AUSTRALIA'S NATIONAL HPV VACCINATION PROGRAM –

ACHEIVEMENTS, CHALLENGES & POSSIBILITIES

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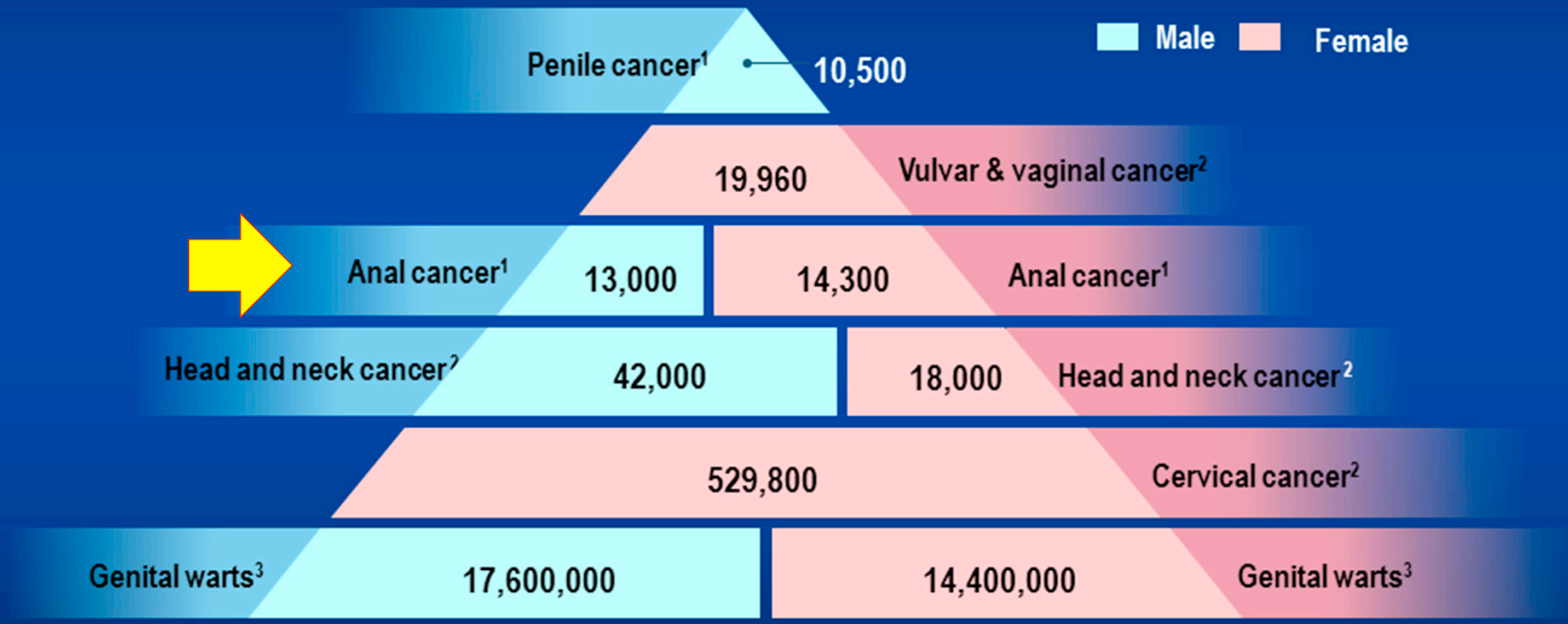
DISCLOSURE SLIDE

- SR Skinner's institution has received:
  - Funding from Sequris and GSK Australia for investigator driven HPV vaccine research
  - Contracts with GlaxoSmithKline as an HPV vaccine clinical trials site
  - Support from GlaxoSmithKline to attend meetings to present original data from clinical trials
  - Honoraria from GlaxoSmithKline and Merck to participate on advisory boards and present at educational meetings

Estimated annual new HPV-related disease cases among Males and Females Globally

5% of all cancers estimated to be caused by HPV



Stanley M. Journal of Infection 2016;72:S23-S28

HPV – THE BASICS

- The majority of sexually active individuals acquire ≥1 HPV genotype during their lifetime
- In most individuals, the HPV infection can be cleared or controlled within 1 or 2 years
- Type-specific HPV infections can reappear among previously exposed individuals
- 60%–70% of women and 40-50% of men who acquire an HPV infection develop a measurable type-specific serum antibody response

CANCER CASES ATTRIBUTABLE TO HPV, AUSTRALIA, 2005

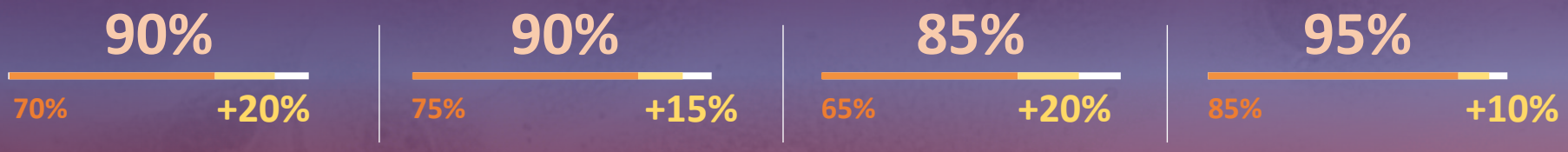
	Women (*n*)	Men (*n*)	% of cases due to HPV (references)	% of HPV associated cases due to HPV-16 and -18 (reference)	Cases potentially preventable by the HPV-16 and -18 vaccine	
					Women (*n*)	Men (*n*)
Cervical cancer	734	–	100[17]	76[65]	558	–
Vulval cancer	264	–	40[31]	86[65]	91	–
Vaginal cancer	76	–	70[31]	88[65]	47	–
Penile cancer	–	69	50[36,38]	87[65]	–	31
Anal cancer	176	149	85[31]	93[65]	140	118
Cancer of the base of tongue and oropharynx	114	395	35[58]	95[65]	38	131
Total	1364	613			874	280

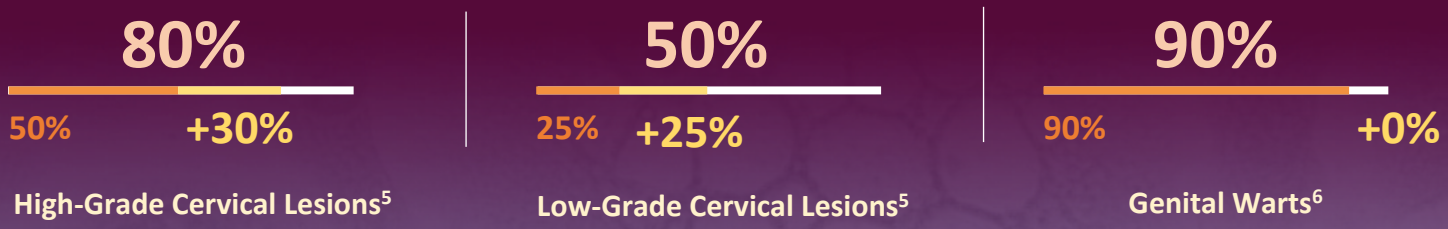
Grulich, Sexual Health, 2010

3 HPV VACCINES- ALL HIGHLY EFFECTIVE

	Bivalent HPV vaccine (Cervarix)	Quadrivalent HPV vaccine (Gardasil)	Nonavalent HPV vaccine (Gardasil 9)
L1 virus-like particle types	HPV 16, 18	HPV 6, 11, 16, 18	HPV 6, 11, 16, 18, 31, 33, 45, 52, 58
Adjuvant	ASO4 (0.5 mg aluminium hydroxide and 50 µg 3-O-desacyl-4”-monophosphoryl lipid A [MPL])	0.225 mg aluminium hydroxyphosphate sulphate	0.5 mg aluminium hydroxyphosphate sulphate
Expression system	Baculovirus-insect cell	Yeast	Yeast
Cross-protection	High against HPV 31, 33, 45[35,36]	Limited; some against HPV 31[37]	Nil known
Registered for use in males	No	Yes	Yes
Schedule	Two doses spaced 6–12 months apart for those aged 14 years and under at first dose Three doses spaced at zero, two and six months for those aged 15 years and over at first dose and immunocompromised individuals with select major medical conditions		

Nearly All HPV-Related Cancers and Diseases Are Caused by 9 HPV Types[a]





Caused by HPV 6, 11, 16, and 18

Additional Cases Caused by HPV 31, 33, 45, 52, and 58

Caused by HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58

[a]Values are approximate.
Not all cervical precancers and lesions, vulvar, vaginal, and anal cancer cases are caused by HPV.

