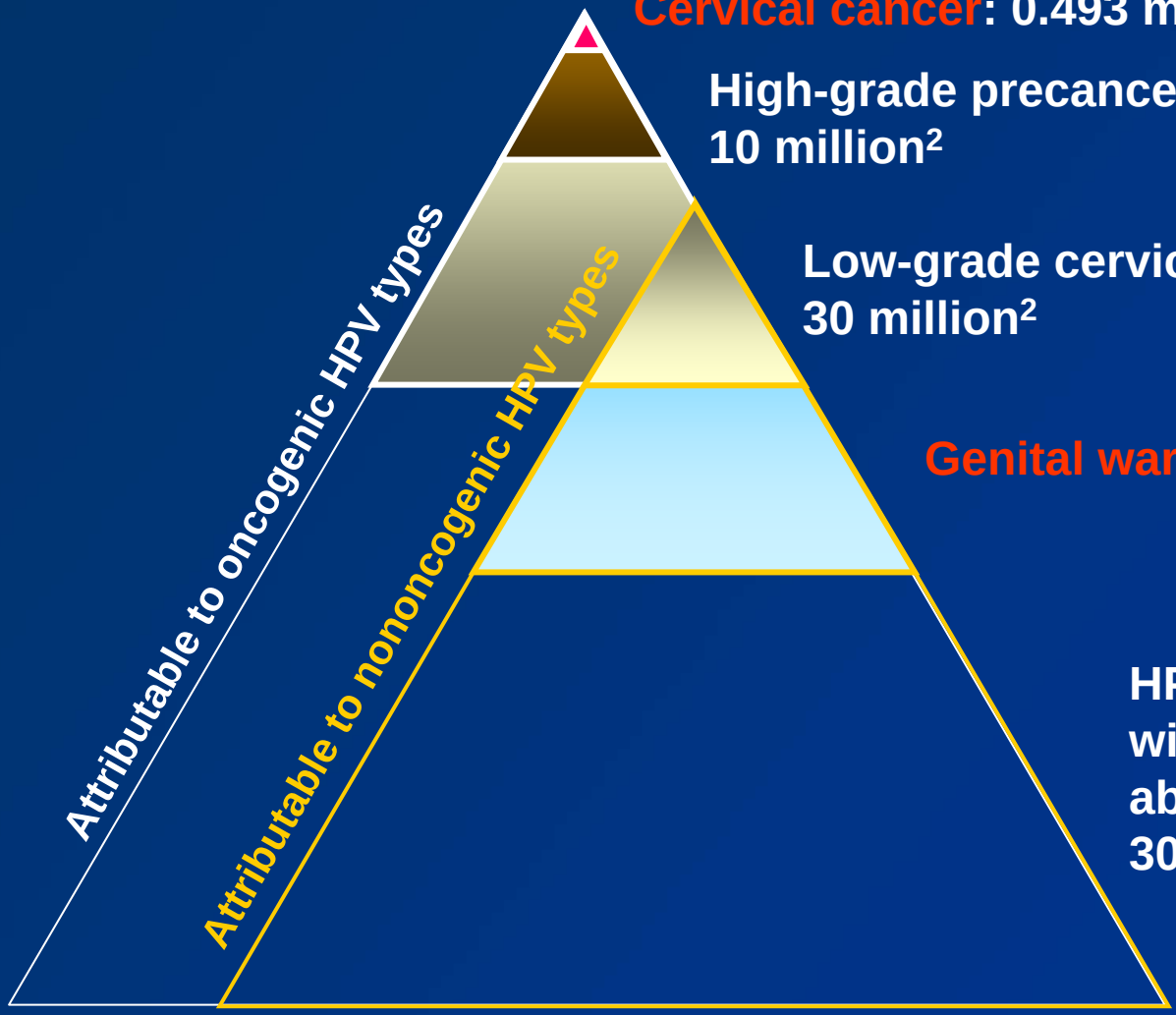
HPV Related Disease and
Quadrivalent HPV 6, 11, 16, 18 Vaccine

Estimated World Burden of HPV-Related Disease and Diagnoses



Cervical cancer: 0.493 million in 2002[1]

High-grade precancerous lesions: 10 million[2]

