Cervical Cancer Screening in Developing Countries

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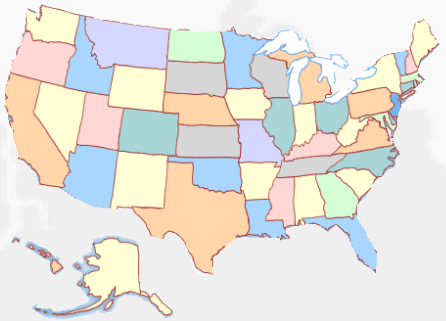
March 11, 2009

Outline

- Epidemiology
- Screening- Cytology, VIA, HPV Test
- Modes of Treatment
- HPV vaccine
- Barriers with Implementation
- Conclusions

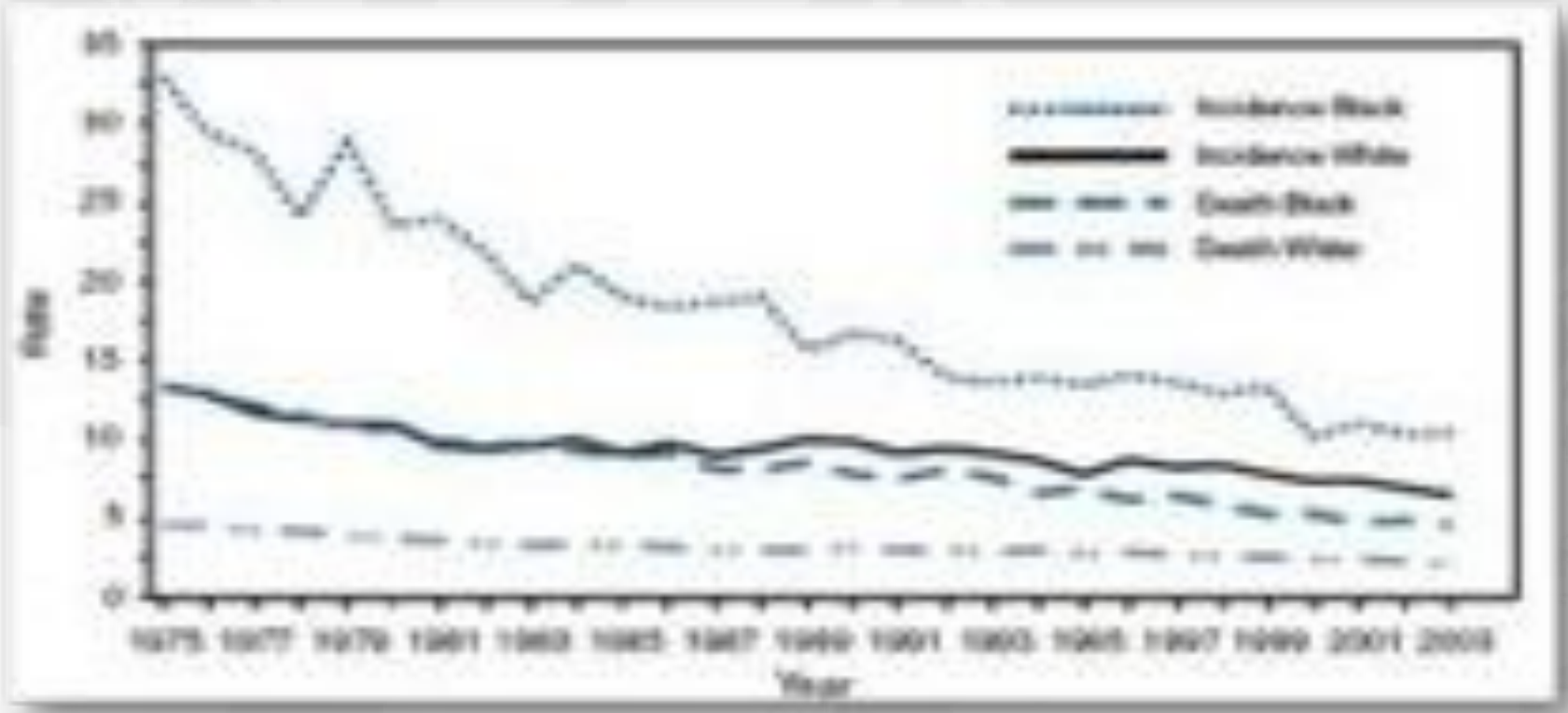
Epidemiology- US



- Ranks 14th in female cancer
- 2003 cervical cancer incidence: 8.1 per 100,000
- Incidence ↓ 75%, and mortality ↓ 70% since 1950s

National Cancer Institute. SEER Cancer Statistics Review, 1975-2003.

Epidemiology- US



Cervical cancer (invasive) SEER incidence* and death rates, by race and year – United States, 1975-2003

National Cancer Institute. SEER Cancer Statistics Review, 1975-2003. Bethesda, MD: National Cancer Institute; 2004.

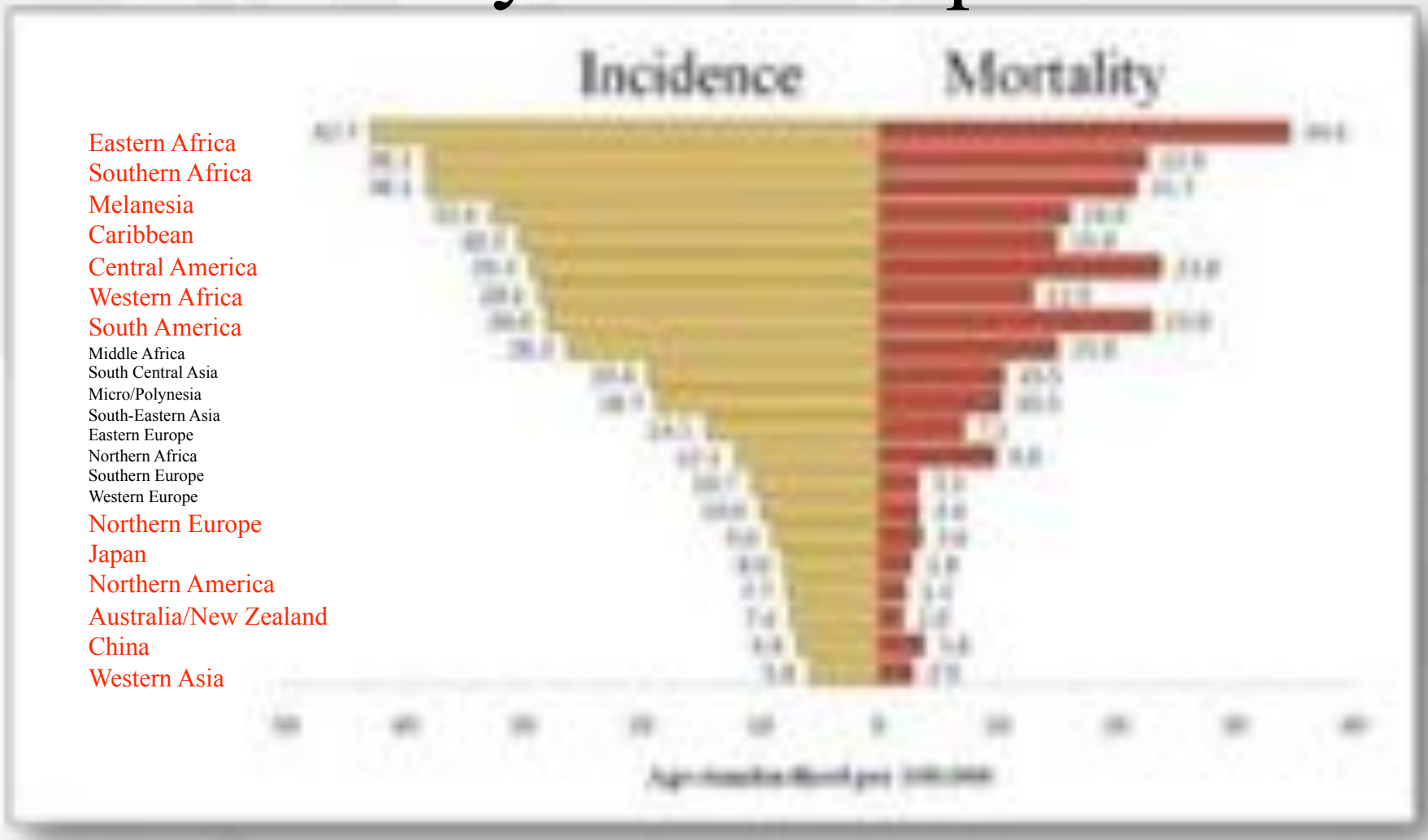
**Per 100,000 persons and age –adjusted to the 2000 U.S. standard population.*

