The concept of HPV tests adapted to emerging Economies

INTERVIEW WITH

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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.

Is really HPV testing in self-collected vaginal samples a game-changer in cervical cancer screening?

It is certainly a game-changer, it 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 if 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.

Other limiting factor for 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 dollars per test. Companies are more willing to offer more affordable prices when they see that the implementation is part of national programs where high number of women are screening; the higher the volume of screening, the more affordable the tests become.

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.

"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 prevention services."

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 of 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.

PATH/XIOMARA CELESTE GONZALEZ

Indigenous lab technician running careHPV in Chimaltenango Province, Guatemala.

Cervical cancer screening in LMIC

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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 the cervical cancer have resulted in very promising new primary and secondary prevention tools that represent a tremendous opportunity in developing countries. For primary prevention, the availability of safe and effective vaccines against the major HPV genotypes promises to dramatically reduce infection, precancer and eventually invasive cancer. This will require mass vaccination programs with high coverage. 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. It is crucial that in the next few years LMIC start vaccination given the long latency of the impact of the vaccine.

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 both in LMIC and in European countries.

The availability of new strategies may be an opportunity for countries interested in reducing the burden of cervical cancer to organize screening programs assuring proper coverage of the population, ideally in the context of population-based (organized) screening where the target population is invited systematically to assure true coverage of at least 80%. Even more important to emphasize is that 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 just 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 women's preferences.

The most radical approach is to treat with ablative procedures (when feasible) all HPV positive women over 30 years of age, proposed as one of the alternatives in the recent WHO recommendations. 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. This approach requires inexpensive and technically simple HPV testing methods, ideally providing immediate results. 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 research. 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 (also need LEEP for those with large lesions). 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. In El Salvador this approach is being used with treatment of about 10% of women. The program has obtained high compliance, is being expanded to the entire country and has been shown to be cost effective. 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.

In order to reduce excessive 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 has suboptimal sensitivity and it is likely to miss an important fraction of lesions and requires extensive training of highly specialized staff and quality assurance.

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 have been shown in some publications to improve the performance of cytology. This method is likely to be effective in areas where cytology is well established but remains to prove 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.

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 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.

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. P16/Ki67 in exfoliated cells has demonstrated good sensitivity and specificity, and detection of E6 oncoproteins appears very promising given their very high sensitivity and specificity. These proteins are currently only available for HPV 16 and 18 proteins, but a new set of HPV types is under investigation.

One of the key issues is the reduction of the number of visits. Thus the ideal method would be a self-administered diagnostic method providing immediate results followed by treatment with oral or topical medication or a therapeutic vaccine. There are important initiatives to investigate these alternatives but in the meantime the provision of access to organized high quality screening, regardless of the screening and triage methods is essential to curb the unacceptable burden of this devastating disease.

TABLE 1

Alternatives for clinical management of HPV positive women

	ADVANTAGES	DISADVANTAGES
	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
Genotyping	Automatic result with the HPV test Sensitivity similar to cytolgy	Similar to conventional
Treat all	High sensitivity Possibility of immediate treatment Prevention of future disease	Limited sensitivity by design (other types)
P16/ki67	Disease specific Training not so complex Automated processing	Experimental
E6 protein	High specificity	Limited sensitivity by design

HPV testing in self-collected samples

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PATH/FRANCESCA HOLME

Lab techs in screening site in Honduras.

Women have problems to access 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 to overcome 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.[1-2] 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).[3]

HPV-self collection is a highly effective method to detect precancerous disease and cancer, especially when compared to cytology.[4] 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.[5] In several studies carried out in middle/low income settings, self-collection was offered at home by a health provider, such as CHWs in Argentina[3] or a nurse in Chile.[1] This strategy is more suitable to those settings considering that using the mail would not be feasible, and in many countries CHWs are already part of the first level of care and have good relation with the community. The possibility of offering self-collection in health centers could be also considered, but in this case the impact on barrier reduction will be limited. In Argentina, self-collection has also been promoted in community fairs, with rooms specially arranged to provide adequate privacy.

