cancer screening through human papillomavirus testing in community health campaigns versus health facilities in rural western Kenya. Int J Gynaecol Obstet, 2018. 141(1): p. 63-69.	Randomized Controlled Trial	4494	Kenya
Jeronimo	2014	Jeronimo, J., et al., A multicountry evaluation of careHPV testing, visual inspection with acetic acid, and papanicolaou testing for the detection of cervical cancer. Int J Gynecol Cancer, 2014. 24(3): p. 576-85.	Cross-Sectional	4710	Uganda
Kamal	2014	Kamal, E.M., et al., HPV detection in a self-collected vaginal swab combined with VIA for cervical cancer screening with correlation to histologically confirmed CIN. Arch Gynecol Obstet, 2014. 290(6): p. 1207-13.	Cross-Sectional	1601	Egypt
Kunckler	2017	Kunckler, M., et al., Cervical cancer screening in a low-resource setting: a pilot study on an HPV-based screen-and-treat approach. Cancer Med, 2017. 6(7): p. 1752-1761.	Cross-Sectional	1012	Cameroon
Mahmud	2012	Mahmud, S.M., et al., Comparison of human papillomavirus testing and cytology for cervical cancer screening in a primary health care setting in the Democratic Republic of the Congo. Gynecol Oncol, 2012. 124(2): p. 286-91.	Cross-Sectional	1528	Democratic Republic of Congo
Manguro	2018	Manguro, G.O., et al., Preference of specimen collection methods for human papillomavirus detection for cervical cancer screening: a cross-sectional study of high-risk women in Mombasa, Kenya. Reprod Health, 2018. 15(1): p. 206.	Cross-Sectional	200	Kenya
Modibbo	2017	Modibbo, F., et al., Randomized trial evaluating self-sampling for HPV DNA based tests for cervical cancer screening in Nigeria. Infect Agent Cancer, 2017. 12: p. 11.	Randomized Controlled Trial	400	Nigeria
Moses	2015	Moses, E., et al., Uptake of community-based, self-collected HPV testing vs. visual inspection with acetic acid for cervical cancer screening in Kampala, Uganda: preliminary results of a randomised controlled trial. Trop Med Int Health, 2015. 20(10): p. 1355-67.	Randomized Controlled Trial	500	Uganda
Mukanyangezi	2018	Mukanyangezi, M.F., et al., Screening for human papillomavirus, cervical cytological abnormalities and associated risk factors in HIV-positive and HIV-negative women in Rwanda. HIV Med, 2018. 19(2): p. 152-166.	Cross-Sectional	206	Rwanda
Obiri-Yeboah	2017	Obiri-Yeboah, D., et al., Self-collected vaginal sampling for the detection of genital human papillomavirus (HPV) using careHPV among Ghanaian women. BMC Womens Health, 2017. 17(1): p. 86.	Cross-Sectional	194	Ghana

Table 3. Continued *= Screened

Author	Year	Citation	Design	N	Country
Ogilvie	2013	Ogilvie, G.S., et al., Results of a community-based cervical cancer screening pilot project using human papillomavirus self-sampling in Kampala, Uganda. Int J Gynaecol	Cross-Sectional	205	Uganda
Snyman	2015	Snyman, L.C., et al., The Vaccine and Cervical Cancer Screen (VACCS) project: Linking cervical cancer screening to HPV vaccination in the South-West District of Tshwane, Gauteng, South Africa. S Afr Med J, 2015. 105(2): p. 115-20.	Cross-Sectional	253*	South Africa
Snyman	2015	Snyman, L.C., et al., The Vaccine and Cervical Cancer Screen project 2 (VACCS 2): Linking cervical cancer screening to a two-dose HPV vaccination schedule in the South-West District of Tshwane, Gauteng, South Africa. S Afr Med J, 2015. 105(3): p. 191-4.	Cross-Sectional	160*	South Africa
Sossauer	2014	Sossauer, G., et al., Impact of an educational intervention on women's knowledge and acceptability of human papillomavirus self-sampling: a randomized controlled trial in Cameroon. PLoS One, 2014. 9(10): p. e109788.	Randomized Controlled Trial	302	Cameroon
Swanson	2018	Swanson, M., et al., Evaluating a community-based cervical cancer screening strategy in Western Kenya: a descriptive study. BMC Womens Health, 2018. 18(1): p. 116.	Cross-Sectional	255	Kenya
Tebeu	2015	Tebeu, P.M., et al., Effectiveness of a two-stage strategy with HPV testing followed by visual inspection with acetic acid for cervical cancer screening in a low-income setting. Int J Cancer, 2015. 136(6): p. E743-	Cross-Sectional	540	Cameroon
Teng	2014	Teng, F.F., et al., Understanding the role of embarrassment in gynaecological screening: a qualitative study from the ASPIRE cervical cancer screening project in Uganda. BMJ Open, 2014. 4(4): p. e004783.	Qualitative	6 health workers, 16 local women	Uganda
Umulisa	2018	Umulisa, M.C., et al., Evaluation of human-papillomavirus testing and visual inspection for cervical cancer screening in Rwanda. BMC Womens Health, 2018. 18(1): p. 59.	Cross-Sectional	764	Rwanda
Untiet	2014	Untiet, S., et al., HPV self-sampling as primary screening test in sub-Saharan Africa: implication for a triaging strategy. Int J Cancer, 2014. 135(8): p. 1911-7.	Cross-Sectional	789	Cameroon
Vassilakos	2016	Vassilakos, P., et al., Use of swabs for dry collection of self-samples to detect human papillomavirus among Malagasy women. Infect Agent Cancer, 2016. 11: p. 13.	Cross-Sectional	449	Madagascar
Viviano	2018	Viviano, M., et al., Self- versus physician-collected samples for the follow-up of human papillomavirus-positive women in sub-Saharan Africa. Int J Womens Health, 2018. 10: p. 187-194.	Cohort-Study	188	Cameroon

