PRIMARY HPV SCREENING

Progress in New Zealand

THE BEGINNING

- 2008 Introduction of Gardasil 4
- 2009 HPV prevalence study initiated
- 2012 Consideration of HPV primary screening as an option for New Zealand
- 2013 HPV prevalence study published
- 2014 Presentation of modelling paper to Monitoring Group
- 2015 Formation of Technical Resource Group
- 2015- present
    - Development of policies and standards

Research article | Open Access | Open Peer Review

Type-specific oncogenic human papillomavirus infection in high grade cervical disease in New Zealand

Leonardo M Simonella ✉, Hazel Lewis, Megan Smith, Harold Neal, Collette Bromhead and Karen Canfell

BMC Infectious Diseases 2013 **13**:114

https://doi.org/10.1186/1471-2334-13-114

Received: 10 September 2012 | **Accepted:** 20 February 2013 | **Published:** 3 March 2013

- HR-HPV types in order of prevalence in NZ
    - 16, 52, 31, 33, 18, 58, 51, 39
- Low ranking of HPV18
- Absence of HPV45 in the top 8
- Gardasil 9 coverage
    - 16,18, 31, 33, 45, 52, 58 plus 6, 11

PLOS | ONE

RESEARCH ARTICLE

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

Jie-Bin Lew[1]*, Kate Simms[1], Megan Smith[1], Hazel Lewis[2], Harold Neal[3], Karen Canfell[1,4]

1 Cancer Research Division, Cancer Council New South Wales, New South Wales, Australia, **2** Public Health Physician, Wellington, New Zealand, **3** National Screening Unit, Ministry of Health, Wellington, New Zealand, **4** School of Public Health, Sydney Medical School, University of Sydney, Sydney, Australia

* jiebin.lew@nswcc.org.au

OPEN ACCESS

Citation: Lew J-B, Simms K, Smith M, Lewis H, Neal H, Canfell K (2016) Effectiveness Modelling and Economic Evaluation of Primary HPV Screening for Cervical Cancer Prevention in New Zealand. PLoS ONE 11(5): e0151619. doi:10.1371/journal.

Abstract

Background

New Zealand (NZ) is considering transitioning from 3-yearly cervical cytology screening in women 20–69 years (current practice) to primary HPV screening. We evaluated HPV-based screening in both HPV-unvaccinated women and cohorts offered HPV vaccination in New Zealand (vaccination coverage ~50%).

Model Features

- Model incorporated
  - Natural history of HPV
  - Natural history of precancer
  - Natural history of cancer
  - Current screening, diagnosis and treatment
  - New Zealand data used for demographics and epidemiology
  - New Zealand cost structures used

- Cytology sensitivity tuned to match NZ output.

Current practice

- Starting age 20
- Interval 3 yearly
- Referral trigger ASCH+ or AG+

  Repeated ASL or LS result
- ASL/LS Pathway with negative history

  Under 30 Repeat cytology 12 months x2

  Over 30 HPV triage

    hrHPV pos refer to colposcopy

    hrHPV neg repeat cytology in 12 months

- HPV also used in return to screening pathway following treatment

Multiple strategies evaluated in detail

- Variables considered
  - Starting age
    - 20 3 yearly with conventional cytology to 30 then 5 yearly
      - (Current practice to 30)
      - 25 with 5 yearly interval
- Primary test
  - HPV test with cytology triage
  - Co-testing with cytology and HPV
  - HPV test with partial genotyping and cytology triage
  - Co-testing with cytology and HPV test with partial genotyping

Intermediate Risk Management

- Low grade cytology and HPV pos (no genotyping)
  - Co-test in 12 months
  - Immediate colposcopy

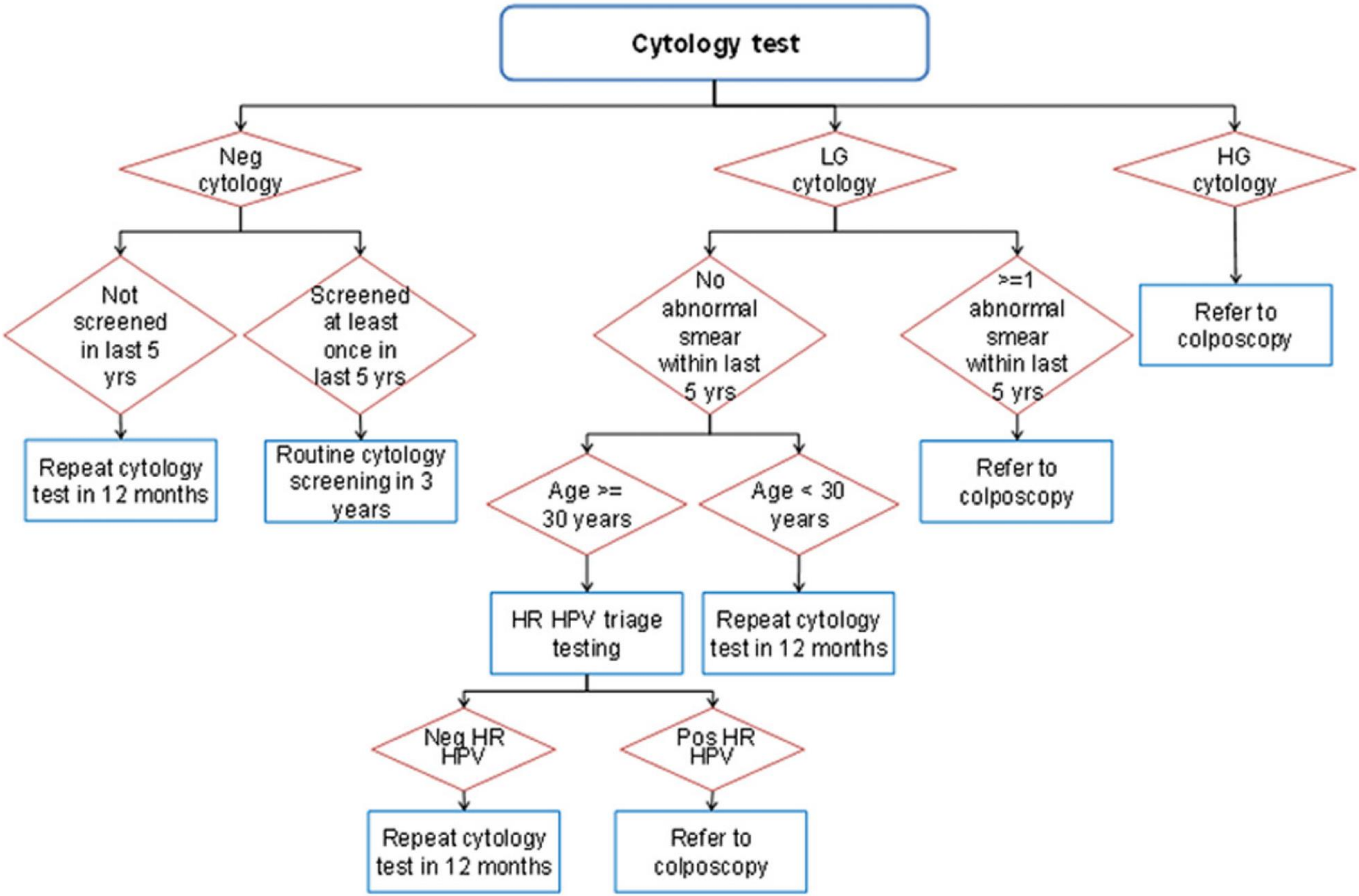
- Low grade cytology and non16/18 HPV pos with partial genotyping
  - HPV in 12 months
  - Immediate colposcopy

