INTEGRATING HPV TESTING IN CERVICAL CANCER SCREENING PROGRAMS

A MANUAL FOR PROGRAM MANAGERS

Pan American Health Organization

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CERVICAL CANCER PREVENTION IN LATIN AMERICA AND THE CARIBBEAN

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INTRODUCTION

KEY MESSAGES

- Cervical cancer is caused by persistent infection with high-risk types of Human Papillomavirus (HPV).
- HPV testing, because of its high sensitivity, offers a great opportunity to improve the effectiveness of cervical cancer screening.
- HPV testing could be considered for incorporation in a national cervical cancer screening program. The decision needs to be based on the scientific evidence, costs, and its potential impact to reduce cervical cancer mortality.
- HPV testing, similar to traditional cytology testing (Pap smear), requires an organized program in which high screening coverage, follow-up care and quality control are achieved.

The World Health Organization (WHO) guideline for cervical cancer screening recommends HPV testing for cervical cancer screening (WHO, 2013). Many countries, however have already established cytology (Pap smear) based screening programs, and while the scientific evidence illustrates that HPV testing is more sensitive than the Pap smear, guidance is needed on how to modify traditional screening programs to incorporate HPV testing.

This guide, *Integrating HPV Testing in Cervical Cancer Screening Programs: A Manual for Program Managers* intends to fill this knowledge gap. It provides information on how to plan and implement a cervical cancer screening program, based on HPV testing as a primary screening test.

The purpose is to provide managers with up-to-date information on HPV testing, and to facilitate strengthening cervical cancer screening programs. It provides information on the natural history of HPV, characteristics of HPV tests, and a summary of WHO recommendations on screening and treatment of precancerous cervical lesions (WHO, 2013).

It also provides general information on HPV test-based cervical cancer screening program issues, such as costs, communication and education, practical laboratory information, and program monitoring. It includes information on the experiences and lessons from other countries that have already introduced HPV testing in national cervical cancer programs.

Why incorporate HPV testing in cervical cancer screening programs?

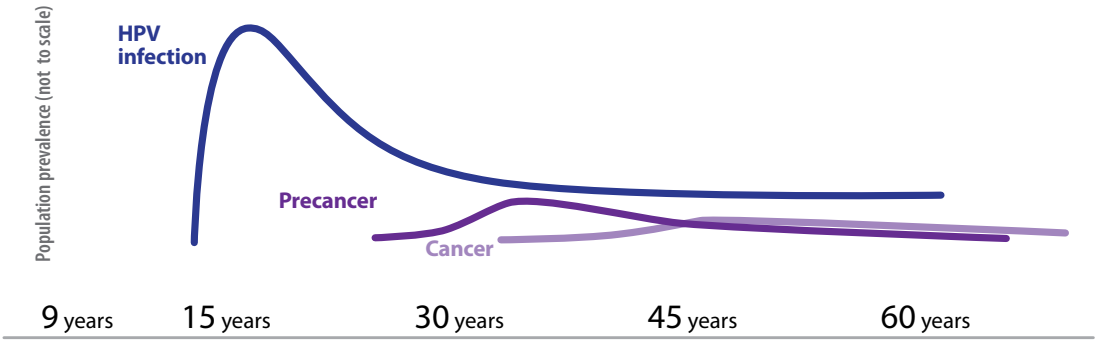
- Scientific evidence shows that it is possible to reduce cervical cancer mortality through screening, with cytology (Pap smears), HPV testing, or visual inspection with acetic acid (VIA) followed by prompt treatment, when indicated.
- The evidence, however, shows that HPV testing is much more accurate and effective in identifying women at greater risk of developing precancerous cervical lesions, and that screening intervals can be longer than with other tests.
- HPV test samples can be taken by a health provider or the woman herself (self-sampling).
- Processing of HPV tests is automated, results do not require subjective interpretation, and thus more objective results are given with HPV testing than other screening tests.
- HPV testing is more cost-effective than VIA or Pap smears, although it may require higher up-front costs for supplies and equipment.
- Some disadvantages, which should be weighed against all the advantages, are the costs of HPV testing, and that HPV test results are currently not immediate and may require several visits to the health center by women, which can result in loss of follow-up for treatment.

COMPREHENSIVE APPROACH TO CERVICAL CANCER PREVENTION AND CONTROL

HPV testing is a key tool for cervical cancer prevention, which requires a comprehensive set of interventions across a woman's life course, and based on the natural history of the disease (Figure 1).

Cervical cancer is caused by persistent infection with high-risk types of human papillomavirus (HPV), which is sexually transmitted. Vaccination against HPV in girls aged 9 to 13 years, combined with screening of precancerous lesions in women aged 30 years and older, followed by appropriate treatment, are key interventions in the prevention of cervical cancer (WHO, 2014). HPV vaccination does not replace cervical cancer screening.

Figure 1: Overview of programmatic interventions over the life course to prevent HPV infection and cervical cancer



Source: WHO, 2013. Comprehensive cervical cancer prevention and control: a healthier future for girls and women.

PRIMARY PREVENTION	SECONDARY PREVENTION	TERTIARY PREVENTION
Girls 9-13 years • HPV vaccination **Girls and boys, as appropriate** • Health information and warnings about tobacco use* • Sexuality education tailored to age & culture • Condom promotion/provision for those engaged in sexual activity • Male circumcision	**Women >30 years of age** **Screening and treatment as needed** • "Screen and treat" with low cost technology VIA followed by cryotherapy • HPV testing for high-risk HPV types (e.g. types 16, 18 and others)	**All women as needed** **Treatment of invasive cancer at any age** • Ablative surgery • Radiotherapy • Chemotherapy

**Tobacco use is an additional risk factor for cervical cancer.*

REQUIREMENTS FOR AN ORGANIZED SCREENING PROGRAM BASED ON HPV TESTING

A population based screening program requires the following components (WHO, 2014):

- An explicit cervical cancer screening policy based on the most up-to-date scientific evidence, and specifying the screening method, screening intervals, and age groups to be screened.
- A cervical cancer program plan, with explicit goals, targets and quality control procedures.
- Allocation of financial resources to carry out HPV testing, diagnostic evaluations and treatment for women with HPV positive results.
- A managerial structure in the Ministry of Health that ensures attainment of the program's goals and targets.
- Clinical guidelines, procedures and protocols for cervical cancer screening, referral, and treatment of precancerous lesions, and invasive cancer.
- Training of health providers who are responsible for delivering the screening and treatment services.
- High screening coverage, typically 70% - 80% of the target population.
- A population-based cancer registry for identification of new cases of cancer and cancer deaths.

Cervical cancer screening services include information and education, a screening test (with or without diagnostic testing), and the treatment of precancer in women. In designing the services, consideration needs to be given to the following:

- Reduce the number of health service visits for screening, treatment, and follow-up, which will increase program effectiveness.
- Increase equitable access and screening coverage, through clinical outreach services to remote areas, as well as static health services, with a focus on reaching women living in vulnerable and disadvantaged communities.
- Ensure continuity of care, through a clear referral pathway, functioning health service networks, as well as ties with the community.
- Assure reliable services and minimize interrupted services resulting from insufficient number of providers, equipment malfunctioning, stock out of supplies, etc.

Process for the Introduction of HPV Testing in a Cervical Cancer Screening Program[1]

PROCESS	CONSIDERATIONS
Confirm political commitment	• Engage high-level stakeholders in the health system. • Invest necessary resources. • Designate program coordinator, with mandate, authority, and resources to direct the program.
Review the current situation	• Analyze the cervical cancer situation in the country (e.g. areas and populations most affected, knowledge and attitudes of health providers, women and their partners, etc.) • Review services available for screening, diagnosis, and treatment of precancerous lesions and invasive cancer. • Assess needs to introduce HPV testing into the screening program. • Identify barriers and opportunities for the introduction of HPV testing.
Develop norms and guidelines for HPV testing	• Establish the target age group for screening and frequency of screening. • Set targets for population screening coverage. • Establish algorithms for follow-up of screened women. • Establish indicators for program monitoring and evaluation. • Engage local stakeholders in evidence-based decision-making for cervical cancer screening and treatment.
Develop the plan for introduction of HPV testing into the cervical cancer program	• Establish a management team for the screening program. • Develop the introduction plan based on the needs assessment. • Establish service delivery strategies including procurement, distribution, and storage of equipment and supplies. • Establish HPV laboratory processes and flow of information and communication between the laboratory and health centers. • Develop a training plan for providers. • Develop communication, information, and education strategies. • Establish program monitoring and evaluation processes and indicators. • Develop the budget and allocate resources according to the action plan.
Get ready for service delivery	• Procure and distribute equipment and supplies. • Develop screening program communication materials. • Provide orientation for community, stakeholders, and health workers. • Ensure provider training and availability for screening, diagnosis, and treatment. • Establish the quality assurance process, including quality indicators and supervision. • Set up the information system for program monitoring and evaluation, according to established indicators.
Launch and implement the program	• Launch the program on a small scale and expand it in line with available resources. • Launch the program with an inaugural event. • Monitor and supervise program processes. • Monitor and evaluate program performance.

1 Adapted from Planning and Implementing Cervical Cancer Prevention and Control Programs: A Manual for Managers. Alliance for Cervical Cancer Prevention. 2004.

SECTION 1:
SCIENTIFIC EVIDENCE ON HPV TESTING FOR CERVICAL CANCER SCREENING

KEY MESSAGES

- Evidence shows that HPV tests are an effective screening test for cervical cancer prevention.
- At a minimum, screening all women aged 30 to 49 years, at least once in their life, is recommended. Screening may be extended to younger or older women, depending on the available resources and women's risk of cervical cancer.
- Regardless of the screening test used, an organized screening program must include high coverage in the group of high-risk women (aged 30-49 years) and prompt follow-up and treatment for all women with abnormal results.

NATURAL HISTORY OF CERVICAL CANCER

The main cause of cervical cancer is persistent infection with high-risk types of human papillomavirus (HPV). HPV 16 and HPV 18 are among the most common high-risk HPV types and are found in approximately 70% of all cervical cancer cases. Low-risk HPV types, such as HPV 6 and HPV 11 are not associated with cancer, but cause genital warts (WHO, 2014).

HPV is primarily sexually transmitted. It is a very common infection and most people are infected shortly after they become sexually active. The risk factors for HPV infection, in both men and women, are related to sexual behavior and include sexual debut at an early age and a high number of sexual partners. A small proportion of women with persistent HPV infection will develop cervical cancer, which can take decades to develop (WHO, 2014).

HPV vaccination in girls aged 9 to 13 years, combined with screening women aged 30 years and older, followed by appropriate treatment are key strategies to prevent cervical cancer (WHO, 2014). HPV vaccination does not replace screening for cervical cancer.

SUMMARY OF WHO RECOMMENDATIONS FOR CERVICAL CANCER SCREENING AND PRECANCER TREATMENT

WHO issued a cervical cancer prevention and control guideline, in 2014, following an extensive review of the scientific evidence. The highlights of the guideline are as follows (WHO, 2014):

- Cervical cancer screening tests include: HPV tests, conventional or liquid based cytology (Pap smear), and visual inspection with acetic acid (VIA).
- Evidence shows that HPV tests are much more sensitive and more effective in identifying women at higher risk of developing precancerous cervical lesions.
- Women aged 30 to 49 years need to be screened at least once in their lifetime, at a minimum. Screening could be extended to younger and/or older age groups, according to available resources.
- For women at average risk -who are HIV negative, not otherwise immunocompromised, and women with no prior abnormal cervical screening test- with negative HPV test results, a minimum of five years is recommended for re-screening.
- Regardless of the test used, an organized screening program needs to assure high screening coverage in the target group (aged 30-49 years), linked to prompt follow-up and treatment for all women with abnormal test results.

