

Alternatives to Cytology: New Perspectives for Screening of Cervical Cancer

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Objective of the Project

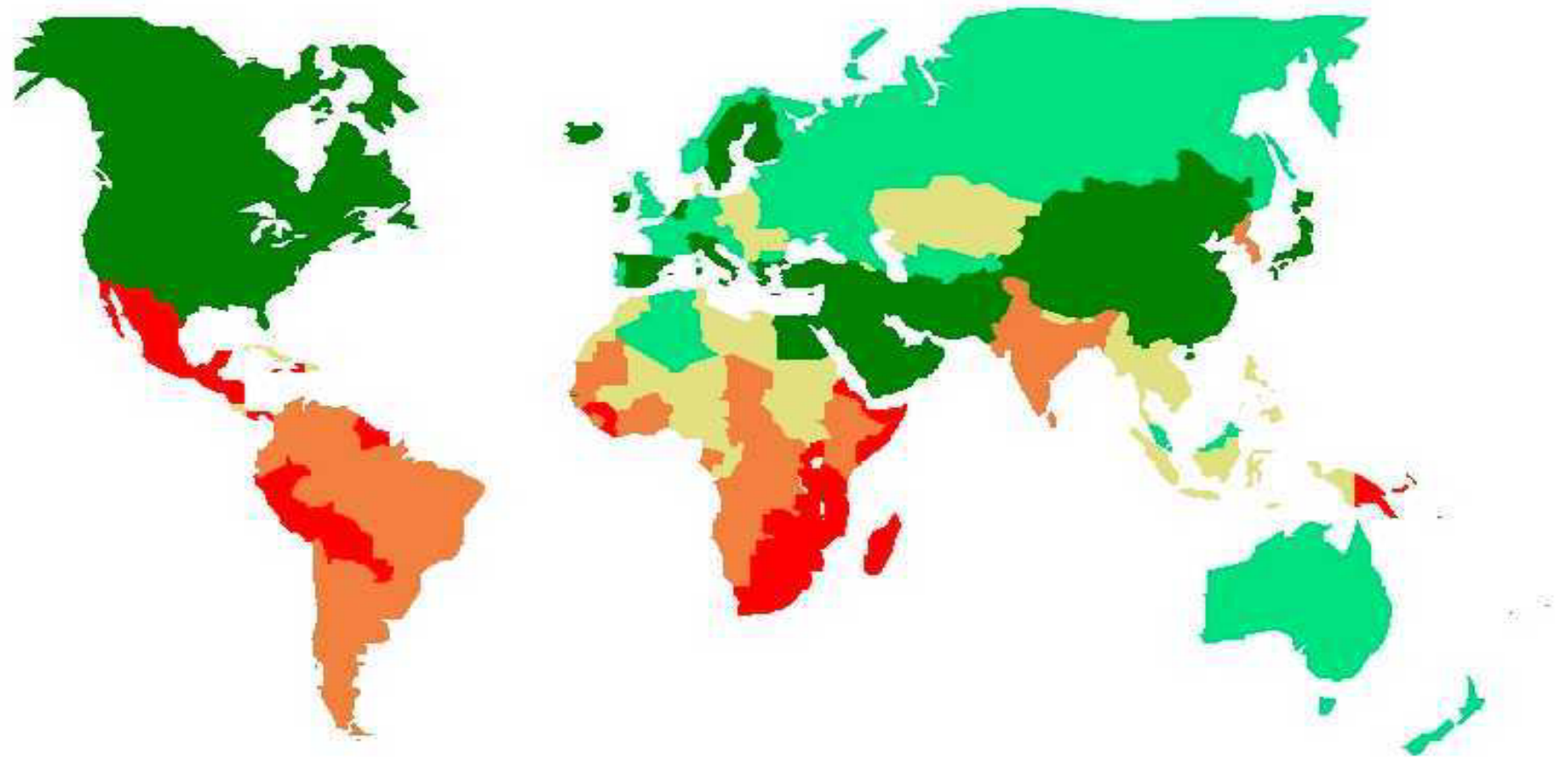
- To evaluate the feasibility, applicability and cost-effectiveness of different approaches to screening of cervical cancer in different resource settings

Annual Estimates of New Cases Globally

| | <u>Incidence</u> | <u>Mortality</u> |
|----------------------|------------------|------------------|
| • Breast Cancer | 795 000 | 313 000 |
| • Cervical Cancer | 450 000 | 300 000 |
| • Ovarian Cancer | 165 000 | 101 000 |
| • Endometrial Cancer | 142 000 | 42 000 |