Table 4. Summary of Participation Studies

Author	Population	N	Study Intervention	Screener	Participation	Attendance
Awua[109]	Local women recruited by home visits	377	Hospital v. community-based HPV screening	Self & Clinician	Reporting for specimen collection: 130/274 (47%) Hospital-based, 98/103 (95%) community-based	NR
Broquet[111]	Women recruited at an urban health center and rural dispensaries	300	Self-sampling in facilities	Self	All approached women participated (100%)	NR
Huchko[105]	Women in 12 rural communities recruited through community outreach or at health facilities	4944	Screening uptake in CHCs v. government clinics	Self	Proportion of attendees undergoing screening: CHC 2898/2943 (99%), Government clinics 2046/3538 (58%)	Proportion of eligible women accessing screening: CHC 60%, government clinics 37%
Modibbo[110]	Women recruited from semi-urban setting via community outreach	400	Clinician-collection in hospital v. Self-collection at home	Randomized: Self or Clinician	Proportion of enrollees undergoing screening: Self-collection 185/200 (93%), Clinician-collection 113/200 (56%) (p<0.001)	NR
Moses[107]	Recruited by local outreach workers	500	Community-based self-sampling v. VIA	Randomized: Self or VIA	Proportion of enrollees undergoing screening: Self-collection arm 248/250 (99%), VIA arm: 121/250 (48%) (p<0.001)	NR
Obiri-Yeboah[112]	Women attending general medicine outpatient and HIV clinics	194	Self-sampling & clinician-collection in a clinic	Self & Clinician	Eligible women participating in screening: 194/195 (99%)	NR
Ogilvie[108]	Women living or working in nearby area recruited by outreach workers	205	Community-based screening program with self-sampling	Self	Proportion of enrolled women undergoing screening: 199/205 (97%)	NR
Snyman (VACCS1)[113]	Parents or guardians of school children who were offered HPV vaccination	253	Cervical Cancer Linked to Vaccination in School by offering self-sampling kits to parents after an information session	Self	253/569 (44%) kits returned/adult females invited, 253/785 (32%) kits returned used/ kits distributed, 253 /1654 (15%) kits returned/students invited for vaccination	NR
Snyman (VACCS2)[114]	Parents or guardians of school children who were offered HPV vaccination.	160	Cervical Cancer Linked to Vaccination in School by offering self-sampling kits sent home with students	Self	160/1135 (14%) kits returned, 160/965 (17%) kits returned/students invited for vaccination	NR
Swanson[106]	Local women recruited with door-to-door strategies and public outreach	255	Screening uptake in CHC with education & self-sampling	Self	Proportion of CHC attendees undergoing screening: 255/267 (96%)	Proportion of eligble women in community attending CHC: 267/870 (31%)

CHC= Community Health Center; VACCS = Vaccine and Cervical Cancer Screen; NR= not reported

