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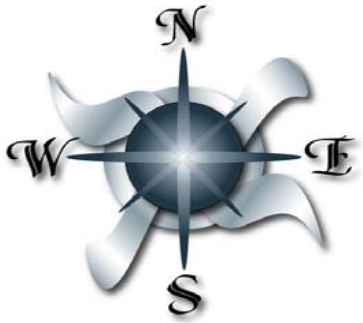


A Randomised Controlled Trial of Primary HPV Screening

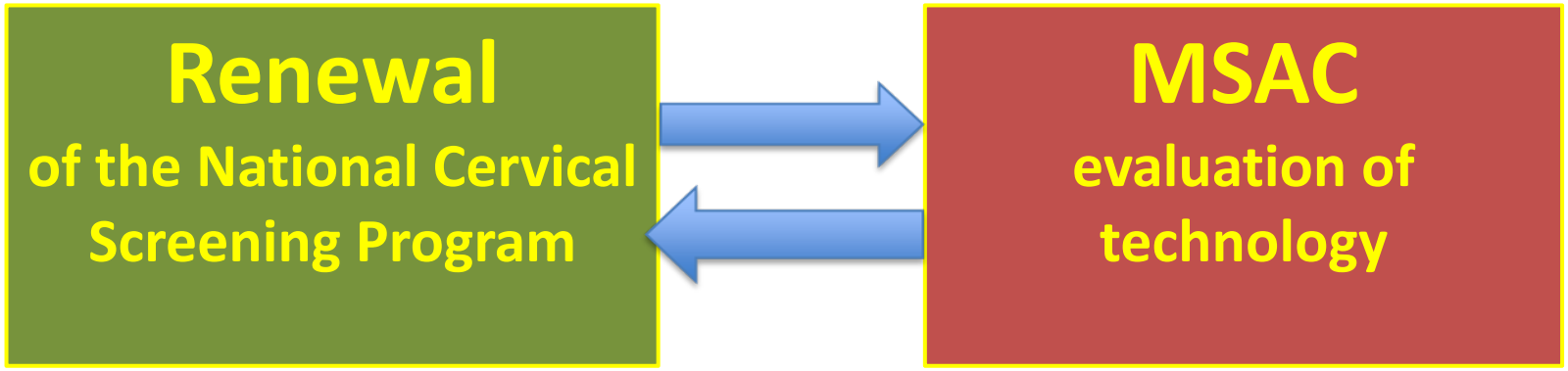
A joint initiative of the Victorian Cytology Service and Cancer Council NSW

A/Prof Karen Canfell and A/Prof Marion Saville

Victorian Cytology Service

Cancer Council NSW

Evaluation in Australia



To assess the impact of new technologies, age range, and screening interval on the Program

Medical Services Advisory Committee (MSAC) evaluation of new screening/triage technologies

<u>Evaluation methods likely to include</u>:

Systematic review of the international literature

Cost-effectiveness modelling for Australia

Local clinical evaluation?

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Some considerations in making any change

- Safety
- Effectiveness
- Cost-effectiveness
- Appropriate screening interval
- Appropriate age of starting screening
- Organisation of screening
- Implementation of triage strategies
- Impact on referral and treatment rates
- Laboratory processing issues
- Acceptability to women
- Acceptability to practitioners

Cost-effectiveness

Fundamentally depends on:

- Ultimate benefit associated with the change:
  - Life Years Saved (LYS) or QALYS
  - Driven by cervical cancer mortality
- Costs:
  - Direct costs associated with new technology
  - Potential cost savings: decreased screening interval
  - Potential cost increases: increased referral rates

Modelling

International data:
Vaccine efficacy
Screening test accuracy

Local information:
Vaccination age
Catch-up range and timing
Vaccination coverage

Screening recommendations
Compliance
Cytology reporting rates
Biopsy rates

Proposed change:
New management pathway or technology

MODEL

Predicted outcomes:
HPV infections
Detected LG, HG
Cancer incidence
Cancer mortality
(life years saved)
Costs and cost-effectiveness

Modelling is a formal mechanism to integrate the existing evidence and make predictions for the future

