Evidencia científica sobre nuevas tecnologías para el cribado del cáncer cervicouterino

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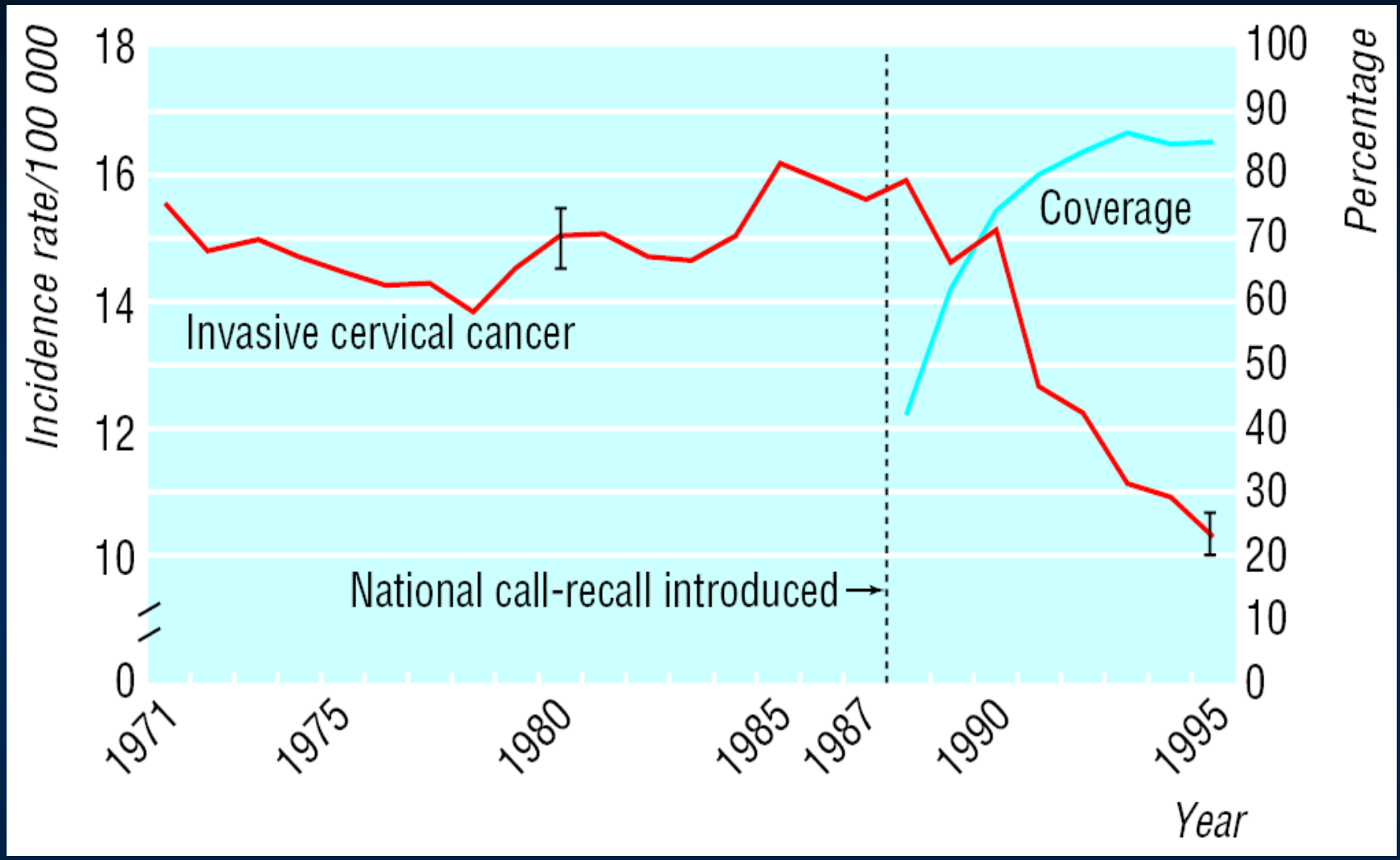
Topics to cover

