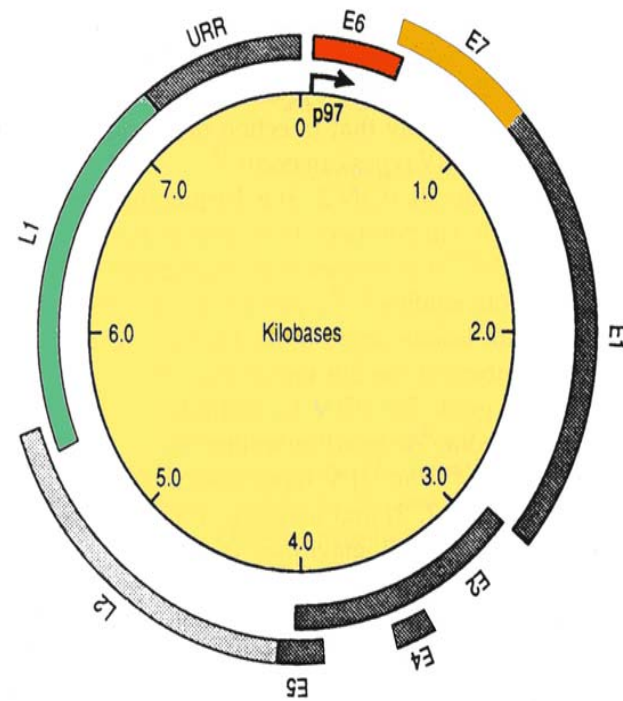
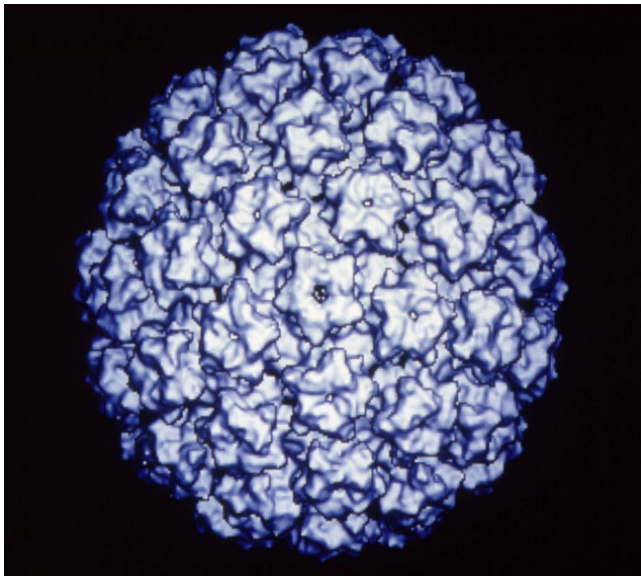


Screening for cervical cancer in Latin America

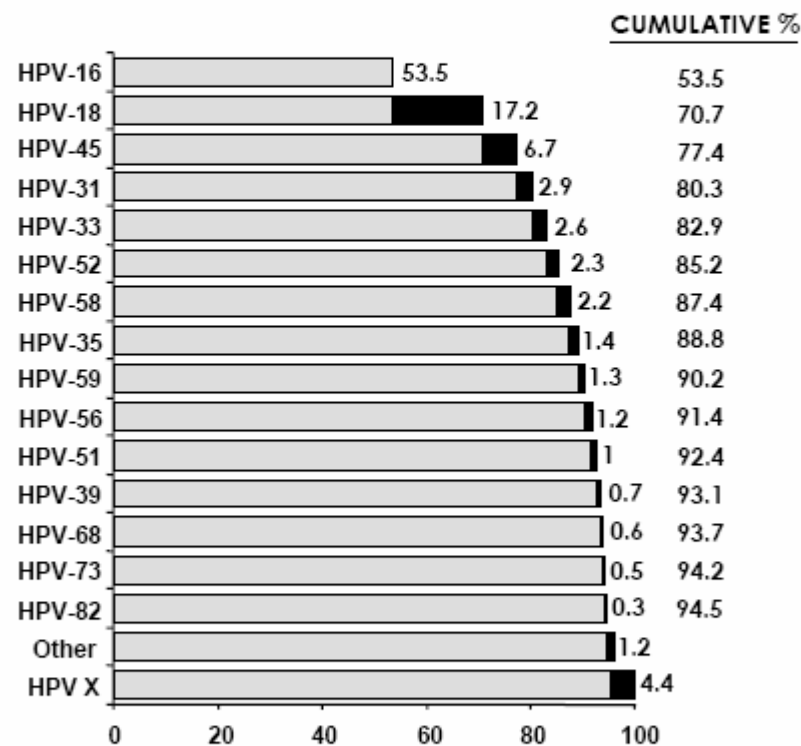
Rolando Herrero
INCTR, Sao Paulo,
2 March 2007

HPV causes all cervical cancers



PERCENTAGES OF CERVICAL CANCER CASES ATTRIBUTED TO THE MOST FREQUENT HPV TYPES IN ALL WORLD REGIONS COMBINED

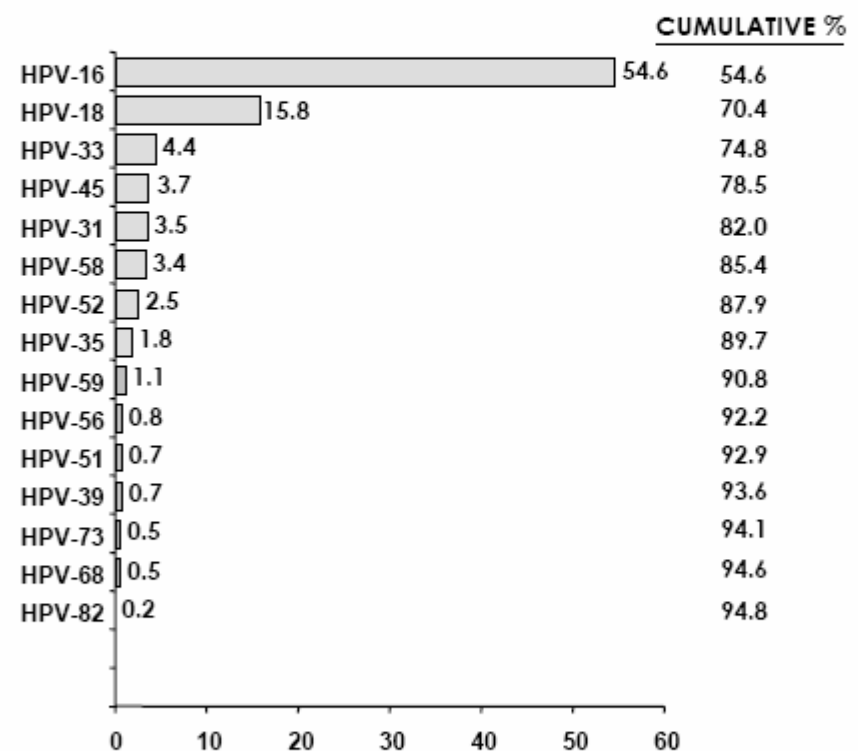
(A) IARC POOLED-ANALYSIS OF 3,085 CASES



Estimates adapted from Munoz N, et al. *Int J Cancer* 2004;111(2):278-85

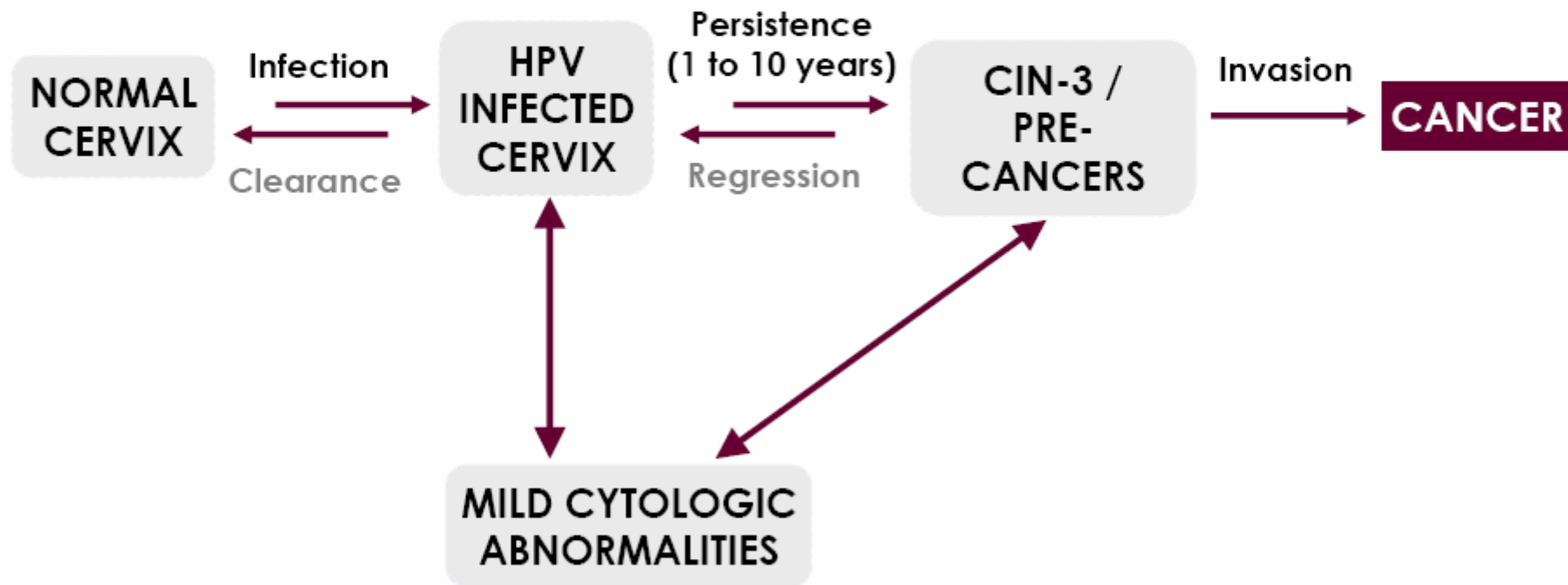
IARC: International Agency for Research on Cancer

