Comprehensive Cervical Cancer Prevention and Control: Strategies and Guidelines

Nathalie Broutet - WHO
Cervical Cancer Worldwide in 2008

- 2\textsuperscript{nd} most common cancer in women and 5\textsuperscript{th} most common cancer overall
- An estimated 529,000 new cases and 274,000 deaths in 2008

Available at http://globocan.iarc.fr/
Over 100 types of HPV, most are not associated with cervical cancer or genital warts.

Most genital HPV infections are transient and are not associated with persistent cervical disease.
Transmission of genital HPV

• Mainly sexual
  – genital warts in couples
  – rare in virgins
  – increases with number of sexual partners
  – HPV concordance in couples
  – Highly contagious

• Vertical transmission
  – rare
HPV Natural History

- Cumulative risk HPV (Woodman, Lancet 2001):
  3 years: 44% / 5 years: 60%
  1075 women (HPV- at entry) / 15-19 years
  - Mean carriage: 4-8 months
  - Multiple infections common
  - Age distribution: generally decreasing in older ages but studies (Lazcano-Ponce, 2000) peak at <25 years, increase from 45 years birth cohort (Peto et al 2000)
Prevalence of HPV DNA in the general female population

Concordia, Argentina

Morelos, Mexico

Ho Chi Minh, Vietnam

Hanoi, Vietnam
Prevalence of cervical HPV DNA by age and HPV type in women with normal cytology: IARC Multi-centre HPV Prevalence Survey

India

Nigeria

Colombia

Mexico
# Conditions associated with HPV types 16, 18, 6, 11

<table>
<thead>
<tr>
<th>HPV 16, 18</th>
<th>Estimated</th>
</tr>
</thead>
<tbody>
<tr>
<td>attributable %</td>
<td></td>
</tr>
<tr>
<td>– Cervical cancer</td>
<td>70 %</td>
</tr>
<tr>
<td>– High grade cervical abnormalities</td>
<td>50 %</td>
</tr>
<tr>
<td>– Low grade cervical abnormalities</td>
<td>30 %</td>
</tr>
<tr>
<td>– Anal cancer</td>
<td>~70 %</td>
</tr>
<tr>
<td>– Vulva / Vagina / Penile</td>
<td>~40 %</td>
</tr>
<tr>
<td>– Head and neck cancers</td>
<td>~3-12 %</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>HPV 6, 11</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>– Low grade cervical abnormalities</td>
<td>10 %</td>
</tr>
<tr>
<td>– Genital warts</td>
<td>90 %</td>
</tr>
<tr>
<td>– Recurrent respiratory papillomatosis (RRP)</td>
<td>90 %</td>
</tr>
</tbody>
</table>

8 most common HPV types in 14,097 cases of invasive cervical cancer by region

- **All cases (n=14,097)**: 70%
- **Africa (n=1,373)**: 72%
- **Asia (n=5,652)**: 67%
- **Europe (n=4,334)**: 74%
- **North America (n=1,311)**: 76%
- **South and Central America (n=1,427)**: 65%
Integration of cervical cancer prevention services

Risk Factor

Prevention (HPV Vaccination)

Cancer Precursor

Sexual Behaviour

HPV and CIN

Early detection and treatment (Screening)

Invasive Cancer

Incidence

Integration of Prevention and Early Detection:
Shared resources, common surveillance systems

Steps in Natural History

E Franco 2009
Cervical Cancer Incidence Worldwide in 2008

Countries with HPV Vaccine in their National Immunization Schedule, 2010

Source: WHO/IVB database, 193 WHO Member States. Data as of April 2011
Date of slide: 03 August 2011
The issue

...we face a formidable gap between innovations in health (vaccines, tests, drugs and strategies for care) and their delivery to communities ...

Madon et al. Science December 2007
Comparison with other cancers: number of deaths among women 25-64 years old

The WHO comprehensive approach to cancer control: no screening without treatment
WHO Comprehensive Cervical Cancer Prevention and Control

- **Primary prevention**
  - Education to reduce high-risk sexual behavior to limit HPV transmission/acquisition
  - Delay age of first sexual intercourse
  - Condom use, limit number of partners, change in sexual behavior
  - HPV vaccination

- **Early detection (secondary prevention)**
  - Screening: Identify and treat precancerous lesions before they progress to cervical cancer
  - Early diagnosis: Identify and treat early cancer while the chance of cure is still good (reduces cervical cancer mortality)

- **Tertiary prevention**
  - Treatment of invasive cancer
  - Palliative care

Economic efficiency and disease-control best practices are in agreement for cervical cancer

Comprehensive approach: Programmatic interventions over the life course to prevent HPV infection and cervical cancer

**PRIMARY PREVENTION**

- **Girls 9-13 years**
  - HPV vaccination
  - From 10 years old and onward

- Health education and services, for example:
  - Sexual health education tailored to the age group
  - Providing contraceptive counseling and services including condoms
  - Prevent tobacco use and support cessation*

**SECONDARY PREVENTION**

- **Women > 30 years of age**
  - Screening and treatment
  - “screen and treat” with low cost technology VIA followed by cryotherapy
  - HPV testing for high risk HPV types (e.g. types 16, 18 and others)

**TERTIARY PREVENTION**

- **All women as needed**
  - Treatment of invasive cancer at any age
  - Ablative surgery
  - Radiotherapy
  - Chemotherapy

