NCPTS

Using hrHPV testing for primary screening: reasons for change

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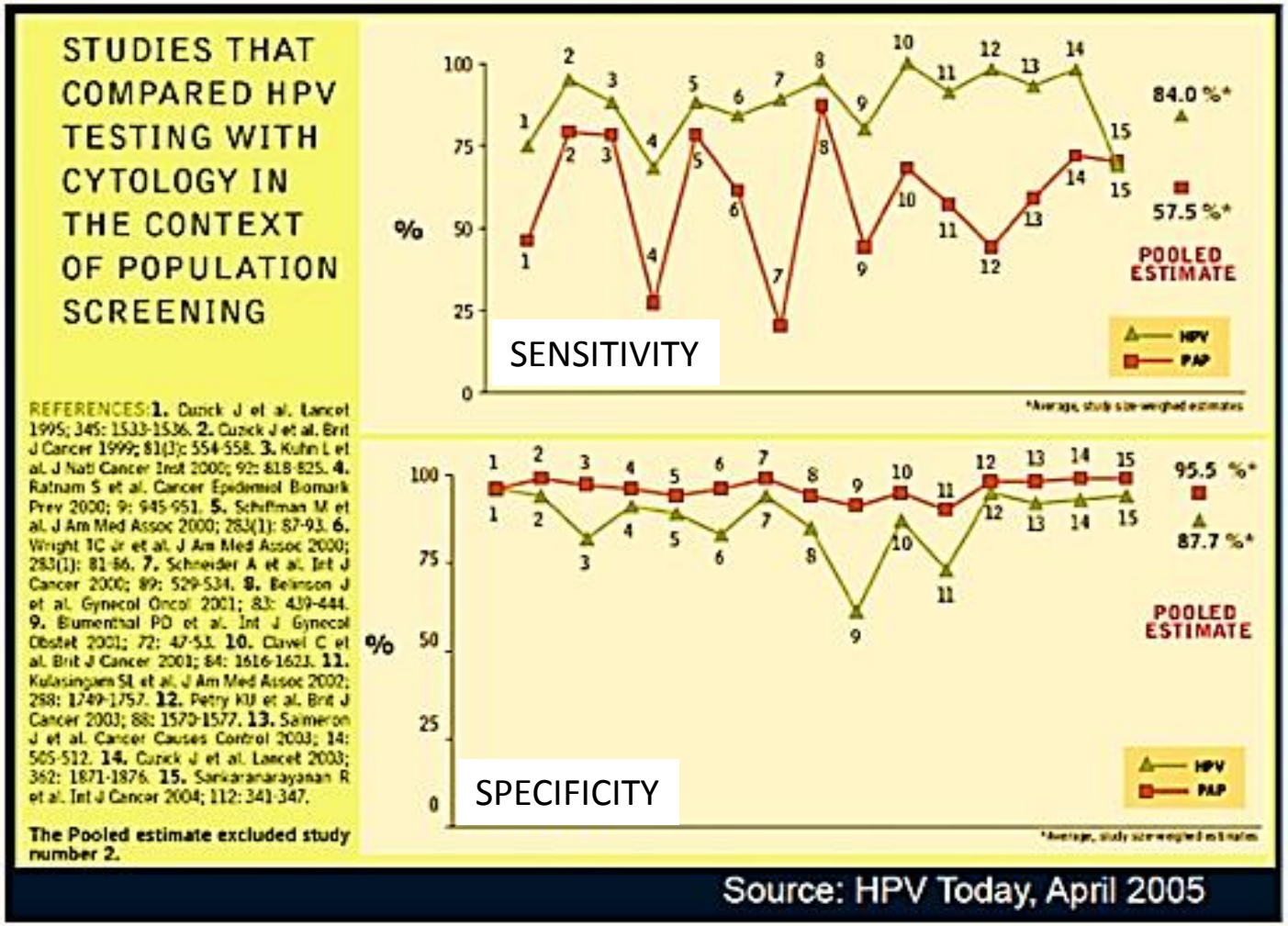
October 2016

1. HPV testing is a more sensitive test



HPV Testing

Cytology

2. A negative HPV test gives greater reassurance than a negative cytology test

Efficacy of HPV-based screening for prevention of invasive cervical cancer: follow up of four European/UK randomised controlled trials comparing HPV screening and cytology-only screening

Italy - NTCC

Netherlands - POBASCAM

Sweden - Swedescreen

England – ARTISTIC

- Detection of invasive cancer was similar for the first 2.5 years but was significantly lower in the HPV screening arm thereafter

- HPV-based screening provided 60-70% greater protection against invasive cancer compared with cytology

