Challenges at the level of HPV prevention

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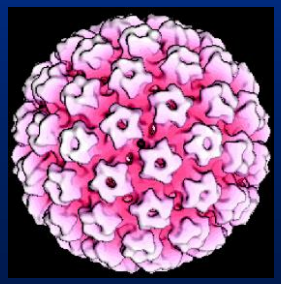
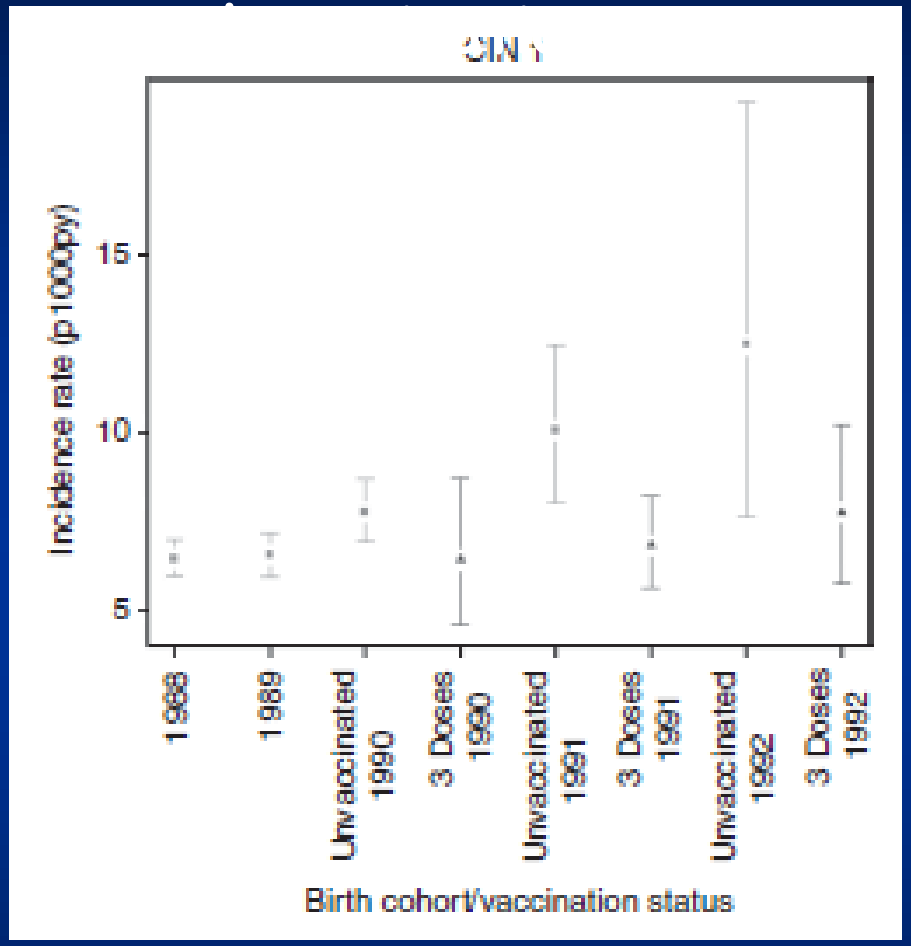
HPV prevention Board Antwerp 01 December 2015

