

Cervical Screening in Vaccinated and Unvaccinated Women

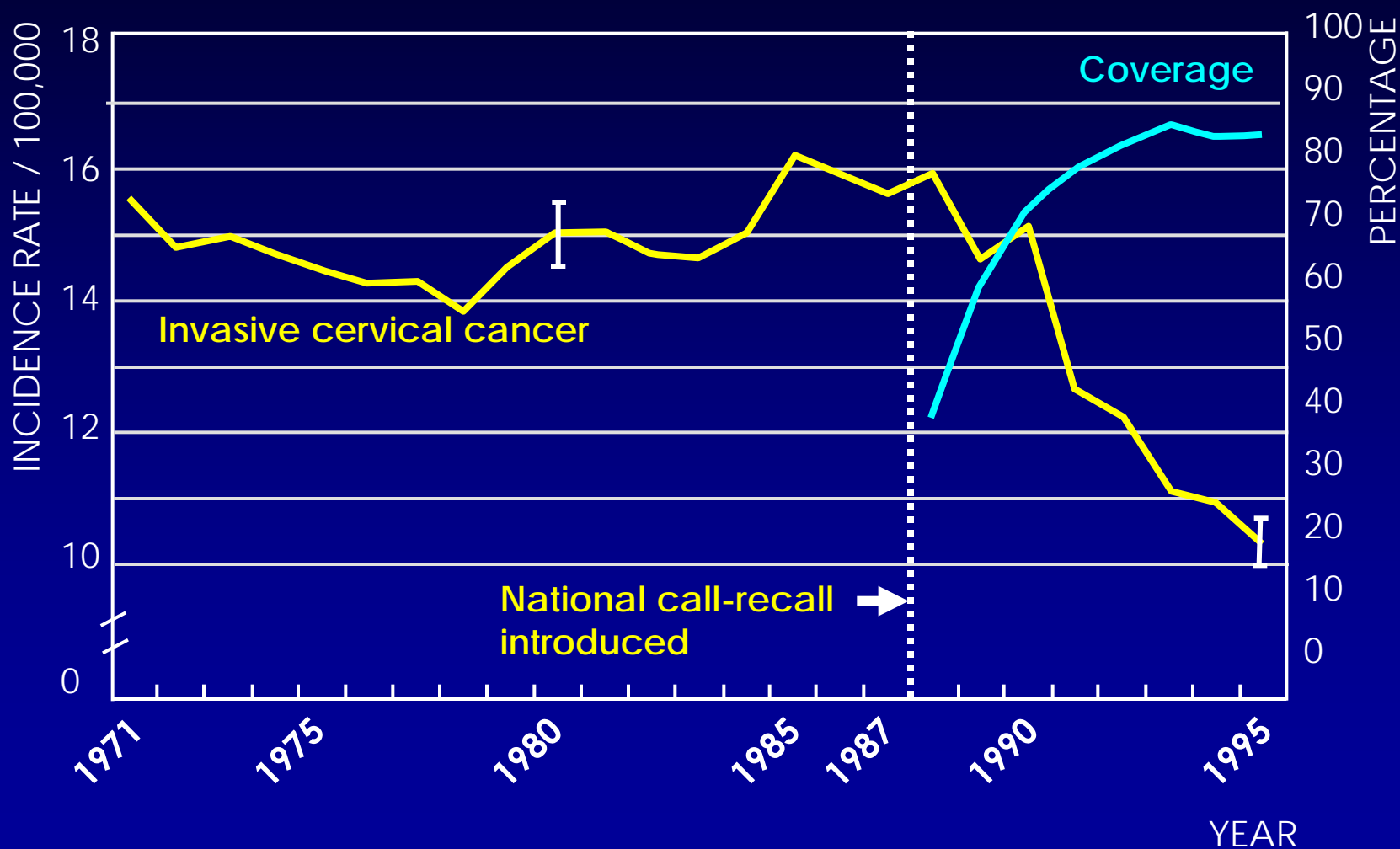
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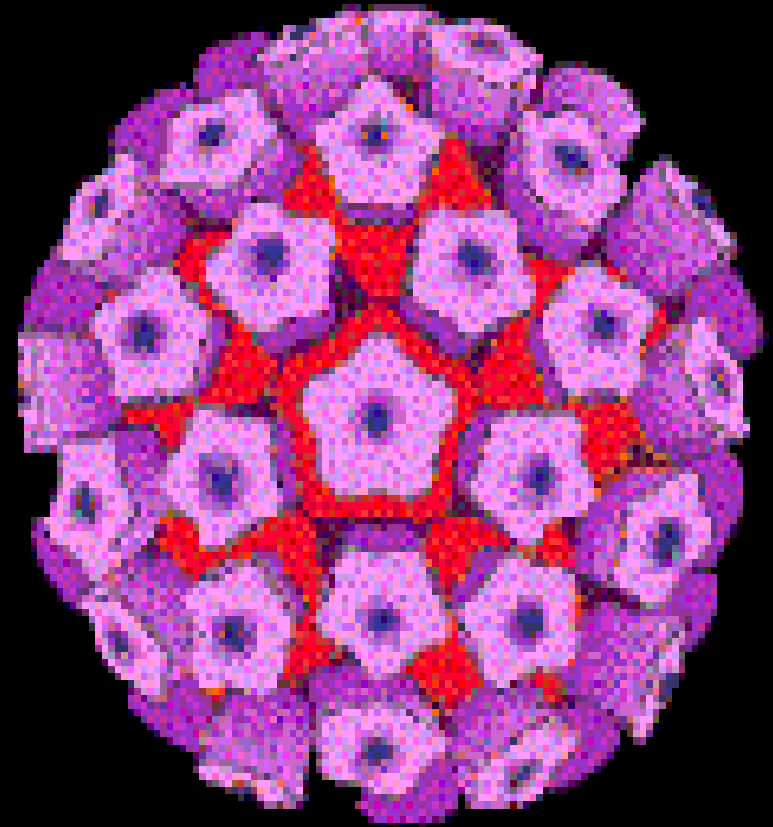
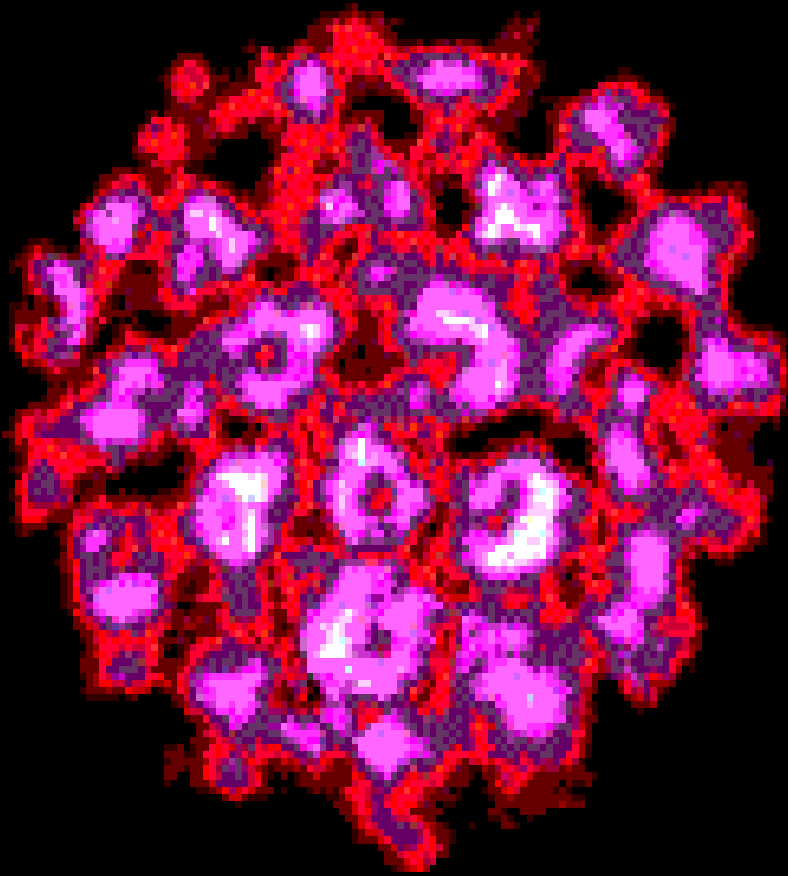
AGE-STANDARDIZED INCIDENCE OF INVASIVE CERVICAL CANCER AND COVERAGE OF SCREENING, ENGLAND, 1971-1995