How do we achieve this success in developing countries?

Epidemiology- Global

- 2nd most common cancer in women worldwide
- Most common cancer among women in developing countries
- 85% of all new cases and deaths occur in developing countries

Globally: Wide Disparities

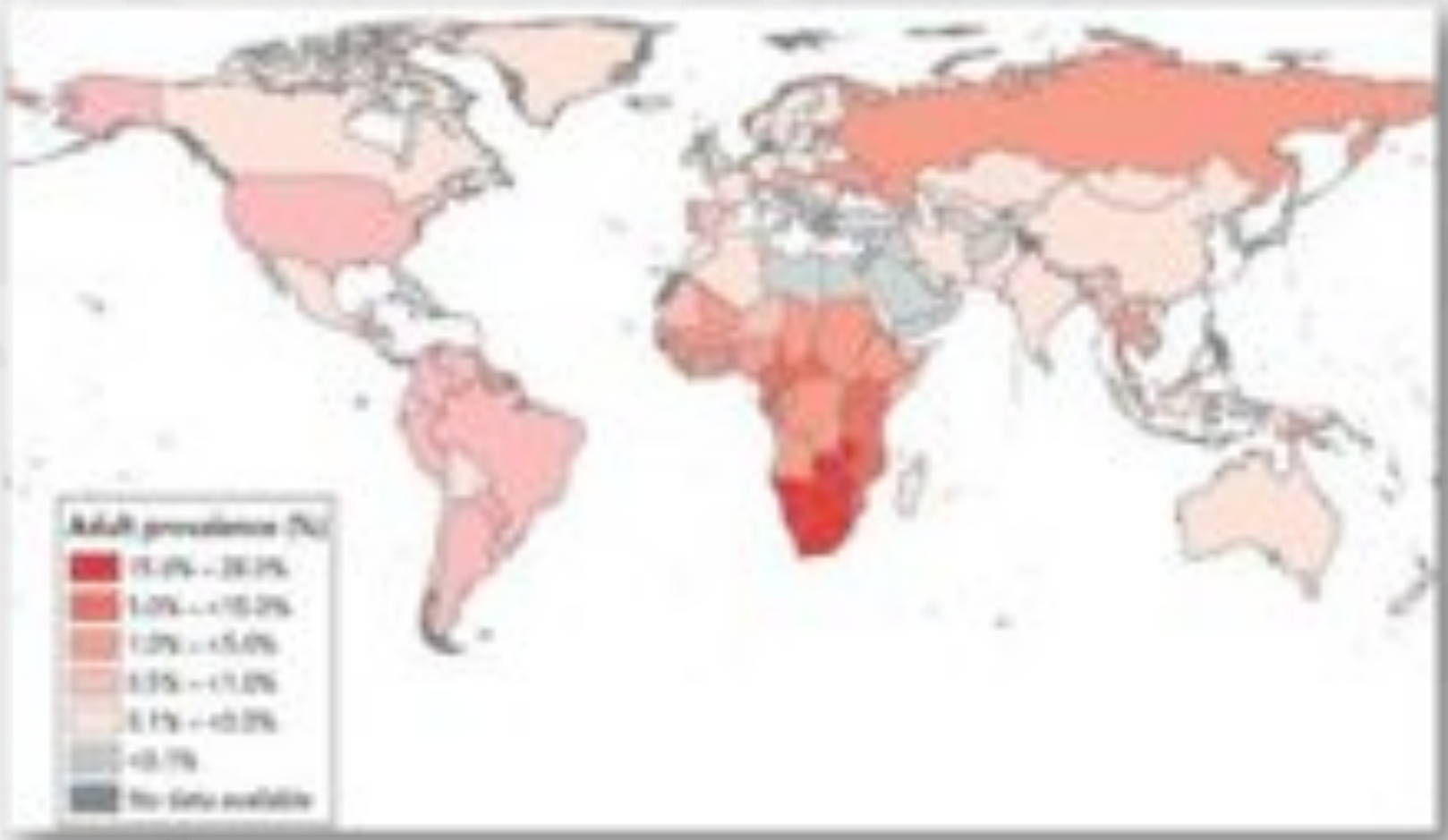


Parkin, D. M. et al. CA Cancer J Clin 2005;55:74-108.

Global Picture of Cervical Ca

Parkin DM, et al. Vaccine 2006;24 Suppl 3:S3/11-25

Global Picture of HIV



WHO/UNAIDS, 2008

Cervical Cancer = Years of Life Lost

- Aim: Compare YLL to AIDS, TB, maternal conditions, and cancers
- Outcome:
  - Responsible for > 150,000 deaths and 2.3 million YLL worldwide
  - Largest cause of YLL from cancer in developing world
  - Latin America, Caribbean, Eastern Europe: cervical cancer contributes more to years of lost life than TB, maternal conditions, or AIDS.

Yang BH, et al. Int J Cancer 2004;109:418-24.