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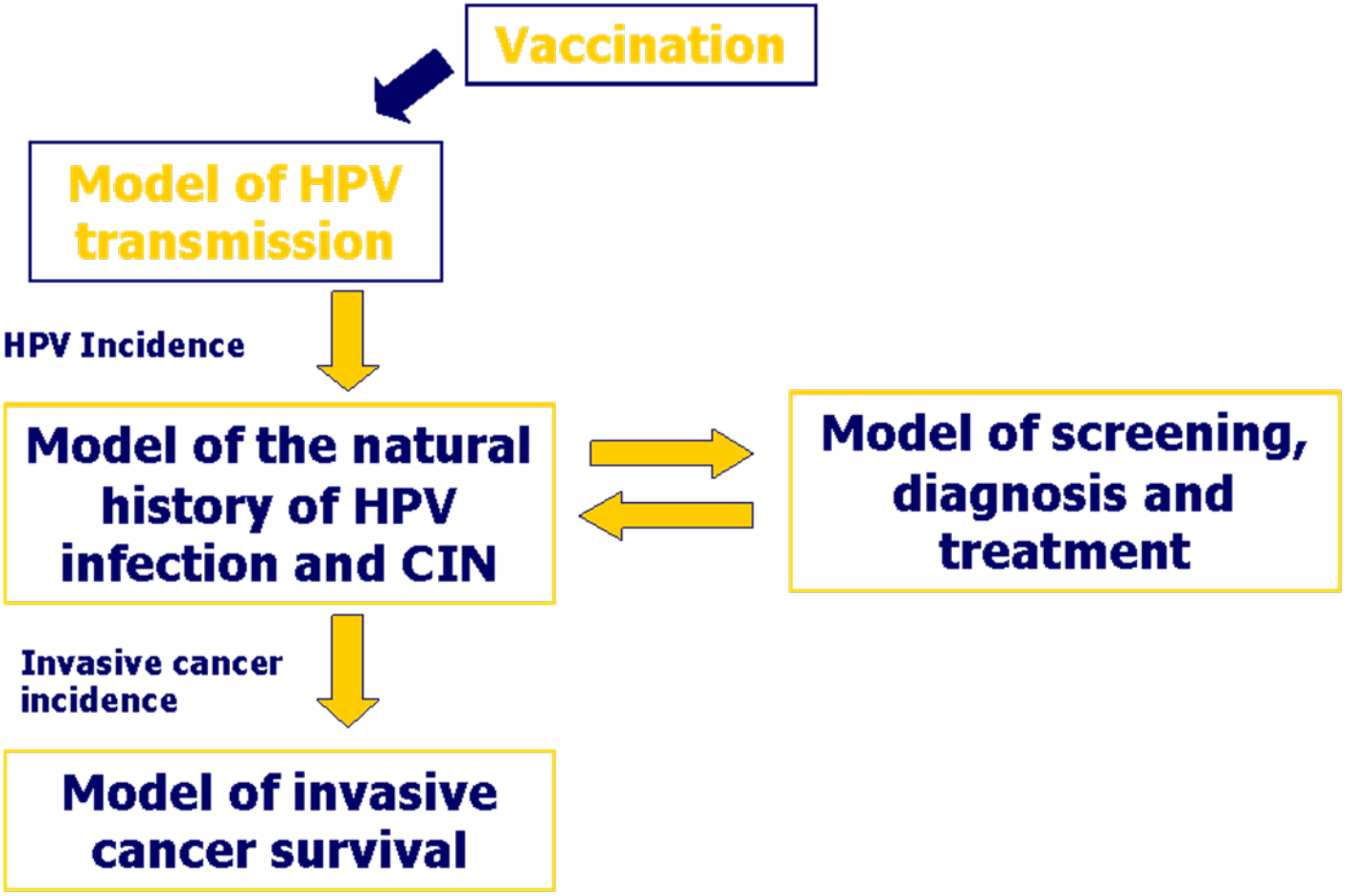
Modelling



Canfell et al, BJC 2004; Smith et al, Int J Cancer 2008;
Report to MSAC #1122 2009; Report to MSAC Ref #39 2009;
Creighton et al, BMC Public Health 2010;
Canfell et al, Vaccine 2011; Smith et al, Vaccine 2011