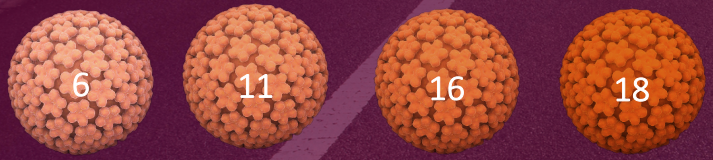
Sanjosé S et al. *Lancet Oncol.* 2010;11:1048–1056. **2.** de Sanjosé S et al. *Eur J Cancer*. 2013;49:3450–3461. **3.** Alemany L et al. *Eur J Cancer*. 2014;50:2846–2854.
emany L et al. *Int J Cancer*. 2015;136:98–107. **5.** Joura EA et al. *Cancer Epidemiol Biomarkers Prev*. 2014;23:1997–2008. **6.** Garland SM et al. *J Infect Dis*. 2009;199:805–814.

GARDASIL®9 PROVIDED BROAD PROTECTION AGAINST CERTAIN HPV-RELATED CANCERS AND DISEASES THROUGH 6 YEARS[1,A]

GARDASIL 9

6 years

Highly efficacious against certain cancers and diseases caused by HPV types



+

High efficacy against certain cancers and diseases caused by HPV types

97%–100%

- High-grade cervical, vulvar, or vaginal disease
- Cervical cancer, CIN2/3, or AIS
- Cervical cancer, CIN3, or AIS
- Persistent infection at 12 months

[a]In females aged 16–26 years.
l = cervical intraepithelial neoplasia; AIS = adenocarcinoma in situ.
uh WK et al. *Lancet*. 2017;390:2143–2159.

Pr Proprietary

NATIONAL HPV VACCINATION PROGRAM[1]

- National HPV Vaccination Program commenced in April 2007
  - School based program for females aged 12 to 13 years as well as a catch up to the age of 18 years (GARDASIL®)
  - GP based program for females up to the age of 26 years (to December 2009)
- In 2013, the program was extended to include 12 and 13 year old boys through school-based programs
- In 2018, the program was updated
  - GARDASIL®9 replaced GARDASIL® as the sole vaccine utilised in the program
  - Students aged 12 to 13 years now receive 2 doses (6 months apart), instead of 3 doses
  - Catch up through GP up to 19 years

NCIRS, Human papillomavirus (HPV) vaccines for Australians. NCIRS Fact sheet: April 2018.

NOT FUNDED

- MSM of any age- recommended
- Immunocompromised- recommended
- Women treated for cervical dysplasia- should be considered
- *3 dose schedule*

- Sexually active women and men over 19 years?

- ***Some adult females and males may gain an individual benefit from HPV vaccination. The decision to vaccinate older people should take into account their likelihood of previous exposure to HPV and their future risks of HPV exposure***

WHO RECOMMENDATIONS

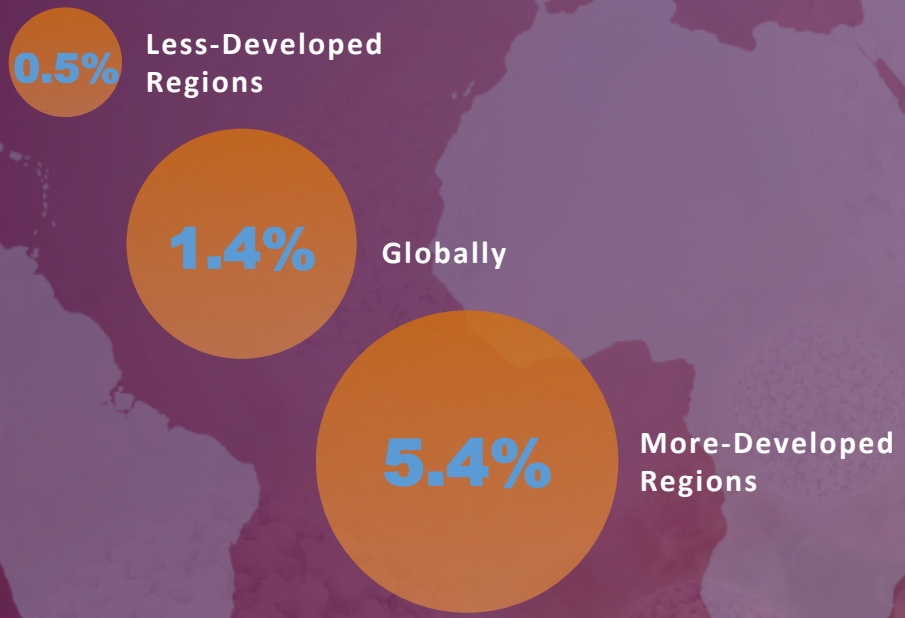
- 2 dose schedule (0, 6-15 months) in females aged 9–14 years
- Females ≥15 years and older – 3-dose schedule
- Individuals known to be immunocompromised and/or HIV infected – 3-dose schedule
- Vaccination of secondary target populations e.g. females aged ≥15 years or males only recommended if:
  - Feasible; Affordable; Cost-effective;
  - Does not divert resources

OTHER COUNTRIES

- US
  - Routine vaccination of females and males aged 11 - 12 years (clinic)
  - Catch up- females to age 26 years and males to age 21 years
  - Routine vaccination of MSM and immunocompromised persons to age 26 years
- UK
  - Routine vaccination of females aged 11-12 years (school)
  - HPV vaccination for MSM ≤ 40 years attending sexual health services
- Most countries only offer vaccination to adolescent females
- Only a small number of developing countries have funded national programs

Global HPV Vaccination Rates Are Low[1]…

Female Full-Course HPV Vaccination Coverage Rate (All Ages)[a]