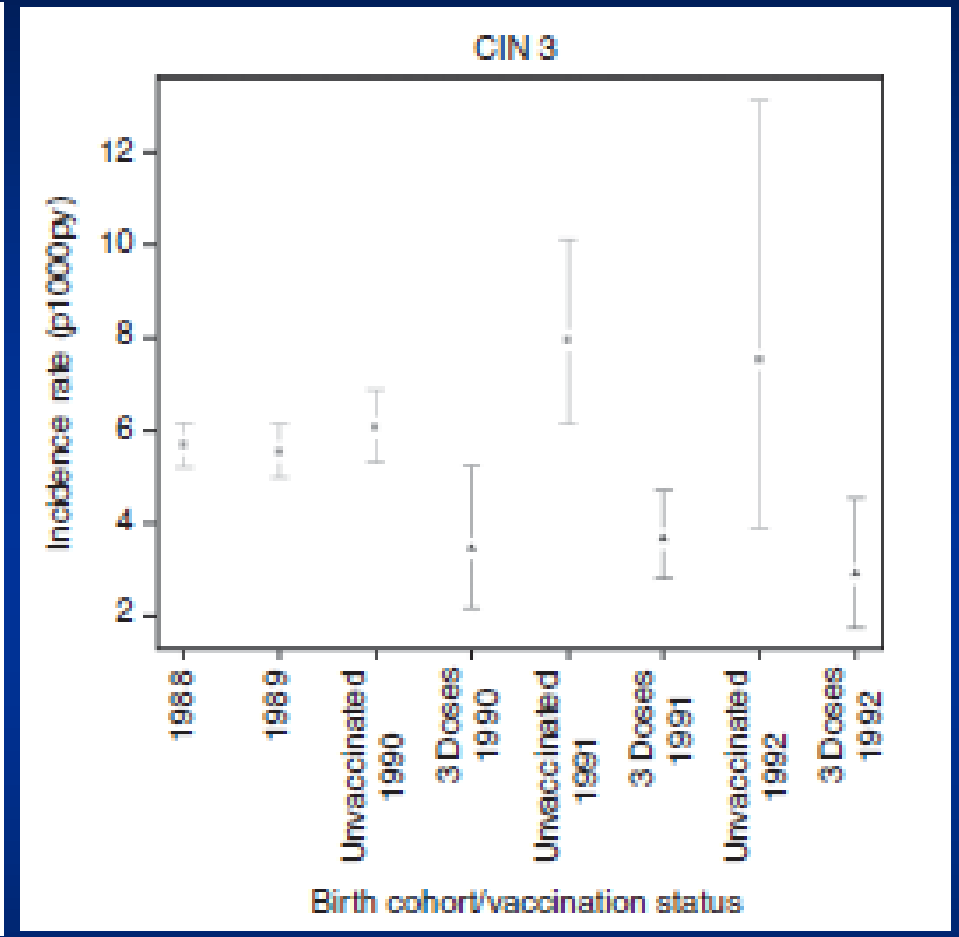


Human papilloma *virus*: key facts for prevention by prophylactic vaccination

- Absolutely restricted host range – humans only
  no animal reservoir
- Mucosal oncogenic HPVs sexually transmitted
  Transmission requires intimate contact
- Vaccine HPV type infection and disease prevented by
  HPV VLP vaccines
  Evidence: RCTs, population effectiveness
- No evidence for HPV type replacement in vaccinated
  cohorts after 10 years
- Genetically stable virus

Incidence rates per 1000 person-year (p1000py) of CIN 1, 2 and 3 stratified by birth cohort



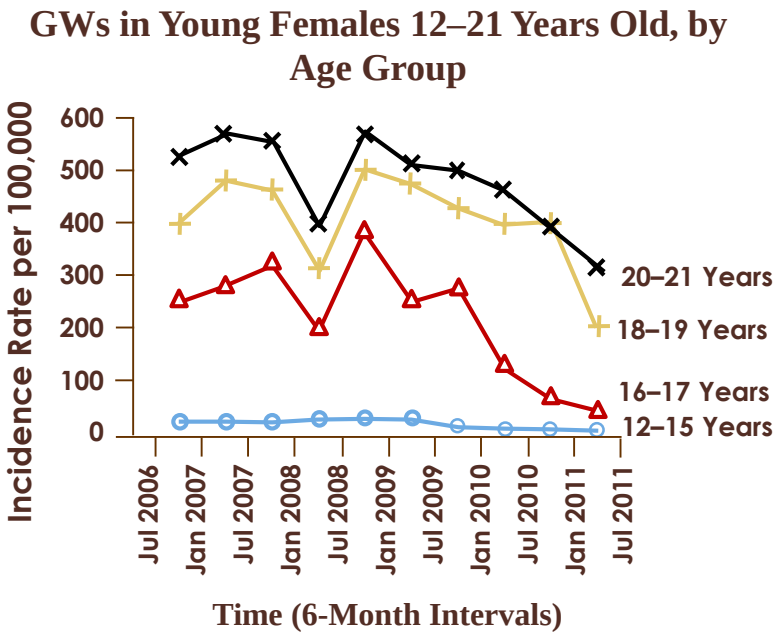


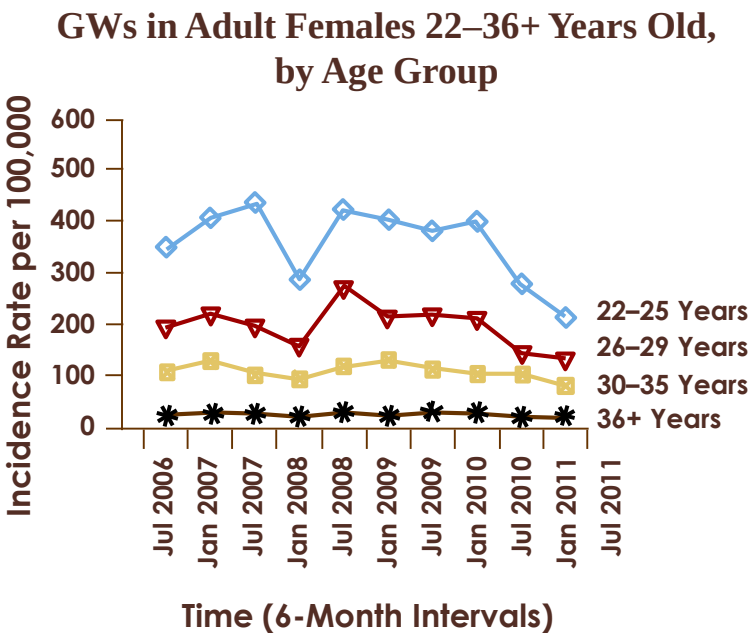
Reductions of CIN1 29%, CIN2 50%, CIN3 55% in 20/21 year old Females in Scotland, catch up cohort mean vaccine coverage 66%

Pollock etal 2014 Br J Cancer 111:1824

Denmark: Incidence of Genital Warts Following Introduction of qHPV Vaccine: Results and Summary[1]

- Near elimination by mid-2011 of GW incidence in females 16 and 17 years old
  - Corresponds to catch-up cohorts, with vaccine coverage >85%
- Gradual but significant decreases observed among women 18 through 29 years old
- No statistically significant change observed in males of any age group





GWs=genital warts; qHPV=quadrivalent human papillomavirus.

Figures reprinted from Baandrup L et al. Significant decrease in the incidence of genital warts in young Danish women after implementation of a national human papillomavirus vaccination program. *Sex Transm Dis*. 2013;40:130–135, with permission of Wolters Kluwer Health.

