

# **Quadrivalent HPV L1 VLP Vaccine: *An update of the Clinical Program***

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*Declaration of conflict of interest: investigator and consultant of Merck, Sharp & Dohme for the quadrivalent HPV vaccine*

# CLINICAL PROGRAM FOR QUADRIVALENT HPV VACCINE (2003 AND LATER)

Protocol 005 (N=2,391)  
16-23 year old women

Protocol 007 (N=1,155)  
16-23 year old women

Yr 5 Immune Memory  
Evaluation

~ 30 000 individuals from 33  
different countries

Different trial designs: Intensive  
or Real World schemes

FUTURE I (N=5,442)  
16-23 year old women

Extension

FUTURE II (N=12,167)  
15-26 year old women

Extension

Duration of Efficacy Registry Study  
Nordic Region \*

Nordic HPV Surveillance  
Disease Burden Study \*

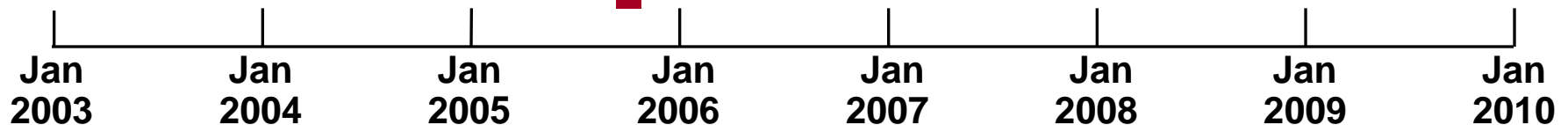
Ph III Adolescent Ig (N=4,800)  
9-15 year olds, both genders

Adolescent Month  
36 Extension

Efficacy Study  
In Adult Women

Male Efficacy  
Program \*

BLA Submission



# PRESENTATION OUTLINE

- Clinical Program Overview
- **Baseline and Efficacy results from Phase III studies in Young Women**
- **Adult Women Study**
- Safety Populations
- Male Program
- Sustained efficacy and Real World results

# HPV 16/18-RELATED CERVICAL, VULVAR, VAGINAL CANCER

Per-Protocol Efficacy Population – Phase III Study Database					
HPV 16/18-Related Cancer	HPV 16/18-Related Surrogate	GARDASIL	Placebo	% Efficacy	95% CI
Squamous Cell Cervical Cancer	CIN 3	1 <sup>†</sup>	51	98	89, 100
Cervical Adenocarcinoma	AIS	0	7	100	31, 100
HPV-Related Vulvar Cancer	VIN 2/3	0	8	100	42, 100
HPV-Related Vaginal Cancer	VaIN 2/3	0	7	100	31, 100

† Single Case - HPV 52/16 CIN 3:

Prevalent, persistent HPV 52 infection with 5/5 biopsies (+) for HPV 52; 1/5 biopsies (+) for HPV 16

FUTURE II Study Group. *Lancet* 2007;369:1861-1868; FUTURE I Study Group. *Lancet* 2007;369:1693-1702

CIN = Cervical Intraepithelial Neoplasia  
AIS = Adenocarcinoma in Situ

VIN = Vulvar Intraepithelial Neoplasia  
VaIN = Vaginal Intraepithelial Neoplasia

# HPV 6/11-RELATED DISEASE

**Only Vaccine to Show Efficacy Against HPV 6/11 Disease**

## Per-Protocol Efficacy Population – Phase III Studies

HPV 6/11-Related	Quad HPV Vaccine	Placebo	% Efficacy	95% CI
CIN (any Grade) or AIS	0	36	100	89, 100
Genital Warts	2 †	156	99	95, 100

† **Cases:**

- HPV 6-related genital wart detected at Month 8
- HPV 6/59 genital wart detected at Month 36

FUTURE II Study Group. *N Engl J Med* 2007;356: 1915-1927; FUTURE I Investigators. *N Engl J Med* 2007;356: 1928-1943

**CIN = Cervical Intraepithelial Neoplasia**

**AIS = Adenocarcinoma in Situ**

# GARDASIL® OFFERS BENEFIT BEYOND HPV 6,11, 16, 18 PROTECTION

**HPV 31/45 - ~10% of cervical cancer**

**10 Tested Non-vaccine HPV types - ~22% of cervical cancers**

HPV type specific Naïve Young Women: Combined Phase III Program				
Causal HPV Type	GARDASIL	Placebo	Efficacy	95% CI
<b>HPV 31/45</b> Primary Endpoint	<b>34</b>	<b>60</b>	<b>43%</b>	<b>12, 64</b>
<b>HPV 31</b>	<b>23</b>	<b>52</b>	<b>56%</b>	<b>26,74</b>
<b>10 Non-vaccine Oncogenic Types</b> HPV 31, 33, 35, 39, 45, 51, 52, 56, 58, 59	<b>162</b>	<b>211</b>	<b>23%</b>	<b>5, 38</b>

# EFFICACY OF GARDASIL® IN WOMEN PREVIOUSLY EXPOSED TO A VACCINE HPV TYPE WHOSE INFECTION HAS CLEARED (Sero+, PCR -)

Combined results from 4 phase II/III trials END OF STUDY–  
MITT-2 Population\* ~4 year follow up in women 16 – 26 years