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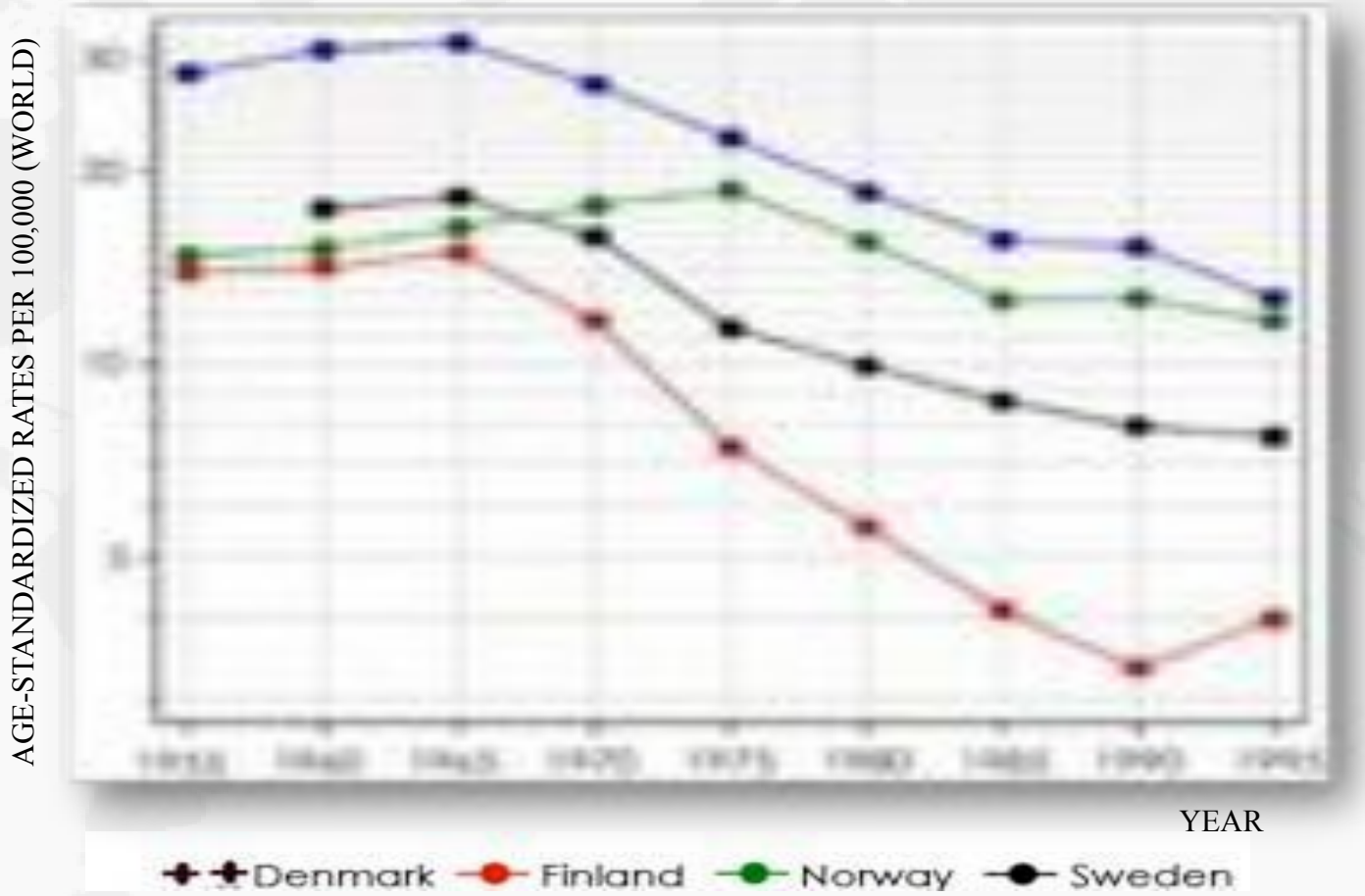
Criteria for Good Screening Test

- High Sensitivity & Specificity
- High Positive Predictive Value
- Simplicity & Low Cost
- Acceptable to Patients & Clinicians

Effect of Screening with Cytology



Parkin DM, et al. Vaccine 2006;24 Suppl 3:S3/11-25.

Screening in Low-Resource Areas

- Screening, dx, tx all on-site
- Low-cost, low-technology screening test
- Wide coverage, accessible to women
- Educational Programs
- Evaluation of Screening Program

Denny L, et al Vaccine 2006;24 Suppl 3:S3/71-7.

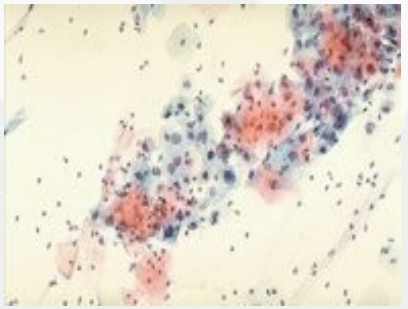
Cytology: Globally Feasible??

Not All Cytology is Equal

- Conventional vs. Liquid Based Cytology
  - Conventional: more common in developing areas, less expensive
  - LBC: used in developed world
- Difference in Sensitivity & Specificity
  - Sensitivity consistently lower in developing countries

Cronje HS. Int J Gynaecol Obstet 2004;84:101-8

Screening- Cytology



- Advantages
  - "Standard of care"
  - Validated & accepted
  - Infrastructure may already be in place
  - Untrained HCW able to perform
  - Common language for referral
  - High specificity
- Disadvantages
  - Infrastructure required
  - High-quality cytology labs & cytopathologists
  - Transport specimen
  - Communication of results
  - Follow-up, colposcopy
  - Low sensitivity
  - ? Cost-effective

Visual Inspection with Acetic Acid (VIA)

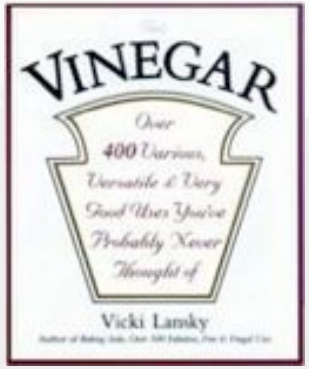
"The detection of intraepithelial or preclinical invasive cervical neoplasias should not depend on the possession of a colposcope."

Ottaviano M, et al. Am J Obstet Gynecol 1982;143:139-42.

Manual for Visual Inspection

International Agency for Research on Cancer
Centre International de Recherche sur le Cancer