- Separate models for vaccinated and unvaccinated cohorts

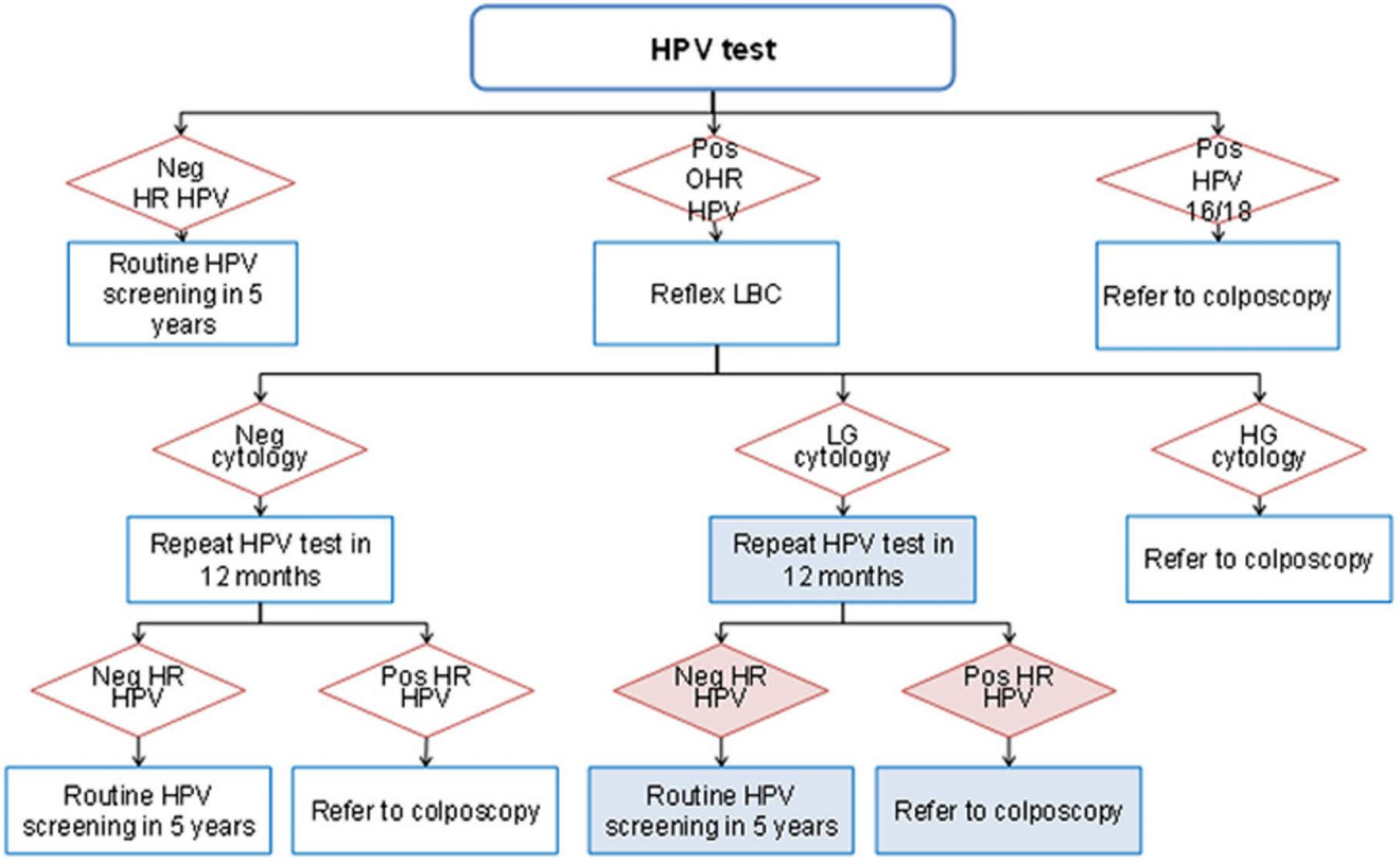
Table 1. List of primary HPV screening strategies evaluated.

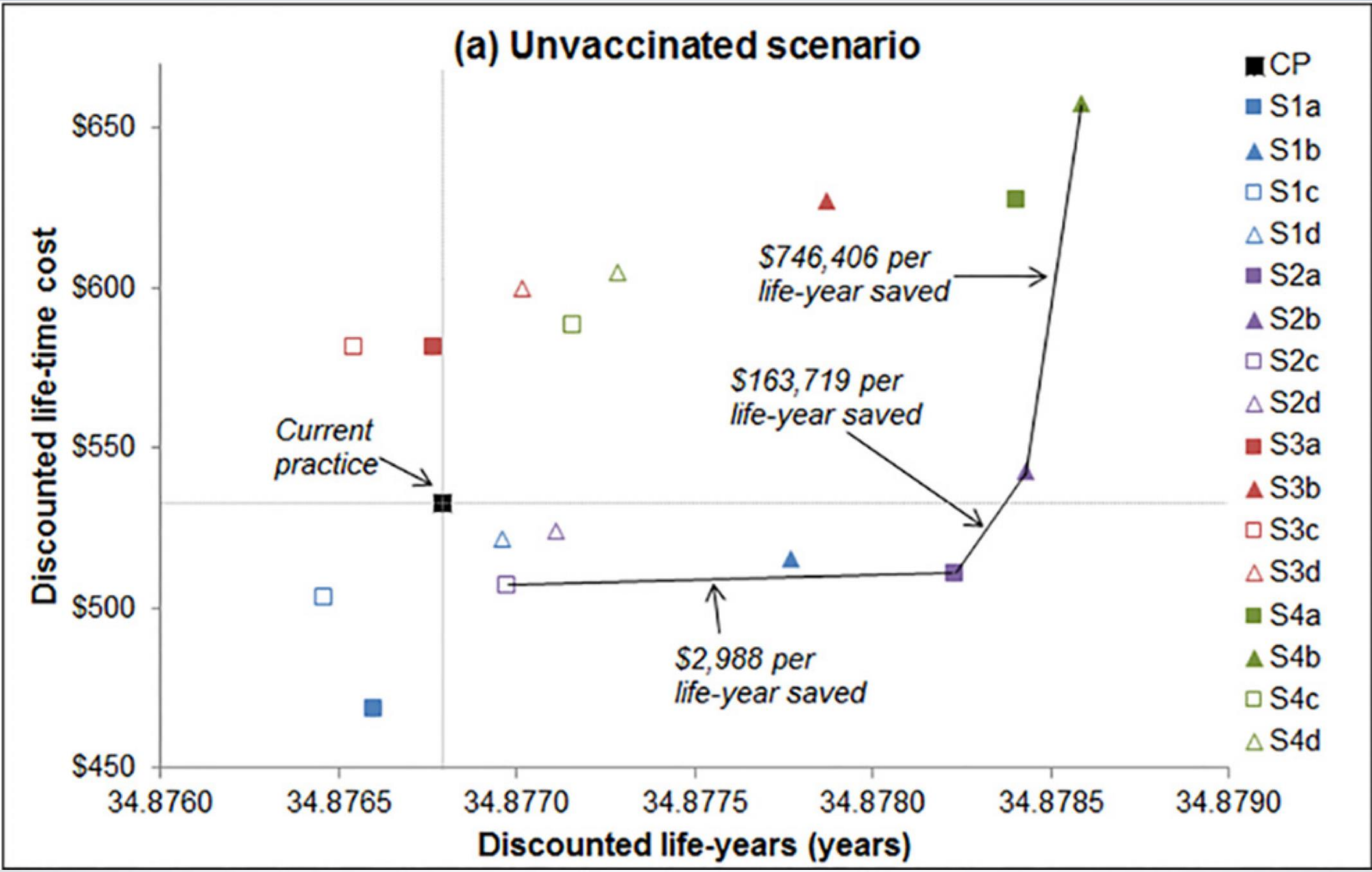
Strategy name	Age of screening starts	Screening test		Management for intermediate risk group*,#
		<30 years	30–69 years	
		Strategy 1 group		
S1a	25	5-yearly HPV test with cytology triage	5-yearly HPV test with cytology triage	Follow-up with co-testing in 12 months
S1b	25	5-yearly HPV test with cytology triage	5-yearly HPV test with cytology triage	Immediate colposcopy
S1c	20	3-yearly cytology screening	5-yearly HPV test with cytology triage	Follow-up with co-testing in 12 months
S1d	20	3-yearly cytology screening	5-yearly HPV test with cytology triage	Immediate colposcopy
		Strategy 2 group		
S2a	25	5-yearly HPV testing with partial genotyping & cytology triage	5-yearly HPV testing with partial genotyping & cytology triage	Follow-up with HPV testing alone in 12 months
S2b	25	5-yearly HPV testing with partial genotyping & cytology triage	5-yearly HPV testing with partial genotyping & cytology triage	Immediate colposcopy
S2c	20	3-yearly cytology screening	5-yearly HPV testing with partial genotyping & cytology triage	Follow-up with HPV testing alone in 12 months
S2d	20	3-yearly cytology screening	5-yearly HPV testing with partial genotyping & cytology triage	Immediate colposcopy
		Strategy 3 group		
S3a	25	5-yearly co-testing with cytology & HPV test	5-yearly co-testing with cytology & HPV test	Follow-up with co-testing in 12 months
S3b	25	5-yearly co-testing with cytology & HPV test	5-yearly co-testing with cytology & HPV test	Immediate colposcopy
S3c	20	3-yearly cytology screening	5-yearly co-testing with cytology & HPV test	Follow-up with co-testing in 12 months
S3d	20	3-yearly cytology screening	5-yearly co-testing with cytology & HPV test	Immediate colposcopy
		Strategy 4 group		
S4a	25	5-yearly co-testing with cytology & HPV test with partial genotyping	5-yearly co-testing with cytology & HPV test with partial genotyping	Follow-up with HPV testing alone in 12 months
S4b	25	5-yearly co-testing with cytology & HPV test with partial genotyping	5-yearly co-testing with cytology & HPV test with partial genotyping	Immediate colposcopy
S4c	20	3-yearly cytology screening	5-yearly co-testing with cytology & HPV test with partial genotyping	Follow-up with HPV testing alone in 12 months
S4d	20	3-yearly cytology screening	5-yearly co-testing with cytology & HPV test with partial genotyping	Immediate colposcopy