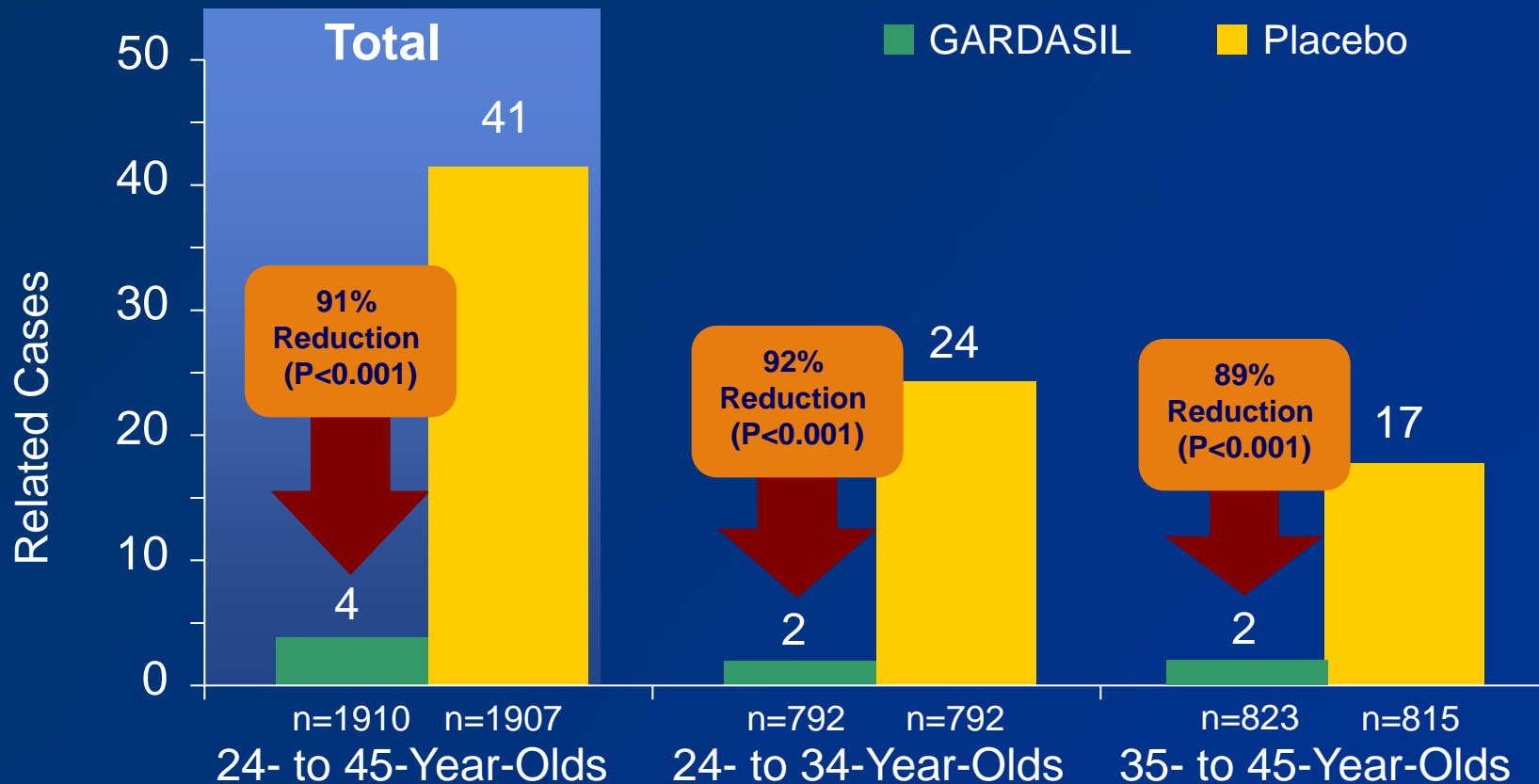
Endpoint	Gardasil®		Placebo		Efficacy (%)	95% CI
	n	Cases	n	Cases*		
CIN (any grade)	1243	0	1283	7	100	(29, 100)
External genital lesions	1268	0	1301	8	100	(40, 100)

\* The 15 placebo cases were due to re-infection or re-activation of a latent infection

This suggests efficacy against recurrence of disease with same vaccine HPV types (re-activation/re-infection)

# Combined Incidence of HPV 6/11/16/18-Related Persistent Infection or Cervical/Vulvar/Vaginal Disease: Results by Age Strata