(B) META-ANALYSIS OF 14,500 CASES

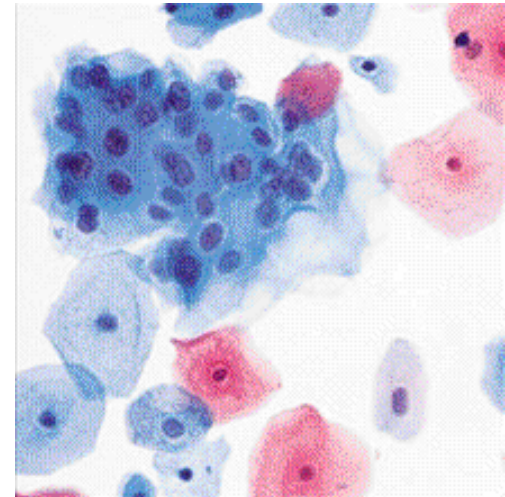
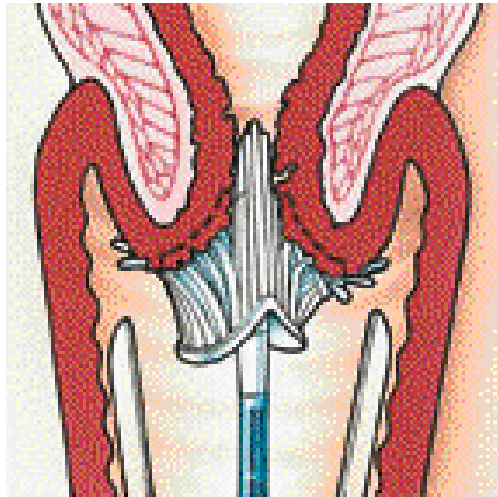


Estimates adapted from Smith JS, et al. *Br J Cancer*, Submitted.

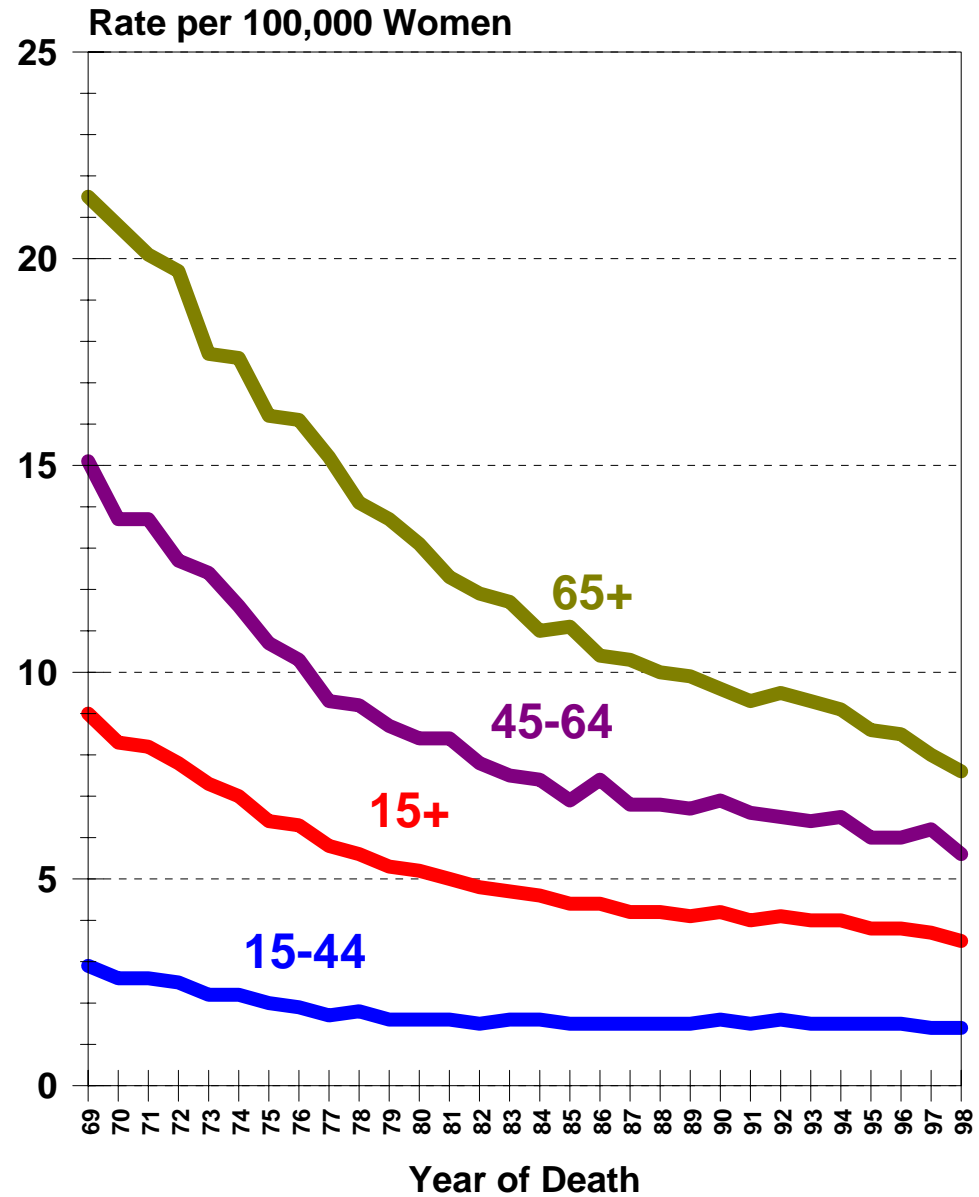
MAJOR STEPS IN CERVICAL CARCINOGENESIS



Screening programs with cytology have helped reduced cervical cancer incidence in developed countries

