The concept of HPV tests adapted to emerging economies

INTERVIEW WITH
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PATH, Seattle, USA

Dr. Jeronimo, why is it important to introduce HPV testing in developing countries?
Cervical cancer is a completely preventable disease, but it is still one of the main killers of women in developing countries; in some areas of the world cervical cancer kills more women than maternal mortality. HPV testing is the only option we have for high-scale population-based implementation of screening. There are several reasons why HPV testing is the best choice: it is highly sensitive for detecting pre-cancer and cancer, and the results are reproducible and do not depend on the operator; its negative predictive value allows us to screen women only a few times in their life; but probably the biggest advantage of HPV testing is that we can use vaginal samples self-collected by women. Self-collection is the only realistic option we have for increasing coverage of screening in countries with limited number of trained health worker.

[Full interview on page 4]

Cervical cancer burden in the 56 poorest countries in the world

- 530,232 new cervical cancer cases are diagnosed annually worldwide
- 254,374 cases are from GAVI-eligible countries (48%)
- Cervical cancer is the leading cause of female cancer in GAVI-eligible countries.
- Age-standardized incidence rates in GAVI-eligible countries are 3-fold higher than in more developed regions and 1.5-fold higher than in less developed ones.
- Cervical cancer peak incidence in GAVI-eligible countries is observed in women aged 60 to 64, with estimated rates of 90 cases per 100,000, 5-fold higher than in more developed countries.

GAVI: Global Alliance for Vaccination and Immunization. GAVI is an international fund-raising institution devoted to facilitate access to vaccines. Adapted from: Human Papillomavirus and related cancers in the GAVI countries. A WHO/ICO HPV Information Centre Report. Vaccine 30, Supp. 4, 2012
Dear Colleagues,

It has become clear in our field that the HPV technologies and HPV-based preventive strategies are dramatically reshaping our understanding of cervical cancer prevention in both developed and developing countries. This interest translates into some 3,500 new scientific publications per year, multiple reviews, guidelines and recommendations that include not minor inconsistencies in the messaging. Modern forms of independent and simplified communication need to be in place to facilitate dissemination of the progress in the field.

We are now entering a down-to-earth period in which decisions are being made and where the state of opinion of the medical and health professionals is critical. This includes practical and implementation issues, such as the introduction of HPV testing or the support to the vaccination programs, but also the challenging research areas such as the implication of HPV in head and neck or skin cancers. At the end of the day, it is the status of the medical opinion that forces public health recommendations and shapes the change.

For the last 15 years the newsletter HPV TODAY has enjoyed a significant success as a reader-friendly and quality-assured source of information for clinicians. This project is now terminated, giving way to a novel project, HPV WORLD, a publication that will be devoted to generating a summaries of the results of complex research areas in a reader-friendly manner, with ample dissemination in the professional networks and interactive features.

HPV WORLD will include a new technical editor and a new team in graphics design/technology that will allow free e-circulation of the materials as well as allowing the production of high quality printed version for targeted distribution at relevant events and meetings. The operational mode will be largely based on invitations to consolidated teams of authors to produce topic-specific compact summaries of the scientific evidence with special interest in the implications in clinical practice. HPV WORLD will preserve its editorial independence in terms of authorship invitations and selection of contents that makes it particularly attractive to medical audiences.

We have an exciting period ahead of us and these academic vehicles of communication are likely to become precious links between science and clinical practice. Building on over 15 years of the HPV TODAY experience, HPV WORLD is geared at being one of these vehicles, perhaps the most consistent and valued in the HPV field. Looking forward to a sustained collaboration with many of you.

Best regards and a healthy 2017.

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The concept of HPV tests adapted to emerging economies

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Is HPV testing in self-collected vaginal samples really a game-changer in cervical cancer screening?
It is certainly a game-changer. HPV testing in self-collected vaginal samples is the only option for breaking some of the barriers for increasing coverage of screening, and HPV testing is the only screening test that can be run using those samples. The other screening tests require a pelvic examination which is not acceptable in many cultural groups. In most places women have a very busy schedule and many other competing obligations, and they do not have time to visit a health facility for a pelvic examination. There is a great experience in Argentina showing that self-collection increased the coverage of screening four times compared with Pap screening. Additionally, multiple studies have shown that HPV testing using self-collected vaginal samples is more sensitive than Pap smear for detecting pre-cancer.

But is self-collection of vaginal samples acceptable by women?
This is great question because there is always some uncertainty about the acceptability of self-sampling by women. In my own experience in several studies in India, Uganda and Central America, self-collecting a vaginal sample is highly acceptable by women from multiple different continents, cultures or beliefs. I also found that the medical community underestimates the acceptability of self-sampling by women in their communities, and also underestimate the proficiency of women for collecting those samples. I participated in several interventions using vaginal self-sampling in almost 100,000 women in multiple countries, and in all of them self-sampling was highly acceptable, and easy to understand and perform by women.

Are the developing countries ready for the introduction of HPV testing?
I think that many developing countries are ready for implementing HPV testing in their populations. One of the barriers in the past was the lack of recommendations for HPV testing for primary screening, but that barrier does not exist anymore; a couple of years ago the World Health Organization published new recommendations and HPV testing is already included as one of the options for screening. More recently in 2016, the American Society of Clinical Oncology (ASCO) published new recommendations for cervical cancer screening and in summary, regardless of the resources available in any given setting, HPV testing is considered the first choice for screening. Countries are now using these new recommendations for updating their own national guidelines. Another limiting factor for the introduction of HPV testing was the price of the tests available in the market; but this is also changing. Now we have countries such as Guatemala, Honduras and Nicaragua using careHPV in their population-based programs at a price of 5 dol-

“The World Health Organization published in 2013, new recommendations where HPV testing is already included as one of the options for screening. More recently in 2016, the American Society of Clinical Oncology (ASCO) published new recommendations for cervical cancer screening and regardless of the resources available in any given setting, HPV testing is considered the first choice for screening.”
“We already have multiple good options for primary and secondary prevention. Now it is the time to think out-of-the-box for planning new options to deliver the services”

Are the HPV current tests suitable for developing countries?
There is always the tendency to wait until we have the “perfect test” to start implementing HPV testing in developing countries, but the HPV test is just one of the several components we need for screening and treating pre-cancerous lesions. We are using careHPV in the national programs of several countries and the test is working very well. It has been mentioned that the problem with careHPV, or any other batch testing, is that we need to have 90 samples to run the test, but in many places there is the need for screening thousands of women, and we have also a limited number of lab technicians. Therefore, being able to run 90 samples in a 3-hour period makes a more efficient use of the limited lab tech capacity.

Delaying implementation of this technology has a huge impact in human life, to be more specific, hundreds of thousands of women die every year due to cervical cancer, and thousands of those lives can be prevented if we do not delay the implementation of the technologies currently available. If any new and better technology comes later, it could be easily incorporated if the other components of the prevention program are already in place.

What could we do for speeding up the reduction of cervical cancer in developing countries?
We do not need more pilots for cervical cancer prevention; we already have multiple good options for primary and secondary prevention. Now it is the time to think out-of-the-box for planning new options for delivering the services. We need to scale-up the implementation of services in more than 100 developing countries in a short period of time, one or two decades at the most. Therefore, we need innovative options for training health care providers in all regions, to make HPV testing available to countries with the higher burden of disease, and to make new treatment options available for those in need. It is urgent to evaluate new strategies for one-in-a-lifetime interventions, strategies such as the HPV Faster approach to do screening and vaccination in one visit. Millions of women will die if we do not act fast within the next few years.
Despite the success of cervical cancer control programs in high income countries, where extensive high quality screening has been in place for decades, the disease is still a leading cause of cancer death among women in low and middle-income countries (LMIC), where 90% of the disease occurs. Large disparities in access to medical services, in particular screening, explain this situation. Repeated screening of a large fraction of women with cervical cytology and referral to colposcopy and treatment of cervical cancer precursors has been the basis of most screening programs. However, it has proven extremely difficult to successfully implement such programs in developing countries.

