- The new European (and Italian) guidelines for cervical screening will recommend

➔ PAP from 25 to 34

➔ HPV (+ triage) from 35 to 64

➔ risk of overdiagnosis and over treatment ➔ Failures in reproductive functioning: pre-term delivery, low birth weight

But….

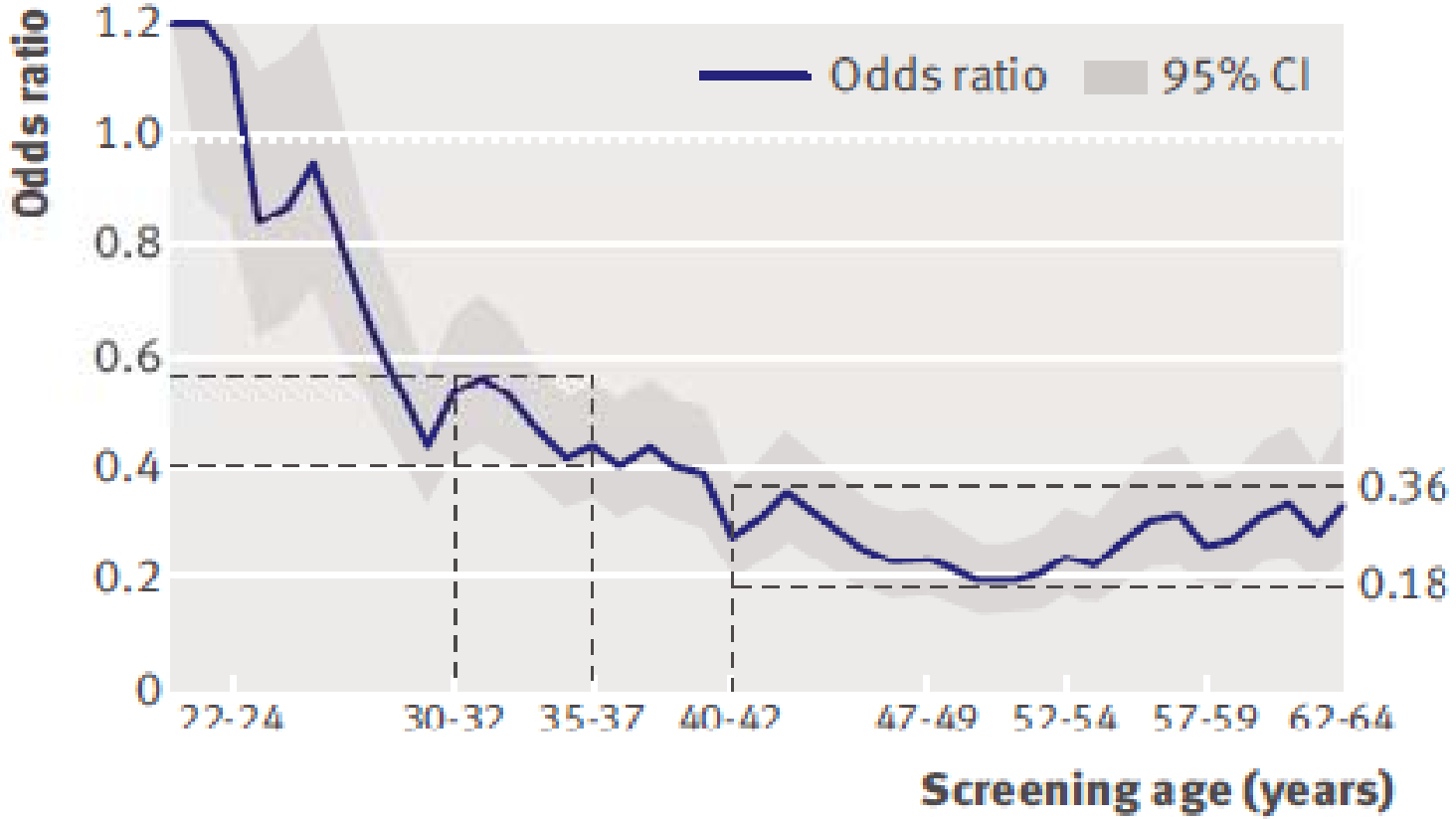


Fig 2 | Odds ratio for developing invasive cervical cancer stage IA or worse (in the next five year interval) in those screened in a given (three year) age band compared with those not screened in that age band (or in two previous years). Odds

Sasieni & Cuzick, BMJ 2009

Table 5. Effects of cervical cancer for attenders compared to non-attenders. The age-specific estimates were obtained from separately fitted models.

