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EPIDEMIOLOGY IN THE CONSTRUCTION OF HEALTH FOR ALL:
TOOLS FOR A CHANGING WORLD

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Expected Impact of HPV Vaccination on Cervical Cancer Screening Practices: *The Need for Synergy between Preventive Strategies*

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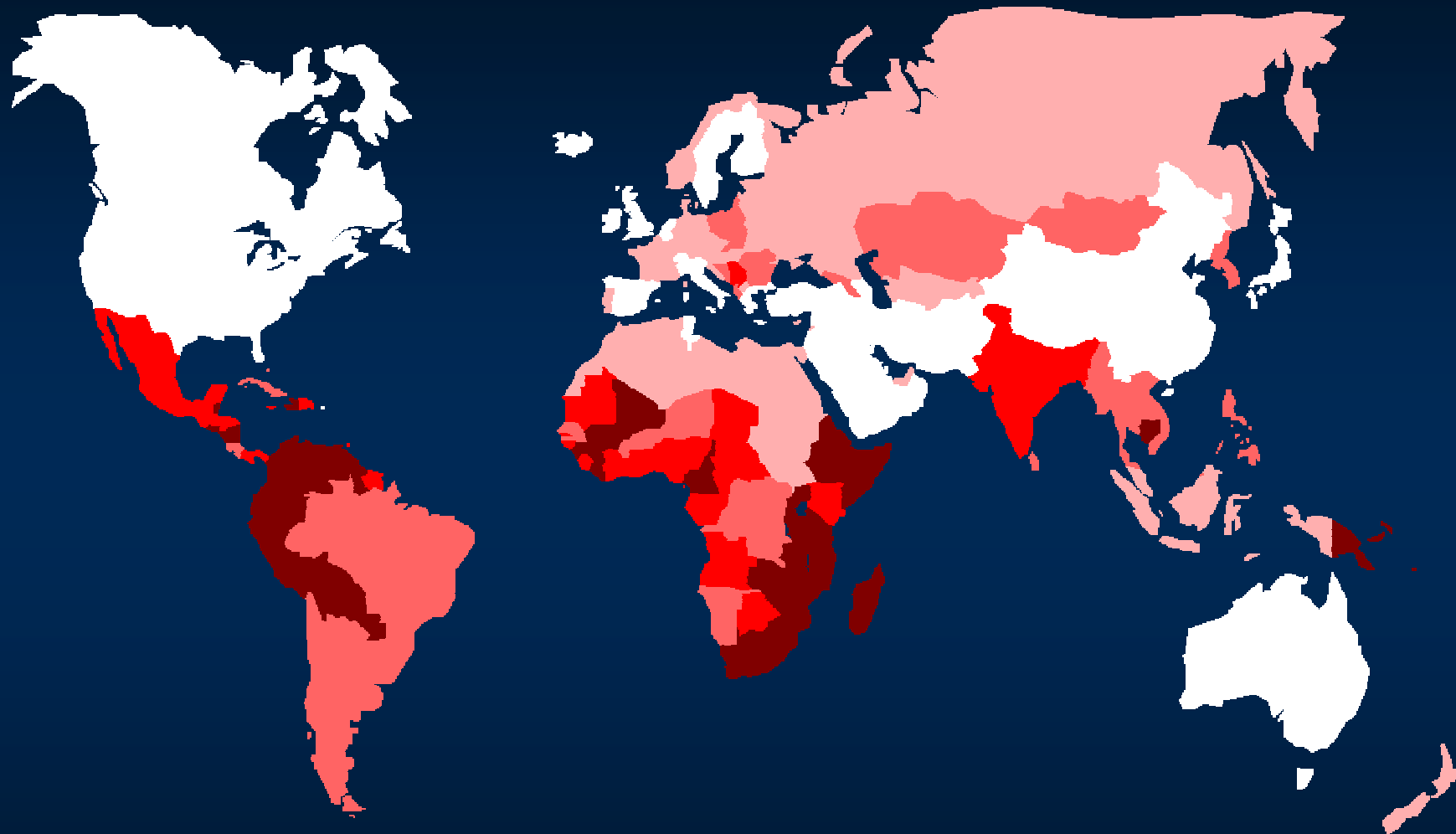
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Points to Cover

- Role of HPV in carcinogenesis: the science driving the changes in prevention strategies
- The cytology screening paradigm before the advent of vaccination
- Expected effects of vaccination on the burden of precancerous lesions and cervical cancer
- Loss of screening performance due to reduction in lesion prevalence: quantitative and qualitative effects
- Advantages of HPV testing as primary screening test followed by cytologic triage

Incidence of Invasive Cervical Cancer



Age-standardized (world population 1960) rates per 100,000 women per year

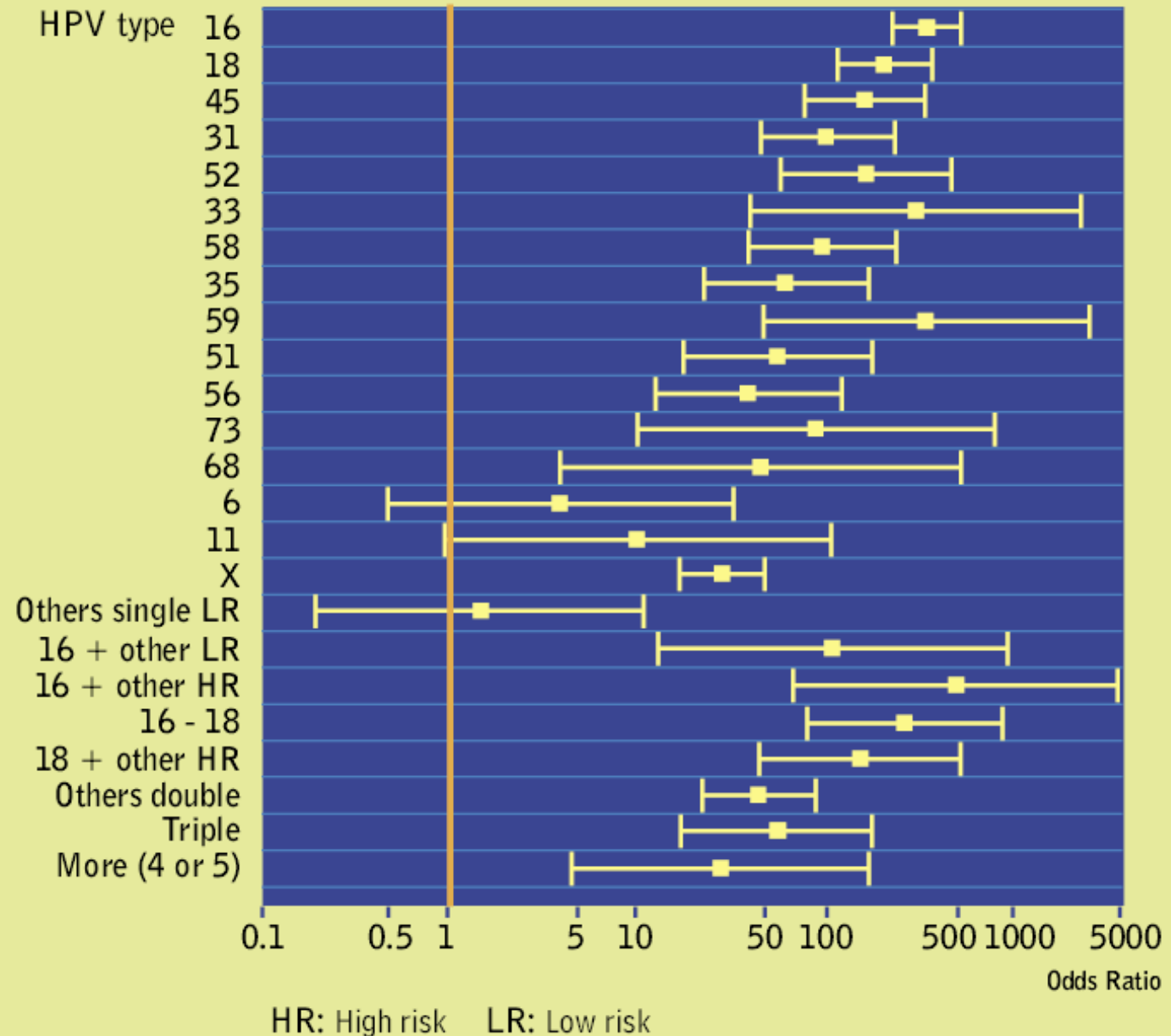
Source: GLOBOCAN 2002 (Ferlay et al., 2004)