WHO/IARC, 1999

Incidence of Cervix uteri cancer ASR (World) All ages



■ < 9.7 ■ < 15.4 ■ < 25.3 ■ < 33.2 ■ < 91.5
(IARC 1998)

Available Control Strategies

| <u>Strategy</u> | | <u>Cases (%)</u> | <u>Deaths (%)</u> |
|-----------------|--------|------------------|-------------------|
| Tobacco | | 20 | 30 |
| Diet | | 25 | 20 |
| Infections | | 15 | 10 |
| Screening | | 3 | 4 |
| | Cervix | 60 | 60 |
| | Breast | 0 | 25 |
| Treatment | | 0 | 20 |

Time to show Important Impact of Different Measures

| <u>Prevention</u> | <u>Time (in yrs)</u> |
|-------------------|----------------------|
| Tobacco | 30 |
| Diet | 10-50 |
| Infections | 40 |
| Screening | 5-10 |
| Treatment | 5 |

Prerequisites of a successful screening programme

A CANCER is suitable for screening if:

- a cancer is a major health problem justifying screening
- natural history of disease - long enough detectable pre clinical phase
- significant proportion of preclinical lesions progress to clinical disease
- available acceptable treatment

Screening Test

- is valid for identifying preclinical lesions
- acceptable (to patient & physician)
- screening interval
- affordable

Characteristics of an Organized Screening Program

- Identification of target Population
- Measures for high coverage and attendance
- Clear screening protocol: health objectives
- Adequate field facilities
- Adequate facilities for diagnosis, Rx and FU
- Information system (cancer registry)
- Evaluation and monitoring (Process and Outcome quality indicators)

Pap Smears

- Sensitivity: 11 to 99%
- Specificity: 14 to 97%
- False negative: 5 to 55%
 - Errors of Commission: laboratory errors-1/3**
 - Errors of Omission: sampling errors-2/3**
- Costs

Fahey et al, 1995

Alternatives to Cytology

- Visual Inspection of the cervix
 - Simple - Clinical Downstaging*
 - Acetic Acid Aided - VIA*
- Gynoscopy
- Cervicography
- Speculoscopy
- Fournier transformed Infrared Spectroscopy
- Laser induced Fluorescence
- HPV Detection / vaccines



WHO COLLABORATING CENTRE
FOR RESEARCH IN HUMAN REPRODUCTION



WHO International Study Group

INTERNATIONAL NETWORK ON CONTROL OF GYNAECOLOGICAL CANCERS (INCGC)



INCGC

The Philosophy/Aims&Objectives

- To establish collaboration amongst International Players
- To standardise research methodology
- To translate research findings into interventions

“Model Protocol for RCT / Demonstration Project”

**Pilot Demonstration Project for
cervical cancer Screening &
Management in a Selected Region in
Pakistan
(Lahore District)**

In collaboration with WHO & MOH
Pakistan

Estimated Cases of Cx Ca in Regions and Selected Countries

Region/Country

New Cases/Year

| | |
|-----------------|-----------|
| • North America | • 15 700 |
| • Latin America | • 44 000 |
| • Europe | • 47 200 |
| • USSR | • 31 300 |
| • Africa | • 36 900 |
| • China | • 131 500 |
| • India | • 120 000 |
| • Japan | • 9 700 |
| • Other Asian | • 70 300 |
| • Australia/NZ | • 1 200 |

source:WHO,1999

Cervical Cancer in Pakistan: Epidemiology

- Total population - 130 million
- Rural population - 70%
- Male/Female ratio - 45:55
- Community - Muslims (90%); Christians; Zorostrians
- Literacy rate - 30%

Cervical Cancer in Pakistan: Epidemiology

Hospital based data:

- 3rd common cancer in women
(following Breast & Oral CA)
- 60% of all genital tract CA
- 70-80% stage III / IV
- 89% in the age group 30-55 yrs
- Majority in low socio-economic class

Objectives of the Project

- evaluate effect of health education
- evaluate VIA as a screening test
- evaluate performance of cytology
- evaluate feasibility, acceptability & cost-benefit of different screening methods

AIM of the Project

- To devise a national screening programme in Pakistan for Cervical Cancer

Materials & Methods

Project Areas:

