New screening strategies for cervical cancer prevention

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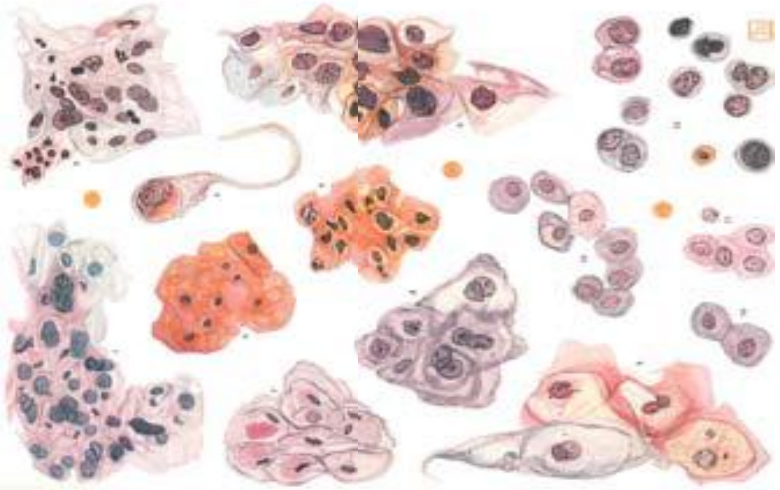
Cervical Cytology Screening

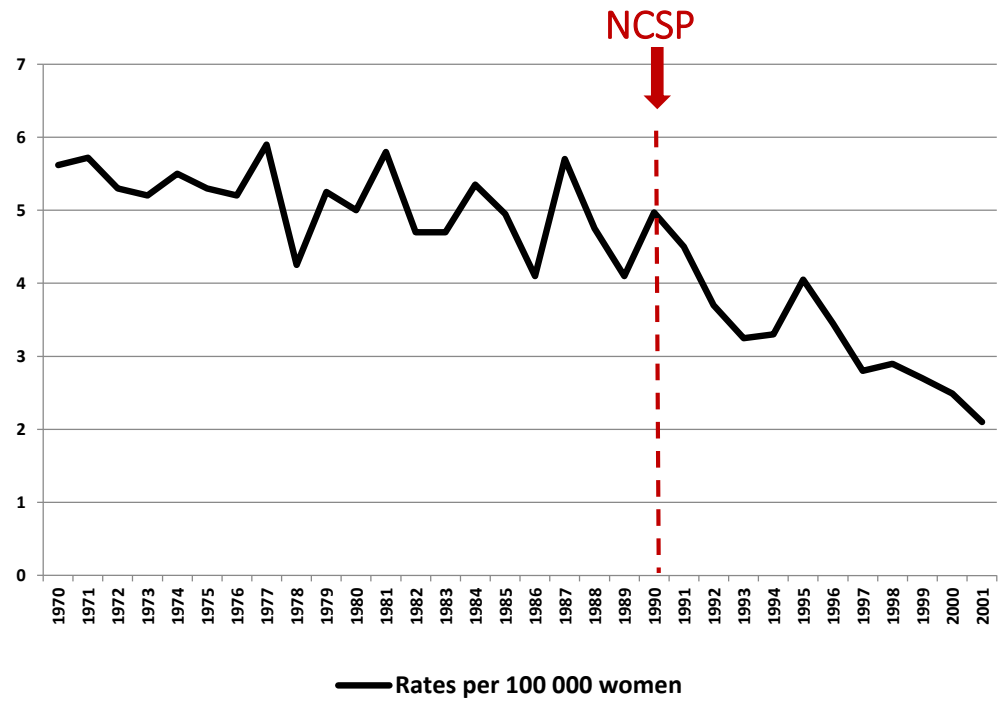
- Has served us extremely well!
- George Papanicoloau: the father of cervical cytology
- Opportunistic screening introduced in the 1950s
- Organised screening was pioneered in Scandinavia: particularly Finland
- NZ: calls for a national cervical screening programme in 1980's but little action until The Cartwright Inquiry (1987 – 1988)
- 1990 the NZ NSCP begins
- Huge push to enrol women: highly successful



Reduction in rates of invasive cancer in NZ

Cervical Cancer Incidence in NZ 1950 - 2002

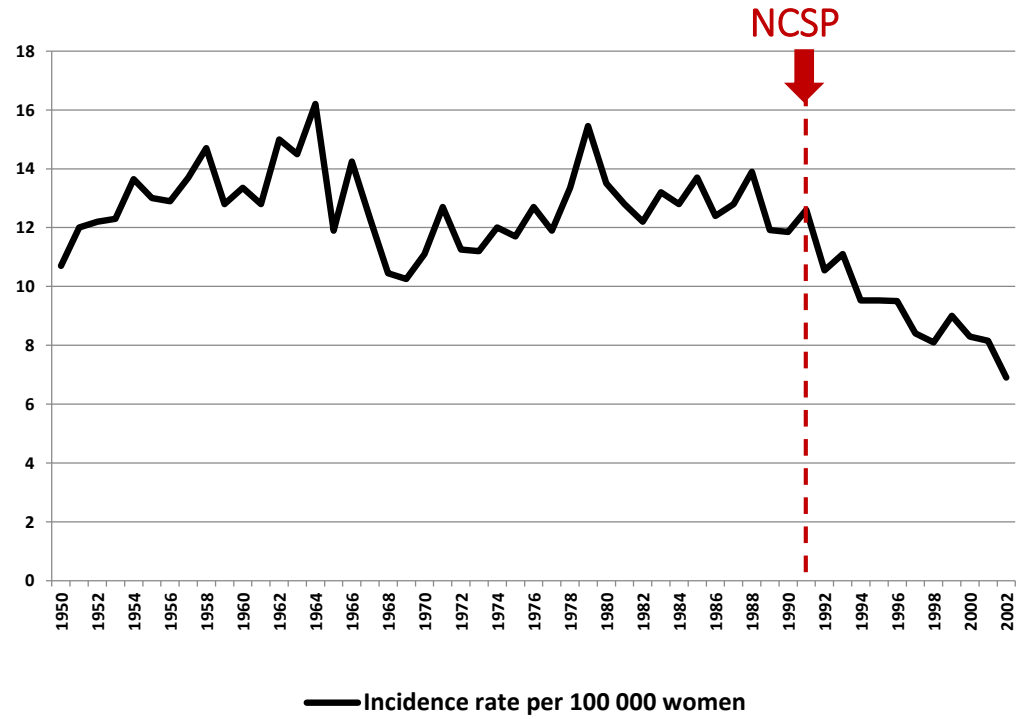
Age-standardised rate (Segi) per 100,000 women



