HPV Vaccine

Not just a cervical cancer vaccine

HPV vaccine

- Only Cervix
- Only female
- Only adolescent

Gardasil Indications

- **Females** aged 9-45* years for the prevention of HPV 16,18, 6 and 11 related:
  - infection
  - cervical, vulval, vaginal and anal precancerous or dysplastic lesions
  - cervical, vulval, vaginal and anal cancer
  - genital warts
- **Males** aged **9- 26 years** for the prevention of anal cancer, precancerous or dysplastic lesions, external genital lesions and infection caused by HPV types 6, 11, 16, and 18

Gardasil data sheet

HPV Vaccine

- Has the potential to reduce the incidence of several cancers
- Has demonstrable herd effect
- In adolescents, two doses are highly immunogenic
- Will be a universal vaccine in due course
- Nothing is really new
  - Hepatitis B vaccine
  - Rubella vaccine

HPV epidemiology

- HPV is responsible for 99% of cervical cancer, genital warts and recurrent respiratory papillomatosis,
- 84% of anal cancers,
- 70% of vaginal cancers, 44% of vulval cancers
- 47% of penile cancers, and
- from 5% to 70% oropharyngeal cancers.

Data presented at IPV conference 2011

Global - Cervical cancer

- In 2004, a global estimate indicated that HPV contributes 3.4 million years of life lost.

Cervical Cancer

- 2008 - 530,000 new cases, 85.5% in less developed regions, and
- 275,000 deaths, 88% from less developed regions
- 15.3% of female cancers behind breast (39%)
- 9.1% of all cancers in more developed regions while it accounts for 17.8% in less developed regions – effect of screening programmes

Data presented at IPV conference 2011

Non cervical cancers

Western countries – Incidence

- Anal cancer – increasing (particularly in MSM)
- vulval cancer - stable or possibly slightly increasing,
- vaginal cancer - stable.
- Penile cancer - varying estimates (stable – decreasing increasing)
- Oro-Pharyngeal cancer – increasing due to HPV decreasing due to smoking.
- In US - 70% OP cancers are caused by HPV.

Data presented at IPV conference 2011

HPV types

- 71% of cervical cancer cases can be attributed to HPV 16-18 and up to 91% to high-risk HPV genotypes.
- Types, 16 and 18 are the most frequent HPV types in HPV positive ano-genital cancers.
- HPV 16 is predominate cause of Oro-pharyngeal cancers
- Genital Warts - 90% caused by types 6 and 11.

Data presented at IPV conference 2011

Vaccine efficacy

- High level of efficacy has been demonstrated against persistent cervical infection, abnormal cytology, anal cancers, and warts (for HPV4)
- CDC (USA) now recommend routine vaccination for males aged 11 or 12 years

- No data on oropharyngeal cancers but it is considered likely that protection will be similar at other sites

- No data on Recurrent Respiratory Papillomatosis

Data presented at IPV conference 2011. MMWR 2011:60(50);1705-1708

GARDASIL Prophylactic Efficacy Females 16 to 26 years

Endpoint	GARDASIL™	Placebo	Efficacy	95% CI
CIN 2/3 or AIS*	2/8493	112/8464	**98%**	94-100
VIN 2/3*	0/7772	10/7744	**100%**	56-100
VaIN 2/3*	0/7772	9/7744	**100%**	50-100
CIN or AIS#	9/7865	225/7865	**96%**	92-98
Genital Warts^	2/6932	189/6856	**99%**	96-100

*Due to HPV 16 or 18 # Due to HPV 6,11,16 or 18 ^Due to HPV 6 or 11
Primary efficacy results with combined database of efficacy studies in per-protocol population.
Mean duration of follow up 4, 3, 3 and 3 years for Protocol 005, Protocol 007, FUTURE I and FUTURE II respectively.
VIN = Vulvar Intraepithelial Neoplasia. VaIN = Vaginal Intraepithelial Neoplasia. CIN = Cervical Intraepithelial Neoplasia .
GARDASIL Product Information 2011.

EGL Efficacy by Lesion Type

Per Protocol Efficacy Population; Males 16 to 26 years

Endpoint	GARDASIL		Placebo		Observed Efficacy (%)	95% CI
	n	# Cases	n	# Cases		
HPV 6/11/16/18-Related EGL	1397	3	1408	31	90.4	69,98
Condyloma	1397	3	1408	28	89.4	66, 98
PIN 1 or worse	1397	0	1408	3	100	<0, 100

1. GARDASIL Product Information 2011. 2. Giuliano et al 2011 NEJM

Duration of Protection

- Data limited by the length of time vaccines available
- Stable protection - around 10 years for each vaccine and expected to be stable long term

- Concept of similar protection to delaying onset of sexual activity even if protection not sustained and booster doses required.