Recent developments in the understanding of the etiology and natural history of cervical cancer have resulted in very promising new prevention tools, representing a tremendous opportunity for developing countries. The availability of safe and effective vaccines against the major HPV genotypes promises to dramatically reduce infection, precancer and eventually invasive cancer. More than 70 countries have already established national programs for adolescent women, but the areas that need it most are still lagging behind in implementation of vaccination (1).

**The challenges and limitations of HPV screening**
For secondary prevention, the main development is the availability of highly accurate and reproducible HPV DNA or RNA methods that permit detection of cervical neoplasia with higher sensitivity than cytology. Consequently, its high negative predictive value for disease development in the following years allows extension of the screening intervals to 5 or more years. Even one HPV test with proper follow-up has been shown to reduce cervical cancer mortality.

The availability of new strategies may be an opportunity for countries to organize screening programs assuring proper coverage of the population, ideally in population-based (organized) screenings to assure true coverage of at least 80% (distributed over the number of years in the screening interval). Even more importantly, programs need to guarantee proper follow-up and treatment of all lesions detected according to the specified protocols, including referral and treatment of advanced cancer and palliative care when required.

The problem with testing for HPV infection, the etiologic agent of cervical cancer, is that only a few women who have HPV infections have or will develop pre-cancerous disease in the future; the vast majority of cervical HPV infections, regardless of age and HPV type, regress spontaneously. Therefore, the specificity of the test is sub-optimal and there is a need to define cost-effective clinical management strategies for HPV positive women, to assure that all those who require an intervention to prevent cervical cancer are treated appropriately.
avoiding excessive and costly referrals and reducing potential overtreatment. The decision has to take into account the resources available, and the feasibility of proper follow-up and the woman’s preferences.

Managing HPV positive women
The most radical approach is to treat with ablative procedures all HPV positive women over 30 years of age, proposed as one of the alternatives in the recent WHO recommendations (2). This option may be considered for areas with limited resources where colposcopy and pathology are not available or difficult to access, and where repeated visits or follow-up are impractical. In El Salvador and other Central American countries, this approach is being used with treatment of about 10% of women. Treating all HPV positive women evidently results in treatment of many women who do not have current disease, possibly up to 80% of those treated, but it also treats a number of women who will develop disease in the future, particularly those who already harbor persistent infections. In addition, ablation of the transformation zone might destroy the specialized cells where cervical cancer originates and thus potentially prevent future disease, although this needs further research3.

The main problem is that this alternative requires setting up treatment facilities for large numbers of women and the logistics for ablative treatment are more difficult than previously thought. New simplified treatment methods promise to solve many of these problems. Another problem is that in some areas (e.g., some locations in Africa) the fraction of HPV positive women is very large even in women over 30, particularly among HIV positive women. The program has reported good compliance and has been shown to be cost effective4. In the context of high prevalence and high frequency of multiple infections with oncogenic HPV types of limited malignant potential, one of the options is to design tests detecting a more restricted group of HPV types. This requires further investigation.

“For secondary prevention, the main development is the availability of highly accurate and reproducible HPV DNA or RNA methods that permit detection of cervical neoplasia with higher sensitivity than cytology. Consequently, its high negative predictive value for disease development in the following years allows extension of the screening intervals to 5 or more years. Even one HPV test with proper follow-up has been shown to reduce cervical cancer mortality.”

The triage choice
In order to reduce overtreatment, we have to include some form of triage, taking into account that, unless the specimen for triage is collected at the same time as the HPV test, it may require additional visits and produce loss to follow-up. The traditional method used in cytology-based screening programs is referring all HPV positive women to colposcopy, biopsy and treatment of histologically confirmed lesions. This is very costly and requires multiple visits, infrastructure and equipment often unavailable in low resource settings. Furthermore, colposcopy is a method of suboptimal sensitivity that requires extensive training of highly specialized staff and quality assurance5.

Cytology
Another triage method, currently in use in several ongoing screening programs is cytology, with referral to colposcopy (or potentially treatment) of all women with abnormalities (usually ASCUS +). The reduction in workload, the knowledge of the presence of HPV by the cytotechnologist and the increase in the frequency of lesions among HPV positive women are expected to improve the performance of cytology. This method is likely to be effective in areas where cytology is well established but it remains to be proven its value in other locations. The protocol for clinical management of HPV positive, cytology negative women remains unresolved and their follow-up is likely to produce losses to follow-up.
HPV World

**HPV typing**
Another alternative for triage is referring to colposcopy or treatment only women with the most carcinogenic genotypes (i.e., HPV 16, 18, 45 or other combinations). This approach has been shown to be at least as sensitive as cytology but by design misses lesions associated with other HPV types. A combination of genotyping with cytology is promising in some settings.

**Visual inspection**
Visual inspection with acetic acid, considered a useful alternative as a primary screening method in settings where other approaches are not available has also been proposed as a triage method and is included in the WHO recommendations', but there are very limited data on its performance as a triage method in the context of an HPV based screening program.

**Molecular biomarkers**
There are a series of molecular methods that have shown promise, particularly if they can be done in the same specimen used for HPV detection, including detection of P16/Ki67 in exfoliated cells and detection of E6 oncoproteins.

A synthesis of the advantages and disadvantages of these alternatives are summarized in Table 1

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**TABLE 1**
ADVANTAGES AND DISADVANTAGES OF CURRENT alternatives for clinical management of HPV positive women

<table>
<thead>
<tr>
<th>ADVANTAGES</th>
<th>DISADVANTAGES</th>
</tr>
</thead>
</table>
| **Treat all** | High sensitivity  
Possibility of immediate treatment  
Prevention of future disease | High overtreatment  
Logistics of ablative treatments |
| **VIA** | Simple, inexpensive | Difficult to standardize  
Variable results  
Loss of sensitivity |
| **Colposcopy-biopsy** | Accepted in medical community  
Specific, limited overtreatment | Complex and expensive  
Specialized staff and training  
Loss of sensitivity |
| **Conventional cytology** | Highly specific  
Present in many areas  
Reduced burden and knowledge of HPV positivity can improve performance | Difficult to achieve quality  
Specialized and highly trained staff  
Poor sensitivity |
| **Liquid based cytology** | Similar to conventional  
Can be done on same specimen as HPV test | Similar to conventional cytology |
| **Limited Genotyping (16/18)** | Automatic result with the HPV test  
Sensitivity similar to cytology | Limited sensitivity by design  
(other HPV types are missed) |
| **Extended Genotyping (i.e. 5+types)** | Further risk stratification based on individual genotypes | May require additional specimen processing. Clinical algorithms not obvious |
| **P16/ki67** | Disease specific  
Training not so complex  
Automated processing | Logistics and technology similar to conventional cytology |
| **E6 protein** | High specificity | Limited sensitivity by design |

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**References**
Mortality rates of the eight most frequent cancer sites in women by level of development

**GRAPHIC 1**

**MORE DEVELOPED REGIONS**

<table>
<thead>
<tr>
<th>Cancer Site</th>
<th>Mortality Rate per 100,000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast</td>
<td>15.3</td>
</tr>
<tr>
<td>Lung</td>
<td>13.6</td>
</tr>
<tr>
<td>Colorectum</td>
<td>9.7</td>
</tr>
<tr>
<td>Ovary</td>
<td>5.1</td>
</tr>
<tr>
<td>Pancreas</td>
<td>5.1</td>
</tr>
<tr>
<td>Stomach</td>
<td>4.7</td>
</tr>
<tr>
<td>Cervix uteri</td>
<td>3.1</td>
</tr>
<tr>
<td>Leukaemia</td>
<td>2.9</td>
</tr>
</tbody>
</table>

