Vaccination of Boys: Is it cost effective?

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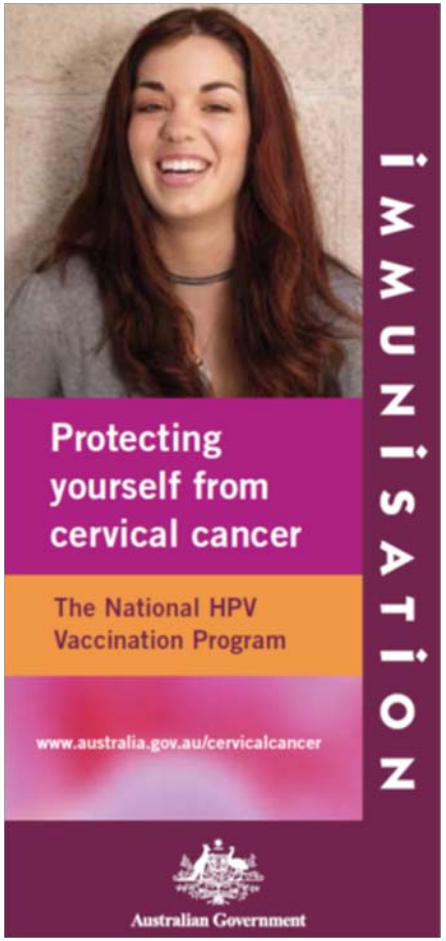
HPV Vaccination to date

- April 2007 –Australian HPV vaccination program (NIP)
  - girls 12 and 13y school based (on-going)
  - girls 13 – 18y school catch-up (ceased end 2008)
  - women up to 26y catch-up (ceased end 2009).
- The National HPV Vaccination Program Register
  - High coverage school based program (>70% girls 12-13y 3 doses)
- Early evidence of benefit of vaccination program in population (GW and high-grade cervical abnormalities)



Brotherton, J et al. (2011). "Early effect of the HPV vaccination programme on cervical abnormalities in Victoria, Australia: an ecological study." The Lancet **377**(9783): 2085-2092
Read, **T** et al. (2011). "The near disappearance of genital warts in young women 4 years after commencing a national human papillomavirus (HPV) vaccination programme." Sexually Transmitted Infections.

HPV vaccines for use in males

- 4vHPV vaccine registered use in males (USA, AUS, Europe).
- **ACIP** draft recommendation of routine vaccination males 11 &12 years, and boys 13 - 21 years who not already received vaccine.
- **Australia**: up-date of the 10th edition of Handbook, HPV chapter is under review.

Factors that impact decision making

- A number of factors must be reviewed when considering recommendations around vaccination
  - local disease burden
  - vaccine efficacy
  - existing programs/ herd benefit
  - implementation
  - cost effectiveness
  - social, ethical considerations
  - safety

Erickson L et al. An analytical framework for immunization programs in Canada. *Vaccine* 2005; 23: 2470-6.
Kimman TG et al, Developing a vaccination evaluation model to support evidence-based decision making on national immunization programs. *Vaccine* 2006**; 24:** 4769-78.
Piso B et al Decision support in vaccination policies. *Vaccine* 2009; **27**: 5923-8.

HPV anogenital infection in males

- majority infections are transient and asymptomatic.
- anogenital HPV infection common among males
  - 1.3% - 72.9% heterosexual men external genital infection (any type)
  - 12% heterosexual men anal HPV infection (any type)
- prevalence greater in men who have sex with men (MSM)
  - **95%** MSM anal HPV infection (any type) (Vadjic et al 2009)
- large proportion due to vaccine HPV types (16/18/6/11)

Dunne, E., et al. (2006). "Prevalence of HPV infection among men: A systematic review of the literature." Journal of Infectious Diseases **194**(8): 1044-1057.
Vajdic, M et al. (2009). "Anal human papillomavirus genotype diversity and co-infection in a community-based sample of homosexual men." Sexually Transmitted Infections **85**(5): 330-335.
Nyitray,G et al.(2011)."Age-specific prevalence of and risk factors for anal human papillomavirus (HPV) among men who have sex with women and men who have sex with men: the HPV in men (HIM) study." Journal of Infectious Diseases **203**(1): 49-57

Natural History HPV infection in males

- Understanding of HPV infection/disease progression limited compared to in females
- No screening program for HPV disease in males
- Lack of prospective cohort studies (increasing!)