Anttila et al. IJC 2010

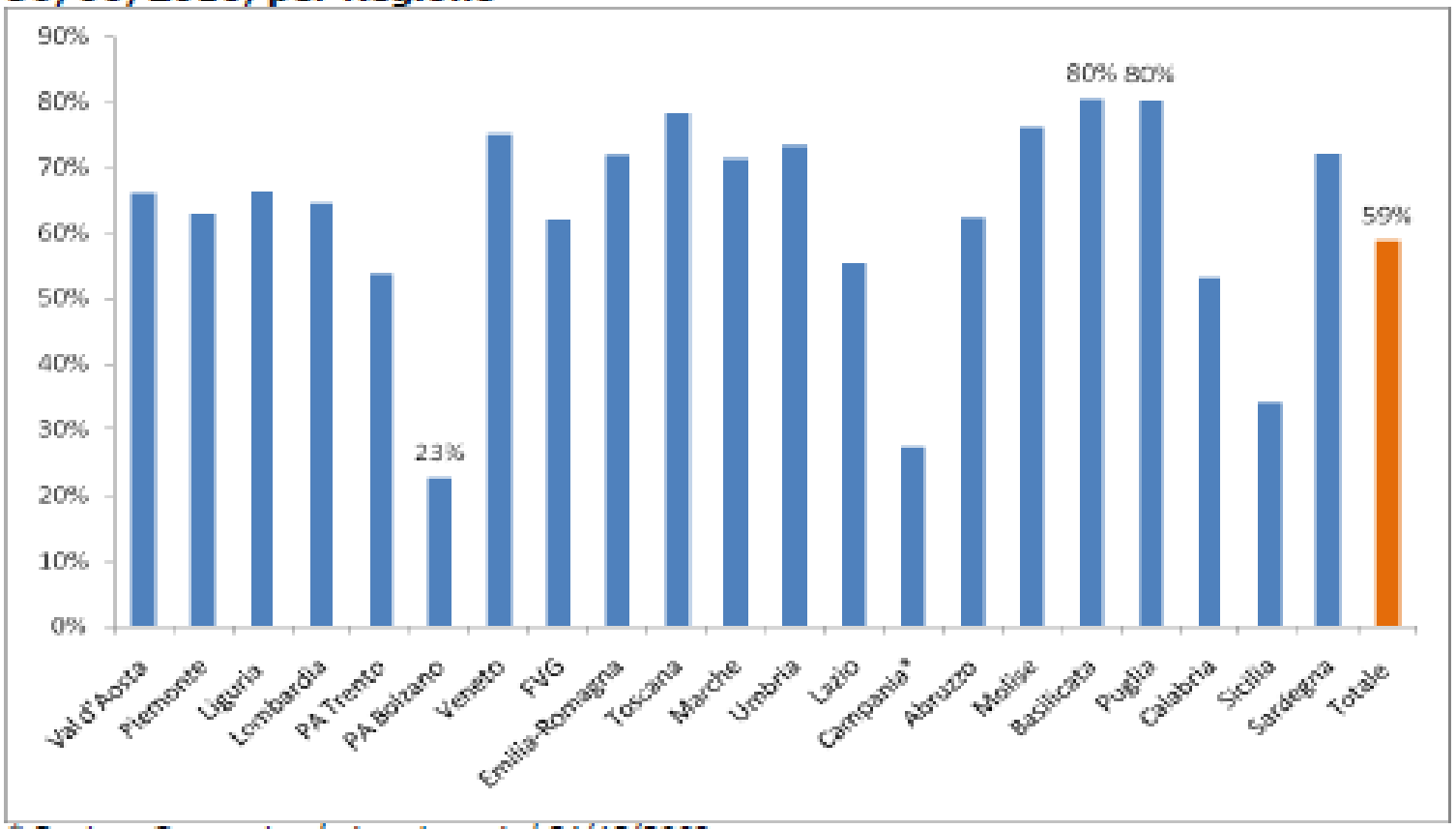
	Cases	Rate	RR	95% CI
Invited at age 20-39 yrs				
Non-attenders	25	8.2	1.00	--
Attenders	**40**	**8.1**	**0.99**	**0.60-1.64**
Screening episode positive	14	431	52.7	26.7-99.8
Recommendation for intensified screening	13	38.1	4.65	2.31-8.93
Screening test negative	13	2.8	0.35	0.17-0.67
Invited at age 40-54 yrs				
Non-attenders	49	13.5	1.00	--
Attenders	**59**	**5.5**	**0.41**	**0.28-0.59**
Screening episode positive	14	485	36.0	19.2-63.5
Recommendation for intensified screening	16	19.9	1.48	0.82-2.55
Screening test negative	29	2.9	0.22	0.13-0.34
Invited at age 55-74 yrs				
Non-attenders	29	14.6	1.00	--
Attenders	**46**	**6.3**	**0.43**	**0.27-0.70**
Screening episode positive	10	973	66.9	31.0-133
Recommendation for intensified screening	8	21.8	1.50	0.64-3.13
Screening test negative	28	4.0	0.28	0.16-0.47