HPV+ women need to be triaged to identify those who need diagnostic follow-up and eventually treatment, adding a visit to the screening process. In several countries, this limitation of HPV-testing has been overcome by taking samples for HPV-test and triage cytology in the same visit, but this is not possible with HPV-self collection, and this is probably its major shortcoming. Women with HPV+ results would need 2-3 visits to the health facility, increasing the risk of not completing the triage/diagnosis/treatment process. See-and-treat approaches can be a solution, but they are not feasible in all settings. Therefore, 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. In the meantime, it is very important to devise strategies and mechanisms to facilitate women access to health services for triage. If self-collection is offered at home it is very important to strengthen the coordination within the health system; then HPV+ women are visualized as patients even if their "point of entry" has not been the health center. The use of mhealth technologies to send reminders to women and health providers should be further explored and investigated.

Self-collection is a tool to overcome barriers to health services, but it is not a magic bullet that makes barriers disappear. This reminds us that screening technologies are only effective if applied in organized programs. This means, among other aspects, having a coordinated referral network, quality health services that are responsive to women needs, well-established responsibilities for each level of the health system, and information systems that allow tracking of the entire continuum of care.

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The care HPV test

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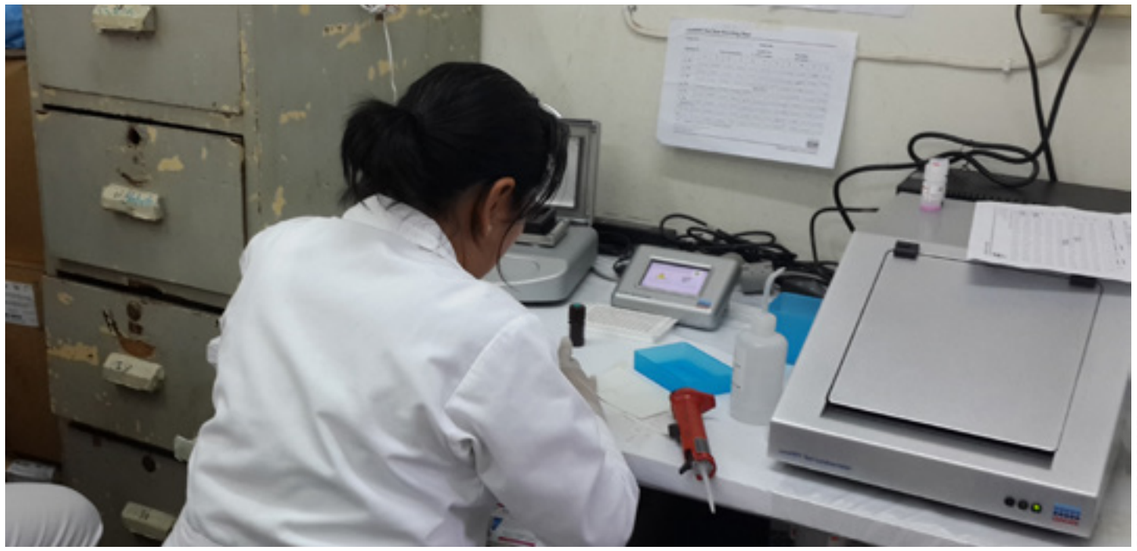

DRA CLAUDIA CAMEL

Labs have very limited infrastructure and resources.

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. (Pictures 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 significantly less (~5 dollars per test), with proven quality standards.

"A screening test for LMICs, must be simple to implement, accepted by the users, and economically sustainable"

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 increased 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 the Central American countries are obtaining with the introduction of careHPV in their public systems give us the opportunity to identify some advantages and limitations when working with that test.

DRA CLAUDIA CAMEL

Lab technician running careHPV in Guatemala.

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.

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 budget of a screening program could also be influenced by the self-sampling strategy, which allows 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.

"The technology is easily adapted to laboratories in different localities, even in places where there is not an actual laboratory"

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 schedules conflict, shame to pelvic exams, etc. Self-sampling with careHPV is accepted by 76% of women in Guatemala.

Finally, our experience shows the need to pilot or demonstrate feasibility within a country, this 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.

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Use of the GeneXpert test in Malawi

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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 TB and drug resistance. The recent availability of Xpert HPV on the same platform may provide a suitable HR-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® HPV is a qualitative in vitro test for the detection of HPV in liquid based cytology (LBC) specimens collected in PreservCyt®. The test detects DNA of 14 high-risk HPV types. Each HPV test can be completed in around 1hour, 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 [5,6]
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 turnaround 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.