Vaccine safety

- 40 million doses distributed in US - adverse events reported similar to those seen in trials
- Vaccine safety data link – 600,000 doses

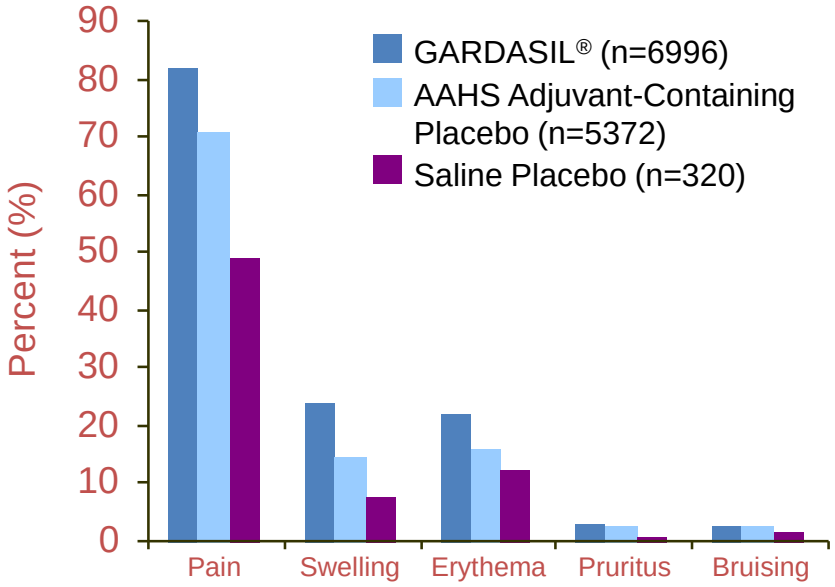
  no increase in GBS, Stroke, VTE, Appendicitis, Seizures, Syncope, Allergic reactions and Anaphylaxis
- Manufacturer sponsored data indicated an increase in risk of fainting on day of vaccination

MMWR 2011:60(50);1705-1708

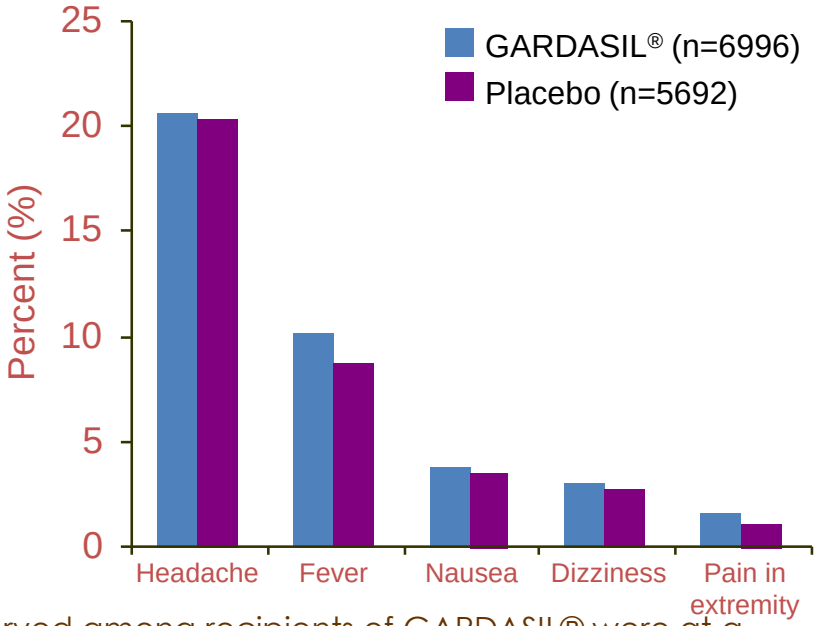
Vaccine-Related Injection-Site and Systemic Adverse Experiences[1]

Females 9 through 45 years of age
(1 to 5 days postvaccination)

Injection Site



Systemic



The vaccine-related adverse experiences that were observed among recipients of GARDASIL® were at a frequency of at least 1.0% and also at a greater frequency than that observed among AAHS control or saline placebo recipients.
AAHS = amorphous aluminum hydroxyphosphate sulfate.

1. Worldwide Product Circular. GARDASIL ® [Quadrivalent human papillomavirus (Types 6, 11, 16, 18) recombinant vaccine]; WPC-GRD-I-122008.

Alternative vaccine schedules

- 0-6 month schedule in 9-13 (or 14) year old girls equivalent to 3 dose schedule in adult women aged 15-25 years[1,2].
- British Columbia and Mexico adopted 2 dose schedule (?+ 3rd dose at 60 months)
- Costa Rica vaccine study indicated that those who received fewer than 3 doses had similar protection for duration of study (4 years)[3]

1.Dobson S,. Abstract presented at International Papilloma Virus Conference, Berlin Sept 2011.
2.Romanowski B Hum Vaccin. 2011;1;7(12). 3.Kreimer et al Data presented at IPV conference 2011