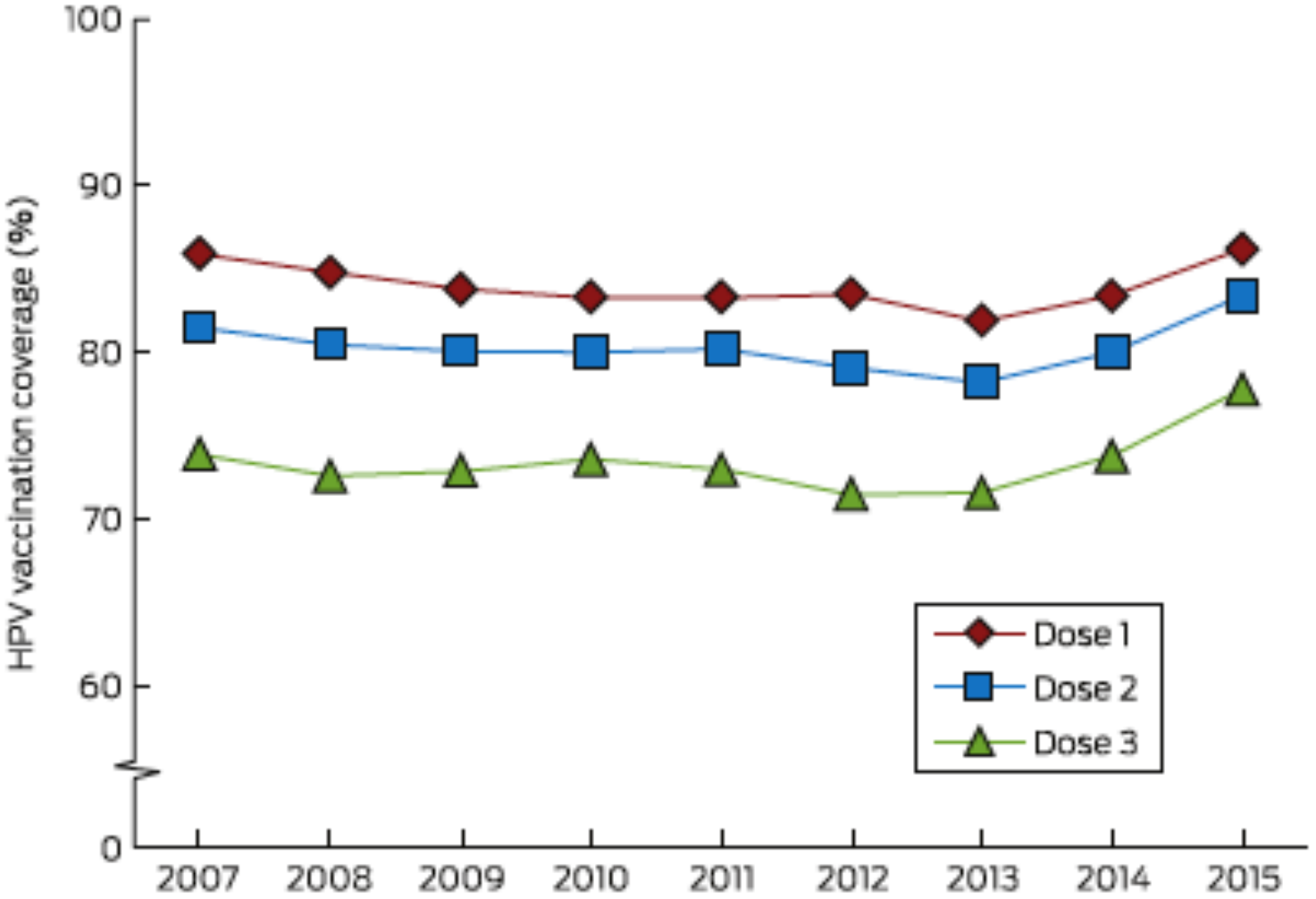


…Can't We Do Better?

[a] proportion of females who received the complete 3-dose HPV vaccine or ≥2 doses within 6 months if consistent with immunization program recommendations.

uni L et al. *Lancet Glob Health.* 2016;4:e453–e463.

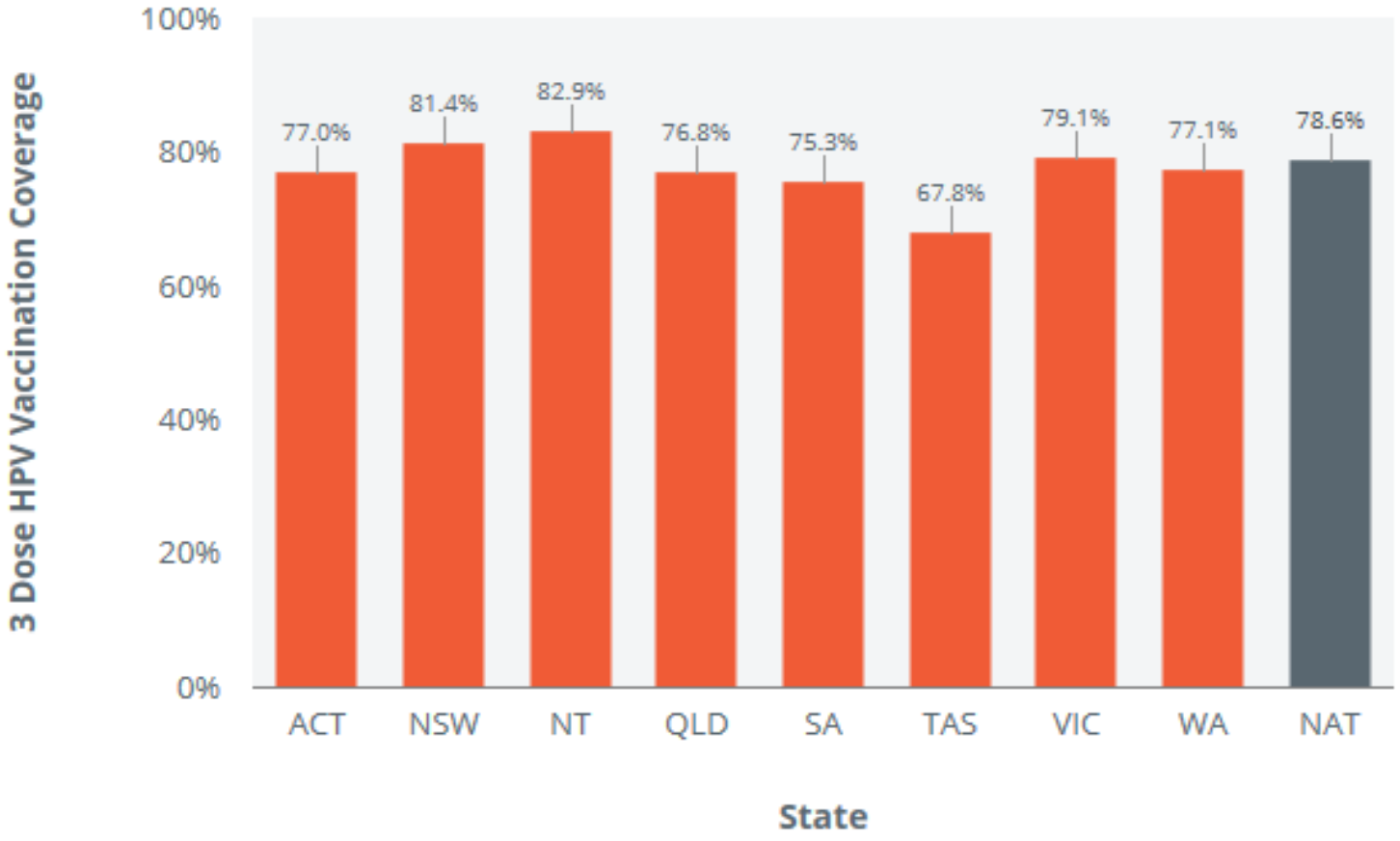
NATIONAL HPV COVERAGE IN GIRLS 15 YEARS, AUSTRALIA 2007-2015



