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Alternatives to Cytology: New Perspectives for Screening of Cervical Cancer

Saloney NAZEER

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

	Incidence	Mortality
• 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

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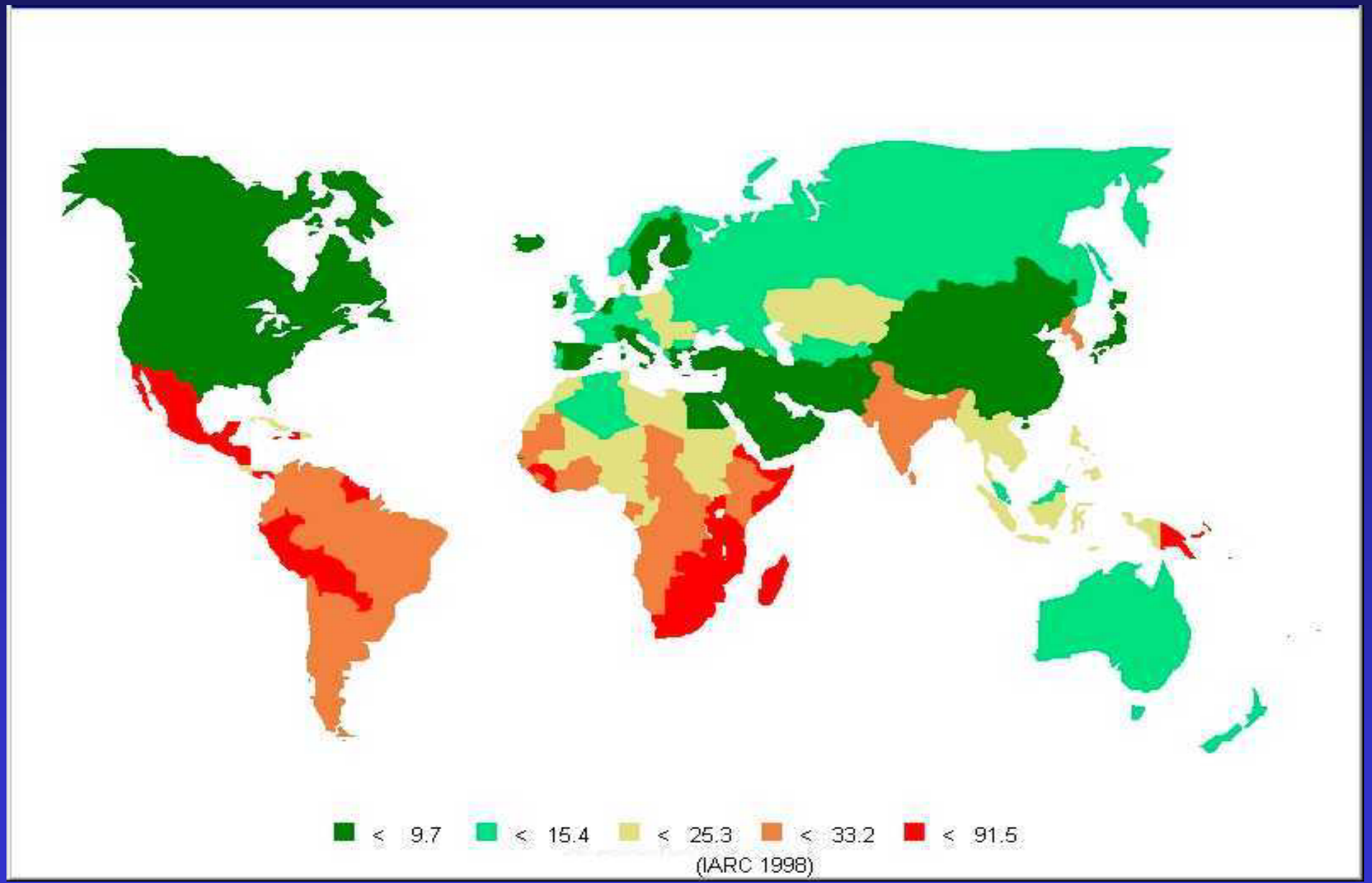
Incidence of Cervix uteri cancer ASR (World) All ages



Available Control Strategies

Strategy		Cases (%)	Deaths (%)
Tobacco		20	30
Diet		25	20
Infections		15	10
Screening		3	4
	Cervix	60	60
	Breast	0	25
Treatment		0	20

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Time to show Important Impact of Different Measures

Prevention	Time (in yrs)
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

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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)

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Pap Smears

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

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WHO COLLABORATING CENTRE
FOR RESEARCH IN HUMAN REPRODUCTION

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WHO International Study Group

INTERNATIONAL NETWORK ON CONTROL OF GYNAECOLOGICAL CANCERS

(INCGC)

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INCGC
The Philosophy/Aims&Objectives

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

"Model Protocol for RCT / Demonstration Project"

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

In collaboration with WHO & MOH Pakistan

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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

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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

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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

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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

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Target Population

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

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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)

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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

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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

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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%	