Table 5. Summary of Acceptability Studies

Author	Design	Population	Testing performed	Collection Preference/Acceptability	Conclusion
Awua[109]	Cross-Sectional	Local women recruited by home visits	Self- & Clinican-HPV	**Pre-Screen Preference** (n=253) : Clinician-HPV 7 (3%) , Self-HPV 20 (8%), Either 226 (89%). **Post-Screen Preference** (n=226): Clinician-HPV 127 (56%), Self-HPV 51 (23%), Either 49 (22%)	Community-based collection increased participation. Women accepted self-HPV but preferred clinician HPV.
Berner[115]	Cross-Sectional	Women invited for free screening campaign at local hospital	Self- &Clinican-HPV, Cytology, VIA	Preference (n=217): Clinican-HPV 135 (62%), Self-HPV 63 (29%)	Women accepted self-HPV, but prefer clinician-HPV often due to concerns of reliability.
Broquet[111]	Cross-Sectional	Women recruited at an urban health center and rural dispensaries	Self-HPV	295/300 (98%) recommended self-HPV	Self-HPV highly acceptable
Chamot[133]	Choice-Based Conjoint Survey	Women recruited from waiting rooms of government run health center that performs screening	VIA	Women preferred urine collection, but also valued wait time, the examiner, and seeing a picture of their cervix.	Most women preferred no wait time (87.5%) and seeing picture of the cervix (99%)
Crofts[117]	Cross-Sectional	Women recruited from a hospital and a village using media campaign.	Self-HPV	Preference for women with prior clinician-HPV(n=86): 64 (74%) self-HPV, 14 (16%) no preference, 8 (9%) clinician-HPV.	Self-HPV is acceptable. Education may positively impact acceptability.
Esber[143]	Cross-Sectional	Subset of women recruited for a community-based cohort study on sexual and reproductive health in rural villages	None	(n=824): 513 (62%) definitely willing to self-collect , 43(5%) probably, 197 (24%) definitely not.	Majority of women are willing to self-collect, but concerns are pain, failure to perform test correctly, and inaccurate tests.
Huchko[105]	Cluster randomized trial	Women in 12 rural communities recruited through community outreach or at health facilities	Self-HPV	99% of women in both arms would test again via self-HPVand recommend testing to a friend	Screening uptake is higher in CHCs vs government clinics. High acceptance of self-HPV
Manguro[116]	Cross-Sectional	Ancillary study from ongoing cohort study of female sex workers	Self- & Clinican-HPV, Cytology, VIA	Preference (n=199): 63(32%) self-HPV, 136 (68%) clinician-HPV	Clinician-HPV preferred. Self-HPV was comfortable and instructions clear, but participants were concerned about correctly performing the collection.
Modibbo[110]	Community-based Randomized Trial	Women recruited from semi-urban setting via community outreach	Randomized: Self- or Clinician-HPV	Preference in Self-HPV arm (n=185): 154 (83%) self-HPV	Self-HPV highly acceptable and resulted in higher rate of screening participation.
Obiri-Yeboah[112]	Cross-Sectional	Women attending general medicine outpatient and HIV clinics	Self- & Clinican-HPV	Preference (n=194) 112 (58%) self-HPV	Self-HPV was acceptable and feasible.
Ogilvie[108]	Pilot Cross-Sectional	Women living or working in nearby area recruited by outreach workers	Self-HPV	189/199 (95%) willing to perform self-HPV	Self-HPV was acceptable and feasible in this community-based setting.
Sossauer[119]	Randomized Controlled Trial	Recruited using local outreach and attendance at 4 health care centers	None	Would agree to regular self-HPV:intervention 150/152 (99%), control 137/149 (92%) (p=0.31) ; Would recommend self-HPV to others: intervention 148/152 (97%), control 147/149 (99%) (p=0.85)	Self-HPV was highly acceptable regardless of whether or not women received the educational intervention.
Swanson[106]	Pilot Cross-Sectional	Local women recruited with door-to-door strategies and public outreach	Self-HPV	98% would repeat self-HPV, 99% would recommend self-HPV	CHC campaigns can increase screening access, but follow-up and linkage to treatment remains challenging.
Teng[118]	Qualitative	Interviews: key stakeholders in ASPIRE Uganda research team. FGD: community women	None	NA	Psychosocial barriers to screening may be addressed with education, particularly with peer-to-peer delivery.

CHC= Community Health Center; FGD= focus group discussion; Self-HPV= Self-collected HPV sample; Clinician-HPV= Clinician-collected HPV sample