1. Baandrup L et al. *Sex Transm Dis*. 2013;40:130–135.

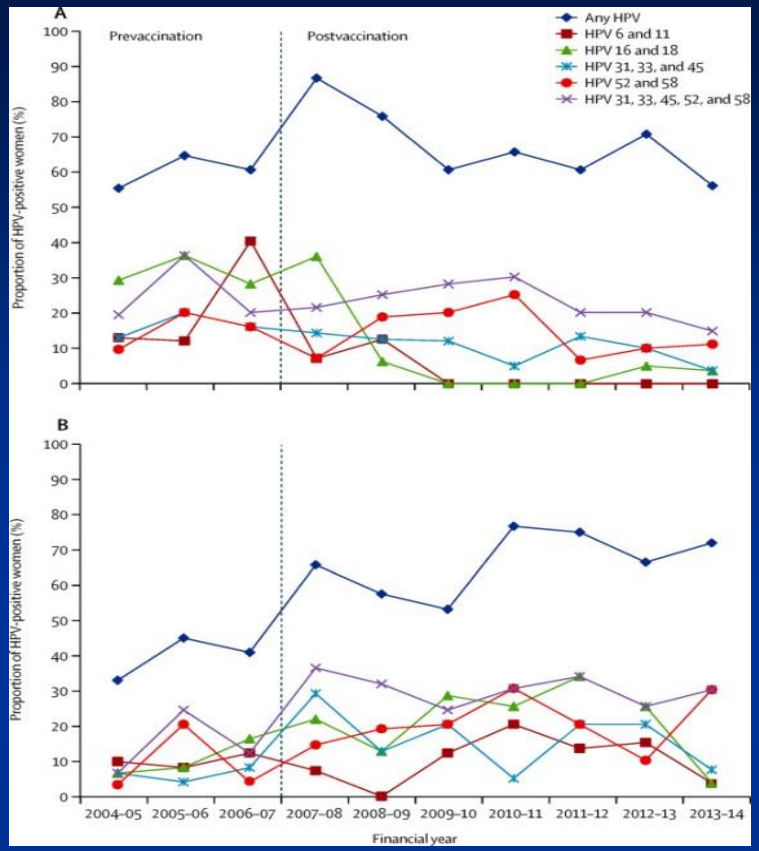


Figure 2. Crude HPV genotype prevalence in women aged 21 years and younger, stratified by (A) Australian-born and (B) overseas-born womenThe dashed line represents when the HPV vaccination programme began. HPV=human papillomavirus.

Eric P F Chow, et al

Human papillomavirus in young women with Chlamydia trachomatis infection 7 years after the Australian human papillomavirus vaccination programme: a cross-sectional study

Volume 15, Issue 11, 2015, 1314–1323

http://dx.doi.org/10.1016/S1473-3099(15)00055-9

Challenge for HPV prevention

Vaccines depend for their impact at the population level by reducing transmission

How can enough population immunity be achieved for $R_0<1$

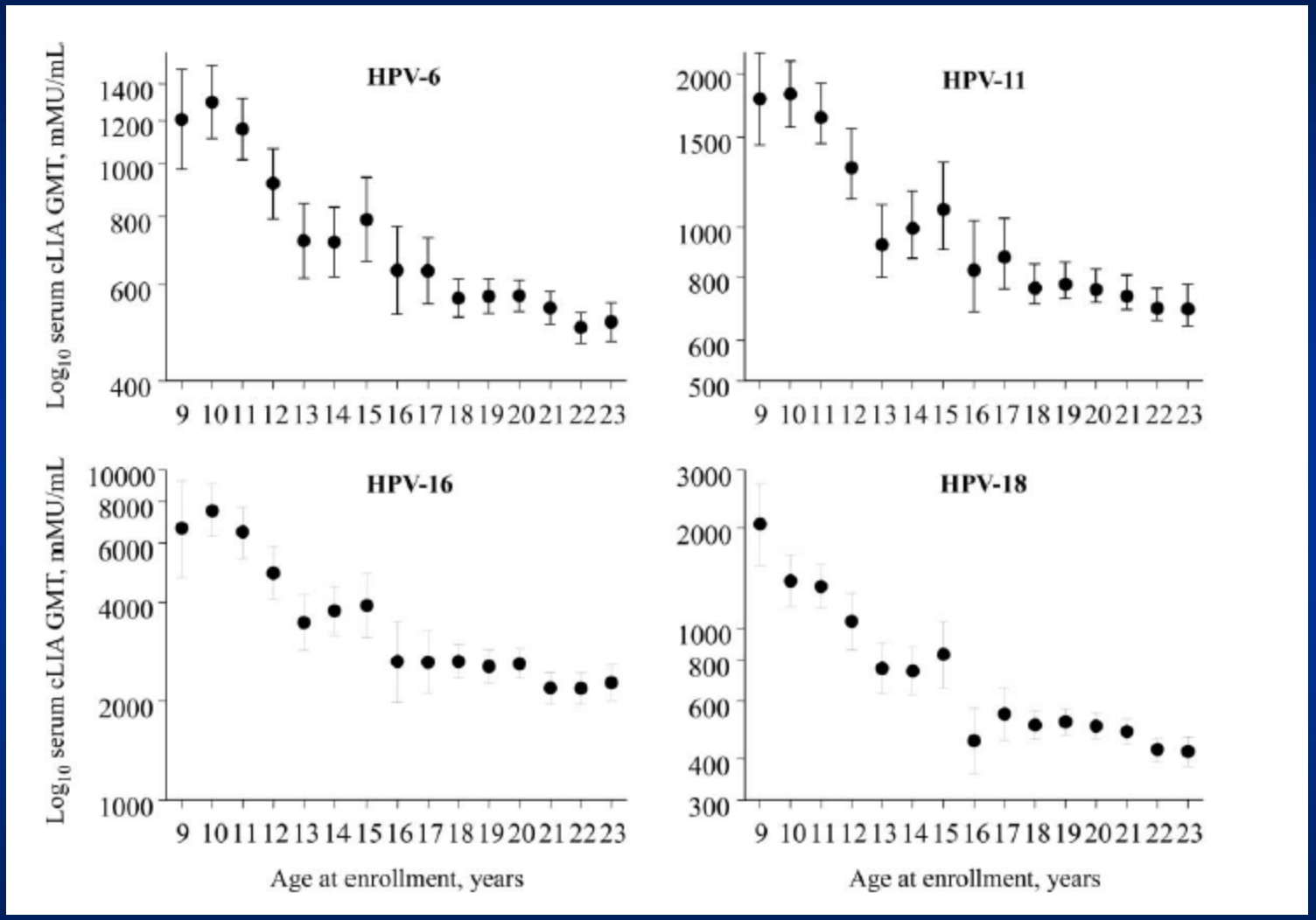
- Cohorts for immunisation
  - Age
  - Males and females
- How many doses
  - 1? 2? 3?
- Cost
  - New vaccines?