The WHO cervical cancer guideline also includes recommendations for screening and precancer treatment strategies. These were developed based on an extensive review of evidence by subject matter experts, as well as modeling where gaps in evidence existed, to compare different service delivery strategies. The highlights of the WHO recommendation for screening and precancer treatment strategies are as follows (WHO, 2013):

1. Use a strategy of screen with an HPV test and treat, over a strategy of screen with VIA and treat. In resource-constrained settings, where screening with an HPV test is not feasible, the panel suggests a strategy of screen with VIA and treatment of precancerous lesions in the same visit, if possible.
2. Use a strategy of screen with an HPV test and treat, over a strategy of screen with cytology followed by colposcopy (with or without biopsy) and treat. However, in countries where an appropriate, high-quality screening strategy with cytology followed by colposcopy already exists, an HPV test or cytology followed by colposcopy could be used.
3. Use a strategy of VIA screening and treatment, over a strategy of cytology followed by colposcopy (with or without biopsy) and treatment. The recommendation for VIA over cytology followed by colposcopy can be applied in countries that are currently considering establishing a screening program.
4. Use a strategy of HPV testing followed by VIA and treatment, over a strategy of VIA screening and treatment.
5. Use a strategy of HPV testing followed by VIA and treatment, over a strategy of cytology screening followed by colposcopy (with or without biopsy) and treatment.

Due to practical reasons and because the WHO subject matter experts prioritized the screen and treat strategy, the option of using HPV testing as the primary screening test, followed by cytology (Pap smear) as a triage test was not included in the revision of evidence nor in the comparison between different strategies. However,

this is a strategy used in several countries where Pap smear programs already exist, and a reason why it can be considered as an option:

- HPV test followed by cytology (Pap smear) and referral of those women with abnormal test results on both tests to colposcopy, biopsy, and treatment, according to biopsy result.

Options for screening strategies using HPV tests

STRATEGY	ADVANTAGES	DISADVANTAGES
HPV, and cytology triage in HPV+ women	• Identifies women at greater risk of precancerous lesions.	• More resources are required for cytology. • Multiple visits required by women and greater risk of loss to follow-up.
HPV, and VIA triage in HPV+ women	• Identifies women at greater risk of precancerous lesions.	• Quality control for VIA is required. • High-grade lesions that are not visible with VIA could be missed.
HPV and treatment (without triage)	• Simplifies the process for completing treatment. • Reduces the number of visits required by the woman. • May lead to more women being treated, and less women being lost to follow-up care.	• Over-treatment may occur. • Treatment costs may be higher.

SECTION 2: SUMMARY OF COMMERCIALLY AVAILABLE HPV TESTS

KEY MESSAGES

- HPV tests vary and use different methods to detect the HPV: some HPV tests will detect the DNA and other HPV tests will detect E6/E7 mRNA.
- Tests that are commercially available at this time, and being used in some countries for cervical cancer screening include: Hybrid Capture 2 (Qiagen), CareHPV (Qiagen), Cobas HPV Test (Roche), Cervista (Hologic), Aptima HPV Assay (Hologic), BD HPV Assay (BD) and Xpert HPV (Cepheid).
- In choosing which HPV test will be used in the screening program, consideration needs to be given to results of clinical trials, clinical validation of the test, and other operational and logistical aspects of the test and its requirements.

GENERAL ASPECTS OF HPV TESTS

Understanding the technical and operational aspects of available HPV tests is an important part of planning an HPV test-based screening program. There are numerous HPV tests available commercially, although only those that have been clinically validated should be used for cervical cancer screening programs.

HPV can be detected through tests that identify high-risk HPV types, either by amplification of a viral DNA fragment (with or without genotyping), or through mRNA detection (Table 1). HPV DNA tests identify the DNA of one or more oncogenic HPV types[2] without prior DNA amplification. Other detection tests amplify a viral DNA fragment using polymerase chain reaction (PCR) to obtain copies, both conventionally and in real-time. HPV genotyping identifies specific viral types (usually HPV 16 and 18). The mRNA tests identify expression of HPV E6 and E7 oncoproteins.

2 At present, over 150 HPV types have been described, of which approximately 50 cause infections of the genital epithelium. HPV types considered oncogenic are 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68.

Table 1. HPV Tests Used for Cervical Cancer Screening

TEST	TECHNIQUE	NAME
DNA	Direct: Genome detection	Hybrid Capture 2
		CareHPV test
	Amplification	GP5+/GP6+ bio PCR-EIA
		Cervista HPV HR
	Amplification and genotyping of HPV-16 and HPV-18	Cervista HPV 16/18
		Cobas HPV test
		Xpert HPV
		Abbott RealTime High Risk (HR) HPV assay
		PapilloCheck
RNA	Amplification of E6/E7 proteins	Aptima HPV Assay
		PreTect HPV-Proofer HV
	Monoclonal antibodies	AVantage HPV E6 Test

The clinical sensitivity of an HPV test is an important consideration for the use of the test in screening programs. A description of the various HPV tests and their performance in screening programs is summarized below.

Direct genome detection tests

Hybrid Capture 2

Hybrid Capture 2 (HC2) is used for cervical cancer screening, and has been clinically validated. This test detects high-risk HPV types (HR-HPV) by means of a probe cocktail for 13 HR-HPV. It is a technique in which DNA hybrids are identified with RNA probes. The Hybrid Capture 2 (HC2) technique was originally developed by the Digene Corporation (Maryland, U.S.A) and is currently produced by Qiagen (Maryland, U.S.A). Since 2000, this kit has the approval of the United States Food and Drug Administration (FDA) for routine use in early detection activities in combination with cytology. In Latin America, this test has been approved and used in public health screening programs in Colombia, Argentina, and Mexico.

Sample collection can be carried out by trained physicians, nurses, or nursing auxiliaries using a brush that is introduced into the endocervical canal, and then placed in a tube that contains a medium for transport to the laboratory.

In the laboratory, cervical cells are subjected to an alkaline denaturation solution that exposes the genetic material. Subsequently, through the use of an RNA probe cocktail (with 13 types of HR-HPV: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68) a viral-RNA: DNA hybrid is formed in the presence of any of these viruses. Hybridization is identified through specific antibodies and a chemiluminescent solution that emits light in the presence of hybrids. A luminometer is required to detect hybrids.

The test is reported as positive when light is emitted and negative when it is not, according to the final reading of the chemiluminescence signal. A positive test means that the woman has been infected by one or more of the 13 HR-HPV types. This test cannot identify the HPV type or whether one or more HPV types are present. The HC2 test is not designed to give a quantitative result; some studies have used the relative light unit (RLU) value as a quantitative evaluation of viral load.

Tests can be processed manually, semi-automatically, or be automated through use of a robot. The semiautomatic processing system has the capacity for 88 samples. Therefore, delivery of results depends on the time needed to fill the machine, which can be approximately 15 days, based on some reports from demonstration areas in Latin America. With the automated method, delivery time is approximately five hours for 352 samples per run.

As with all HPV tests, the advantages include high sensitivity and high negative predictive value. Therefore, a woman with a negative HPV test result has an extremely low probability of developing any cervical lesions in the next 5 years. The disadvantages include lower specificity and cross-reactions with low-risk probes.

CareHPV

The CareHPV test uses the same principle as the Qiagen HC2 technique and detects 14 high-risk HPV types in an automated, faster process. The test has been clinically validated. The sample collection is done the same way as HC2, which was previously described. It includes DNA denaturation, hybridization with an RNA probe, hybrid capture and detection, and signal amplification. This technique has limitations similar to those of the HC2 test. CareHPV is a rapid test that requires 2.5 hours to process the 90 samples that fit in the well. It is commercially available in China and India and it is currently being used in several implementation studies in Latin America and other countries.

DNA Amplification Tests

PCR gene amplification is another important molecular technique that makes it possible to obtain millions of copies from a specific DNA fragment. Different primer sets have been designed, which for the most part target region L1 and make it possible to differentiate, through specific probes, the most frequent types of high, intermediate, and low risk HPV, by doing plate hybridization of the biotinylated products previously amplified by PCR. This technique is very sensitive with a detection level down to one viral copy. However, due to its high sensitivity, this method is very susceptible to contamination. At present, in addition to generic PCR, there are specific tests that report certain viral HPV types and multiple PCR that identify several genome fragments. Tests include, among others, GP5+/GP6+, Cervista, Cobas Test, and Abbott RealTime High Risk (HR) HPV assay.

GP5+/bio-GP6+ PCR-EIA

This technique was developed using GP5+/bio-GP6+ primers that amplify a fragment from the HPV L1 region; it has been clinically validated. This technique detects 37 viral types: 14 HR-HPV and 23 low-risk HPV (LR-HPV). This test is used in trials and has the advantage that the PCR products for the specific high-risk HPV types can be genotyped by reverse line blot analysis. It is one of the most frequently used techniques in research studies around the world. This technique is NOT for commercial use, nor for cervical cancer screening programs.

PCR products hybridize with a mixture of specific oligonucleotides. An enzyme immunoassay (EIA) is used for detection. Use of the GP5+/6+ PCR-EIA technique on raw extracts has high analytical sensitivity.

It has the advantages that in a simple format, up to 42 PCR products can be simultaneously typed per membrane per day, and that membranes can be easily rehybridized at least 15 times without loss of specificity or sensitivity. Its limitation is that it is not available commercially.

Cervista HPV HR and Cervista HPV 16/18

The Cervista HPV HR test is an analytically and clinically validated in vitro diagnostic test for the qualitative detection of 14 HR-HPV types in cervical specimens. Cervista cannot determine the specific HPV type. Cervista HPV 16/18 detects HPV 16 and 18. The test was approved by the FDA in 2009 to be used together with cervical cytology in women aged ≥30 years.

Cervista uses Invader chemistry, a signal amplification method for detection of specific nucleic acid sequences. This method uses two types of isothermal reactions that occur simultaneously: a primary reaction that occurs on the targeted DNA sequence and a secondary reaction that produces a fluorescent signal. The instrument has an internal control that reduces false negatives produced by a low number of cells. Cervista HPV 16/18 uses the same technology as Cervista HPV HR for genotyping.

One of the advantages is that this technique is highly reproducible and sensitive. The internal quality control to confirm sample quality is one of its greatest advantages in the market. However, according to the manufacturer it has certain limitations, including cross-reactivity to two HPV types of unknown risk; more specifically is positive for HPV-67 with 5,000 copies/reaction and positive for HPV-70 with 50,000 copies/reaction. Furthermore, low levels of infection or sampling error may cause false negatives.

Cobas HPV Test

The Cobas HPV test detects 12 high-risk HPV types (31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68), and specifically reports on HPV 16 and 18. This is a clinically validated in vitro qualitative test. The system uses the β-globin gene as an internal control for specimen integrity, extraction, and amplification. The system is totally automated, facilitating laboratory workflow. It consists of a Cobas Z thermocycler and the necessary software for real-time PCR, using primers for the HPV L1 region. The procedure includes processing of DNA extraction samples and real-time PCR analysis. The technique does not cross-react with non-carcinogenic genotypes. Furthermore, the operator has minimal contact with the sample, preventing contamination. This system can carry out 96 tests in approximately five hours.

The advantages of this system are reduction in processing and work time; reduction in repetitive motions; reduction in the risk of errors due to fatigue; reduction in the production of biohazard waste; and reduction in costs by eliminating the need for additional reagents.