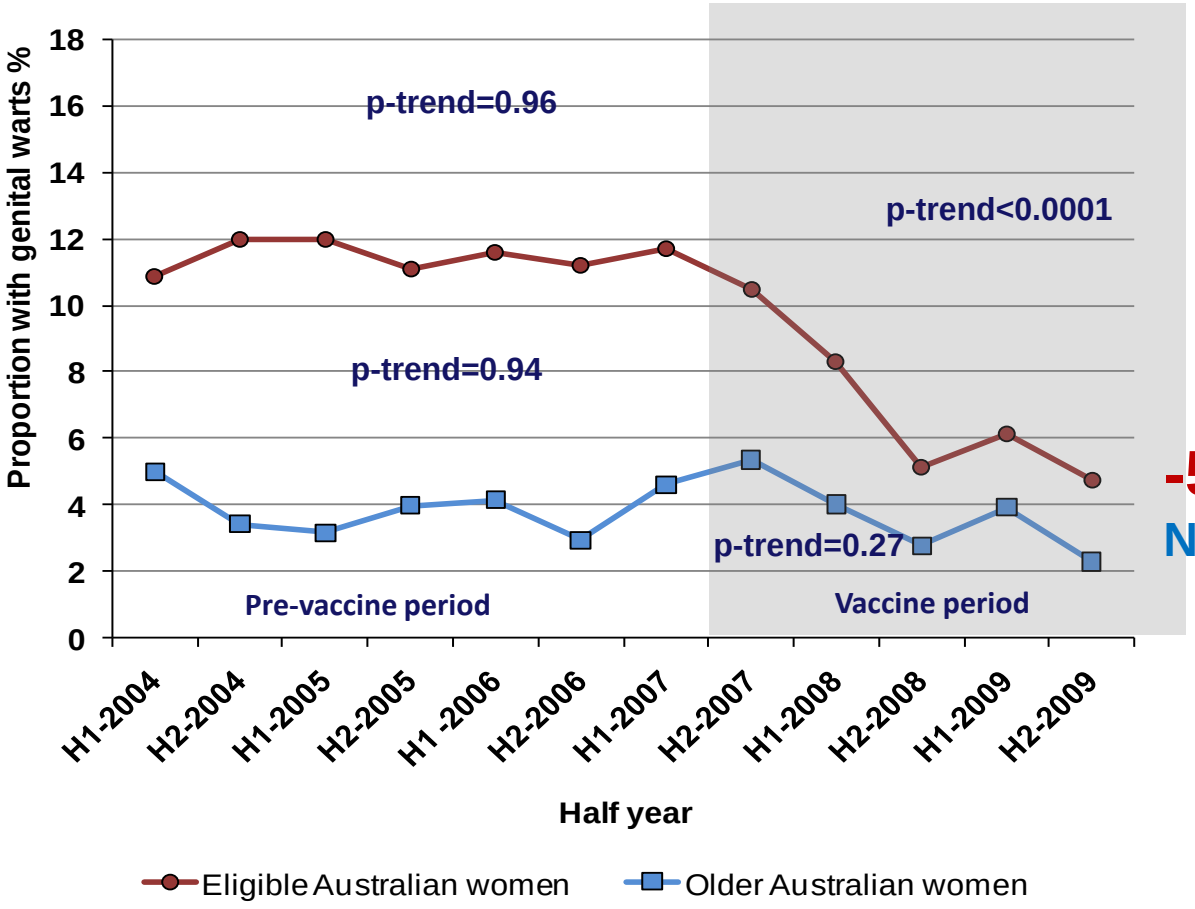
Herd protection

- Australian data
- 59% reduction in consultations for genital warts in women eligible to receive vaccine
- No reduction in women not eligible to receive vaccine
- 28% reduction in Wart consultations in heterosexual men
- No reduction in MSM

