Cervical Cancer Screening in Low Resource Settings

The Honorable Minister of Health
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Declaration of Conflict of Interest

• Current Minister of Health, Nigeria

• Served as Consultant/Speaker’s Bureau and supported by GSK

• Served on IDMC for HPV Studies
Outline

• Role of Screening in CC control
• Global Spread of Screening
• Peculiarities of Low Resource Settings
• Feasible Evidence-based Options for LRS
• Imperatives for establishing a sustainable CC Screening Programme in LRS
• Recommendations
• Concluding remarks
Acknowledgements

• The President of RCOG
• LOC
• Greetings from Nigeria
• The High Commissioner of Nigeria in South Africa
Cervical cancer in Low Resource Settings

- 85% of incident CC occur in less developed regions (low and middle-income countries)
  - Represent 12% of women’s cancers in those regions

- 87% CC of deaths resulting from cervical cancer occur in these less-developed regions

- Regions with the highest mortality rates: Southeast Asia, Western Pacific regions, followed by India and Africa

Cervical Cancer Prevention...

- A preventable disease
- Well recognized causative factor
- Well defined pathologic pathway
- Accessible Cervix
- Easily detectable precursor lesions
- Treatable pre-malignant phase
The philosophy of cervical cancer prevention is based on key drivers

**SEX**
- Sexual activity

**HPV**
- Persistence of HPV infection

**CANCER**
- Premalignant lesion of the cervix
- Cervical cancer
Primary Goal of CC Screening

• Accurate detection and timely treatment of CIL at Population level for the purpose of CC Prevention.

.........Jeronimo J et al., Journal of Global Oncology POBP dl on 180317.
Cervical Cancer and Underdevelopment

- **Economies**
  - Reduced labor supply
  - Reduced labor outputs (e.g., cost of absenteeism)
  - Additional costs to employers (e.g., productivity, insurance)
  - Lower returns on human capital investments
  - Lower tax revenues
  - Increased public health and social welfare expenditures

- **Health systems**
  - Increased consumption of NCD-related healthcare
  - High medical treatment costs (per episode and over time)
  - Demand for more effective treatments (e.g., cost of technology and innovation)
  - Health system adaptation (e.g., organization, service delivery, financing, and adaptation costs)

- **Households and individuals**
  - Reduced well-being
  - Increased disabilities
  - Premature deaths
  - Household income decrease, loss, or impoverishment
  - Higher health expenditures, including catastrophic spending
  - Savings and assets loss
  - Reduced opportunities

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**Country productivity and competitiveness**

**Fiscal pressures**

**Health outcomes**

**Poverty, inequity, and opportunity loss**
The progression: ‘A failure of strategic approach!'
Typical Health system in Low Resource Settings

- Weak Health system
  - Tertiary more functional than Primary Health Care system
  - Lack of well organized follow-up system
- Poor referral system
- Weak coordination
- Human Resource gaps
  - Shortage of pathologists, laboratories, colposcopists and other health providers, which limits the establishment of a traditional screening program.
  - For example, some countries in sub-Saharan Africa have no pathologists, and/or laboratories.
- Sub-optimal infrastructure
- Heavy economic and psychosocial burden
- Poor Funding
  - Health insurance guarantee access & coverage
Principles of Cervical cancer prevention

- **Primary prevention**
  - Behavioural change communication: Responsible sexual behaviour
  - HPV vaccination

- **Secondary prevention**
  - Cytological screening (Pap smear)
  - Visual inspection techniques
  - HPV DNA testing

- **Tertiary prevention**
  - Detection of early disease
  - Radiotherapy
  - Radical surgery
Age Standardized Incidence and Mortality Rates in British Columbia, 1955-1995

Number per 100,000 by Year:
- Incidence
- Mortality
Organized versus opportunistic cervical cancer screening

- Cervical cancer mortality trends indicate organized screening programmes are more effective than opportunistic screening\(^1,2\)
  - A case-control study in Finland demonstrated organized screening gave a greater reduction in the relative risk of cervical cancer than opportunistic screening:\(^3\)
    - Organized screening, odds ratio = 0.25; 95% CI: 0.1–0.5
    - Opportunistic screening, odds ratio = 0.57; 95% CI: 0.3–1.1
  - The EU and IARC guidelines on cervical cancer screening recommend organized screening programmes\(^2\)

<table>
<thead>
<tr>
<th>Country</th>
<th>Screening modality (1960s–1990s)</th>
<th>Decrease in cervical cancer mortality, 1960s–1990s*, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Finland</td>
<td>Organized</td>
<td>82</td>
</tr>
<tr>
<td>Sweden</td>
<td>Organized</td>
<td>65</td>
</tr>
<tr>
<td>Norway</td>
<td>Opportunistic</td>
<td>41</td>
</tr>
</tbody>
</table>

* In the late 1960s, Finland and Sweden introduced nationwide organized cervical cancer screening programmes; Norway had organized screening in one only county covering ~ 5% of the population.