Brotherton, MJA 2017

COVERAGE IN FEMALES

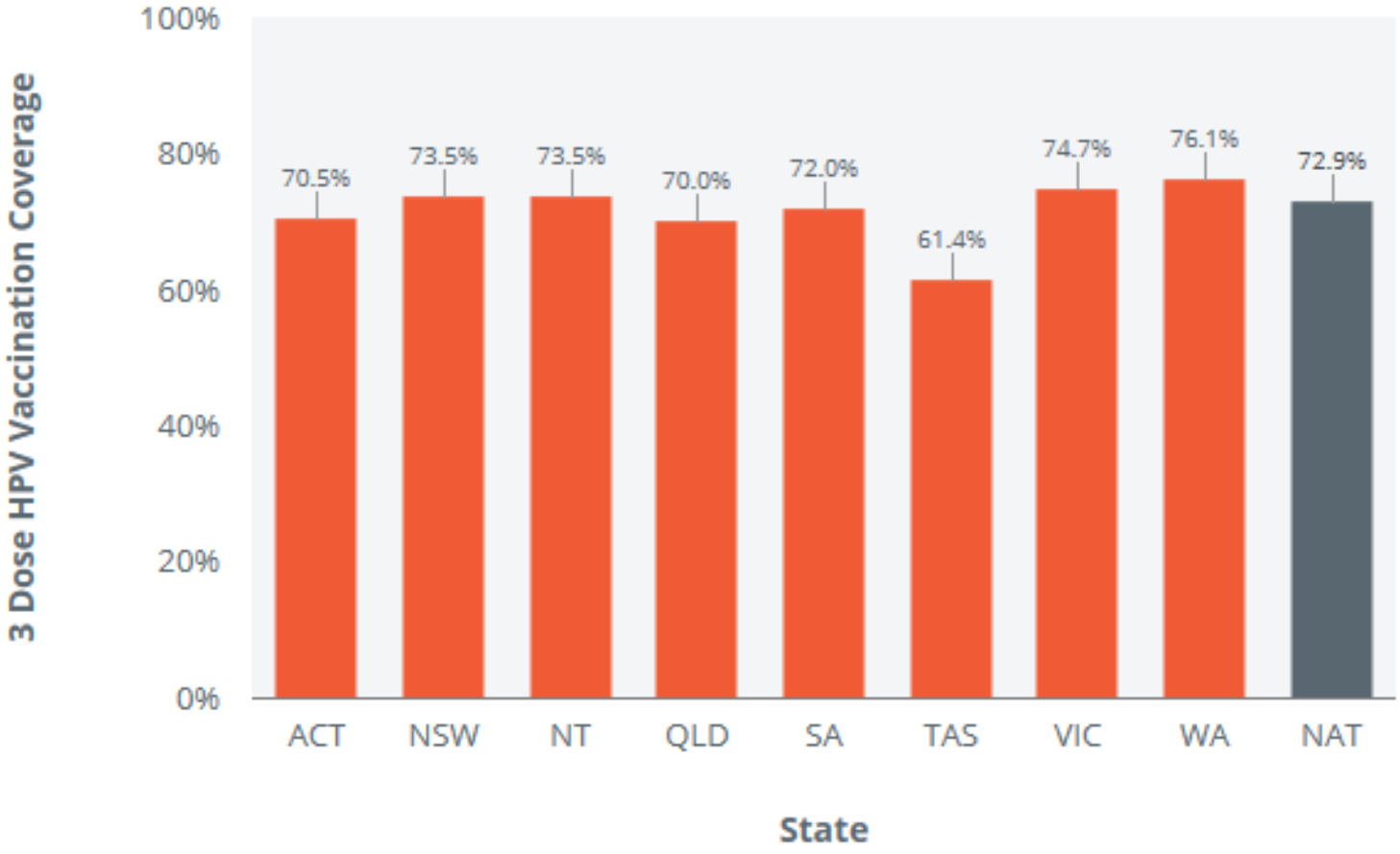
Australian HPV 3 dose vaccination coverage for females turning 15 years of age in 2016



http://www.hpvregister.org.au/research/coverage-data/HPV-Vaccination-Coverage-2016

COVERAGE IN MALES

Australian HPV 3 dose vaccination coverage for males turning 15 years of age in 2016



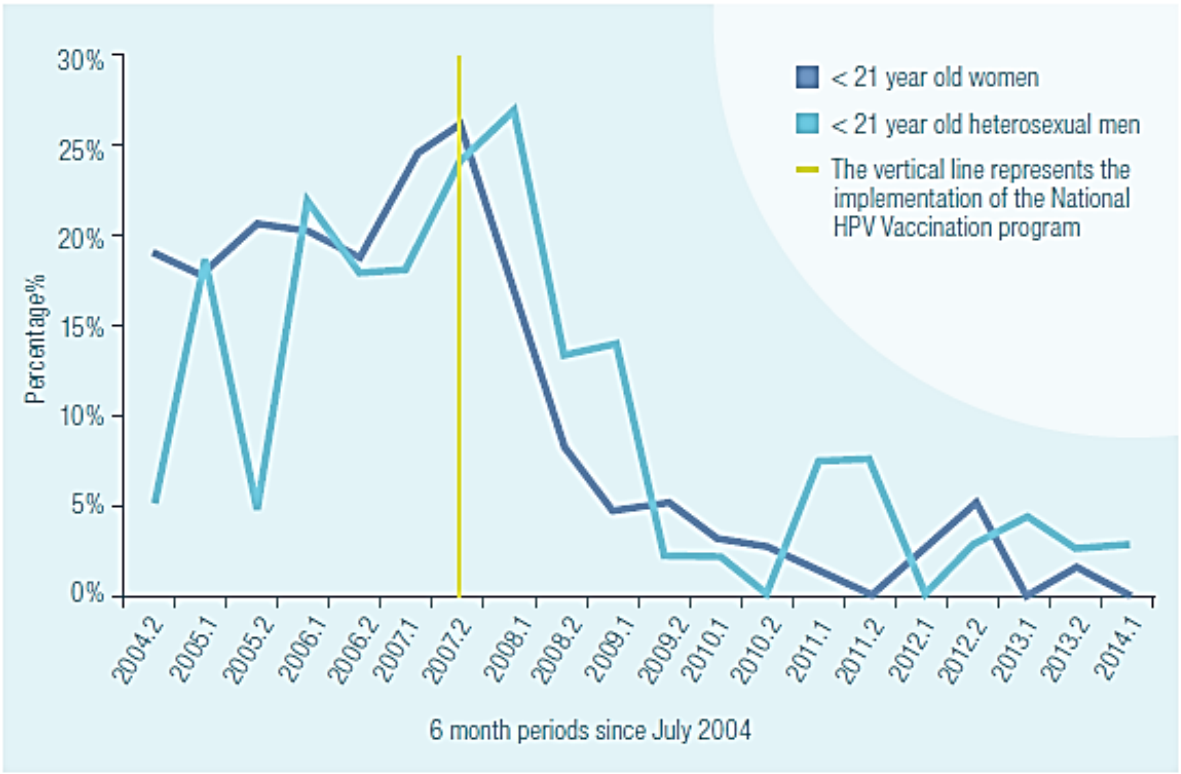
http://www.hpvregister.org.au/research/coverage-data/HPV-Vaccination-Coverage-2016---Male

IMPACT OF NATIONAL HPV VACCINATION PROGRAM

- **Genital warts**
- **Cervical abnormalities**
- **HPV Prevalence**

GENITAL WARTS - AUSTRALIA

PROPORTION OF AUSTRALIAN MALES AND FEMALES (<21 YEARS) WITH GENITAL WARTS BY HALF YEAR 2004-2014[18]



Retrospective analysis of new patients attending Melbourne Sexual Health Centre (MSHC); among 81,939 new patients, 4282 (10.2%) cases of genital warts identified. 1=January to June; 2=July to December.

Diagnosis of Genital warts has decreased:

- In women < 21 years from 18.4% in 2004/5 to 1.1% in 2013/14 ($p<0.001$)
- In males <21 years from 11.3% to 2.8%; ($p_{trend}<0.001$)