Genital HPV infection is usually but not always sexually transmitted

Infection occurs early after the onset of sexual activity

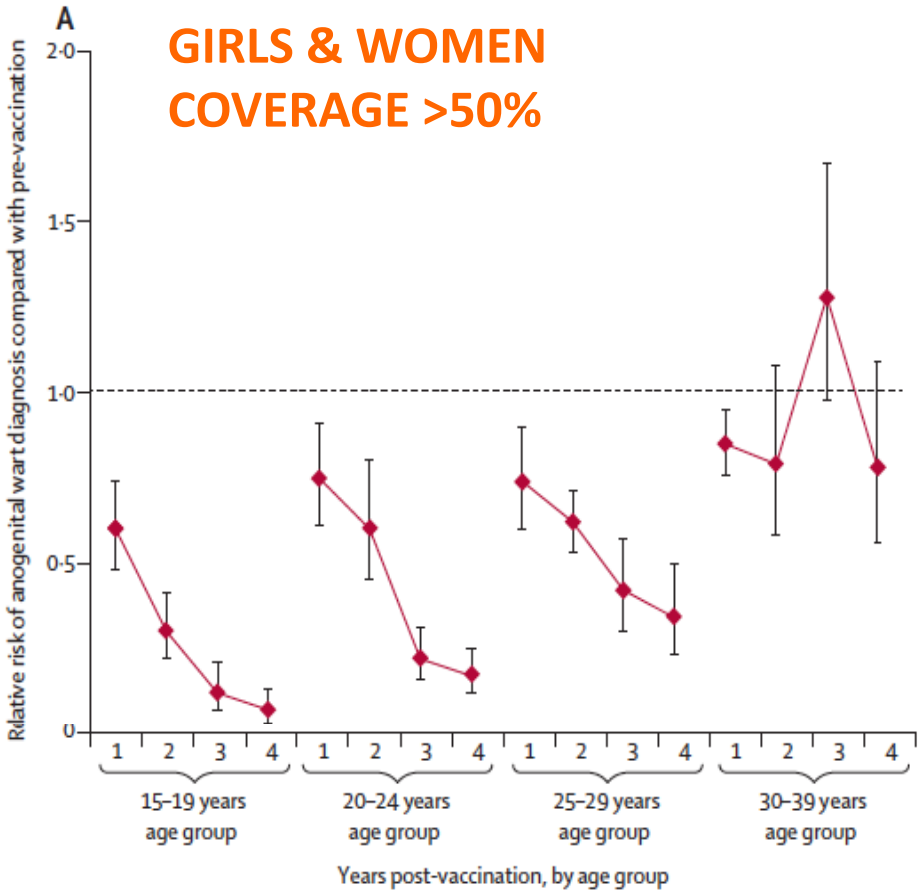
Immune responses to the vaccines are optimal in 9-13 year olds

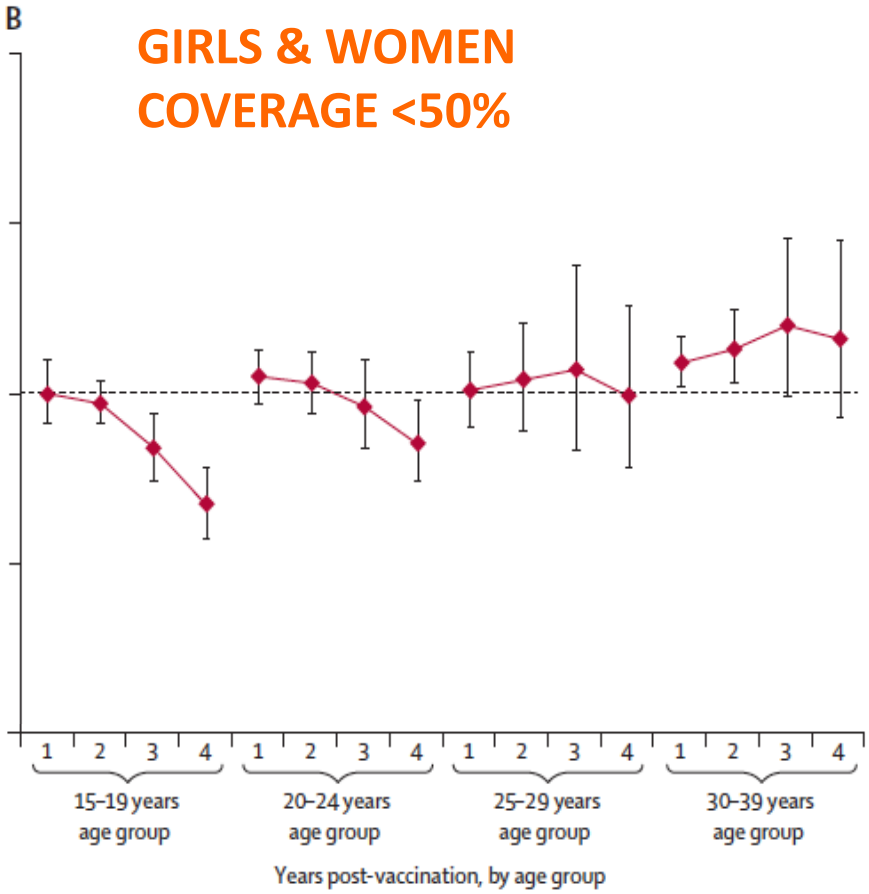
Antibody responses in females by age group at month 7 post vaccination