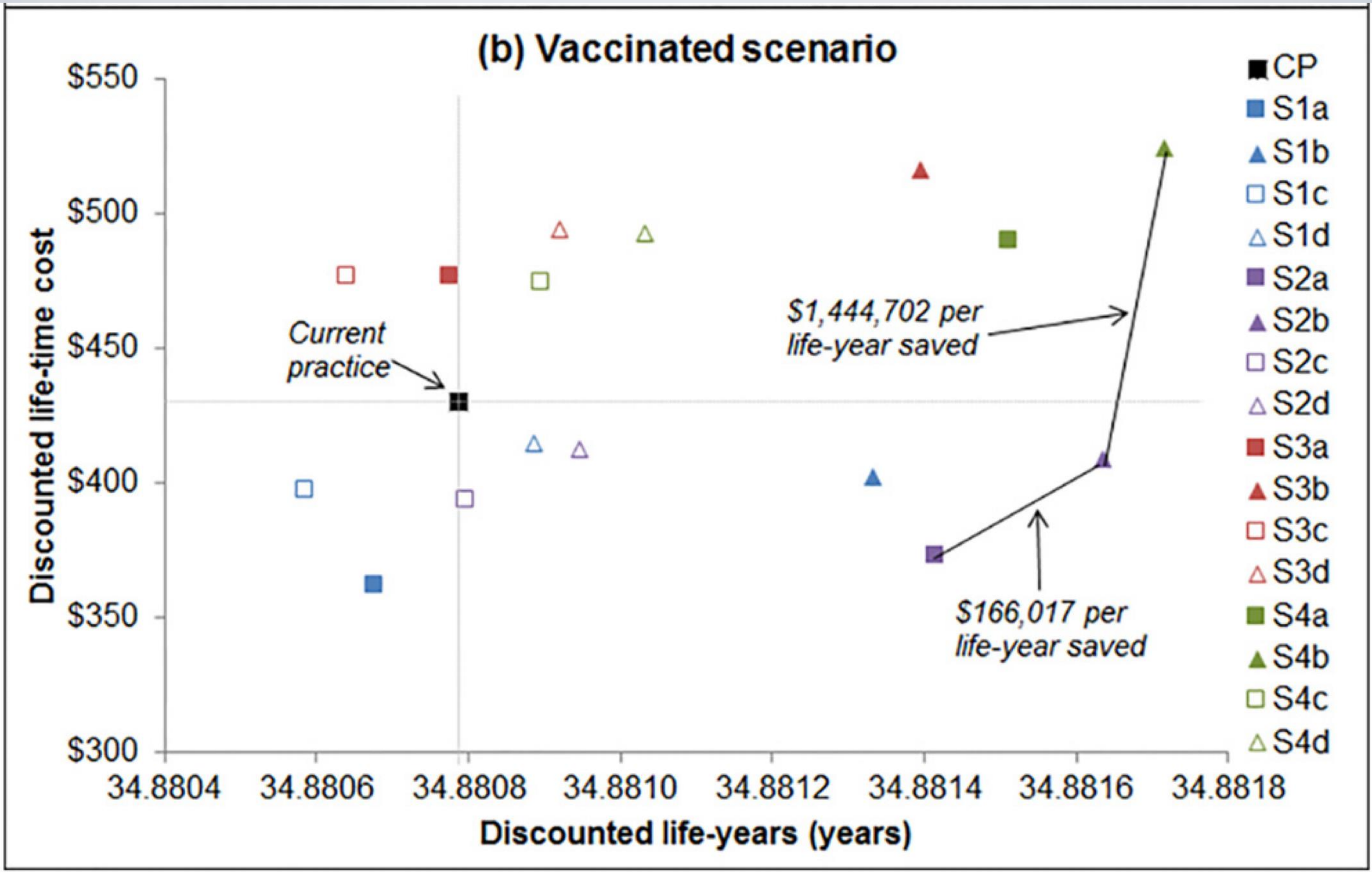
(a) Modelled screening pathway of current practice



(c) Modelled screening pathway of S2a




(a) Unvaccinated scenario
Discounted life-time cost
$650
$600
$550
$500
$450
34.8760
34.8765
34.8770
34.8775
34.8780
34.8785
34.8790
Discounted life-years (years)
Current practice
$746,406 per life-year saved
$163,719 per life-year saved
$2,988 per life-year saved
CP
S1a
S1b
S1c
S1d
S2a
S2b
S2c
S2d
S3a
S3b
S3c
S3d
S4a
S4b
S4c
S4d