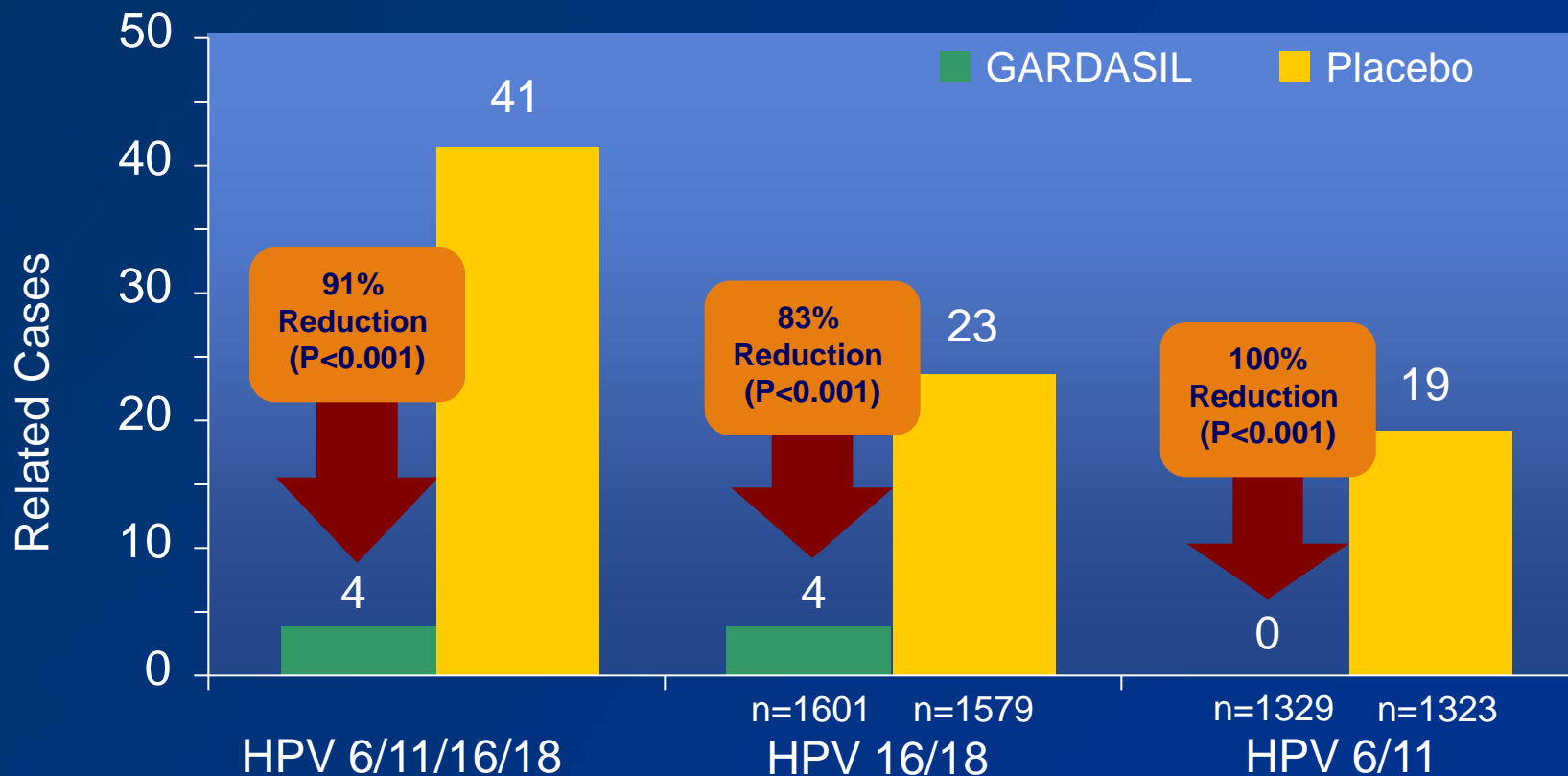
Per-Protocol Efficacy Population



1. Luna J et al. Poster presented at: 24th International Papillomavirus Congress; November 3-9, 2007; Beijing, China. Presentation No. PA1-04. 2. Worldwide Product Circular. GARDASIL™ [Quadrivalent human papillomavirus (Types 6, 11, 16, 18) recombinant vaccine]; WPC-GRD-I-122007.

# Combined Incidence of HPV 6/11/16/18-Related Persistent Infection or Cervical/Vulvar/Vaginal Disease: Results by Vaccine HPV Type

Per-Protocol Efficacy Population



Women 24 to 45 years of age

Worldwide Product Circular. GARDASIL™ [Quadrivalent human papillomavirus (Types 6, 11, 16, 18) recombinant vaccine]; WPC-GRD-I-122007.

# Reduction in HPV 16/18-Related Abnormal Pap Test Results

## Per-Protocol Efficacy Population

	<b>GARDASIL</b>	<b>Placebo</b>	<b>% Reduction</b>	<b>95% CI</b>
<b>ASC-US (HR+) or Worse</b>	<b>1</b>	<b>17</b>	<b>94%</b>	<b>63, 100</b>
ASC-US HR(+)	1	7	86%	-10, 100
LSIL or Worse	0	11	100%	61, 100
LSIL	0	10	100%	56, 100
ASC-H	0	1	100%	—
HSIL	0	0	—	—

ASC-US = atypical squamous cells of undetermined significance; LSIL = low-grade squamous intraepithelial lesions; HSIL = high-grade squamous intraepithelial lesions; ASC-H = atypical squamous cells, cannot exclude HSIL

Women 24 to 45 years of age

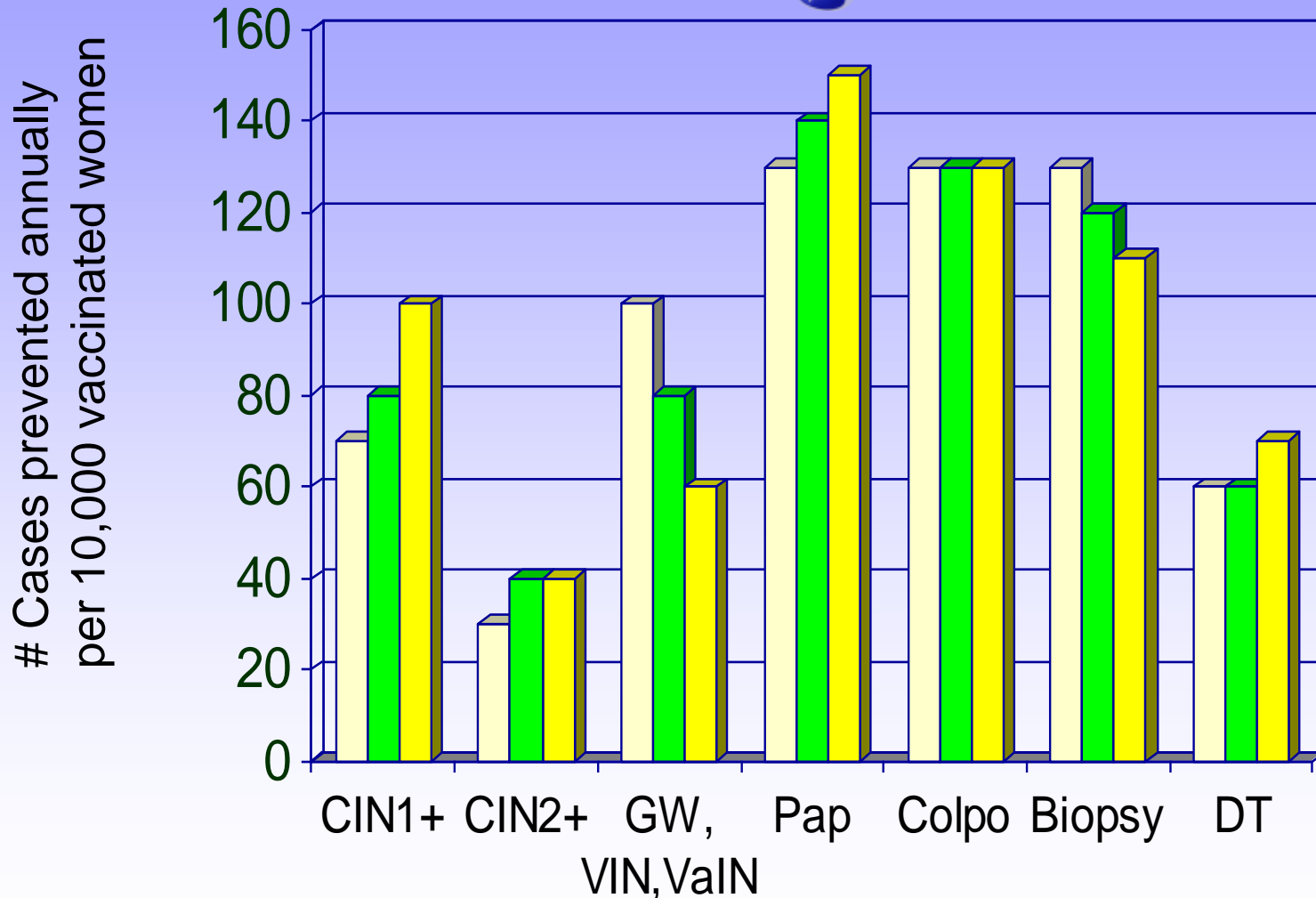
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**25th of September 2009**