Limitations mentioned by the manufacturer include that testing needs to be done by personnel with experience in PCR techniques and with the Cobas HPV test system. Furthermore, only the Cobas x 480 instrument and the Cobas z 480 analyzer have been validated for use with this product. No other sample preparation instrument

or PCR system can be used with this product. The presence of PCR inhibitors, as well as a low number of virus copies in the sample, may cause false negatives or invalid results.

Abbott RealTime High Risk (HR) HPV assay

The Abbott RealTime High Risk (HR) HPV assay test detects 14 HR-HPV types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68). This test reports on HPV 16 and 18 separately from the other high-risk HPV types.

This is a completely automated in vitro qualitative process that is clinically validated according to international requirements for use in screening in women starting at age 30 years.

The system consists of an m2000sp instrument that prepares the nucleic acid and an m2000rt analyzer that carries out real-time PCR using a mixture of multiple primers and probes for amplification and detection of HR-HPV DNA and for the β-globin gene, as an internal quality control of cervical cells collected in liquid-based cytology.

The response time of the process is from six to eight hours for 96 samples and depends on the DNA extraction method used.

The advantages of this technique are the automation of the multiple steps—reducing personnel—time used, and risk of contamination. Subjective interpretation is one of the test's limitations. In recent years, real-time PCR has been introduced in molecular HPV diagnosis as a tool for quantitative determination of viral load as well as for diagnosis of infection. Real-time detection of amplified products can be carried out using fluorescent molecules that are inserted in double chain DNA, such as SYBR Green, or through hybridization with different types of probes, such as Taqman probes, fluorescent primers, or molecular beacons and hydrolysis probes. Probe use increases reaction specificity.

BD HPV Assay

The BD HPV test is a real-time PCR that amplifies the region that codes HR-HPV E6/E7 oncoproteins. It has been clinically validated. These regions are present throughout the stages of the disease's progression and the assay has been designed to detect specific regions according to virus type, instead of amplification of gene regions detected with L1 primer sets. The test provides individual information for six HPV types (16, 18, 31, 45, 51, and 52), as well as detection of all 14 HR-HPV. The BD HPV test performs as well as other tests approved by the FDA and those with European Commission CE (Conformité Européenne) marking—including HC2—and using cervical specimens collected in PreservCyt medium (Hologic, Marlborough, MA, U.S.A.).

The samples are processed in the BD Viper system, which has an internal quality control. This technique achieved CE approval in January 2015 and is available for commercial use. The system is totally automated and can process 1-30 samples per run and 120 results per patient per day, including genotyping.

Xpert HPV

The Xpert HPV test is a real-time PCR that simultaneously detects DNA encoding for E6/E7 oncoproteins of 14 HPV types (HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68). The samples are processed as individual

cartridges in the GeneXpert platform from Cepheid (Sunnyvale, CA, U.S.A.). This is a molecular diagnostic platform with a capacity to process one test at a time, to 80 tests, in one hour. Test results are reported for overall high-risk HPV status, as well as the presence of high-risk HPV genotypes.

E6/E7 mRNA Detection

The carcinogenic process is regulated by HPV E6 and E7 oncoproteins and, as a result, excessive expression of these genes is a risk marker for cervical cancer. It has been postulated that detection of E6/E7 oncogene expression could be more specific and be a better cancer risk predictor than the HPV-DNA test. At least two methods use RNA detection: the Aptima HPV Assay test of E6/E7 messenger RNA (Gen-Probe), which detects 13 HR-HPV types and HPV-66; and the PreTect HPV-Proofer (NorChip) test, which detects RNA of HPV types 16, 18, 31, 33, and 45.

APTIMA HPV Assay

This qualitative test is based on direct detection of the expression of E6 and E7 mRNA oncoproteins, from the 14 types of HR-HPV (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68) through real-time amplification (48, 49). The APTIMA HPV Assay does not discriminate among the 14 types. The test can analyze cervical samples collected in tubes for ThinPrep cytology with PreservCyt solution. The assay includes an internal control to oversee nucleic acid capture, amplification, detection, as well as user or APTIMA HPV E6/E7 instrument errors. This system can carry out up to 250 tests in approximately five hours.

This technique was approved by the FDA in 2011 for screening women starting at age 30 years, in combination with Pap smears.

It has several limitations, such as, that the test has not been evaluated in HPV-vaccinated individuals; that detection of high-risk HPV mRNA depends on the number of copies in the specimen and that, in addition and according to the literature, false positives can occur with low-risk HPV.

Arbor Vita OncoE6 Cervical Test

The OncoE6 test is a lateral flow strip test that detects high levels of viral E6 oncogene as a biological marker and it could be used as a triage test in women positive for the HPV test. The product has been evaluated in a large-scale study in China. It has CE approval and is ready for marketing.

Sample collection is done using a Dacron swab and PreservCyt media. It does not require complex equipment for processing. The equipment costs around US$2,000 and can process 45 specimens per operator per day, a volume that can be processed in a clinic within 2-2.5 hours.

Performance of HPV tests

The scientific evidence to demonstrate that HPV tests are effective in reducing cervical cancer mortality is available from cross-sectional studies in which the HPV tests are evaluated alongside cervical cytology to evaluate test sensitivity and specificity. Evidence is obtained from randomized clinical trials in which women are assigned to two groups: an HPV test intervention group and a Pap smear control group. This makes it possible to evaluate test sensitivity and specificity as well as reduction in cancer mortality. Table 2 shows the HPV test sensitivity and specificity of the tests described above.

Table 2. Performance of HPV tests used for cervical cancer screening

TEST	SENSITIVITY (%)	SPECIFICITY (%)
Hybrid Capture 2	97.5	84.3
CareHPV	90.0	84.2
Cervista HPV	100	
Cobas HPV Test	97.3	84.5
Abbott RealTime High Risk (HR) HPV assay	95.0	87.2
Aptima HPV Assay	97.6	90.2
Xpert HPV	100	81.5

Source: Cuzick J et al. 2013.

Selection of the HPV test for the cervical cancer screening program

Once the decision has been made to introduce HPV testing into the screening program, the most suitable HPV test can be chosen from the options available on the market. The selection needs to be based on clinical validation of the test, operational and logistical aspects, and the test's costs and benefits. Some questions to consider are as follows:

- What HPV types are detected by the test?
- How are the results presented: by HPV type or as HPV positive/negative?
- What are the manufacturer requirements and costs of the HPV test, equipment and supplies?
- What is the appropriate lot size to process samples?
- How long does specimen processing take?
- What type of training is needed to process the tests?
- What in-country support is available for equipment installation and maintenance?
- How is the quality of the test result controlled?
- Can self-sampling be used with the HPV test?
- What are the requirements for storage, and other supply chain management issues?
- With the local distributor of the HPV test, are there any conditions, arrangements and additional costs to consider?

Considerations for choosing an HPV Test

- Before selecting an HPV test from among the wide range available on the market, conduct a cost-benefit analysis and consider the feasibility of implementing the HPV test in the context of the screening program.
- Choose an HPV test that has been clinically validated.
- HPV tests authorized by regulatory agencies, such as the U.S.A. Food and Drug Administration and/or the European Medicines Agency (EMA) would be prudent options.
- Introducing a specific HPV test into the screening program, and then later changing to another HPV test may be logistically difficult and will have cost implications.
- HPV tests have expiration dates—for example, 9 months or 12 months—and supply chain management aspects need to be considered when choosing the HPV test for use in the conditions and context of the screening program.

SECTION 3:
COSTS TO CONSIDER FOR AN HPV TEST-BASED CERVICAL CANCER SCREENING PROGRAM

KEY MESSAGES

- Two types of costs are typically considered in developing cervical cancer screening programs: the cost per person screened, and the total cost of the program.
- Planning and consideration must be given to the costs of the initial investment to set up an HPV test-based program, recurring costs, and operational aspects of the program.
- Costs to consider range from the purchase of HPV tests, equipment and supplies, training, community education, and treatment, among others.
- The WHO Cervical Cancer Prevention and Control Costing Tool can be used to estimate the costs for setting up and operating an HPV test-based screening program.

COSTS TO BE CONSIDERED

How much will an HPV test-based screening program cost? In order to answer this question, one must consider that the program will have initial capital costs, as well as recurring costs. Some costs will be specific to the use of the HPV test, but most costs are related to an organized screening program, regardless of the screening test used.

Several tools are available to help calculate a country's screening program. One such tool is the WHO Cervical Cancer Prevention and Control Costing Tool[3].

Costs are influenced by the screening algorithm that is chosen. For example, costs are different if HPV testing is used in a screen-and-treat strategy, or if HPV testing is done first, followed by cytology triage in HPV positive women.

Calculating the costs of a screening program is not straightforward, since some expenses may not be obvious. To determine program costs, the fixed costs of the health system need to be considered (e.g., health worker wages) and the specific additional costs for inclusion of HPV testing need to also be considered. The following is a suggested list of items to consider in costing an HPV test-based screening program.

3 Available at: http:/www.who.int/immunization/diseases/hpv/cervical_cancer_costing_tool/en/

- **Cost of education and community mobilization programs:**
  - Community educator wages, based on country standards
  - Training of community educators
  - Transportation for community educators
  - Printing and distribution of educational materials
- **Cost of specimen collection:**
  - Wages of health workers
  - Training of health workers
  - HPV test materials: brushes, specimen tubes, etc.
  - Transport of specimen collection materials to and from the health center
  - Transport of HPV tests to the laboratory
  - Other materials: gloves for personnel who handle samples, data collection forms, etc.
- **Cost of specimen processing:**
  - Wages of laboratory staff
  - Training of technicians and laboratory staff
  - HPV test equipment
  - HPV test processing supplies
- **Reporting HPV test results:**
  - Wages of personnel responsible for patient follow-up
- **Evaluation and treatment of women with HPV positive results:**
  - Pelvic examination: required materials and equipment, such as a table, lamp, etc.
  - Supplies for VIA: acetic acid, etc.
  - Colposcopy: equipment, training, wages of providers
  - Biopsy: biopsy forceps, materials for processing and reading specimens
  - Cryotherapy: cryotherapy equipment, gas
  - LEEP (loop electrosurgical excision procedure): equipment, wire loops, anesthesia
- **Treatment of patients with invasive cancer:**
  - Equipment and health worker wages for radical surgery, radiation therapy, and chemotherapy.

Although screening will be done on all women who agree to participate, follow-up and treatment will only be required in a smaller percentage of women, those with abnormal results. The proportion will vary by populations, but typically 10%-15% of all screened women will require follow-up care. This needs to be considered in the calculation of program costs and the calculation of costs per person screened.

The budget for the screening program needs to be ensured over the long term, along with the consistent availability of supplies and equipment to ensure access to HPV testing and treatment. This is an investment that can cost more at the beginning of a program, especially due to the purchase of the test, equipment and training of the health team. But, the prevention of invasive cancer, through HPV testing and treatment of precancerous lesions, in addition to HPV vaccination of girls aged 9-13, will bring considerable savings from the reduced number of women who need cancer treatment, and economic gains in preventing avoidable deaths.

SECTION 4:
PLANNING AN HPV TEST-BASED CERVICAL CANCER SCREENING PROGRAM: WHERE TO BEGIN?

KEY MESSAGES

- The decision to introduce HPV testing into a cervical cancer screening program should be taken at the highest level of the public health authority and as part of a public health strategy to improve the program.
- Engaging the main stakeholders from the beginning of the planning process, and building consensus among them, are key components to ensure effective introduction of this new technology.
- HPV testing is an attractive technology and can be used to mobilize resources and motivate stakeholders to improve the program. HPV testing does not replace the need for an organized screening program.

