HPV Tests:
The key to universal screening for cervical cancer?
Wednesday, September 10, 2014

Presenters

Dr. Jose Jeronimo, Senior Advisor for Women’s Cancers, and Director of the START-UP Project, PATH (USA).

Dr. Debbie Saslow, Director of Breast and Gynecologic Cancer, American Cancer Society (USA).

Dr. Silvina Arrossi, Scientific Coordinator, National Program on Cervical Cancer Prevention, Centro de Estudios de Estado y Sociedad/National Council for Scientific and Technologic Research (Argentina).

Dr. Carolyn Nakisige, Gynecologist, Mulago Teaching and National Referral Hospital, Department of Obstetrics and Gynecology, Gynecological Oncology Unit, (Uganda).

Dr. Joanna Cain, Professor and Vice-Chair, OB/GYN, and Director of Faculty Talent Management, University of Massachusetts Medical School and Chair of the WHO Committee on the revision of the C4GEP manual, WHO’s new guidelines on cervical cancer control (USA).
Natural History of HPV Infections

- HPV infections are extremely common
- HPV infections cannot be treated, but cervical changes and warts CAN be treated
- Most HPV infections are transient: they are cleared by the immune system
  - 70%-90% will clear within 1-2 years
- Persistent viral infections may lead to cancer and its precursors
- While most HPV infections do not lead to cancer, virtually all cervical cancers are caused by HPV
What is an HPV test?

- Cells are collected just like a Pap test (using the same swab or a second swab)

- It checks for high-risk HPV

- In countries that screen with Pap tests, the HPV test sometimes is used to determine if a woman needs further evaluation, i.e. for an ASC-US Pap result

- When both the HPV test and the Pap test are done together for screening, it is called “cotesting”
WHEN AND HOW SHOULD WOMEN GET SCREENED FOR CERVICAL CANCER?

NEW U.S. SCREENING GUIDELINES...
# Cervical Screening Recommendations (2012)

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Screening Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women &lt;21</td>
<td>No screening</td>
</tr>
<tr>
<td>Women ages 21-29</td>
<td>Cytology alone every 3 years (liquid or conventional)</td>
</tr>
<tr>
<td></td>
<td>Recommend AGAINST annual cytology</td>
</tr>
<tr>
<td>Women ages 30-65</td>
<td>HPV + cytology “cotesting” every 5 years (preferred)</td>
</tr>
<tr>
<td></td>
<td>or Every 3 years with cytology alone (acceptable)</td>
</tr>
<tr>
<td></td>
<td>Recommend AGAINST more frequent screening</td>
</tr>
<tr>
<td>Women ages &gt;65</td>
<td>Discontinue after age 65 if 3 negative cytology tests or 2 negative HPV tests in last 10 years with most recent test in last 5 years</td>
</tr>
<tr>
<td>Post-Hysterectomy</td>
<td>Discontinue if for benign reason</td>
</tr>
<tr>
<td>Screening after HPV vaccination</td>
<td>Follow age-appropriate recommendations (same as unvaccinated women)</td>
</tr>
</tbody>
</table>
Key Evidence Supporting New Recommendations

- Several large studies showing greater benefits and reduced harms of co-testing (HPV plus Pap) at longer screening intervals
- Modeling studies showing harms of over-screening
- Emerging evidence on HPV testing alone and screening after vaccination
Why is HPV testing an attractive option for cervical cancer screening?

- More sensitive and reproducible than the Pap test
- More “upstream” in the carcinogenic process, thus enabling a longer safety margin for screening intervals
- Can be automated, centralized, and be quality-checked for large specimen throughput
- May be more cost-effective than cytology if deployed for high volume testing, such as in primary screening
- A more logical choice for screening women vaccinated against HPV infection
Why is HPV testing an attractive option for cervical cancer screening?