***Approval by EMEA and inclusion of  
efficacy data for  
women between 24 and 45 yrs  
in the Local Product Circular***

We observe similar disease reductions in ALL populations

naive   mixed    exposed  



CIN = cervical intraepithelial neoplasia; GW = genital wart; VIN = vulvar intraepithelial neoplasia; VaIN = vulvar intraepithelial neoplasia; Colpo = colposcopy; DT = definitive therapy

- The quadrivalent vaccine was similarly efficacious when offered to
  - a population of women who are HPV naïve
  - a mixed population of naïve and exposed
  - a population of previously exposed women

*THEREFORE, we could expect to have similar public health impacts in terms of disease reduction in the years immediately following vaccination*

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# SAFETY POPULATION FOLLOW-UP

- All SAEs Day 1 to 15 Postdose 1, 2, 3
- At all times in the study
  - All SAEs that were Vaccine-Related (poss, prob, def)
  - All SAEs that were Procedure-Related (poss, prob, def)
  - All Deaths
  - All new medical conditions reported as “medical history”
  - All spontaneously reported non-serious AEs
  - All Pregnancy-related SAEs
    - In mom during the pregnancy
    - In baby during delivery
    - In baby during follow-up
    - In baby if mom breastfeeding
  - Pregnancy and Breast-feeding outcomes
  - Deaths
  - Overdoses

# INTEGRATED DETAILED SAFETY DATABASE CLINICAL ADVERSE EXPERIENCE SUMMARY

	Quadrivalent vaccine (N = 6160)	Placebo (N = 4064)
<b>Subjects with Follow-up</b>	<b>6069</b>	<b>3994</b>
<b>Subjects With at Least 1 Adverse Experience (AE)</b>	<b>89.9%</b>	<b>85.5%</b>
<b>Subjects With at Least 1 Injection-Site AE</b>	<b>83.0%</b>	<b>73.4%</b>
<b>Subjects With at Least 1 Systemic AE</b>	<b>35.3%</b>	<b>36.6%</b>
<b>Subjects With at Least 1 Serious AE (SAE)</b>	<b>0.6%</b>	<b>0.7%</b>
<b>Discontinued Due to an Adverse Experience</b>	<b>0.2%</b>	<b>0.2%</b>

Day 1 to 15 Following Any Vaccination

# SAFETY POST-LICENSURE

(VAERS, USA)

***“All serious reports (6%)\* for Gardasil have been carefully analyzed by medical experts. Experts have not found a common medical pattern to the reports of serious adverse events reported for Gardasil that would suggest that they were caused by the vaccine”.***

Slade et al., JAMA 2009

\*rates comparable to SAEs reported for other vaccines

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## MALE VACCINE EFFICACY STUDY

- Randomized (1:1), placebo-controlled
- 3 doses of GARDASIL™ or placebo at 0, 2, and 6 months
- 36 months follow-up
- Heterosexual men (HM)
  - 16-23 year old
  - 3400
- Men having sex with men (MSM)
  - 16-26 year old
  - 600

## PRIMARY OBJECTIVES

- Safety
- Efficacy: Combined incidence of HPV 6/11/16/18-related
  - Main study: HM + MSM
    - External genital warts
    - Penile/perianal/perineal intraepithelial neoplasia (PIN)
    - Penile, perianal, or perineal cancer
  - Sub-study: MSM
    - Anal intraepithelial neoplasia (AIN)
    - Anal Cancer
- Immunogenicity
  - GMT, seroconversion rates

# EFFICACY AGAINST HPV 6/11/16/18-RELATED EGL IN MEN

## Per-protocol population

Severity	GARDASIL (n = 1,397)		Placebo (n = 1,408)		% Efficacy	95% CI
	Cases	Rate	Cases	Rate		
<b>All EGLs</b>	3	0.1	31	1.1	<b>90.4</b>	69.2, 98.1
<b>Condyloma</b>	3*	0.1	28	1.0	<b>89.4</b>	65.5, 97.9
<b>PIN 1</b>	0	0.0	2	0.1	--	--
<b>PIN 2/3</b>	0	0.0	1	0.0	--	--

Based on these data, the US FDA Advisory committee has recommended the approval of the quadrivalent HPV vaccine to prevent HPV infection and genital warts in boys and young men aged 9-26 yrs

Giuliano and Palefski, IPV Conf, Malmo, 2009)

*n* = number of subjects randomized who received at least one injection and have follow-up after month 7; rate= incidence per 100 person years at risk; CI = confidence interval; EGL = external genital lesion; PPP = penile, perianal, perineal; PIN = penile/perianal/perineal intraepithelial neoplasia; case counting began after month 7.