Relative Risk estimates from the pool of IARC case-control studies:

Muñoz et al., NEJM 2003

Graph kindly provided by the Editors of HPV Today

HPV TYPE-SPECIFIC RISK ESTIMATES FOR CERVICAL CANCER



Proportion of a given cancer that is preventable by elimination of the exposure to the causal agent

Cancer prevention target	Population attributable risk
HPV infection and cervical cancer	> 99%
Smoking and lung cancer	75%-85%
Chronic HBV infection and liver carcinoma	10%-30% (low risk areas) 50%-90% (high risk areas)
Alcohol drinking and oral cancer	25%-70%
HRT and endometrial cancer	15%-50%

HPV Vaccination

- Phase II and III trial findings already in the public domain.
- Safety and efficacy of VLP vaccines documented by numerous peer-reviewed publications in leading medical journals.
- Although clinical experience has just passed 6 years, the evidence base is one of the strongest in disease prevention.
- The standard of proof is far more rigorous than that used in the evaluation of candidate vaccines of the past.
- Possibly, the most scrutinized vaccine by the public and media concerning need and safety.

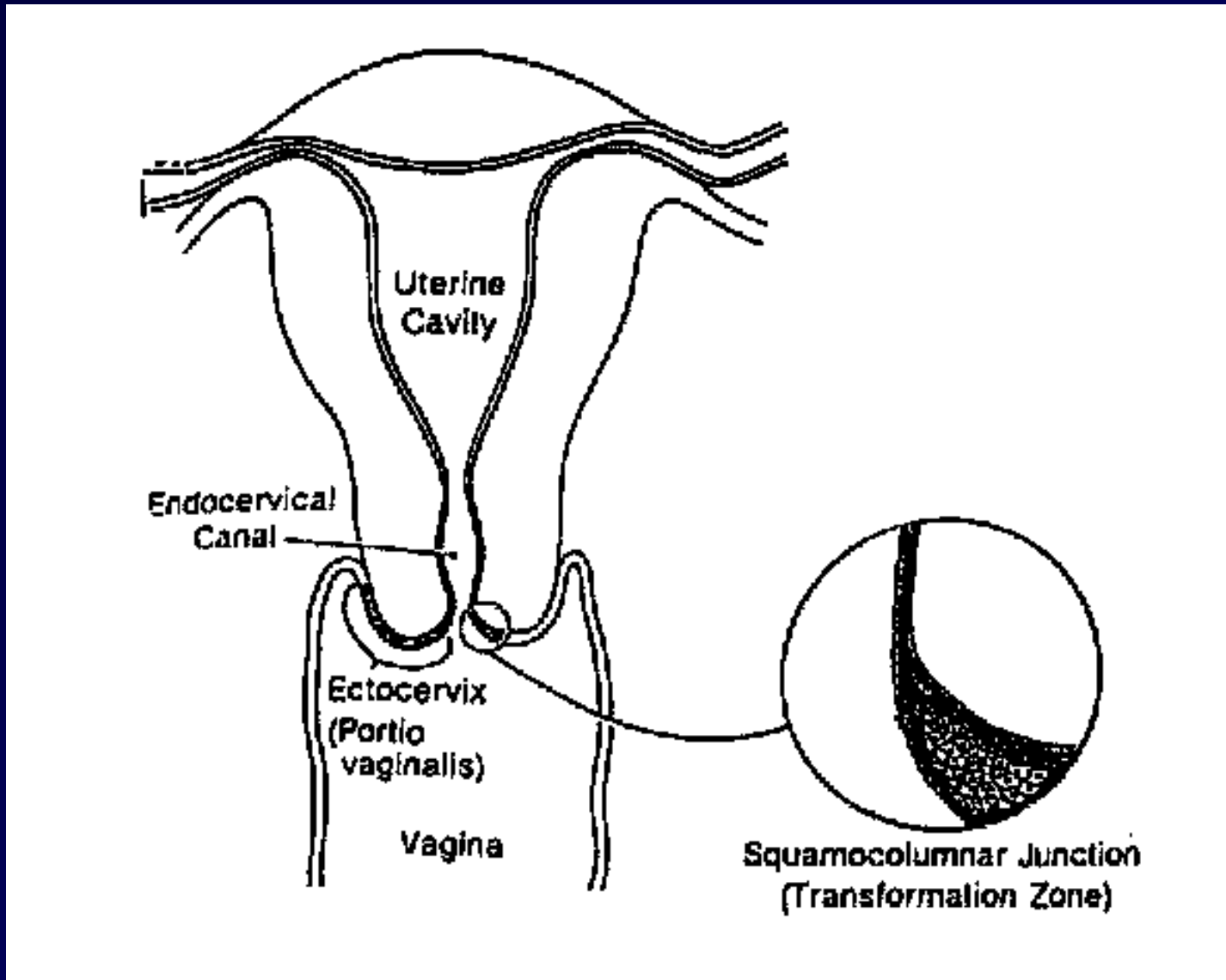
Is Screening Needed After Vaccination?

Yes!!!

