Implementation of HPV based cervical cancer prevention strategies

A/Prof. Marion Saville
Executive Director

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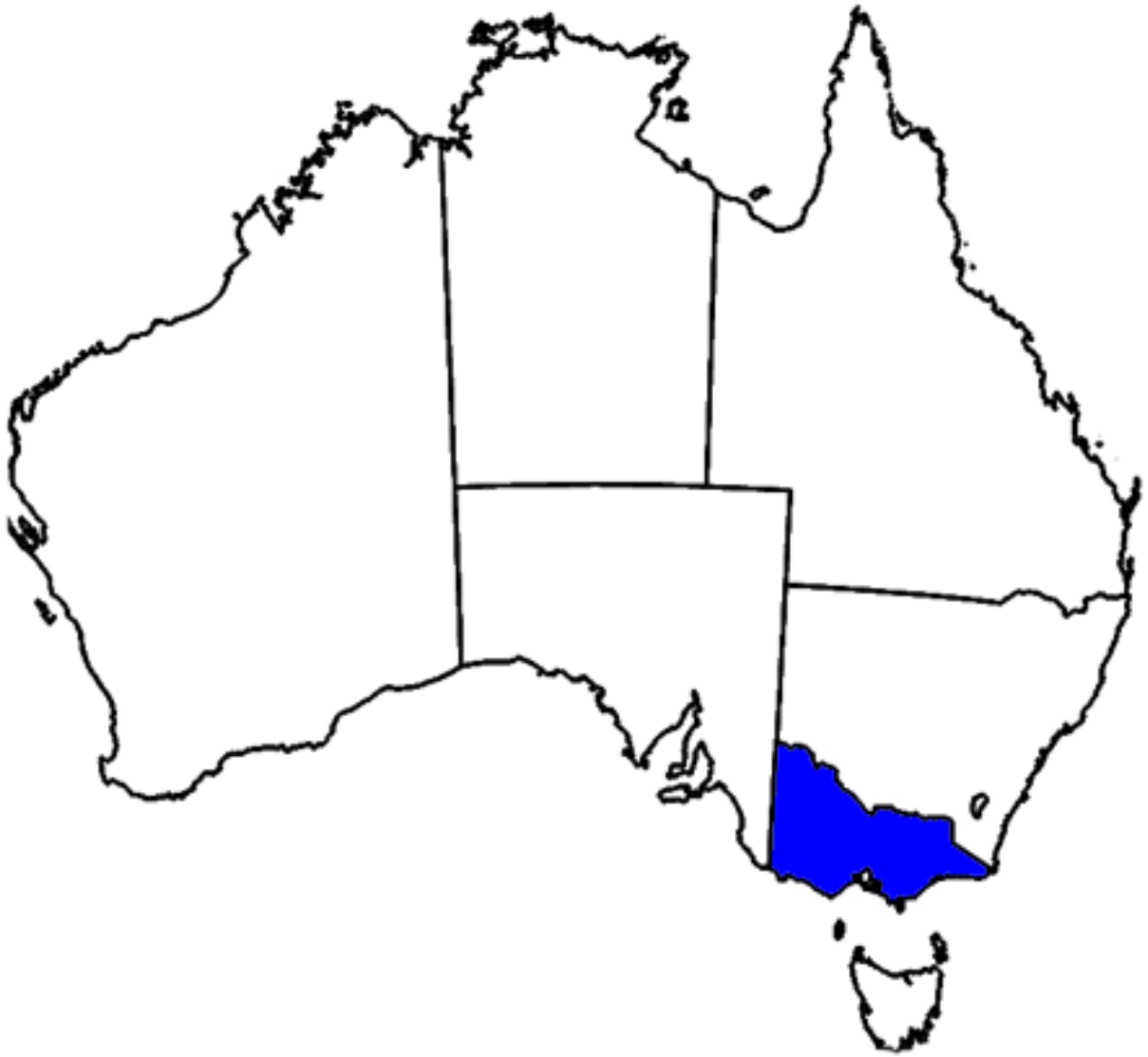
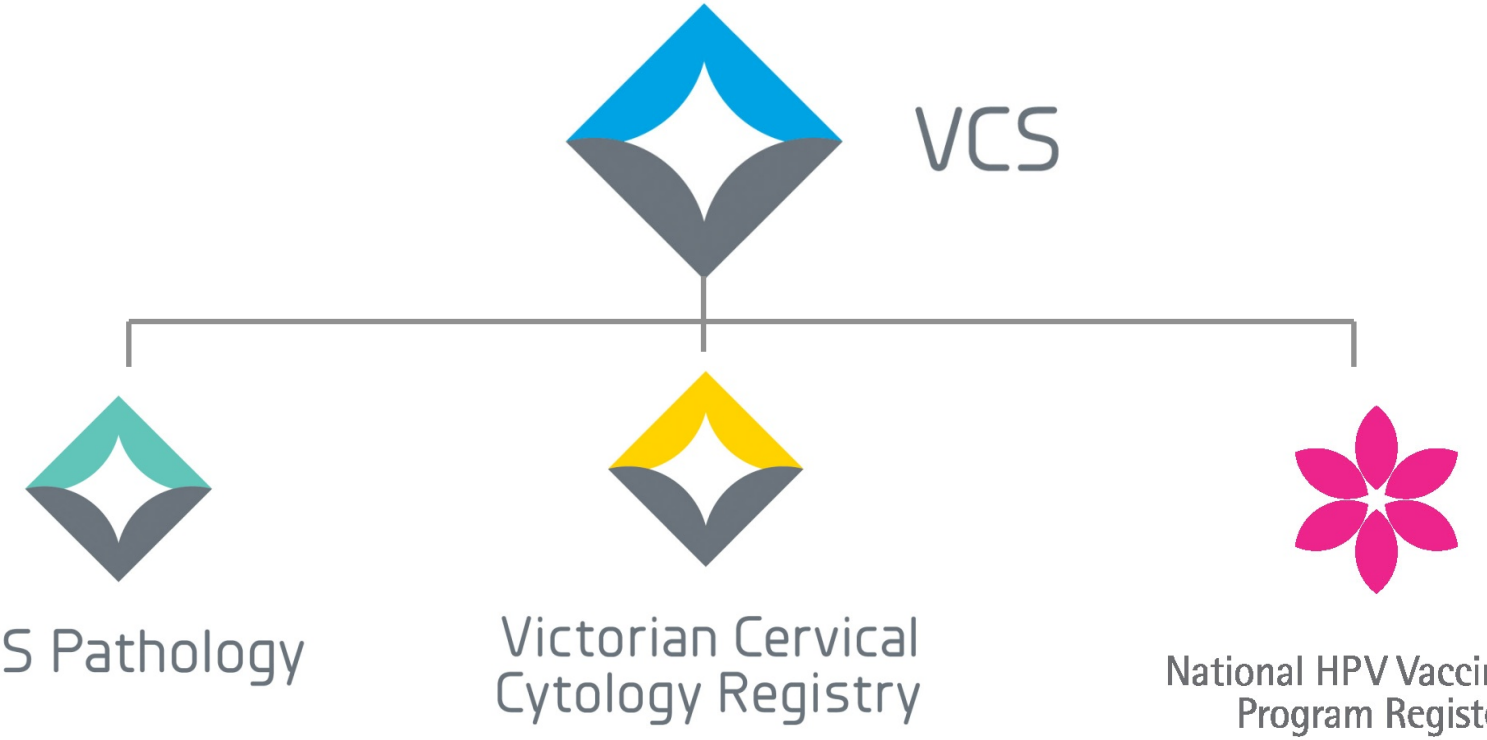




A specialist gynecological pathology laboratory

- Cervical cytology 300,000 per annum, predominantly conventional
- Cervical histopathology
- HPV testing

A state based Pap test registry

- Follow up, reminders
- Supports programme monitoring and evaluation
- Provides framework for quality monitoring of laboratories

A **national** register recording HPV dose information

- Course completion statements
- Reminder functions
- Supports programme monitoring and evaluation