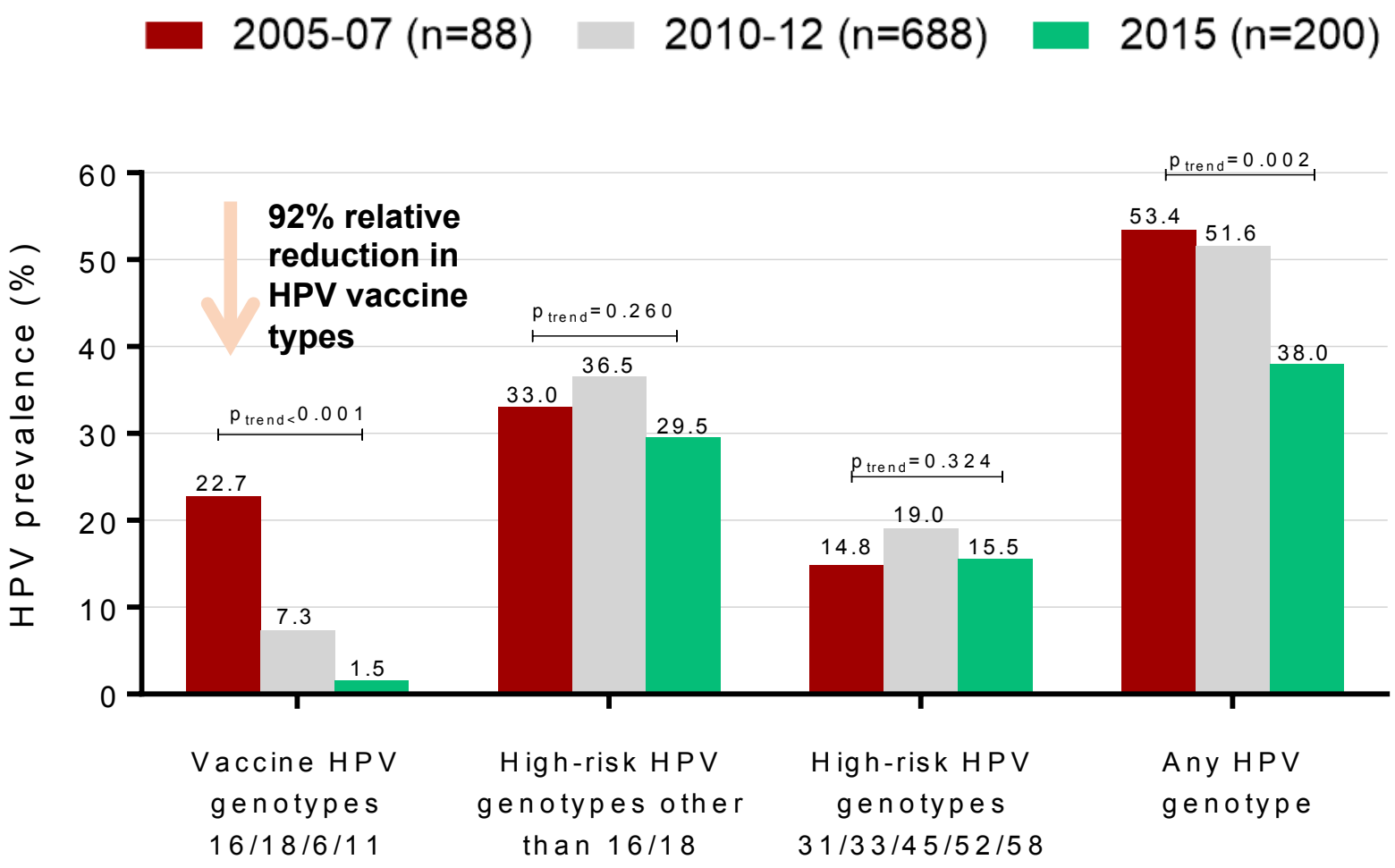
Adapted from Chow et al STI 2015.

3 DOSE COVERAGE IN WOMEN ATTENDING FAMILY PLANNING CLINICS FOR CERVICAL SCREENING

	2005-07	2010-12	2015
18-24 year olds	0%	51.2%	65.5%
25-36 year olds	0%	-	40.3%

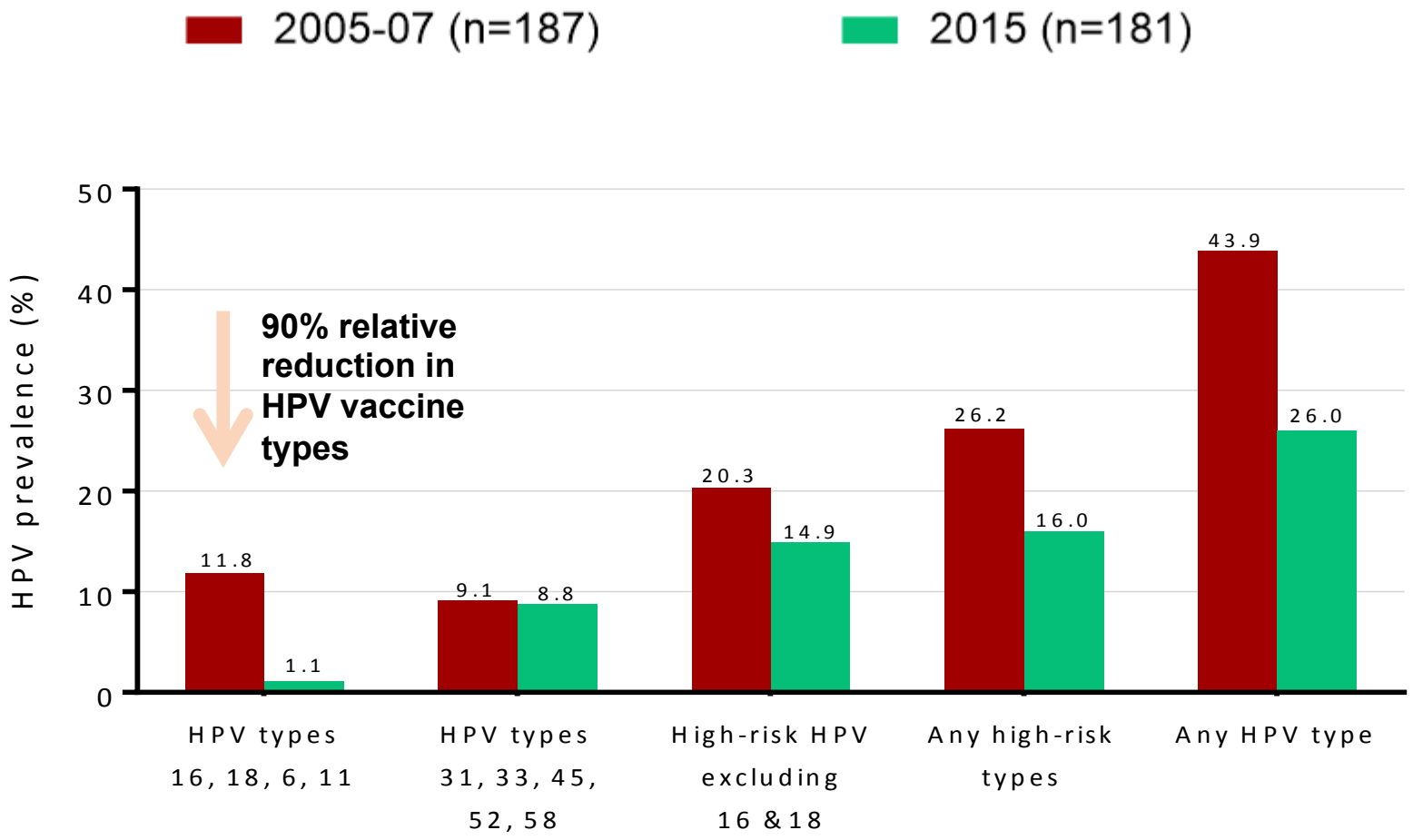
Machalek, JID 2018

92% REDUCTION IN HPV VACCINE TYPE INFECTIONS AMONG 18-24 YEAR OLD WOMEN



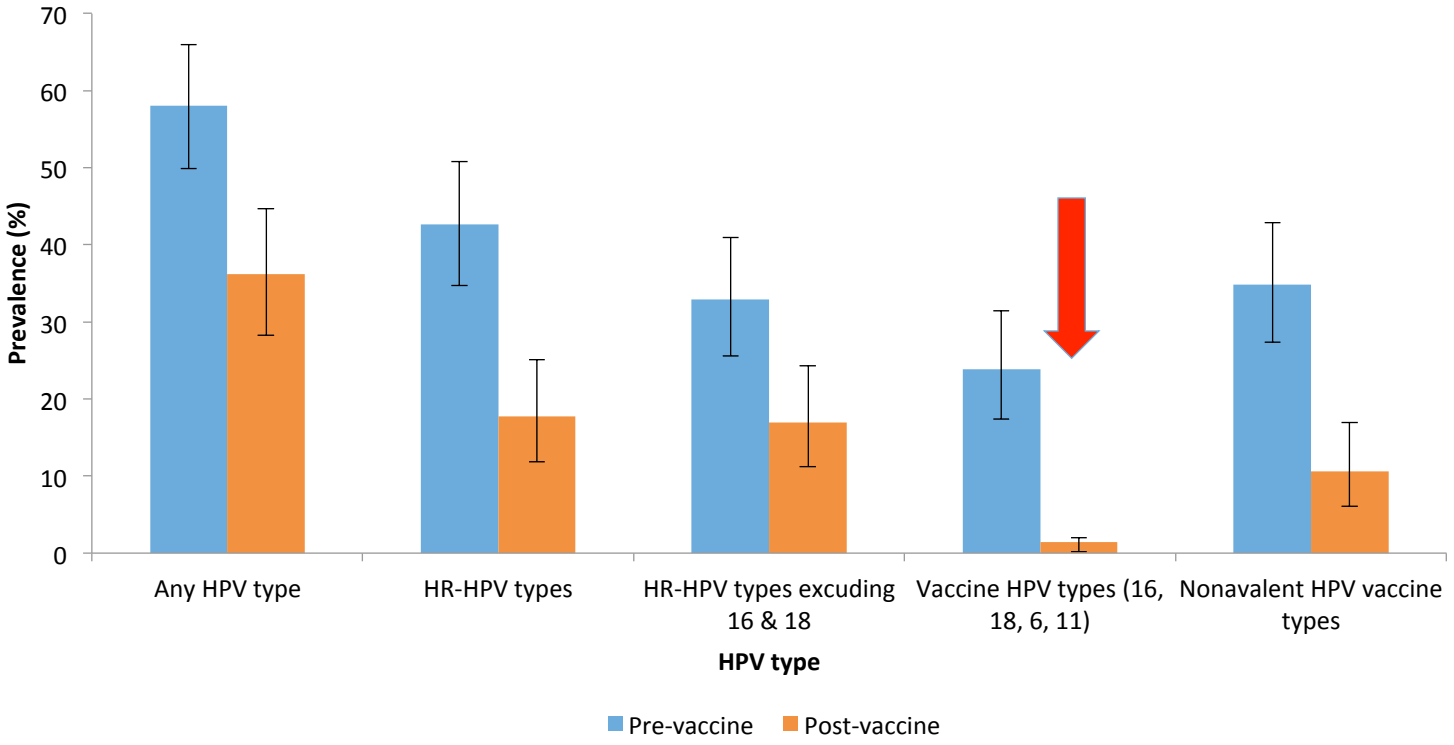
Machalek DA, Garland SM, Brotherton JM et al. JID 2018