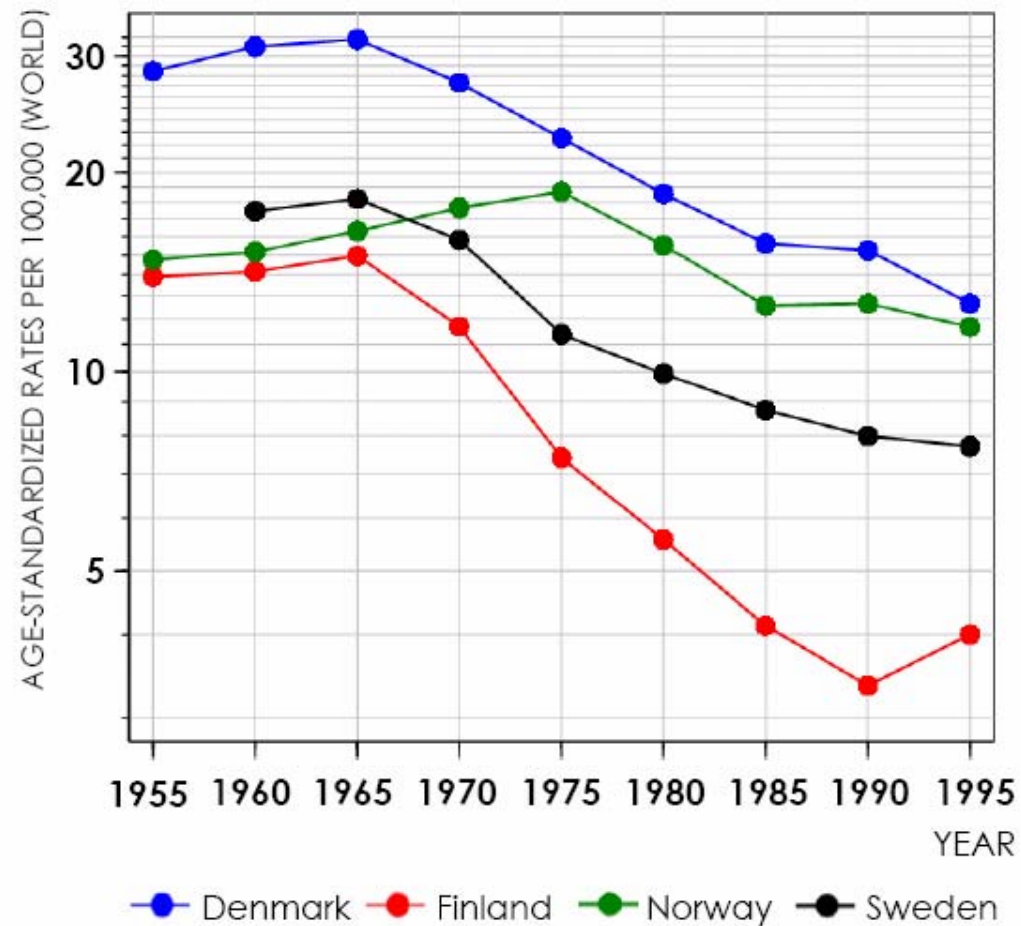


U.S. Mortality Cervical Cancer



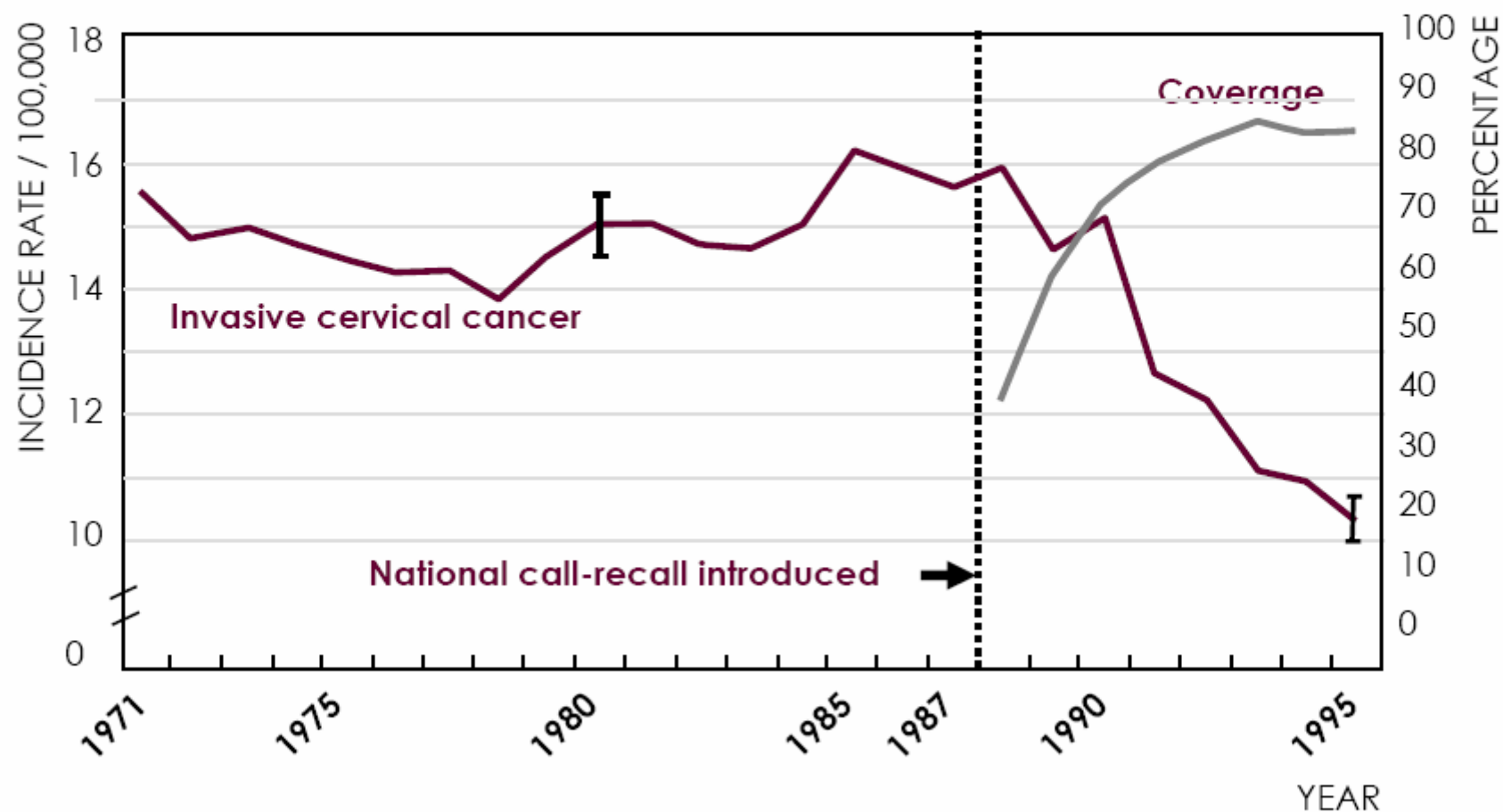
Source: NCHS Mortality Data
Age-Adjusted to 1970

TIME TRENDS IN AGE-STANDARDIZED (WORLD) INCIDENCE RATES OF CERVICAL CANCER IN FOUR NORDIC COUNTRIES



Parkin DM, et al. Cancer incidence in five continents, vol. I-VIII. Lyon: IARC CancerBase No. 7; 2005.

AGE-STANDARDIZED INCIDENCE OF INVASIVE CERVICAL CANCER AND COVERAGE OF SCREENING, ENGLAND, 1971–1995



Reprinted from Castle et. al. J Natl Cancer Inst 2005;97(14):1066-71 with permission from BMJ Publishing group.

Characteristics of successful programs

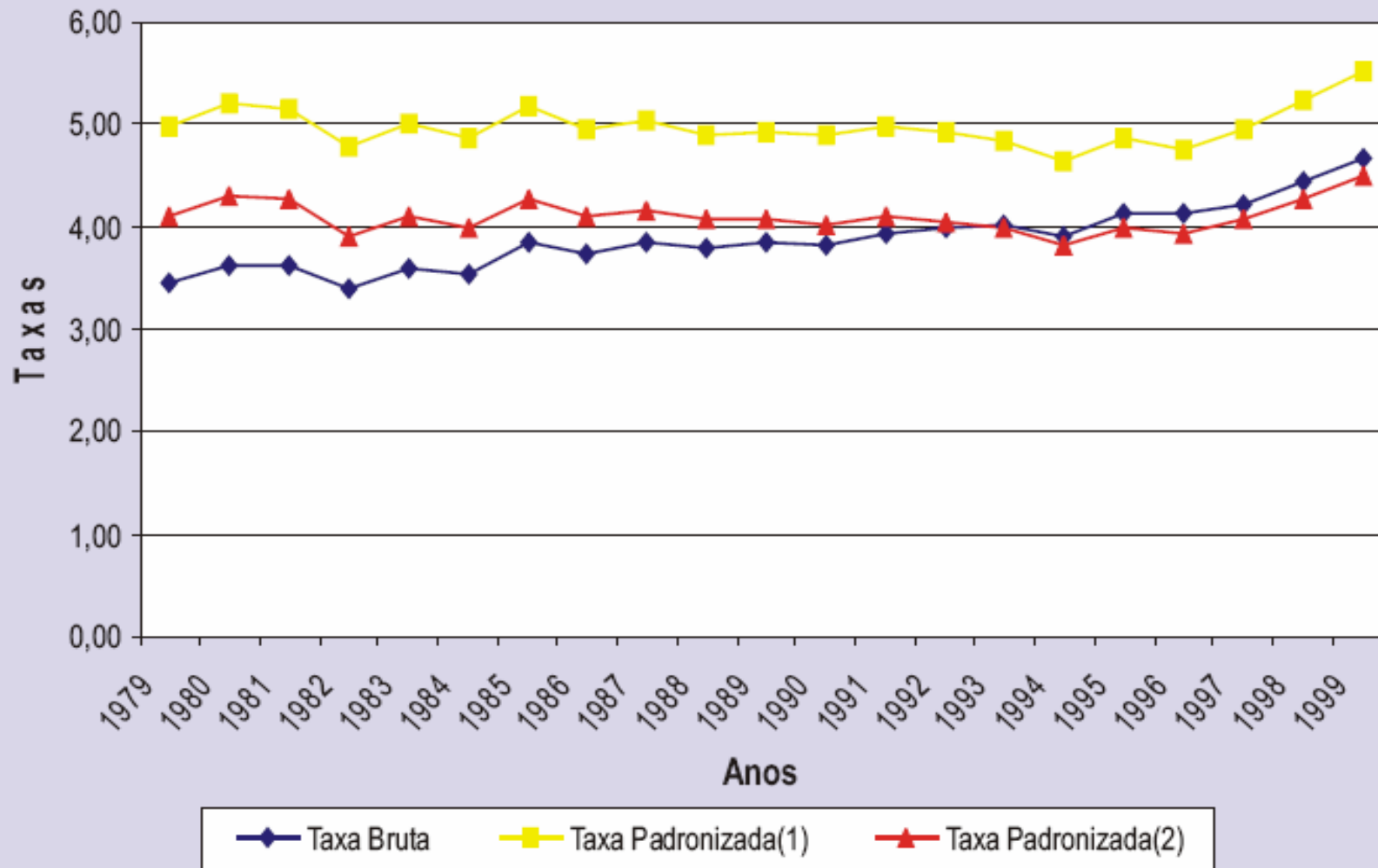
- Organized
- Call-recall systems
- Quality Control
- Permanent training
- Multidisciplinary teams
- Performance evaluation
- Political and community support