*Prevent tobacco use and support cessation is a reference to strategies or services that may be included in the comprehensive approach, but it is not specified in the provided text.
Opportunities

• New vaccines
  – Offer a completely new strategy for prevention

• New assays and new algorithms for improved cervical cancer screening
  – May permit identification of precancerous and cancerous lesions with greater accuracy, less complexity, and fewer barriers to access

• New technology offers new possibilities for widespread access to effective prevention, i.e., ability to reduce inequity

• New advocates, new interest, new energy
Primary Prevention: new opportunities

New target population: not one previously served routinely by immunization programs

Since 2006: Current WHO recommendations for HPV Vaccines

- HPV vaccines are prepared from virus-like particles using recombinant technology and are non-infectious.
- Two vaccines currently available and as of July 2009 both WHO prequalified (means UN can procure):
  - Cervarix® (bivalent): Prevents precancerous lesions/cancers from HPV types 16 and 18.
  - Gardasil®/Silgard® (quadrivalent): Prevents precancerous lesions, cancer, and anogenital warts from four HPV types 6, 11, 16 and 18.
- Neither vaccine will treat women with current HPV infection.
- Work best in HPV naïve individuals to the vaccine types.
- Quadrivalent vaccine licensed in >100 countries and bivalent vaccine licensed in >60 countries.
- Cost >US$100/dose in developed; reports of US$30/dose in some selected developing countries. (Needs to be in the order of <US$5/dose to be cost-effective)
<table>
<thead>
<tr>
<th></th>
<th>Gardasil®/Silgard®</th>
<th>Cervarix®</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Manufacturer</strong></td>
<td>Merck &amp; Co., Inc.</td>
<td>GlaxoSmithKline (GSK) Biologicals</td>
</tr>
<tr>
<td><strong>Prophylactic Vaccine</strong></td>
<td>VLP vaccine based on recombinant yeast technology</td>
<td>VLP vaccine based on recombinant baculovirus technology</td>
</tr>
<tr>
<td><strong>HPV types</strong></td>
<td>6, 11, 16, and 18 -- protects against cervical cancer and genital warts</td>
<td>16 and 18 -- protects against cervical cancer</td>
</tr>
<tr>
<td><strong>Adjuvant</strong></td>
<td>Alum (aluminium salt): 225 µg Aluminum Hydroxyphosphate Sulfate</td>
<td>AS04 (alum plus proprietary adjuvant MPL): 500 µg Aluminum Hydroxide 50 µg 3-deacylated Monophosphoryl Lipid A</td>
</tr>
<tr>
<td><strong>Regulatory status</strong></td>
<td>Country of manufacture: USA. Licensed by FDA (USA) in 2006 Licensed in &gt;100 countries</td>
<td>Country of manufacture: Belgium Approved by EMEA (EU) in 2007 Licensed &gt;60 countries</td>
</tr>
<tr>
<td><strong>Population licensed</strong></td>
<td>Females aged 9-26 yrs (age varies by country) Males aged 9-15 yrs few countries</td>
<td>Females aged 10-55 yrs (age varies by country)</td>
</tr>
<tr>
<td><strong>Composition</strong></td>
<td>20 µg HPV 6 / 40 µg HPV 11 / 40 µg HPV 16 20 µg HPV 18</td>
<td>20 µg HPV 16 20 µg HPV 18</td>
</tr>
<tr>
<td><strong>Schedule</strong></td>
<td>3 injections at months 0, 2, and 6</td>
<td>3 injections at months 0, 1, and 6</td>
</tr>
<tr>
<td><strong>Administration</strong></td>
<td>Liquid, intramuscular 0.5 mL injection</td>
<td>Liquid, intramuscular 0.5 mL injection</td>
</tr>
<tr>
<td><strong>Cold chain</strong></td>
<td>Storage +2°C to +8°C; must not be frozen</td>
<td>Storage +2°C to +8°C; must not be frozen</td>
</tr>
</tbody>
</table>
WHO Vaccine Policy

2009, 84, 117–132

Contents
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   WHO position paper
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OUTBREAK NEWS

Meningococcal disease, African meningitis belt

During the first 11 weeks of 2009 (1 January – 15 March), a total of 24 868 suspected cases of meningococcal disease, including 1513 deaths, were reported to WHO by countries of the African meningitis belt. Of these cases, >85% occurred in one epidemic focus encompassing northern Nigeria and Niger and were characterized by the predominance of Neisseria meningitidis serogroup A.

LE POINT SUR LES ÉPIDÉMIES

Méningococcie, ceinture de la méningite en Afrique

Au cours des 11 premières semaines de 2009 (du 1er janvier au 15 mars), un total de 24 868 cas présumés de méningite, dont 1513 mortels, ont été notifiés à l’OMS par les pays de la ceinture de la méningite. Parmi ces cas, >85% de ces cas se sont produits dans un seul foyer épidémique englobant le nord du Nigéria et le Niger et ils se caractérisent par une prédominance du sérogroupe A de Neisseria meningitidis.
WHO Position Paper — Primary Target

- WHO recommends that HPV vaccination should be introduced into national immunization programmes where:
  - prevention of cervical cancer & other HPV-related diseases is a public health priority,
  - vaccine introduction is programmatically feasible, and financially sustainable;
  - the cost-effectiveness aspects have been duly considered.
- Initially prioritize high coverage in primary target population of girls 9-10 through 13 years.
- Three doses over 6 months
- Need for booster doses not established. Still monitoring but very effective and likely long lasting protection.
WHO Position Paper – Other Groups

- Vaccination of older adolescent females or young women only recommended if a significant proportion likely to be naïve to vaccine-related HPV types; feasible, affordable, and cost-effective; does not divert resources from primary target or screening programmes.