- Increased detection of CIN3+ initially
- Decreased detection of CIN3+ and cancers in subsequent screening rounds
- Negative test result has high negative predictive value and low risk of CIN3+ or cancer for a number of years
- Allows longer screening intervals
- Increased detection of adenocarcinoma
Why prefer cotesting?

Pooled analysis of 7 European studies:
Risk of CIN3+

<table>
<thead>
<tr>
<th>6 years after negative co-test</th>
<th>3 years after negative cytology</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.28%</td>
<td>0.51%</td>
</tr>
</tbody>
</table>
CIN3+ Risk Following a Negative Test

- Cytology-
- HPV-
- Cytology-/HPV-

Cumulative incidence of CIN3+ (per 10,000)

Time since initial testing (mos.)
HPV Screening for Cervical Cancer in Rural India

Figure 2. Cumulative Incidence of Cervical Cancer of Any Stage (Panel A) and Stage II or Higher (Panel B) and Mortality (Panel C). HPV denotes human papillomavirus, and VIA visual inspection of the cervix with acetic acid.
HPV Test Options

- Arbor Vitae OncoE6 test
- Becton Dickinson (BD) Onclarity HPV assay
- Cepheid GeneXpert
- General Electric Healthcare FTA Elute card self-sample collection kit
- Hologic Aptima HPV test
- Qiagen
  - CareHPV
  - Hybrid Capture 2
- Roche Cobas HPV test
Global Progress in HPV Testing

February 2014

National programs
- Argentina
- Italy
- Mexico
- Netherlands
- United States

Pilot programs
- China
- Colombia
- El Salvador
- Germany
- India
- Nicaragua
- Paraguay
- Peru
- Republic of Georgia
- Rwanda
- Spain
- Uganda
Global Progress in Visual Inspection (VIA) for Cervical Cancer Screening

February 2014

National programs
Bangladesh
Bolivia
Cambodia
China
Colombia
El Salvador
Guatemala
Guyana
Indonesia
Kenya
Malawi
Morocco
Mozambique
Nicaragua
Panama
Paraguay
Peru
Philippines
Rwanda
Suriname
Tanzania
Thailand
Uganda
Vietnam
Zambia

Pilot programs
Angola
Benin
Bhutan
Botswana
Burkina Faso
Cameroon
Côte d’Ivoire
Ethiopia
Gambia
Ghana
Grenada
Guinea
Haiti
Honduras
India
Lesotho
Madagascar
Maldives
Mali
Mauritania
Myanmar
Namibia
Nepal
Niger
Nigeria
Republic of Congo
Senegal
Sierra Leone
South Africa
St. Lucia
Sudan (North)
Togo
Turkey
Vanuatu
Zimbabwe
Cost effectiveness

- Cost per LYS for a single lifetime screen with either single visit VIA or 2-visit HPV testing ranged from $10 to $467 per LYS for all countries studied.

- A once per lifetime screening strategy is highly cost-effective.

- When screening twice per lifetime at age 35 and 40, the cost per LYS remained less than the per capita GDP in each country for VIA or HPV testing depending on the country.
Cost effectiveness

- All of the cost-effectiveness analyses suggest that cervical cancer screening is cost-effective even in resource-poor nations with the potential to reduce cervical cancer incidence by at least 25% to 30%.

- Cervical cancer mortality reduction is most sensitive to:
  - quality of screening
  - coverage rates (screen more women rather than less women more frequently)
  - minimizing loss to follow-up of women with positive results
Introduction of HPV-testing in programmatic settings: Argentina model

SILVINA ARROSSI, Msc, PhD
Scientific Coordinator PNPCC/ INC
CERVICAL CANCER IN ARGENTINA

4,000 CASES DIAGNOSED ANNUALLY
2,000 WOMEN DIE ANNUALLY

CERVICAL CANCER MORTALITY RATES (ARS) by PROVINCES (2009-2011)
BENEFITS BASED ON HPV TEST SCREENING

- HIGHLY SENSITIVE (95%) AND REPRODUCIBLE TEST, ITS READING IS AUTOMATIC

- HIGH NEGATIVE PREDICTIVE VALUE, ALLOWING TO INCREASE THE SCREENING INTERVAL, SIMPLIFYING ACTIVITIES TO ACHIEVE HIGH SCREENING/TREATMENT COVERAGE