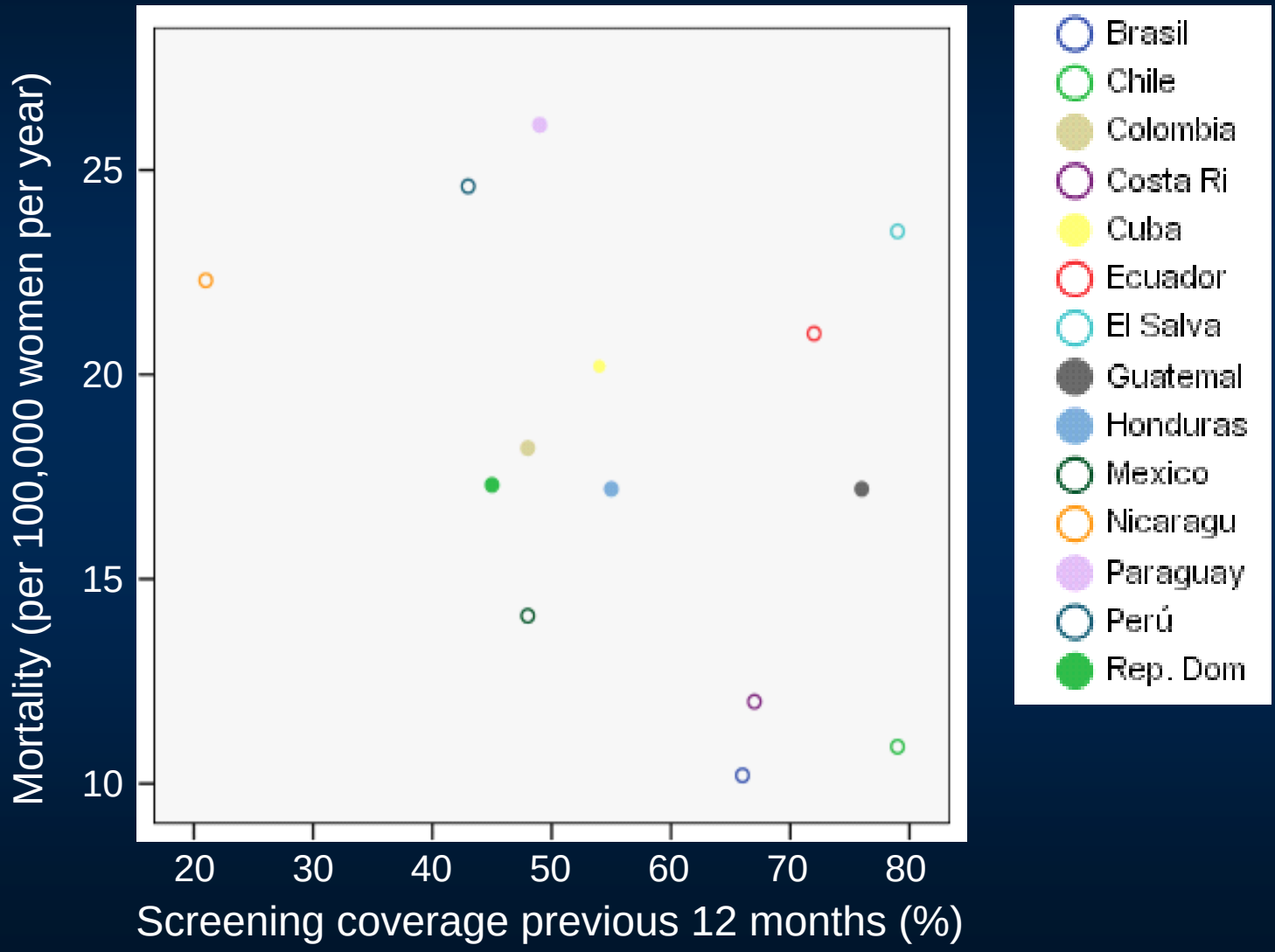
- Cytology screening as the paradigm of cervical cancer control: Glory for some, failure for many.
- Cervical cancer screening technologies.
- Rationale and burden of proof for HPV DNA testing in primary screening for cervical cancer.
- Post-HPV vaccination era: need for a paradigm change that combines primary and secondary prevention.



Age standardized incidence of invasive cervical cancer and coverage of screening, England, 1971-95

(Quinn et al., BMJ 1999; 318: 904-8)

Pap Cytology Screening Coverage and Cervical Cancer Mortality in Latin America



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

Screening has multiple interconnected components, all of which must function

- Without an organized programme, Pap cytology coverage is misleading as indicator of success because it reflects access to care for women at lowest risk.
- Failure of other components of a screening programme: quality assurance, patient treatment and follow-up, sustainability.

How good is Pap cytology in cervical cancer screening?

- Duke Report (Nanda et al., 2000): Considering only studies free of verification bias: sensitivity: 51%, specificity: 98%
- Pooled analysis of European and Canadian studies (Cuzick et al., 2006): sensitivity = 53% (CIN2+) and specificity = 96%
- 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% of 49% = 76%
  3 consecutive annual Pap tests: 76% + 51% of 24% = 88%

Adjunctive or alternative screening techniques in cervical cancer

Cytology preparation and microscopic assessment:

- Liquid-based thin-layer techniques
- Computer-assisted microscopical scoring
- Automated smear processing and reading

In vivo, real-time techniques:

- Screening colposcopy
- Cervicography
- Visual inspection (VIA, VILI)
- Physical/Optical methods: Polar probe, Spectroscopy, Speculoscopy

Detection of human papillomavirus DNA:

- Signal amplification: Hybrid Capture™ 2 assay
- Target amplification: polymerase chain reaction (MY09/11, PGMY, GP5+/6+, SPF-10)

Other molecular methods:

- mRNA expression of E6/E7 transcripts
- p16 immunostaining
- Proliferation or DNA replication markers Ki-67 and PCNA; cdc6 and mcm5
- Genome-wide comparative genomic hybridisation (CGH)

Franco et al., CEBP 1996; Cuzick et al., Vaccine 2006

What is controversial in cervical cancer screening?

Current Pap cytology paradigm:

- ✓ Age at initiation: 18, 21, 25, or later?
- ✓ Frequency of screening: annual, 2-year, 3-year, 5-year intervals?
- ✓ Is liquid-based cytology more accurate than conventional Paps?

Screening in low-resource settings:

- ✓ Effectiveness and sustainability of VIA screening followed by cryotherapy

New paradigm based on molecular testing:

- ✓ Should HPV DNA testing be used to triage borderline and low grade abnormalities?
- ✓ Should Pap cytology be replaced by HPV DNA testing as the primary screen?

Pruebas de tamizaje

Características	Prueba de Pap	Prueba de ADN de VPH	IVAA
Sensibilidad	47-62%	66-100%	67-79%
Especificidad	60-95%	62-96%	49-86%
Numero de visitas	2 o más	2 o más	1

Fuente: Sankaranarayan et al. *Int J Obstet Gynaecol,* 2005; courtesy of Dr. Silvana Luciani.