Increased screening has greatly reduced the incidence of cervical cancer in England

- Improvements in cervical screening coverage in England have led to a 35% decrease in cervical cancer cases in under a decade

Age-standardized incidence of invasive cervical cancer and coverage of screening; England, 1971–1995

Screening Is Vital
But Screening Programmes Are Not Available In Low-Resource Settings
The great question!

- Why are there almost no developing countries with an effective screening program?
Organization and Politics

- Cancer screening is a complex process
- It is not the sum of all individual diagnostic tests
- Compliance and Coverage are critical
- Feedback is crucial
- It is a public intervention with responsibility
- It involves commitment and money
- A major challenge is the effective linking of communities to screening services
Obstacles on the Path of Screening

• Factors in the Community
• Choice of Appropriate Screening Method
• Trained Personnel to Handle the Various Aspects of Screening and Subsequent Management of those Detected to have Lesions at the time of Screening
The Community

• Ignorance about Cancer
• Lack of Awareness that Screening Methods Were Available for some Cancers
• Cultural Reliance on Traditional Healers
• Prejudices about Orthodox Health Services
• Reluctance of Women to have Strangers Examining their Genitalia because of Cultural and Religious inhibitions
Facilities

- Staining Equipment
- Colposcopy
- Treatment
  - Cryotherapy
  - LEEP
Cervical cancer prevention and control

Comprehensive Cervical Cancer Prevention & Control

INTEGRATION

**PRIMARY PREVENTION**
Girls 9-13 years
- HPV vaccination

**SECONDARY PREVENTION**
Women >30 years of age
- Screening and treatment as needed
  - "Screen and treat" with low cost technology VIA followed by cryotherapy
  - HPV testing for high risk HPV types (e.g. types 16, 18 and others)

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

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

• Reduce the burden of CC

• Early diagnosis

• Treatment is cheap when picked early

• Choice of screening method
  • High sensitivity
  • High specificity
  • High predictive values
Target population to be considered

- General population
- HIV Population
- Other immunosuppressed populations
- Pregnancy
- Postpartum mothers
- Post-hysterectomy women (Total vs sub-total)
- Follow-up care
Issues to consider before making a choice

• Available resources

• Cost effective methods

• Capacity of health care providers

• Infrastructure
Tests Available

- Visual Inspection
- VIA
- VILI
- Pap Smear
  - Conventional
  - LBC
  - Pap Net
- HPV DNA Testing
- Cervicography
- Polar Probe
- Biomarkers
The Pap Smear

- Identifies Abnormal And Pre-cancerous Cells On The Cervix
- These Can Be Monitored and Treated Before They Progress To Cervical Cancer

Expensive And Time-consuming For Healthcare Professionals And Individuals

Dr Papanicolaou

Imperatives for sustainable National CC screening programme

- **Catchment Age**
  - HPV DNA testing – 30 – 49 years
  - VIA - ≥ 35 years

- **Intervals of screening**
  - General population: HPV DNA testing every 10 years (2 – 3 times per lifetime)
  - HIV or Immunosuppressed – Intervals halved

- **Choice of Screening**
  - Primary Screening – HPV DNA test alone or VIA alone
  - Co-testing – HPV DNA test & VIA

- **Age to stop screening** – 55 – 65 years

- **Sample collection techniques (Provider vs self sampling)**
Imperatives for sustainable National CC screening programme

• Develop the Health System
• Strengthen Capacity for Surgery and Radiotherapy
• Develop Public Health Education programme
• Start Small
• Grow Big
### Test Qualities of VIA When Performed as Primary Screening in Low-Resource Settings

