NCPTS

Using HPV Testing for primary screening for cervical cancer prevention

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August/September 2017

Preventing cervical cancer

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.

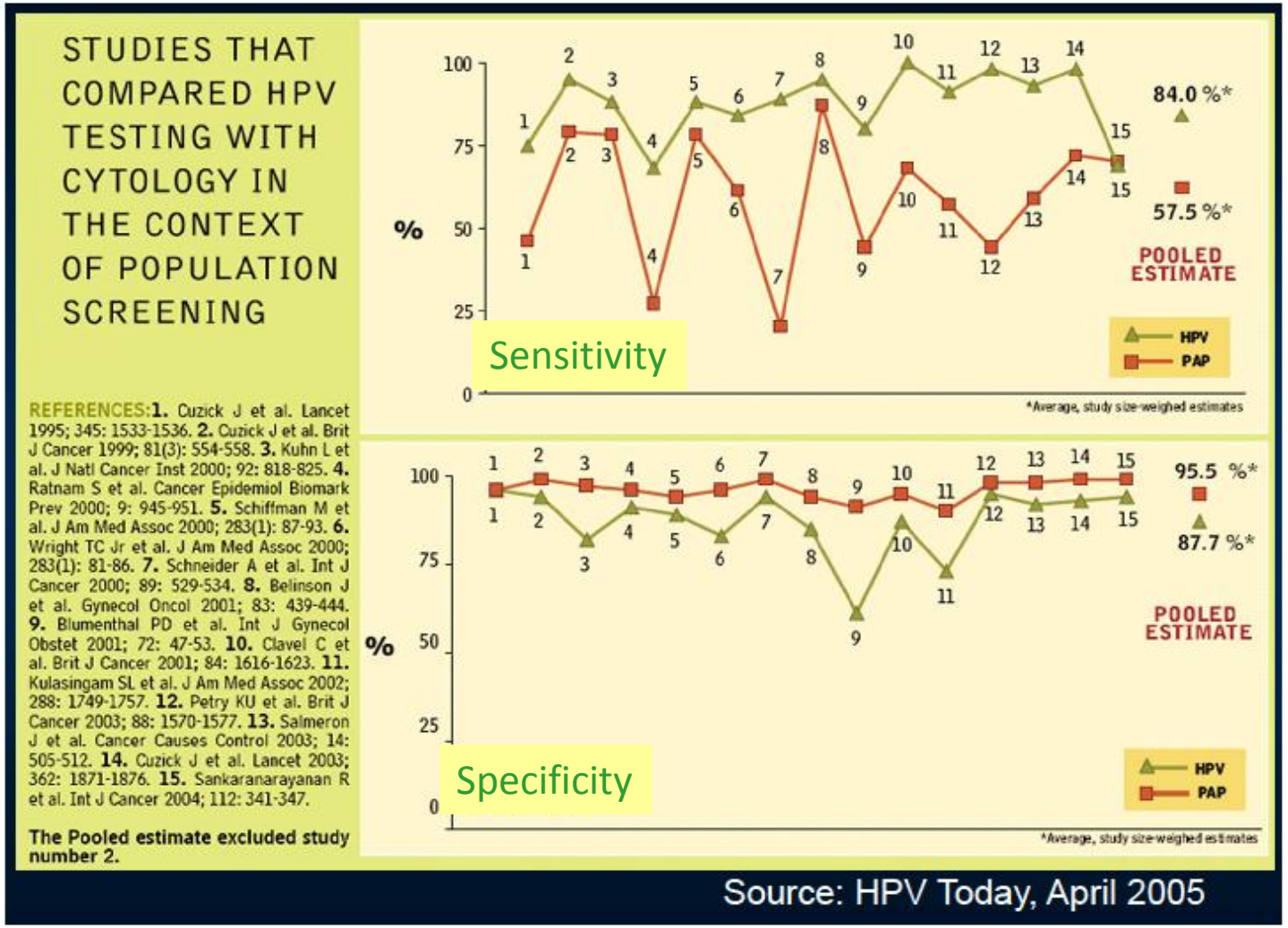