Screening programs are not
existent or have largely failed in
Latin America



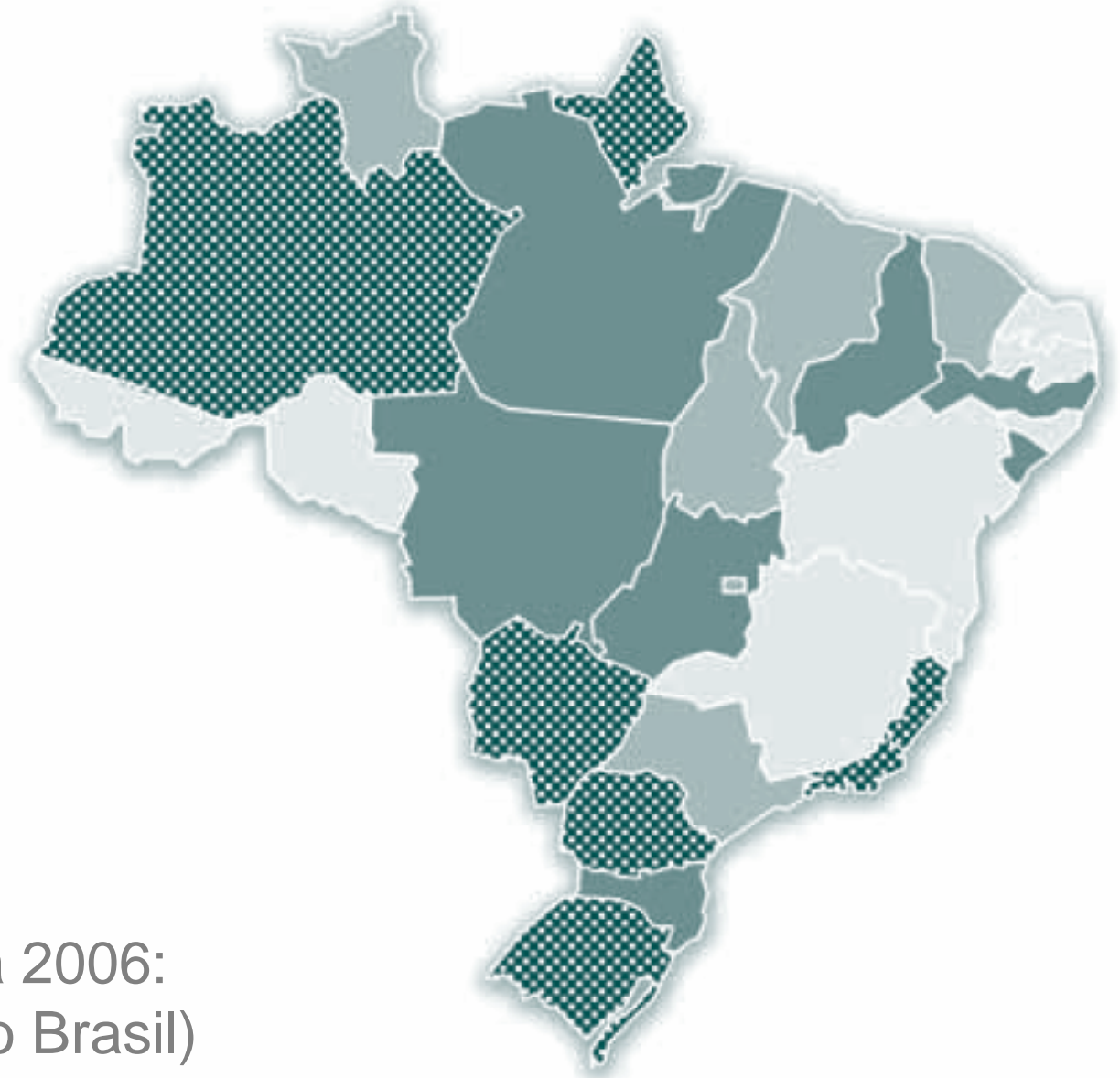
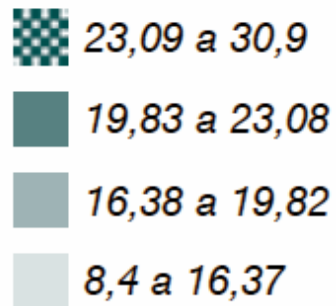
Taxas de mortalidade por **câncer do colo do útero**, brutas e ajustadas por idade pelas populações mundial e brasileira, por 100.000 mulheres, Brasil, entre 1979 e 1999.



Source: SIM/DATASUS/MS, Fundacao IBGE, Divisao de Epidemiologia CONPREV/INCA/MS. Courtesy of Dr. Eduardo Franco

Representação espacial das taxas brutas de incidência por 100.000 mulheres, estimadas para o ano 2006, segundo a Unidade da Federação (neoplasia maligna do colo do útero).

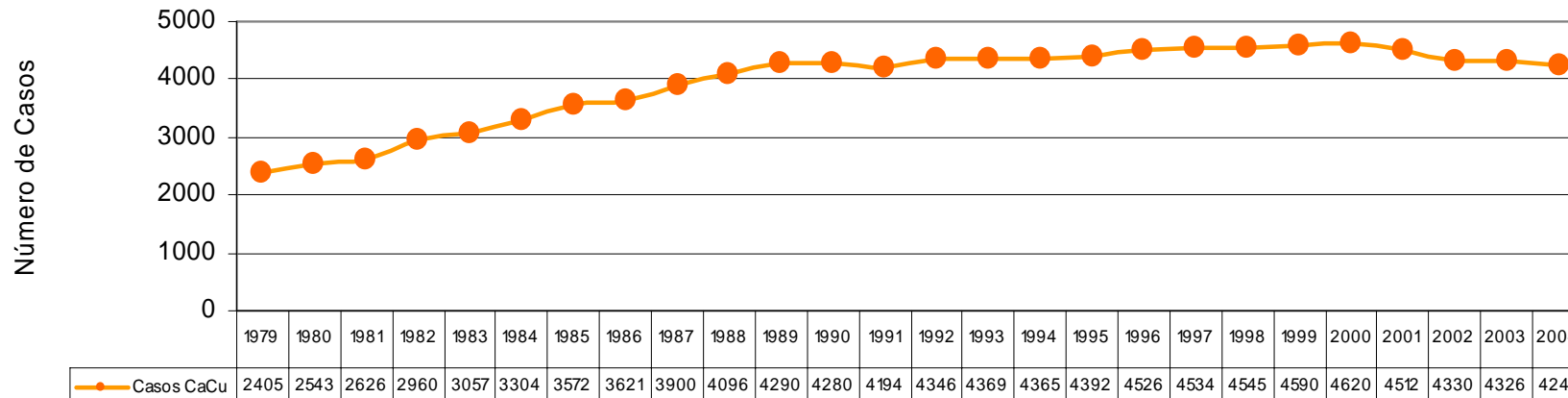
Mulheres



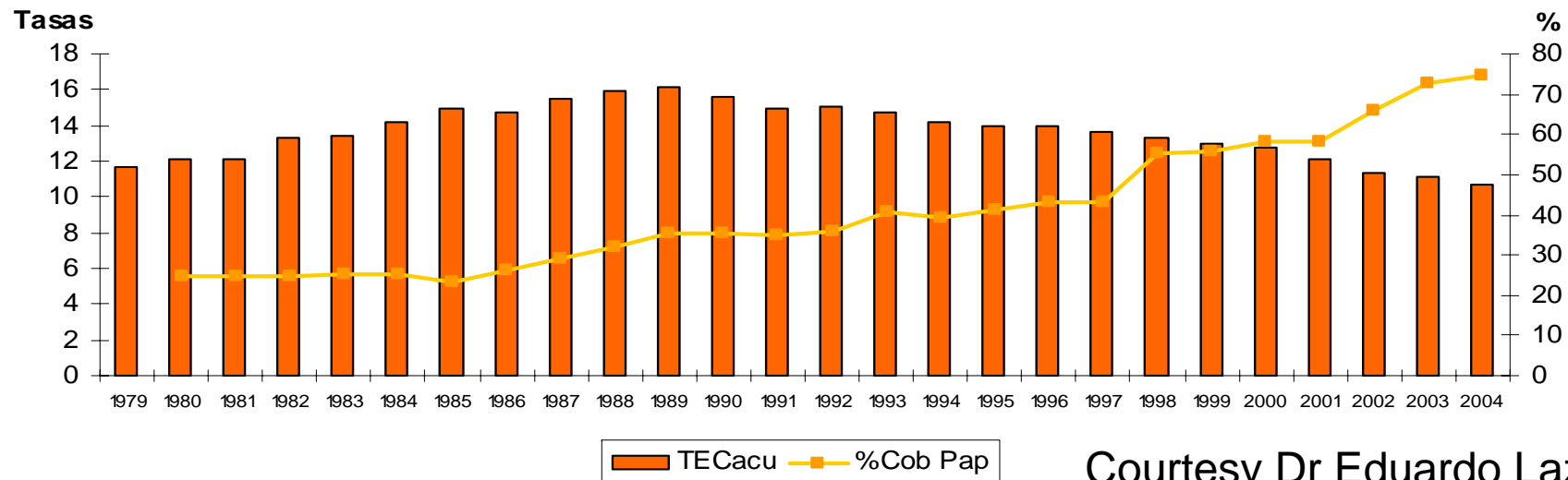
INCA, 2005 (Estimativa 2006:
Incidência de câncer no Brasil)

Cervical cancer mortality rates and Pap smear coverage, México:1979-2004.