90% REDUCTION IN HPV VACCINE TYPE INFECTIONS AMONG 25-35 YEAR OLD WOMEN



Machalek DA, Garland SM, Brotherton JM et al. JID 2018

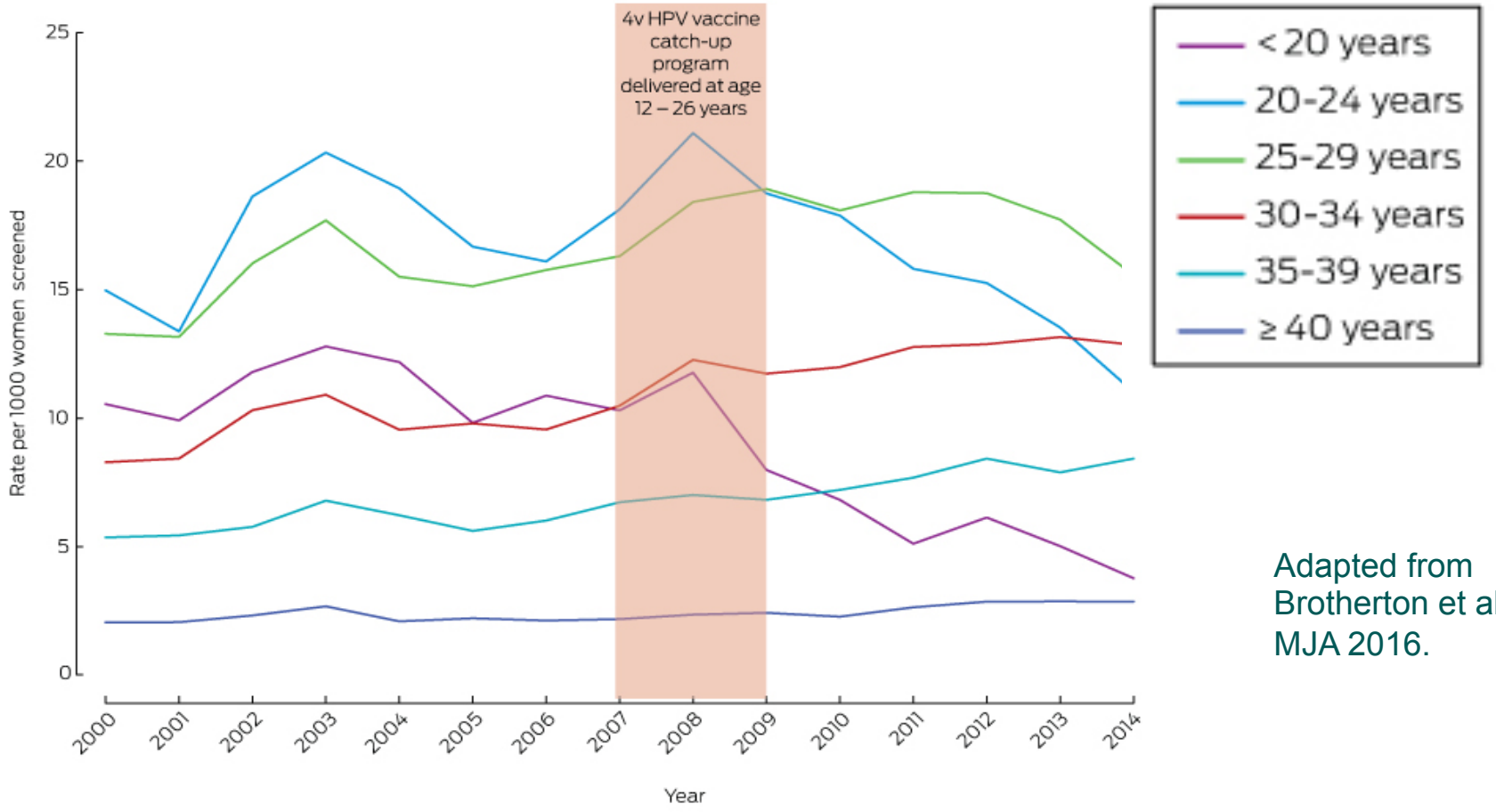
DECLINE IN HPV INFECTIONS IN INDIGENOUS WOMEN 18-26
PRE-VACCINE (2005-2007) AND POST-VACCINE (2014-2015)



*p < .05 for difference in percentages between groups. HR-HPV types are 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 68; nonavalent vaccine types are 6, 11, 16, 18, 31, 33, 45, 52, and 58