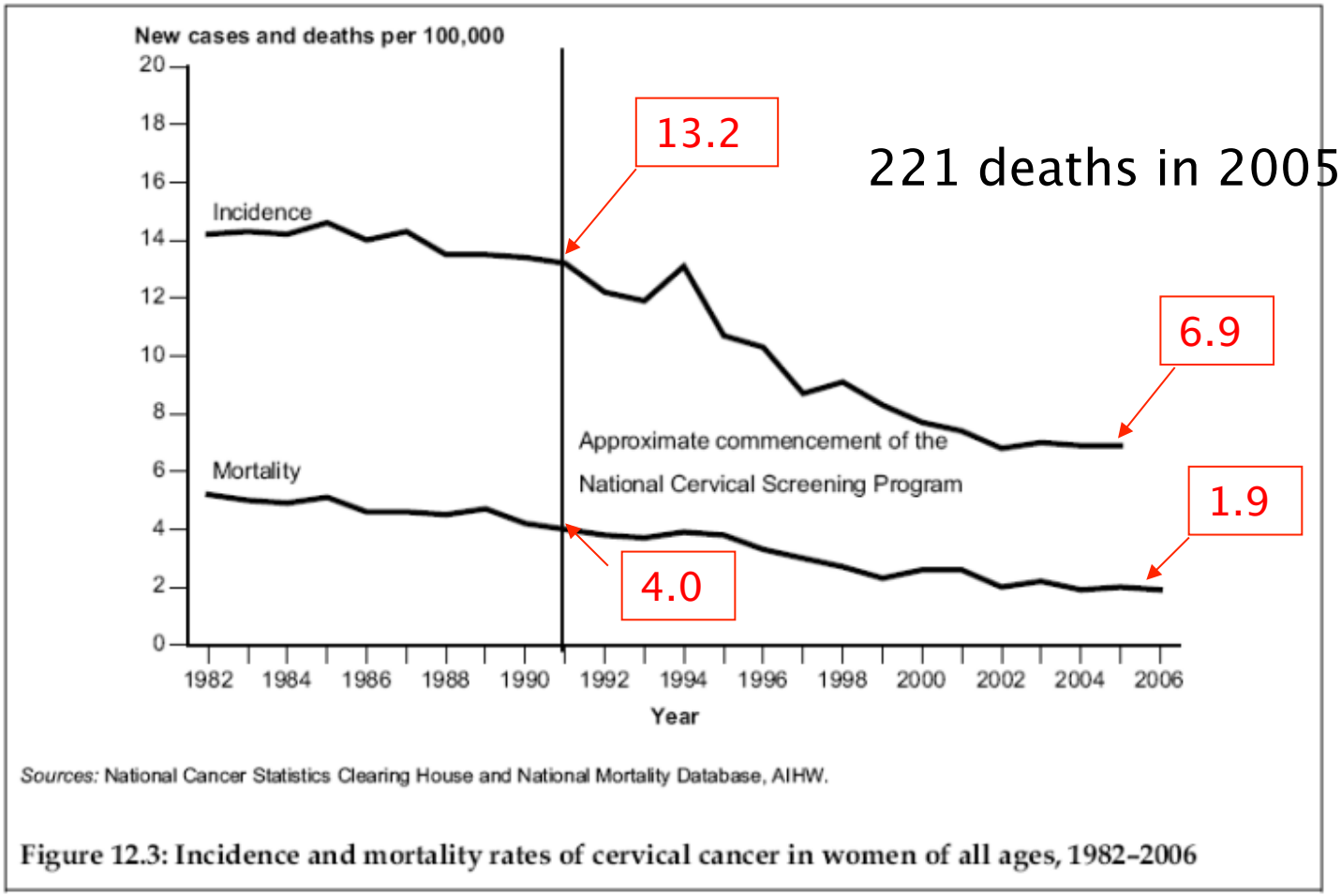
Cervical cancer prevention in Australia

- National Cervical Screening Programme
  - Impact
  - Participation
- National HPV vaccination programme
  - Participation/ Equity
  - Impact
- Integrating screening and vaccination
  - Evidence for HPV primary screening
    - Policy response
    - Research initiatives

Our National Cervical Screening Programme

- In place as an organised programme for 20 years
  - Based on conventional cytology (Papanicolaou smear)
  - Women aged 18-69 years
  - Screening recommended every 2 years

Incidence and mortality rates of cervical cancer in Australia



Sources: National Cancer Statistics Clearing House and National Mortality Database, AIHW.

Figure 12.3: Incidence and mortality rates of cervical cancer in women of all ages, 1982–2006

Source: AIHW (Australian Institute of Health and Welfare) & AACR (Australasian Association of Cancer Registries) 2008. Cancer in Australia: an overview, 2008. Cancer series no. 46. Cat. no. CAN 42.Canberra: AIHW.

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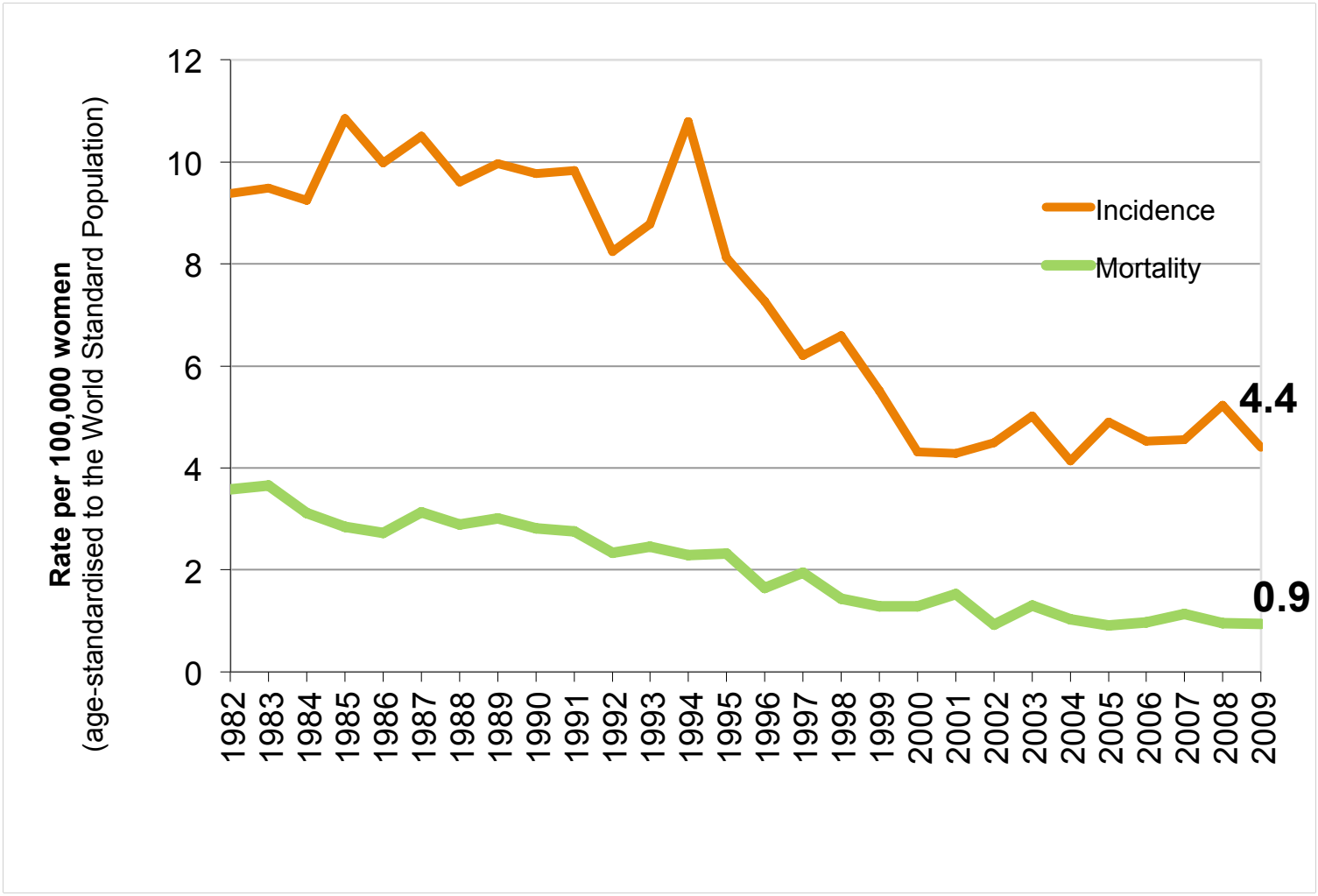
In Victoria 2009



Victorian Cervical Cytology Registry

The vast majority of cervical cancers occur in underscreened women

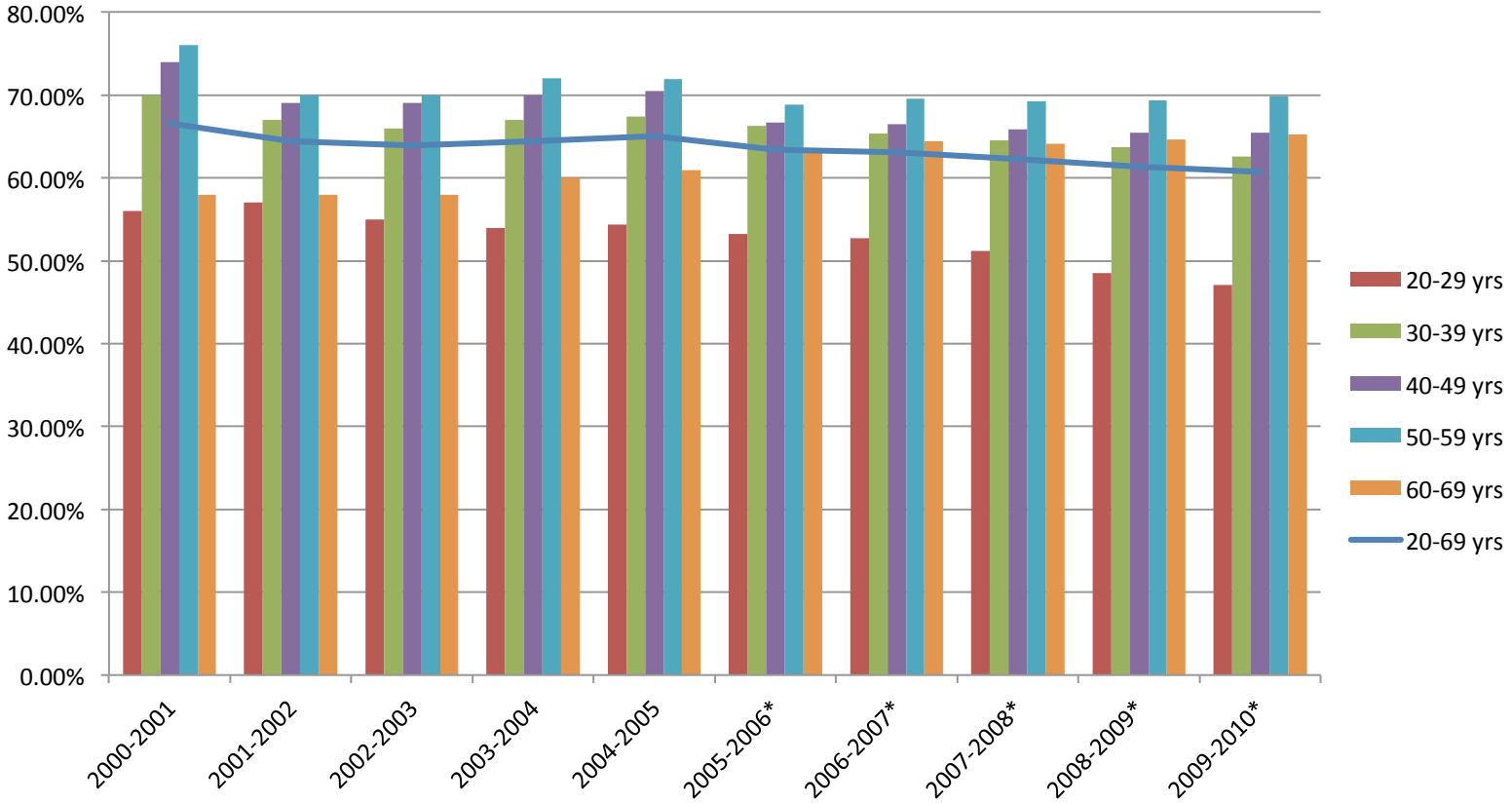
Table 9: Screening history of Victorian women diagnosed with cervical cancer for the period 1 January 2008 to 31 December 2008.