Table 6. Summary of Feasibility Studies

Author	Design	N	Screening Location	HPV Collection	HPV Samples Missing or Invalid	HPV Test Locale	HPV Test	Result Notification	Additional Findings
Awua[109]	CS	377	Hospital or Community	Self & Clinician	2/246 (0.8%) Self, 2/233 (0.9%) Clinician	NR	Xpert	NR	NA
Cubie[122]	CS	763	Facilities	Clinician	13/763(1.7%) invalid	Local	Xpert	NR	Kit expensive; cytology-based medium wasteful & hard to dispose
Huchko[105]	RCT	4494	CHC or Facilities	Self	1/4944 (<0.0%) inconslusive	Local	careHPV	NR	CHC's may provide more coverage if linked to delivery of other health services. Challenges in measuring coverage
Jeronimo[123]	CS	4710	Facilities	Self & Clinician	Missing results or lost to follow up: 1564/4710 (33.2%)	Local	careHPV	NR	Cytology results unreliable in Uganda despite having a senior pathologist
Kunckler[120]	CS	1012	Hospital	Self	9/1012 (0.9%) invalid	Local	Xpert	NR	Xpert HPV assay easy to use. A generator may be needed for outages. Dry swabs worked well and easier than wet medium.
Moses[107]	RCT	500	Community (HPV)	Randomized: Self or VIA	Self: 0 samples invalid, VIA: 26/121 (21.5%) unsatisfactory or missing	Local	Ecoli s.r.o real-time PCR	34/73 (47%)*	33/34 women receiving test results attended follow-up
Obiri-Yeboah[112]	CS	194	Facilities	Self & Clinician	3/194 (1.5%) invalid	Burkina Faso	careHPV	NR	NR
Ogilvie[108]	CS	205	Community	Self	0 invalid	Local	careHPV	30/35 (85%)*	22/35 attend follow up appointment (62.8%)
Snyman (VACCS1)[113]	CS	569	Home	Self	9/253 (3.6%) invalid	NR	Roche linear array	100%	School infrastructure & mobile phones effective for result communication
Snyman (VACCS2)[114]	CS	519	Home	Self	2/160 (1.3%) invalid	NR	Roche Cobas 4800	100%	School infrastructure & mobile phones effective for result communication
Swanson[106]	CS	255	CHC	Self	12/255 (4.7%) invalid	Local	careHPV	183/ 243 (75%)	Women unable to be reached with test results were more likely to not have a mobile phone (40% v. 5%, p<0.001)
Vassilakos[121]	CS	449	Community	Self	Invalid: Cobas 44/449 (9.8%), H28 38/449 (9.8%)	Switzerland	cobas, Anyplex II HPV28	NR	Dry swabs stored at room temperature adequate if specimens processed within 2 weeks

CS= cross-sectional; RCT= randomized controlled trial; CHC= Community Health Campaign; Local= run in country of sampling; NR= not reported; * Received Positive Test Results

Table 7. Conclusions and Limitations of Feasibility Studies

Author	Study Intervention	Conclusions	Limitations
Awua[109]	Hospital-based v. community-based HPV screening	Low initial response rates to hospital-based collection prompted addition of community-based collection. Community-based collection increased participation.	The community based strategy adopted during the study and distribution of two strategies not even or randomised.
Cubie[122]	10% of women attending screening clinics tested with cytology and Clinician-HPV	XpertHPV test proved easy to use, reproducible and had a result turnaround time of two hours.	The kit is expensive and the transport medium is wasetful and hard to dispose.
Huchko[105]	HPV screening attendance compared for CHCs vs. government clinics	Screening uptake is higher in CHCs vs government clinics. Self-collection was feasible and yielded valid test results.	Performance of HPV test not assessed (no reference test or alternative standard) Possible some women came to health facility for symptoms. No information on time from screen to results.
Jeronimo[123]	Screening comparison: Self-HPV, clinician-HPV, VIA, Cytology	HPV tests (self- and clinician-collected) perform better than subjective tests. Performance varied by geographic site.	Verification bias due to screen negative women not getting colposcopy or histology. Follow-up not specifically reported. Treatment rates not reported.
Kunckler[120]	Self-sampling HPV test with positive women evaluated with VIA/VILI for screen-and-treat	HPV screen with VIA triage and treat in same day is feasible (1.1% lost to follow up). Xpert HPV assay easy to install and operate.	Low number of CIN2+ cases. Pilot study.
Moses[107]	Community-based self-HPV v. VIA	Self-collection improved uptake as compared to VIA. Challenges: communicating results (<50% received) and follow-up attendance.	Some follow-up data incomplete
Obiri-Yeboah[112]	Self-HPV v. Clinician-HPV in general medicine and HIV clinics	Self-collection for careHPV testing is feasible.	No qualitative assessment of acceptance. Women recruited in clinic setting
Ogilvie[108]	Outreach screening program with survey and self-sampling	Self-collection with mobile phone result reporting is feasible. With transportation support, attendence to follow-up was good.	Not a random sample. Women all had access to mobile phones. Reimbursed for travel cost to colposcopy. No long-term follow up
Snyman (VACCS1)[113]	Cervical Cancer Linked to Vaccination in School by offering self-sampling after information session	Linking cervical cancer screening to school vaccination programs is feasible. 68.2% screen kits not returned.	Limited info on screenees. No follow-up. No comparison to alternative screening tests.
Snyman (VACCS2)[114]	Cervical Cancer Linked to Vaccination in School by offering self-sampling kits sent home with girls.	Linking cervical cancer screening to school vaccination programs is feasible. Almost 50% screen kits not returned.	Limited info on screenees. No follow-up. No comparison to alternative screening tests.
Swanson[106]	CHC with education, self-HPV, to test screening uptake, HPV prevalence, and follow-up	CHC campaigns can increase screening access, with almost 1/3 population screened. Greater 3/4 of the screened received results.	Sample Size. Didn't look at CIN as an outcome. Number of indeterminate results and slow turn-around time of results.
Vassilakos[121]	Screening comparisons: self-HPV swab analyzed with two HPV tests	Self-collection with dry swabs is feasible , but HPV analysis should be performed within 2 weeks as delay can increase invalid results.	Methodology not applicable to real-world given invalid samples and delay from screening to reporting. Lack of histology for all tested women.