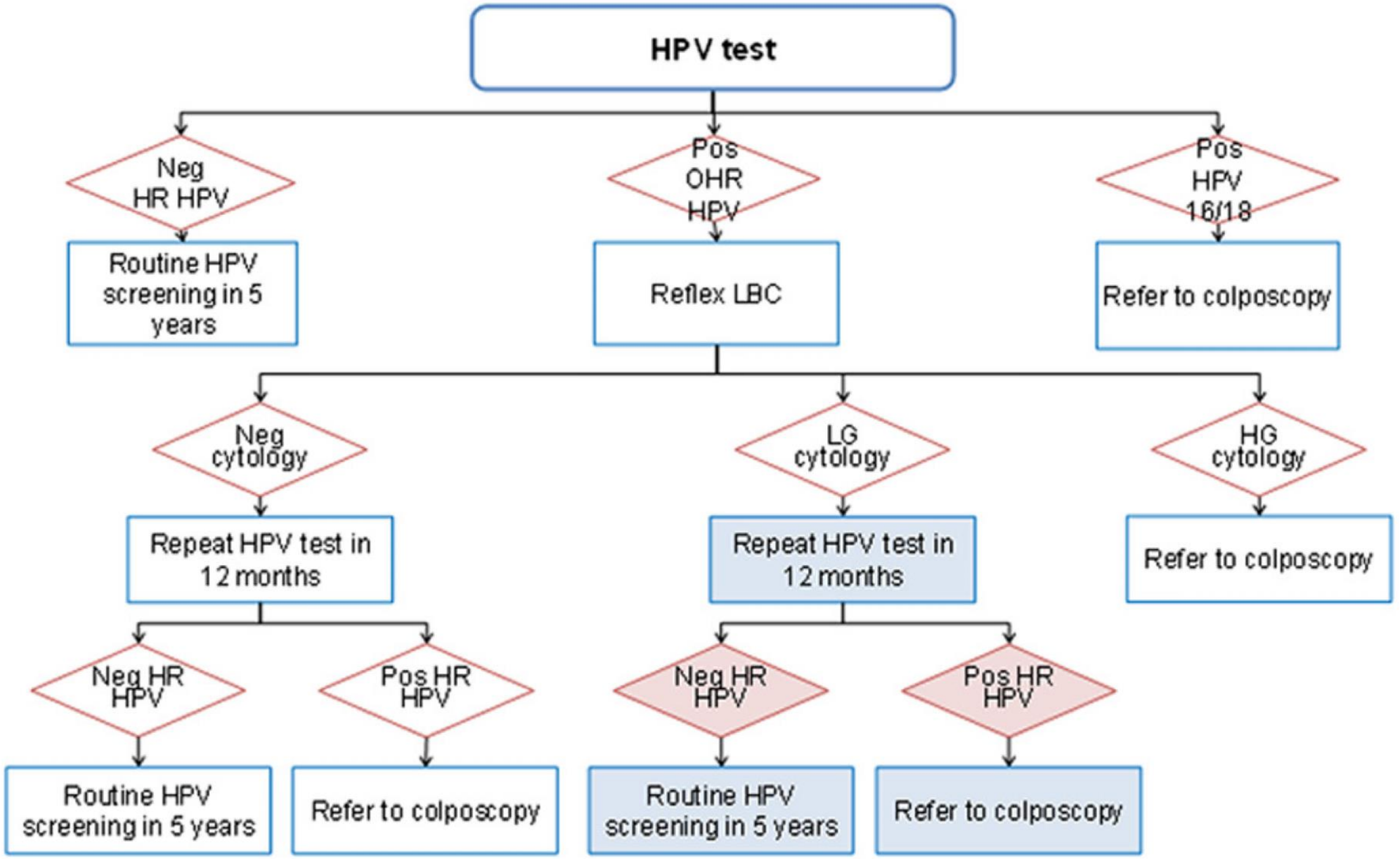

(b) Vaccinated scenario
$550
$500
$450
$400
$350
$300
Discounted life-time cost
34.8804
34.8806
34.8808
34.8810
34.8812
34.8814
34.8816
34.8818
Discounted life-years (years)
Current practice
$1,444,702 per life-year saved
$166,017 per life-year saved
CP
S1a
S1b
S1c
S1d
S2a
S2b
S2c
S2d
S3a
S3b
S3c
S3d
S4a
S4b
S4c
S4d

Selected Strategy

- Primary HPV testing with partial genotyping and cytology triage
- All HPV results triggering referral generate a cytology slide to assist management, not to influence referral
  - HPV 16/18 pos primary screen
  - HPV pos (non 16/18) in intermediate risk
    - 12 month repeat if Neg or LSIL cytology

- Pathway same as Australia

(c) Modelled screening pathway of S2a



The path to primary HPV screening

- Conversion to 100% LBC
- Introduction of HPV triage
- Introduction of HPV vaccination
- HPV prevalence study
- Modelling of HPV Screening in NZ
- Formation of TRG
- Development of initial proposal
- Initial consultation
- Ministerial approval to progress
- Development of screening pathway, policies and standards
- Clinical working group
- Cytology working group
- Histology working group
- HPV working group
- Final draft policies and standards

Implementation
Australia vs New Zealand

- Australia
  - Development of new pathway and standards
  - Start 25, 5yrly
  - Convert to LBC
  - Introduce HPV testing
  - Up to 95% cytology volume reduction
  - New register required
- New Zealand
  - Development of new pathway and standards
  - Start 25, 5yrly
  - 100% LBC in place
  - HPV testing in place
  - Up to 80% volume reduction
  - New register required

2018 Status
New Zealand

- Draft policies and standards complete
- One critical component missing
- Current register unable to accomodate HPV primary screening pathway
- Proposal to develop a new screening IT platform comprising a shared base (demographic data, external interfaces) with program specific databases (bowel, cervical, breast, etc)
- Procurement process initiated.
- 2018 Budget. Approval for base and bowel only.
- HPV primary screening on hold.

Progress since 2018

- Analysis of requirements for "Self Testing"
  - Self testing was always identified as an option for the NCSP
  - Built into the HPV testing requirements (requiring DNA PCR)
  - Significant unanswered issues precluded incorporation in 2018

- Development of Extended and Full Genotyping assays
  - Does the greater resolution of these tests offer advantages?

- RFP evaluation in progress
  - Start primary HPV screening mid 2023
  - Self testing (clinician supervised) available to all

Key Issues for "Self Testing"

- Is test sensitivity preserved?
  - Yes for DNA PCR
  - No for HC-2 and RNA PCR
- Is self testing an acceptable option for those currently resistant to cervical screening?
  - Yes, according to multiple studies in NZ and Australia
- Will resistant women with a positive HR-HPV result engage with followup?
  - Yes, according to multiple studies in NZ and Australia
- How to triage positive (Non-16/18) positive HR-HPV

Self Testing
Triage Options

- Recall for Cytology
  - Default option
    - Who pays?
- Methylation
  - Can be done as a reflex test on HPV sample
    - Years away (2-4)
- Extended/Full genotyping
  - Use genotype information to modify referral and followup
    - Adds complexity

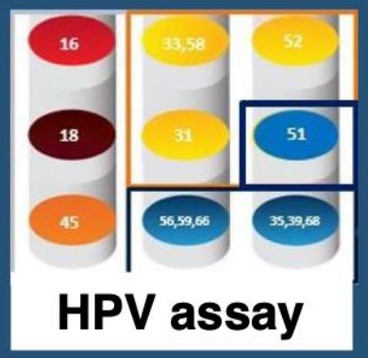
Extended / Full Genotyping

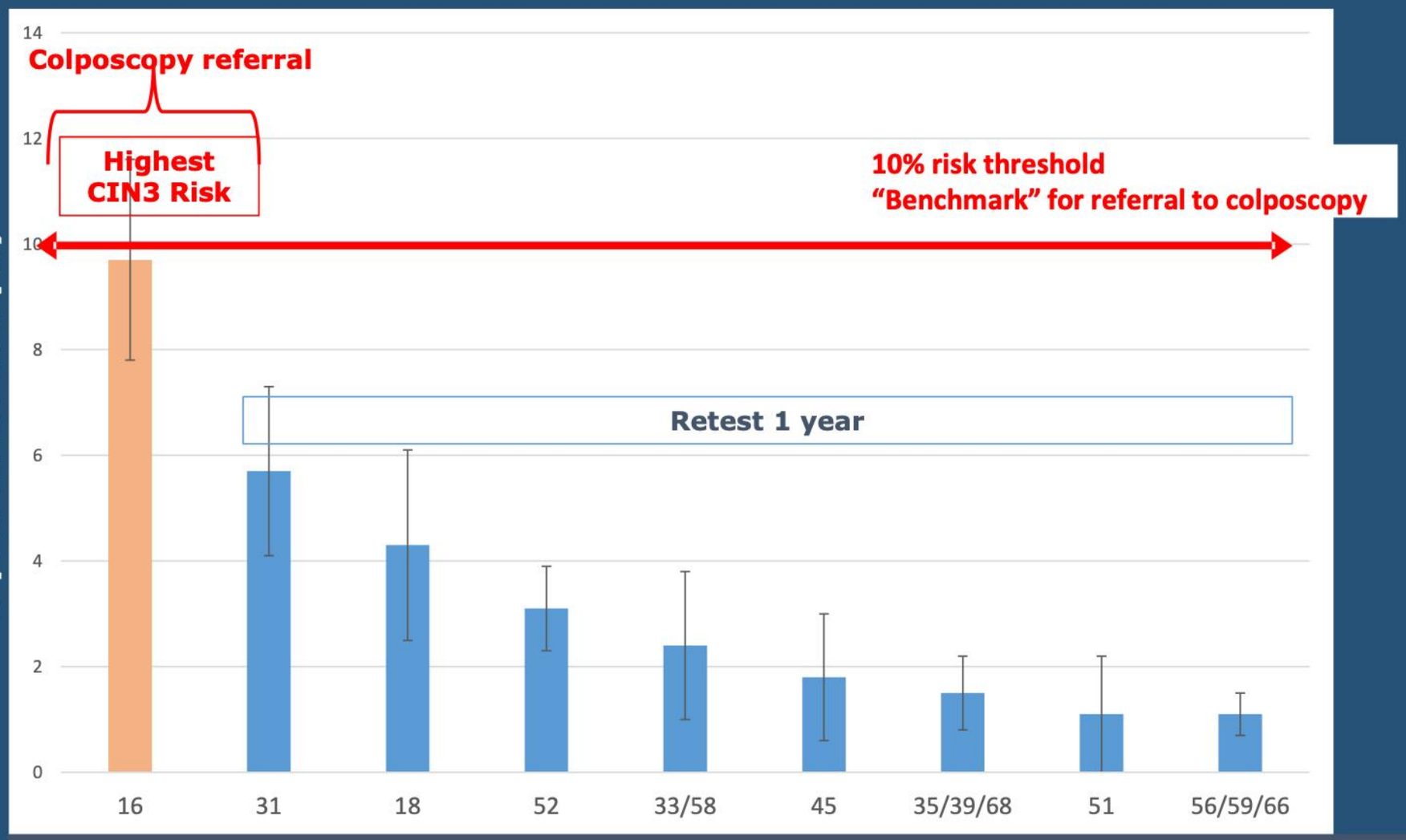
- Risk stratification options
  - Hierarchy of risk for identification of HSIL or Cancer
    - HPV 16 highest risk for both
    - HPV 18 second highest risk for cancer
    - HPV 18, 31, 52, 45, 33 similar risk grouping for HSIL