Screening History	Invasive Squamous cell carcinoma Number	(%)	Other invasive cervical cancer Number	(%)	Invasive Sub-Total		Micro-invasive Sub-Total		Invasive & Micro-invasive Total	
A. Never screened	46	61%	36	56%	82	59%	13	32%	95	52%
B. Lapsed screeners (last screen greater than 2.5 years)	17	22%	14	22%	31	22%	9	22%	40	22%
C. Adequately screened (last screen within 2.5 years)	5	7%	12	19%	17	12%	11	27%	28	15%
D. Delayed diagnosis	3	4%	1	2%	4	3%	7	17%	11	6%
E. Not eligible	5	7%	1	2%	6	4%	1	2%	7	4%
Total	76	100%	64	100%	140	100%	41	100%	181	100%

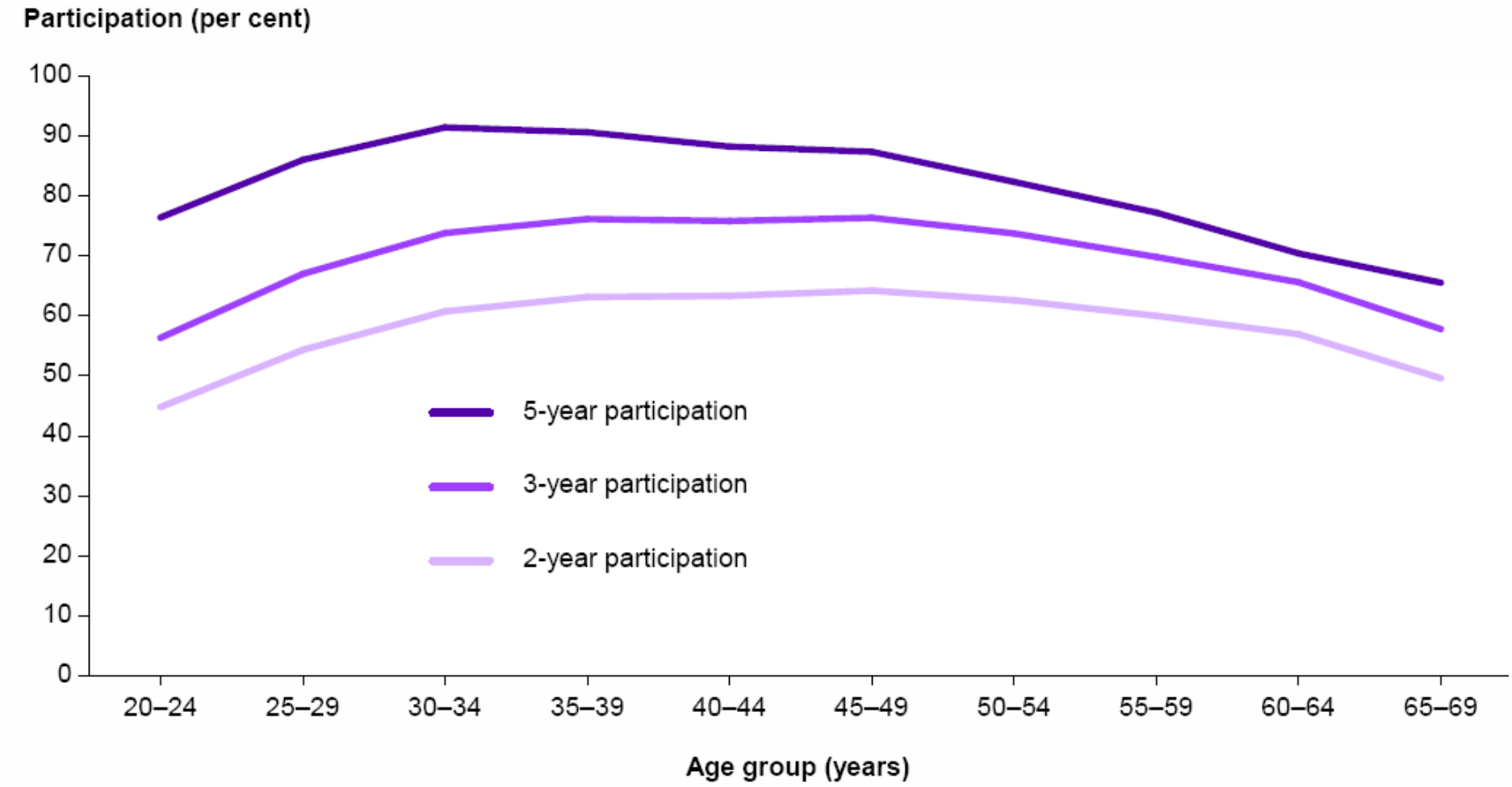
1 Women over 70 years and with a negative screening history are outside the eligible range for the screening program. Refer to the National Cervical Screening Program at www.cancerscreening.gov.au

Victorian Cervical Cytology Registry

2-yearly participation, by age, Victoria



Victorian Cervical Cytology Registry



Source: AIHW analysis of state and territory cervical cytology register data; data for figure are available in Table A1.

Figure 1.4: Participation of women aged 20–69, by age over 2 years (2009–2010), 3 years (2008–2010), and 5 years (2006–2010)

National HPV Vaccination Program: Australia

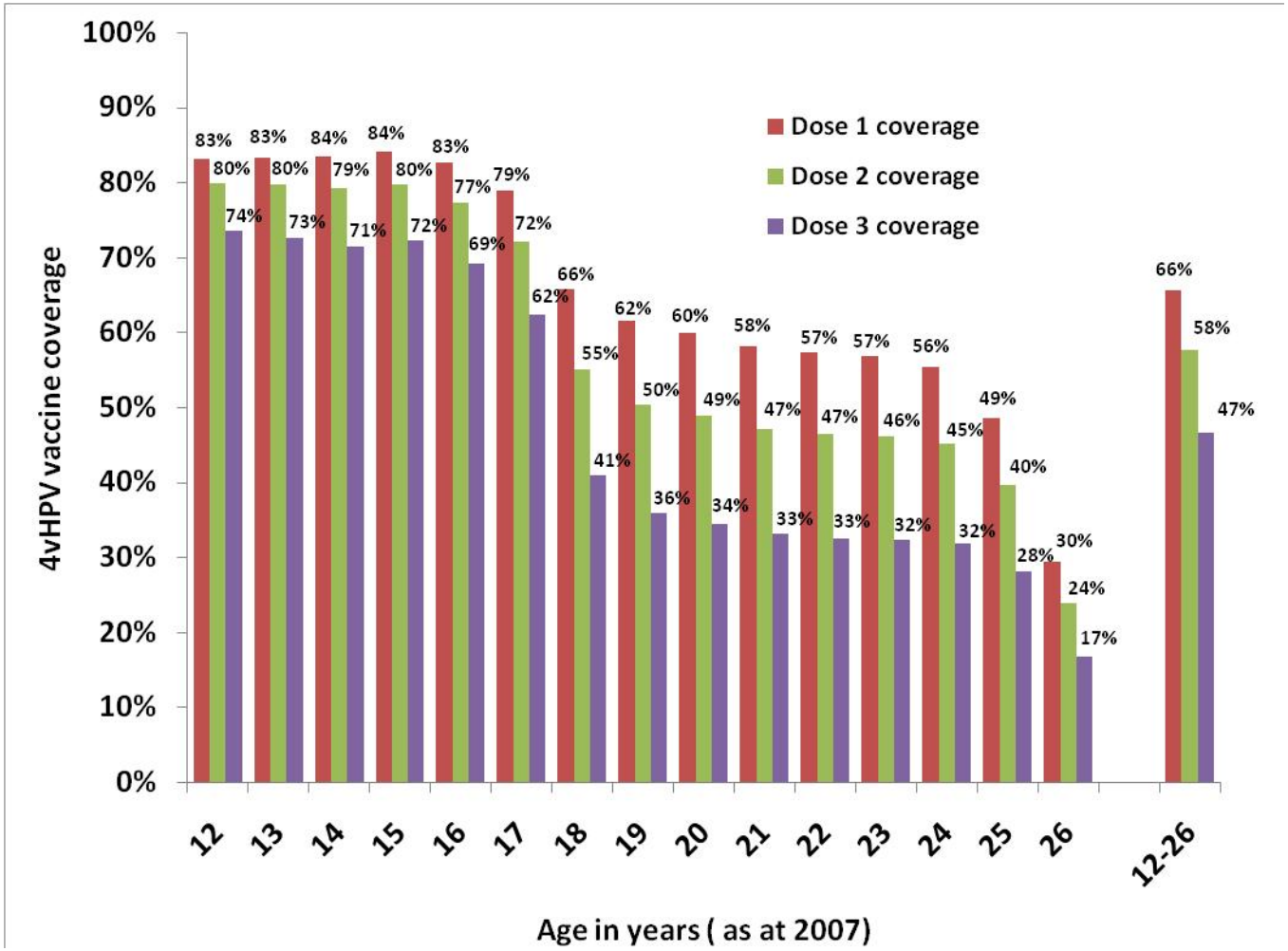
- Commenced 2007
  - Ongoing routine vaccination of 12-13 year old girls
  - School and GP-based catch-up to age 26 from 2007-9
- 3 doses over ~4-6 months; Gardasil
- Recommended inclusion of males in program in Nov 2011

Vaccination coverage in females

Age in 2007	12-13	14-15	16-17	18-19	20-26
3-dose coverage*	73%	72%	66%	38%	30%

**** Data extracted from the NHVPR as at 22 March 2011. See: http://www.health.gov.au/internet/immunise/publishing.nsf/Content/immunise-hpv***

National notified coverage Australia



As held at Sept 2011. Excludes consumers who have opted off.