**GRAPHIC 2**

**LESS DEVELOPED REGIONS**

<table>
<thead>
<tr>
<th>Cancer Site</th>
<th>Mortality Rate per 100,000</th>
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<tbody>
<tr>
<td>Breast</td>
<td>10.8</td>
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<tr>
<td>Cervix uteri</td>
<td>9.8</td>
</tr>
<tr>
<td>Lung</td>
<td>9.7</td>
</tr>
<tr>
<td>Stomach</td>
<td>8.1</td>
</tr>
<tr>
<td>Liver</td>
<td>7.2</td>
</tr>
<tr>
<td>Colorectum</td>
<td>5.4</td>
</tr>
<tr>
<td>Oesophagus</td>
<td>4.7</td>
</tr>
<tr>
<td>Ovary</td>
<td>3.1</td>
</tr>
</tbody>
</table>

**GRAPHIC 3**

**GAVI-ELIGIBLE COUNTRIES**

<table>
<thead>
<tr>
<th>Cancer Site</th>
<th>Mortality Rate per 100,000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cervix uteri</td>
<td>15.9</td>
</tr>
<tr>
<td>Breast</td>
<td>12.3</td>
</tr>
<tr>
<td>Stomach</td>
<td>4.0</td>
</tr>
<tr>
<td>Lung</td>
<td>3.9</td>
</tr>
<tr>
<td>Ovary</td>
<td>3.7</td>
</tr>
<tr>
<td>Liver</td>
<td>3.7</td>
</tr>
<tr>
<td>Oesophagus</td>
<td>3.7</td>
</tr>
<tr>
<td>Colorectum</td>
<td>3.3</td>
</tr>
</tbody>
</table>

HPV and related cancers in the GAVI countries. Vaccine Vol 30, Supp 4 2012
Women have problems accessing screening services due to a complexity of factors that include socio-economic conditions, subjective factors and cultural values and norms, and health services organization and management. Self-collection of a vaginal sample for HPV testing gives them the possibility of collecting the sample by themselves, in a private room, with no other person looking at their body. This unique characteristic of HPV-testing makes it a revolutionary tool for screening programs. After decades of work to understand and try to overcome barriers faced by women to access screening, the medical community has a tool that allows overcoming some of the most important problems, for example the shame of the gynecological visit or the scarcity of sample takers in remote areas. Studies carried out in different settings have shown that it is highly accepted by women. A study carried out in Argentina where women had the option to choose showed that women preferred self-collection to clinician-collected HPV testing, even when they lived in rural areas and when self-collection was offered by male community health workers (CHWs).

HPV-self collection is a highly effective method to detect precancerous disease and cancer, especially when compared to cytology. It is less sensitive than clinician collected HPV-testing, and that is why self-collection has been mainly recommended for screening under-users. However, women get screened at great cost in terms of loss of workdays, childcare limitations, and psychological stress. Therefore, self-collection could be offered to all women and allow them to choose based on their preference. This would allow including women preferences as a decisive factor in the equation to recommend and choose between two screening methods that are both highly effective. As the difference in sensitivity might be reduced with PCR based methods, more evidence is needed about how these tests perform for self-collection in programmatic conditions.

Several studies have used different methods to offer women HPV self-collection. In European studies, women received self-collection through the mail system, and this has resulted in a moderate increase in screening uptake. In several studies carried out in middle/low income settings, self-collection was offered at home by a health provider, such as CHWs.

“The ideal self-collection test would allow for screening and triage in the same sample and provide results immediately. This would not only reduce the number of visits, but also give health providers the possibility of providing on-the-spot appointments for next steps, and specific counseling targeted at increasing adherence to follow-up among women at high risk of cervical cancer.”

Laboratory technicians in a screening site in Argentina
“Self-collection of a vaginal sample for HPV testing gives women the possibility of collecting the sample by themselves, in a private room, with no other person looking at their body. This unique characteristic of HPV-testing makes it a revolutionary tool for screening programs”

In this randomized trial in Mexico, some 25,000 women were offered either self sampling advise and devices or conventional gynecological examination for a PAP smear test. Participation rates were 98% in the self sampling arm vs. 87% in the Pap test arm. Self samples were then tested for HPV DNA using Hybrid Capture 2 (HC2) in a centralized laboratory. The number of screen-positive women was 9.8% in the HPV arm vs. 0.38% in the Pap smear arm ( cutoff ASCUS+). However the number of CIN 2+ cases or invasive cancer cases was 3 to 4-fold higher in the self sampling and HPV testing arm (RS: 3.4 and 4.2) compared to the Pap smear arm. Although the PPT of a positive cytology was much higher than the one for HPV The authors concluded that the high sensitivity of the self sampling and HPV test was a strong asset in populations with limited opportunities for screening in their lifetime.

**TABLE 1**
Self-collection of vaginal specimens for HPV testing in cervical cancer prevention (MARCH study): a community-based randomised controlled trial in Mexico

<table>
<thead>
<tr>
<th></th>
<th>SELF SAMPLING AND HPV SCREENING</th>
<th>INVITATION FOR A PAP SMEAR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number</strong></td>
<td>12.330</td>
<td>12.731</td>
</tr>
<tr>
<td><strong>Positive Test</strong></td>
<td>9.8%</td>
<td>0.38%*</td>
</tr>
<tr>
<td><strong>CIN 2+ x10^4</strong></td>
<td>117.4 (RS: 3.4)</td>
<td>34.4 (Ref.)</td>
</tr>
<tr>
<td><strong>Invasive cancer x10^4</strong></td>
<td>30.4 (RS: 4.2)</td>
<td>7.2 (Ref.)</td>
</tr>
<tr>
<td><strong>PPV CIN 2+</strong></td>
<td>12.2%</td>
<td>90.5%</td>
</tr>
</tbody>
</table>

HPV= human papillomavirus. CIN=cervical intra-epithelial neoplasia. PPV=positive predictive value. (RS, Ref) = relative sensitivity compared to the reference | *: threshold of abnormality defined as ASCUS+

References


Hybrid Capture 2 (HC2) was the first FDA approved HPV test in early 2000s, but for multiple years this technology was cost prohibitive for low and middle-income countries (LMICs). Due to the need of having a more affordable HPV test, the careHPV test was developed by Qiagen with support from PATH and the Bill and Melinda Gates foundation. This technology does not require running water, air conditioning or sophisticated lab infrastructure. (Figures 1 and 2) Processing careHPV testing has been relatively easy to learn and implement by different health system providers including cytologists and laboratory technicians. The other major advantage is that the price of the test is expected to be in the range of ~5 dollars per test, with proven quality standards.

The 2013 WHO Guidelines include HPV testing for primary screening, and a variety of follow-up options for HPV positive women, and countries can now consider restructuring their national programs using HPV testing. The high sensitivity of the test allows increasing the screening intervals, and provides an opportunity to increase coverage in high-risk populations by using self-collected vaginal samples. Self-collection of vaginal samples can be done within the privacy of their home, close to their work places, or other facilities in the community.

Our experience with the careHPV test is based on the implementation of HPV testing we are doing in Guatemala and El Salvador. These are essential projects because it is the first time in LMICs that HPV testing is being implemented in their public health systems through national governments. The experience that the Central American countries are obtaining with the introduction of careHPV in their public systems gives us the opportunity to identify some advantages and limitations when working with that test.

Advantages of the careHPV test

A screening test for LMICs must be simple to implement, accepted by the users, and economically sustainable. Currently the careHPV test is the only test that has been proven to have such characteristics.