Casos de Mortalidad por Cáncer Cervicouterino en México, 1979 - 2004

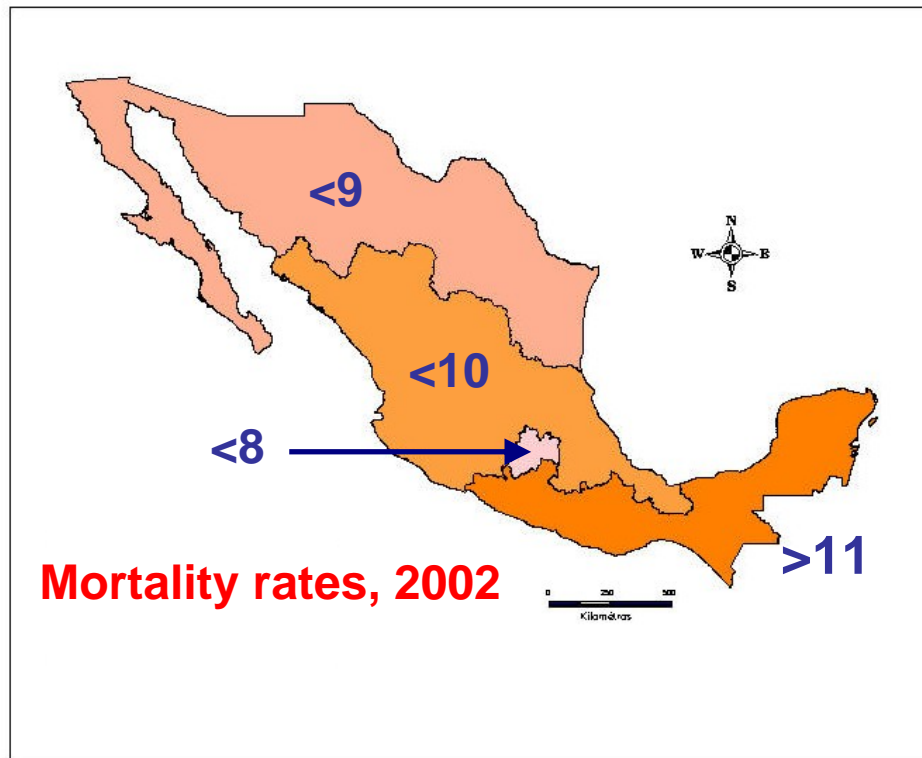


Tasas Estandarizadas de Mortalidad por Cacu y Coberturas trianuales de Pap en México, 1979-2004