UK audit - cases

- **62% of women with fully invasive cancer (age <70) had been screened within 5 years of diagnosis: 60% of squamous, 70% of adenocarcinoma.**
- **10% of cases under age 65 were diagnosed >6 months after positive cytology.**
- **52% had only negative smears**

HPV



HPV positivity in a large international study

HPV type	Number Positive (%)
HPV 16 and related	HPV16 482 (53.0)
	HPV 31 54 (5.9)
	HPV 33 28 (3.1)
	HPV 35 16 (1.8)
	HPV 52 26 (2.9)
	HPV 58 20 (2.2)
HPV 18 and related	HPV 18 140 (15.4)
	HPV 39 15 (1.6)
	HPV 45 81 (8.9)
	HPV 59 15 (1.7)
	HPV 68 11 (1.2)
Other	HPV 6/11 2 (0.2)
	HPV 56 16 (1.8)
Miscellaneous	26 (2.9)
Undetermined	14 (1.5)
Positive	907 (99.8)
Negative	2 (0.2)
Total Adequate	909 (100)

(From Bosch, *et al.* 1995 and Walboomers, *et al.* 1996)

Impact of Vaccination

Invasive Cancer

- Estimated at 73% due to HPV 16/18 (all ages) by Clifford, 2005
- Potential for Cross-protection against 45/31 -- another 14% = 87%

CIN 3

- Moderate or worse cytology (Sergeant et al) - 53% in women of all ages
- In FUTURE I & II - 63.5% of women aged 15-26

Abnormal Smears

- 53% of high and 28% of low grade due to HPV 16/18
- Weighted average - 30% can be prevented by vaccination

The English HPV vaccination programme

Academic year HPV vaccine given	School Year 7	School Year 8 Age 12-13	School Year 9	School Year 10	School Year 11 Age 15-16	School Year 12 Age 16-17	School Year 13 Age 17-18
2008/09		1/9/1995 to 31/8/1996					1/9/1990 to 31/8/1991
2009/10		1/9/1996 to 31/8/1997		1/9/1994 to 31/8/1995	1/9/1993 to 31/8/1994	1/9/1992 to 31/8/1993	1/9/1991 to 31/8/1992
2010/11		1/9/1997 to 31/8/1998					
2011/12		1/9/1998 to 31/8/1999					

Uptake of HPV vaccines

- HPV vaccine uptake rate varies by country
- School-based HPV vaccination programmes have the highest uptake rates

Country	3 rd dose vaccine uptake %
Australia ¹	70.0*
Canada ²	80 [†]
England (UK) ³	80.1
USA ⁴	17.9 [‡]