Uncertainty around:

- Proportion of HPV anogenital infections that progress to pre-cancerous lesions (intra-epithelial neoplasia).
- Progression of pre-cancerous lesions to cancer

  ie. AIN 1 → AIN 2 → AIN 3 → Anal Cancer
- Time to progression / clearance

HPV attributable cancer, by site

Cancer	Proportion Attributable any HPV (%)	Proportion HPV+ associated HPV16/18 (%)
Penile *	50*	87
Anal	85	93
Oropharyngeal	35	90
Oral Cavity	24	85
Cervical	95	70

*Varies by cancer sub-type (~ 65%) basaloid/warty subtype and rare to absent in keratinising/verrucous subtypes)

- HPV 6/11 associated ~90% genital warts, and 100% Recurrent respiratory papillomatosis

Table 1: HPV-associated cancers and proportion HPV 16/18 positive (modified from Grulich et al 2010)

Male HPV disease burden Australia

- Number of HPV associated cancers in males is low
  - 2005 ~ 300 HPV associated cancers in males
- Increase in incidence of anal cancer and HPV associated oral and oropharyngeal cancers in males
  - ↑ **23%** in females and **50%** in males in 2005 from that in 1990.
- MSM are at a greater risk of HPV-associated disease
  - Anal cancer ~12.5 – 25.8/100 000 population

Grulich, A et al (2010). "Cancers attributable to human papillomavirus infection." Sexual Health **7**(3): 244-252.
Jin, F., A. N. (2011). "Trends in anal cancer in Australia, 1982-2005." Vaccine **29**(12): 2322-2327.

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Efficacy of Quadrivalent HPV Vaccine against HPV Infection and Disease in Males

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Efficacy of 4vHPV vaccination in males

- 4065 males 16–26 years, 18 countries (sub-population 602 MSM) followed 36 months
  - Primary efficacy endpoint
    - HPV 6, 11, 16, 18 external genital lesions (EGL)
    - HPV 6, 11, 16, 18 AIN and anal cancer (MSM sub-study)
  - Secondary efficacy endpoint
    - Incident & persistent genital HPV 6,11,16,18 infection
    - Incident & persistent intra-anal HPV 6,11,16,18 infection (MSM sub-study)

Study endpoint	Cases (vaccine)	Cases (control)	Efficacy % [95% CI]
HPV 6/11/16/18 associated EGL	3	31	90·4% [69·2 – 98·1]
Condyloma	3	28	89·4% [65·5 – 97·9]
PIN 1 or worse	0	3	100% [<0 – 100]
Penile, perianal or perineal cancer	0	0	n/a
AIN 1 or worse*	5	24	77·5% [39.6 – 93·3]
Anal cancer*	0	0	n/a
HPV 6/11/16/18 persistent infection	15	101	85·6% [73·4 – 92·9†]
HPV 6/11/16/18 persistent intra-anal infection*	2	39	95% [80 – 99]

* Vaccine efficacy against persistent intra-anal HPV infection, AIN and anal cancer was determined in MSM sub-study participants only

Table 2: Summary of 4vHPV vaccine efficacy in male study participants in the per protocol population (PPE), against multiple clinical end points (end of study; month 36)
(Guilano A, 2011, Palefsky 2010)

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Uncertainties around vaccine efficacy

Current efficacy data:

- provides strong evidence of effect against GW
- some evidence of effect against intra-epithelial neoplasia (AIN)
- no evidence of penile/anal cancer (lack of cases)

Is demonstrated efficacy against pre-cursor lesions (ie PIN/AIN) enough translate efficacy against cancer?

Same approach adopted for female program

- Inferences based on surrogate outcomes less certain in males

Immunogenicity in adolescent males

- Immunogenicity has been used as a proxy to predict vaccine efficacy in adolescent males (<16 years).

- Antibody response in adolescent boys (9 – 15 years) is **≥** that in young adult males

  - 99% seroconversion all vaccine HPV types

- Antibody response in adolescent boys (9-15 years) is also non-inferior to that achieved in girls of same age.