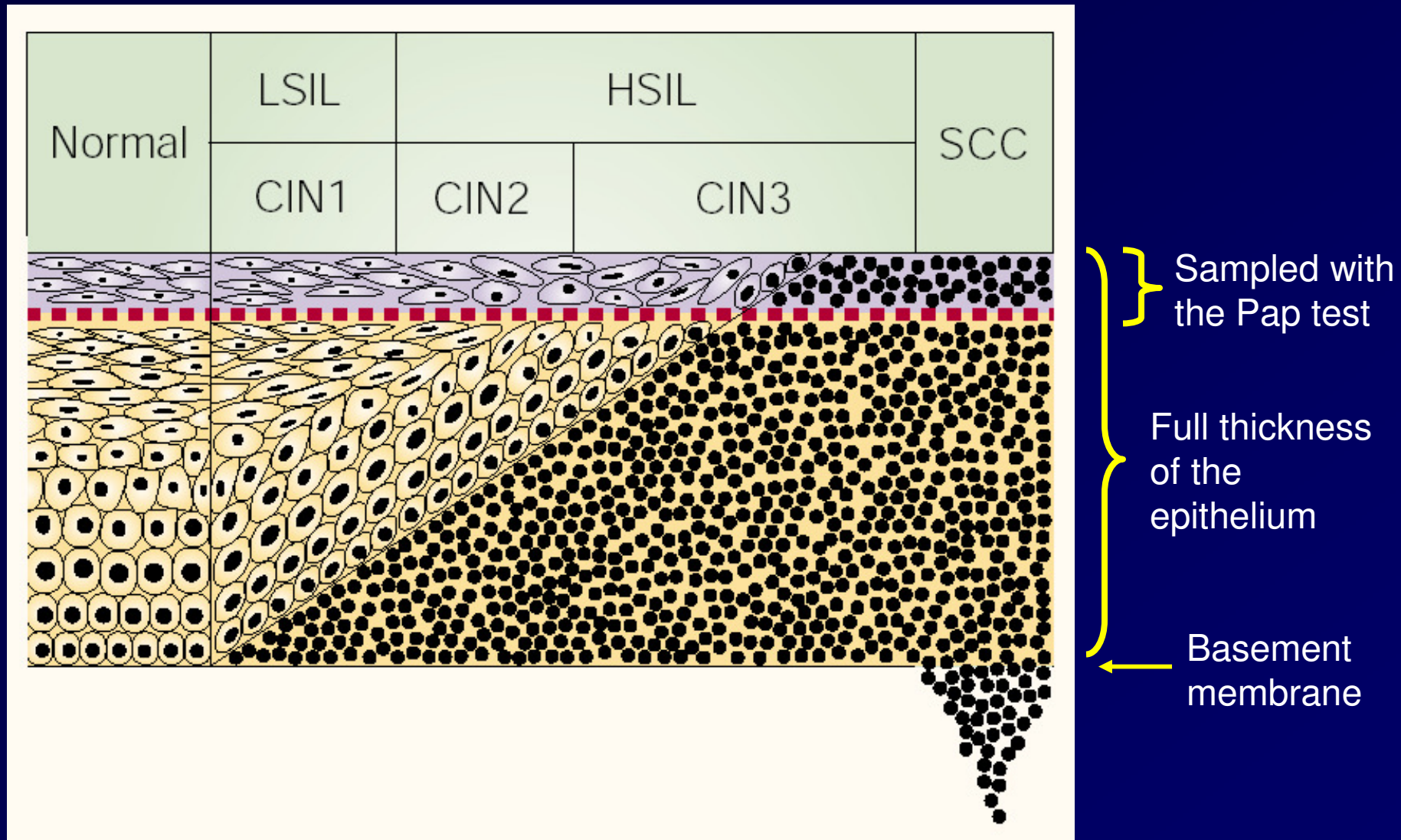
- Vaccines protect against HPVs 16 and 18 which cause at most 75% of all cervical cancers
- Vaccination is for pre-exposure prophylaxis; most women will continue to rely on screening

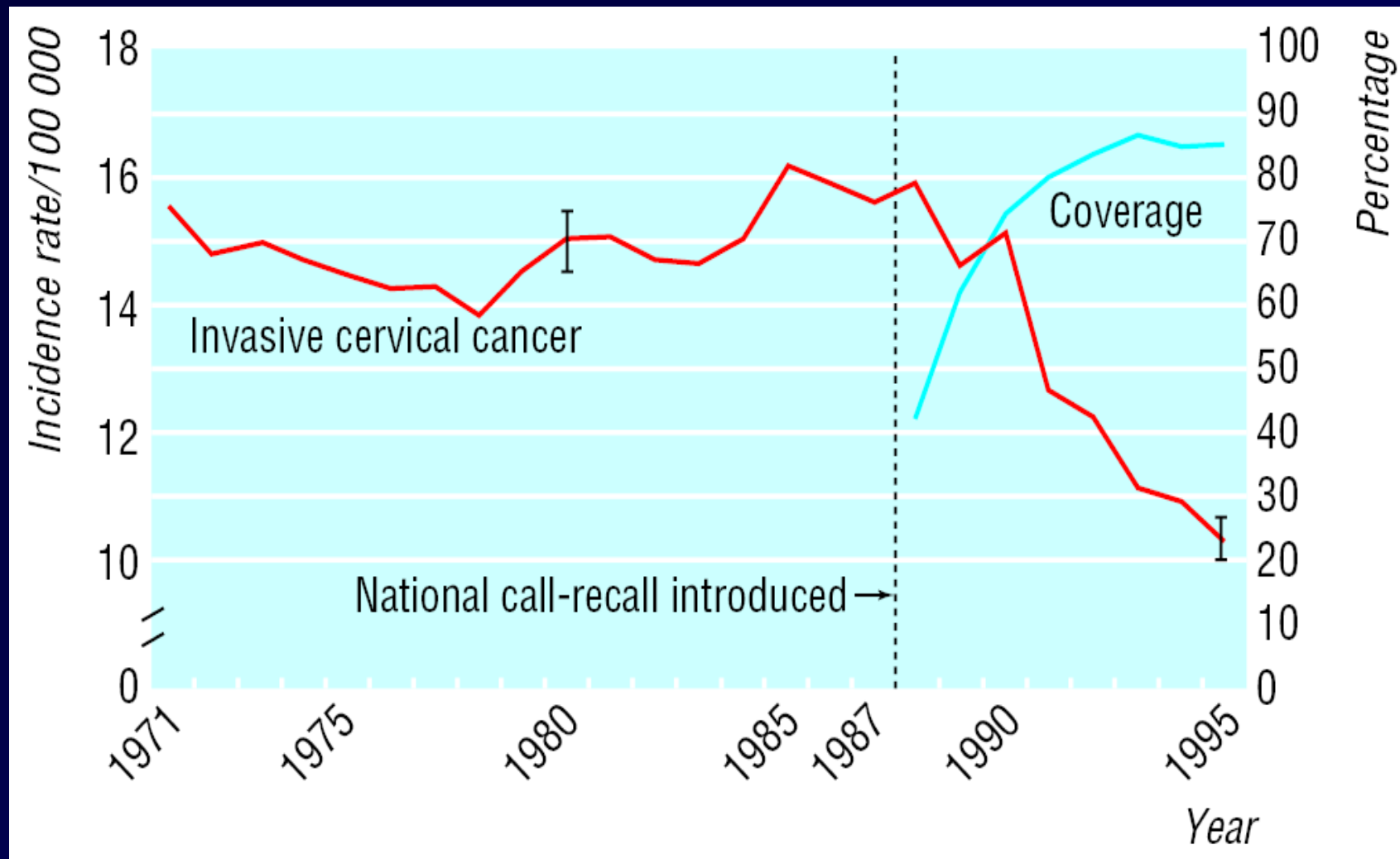
But How?