Ronco et al Lancet 2014:383:524053

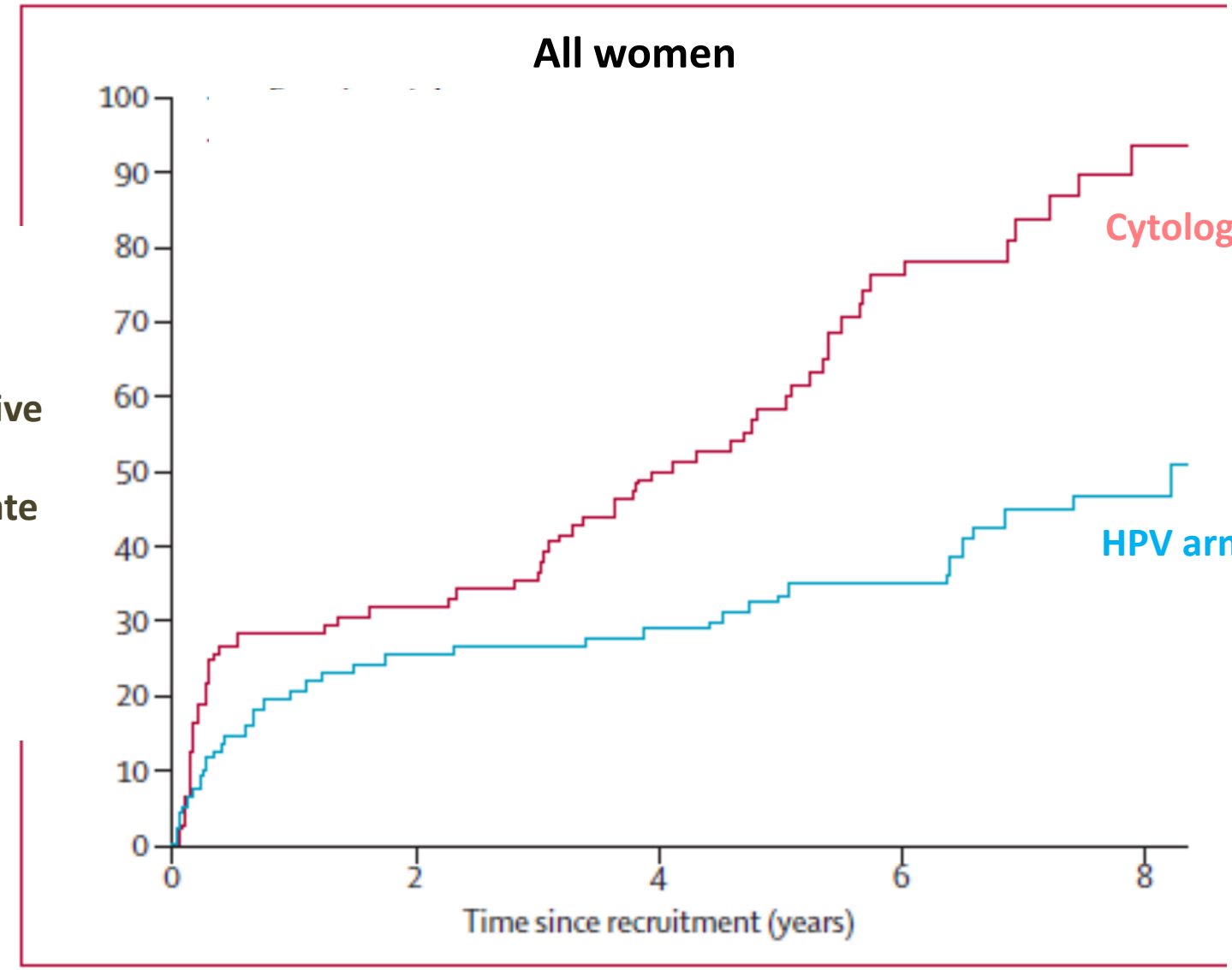
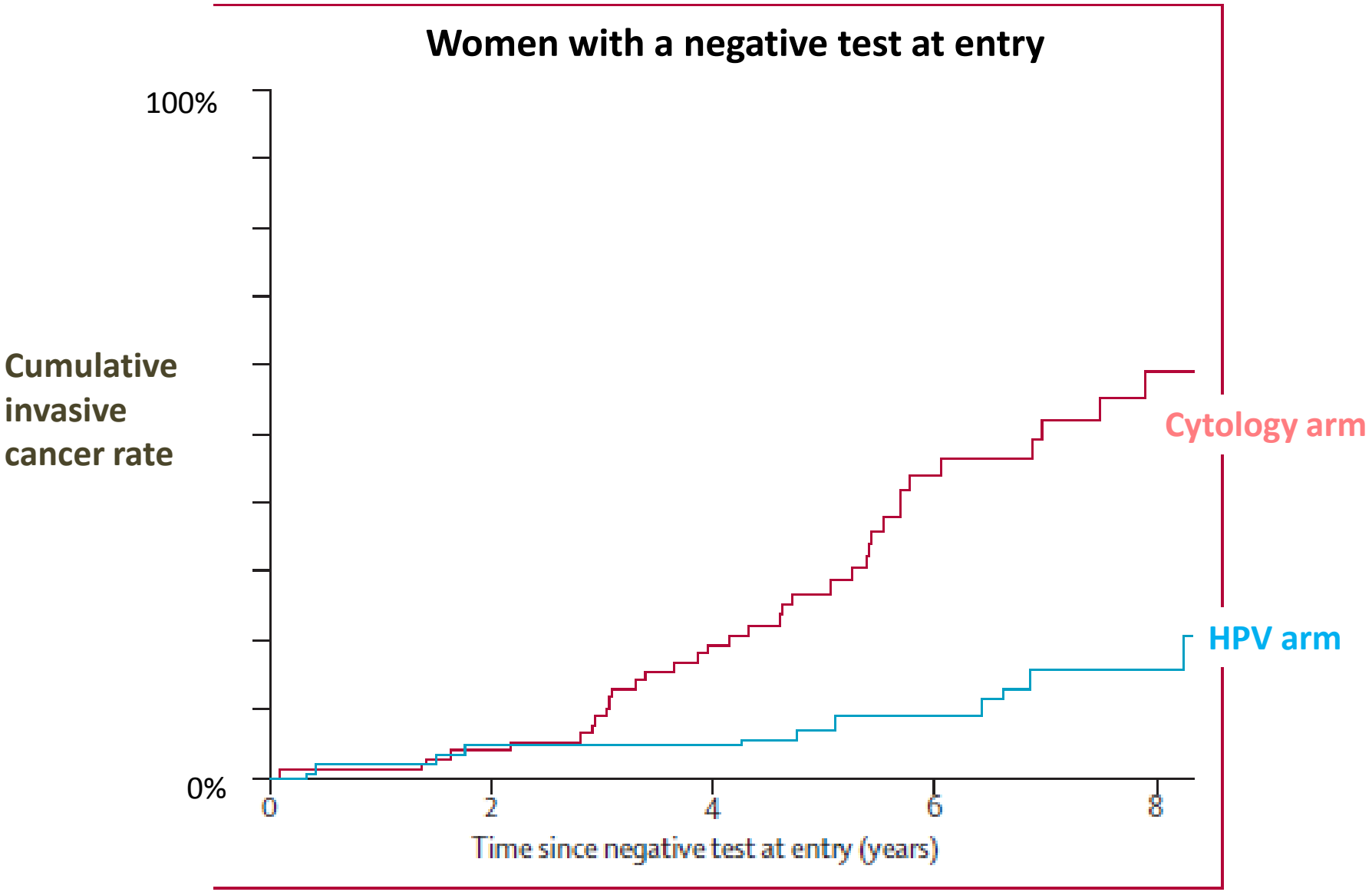