Block, T.. (2006). "Comparison of the immunogenicity and reactogenicity of a prophylactic quadrivalent human papillomavirus (types 6, 11, 16, and 18) L1 virus-like particle vaccine in male and female adolescents and young adult women." Pediatrics **118**(5): 2135-2145.
Reisinger, K.. (2007). "Safety and persistent immunogenicity of a quadrivalent human papillomavirus types 6, 11, 16, 18 L1 virus-like particle vaccine in preadolescents and adolescents: a randomized controlled trial." Pediatric Infectious Disease Journal **26**(3): 201-209

Herd effect of HPV vaccination

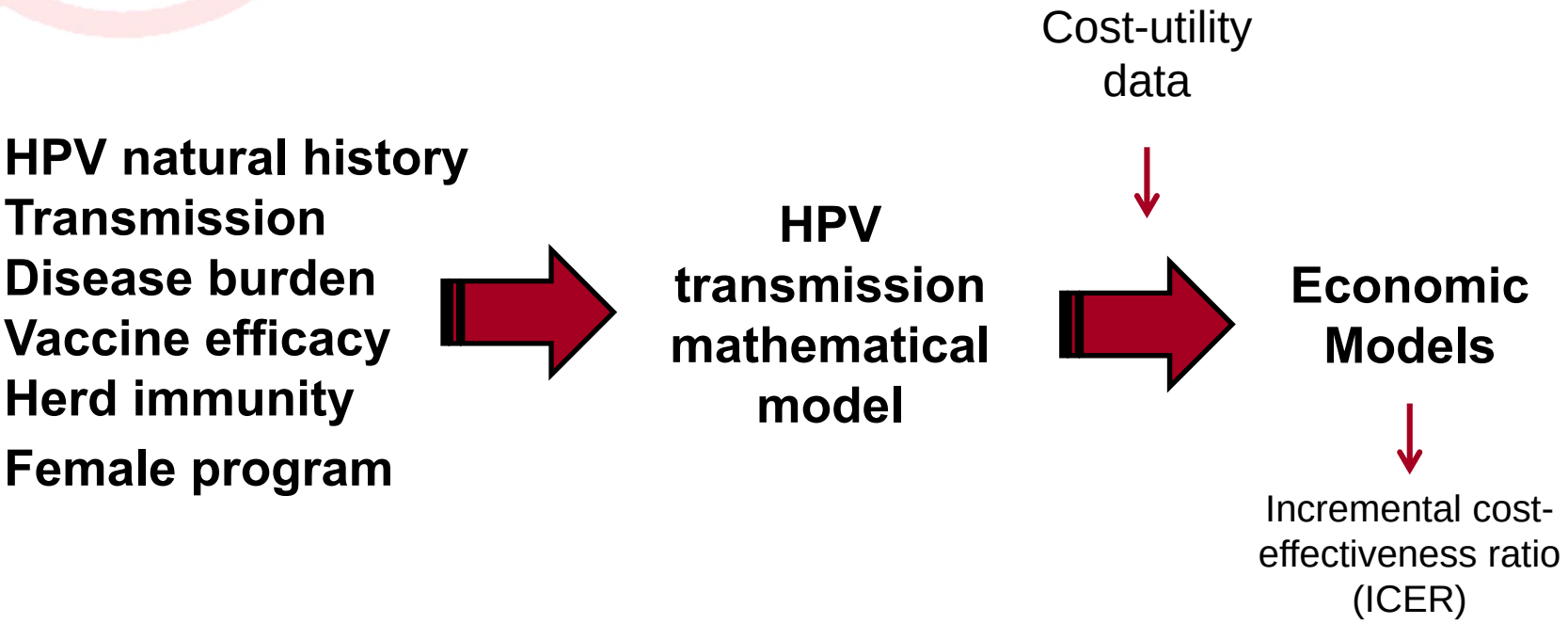
- Herd effect of female vaccination has already been demonstrated for HM males (not MSM) (Read et al 2011)
- Vaccination of males expected provide indirect benefit
  - to un-vaccinated females
  - to un-vaccinated MSM

How much extra health benefit would be gained if males included into female only HPV vaccination programs?

Read, T. (2011). "The near disappearance of genital warts in young women 4 years after commencing a national human papillomavirus (HPV) vaccination programme." Sexually Transmitted Infections.