"The most efficient and effective strategy for finding and treating precancerous lesions in low-resource settings is screening with either VIA or HPV DNA testing, and treating immediately using cryotherapy." (PATH, Outlook Newsletter, Volume 27, Number 2, May 2010)

VIA, VILI, Pap screening performance in Kinshasa

(Lugoma et al., Int. J. Cancer 2006)

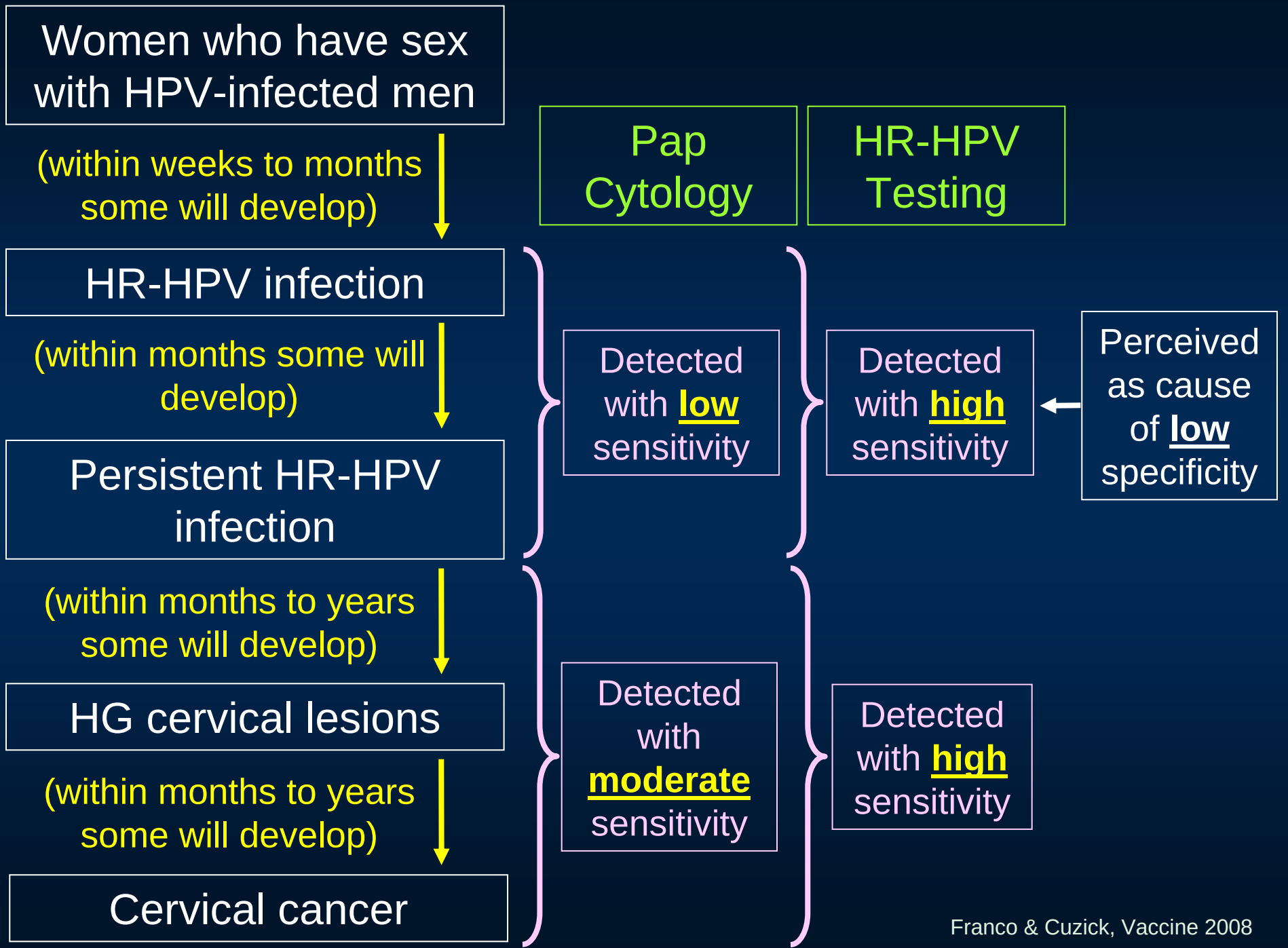
Index (%)	VIA-Nurse	VIA-MD	VILI-nurse	VILI-MD	Pap (ASCUS)
Sensitivity	55.5	71.1	44.0	68.3	71.9
Specificity	64.6	71.3	74.6	76.2	94.7

N=1528 women; colposcopy performed in all women; outcome: histologically-confirmed CIN2/3; indices corrected for verification bias.

HPV testing in cervical cancer screening

(for DNA of high oncogenic risk types)

- **Approaches already implemented or being evaluated:**
  - Serial: Cytology screening followed by HPV testing to triage ASC-US (approved by many professional societies in North America, FDA)
  - Parallel: Cytology and HPV cotesting (approved by some professional societies in North America, FDA)
  - Serial: HPV testing followed by cytologic triage (being examined in the Finnish trial, BC RCT, a.k.a., HPV FOCAL Study)



Franco & Cuzick, Vaccine 2008

Why is HPV DNA testing an attractive option for cervical cancer screening?

- More sensitive and reproducible 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
- A more logical choice for screening women vaccinated against HPV infection

Conclusions of the IARC Cervix Cancer Screening Meeting, 20-27 April 2004

- There is ***sufficient evidence*** that screening by **conventional cytology** has reduced cervical cancer incidence and mortality rates.
- There is ***sufficient evidence*** that screening by **liquid-based** or **automated cytology** can reduce cervical cancer incidence and mortality rates.
- There is ***sufficient evidence*** that **testing for human papillomavirus** infection **as the primary screening** modality can reduce cervical cancer incidence and mortality rates.
- There is ***limited evidence*** that screening by **visual inspection with** application of **acetic acid** or **Lugol's iodine** can reduce cervical cancer incidence and mortality rates.

http://www.iarc.fr/ENG/Press_Releases/archives/pr151a.html

Validation of HR-HPV DNA testing in primary screening for cervical cancer: Burden of proof

- ✓ Increased cross-sectional sensitivity and acceptable specificity relative to Pap.
- ✓ More reproducible across settings.
- ✓ Increased detection of HG-CIN that is likely to persist or progress.
- ✓ Increased safety during follow-up for women with negative results at initial screen.
- ✓ Reduced incidence of advanced cervical cancers and mortality.