* All school cohorts vaccinated in New South Wales and Victoria

[†] Atlantic provinces

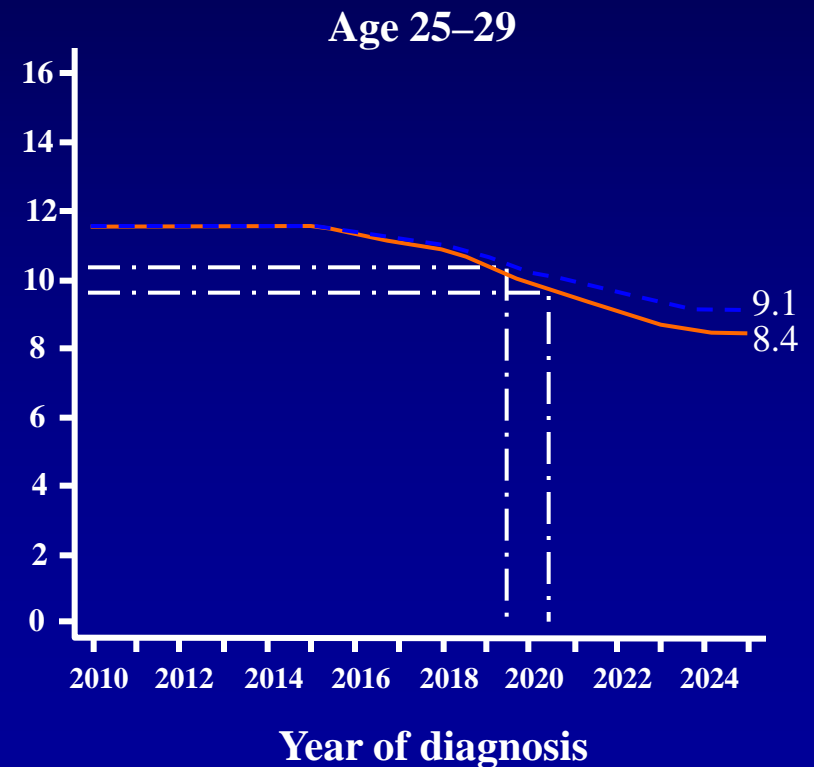
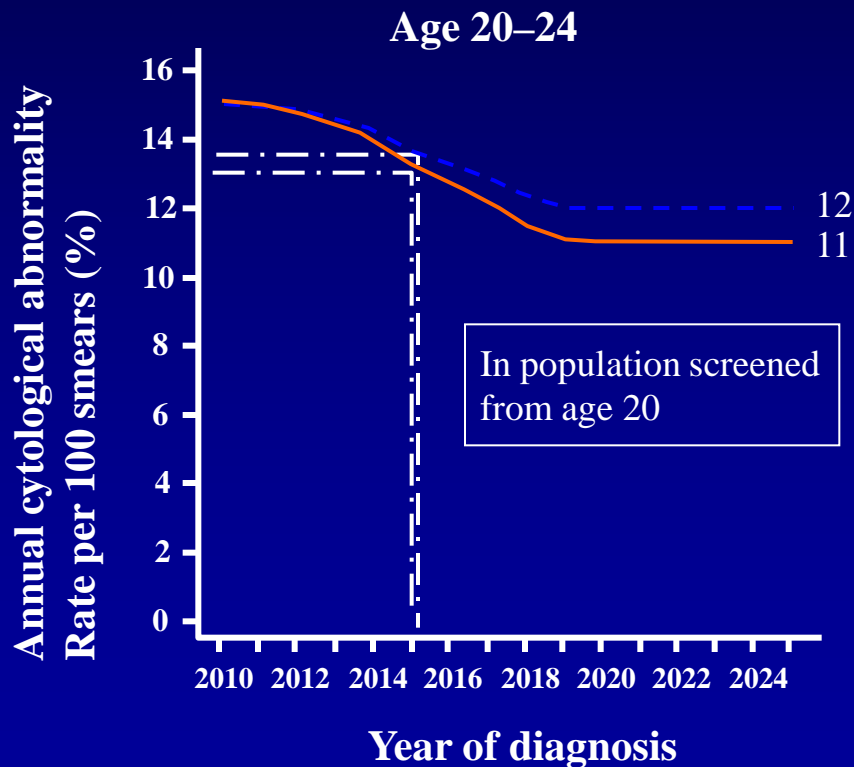
[‡] General practice vaccination of 13–17-year-olds

1. Brotherton J, *et al.* *CDI* 2008; **32**:457–461; 2. Colucci R, *et al.* Report Card on Cancer in Canada, 2008. Available at: <http://www.canceradvocacy.ca/reportcard/2008/reportcard-2008.pdf> (Accessed 21 May, 2010); 3. Department of Health. Annual HPV vaccine uptake in England: 2008/09. Available at: http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_111675. Accessed 21 May, 2010; 4. Stokley S, *et al.* *MMWR Weekly* 2009; **58**(36):997–1001.

Predicted impact of UK vaccination programme: cytological abnormalities

Predicted reduction in cytological abnormalities
(with 80% vaccination coverage)

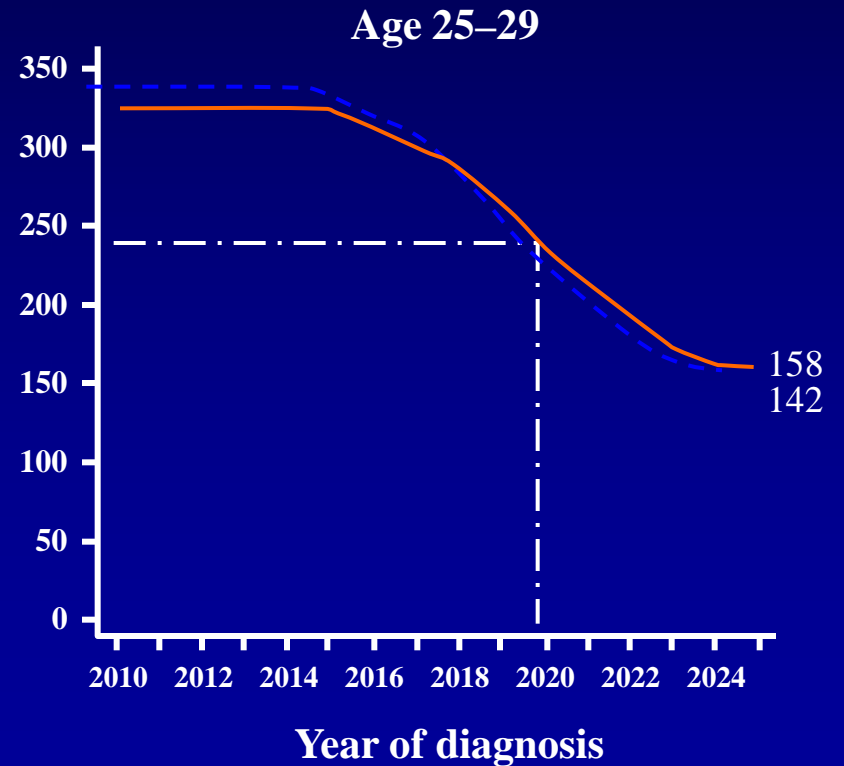
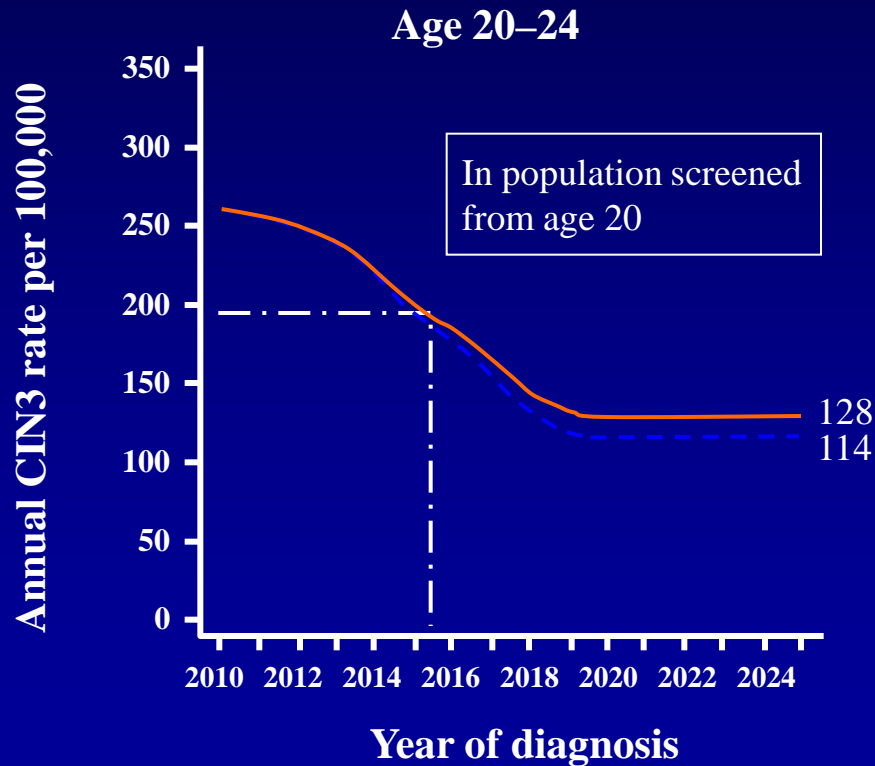
- No cross-protection
- - - With cross-protection
- · - · 50% benefit achieved