- IT ALLOWS SELF-COLLECTION BY WOMEN, REDUCING BARRIERS TO SCREENING

- HPV VACCINATION
INTRODUCTION OF HPV-TESTING

PROGRAMME ORGANIZATION

- HIGH COVERAGE
- QUALITY LABORATORIES
- ACCESS TO DIAGNOSIS AND TREATMENT
- ADEQUATE COMMUNICATION/TRAINING/EDUCATION
- INFORMATION SYSTEM
CONSENSUS AND PARTICIPATION

- Consensus and involvement of main actors
  - Main Scientific Societies
  - International agencies (PAHO, UNFPA, IARC)
  - Malbrán Institute
  - National Council of Women
  - Universities
  - Health research centers: University of BUENOS AIRES, CEDES
  - Regional health research networks (Colombia, México, Costa Rica)
HPV TESTING IN ARGENTINA

**STRATEGY**

- **HPV TEST**
  - **HPV (+) AND ABNORMAL PAP:** COLPOSCOPY
  - **CYTOLOGY FOR HPV (+) WOMEN**
  - **y más**

  - HPV Negative: Re-screening in three years
  - HPV+, Normal Pap: Re-screening in one year
REORGANIZATION OF LABORATORY NETWORK

HPV LABORATORY

CYTOLOGY LABORATORY

PATHOLOGY LABORATORY

CENTRALIZATION OF HPV TESTING AND CYTOLOGY
TRAINING ACTIVITIES

- TRAINING FOR SAMPLE TAKERS
  TRAINING FOR 10 PROVINCIAL TRAINERS IN CHARGE OF TRAINING ALL 150 SAMPLE TAKERS

- REFRESHER COURSES ON COLPOSCOPY AND TREATMENT TECHNIQUES FOR CERVICAL PATHOLOGY SERVICES (around 20 dx/tx units)

- TRAINING WORKSHOPS ON HPV TESTING FOR HEALTH SERVICE DIRECTORS (more than 200 participants)

- TRAINING OF MORE THAN 700 COMMUNITY HEALTH WORKERS
DEVELOPMENT OF COMMUNICATION MATERIALS FOR WOMEN AND HEALTH PROFESSIONALS

Key messages:
• informing women about the test, the link between HPV and cervical cancer prevention,
• decreasing possible anxiety and fear of a positive HPV result,
• stressing the fact that HPV is a common disease
• pre-cancerous lesions can be treated
INCORPORATION OF MODULE “HPV” IN SITAM

CANTIDAD DE TEST DE HPV POR DEPARTAMENTO
PCIA DE JUJUY, Período 01/01/2012 - 31/12/2012
Rango de Edad --> Desde 0 hasta 105