HPV TEST AS AN OPPORTUNITY FOR PROGRAM IMPROVEMENT

Introduction of HPV testing provides an opportunity to improve the efficiency and effectiveness of a cervical cancer screening program. Its introduction involves changes in ways of working, in addition to changes in the organization of health services. The following provides guidance on how and where to begin with the introduction of HPV testing into screening programs.

Specific aspects to consider for an HPV test-based screening program:

- Define the HPV testing target age group, frequency of screening, and algorithms that may include: HPV screen-and-treat, or HPV followed by VIA, or HPV followed by cytology.
- Establish screening coverage goals and define the strategies to be used to achieve a high coverage of the target age group.
- Establish strategies to ensure all women with HPV positive test results will receive follow-up care, and ensure service availability to avoid overload and a backlog in colposcopy and biopsy services.

- Consider logistical issues, such as the fact that HPV tests have an expiration date and need to be used prior to their expiration.
- Consider the psychosocial impact of HPV test results on women. For this, it is vital to ensure that health teams, responsible for delivering HPV test results, have a deep understanding about HPV, HPV testing and cervical cancer.

How to begin to introduce HPV testing in a cervical cancer screening program:

- Review the current situation of the screening program, analyze the current capacity and resources in the health system, and identify gaps and needs to improve the screening program.
- Build the political will to introduce HPV testing among health decision-makers and leaders.
- Establish clinical guidelines for HPV testing.
- Publicize and promote the introduction of HPV testing with relevant stakeholders, including medical associations, governmental and nongovernmental health agencies, civil society groups, and universities.
- Establish an advisory committee, with key stakeholders, to design and monitor the HPV test-based screening program.
- Involve the mass media to raise public awareness about HPV and HPV testing.
- Begin to introduce HPV testing on small scale demonstration or pilot programs, and expand as resources permit.

Review the current cervical cancer program

First, begin with an analysis of the cervical cancer situation in the country by identifying the women most affected, geographical areas with the greatest incidence, knowledge and attitudes of women and their partners, as well as health providers, etc. Then review the health service capacity and needs for screening, diagnosis, and treatment of precancerous lesions and invasive cancer. Finally, evaluate the specific needs for the introduction of HPV testing into the screening program, including identifying the barriers and opportunities for introduction of HPV testing.

Establish HPV testing guidelines

It is critical to establish clinical guidelines for HPV testing, based on evidence, including the target age group for screening and frequency of screening. The guidelines should also establish algorithms for the management of women with HPV test results, and especially how women with HPV positive test results will be managed. Program monitoring and evaluation indicators, including screening coverage targets, should be established. This should be done with the involvement of local stakeholders and leaders.

Ensure political will for the introduction of HPV testing

The political will to introduce HPV testing in an organized cervical cancer screening program is critical. This should be reflected at the highest level of the public health system, that is the Ministry of Health, and be reflected in the national program budget and management processes. Political will is also required among the

professional associations and public health workforce to support the change of practice needed to integrate HPV testing into screening programs.

Publicize the introduction of HPV testing among stakeholders

Publicize the introduction of HPV testing among scientific societies, governmental and nongovernmental health agencies, civil society groups, and universities, among other stakeholders. This will involve scientific presentations, especially in the early stages of the process, to build institutional commitments for HPV testing, and discussions to ensure that criticism and dissent contribute to the project's development and do not become obstacles to successful implementation.

Present the plans for HPV testing to health administrators and providers in the jurisdiction where it will first be implemented

A meeting with local health administrators and providers should be held, and following meetings with the highest health authorities, to present scientific information and the plans for HPV testing. These planning meetings should be as participatory as possible to involve all stakeholders in the planning, and to strengthen their commitment to the roll out of HPV testing.

Establish an external advisory group

An external advisory group, with experts and professionals experienced in HPV testing, can be established to help plan the introduction of HPV testing and ensure the credibility and viability of the plans. The advisory group may be composed of representatives from scientific societies, academia, nongovernmental organizations and international health agencies with experience in introducing new technologies. The advisory group can also assist in evaluating the program's implementation and suggest improvements.

Disseminate scientific evidence

Presentation of the plans for HPV testing to national and international scientific agencies, and during professional meetings and conferences, can be a useful way to gain widespread support for the HPV testing program.

Involve mass media

Involving the mass media to promote messages about HPV testing can help to obtain a greater commitment from the public and health providers when the program is rolled out. There is generally little media information about HPV and cervical cancer screening, and many biased reports about HPV vaccines have emerged. So it is necessary to provide journalists with current and scientific information to help raise awareness and understanding of HPV testing.

Begin implementation on a small scale

Introducing HPV testing may require changes in the health services. Therefore, small scale demonstration or pilot projects are recommended to begin implementation. Then, based on lessons learned, the program can be expanded to other geographical areas as resources permit.

SECTION 5:
TRAINING HEALTH WORKERS IN HPV TESTING

KEY MESSAGES

- Health workers need to be well informed about the natural history of cervical cancer, as well as HPV testing, interpreting HPV test results, follow-up, and counseling for women.
- In-depth training, involving theory and practice, is extremely important for program success. It requires an investment of time and designated funding.
- All health workers involved in cervical cancer screening, particularly in the primary care level, will need training. This includes informing community health workers, general practitioners, gynecologists, pathologists, and laboratory technicians about HPV and HPV testing.
- Health workers who provide screening services to women will need to be trained on how to take HPV test samples and how to communicate results to women.

TRAINING HEALTH CARE WORKERS

Prior to rolling out the HPV test in the cervical cancer screening program, all health workers will require information and training on HPV and cervical cancer. This will involve mainly health professionals working at the primary care level - physicians, nurses, and community health workers – as well as specialists such as gynecologists, pathologists, and laboratory technicians.

Training can include different teaching techniques such as lectures, role playing, practice sample-taking with gynecological models and discussion of different situations or questions that can arise from women participating in HPV testing. It will be important to evaluate participants' knowledge at the end of the training, as well as to routinely supervise and monitor clinical skills, and hold refresher trainings if needed.

Training objectives

The objectives of training health professionals are to ensure that they can provide the following:

- Communicate information about HPV testing and cervical cancer screening to women in plain, clear language.
- Take a cervical sample for HPV testing.
- Provide information and counseling to women, before and after the HPV test is taken.
- Appropriately communicate HPV test results.
- Ensure follow-up care is provided to women, according to the HPV testing guidelines.

Who should be trained?

The following health care workers are suggested to be informed about HPV testing and cervical cancer screening:

- Physicians (general practitioners, gynecologists).
- Nurses (licensed nurses, nurse technicians).
- Community health workers (if applicable).

Training topics

The following topics are suggested to be included in training modules on HPV testing and cervical cancer screening:

Anatomy of the female reproductive system

This information is necessary for health workers to understand and explain to women, in a simple manner, the part of the body from which the tissue sample will be taken to test for the virus.

Natural history of cervical cancer

Health providers need to have a deep understanding of how cervical cancer develops, the role of HPV infection in the development of cervical cancer, how precancerous lesions are detected, and the role of HPV testing to prevent cervical cancer.

Human papillomavirus (HPV)

Health providers will need to know about the different types of HPV, how the virus is transmitted, the health consequences of HPV infection, and general information about the various types of HPV tests.

HPV tests

Health workers need to have a good knowledge on the following information about HPV tests:

- Basic principles of how HPV tests detect the virus.
- Populations that need to be screened: recommended ages for screening and frequency of screening.
- Supplies and materials needed for HPV testing, and how it will be done.
- Who will take the sample for HPV testing, and how the tests will be processed.
- How HPV test results are provided to women.
- What an HPV test result, positive or negative, means.
- How to communicate HPV test results to women.

HPV testing using self-sampling

HPV tests have the advantage that the test sample can be taken by the woman herself, without a gynecological exam (See Section 10: HPV testing using self-sampling). If the HPV test will be used in this manner, health workers should also be trained in the following aspects:

- The technique, procedures and effectiveness of HPV self-sampling.
- How to explain to women, step by step, how to take the sample themselves for HPV testing.
- How the tests will be processed and results provided.

Training in the use of data collection materials

A screening program, regardless of the test used, needs a data collection system and clinical reporting forms, based on the indicators and variables relevant to the program (see Section 11: Information Systems and Program Evaluation). Laboratory forms will also need to be sent with the respective, duly labeled, samples for HPV testing. Health providers will need to be trained in how to use these forms and complete the information, emphasizing the importance of completely filling out the forms to assure patient follow-up and program monitoring.

Training in the use of educational materials and counseling

Educational materials for the public should be part of the HPV test-based screening program (see Section 9: Communicating results about HPV testing). During the training of health providers, these materials should be distributed with explanations about how, and with whom, the educational materials should be used.

Counseling is a fundamental component of a screening program (see Section 9: Communicating results about HPV testing). In this regard, health workers should be trained in the following aspects:

- The concept of pre- and post- HPV test counseling.
- Essential techniques for counseling women on sexual health matters, such as HPV infection and HPV testing.
- The characteristics of a good counselor.
- The key points to convey about HPV infection, HPV testing and cervical cancer prevention.
- How and what to communicate to women about their HPV test result.

SECTION 6:
PROCEDURES FOR HPV TEST SAMPLE COLLECTION AND SHIPMENT TO THE LABORATORY

KEY MESSAGES

- Once a sample is taken for HPV testing, it will generally require transportation to the laboratory for testing.
- The quality of the test results will depend on the quality of the sample taken.
- Health workers, therefore, need proper training on how to take the HPV test sample, as well as the procedures for transporting the sample to the laboratory.
- HPV tests have expiration dates and can be sensitive to temperature changes. Therefore, attention is needed to use the tests within the date, as well as to ensure proper storage and transportation.

PROCEDURE FOR SAMPLE COLLECTION FOR HPV TESTING

HPV testing can be performed in any health facility that has the appropriately trained health providers and necessary supplies and equipment. Sample collection for HPV testing is typically performed during a gynecological examination, where the health worker, after inserting the speculum, removes a sample of cervical cells using a specially designed brush. During sample collection, it is important to ensure the woman's privacy and to promote mutual trust and minimize the fear and embarrassment this test might cause.

Depending on the type of HPV test used, the sample is then placed in a collection tube that contains a liquid transport medium. The tube should be properly labeled with the person's first and last names and a personal identification number. The tube is then sent, in a timely and secure manner, for analysis to a molecular biology laboratory that has the capacity to process the HPV test. Samples need to be sent to the laboratory in less than 14 days following collection, to avoid having to be discarded. Coordination is vitally important between the health facilities, where specimens are collected, and the laboratory where the tests are processed.

The following describes the steps for taking a sample for HPV testing:

Preparation

1. Explain HPV testing to the woman and the meaning of results. Make sure that the woman has understood the explanation.
2. Perform a gynecological examination.

Sample collection

3. Obtain a sample from the cervix with the brush or swab, following the instructions corresponding to the type of collecting device.
4. Place the brush or swab in the collection tube with the preservative solution.
5. Close and gently remove the speculum.
6. Place used instruments in a decontamination solution.
7. Label the collection tube with the woman's first and last names, personal identification number, and the date.

After obtaining the sample

8. In the patient's chart, write that the HPV test sample was taken, and any observations during the gynecological exam.
9. Instruct the woman about when to return to receive her test results.

Storage and transport of HPV test samples

This is an example of the procedures for storage and transportation of HPV test samples, but always refer to, and follow the manufacturer's instructions for the specific product used.

Storing and transportation of collection tubes:

- Store collection tubes at room temperature (15-30 °C).
- Transport to the laboratory does not require refrigeration.
- The tubes can be preserved for 2-3 weeks at room temperature.
- In the laboratory, samples can be preserved for up to one additional week at 4 °C and up to 3 months at -20 °C.
- Do not use the test after the indicated expiration date.