- Lahore District - population of 700 000
- Three rural and periurban areas - **CHUNG**, **RAIWIND** and **BURKI**
- Comparable socio-economic & demographic backgrounds
- Similar health care facilities
- Equal access to the district's teaching hospitals , namely Sir Ganga Ram Hospital and Mayo Hospital

Project Phases:

- **PHASE I PREPARATORY**
June 1996 - September 1996
- **PHASE II INTERVENTION**
January 1997- June 1997
 - *Knowledge Attitude and Practice (KAP) Survey*
 - *Health Education*
 - *Training*
- **PHASE III - Data Collection**
July 1997 - December 1998

Target Population

- Total female Population: $\pm 50\ 000$
- Target Population (*WHO criteria*)
- Sexually active women aged 30-60 years: $\pm 15\ 000$
- Population census data

Data Collection

- *KAP Survey*

Preprepared questionnaire by lady health workers

- *Screening & Management*

All women aged 30-60 yrs, who presented at the hospital gynae.out-patient clinics

(June 1997 - Dec. 1998)

Methodology

1080 women - aged 30-60 yrs
M/H - Gynae examination

VIA - 3% A.A.

Acetowhite lesion

No Acetowhite lesion

Papsmear conventional

Colposcopy - SGRH

Recall 3 yrs

Punch Bx/histology

CIN I: Rx infec. Rpt 12 wks

CIN II: Cryo or elec. Coag

CIN III: Cold knife cone

RESULTS

KAP Survey

- No. of women (30-60 yrs): 15 000
- Education: 85% uneducated / 15% primary school
- Mean age at marriage: 20.6 yrs
- Parity: 0-15 (>25% had >5 children)
- Low socio-economic status
- Knowledge about general health: poor
- Knowledge about cervical cancer: 0%
- Reluctance to visit a clinic if not ill: 100%

RESULTS

Screening & Management

- No.of women: 1080
- Age: 30-60 yrs (median 40.2)
- All were married with median parity of 7.5

Results of VIA and Pap-smears compared with Histologic diagnosis

| VIA | PAP | No. | Lost | Colposcopy | Biopsy | Mild Disp. | Mod. Disp. | Severe Disp | CIS | Inv. Ca | Other |
|-------|-----|------|------|------------|--------|------------|------------|-------------|-----|---------|-------|
| + | + | 100 | 10 | 90 | 66 | 4 | 6 | 24 | 16 | 12 | 4 |
| + | — | 212 | 32 | 180 | 90 | 6 | 56 | 8 | 2 | 0 | 18 |
| — | + | 56 | 16 | 40 | 10 | 6 | 2 | 2 | 0 | 0 | 0 |
| — | — | 712 | 20 | 204 | 12 | 4 | 4 | 0 | 0 | 0 | 4 |
| TOTAL | | 1080 | 78 | 514 | 178 | 20 | 68 | 34 | 18 | 12 | 26 |

Results (contd.)

- Histology was the reference point
- Dysplasia all grades: 14 %
 - LSIL - 2%
 - HSIL - 12%
- Invasive cancer: 1.2%

Comparison of VIA and Histology

| | Histology | | |
|-------|-----------|----|-------|
| VIA | + | — | Total |
| + | 134 | 22 | 156 |
| — | 18 | 4 | 22 |
| Total | 152 | 26 | 178 |

Comparison of Pap-smear and Histology

| | Histology | | |
|-----------|-----------|----|-------|
| Pap Smear | + | — | Total |
| + | 72 | 4 | 76 |
| — | 80 | 22 | 102 |
| Total | 152 | 26 | 178 |

RESULTS

| | sensitivity | specificity | false neg |
|-------------|-------------|-------------|-----------|
| • Pap-smear | 47.4% | 84.6% | 53.6% |
| • VIA | 88.1% | 15.4% | |

Consensus Conference, Tunis 1999

AIMS & OBJECTIVES

- **Review & assess completed & ongoing research studies on Cx Ca /HPV/STD and their relevance to screening for Cx Ca**
- **Review & revise, current WHO Guidelines**
- **Revise strategies to successfully carry out these recommendations esp. in DCs**