Screening- VIA/VILI

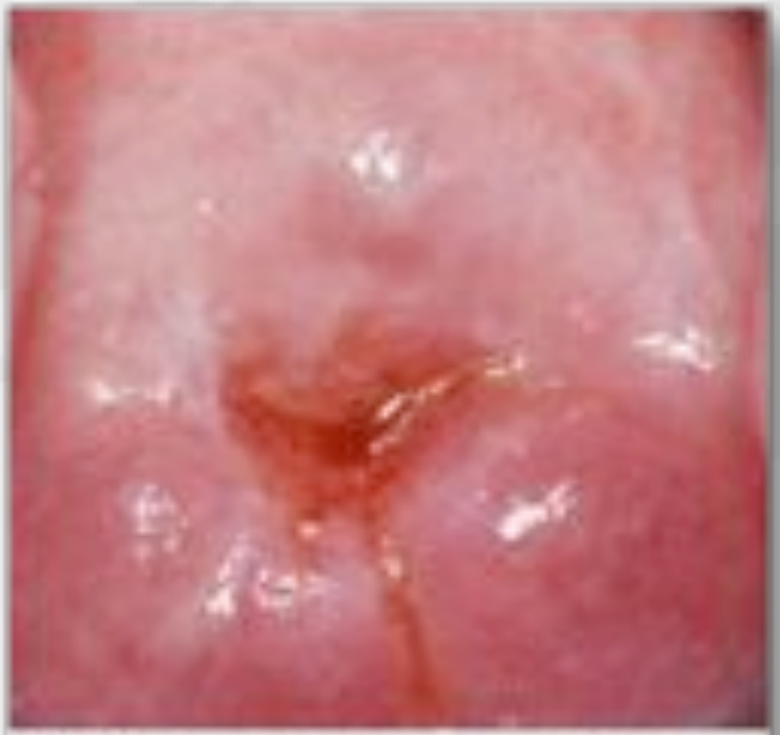


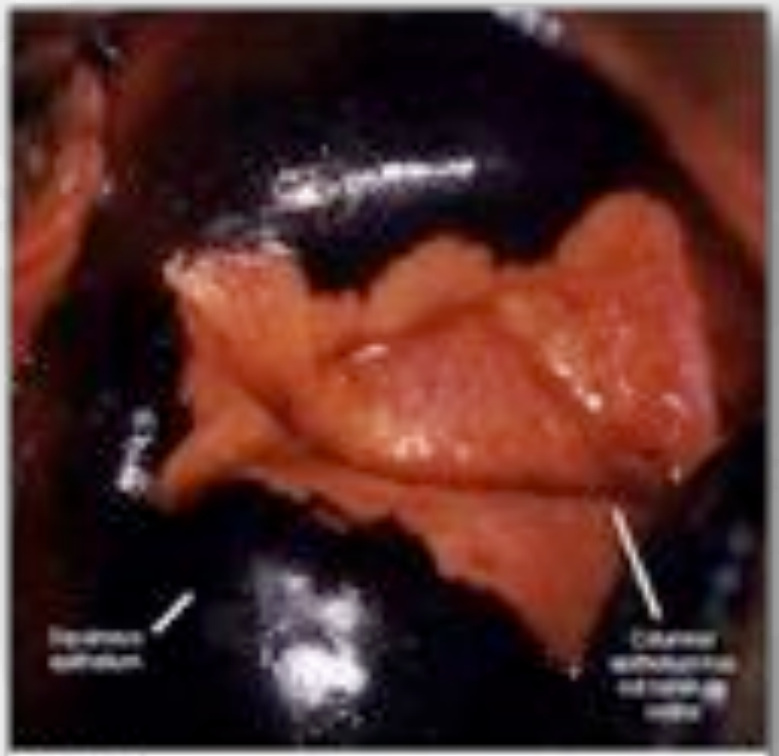
- Visual Inspection with acetic acid (VIA): can be done with naked eye or low magnification
  - Speculum exam
  - Application of dilute 3-5% acetic acid to the cervix
  - Abnormal tissue appears white
- Visual Inspection with Lugol's Iodine (VILI)
  - Uses Lugol's Iodine instead of acetic acid
  - Abnormal tissue appears unstained

VIA Reporting

VIA Result	Clinical Findings
Negative	No AWE, polyp, cervicitis, inflammation, Nabothian cysts; metaplasia
Positive	Sharp, well-defined AWE usually touching SCJ, leukoplakia, warts
Suspicious for cancer	Visible ulcerative, warty growth, bleeding to touch

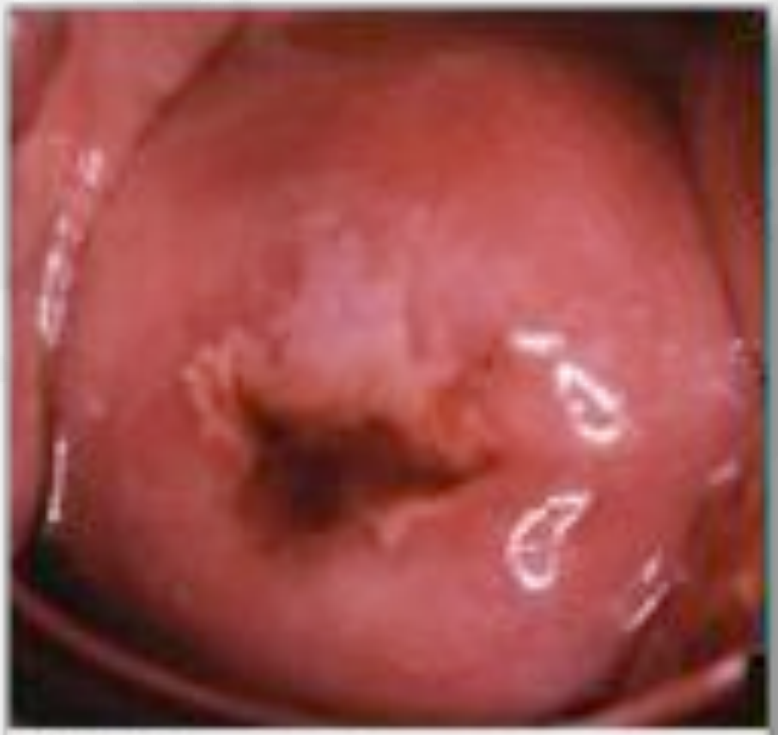
VIA/VILI negative

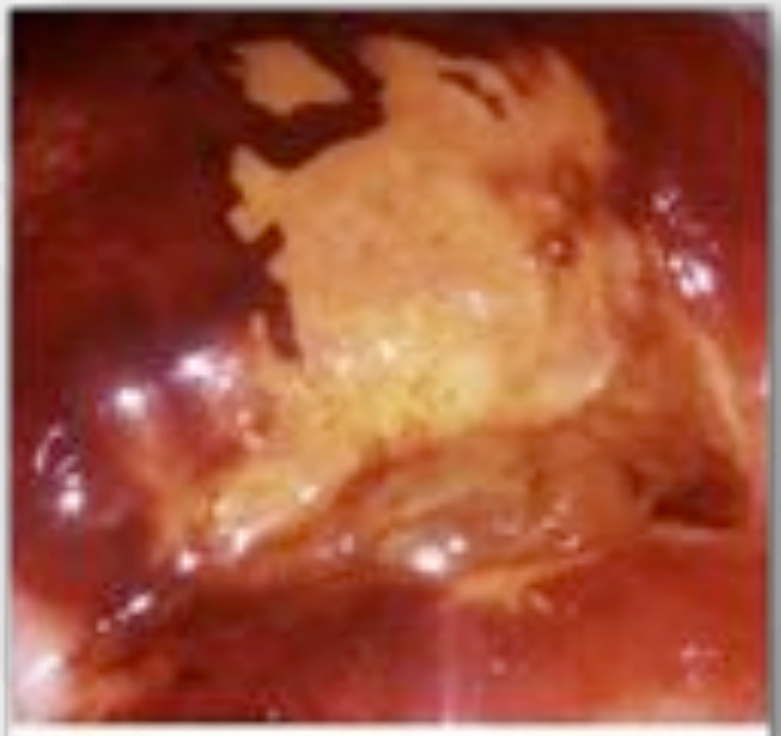




International Agency for
Research on Cancer (IARC)

VIA/VILI positive





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Research on Cancer (IARC)