HPV vs. Pap in Primary Screening

- Pooled analysis of European and North American studies (Cuzick et al., IJC 2006): 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 (Arbyn et al., Vaccine 2006): HPV 1.23 times more sensitive and 0.94 times less specific than cytology.
- Comparable if not better results from emerging RCT data.

RCTs of HPV testing in screening

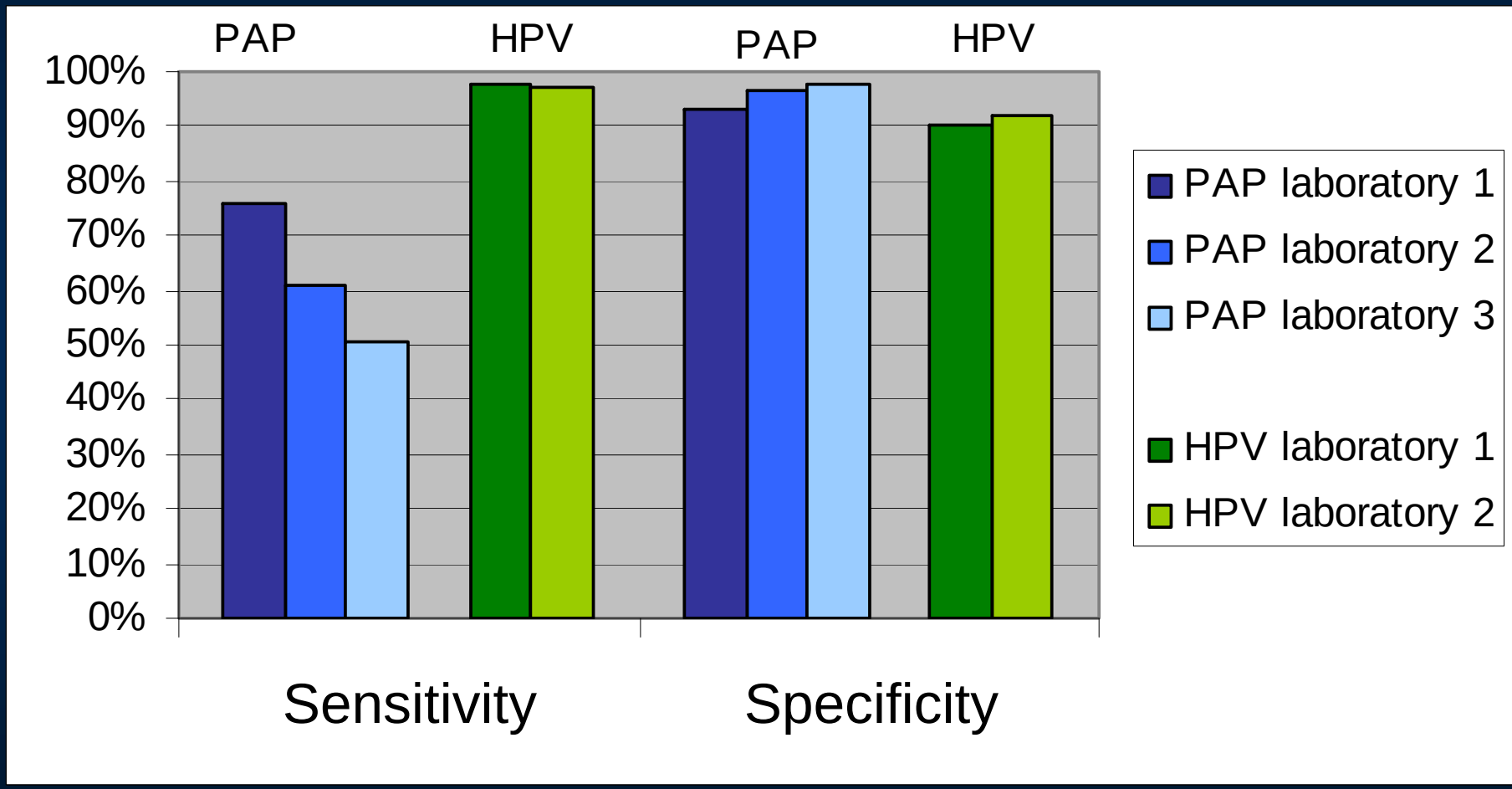
- POBASCAM study: The Netherlands (Meijer et al., Int J Cancer 2004; Bulkmans et al, Lancet 2007)
- Indian Trial (Osmanabad) (Sankaranarayanan et al. NEJM 2009)
- ARTISTIC trial: UK (Kitchener et al. Lancet Oncol 2009)
- NTCC Italian Study (Ronco et al., Lancet Oncol, 2006; JNCI 2006)
- SWEDESCREEN: Swedish trial (Elfgren et al. AJOG 2005; Naucler et al., NEJM 2007; JNCI 2009)
- Finnish RCT (Kotaniemi et al., BJC 2005; Eur J Cancer 2008; IJC 2008; Leinonen et al., JNCI 2009)
- CCCaST study: Canada (Mayrand et al., IJC 2006; NEJM 2007)
- BC RCT (HPV FOCAL): Canada (Ogilvie 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; detection of CIN2+; estimates corrected for verification bias (Mayrand et al., NEJM 2007)

Influence of laboratory performing the test on Pap and HPV testing performance (CCCaST Study)



(Mayrand et al., unpublished data)

Reduction in incidence of HG-CIN or cancer (HPV+Pap cotesting vs. Pap)

Outcome	Swedish Study*: Lesions detected at follow-up (mean: 4.1 years)			Dutch Study**: Lesions detected at follow-up (median=7.1, range:6.5-8.5)		
	Intervention	Control	RR (95%CI)	Intervention	Control	RR (95%CI)
CIN 2+	25	43	0.58 (0.36-0.96)	39	74	0.53 (0.36-0.78)
CIN 3+	16	30	0.53 (0.29-0.98)	24	54	0.45 (0.28-0.72)