Topics

1. The path to introducing HPV testing for primary screening

2. Using HPV testing for primary screening: The ARTISTIC trial

3. Introducing HPV primary screening in New Zealand

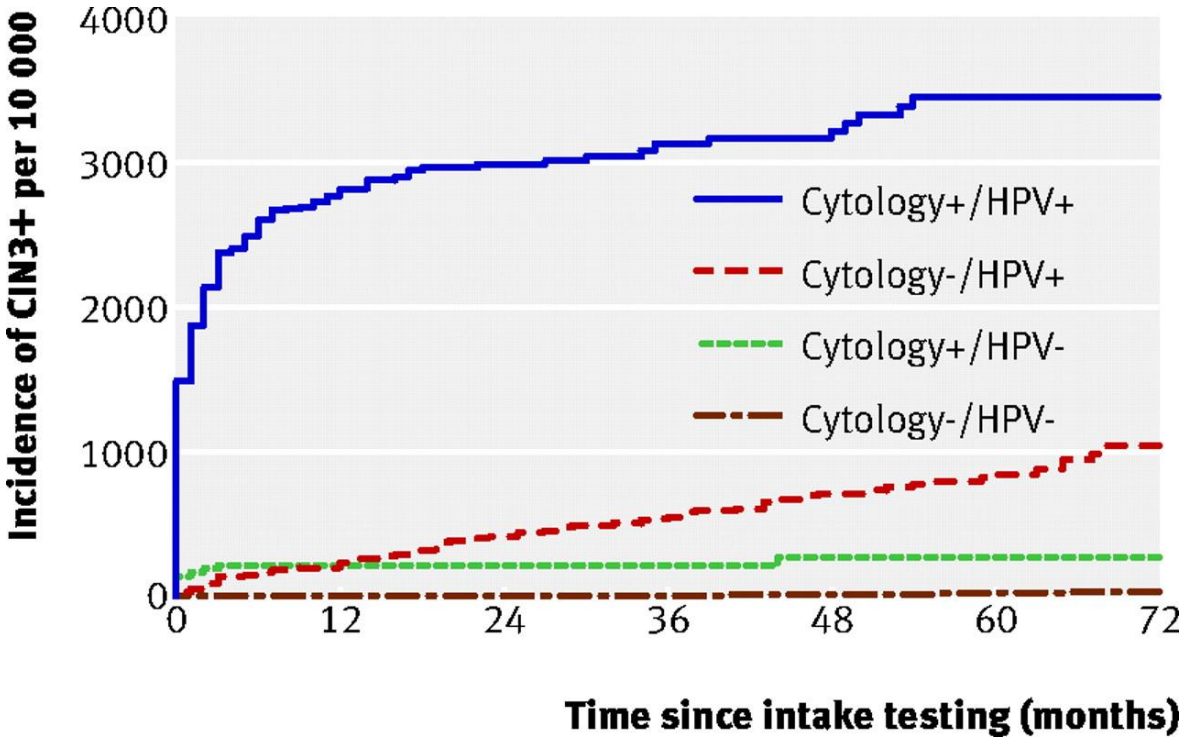
HPV testing is a more sensitive test than cytology