Figure 2: Cumulative detection of invasive cervical carcinoma

Ronco et al Lancet 2014:383:524053



Ronco et al Lancet 2014:383:524053

The ARTISTIC trial: high quality LBC UK

- A randomised trial comparing **cytology *vs.* cytology + HPV screening**

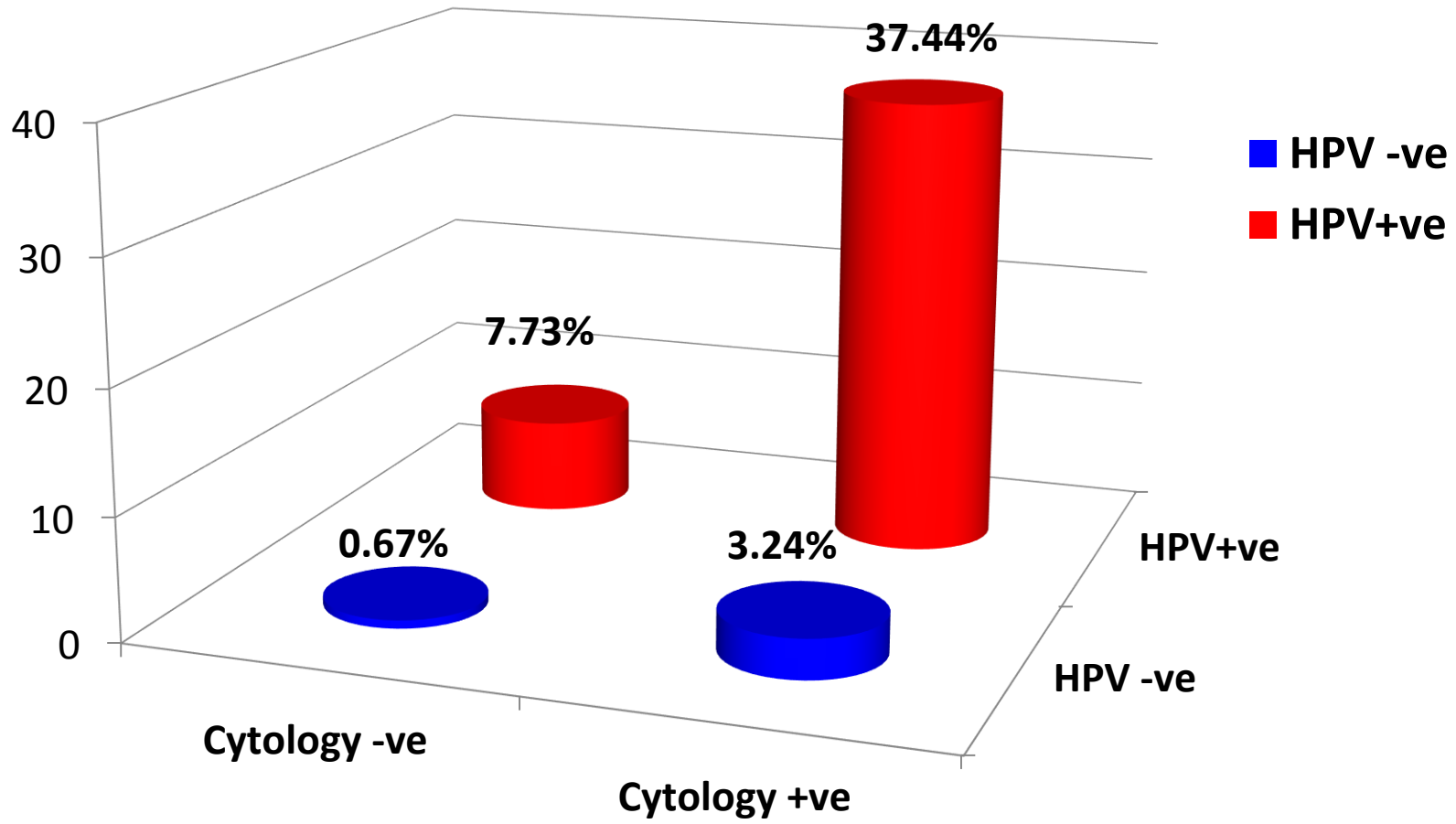
Two initial screening rounds, three years apart with a third round as an extended trial: Primary outcome: CIN 3+

- Performed in the setting of the in England
- Women were undergoing routine cervical screening in the English cervical screening programme in general practices and family planning clinics in the Greater Manchester area
- 24,510 women aged 20-64 years were enrolled between July 2001 and September 2003
- Cytology and an HPV test were performed on an LBC sample
  - mostly ThinPrep, some SurePath in round 2
  - Hybrid Capture 2 was used for the HPV tests
    (13 high-risk subtypes)