The HPV Register

Equity in screening vs vaccination

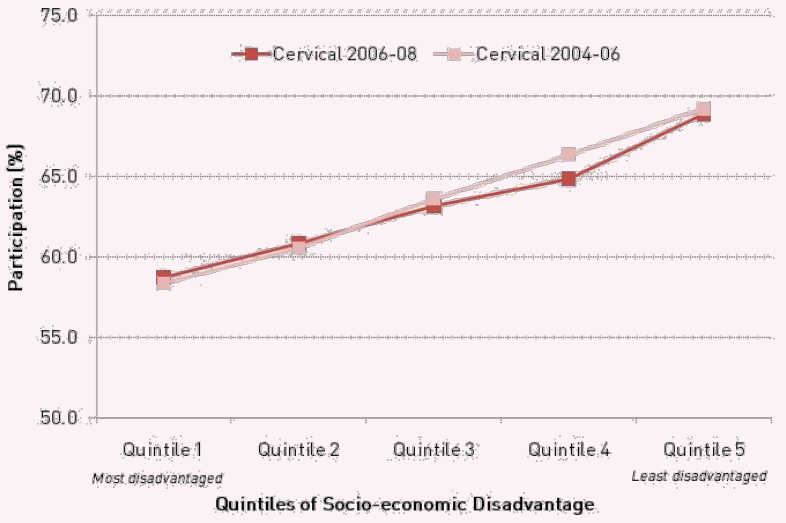
- Women of low SES are less likely to participate in screening
- If HPV vaccine coverage lower among low SES women, existing inequities could widen

Victorian Cervical Cytology Registry

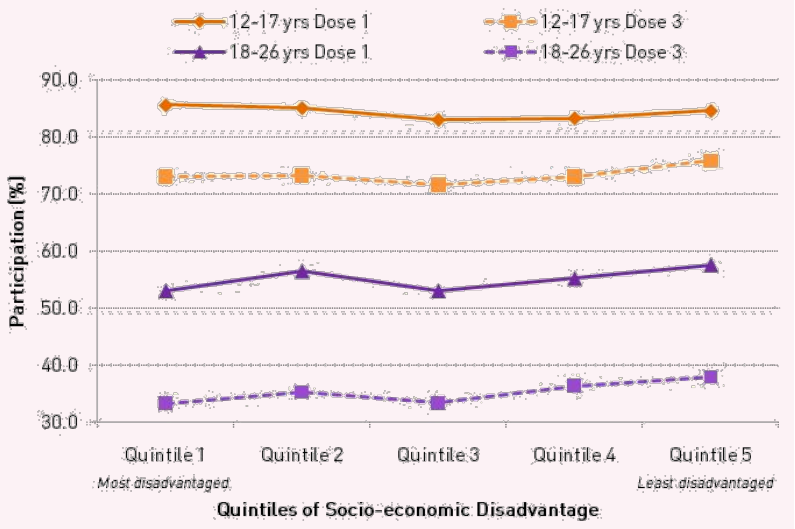
Equity In Screening vs Vaccination

Victoria, Australia (Barbaro, Brotherton and Gertig Med J Aust 2012)

National Cervical Screening Program by socioeconomic status, Victoria



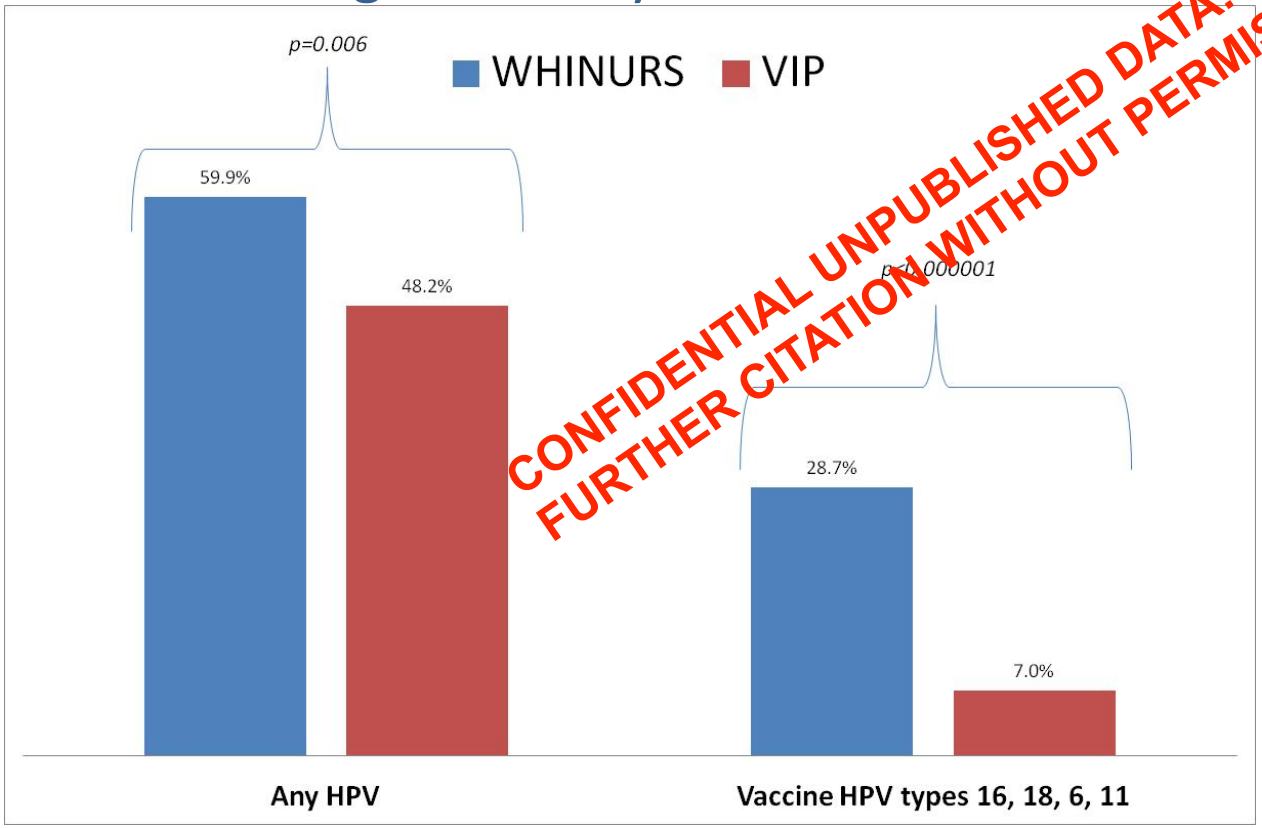
National HPV Vaccination Program by socioeconomic status, Victoria



Victorian Cervical Cytology Registry

Interim VIP results

Women aged 18-24 years VIP n= 446



Preliminary results show that the differences remain highly significant when adjusted for age, OCP use, smoking, SES and remoteness.

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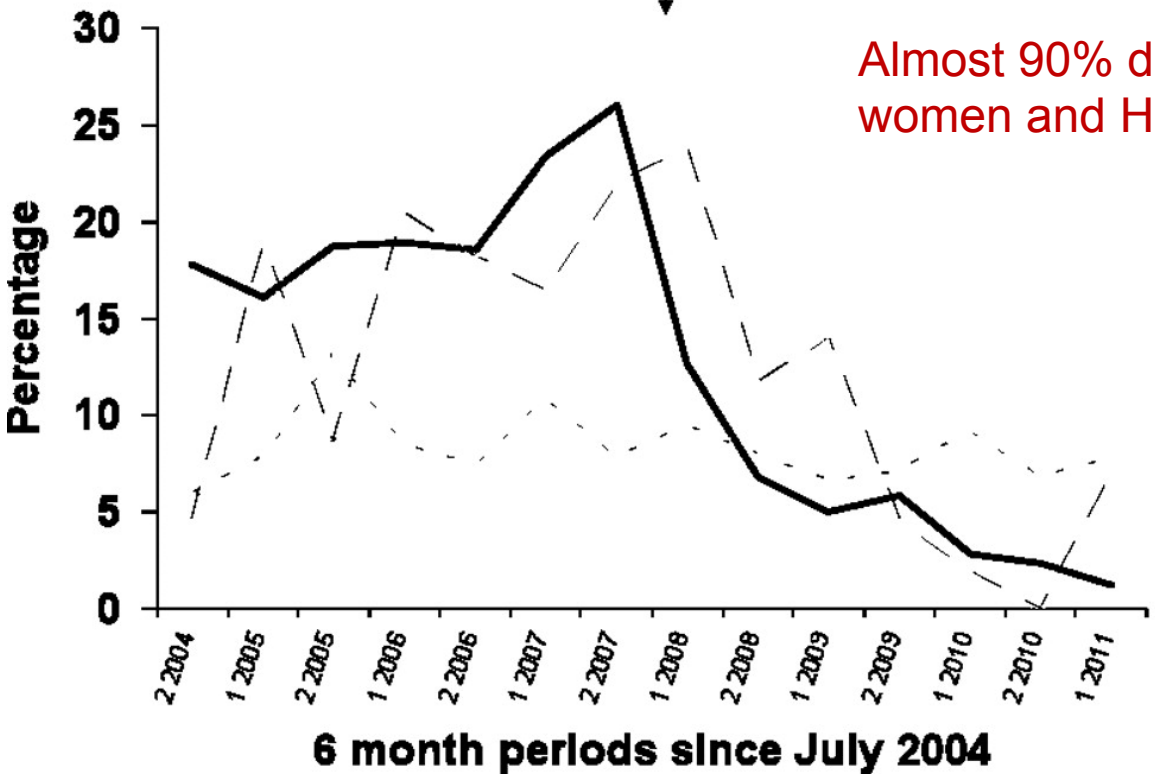
Presentations with warts in men and women <21 years, and MSM all ages, July 2004 to end June 2011