VIA Suspicious for Cancer

International Agency for
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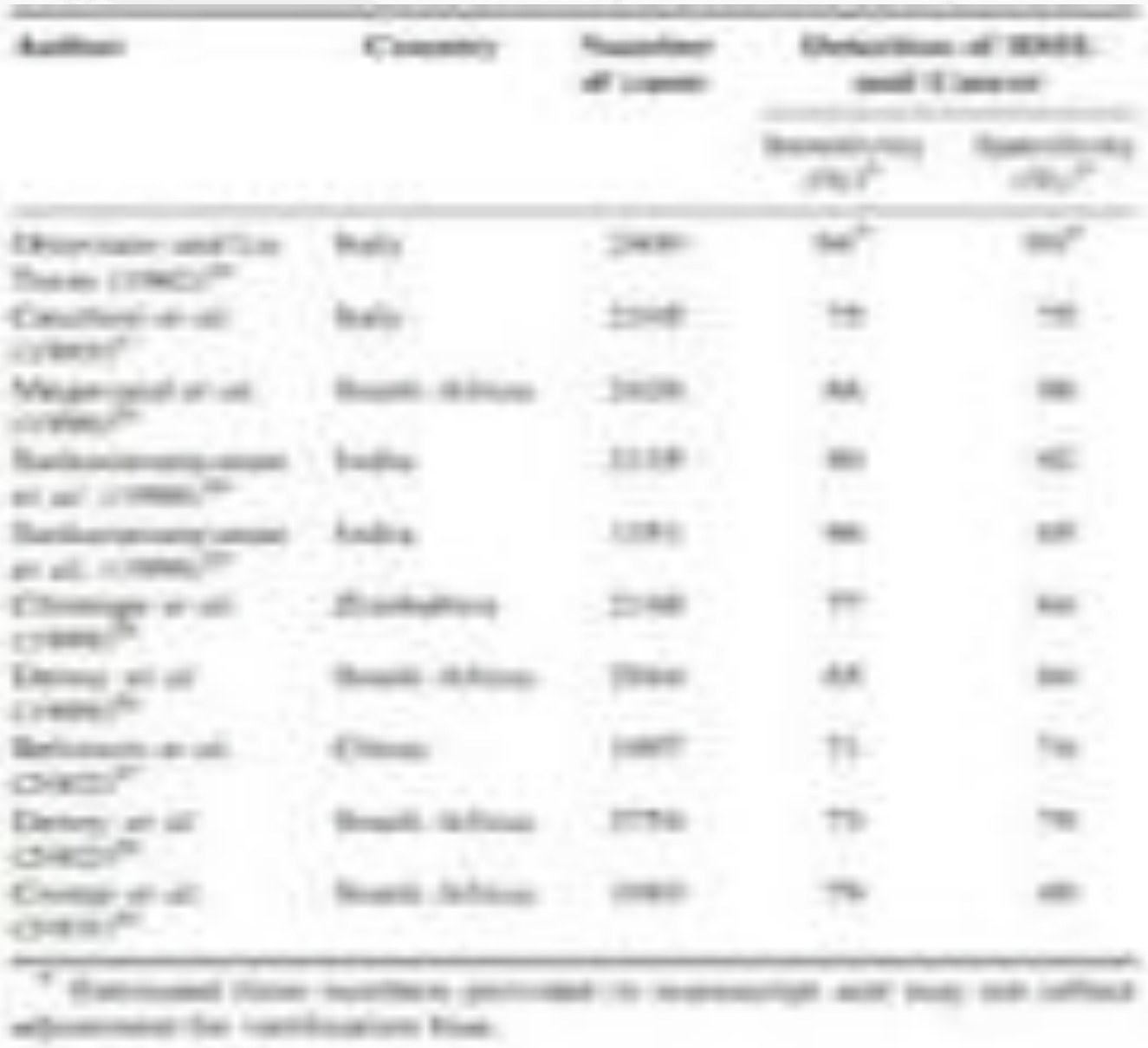


Denny L. BJOG 2005;112:1204-12.

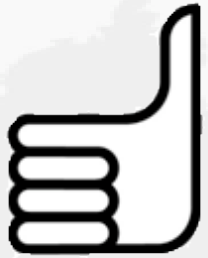
VIA vs. Cytology

- Cross-sectional study, Zimbabwe
  - n=10,934 screened with both cytology & VIA
  - Screening done by 6 trained nurse-midwives
  - 15 primary care clinics.

Test	Sensitivity (95% CI)	Specificity (95% CI)
VIA (n=2130)	76.7 (70.3-82.3)	64.1 (61.9-66.2)
Pap (n=2092)	44.3 (37.3-51.4)	90.6 (89.2-91.9)

University of Zimbabwe/JHPIEGO Cervical Cancer Project. Lancet 1999;353:869-73.

VIA Advantages



- Simple, easy to learn
- Different healthcare workers can be trained
- Minimal lab infrastructure needed
- Inexpensive, low costs to start-up & sustain
- Requires 1 visit, immediate result
- Screen & Treat
- Integrate into primary health care services

VIA Disadvantages

- Moderate specificity, unnecessary tx in single visit approach
- Health, cost implications of over-treatment
- Need for training & quality control
- Evaluator dependent
- Less accurate in post-menopausal women
- Not uniformly accepted

VIA appears to be a more appropriate screening modality for resource-poor areas, but is it cost-effective?

What is Most Cost-Effective?

- Computer-based model applied to 5 countries: India, Kenya, Peru, S. Africa, Thailand
  - Screening methods: cytology, VIA, HPV Test
  - Number of visits: 3 vs. 2 vs. 1- visit strategies
  - Outcomes: lifetime risk of cancer, years of life saved, lifetime costs, and cost-effectiveness ratios (cost per year of life saved).

Goldie SJ, et al. N Engl J Med 2005;353:2158-68.

VIA is Cost Effective

- VIA or HPV test in 1 or 2 visits are cost-effective alternatives to 3-visit cytology-based screening.
  - Screened women once @ age 35 yr
  - Decrease cervical cancer risk by 25-36%
  - Cost < $500 per year of life saved

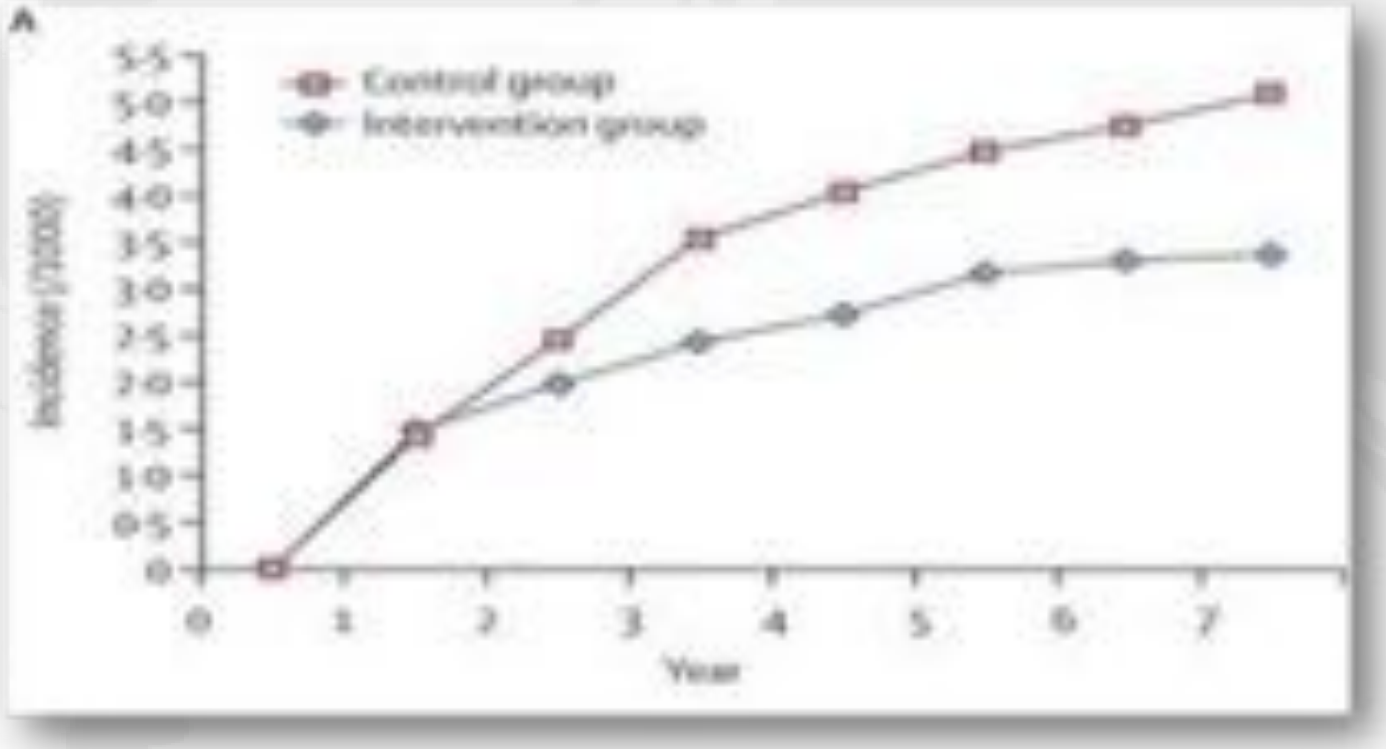
Goldie SJ, et al. N Engl J Med 2005;353:2158-68.