Totales Absolutos

<table>
<thead>
<tr>
<th></th>
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<th></th>
<th></th>
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<tbody>
<tr>
<td>COCHINOCAP</td>
<td>680</td>
<td>65</td>
<td>9.56</td>
<td>615</td>
<td>90.44</td>
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<tr>
<td>EL CARMEN</td>
<td>2,842</td>
<td>345</td>
<td>12.14</td>
<td>2,497</td>
<td>87.86</td>
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<td>GRAL MANUEL BELGRANO</td>
<td>10,497</td>
<td>1,472</td>
<td>14.02</td>
<td>9,021</td>
<td>85.94</td>
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<tr>
<td>HUMAHUACA</td>
<td>891</td>
<td>87</td>
<td>9.76</td>
<td>804</td>
<td>90.24</td>
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<td>LEDESMA</td>
<td>2,769</td>
<td>347</td>
<td>12.53</td>
<td>2,421</td>
<td>87.43</td>
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<tr>
<td>PALPALA</td>
<td>1,553</td>
<td>212</td>
<td>13.65</td>
<td>1,341</td>
<td>86.35</td>
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<tr>
<td>RINCONADA</td>
<td>6</td>
<td>0</td>
<td>0.00</td>
<td>6</td>
<td>100.00</td>
</tr>
<tr>
<td>SAN ANTONIO</td>
<td>43</td>
<td>5</td>
<td>11.63</td>
<td>38</td>
<td>88.37</td>
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<tr>
<td>SAN PEDRO</td>
<td>2,700</td>
<td>336</td>
<td>12.44</td>
<td>2,364</td>
<td>87.56</td>
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<tr>
<td>SANTA BARBARA</td>
<td>644</td>
<td>66</td>
<td>10.25</td>
<td>577</td>
<td>89.60</td>
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<tr>
<td>SANTA CATALINA</td>
<td>12</td>
<td>1</td>
<td>8.33</td>
<td>11</td>
<td>91.67</td>
</tr>
<tr>
<td>SUSQUES</td>
<td>327</td>
<td>39</td>
<td>11.93</td>
<td>288</td>
<td>88.07</td>
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<tr>
<td>TILCARA</td>
<td>792</td>
<td>92</td>
<td>11.62</td>
<td>700</td>
<td>88.38</td>
</tr>
<tr>
<td>TUMBAYA</td>
<td>138</td>
<td>10</td>
<td>7.25</td>
<td>128</td>
<td>92.75</td>
</tr>
<tr>
<td>VALLE GRANDE</td>
<td>82</td>
<td>5</td>
<td>6.10</td>
<td>77</td>
<td>93.90</td>
</tr>
<tr>
<td>YAVI</td>
<td>680</td>
<td>71</td>
<td>10.44</td>
<td>609</td>
<td>89.56</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>24,030</strong></td>
<td><strong>3,153</strong></td>
<td><strong>12.79</strong></td>
<td><strong>21,497</strong></td>
<td><strong>87.19</strong></td>
</tr>
</tbody>
</table>

Bajar listado en formato: [Excel][CSV][XML][Texto]
HPV self-collection offered by community health workers during home visits
TOTAL CHWs
$\approx 700$

CLINICIAN-COLLECTION AT HEALTH CENTERS
n= 97
2964 WOMEN

SELF-COLLECTION
n= 94
3049 WOMEN
RESULTS

- Four times more women screened in the self-collection group*

- Three times more CIN2+ cases detected in the self-collection group even if detection rate was slightly lower

- Self-collection for HPV testing offered by CHWs is an acceptable and highly effective method to increase screening uptake and increase the number of detected precancerous lesions.

*Results submitted for publication
MAIN LESSONS

HPV TESTING INTRODUCTION MUST BE PART OF A POLITICAL DECISION AND A OF A PUBLIC HEALTH STRATEGY

CONSENSUS IS AN KEY PROCESS COMPONENT, KEY ACTORS MUST BE PART OF THE PROJECT FROM THE VERY BEGINNING

HPV TESTING IS AN ATTRACTIVE TECHNOLOGY AND IT CAN BE USED TO MOBILIZE RESOURCES, MOTIVATE ACTORS... BUT IT CANNOT REPLACE THE NEED FOR ORGANIZATION...

WE STILL NEED TO HAVE ORGANIZED PROGRAMS!
Thanks!
The promise of self sampling

Dr. Carolyn Nakisige
Mulago National Referral and Teaching Hospital, Kampala, Uganda

“HPV test the key to universal screening for cervical cancer?”
10th September 2014
Challenges for screening

- 1 billion women >30 years-old who have not been screened
- Lack of trained personnel for pelvic evaluation
- Resistance to pelvic evaluation
- Competing priorities

Self- or vaginal sampling
START-UP Demonstration Project

- Screening methods compared
  - Pap smear
  - Visual inspection with acetic acid (VIA)
  - careHPV™ Test with cervical samples (collected by clinicians)
  - careHPV™ Test with vaginal samples (collected by women)
Study Results

- Enrollment August 2010 to November 2011.