Almost 90% decline in genital warts in women and HSM < 21 years since July 2007

Adjusted OR pre and post July 2007(no. of sex partners)

Females <21 Pre 1.11 (0.9-1.4)
Post 0.44 (0.3-0.6)
MSW <21 Pre 1.32 (0.9-1.9)
Post 0.42(0.3-0.6)

Non residents excluded

Read T R H et al. Sex Transm Infect doi:10.1136/sextrans-2011-050234

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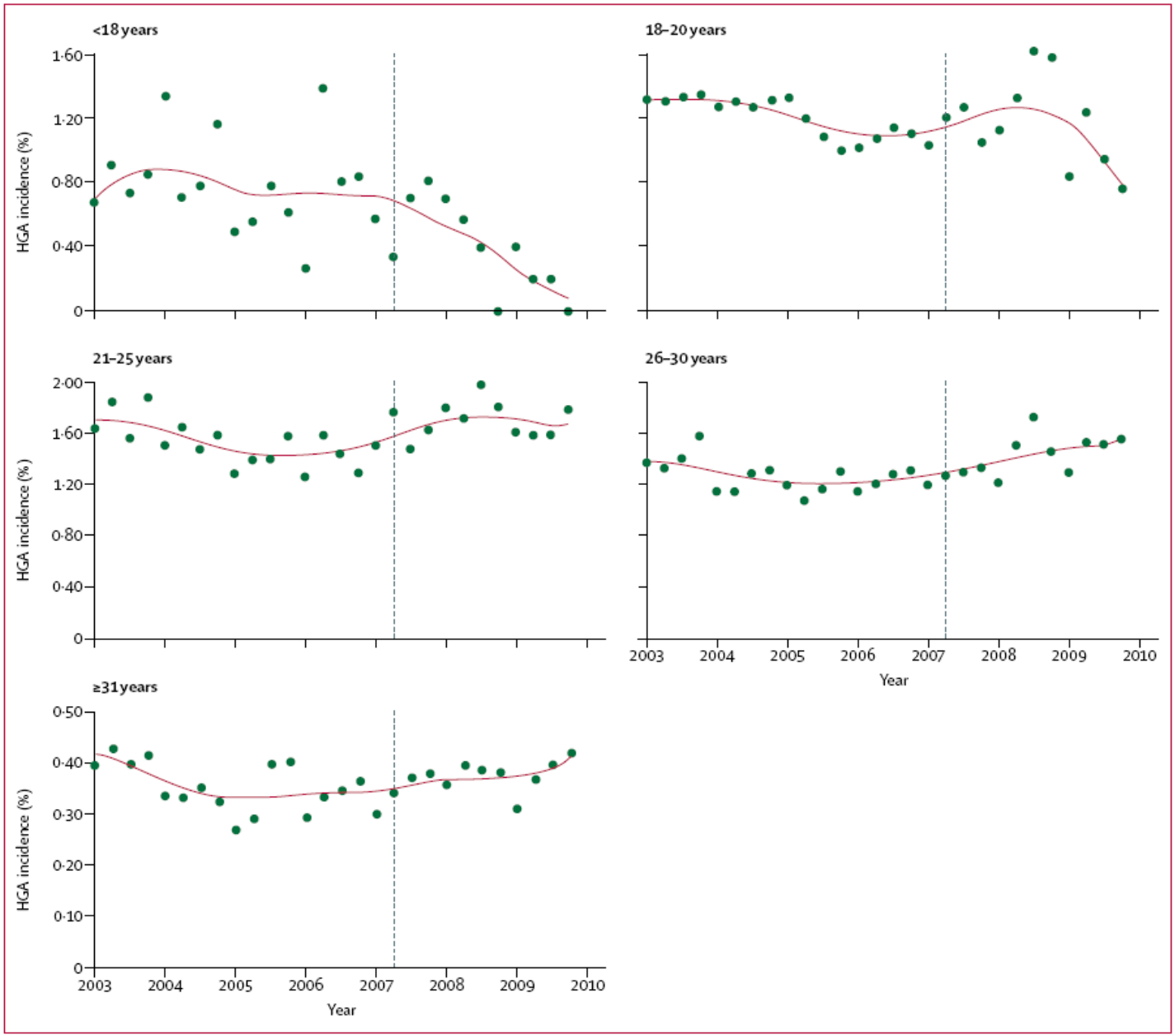


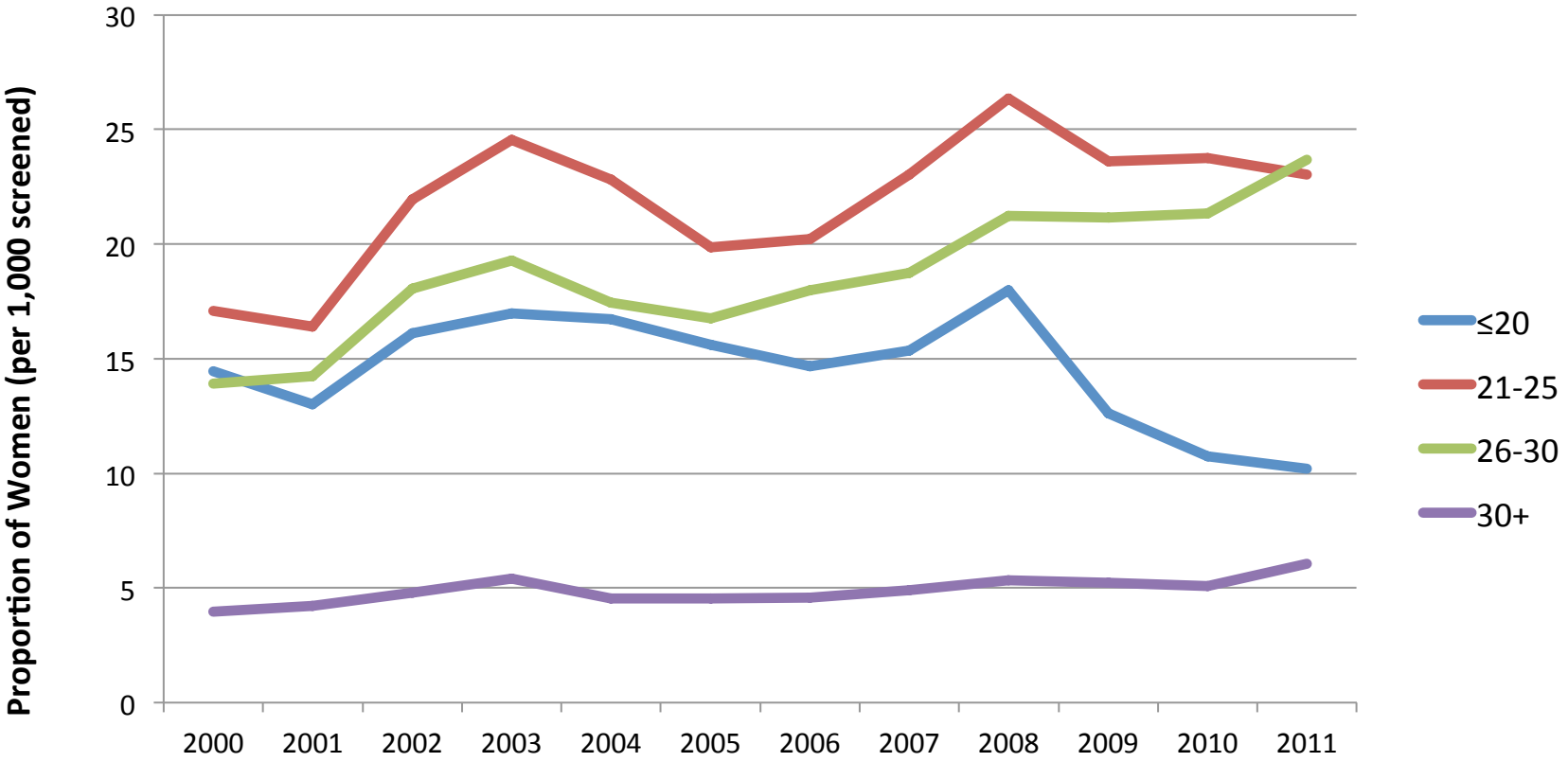
***Figure 2*: Incidence of high-grade cervical abnormalities, by age group**

Incidence of high-grade cervical abnormalities (HGA; green dots) is the number of new diagnoses within a 3-month period per 100 women tested. Lowess smoothing trends are shown with red lines. The vertical lines, at the start of the second quarter in 2007, signify the introduction of human papillomavirus vaccination.