- Vaccination of males for prevention of cervical cancer not recommended at this time.
  - Strategies that achieve >70% of young adolescent girls are more cost-effective than vaccinating both boys & girls.

- Immunocompromised females – limited data (more soon). HIV testing not needed. Vaccine benefits because of increased risk.
WHO Position Paper – Implementation

- HPV vaccination to be part of a coordinated cervical cancer and other HPV-related diseases prevention strategy including:
  - Education to reduce risk behaviours;
  - Screening;
  - Diagnosis and treatment.
- Seek opportunities to link with other adolescent health services.
- Not replace, undermine or divert funding from effective cervical screening programmes (30% of cervical cancer caused by HPV types other than 16 & 18).
- HPV vaccination should not be deferred in countries if above cannot be implemented at the time when vaccination could be introduced.
NHS Trust suspends cervical cancer vaccinations after girl, 14, dies within hours of jab

By DANIEL MARTIN
Last updated at 1:43 PM on 02nd October 2009
HPV vaccine: an entry point for integrated services to adolescents

- Adolescents represent 1 in 5 of the world's population.
- Adolescent girls are particularly vulnerable and deserve special attention.
- HPV vaccine is an effective new tool that targets adolescent girls.
- The HPV vaccine provides an opportunity to reach adolescents with a wider range of proven health information and services.
- The tools are available.
Education of patients, parent and communities

- Messages and patient or parental notification, approval or consent methods, should be tailored to local cultural context and information needs of various audiences (e.g., candidates, parents, clinicians).

- Messages should stress that vaccines:
  - Do not cure cancer
  - Prevent some HPV-related cancers
  - Are most effective when given before onset of sexual activity
  - Require 3 doses
  - Not recommended for pregnant females
  - Will not prevent HIV, other STI, or pregnancy
  - Quadrivalent vaccine programmes may note wart prevention.

- Educational campaigns are recommended to improve knowledge about cervical cancer and HPV to increase vaccine acceptance.
Still... secondary prevention is needed at adult age

- Up to 30% of all cervical cancer cases caused by HPV types other than 16 and 18: need for future cervical cancer screening
- Unknown on cx ca
- Screening of the non vaccinated population
Which screening test for which population and where?

- Conventional pap smear
- Hybrid Capture® 2 DNA test

Visual inspection with acetic acid (VIA)

Visual inspection with Lugol’s iodine (VILI)

CareHPV rapid DNA test
Secondary prevention: why new approaches are needed?

- Clinical expertise limited
- **Very** limited capacity for confirmatory or diagnostic testing
- Poor Infrastructure
  - Limited reporting, monitoring
  - Difficult to contact patients
- Available and accepted screening methods (pap smear) are not practical or accessible to the majority of women living in many countries
- Predictive value of actual screening tests will change with implementation of HPV vaccination
Alternative programmatic approaches for cervical cancer screening

- Conventional approach: screen, diagnose, confirm, and treat
- New paradigms: "screen and treat approaches" (ACCP)
  - Screen and treat (1 or 2 visits)
  - Screen, see (colposcopy), and treat (1 to 2 visits) (with later histological confirmation)
- Appropriate use of screening tests: cytology, visual methods, HPV DNA assays
- Supporting Ministries of Health to strengthen evidence-based cervical cancer screening programmes – different combinations may be used in different countries

RTCOG/ JHPIEGO Lancet, 2003; 361: 814-20
Denny et al., 2005 JAMA 294: 2173-81
Sankaranarayanan et al., Int J Cancer, 2004; 109: 461-7
## Characteristics of screening tests for secondary prevention

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Conventional cytology</th>
<th>HPV DNA tests</th>
<th>Visual inspection tests</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>VIA</td>
</tr>
<tr>
<td><strong>Sensitivity</strong></td>
<td>47-62%</td>
<td>66-100%</td>
<td>67-79%</td>
</tr>
<tr>
<td><strong>Specificty</strong> (for high-grade lesions and invasive cancer)</td>
<td>60-95%</td>
<td>62-96%</td>
<td>49-86%</td>
</tr>
<tr>
<td><strong>Comments</strong></td>
<td>Assessed over the last 50 years in a wide range of settings in developed and developing countries</td>
<td>Assessed over the last decade in many settings in developed and relatively few in developing countries</td>
<td>Assessed over the last decade in many settings in developing countries</td>
</tr>
<tr>
<td><strong>Number of visits required for screening and treatment</strong></td>
<td>2 or more visits</td>
<td>2 or more visits</td>
<td>Can be used in single-visit or 'see and treat' approach where outpatient treatment is available</td>
</tr>
</tbody>
</table>

Cluster Randomised Controlled Trial of VIA Screening, Dindigul District, India

- 113 Village clusters
- 80,252 eligible women aged 30-59 years
- Intervention: Single screening
- Follow-up: 7 years

Overall and age-specific hazard ratio for incidence for all cervical cancers and for cervical cancer deaths