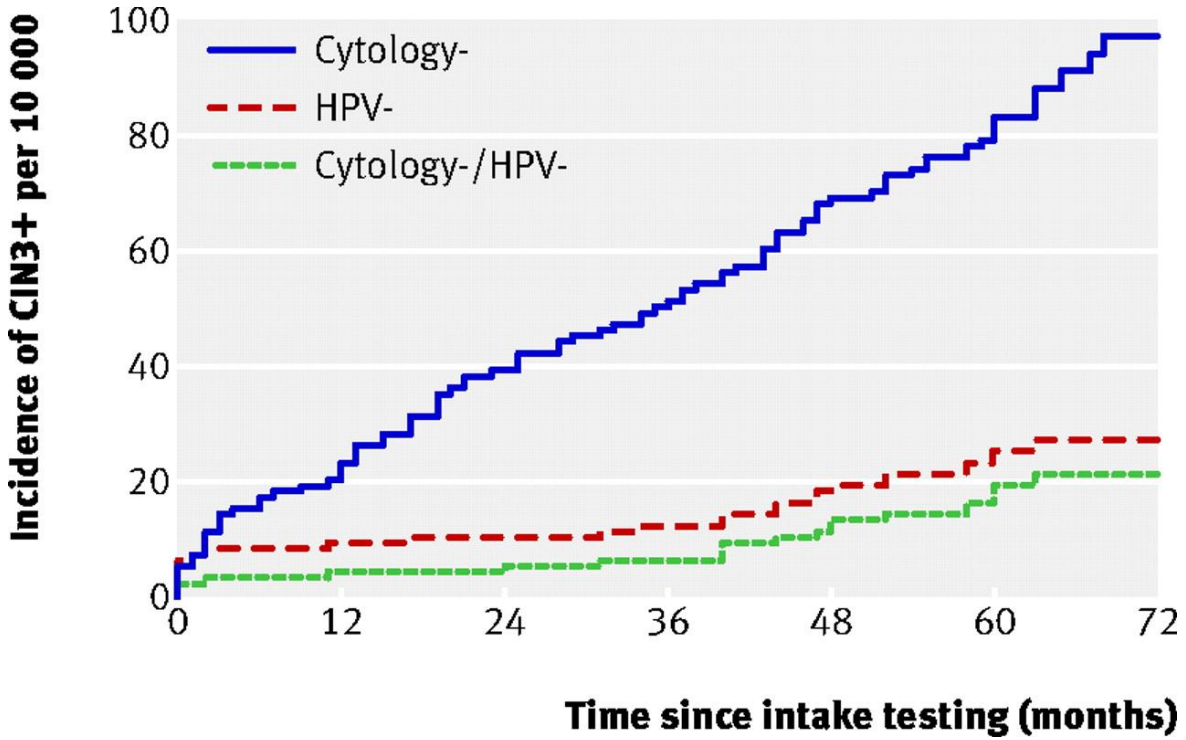


HPV Testing

Cytology (conventional)

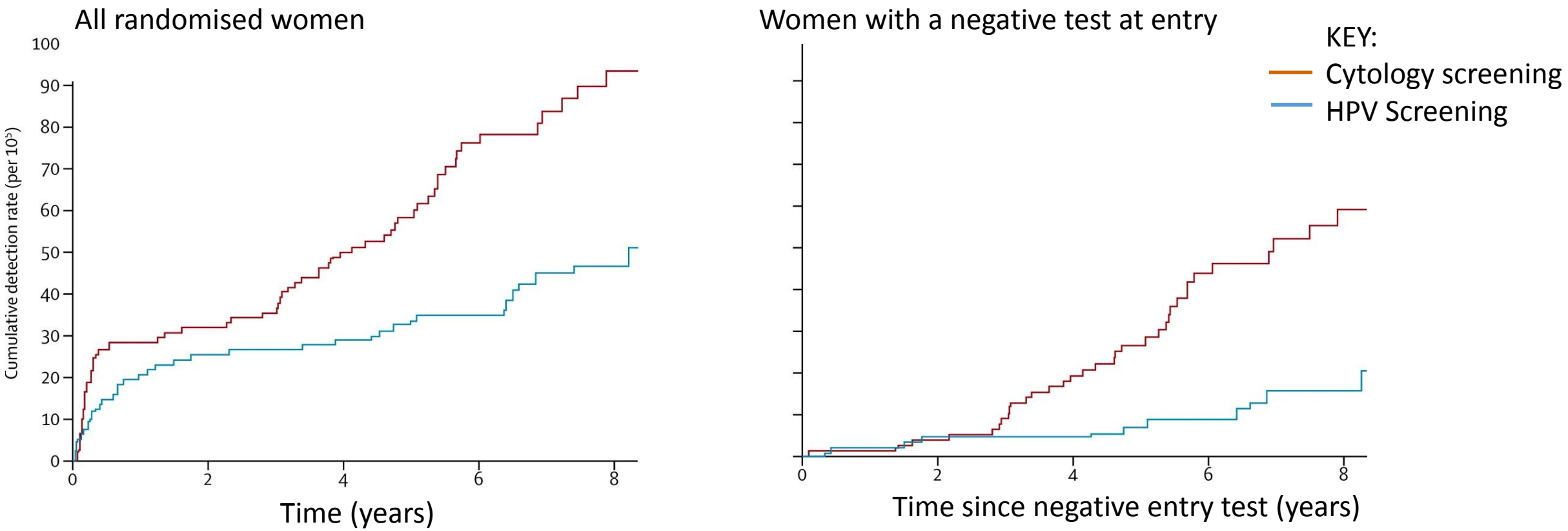
HPV Test screening results in lower CIN3+ rates compared with cytology screening





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:

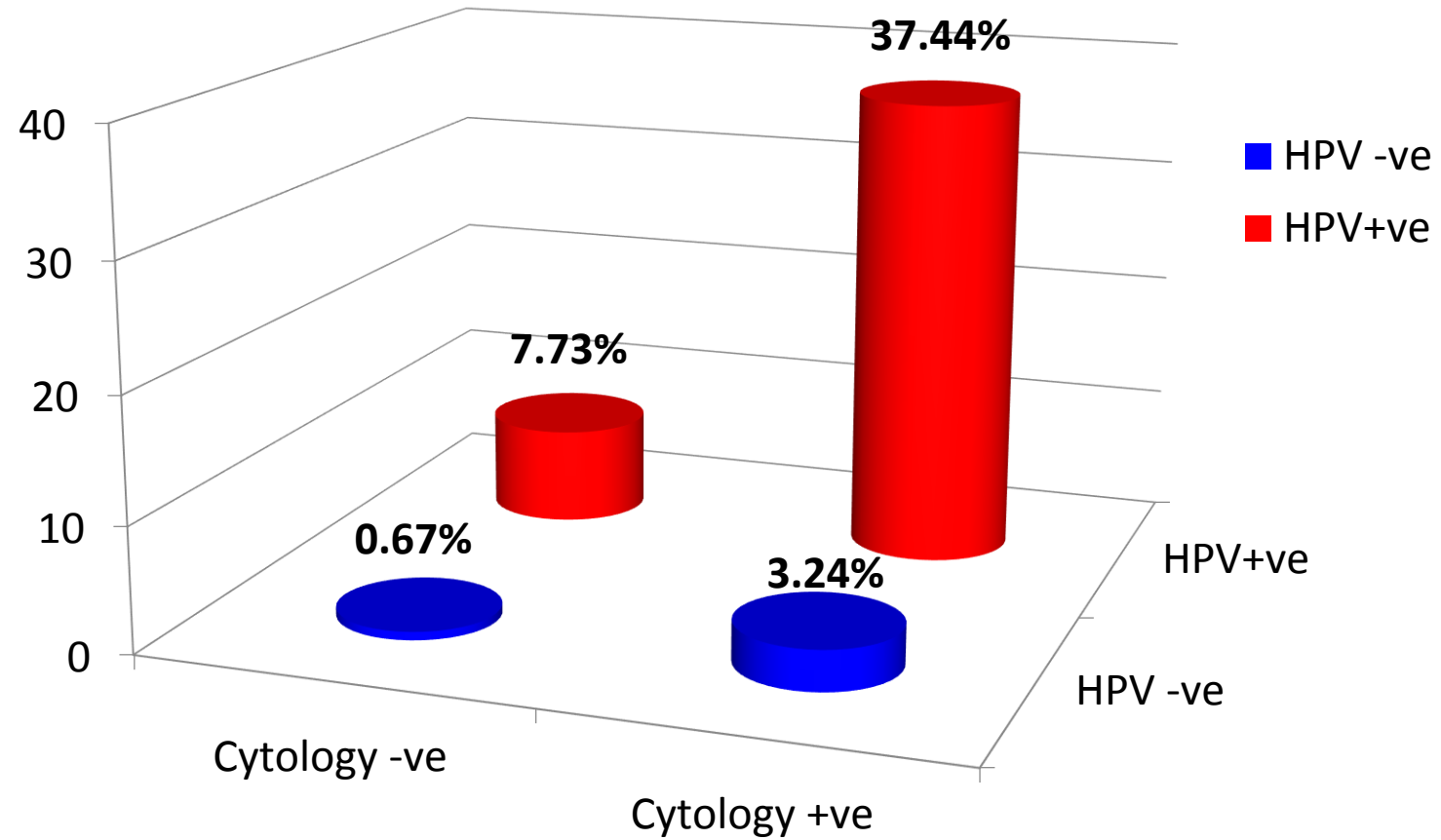
Cumulative CIN2+ rates: after negative cytology = 1.41%

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



Women with invasive cancer

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

HPV (HC2)-negative women who developed CIN3+

Nine in the study: HPV genotyping performed

- Three contained HPV 16
- One contained HPV 6
- Four were negative
- One insufficient material for genotyping

Roche AMPLICOR: 8 tested, three positive

HPV partial genotyping

Cumulative rate of CIN2+ @6 years for women who at baseline were:

"Any hrHPV" positive was 20.1%

HPV 16 positive was 43.6%

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

World Health Organisation (WHO) Guidelines for screening and treatment of precancerous lesions for cervical cancer prevention (2013)

Recommended screening with an HPV test over screening with cytology before colposcopy.