CHC= Community Health Campaign; Self-HPV= Self-collected HPV sample; Clinician-HPV= Clinician-collected HPV sample; VACCS = Vaccine and Cervical Cancer Screen

Table 8. Summary of Accuracy Studies

Author	Design	N	Country	Age	Screening Test	WHO Prequalified POC HPV Test	HPV Test Locale	Limitations
Jeronimo[123]	Cross-Sectional	4710	Uganda	25-60	Self-HPV, Clinician-HPV, VIA, Cytology	Yes	Local	Verification bias due to screen negative women not getting colposcopy or histology.
Kamal[126]	Cross-Sectional	1601	Egypt	25-65	Self-HPV, Clinician-HPV, VIA	No	NR	HPV test may be challenging to implement on a large-scale. Verification bias due to screen negative women not getting colposcopy or histology. (almost 60%)
Kunckler[120]	Cross-Sectional	1012	Cameroon	30-49	Self-HPV	Yes	Local	Low number of CIN2+ cases. Pilot study.
Mahmud[128]	Cross-Sectional	1528	Democratic Republic of Congo	>=30	Clinician-HPV, cytology, VIA, colposcopy	No	United States	Cytology and HPV tests assessed out of country.
Mukanyangezi[124]	Cross-Sectional	206	Rwanda	>=18	Cytology, Clinician-HPV	No	Sweden	Recruitment differences in HIV-positive and negative meant that some HIV-negative women participated in study due to gynecologic symptoms.
Tebeu[127]	Cross-Sectional	540	Cameroon	30-65	Self-HPV	No	Switzerland	Small size. Verification bias due to not all women getting reference standard.
Umulisa[125]	Cross-Sectional	764	Rwanda	30-69	Clinician-HPV, cytology, VIA.	Yes	careHPV(Local), GP5+/6+-mediated PCR (The Netherlands)	Small numbers of cases (HSIL+).

Self-HPV= Self-collected HPV sample; Clinician-HPV= Clinician-collected HPV sample; Local= run in country of sampling; NR= not reported