Reporting results

- Cytology results were reported for all women
- Women were randomised in a 3:1 ratio to have their HPV result revealed (reported) or concealed.
  - In the HPV-revealed arm women were followed up on the basis of their cytology result + the cytology negative women had their HPV-revealed results acted on if persistently positive
  - In the HPV-concealed arm, women were managed on the basis of their cytology result alone

Cumulative % CIN 2+ outcome @ 6 years by cytology and HPV status at entry



Extending the screening interval

The greater negative predictive value of a negative result with HPV testing compared with LBC Cytology is the reason why we can safely extend the screening interval

ARTISTIC: the cumulative CIN2+ rate after a negative hrHPV test was the same at 6 years as it was after 3 years following a negative LBC Cytology result

3. HPV testing is fully automated and not affected by how common the disease is

- HPV testing is an automated predictable test whereas cytology relies on humans who vary in skill, and whose performance can vary over time.

- The accuracy of HPV testing isn't affected by how many positive samples there are in the screened population whereas cytologists will be less accurate at correctly identifying lesions when very few positive samples are present.

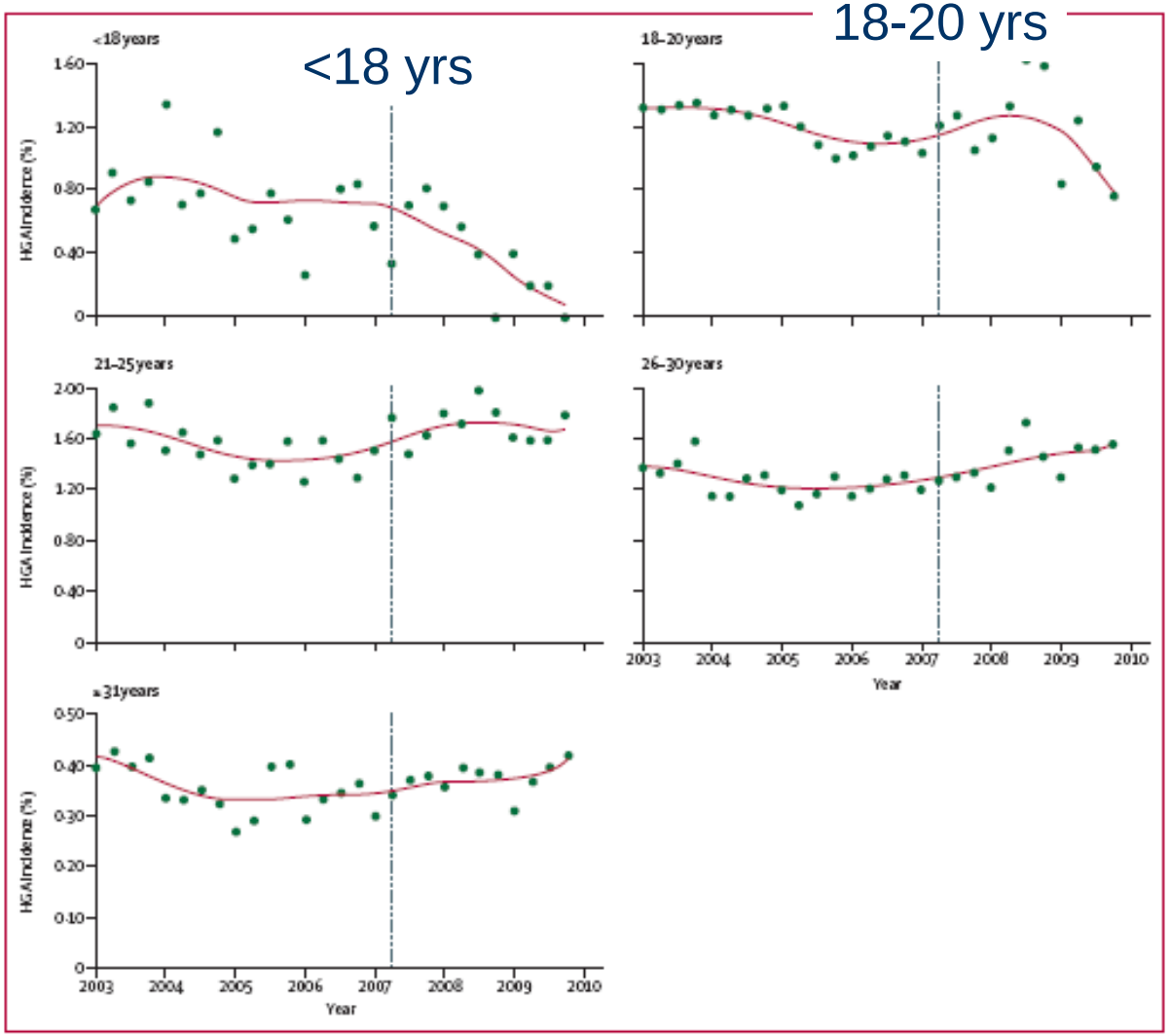
Why the rush?