Control of opportunistic screening

- Legal frameworks enabling QA and organised activity
- Modifications to the laboratory systems also required
- Efficacy ?

HPV VACCINATION – ITALY 2010

Figura 1. Coorte 1997: dati di copertura per 3 dosi di vaccino HPV aggiornati al 30/06/2010, per Regione



** Regione Campania: dati aggiornati al 31/12/2009*

future. We modeled a scenario in which the likelihood of vaccination and screening in an individual girl was unrelated; in this case, approximately 30% of girls who were not vaccinated would account for 40% (95% CI = 30% to 45%) of invasive cervical cancers. However, if unvaccinated girls were less likely to be screened later in their lives, then 69% (95% CI = 60% to 76%) of invasive cervical cancers occurred in unvaccinated women. This finding highlights the importance of achieving high and equitable coverage.

JEREMY D. GOLDHABER-FIEBERT
SUE GOLDIE

- The same screening policy either for vaccinated or not vaccinated women?

Cervical cancer screening in Finland

- Organised programme from 1963, nation-wide 1971
- Women in ages 30-64 targeted nationally (25-69 in some regions), five-year interval
- Seven tests lifetime (nine in some regions)
- Age-specific invitational coverage 98% in 2007; attendance rate at 70%
- Estimated 5-year coverage of ***any*** smears 90% (surveys)
- Estimated coverage of ***any*** smears lifetime 98% (surveys)

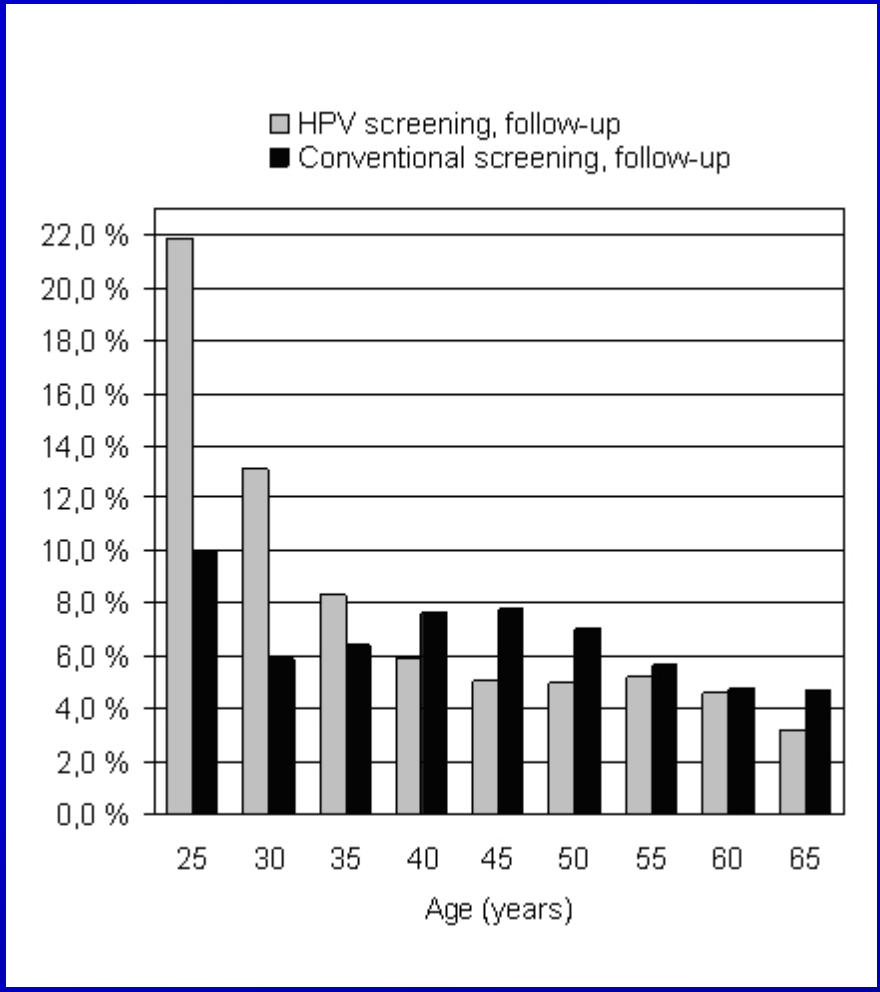
Cervical cancer screening programme in Finland in 2008