Giuliano etal 2007 JID 196

RR OF GW DURING THE FIRST 4 YEARS AFTER GARDASIL INTRODUCTION RELATIVE TO PRE-VACCINATION PERIOD

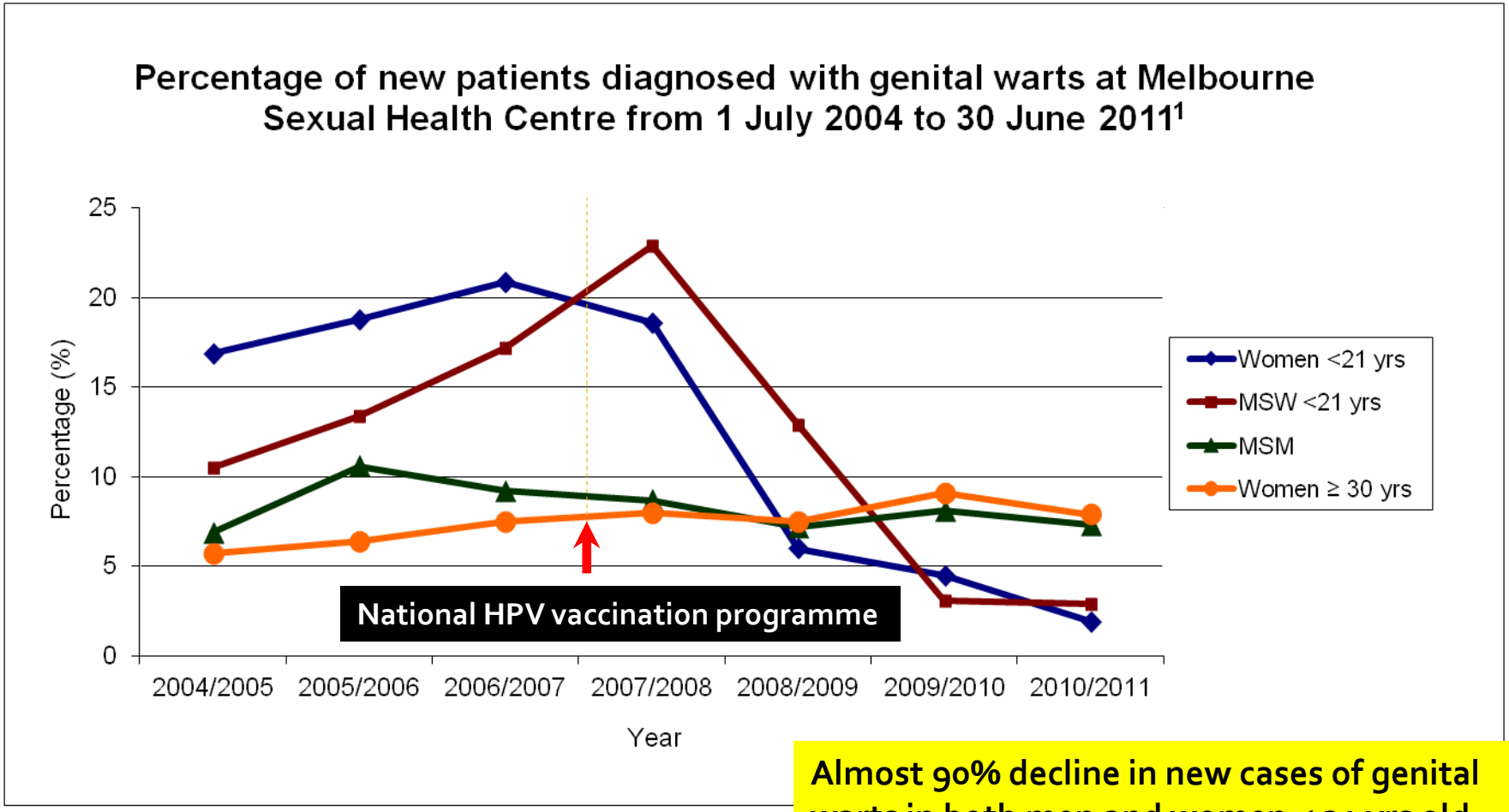




Drolet et al, Lancet Infect Dis 2015

Gender Neutral Vaccination

Australia: Near disappearance of genital warts after commencement of national HPV program