Can VIA Prevent Invasive Cancer?

- Cluster randomized trial in India
  - 49,311 intervention grp (VIA); 30,958 control grp
  - Intervention grp: VIA, Colpo/Bx, Immediate Cryo
  - Control grp: education on screening & cervical ca
  - Intention to treat analysis
  - **Primary outcome**: VIA affects cervix cancer incidence and mortality

Sankaranarayanan et al. Lancet 2007;370:398-406.

VIA Decreases CIN 2+



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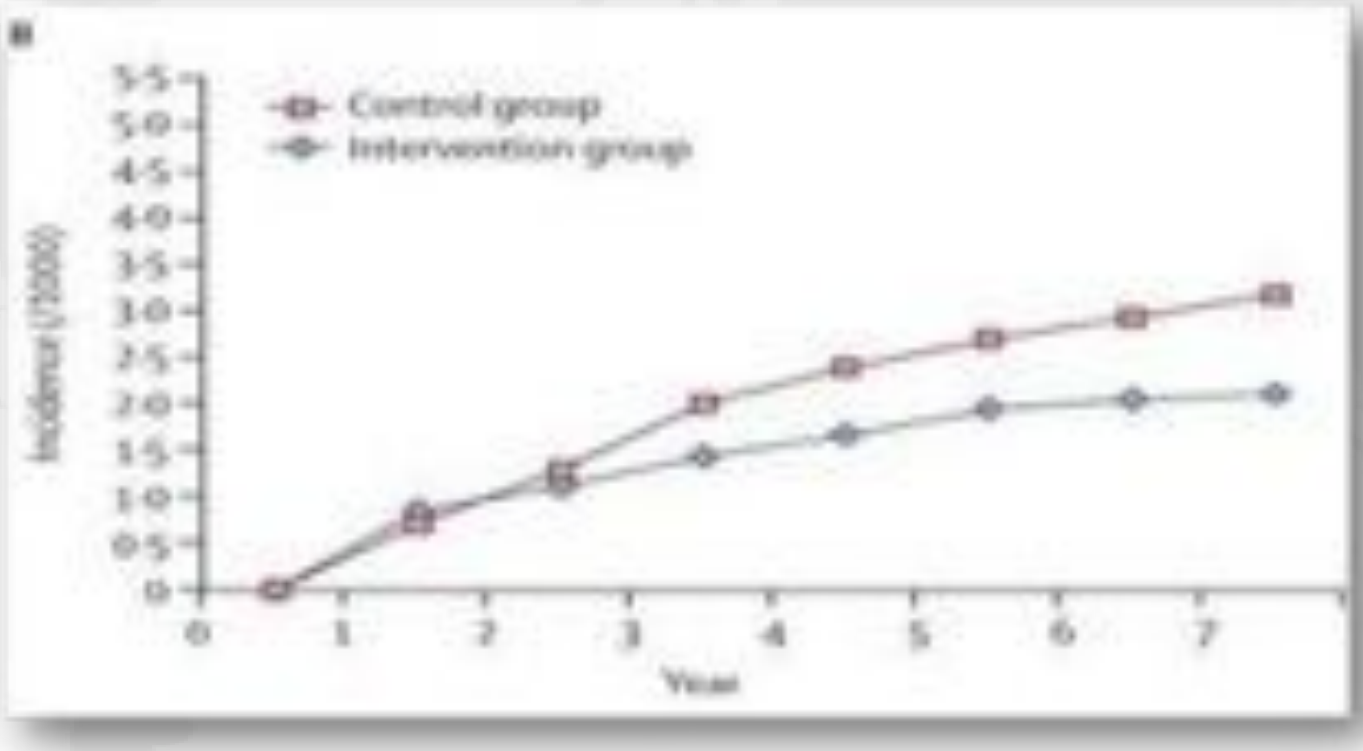
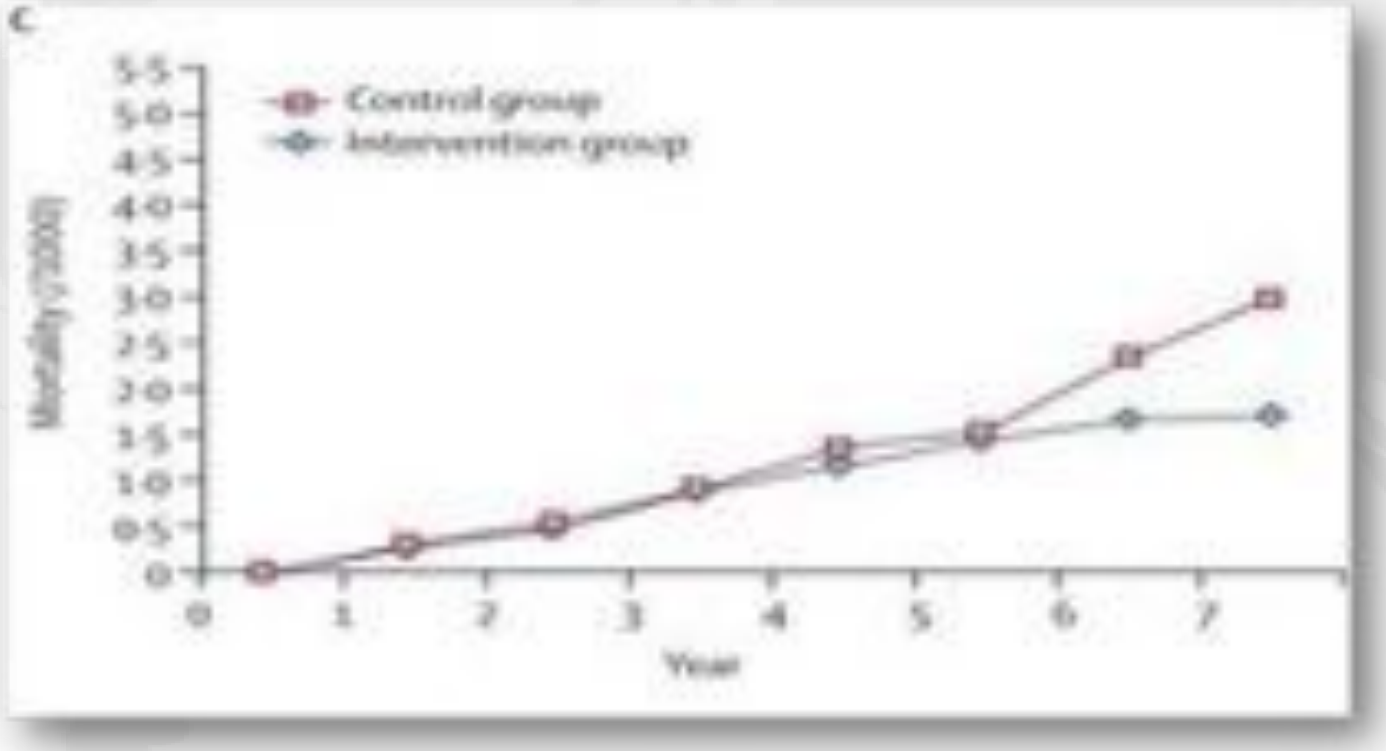
VIA Decreases Cervical Cancer



Sankaranarayanan et al. Lancet 2007;370:398-406.