Brotherton J, Fridman M, May CL, Chappell G, Saville AM, Gertig D, Early effect of the HPV vaccination program on cervical abnormalities in Victoria, Australia; Ecological Study. Lancet 2011

Victorian Cervical Cytology Registry

Trends In High-grade Cervical Abnormalities (Histologically-confirmed) By Age



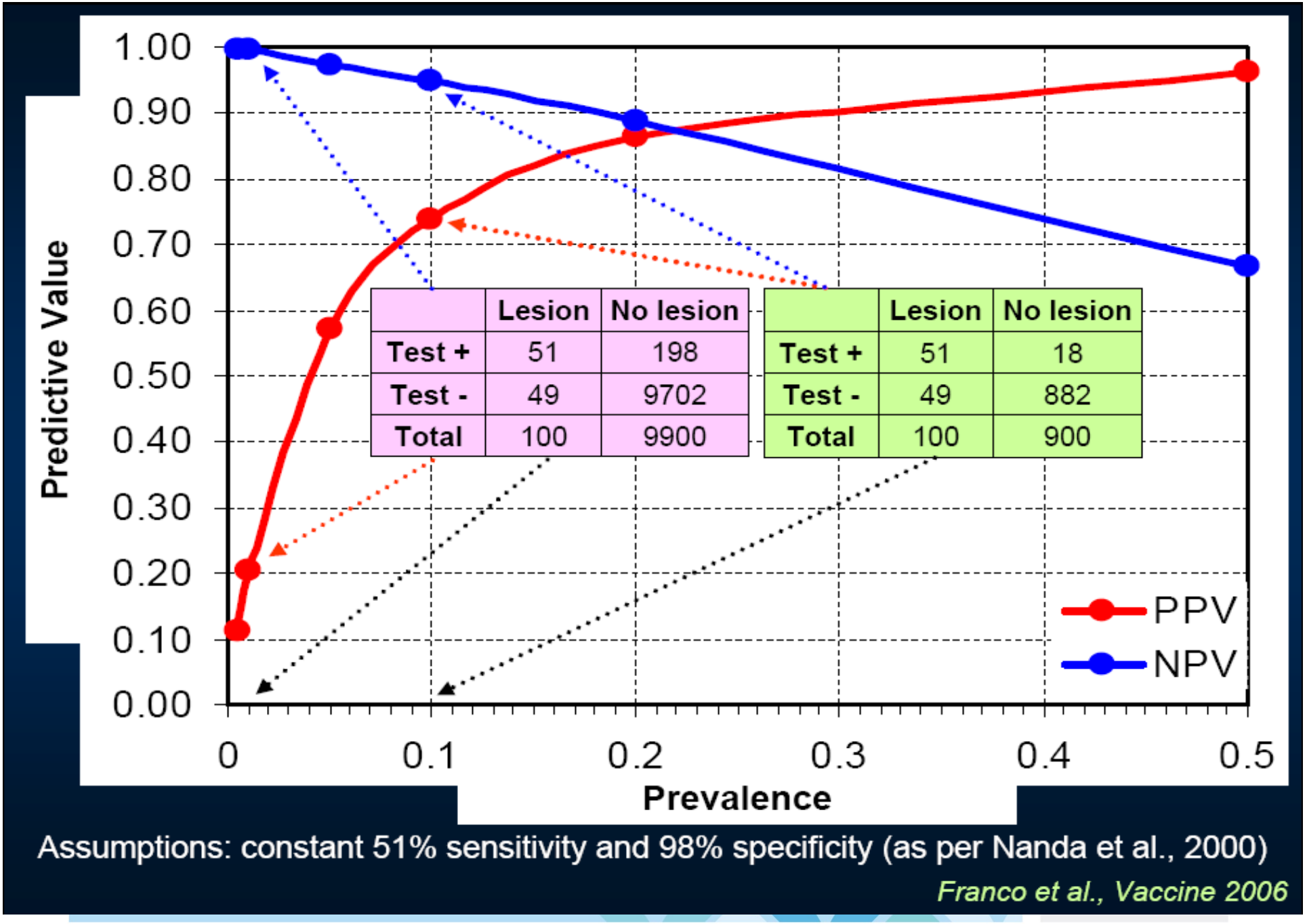
Victorian Cervical Cytology Registry

The need for linkage

- We are in the process of linking the HPV vaccine register to the Pap test register
  - We intend to examine abnormality rates by vaccine status
  - We will also examine screening participation by vaccine status

Vaccine impact on screening

- Average risk of invasive cervical cancer in population will decline
- Cost-effectiveness of existing screening programs will decline
- The test performance characteristics of cytology are likely to decline as the prevalence of screening target (HSIL) falls



Assumptions: constant 51% sensitivity and 98% specificity (as per Nanda et al., 2000)

Franco et al., Vaccine 2006

Pap smear and HPV testing

- Cervical cytology
  - Conventional cytology
  - Liquid-based cytology (LBC)
  - Image-read LBC

- HPV DNA/mRNA testing
  - Plethora of emerging technologies
  - Performance benchmark established (HC2™ Qiagen)*

Meijer C et al. Guidelines for human papillomavirus DNA test requirements for primary cervical cancer screening in women 30 years and older. Int J Cancer 2009

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Cervical screening in the era of HPV vaccination

- Do we have different screening programmes for vaccinated and unvaccinated women?
  - too complex
    - Will practitioners contact a register on a woman by woman basis before collecting a Pap smear?
    - Will practitioners rely on women's recall?

Cervical screening in the era of HPV vaccination cont/..

- Do we screen all women less intensively?
  - **equity issues**
    - This approach will not deliver a screening programme that is appropriate for individual women's risk of developing cervical cancer.

Why might a women in a vaccinated cohort develop cancer?

- Not vaccinated
- Missed some doses
- Vaccine failure
- Other oncogenic types

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All will have acquired high risk HPV infections and developed persistence

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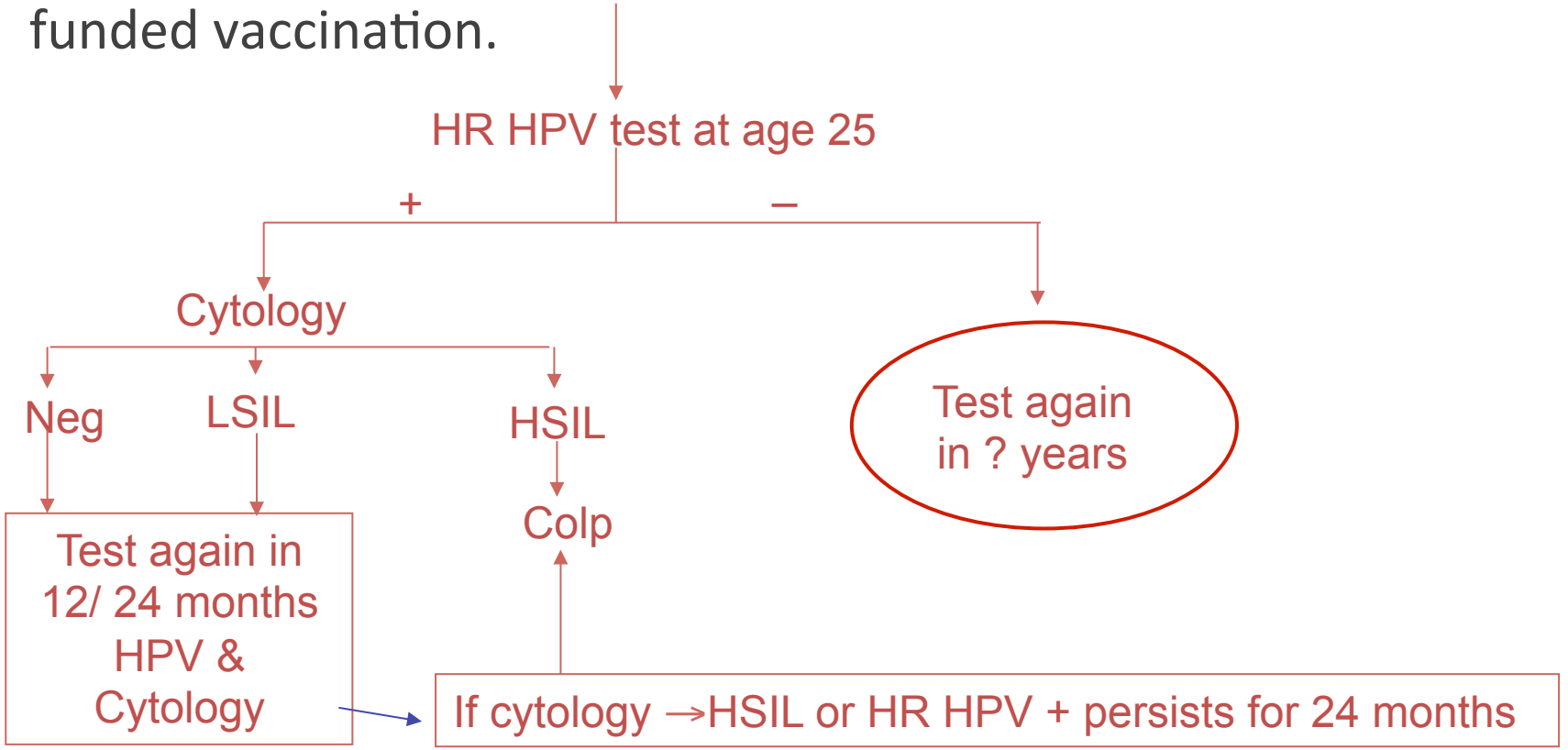
Proposed screening algorithm

Start with all women who are of an age to be offered publicly funded vaccination.