Cervical cancer 1990-2001
Incidence fell by 40%

Cervical Cancer Mortality in NZ 1970 - 2001

Age-standardised rate (Segi) per 100,000 women



Cervical cancer 1990-2001
Mortality fell by 60%

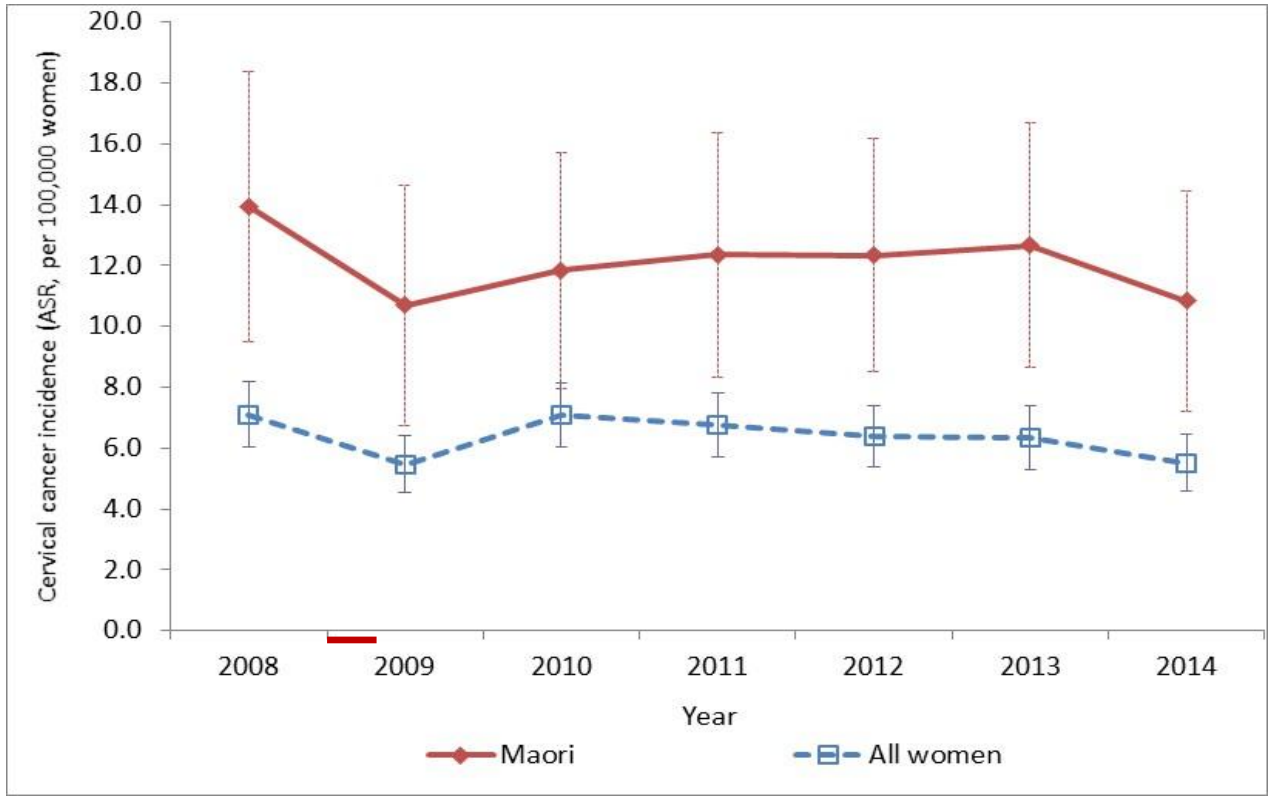
Why has cervical screening worked despite a significant false negative rate?

- long pre-invasive phase of preclinical disease
- cervix is accessible
- simple test can detect pre-invasive disease with reasonable sensitivity and good specificity
- the screening test is cheap and can be carried out in primary care
- effective treatment is available for precursor lesions that has a significant impact on incidence of invasive disease and mortality

So where are we now?

NCSP Annual Report 2014: Incidence

Age-standardised cervical cancer incidence rates, 2008 to 2014, by ethnicity



Vertical bars represent 95% confidence intervals

Incidence and Mortality by Cancer type for NZ women 2012

	Incidence	Mortality
Breast	85.0	17.1
Colorectal	33.5	13.7
Melanoma	33.1	2.8
Lung	23.2	19.2
Uterine Body	13.9	2.4
NH Lymphoma	9.6	2.9
Ovary	8.0	5.1
Leukaemia	7.3	2.7
Thyroid	7.2	0.3
Kidney	5.4	1.4
Pancreas	5.4	5.1
Uterine Cx	5.3 (12th)	1.4 (16th)

Ref: GLOBOCAN

New advances have all arrived at the same time

- HPV vaccines produced and have proved to be highly successful
- Molecular science has exploded our knowledge about how HPV causes disease
- HPV testing to identify the presence of HPV DNA has proven to be more sensitive than cytology at detecting high-grade lesions
- Advances in IT systems now allow
  - large scale clinical trials to investigate different screening strategies
  - complex modelling to study and compare different potential strategies.