Table 9. Performance of HPV Tests

Author	Screening Tests	HPV Test	Reference Test	Population Offered Reference Test	Reference Test Missing/Lost to Follow-Up	Sensitivity, % (95% CI)	Specificity, % (95% CI)	PPV, % (95% CI)	NPV, % (95% CI)
Jeronimo[123]	Self-HPV, Clinician-HPV, VIA, Cytology	careHPV	Histology CIN2+	Screen positive (n=3835)	1564/3835 (40.8%)	**Self-HPV:** 77 (66.8, 85.4), **Clinician-HPV:** 88.5 (79.9, 94.3), **VIA:** 73.6 (63, 82.4), **Cytology:** 69 (58.1, 78.5)	**Self-HPV:** 82 (80.5, 83.3), **Clinician-HPV:** 81.8 (80.3, 83.1), **VIA:** 66.6 (64.9, 68.3), **Cytology:** 48.6 (46.8, 50.4)	**Self-HPV:** 10.8 (8.5, 13.5), **Clinician-HPV:** 12.1 (9.7, 14.9), **VIA:** 5.9 (4.6, 7.5), **Cytology:** 3.7 (2.8, 4.7)	**Self-HPV:** 99.3 (98.9, 99.6), **Clinician-HPV:** 99.6 (99.3, 99.8), **VIA:** 99.0 (98.4, 99.4), **Cytology:** 99.6 (99.1, 99.9)
Kamal[126]	Self-HPV, Clinician-HPV, VIA	HC2	Histology CIN2+	Screen positive (n=640), 5% screen negative (n=48)	58/688 (8.4%)	**Self-HPV:** 89.2 (3.4, 7.8) , **Clinician-HPV:** 90.0 (93.5, 96.1), **VIA:** 67.3	**Self-HPV:** 84 , **Clinician-HPV:** 86 , **VIA***:* 67	**Self-HPV:** 36, **Clinician-HPV:** 34 , **VIA:** 57	**Self-HPV:** 98 , **Clinician-HPV:** 98, **VIA:** 89
Kunckler[120]	Self-HPV	Xpert	Histology CIN2+	Screen positive (n=187)	2/187 (1.1%)	**VIA/VILI:** 84.2 (57.8, 95.3) **HPV 16/18/45(+)**: 63.2 (38.0, 82.7)	**VIA/VILI:** 45.6 (38.0, 53.5) **HPV 16/18/45(+):** 71.3 (63.7,77.8)	**VIA/VILI:** 15.6 (9.7,24.0) **HPV 16/18/45(+):** 20.7 (11.9, 33.4)	**VIA/VILI:** 96.1 (88.2, 98.8) **HPV 16/18/45(+):** 94.2 (88.2,97.2)
Mahmud[128]	Clinician-HPV, cytology, VIA, colposcopy	HC2, HC2+4	*Histology CIN2+	Colposcopy: all (n=1528). All colposcopy (+) offered biopsy (n=290). 19% colposcopy (-) offered biopsy (n=290)	24/290 (8.3%)	**HC2:** 83.4 (66.8, 100) **HC2+4:** 83.5 (67.0, 100) **Cytology (ASCUS+):** 71.9 (54.0, 89.7)	**HC2:** 90.8 (89.0, 92.7) **HC2+4:** 91.0 (89.1, 92.8) **Cytology (ASCUS+):** 94.7 (93.3, 96.2)	**HC2:** 30.0 (19.6,42.1) **HC2+4:** 30.4 (19.9, 42.7) **Cytology (ASCUS+):** 40.0 (27.0, 54.1)	**HC2:** 99.3 (97.8, 99.8) **HC2+4:** 99.3 (97.9, 99.8) **Cytology (ASCUS+):** 98.7 (97.1, 99.5)
Mukanyangezi[124]	Cytology, Clinician-HPV	37-HPV strain Multiplex Luminex	Cytology HSIL+	All participants (n=400)	16/400 (4%)	**PHR-HPV/HR-HPV:** 78 (49, 95)	**PHR-HPV/HR-HPV:** 87 (83, 90)	NR	NR
Tebeu[127]	Self-HPV	Abbott RealTime High Risk	*Histology CIN2+	Screen positive (n= 146) and random sampling screen negative (n=146)	83/292 (28.4%) [Screen (+) 37/146 , Screen (-)38/146]	**HPV:** 100.0 (79.6, 100.0) **VIA (HPV+):** 36.4 (15.2, 64.2) **VIA (HPV-):** No HPV- CIN2+	**HPV:** 74.5 (70.6, 78.1) **VIA (HPV+):** 87.4 (79.2, 92.6) **VIA (HPV-):** 93.1 (86.5, 96.6)	**HPV:** 10.3 (6.3, 16.3) **VIA (HPV+):** 25.0 (10.2,49.5) **VIA (HPV-):** 00.0 (00.0, 35.4)	**HPV:** 100.0 (99.0, 100.0) **VIA (HPV+):** 92.2 (84.8,96.2) **VIA (HPV-):** 100.0 (96.1,100.0)
Umulisa[125]	Clinician-HPV, cytology, VIA	careHPV, GP5+/6+-mediated PCR	**Histology HSIL+	Screen positive (n=177). Screen negative women inadvertent (n=6)	44/183 (24%)	**careHPV:** 59 (33, 82) **PCR:** 77 (50, 93)	**careHPV:** 89 (87, 92) **PCR:** 88 (86, 91)	**careHPV:** 11 (6, 20) **PCR:** 13 (7, 21)	**careHPV:** 99 (97.9, 99.6) **PCR:** 99.4 (98.5, 99.8)

95% CI= 95% Confidence Interval; PPV= positive predictive value; NPV= negative predictive value; Self-HPV= Self-collected HPV sample; Clinician-HPV= Clinician-collected HPV sample; NR= not reported; *Correction for verification bias; **Imputation for missing

Table 10. Summary of Agreement Studies

Author	Design	N	Country	Screening Tests	HPV Test Locale	HPV Test	Concordance/Agreement	Kappa statistic	Measure of Agreement
Ajenifuja[129]	Cross-Sectional	194	Nigeria	Self-HPV & Clinician-HPV	Local	Hybribio HPV GenoArray	93.80%	0.47	Genotype Agreement
Jeronimo[123]	Cross-Sectional	4710	Uganda	Self-HPV, Clinician-HPV, VIA, Cytology	Local	careHPV	NR	NR	NR
Kamal[126]	Cross-Sectional	1601	Egypt	Self-HPV, clinician-HPV, VIA	NR	HC2	94.80%	0.89	HR-HPV presence
Modibbo[110]	Randomized Controlled Trial	400	Nigeria	Randomized: Self-HPV or Clinician-HPV	Netherlands	GP5+/6+-mediated PCR with LMNX genotyping	Prevalence of HR-HPV: Self-HPV 19/185 (8.9%), Clinician-HPV 10/113 (10.3%)	NR	Prevalence of HR-HPV
Obiri-Yeboah[112]	Cross-Sectional	194	Ghana	Self-HPV & Clinician-HPV	Burkina Faso	careHPV and Anyplex II HPV HR Detection assay	94.20%	0.88	HR-HPV presence (careHPV Agreement)
Untiet[130]	Cross-Sectional	789	Cameroon	Self-HPV, Clinician-HPV, cytology	Switzerland	Abbott RealTime High Risk	NR	0.74	HR-HPV presence
Vassilakos[121]	Cross-Sectional	449	Madagascar	Self-HPV swab analyzed with two HPV tests	Switzerland	cobas, Anyplex II HPV28	% Total agreement 89.9, % Positive Agreement 84.8	0.77	HR-HPV presence