* Adapted from table 2 of Naucler et al., NEJM 2007;357:1589

** Calculated using data from Bulkmans et al., Lancet 2007;370:1764

Efficacy of human papillomavirus testing for the detection of invasive cervical cancers and cervical intraepithelial neoplasia: a randomised controlled trial

Lancet Oncol 2010; 11: 249–57

*Guglielmo Ronco, Paolo Giorgi-Rossi, Francesca Carozzi, Massimo Confortini, Paolo Dalla Palma, Annarosa Del Mistro, Bruno Ghiringhello, Salvatore Girlando, Anna Gillio-Tos, Laura De Marco, Carlo Naldoni, Paola Pierotti, Raffaella Rizzolo, Patrizia Schincaglia, Manuel Zorzi, Marco Zappa, Nereo Segnan, Jack Cuzick, and the New Technologies for Cervical Cancer screening (NTCC) Working Group**

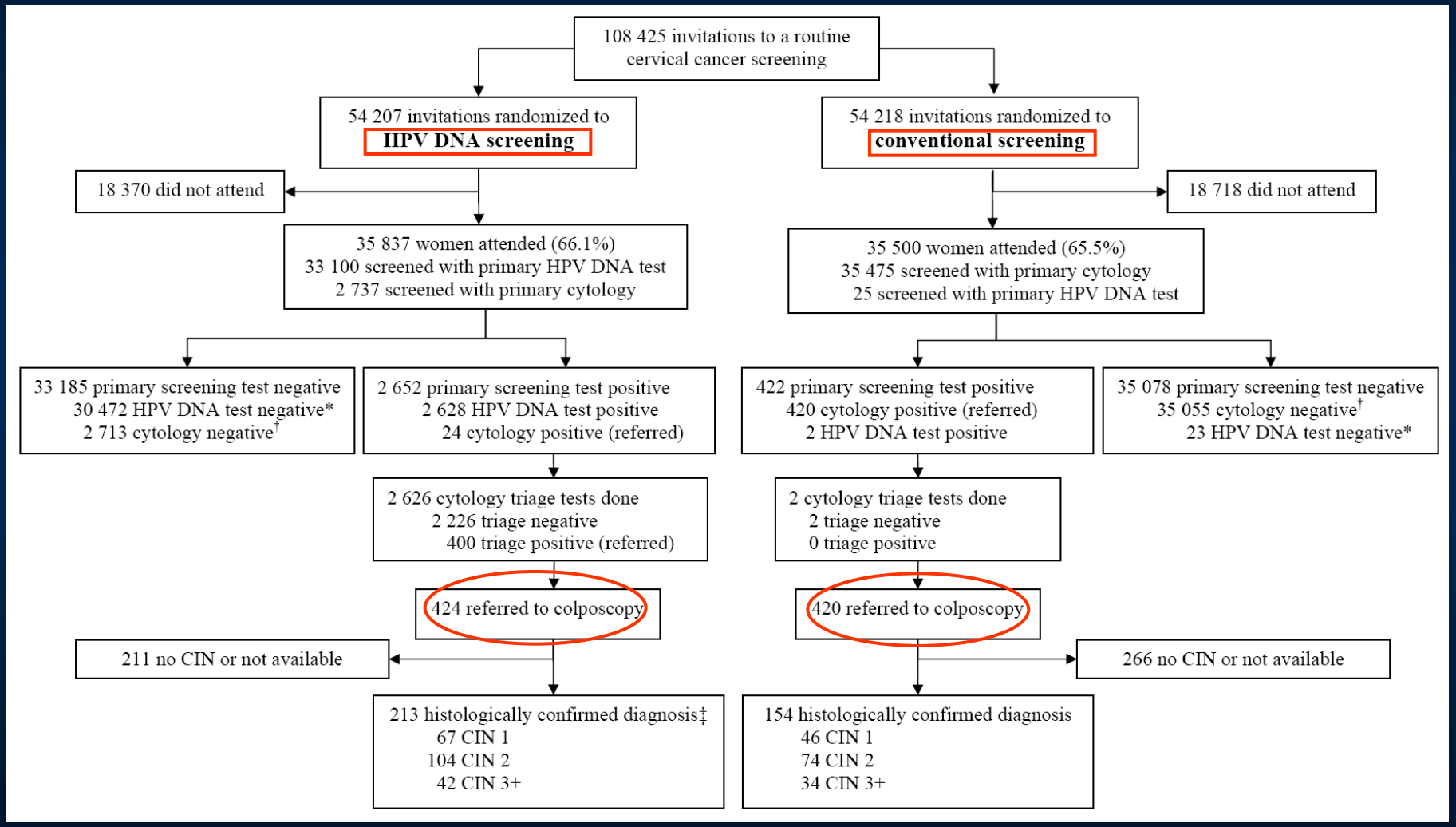
- Two-phase RCT in Italy: HPV (HC2) vs. cytology
- Women aged 25-60 years randomized to conventional cytology or to HPV testing in combination with LBC (1st phase) or HPV alone (2nd phase)
- N=47,001 for cytology and N=47,369 for HPV

RR of lesions at round 2 (HPV vs. Pap) (median F/up=3.5 years)

Age (years)	Lesion outcome at round 2	RR (95%CI)
25-34	CIN2	0.54 (0.23-1.27)
	CIN2/3/AIS	0.59 (0.33-1.05)
35-60	CIN2	0.54 (0.23-1.28)
	CIN2/3/AIS	0.51 (0.28-0.93)

Finnish Study

(Leinonen et al., JNCI 2009)