- When immunisation is widespread and particularly when those immunised with the nonavalent vaccine reach the screening age, the prevalence of disease in the population will fall.
- The problem: cytology will no longer be the good performer that it has been in the past
- If HPV testing is used as the primary screening test followed by cytology only for those women who are hrHPV positive, the frequency of abnormality will again be high enough to allow cervical cytology to be effective at detecting high-grade lesions

Early effect of the HPV vaccination programme on cervical abnormalities in Victoria, Australia: an ecological study

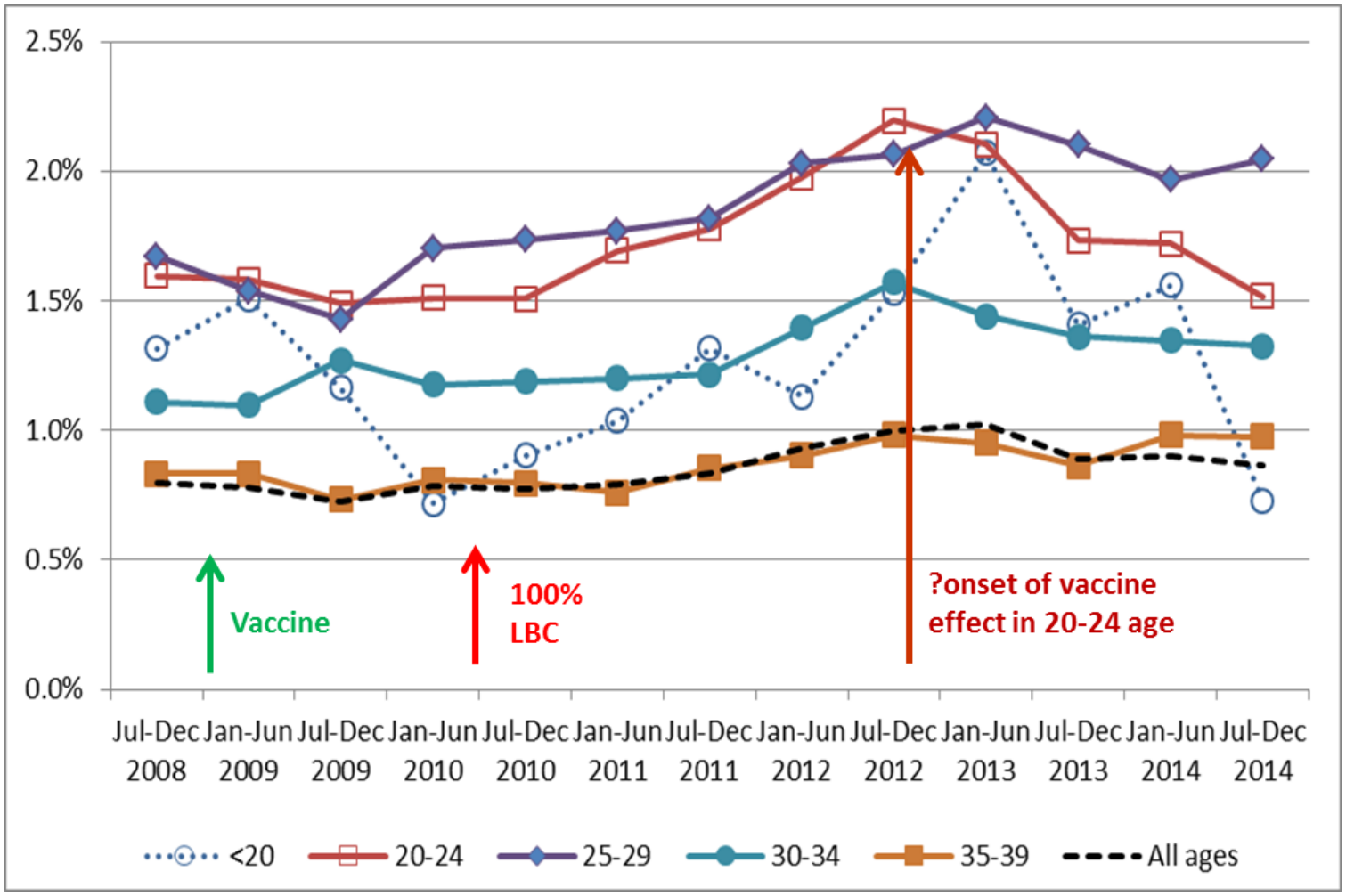
Lancet 2011; 377: 2085–92
Julia M L Brotherton et al

HG Rates against year
2003 – 2010
by age group



Incidence of high-grade cervical abnormalities, by age group

HSIL rates by age: NZ Data 2008-2014



Future cervical cancer prevention strategy 2018

Primary prevention:

HPV Immunisation

Secondary Prevention:

hrHPV testing followed by cervical cytology if HPV positive

HPV immunisation currently

- Offered free to 12-13 year girls from 2009
- Mainly a school-based programme. Also GP's, local health centres and some Family Planning clinics. Primary care can follow up girls who were not vaccinated at school
  - Currently free for girls and young women up to their 20th birthday.
- protects against hrHPV types 16 and 18 (70% of cervical cancers) and low-risk types 6 and 11 (90% of genital warts)
- HPV immunisation 2-dose coverage currently 68% for all ethnicities – better for Pacific, Asian and Māori (78%) women
- Immunised or not, women still need to participate in regular cervical screening. The vaccine does not protect against all hrHPV types.