Incremental benefit of vaccinating males

Can be estimated through modelling



Australian Context (Smith et al 2011)

Model reduction of male HPV associated cancers through current female only program and the additional reduction expected with addition male vaccination

Base Assumptions: VE 100%, lifelong immunity, 78% coverage females

- **73%** of max vaccine conferred benefit to males from female/male program will be achieved by female only program

- Additional benefit from male vaccination sensitive to:
  - Coverage
  - Vaccine efficacy
  - Duration of protection

Smith, M.et al. (2011). "The predicted impact of HPV vaccination on male infections and male HPV-related cancers in Australia." Vaccine In Press.

Models of cost-effectiveness

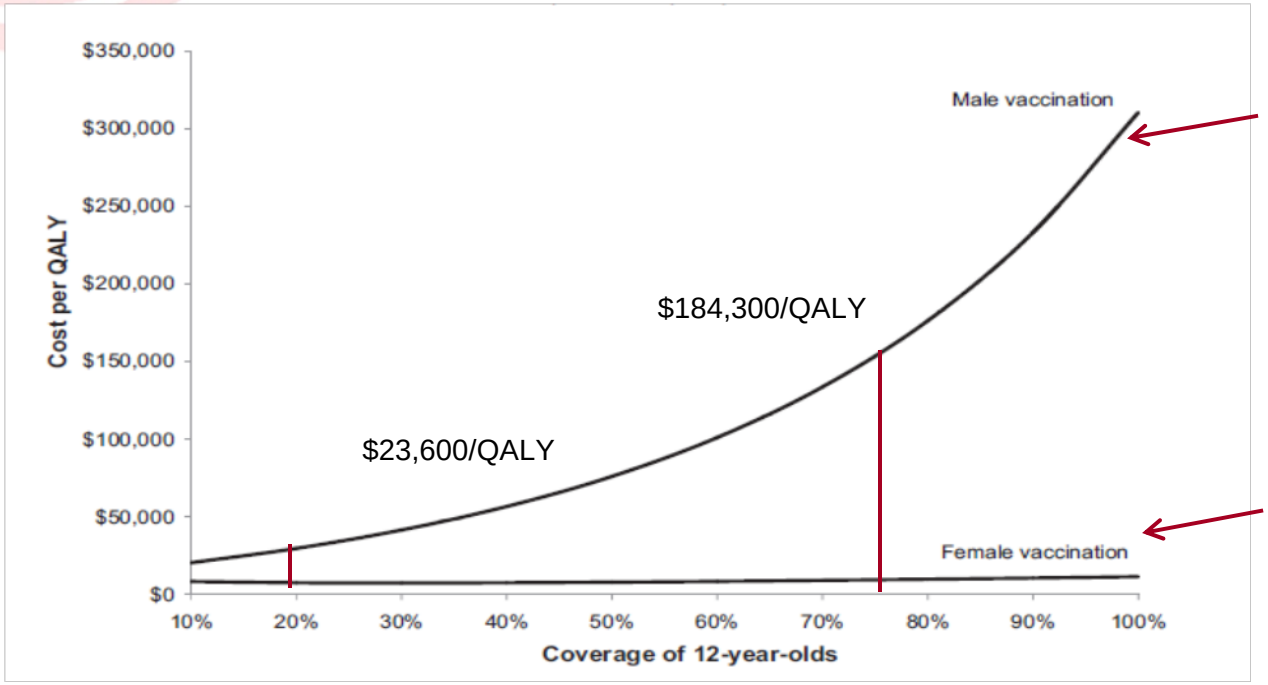
- Estimate additional cost of health intervention per additional unit of health benefit (ICER: $/QALY)
- Cost-effectiveness of male vaccination females varies

  (methodology, assumptions, local situation)
- Majority found male vaccination “not cost-effective”
- Cost effectiveness of vaccinating males increases when:
  - Benefit of all HPV associated disease in males considered
  - Vaccine efficacy, persistence and coverage is reduced females
  - Cost of vaccine is reduced

Kim, J. et al (2009). "Cost effectiveness analysis of including boys in a human papillomavirus vaccination programme in the United States." BMJ **339**(b3884): 1-10.
Brisson, M., et al. (2009). "Economic Evaluation of Human Papillomavirus Vaccination in Developed Countries." Public Health Genomics **12**(5-6): 343-351.