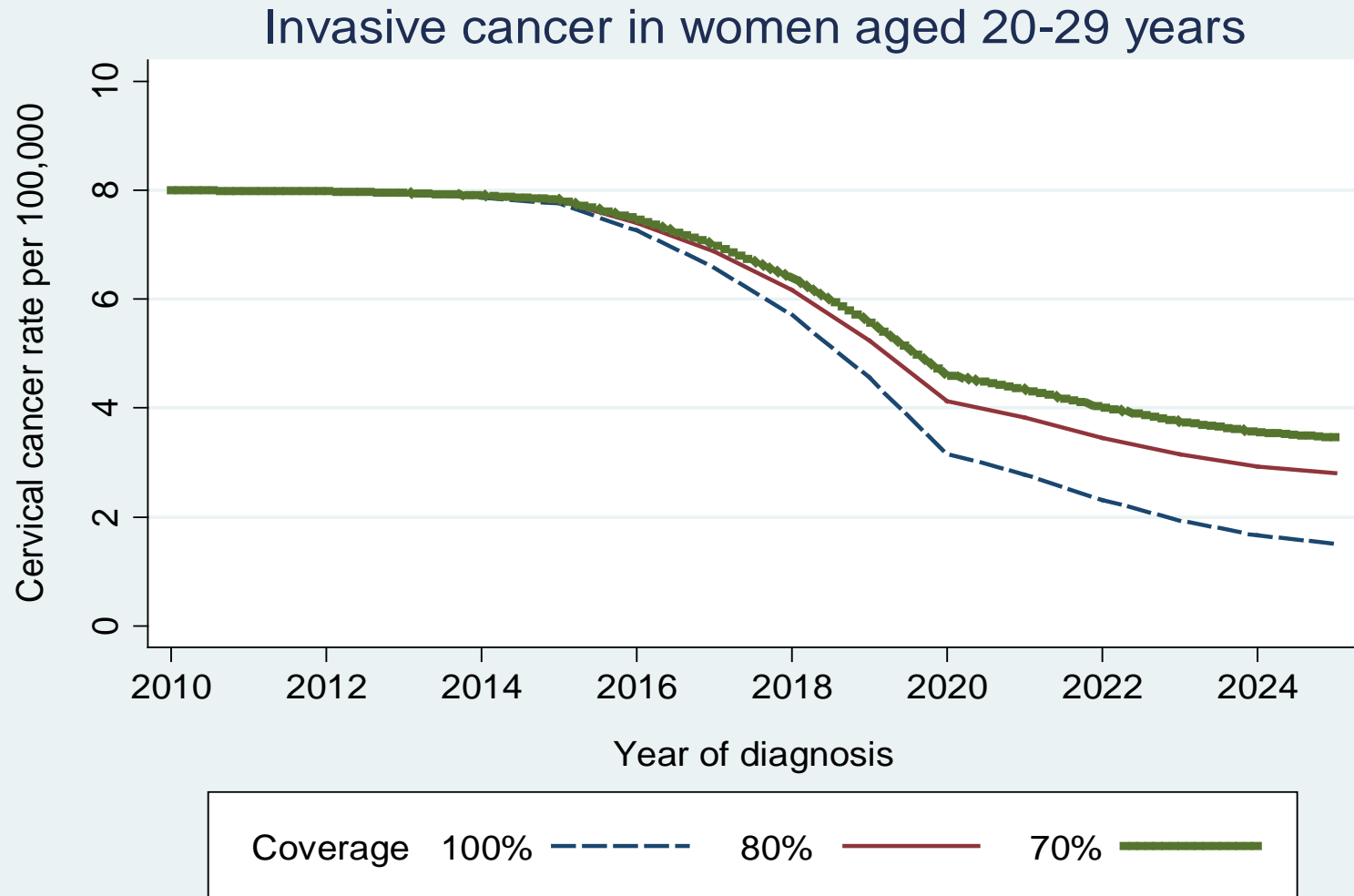
Predicted impact of UK vaccination programme: CIN3

Predicted reduction in CIN3
(with 80% vaccination coverage)

- No cross-protection
- - - With cross-protection
- · - · 50% benefit achieved



Effect of vaccine over time – invasive cancer



Potential Role of HPV Testing in Cervical Screening

- **Primary Screening**

- Adjunct to Cytology
 - Higher Sensitivity
 - Longer Screening Interval
 - Reduced Inadequate Rate
- Sole Primary Test
 - Use of Cytology for Triage
- Self Sampling
 - Improved Coverage