'http://www.cancer.fi/syoparekisteri/en/mass-screening-registry/'

- Target population 1.3 million women
- About 260,000 women invited (98%)
- >180,000 screened (70%)
- Follow-up cytology recommended: 5.4%
- Referral: 1.1%
- CIN1+ cases treated: 0.4% of screened
- Appr. 10% of the screening tests primary HPV screening with cytology triage

Frequency of recommendations for intensified screening (Leinonen et al. JNCI 2009)

- 2581 recommendations in the HPV arm, 2340 in the conventional arm
- 9% more recommendations in the HPV arm overall (95% CI 3-15%)
- From age 40 onwards, rate was constantly lower in HPV arm
- The rate was modified by age in both arms (p-value for age, and for the interaction term 'age x arm' < 0.001)



Discussion on HPV screening

- There is an increase in over-diagnosis of pre-cancer lesions in HPV screening, compared with cytology, during the first screening round
- The risk of over-diagnosis is particularly pronounced in women aged below 35
- In women aged 35-65 at index screen, overdiagnosis in a woman's lifetime can be avoided if control over other uses of cytology (particularly opportunistic screening in women below age of 30) can be reduced
- Self-sampling could be integrated as the first or second reminder

Efficacy of HPV vaccination against CIN2+ irrespective of HPV type in lesion: phase III estimates using *Cervarix*®

Endpoint Phase III study	Cohort	VE %	95% CI
CIN2+ irrespective of HPV type in lesion, irrespective of baseline HPV DNA status	TVC-1	**30.4**[1]	**16.4–42.1**
CIN2+ irrespective of HPV type in lesion, DNA negative for all high-risk HPV types at baseline	TVC naïve	**70.2**[1]	**54.7–80.9**

Estimated worldwide prevalence of HPV 16/18 in high grade lesions (CIN 2/3) is 52%[2]

1. Paavonen J et al. Lancet 2009; 374 (9686): 301 - 314.
2. http://www.who.int/hpvcentre/statistics. Accessed 1 May, 2009.