SECTION 7:
OPERATIONAL ASPECTS OF THE LABORATORY

KEY MESSAGES

- HPV tests need to be processed in a centralized laboratory, using the processing equipment associated with the particular test.
- HPV testing procedures need to be integrated into a pathology laboratory.

OPERATIONAL ASPECTS OF THE LABORATORY

A centralized pathology laboratory, with qualified personnel and quality assurance procedures, will be necessary to process HPV tests. Laboratory software is essential to record women's information including the HPV test results, as well as any additional test results (if applicable) such as colposcopy, biopsy and treatment.

HPV test results are used to identify two groups of women:

a) Women who are HPV negative, which, given the test's high negative predictive value, do not need to be re-screened for at least 5 years; and
b) Women who are HPV positive, and will require follow-up care or treatment. In this regard, timely and close communication between the pathology laboratory and health facilities will be important to communicate results.

The physical space in the laboratory

A bright room is needed to enable HPV test processing, that requires microplate techniques. The room should be enclosed, with no fast moving air, dust, or other substances that could contaminate the results. The room temperature should be constant at 20-22 ˚C.

The countertops should be approximately 70 cm wide and long enough to hold the different HPV testing components. Since the homogenization process makes the countertop vibrate, it is advisable to have one countertop for the various instruments; another countertop for the hot-water bath area, preferably close to a water faucet and sink; and a countertop for the luminometer. A central island is an extremely useful space for carrying out sample preparation, transferring reagents to pipettes, and various other operations, before taking samples to the testing instruments.

HPV test samples can be stored for two weeks at room temperature, an additional week in the laboratory at 2-8 ˚C, and up to 3 months at -20 ˚C. Therefore, there should be a refrigerator and freezer with capacity to store HPV test samples. Since refrigerators increase the temperature in the room where they are in use, due to heat given off by their motors, they should be kept in a location physically separated from the room where HPV processing is done.

Personnel working in the HPV testing room should observe stringent hygiene standards and always work with talcum powder-free gloves, because it could contaminate the samples. No smoking, eating, or drinking should be allowed in the work area. Unauthorized laboratory personnel should not be permitted in the processing room.

Considerations in processing HPV tests

The specific methods used to process the HPV tests will depend on the particular test used, and the manufacturer's recommendations for processing tests should always be followed. A general description of HPV test processing, its limitations and precautions is described below.

a) General considerations and limitations of HPV testing:

- The HPV test is designed to detect high-risk HPV types, typically including HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68.
- The test may not detect low-risk HPV types, such as HPV 6, 11, 42, 43, and 44.
- The test cannot differentiate between infection with one HPV type and infection with several HPV types; nor can the test identify a new infection from a re-infection.
- An HPV negative test result does not completely rule out presence of HPV, since there may be a small chance of sampling errors, or from very low levels of HPV infection (that is, less than 5,000 copies per sample).
- Samples need to be obtained using the cervical brush that accompanies the specific HPV test.
- At the time the HPV test sample is taken, if there is presence of anti-mycotic creams, contraceptive gel, or vaginal hygiene products, these may contaminate the sample and the HPV test result may be a false negative.
- The brush should not be used in pregnant women.
- There is a small chance of cross-hybridization with HPV strains 6, 11, 40, 42, 53, 54, 55, 56, MM4, MM7, MM8, and MM9, which may affect test results.
- Cross-reaction with the plasmid pBR322 may occur, which could result in false positives, since it has some analogous sequences, especially if concentrations of this bacterial plasmid are high.

b) Precautions to maximize quality of HPV test processing:

- Mouth pipetting should not be done.
- No smoking, eating, or drinking should be permitted in areas where reagents are being used.
- Talcum powder-free latex gloves should be used in all steps of the procedure.
- Spills should be cleaned up immediately, using disinfectants such as sodium hypochlorite.

- HPV test reagents should not be used after their expiration date.
- Processing tests that have passed their expiration date, or processing tests in conditions outside the recommended temperature range can lead to invalid test results.
- Quality control procedures, test calibration and verification criteria, and interpretation of test results should be carefully carried out.
- Pipetting exact amounts of reagents specified in the manufacturer's instructions and ensuring the correct blend of the various reagents are important for quality testing.
- False positives can be produced by inadequate pipetting if aliquots are not properly transported, and in the process of hybridization, the pipette should not touch the sides of the tube or the contents of the probe.
- Nucleic acids are very sensitive to degradation by environmental nucleases and nucleases on human skin. Therefore, surfaces should be covered, with no dust, and talcum powder-free gloves should be used in the processes.
- The denaturation step should be done immediately after opening the equipment. Failure to observe this precaution may produce false negative results.
- Improperly done homogenization steps and inverting or inadequately shaking tubes can result in false positives. The technique should be done meticulously and systematically, following manufacturer instructions.
- Contamination of the microplate with bacteria, saliva, hair, or skin oils should be prevented.
- Samples can be kept at room temperature for a maximum of two weeks.
- Unauthorized laboratory personnel should not be allowed to enter the processing room and untrained personnel should never be allowed to participate in the process.

SECTION 8:
MANAGEMENT OF HPV TEST RESULTS

KEY MESSAGES

- HPV testing can identify women at risk of developing cervical cancer, and when coupled with appropriate treatment, can reduce cervical cancer incidence and mortality.
- Women with HPV positive test results need follow-up care. There are several options: immediate treatment, or triage with another test -cytology or VIA- or referral for colposcopy. The choice will depend on the resources available in the health system, and the country guideline.
- All efforts are needed to ensure women with HPV positive test results receive follow-up care. Loss to follow-up is a reflection of the barriers to access to health services.

MANAGEMENT OF HPV TEST RESULTS

HPV testing is only effective if the corresponding follow-up and treatment is provided to all women. In fact, appropriate follow-up care and treatment has a greater impact on mortality reduction than a high screening coverage. For example, follow-up and treatment of 50% of women detected with precancerous lesions in a setting with 100% screening coverage has been estimated to reduce mortality by 50%; while 100% follow-up and treatment in a context of 50% screening coverage has been estimated to reduce mortality by 70% (Murillo R *et al.* 2008).

Despite this fact, follow-up care after screening continues to be a challenge. Several studies in high-income countries report 10%-45% of screened women with incomplete diagnosis and treatment (Spence A, Goggin P and Franco EL. 2007). In Latin American settings, with weaker health systems, follow-up care is more challenging and an estimated 18%-75% of screened women do not complete their diagnosis and treatment (Arrossi S *et al.* 2012; Wiesner C *et al.*2010).

This loss to follow-up care is a reflection of the barriers to access to health services. Also, social determinants of health have an impact on the completion of diagnosis and treatment procedures. For example, women's position in the socioeconomic structure, older age, low educational level, low income level, lack of transportation, and lack of social support are factors that can affect whether a woman is screened, or completes the diagnosis and treatment procedure, when results are abnormal.

Women's knowledge and perceptions regarding cervical cancer, HPV, and how to prevent it and treat it are also factors affecting follow-up care. For this reason, information received during the medical visit, and how HPV test results are communicated to women are important factors in ensuring continuity in the process of care (see Section 9: Communicating results about HPV testing).

In addition to patient-related barriers to follow-up and treatment, there are also health system factors related to the availability, organization, and operation of health services. Barriers include long delays in delivering test results back to the patient, lack of appropriate guidance concerning the steps to follow after receiving a positive HPV test result, difficulties with obtaining a medical appointment for treatment, and long waiting times for care (Arrossi S *et al*. 2012). In addition, many screening programs tend to lack effective follow-up systems to contact patients, have problematic referral and counter-referral systems, or lack human resources to respond to the demands for care.

These barriers need to be considered when planning and implementing a cervical cancer screening program based on HPV testing. This section offers information to help plan services to manage women with HPV positive test results.

MANAGING WOMEN WITH AN HPV POSITIVE TEST RESULT

There are several strategies that can be used to manage women with HPV positive test results: immediate treatment, or triage with another test -cytology or VIA- or referral to colposcopy. There are also options to consider regarding a diagnosis -with or without biopsy- and regarding treatment for precancerous lesions-cryotherapy, LEEP, conization. These decisions need to be made as part of establishing national guidelines for cervical cancer screening, and in planning the program. The decisions should be made based on an assessment of the health system capacity, human and financial resources available and other contextual factors. In addition, the strategies selected should take into account the number of visits that women will have to make to complete the screening and treatment process, since a greater number of visits may lead to a greater loss of women and increase program costs.

Table 1 shows several regimens for triage, diagnosis, and treatment by the number of visits required.

Table 1. Examples of strategies to manage women with HPV positive test results, by number of required visits

VISIT 1	VISIT 2	VISIT 3	VISIT 4
HPV test, followed by treatment for women with positive results			
HPV test, with VIA as a triage test in HPV positive women, then followed by treatment for women with HPV and VIA positive results			
HPV test	Colposcopy -with or without- biopsy	Treatment	
HPV test, and cytology at the same time	Colposcopy for all women with test results of HPV positive and abnormal cytology -with or without biopsy	Treatment	
HPV test	Cytology for all women with HPV positive test results	Colposcopy/confirmatory biopsy	Treatment

Source: Adapted from Planning and Implementing Cervical Cancer Prevention and Control Programs: A Manual for Managers. Alliance for Cervical Cancer Prevention. 2004.

ENSURING ACCESS TO DIAGNOSIS AND TREATMENT SERVICES

Planning and estimating resources needed

When planning the introduction of HPV testing, it is crucial to estimate the number of women who will need services for follow-up diagnosis and treatment; and then accurately assess the human, financial and material resources needed to respond to the demand. The following factors should be considered:

- Number of women estimated to need services at each stage screening, diagnosis, treatment, post-treatment follow-up. After estimating the program's target population, estimate the number of women expected to be referred to diagnosis (e.g., colposcopy/confirmatory biopsy), treatment (e.g., LEEP), and post-treatment follow-up services. Based on this estimate, decide what will be needed to ensure equitable access to these services. As an example, see the box below on how to calculate the number of women who will require colposcopy services.
- Availability of human resources trained to perform the diagnosis and treatment. It will be important to plan for the right number of trained providers, as well as ensure that the location of diagnostic and treatment services are distributed across geographical areas, in order to be accessible and meet the service demand.
- Availability - type and quantity - of diagnostic and treatment equipment, such as colposcopes, cryotherapy equipment, LEEP, etc.

Example of how to calculate the number of women that will require colposcopy services

- Total number women aged 30 to 64 years to be screened: 12,500 women
- Estimated screening program coverage (80%): 10,000 women
- An estimated 12% of women screened will be HPV positive: 1,200 women will need additional evaluation.
- If colposcopy is the chosen method for further evaluation: 1,200 women will need access to the service.
- If cytology will be used as a triage test before further evaluation: 1,200 Pap smears will need to be taken and processed.
- Calculation of women that may need to be treated (e.g. 2% of women screened with HPV testing): 200 women

Depending on the health system capacity, a decision will be needed about which service delivery model will be used: vertical services, in which providers and facilities provide a single service; or integrated services, in which providers deliver a range of health services. Also, based on the characteristics of the country or region, a decision will need to be made about whether the service will be static services, at a health center or hospital, or whether it will be outreach services, also called mobile services.

Diagnostic and treatment service networks

For the diagnosis and treatment process to be effective, trained human resources and equipment must be coordinated and be part of an efficient service network that facilitates continuity of care for women, following screening.