With HPV Testing the frequency of screening will decrease. Once a woman has been screened negative she should not be rescreened for at least 5 years but should be rescreened within 10 years

Report of the Parliamentary Review Committee regarding the New Zealand Cervical Screening Programme June 2011

- large randomised clinical trials: convincing evidence is emerging to support the use of hrHPV testing as a primary screening test

- "..it is timely for any cervical screening programme to move to this new paradigm."

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

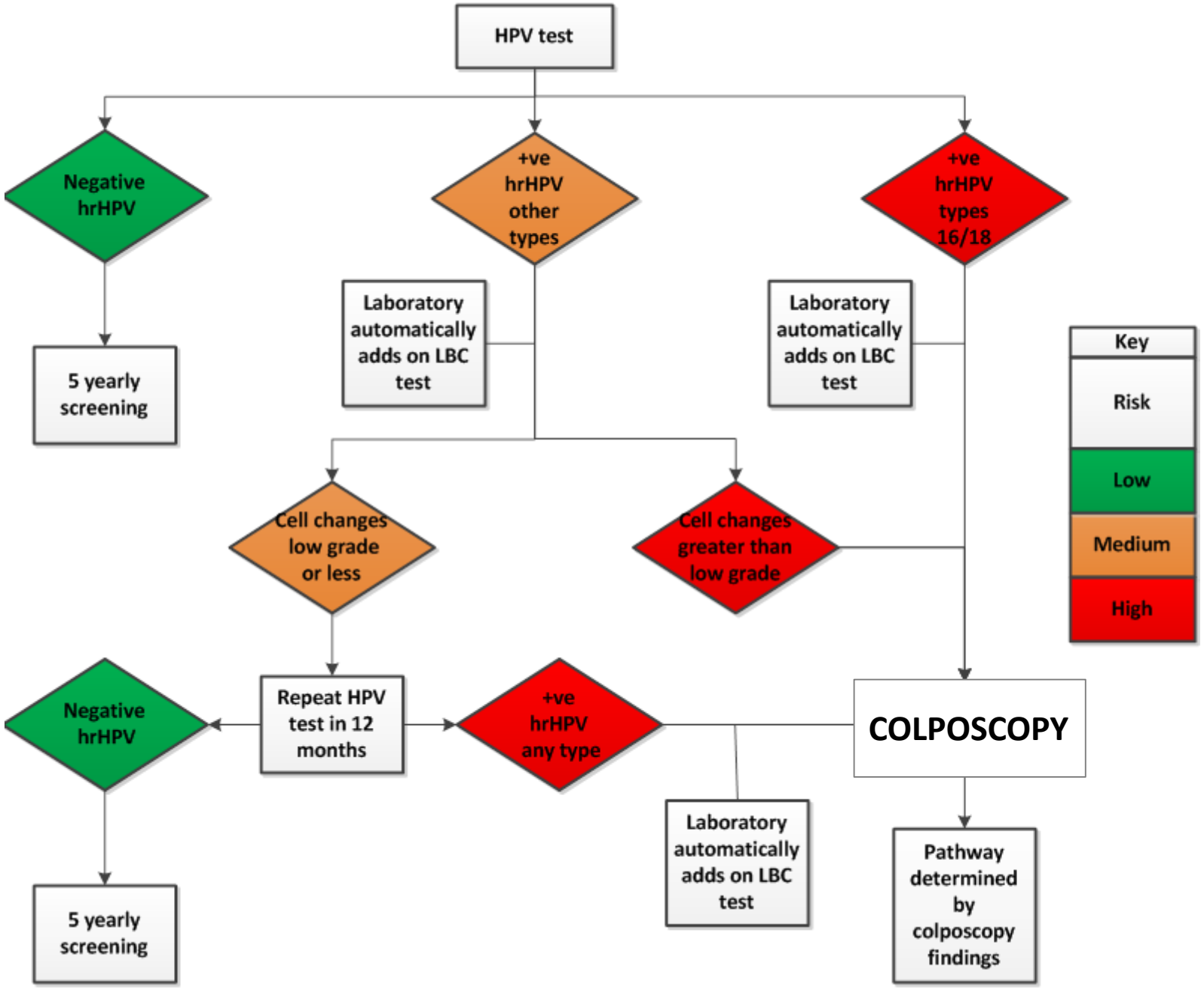
Effectiveness Modelling and Economic Evaluation of Primary HPV Screening for Cervical Cancer Prevention in New Zealand