Why will it work?

Over 99% of cervical cancer cases are caused by HPV viruses.

Preventing cervical cancer

Currently:

Screening with cervical cytology

Immunisation programme commenced in 2008

HPV testing introduced for use after cytology in 2009 to assist with patient management

The future is:

Primary prevention is by immunisation as this prevents lesions from developing.

Secondary prevention is by screening to detecting pre-invasive high-grade lesions that have developed so they can be treated before they become invasive.

The new screening strategy will be:

HPV primary screening with partial genotyping and cytology triage.

Primary prevention is by immunisation

Gardasil 9 (9-valent vaccine): introduced 1 January 2017

Funded for both males and females aged 9-26 years (inclusive)

- 9-14 years: two-dose schedule
- 15-26 years: three-dose schedule

Potential to prevent:

Gardasil 4: 70% of invasive cervical cancers

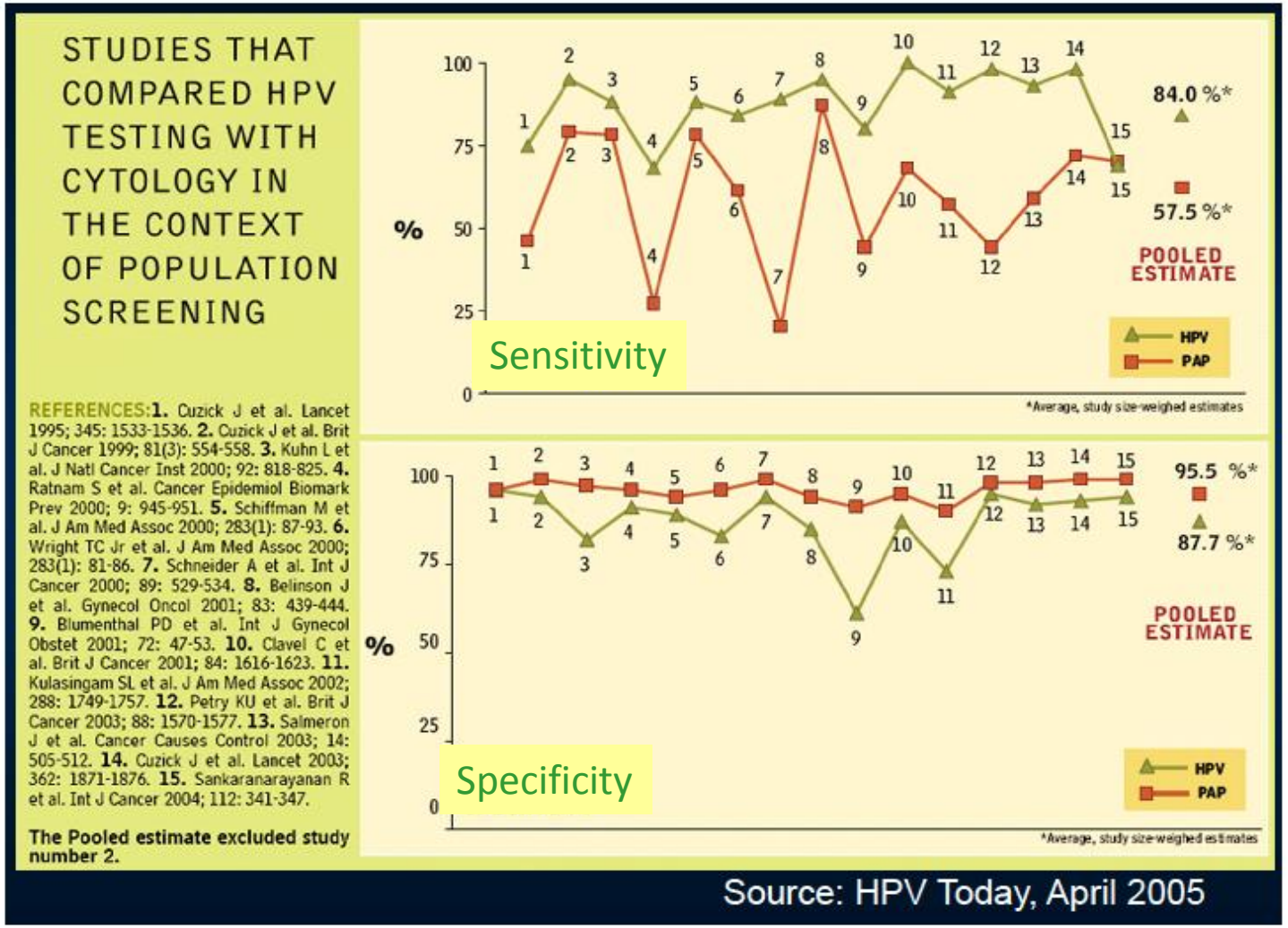
Gardasil 9: 90% of invasive cervical cancers

NZ Immunisation rates @ 31 Dec 2016: 2002 birth cohort (girls aged 15 years)