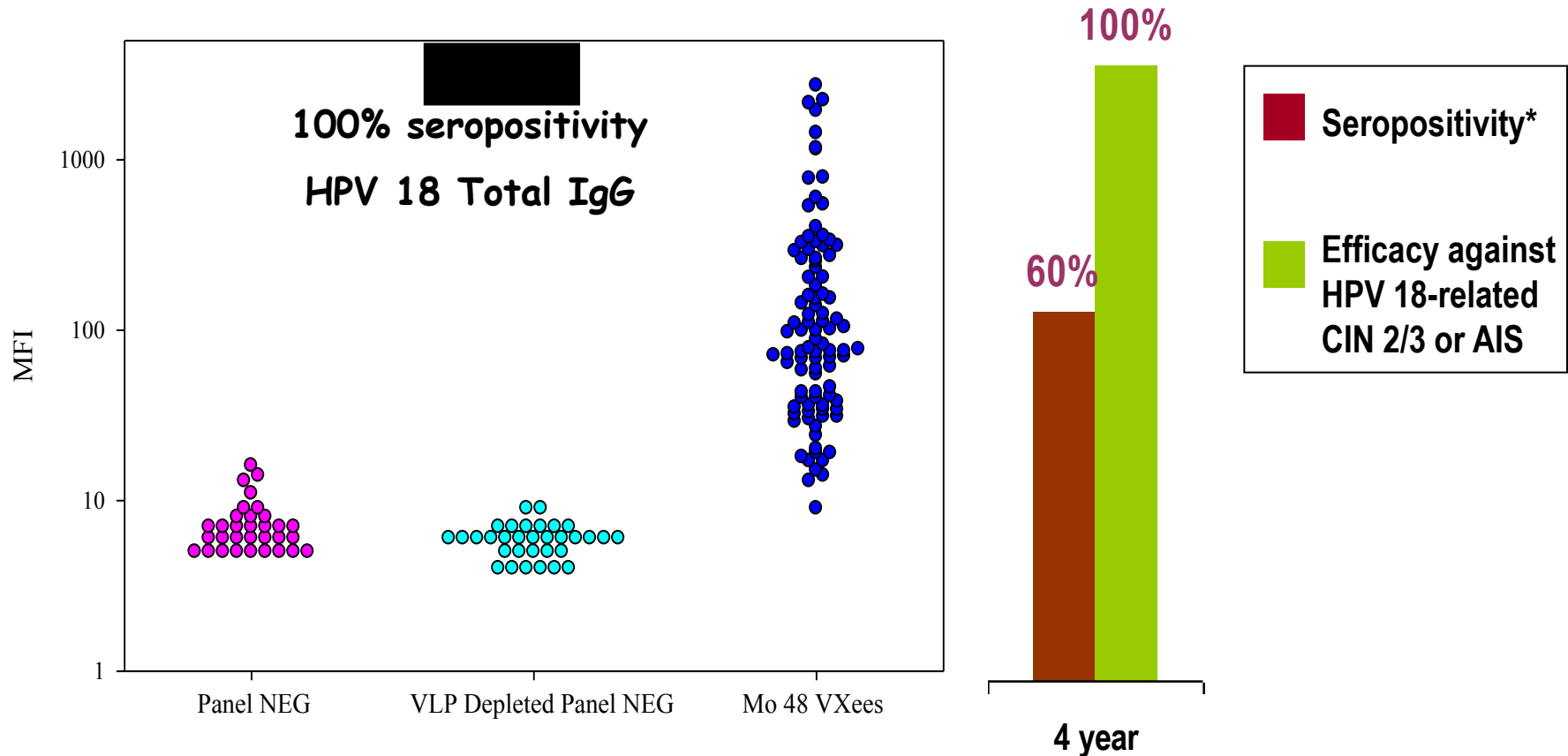
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## DURATION OF PROTECTIVE EFFICACY

- Demonstration of an **anamnestic response** in vaccinees after an antigen challenge confirms the presence of immune memory.
- Sustained efficacy despite seronegativity in a proportion of subjects strongly suggests that **immune memory will account for long-term protection**
- ***The exact duration of protective efficacy for any prophylactic HPV vaccine will only be determined after decades of follow up of vaccinees***

# Seropositivity and efficacy of Quadrivalent HPV L1 VLP Vaccine against HPV 18-related cervical disease (HPV 18-related CIN 2/3 or AIS) in women 16–26 years