Baseline Results of HPV Testing in European & North American Screening Studies

Jack Cuzick

Christine Clavel, Ulli Petry, Peter Sasieni

Chris Meijer, Sam Ratnam

Philippe Birembaut, Anne Szarewski

Shalini Kulasingam, Heike Hoyer

Thomas Iftner

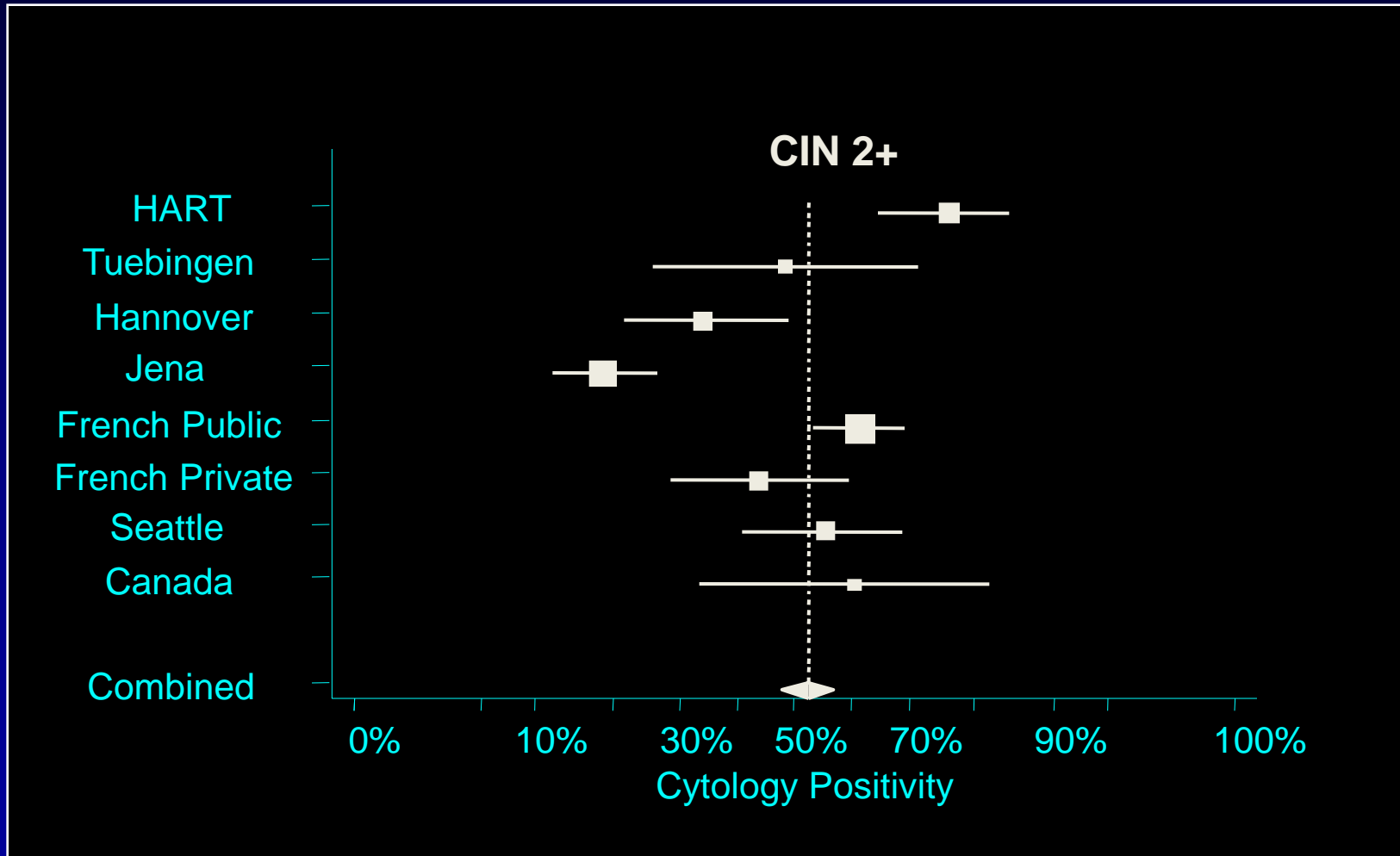


Barts and The London
Queen Mary's School of Medicine and Dentistry

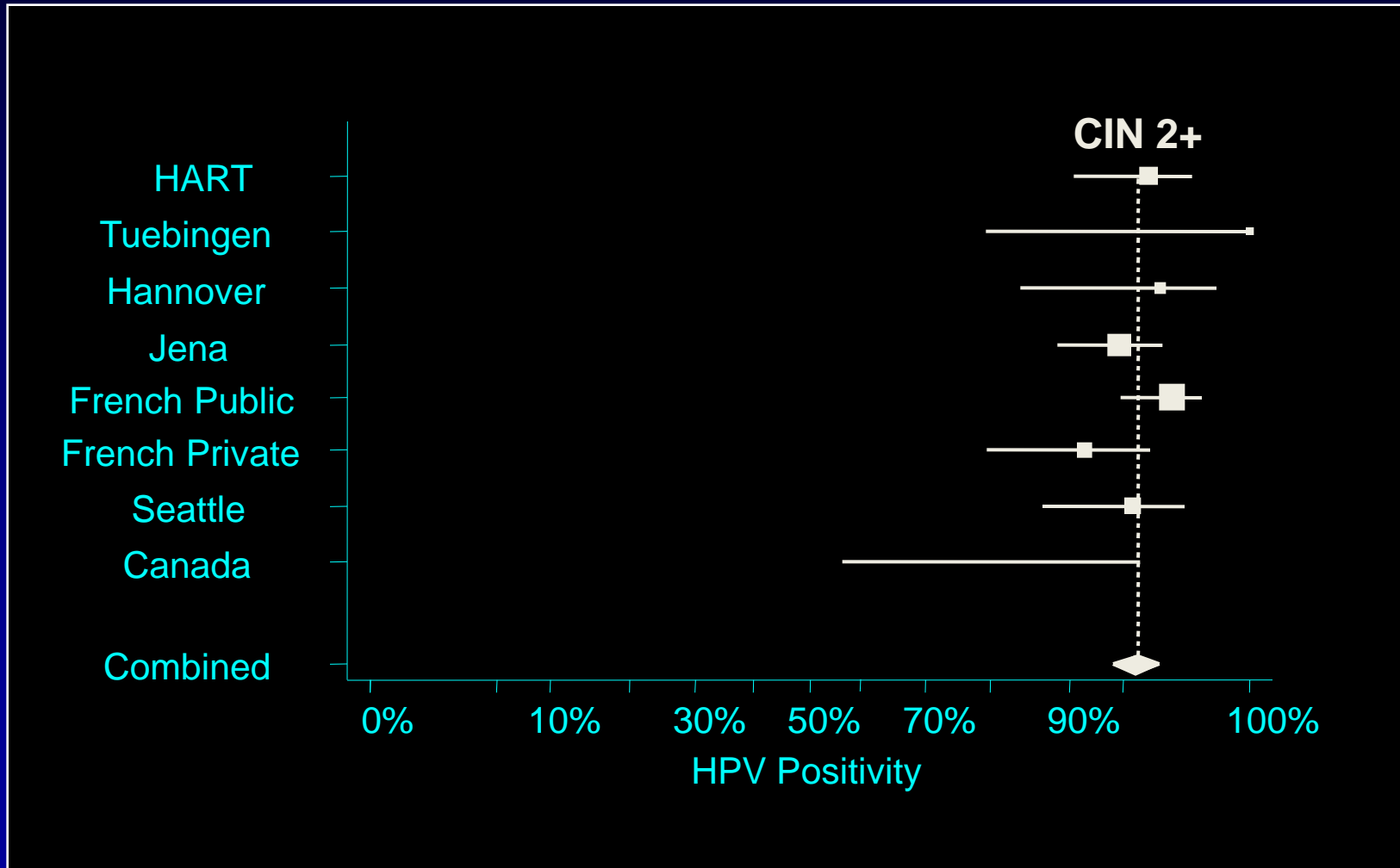
Int J Cancer 119:1095-1101,2006



Cytology Sensitivity - CIN2+ (all ages)