<table>
<thead>
<tr>
<th>Group</th>
<th>Hazard ratio (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control group</td>
<td>1.0</td>
</tr>
<tr>
<td>Intervention group (VIA)</td>
<td></td>
</tr>
<tr>
<td><strong>Overall</strong></td>
<td></td>
</tr>
<tr>
<td>Cervical cancer incidence</td>
<td>0.75 (0.59-0.95)</td>
</tr>
<tr>
<td>Cervical cancer death</td>
<td>0.65 (0.47-0.89)</td>
</tr>
<tr>
<td><strong>30-39 years</strong></td>
<td></td>
</tr>
<tr>
<td>Cervical cancer incidence</td>
<td>0.62 (0.40-0.96)</td>
</tr>
<tr>
<td>Cervical cancer death</td>
<td>0.34 (0.18-0.66)</td>
</tr>
<tr>
<td><strong>40-49 years</strong></td>
<td></td>
</tr>
<tr>
<td>Cervical cancer incidence</td>
<td>0.82 (0.55-1.24)</td>
</tr>
<tr>
<td>Cervical cancer death</td>
<td>0.55 (0.31-1.00)</td>
</tr>
<tr>
<td><strong>50-59 years</strong></td>
<td></td>
</tr>
<tr>
<td>Cervical cancer incidence</td>
<td>0.76 (0.50-1.16)</td>
</tr>
<tr>
<td>Cervical cancer death</td>
<td>0.99 (0.58-1.66)</td>
</tr>
</tbody>
</table>

*C.I.: Confidence interval*
Efficacy of visual screening

- VIA has been associated with a **37% reduction** in the prevalence of CIN 2 and 3 lesions in a randomized trial in South Africa, when VIA positive women were treated with cryotherapy.

- A single round of **VIA screening followed by cryotherapy** has been associated with a **30% reduction in cervical cancer incidence** and 35% reduction in cervical cancer mortality in a randomized trial in Dindigul district, India.

Denny et al., JAMA 2005;294:2173-81
Sankaranarayanan et al., Lancet 2007;37:398-406
Example of the introduction of a VIA-cryo based programme in six African countries.
Sub Saharan Africa / WHO Pilot projects
Madagascar, Malawi, Nigeria, Tanzania, Uganda, Zambia 2007-2010
Basic Planning steps:

- Analysis the policies
- Assess magnitude of the problem;
- Create a National steering committee;
- Discuss and agree on cost effective intervention adequate to country context;
- Identify pilot sites;
- Implement intervention.
Strengthening Cervical Cancer Prevention Programme – Operational framework

- VIA
- VIA
- VIA
- VIA

- Palliative care
- Community level
- Awareness, Communication

- PHC level
- Secondary level
- Tertiary level

- VIA and cryotherapy
- Treatment

- Monitoring and evaluation
- Training

World Health Organization
encourage eligible women to have cervical cancer screening

counsel women about cervical cancer, risk factors and prevention

VIA

normal (-)
already in 3-5 years

abnormal (+)
eligible cryo

not eligible cryo

cancer (++)
refer for further evaluation or cancer treatment

cryo

follow-up at 1 year
## Sites activity

<table>
<thead>
<tr>
<th>Site</th>
<th>Country</th>
<th>No Screened</th>
<th>Screened</th>
<th>Positive N (%)</th>
<th>Final data collect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moshi</td>
<td>Tanzania</td>
<td>2,636</td>
<td>311</td>
<td>(11.8)</td>
<td>December 2008</td>
</tr>
<tr>
<td>Antananarivo</td>
<td>Madagascar</td>
<td>3,746</td>
<td>422</td>
<td>(11.3)</td>
<td></td>
</tr>
<tr>
<td>Blantyre</td>
<td>Malawi</td>
<td>1,221</td>
<td>151</td>
<td>(12.4)</td>
<td>February 2008</td>
</tr>
<tr>
<td>Sagamu</td>
<td>Nigeria</td>
<td>5,529</td>
<td>317</td>
<td>(5.7)</td>
<td>January 2008</td>
</tr>
<tr>
<td>Peramiho</td>
<td>Tanzania</td>
<td>2,754</td>
<td>213</td>
<td>(7.7)</td>
<td>December 2008</td>
</tr>
<tr>
<td>Masaka</td>
<td>Uganda</td>
<td>2,312</td>
<td>180</td>
<td>(7.8)</td>
<td>January 2009</td>
</tr>
<tr>
<td>Lusaka</td>
<td>Zambia</td>
<td>1,381</td>
<td>386</td>
<td>(28.0)</td>
<td>November 2008</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>19,579</strong></td>
<td><strong>1,980</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Note: The table above summarizes the sites activity with the number of people screened and the percentage of positive cases.*
Cervical cancer screening counsel in Tanzania

Visual inspection with acetic acid in Zambia

Interview of eligible women in Uganda

Woman reassurance in Madagascar
Preliminary results: Project summary

Total number of clients = 19,665

Clients not screened = 89 (0.4%)

Number of clients screened = 19,579 (99.6%)

Negative = 17,273 (88.2%)

Positive = 1,980 (10.1%)

Suspicious of cancer = 326 (1.7%)

Eligible for Cryo = 1,745 (88.1%)

Not eligible for Cryo = 236 (11.9%)