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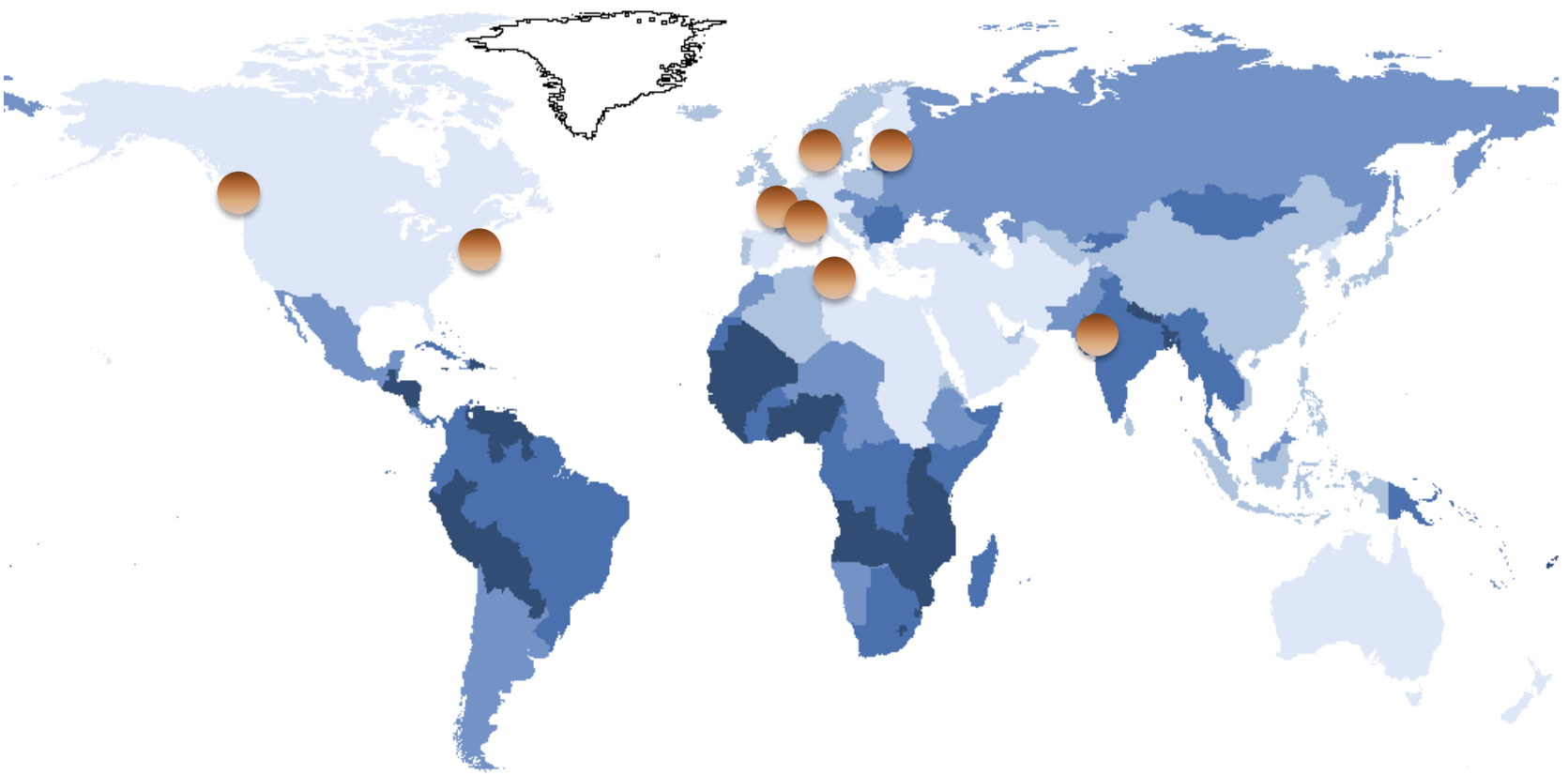
Estimated age-standardised incidence rate per 100,000
Cervix uteri, all ages



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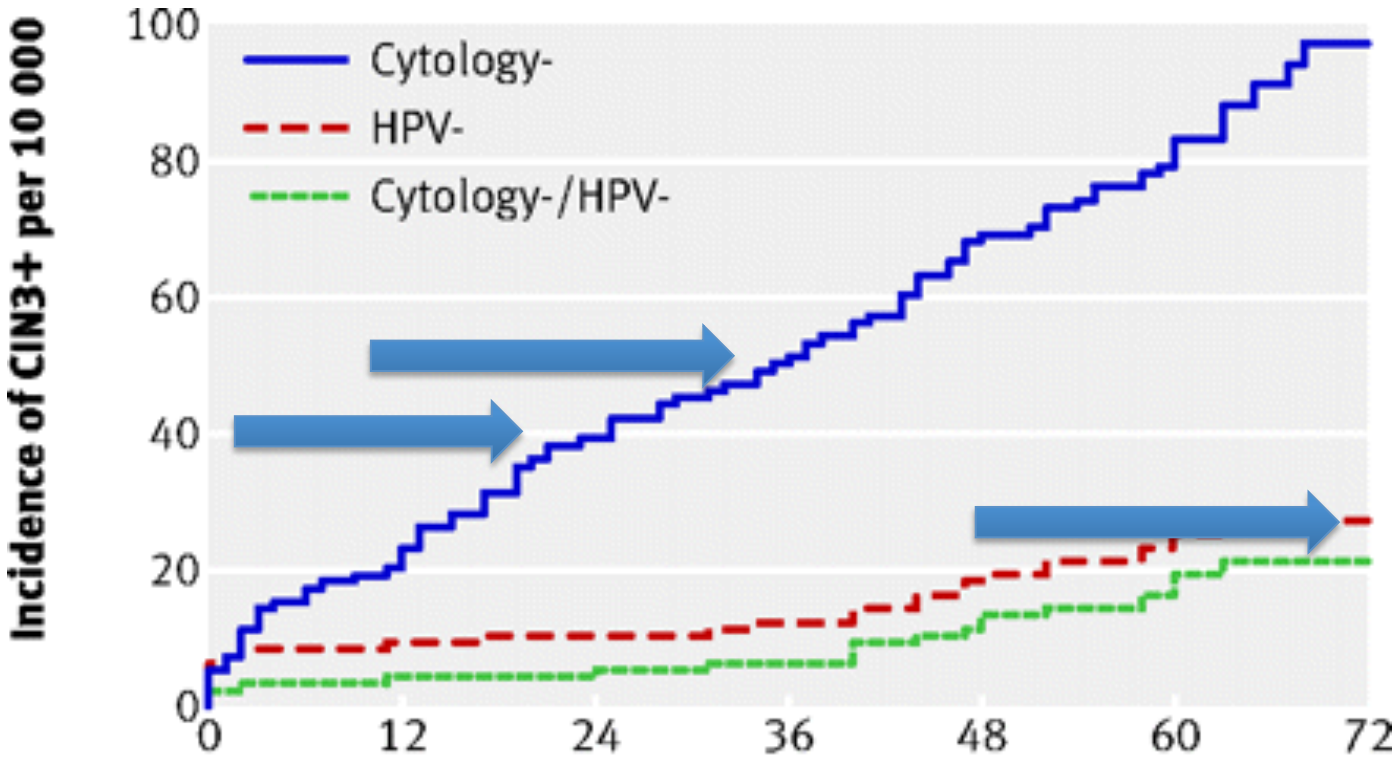
Estimated cervical cancer incidence 2008

Longitudinal outcomes:

HPV and cytology negative women



"Low risk"

BMJ

Dillner, J. et al. Joint European** Cohort **Analysis. BMJ 2008;337:a1754

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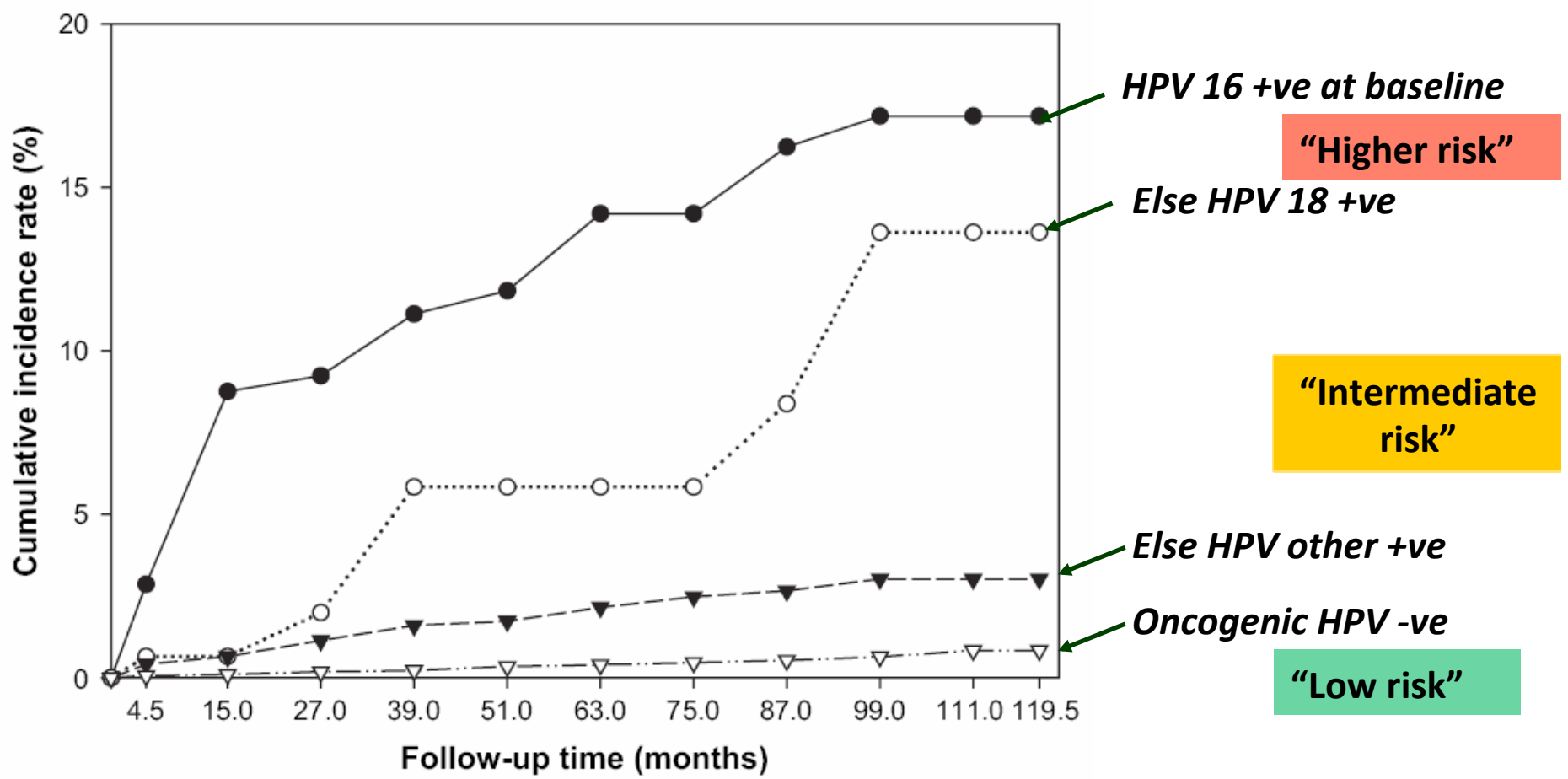
Pobascam trial: Netherlands