Current status

LBC

- MSAC has reviewed LBC twice
  - A 2002 review concluded ‘there is currently insufficient evidence pertaining to liquid based cytology for cervical screening’
  - The second review in 2009 led MSAC to conclude ‘in comparison to Papanicolaou (Pap) test that LBC is safe, is at least effective, is not cost effective at the price requested’

LBC – MSAC 2009

Scenario compared to conventional cytology @$19.60	% reduction in cancer cases	Additional CIN 2/3 treatments required to prevent one cancer case	Cost-effectiveness relative to current practice ($/LYS)
Manually read LBC @$22.00	3.2%	32	$126,315
@$30.50	3.2%	32	$385,982
Image read LBC (@$36.00)	9.5%	26	$194,835

Under favorable assumptions for new technologies

Dyer S, Howard K, Lord S, Canfell K, Smith M, Creighton P, Lew JB, Clements M (Health Technology Assessors) . MSAC Application #1122; http://www.msac.gov.au/. March 2009

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LBC – MSAC 2009

- 2009 reports demonstrated that the following modifiable factors would increase cost-effectiveness of manually or image-read LBC
  1. Price
  2. HPV triage testing of low grade smears (p/dLSIL)
  3. Increase screening interval to 3 years

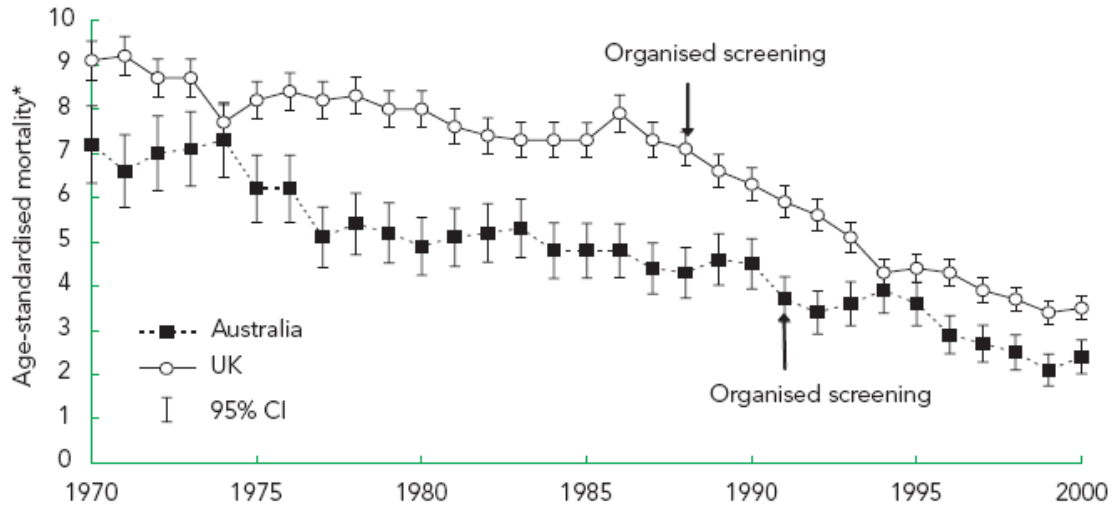
Dyer S, Howard K, Lord S, Canfell K, Smith M, Creighton P, Lew JB, Clements M (Health Technology Assessors) . http://www.msac.gov.au/. March 2009:

MSAC Application #1122 (LBC)

MSAC Reference #39 (HPV triage)

3-yearly screening: cytology

4 Age-standardised mortality from cervical cancer in women aged 20–69 years in Australia and the United Kingdom (England and Wales)



* Rates per 100 000 women. Although data are shown for England and Wales, annual age-standardised mortality rates for the UK were within 3% of those for England and Wales in each year for which data were available.

"Since the introduction of organised screening, similar reductions in cervical cancer incidence and mortality have been achieved in Australia and the UK. Therefore, the 2-yearly screening policy in Australia and the predominantly 3-yearly screening policy in the UK have been of similar effectiveness"

Canfell K, Sitas F and Beral V, Med J Aust 2006

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3-yearly screening: cytology

	Total cytology tests (and change from current practice)	Total colposcopies (and change from current practice)	Total biopsies (and change from current practice)	Total CIN 2/3 treatments (and change from current practice)
Current practice, 2-yearly recommendation	1.90M	66,000	32,000	17,600
Continue reminder system, 3-yearly recommendation	1.76M (140,000 fewer)	63,300 (2,700 fewer)	30,600 (1,400 fewer)	17,300 (300 fewer)
Call-and-recall, 3-yearly recommendation	1.65M (250,000 fewer)	59,600 (6,400 fewer)	28,800 (3,200 fewer)	17,000 (600 fewer)

Note: (1) Estimated for women of all ages using the resident Australian female population in 2007.