“The learning curve for technicians in the processing of the tests has been easily achieved during training. Multiple healthcare professionals have been trained in our countries, including laboratory technicians and cytotechnologists. Trained technicians have also shown that competencies are also easily replicable in training.”
Laboratories in many developing countries often have very limited infrastructure and resources.

Cost
The cost of the careHPV is one of the biggest advantages and should be independently analyzed at the time of implementing a strategy for screening of cervical cancer with DNA tests in places where resources are limited. In addition, the cost of a screening program could also be influenced by the self-sampling strategy, which allows for the reduction of other costs associated with sample collection (speculum, gloves and personnel time). Several studies have shown that careHPV testing with proper follow up is a very cost effective option.

Adaptability
In our experience, the technology is easily adapted to laboratories in different localities, even in places where there is not an actual laboratory. The minimum requirements for the testing site consist of a table of 2 meters by 60 centimeters, three electrical outlets, a backup battery and a chair. The learning curve for technicians in the processing of the tests has been easily achieved during training. Multiple healthcare professionals have been trained in our countries, including laboratory technicians and cytotechnologists. Trained technicians have also shown that competencies are also easily replicable in training.

We want to emphasize the importance of self-sampling in a population-based national screening program. Self-sampling closes many of the cultural, behavioral and practical gaps that are found in cervical cancer screening, improves adherence to screening, and facilitates access to screening overcoming limitations such as distance to health facilities, lack of transportation to health services, work schedule conflicts, shame of pelvic exams, etc. Self-sampling with careHPV is accepted by 76% of women in Guatemala (4).

Finally, our experience shows the need to pilot or demonstrate feasibility within a country, which is essential in order to learn as the intervention grows in scale. It is crucial to emphasize that even though there are new options for screening, it is as important to ensure that proper management must be conducted for HPV positive women. Now with the new WHO Guidelines as a reference, HPV screening and follow up algorithms can be assessed based on each country’s resources.

References
Cancer of the cervix uteri is the 4th most common cancer among women worldwide, with the highest incidence in low and middle income countries (LMIC), particularly in Sub-Saharan Africa\(^1\). Affordable, practical and effective cervical screening strategies are urgently needed in many LMIC with WHO recommending introduction of HPV testing as a primary screening tool (rather than cytology), with or without Visual Inspection with acetic acid (VIA)\(^2\).

However, there are few HPV tests suited to LMIC. The well-established Hybrid Capture 2 (HC2) assay led to development of careHPV\(^3\) which uses minimal electricity and water, which is now readily available. The GeneXpert Instrument System (Xpert) (Cepheid, Sunnyvale, CA, USA) offers real-time polymerase chain reaction (PCR) based assays with all reagents and process contained within a single-use test cartridge. Instruments are available in 1, 2, 4 or 16-module configurations. Xpert MTB/RIF assay has become widely used in LMIC for rapid identification of \(\text{ra}\) and drug resistance. The recent availability of Xpert HPV on the same platform may provide a suitable \(\text{ra}-\text{HPV}\) test for LMIC as it requires minimal training, can be done in clinic side-rooms and gives highly reproducible results\(^4\).

**Xpert HPV Assay**

Xpert\(^\circledR\) HPV is a qualitative in vitro test for the detection of HPV in liquid based cytology (LBC) specimens collected in PreservCyt\(^\circledR\). The test detects DNA of 14 high-risk HPV types. Each HPV test can be completed in around 1 hour, allowing same day screening and treatment. A specimen adequacy control (SAC) is provided which detects a single copy human reference gene in a separate channel. Three channels provide partial genotyping: HPV 16; HPV 18 and 45 in a pooled result; and other hr-HPV types in an aggregate result for three groups: [HPV 31, 33, 35, 52, 58]; [HPV 51/59]; and [HPV 39, 56, 66, 68].

**Results from Nkhoma Hospital, Central Malawi\(^5\)**

Xpert HPV proved simple to perform in a small peripheral laboratory. Training of laboratory staff proved straightforward and could be cascaded to lower skilled personnel. Hands-on time per sample was only a few minutes. Multiple internal quality control (IQC) samples showed high reproducibility and consistent Ct readings (Cycle threshold for positivity). Few errors were reported, usually due to failure to add sample or inadequate mixing. Valid HPV results were available from 98.3% of sampled women.

Over 92% of 750 specimens came from unscreened women aged 20-60 years. Overall HPV positivity was 19.9%, with detection of HPV ‘other’ being more than twice as frequent as HPV 16 or HPV 18/45 (64.4 % versus 24.2% for each of HPV 16 or 18/45. HPV 31-related types (HPV 31, 33, 35, 52 or 58) were the most prevalent. HPV positivity was much higher in women known to be HIV positive (43.4%).

**Advantages and disadvantages of Xpert HPV in Africa/LMIC**

Our Nkhoma results showed that results could be returned to the clinic within 2 hours of sample collection. This time frame may be acceptable to many women who come early to clinics and are willing to wait, in preference to returning for a second visit should treatment be necessary. Xpert HPV could
therefore be added into a same day ‘screen and treat’ service, but would be more sensitive and specific than VIA. However, with provider taken specimens, HPV positive women have to be examined twice. Self-sampling by women in a private cubicle as soon as they arrive at the clinic would overcome this problem. While the low specificity of HPV tests for significant disease is a major limitation to use as the only screening test, the objectivity and high reproducibility linked to VIA of positives would avoid many false interpretations, while improving utility and saving costs in a screen and treat programme. All HPV tests remain expensive and although Cepheid has a separate pricing system for LMIC, the cost is far beyond the budget available for screening in many countries. Furthermore, there is considerable wastage with the assay as currently validated. PreservCyt pots are expensive, designed for cytology screening regimes and their use for HPV screening alone is wasteful. Availability and use of a high alcohol content transport medium is also not ideal and the pots come with 20mls PreservCyt when only 1ml is needed for Xpert HPV. These practical issues need to be addressed.

Conclusions
Xpert HPV offers several advantages, particularly in its ease of use by non-laboratory staff with minimal training, rapid turn-around time and reproducible results with the added bonus of partial genotyping. A 1-2 hour turn-around time between clinic and testing environment would allow integration into a same day ‘screen and treat’ service. However the cost of Xpert HPV kits remains prohibitive for most LMIC and much more attention to the collection of specimens rather than performing the test is required if Cepheid is to obtain a significant slice of a potentially lucrative, future HPV market in LMIC.

References


**FIGURE 1**
Xpert HPV process from specimen collection to test result

**FIGURE 2**
Example of result output from a clinical sample from Nkhoma Hospital. Multiple infection detected with HPV 16 (blue), HPV 18/45 (pink) and HPV ‘other’ (green; P3=HPV 31 related)

**TABLE 1**
Xpert HPV results in PreservCyt specimens from women attending VIA clinics in 2014-15 at Nkhoma Hospital Central Malawi

<table>
<thead>
<tr>
<th>Collection date</th>
<th>No of specimens with valid HPV results</th>
<th>No of specimens where HPV not detected</th>
<th>No of specimens where HPV detected</th>
<th>HPV 16</th>
<th>HPV 18/45</th>
<th>HPV Other</th>
<th>HPV 31+</th>
<th>HPV 51/59</th>
<th>HPV 39+</th>
<th>Multiple infections</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jan- Dec 2014</td>
<td>604</td>
<td>484</td>
<td>120</td>
<td>30</td>
<td>27</td>
<td>77</td>
<td>47</td>
<td>15</td>
<td>21</td>
<td>17</td>
</tr>
<tr>
<td>Jan - April 2015</td>
<td>146</td>
<td>117</td>
<td>29</td>
<td>6</td>
<td>9</td>
<td>19</td>
<td>12</td>
<td>2</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Total</td>
<td>750</td>
<td>601</td>
<td>149</td>
<td>36</td>
<td>36</td>
<td>96</td>
<td>59</td>
<td>17</td>
<td>26</td>
<td>23</td>
</tr>
</tbody>
</table>

Percentage of total collected: 98.3% 80.1% 19.9% 4.8% 4.8% 12.8% 7.9% 2.3% 3.5% 3.1%

Percentage of total valid specimens: 24.2% 24.2% 64.4% 39.6% 11.4% 17.5% 15.4%

* HPV 31+: 31,33,35,52,58 | HPV 39+: 39,56,66,68
Experience with careHPV implementation in China

Between the years 1989 and 2008, the morbidity and mortality of cervical cancer among Chinese women increased continuously, especially for rural women which the age-adjusted morbidity in 2008 was three times higher than 1989 and the adjusted mortality nearly doubled. The average age of women diagnosed as cervical cancer was five years younger. Effective preventive measures were imminently needed to curb the deterioration.