McGregor et al, Vaccine 2018

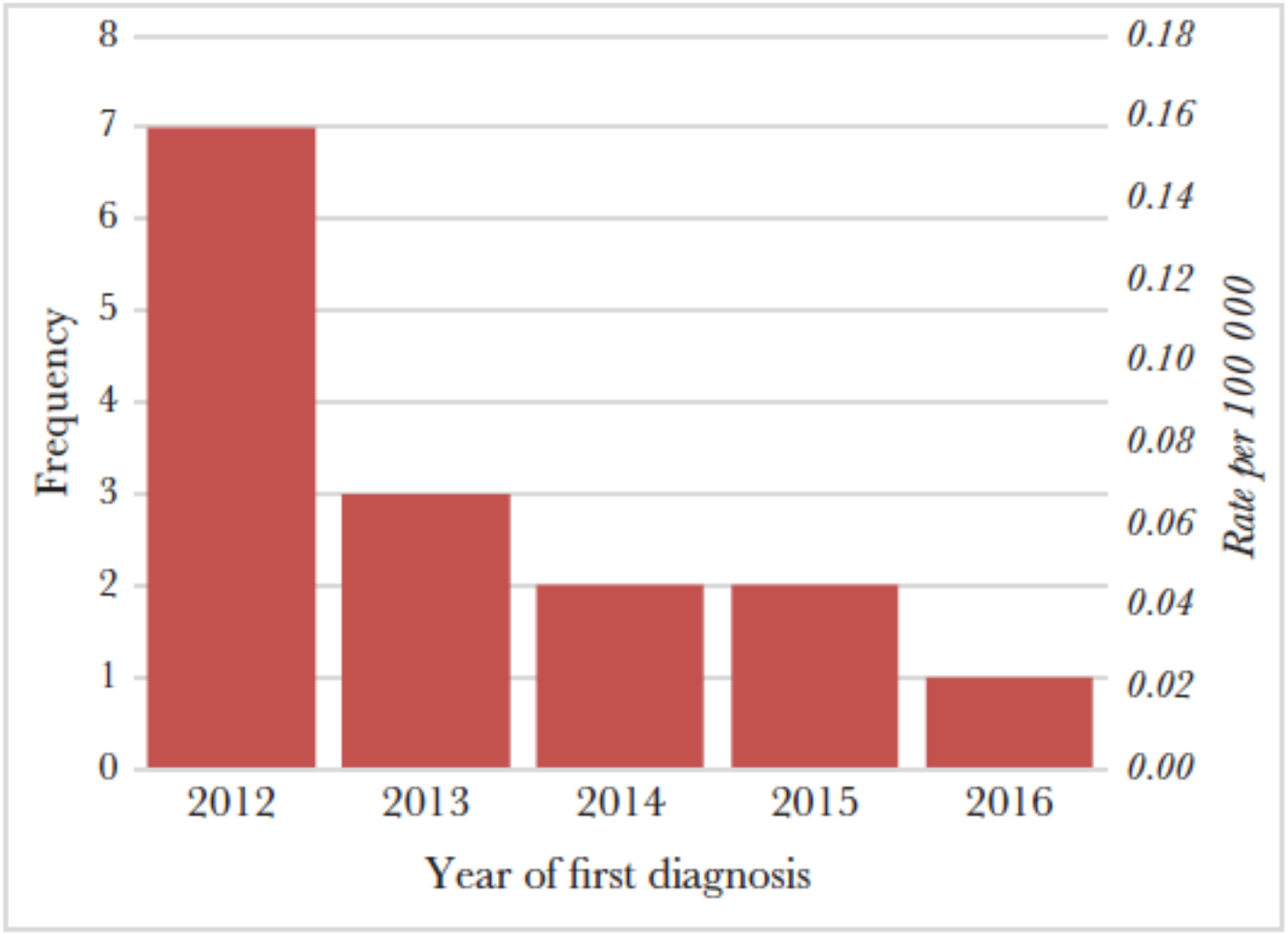
HG CERVICAL LESIONS 5-6 YEARS POST VACCINE



Adapted from Brotherton et al MJA 2016.

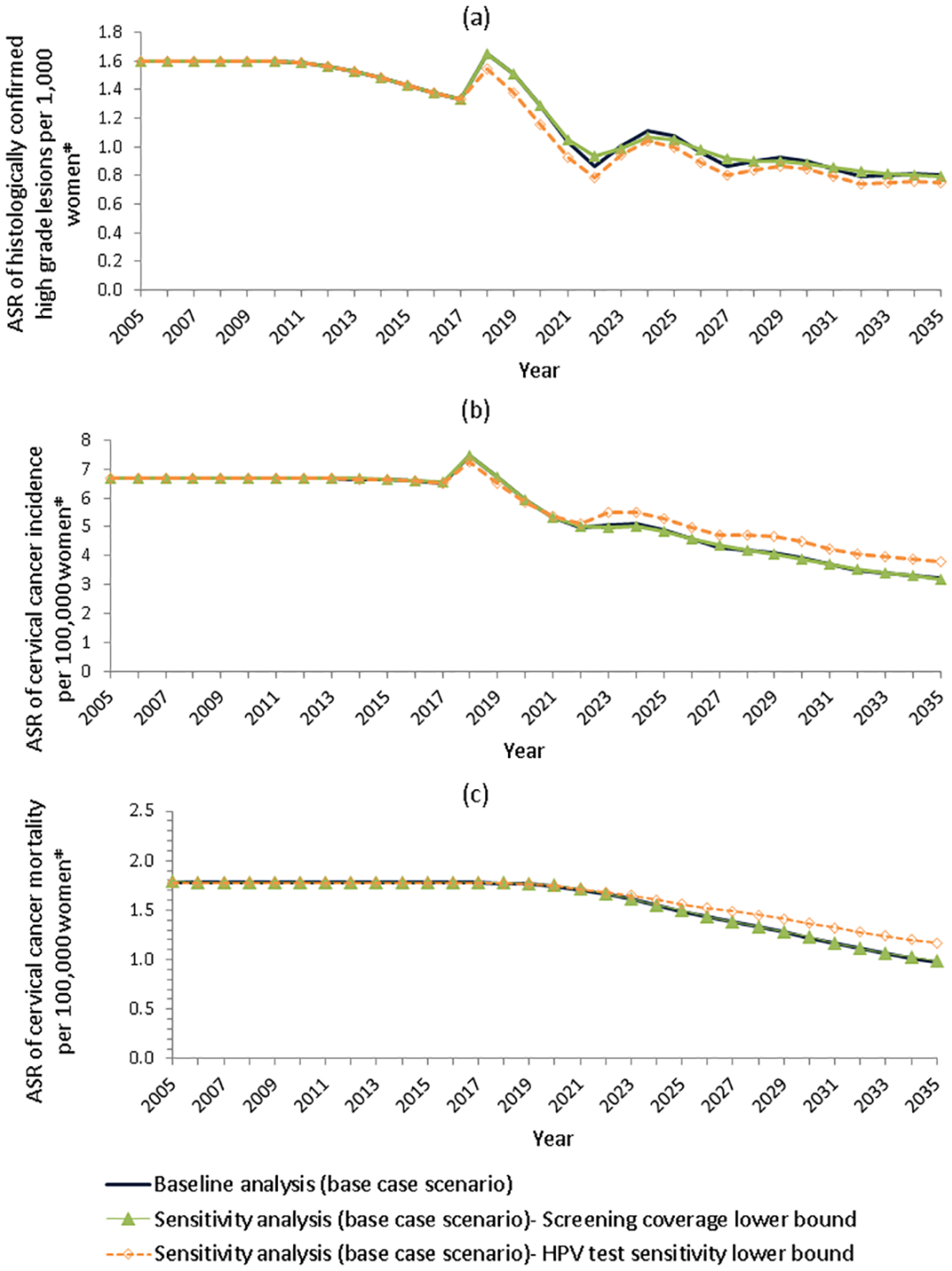
Trends in prevalence rates of high-grade histologically confirmed cervical abnormalities diagnosed in Victorian women, by age group, 2000-2014