The squamo-columnar Junction and Transformation Zone of the Uterine Cervix



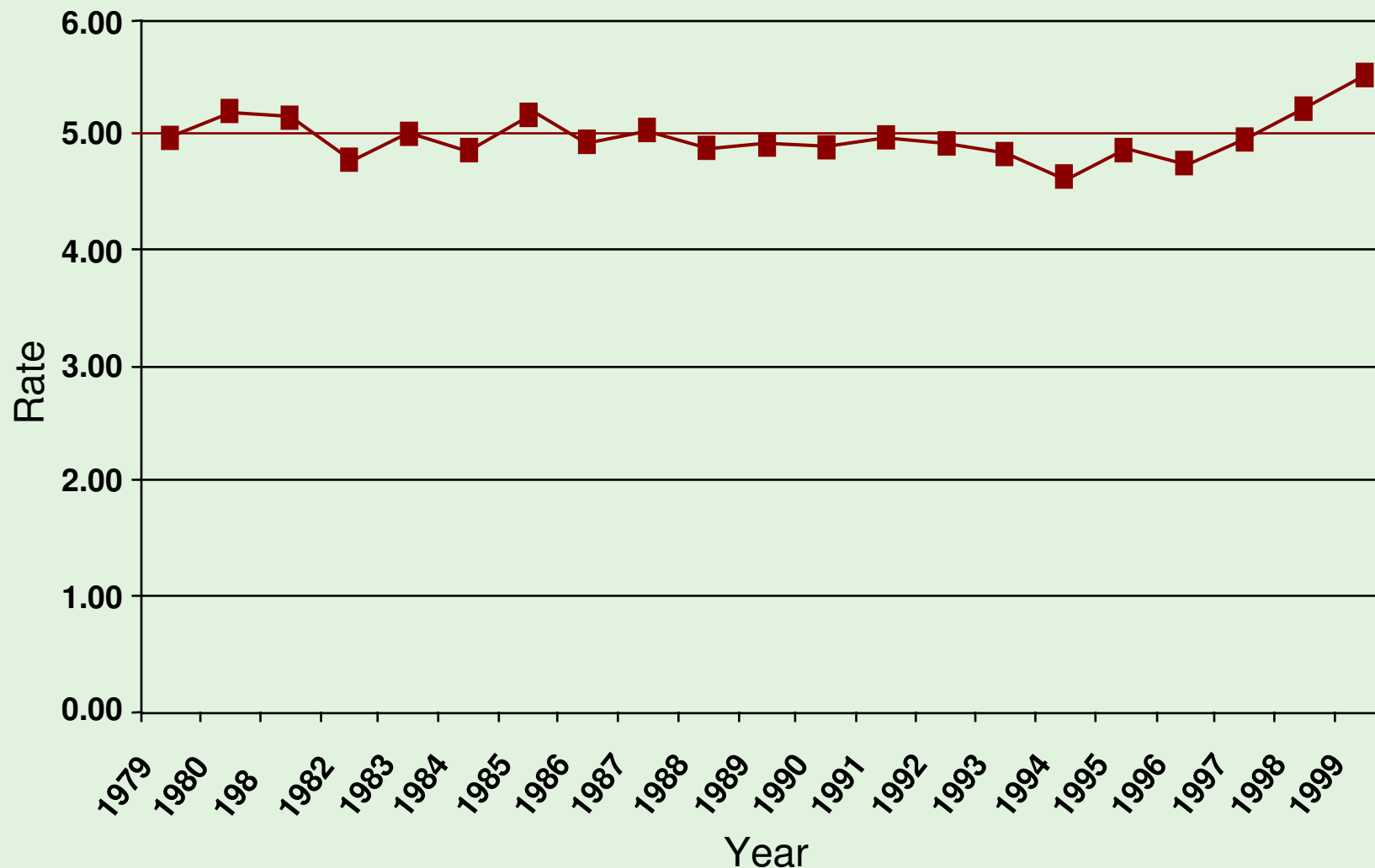
Spectrum of morphological abnormalities in the cervical squamous epithelium





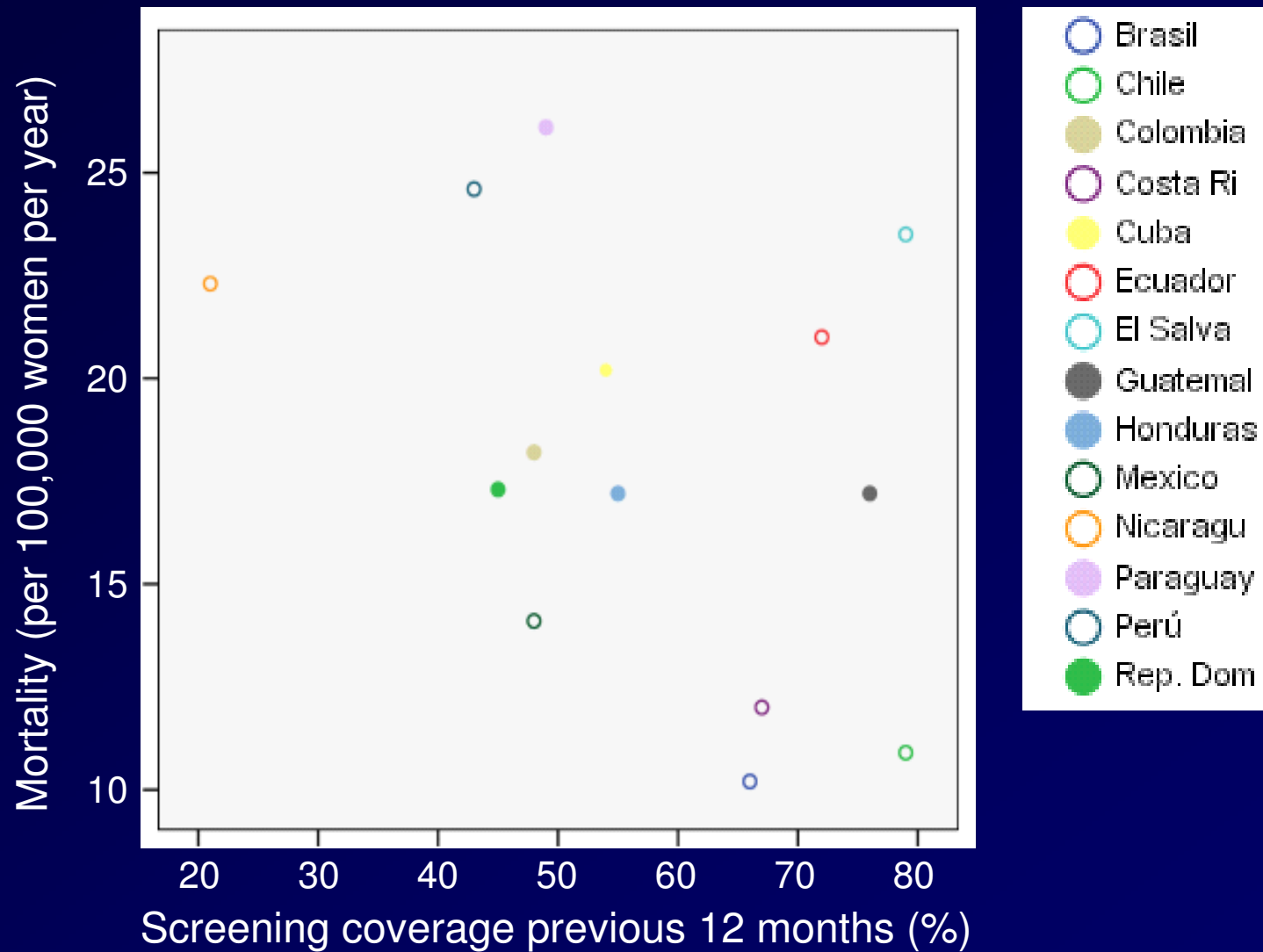
Age standardized incidence of invasive cervical cancer and coverage of screening, England, 1971-95
 (Quinn et al., *BMJ* 1999; 318: 904-8)