In 2005, Shenzhen, a prosperous special economic zone, and Xiangyuan, a poverty-stricken county in Shanxi province, were firstly provided resources for early diagnose and treatment for women at risk of cervical cancer, aiming to evaluate different screening models for abundant urban areas and underdeveloped regions respectively. Shortly after that, in 2006-2009, the central government expenditure transfer project for cervical cancer early detection and treatment was conducted in 43 rural sites, covered more than 80,000 women. Health providers were trained to use visual inspection via acetic acid or Lugol’s iodine (VIA/VILI) for primary screening and diagnosed by biopsy after colposcopy. In 2009, the
government announced a more ambitious screening project for cervical cancer, which 10 million aged 35–59 women living in 220 rural county areas were screened by VIA/VILI or cytology in three years. This project was tripled since 2012 that screen 10 million women in over 1,100 counties every year. Cytology and VIA/VILI were used for primary screening, but at that time costly and complicated HPV testing was not an option. Therefore, seeking for efficient and affordable technology for cervical cancer screening in low-resource settings has been an important issue in the last two decades.

In 2007, careHPV was successfully shown to be accurate, fast, reproducible, and low-cost by our team, cooperating with PATH and QIAGEN Inc. Personnel with limited laboratory experience could perform it correctly after a simple training procedure, which is promising for use in low- and middle-income countries (LMICs). Besides, the following study implied that careHPV 16/18/45 might be used in LMICs for triaging HPV-positive women.

In 2007, careHPV was successfully shown to be accurate, fast, reproducible, and low-cost by our team, cooperating with PATH and QIAGEN Inc. Personnel with limited laboratory experience could perform it correctly after a simple training procedure, which is promising for use in low- and middle-income countries (LMICs). Additionally, the study implied that careHPV 16/18/45 might be used in LMICs for triaging HPV-positive women.

The delegates from International Agency for Research on Cancer (IARC)/World Health Organization (WHO) and Union for International Cancer Control (UICC) site-visited the careHPV manufacturer located in Shenzhen in 2010 and the test was approved by China Food and Drug Administration (SFDA) in the year 2012 after finishing registration clinical trials. Inspired by the experience from China, more implementing studies were conducted in LMICs, such as Nicaragua, Uganda, and Laos. We believe more women from developing countries would be benefited after careHPV test get the pre-qualification from WHO. HPV testing is now recommended in the WHO guidelines as primary screening and it hopefully will be gradually implemented in the government supported screening program in China. In the year 2015, a nationwide implementing demonstration program of HPV testing as the primary screening was launched, aiming at evaluating the real world performance by local health providers and Women-Children Health Center with fundamental infrastructures. A total of 33,000 women 35–64 years old in 11 rural sites were randomized into three arms and screened by pap smears, VIA/VILI or careHPV test respectively in the first year. Then, in the third year, the participants will be screened by the three tests simultaneously. The clinical utility, health economic effectiveness, and acceptability of careHPV test among screened women, health providers, and government officials will be evaluated. The final results of the 3-years study are expected to provide more convincing evidence and practical advice for policy maker in future population-based HPV screening programs for about 280 million women age 35–64 in whole China.

Another inspiring news is that Ordos, a city located in Inner Mongolia which consisted of 9 counties/districts and nearly 2 million residents, is the first city in China to use careHPV test as primary screening for all women age 35–64 years. HPV-positive women are triaged with VIA/VILI or cytology, dependents on the capability of the local Women-Children Health Center. Approximately 340,000 eligible women will be screened in five years interval. QIAGEN offers the testing kits at an affordable price as promised for public health program and the onsite technical support. The screening cost will be covered by the government expenditure of Ordos. By multi-efforts, the implementing of careHPV has made a great improvement in China. It is the most promise candidate test for HPV as primary screening of cervical cancer among 5 million women in fiscal year 2016–2017.

References


Incidence and mortality from cervical cancer remain high in Central America; worldwide, only Africa and Melanesia experience higher rates of this largely preventable disease. Although many Central American ministries of health invested in Pap-based cervical cancer screening programs for several decades, these efforts had limited impact. Highly-sensitive HPV testing for primary screening, at increasingly accessible prices, and the option of using self-collected vaginal samples caused Central American countries to look to HPV testing to overcome infrastructure barriers and improve the efficacy of their screening programs. El Salvador, Guatemala, Honduras, and Nicaragua are now implementing and evaluating HPV screening in select areas, with plans to scale up this strategy nationally if results are favorable. Other emerging economies can learn from the Central American experience of planning for and implementing HPV testing, including benefits and challenges identified to date. Months of planning for test introduction preceded the implementation. Key preparatory activities included updating national guidelines to include HPV screening and treatment algorithms; training personnel in HPV testing basics and laboratory procedures; distribution of necessary supplies; updating or developing health information systems; and strengthening triage and treatment networks. Most countries are implementing HPV testing in self-sampling modality to make the test more accessible for women and alleviate congested health facilities. This required developing community outreach strategies including visual materials with self-sampling instructions. Common challenges across the countries emerged during the planning process and initial implementation. Since these countries had some Pap infrastructure in place, implementing HPV testing required a paradigm shift for health personnel and women. This required training in the latest evidence in cervical can-
In the course of planning for and implementing HPV screening, several advantages for emerging economies implementing this strategy have become increasingly apparent. Preliminary data on positivity rates for HPV tests in these countries, as well as follow-up and treatment rates, indicate that the detection rate for CIN2+ is higher with HPV testing than what the countries were achieving with the Pap-based programs. Self-sampling is highly accepted by health workers and women in the community. Countries are also finding that it is easier to reach women at locations such as basic health posts, homes, and markets. Additionally, they observed that women never screened before, or hesitant to undergo pelvic examination, are accepting self-collection of vaginal samples for HPV testing. Since HPV testing permits a longer interval between screenings of HPV-negative women (5 years), countries are increasingly able to focus their cervical cancer prevention resources on HPV positive women.

The challenges we observed in Central America also provide important lessons for other emerging economies. The up-front costs of changing an HPV screening strategy are significant and need to be carefully quantified. The least expensive commercially available test—careHPV™—costs US$5 per test and also requires the purchase of ancillary supplies; this is in reach for Central American countries, but could be difficult for other economies to afford. Pooled procurement mechanisms such as the Pan American Health Organization’s Strategic Fund, or the United Nations Population Fund (UNFPA) procurement system, represent possible opportunities to obtain more preferential pricing in the future.

Additional initial costs include training of health care personnel, as well as making infrastructure adjustments such as creating capacity for cold storage of test reagents. In addition, countries must be prepared to undergo the challenging work of changing paradigms from previous screening strategies or building from a weak or non-existent screening system.