Care networks vary depending on the services available, the institutions involved, and the structure of the health system. Prevention of cervical cancer is a process that necessarily requires the involvement of all levels of the health care system: primary, secondary, and tertiary care and, in some cases, involves both the public and private systems.

The stages of screening, diagnosis, and treatment need to be well coordinated to make the process effective. These stages include necessary procedures for: screening (HPV testing) and delivery of results; referral for diagnostic confirmation (e.g., colposcopy and biopsy); and treatment for precancer (e.g., LEEP) and cancer (e.g., brachytherapy, chemotherapy) or palliative care, as appropriate.

The interactions between levels of care that link the different procedures are called *interfaces*. These include the transfer of information and responsibilities among the users, health workers, and institutions involved. Interfaces are critical to establish the process, fulfilling the objectives of each step, and achieving the best possible outcomes (Zapka J *et al.* 2010).

The health management team needs to identify facilities and services that are available to be part of the diagnosis and treatment network. Facilities need to be accessible with regard to hours, services and location. The management teams must seek agreements for the organization and maintenance of these health networks.

To be effective, all key actors in the health system need to be involved from the beginning of the screening process. Good relationships among the personnel at the different services and facilities, clear referral protocols and communications, and clear responsibilities at each stage of the process are essential (ACCP, 2004). One possible strategy is to organize a working team that includes stakeholders and representatives from the facilities involved (e.g., hospital directors, chief of gynecology services) to strengthen and maintain ties. This team can meet periodically to define protocols, establish goals, evaluate processes, and solve problems.

The personnel involved in the process at all levels of care need to be familiar with the diagnosis and treatment network and have written protocols that include accurate information on:

- Which cases require women to be referred.
- Name, address, and hours open to the public of the service and facility where the women are referred.
- Referral mechanisms (e.g. letters, phone calls, etc.).
- How to make appointments.
- Form of communication among services.

Strategies to reduce loss to follow-up care

The fact that services are available does not necessarily guarantee that women can access the service or will use them. Several geographic, socioeconomic, and health system barriers exist that cause loss of follow-up care for women with HPV positive test results. These barriers cannot be ignored by the health care team. To ensure continuity of care for women during the diagnosis and treatment process, an effective follow-up system should be ensured. This includes:

- Contact information on women at the first visit and updated at each subsequent visit.
- A registry system for women in follow-up care. Services need to clearly identify HPV positive women and establish priorities for their care. Systems can vary, ranging from computerized systems to index card files of women to be followed-up.
- Mechanisms to contact and follow-up women who miss a scheduled appointment. Telephone calls, letters, or personalized methods can be used, such as visits by health agents or "navigators" (see box below).

Using patient navigators to overcome health system barriers

Patient navigation involves the provision of logistical and emotional support to ensure continuity of care in the diagnosis and treatment processes for women with abnormal screening test results, or women diagnosed with cancer. Patient navigation also includes support for gaining access to health services and overcoming barriers to attaining appropriate and timely care (Wells KJ *et al*. 2008). The objective is to reduce delays in access to the care process, emphasizing timely access to diagnosis and treatment, and the reduction of dropouts from the process.

The origin of this strategy comes from a case management model that includes four components:

1. Case identification: establish a systematic procedure to identify individuals with abnormal results or cancer that need follow-up care.
2. Contact patients and gather information concerning the barriers to the continuity of care for diagnosis and treatment.
3. Individualized strategy to overcome the barriers identified.
4. Systematic follow-up of each case until the problem is resolved and the woman receives complete diagnosis and treatment.

SECTION 9: COMMUNICATING RESULTS ABOUT HPV TESTING

KEY MESSAGES

- Communicating information about HPV and HPV testing are critical aspects of a cervical cancer prevention program.
- Information needs to be provided on HPV, its relationship to cervical cancer, and the role of HPV testing to prevent cervical cancer.

COMMUNICATIONS IN THE CONTEXT OF HPV TESTING

The introduction of HPV testing in cervical cancer screening programs includes developing communication strategies and messages that target a range of audiences: women, their partners and families, community leaders, health providers, and journalists.

Communication strategies are needed to ensure that the cervical cancer program objectives and priorities are met, particularly to inform and encourage women to seek screening services and adhere to follow-up care.

Women's perceptions and knowledge about HPV and cervical cancer

In developing a communications strategy, it is important to take into consideration women's knowledge, understanding and perceptions about cervical cancer and to tailor messages and strategies accordingly. Some considerations include the following:

- Women generally identify the cervix with the reproductive tract, without specifying its location, anatomy, or function.
- Women perceive cervical cancer as a disease that is severe, invasive, incurable, and associated with death. It is seen as a disease that remains latent and is activated by chance or by a specific incident, such as being hit, having a miscarriage, or pregnancy.
- Women generally describe Pap smears as an uncomfortable and annoying experience, rather than painful.

In general, knowledge about HPV is limited among the general population and health professionals. Information about HPV tends to be infrequent, inadequate and can be confusing to women, without responding to their information needs. Many people have not yet learned about HPV infection and its link to cervical cancer.

Some media attention has been given to HPV, but without details or important aspects covered. For example, a survey of media stories on HPV showed that 50% of stories explained that HPV is a very common sexually transmitted virus, but only 8% of the media content differentiated between HPV that cause warts and high-risk HPV that cause cancer, and only 13% of stories included information that HPV infection generally disappears on its own. In addition, an analysis of 75 brochures on cervical cancer screening revealed that the materials addressed medical, more than psychological concerns about HPV testing; and the least mentioned topics were the feelings that women might experience in response to an HPV positive test result, such as stigma, fear, guilt, helplessness, anger, and anxiety (Mast TC *et al.* 2009).

Communication on HPV and HPV testing

Primary audiences

There are two main audiences to consider in developing a communication strategy: women and health teams. Other audiences that need to be considered are community health workers, professionals in nongovernmental health organizations, and journalists. Messages to consider are described in the table below and in the Annex: Women's Frequently Asked Questions.

Key messages for women

TOPIC	KEY MESSAGES FOR WOMEN
CERVICAL CANCER	• Cervical cancer occurs when there is an abnormal growth of cervical cells. • Cervical cancer is caused by persistent infection by high-risk HPV types.
HUMAN PAPILLOMAVIRUS	• HPV is a very common virus, transmitted by sexual contact. • The majority of people will have an HPV infection during their lifetime. • In most cases, HPV infection clears by itself, from the body's own immune response. • Some HPV infections may not clear, and will become persistent. This can cause lesions on the cervix.
RELATIONSHIP BETWEEN HPV AND CERVICAL CANCER	• Persistent infection with high-risk HPV types is the cause of cervical cancer. • If not detected and treated, HPV infections can cause precancer lesions in the cervix, that can develop into cervical cancer. It is estimated to take 10-15 years from HPV infection to the development of cervical cancer. • Having an HPV infection does not mean having cancer.
HPV TEST	• The HPV test determines whether there is an HPV infection in the cervix. • The HPV test is taken during a gynecological examination. A small brush is used to collect a sample of cells from around the cervix. The brush is placed in a tube that is sent to the laboratory for analysis.
HPV TEST RESULTS	• Test results are generally given as HPV positive or HPV negative. • A **negative result** means that an HPV infection was not found in the cervix. • A **positive result** means that an HPV infection was found, and that other tests or treatment are needed.

Considerations for health providers, when talking to women about HPV and cervical cancer

- Explain to women the reproductive system, the location of the cervix, and its function.
- Use clear and plain language, without jargon or highly technical terms.
- Utilize pamphlets, posters, flipcharts, or other visual materials.
- Ask the woman about her knowledge of HPV, cervical cancer, screening and treatment. This would be a good starting point for a discussion on HPV testing and cervical cancer prevention.
- Inquire about whether the woman has heard about the HPV test and what she expects from the testing. Ask her whether she has previously had a Pap test and is familiar with the procedure.
- Consider that women may feel embarrassed to talk about HPV and cervical cancer.
- Cervical cancer is a serious disease and often associated with death. It is important to emphasize that cervical cancer can be prevented and the HPV testing is a tool to detect whether women are at risk for cervical cancer.
- Because it is a sexually transmitted virus, a woman may ask how she became infected, or whether she could infect someone else. Clarify that HPV is a common virus that most people will have at some point in their lives.
- Explain that the woman has a right to a private examination room, and that the HPV test might be taken by a male or female health provider (whichever is the case).
- Allow the woman to see and touch the HPV test materials, which may help reduce fear and anxiety.
- Waiting for the HPV test result can cause distress and anxiety. Minimize any delays in providing HPV test results.
- Clearly communicate the HPV test results and what they mean for the woman. Make sure that the woman understands the information provided about her HPV test result.

Using Mass Media

Information about HPV and cervical cancer provided to the public through mass media can have a great impact on the way HPV testing is perceived by women, health professionals, and the general public. Prior to rolling out the HPV test-based screening program, contact the different media outlets in the area, especially newspapers and radio, and provide journalists with basic information about HPV, HPV testing, cervical cancer, and the epidemiological situation in the country/region.

Counseling Strategies

Counseling is a strategy for interpersonal communication between the health provider and the woman. It allows women to become more informed and knowledgeable about HPV and cervical cancer prevention and encourages them to adopt preventive practices. Counseling can be done individually, or in groups. Individual counseling is suggested for cervical cancer prevention, since sensitive topics, such as sexuality, disease, and death will be discussed. These topics can cause anxiety, fear, and embarrassment in women. Therefore, a private space needs to be used during counseling to create an environment of trust and confidentiality.

Counseling is based on active listening by the health provider. It is an opportunity for women to ask and be asked questions, and to put into words her fears and anxieties related to HPV testing and cervical cancer

prevention. Counseling is done without judgment, and to build new knowledge and confidence in women to support HPV testing and promote health seeking behaviors.

Counseling can begin with a discussion about the woman's knowledge of HPV and cervical cancer, and her experience with gynecological examinations. It is important to listen to the woman's doubts, fears, and concerns and provide her with information in clear and straightforward language.

Counseling can be done in a fixed space in a health facility, or in a space that is created for counseling at another location where health services are offered. Counseling can be done during communication and outreach activities, during home visits, at health facilities, among other locations.

Communicating HPV test results

At the time of receiving her HPV test result, a woman may feel a high level of stress. When the test result is HPV positive, she may feel fear, shame, guilt, and other feelings. These emotions can have an impact on whether the woman adheres to the referral for diagnostic and treatment services. Therefore, the most important moment for counseling is at the time of providing HPV test results to women. It is important to deliver the HPV test results in a calm and non-judgmental manner, and to minimize any fears and anxiety. The woman could be probed for any doubts or questions about what the HPV test result means for her.

All women have the right to receive their HPV test results in a timely manner. Women should receive their HPV test result in less than 30 days of sample collection, whether the result is HPV negative or HPV positive.

Counseling is also required during the follow-up and treatment services. It is important to convey information about the procedures to women, how the procedures will be done and what the intended outcomes are of the procedures.

WHO PROVIDES COUNSELING	COUNSELING SKILLS	PRINCIPLES FOR COUNSELING	TOPICS FOR COUNSELING
• Trained health providers: physicians, nurses, and social workers.	• Active listening, clear language, command of nonverbal communication. • Paraphrase to clarify, identify, and reflect feelings. • Formulate meaningful questions. • Empathy, comprehension, discretion, social skills.	• Respect. • Non-judgmental. • Privacy. • Truthfulness. • Confidentiality. • Open mindedness.	• Reproductive health anatomy. • HPV and HPV infection. • HPV testing. • Cervical cancer prevention. • Follow-up and treatment.