Male vaccination when female coverage is low

CE model of male HPV vaccination in US (~30% coverage)



Male vaccination compared with female only

Female only compared with no vaccination

- better use of health care dollar to increase coverage in females?

Chesson et al (2011) The cost-effectiveness of male HPV vaccination in the United States (29) 8443 – 8450

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Forgotten population - MSM

- All models include heterosexual HPV transmission.
- Male benefit due to female only HPV vaccination program might be over-estimate.
- MSM have largest burden of HPV disease

In Australia:

- 44 – 73% of anal cancer cases in men occurs in MSM

Herd benefit gained in heterosexual males have limited impact of the burden anal cancer?

Smith AM, et al (2003). Sex in Australia: sexual identity, sexual attraction and sexual experience among a representative sample of adults. *Aust N Z J Public Health* 27(2):138-145.
Grulich AE, et al (2003). Sex in Australia: Homosexual experience and recent homosexual encounters. *Aust N Z J Public Health* 27(2):155-163.

Cost-effectiveness in Australia?

- Process for assessing and funding new vaccines
  - Australian Technical Advisory Group on Immunisation (ATAGI)
  - Pharmaceutical Benefits Advisory Committee (PBAC)

- In 2010, an application was made to the PBAC to extend current NIP funded HPV program

  "to *include males 12 to 13 years of age and a catch-up program over two years for Year 9 males*"

- The PBAC rejected the requested extension because of *"unacceptably high and uncertain cost-effectiveness"*

  March 2011 PBAC Meeting Public Summary Document

Alternative delivery to males

- Individual benefit**:** vaccination of males who have not commenced sexual debut

- Targeted vaccination: particularly for MSM
  - minimal in-direct benefit from female program
  - feasibility – Majority MSM would disclose their sexual orientation to receive free HPV vaccine (at 20 years of age, median of 15 sexual partners) (Simatherai et al)

Simatherai D, Bradshaw CS, Fairley CK, Bush M, Heley S, Chen MY. What men who have sex with men think about the human papillomavirus vaccine. *Sex Transm Infect* 2009; **85**: 148-9.

Ethical / social considerations

- Share of sexual health burden between genders
  - both genders transmit HPV
  - lesser responsibility males
  - less understanding HPV infection/disease
- Opportunity health discussions adolescent males?
- Non-discriminatory to sexual preferences (best way to offer benefit to MSM)
- No screening program for anal cancer in Australia

Rae M et al Vaccines – but not as we know them: an ethical evaluation of HPV vaccination policy in Australia (2011) Aus &NZ J of Pub Health 35 (2) 176 – 179).

Conclusion

- HPV vaccination prior to sexual debut will offer individual benefit to males
- Cost effectiveness of universal HPV vaccination of males is variable
  - High coverage in females: Majority reduction of disease burden in males from female programs
  - Low coverage females: Including males is more cost effective
- Ethics/social considerations can be as influential as cost
  - Gender equity, extending benefit to MSM