Based on our experience in Central America to date, we expect the benefits of HPV screening to justify the costs in emerging economies. Over time, we expect HPV testing to lead to a decrease in cervical cancer cases in Central America, especially for women with limited health care access, benefitting women and families and avoiding the economic and social losses caused by this preventable disease.

Self-sampling for HPV testing is allowing cervical cancer screening programs to reach women that were never screened in the past or had irregular screening. In Nicaragua 85% of women that are being screened using self-collection approach are under-screened or never-screened women, and that is the result of the commitment from the government. That political will was translated into a clear directive from the government officials to go to the communities and look for women with inadequate screening history. There were multiple factors why these women were not screened in the past, most commonly was the resistance to get a pelvic evaluation, as well as having multiple obligations at home and work. Even though self-sampling is being very effective reaching these women, we have the need to create innovative approaches to follow and treat women with a positive HPV result to overcome the factors limiting the access of these women to the health facilities. Some approaches to consider is to create campaigns for treatment at the community level.

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References

Cervical cancer in Uganda is the most common cancer among women in Uganda, a country with one of the highest rates in the world (age standardized incidence rate 44.4 per 100,000)\(^1\). More than 80% of women are diagnosed with late-stage cancer, and women living with HIV (WHIV) are at greater risk of developing cervical cancer. Despite being entirely preventable, cervical cancer education, prevention and care remain under-funded, which is compounded by a shortage of trained healthcare personnel in the country\(^2\). At present, the standard for screening in Uganda is visual inspection using acetic acid (VIA). However, training providers to offer screening, the invasiveness of a pelvic examination, and user variability (56%-90%) are barriers led to an examination of use of HPV-DNA, either as a clinician or self-collected option to improve access to screening. Self collection reduces the burden on skilled professionals, decreases the need for travel to clinics, obviates the embarrassment of the pelvic exam and has shown exceptional promise for LMIC. Two important research programs in Uganda indicating the feasibility of self collection are highlighted in this paper.

Screening Technologies to Advance Rapid Testing (START-UP): Project 1 CareHPVTM test, a low-cost HR-HPV screening tool that yields results rapidly and with minimal equipment needs was used in a study by Makerere University in 2009\(^2\). Clinician-collected (cervical) and self-collected (vaginal) CareHPVTM specimens, VIA, and cytology tests were evaluated among 4710 Ugandan women (Table 1). A sub-group analysis demonstrated high sensitivity of CareHPVTM in both HIV positive and negative women in Uganda. In the study of 2,337 Ugandan women with known HIV status, positivity rate was higher among WHIV (44.9%) compared to HIV negative women (19.0%). CareHPVTM sensitivity for both cervical or vaginal samples was better than VIA or Pap.

Figure 1: Sensitivity and specificity of the 4 screening tests for detection of CIN2+ and CIN3+ among Ugandan participants

In Uganda, 99.5% of women enrolled accepted to self collect vaginal samples. Interestingly, women preferred clinic based screening as opposed to home based self sampling. Self sampling acceptance was higher when provider prepared women through health education, allowed women to feel the brush and were present during the self collection process. During field implementation, additional use of culturally appropriate educational aid would promote self sampling.

Community based HPV self collection

The Advances in Screening and Prevention in Reproductive Cancers (ASPIRE) project integrates cervical cancer screening with STI & HIV testing and...
reproductive health education and offers screening at the community level. Outreach workers, who are known and trusted community members trained in self-collection based screening, recruit women at their homes or places of work. They provided self collected specimens: one for HR-HPV testing, and a second for STI screening (gonorrhea and Chlamydia). Women provide the specimen at the place of recruitment, and do not need to attend a clinic. Women who test HR-HPV positive are referred to the local health unit for follow up VIA screening with a nurse. Using a see-and-treat approach, women who screen positive are treated using cryotherapy in the same visit.

“Integration of cervical cancer prevention with reproductive health services is recommended by the WHO to maximize resources and improve access in low resource settings. It has been demonstrated that integrating interventions for HIV, reproductive health, and maternal health has successfully improved the uptake of services, and improved the quality of care received by women.”

Future Directions
Screening for cervical pre-cancer using low cost HPV DNA testing like CareHPV on self-collected vaginal specimen could be the game changer for cervical cancer prevention in Uganda and other LMIC. Use of self-collected specimens could result in a rapid increase in screening coverage, does not require an expansive clinical infrastructure, and does not need highly trained personnel. Self-collection has the potential for rapid scaling at the community level and trained, female village health workers or volunteers could be mobilized for mass sample collection.

### REFERENCES


### TABLE 1

**Sensitivity and specificity of the 4 screening tests for detection of CIN2+ and CIN3+ among Ugandan participants.**

<table>
<thead>
<tr>
<th></th>
<th>SELF-COLLECTED CAREHPV™</th>
<th>CLINICIAN COLLECTED CAREHPV™</th>
<th>VIA</th>
<th>CYTOLOGY</th>
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<tr>
<td><strong>Number with CIN2+</strong></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>N=87</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensitivity, % (95% CI)</td>
<td>77.0 (66.8, 85.4)</td>
<td>88.5 (79.9, 94.3)</td>
<td>73.6 (63.0, 82.4)</td>
<td>69.0 (58.1, 78.5)</td>
</tr>
<tr>
<td>Specificity, % (95% CI)</td>
<td>82.0 (80.5, 83.3)</td>
<td>81.8 (80.3, 83.1)</td>
<td>66.6 (64.9, 68.3)</td>
<td>48.6 (46.8, 50.4)</td>
</tr>
<tr>
<td><strong>Number with CIN3+</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N=25</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensitivity, % (95% CI)</td>
<td>72.0 (52.0, 87.9)</td>
<td>84.0 (63.9, 95.5)</td>
<td>80.0 (59.3, 93.2)</td>
<td>72.0 (50.6, 87.9)</td>
</tr>
<tr>
<td>Specificity, % (95% CI)</td>
<td>80.7 (79.3, 82.1)</td>
<td>80.3 (78.9, 81.7)</td>
<td>65.9 (64.2, 67.5)</td>
<td>48.3 (46.5, 50.1)</td>
</tr>
</tbody>
</table>

Integration of cervical cancer prevention with reproductive health services is recommended by the WHO to maximize resources and improve access in low resource settings. It has been demonstrated that integrating interventions for HIV, reproductive health, and maternal health has successfully improved the uptake of services, and improved the quality of care received by women.
Screen & Treat with HPV testing in Low and Medium-Income Countries: pros & cons

A round 85% of cervical cancer deaths occur in low and medium-income countries (LMIC) essentially because of the lack of screening. Cytology-based cervical cancer screening programs have successfully reduced cervical incidence in high-income countries, but not in LMIC, essentially because of high-cost and logistic limitations.

A “screen-and-treat” approach for cervical prevention is based on a screening test result followed by treatment in the same visit. This strategy allows reducing travel time, minimizing the number of visits, transport, childcare needs and reducing the cost. It has been demonstrated in the LMIC context that adding a delay between screening, obtaining results and proposing treatment induces a loss of follow-up. Therefore, an approach incorporating diagnosis procedure followed by an immediate management should be prioritizing to optimize cervical cancer screening program in LMIC.

An approach incorporating a diagnosis procedure followed by an immediate management should be prioritized to optimize cervical cancer screening programs in LMIC.”