Courtesy Dr Eduardo Lazcano

Geographic variation of cervical cancer in Mexico

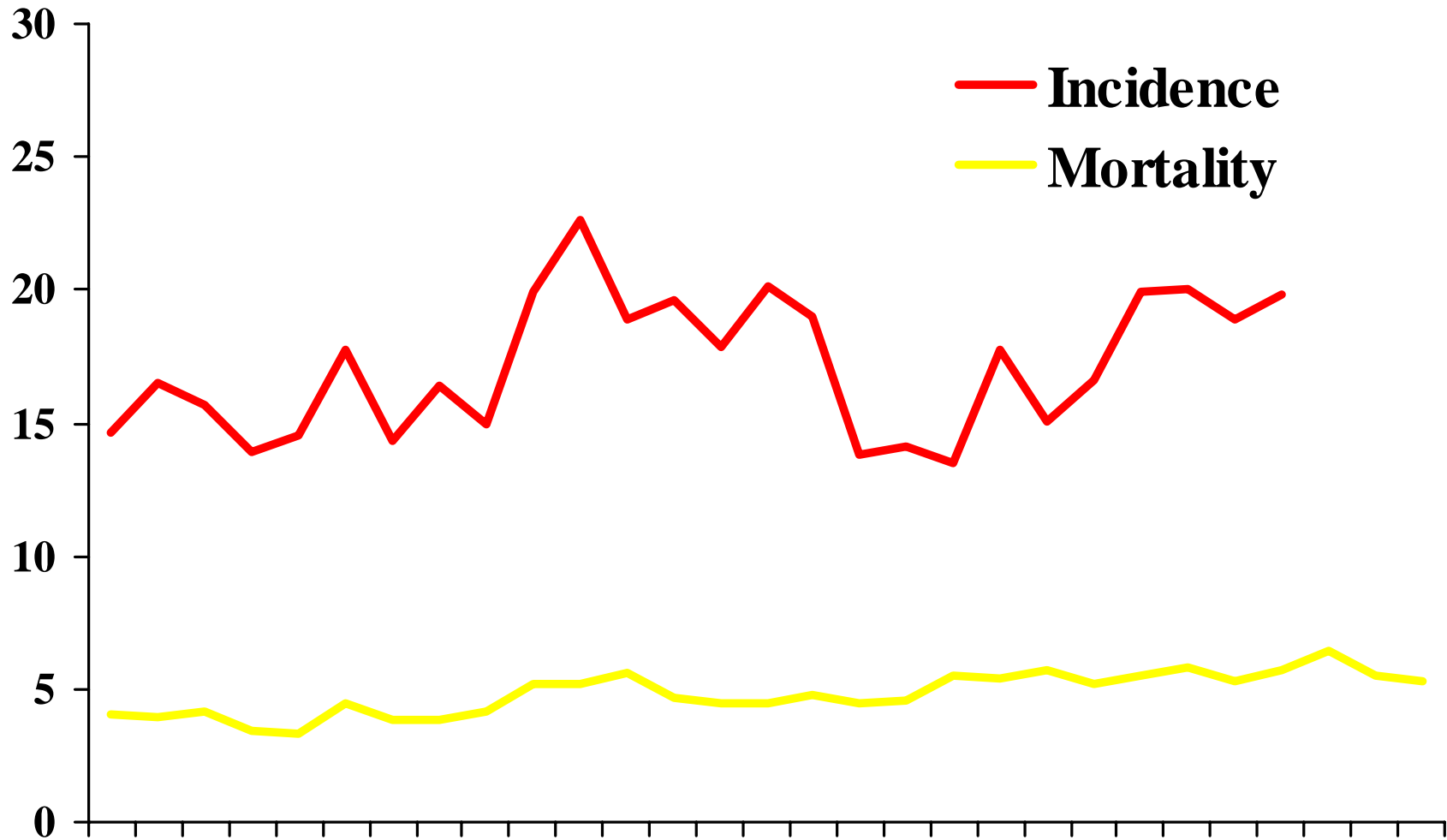


**102, 544 deaths
in the last 25 years**

Higher mortality

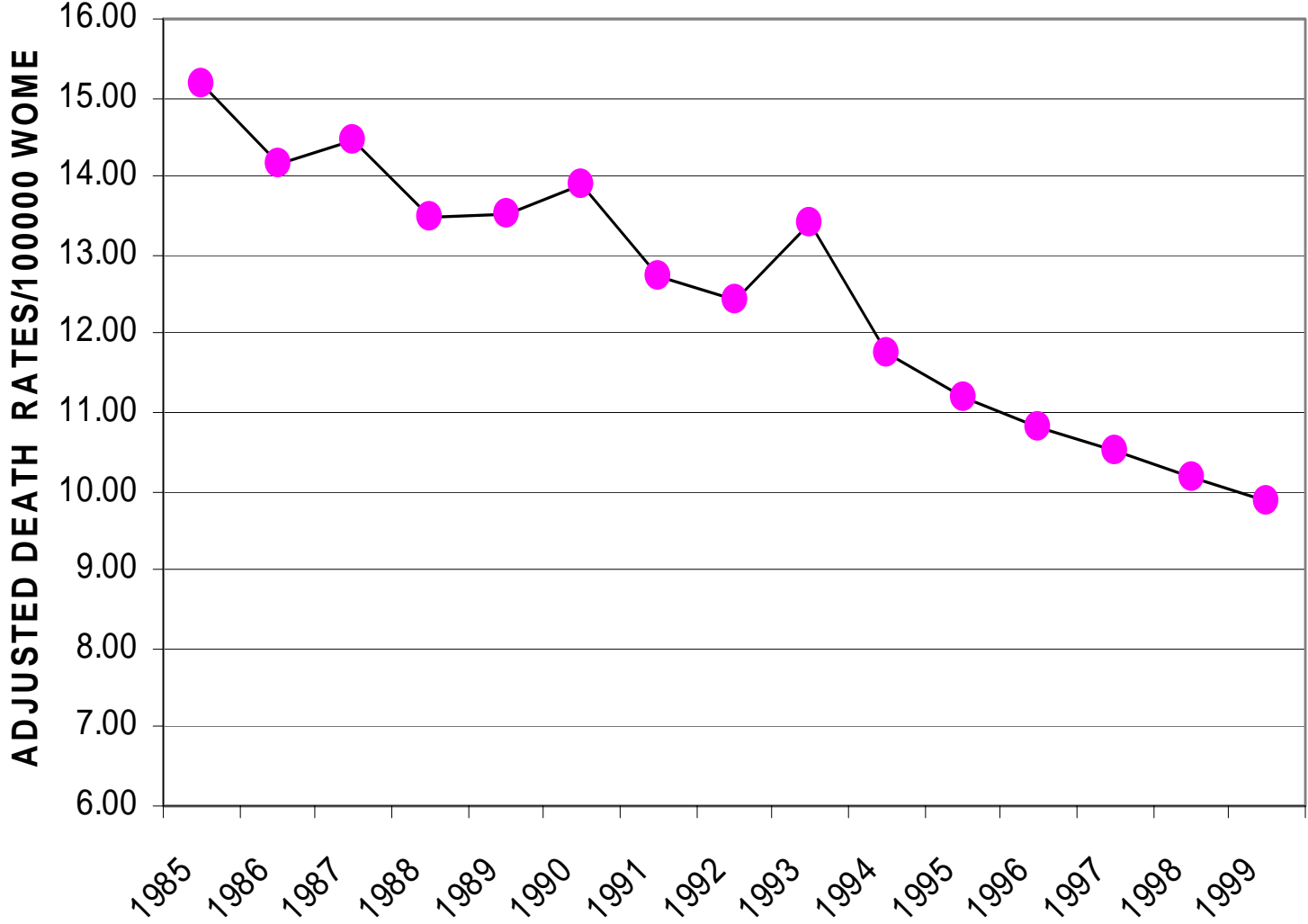
- Rural
- Low Pap coverage
- Multiparity
- No social security
- Illiteracy
- South of México

INCIDENCE AND MORTALITY RATES FROM CERVICAL CANCER IN CUBA 1976-2004



Courtesy Dr Juan Lence

Cervical cancer mortality rates in Chile 1985-1999



Courtesy Dr Catterina Ferreccio

The Chilean Cervical Cancer Program

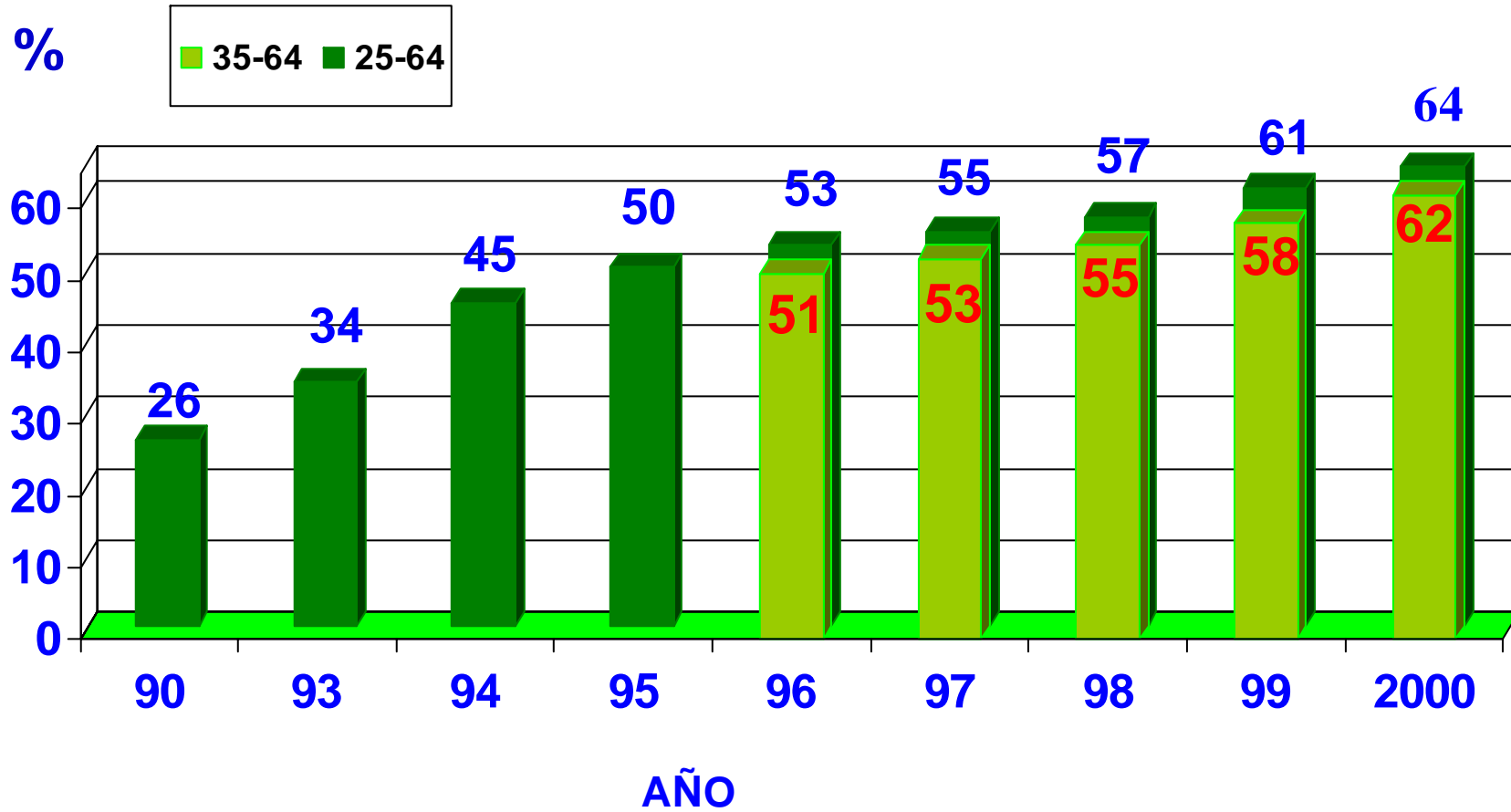
- 1960-** Opportunistic screening
- 1986**
- 1987** Reformulation of the National Program: ages: 25-64; every three years.
- 1994** Expansion of screening coverage
- 1997** Surgical treatment and 100% free Radiotherapy
- 1998** Review of national guidelines
- 1999** Consensus protocol for Chemotherapy and Radiotherapy
- 2003** Ca Cx one of the 5 health problems with treatment guaranteed in some stated period.

Strengths of the Chilean program

1. CaCx is a National Priority
2. Is part of Cancer Program
3. Linked with a National citopathology network
 - ☺ Quality control Information
4. 100% coverage of surgical treatment (< 30 days);
Radiotherapy and pain relief
5. Annual Evaluation with the 28 responsible.
6. Integration from primary to tertiary care
7. Continuous training.