VIA Decreases Mortality



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VIA does seem to have a promising role in decreasing disease burden, but what other methods can be used?

Screening- HPV Test

- HPV Test: Hybrid Capture 2 (HC2)
  - High-risk HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68
  - Sensitivity/Specificity depends on the use of the test
- Uses of HPV Test
  - Triage for ASCUS
  - Follow-up treatment for CIN
  - Primary screening

HPV Test Sensitivity/Specificity

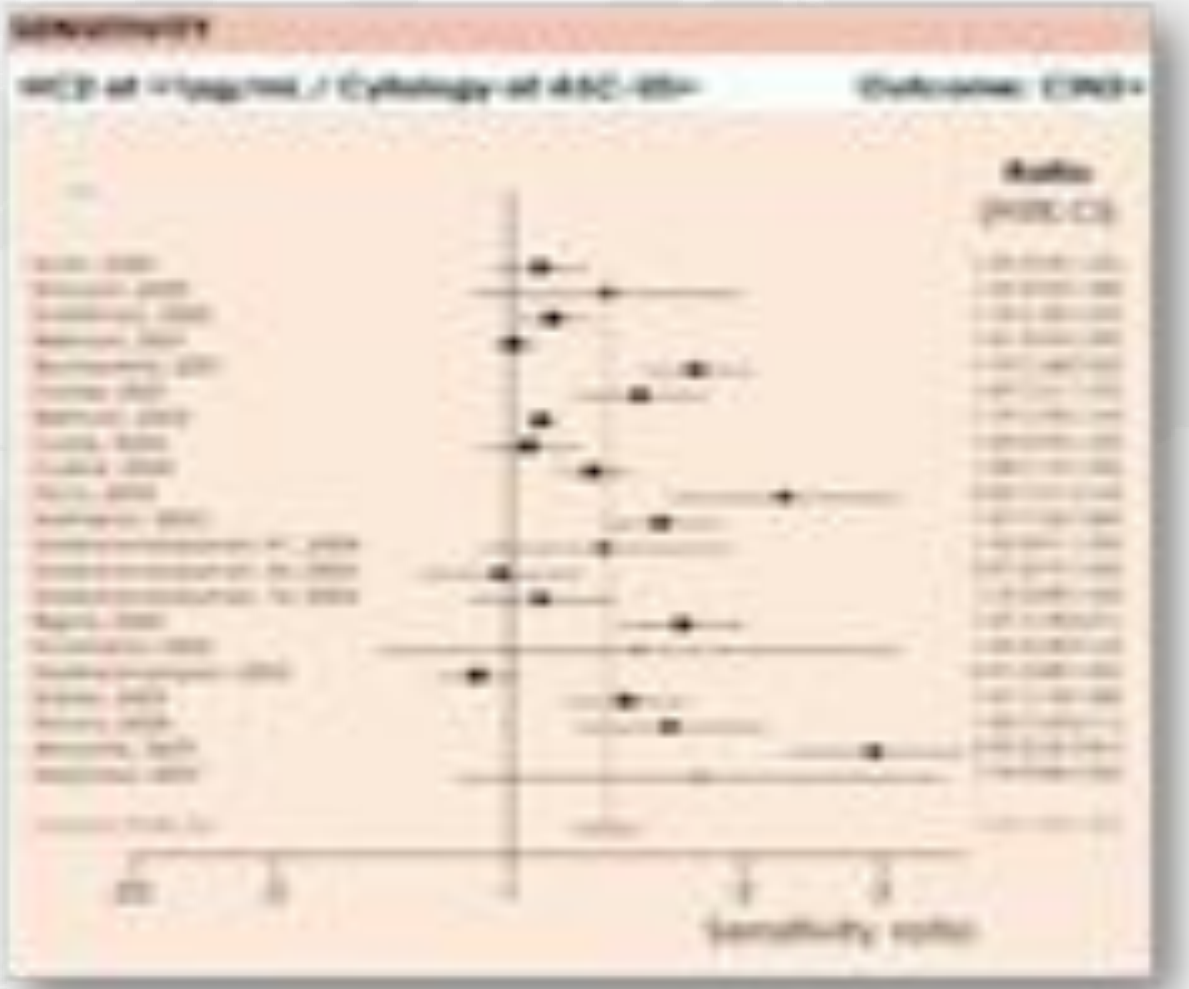
- Primary Screening: 25 cross-sectional studies (US, Europe, India, Peru, Brazil Zimbabwe, S. Africa)

:

	Sensitivity	Specificity
Overall	89.7%	88.2%
N.Amer/Europe	98.1%	91.7%

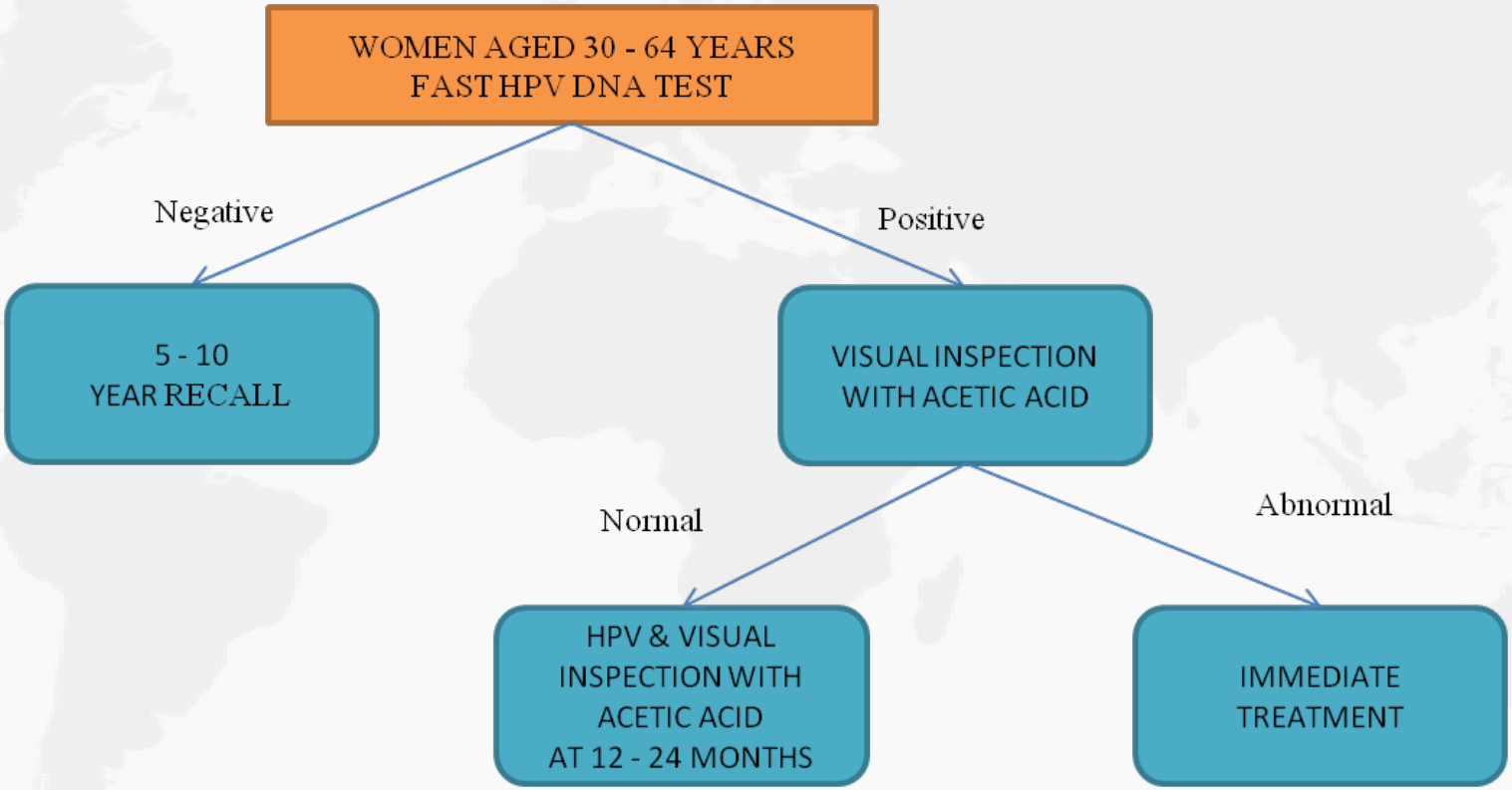
Cuzick J, et al. Vaccine 2008;26 Suppl 10:K29-41.