HPV Sensitivity - CIN2+ (all ages)



Summary

	Sensitivity	Specificity
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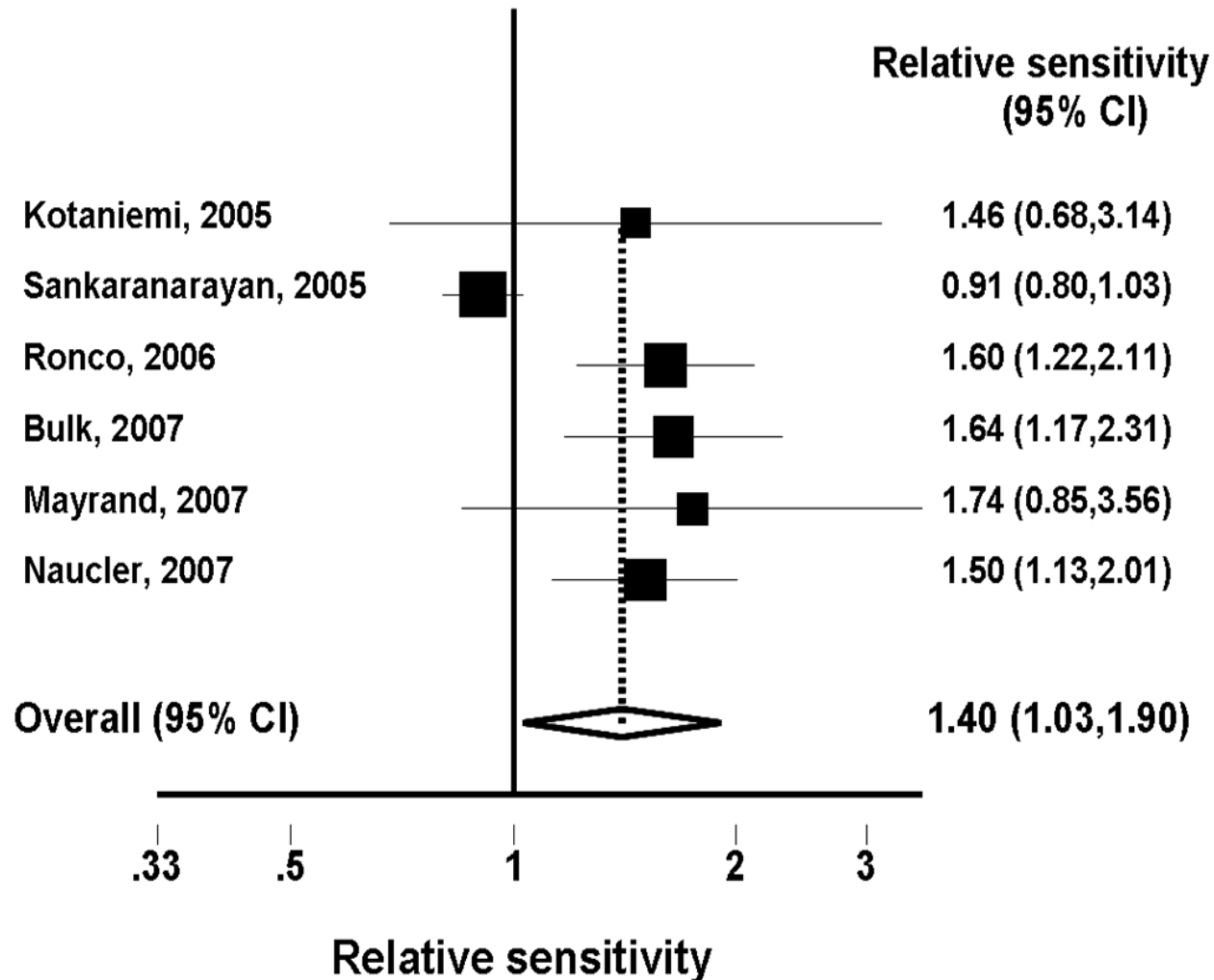
HPV	96%	92%
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CYTOLOGY	53%	97%
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Double-testing studies after overview (CIN2+)

		Sensitivity	Specificity
Italian Phase I	HPV	97.3	93.2
(experimental arm)	Cytology	74.0	94.8
Canadian	HPV	94.6	94.1
	Cytology	55.4	96.8