**\*Seropositivity to HPV 18 neutralizing antibodies to a single neutralizing epitope measured by cLIA**

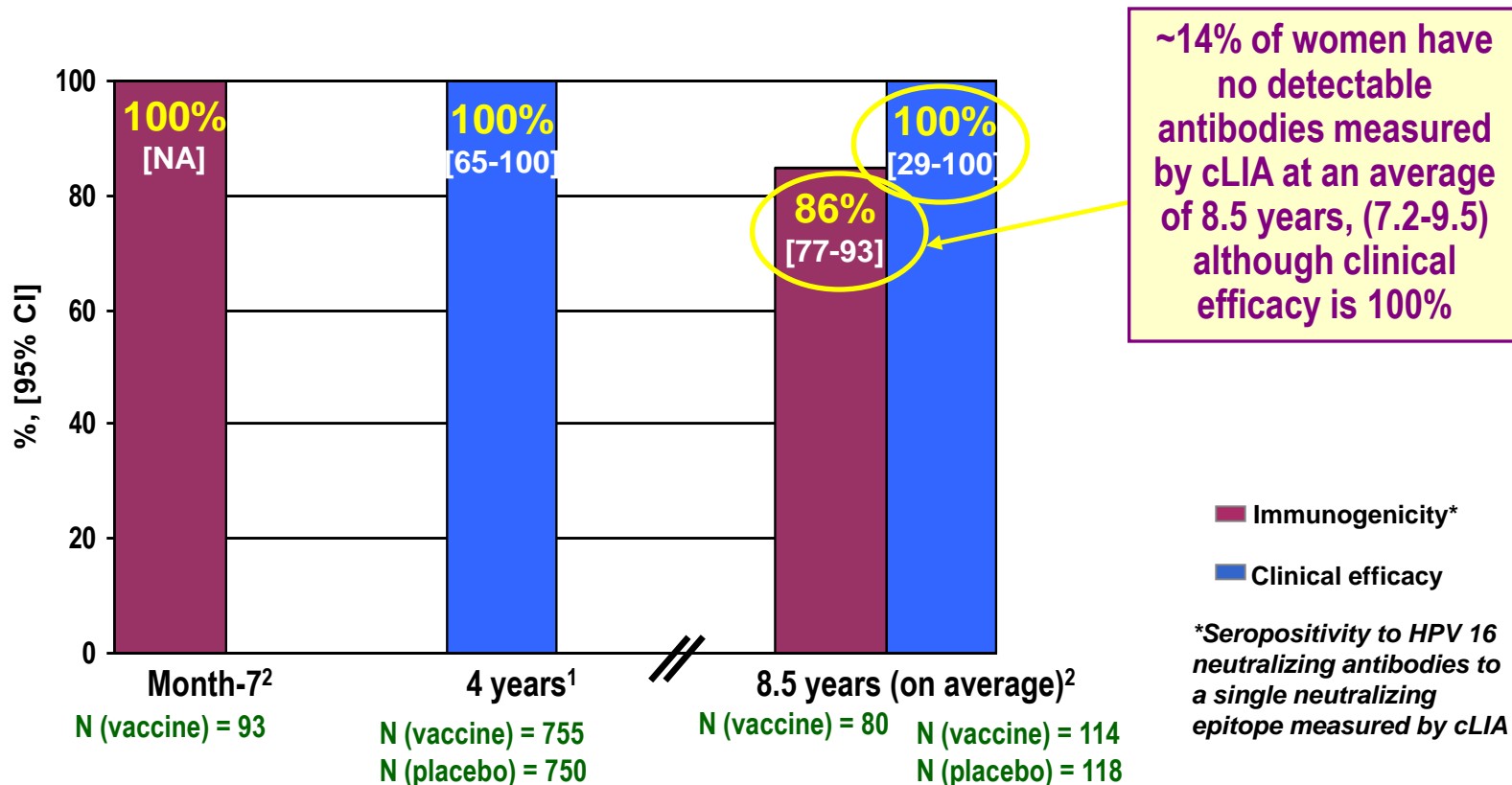
# CASES OF HPV 18-RELATED CIN 2/3 OR AIS BY VISIT INTERVAL

PPE Population: 007/FUTURE I/FUTURE II End-of-Study Database

Visit Interval	Vaccine	Placebo	Vaccine % Seropositive
D1 to <M12	0	1	Month 7: 99.5%
M12 to <M24	0	6	Month 24: 71.1%
M24 to <M36	0	9	*
M36 to <M48	0	10	Month 44: 60.2%
M48 or Beyond	0	3	*
<b>Cumulative</b>	<b>0</b>	<b>29</b>	