- ***Number of colposcopies and biopsies would reduce by 4-10%***
- ***Number of treatments for CIN 2/3 would reduce by 2-4%***
- ***No significant increase in cervical cancer cases and deaths***

Creighton P , Lew JB, Clements M, Smith M, Howard K, Dyer S, Lord S and Canfell K. BMC Pub Health 2010

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No changes to recommended screening technology, age range or interval in the 20 years the organised program has existed

Why change now?

National HPV Vaccination Program

- Commenced 2007
  - Ongoing routine vaccination of 12-13 year old girls
  - School-based and GP-based catch-up to age 26 years from 2007-9
- Vaccination coverage:

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***

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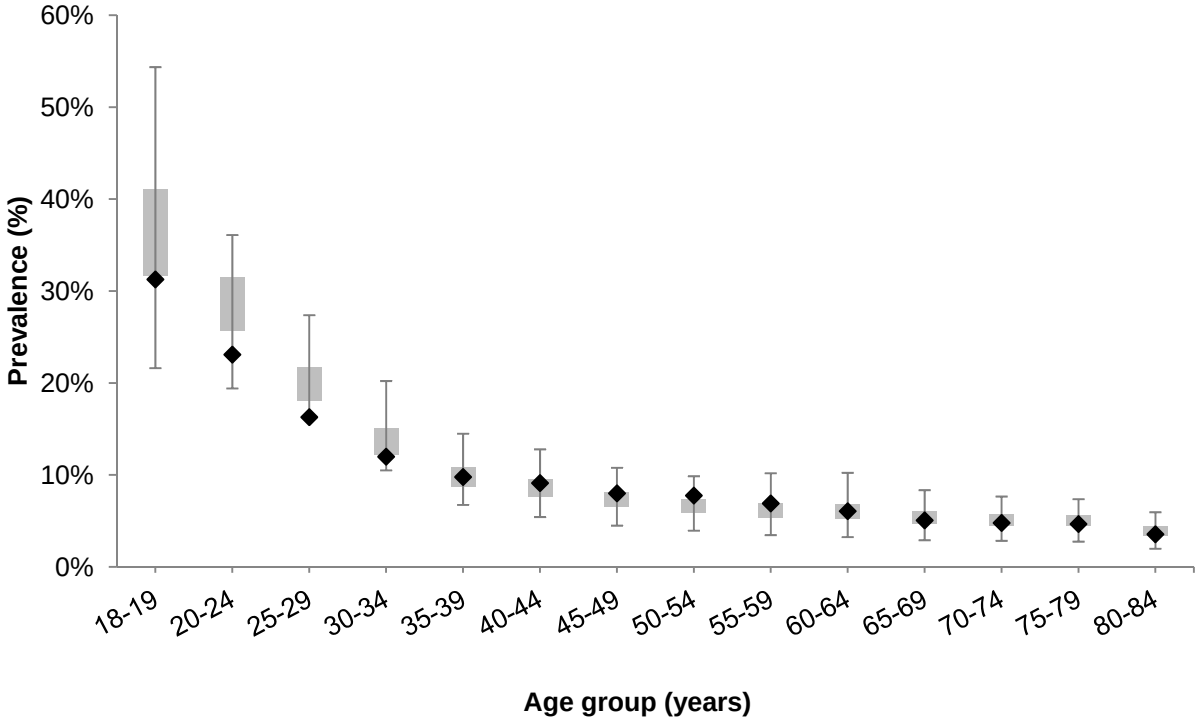
Pre-vaccination HPV prevalence



Modelled results for female HPV prevalence for all oncogenic types in sexually active women in Australia, after fitting to data from the WHINURS study

Smith MA, Lew JB, Walker RJ, Brotherton JM, Nickson C, Canfell K. The predicted impact of HPV vaccination on male infections and male HPV-related cancers in Australia. Vaccine 2011