- Strain specific persistence
  - Strain specific persistence is key for risk assessment on followup testing

Extended Genotyping
Negative cytology

NILM+, risk-based management with extended genotyping





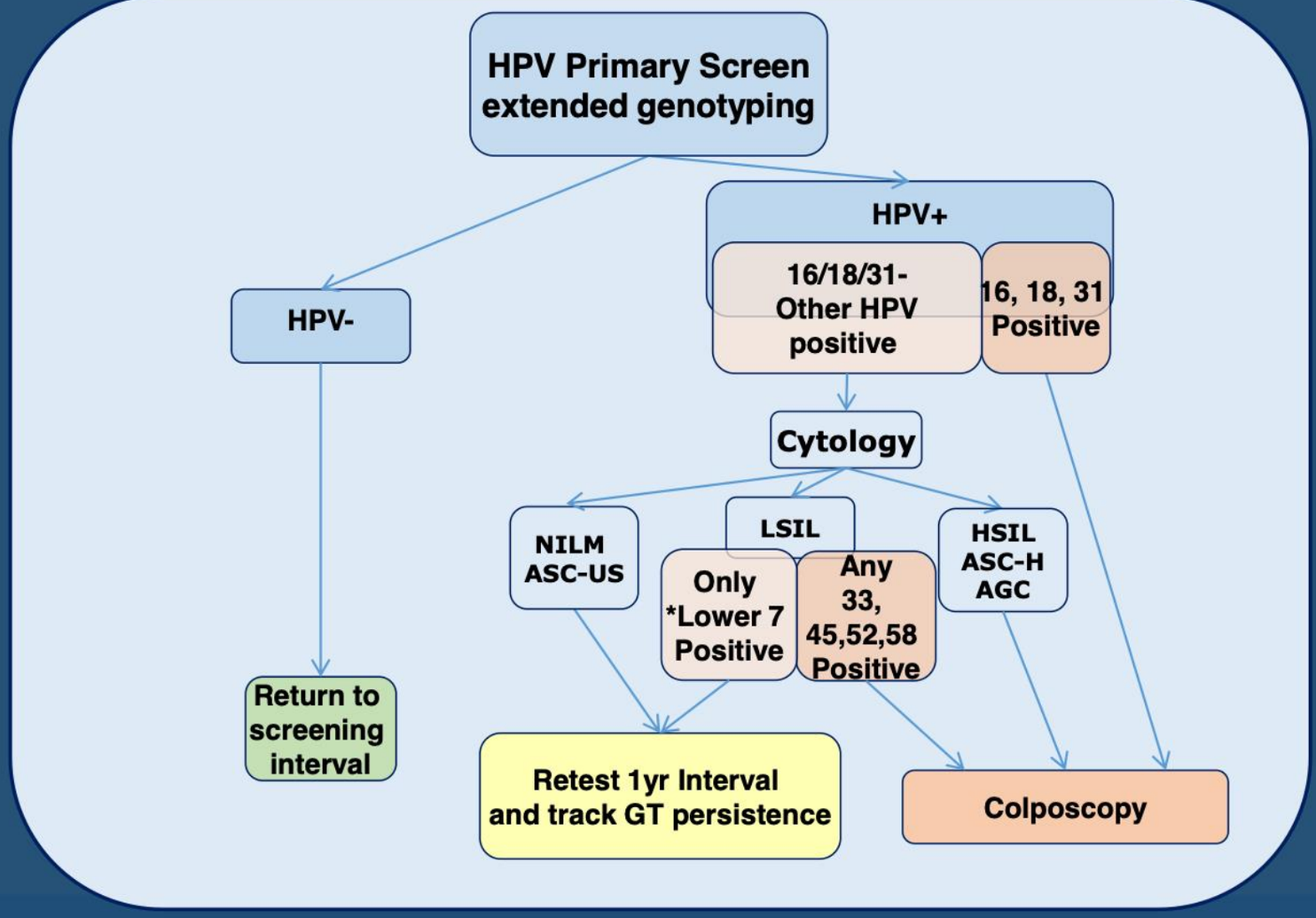
Total NILM+ women = 16,801 (N=840,380)

Composite from:
Onclarity 2018,
Schiffman 2015 JCM,
Wheeler 2014 IJC,
Monsonego 2015 GO,
Schiffman 2016 IJC

Under the principle of equal management for equal risk, HPV18+ should be managed like HPV31+