Relative Sensitivity of HPV vs cytology for CIN2+ in randomised trials

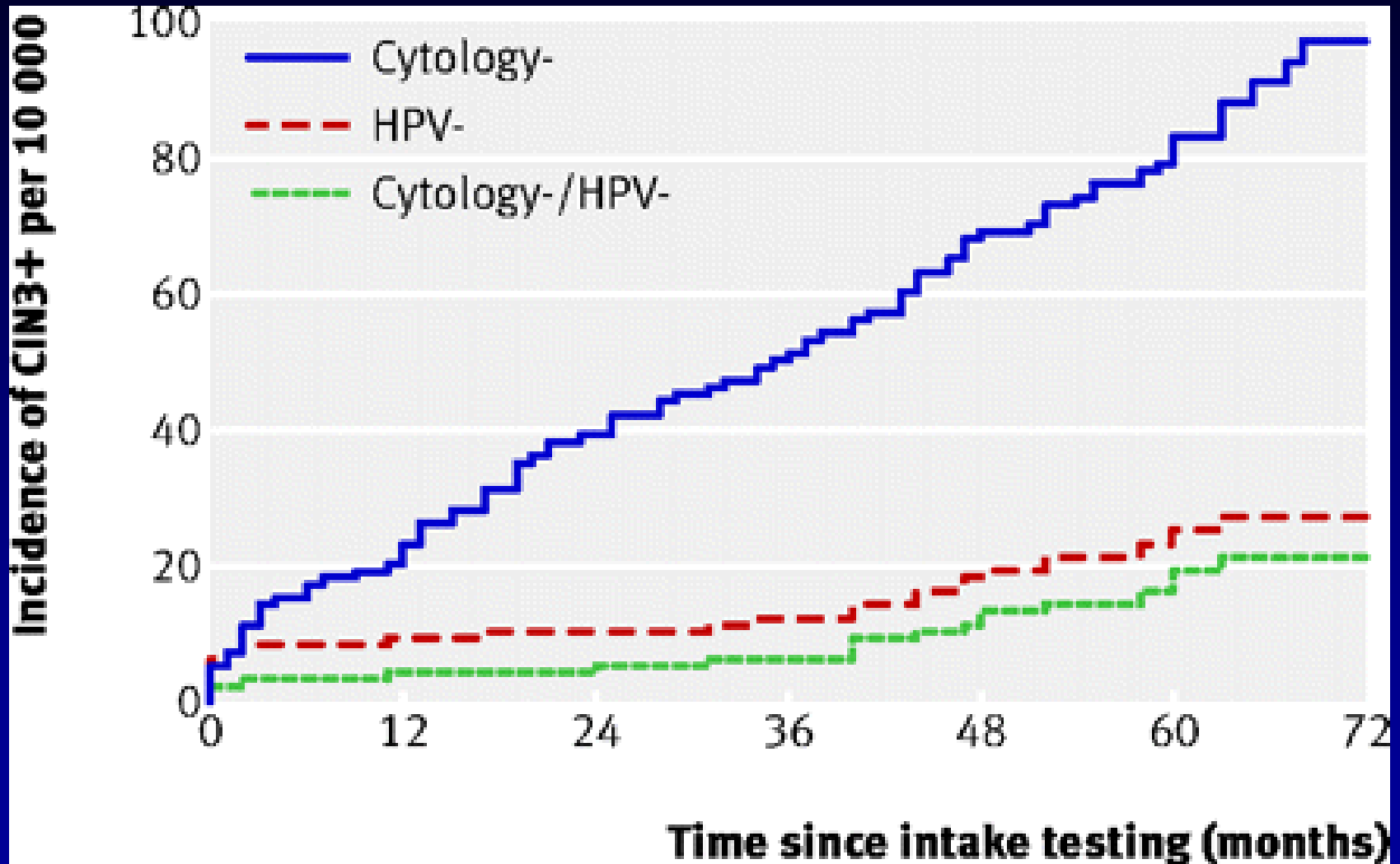


**Long term predictive values of
cytology and human papillomavirus testing
in cervical cancer screening:
Joint European cohort study**

Joakim Dillner, Matejka Rebolj, Philippe Birembaut, Karl-Ulrich Petry, Anne Szarewski, Christian Munk, Silvia de Sanjose, Pontus Naucler, Belen Lloveras, Susanne Kjaer, Jack Cuzick, Marjolein van Ballegooijen, Christine Clavel, Thomas Iftner,

Br Med J. 2008

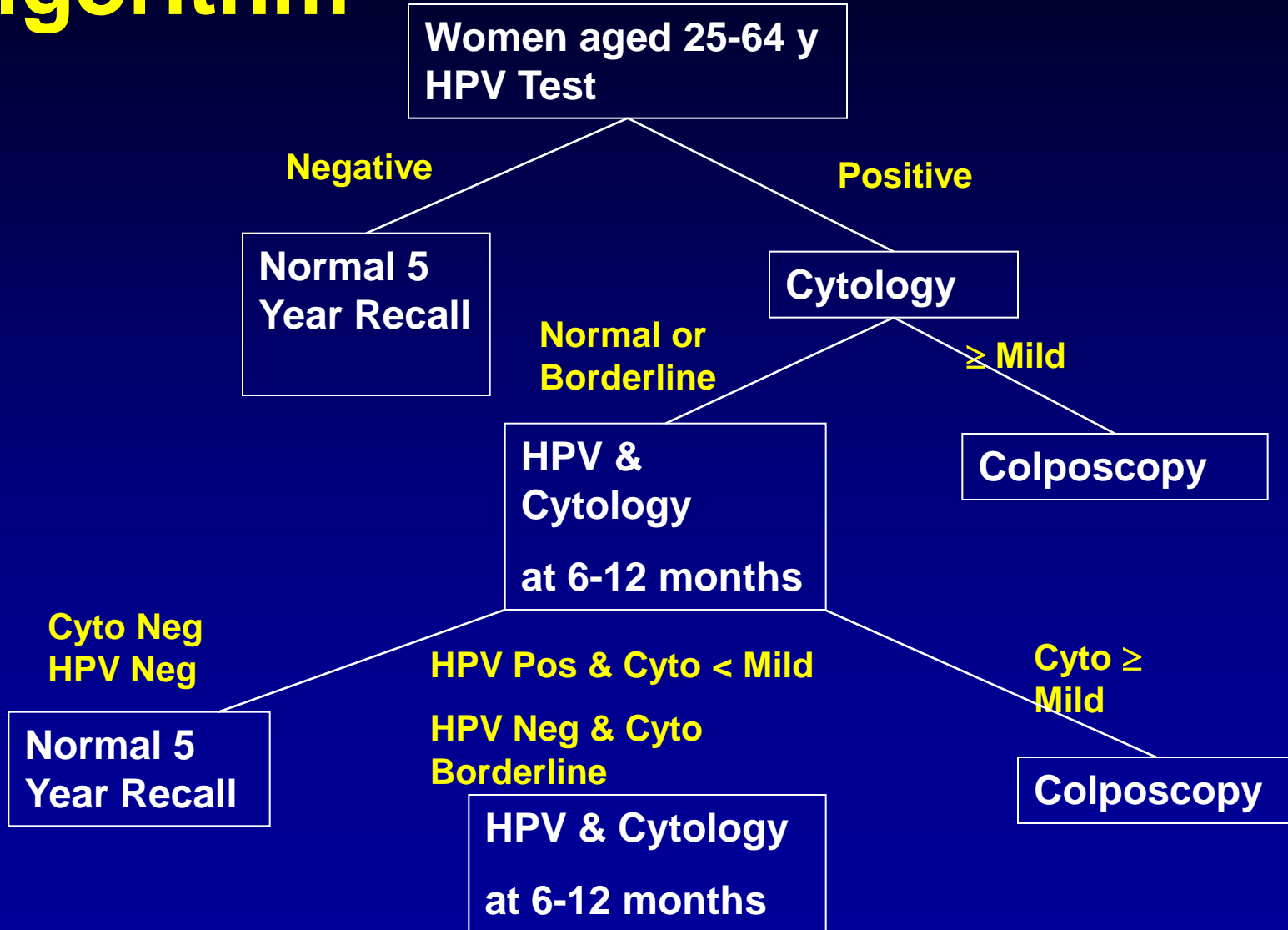
Cumulative incidence rate for CIN3+ according to baseline test results excluding Denmark and Tübingen