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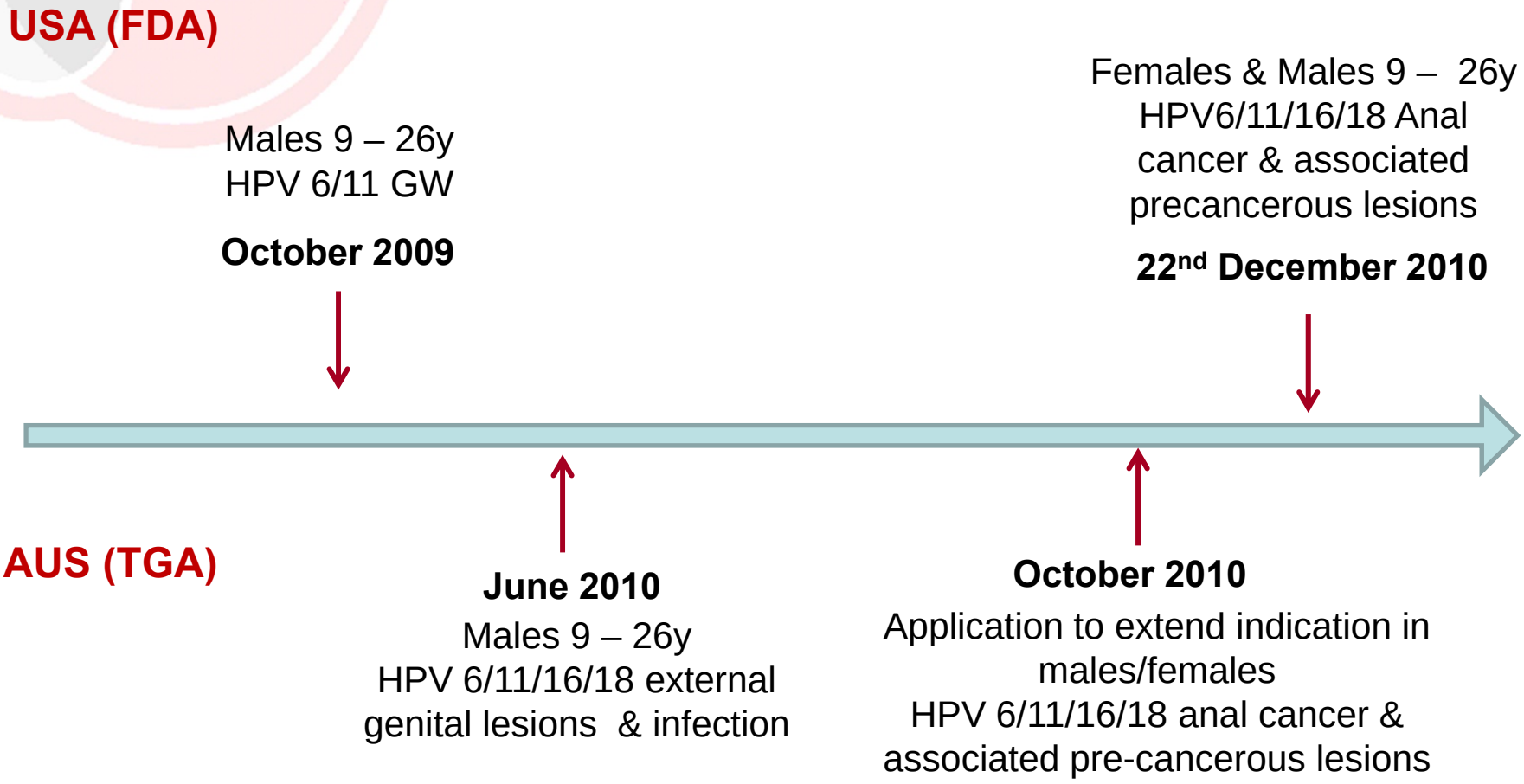
Registration of HPV vaccines for males



Acceptance

- Framing of HPV vaccination programs around cervical cancer
- Males generally have a poorer understanding of HPV, its associated diseases and the available vaccines.

  Australian population-based survey: more participants were aware of the association HPV and cervical cancer than HPV and other disease (Pitts et al 2010)
- Re-branding of program to reduce disparity in understanding between genders – without dilution current up-take in females
- Reported knowledge of HPV and available vaccines in MSM is higher than in heterosexual males

Pitts MK, Heywood W, Ryall R, et al. Knowledge of human papillomavirus (HPV) and the HPV vaccine in a national sample of Australian men and women. *Sex Health* 2010; **7**: 299-303.

Cost-effectiveness of targeted vaccination MSM

- **Model of USA scenario** (Kim J et al)

50% vaccine coverage, 90% vaccine efficacy, benefit of anal cancer and GW modelled only.

  - vaccination of MSM at 12yo $15 290/QALY gained (0% HPV exposure)
  - vaccination of MSM at 20yo $35 740/QALY gained (50% HPV6,11,16 and 18 exposure)

- ICER were sensitive to:
  - **Previous HPV exposure**
  - **Duration vaccine induced protection**
  - **Incidence of anal cancer**
  - **HIV status**

Kim J Targeted human papillomavirus vaccination of men who have sex with men in the USA: a cost-effectiveness modelling analysis, 2010; 10(12) 845 - 852