A randomized trial conducted in South Africa having adopted a HPV–based approach, demonstrated that it is a highly effective strategy with a significant reduction of CIN2+ lesion. This approach is far more accurate, sensitive and robust than VIA in detecting cervical intraepithelial neoplasia grade 2 and worse (CIN2+). After 36 months of follow-up, the cumulative risk of CIN2+ was reduced by 73% in HPV-negative women as compared to the control (untreated) arm1.
women and 32% in VIA-negative women as compared to the control (untreated) arm. Other report demonstrated that HPV testing strategy conducted in LMIC is associated with decreased cervical cancer-related mortality. HPV-based screening is recommended by WHO as an alternative for cervical cancer screening (WHO 2014). Until recently, the greatest limitations of HPV testing were the need for expensive laboratory infrastructure and the 4-7 h time to process the test. The development of rapid molecular methods for detecting HPV DNA (e.g., careHPV® - Qiagen, GeneXpert® - Cepheid) for screening or other point-of-care type of tests make a “screen and treat” strategy more feasible. Limitation of HPV-based screening is its low positive predictive value, since it does not directly test for cancer, but for HPV infection. This indicates that a triage test following a positive HPV results may be necessary to limit the rate of false positive and consequently reduce the harm of overtreatment. Integrating HPV screening with a VIA triage test may offer the dual benefits of HPV screening to maximize the detection and VIA for treatment triage of HPV-positive women (Figure 1).

The START UP study conducted in Hyderabad, India has evaluated the careHPV test as primary screening test (HPV self-sampling). HPV-positive women were triaged with VIA and VIA-positive treated by cryotherapy. Cytology, colposcopy, biopsies were used as quality control and to calculate tests performance. These data support that VIA used as a triage test for HPV positive women reduce the number of overtreatment with 19% of HPV-positive being treated. However, VIA used as a triage test have missed 40% of CIN2+ lesion in this study. But VIA performed similar to colposcopy in detection of CIN 3 and invasive cancers. Hence VIA can be used for treatment triage. Similar results have been reported in a study conducted in sub-Saharan Africa using VIA/VILI as triage test for HPV-positive women with an extremely low sensitivity (25%) for CIN2+ detection. There is probably room for VIA improvement that still need to be investigated like the use of cervicography to assure quality assurance of the method.

In conclusion, new laboratory-independent and affordable HPV tests are available, providing immediate results and making it possible to screen and treat women during the same visit. Adding VIA to HPV primary testing may be a well-suited method for LMIC, provides an unprecedented opportunity to develop cervical screening programs in LMIC with a single-visit approach. However, questions are still open as how such a test could be introduced in an effective manner in LMIC.

References

Treatment of precancer lesions: overcoming the bottleneck

Background
Cervical cancer is the first or second most common cancer and a leading cause of cancer deaths among women in low- and middle-income countries (LMICs) where nearly 90% of the deaths occur. The primary reason for this inequitable burden of disease is the absence of routine screening services in most LMICs. In 2012, Malawi was estimated to have the highest rate of cervical cancer in the world with an age-standardized rate of 75.9 per 100,000 women. In 2014, only 22% of Malawian women had access to cervical cancer screening using visual inspection with acetic acid (VIA). While many LMICs have started pilot screening programs in recent years, only a few programs have expanded to reach more than a small proportion of the women who need them.

Even when screening services are available, women identified as positive on screening tests often have little or no access to effective precancer treatment. In Malawi, 60% of precancerous lesions in 2014 were not treated due to the unavailability of standard treatment (cryotherapy using carbon dioxide or nitrous oxide gas). Factors constraining treatment availability include the initial cost of equipment, the cost of ancillary supplies, and the burden of initial training and maintenance of skills when treatment is needed for only a fraction of women screened. While cryotherapy was seen as holding great promise, it has proven to be unsustainable due to the high cost and limited supplies of gas and the difficulty in central procurement and distribution of gas cylinders. In Malawi, in 2014, a cryotherapy unit cost US$1,350, and a cylinder of nitrous oxide gas cost $930, which provides 20 treatments on average ($46.50 per treatment in a country with a health expenditure of $14.50 per capita in 2010).

New technology options
Two non-gas-based treatment technologies have been identified. The CryoPen® Surgical System (CryoPen, Inc., Texas, USA) uses the same ablative principle of freezing abnormal tissue, but creates freezing temperatures using a recirculated refrigerant gas system powered by electricity. The device has been available in the United States for several years, but the company recently modified the design to make it more robust, easier to transport, and affordable for LMICs. An alternative ablative approach previously known as cold coagulation (also called thermal coagulation because it uses heat rather than cold) uses a metallic probe at 100 to 120 degrees centigrade for 30 to 60 seconds to destroy precancerous lesions. One version of the coagulator with probes (WISAP Medical Technology GmbH, Germany) requires electricity and costs about $3,400 (2015 discount by WISAP for Malawi). Another version being developed by a United States company (Liger Medical, LLC, Utah, USA) is a patent-pending hand-held battery-powered device that is anticipated to sell for about $1,000. Development of the Liger Medical unit is expected to be completed in 2016. Thermal coagulation is shown to be safe, effective, and suitable for low- to mid-level health providers in LMICs. With the availability of these new treatment options, both static and outreach services can be carried out more readily.

Experience with alternative treatment approaches
Experience with CryoPen in low-resource settings is limited, although a few small exercises were conducted in countries in Africa and Latin America.
Nkhoma Hospital screened 7,088 women from October 2013 through March 2015, with 429 (6.1%) VIA positive, of whom 361 (84.1%) had same-day treatment with thermal coagulation. Of those treated, 234 (62.4%) returned for a 6-month follow-up, and of these, 220 (94%) were healed with no evidence of persistent lesions. The procedure was well tolerated with minimal complaints of discomfort and few return visits for complications.

A field evaluation is planned for Uganda in 2016. The bulk of the experience with thermal coagulation comes from the United Kingdom and a few scattered individual users in Africa and Asia. The most extensive experience comes from Nkhoma Hospital in rural Central Malawi, where a cervical cancer program in partnership with the Scottish Government, the University of Edinburgh, and NHSScotland turned to thermal coagulation in response to challenges with conventional cryother-apy. Nkhoma Hospital screened 7,088 women from October 2013 through March 2015, with 429 (6.1%) VIA positive, of whom 361 (84.1%) had same-day treatment with thermal coagulation. Of those treated, 234 (62.4%) returned for a 6-month follow-up, and of these, 220 (94%) were healed with no evidence of persistent lesions. The procedure was well tolerated with minimal complaints of discomfort and few return visits for complications.

Next steps
To ensure wide availability of treatment options in LMICs, several parallel activities are needed. The development of technologies like CryoPen and the Liger Medical thermal coagulation unit must be completed and the units validated. A more diverse evidence base on efficacy is needed, particularly for thermal coagulation since there has been less experience with it. Nkhoma Hospital is currently working with the Malawi National Cervical Cancer Program to provide data on safety and effectiveness of thermal coagulation, but data from other sites would also be needed. Training programs will require materials for new treatment methods. Nkhoma Hospital has developed a training manual for thermal coagulation users that can serve as a starting point. Since many countries rely on World Health Organization (WHO) guidelines, it will be important to present essential information on equipment specifications and clinical performance to WHO for official endorsement. Only by overcoming the current bottlenecks to precancer treatment can we ensure that screening programs achieve their intended purpose and reduce the burden of this disease.

References
Cervical cancer mortality is a reflection of social inequity in health care. Innovative strategies that combine HPV vaccination with HPV testing should be implemented in order to transform screening paradigms which have been inefficient in lower and middle-income countries. This approach will reduce the burden of disease at local and national levels while also contributing to a rapid decrease in the spectrum of HPV-related diseases at the global level.

Reframing HPV-driven cancer control objectives

Ten years after the introduction of the HPV vaccine, its impact in real-world conditions with at least 60% coverage has been a 90% reduction in the prevalence of HPV 6/11/16/18; a 45% reduction in low grade cytological abnormalities as well as an 85% reduction in high grade histological lesions. In spite of this impressive progress, optimal protection through population-level HPV vaccination has not been reached. Lesions produced by HPV infection remain a significant cause of morbidity and mortality worldwide, and especially in poor countries.