Cryo done = 1,071 (61.3%)

Lost/didn't go yet for cryo = 501 (29.8%)

Cryo not done = 173 (9.9%)

- To get permission
- Equipment not in order
- Other treatment offered
- Extensive lesion

Refer/Other management
Time lag between initial screening and cryotherapy

Time lag between initial VIA screening and cryotherapy

<table>
<thead>
<tr>
<th>Time between VIA and cryo</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Same day</td>
<td>43.8%</td>
</tr>
<tr>
<td>In one week</td>
<td>21.4%</td>
</tr>
<tr>
<td>7-29 days</td>
<td>17.0%</td>
</tr>
<tr>
<td>30-59 days</td>
<td>5.8%</td>
</tr>
<tr>
<td>60-90 days</td>
<td>3.3%</td>
</tr>
<tr>
<td>90+ days</td>
<td>8.7%</td>
</tr>
</tbody>
</table>

Note: The percentages indicate the distribution of time lags between initial VIA screening and cryotherapy.
Reasons why cryotherapy was not done

- Client refused, reason given: 29.5%
- Client decided to postpone: 28.8%
- Dense white lesion: 17.8%
- Lesion extends into endocervix: 15.3%
- Suspicious for cancer: 3.7%
- Client pregnant: 3.7%
- Other: 1.2%

N=163 (missing data 10)
Suspected Cancer at screening

Suspected cancer as at time of screening = 326

- Investigated = 131
  - Cancer = 108
    - Final treatment given = 104
  - No cancer = 10
    - Treatment given not known = 4
  - Outcome not known = 13
- No information about them = 195

Final treatment given = 104
Treatment given not known = 4
Sub Saharan Africa / WHO Pilot projects
Madagascar, Malawi, Nigeria, Tanzania, Uganda, Zambia

Challenges:

• Monitoring performance and quality of the programme
• Feed back from referral
• Lag between screening and treatment is long (waiting list)
• A too important proportion of cryotherapy eligible have not been treated
• Cryotherapy equipment shortage: frequent break down interrupts work
Challenges:

- Lack of human resources;
- Low coverage of health facilities;
- Lack of awareness, even among health care workers;
- Implementing supervision;
- Integration with other services at the primary health care level;
- Lack of funding.

Sub Saharan Africa / WHO Pilot projects
Madagascar, Malawi, Nigeria, Tanzania, Uganda, Zambia
Key issues for programmes

- Choice of the algorithm to increase screening and treatment coverage
- VIA/Cryotherapy is acceptable, but procurement is an issue
- Important lessons learnt for scaling-up in countries
  - Importance of supervision
  - Organisation of training
  - Monitoring and evaluation (lack of cancer registry)
  - Feedback of referral
- Access to treatment for high grade lesions and cervical cancer has to be in place
- Implementation of policy should include linkages with HIV and SRH as well as related programmes.
Key recommendations on screen and treat

For the update of the C4-GEP
Screening options (with or without triage or diagnosis confirmation), subpopulations and outcomes

<table>
<thead>
<tr>
<th>Screening options to evaluate</th>
<th>Subpopulations</th>
<th>Outcomes (after treatment)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. VIA</td>
<td>1. HIV+</td>
<td>1. Mortality from cervical cancer</td>
</tr>
<tr>
<td>2. HPV</td>
<td>2. Age (&lt;25, 25-30, 30-50, &gt;50)</td>
<td>2. Cervical cancer Incidence,</td>
</tr>
<tr>
<td>3. HPV (and if positive)</td>
<td></td>
<td>3. Detected CIN 2,3</td>
</tr>
<tr>
<td>followed by VIA</td>
<td></td>
<td>4. SE of treatment: Infections,</td>
</tr>
<tr>
<td>4. HPV (and if positive)</td>
<td></td>
<td>fertility/ prematurity, bleeding</td>
</tr>
<tr>
<td>followed by colposcopy +/- biopsies</td>
<td></td>
<td>5. Compliance to Treatment (vary by test)</td>
</tr>
<tr>
<td>5. Cytology (and if positive)</td>
<td></td>
<td>6. Coverage with screening method: does it actually improve coverage or acceptability (surrogate)</td>
</tr>
<tr>
<td>followed by colposcopy +/- biopsies</td>
<td></td>
<td>7. Secondary health benefits of screening visit (identify other diseases for example infections particularly STI, family planning information, sexual health information)</td>
</tr>
<tr>
<td>6. HPV (and if positive)</td>
<td></td>
<td>8. Compliance to Treatment (vary by test)</td>
</tr>
<tr>
<td>followed by reflex cytology, followed by colposcopy +/- biopsies</td>
<td></td>
<td>9. Secondary health benefits of screening visit (identify other diseases for example infections particularly STI, family planning information, sexual health information)</td>
</tr>
</tbody>
</table>
## Treatment options, subpopulations and outcomes

<table>
<thead>
<tr>
<th>Treatment options to evaluate</th>
<th>Subpopulations</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Cryotherapy</td>
<td>1. Size of lesion: &lt;&gt;75% portio or 3 out of 4 quadrants</td>
<td>1. CIN 2,3 (6 or 12 months, 24 months of follow up)</td>
</tr>
<tr>
<td>2. LEEP</td>
<td>2. HIV status</td>
<td>2. HPV negative (6,12 and 24 months)</td>
</tr>
<tr>
<td></td>
<td>5. Age &lt;&gt;50</td>
<td>5. Bleeding: two groups: Major (requires hospitalization/blood transfusion); and Minor (requires packing or suturing)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6. Damage to other organs/other surgery required – such as injury to bladder or urethra.</td>
</tr>
</tbody>
</table>
Traditional evaluation of screening tests