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

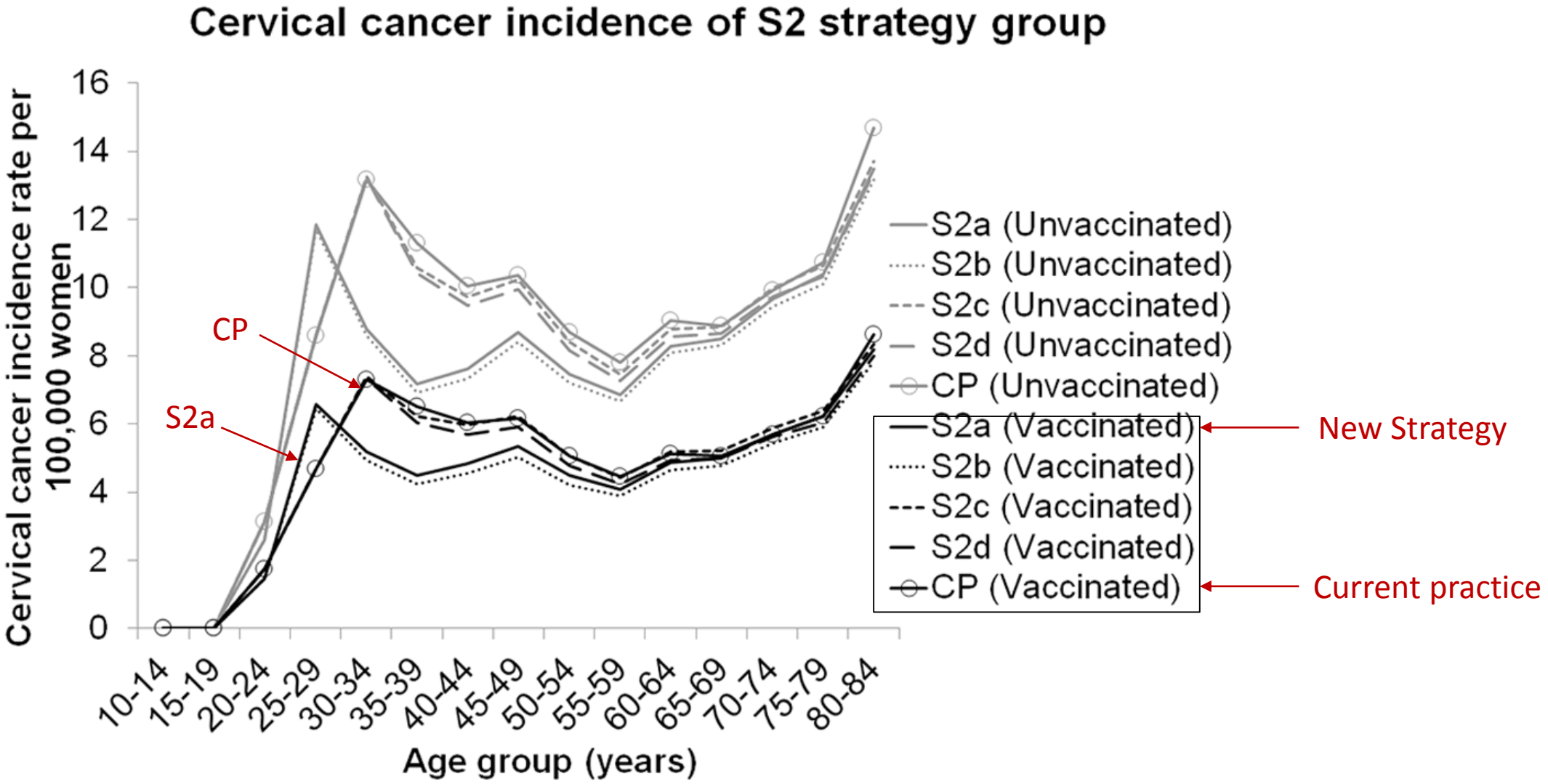
Conclusion: Recommended screening strategy for New Zealand was