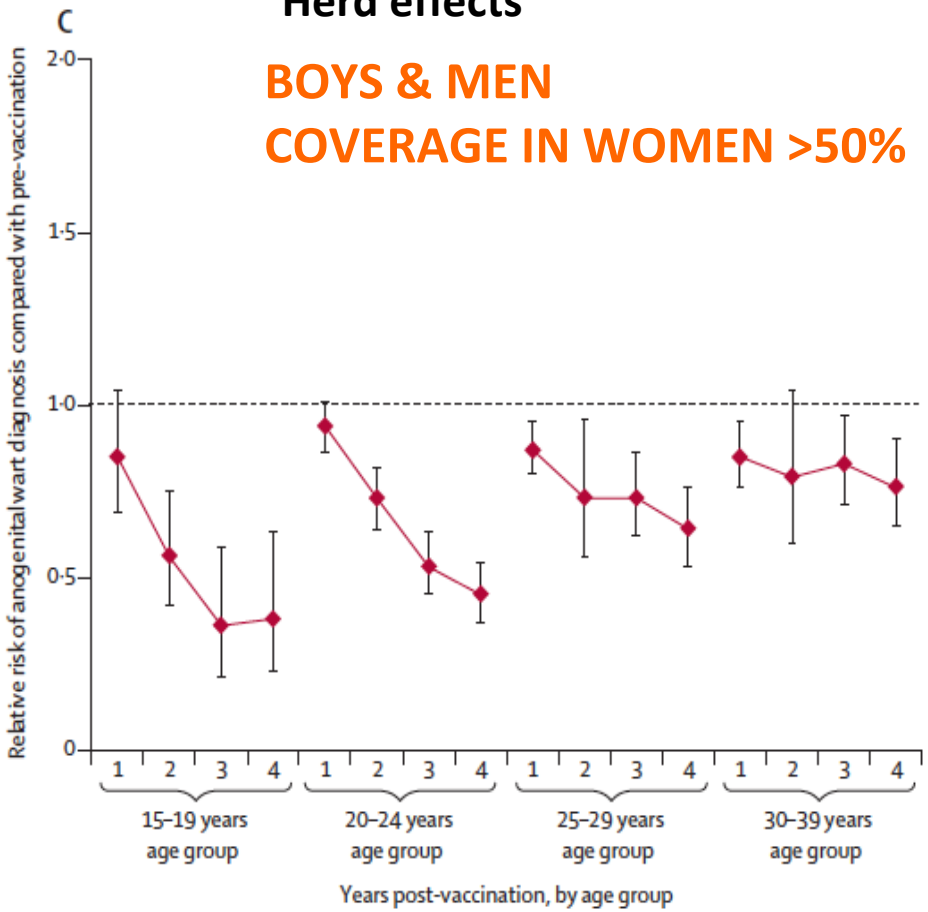


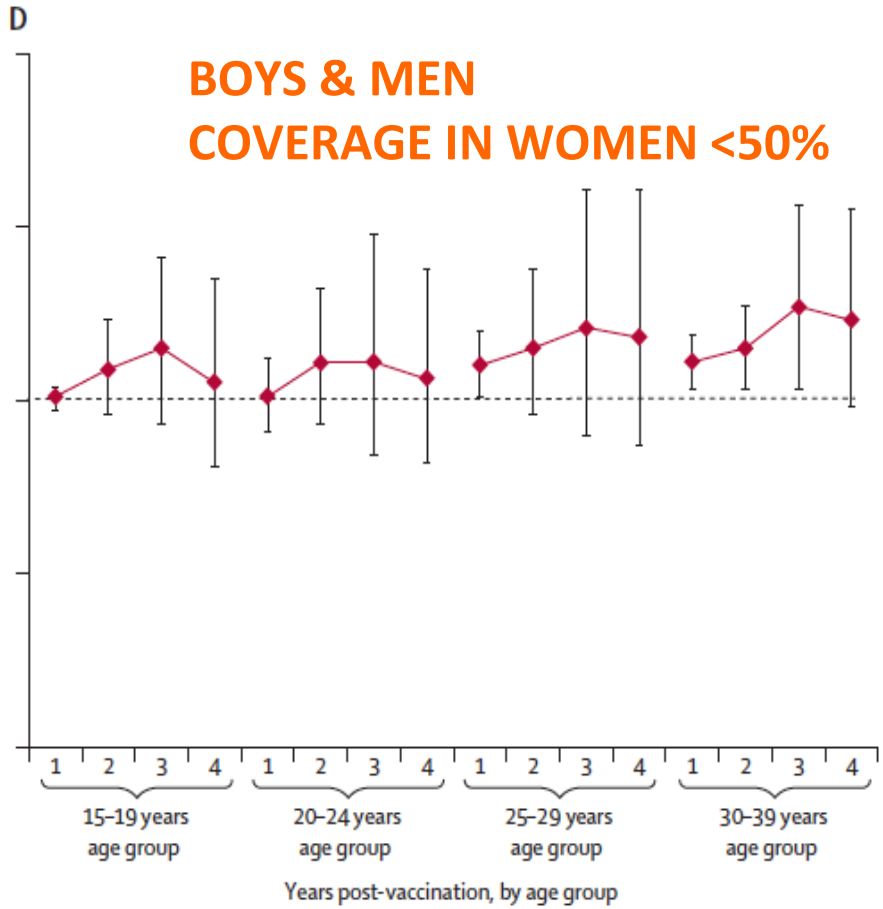
Almost 90% decline in new cases of genital warts in both men and women < 21 yrs old

1. Read et.al., *Sex Transm Infect 2011*; 87:544e547. doi:10.1136/sextrans-2011-050234

RR OF GW DURING THE FIRST 4 YEARS AFTER GARDASIL INTRODUCTION RELATIVE TO PRE-VACCINATION PERIOD

Herd effects





Drolet et al, Lancet Infect Dis 2015

Gender neutral vaccination

- MSW get herd protection from female only vaccination when coverage >70% - not cost effective

- Herd protection is not herd immunity – by definition female only immunisation cannot give herd immunity

- MSM not protected by female only vaccination but can be vaccinated as a high risk group

- Sustainability of herd protection in men depends upon sustained high coverage in women

- Reduction in coverage in women and a reservoir of virus in men would lead to a loss of vaccine effectiveness

Challenges for HPV prevention

Increasing coverage in girls
Extending catch up

Immunising at a younger age
- children
- infants

Immunising boys and girls

How many shots do we really need for long term protection -1?, 2? 3?