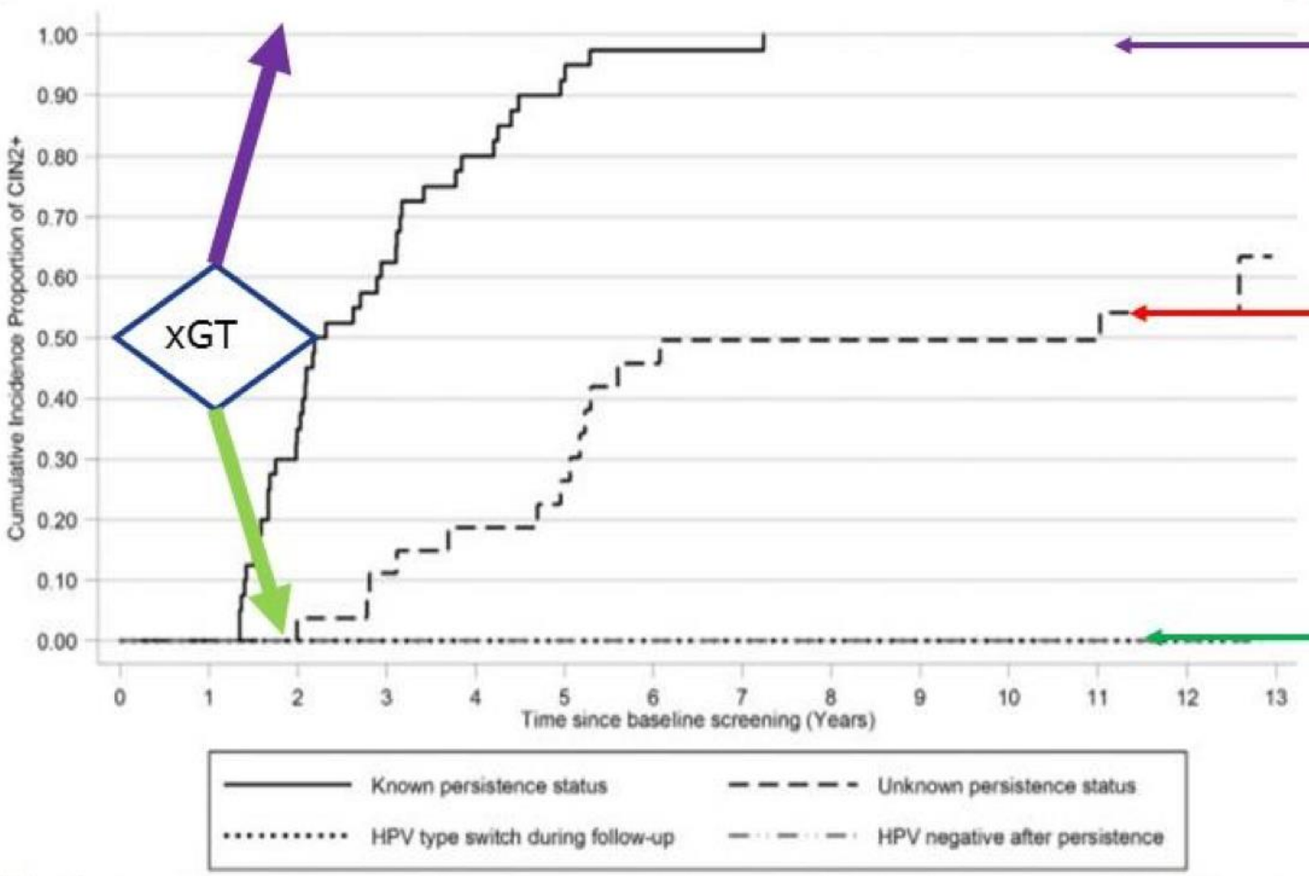
Extended Genotyping
Australian/NZ pathway

Primary HPV Screening with extended genotyping (apply tradition + equal management for equal risk)



Extended Genotyping
Persistence vs New

FIGURE 4
Cumulative proportion of CIN2+ among women with type-specific persistence



The lines represent women with a known persistence status (black line; n = 40), unknown persistence status (dashed line; n = 27), HPV type switch (clearance of the previously persistent type; dotted line; n = 4), and HPV negativity after persistence (dash-dot line; n = 31). The last 2 lines are entirely overlapping because there were no events detected during follow-up for both the latter 2 groups.

CIN2+, cervical intraepithelial neoplasia grade 2 or worse; *HPV*, human papillomavirus.

Elfgren et al. Management of women with human papillomavirus persistence. Am J Obstet Gynecol 2017.

Represents the value of knowing differentiated risk of extended genotype persistence

Represents the undifferentiated risk of genotype masking

Represents the value of knowing the low risk of genotype-specific clearance by unmasking results

BD

Extended Genotyping
Persistence vs New

Conclusions

- The risk posed by a new genotype (de novo or reactivated) infection is significantly lower than the risk posed by a type-specific persistent infection
  - Type-specific hrHPV infection is associated with highest risks
- Women directed to 12-month testing after an abnormal screening result may have type-specific persistence, or clearance or a new hrHPV infection
  - Management should differ between these
  - Genotype results could be grouped into 4 risk tiers stratification for NILM and persistent same genotype positive

• HPV 16	highest risk	26-30%
• HPV 18, 31, 33	high risk	14-19%
• HPV 45, 52, 58	intermediate risk	9-10%
• HPV 35, 39, 51, 56, 59, 66, 68	lesser risk	0-3%

- The genotypes will be grouped into tiers according to similar risk values, based on local thresholds for management actions

BD Onclarity

- Individual wells for HPV 16, 18, 31, 45, 51, 52
- Shared well for HPV 33 and 58 (P1)
- Shared well for HPV 35, 39 and 68 (P2)
- Shared well for HPV 56, 59 and 66 (P3)

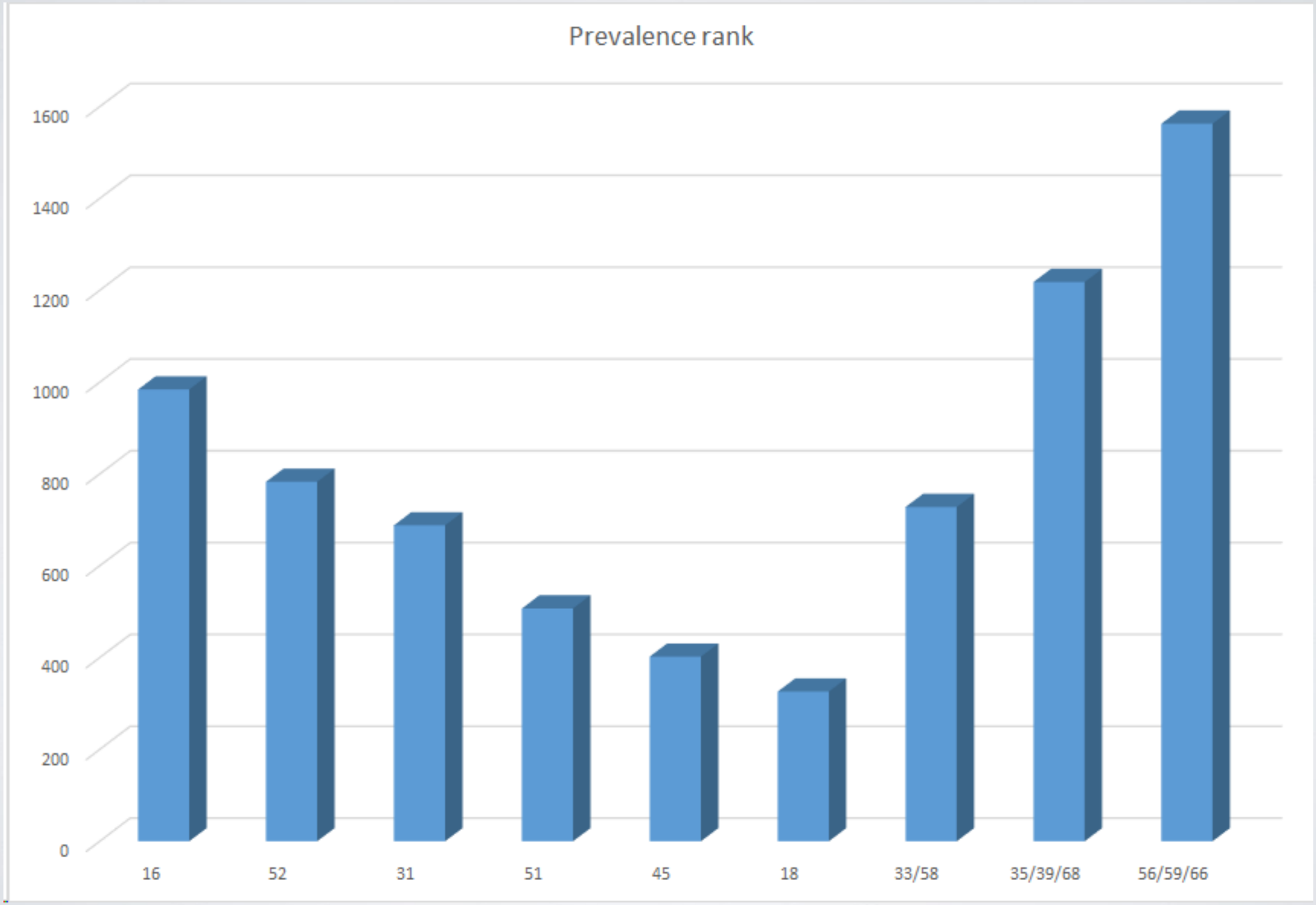
Pathlab experience with Onclarity

- Introduced late 2017
- LSIL and ASL triage for women over 30
- Return to normal screening post treatment