Gardasil 4 three-dose vaccination coverage

Maori: 74% Pacific: 70% Asian: 74% Others: 60% Total: 66%

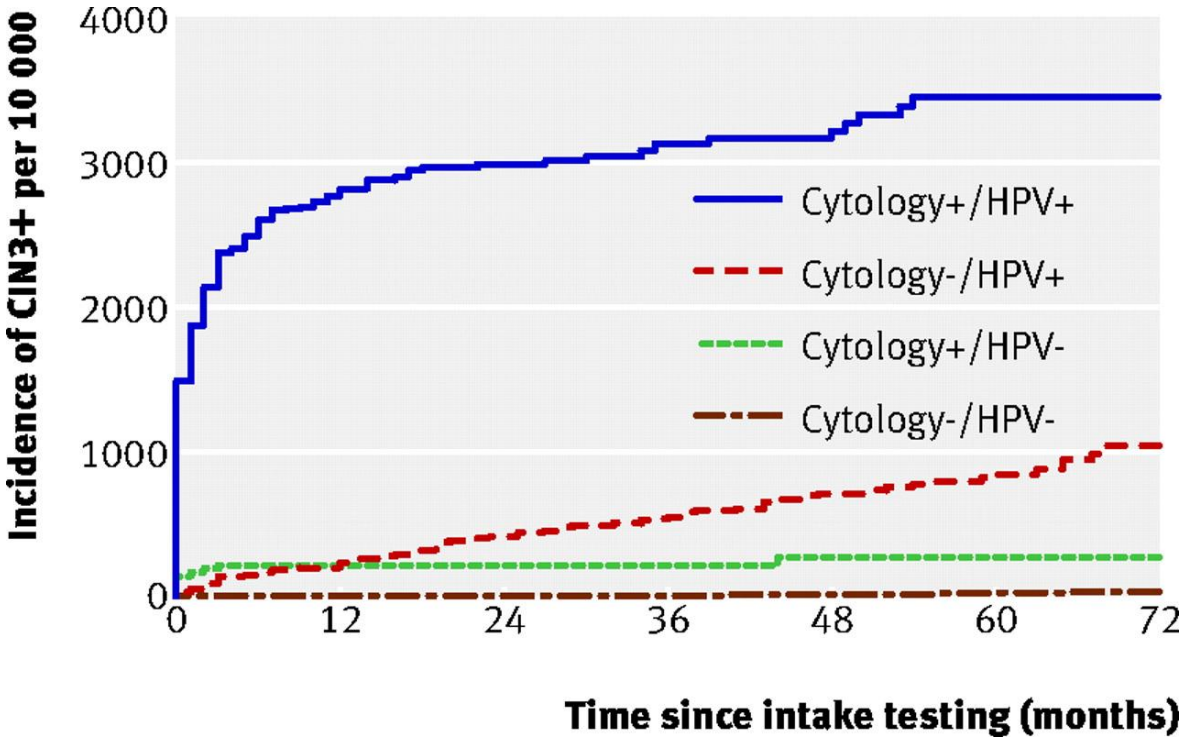
HPV testing is a more sensitive test than cytology

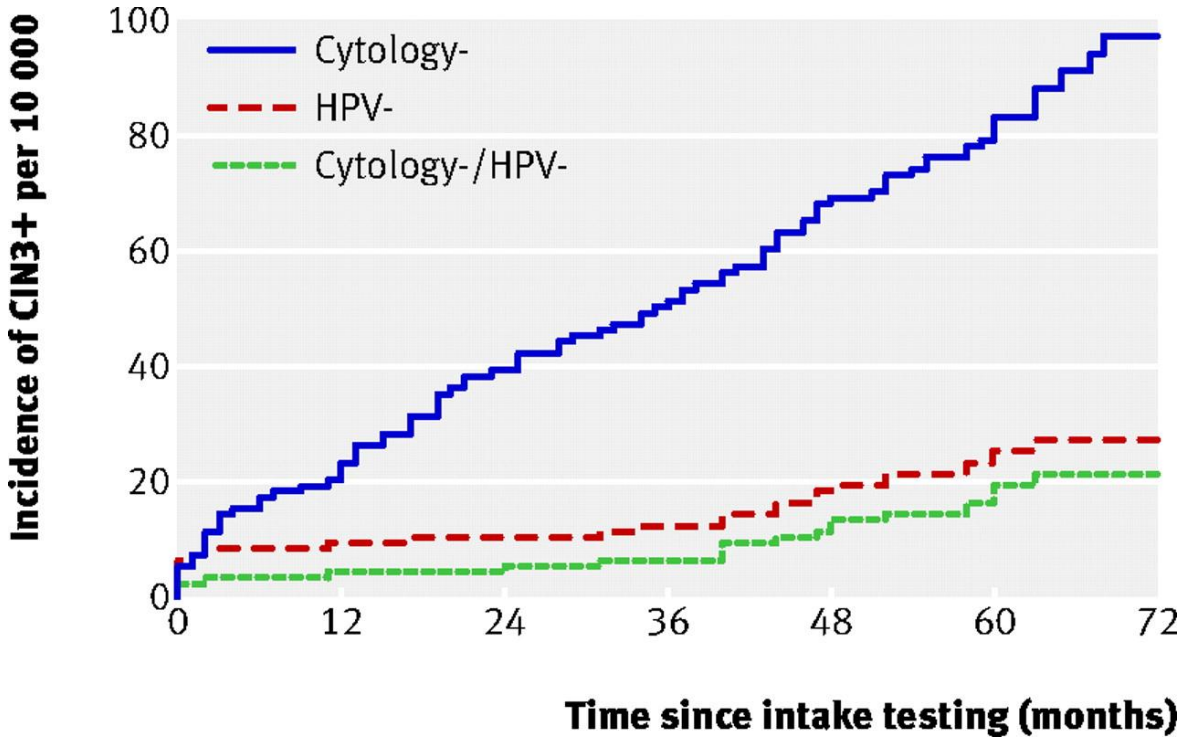


HPV Testing

Cytology (conventional)