# IMMUNOGENICITY AND EFFICACY AGAINST HPV 16-RELATED CIN2+ OF HPV-16 MONOVALENT VACCINE

Per protocol population



## Immunogenicity and efficacy against HPV-16 CIN2+ of HPV 16 monovalent vaccine in the per protocol population

NA: Not available

1. Mao C et al. *Obstet Gynecol* 2006;107:18-27

2. Rowhani-Rahbar A et al. *Vaccine* 2009 Epub ahead of print

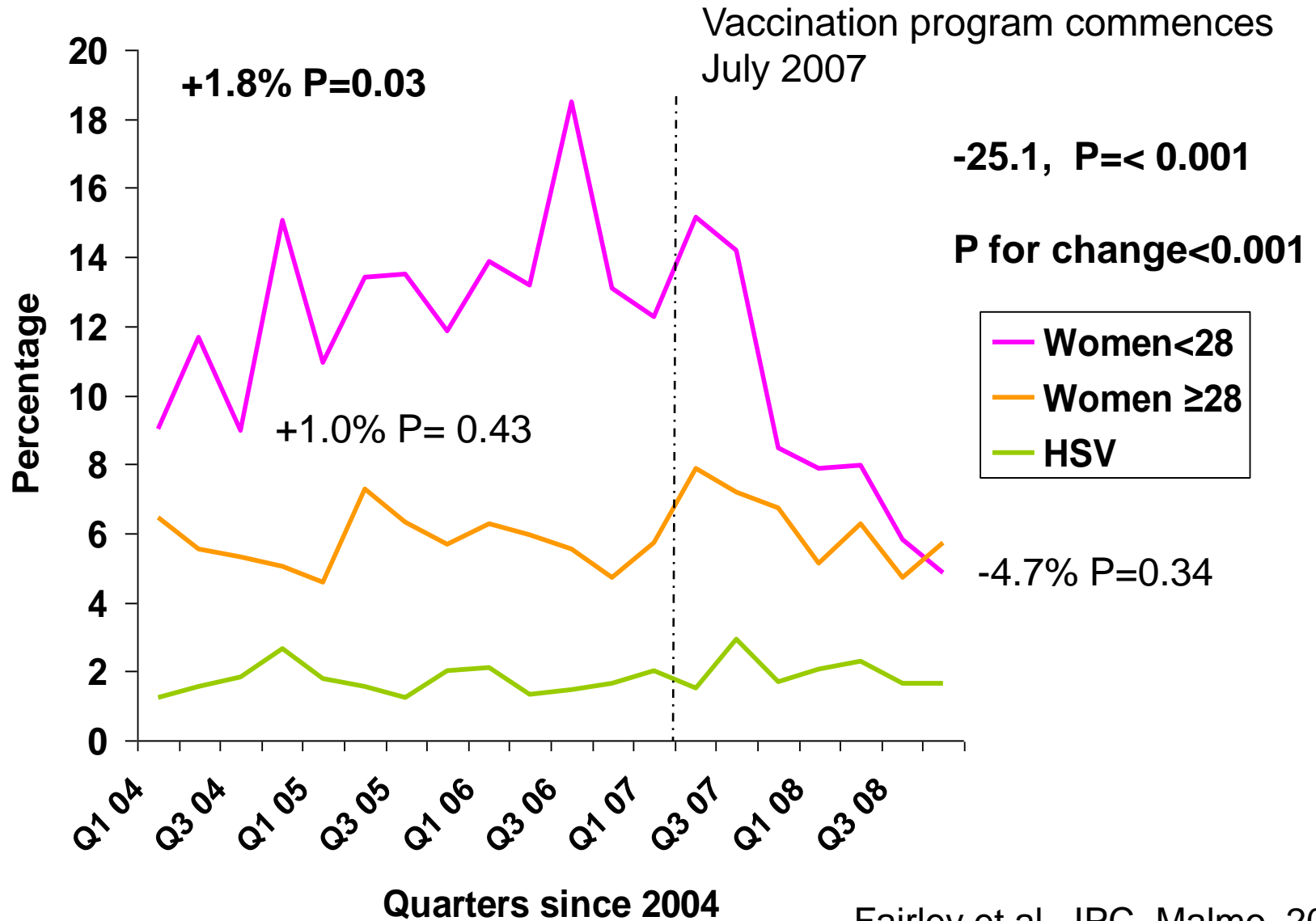
# FIRST EFFICACY RESULTS IN REAL WORLD

- Australia provided free quadrivalent human papillomavirus (HPV) vaccine\*
  - **12-18 year old girls** in a school-based program from April 2007, (coverage end of 2007 between 69% and 75% of girls in years 7, 10,11 and 12)(1)
  - **women ≤26 years** through general practices from July 2007 (coverage 18 and 26 years of age is estimated to be 65% to 70% by end 2008)

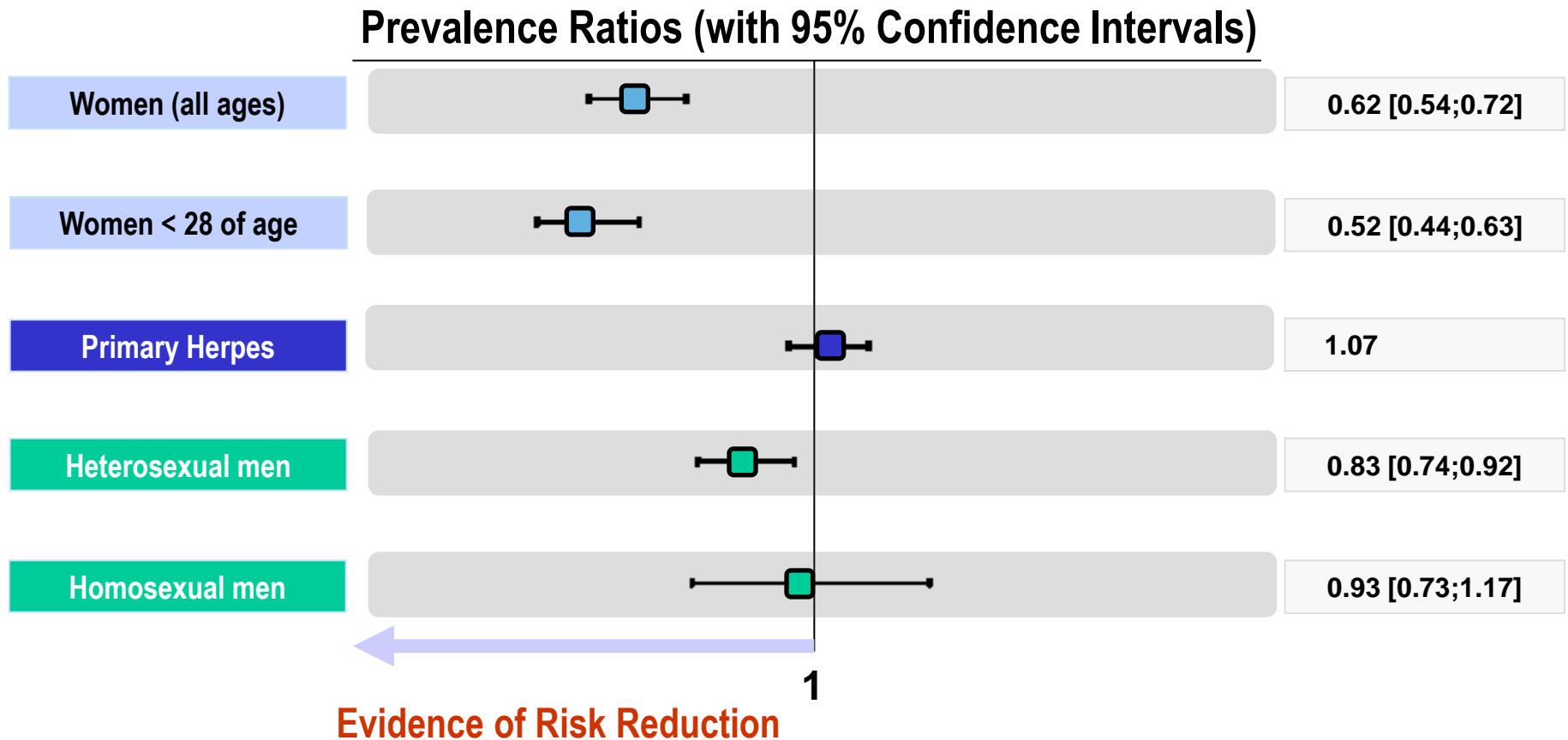
**New clients with genital warts were studied at the Melbourne largest clinic for STD (2004-2008)**  
(Fairley et al., IPC Malmo, May 2009)