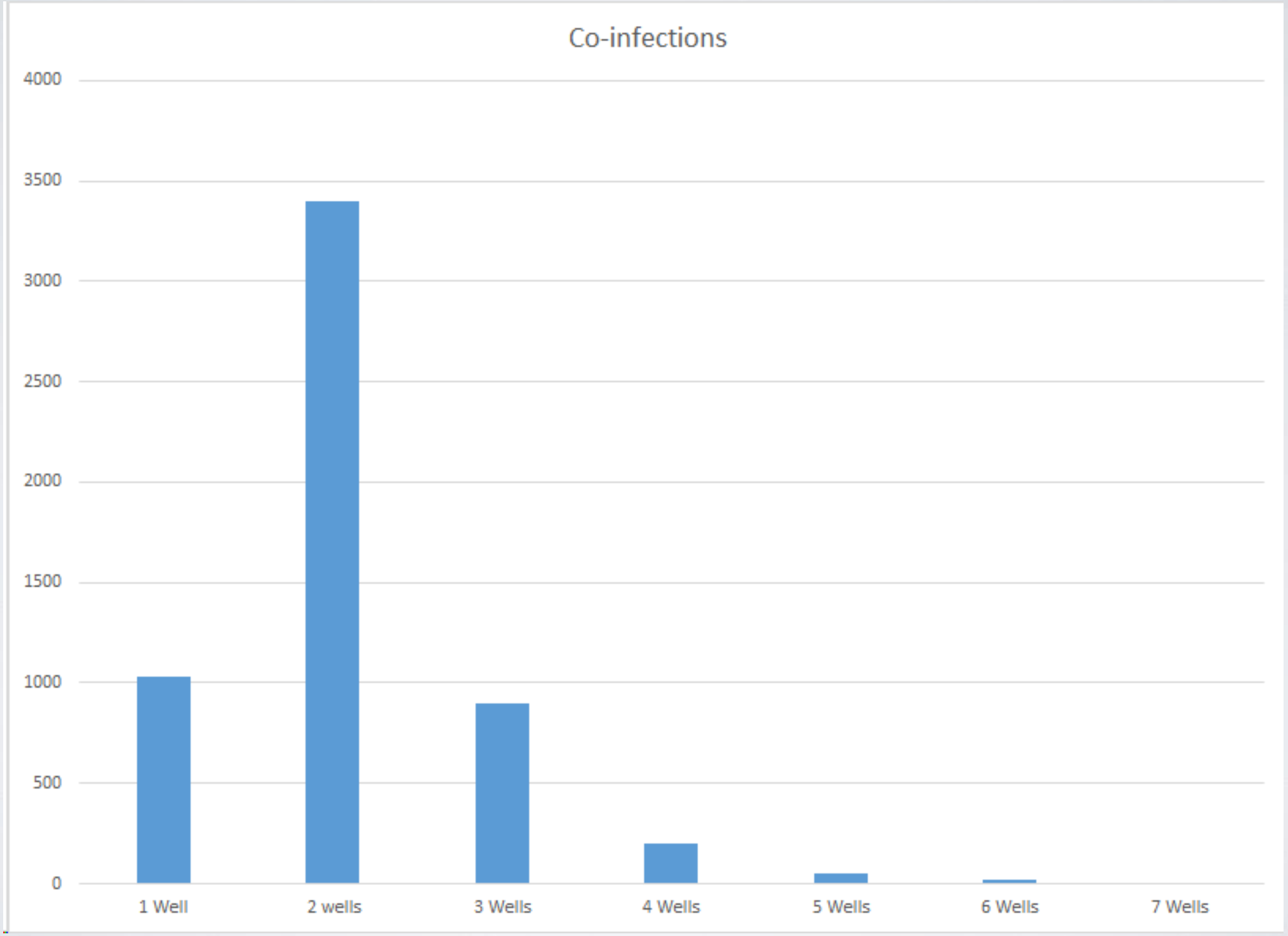
- NOT REPRESENTATIVE OF NZ FEMALE POPULATION

Total tests	19,446	
Not Detected	13,770	71%
Detected	5,613	29%
Invalid	63	0.3%

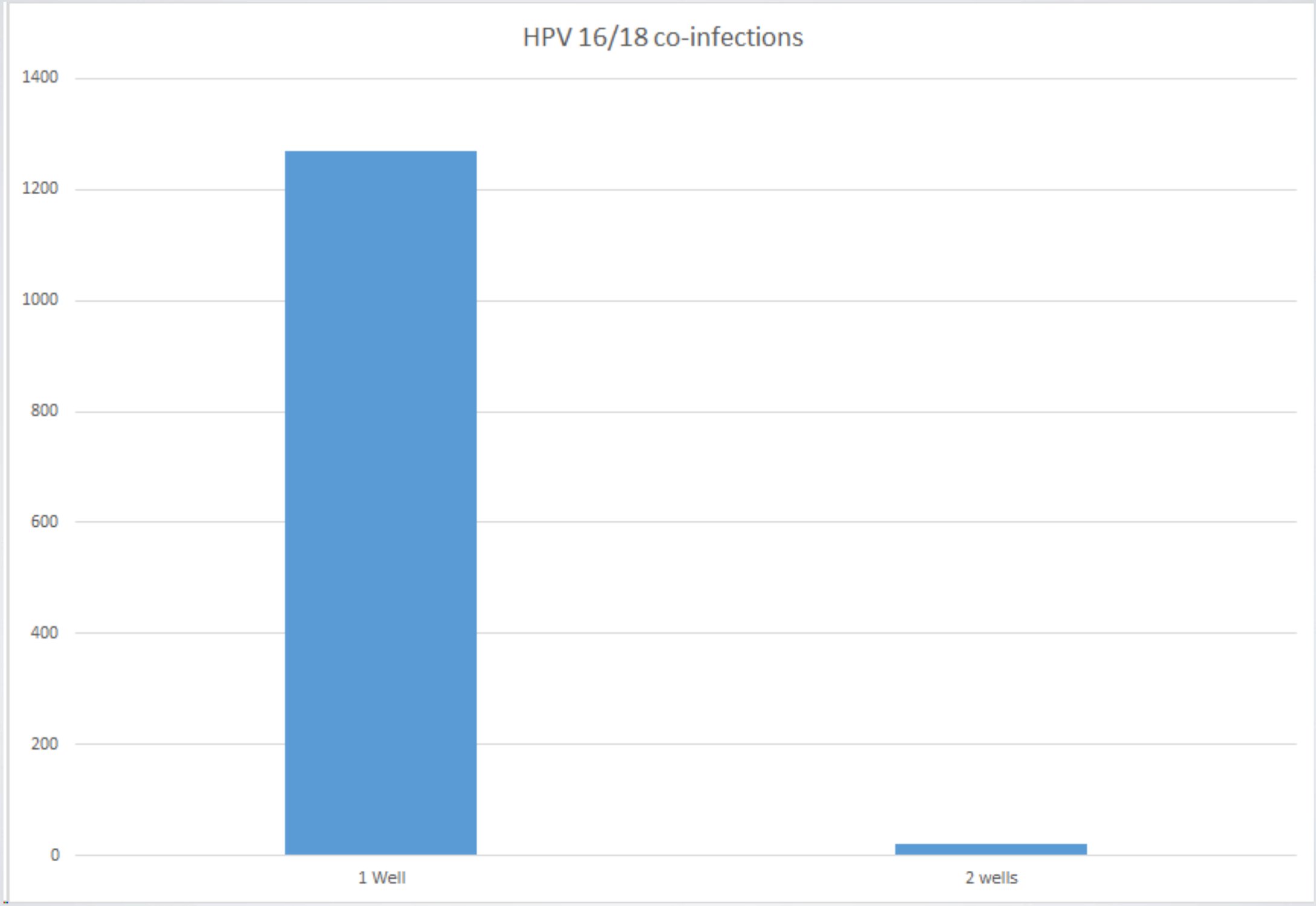
Prevalence ranking comparable to prior studies