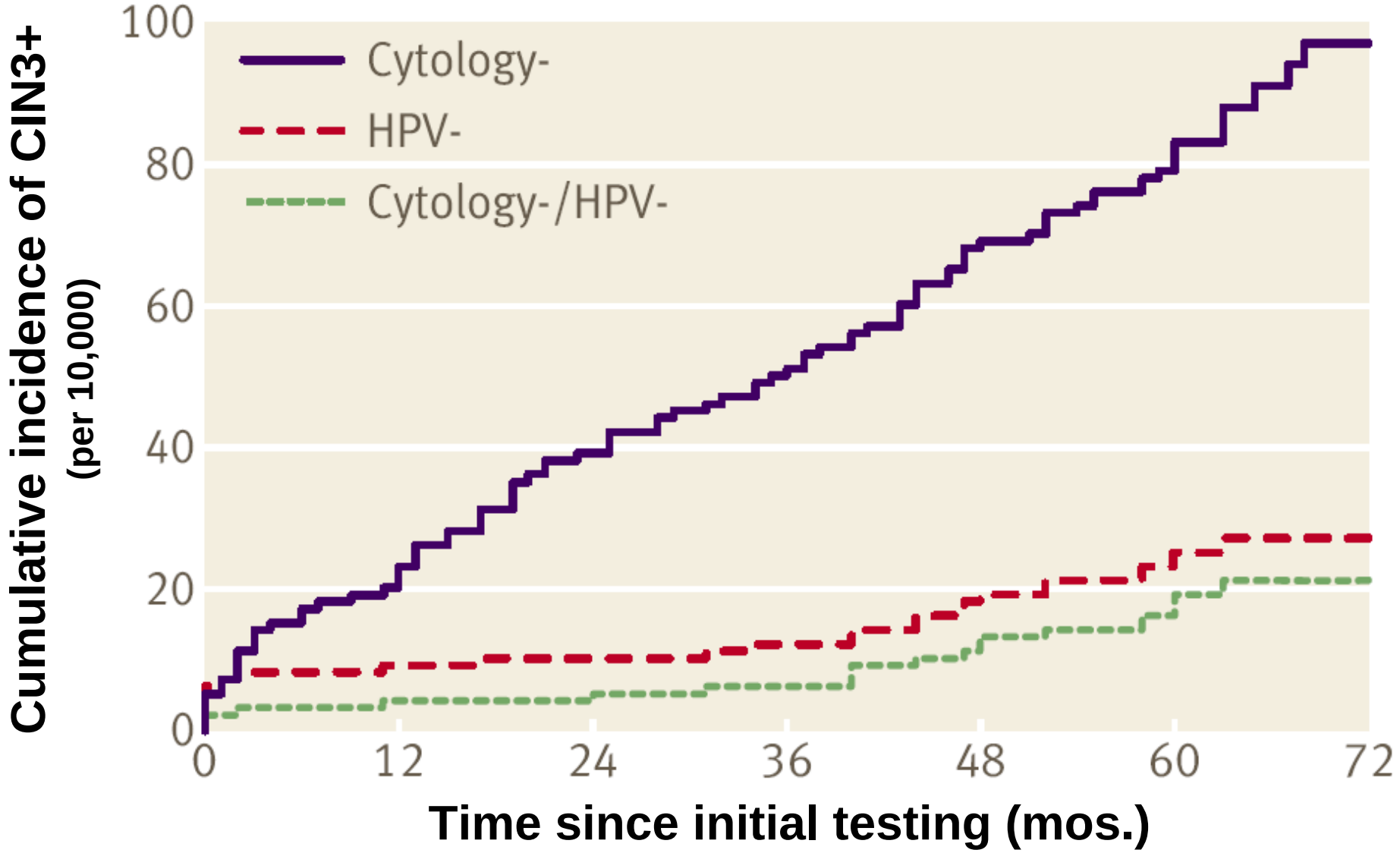
Safety for women who are screen-negative:

Cumulative proportion of HG-CIN or cancer detection in the Dutch Study

Group	Screening results at baseline	CIN3+	CIN2+
Intervention	Pap and HPV negative (n=7980)	0·1% (0·1–0·2)	0·4% (0·2–0·5)
	HPV negative (n=8113)	0·2% (0·1–0·3)	0·5% (0·3–0·6)
Control	Pap negative (n=8330)	0·8% (0·6–1·0)	1·1% (0·8–1·4)

(adapted from table 5 in Bulkmans et al., Lancet 2007;370:1764)

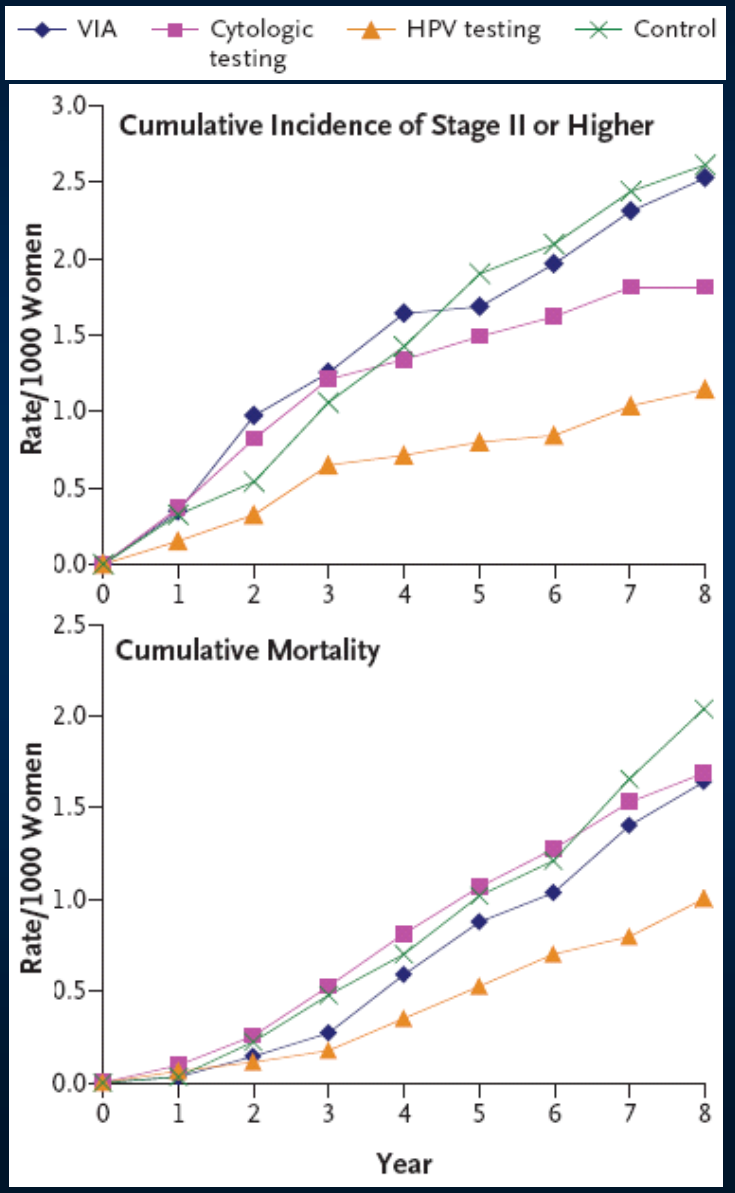
Cumulative incidence of CIN3+ according to baseline test results in European sites (excluding Denmark and Tubingen)