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th># Cases</th>
<th>Detection of HGSIL &amp;</th>
<th>Sensitivity a</th>
<th>Specificity a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Megevand et al (1996)</td>
<td>South Africa</td>
<td>2,426</td>
<td></td>
<td>65%</td>
<td>98%</td>
</tr>
<tr>
<td>Sankaranarayanan et al (1998)</td>
<td>India</td>
<td>2,935</td>
<td></td>
<td>90%</td>
<td>92%</td>
</tr>
<tr>
<td>Sankaranarayanan et al (1999)</td>
<td>India</td>
<td>1,351</td>
<td></td>
<td>96%</td>
<td>68%</td>
</tr>
<tr>
<td>University of Zimbabwe/JHPIEGO (1999)</td>
<td>Zimbabwe</td>
<td>2,148</td>
<td></td>
<td>77%</td>
<td>64%</td>
</tr>
<tr>
<td>Belinson (2001)</td>
<td>China</td>
<td>1,997</td>
<td></td>
<td>71%</td>
<td>74%</td>
</tr>
<tr>
<td>Denny et al (2002)</td>
<td>South Africa</td>
<td>2,754</td>
<td></td>
<td>70%</td>
<td>79%</td>
</tr>
<tr>
<td>Sankaranarayanan &amp; Wesley (2003)</td>
<td>India</td>
<td>4,444</td>
<td></td>
<td>83%</td>
<td>87%</td>
</tr>
</tbody>
</table>

*aEstimated from the number provided in the manuscript and does not reflect adjustment(s) for verification bias.

*Modified from JHPIEGO Corporation*
Evidence that VIA alone reduced CC morbidity & Mortality

Effect of VIA Screening by Primary Health Workers: Randomized Controlled Study in Mumbai, India

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Effectiveness of VIA, Pap, and HPV DNA Testing in a Cervical Cancer Screening Program in a Peri-Urban Community in Andhra Pradesh, India

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Abstract

Background: While many studies have compared the efficacy of Pap cytology, visual inspection with acetic acid (VIA) and human papillomavirus (HPV) DNA assays for the detection of cervical intraepithelial neoplasia and cancer, few have evaluated the program effectiveness.

Methods and Findings: A population-based sample of 5603 women from Medchal Mandal in Andhra Pradesh, India were invited to participate in a study comparing Pap cytology, VIA, and HPV DNA screening for the detection of CIN3+. Participation in primary screening and all subsequent follow-up visits was rigorously tracked. A 20% random sample of all women screened, in addition to all women with a positive screening test result underwent colposcopy with directed biopsy for final diagnosis. Sensitivity, specificity, positive and negative predictive values were adjusted for verification bias. HPV testing had a higher sensitivity (100%) and specificity (90.6%) compared to Pap cytology (sensitivity = 78.2%; specificity = 86.0%) and VIA (sensitivity = 31.6%; specificity = 87.5%). Since 58% of the sample refused involvement and another 28% refused colposcopy or biopsy, we estimated that potentially 87.6% of the total underlying cases of CIN3 and cancer may have been missed due to program failures.

Conclusions: We conclude that despite our use of available resources, infrastructure, and guidelines for cervical cancer screening implementation in resource limited areas, community participation and non-compliance remain the major obstacles to successful reduction in cervical cancer mortality in this Indian population. HPV DNA testing was both more sensitive and specific than Pap cytology and VIA. The use of a less invasive and more user-friendly primary screening strategy (such as self-collected swabs for HPV DNA testing) may be required to achieve the coverage necessary for effective reduction in cervical cancer mortality.

Next generation biomarkers for screening

• p16INK4a immunocytochemistry (p16 ICC)
  • p16 ICC has demonstrated high sensitivity and specificity that is similar to or better than cytology testing for > CIN2 and > CIN3 among women with hrHPV-positive results.

• Ki-67, a cell proliferation marker, has been included with p16 ICC (p16/Ki-67 ICC) as a dual stain to create a morphology-independent test
Global Progress in Visual Inspection (VIA) for Cervical Cancer Screening as of November 2016
Global Progress in HPV DNA Testing for Cervical Cancer Screening as of November 2016
Coverage for cervical cancer screening programmes

% of countries reporting each range of participation for cervical cancer screening programmes

% age countries reporting cervical cancer screening programmes as organised / population-based or opportunistic
Countries with available policies for Cervical Cancer Prevention and Control in Africa

<table>
<thead>
<tr>
<th>Health promotion</th>
<th>HPV service delivery</th>
<th>HPV vaccine</th>
<th>Cervical cancer</th>
<th>Cancer</th>
<th>NCDs</th>
<th>Women and Gender</th>
<th>RH</th>
<th># of Countries</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>8</td>
<td>10</td>
<td>5</td>
<td>6</td>
<td>3</td>
<td>8</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>2</td>
<td>0</td>
<td>6</td>
<td>4</td>
<td>2</td>
<td>8</td>
<td>10</td>
<td>0</td>
</tr>
</tbody>
</table>

Source: WHO AFRO-10 baseline report

Policy not Available  ■ Policy Available

COPYRIGHT OF SPEAKER
In line with its Global health mandate, guidance and normative documents on cervical cancer have been developed/updated.