Data presented at IPV conference 2011

FEMALE REDUCTION IN GENITAL WARTS

Proportion of Australian women with genital warts by age, by half-year 2004-2009



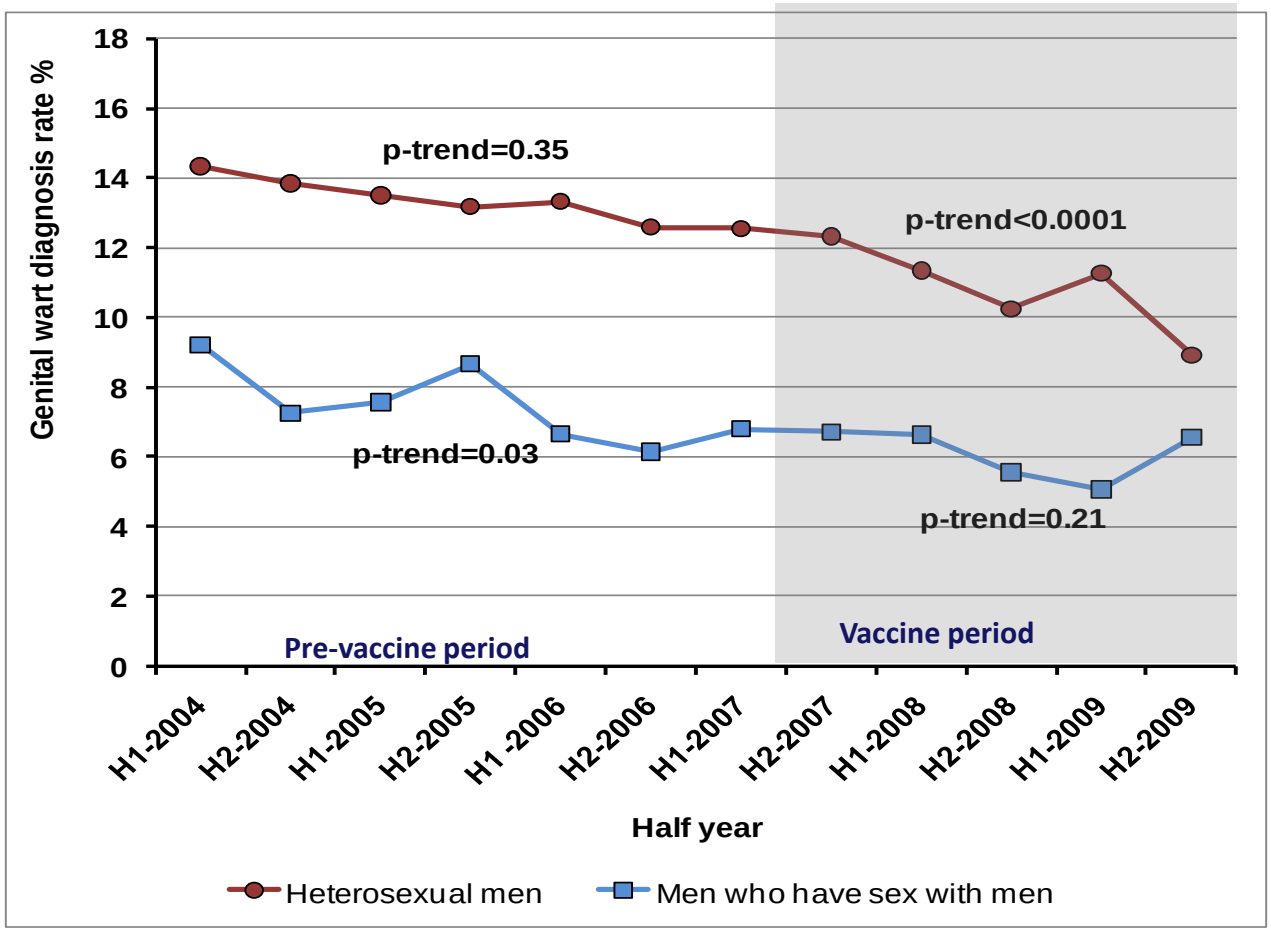
-59%

No change

Donovan et al. Lancet 2011

HETROSEXUAL MALES: SOME PROTECTION FROM FEMALE VACCINATION

Proportion of men with genital warts by gender of sexual partners, by half year 2004-2009