PAP COVERAGE WOMEN AGES 25 - 64 CHILE 1990 - 2000



Fuente: Informe Servicios de Salud

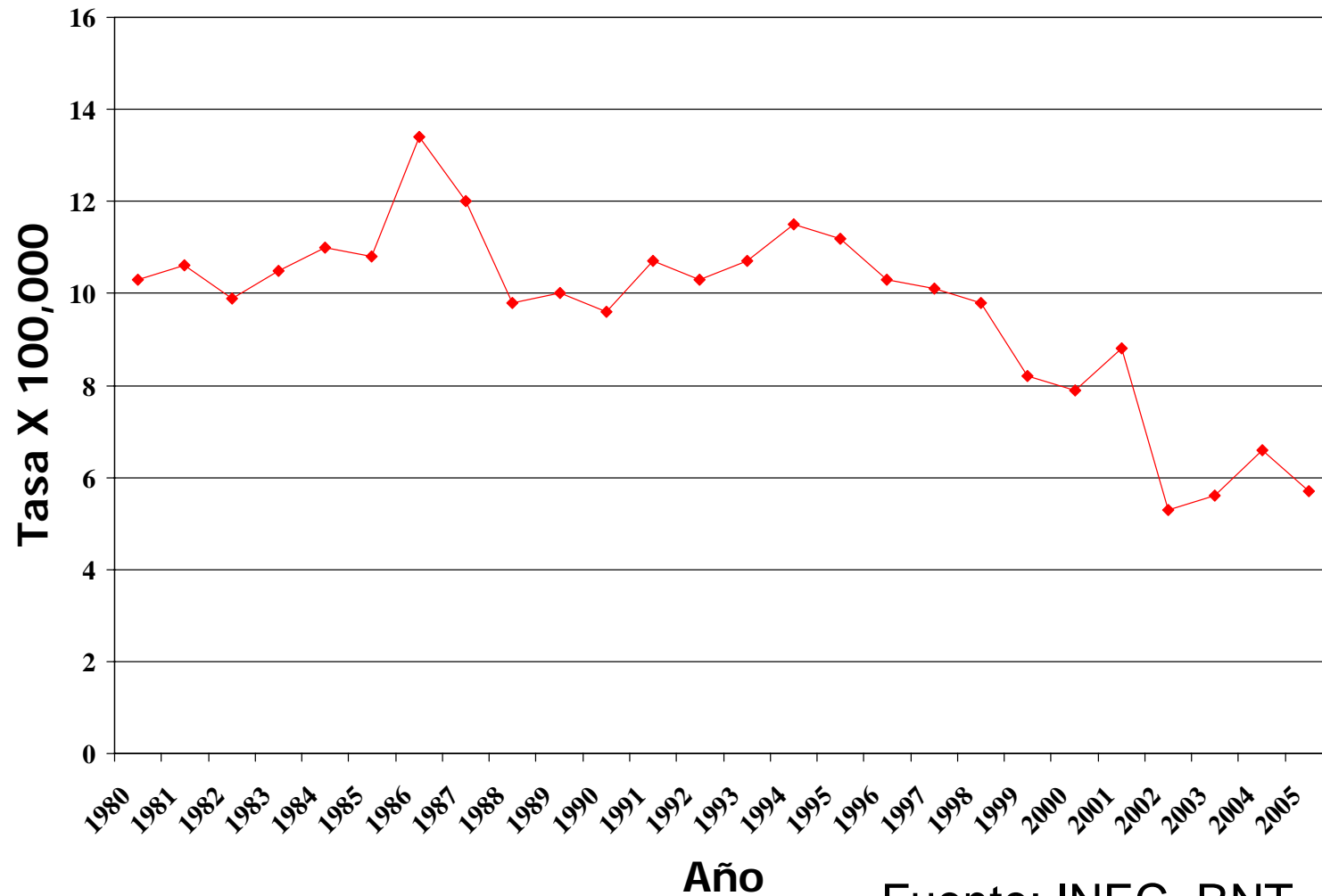
Unidad de Cáncer-Matrona Marta Prieto M.

**Cervical Cancer mortality rate (x 100,000) by education
age adjusted to 1992. Chile 1985-1996**

Education years	1985-87	1994-96	Decrease	
Basic (1-8 years)	21.9	19.2	12.5	
Media (9-12 years)	16.0	13.0	18.7	
Superior (13 and more)	9.9	4.8	51.6	

Cortesy of Dr Catterina Ferreccio

Standardized cervical cancer mortality rates in Costa Rica, 1980-2005



Fuente: INEC, RNT

Reasons for reductions in mortality in Costa Rica

- Program reorganization 90's
 - Change of collection instrument
 - National Cytology Lab
 - Increase in coverage
 - Improvements in follow up
- Acces to medical services
- Reduction in cofactors
- Socio-economic improvement

Limitations of cytology

- Low sensitivity – needs to be repeated
 - 51% (30-87%) Nanda et al, 2000
 - 53% Cuzick et al, 2006
- Low reproducibility – needs quality control
- Can not be made automatic – needs multiple visits
- All this increases cost and reduces access

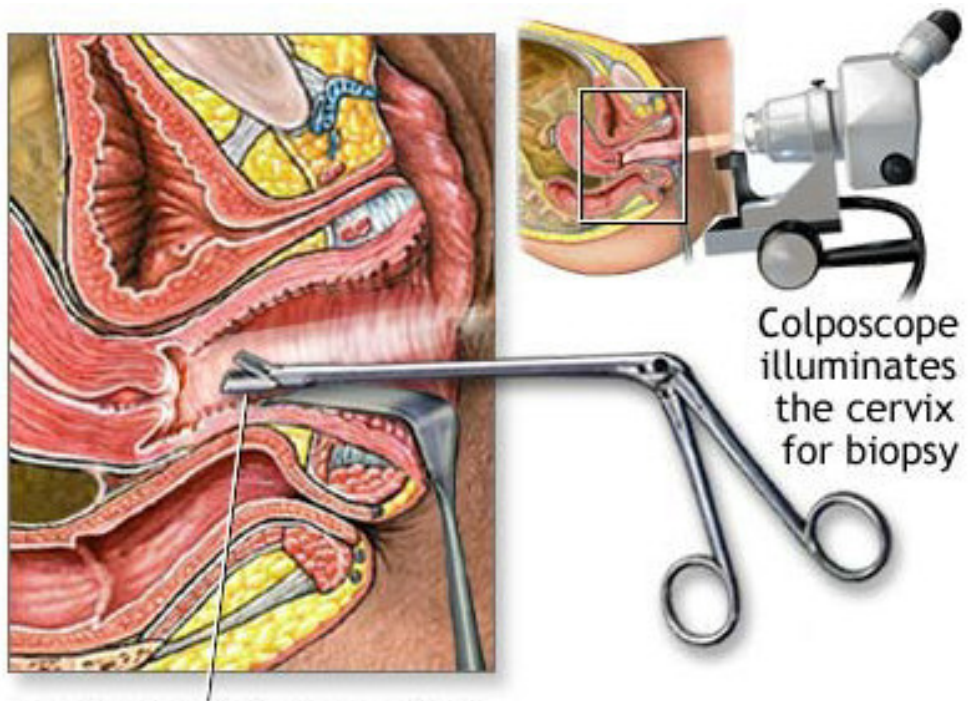
Abnormal Pap



Colposcopy/Biopsy



Treatment



Limitations of colposcopy

- Bad correlation between visual changes and severity of the lesion.
- Limited sensitivity for high grade disease. ALTS:
~40 Colposcopists – Sensitivity 54.8%
- Problems of reproducibility of histopathology

New methods are required to overcome limitations of current screening methods

- Better performance
- Reduction in number of visits
- Low cost

PERFORMANCE AND CHARACTERISTICS OF DIFFERENT SCREENING METHODS

SCREENING TEST	SENSITIVITY	SPECIFICITY	CHARACTERISTICS
Conventional cytology ^a	Moderate (44–78%)	High (91–96%)	Requires adequate health care infrastructure; Laboratory based; Stringent training and quality control
HPV-DNA testing ^a	High (66–100%)	Moderate (61–96%)	Laboratory based; High throughput; Objective, reproducible and robust; Currently expensive
Visual Inspection Methods ^a			Low technology; low cost
VIA	Moderate (67–79%)	Low (49–86%)	Linkage to immediate treatment possible; Suitable for low-resource settings
VIAM	Moderate (62–73%)	Low (86–87%)	
VILI	Moderate to high (78–98%)	Low (73–93%)	
Colposcopy	Low (44–77%)	Low (85–90%)	Expensive; Inappropriate for low-resource settings
Polar Probe	Moderate (67–74%)	Low (65–72%)	High technology but gives immediate result and could be linked to immediate treatment

^a Ranges of sensitivity and specificity adapted from reference Sankaranarayanan R, et al. Int J Gynaecol Obstet 2005; 89(Suppl. 2):S4–S12.

VIA: Visual inspection with acetic acid; VIAM: VIA with magnification; VILI: Visual inspection with Lugol's iodine

Potential uses of HPV testing

- Based on the premise that 100% of lesions are caused by HPV
- However, infection is very common and only a fraction progresses to cancer (1-2%)

Uses of HPV testing

- Triage of ASCUS-LSIL to colposcopy
- Post treatment
- Primary screening

HPV for triage of ASCUS ALTS: 2 year follow up

- Sensitivity of 1 HPV test: 92%
- Colposcopic referral: 53%

- Sensitivity of 3 Paps (HSIL): 60%
- Colposcopic referral: 12%

- Sensitivity of 3 Paps (ASCUS): 97 %
- Colposcopic referral: 73 %

HPV for LSIL triage

- More than 80% of LSIL have HPV so it is not recommended
- Recommendation: colposcopy or short term follow up