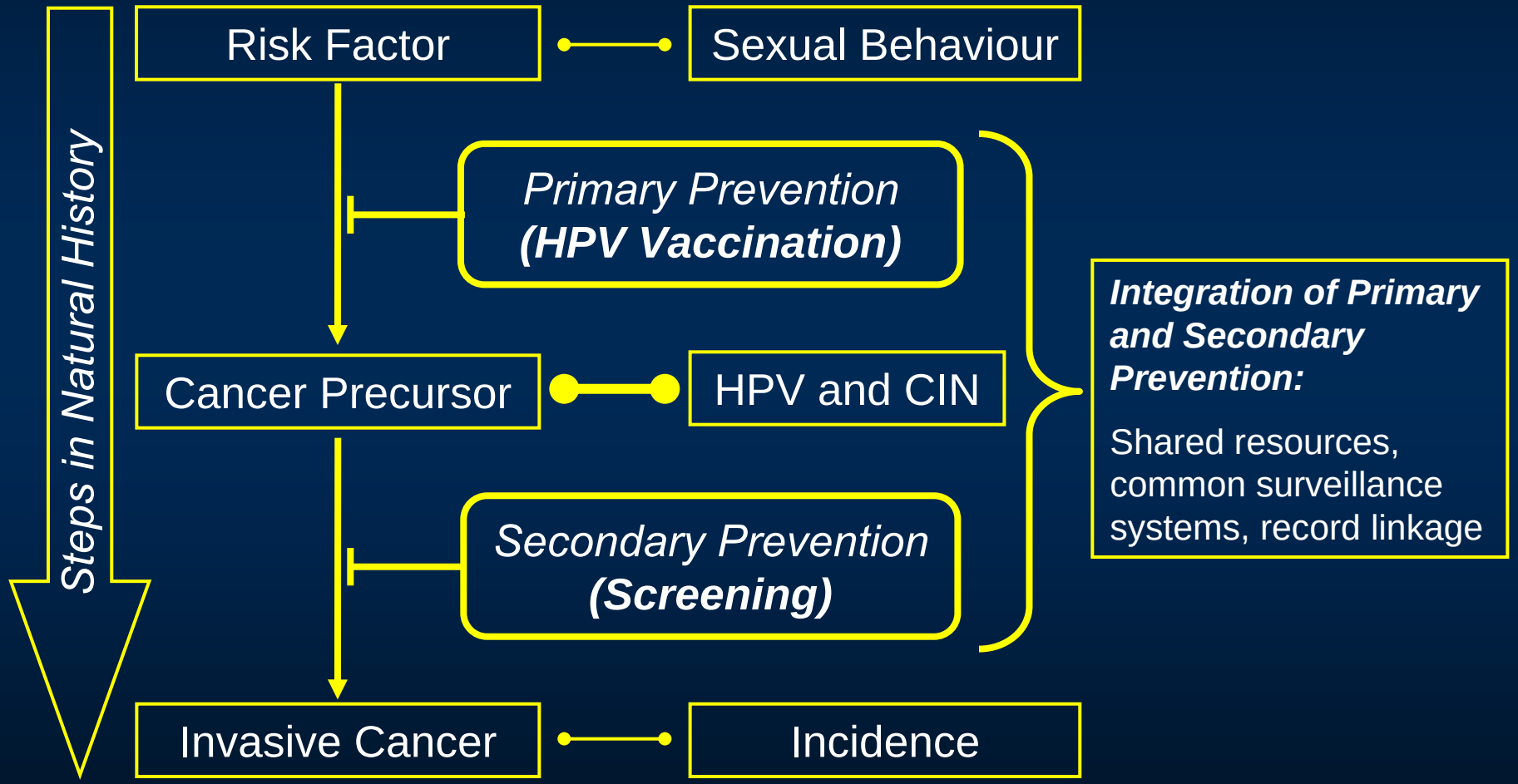
Dillner, J. et al. BMJ 2008;337:a1754

Osmanabad Cluster-RCT: Summary of Findings (Sankaranarayanan et al., NEJM 2009)

	Control	Cytology	VIA	HPV Testing
Any cancers	118	152	157	127
Person-years	247,895	250,523	267,326	268,185
Rate per 100,000	47.6	60.7	58.7	47.4
HR (95%CI)	1 (ref)	1.34 (0.99–1.82)	1.30 (0.95–1.78)	1.05 (0.77–1.43)
Advanced cancers stage II+)	82	58	86	39
Person-years	247,895	250,523	267,326	268,185
Rate per 100,000	33.1	23.2	32.2	14.5
HR (95%CI)	1 (ref)	0.75 (0.51–1.10)	1.04 (0.72–1.49)	**0.47 (0.32–0.69)**
Deaths	64	54	56	34
Person-years	248,175	251,144	267,917	268,674
Rate per 100,000	25.8	21.5	20.9	12.7
HR (95%CI)	1 (ref)	0.89 (0.62–1.27)	0.86 (0.60–1.25)	**0.52 (0.33–0.83)**