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

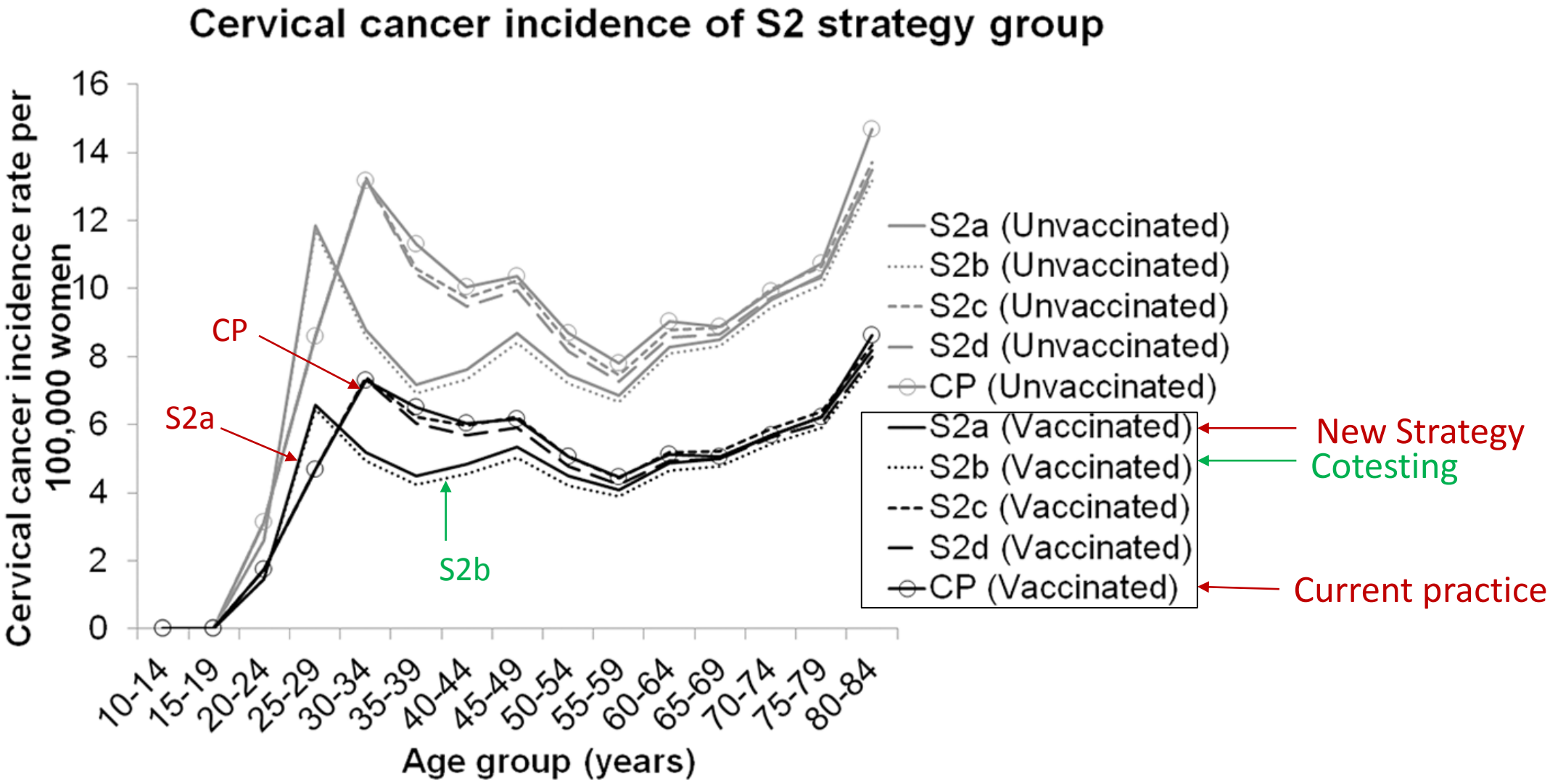
If 60 deaths annually: 12% reduction prevents 7 deaths

- 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

Proposed new NCSP Clinical Management Guidelines

https://www.nsu.govt.nz/health-professionals/national-cervical-screening-programme/cervical-screening-guidelines/updated

- available on the NSU website for comment
- acknowledgement: Harold Neal and Gary Fentiman lead the development of these guidelines in 2016/17

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