SECTION 10:
HPV TESTING USING SELF-SAMPLING

KEY MESSAGES

- One of the advantages of HPV testing is that it can be done by the woman herself, without undergoing a gynecological examination.
- HPV self-sampling has high sensitivity and specificity, similar to that of HPV testing conducted by a physician or nurse.

ADVANTAGES OF HPV SELF-SAMPLING

One of the advantages of HPV testing is that it is the only screening test that can be done with a vaginal sample taken by the woman herself. HPV test sensitivity and specificity using a vaginal sample, taken by the patient, is similar to that taken by a health provider (Lazcano-Ponce E *et al.* 2011).

HPV self-sampling is widely accepted in countries of Latin America, Africa, and Asia. Studies in China, Uganda, India, Nicaragua (even among the indigenous population in the Masaya region) have shown that acceptance by women for HPV self-sampling is high (Jeronimo J *et al.* 2014).

Health workers may be resistant to an HPV test-based screening program that relies on HPV self-sampling. This may be due to the uncertainties about the woman's acceptability and quality of the sample for testing. But it is important for health workers to understand that HPV infection is not limited to the cervical epithelium, and that the infection can also be in the vagina, vulva, and even the anal region. Therefore, even if the self-sample does not collect an adequate amount of cells from the cervix, a sample of vaginal cells will be sufficient to determine whether or not the woman has an HPV infection.

Another advantage of HPV self-sampling is that it can increase screening coverage. This is because it does not require women to go to a health service and can be done in the convenience of a woman's home, or in community settings that offer sufficient privacy. Women can take the HPV test, send the sample by mail to the health center or laboratory for processing, and the health workers at the health center can then contact them to provide results or schedule an appointment for further evaluation.

Many women choose not to undergo a gynecological examination, for many reasons including modesty, or unwillingness to be examined by a male health provider. HPV self-sampling helps to overcome these barriers.

HPV self-sampling can also facilitate cervical screening in health centers where there is limited capacity for screening, such as no physicians, no gynecological tables or no vaginal specula.

Eligibility for HPV self-sampling

All women in the screening program's target age group are eligible for HPV self-sampling, if they agree and understand the instructions. Although acceptability by women for HPV self-sampling is high, there are women who may prefer that a health provider take the cervical sample. The most common reasons a women rejects HPV self-sampling are (Bansil P *et al.* 2014):

- Fear of hurting herself. Appropriate counseling can alleviate a woman's fear, although the health provider may have to take the sample if the patient is still afraid and does not agree to take the sample herself.
- Fear that the sample will not be of good quality. Appropriate counseling can relieve a woman's uncertainty.
- Resistance to touching her genitals.
- Fear of not using the sampling brush or tube properly. Appropriate training of women can decrease this fear.

Instructions for HPV self-sampling

It is important that instructions on how to take the HPV self-sample are explained in a simple, straightforward way, ideally with visual aids. It is important to consider the cultural and social characteristics of the populations, and be aware that some women may feel offended by the illustrations showing how to collect a sample for HPV testing.

Training health providers on HPV self-sampling

All health providers that will offer women the choice of a self-sampled HPV test should be well informed about this procedure. Health providers need to understand the procedure and be prepared to discuss it with women and answer any questions or concerns they may have.

Topics to address during training include the natural history cervical cancer, emphasizing that HPV infection is very common, HPV testing and the advantages of HPV self-sampling. Additional information to give health providers is as follows:

- Information about the supplies used in HPV self-sampling.
- Eligibility for HPV testing and self-sampling.
- Instructions for how to take a self-sample, label the collection tube and where to send it for processing.
- The meaning of HPV positive and HPV negative results.
- Follow-up steps for women with HPV positive results.
- Specific instructions for the woman doing self-sampling.

Reporting results to women

It is necessary to develop appropriate and timely strategies to inform women about their HPV test result in a timely manner. If the sample was taken at the health center, the woman can be asked to return at a

predetermined date to receive the result. If the woman took the sample at her home, community health workers can contact women at their home to deliver the results. HPV test results are private and need to be only be given to the woman directly, and not discussed with anyone else. Protection of privacy is important, especially given the possibility that community health workers may have close community relationships with the patient and her family.

Follow-up of women with HPV positive results

HPV self-sampling has the advantage that women can take the test by themselves without having to go to a health facility and undergoing a gynecological examination. However, if the HPV test result is positive, the woman will need to go to the health center for further follow-up care. Therefore, if HPV self-sampling will be used as a strategy in the program, it is necessary to build in systems to ensure all women with positive test results will receive follow-up. This includes providing women with appropriate counseling and education so that they understand the need to complete the required follow-up steps, after a positive test result.

SECTION 11: INFORMATION SYSTEMS AND PROGRAM MONITORING

KEY MESSAGES

- A cervical cancer program needs an information system to be able to monitor patient outcomes and program indicators.
- Information systems can be based in each health facility or centralized in an office that serves several health facilities.
- Their essential function of the information system is to systematically collect patient data and results of tests and procedures, and to periodically produce monitoring reports.

OBJECTIVES OF THE INFORMATION SYSTEM

The cervical cancer screening program will require an information system to enable monitoring patient outcomes and program indicators. The information system can be used to record information about the care and HPV test results of each woman participating in the screening program, as well as to produce periodic reports on program indicators, as suggested in Table 1.

The information system should be used to generate information on woman's HPV test results, categorized as follows:

- Group A: Women with HPV negative test results.
- Group B: Women with HPV positive test results, and who have been diagnosed and treated (completed care).
- Group C: Women with HPV positive test results, and who did not receive results and/or were not treated (incomplete care).

The purpose is to monitor quality of care and, if indicated, adopt measures that minimize the number of women in Group C.

Table 1: Cervical cancer screening program indicators (WHO, 2014)

Performance Indicators

a) Screening coverage of the eligible population: Percentage of eligible women in the target group with at least one HPV test in a period of three to five years, according to the screening interval established in the country.
b) HPV test positivity rate: Percentage of women with an HPV positive result in the past 12 months.
c) Treatment rate: Percentage of women with an HPV positive test who have completed appropriate treatment in the past 12 months.

Impact Indicator

d) Cervical cancer incidence and mortality: Cervical cancer incidence and mortality by age group in the program's target population.

FACTORS TO CONSIDER IN SETTING UP AN INFORMATION SYSTEM

Measurement of program indicators requires an information system that produces quality data in a timely fashion. When setting up an information system, consider the following:

- Create clinical data collection forms to record information about women in the screening program.
- Train health providers on data collection and how to enter these data into the information system.
- Designate a responsible person(s) at each level of care who will manage the information system, data collection, and reporting.
- Ensure that data are collected across all levels of care -primary, secondary, and tertiary- linking information systems if necessary. Such a linkage will enable health personnel to track users across the health system and evaluate overall program impact.

A computerized information system can link various health facilities, laboratories, and data processing centers, enabling them to produce periodic automated reports on basic indicators, such as coverage, treatment, and follow-up rates.

FACILITY-LEVEL HEALTH INFORMATION SYSTEM

At the health facility level, the information system is used to monitor and evaluate screening and treatment services provided at that facility. Although secondary and tertiary level health care facilities may have computers available, some facilities may need a simple manual log or registry to record data. The following information is suggested to be recorded in the registry:

Registry for participation in screening services

Basic information and test results are recorded for all screened women. It can be used to monitor laboratory results, identify when they are missing, and be used to call back women to receive their HPV test results.

Laboratory registry

It is located in the laboratory and is used to record all incoming HPV test samples and record results after processing. It helps to monitor results that have not yet been reported to the health facility.

Referral-care registry

It records all users who receive diagnostic and treatment services after receiving HPV positive test results. It helps to monitor treatment rates.

In each facility, the information on the women obtained from the registries is used to calculate the monthly statistics for a limited number of indicators that are feasible for a facility-level health information system (see Table 2). The monthly statistics from the different facilities in a district can then be grouped to evaluate program performance at the district level.

Table 2: Elements for monitoring a cervical cancer screening program

DATA COLLECTION SITE	PARAMETERS	DESCRIPTION
Screening facilities	Women's participation in screening.	Number of women tested for the first time in the year in the screening program.
	Appropriate target age group.	Divide the number of women screened in the target age group, divided by the total number of women tested for the first time in the year.
Laboratory	Percentage of women with HPV positive results.	Number of women with HPV positive test results, divided by the total number of women with HPV test results in the year.
	Quality of HPV testing.	Divide the number of HPV positive tests by the total number of HPV tests processed in the year.
	Laboratory processing time.	Divide the number of test results processed and sent to the health facility, in the three weeks following sample receipt in the laboratory, by the total number of samples received for processing in the laboratory in the same time period.
Diagnosis and treatment facilities	Percentage of women with precancerous lesions.	Divide the number of women diagnosed with precancerous lesions, by the number of women who received colposcopy. **Note:** Colposcopy quality can also be evaluated seeking the correlation between colposcopy results and histological study results.
	Treatment of women with HPV positive results.	Divide the number of women treated, by the number of women with HPV-positive results in the year.
	Percentage of women with invasive cancer results.	Divide the number of women diagnosed with invasive cancer, by the number of women receiving colposcopy in the year.
	Treatment of women with cancer.	Divide the number of women treated for cancer, by the number of women diagnosed with cancer in the year.

SECTION 12: COUNTRY EXPERIENCES WITH INTEGRATING HPV TESTING IN NATIONAL CERVICAL CANCER SCREENING PROGRAMS

UNITED STATES OF AMERICA

Through the first half of the 20th century, the United States (U.S.) had a high burden of cervical cancer, similar to the current situation in many low- and middle-income countries. The introduction of Pap smears in the 1950s was the starting point for screening in the U.S. (Benard VB *et al.* 2014). Although clinical trials to evaluate its potential effectiveness were not carried out before its implementation (Cuzick J *et al.* 2008), opportunistic Pap tests resulted in the first successes in early detection of cervical cancer. The drastic reduction in cervical cancer cases and deaths in the ensuing decades (Benard VB *et al.* 2014) demonstrated the effectiveness of Pap tests and led to the preparation of clinical guidelines. Although the cervical cancer incidence rate continues to decline, over 12,000 women develop the disease every year (Benard VB *et al.* 2014). In 2011, over 4,000 women died from this very preventable disease. In 2012, while 88.8% of women in the U.S. had been screened in the preceding five years, approximately 8,000,000 women had still not been screened for cervical cancer.

To date, the U.S. does not have an organized national cervical cancer screening program. There is, however, the National Breast and Cervical Cancer Early Detection Program (NBCCEDP) which provides screening services to women living at, or below, 25% of the federal poverty line and who do not have health insurance or sufficient coverage (Lee NC *et al.*2014).

Introduction of HPV testing

In 1999, the U.S. Food and Drug Administration (FDA) approved the use of an HPV test (Digene Hybrid Capture 2) as a triage method, for follow-up of women screened by cytology and with atypical squamous cells of undetermined significance (ASCUS) (Saraiya M *et al.* 2013). Its use grew after a large study confirmed its effectiveness for triage (Solomon D *et al.* 2001). NBCCEDP began to authorize HPV test triage as part of its program in 2002 (Saraiya M *et al.* 2007). In 2003, the FDA approved dual testing with HPV and Pap tests in women aged 30 years and older. Immediately afterwards, the American College of Obstetricians and Gynecologists (ACOG) and the American Cancer Society (ACS) changed their screening guidelines to recommend screening with dual testing or the Pap test alone, both at an interval of three years (Saraiya M *et al.* 2013).