Self-HPV= Self-collected HPV sample; Clinician-HPV= Clinician-collected HPV sample; NR= not reported

Table 11. Summary of HPV Screen-and-Treat Studies using a Triage Test

Author	Triage Test [Population Receiving]	Triage Attendance	Reference Test	Sensitivity, % (95% CI)	Specificity, % (95% CI)	PPV, % (95% CI)	NPV, % (95% CI)
Bigoni[131]	Randomized: VIA or Cytology [Screen +] Both arms had cervical biopsy & ECC	**VIA:** 97/ 129 (75.2%) **Cytology:** 99/130 (76.2%)	Histology CIN2+	**Cytology (ASCUS+):** 90.0 (59.6, 98.2) **Cytology (HSIL+):** 60.0 (31.3, 83.2) **VIA:** 25.0 (7.1, 59.1)	**Cytology (ASCUS+):** 85.2 (76.3,91.2) **Cytology (HSIL+):** 97.7 (92.1, 99.4) **VIA:** 74.2 (64.2, 82.1)	NR	NR
Kunckler[120]	VIA/VILI with Biopsy [Any HPV +]	185/187 (98.9%)	Histology CIN2+	**HR-HPV+ & VIA/VILI :** 84.2 (57.8, 95.3) **†HPV 16/18/45(+):** 63.2 (38.0, 82.7)	**HR-HPV+ & VIA/VILI** 45.6 (38.0, 53.5) **†HPV 16/18/45(+):** 71.3 (63.7,77.8)	**HR-HPV+ & VIA/VILI** 15.6 (9.7,24.0) **†HPV 16/18/45(+):** 20.7 (11.9, 33.4)	**HR-HPV+ & VIA/VILI** 96.1 (88.2, 98.8) **†HPV 16/18/45(+):** 94.2 (88.2,97.2)
Tebeu[127]	VIA with biopses [All screen (+) (n= 146); random sampling screen (-)(n=146)].	109/146 (74.7%) HPV+, 108/146 (73.9%) HPV-	^Histology CIN2+	**HPV alone:** 100.0 (79.6, 100.0) **HPV with VIA Triage:** 33.3 (15.2, 58.3)	**HPV alone:** 74.5 (70.6, 78.1) **HPV with VIA Triage:** 96.7 (94.8, 97.9)	**HPV alone:** 10.3 (6.3, 16.3) **HPV with VIA Triage:** 22.7 (10.1, 43.4)	**HPV alone:** 100.0 (99.0, 100.0) **HPV with VIA Triage:** 98.0 (96.4, 99.9)
Umulisa[125]	VIA with biopsies [Screen (+) via VIA, careHPV, PCR HPV]	148/177 (83.6%)	^^Histology HSIL+	***1-visit screen-and-treat:** careHPV 71 (44, 90); VIA 41 (18, 67) ****2-visit:** careHPV & VIA triage 35 (14, 62)	***1-visit screen-and-treat*:** careHPV 88 (85, 90); VIA 96 (94, 97) ****2-visit:** careHPV & VIA triage 98 (97, 99)	***1-visit screen-and-treat:** careHPV 12 (6, 20); VIA 18 (8, 34) ****2-visit:** careHPV & VIA triage 27 (11, 50)	***1-visit screen-and-treat:** careHPV 99.2 (98.2, 99.8); VIA 98.6 (97.5, 99.3) ****2-visit:** careHPV & VIA triage 98.5 (97.4, 99.3)

95% CI= 95% Confidence interval; PPV= positive predictive value; NPV= negative predictive value; NR= not reported; ^Correction for verification bias ; ^^Imputation for missing histology; *hypothetical; **performed, †Results for screening test only