Immunisation against HPV: the future

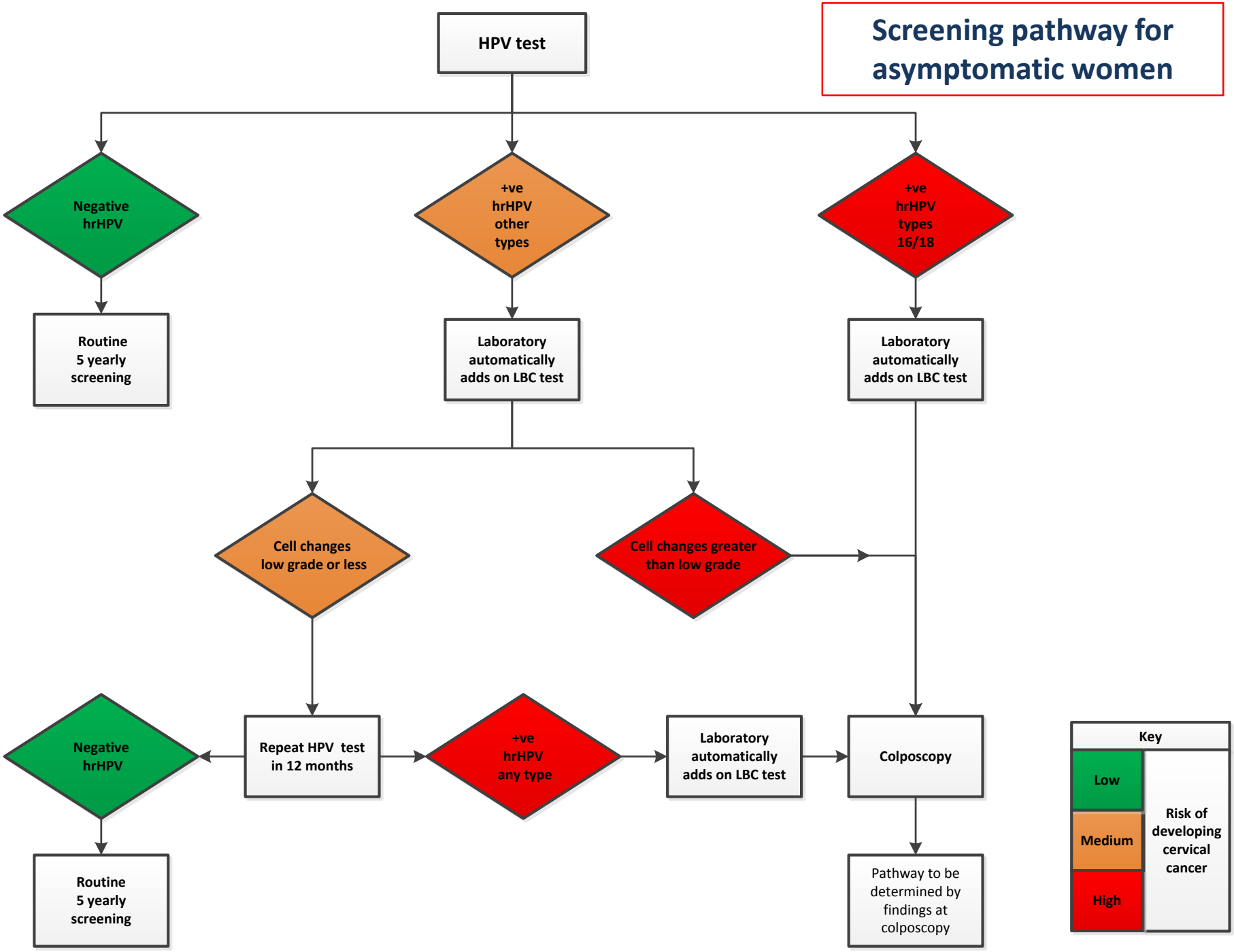
From 2017 immunisation against HPV will be funded for:

- Girls and boys
- school based programme at 12-13 years of age with free vaccination up to the age of 26 years
- Nonavalent (Gardasil-9) will be used; includes 7 high-risk types plus 6 and 11
- Two doses at least 6-months apart will assist with coverage