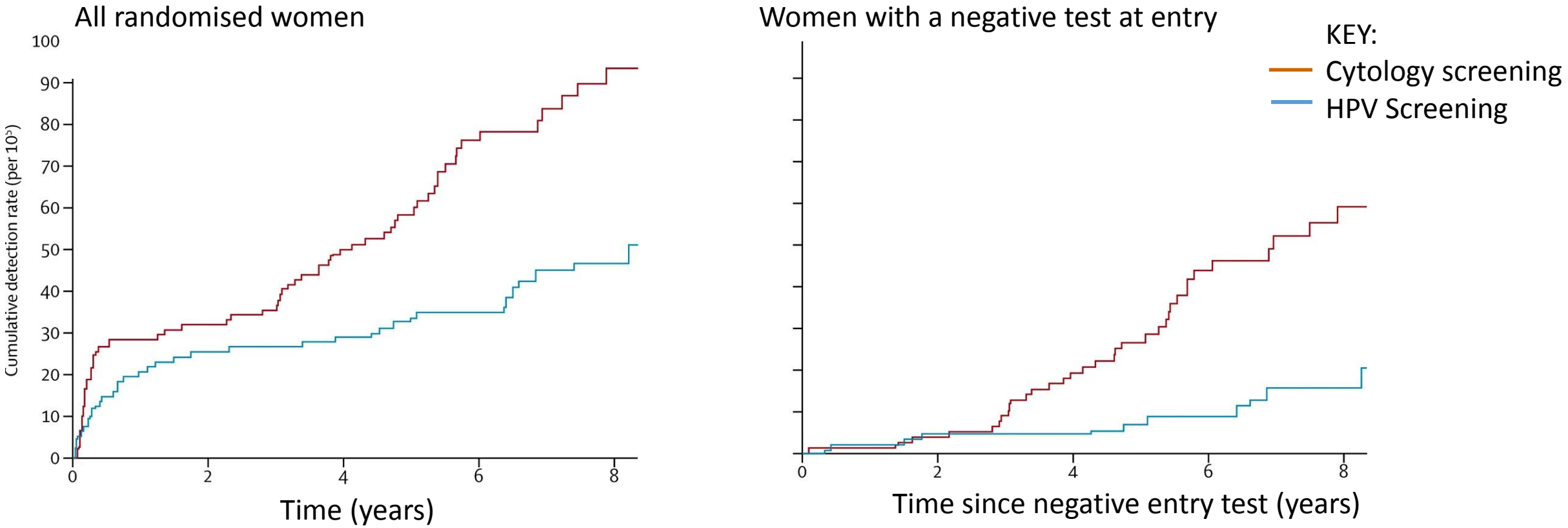
HPV Test screening results in lower CIN3+ rates compared with cytology screening





Long term predictive values of cytology and human papillomavirus testing in cervical cancer screening; joint European cohort study
Dillner J BMJ 2008;377:a1754

HPV test screening results in lower invasive cancer rates compared with cytology screening



Efficacy of HPV-based screening for prevention of invasive cervical cancer: follow-up of four randomised controlled trials
Ronco G et al Lancet 2014;383:524-32

How does HPV testing using LBC perform as a primary screening test?

The ARTISTIC Trial (UK): A Randomised Trial In Screening to Improve Cytology

- It used high quality LBC: the study showed that it is possible to achieve high levels of sensitivity for detecting high-grade lesions using LBC cytology (around 90%)
- The UK has a very high standard of cytology reporting
- The trial was conducted rigorously within the setting of a screening programme

The LBC type was mainly ThinPrep (some SurePath towards the end of the study). HPV Test technology was Hybrid Capture 2

Design

- The trial was run in the setting of the cervical screening programme in England
- Women were undergoing routine cervical screening from 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
- A randomised trial comparing

  cytology *vs.* cytology + HPV screening

- Extended trial: three screening rounds, each three years apart (6 years)

ARTISTIC: Results

At baseline: All women had both cytology and hrHPV testing

16% of women overall were hrHPV+ve: Age 20-24 years = 40% group

over 50 years = 7%

13% had abnormal cytology (2%= CIN2+)

9.1% of women (revealed arm) were cytology-negative, hrHPV-positive

All had their cytology results reported, whereas some had their HPV result reported (revealed) and others had their HPV results concealed.

After 6 years:

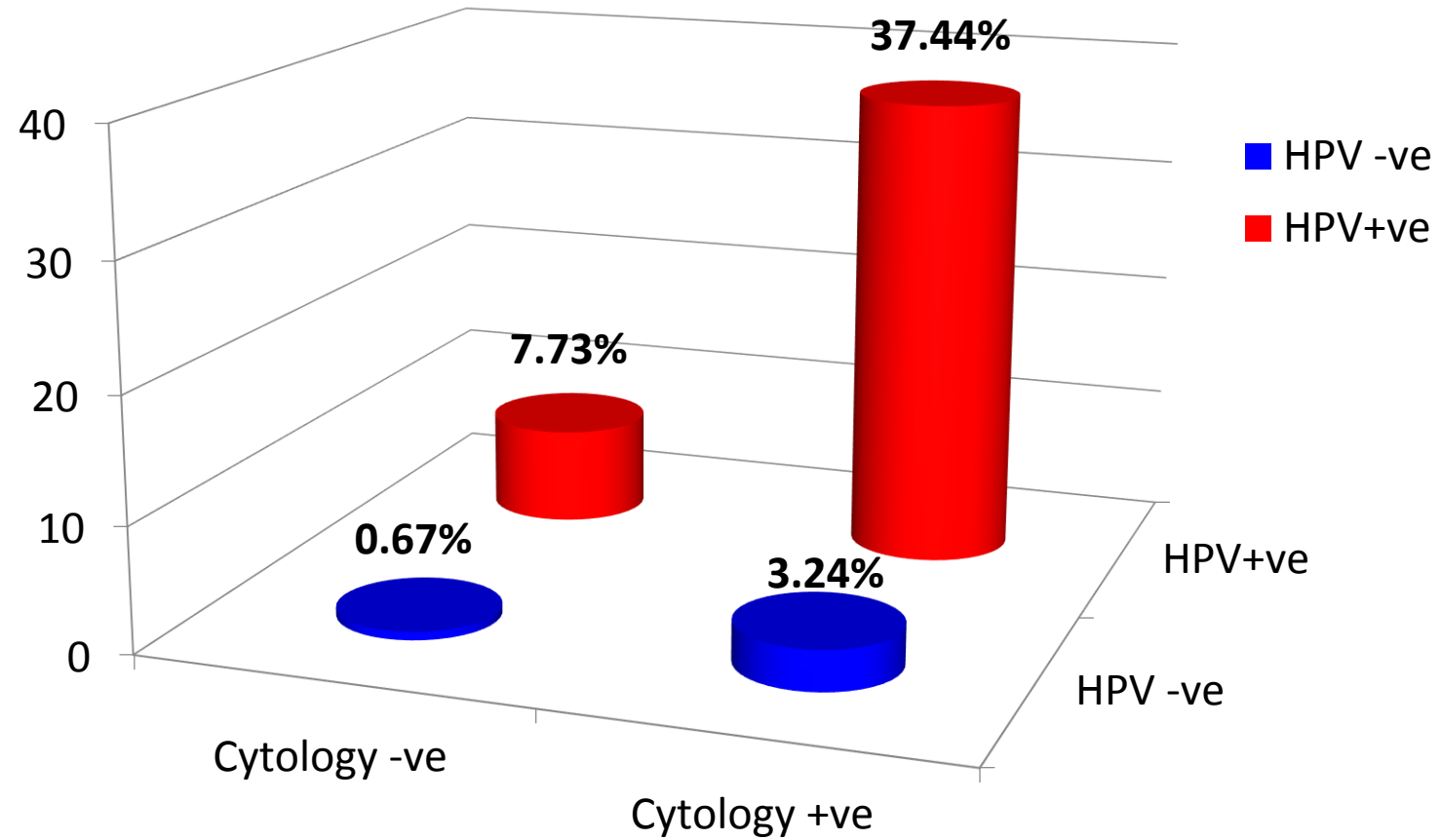
Cumulative CIN2+ rates: after negative cytology = 1.41%