Evaluating the incorporation of HPV vaccination of adult women into screening programs based on high-risk HPV (hrHPV) testing is the cervical cancer prevention strategy with the greatest potential impact in the immediate future.

Vaccination of adult women: additional lessons from Phase III trials

Results of Phase III HPV vaccination trials documented that the vaccine’s efficacy among adult women is excellent amongst HPV screening-negative women (efficacy >80% to prevent resultant HPV-related cervical intraepithelial neoplasia). Broad-spectrum protection such as this may lower the need for subsequent screening, warrant longer screening intervals than those currently used and offer novel prevention policies against HPV-related cancers.

The combination of vaccination and screening strategies to prevent cervical cancer may be particularly appropriate in countries with high incidence of cervical cancer that have already implemented hrHPV-based screening programs. These criteria are satisfied in Mexico. A broader age range of women in population-based HPV vaccination programs could have direct benefits for vaccinated women and indirect benefits for non-vaccinated women and male sexual partners via increased herd immunity, leading to a reduction in all HPV-related cancers.

The HPV FASTER proposal

Based on the high efficacy of the HPV vaccine in older women, a novel strat-
If a combined screening and vaccination strategy is widely adopted, we expect promising results. This strategy has the potential to: 1) mitigate the screening demand for both women and healthcare services by extending screening intervals; 2) improve the cost-benefit balance of screening programs; and 3) provide greater protection and quality of life to a large number of women through a reduction of cervical cancer incidence. An intervention such as this may not only save many lives in the next 30 years but also be cost-effective.

### The HPV FASTER trial in Mexico

We are initiating a population-based study to assess the efficacy of a 2-dose HPV vaccination schedule with [HPV16/18 AS04-adjuvanted vaccine (Cervarix®) and HPV 6/11/16/18 vaccine (Gardasil®)] against HPV-persistent infection and HPV-related cervical disease in women 25 to 45 years of age attending clinics for hrHPV-based screening. A total of 18,000 women aged 25-45 years, attending the regular cervical cancer-screening program in primary health care services in the Tlalpan borough of Mexico City, will be invited to the study. Eligible participants will be assigned to one of three comparison groups: 1) HPV16/18 vaccine and hrHPV-based screening; 2) HPV6/11/16/18 vaccine and hrHPV-based screening; 3) a control group who will receive only hrHPV-based screening. Strict surveillance of hrHPV persistent infection and occurrence of precancer-
ous lesions will be conducted to estimate safety profiles at different screening intervals; participants will undergo diagnostic confirmation and treatment as necessary. Current evidence establishes HPV vaccination as an effective and cost-reducing strategy for cervical cancer prevention.

We are initiating a population-based study to assess the efficacy of a 2-dose HPV vaccination schedule with [HPV16/18 AS04-adjuvanted vaccine (Cervarix®) and HPV 6/11/16/18 vaccine (Gardasil®)] against HPV-persistent infection and HPV-related cervical disease in women 25 to 45 years of age attending clinics for hrHPV-based screening. However, in countries such as Mexico the optimal effect of HPV vaccination is expected when over 60% coverage is reached in age cohorts including young women up to 24 years of age. These results will only be observed in 15+ years’ time. The dilemma we face is how to speed this impact up through implementation of an innovative public health intervention that will largely attenuate the burden of cervical cancer.

The FASTER Tlalpan Study5,6 will provide insights into new approaches to cervical cancer prevention. This will be the first assessment in real-world conditions of the impact of HPV vaccination incorporated into a hrHPV-based primary screening program, including allowing extended screening intervals. This demonstration study will also help to identify the determinants of participation, barriers, acceptability and compliance of the different clinical practices as well as programmatic and logistic difficulties. In addition, the study will allow assessment of the incorporation of epidemiological surveillance strategies to evaluate the future impact of combined cervical cancer screening and HPV vaccination in women between 25 and 45 years of age in Mexico.

References

HPV vaccination status is not associated with increased risky sexual behavior

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Despite the recommendations made by national immunization advisory committees around the world, HPV vaccination rates, especially in the United States, remain suboptimal. For example, in the United States in 2015 only 62.8% of 13-17 year old girls and 49.8% of 13-17 year old boys had received at least one dose of the HPV vaccine and the numbers are even lower for series completion (41.9% and 28.1% respectively). When asked about barriers vaccinating their children for HPV, some parents cite concerns about Risk Compensation. That is, they are concerned that vaccinating their children against a sexually transmitted infection (STI) will result in increased risky sexual behaviors. Critics of the vaccine have expressed this concern throughout the world, from the U.S., to Canada, to the United Kingdom. However, our recent systematic review of the literature found no evidence of risky sexual behavior after vaccination. When asked about barriers vaccinating their children for HPV, some parents cite concerns about Risk Compensation. That is, they are concerned that vaccinating their children against a sexually transmitted infection (STI) will result in increased risky sexual behaviors.

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vaccination status and subsequent sexual activity. In fact, there were some longitudinal studies that found decreased sexual activity after vaccination. Although some cross-sectional studies did find vaccinated participants were more likely to have engaged in sexual intercourse than unvaccinated participants, these studies also noted that many of their participants (between 45% and 62%) were sexually active prior to HPV vaccination. Therefore, these results may be more indicative of a woman engaging in sexual behavior, then seeking out protective measures as opposed to vaccination causing increased sexual behavior. Furthermore, previous studies have shown that providers are more likely to recommend HPV vaccine to patients they believe are sexually active or not in a monogamous relationship. Other studies examined more specific risky sexual behaviors, finding no association between HPV vaccination and behaviors such as: age at sexual debut, number of sexual partners, and contraception use. In fact, some studies found that vaccinated participants reported less risky sexual behavior as compared to the unvaccinated participants. These results provide compelling evidence that there is no increase in risky sexual behaviors after HPV vaccination.

Behavioral Outcomes
Almost all of the behavioral outcome studies found no association between...
Biological Outcomes
Several studies have examined biological/health markers of risky sexual behavior, including STI/HIV testing, STI/HIV diagnosis, pregnancies, and abortions. There was no evidence of increased STI/HIV testing or diagnosis in the vaccinated sample. Furthermore, one study found that participants who did not receive HPV vaccine had higher rates of chlamydia. Two studies examined a composite measure of STIs and pregnancies and neither found any relationship with vaccination status. Other studies found no associations between vaccination and pregnancy or abortion, and one reported that among participants who had a history of abortion, none of them had received HPV vaccine. These biological/health outcome studies lend further support to the findings of the sexual behavior studies that show no association of HPV vaccination with increased risky sexual behavior.

Conclusions
The consistent, replicated findings across the 20 studies examined in our systematic review provide strong evidence refuting the proposed association between HPV vaccination and risky sexual behavior. The 20 studies, which utilizing at least four distinct study designs and included a total of 521,879 participants, found no evidence for increased numbers of sexual partners, younger age of sexual initiation, decreased use of contraception (including both condoms and hormonal contraceptives), increased STI diagnoses, increased pregnancy rates, or increased history of abortion among those vaccinated against HPV. In fact, some studies found that vaccinated women engaged in fewer risky behaviors than unvaccinated women. The findings from our systematic review should alleviate any parental concerns that HPV vaccination will lead to risky sexual behaviors.

References
A new scientific Journal devoted to HPV and other small DNA tumor viruses and the official journal of the International Papillomavirus Society.

In 2016, PVR received and evaluated 118 manuscripts and published 36. The request of inclusion of the published materials into Pubmed is being filed and successful resolution is expected in 2017.

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