INCIDENT CASES JORP 2012-2016, AUSTRALIA



0.16/100,000 in 2012 to 0.02 cases/100,000 in 2016, p=.034

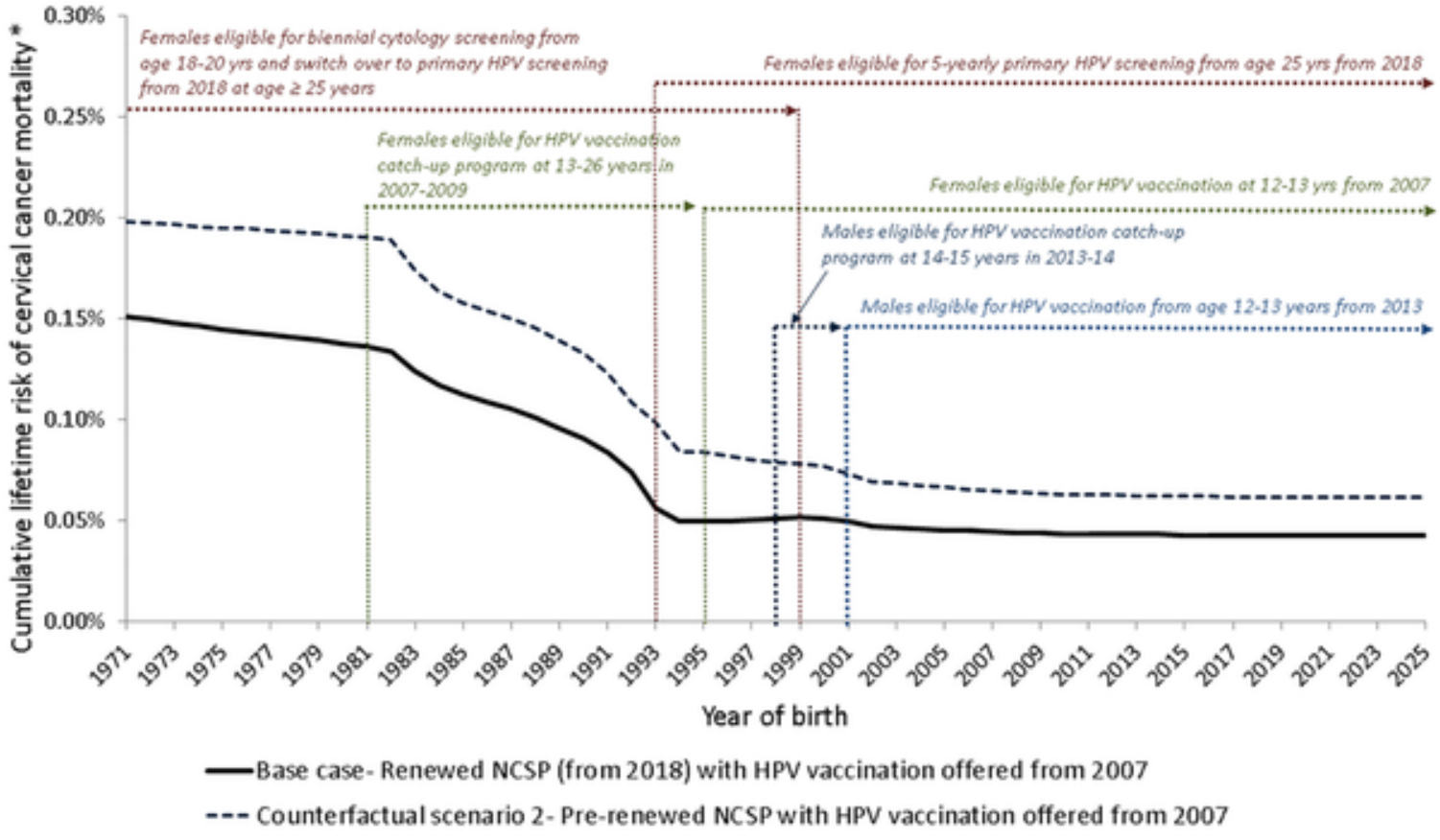
Novakovic et al, JID 2018



Predicted cases of HGL, CC incidence and mortality

Hall et al, PLOS ONE, 2018

Modelled cumulative lifetime risk of cervical cancer mortality by birth year in Australia



Hall MT, Simms KT, Lew JB, Smith MA, Saville M, et al. (2018) Projected future impact of HPV vaccination and primary HPV screening on cervical cancer rates from 2017–2035: Example from Australia. PLOS ONE 13(2): e0185332. https://doi.org/10.1371/journal.pone.0185332
http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0185332

PLOS ONE

HPV VACCINE SAFETY

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Breaking News: Japan Suspends Recommendation Vaccines

June 16, 2013 By admin — 7 Comments

Japan Suspends Recommendation

By Norma Erickson

14 June 2013: M
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Mrs. Tomoko Saito, reporter for *The Asahi Shi*

Immunol Res
DOI 10.1007/s12026-016-8820-z

ENVIRONMENT AND AUTOIMMUNITY

Severe somatoform and dysautonomic syndromes after HPV vaccination: case series and review of literature

Reduced confidence in vaccine safety has impacted vaccine uptake in some countries

BMJ Case Reports

ossible pathogenesis of a disease

3 years after menarche in a
uman papillomavirus vaccination

nville Ward[2]

Pharmaceutical Regulatory Affairs: Open Access

Tomljenovic and Shaw, Pharmaceut Reg Affairs 2012, S12:001
http://dx.doi.org/10.4172/2167-7689.S12-001

Research Article Open Access

Death after Quadrivalent Human Papillomavirus (HPV) Vaccination: Causal or Coincidental?

Lucija Tomljenovic[1*] and Christopher A Shaw[1,2,3]

[1]Department of Ophthalmology and Visual Sciences, University of British Columbia, Canada
[2]Program in Experimental Medicine, University of British Columbia, Canada
[3]Program in Neuroscience, University of British Columbia, Canada

ELSEVIER

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

3

IMMUNITY

of a pseudo-neurological syndrome 3 AS04-adjuvated vaccine: might it ine/inflammatory syndrome vants (ASIA) presenting n disorder?

Castelli ·
aola Bruni

Orthostatic intolerance and postural tachycardia syndrome as suspected adverse effects of vaccination against human papilloma virus

CrossMark

Louise S. Brinth, Kirsten Pors, Ann C. Theibel, Jesper Mehlsen*

Coordinating Research Centre, Frederiksberg Hospital, Nordre Fasanvej 57, 2000 Frederiksberg, Denmark

UPDATED REVIEW HPV VACCINE SAFETY: 2012-2016

Drug Saf (2013) 36:393–412
DOI 10.1007/s40264-013-0039-5

REVIEW ARTICLE

Safety of Human Papillomavirus Vaccines: A Review

Kristine K. Macartney · Clayton Chiu ·
Melina Georgousakis · Julia M. L. Brotherton

Drug Saf (2018) 41:329–346
https://doi.org/10.1007/s40264-017-0625-z

REVIEW ARTICLE

Safety of Human Papillomavirus Vaccines: An Updated Review

Anastasia Phillips[1] · Cyra Patel[2] · Alexis Pillsbury[2] · Julia Brotherton[3,4] ·
Kristine Macartney[1,2]

HIERARCHY OF STUDY DESIGN

Decreasing quality of evidence

Study type	REVIEW 1 (2013) Up to May 2012	REVIEW UPDATE (2018) May 2012– August 2016
Pooled or meta-analyses	3	2
Randomised clinical trials	38	26
Non-randomised clinical trials	6	13
Population-based observational studies	8	16
Spontaneous reporting systems	16	29
Case series/reports	21	23

Provides evidence to inform causality assessment

Can inform hypothesis

OVERALL SAFETY OF HPV VACCINES

- ISR (injection site reaction) most common AE in clinical trials (absolute rates 22%-85%) and SRS
- Slightly higher ISRs in 2vHPV vs 4vHPV; females vs males
- Systemic, unsolicited and severe AEs similar to control for both 2 v and 4v (similar in head to head) in clinical trials
- SAEs generally low in SRSs (2.5/100,000 to 8.4/100,000 across countries)
- Syncope not uncommon AE esp in younger adolescents, not specific to HPV vaccines
- Relative risk of death (VSD from 2005-2011, 1.4M doses) significantly lower than expected, none causally associated. Pooled clinical trials data, SRS raise no concern.
- 9valent: ISR more frequent than with 4valent (90.7% vs 85%); SAEs similar rate 2%; population surveillance not yet reported

ADVERSE EVENTS OF SPECIAL INTEREST REVIEWED

- Guillain-Barre Sydrome (GBS)
- Postural orthostatic tachycardia syndrome (POTS)
- Premature ovarian insufficiency (POI)
- Autoimmune disease (AID)
- Acute disseminated encephalomyelitis (ADEM)
- Multiple sclerosis (MS)
- Complex regional pain syndrome (CRPS)
- Venous thromboembolism (VTE)

No association between vaccination and adverse event found

SAFETY ‘TAKE HOME MESSAGES’

- Robust evidence supports safety of the HPV vaccine & GACVS has ‘‘not found any safety issue that would alter its recommendations for the use of the vaccine’’.

- Baseline prevalence of new onset AID is high among adolescent girls, who are the target group for HPV vaccination.

- Case studies can assist hypothesis generation but allegations based on poor-quality evidence may lead to unjustified loss of confidence with an impact on vaccine coverage that ‘‘will result in real harm’’ (WHO, GACVS 2017)

- Communication regarding vaccine safety should be based on comprehensive review of the body of quality scientific evidence.

CONCLUSIONS

- Sustained high coverage achieved in Australia, with moderate coverage in catch up
  - Marked and rapid impact across populations and disease
- 2 dose schedule from 2018- GARDASIL®9
- National register key to accurate measurement of coverage, vaccine effectiveness
- Very safe vaccine, continued high community support
  - Threats need rapid response
- Need to ensure continued high coverage across all populations, including in high risk groups
- Lessons from our success may inform programs around the world