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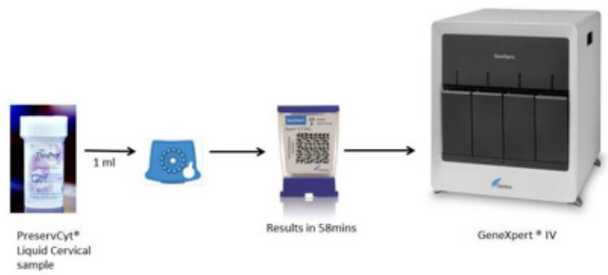
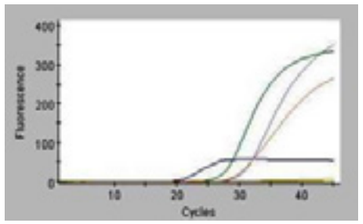
FIGURE 1

Xpert HPV process



a. from specimen collection to test result



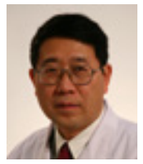
b. Example of result output from clinical sample from Nkhoma Hospital. Multiple infection with HPV 16, HPV 18/45 and HPV 'other' detected

TABLE 1

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

COLLECTION DATE	NO OF SPECIMENS WITH VALID HPV RESULTS	NO OF SPECIMENS WHERE HPV NOT DETECTED	NO OF SPECIMENS WHERE HPV DETECTED	HPV 16	HPV 18/4	HPV 'OTHER'	HPV 31+	HPV 51/59	HPV 39+	MULTIPLE INFECTIONS
Jan-Dec 2014	604	484	120	30	27	77	47	15	21	17
Jan –April 2015	146	117	29	6	9	19	12	2	5	6
Total	**750**	**601**	**149**	**36**	**36**	**96**	**59**	**17**	**26**	**23**
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%

Experience with careHPV implementation in China



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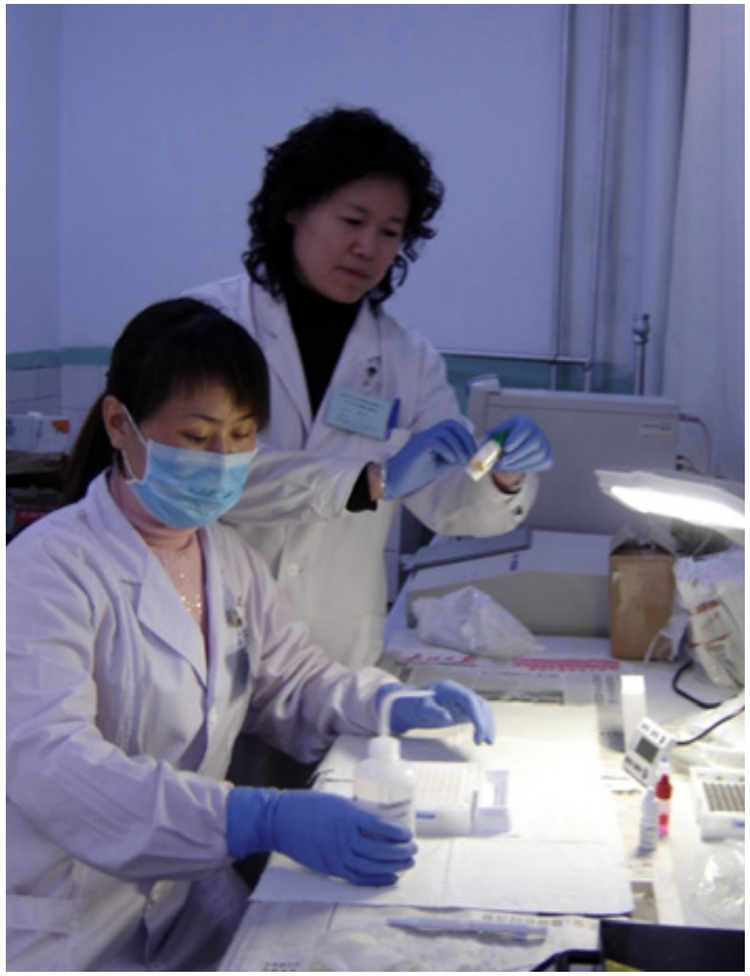
Between the year 1989-2008, the morbidity and mortality of cervical cancer among Chinese women increased continuously, especially for rural women which the age-adjusted morbidity in 2008 was three times higher than 1989 and the adjusted mortality nearly doubled. The average age of women diagnosed as 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.