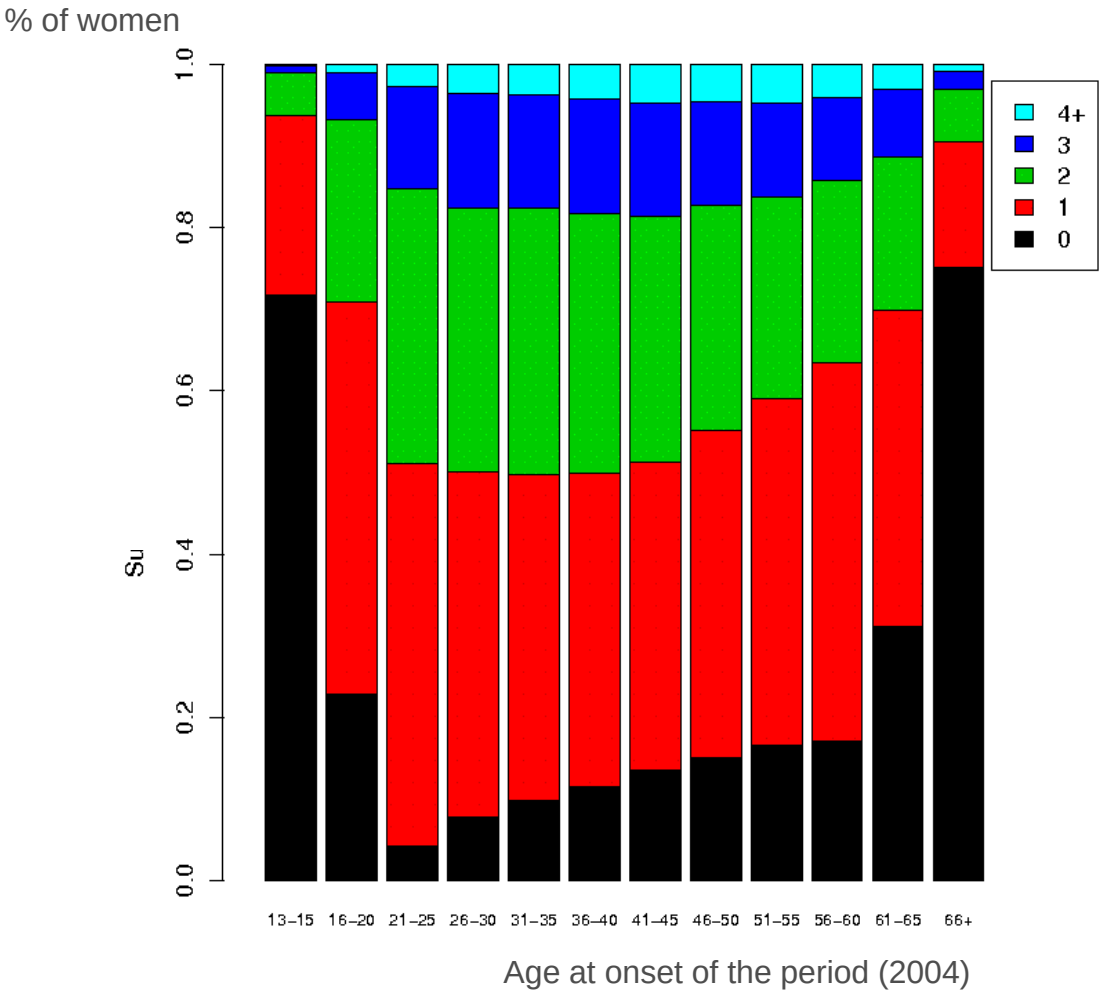
Efficacy on CIN3+/Referral/Local therapy /hrHPV

TVC naive cohort, *Cervarix*®

Final Analysis, Phase III study		HPV	Control	VE (%)	LL	UL	P-value
CIN3+ irrespective HPV DNA results		3	**23**	**87**	55	98	<0.0001
Colposcopy referrals		354	**476**	**26**	15	36	<0.0001
Number of cervical excision procedures		26	**83**	**69**	50	81	<0.0001
Any oncogenic HPV, 12 month persistent infection		585	**803**	**28**	19	36	<0.0001