- 4,726 women enrolled.

- 4,710 (99.7%) with complete screen results available.

- 4,701 (99.5%) provided a self-collected sample.

- 2,340 (49.5%) women provided self-reported HIV status at time of screening.
## Sensitivity and Specificity: CIN2+ Total population (N=3,146)

<table>
<thead>
<tr>
<th>Method of screening</th>
<th>Sensitivity* (95% CI)</th>
<th>Specificity (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>cervical careHPV™</td>
<td>88.5% (79.9, 94.3)</td>
<td>81.8% (80.3, 83.1)</td>
</tr>
<tr>
<td>vaginal careHPV™</td>
<td>77.0% (66.8, 85.4)</td>
<td>82.0% (80.5, 83.3)</td>
</tr>
<tr>
<td>VIA</td>
<td>73.6% (63.0, 82.4)</td>
<td>66.6% (64.9, 68.3)</td>
</tr>
<tr>
<td>Pap smear (ASCUS+)</td>
<td>69.0% (58.1, 78.5)</td>
<td>48.6% (46.8, 50.4)</td>
</tr>
</tbody>
</table>
Self-sampling: Acceptance

<table>
<thead>
<tr>
<th>Close-ended questionnaire</th>
<th>(N=913)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Self-sampling acceptability</strong></td>
<td></td>
</tr>
<tr>
<td>Sample collection was easy</td>
<td>89.7%</td>
</tr>
<tr>
<td>Prefer providing sample herself</td>
<td>64.5%</td>
</tr>
</tbody>
</table>

**Qualitative interviews:**

“I prefer self-sampling because it is easy, comfortable and simple to follow the instructions. If I had to go through it again, I would do self-sampling ten times more than provider sampling.”

“Although I was worried about the brush, the experience was not painful.”
Self-sampling: Concerns

<table>
<thead>
<tr>
<th>Concerns about sample collection*</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Not providing a ‘good sample’</td>
<td>46.7%</td>
</tr>
<tr>
<td>Hurting themselves</td>
<td>30.9%</td>
</tr>
<tr>
<td>Dropping brush/equipment to collect the sample</td>
<td>6.8%</td>
</tr>
</tbody>
</table>

Qualitative interviews:
“Most women accepted self-sampling, but for those who did not, the main reason they gave was not wanting to touch themselves.”
“The only worry I had was about the pain but there was no pain. It was with the help of the nurse which made it very easy”

*Respondents were able to provide multiple responses
Results from other sites

- **Self sampling:**
  - 99.5% Rural Uttah Pradesh
  - 82.8% Nicaragua
  - 78.6% Hyderabad.

- **Preferred self sampling as opposed to provider sampling:**
  - 93.1% Uttah Pradesh
  - 95.5% Hyderabad
  - 50% Nicaragua
Lessons learned

- HPV testing performed well in this demonstration study conducted in a resource-limited setting and its sensitivity for both cervical or vaginal samples was better than VIA or PAP.

- Self collected vaginal sampling was feasible and well accepted in low resource settings.

- During field implementation, additional use of culturally appropriate educational aid would promote self sampling.