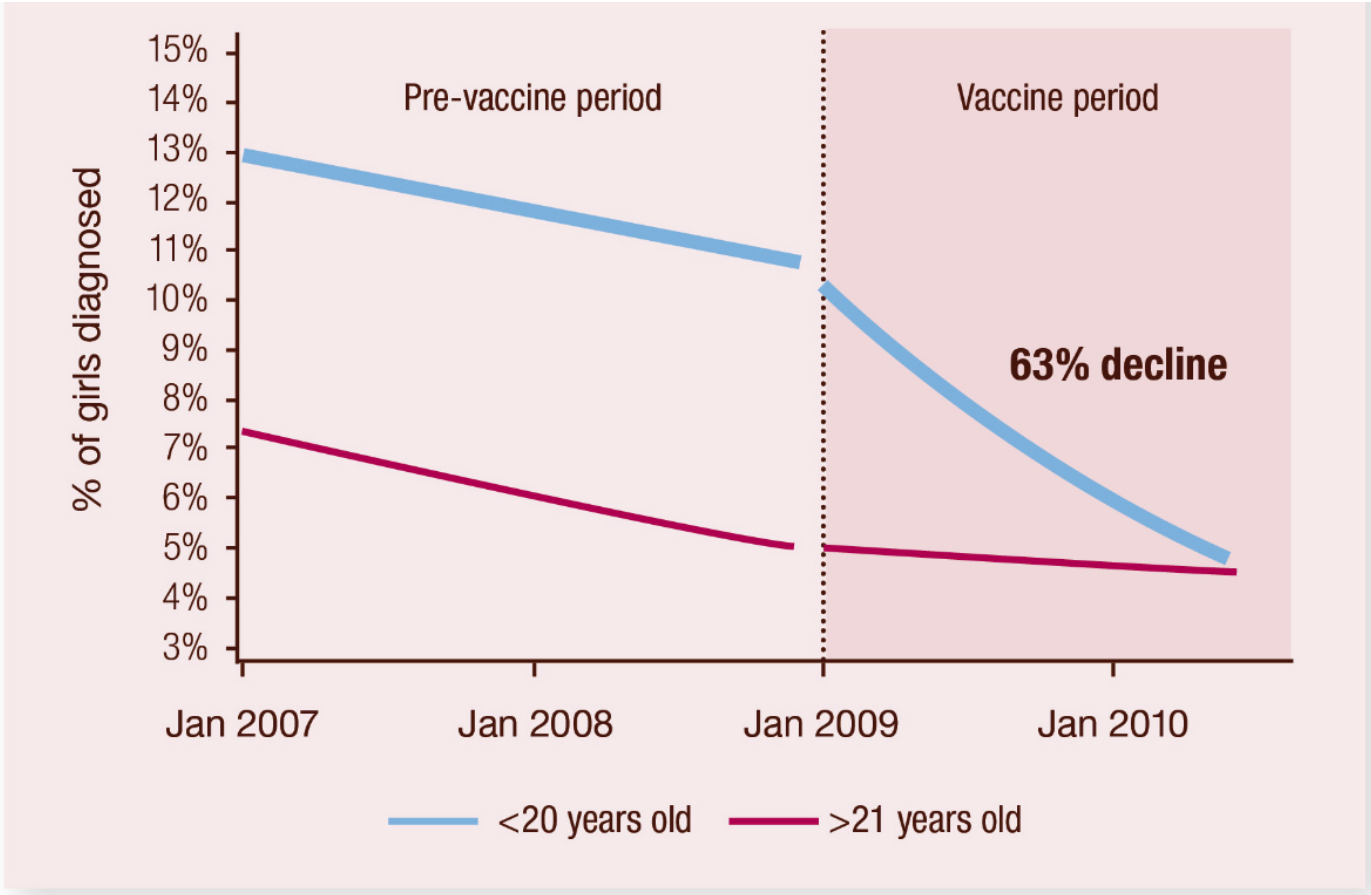


-28%

no Change

Donovan et al. Lancet 2011

Reduction of Genital Warts in New Zealand



Reference: Oliphant J and Perkins N, Impact of the human papillomavirus (HPV) vaccine on genital wart diagnoses at Auckland Sexual Health Services, NZMJ, 2011;124:1339, 51-58.

Other issues

- Reduction in high grade cervical abnormalities in Women in Australia
- Cervical procedures increase risk of premature labour – vaccination should reduce that risk
- Likelihood of genotype replacement is low

Data presented at IPV conference 2011

Universal vaccination

- MSM higher risk of HPV related cancer
  - RR 30 for anal cancer
  - RR 2 for orpharyngeal cancer
  - RR 6 for genital warts
- Herd immunity implies that universal vaccination will provide greater protection for females
- Universal (male and female) vaccination of adolescents (probably with 2 doses) is inevitable as vaccine cost declines

Data presented at IPV conference 2011

Vaccination Post Colposcopy?

- No direct study to answer this but some indirect evidence.

- Previous vaccination with Q4HPV vaccine in women who had surgical treatment for HPV related disease significantly reduced incidence of subsequent HPV related disease. (~46% - 95% CI 22.5%- 63.2%)

Joura et al BMJ 2012 27/3/12

Vaccination Post Colposcopy?

- Efficacy against persistent infection, CIN and EGL, caused by HPV 6,11,16,18, was 66.9% (95% CI 4.3% - 90.6%) in women aged 24-45 who were seropositive but DNA -ve at time of vaccination. Castellsague et al British Journal of cancer 2011

- The immune response to HPV 6,11,16,18 vaccine appears to prevent reinfection or reactivation of disease with vaccine HPV types. Olsson et al Human vaccines October 2009

Coverage in NZ

- Uptake ~ 50%
- Why?
  - concerns about duration of immunity
  - reluctance to accept that early onset sexual activity occurs
  - persistent anti vaccine publicity
  - opposition from faith based groups

Improving Coverage

- No magic bullet
- Accumulation of data on safety and duration of immunity
- Vaccine will gradually become “normal” and universal
- At present the decision to vaccinate adolescent girls seems very straightforward to me

HPV Vaccine - conclusions

- Has the potential to reduce the incidence of several cancers
- Has demonstrable herd effect
- In adolescents, two doses are highly immunogenic
- Will be a universal vaccine in due course
- Coverage will gradually improve


UNATTENDED
CHILDREN
WILL BE GIVEN
AN ESPRESSO
AND A FREE PUPPY

The End

GARDASIL Prophylactic Efficacy Females 27 to 45 years

Per Protocol Efficacy Population

Endpoint	GARDASIL (N=1,601) # of Cases	Placebo (N=1,599) # of Cases	Observed Efficacy (%)	95% CI
HPV 6/11/16/18-Related Persistent Infection, CIN, or EGL	10	86	**84.7**	(67.5,93.7)