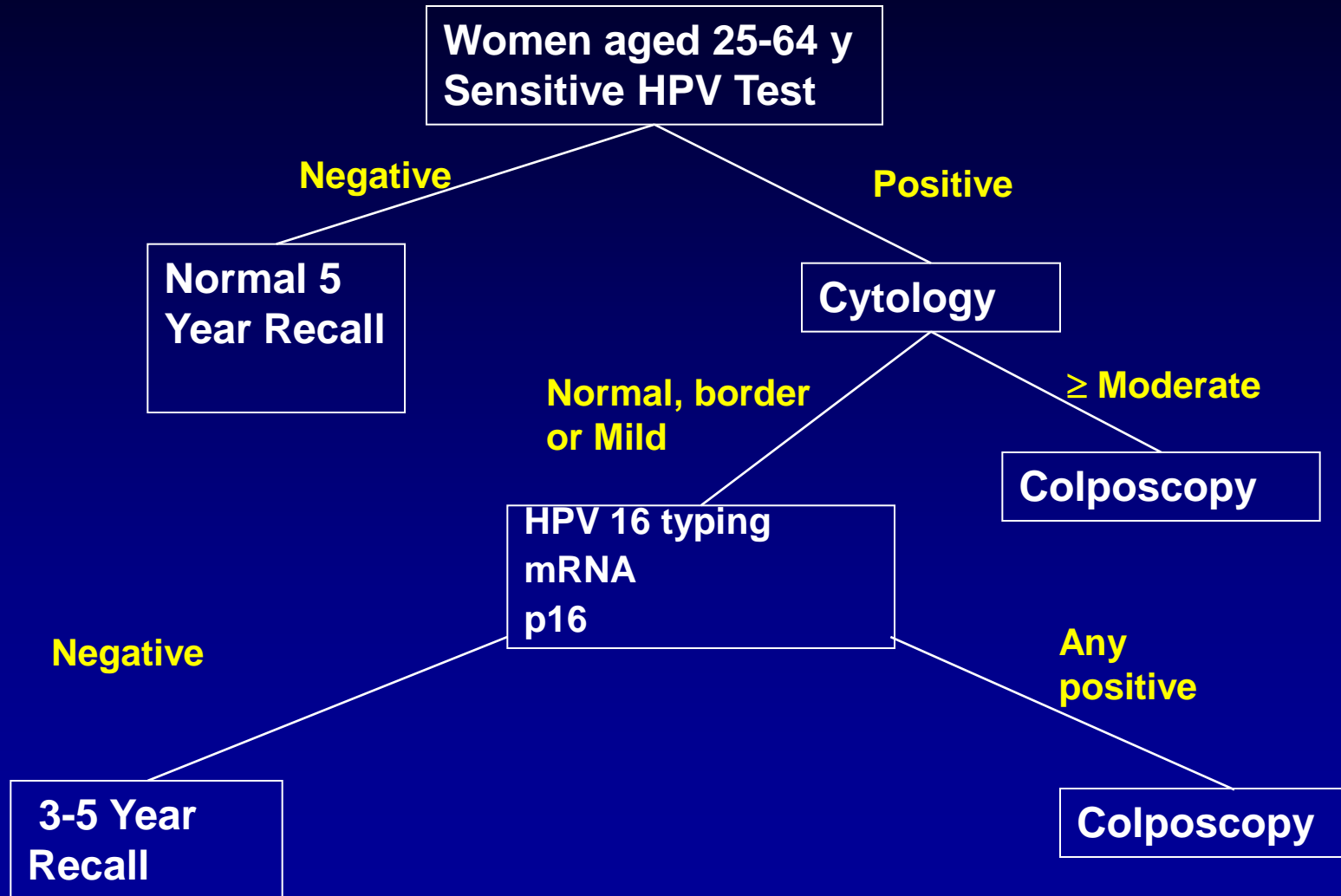
CIN3+ rates after a negative screening test

- Cytology @ 3 yrs 0.51% (0.23 – 0.77%)
- HPV @ 6 yrs 0.27% (0.12 – 0.45%)

Proposed New Screening Algorithm



Potential Future Screening Algorithm



Screening – Post Vaccination

- Lower Prevalence of CIN2+ due to lack of HPV 16/18 induced lesions
 - Decreased PPV
 - True positives decreased – false positives unchanged
 - Decreased Sensitivity for cytology
 - Abnormalities rarer – loss of concentration

Screening – Post Vaccination

- **Screening less cost effective**
- **Objective, automated methods of HPV testing will be even more important for low prevalence setting**
- **May be a role for computer assisted cytology based primary screening (with new IHC markers) – not yet proven**

Screening – Post Vaccination

- **Longer screening intervals**
 - Requires knowledge of vaccination history
 - Older women beyond vaccination age still need screening for 40+ years
- **Self –Sampling ??**
 - Only sensitive with HPV testing

Screening – Post Vaccination

- **Better (more specific, but highly sensitive) molecular markers for testing??**
 - HPV typing ??
 - HPV mRNA testing
 - Proliferation markers (mcm)
 - Improved cytology
 - Computer assisted reading
 - p16
 - Proliferation markers

Cervical cancer is preventable!

- **Cervical cancer is the only cancer with a single, known cause - the Human Papillomavirus**
- **Only when infection with high-risk types persists can cervical cancer develop**
- **Vaccination can prevent infection (currently against HPV 16/18), but not eliminate it once it occurs**
- **Screening can identify precursor lesions which are treatable**

Overall Conclusions

- **Vaccines are effective, but are mostly for the next generation of women**
 - Current generation of women will need screening
- **Screening will be more difficult and less cost effective in vaccinated women**
 - Longer intervals and ? Self sampling?
 - Registries of vaccinated women needed to inform screening
- **Screening will benefit from use of HPV testing as the primary screen**
 - Newer more specific tests even more critical
 - HPV testing before vaccination in women aged 16+ ?
- **Until truly multivalent vaccines become widely available, screening will remain an important part of cervix cancer prevention**