after negative HPV result = 0.87%

Women who were HPV negative at baseline had similar protection from CIN2+ after 6 years as women who were cytology negative at baseline after 3 years

ARTISTIC: Results after 6 years

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



ARTISTIC trial: Conclusions

- A negative HPV test provides a similar degree of protection from CIN2+ over 6 years as a negative LBC does over 3 years, indicating that the screening interval could be safely extended
- Cytology and HPV testing combined would not add significantly to HPV as a stand alone screen with cytology triage for HPV positive women

References:

1. HPV testing in combination with liquid-based cytology in primary cervical screening (ARTISTIC): a randomised controlled trial **Kitchener HC** et al **Lancet Oncology 2009** Jul;10(7):672-82
2. A comparison of HPV DNA testing and liquid based cytology over three rounds of primary cervical screening: extended follow up in the ARTISTIC trial. **Kitchener HC** et al **Eur J Cancer 2011** Apr;47(6):864-71

NCSP: Changing the Primary Laboratory test
Public consultation papers released October 2015

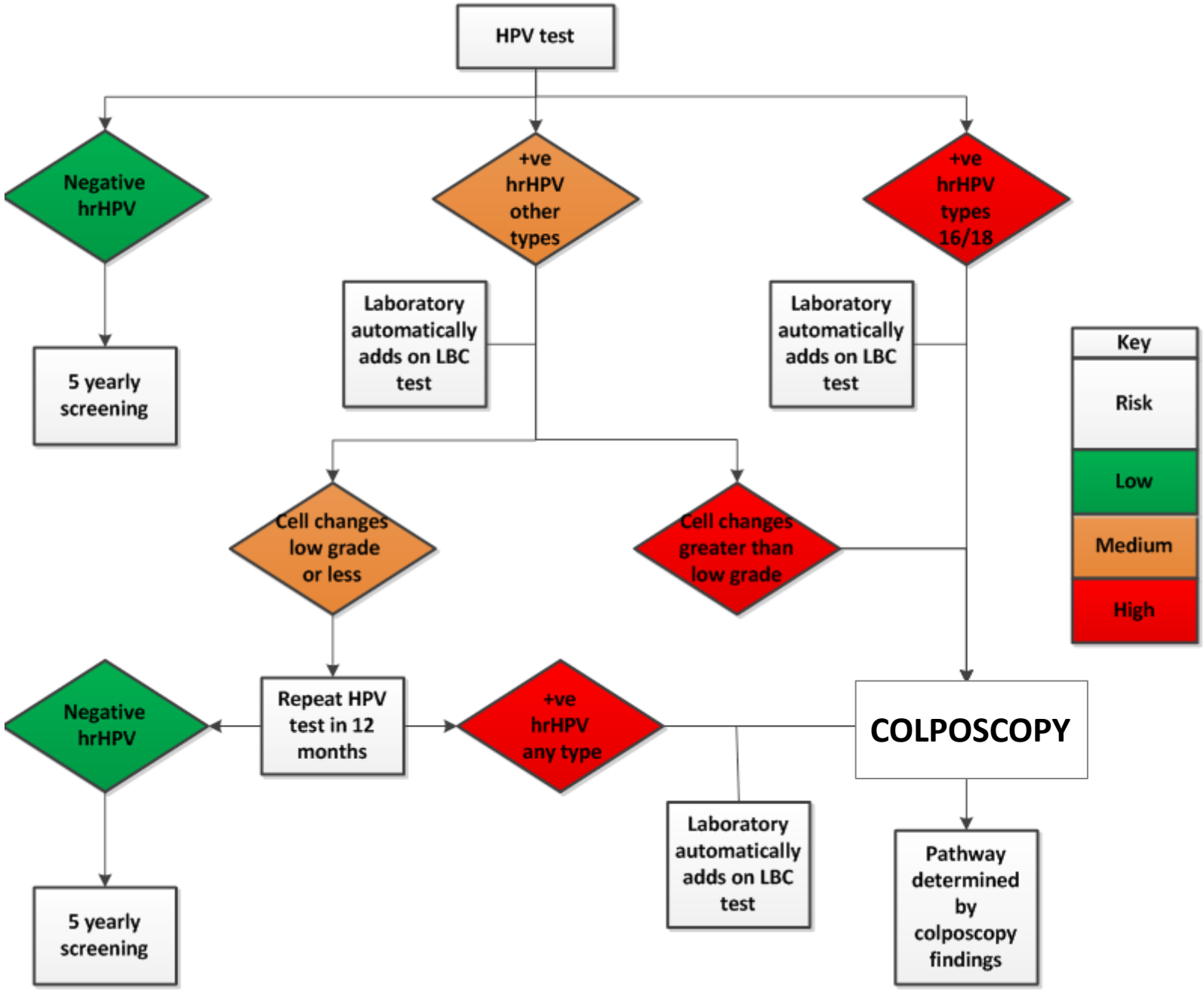
Effectiveness Modelling and Economic Evaluation of Primary HPV Screening for Cervical Cancer Prevention in New Zealand