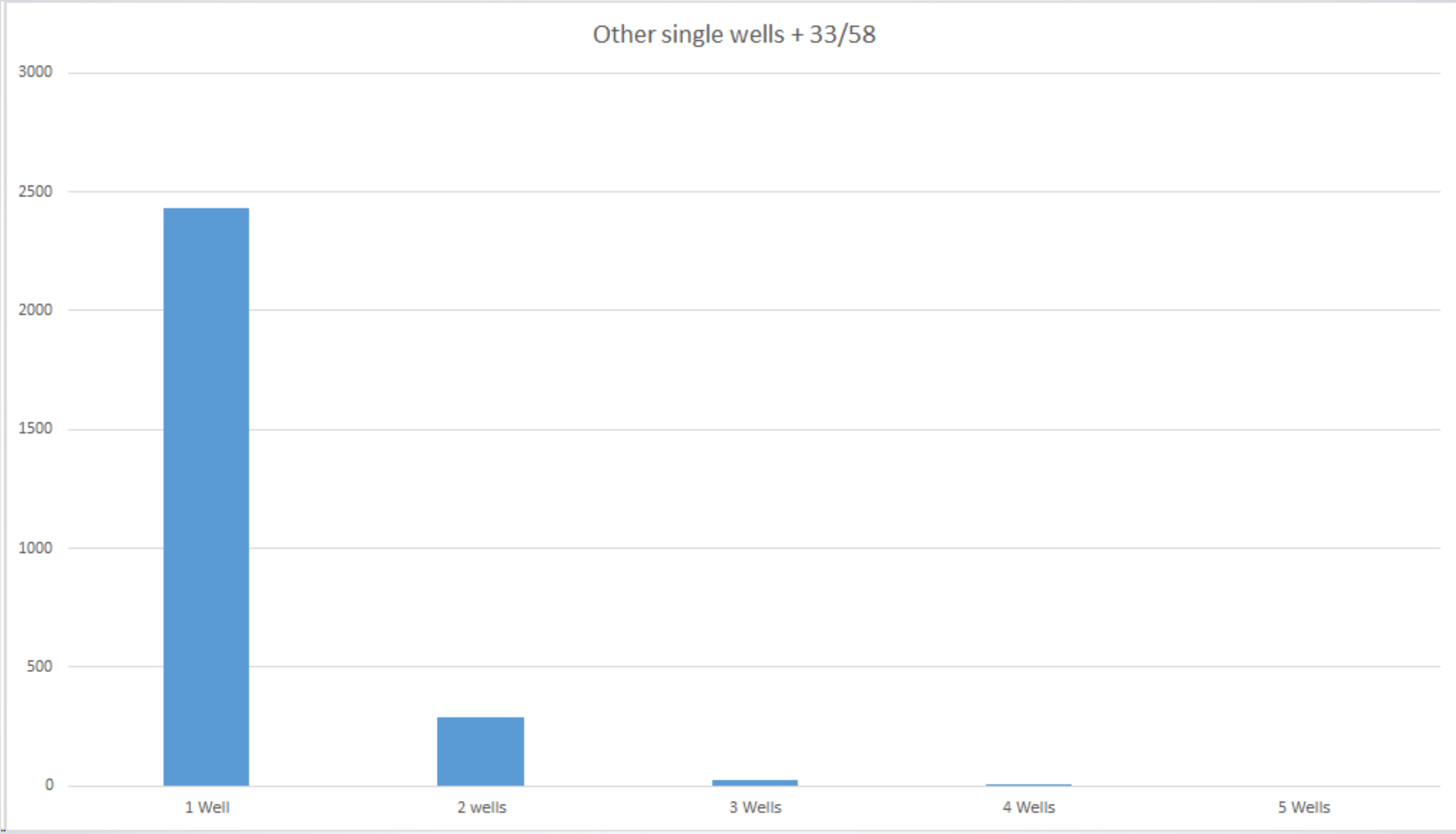
Co-infections are common



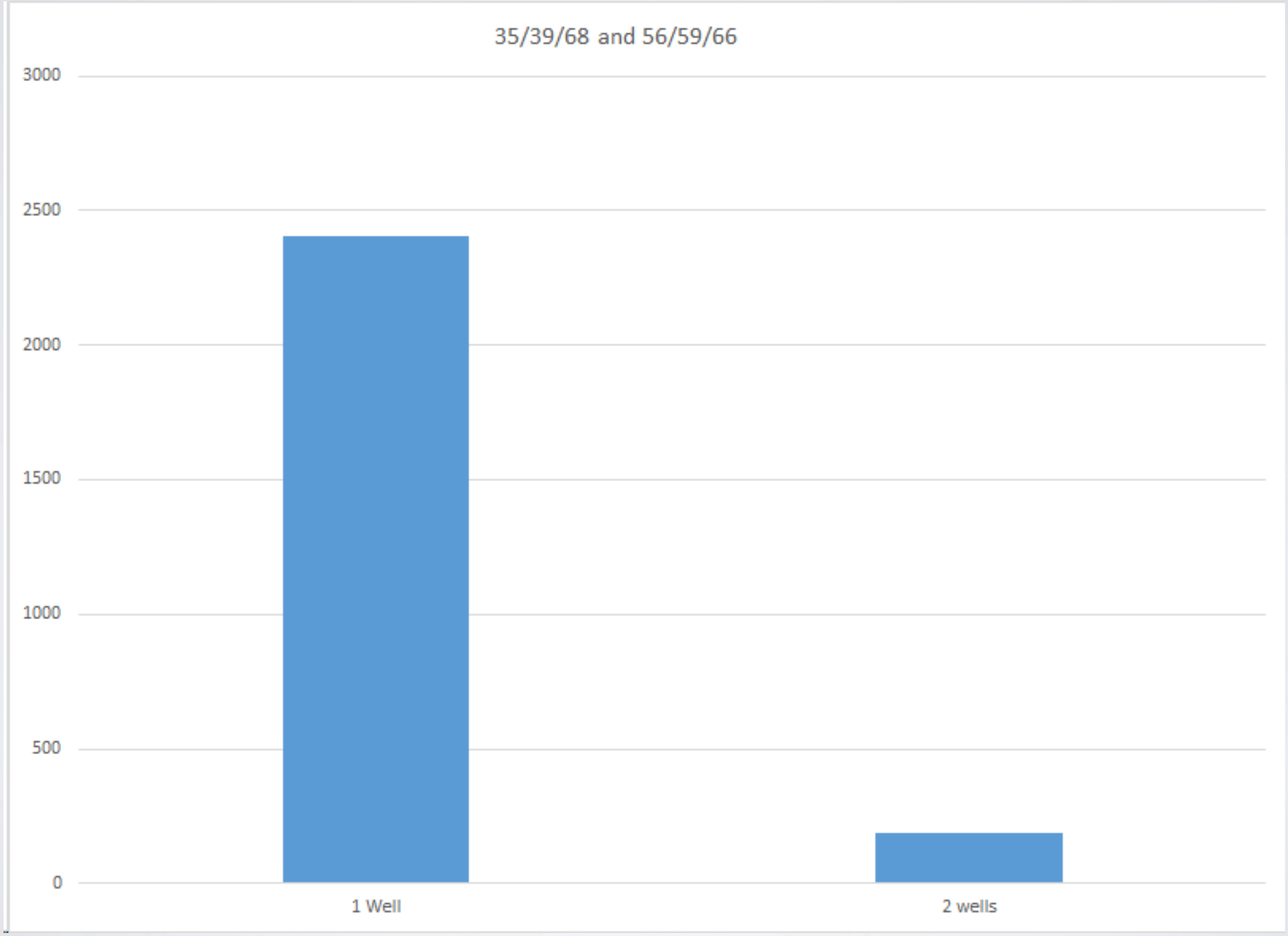
HPV 16 and 18 co-infections are rare



Co-infections
Other single wells plus P1



Co-infections
P2 and P3



Summary observations

- Prevalence ranking similar to 10 years previously
- Partial genotyping masks true extent of Co-infections

- Other comments
- Type specific clearance has been observed
- Type specific persistence has been used in management decision making
- Multiple infection a feature of older women
  - Consistent with same previous studies

- Real possibility to improve both clinical outcomes and monitoring.