Cervical cancer prevention activities are inherently a single process



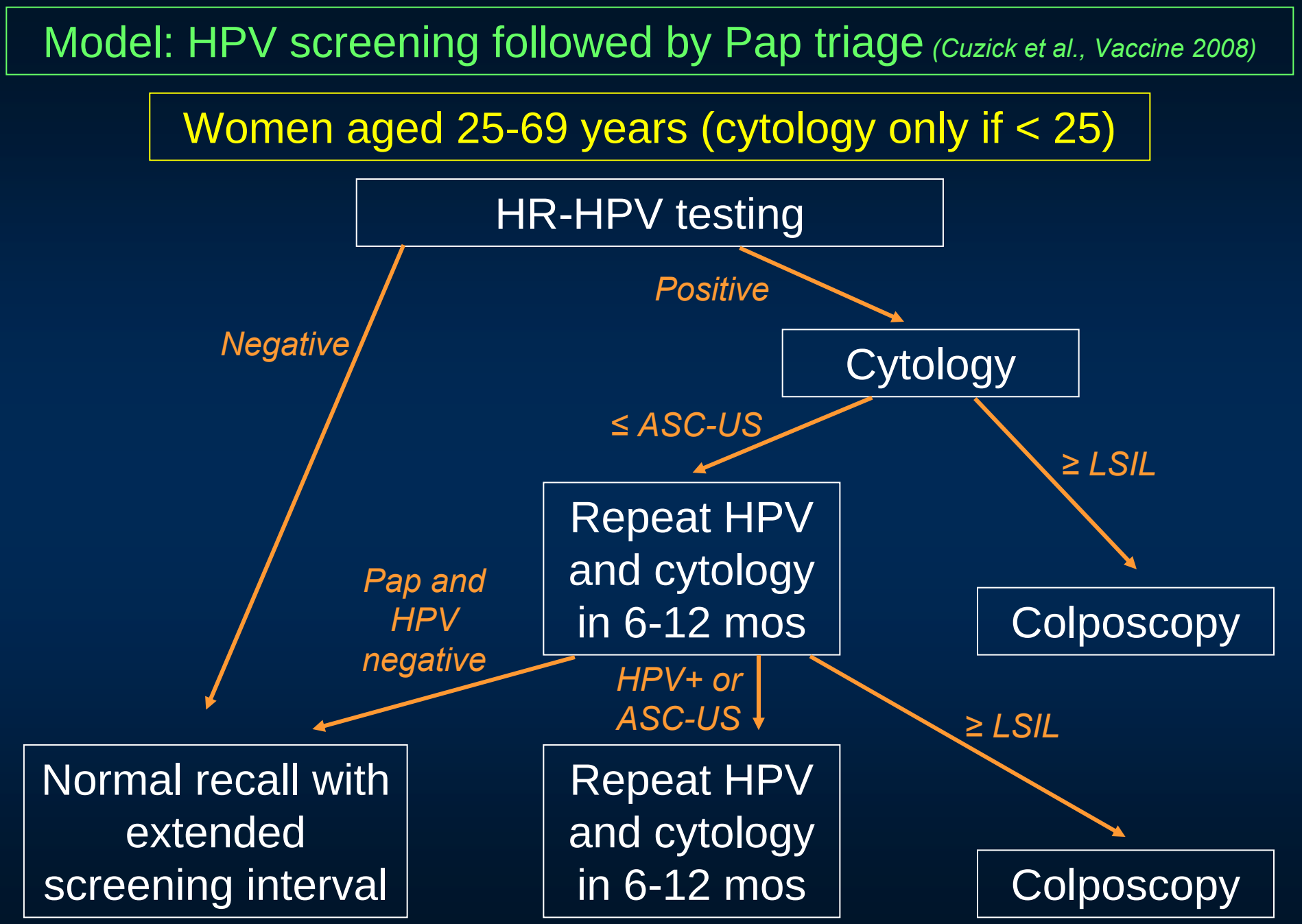
Franco et al., Vaccine 2008

Need for a paradigm change in screening following vaccination

- Pap cytology will not be the same if left as primary test
- **Potential solution:** HR-HPV DNA testing as primary screening test followed by cytologic triage:
  - HPV testing more "upstream" than cytology → longer latency safety window
  - HPV testing more sensitive and reproducible 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

Franco et al., Vaccine, 2006

Model: HPV screening followed by Pap triage *(Cuzick et al., Vaccine 2008)*



Additional benefits of an “HPV followed by Pap” strategy in populations with high vaccine uptake

- **Serving a second purpose:** A surveillance system integrated with vaccination registries to monitor vaccine efficacy, duration of protection, and cross-protection.
- **Impact on adenocarcinomas:** Improved detection of glandular lesions.
- **Reaching remote areas:** Potential for using self-collected cervical samples and increase coverage.
- **Simplicity for guidelines:** Proposed approach valid also for unvaccinated populations.
- **Safety in increasing screening intervals**
- **Preserves workforce:** Cytology too important to be used as screening test; should be reserved for diagnostic triage.

Conclusions

- ✓ Despite its pitfalls Pap cytology continues as the favoured approach in countries with opportunistic or organized screening.
- ✓ Over time, HPV vaccination will have a negative impact on the performance of cytology, thus further straining the efficacy of screening in middle and low resource settings.
- ✓ HR-HPV DNA testing a more efficacious and robust screening test than cytology, especially post-vaccination.
- ✓ VIA a promising strategy in low-resource settings.
- ✓ A new paradigm of HPV testing followed by Pap triage or VIA can provide a double role as a screening approach and surveillance system to monitor the effectiveness of HPV vaccination.