Castellsague et al 2011; Mean follow up time 3.8 years

Efficacy Against HPV 6/11/16/18-related Persistent Infection and Disease in Seropositive/DNA negative Subjects

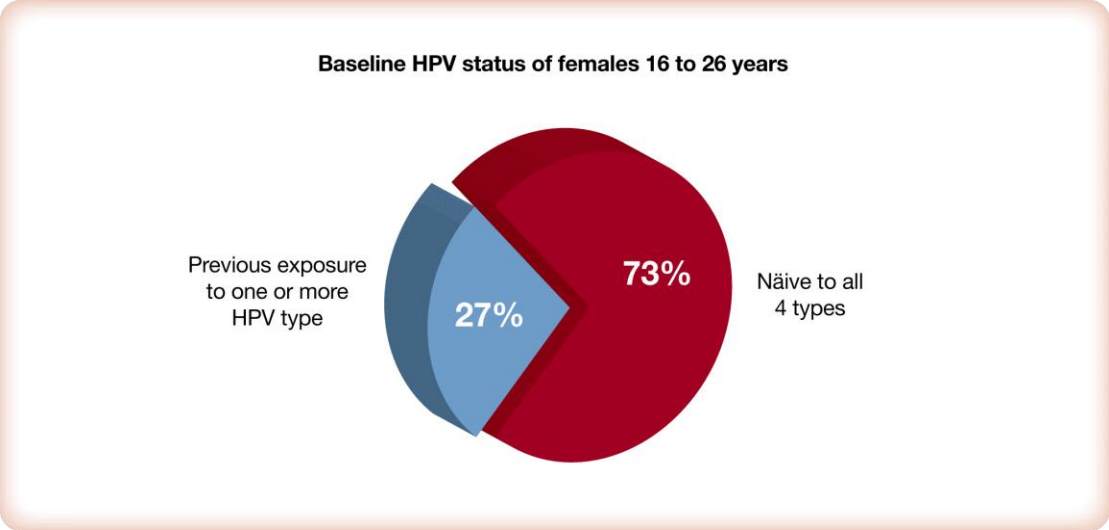
Females aged 27 to 45 years; Post Hoc Analysis

Endpoint	GARDASIL (N=1,910) # of Cases	Placebo (N=1,907) # of Cases	Observed Efficacy (%)	95% CI
HPV 6/11/16/18-related Persistent Infection, CIN, or EGL	5	15	**66.9**	(4.3, 90.6)
Persistent Infection	5	15	**66.8**	(3.8, 90.5)
CIN (any grade) or EGL	0	0	**NA**	NA

Castellsague et al 2011

Efficacy in Sexually Active Women

- Clinical trial subjects were ~20,000 mostly sexually active women, 16 to 26 years



- Women infected with vaccine HPV types prior to vaccination were protected from clinical disease due to remaining vaccine HPV types[1]

1. GARDASIL Product Information 2011

GARDASIL®: FUTURE I-II End-of-Study Results

Impact on Rates of Pap Test Abnormalities and Cervical, Vulvar, and Vaginal Procedures in 16- through 26-Year-Old Women[1]

FUTURE I-II Generally Naïve Population = R-MITT2 Population

Population	Endpoint	GARDASIL®		Placebo		% Reduction (95% CI)
		n	cases	n	cases	
Generally HPV-Naïve R-MITT2 (Protocols 007, FUTURE I, FUTURE II)	ASC-US (positive for high-risk types by HC2 probe)	4870	285	4758	359	22.7 (9.4, 34.0)
	ASC-H	4870	59	4758	89	35.2 (8.9, 54.2)
	LSIL	4870	864	4758	1000	16.1 (8.1, 23.5)
	HSIL	4870	24	4758	41	42.7 (2.9, 66.9)
	Colposcopy With Biopsy	4696	741	4759	950	21.8 (13.9, 29.1)
	Definitive Cervical Therapy	4696	132	4759	230	41.9 (27.7, 53.5)

Generally naïve population: R-MITT2 = naïve to all vaccine HPV types at day 1 (polymerase chain reaction [PCR] and serology), naïve to 10 common HR nonvaccine HPV types at day 1 (PCR), day 1 Pap test = negative.