- HPV+ cytology co-testing (intervention) vs. cytology alone
- Women aged 29-56 years
- Follow-up on ~34,000 women
- Two rounds of screening @5 years

	Detection of…	RR intervention vs control
Baseline round	CIN2+	1.25 (1.05-1.50)
Second round @5 years	CIN3+	0.73 (0.55-0.96)
	Invasive cervical cancer	0.29 (0.10-0.87)

Rijkaart et al, Lancet Oncology 2012

Longitudinal outcomes:
HPV positive women



Cumulative CIN3+ in 20,514 women (median age 34 years)

Khan MJ, Castle PE, et al. The elevated 10-year risk of cervical precancer and cancer in women with human papillomavirus (HPV) type 16 or 18 and the possible utility of type-specific HPV testing in clinical practice. JNCI 2005

National Cervical Screening Program

A joint Australian, State and Territory Government initiative

Renewal of the National Cervical Screening Programme

- **Aim**
  - To ensure that all Australian women, HPV vaccinated and unvaccinated, have access to a cervical screening program that is safe, acceptable, effective, efficient and based on current evidence
- **Objectives**
  - Assess the evidence for screening tests and pathways, the screening interval, age range and commencement for both vaccinated and non-vaccinated women;
  - Determine a cost-effective screening pathway and program model;
  - Investigate options for improved national data collection systems and registry functions to enable policy, planning, service delivery and quality management; and
  - Assess the feasibility and acceptability of the renewed program for women.

	Comparator	Scenario 1	Scenario 2	Scenario 3
Primary screening test	Conventional Cytology	Conventional Cytology	LBC (cell filtration and cell enrichment separately)	HPV DNA testing
Age range	Women aged 18/69 years	Women aged 25-64 years (IARC recommendations)		
Interval	2 years	3 years (aged 25-49) and 5 years (aged 50-65) (IARC recommendations)		No less than 5 years (a range of intervals should be considered)

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Future directions
in cervical screening

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Why another primary HPV RCT?

- Evaluate primary HPV in partially vaccinated population using updated testing technology
- More focus on optimal management of HPV positive women
- Specific evaluation of safety, effectiveness and costs in Australian context
- **Pragmatic trial/demonstration of concept**

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Future directions
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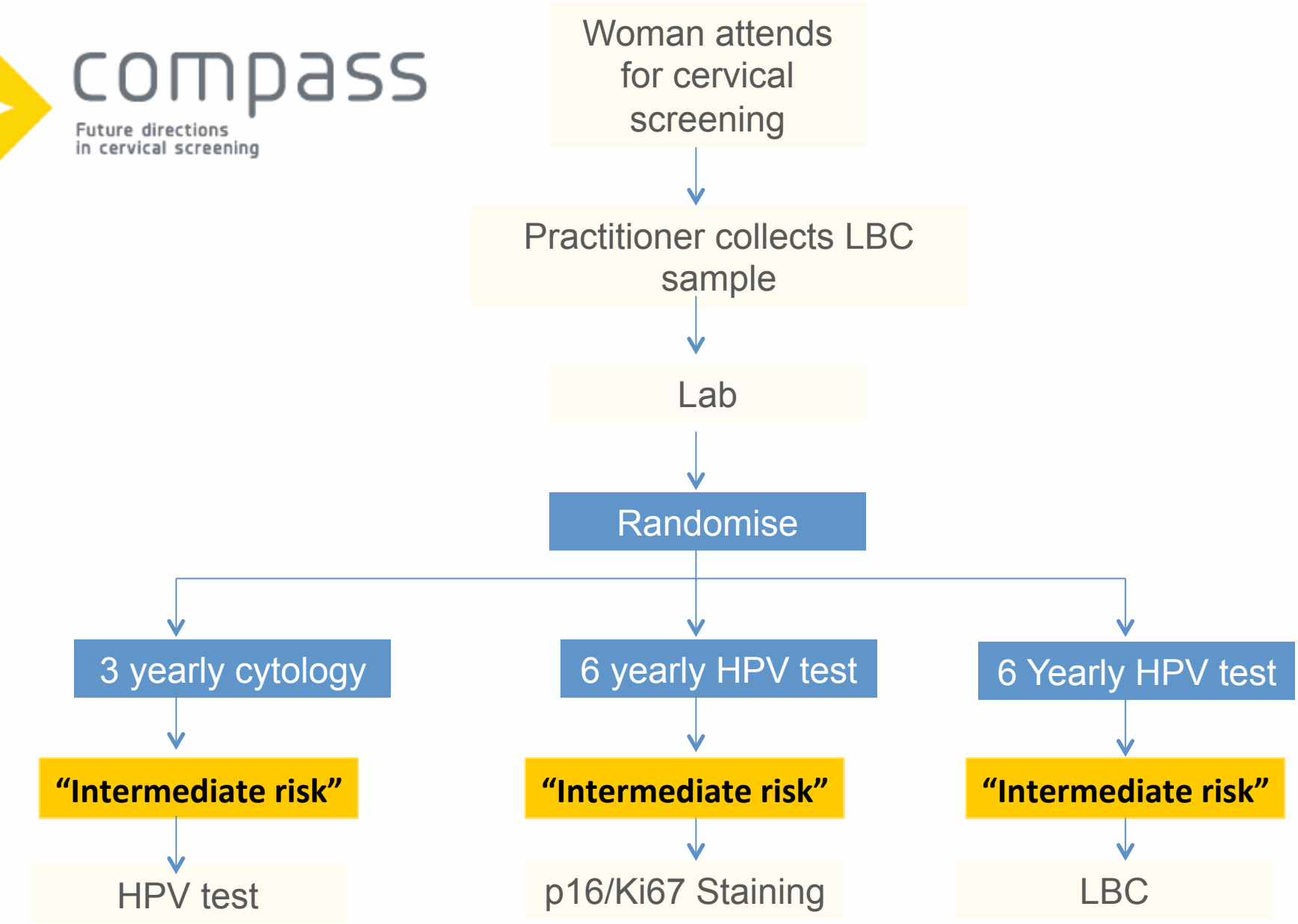

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Key elements

- Women aged 25-64 years recruited through primary care practices in Victoria
- 6-yearly HPV screening (with safety monitoring)
- Consenting women will have LBC sample taken, with laboratory-based randomization
- Management of follow-up via VCCR
- Active recall for rescreening prior to six years
- Stratification by <30, 30+ years
  - Post-hoc linkage to NHPVR (vaccination register)
- Disease status ascertainment in random sample of screen-negative women
- Post-hoc age/LGA matched analysis with non-participating women on VCCR

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Pilot study

- 5,000 women at 1:2:2 randomisation allocation
- 2 primary screening technologies involved
- 4 practices recruiting

Aims of the Pilot:

- To assess recruitment rate
  - Overall and by practice
  - To quantify participant and GP acceptance of randomization process and use of longer routine screening intervals
- Assess laboratory feasibility for 2 technologies
  - Time and motion study
  - Volumetric process assessment
- To quantify test positivity rates for women <30, 30+ years
  - Preliminary cross-sectional analysis to assess positivity rates and diagnostic yield in the baseline screening round for histologically-confirmed CIN3

Conclusions

- In developed countries, several factors driving a move towards less intensive screening and older age of starting screening
- Primary HPV extremely promising – but still there are unanswered questions about implementation
- Need to evaluate screening technology changes in an integrated fashion:
  - Consider in conjunction with effect of vaccination, interval and age range changes
- Evaluation will involve:
  - Modelling for near term answers
  - Local clinical evaluation (Compass)

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- Jessica Darlington-Brown
- Dr Phil Castle
- Prof Bruce Armstrong
- Denise Walsh

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Future directions
in cervical screening

Co-Principal Investigators
•A/Prof Karen Canfell
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•A/Prof. Dorota Gertig (VCS)
•Dr. Julia Brotherton (VCS)
•Dr. David Wrede (RWH)
•Dr. Jeffery Tan (RWH)
•Dr. Sally Lord (CTC)
•Dr. Andrew Martin (CTC)
• A/Prof Kirsten Howard (USyd)

Key Responsibilities
•Protocol development , review and revision.

Associate Investigators
•Dr. Stella Heley
•Dr. Lara Roeske
•Gillian Phillips
•Dr. Jane Collins
•Sandy Anderson
•Jessica Darlington-Brown
•Others to be determined

Key Responsibilities
•Give advice on protocol and operational aspects of trial

Quality Assurance Panel Histopathology
Chair: A/Prof. Annabelle Farnsworth

Key Responsibilities
•Review histopathology slides in a blinded manner

Data Safety Monitoring Board (Chair: Prof. Michael Quinn)

Key Responsibilities
•Regularly review safety data in a blinded manner
•Recommend study termination if pre specified stopping criteria are met
•Make safety or monitoring recommendations as appropriate

Scientific Advisory Committee (Chair: Prof. Bruce Armstrong)

Key Responsibilities
•Advise on study protocol development
•Annual progress meetings (more frequent if required)
•Review pilot and main trial analysis

NHMRC Clinical Trials centre

Key Responsibilities
•Provision of randomisation mechanism
•Contribute to statistical aspects of protocol design

VCS

Key Responsibilities
•Laboratory Management
•GP Recruitment
•Participant recruitment
•Implement linkage to VCCR & NVPR

Cancer Council NSW

Key Responsibilities
•Lead protocol design
•Data management
•Lead data analysis and write-up

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