Age-Standardized Cervical Cancer Mortality, per 100,000 Women in Brazil (1979-99)



Population World Standard; Sources: System of Information on Mortality - SIM/DATASUS/MS; Foundation IBGE; Division of Epidemiologia and Vigilância - CONPREV/INCA/MS

Pap Cytology Screening Coverage and Cervical Cancer Mortality in Latin America



Courtesy of Dr. Raul Murillo, Nat'l Cancer Inst, Colombia

How good is Pap cytology in cervical cancer screening?

- Duke Report (AHRQ, 1999; Nanda et al., 2000): Considering only studies free of verification bias: sensitivity: 51%, specificity: 98%
- Cytology screening programmes have to compensate for the low sensitivity by requiring 2-3 annual Pap tests before screening can be done less frequently
- Approximate programme sensitivity for:
 - 2 consecutive annual Pap tests: $51\% + 51\% \text{ of } 49\% = 76\%$
 - 3 consecutive annual Pap tests: $76\% + 51\% \text{ of } 24\% = 88\%$

Expected **short-term** outcomes

Settings with organized or opportunistic Pap screening:

- Reductions of case loads of ASC, LSIL, and HSIL to be triaged or managed; reductions of colposcopy referrals
- Plausible estimates with empirical backing from RCTs: 40% for those vaccinated against 16/18 and 50% for those protected against 6/11/16/18

Expected **short-term** outcomes

- Reductions in case loads a function primarily of two factors:
 - Uptake of HPV vaccination by successive cohorts of adolescents and young women
 - Time it will take for protected women to reach screening age
- Impact on case loads initially minimal for women vaccinated between the ages of 11 and 18 years

Expected **long-term** outcomes

Settings with organized or opportunistic Pap screening:

- Reduction of cervical cancer burden unlikely to be observed for at least a decade because of the latency for averted HSILs to progress to invasive lesions
- Lack of equitable access to benefit: High vaccine uptake may happen mainly among women who will eventually comply with screening

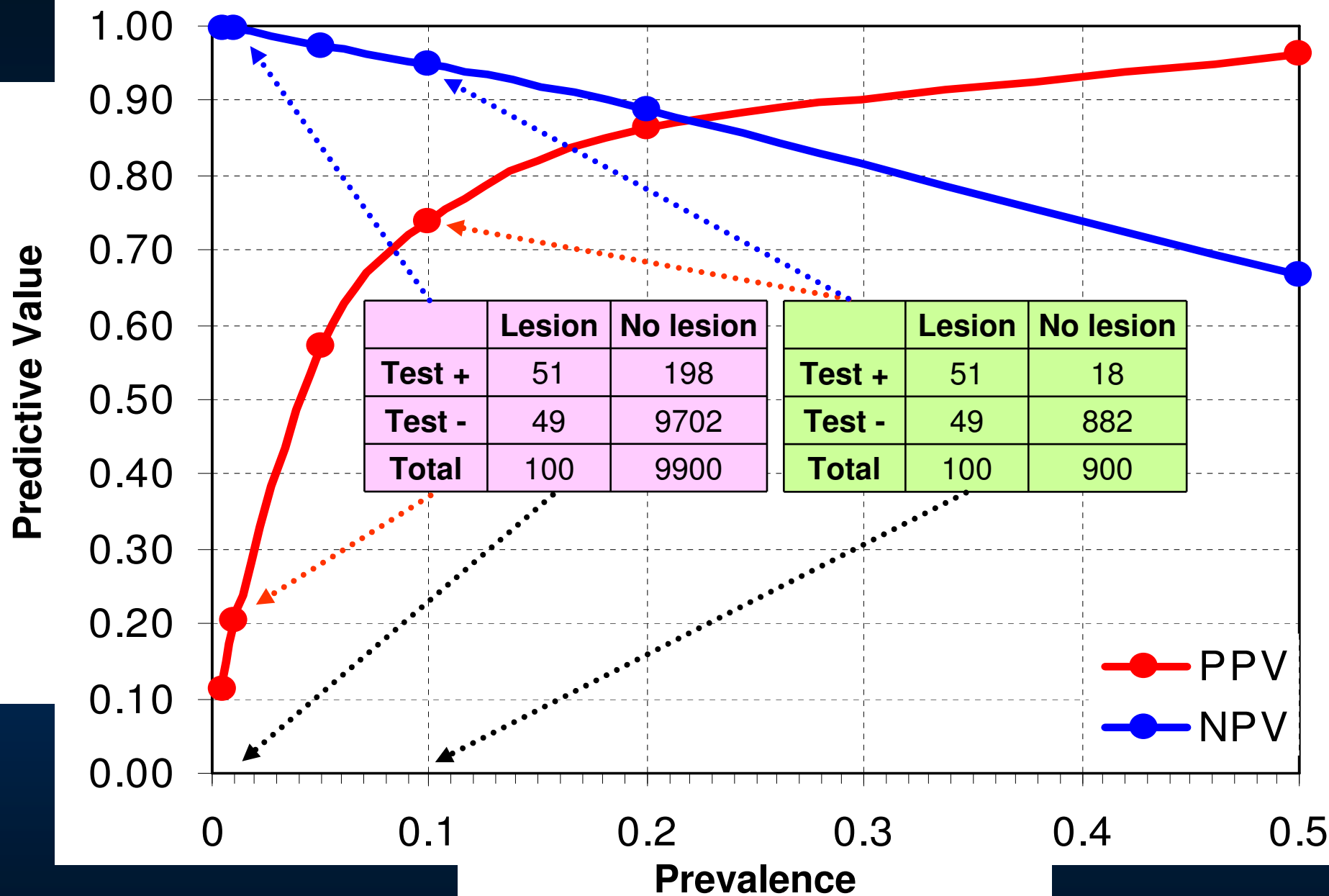
Expected **long-term** outcomes

Lack of equitable access to benefit:

- Like mothers, like daughters...
 - Young women who are vaccinated are likely to comply with screening later in life
 - Initial enthusiasm with reduction in cervical abnormalities; however, because of their high compliance with screening these women would not be likely to develop cervical cancer
 - Non-vaccinated women less likely to be screened → their lesions will progress undetected → cytology surveillance oblivious to their occurrence until cancer is diagnosed

Loss of Pap screening performance due to vaccination

- **As successive cohorts of women are vaccinated:**
 - Reduction in prevalence of cytological abnormalities
 - End result: decrease in positive predictive value of cytology
 - Increase in false positive rates will lead to non-rigorous diagnostic work-up
 - Impact on cytotechnician training and quality assurance



Assumptions: constant 51% sensitivity and 98% specificity (as per Nanda et al., 2000)
 $PPV = \frac{Se \times P}{Se \times P + (1 - Sp) \times (1 - P)}$ and $NPV = \frac{Sp \times (1 - P)}{(1 - Se) \times P + Sp \times (1 - P)}$

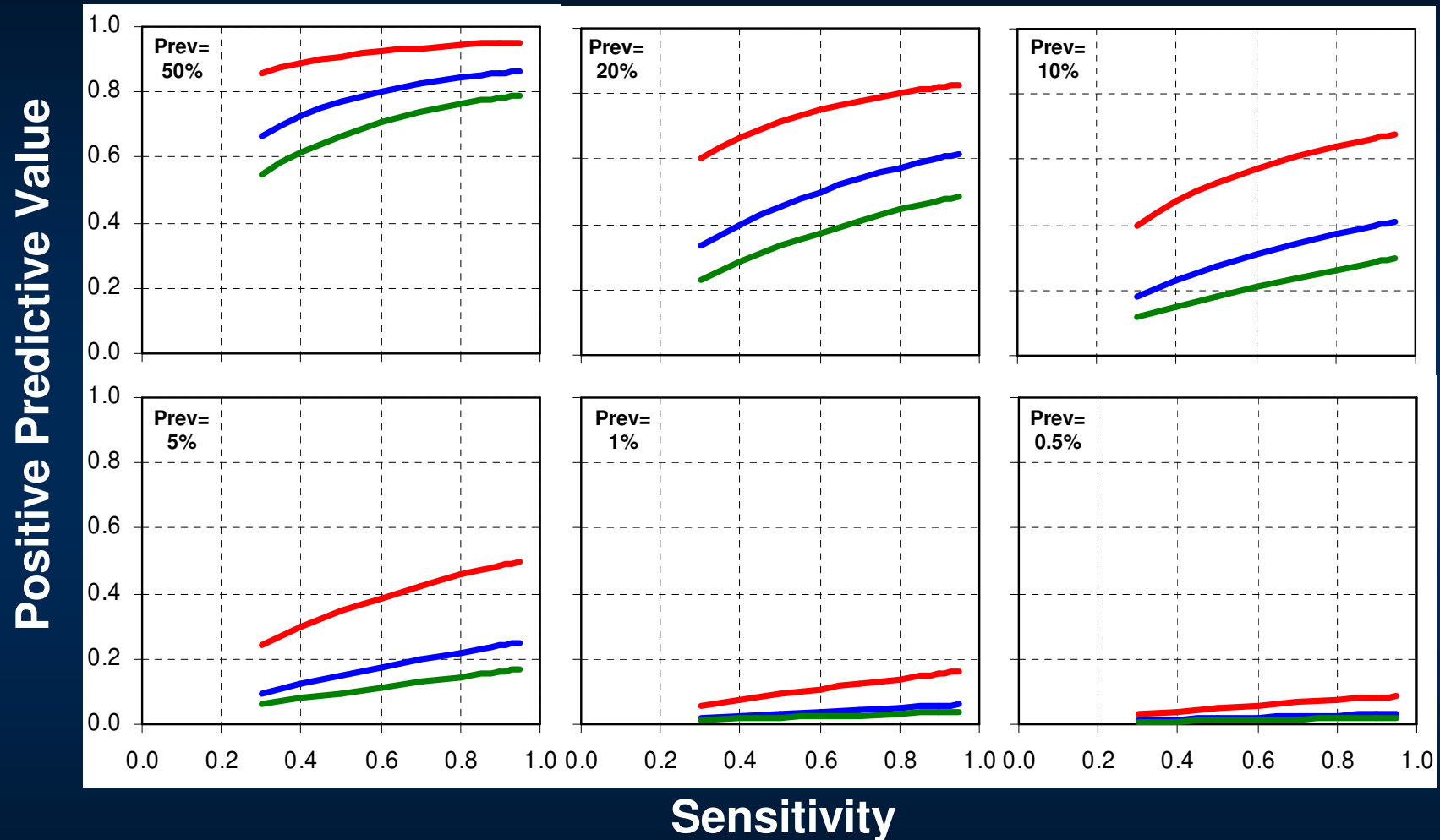
Possible qualitative changes in Pap cytology performance

- **Sensitivity will be negatively affected:**
 - Today's typical case load: approximately 10% of all smears contain abnormalities that are serious enough to merit slide review
 - Reduction in lesion prevalence → fatigue will set in given expectation that abnormalities will be rare → smears may not be read as thoroughly → more false negatives
 - **End result:** further decline in the PPV of cytology
 - *(some of the lowest estimates of Pap sensitivity are in frequently screened, low risk populations of developed countries)*

Possible qualitative changes in Pap cytology performance

- **But specificity may suffer as well...**
 - Decrease in signal-to-noise ratio of cytology → due to rarity of squamous abnormalities and koilocytotic atypias (the signal) inflammatory changes or reactive atypias (the noise) may be *overcalled*
 - Could be aggravated by cytotechnician's fear that relevant abnormalities will be missed
 - Heightened awareness of the potential for false-negative diagnoses may lead to more false-positive reports → loss in specificity
 - **End result:** further decline in the PPV of cytology

Joint effects of changes in sensitivity, specificity, and lesion prevalence on the PPV of a screening test