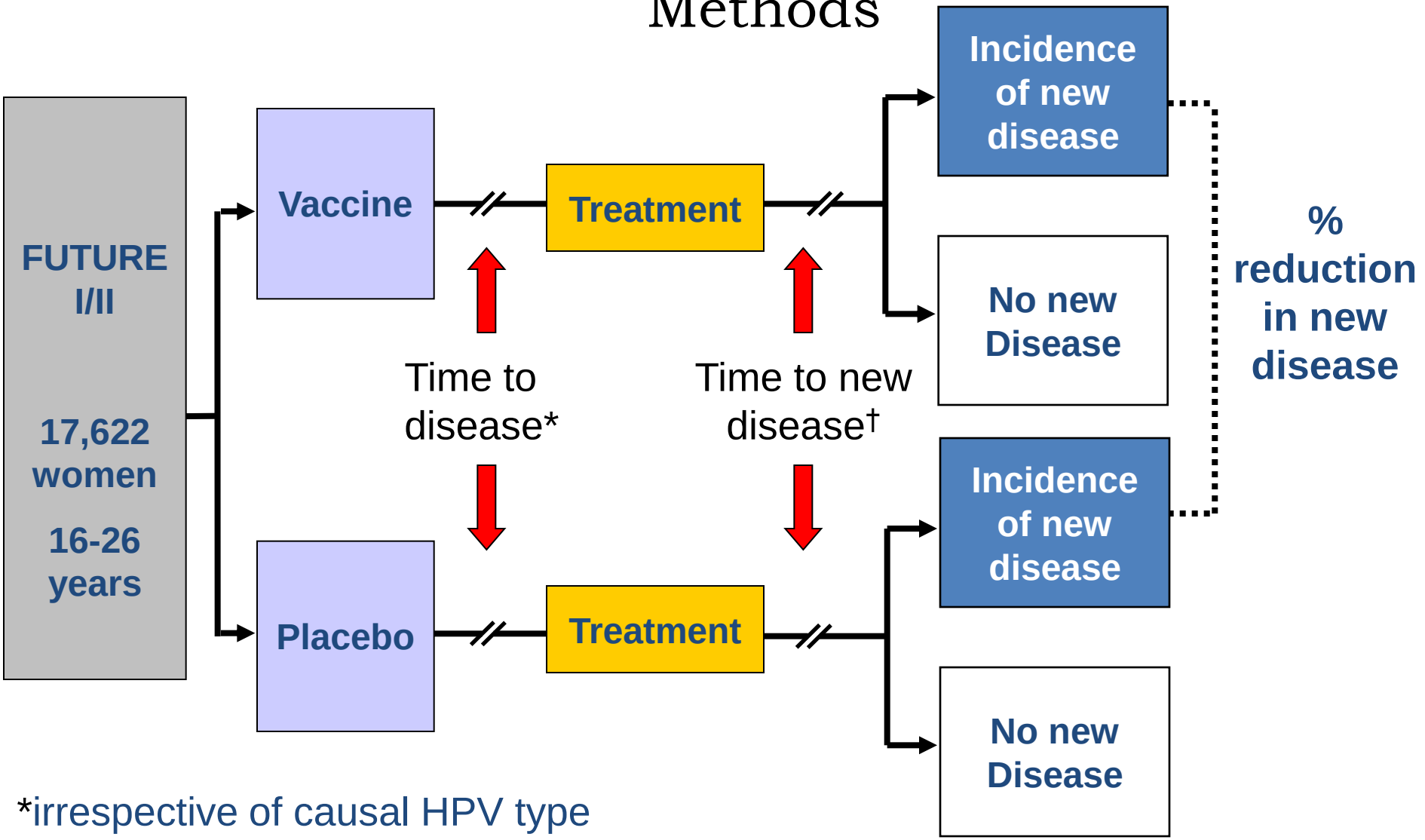
ASC-US = atypical squamous cells of undetermined significance.
HC2 probe = positive reflex HPV test (hybrid capture 2, Digene, Boxborough, MA, USA).
ASC-H = atypical squamous cells – cannot rule out HSIL.
LSIL = low-grade squamous intraepithelial lesion.
HSIL = high-grade squamous intraepithelial lesion.
CI = confidence interval.

1. Huh WK. Data presented at: Society of Gynecologic Oncologists 39th Annual Meeting on Women's Cancer™; March 9–12, 2008; Tampa, FL.

Rationale for Universal Vaccination

- Gender equity for the prevention of HPV disease
- Female only vaccination programmes single out females as the sole target for sexual health interventions
- Burden of HPV disease in men (head and neck, penile, anal) and genital warts
- No method of screening HPV disease in men
- Unethical for males not to receive direct benefit from vaccination
- MSM population only gain from direct vaccination
- Depending on female vaccine uptake and cost of HPV vaccine, universal vaccination is cost effective

Methods



*irrespective of causal HPV type

†New HPV disease is defined as any disease that was detected at least 60 days post-treatment/diagnosis.