In 2012, the U.S. Preventive Services Task Force (USPSTF), ACOG, and ACS consolidated their cervical cancer guidelines (Saraiya M *et al.* 2013) While the new guidelines maintained the option of Pap tests at a three-year interval, they gave preference to co-testing with HPV tests and Pap test in women aged 30 and older and increased the screening interval to every five years due to the high negative predictive value of the HPV tests (Bulkmans NW *et al.* 2007; Dillner J *et al.* 2008; Naucler P *et al.* 2007). That same year, NBCCEDP included co-testing in its program (Benard VB *et al*. 2014). In 2014, the FDA approved the first HPV test for primary cervical cancer screening in women aged 25 years and older, after a large study confirmed effectiveness similar to the Pap test. Immediately, the Society of Gynecologic Oncology (SGO) and the American Society for Colposcopy and Cervical Pathology (ASCCP) recommended HPV testing as primary screening for women starting at age 25 years, with three-year intervals after a negative result (Huh WK *et al.* 2015).

Lessons learned

The following lessons, based on the experience of the United States with opportunistic screening, can be important for other countries in their first steps to integrate HPV testing into a screening program.

Over the years, groups of experts made changes to U.S. cervical cancer screening recommendations to keep them updated with scientific advances and better understanding of the disease. Unfortunately, these continuous changes resulted in major confusion among health care providers about the screening methods they should use, which intervals are appropriate, and the target age groups. Many providers hurried up to adopt HPV testing in their practice, but without following the recommended increase in screening interval. Some even started doing yearly co-testing instead of adhering to the three and now five-year interval. Cervical cancer screening recommendations need to be clear and consistent since their implementation time tends to be long, and years can go by before physicians and other health care providers begin to use the guidelines in their practice.

There are disparities in cervical cancer screening in the U.S. The screening coverage is generally high, but it is notably lower in areas of the country with less infrastructure and economic resources. The southern region reports more cases and more deaths from cervical cancer and a greater percentage of women who have not been screened in previous years in comparison with other regions of the country (Benard VB *et al.* 2014). The United States Affiliated Pacific Island Jurisdictions (USAPI) are another example where health care providers recognize the lack of resources and the high cost of Pap tests as important barriers to cervical cancer screening (Townsend JS *et al.* 2014). HPV testing can be a feasible screening option in low resource environments since testing can be done by self-sampling, and it usually requires fewer financial, technical, and human resources to obtain results.

MEXICO:
Introducing HPV testing and lessons learned

National and international scientific evidence shows that the human papillomavirus (HPV) test offers several advantages, among them:

- Greater sensitivity and specificity for detection of precursor lesions.
- Greater ease in sample collection.
- Greater screening coverage, especially in marginalized areas.

Furthermore, in a study in rural Mexico, comparing the effectiveness of HPV self-sampling with Pap tests, the HPV test was found to detect 4.2 times more women with invasive cancer than when using the Pap test (Lazcano-Ponce E *et al.* 2011).

For these reasons, Mexico first introduced HPV testing into the cervical cancer screening program in 2008, when Hybrid Capture 2 (HC2) was introduced in a pilot program in Morelos. HPV testing was expanded in 2009 to 21 states with 12 regional laboratories, prioritizing municipalities with a lower Human Development Index. In 2010, 32 states integrated HPV testing with HC2 for primary screening into their cervical cancer screening programs.

The introduction of this new technology in Mexico offers several lessons. These lessons are primarily related to the actual conditions in the health system where the technology is implemented. In particular, it was necessary to ensure that testing can be sustained over time without interruption and that follow-up and treatment services were available in the health system networks. Furthermore, health workers and the public needed to learn about HPV testing and accept the new technology. The following is a summary of the lessons learned:

- The biggest challenge was health worker acceptance of HPV testing, and changing the paradigm from Pap testing to HPV testing.
- Funding for the purchase of HPV test equipment and supplies needs to be ensured.
- An operational "platform" that ensures follow-up and treatment needs to be ensured.
- It is important to disseminate information among both physicians and the public about HPV infection, its relevance and meaning and the burden of cervical cancer.
- An algorithm for care needs to be developed and followed by all providers. The choice of follow-up algorithm is fundamental to the strategy's success.
- Planning services need to consider the increase in number of women who will need follow-up care.
- The HPV test results given to women need to be accompanied by appropriate counseling to decrease loss to follow-up care.

ARGENTINA:
Implementation of the demonstration project for the introduction of HPV testing in the province of Jujuy

In Argentina, the National Cervical Cancer Prevention Program was re-launched in 2008, with the view to increase screening coverage in the target population, assure laboratory quality, timely diagnosis and treatment for women with precancerous lesions, and to implement an information system for monitoring and evaluation (Arrossi S *et al.* 2015). This work was initiated in Jujuy, in Northwest Argentina, one of the provinces with the highest cervical cancer mortality. Initially, the cytology based screening program was strengthened by equipping pathology laboratories, providing them with computers and implementing a screening information system, a nationwide online database. By the end of 2011, Jujuy had successfully met the screening program goals for coverage, diagnosis, and treatment rates. All Pap tests and biopsies had been registered into the information system, enabling all stages of the screening process to be monitored, from determining the screening coverage, to actively searching women to provide results and assure follow-up care.

Based on this experience, the National Cervical Cancer Prevention Program began the Demonstration Project for the Introduction of HPV Testing in Jujuy Province in 2011. The project is part of a national strategy that also includes introduction of HPV vaccination for girls aged 11 years.

The four-year Jujuy Project (2011-2014) was a project to develop, implement, and evaluate the programming components of a screening strategy based on HPV testing. It involved the introduction of screening based on HPV testing for all women aged 30 years and older, along with cytology as a triage test in HPV positive women. Cytology is taken together with the HPV testing, but it is only processed in the laboratory if the HPV test result is positive. All women with abnormal cytology results are referred to colposcopy and biopsy if necessary.

The goals of the Jujuy Project were to introduce HPV testing in all of the 270 health facilities and to achieve 80% screening coverage of the target population -women aged 30 to 64 years- which corresponds to an annual screening goal of 18,700 women.

Project implementation included the following activities as key components:

1. Presentation of the proposal to the national authorities and to representatives of provincial health programs and healthcare providers.
2. Establishment of a scientific advisory council, with representatives from scientific societies, national universities, NGOs involved in cervical cancer prevention, and international organizations, such as PAHO and IARC.
3. Development of screening, diagnosis, treatment algorithms in consensus with the country's main scientific societies and design of the provincial referral and counter-referral network.
4. It was established that the HPV laboratory would be set up as a service of the cytopathology laboratory centralizing the reading of all cytologies for women aged 30 years and older.

5. Communications materials were designed, and trainings were held for all healthcare providers involved in cervical cancer prevention in the province, including health center directors, gynecologists, and more than 700 health agents who belong to the provincial health system.

An evaluation of the first year of implementation showed that by the end of 2012, all provincial health centers were offering the HPV test and that 22,834 women had been screened, of which 99% were aged 30 years and older. Of these women, 13% were HPV positive and in this subgroup, 807 women had an abnormal cytology. In total, 191 CIN2+ lesions were found, of which 68% had been treated by December 2013 (Arrossi S *et al.* 2015).

As part of the Jujuy Project, the EMA study was carried out to evaluate the acceptability and effectiveness of HPV self-sampling to increase screening coverage. This was a population-based cluster-randomized study, which compared the effectiveness of HPV self-sampling with HPV testing performed in health facilities by medical professionals. The EMA study found that 86% of women accepted HPV self-sampling, and four times more women were screened as a result of the self-sampling strategy as compared to facility based screening (86% versus 20%) (Arrossi S *et al*. 2015).

The Argentine Ministry of Health then decided to expand HPV testing to the rest of the country, phasing in implementation. In 2015, the provinces of Tucumán, Neuquén, Misiones, and Catamarca were added, and extension of the program to the province of Buenos Aires is expected in 2016.

Main lessons

- The introduction of testing needs to be part of a public health decision and strategy to reduce cervical cancer. Political commitment from health authorities is essential. Political commitment should result in actions to ensure coverage: the HPV test has an expiration date and needs to be used!
- Introducing HPV testing strengthens the impact of prevention activities but does not solve organizational problems; certain organizational conditions are prerequisites to testing implementation.
- Inclusion of testing needs the greatest consensus, agreement, and support possible from stakeholders in cervical cancer prevention.
- Inclusion of HPV testing boosts will, it is a mobilizing agent, but it does not supplant organizational work, with services, healthcare providers, and the community, necessary for taking a qualitative leap in cervical cancer prevention.
- It is possible to achieve high adherence to screening ages by professionals, but this can only be achieved through the coordinated action of all healthcare providers.
- Training/information of health professionals is essential to ensure they are all familiar with the test, its scientific basis, and that it is used as part of an organized program with a public health approach.

ANNEX:
FREQUENTLY ASKED QUESTIONS ABOUT HPV

What is the link between HPV and cervical cancer?

Cervical cancer is caused by persistent infection with high-risk HPV types. The infection can cause lesions on the cervix, which, over time, if they are not detected and treated, will lead to cancer. Lesion is the name given to changes in the cells of the cervix, caused by the HPV infection - they are painless, invisible, and cannot be felt.

Can all HPV types cause cervical cancer?

There are over 100 types of HPV. There are low-risk HPV types which can cause genital warts. **THESE ARE NOT RELATED TO CANCER**. There are high-risk HPV types which can cause precancerous lesions. **IF THE LESIONS ARE NOT DETECTED AND TREATED, THEY CAN SLOWLY DEVELOP INTO CANCER.**

How is HPV transmitted?

HPV is a virus that is transmitted through sexual contact. It is very common and most people will have an HPV infection at some point in their life, without having any symptoms.

Can men also be infected by HPV?

Yes, men can have an HPV infection, just like women. Cancers associated with HPV in men, include anal, penile and oral cancers, but these are less common.

Can HPV infection be prevented?

Yes, there are HPV vaccine which can prevent infection from HPV. They are safe and effective to prevent infection with high-risk HPV types that can cause most cases of cervical cancer. As a method, condoms help reduce the chances of infection but do not eliminate it completely, since the virus can be harbored in places in the genital and anal area that are not protected by a condom. Condom use is advisable since they can prevent other sexually transmitted infections and unplanned pregnancies.

Does HPV produce symptoms?

No, an HPV infection does not produce symptoms, which is why it is important for women to be screened for cervical cancer and be tested for HPV infection. HPV infection will most often disappear on its own, from the body's natural immune response, particularly in younger women.

Can HPV be treated?

There is no treatment for HPV infection, but there is treatment for the health effects of HPV infection. Warts can be removed. Cervical lesions can be treated, depending on the extent of the lesion, with freezing (cryotherapy), or removing (with LEEP or other methods) the HPV infected cervical cells.

Can a pregnant mother transmit HPV to her child?

This is infrequent, but in some cases if the woman has visible genital warts in the birth canal, she can transmit the virus to the baby.

Can pregnant women be tested for HPV?

No.

If the result of the test is positive, what does that mean?

It means that the presence of high-risk HPV has been detected in the cervix. A Pap test will detect whether the virus has caused any lesions. **HAVING HPV DOES NOT MEAN HAVING CANCER.**

If my HPV test was positive, what can I tell my partner?

Infection by HPV is very common. Most people are going to have it at some point in their lifetime. HPV can remain "silent" for many years before it is detected. This means that a person can become infected with the virus at some earlier time through sexual activity, and several years can go by before it is detected. As a result, ascertaining when the infection occurred does not make sense. This test detects high-risk HPV. It is important to remember that even though the man may have some of these HPV types, the virus is not treated. Hence, the woman will only receive treatment in the event that a precancerous lesion is detected in the cervix. In the event warts are diagnosed during the exam, caused by some low-risk HPV types, it is recommended that the partner sees a physician.

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