Specificity: red: 95%, blue: 85%, and green: 75%

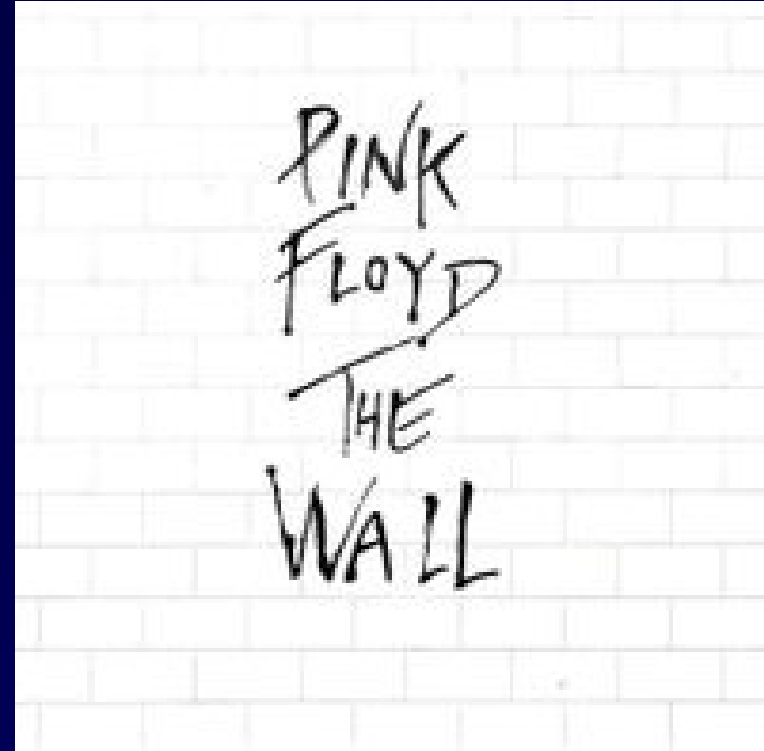
Graphs represent decreasing hypothetical situations of lesion prevalence: Africa and Latin America: 10%-20%, Western countries: 5%-10%, Triage: 50%

Quantitative and qualitative penalties on the PPV of cytology

- **In consequence:**
 - Cytology laboratories will tend to err on the side of conservatism to decrease risk of malpractice suits
 - Safeguard: to maintain unnecessarily frequent screening visits as policy to provide protection against false-negatives
- Conclusion: costly and ineffective way of combining screening to vaccination

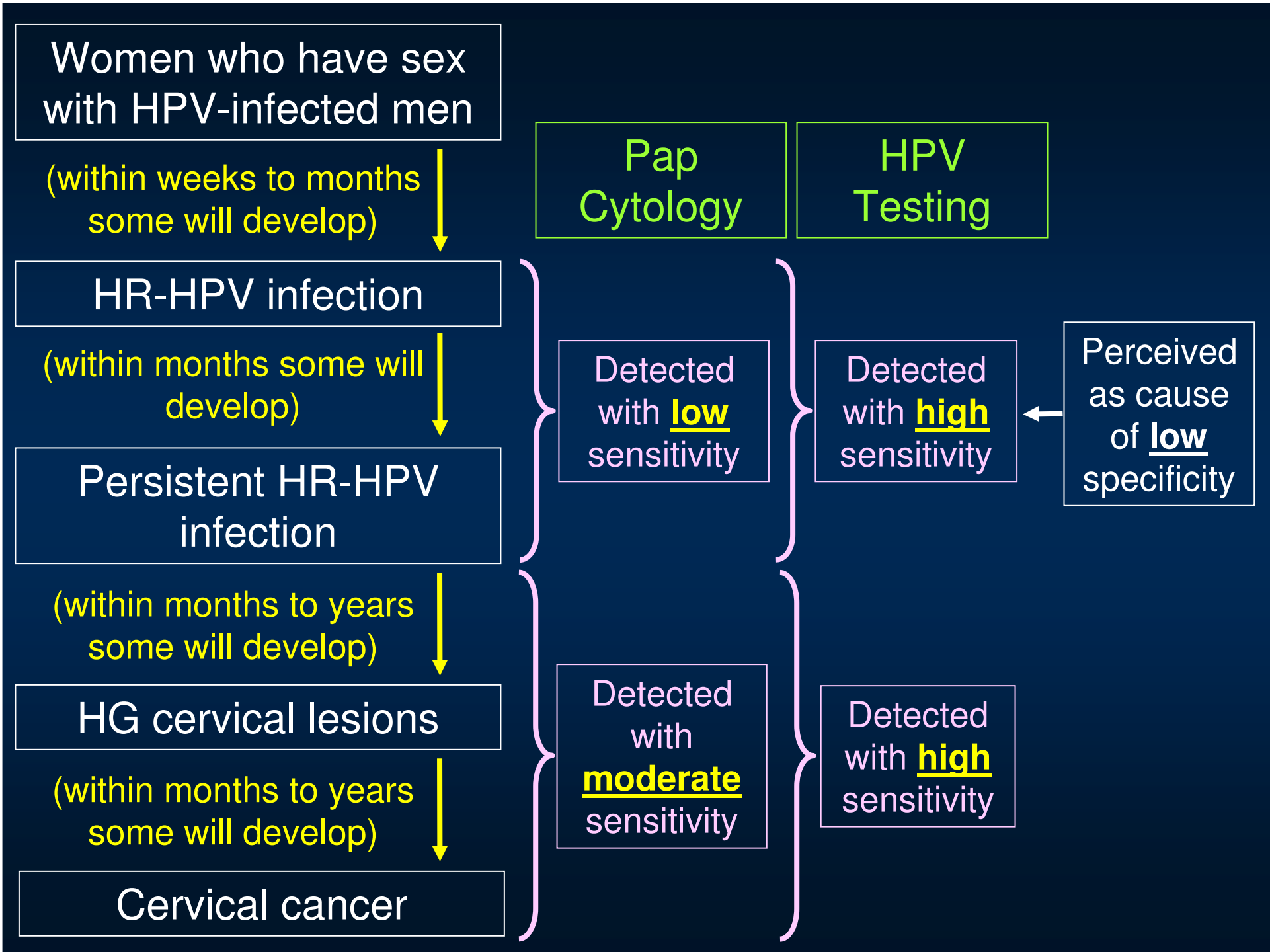
HPV vs. Pap in Primary Screening

- Pooled analysis of European and North American studies: HPV testing substantially more sensitive in detecting CIN2+ than cytology (96.1% vs. 53.0%) but less specific (90.7% vs. 96.3%).
- Meta-analysis of all available studies: HPV 1.23 times more sensitive and 0.94 times less specific than cytology.
- Comparable if not better results from emerging RCT data (e.g., POBASCAM, NTCC, CCCaST)



*“...The child is grown, the dream is gone.
I have become comfortably numb.”*

David Gilmour & Roger Waters



RCTs of HPV Testing in Screening

- HART trial: UK (Cuzick et al., Lancet, 2003)
- POBASCAM study: The Netherlands (Meijer et al., IJC 2004)
- Indian Trial (Osmanabad) (Sankaranarayanan et al.)
- ARTISTIC trial: UK (Kitchener et al.)
- NTCC Italian Study (Ronco et al., Lancet Oncol, 2006)
- SWEDESCAN: Swedish trial (Naucler et al., NEJM 2007)
- CCCaST study: Canada (Mayrand et al., IJC 2006; NEJM 2007)
- BC RCT (HPV FOCAL): Canada (Coldman et al.)