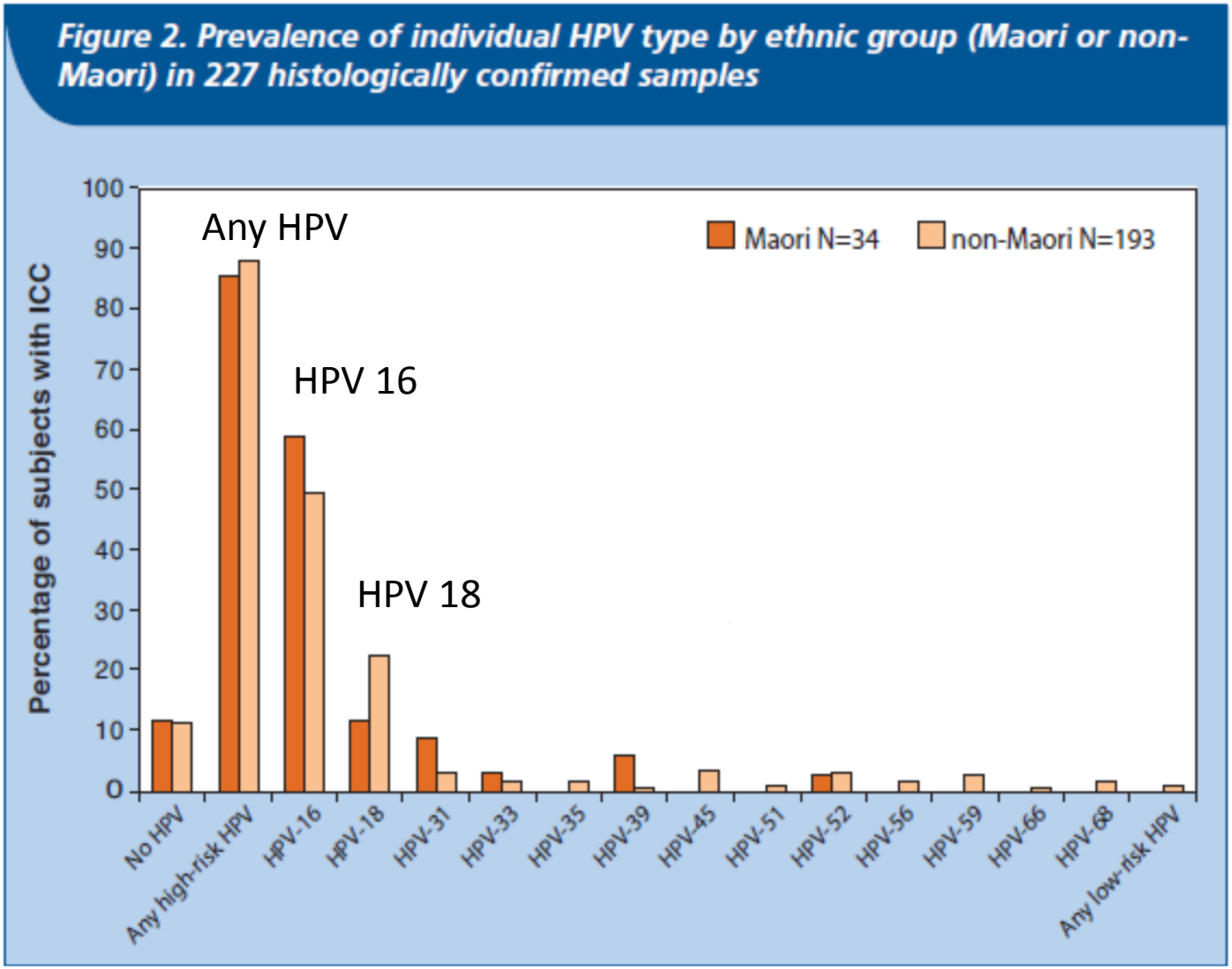
Primary HPV Screening: NZ 2018

- High risk HPV testing (hrHPV) with partial genotyping and cytology triage every 5 years
  - a *hrHPV test:* reported as "Detected" if at least one of 14 different subtypes of hrHPV are present
  - *partial genotyping :* identifies whether hrHPV subtypes 16 or 18 are present. The other subtypes are collectively reported as "other".
  - *Cytology triage* means using cytology to determine the management of some women who are hrHPV positive.

Screening pathway for asymptomatic women



Why partial genotyping?



Sykes et al BMC Infectious diseases 2014 14:374

ARTISTIC trial data
HPV genotyping

- Cumulative rate of CIN2+ for women who at baseline were:

  HPV 16 +ve was 43.6%

  Any hrHPV +ve was 20.1%

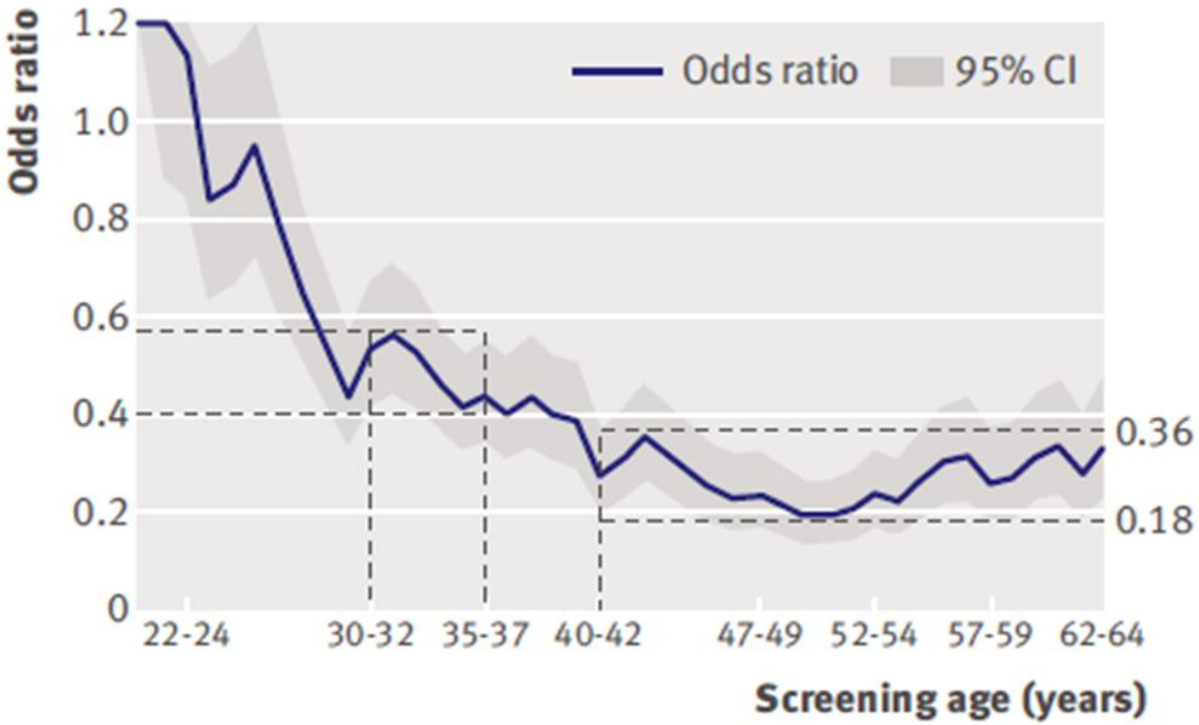
Why cytology triage?

- many women who are “hrHPV other” positive will have a productive viral infection that will clear naturally
- cytology is more specific than HPV testing for identifying women with cervical lesions
  - Women with high-grade cytology will go to colposcopy
  - Those with normal or low-grade cytology will have a repeat HPV test at 12 months to see if the HPV infection has persisted.