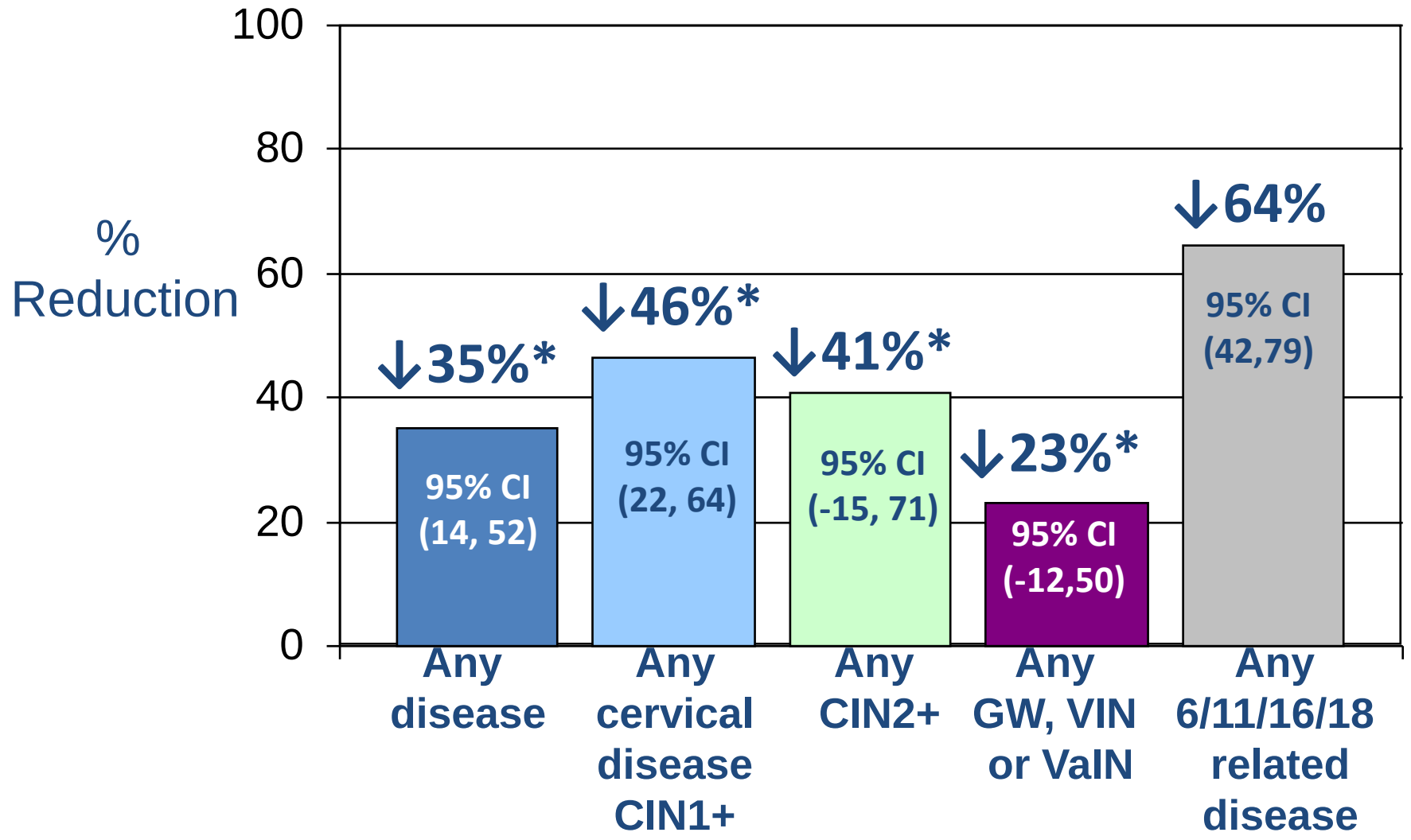
Efficacy Against HPV 6/11/16/18 Anal Disease

Per Protocol Efficacy Population

Endpoint	GARDASIL (N=194) # of Cases	Placebo (N=208) # of Cases	Observed Efficacy (%)	95% CI
HPV 6/11/16/18 - Related AIN	5	24	**77.5**	(39.6, 93.3)
HPV 6/11/16/18 - Related AIN 2/3	3	13	**74.9**	(8.8, 95.4)

Palefsky et al 2011; Mean follow up time 2.2 years

Impact of qHPV Vaccine on new HPV disease – after a pathology panel diagnosis of GW, VIN, VaIN



*Irrespective of HPV type

What is the biological mechanism for the observed reductions?

- Women infected with 1-3 vaccine HPV types benefit from the vaccination*
  - 66% of the HPV6/11/16/18 related CIN cases in the placebo arm did not have the same type detected in the original definitive therapy specimen, suggesting disease from new infection
- The vaccine generates an anamnestic response in women who are seropositive pre-vaccination, and prevents re-infection or disease. †
- Vaccination of women negative to 14 HPV types reduced the incidence of CIN2+ associated with 10 non-vaccine HPV types by 32.5% (95% CI: 6.0, 51.9)°
  - Disease prevented post-surgery may be due to cross-protection

* J Infect Dis 2007; 196:1438-1446
† J Infect Dis 2007; 196:1438-1446
° J Infect Dis 2009; 199:926-935.

Conclusions

- Women who have been treated for HPV-related disease are at high risk for developing additional disease post-treatment
- Quadrivalent HPV Vaccine significantly reduced the incidence of “new” disease
- Although the exact underlying mechanism is not fully known, these observed reductions are clinically significant
- On an individual level, vaccination of a woman with past or existing HPV-related disease is warranted and should be considered
- These data to not indicate that vaccination provides a therapeutic effect. It is likely that most of the new disease which is detected post-treatment is from a new infection.