- Conduct systematic reviews of cohort studies of screening tests
- Calculate pooled sensitivity and specificity
- Compare tests

<table>
<thead>
<tr>
<th></th>
<th>HPV</th>
<th>VIA</th>
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<tbody>
<tr>
<td>Pooled sensitivity</td>
<td>95% (95% CI: 84 to 98)</td>
<td>69% (95% CI: 54 to 81)</td>
</tr>
<tr>
<td>Pooled specificity</td>
<td>84% (95% CI: 72 to 91)</td>
<td>87% (95% CI: 79 to 92)</td>
</tr>
</tbody>
</table>
What are the downstream consequences of screening?

Sensitivity

Specificity

TP
FP
TN
FN

Treated
Not treated

Mortality
Cervical cancer
CIN recurrence
Bleeding
Infection
Premature delivery
Over treatment
Pooled sensitivity and specificity of HPV and VIA - 2013

• Conduct systematic reviews of cohort studies of screening tests
• Calculate pooled sensitivity and specificity
• Compare tests

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FLOWCHARTS FOR SCREEN AND TREAT STRATEGIES WITH VIA

- **Negative**
  - Rescreen every 5 or more years
  - **HIV+ rescreen before 3 years**

- **Positive**
  - Eligible for cryotherapy, treat with cryotherapy

- **Suspicious for cancer**
  - Refer to appropriate diagnosis and treatment

- **Post-treatment follow-up at 1 year**
FLOWCHARTS FOR SCREEN AND TREAT STRATEGIES for HPV followed by VIA as triage

HPV

Negative
- Rescreen every 5 or more years
- HIV+ rescreen before 3 years

Positive

VIA

VIA negative
- Rescreen after 1 year

VIA positive
- Eligible for cryotherapy, treat with cryotherapy
- Not eligible for cryotherapy, treat with LEEP

Suspicious for cancer
- Refer to appropriate diagnosis and treatment

Post-treatment follow-up at 1 year

Rescreen every 5 or more years

HIV+ rescreen before 3 years
FLOWCHARTS FOR SCREEN AND TREAT STRATEGIES WITH HPV alone – VIA used to determine eligibility for cryotherapy

HPV

- Negative
  - Rescreen every 5 or more years
    - HIV+ rescreen before 3 years
  - Eligible for cryotherapy, treat with cryotherapy
  - Post-treatment follow-up at 1 year

- Positive
  - Visual inspection with acetic acid
    - Suspicious for cancer
      - Refer to appropriate diagnosis and treatment
    - Not eligible for cryotherapy, treat with LEEP
FLOWCHARTS FOR SCREEN AND TREAT STRATEGIES WITH HPV or cytology followed by colposcopy with or without biopsy

HPV or cytology

HPV negative or normal cytology

- Rescreen every 5 years or more
- HIV+ rescreen before 3 years

HPV+ or ASCUS+

- Colposcopy positive
  - Biopsy
    - Eligible for cryotherapy, treat with cryotherapy or LEEP
      - If CIN 2-3, treat according to recommendations
    - Not eligible for cryotherapy, treat with LEEP
      - Post-treatment follow-up at 1 year
  - Colposcopy negative
    - Suspicious for cancer
      - Refer to appropriate diagnosis and treatment
    - Rescreen every 5 years or more
      - HIV+ rescreen before 3 years

- Colposcopy negative
  - Eligible for cryotherapy, treat with cryotherapy or LEEP
  - Not eligible for cryotherapy, treat with LEEP
  - Post-treatment follow-up at 1 year
  - Rescreen every 5 years or more
    - HIV+ rescreen before 3 years
  - Suspicious for cancer
    - Refer to appropriate diagnosis and treatment
Strengthening Cervical Cancer Prevention Programme – Operational framework

- Palliative care
- Community level
  - VIA or HPV
  - VIA or HPV
  - VIA or HPV
  - VIA or HPV
  - VIA and cryotherapy
- Awareness, Communication
- PHC level
  - Cyto / colo and biopsies
  - VIA and cryotherapy
- Secondary level
  - Treatment
- Tertiary level
- Training
- Monitoring and evaluation
Choice of a test should be based on:

• Effectiveness of the test (sensitivity/specificity) in the target women.