Potential for self sampling for hrHPV screening

- Cytology needs to be taken from the transformation zone so that abnormal cells are sampled: hrHPV testing doesn't require such a specific sample – a high vaginal swab can be used
- Opens up the possibility for self-sampling, particularly as a way to increase screening coverage for women who aren't currently being screened
- If the hrHPV test is positive, the woman will need to have a speculum examination for a clinician-taken sample for cytology
- Need to ensure: a self-sample is as good or nearly as good as a clinician-taken sample, accurate sample identification can be assured, that increased screening coverage will result
- NZ research projects are about to commence to investigate the acceptability of this option for NZ women

Commencing screening at age 25



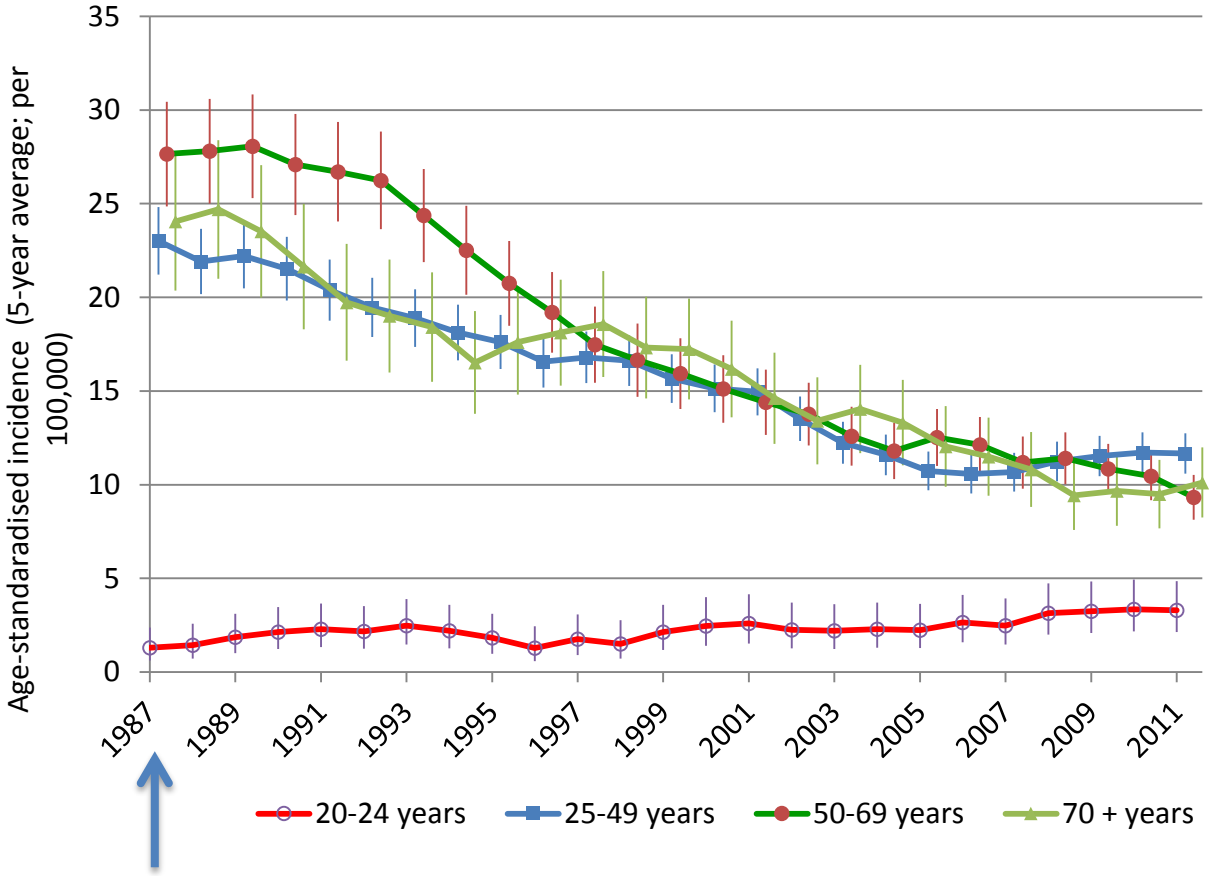
Sasieni BMJ 2009;339:b2968

Women 20-24 years

- High incidence of HPV and CIN but
  low risk of cancer.
- Spontaneous regression frequent
- Potential harm of intervention
- Becoming vaccinated

NZ cervical cancer incidence by age

Five-year average cervical cancer incidence*, by age



% change in cervical cancer incidence in 2009-2013 compared to pre-NCSP (1985-1989):

25-49 yrs: decr 49%

50-69 yrs: decr 66%

70+ yrs: decr 58%

20-24 yrs: increase

Average for five-year period prior to NCSP (1985-1989)

**(age-standardised, per 100,000)*

Key points and questions

- Woman still need to have regular samples taken but once every 5 years (if negative) rather than 3- yearly
- cytology will be performed as a second test for all hrHPV positive women
- all women who are referred for colposcopy will have their cytology reported
- same screening pathway for unvaccinated and vaccinated women

- The recommended age to commence screening will rise to 25 years
- Self-sampling will NOT be introduced in 2018

The NCSP Register will need significant change

What will reporting be like with HPV primary screening for anatomic pathologists?

- less abnormal cytology, gradually (immunisation)
- initial increase in histology (more sensitive screening test)
- lesions will be detected earlier so gradually smaller and more difficult to detect
- histo-cyto correlations increasingly important
- Specialise in cervical pathology: cyto and histo

Invasive cancer: Rounds 1 and 2 of ARTISTIC

There were 12 invasive cancers in the CIN3+ group

- Round 1 = 9 cases
  - 8 detected with CIN2+ cytology and all were HPV +ve
  - 1 (adenocarcinoma) had “borderline” cytology and was HPV -ve
- Round 2 = 3 cases
  - One had negative cytology and was HPV +ve in both rounds
  - One (adenocarcinoma) had negative cytology in both rounds, was HPV -ve in round 1 and HPV +ve in Round 2
  - One had borderline cytology in both rounds, was HPV negative in round one and didn’t have a round 2 HPV result