VIA

| STUDY | TYPE of STUDY | SCREENING TESTS | PATIENT POPULATION | RESULTS |
|--|-----------------|---|---|---|
| University of Zimbabwe and JHPIEGO Zimbabwe 1999 | Cross-sectional | <ul style="list-style-type: none"> VIA Pap Colposcopy/Biopsy | Age 25-55yrs attending PHC clinics. | Sensitivity: 76.7% Specificity: 64.1% 44.3% 90.6% |
| <i>T.Wright et al</i> Cape Town 1999 | Cross-sectional | <ul style="list-style-type: none"> Pap VIA HPV Cerviography | 35-60 yrs Peri-urban community unscreened | 78/95% 67/84% 58/92% 73/86% |
| <i>Singh et al</i> Delhi 1999 ongoing..... | ??? | <ul style="list-style-type: none"> VIA Gyno Cyto (colpo/histo) | 3000 women | HSIL 81.5% 88.9% 88.9% 80% |
| <i>Croijs et al</i> Bloemfontein 1997-1999 ongoing..... | ?? | <ul style="list-style-type: none"> Cyto Cervico VIA Cyto Cervico VIA Speculo | 3000 women 1000 women | 37.8%/99 50.3% /77% 51.2%/ 49% 60/96% 48.9/86.8% 80/46.3% 82/ 39.5% |

Human Papilloma Virus (HPV)

| STUDY | TYPE of STUDY | SCREENING TEST | PATIENT POPULATION | RESULTS |
|---------------------------------------|----------------------|--|--|---|
| <i>Lorincz et al</i> New York 1998 | Cohort Study | Hybrid Capture Liquid Based Cytology Biopsy | 265 women with ASCUS and LSIL by Colposcopy (mean age 27yrs) | Sensitivity: LSIL 86% HSIL 93% |
| <i>Kinney et al</i> USA 1999 | Cohort Study | Liquid based cytology Hybrid Capture Histology | 995 women with ASCUS from Gynae Clinics | Sensitivity HPV – 89.2% Repeat Pap 76.2% |
| <i>Cuzick et al</i> UK 1999 | Cross - sectional | Conventional Pap PCR /SHARP Hybrid Capture | 3103 women, > 35 yrs Routine GP Clinics | PCR= 87.3% HPV Hybrid Capture =88.9% Pap –79% |
| <i>T.Wright et al</i> Cape Town | Cross- sectional | Cytology VIA Hybrid Capture Cervicography | 1415 women 36-60 yrs | 67.9% sensitivity of both HPV Hybrid Capture (self collected) and Pap |

Different Screening Methods Compared to PapSmear

| <u>TEST</u> | <u>LINKS</u> | <u>SCIENTIFIC</u> | <u>T</u> | <u>SE/SP</u> | <u>C</u> | <u>TE</u> |
|---------------|--------------|-------------------|----------|--------------|----------|-----------|
| Pap | | | + | ++ | ? | ? |
| Polar Probe | + | | ■ ? | ?? | ? | + |
| VIA | + | | + | + - | ? | = |
| Automation | - | | + | ++ | + | + |
| Speculoscopy | + | | + | ?? | + | - |
| Tumor Marker | - | + | ? | ?? | + | + |
| Cervicography | - | | + | + - | + | - |
| Thin Prep | - | | + | ++ | ? | + |
| HPV Test | - | | + | -- | ? | + |
| HPV Vaccine | ++ | + | | | | |
| Down Staging | + | | | -- | | |

T = Training - SE = Sensitivity - C = Cost - TE = Technology

Links = Means referrals when compared to Pap test

Conclusion / Discussion

Conclusion / Discussion

- Screening for cervical cancer reduces incidence of & mortality from invasive disease (upto 90%)
- Is applicable as a public health policy
- However, a single format cannot be applicable for all countries / regions

Conclusion / Discussion

- Limitations of cytology based screening programmes (*esp in DCs*):
 - *cost for population based application*
 - *lack of quality assurance - suboptimal*
 - *logistical issues*
- Low compliance / High drop out rate

Conclusion / Discussion

New alternative techniques - holding promise

- VIA sensitivity comparable (70%)
specificity low (14-30%)

? PPV & NPV

? Efficacy & QC

? Cost (overtreatment)

Conclusion / Discussion

- HPV sensitivity comparable (80-90%)
specificity lower (high false + < 30 yrs)

? PPV & NPV (risk of reduced surveillance)

? Efficacy & QC

? Cost (pop. based screening)

? Benefit independent of cytology

Conclusion / Discussion

- Sequential screening with a low cost, simple test e.g. Visual Inspection with Acetic Acid (VIA)
- Followed by a more objective test e.g. Pap smear or HPV detection on selected sub-group
- Disinvest in screening programme (screen 10 yrly)

Conclusion / Discussion

- All new techniques need to be evaluated in RCTs for specificity; quality control; cost-effectiveness; efficacy
- HPV vaccines: 30 years to evaluate; logistics not defined