Zhixia Li, a local laboratory worker (left) was trained by senior technician, Feng Chen (right) from CICAMS

In 2007, careHPV was successfully proved to be accurate, fast, reproducible, and low-cost by our team cooperated with PATH and QIAGEN Inc. Personnel with limited laboratory experience could perform it correctly after 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.

"Ordos, in Inner Mongolia, is the first city in China to use careHPV test as primary screening"

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.

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Programmatic implementation of HPV testing in Central America

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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 cancer prevention, including data on the limitations of Pap testing, at various levels of the health care system from central leadership to community nurses. Additionally, countries had to develop and prepare for new screening and treatment algorithms incorporating HPV testing in anticipation of an influx of screen-positive women. Each country independently determined that HPV screening algorithms should require few steps in order to avoid bottlenecks in treatment delivery. All countries are therefore sending most HPV-positive women to visual inspection with the goal of facilitating immediate treatment with cryotherapy when possible. Most countries had to significantly expand visual inspection and cryotherapy capacity beyond existing levels in order to adequately manage the expected volume of HPV-positive women.

PATH/MICHAEL WANG

Women receiving Health education in Honduras

> **"Countries have some Pap infrastructure in place, but implementing HPV testing required a paradigm shift for health personnel and women"**

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 heath 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.

nges we observed in Central America also provide important lessons for other emerging economies. The up-front costs of changing to 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.

> **"The challenges we observed in Central America provide important lessons for other emerging economies"**

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.

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HPV Testing in self collected samples in Uganda

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Cervical cancer in Uganda
Cervical cancer 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 underfunded, which is compounded by a shortage of trained healthcare personnel in the country2. 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 has shown exceptional promise for LMIC"

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 20093. Clinician-collected (cervical) and self-collected (vaginal) CareHPVTM specimens, VIA, and cytology tests were evaluated among 4710 Ugandan women (Figure 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.
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.

DR CAROL NAKISIGE

Group education of women waiting for screening in Uganda.

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.

Integrated cervical cancer screening with reproductive health services
ASPIRE conducted a randomized controlled trial of 500 women comparing community-based HR-HPV self collection to VIA in Kisenyi, Uganda4. In this study, self collection-based high risk HPV testing had a significantly higher uptake (99.2%) compared to VIA alone (48.4%). This trial demonstrated that self-collection based screening is both feasible and acceptable among women in this setting, and suggests this method improve access compared to VIA. Similar to the study at Makerere, rates of HR-HPV were high in the study population (29.4%), and were significantly higher among WHIV compared to HIV negative women, including rates of HR-HPV types 16 and 18.
Integration of cervical cancer prevention with reproductive health services is recommended by the WHO to maximize resources and improve access in low resource settings5. It has been demonstrated that integrating interventions for HIV, reproductive health, and maternal health has successfully improved uptake of services, and improved the quality of care received by women.

"CareHPV on self-collected vaginal specimen could be the game changer for cervical cancer prevention"

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.

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Screen & Treat with HPV testing in Low and Medium-Income Countries: pros & con

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Around 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.

The visual inspection with acetic acid (VIA) or Lugol's iodine (VILI) testing as an alternative to cytology has the advantage of being low-cost, easy to be carried out by nurses of midwifes after short training and offer the option of treatment immediately or shortly after diagnostic testing. Limitation of VIA-based screening is that it is health-care provider dependent and lacks of reliable assurance control. These limitations have favored the search of alternative approach for LMIC like HPV testing. This method should add objectivity and performance by detecting cases of neoplasia that visual approach has failed to detect and offer the possibility, that sample collection can be performed by the patient herself, not requiring trained personnel and infrastructure to perform a pelvic examination thus increases acceptability and screening coverage.