Lew JB et al Plos One doi:10.1371/journal.pone.0151619 May 17 2016

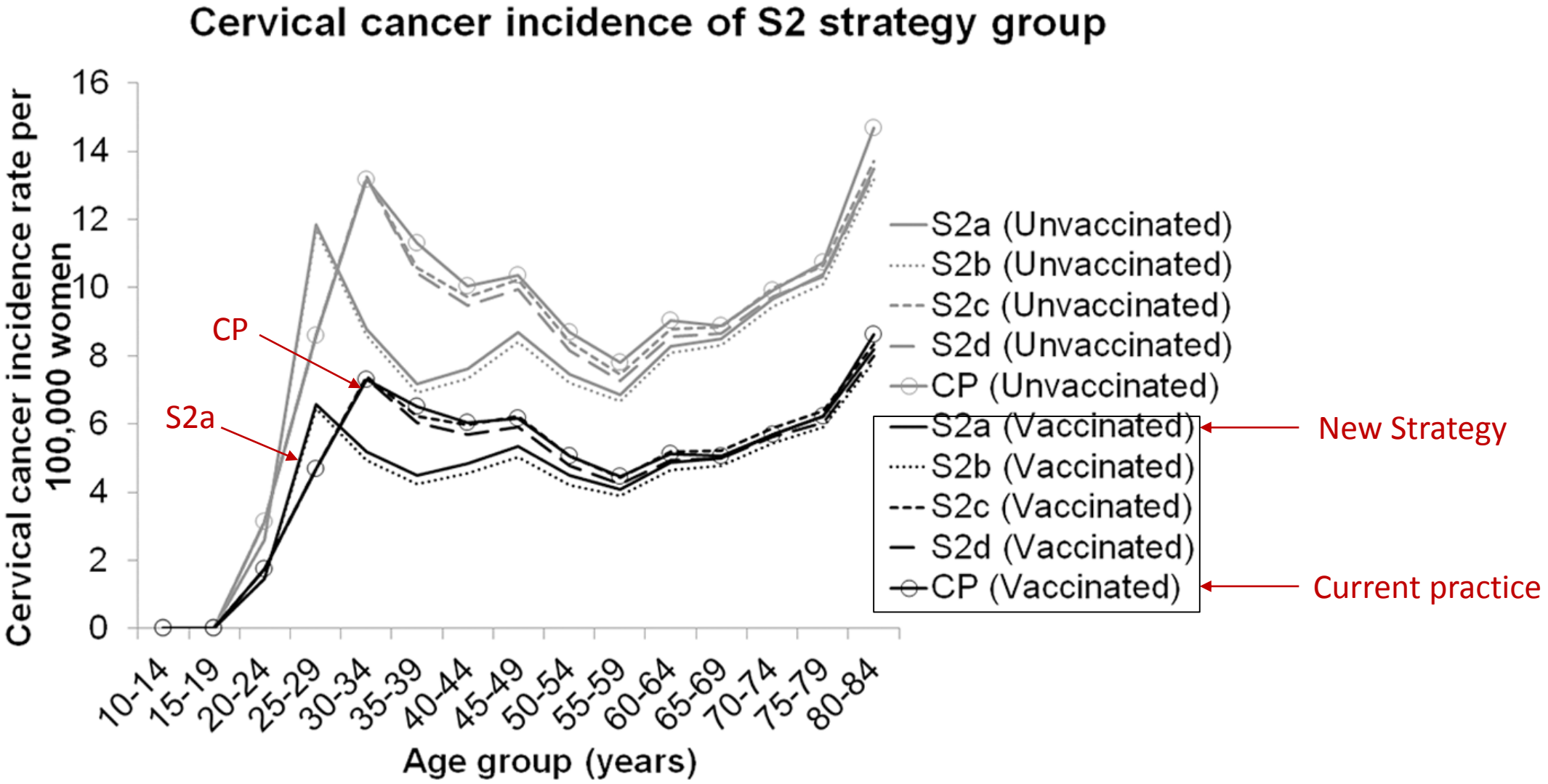
Conclusion: Recommended screening strategy for New Zealand was

HPV primary screening with partial genotyping and cytology triage

HPV primary screening in New Zealand: for asymptomatic women



Predicted outcomes for the impact on cervical cancer incidence in New Zealand



Predicted reductions in cervical cancer rates (Vaccinated scenario)