The antibody quantity and quality in 9-13 year olds after 2 vaccine doses at 0-6months is as good as that generated after 3 doses 0,2,6 months in 16-23 year olds in whom efficacy has been shown

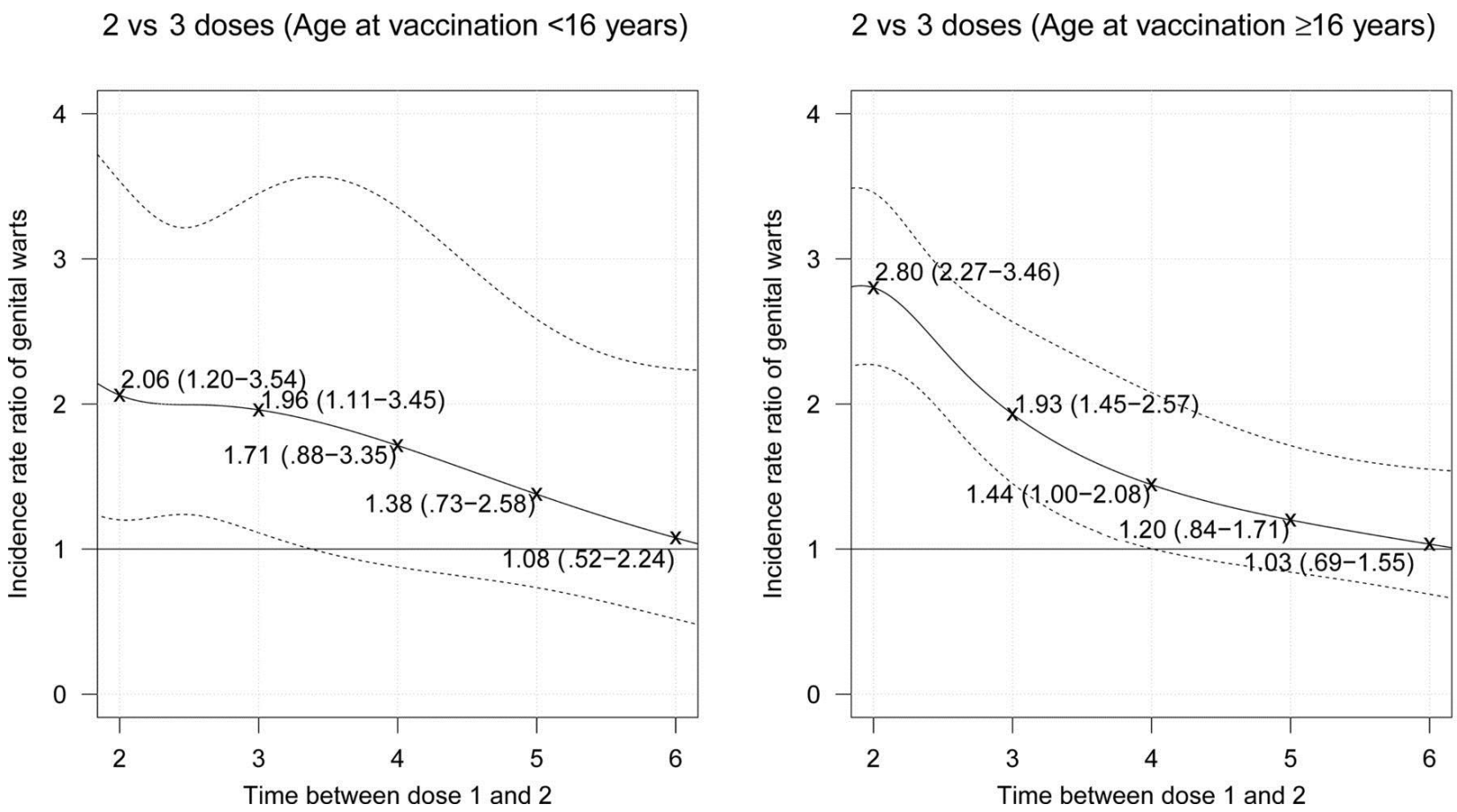
SAGE April 2014 meeting

Upon review of the evidence, SAGE recommended a 2-dose schedule for girls, if vaccination is initiated prior to 15 years of age.
The recommended minimal interval between the 2 doses is 6 months.

A 3-dose schedule remains necessary if immunization is initiated after the girls' 15th birthday.

This interval may be extended to 12 months if this facilitates administration
A 3-dose schedule (i.e. at 0, 1-2, and 6 months) remains recommended for immunocompromised individuals, including those known to be HIV-infected."

Influence of interval between first and second dose of human papillomavirus vaccine on the incidence of genital warts (GWs): 2 doses compared with 3 doses.