CCCaST Study: First Screening Round Results*

Indices	Screening test	Estimate (95%CI)
Sensitivity	Pap	55.4 (33.6-77.2)
	HPV	94.6 (84.2-100)
Specificity	Pap	96.8 (96.3-97.3)
	HPV	94.1 (93.4-94.8)
PPV	Pap	7.1 (4.8-10.3)
	HPV	6.4 (5.0-8.0)
NPV	Pap	99.8 (99.7-99.9)
	HPV	100 (98.6-100)

* 10,171 women in Montreal and St. John's, aged 30-69 years, randomized to Pap or HPV as primary screening method; estimates corrected for verification bias (Mayrand et al., NEJM 2007)

Why is HPV Testing an Attractive Option for Cervical Cancer Screening?

- More sensitive than the Pap test
- More “upstream” in the carcinogenic process, thus enabling a longer safety margin for screening intervals
- Can be automated, centralized, and be quality-checked for large specimen throughput
- May be more cost-effective than cytology if deployed for high volume testing, such as in primary screening
- More logical choice for screening women vaccinated against HPV infection

Concerns about Adopting HPV Testing in Cervical Cancer Screening

Important:

- Modifications to existing screening programs will be necessary
- At present, the unit cost for HPV testing is higher than that for Pap cytology
- Screening for HPV will create a dependence on commercial interests
- Health education issues

Irrelevant Concerns about HPV Testing in Cervical Cancer Screening

- Will lead to excess in referrals and uncertainties about follow up of HPV+ women with no CIN
- No change needed: Pap cytology screening shown to reduce cervical cancer incidence and mortality
- There is no evidence that screening with HPV testing may reduce cervical cancer incidence and mortality
- Women prefer annual visits anyway
- Stigmatization

Need for assessing the basis of screening programs following vaccination

- Pap cytology will not be the same if left as primary test
- Solution: HPV testing as primary screening test followed by cytologic triage:
 - HPV testing more “upstream” than cytology → longer latency safety window
 - HPV testing more sensitive and not prone to the vagaries of a test based on subjective interpretation
 - HPV testing less likely to vary in sensitivity and specificity as a function of decreasing prevalence in infections and lesions
 - Cytology will perform better in the artificially high lesion prevalence when triaging HPV+ women

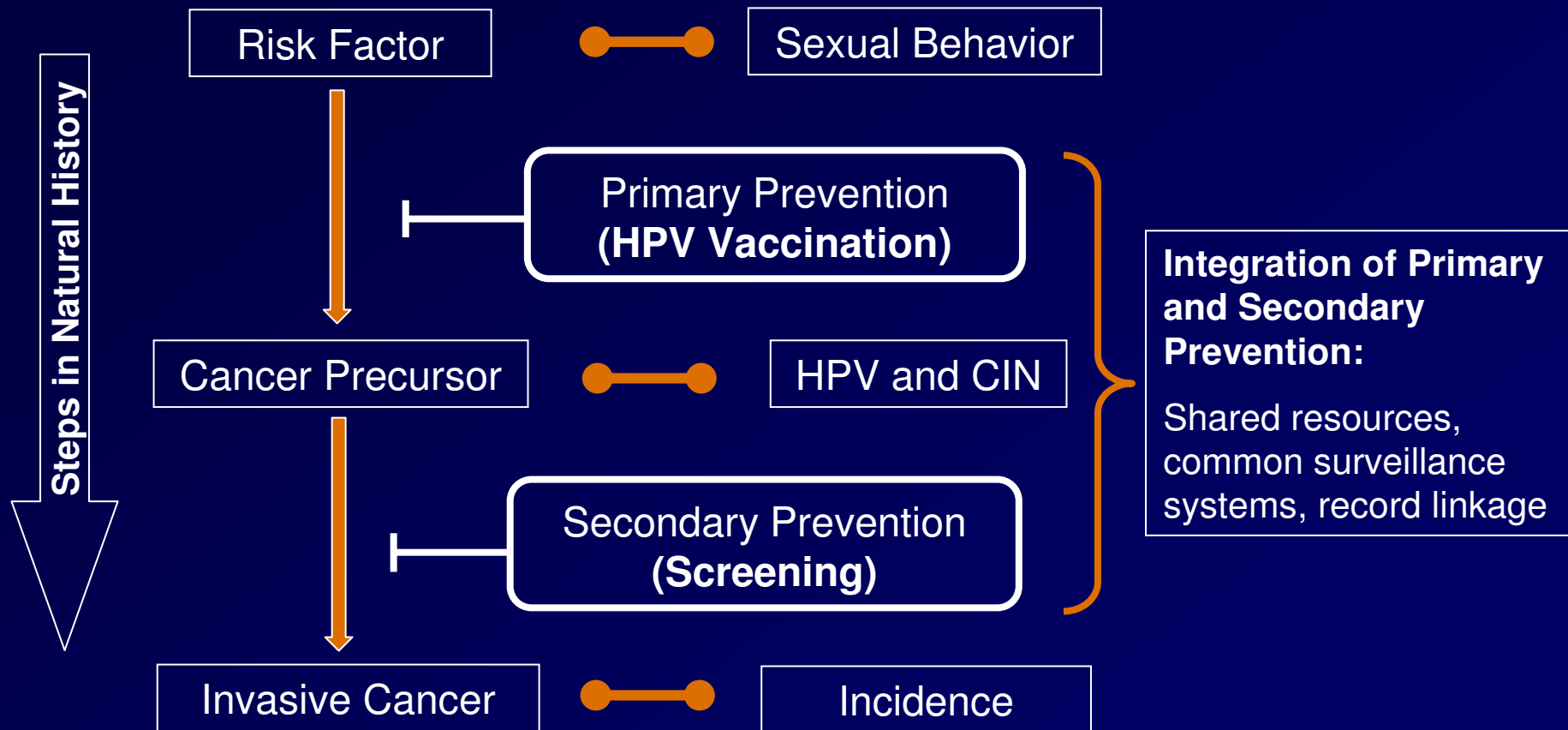
Other benefits from the HPV-Pap screening algorithm

- **Dividend:** A surveillance system integrated with vaccination registries to monitor vaccine efficacy, duration of protection, and cross-protection
- Rational approach to assuage concerns that frequency of screening must not be changed to avoid missing lesions caused by other oncogenic HPV types
- Improved detection of glandular lesions
- Potential for using self-collected cervical samples
- Cytology too important to be used as screening test; it should be reserved for diagnostic triage

The case for synergy in prevention modalities

1. Screening will have to continue in the HPV vaccination era
2. Opportunistic (as opposed to universal) vaccination will create (further) inequity in access to benefit
3. Cytology screening performance will degrade following vaccination
4. HPV infection surveillance will be needed post-vaccination
5. Proposal: reformulate screening as an integrated approach complementing vaccination

Integrated Approach to Screening





*Muito obrigado
pela amável
atenção, Tchê !*