Incidence reduction:11.7%

Mortality reduction: 11.9%

If 160 new cases annually: 12% reduction prevents 19 cases

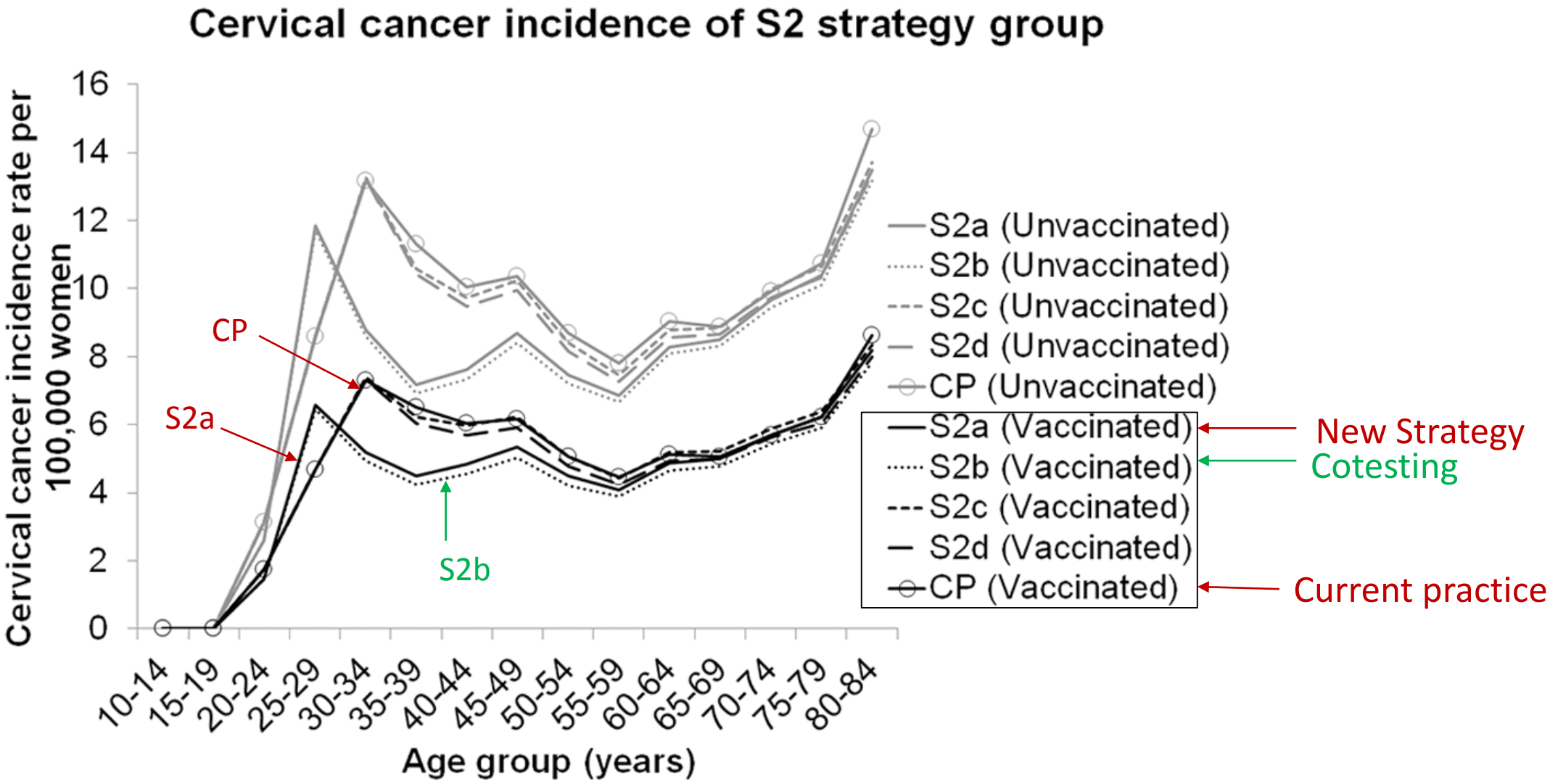
If 60 deaths annually: 12% reduction prevents 7 deaths

- Vaccination will reduce the cancer risk for everyone who is immunised and also considerably reduces the risk for those who are not immunised because of herd immunity
- The risk reductions associated with changing the screening strategy will only occur for women who have screening tests, although there is likely to be some added protection for women who are underscreened.

No test is perfect: Why not use both HPV testing and cytology (cotesting)?

- both cytology and HPV testing will miss some women with high-grade lesions: using both cytology and HPV testing as a co-test maximises early detection
- But:
  - most of the benefit of a cotest is achieved with the HPV test
  - it is very expensive to use two screening tests
  - cotesting results in highly complex management algorithms because of the high number of possible outcomes of testing
  - a lot more women would be referred for colposcopy, and more treatments would occur.

Predicted outcomes for cotesting with partial genotyping (S2b)



Cotesting women who are at higher risk of having invasive cancer makes sense

Selective cotesting will be used for women who:

- have symptoms suspicious of invasive cancer
- have a positive hrHPV screening test (any HPV subtype)
- have been treated for a high-grade lesion (test of cure)
- are at greater clinical risk (e.g. immune-deficient women)

This is investigation of increased individual risk, not population-based screening of asymptomatic women

Type distribution of human papillomavirus among adult women diagnosed with invasive cervical cancer (stage 1b or higher) in New Zealand

Peter Sykes, Kusuma Gopala, Ai Ling Tan, Diane Kenwright, Simone Petrich, Arico Molijn, and Jing Chen

BMC Infectious Diseases 2014,14:374

HPV genotyping was performed on cervical tissue specimens for 227 cases of cervical cancer diagnosed in 2004 - 2010 from five NZ hospitals.

HPV was detected in 201 cases (88.5%) with multiple infections present in 11 cases (5.5%).

HPV Subtype	No. of cases
HPV-16	116
HPV-18	47
HPV-31	9
HPV-45	7
HPV-52	7
HPV-59	5
HPV-33	4
HPV-35	3
HPV-39	3
HPV-51	2
HPV-56	3
HPV-66	1
HPV-68	3
Unidentifiable subtype (technical reasons)	2
Low-risk HPV types (HPV-11,HPV-70)	2 (1)

Red highlighted HPV subtypes are those included in Gardasil-9

i.e. 191/212 infections could have been prevented by Gardasil-9

HPV Testing covers the red HPV types as well as the green types