Maria Blomberg et al. Clin Infect Dis. 2015;61:676-682

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Clinical Infectious Diseases

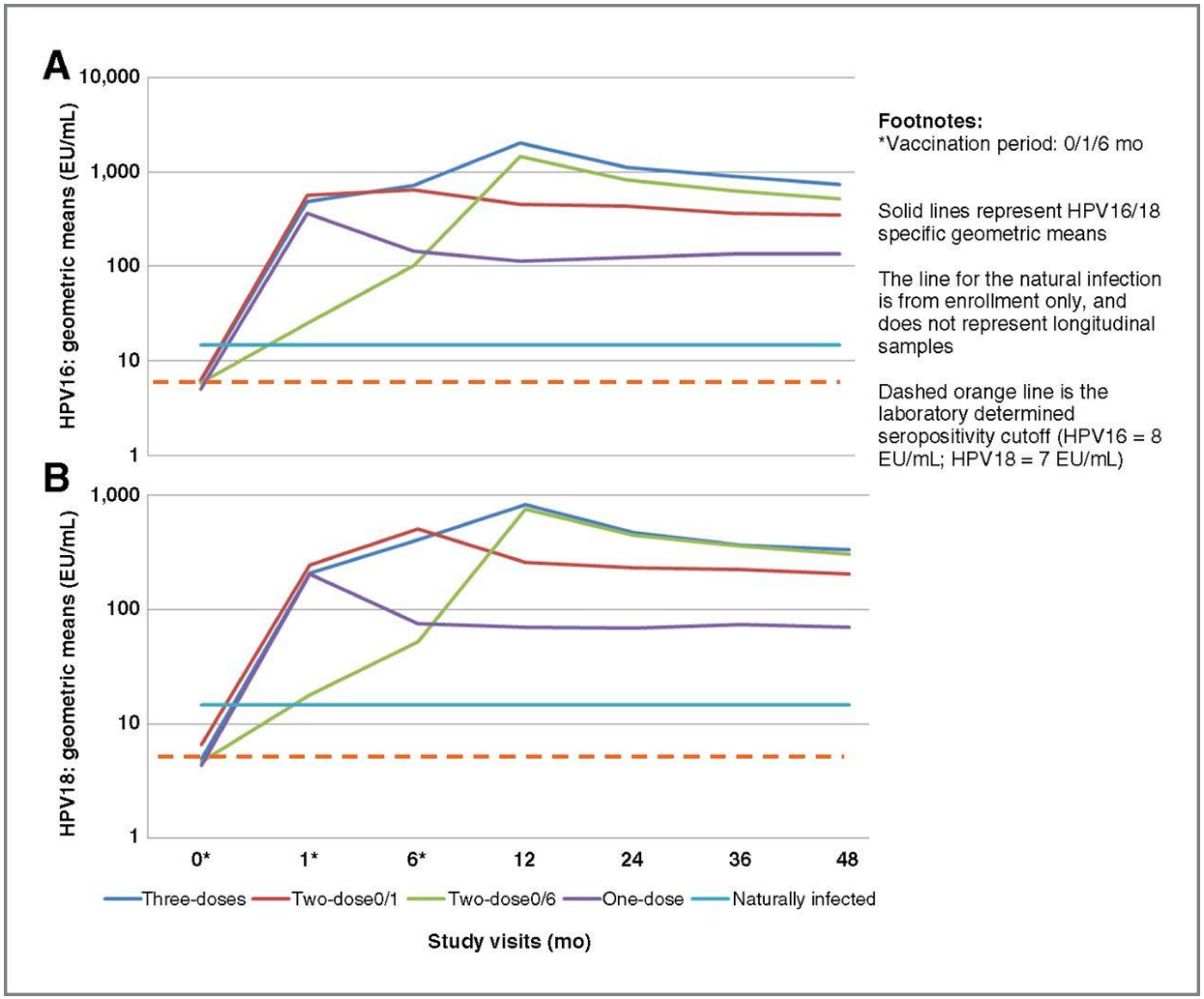
Efficacy of fewer than three doses of an HPV-16/18 AS04-adjuvanted vaccine: combined analysis of data from the Costa Rica Vaccine and PATRICIA trials

Aimée R Kreimer, Frank Struyf*, Maria Rowena Del Rosario-Raymundo, Allan Hildesheim, S Rachel Skinner, Sholom Wacholder, Suzanne M Garland, Rolando Herrero, Marie-Pierre David, Cosette M Wheeler, for the Costa Rica Vaccine Trial and the PATRICIA study groups†*

Lancet Oncology June 10 2015

"**We assessed vaccine efficacy against incident HPV-16/18 infection in the modified total vaccinated cohort (22 327 received three doses, 1185 two doses, 543 one dose). Vaccine efficacy against incident HPV-16/18 infections for three doses was 77·0% (95% CI 74·7–79·1), two doses was 76·0% (62·0–85·3), and one dose was 85·7% (70·7–93·7). "**

A and B, HPV16 (top) and HPV18 (bottom) specific antibody geometric means: by number of vaccine doses and study visit.



Safaeian M et al. Cancer Prev Res 2013;6:1242-1250

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Cancer Prevention Research

Challenges for one dose

No immune correlate

Kinetics of antibody response – limited data for 1 dose from post hoc analysis

Evidence restricted to immunogenicity

More data on antibody affinity and avidity maturation in natural infection and after immunisation needed

At the present there is no evidence from randomised control trials demonstrating efficacy and duration of protection.

Challenge for HPV prevention

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How can enough population immunity be achieved for $R_0 < 1$

- Cohorts for immunisation
  - Age
  - Males and females
- How many doses
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- Cost
  - New vaccines?

Many 2nd Generation Candidates Are Being Developed

Protein:

- Alternative VLP production systems:
  E. coli in Phase III trial *Cecolin™*
- Pichia, Hansenula, Plants
- L1 pentameric subunits
- L2-polypeptides – many variations

Vectored:

- L1 recombinant AAV
- L1 recombinant Salmonella vaccine
- L1 recombinant Measles vaccine
- L1 AcHERV