- Trained providers should be available to collect or assist the women to collect the vaginal specimen.
How Uganda can benefit from this:

- Increased screening coverage.
- Given the limited resources like speculums, trained personnel and examination beds, self-sampling could benefit by collecting samples from more women.
- Potential for screening at scale in the community.
- Trained, female village health workers or volunteers could be mobilized for mass sample collection.
Thank you

- Dr. Carolyn Nakisige
carolynnakisige@yahoo.com
Global recommendations for HPV testing

Joanna M. Cain, MD, FACOG
Professor and Vice Chair, Ob/Gyn
Director, Office of Faculty Talent Management
University of Massachusetts School of Medicine
Chair, Subcommittee on Cervical Cancer Control, FIGO
Screening Options have clear parameters

- Goal is to SCREEN for precancer and treat
- At lowest cost
- At longest interval
- With highest sensitivity/Specificity
- WITH the resources that are available
- WHO Spring 2013 recognizes this as an ESSENTIAL health care service
Time lags with WHO guidance led to FIGO Global Guidance Oct 2009

• Key assumptions:

• “FIGO endorses a rights-based approach ..., where every woman has the right to the highest attainable standard of health care and the right to quality of life”

• Choose diverse tools that will have a significant and sustainable impact

• CREATE A BUNDLE OF SERVICES
FIGO: Stresses application to setting

- “the approach taken to screening can be as, or more, important than the test used…”
- “the most accessible and effective modality for a single visit approach is VIA/ cryo”
- Pointed to HPV tests as the next step, particularly if single visit, adequate personnel and low costs developed
- In the absence of those factors, VIA still important
There are new US screening guidelines: 2012

<table>
<thead>
<tr>
<th>Age and Test</th>
<th>Intervals</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>21 to 29</td>
<td>Every 3 years</td>
<td>HPV testing reflex only</td>
</tr>
<tr>
<td>Cytology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>30 and older</td>
<td>Every 3 years</td>
<td>If neg/neg: ? Possibly Longer intervals</td>
</tr>
<tr>
<td>Cytology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HPV and cytology</td>
<td>Every 5 years</td>
<td>Recent FDA 2014: HPV alone</td>
</tr>
<tr>
<td>65 and over, neg history or</td>
<td>Stop screening</td>
<td>10 years past last abnormal screen</td>
</tr>
<tr>
<td>Hyst , no CIN</td>
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</tbody>
</table>
2013: WHO guidelines for screening and treatment of precancerous lesions for cervical cancer prevention

• 2011 to 2013: Revision of the 2006 C4-GEP

• Systematic review of different treatment strategies

• 9 Final recommendations to evaluate present strategies or to consider in development of a strategy where none exists
Outcomes considered

- Cancer mortality
- Cervical cancer incidence
- Detected CIN2,3
- Major infections
- Maternal bleeding/ premature delivery
- Fertility
- Concurrent identification of STI with exam
- Minor infections post treatment
Strategies that emerged

• Targeted at women 30 and over
• Screening intervals depend on resources
• Even one lifetime screen makes a difference
• Prefer to Screen with HPV and treat, over VIA and treat.
• Where screening with HPV not feasible, then VIA and treat
Screening programme in place?

YES, VIA

NO

YES, Cytology f/u Colposcopy

Do you have enough resources to provide an HPV test?

Does not

Meets Quality Indicators

YES

NO

Resources for a sequence of tests?

yes

HPV followed by VIA

HPV alone

VIA alone

no

Cytology or HPV followed by colposcopy

Cryotherapy and/or LEEP must be part of a screen and treat programme
Additional findings

Don’t

• Use CKC as a standard treatment in screen and treat strategy
• Use cytology unless adequate coverage of population and meeting ALL quality/ performance testing

Think about

• **Intervals**: negative VIA or cytology: 3 to 5 years
• HPV negative: 5 or > years
• HIV+ or high endemic HIV: at least every 3 years if negative
• Post treatment screen: at 1 year
Screening is part of a BUNDLE of cervical cancer control

- HPV testing alone, mobile format, self testing
- Visual Inspection/ Acetic Acid (VIA)+RX
- With concurrent immediate treatment
- If only once, ? 30, 40, 50? (WHO between 30 and 49)
- Treated women need f/u 1 year (WHO)
- Vaccine, screen, treat pre invasive, treat invasive, quality control, track outcomes.........
This webinar and others in the series will be available on our website.

New issue briefs are also available!

www.CervicalCancerAction.org