• Capacity to reach (coverage) a significant proportion (at least 80%) of target women
  – Local infrastructure where the test will be used

• Cost
What coverage requires

• Increase availability and access to quality services: tests should be easy to perform and acceptable at the level of the health system where they are intended to be used

• Treatment has to be available

• Information and knowledge about the existence of quality services to ensure women to go to services
WHO standards for cervical cancer prevention and control

[Link to WHO standards]

http://www.who.int/reproductivehealth/en/
<table>
<thead>
<tr>
<th>Context</th>
<th>Recommendation</th>
<th>Quality of evidence</th>
<th>Strength</th>
</tr>
</thead>
<tbody>
<tr>
<td>Use of cryotherapy for prevention of CIN</td>
<td>1a. The expert panel recommends cryotherapy over no treatment</td>
<td>★★★★</td>
<td>Strong</td>
</tr>
<tr>
<td></td>
<td>1b. In settings where LEEP is available and accessible, the expert panel suggests treatment with LEEP over cryotherapy</td>
<td>★★★★</td>
<td>Conditional</td>
</tr>
<tr>
<td>Lesion size</td>
<td>2. Among women with CIN lesions covering more than 75% of the ectocervix, or with lesions extending beyond the cryo tip being used, the expert panel suggests performing or referring for excisional therapy</td>
<td>★★★★</td>
<td>Conditional</td>
</tr>
<tr>
<td>Lesions extending into the endocervical canal</td>
<td>3a. In settings where LEEP is available and accessible, and women present with CIN lesions extending into the cervical canal, the expert panel suggests treatment with LEEP over cryotherapy</td>
<td>★★★★</td>
<td>Conditional</td>
</tr>
<tr>
<td></td>
<td>3b. In settings where excisional procedures (e.g. LEEP, laser or CKC) or referral to additional treatment are not available, the expert panel suggests that women with lesions extending into the endocervical canal be treated with cryotherapy</td>
<td>★★★★</td>
<td>Conditional</td>
</tr>
<tr>
<td>Cryotherapy technique and procedure</td>
<td>4. The expert panel suggests double freeze using a 3 minute freeze, 5 minute thaw, 3 minute freeze cycle over single-freeze cryotherapy</td>
<td>★★★★</td>
<td>Conditional</td>
</tr>
<tr>
<td></td>
<td>5. The expert panel recommends cryotherapy using either carbon dioxide ($CO_2$) or nitrous oxide ($N_2O$) gas</td>
<td>★★★★</td>
<td>Strong</td>
</tr>
<tr>
<td></td>
<td>In settings where both gases are available, the expert panel suggests cryotherapy with $CO_2$ rather than with $N_2O$</td>
<td>★★★★</td>
<td>Conditional</td>
</tr>
<tr>
<td></td>
<td>6. The expert panel recommends that the “cough technique” should not be used during cryotherapy</td>
<td>★★★★</td>
<td>Strong</td>
</tr>
<tr>
<td></td>
<td>7. The expert panel suggests that prophylactic antibiotics should not be used when providing cryotherapy</td>
<td>★★★★</td>
<td>Conditional</td>
</tr>
<tr>
<td>Context</td>
<td>Recommendation</td>
<td>Quality of evidence</td>
<td>Strength</td>
</tr>
<tr>
<td>----------------------------------------------</td>
<td>------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
<td>---------------------</td>
<td>----------</td>
</tr>
<tr>
<td>Providers</td>
<td>8. The expert panel recommends that health-care workers (including non-physicians) trained in cryotherapy perform the procedure for women when it is indicated. The expert panel also suggests that trained nurses or trained midwives rather than physicians may perform cryotherapy.</td>
<td>☄️☄️☄️☄️</td>
<td>Strong</td>
</tr>
<tr>
<td>Use of cryotherapy during pregnancy</td>
<td>9a. In pregnant women, the expert panel suggests deferring cryotherapy until after pregnancy.</td>
<td>☄️☄️☄️☄️</td>
<td>Conditional</td>
</tr>
<tr>
<td>Use of cryotherapy during pregnancy</td>
<td>9b. In women whose pregnancy status is unknown (or there is no clinical evidence of pregnancy), the expert panel suggests using cryotherapy.</td>
<td>☄️☄️☄️☄️</td>
<td>Conditional</td>
</tr>
<tr>
<td>Retreatment of CIN lesions with cryotherapy</td>
<td>10a. The expert panel recommends cryotherapy over no treatment for women who screen positive after prior cryotherapy treatment.</td>
<td>☄️☄️☄️☄️</td>
<td>Strong</td>
</tr>
<tr>
<td>Retreatment of CIN lesions with cryotherapy</td>
<td>10b. In settings where LEEP is available and accessible, the expert panel suggests treatment with LEEP over cryotherapy for women who screen positive after prior cryotherapy treatment.</td>
<td>☄️☄️☄️☄️</td>
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Technical specifications for cryotherapy equipment

Technical specification for cryotherapy equipment

This manual addresses key issues that will ensure the procurement and effective use of quality assured cryotherapy equipment to support the early management of precancerous cervical lesions as part of a comprehensive cervical cancer prevention programme.

Contents:
- Technical Basis Paper. Cryotherapy equipment for the treatment of pre-cancerous cervical lesions
- Generic Specification. Cryotherapy equipment for the treatment of pre-cancerous cervical lesions
- Advice and guidance. gas supplies for cryotherapy treatment of precancerous cervical lesions
- Recommendations for handling gas cylinders
- Procurement guidance.
QA/QC for VIA-cryotherapy based programmes

Companion guides to (C4GEP)

Quality control and quality assurance for visual inspection with acetic acid (VIA) and for cryotherapy for cervical cancer prevention and control

Intended primarily for programme managers and other stakeholders working in public health programmes for cervical cancer prevention and control.

Purpose

This guide focuses on quality control and quality assurance for VIA and cryotherapy, given that both have been extensively evaluated through cross-sectional studies, prospective randomized trials and demonstration programmes.