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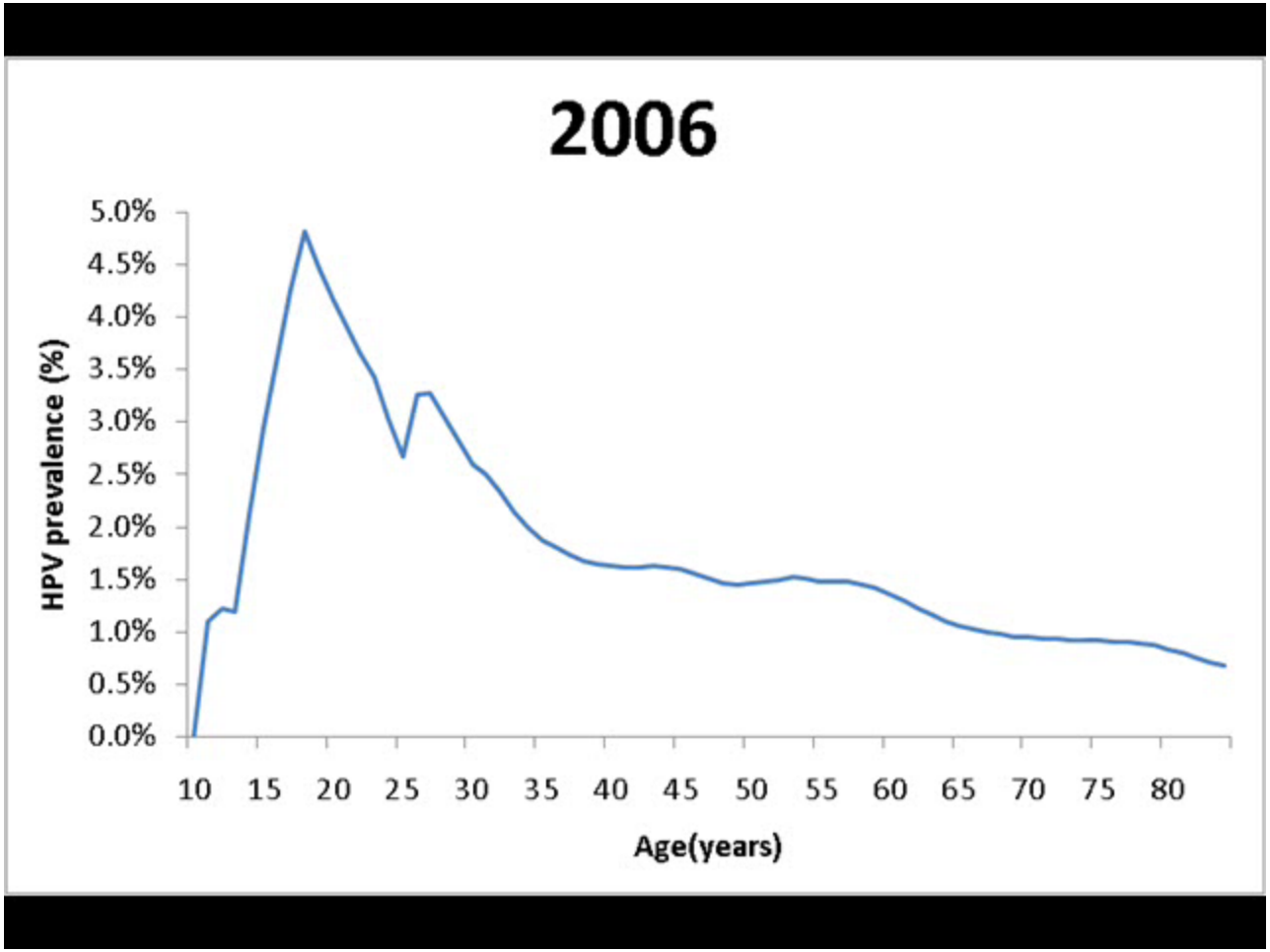
Impact of vaccination on HPV16/18



Adapted from: Smith MA, Canfell K, Brotherton JM, Lew JB, Barnabas RV. The predicted impact of vaccination on human papillomavirus infections in Australia. Int J Cancer 2008.