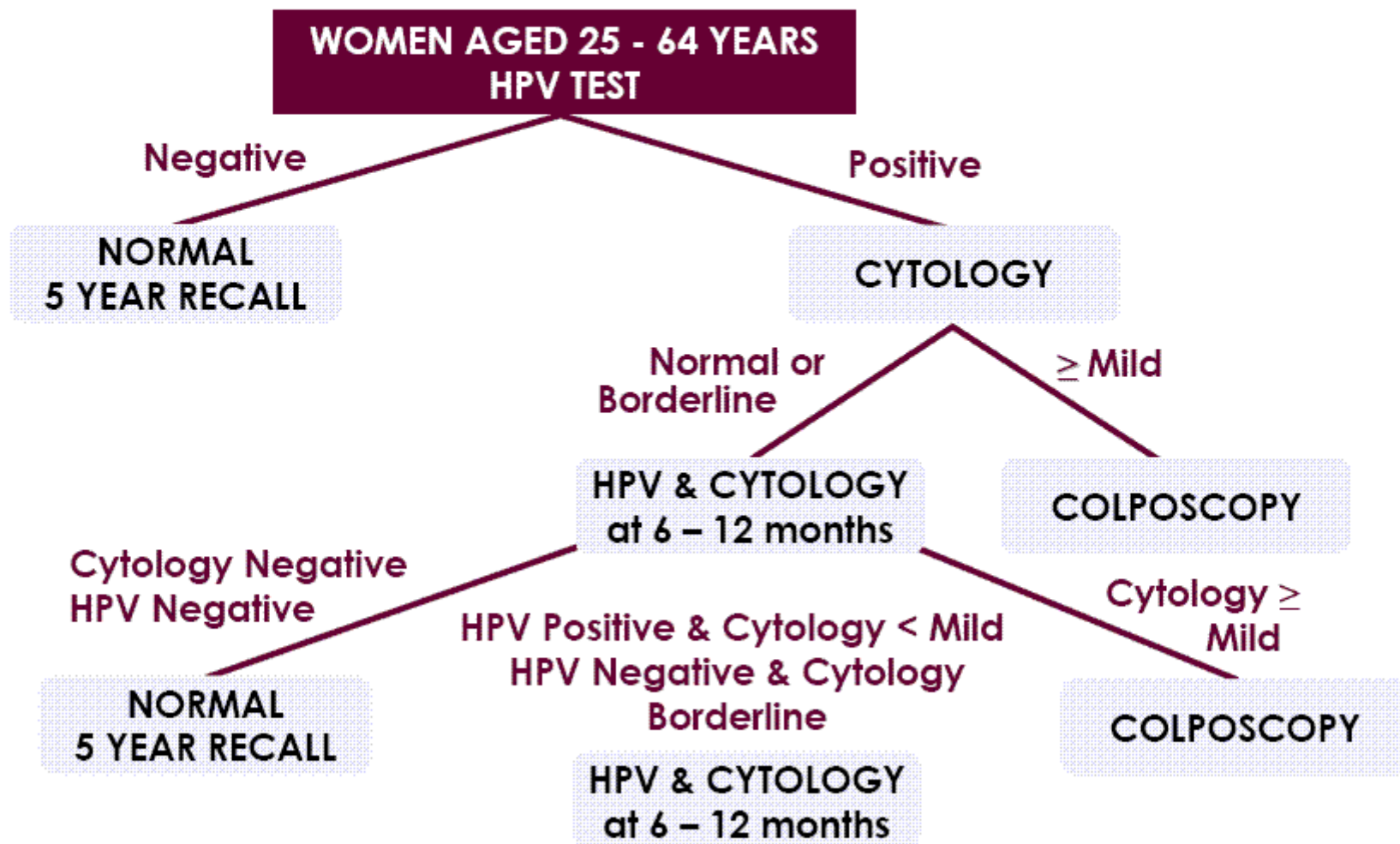
HPV for primary screening

- Sensitivity for high grade disease higher than Pap
 - 98% USA and Europe
 - 50-88% in India and Zimbabwe (Arbyn 2006)
- Specificity lower than Pap
- Approved by FDA for women over 30

Perspectives for screening in the future

- Primary screening with HPV followed by cytology in positives
- Increase interval in HPV negatives
- Fast HPV tests with immediate treatment
 - Hybrid capture
 - Detection of E6 protein

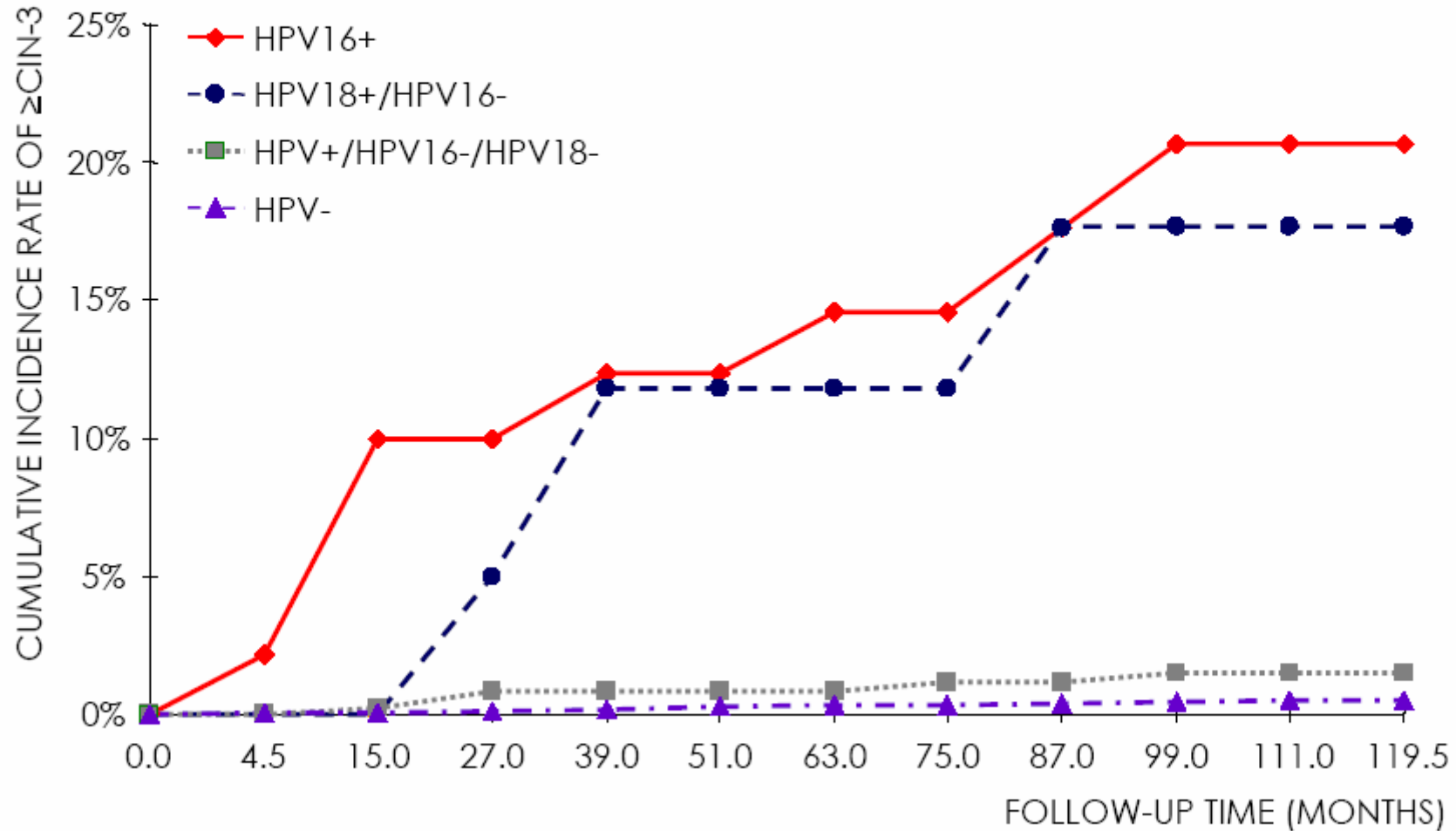
POSSIBLE ALGORITHM FOR THE USE OF HPV TESTING AS THE SOLE PRIMARY SCREENING MODALITY FOR WOMEN AGES 25-64, FOLLOWED BY PAP TRIAGE OF HPV POSITIVE WOMEN



Alternatives for management of HPV positives with negative cytology

- Viral persistence
- HPV type
- Viral load
- mARN of E6-E7 (16 18 31 33 45)
- Immunohistochemistry of p16
- Other markers

THE CUMULATIVE INCIDENCE OF CIN-3 OR GREATER OVER A 10-YEAR PERIOD AS A FUNCTION OF A SINGLE HPV TEST RESULT AT ENROLMENT



Reprinted from Khan MJ, et al. J Natl Cancer Inst 2005;97(14):1072-9 with permission from Oxford University Press.

CIN: Cervical intraepithelial neoplasia

Alternatives for management of HPV positives with negative cytology

- Viral persistence
- HPV type
- Viral load
- mARN of E6-E7 (16 18 31 33 45)
- Immunohistochemistry of p16
- Other markers

The search for low cost alternatives

- Visual inspection with acetic acid and immediate cryotherapy.
- Visual inspection with lugol and immediately cryotherapy

Reaction to acetic acid



Advantages of visual inspection

- Simple, non invasive, economic
- No need for special equipment
- Immediate results

Limitations of visual inspection

- Hard to achieve appropriate training.
- High percentage of positives
- Low sensitivity in some studies.
- Requires frequent screening
- Results of large trials by award winning Sankar coming up soon

Conclusions

- Cytology screening works in the context of high investment and technology, not feasible in less developed areas
- New methods with HPV testing can reduce costs with high efficacy
- Screening must go on and be improved despite availability of prophylactic vaccines