The recommendations provided in this document need to be adapted to national policies, health systems, needs, language and culture.
Cervical cancer indicators

Performance indicators

**Screening rate of the target population** (women aged 30–49 years): Percentage of women aged 30–49 years who have been screened for the first time with VIA in the previous 12-month period.

**Positivity rate**: Percentage of screened women aged 30–49 years with a positive VIA test result in the previous 12-month period.

**Treatment rate**: Percentage of VIA-positive women receiving treatment in the previous 12-month period.

Result indicator

**Coverage rate indicator**: Percentage of women aged 30–49 years who have been screened with VIA or another screening test at least once between the ages of 30 and 49 years.

Impact indicator

Cervical cancer age-specific incidence.
Purpose of the update

- Health education to be expanded
- HPV vaccines to be included
- New data on use of screening tests and algorithms
- New data on HIV and cervical cancer:
  - Natural history of HPV infection in HIV+ women
  - Age of first screening
  - Frequency of screening tests
  - Management of positive screening tests in HIV positive women (cryotherapy, LEEP) and follow-up, also safety issues
- HIV screening in women undergoing cervical cancer screening – how to incorporate?
Why offer counselling and testing for HIV at cervical cancer screening?
Objectives of a national programme

• **General Objective:**
  Contribute to reducing the incidence of cervical cancer in the region X (or in the country Y)
  = Reduce the incidence of cervical cancer by 50% within 20 years

• **Specific objectives:**
  – Inform 90% of the target population in 5 years
  – Detect 30% of women 35-50 years old the first year and 90% after 5 years
  – Treat 100% of cases of precancerous lesions detected
  – Treat 100% of cases of cervical cancer diagnosed
Process measures

Monitor the level of coverage

Proportion of women screened

Target population

Guinea
Process measures

Related interventions screening, diagnosis, treatment and follow-up

- Detection rate

- Proportion of women with positive test eligible for cryo

- The proportion of women with positive screening tests / cryo / referral visit for further investigation
Process measures

Information about the performance and the quality

- Proportion of women with inadequate/inconclusive tests

- Proportion of women with inadequate/inconclusive screening tests receiving repeat tests

- Time taken to deliver the screening test results, diagnosis and/or treatment

- Proportion of women with absence of treatment management
Impact measure

Cancer registry
Information system: Recommendations

- for positive cases: keep full data
- for negative cases: count only the cases

Advantages:

- System not overloaded
- Data quantity highly reduced
- Simple programme monitoring
Cervical cancer data linkage

Screening programme / District A

Primary Health services

Laboratory

Regional monitoring & surveillance system

District services

Screening programme / District X

Regional monitoring & surveillance system

Screening programme / District Y

National monitoring & surveillance system
Model for a comprehensive cervical screening information and reporting system

- Visual inspection clinic (VIA)
  - personal identifiers
  - basic test data

- Cytology/HPV laboratories
  - personal identifiers
  - other personal data
  - basic smear data
  - added smear data

- Histopathology laboratories
  - personal identifiers
  - basic biopsy/treatment data
  - added specimen data

- Colposcopy/treatment centres
  - personal identifiers
  - colposcopic impression
  - treatment data

Process measures

- Select Edit Standardize Link
- Cervical Screening Database
- Periodic linkages with external databases

Impact measures

- Health centres, physicians
- Cytology/HPV laboratories
- Histopathology laboratories
- Screening programme
- Government, researchers
- Women

- Hospital discharges
  - list of target population
  - cervical cancers
  - deaths
  - hysterectomies
New stakeholders and partners for cervical cancer prevention and control

- Ministry of health: Immunization, sexual and reproductive health, adolescent health, cancer control, and HIV prevention partners,
- Ministry of education: school health,
- Women's groups
- Community based group to reach girl out of school

Interdisciplinary coordination needed
Challenges

• Human resources
  – Shortage of trained health workers for vaccinating, screening, treating

• Organization
  – Need coordination between partners who are not used to working together: immunization, sexual and reproductive health, cancer control, child and adolescent health, school health, health systems strengthening

• Identifying best affordable programmatic practices for a given country
  – Vaccine delivery
  – Screening-treatment algorithms
  – Cancer treatment center

• Establishing monitoring and evaluation

• Financial resources
  – High costs of new technologies
  – New costs for new delivery systems
  – Economic downturn so government and donor resources limited
Gaps in sexual and reproductive health

- High unmet need for family planning: estimated 215 million women
- Uneven and slow progress on maternal mortality: 2.3% annual reduction (5.5% for MDG)
- High rates of unsafe abortion: 47,000 deaths annually
- High rates of teenage pregnancy and unsafe sex
- High rates of sexually transmitted infection: 448 million cases
- Gender inequality and human rights issues
- +/- 500,000 new cases of cervical cancer with 275,000 deaths
Example of programmatic linkages: sexual and reproductive health and HIV services

Existing services

Primary health care (PHC) services

Proposed linkages

Family planning services

Antenatal care (ANC)

STI services

Cervical / breast cancer screening

VCT/PITC

BCC

Expected outcome

Increased access to prevention and care

Improved quality of sexual and reproductive health services

$voluntary counselling and testing (VCT); provider-initiated testing and counselling (PITC); behaviour change communication (BCC):
Challenges

Overcoming the transfer and application of knowledge gap

To take evidence into practice
Acknowledgments

http://www.who.int/reproductivehealth/topics/cancers/index.html

WHO Working group
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Eric Lucas