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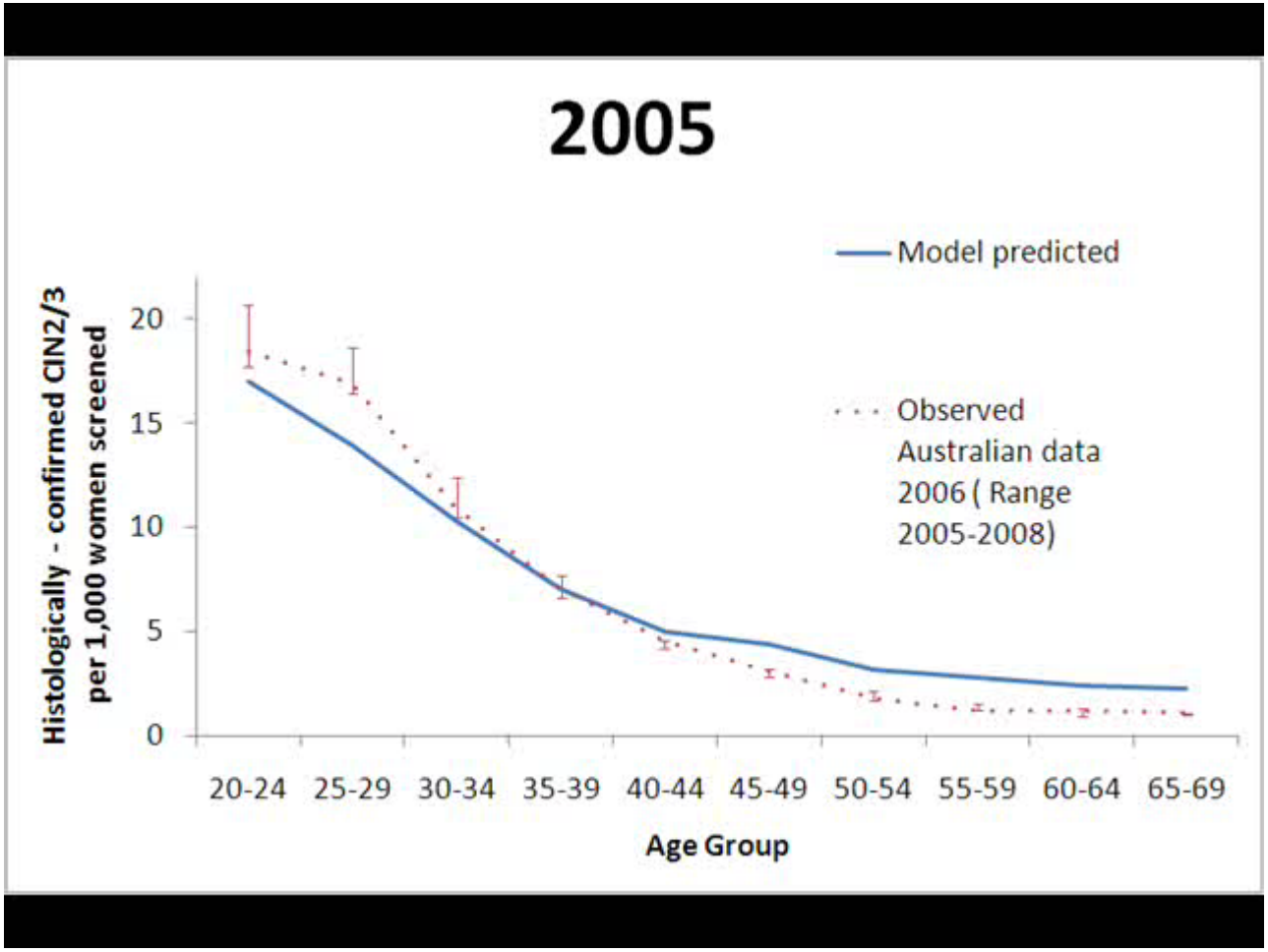
Impact of vaccination on HG lesions

Detected and histologically confirmed CIN2/3



"Most extreme" assumptions about vaccine efficacy. Assumes full cross-protection, 100% efficacy in HPV naïve women, and that vaccine effective in women exposed but without current infection

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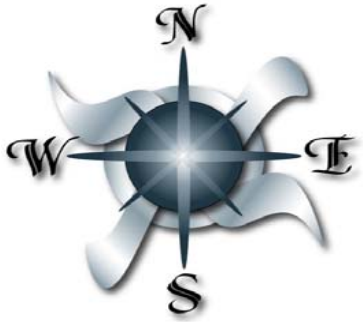

Large-scale trial of HPV screening vs. cytology

Pragmatic trial/ “real world” demonstration

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Why another primary HPV RCT?