\*Personal communication Dr Rosemary Lester (1) and Greg Whiteside (2), CSL Biotherapies

# PROPORTION OF NEW CLIENTS WITH WARTS PER QUARTER CHANGE



# DEMONSTRATION OF THE DECLINE IN THE RISK OF GW



Relative Risk (CI 95%) for genital warts in 2008 (1-year period post-vaccine introduction) vs. 2004-2007 (pre-vaccine introduction period) in patients attending Melbourne Sexual Health Centre, Australia



## Recommended Adult Immunization Schedule – United States, 2009

Weekly

January 9, 2009 / Vol. 57 / No. 53

**HPV vaccination: Recommended for all females aged 11 through 26 years, regardless of sexual activity or clinical evidence of previous HPV infection, who have not completed the vaccine series.**

<http://cme.medscape.com/viewarticle/586678> (ACIP issues 2009Adult ImmunizationSchedule)

2009, 84, 117–132

No. 15



World Health  
Organization

Organisation mondiale de la Santé

Weekly epidemiological record  
Relevé épidémiologique hebdomadaire

10 APRIL 2009, 84th YEAR / 10 AVRIL 2009, 84<sup>e</sup> ANNÉE

No. 15, 2009, 84, 117–132

<http://www.who.int/wer>

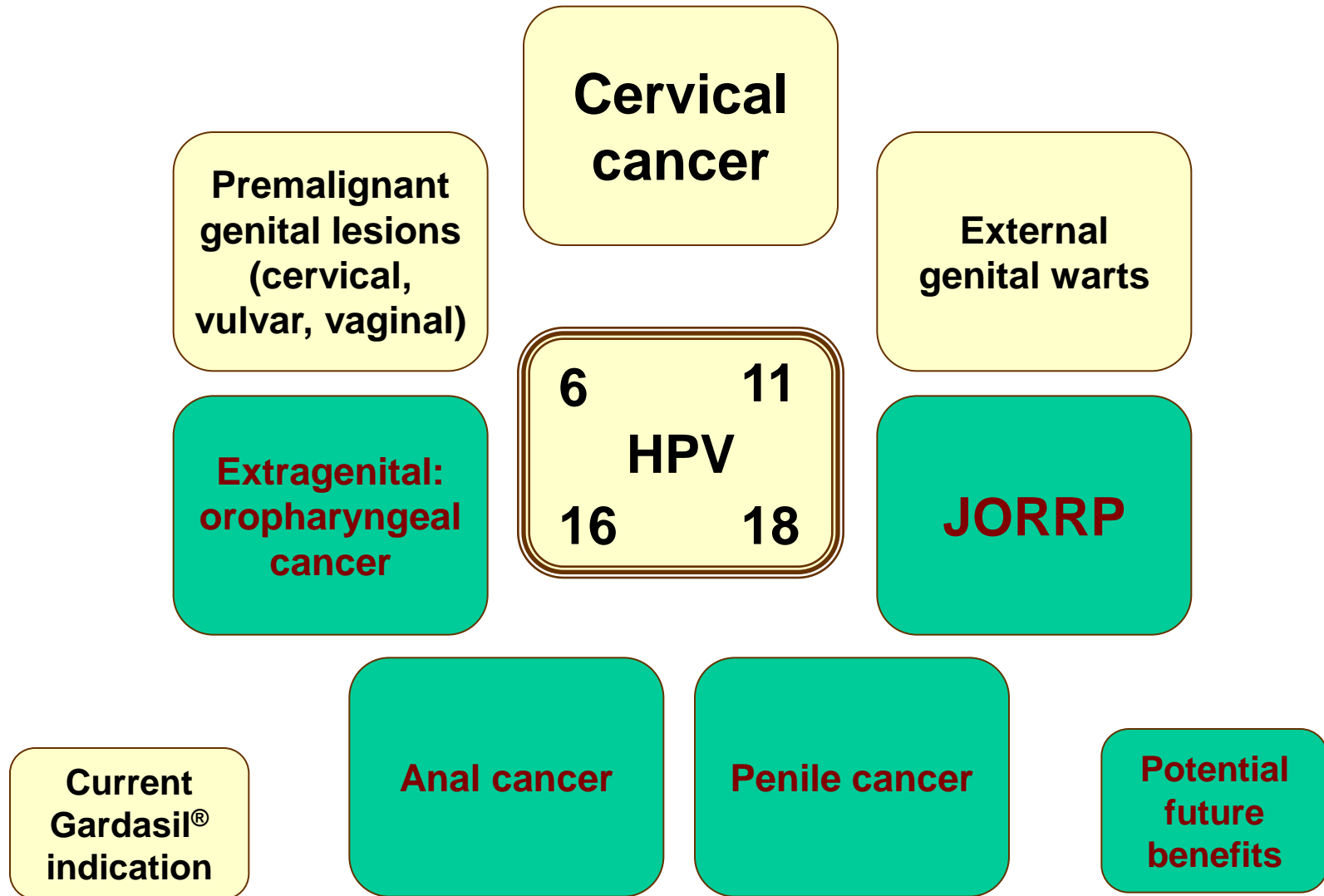
**Human papillomavirus vaccines  
WHO position paper**

# Growing Evidence of HPV in Non-Cervical Diseases

- Vulvar cancer and precancerous or dysplastic lesions
- Vaginal cancer and precancerous or dysplastic lesions
- Genital warts (condyloma acuminata)
- Recurrent Respiratory Papillomatosis 100% HPV 6/11
- Baş & Boyun Kanserleri ~ 40% HPV positive
- Anal Kanser ~80% HPV positive
- Penis Kanseri ~50% HPV positive



# THE PROMISE OF A QUADRIVALENT VACCINE



*Teşekkür ederim*