Purpose
To provide resource-stratified, evidence-based recommendations on the secondary prevention of cervical cancer globally.

Methods
ASCO convened a multidisciplinary, multidimensional panel of oncology, primary care, epidemiology, health economic, cancer control, public health, and patient advocacy experts to produce recommendations reflecting four resource-tiered settings. A review of existing guidelines, a formal consensus-based process, and a modified ADAPTE process to adapt existing guidelines were conducted. Other experts participated in formal consensus.

Results
Seven existing guidelines were identified and reviewed, and adapted recommendations form the evidence base. Four systematic reviews plus cost-effectiveness analyses provided indirect evidence to inform consensus, which resulted in ≥ 75% agreement.

Recommendations
Human papillomavirus (HPV) DNA testing is recommended in all resource settings; visual inspection with acetic acid may be used in basic settings. Recommended age ranges and frequencies by setting are as follows: maximal: ages 25 to 65, every 5 years; enhanced: ages 30 to 65, if two consecutive negative tests at 5-year intervals, then ages 30 to 49, every 10 years; and basic: ages 30 to 49, one to three times per lifetime. For basic settings, visual assessment is recommended as triage; in other settings, genotyping and/or colposcopy are recommended. For basic settings, treatment is recommended if abnormal triage results are present; in other settings, colposcopy is recommended for abnormal triage results. For basic settings, treatment options are cryotherapy or loop electrosurgical excision procedure (or ablation) is recommended. Twelve-month post-treatment follow-up is recommended in all settings. Women who are HIV positive should be screened with HPV testing after diagnosis and screening should be many times per lifetime as the general population. Screening is recommended at 6 weeks postpartum in basic settings; in other settings, screening is recommended at 6 months. In basic settings without mass screening, infrastructure for HPV testing, diagnosis, and treatment should be developed. Additional information can be found at www.asco.org/ts-cervical-cancer-secondary-prev-guideline and www.asco.org/guidelineswiki.

In the view of ASCO that health care providers and health care system decision makers should be guided by the recommendations for the highest stratum of resources available. The guideline is intended to complement, but not replace, local guidelines.
Requirements to achieve WHO’s 2025 goals and indicators on Cervical Cancer

- **Governance**: CxCa control policy, strategies and programmes
- **Financing**: Innovative funding strategies
- **Human resources**: National capacity including at peripheral level
- **Services provision**: Early detection through VIA; accessibility of therapeutic resources; referral mechanisms; HPV vaccination
- **Surveillance**: Comprehensive national data
Cervical cancer policy should address all aspects of prevention and control in line with the WHO recommendation for a comprehensive approach that takes into consideration the natural history and progression of HPV infection.

1. **Prevention**
   - ASRH
   - HPV Vaccine
   - Community
   - Education/mobilization

2. **Early Diagnosis**
   - Screening
   - Early diagnosis
   - Laboratory services

3. **Treatment**
   - Surgery
   - Radiotherapy/Brachytherapy
   - Chemotherapy

4. **Palliative Care**
   - Opioid availability
   - Community support
   - Survivorship support
Concluding remarks

- Take CC as a public challenge
- Each country should develop a strategic plan for CC at the population level
  - Evidence based; Feasible & Provide opportunity for periodic review
- Each country should set targets for their screening policy
  - Methods
  - Population group (could be in phases); Age & Interval
- Develop a robust Monitoring & Evaluation to generate National data that will shape policy
- Develop framework for Capacity building
- Incorporate CC screening into health insurance coverage
- We shall continue to screen even with universal HPV vaccination coverage
Imperatives for sustainable National CC screening programme

- Develop the Health System
- Strengthen Capacity for Surgery and Radiotherapy
- Develop Public Health Education Programme
- Start Small.....HPV / DNA or VIA
- Grow Big........Scale Up to Population Level
Thank you