Table 12. Summary of HPV Screen-and-Treat Studies without Triage Tests

Author	Design	Screening Tests	Management Screen Positive	Follow-Up/Treatment Rates	Time screening to follow-up/treatment	Follow-up attendees not treated	Reasons not treated
Huchko[105]	Cluster randomized trial	Self-collected HPV	Screen-and-treat with VIA/VILI for eligibility	372/1043 (35.7%) HPV+ receiving treatment	Screening to treatment: mean 47 days (IQR, 31-77 days)	Not reported	Not reported. HPV testing performed within 2 weeks of collection.
Kunckler[120]	Cross-Sectional	Self-collected HPV	VIA/VILI with Biopsy (Any HPV +). Immediate Treatment for: (HPV 16/18/45 +) or (other HR-HPV + AND VIA/VILI +)	185/187 (98.9%) HPV + women underwent VIA/VILI	110/121 (90.9%) women requiring treatment had same day treatment	n=11	Equipment failure (n=1), Ineligible based on disease (n=8), Ineligible due to pregnancy (n=1), No visualization SCJ (n=1)
Swanson[106]	Pilot Cross-Sectional	Self-collected HPV	Screen-and-treat with VIA for eligibility	24/47 (51.1%) screen positive attended follow-up. 20/24 attendess received treatment at first visit	Testing to receiving results: median and mean 28 days. Result notification to treatment: median 7 days (IQR 4-15)	n=4	Pregnant or study ineligible (n=3), Ineligible based on disease (n=1)

IQR = Interquartile Range

Table 13. Quality Assessment using the Mixed Methods Appraisal Tool (MMAT)

Author	1. QUALITATIVE STUDIES					COMMENTS
	1.1. Is the qualitative approach appropriate to answer the research question?	1.2. Are the qualitative data collection methods adequate to address the research question?	1.3. Are the findings adequately derived from the data?	1.4. Is the interpretation of results sufficiently substantiated by data?	1.5. Is there coherence between qualitative data sources, collection, analysis and interpretation?	
Teng	Yes	Yes	Yes	Yes	Yes	
	2. RANDOMIZED CONTROLLED TRIALS					
	2.1. Is randomization appropriately performed?	2.2. Are the groups comparable at baseline?	2.3. Are there complete outcome data?	2.4. Are outcome assessors blinded to the intervention provided?	2.5 Did the participants adhere to the assigned intervention?	
Bigoni	Yes	Yes	Yes	Yes	Yes	
Huchko	Yes	No	Can't tell	Can't tell	Can't tell	12 communities randomized to screening via a health facility or a community health campaign (CHC). Women screened in the CHCs were older, more likely to have had prior screening, and more likely to be HIV negative.
Modibbo	Yes	Yes	Yes	Can't tell	Yes	
Moses	Yes	Yes	Yes	Can't tell	Yes	
Sossauer	Yes	Can't tell	Yes	Can't tell	Yes	
	3. NON-RANDOMIZED STUDIES					
	3.1. Are the participants representative of the target population?	3.2. Are measurements appropriate regarding both the outcome and intervention (or exposure)?	3.3. Are there complete outcome data?	3.4. Are the confounders accounted for in the design and analysis?	3.5. During the study period, is the intervention administered (or exposure occurred) as intended?	
Ajenifuja	Yes	Yes	Yes	Can't tell	Yes	
Awua	Yes	Yes	Yes	Can't tell	No	The community based strategy adopted during the study and distribution of two strategies not even or randomised.
Berner	Yes	Yes	Yes	Can't tell	Yes	
Broquet	Yes	Yes	Yes	Can't tell	Yes	
Jeronimo	Yes	Yes	Yes	Can't tell	Yes	
Kamal	Yes	Yes	Yes	Can't tell	Yes	
Kunckler	Yes	Yes	Yes	Yes	Yes	
Mahmud	Yes	Yes	Yes	Can't tell	Yes	
Manguro	No	Yes	Yes	Yes	Yes	
Mukanyangezi	Yes	Yes	Yes	Yes	Yes	
Obiri-Yeboah	Yes	Yes	Yes	Yes	Yes	
Ogilvie	Yes	Yes	Yes	Can't tell	Yes	
Snyman	Can't tell	Yes	Yes	Can't tell	Yes	
Snyman	Can't tell	Yes	Yes	Can't tell	Yes	
Tebeu	Yes	Yes	Yes	Can't tell	Yes	
Umulisa	Yes	Yes	Yes	Can't tell	Yes	
Untiet	Yes	Yes	Yes	Can't tell	Yes	
Vassilakos	Yes	Yes	Yes	Can't tell	Yes	
Viviano	Yes	Yes	Yes	Can't tell	Yes	

Table 13. Continued

Author	4. QUANTITATIVE DESCRIPTIVE STUDIES					COMMENTS
	4.1. Is the sampling strategy relevant to address the research question?	4.2. Is the sample representative of the target population?	4.3. Are the measurements appropriate?	4.4. Is the risk of nonresponse bias low?	4.5. Is the statistical analysis appropriate to answer the research question?	
Chamot	Yes	No	Yes	Can't tell	Yes	Participants were women who had previously undergone visual inspection screening. No screening naiive
Crofts	Yes	Yes	Yes	Yes	Yes	
Cubie	Yes	Yes	Yes	Yes	Yes	
Esber	Yes	Yes	Yes	Can't tell	Yes	
Swanson	Yes	Yes	Yes	Yes	Yes	

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