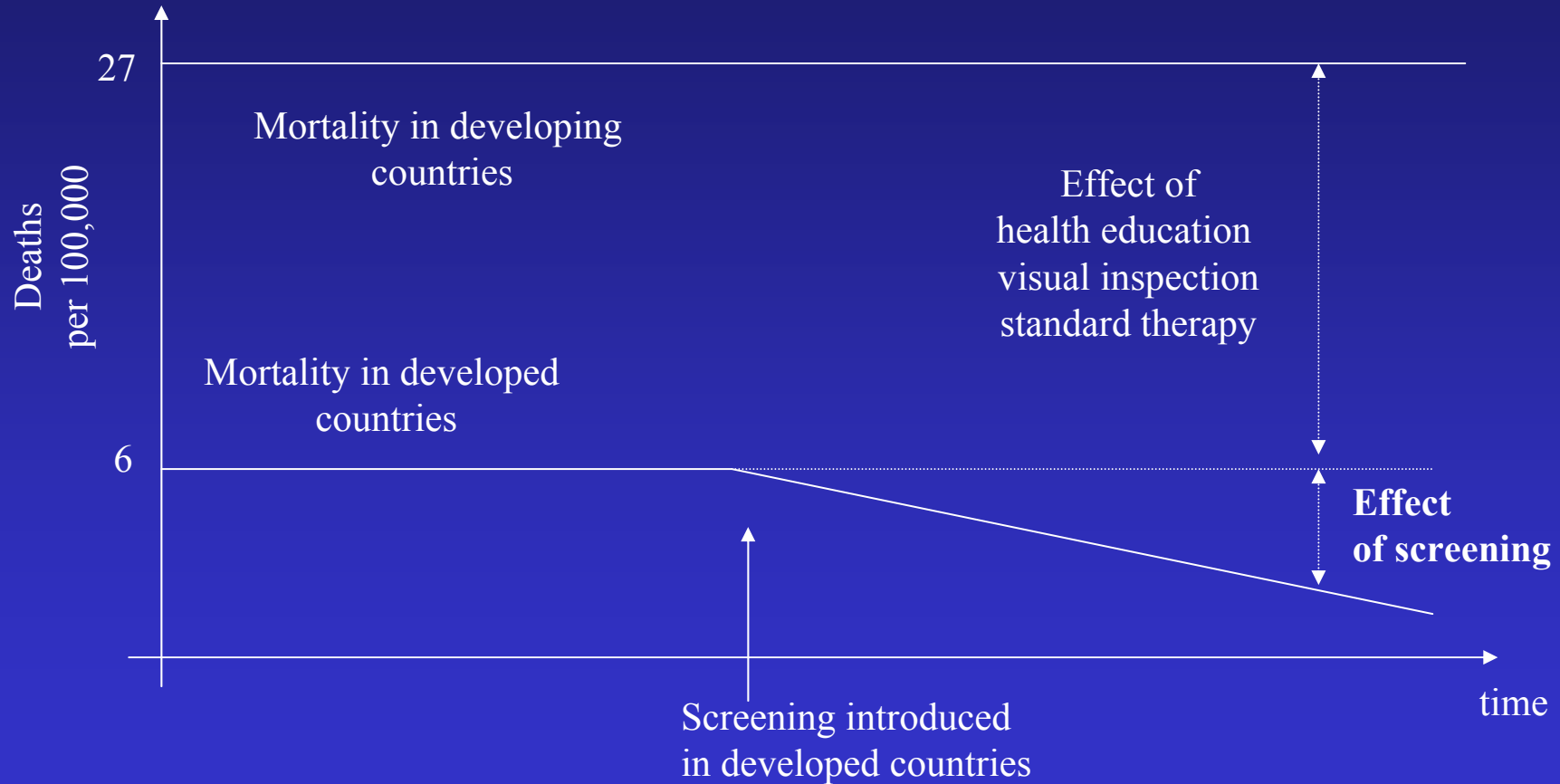
Conclusion / Discussion

Pap smear the only proven method

Step-up approach

- Screen every woman at age 45
- When resources permit screen 10 yrly at age 35, 45, 55
- If resources available, screen 5 yrly age 35-59
- Once coverage achieved (80%)- expand to age 25 (if resources available)

Cervical Cancer Control



Parting Comment

The decision to establish and continue screening programmes depends on:

- the factual evidence
- a compromise between different elements of programmes, individualised to the needs of different populations