HPV is more sensitive than Pap



Cuzick J, et al. Vaccine 2008;26 Suppl 10:K29-41.

Screening Algorithm- HPV Test



Cuzick J, et al. Vaccine 2008;26 Suppl 10:K29-41.

Screening- HPV Test

- Advantages
  - High sensitivity
  - Automated, objective test
  - Local labs
  - Screen & Treat
  - Self sampling
- Disadvantages
  - Lower specificity
  - Geographic heterogeneity of results
  - Quality control, test parameters
  - Expensive cost $

VIA vs. HPV Test

- RCT for non-cytology based screen & treat to determine safety & efficacy of VIA, HPV testing
  - South Africa: 6,555 women; 35-65 years
  - All had both HPV test & VIA then randomized
    - Cryo if HPV⊕ ***OR*** Cryo if VIA⊕ ***OR*** delayed eval
  - Outcome measured CIN2+ @ 6, 12 mo

Denny L, et al. JAMA 2005;294:2173-81.

	HPV DNA Group	VIA Group	Delayed Evaluation (Control) Group
Cumulative Prevalence at 6 or 12 mo After Randomization			
CIN 2+			
Total No.	25	54	93
% (95% CI)*	1.42 (0.87-1.97)	2.91 (2.12-3.69)	5.41 (4.32-6.50)
At 6 mo After Randomization			
Evaluated, No.	1879	1929	1859
CIN 1	45	58	44
Neoplasia in endocervical curettage	4	5	5
CIN 2	4	20	33
CIN 3	7	18	27
Cancer	0	0	1
CIN 2+			
Total No.	15	43	66
% (95% CI)	0.80 (0.40-1.20)	2.23 (1.57-2.89)	3.55 (2.71-4.39)
At 12 mo After Randomization†			
Evaluated, No.	897	950	861
CIN 1	21	27	25
CIN 2	7	8	18
CIN 3	2	3	8
Cancer	1	0	1
CIN 2+			
Total No.	10	11	27

Table 3. Pathological Diagnoses of Cervical Intraepithelial Neoplasia

Denny L, et al. JAMA 2005;294:2173-81.

JAMA

Screening Summary

Screening Test	Sensitivity	Specificity
Cytology	44-78%	91-96%
VIA	67-79%	49-86%
HPV DNA	66-100%	61-96%
VIAM	62-73%	86-87%
Colposcopy	44-77%	85-90%

Cuzick J, et al. Vaccine 2008;26 Suppl 10:K29-41.

Rapid HPV Test

- Batch Test: *care*HPV
  - HPV DNA
  - Vaginal/cervical specimen
  - <2.5 hours
- Strip test
  - E6 protein biomarker
  - Cervical specimen
  - 15 min

Rapid HPV Test in Rural China

- Cross-sectional Study
  - n=2530 women, 30-54 years
  - All women examined with
    - *care*HPV vaginal, cervical swabs,
    - LBC
    - HC2
    - VIA
    - Colpo
  - Outcome: clinical accuracy of *care*HPV as rapid screening test?

Qiao YL, et al. Lancet Oncol 2008;9:929-36.

Rapid HPV Test: a Promising Screening Test

Screening Test	Sensitivity (95% CI)	Specificity (95% CI)
*care*HPV cervical	90.0 (83-97)	84.2 (82.7-85.7)
*care*HPV vaginal	81.4 (72.3-90.5)	82.4 (80.8-83.9)
HC2	97.1 (93.2-100)	85.6 (84.2-87.1)
LBC	85.3 (76.9-93.7)	97.0 (96.3-97.7)
VIA	41.4 (29.9-53.0)	94.5 (93.6-95.4)

Qiao YL, et al. Lancet Oncol 2008;9:929-36.

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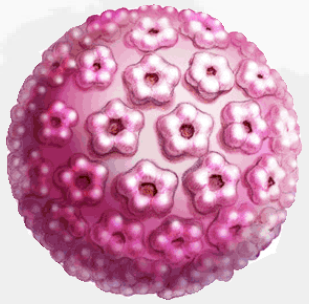
Modes of Treatment

- Cryotherapy
- LEEP
- Cervical conization
- Hysterectomy
- Chemoradiation

1st Symposium on Prevention of Cervical Cancer, Nicarauga

Outline



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HPV Vaccine

- Quadravalent vaccine HPV 6,11,16,18
  - FDA approved June 2006, ages 9-26 yr
  - 3 IM injections 0, 2, 6 months
  - $360 for 3 injections
  - Cross protection again other HPV types (45,31)
- Bivalent Vaccine HPV 16, 18
  - 3 IM injections 0, 1, 6 months
- Primary prevention: for prophylaxis not therapeutic
- Both vaccines > 90% efficacious against ≥ CIN 2

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Barriers

Barriers to HPV Vaccine

- Target: prior to onset of sexual activity (9-13 yr)
  - Vaccinating adolescents for a STI
- Vaccinating school-age children and adolescents
- Duration of vaccine
- Cancer vaccine, prophylactic vaccine for a cancer not likely to develop for decades
  - Full effect of vaccination will take 30-40 yrs
- Competing with other new vaccines

Barriers to HPV Vaccine

- Gender-specific immunization
- Costs: 2.2 billion people live in countries which have GNI < $825 per capita

World Bank 2006

Solutions?

- Bridge pediatric immunization, sexual & reproductive health, cancer communities
  - May serve as a future model for HIV vaccine
- Manufacture vaccine locally to reduce costs
- More outreach, mobile vaccination programs

So what is the answer for developing countries?

Conclusions

- Country-specific solutions need to be found, while being aware of criteria that enabled successful screening programs.
- VIA or HPV test in 1 or 2 visits are cost-effective alternatives to 3 visit pap based screening.
- Aim to screen women once in their lifetime, 30-40 years old

Conclusions

- Additional work is needed to develop rapid, user-friendly, low-cost HPV tests.
- Increase distribution of HPV vaccine.
- Increase accessibility of services and quality care

Sources

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Online resources:

http://www.path.org/cervical-cancer.php

http://www.iarc.fr/

Thank you!

- Dr. Jennifer Unger
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