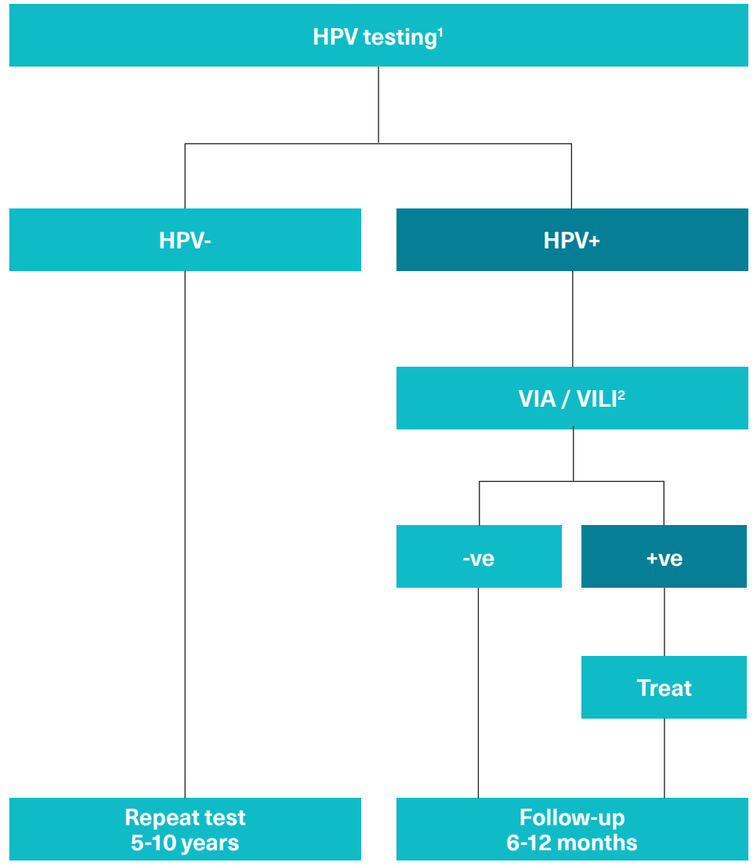
A randomized trial conducted in South Africa having adopted a HPV–based approach, demonstrated that it is a highly effective strategy with a significant reduction of CIN2+ lesion. This approach is far more accurate, sensitive and robust than VIA in detecting cervical intraepithelial neoplasia grade 2 and worse (CIN2+). After 36 months of follow-up, the cumulative risk of CIN2+ was reduced by 73% in HPV-negative women and 32% in VIA-negative women as compared to the control (untreated) arm(1). Other report demonstrated that HPV testing strategy conducted in LMIC is associated with decreased cervical cancer-related mortality[2].

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., care HPV® - 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)[3]. 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[4]. 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 LIMIC, 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.

FIGURE 1
Suggested algorithm for cervical cancer screening in low and medium-income countries



1 Possibility to perform a HPV self-sampling; 2 Inspection for eligibility for cryotherapy or cold coagulation. HPV: Human papillomavirus; VIA/VILI: Visual inspection with acetic acid/visual inspection with Lugol's iodine

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Treatment of precancer lesions: overcoming the bottleneck

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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.[1] 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 (2013 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.[2,3] 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. 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 cryotherapy. 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.[4] 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.

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HPV vaccination impact on a cervical cancer screening program: the HPV faster-tlalpan study in Mexico

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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.[1]. 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. (Table 1) [2].[3].

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 strategy combining vaccination and screening, HPV FASTER, has been proposed (referencia 4). In accordance with this proposal, HPV vaccination of women in a broad age range could offer protection to women who are not currently infected, but could also protect against subsequent HPV infections by the vaccine HPV types. As a result, a combined strategy of HPV vaccination and screening may reduce the lifetime number of screens used by HrHPV-based screening programs currently.

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 in cervical cancer. An intervention such as this may not only save many lives in the next 30 years but also be cost-effective.

However, data on efficacy of HPV vaccination in older women to reduce cervical cancer risk, and not just the risk of precancerous lesions, are lacking. That is, currently there is insufficient knowledge regarding the role of HPV vaccination in older women to permit screening intervals to be extended safely following a negative screening.

A significant challenge for HPV-vaccine uptake is the number of doses required in the standard vaccine schedule. Although licensed in some countries for use among older individuals (i.e. in the European Union), most national HPV vaccination programs target teenagers and young adults. Recent studies found that fewer than three doses of the two commercially available prophylactic HPV vaccines seem to provide similar protection against cervical HPV16 and HPV18 infections as the three-dose schedule in women older than 25 years old.

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 precancerous 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. 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 Study[5]. [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.

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