- Evaluate primary HPV in partially vaccinated population
- More focus on optimal management of HPV positive women
- Specific evaluation of safety, effectiveness and costs in Australian context

COMPASS

- Call-and-recall screening
- 6-yearly HPV screening (with safety monitoring)
- Women aged 25-69 years recruited through GP practices in Victoria
- Consenting women will have LBC sample taken, with laboratory-based randomization
- Stratification by <30, 30+ years
- Disease status ascertainment in random sample of screen-negative women
- Post-hoc age and LGA matched analysis with non-participating women on VCCR
- Possible future extension to other states

Study Arm 1

- Image read cytology screening "Low risk"
  - Cytology-negative to 3-yearly recall
  - Cytology p/d HSIL to colposcopy "Higher risk"
- Reflex HPV triage testing for low grade smears (p/dLSIL)
  - Oncogenic HPV positive to colposcopy "Higher risk"
  - HPV negative to 12 month follow-up

"Intermediate risk"

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Study Arm 2

- HPV screening
  - HPV negative to 6–yearly recall **"Low risk"**
  - (Safety monitoring at 3 years)
- For HPV positive, type 16/18 (+/-45) genotyping
  - HPV 16/18 positive to colposcopy **"Higher risk"**
- For HPV 16/18 neg, positive other oncogenic type
  - Cytology triage testing
  - Cytology HSIL to colposcopy **"Higher risk"**
  - Cytology negative or p/dLSIL to 12 month follow-up

"Intermediate risk"

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Study Arm 3

- HPV screening
  - HPV negative to 6–yearly recall **"Low risk"**
  - (Safety monitoring at 3 years)
- For HPV positive, type 16/18 (+/-45) genotyping
  - HPV 16/18 positive to colposcopy **"Higher risk"**
- For HPV 16/18 neg, positive other oncogenic type
  - Dual-stained cytology (p16/Ki-67, mtm assay)
  - Dual-stained cytology positive to colposcopy **"Higher risk"**
  - Dual-stained cytology negative to 12 month follow-up **"Intermediate risk"**

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Pilot study

- 5,000 women at 1:2:2 randomisation allocation

Aims of the Pilot:

- To assess participant acceptance of randomization process and use of longer routine screening intervals
- Assess laboratory feasibility
- To quantify test positivity rates for the primary screening test in each arm in women <30 and 30+ years
  - Perform preliminary cross-sectional analysis to assess diagnostic yield in the baseline screening round for histologically-confirmed CIN3

Some considerations in making any change

- Safety
- Effectiveness
- Cost-effectiveness
- Appropriate screening interval
- Appropriate age of starting screening
- Organisation of screening
- Implementation of triage strategies
- Impact on referral and treatment rates
- Laboratory processing issues
- Acceptability to women
- Acceptability to practitioners

Trial outcomes

Pilot, baseline round, sub-studies, longitudinal follow-up

- Primary effectiveness endpoint based on cumulative detection of confirmed CIN3 in screen-negative women at 6 years in each arm

- Safety (3-yearly follow-up)
- Effectiveness (cross-sectional sens/spec and diagnostic yields)
- Cost-effectiveness (early assessment)
- Appropriate screening interval
- Appropriate age of starting screening
- Organisation of screening (compliance with longer intervals)
- Implementation of triage strategies
- Impact on referral and treatment rates (from pilot/baseline)
- Laboratory processing issues
- Acceptability to women (QoL studies)
- Acceptability to practitioners

Conclusions

An integrated approach is required…

New technologies cannot be considered in isolation from other aspects of screening

Need to focus on building the evidence base required for decision making

Australia can build on a very successful cervical cancer prevention program

and is in a position now to consider the optimal combination of vaccination, HPV testing and the role of cytology into the future