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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	• VIA • Pap Colposcopy/Biopsy	Age 25-55yrs attending PHC clinics.	Sensitivity: 76.7% Specificity: 64.1% 44.3% 90.6%
T.Wright et al Cape Town 1999	Cross-sectional	• Pap • VIA • HPV • Cerviography	35-60 yrs Peri-urban community unscreened	78/95% 67/84% 58/92% 73/86%
Singh et al Delhi 1999 ongoing……	???	• VIA • Gyno • Cyto • (colpo/histo)	3000 women	HSIL 81.5% 88.9% 88.9% 80%
Croije et al Bloemfontein 1997-1999 ongoing…..	??	• 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%

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Human Papilloma Virus (HPV)

STUDY	TYPE of STUDY	SCREENING TEST	PATIENT POPULATION	RESULTS
Lorincz et al 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%
Kinney et al 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%
Cuzick et al 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%
T.Wright et al 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

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Different Screening Methods Compared to PapSmear

TEST	LINKS	SCIENTIFIC	T	SE/SP	C	TE
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

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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

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Conclusion / Discussion

New alternative techniques - holding promise

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

  ? PPV & NPV
  ? Efficacy & QC
  ? Cost (overtreatment)

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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

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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)

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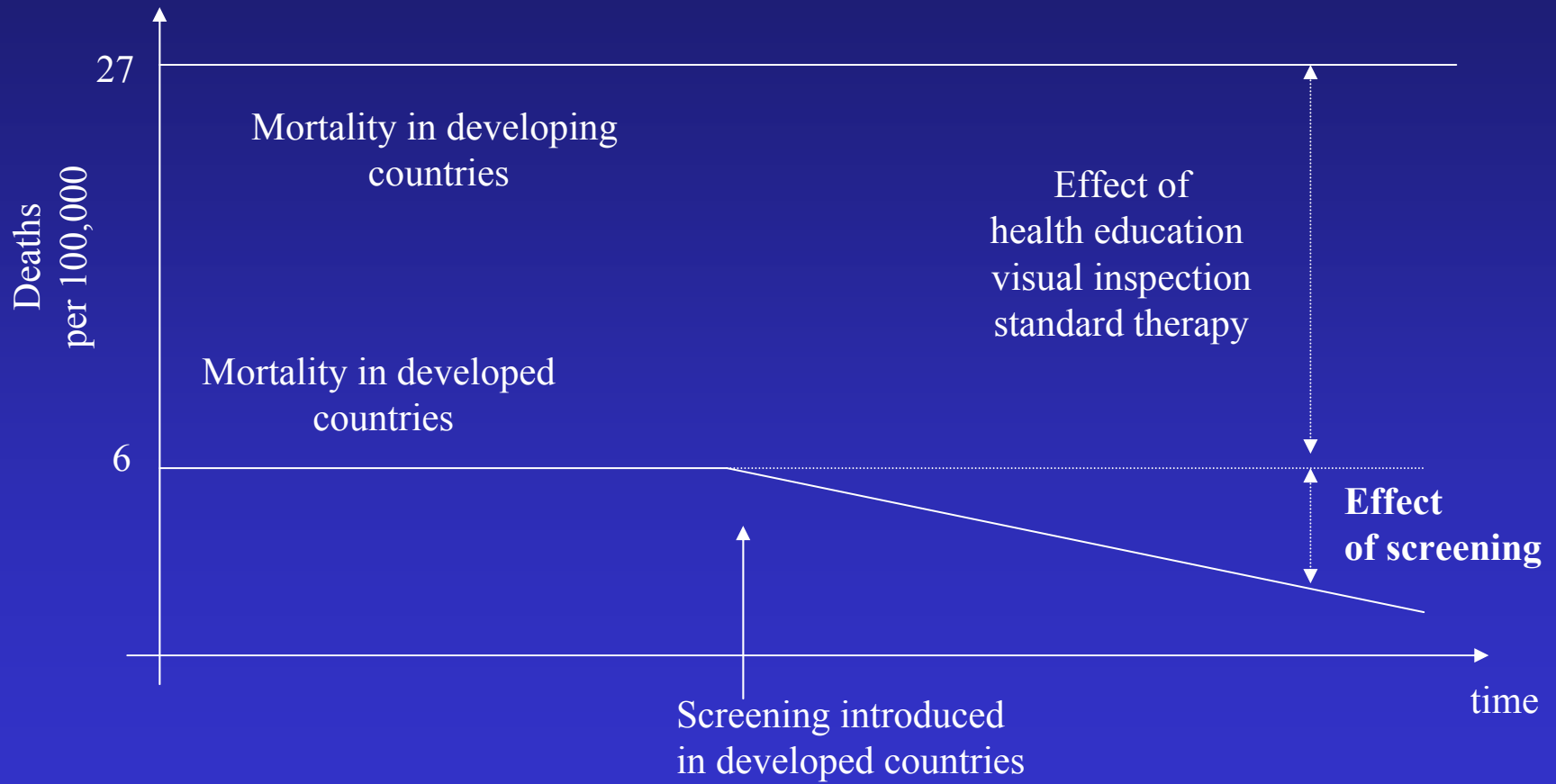
Cervical Cancer Control



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Parting Comment

The decision to establish and continue screening programmes depends on:

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