Paavonen J et al. Lancet 2009; 374 (9686): 301 - 314

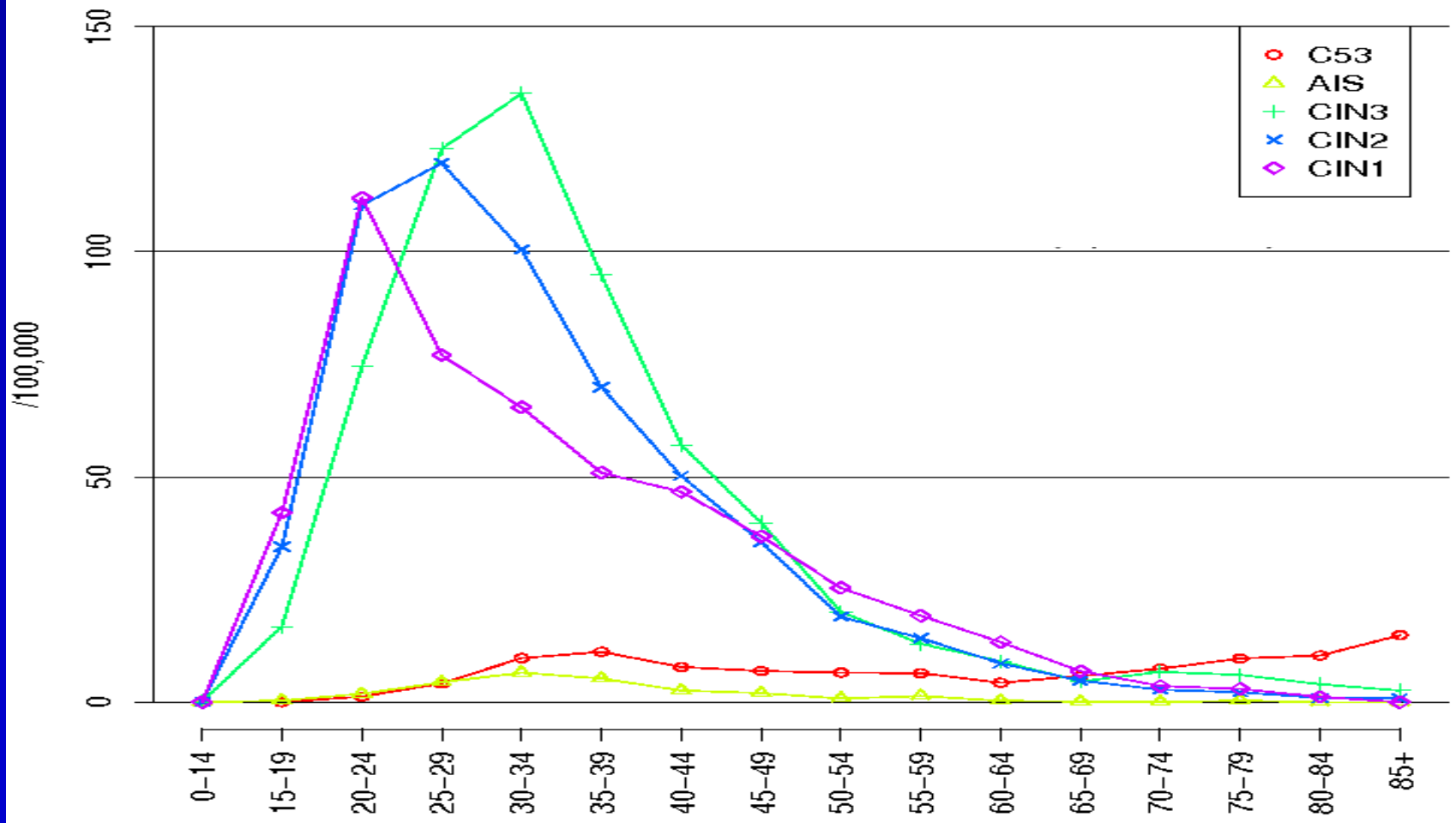
Proportion of women with a Pap smear test at least once within five years, by age and number of smears within the period (H.Salo et al. THL, June 2011)



Age-specific rates of cervical cancers and pre-cancers

Finnish Cancer Registry and Hospital/Outpatient Treatment Register 2004-2008

H.Salo et al., THL, June 2011



Consequences for screening

- Even though a highly cost-effective screening programme, the current practice including a high burden of CIN treatments and of mild cytological abnormalities among women below age of the start of the programme probably not cost-effective
- In order to improve overall cost-effectiveness of the services, opportunistic screening must be reduced

Consequences for screening

- If directed towards proper target ages & intervals, introduction of HPV screening would not increase the CIN burden
- Information on effectiveness of screening among young women (below age of 35) is still uncertain, difficult to evaluate thoroughly in absence of trials
- More research is needed also on most optimal policies of screening and management in the old female population, also after the age of last screen of the current programme

Challenges in introducing HPV-screening

- To improve adherence to population-based models
  - Education, training, attitudes among medical groups
  - Building up invitational & information systems, reduce numbers of non-screened and under-screened
  - Legal frameworks enabling QA and organised activity
- Reducing overuse of services and adverse aspects
  - Not to start screening at too early age
  - To reduce lifetime tests provided for healthy women
  - Include all tests and treatments in the evaluation systems
  - Modifications to the laboratory systems also required

Consequences for vaccination

- Magnitudes in the effectiveness of vaccination not completely clear yet, depend e.g. on coverage by vaccinated age groups, and screening intensity among vaccinees
- Vaccination alone, without other simultaneous changes improving overall cost-effectiveness, would likely not be enough to reduce the current excess burden of CIN/mild abnormalities in the young female population
- Instead of incremental cost-effectiveness, guidance should be based on overall cost-effectiveness taking all prevention strategies and options simultaneously into account

European Challenge

- Gradual implementation: Feasibility, careful planning & pilots recommended to demonstrate that the components of the screening programme work with a sufficient quality
- Countries with effective organised screening and large-scale RCTs/pilots have highest readiness for HPV screening
- In the settings without an organised programme, introduction of HPV-based screening should take place only in context of piloting an organised population-based programme ; otherwise harms and adverse effects would increase tremendously
- Important to consider possible synergies between screening programme and HPV vaccination