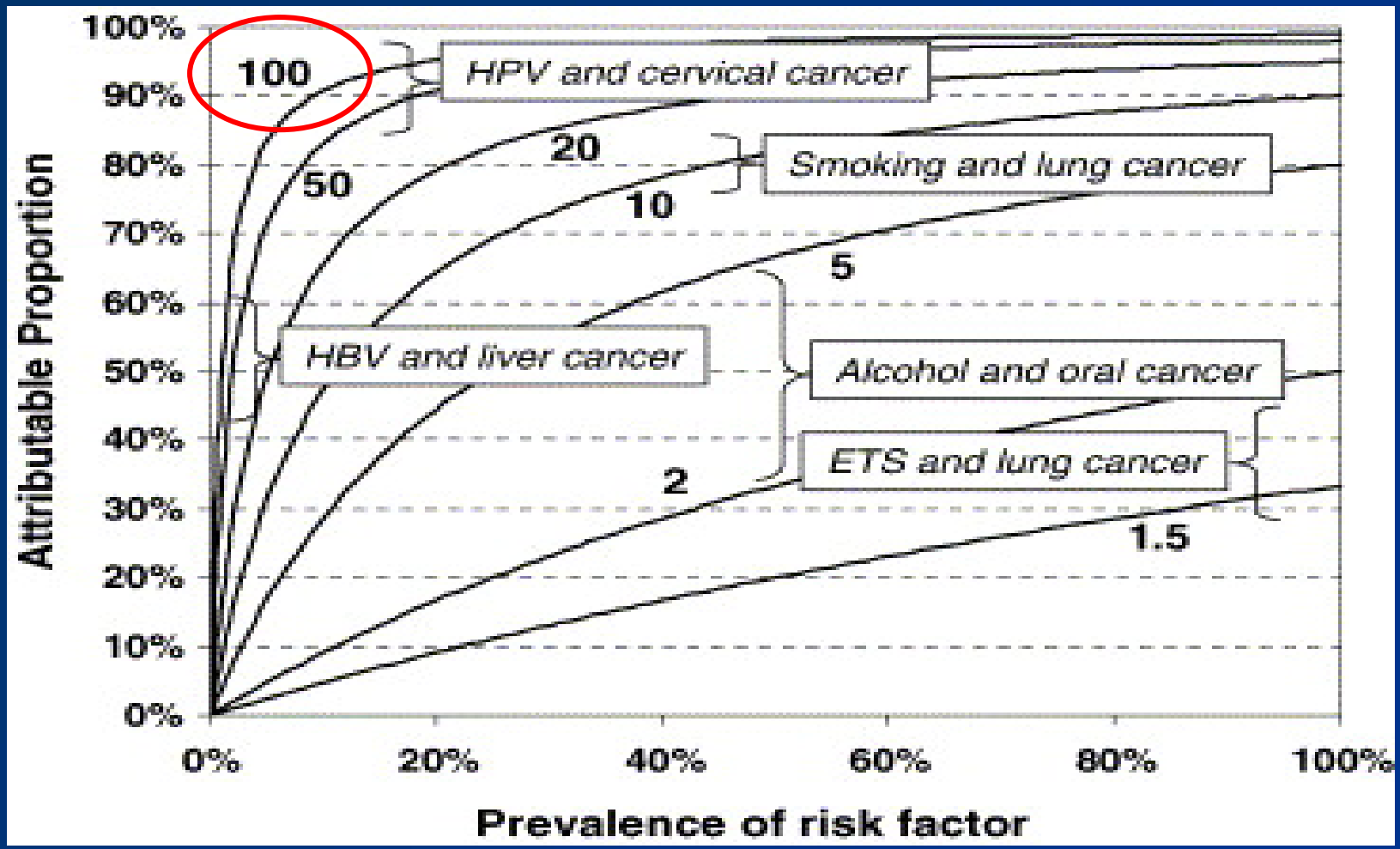
Low-grade cervical lesions: 30 million[2]

Genital warts: 30 million[3]

HPV infection without detectable abnormalities: 300 million[2]

1. Parkin DM, Bray F, Ferlay J, Pisani P. *CA Cancer J Clin*. 2005;55:74–108. 2. World Health Organization. Geneva, Switzerland: World Health Organization; 1999:1–22. 3. World Health Organization. WHO Office of Information. *WHO Features*. 1990;152:1–6.

HPV Accounts for Virtually All Cervical Cancer



Franco and Harper, 2005

HPV and Cancer: A Broader Picture[1]

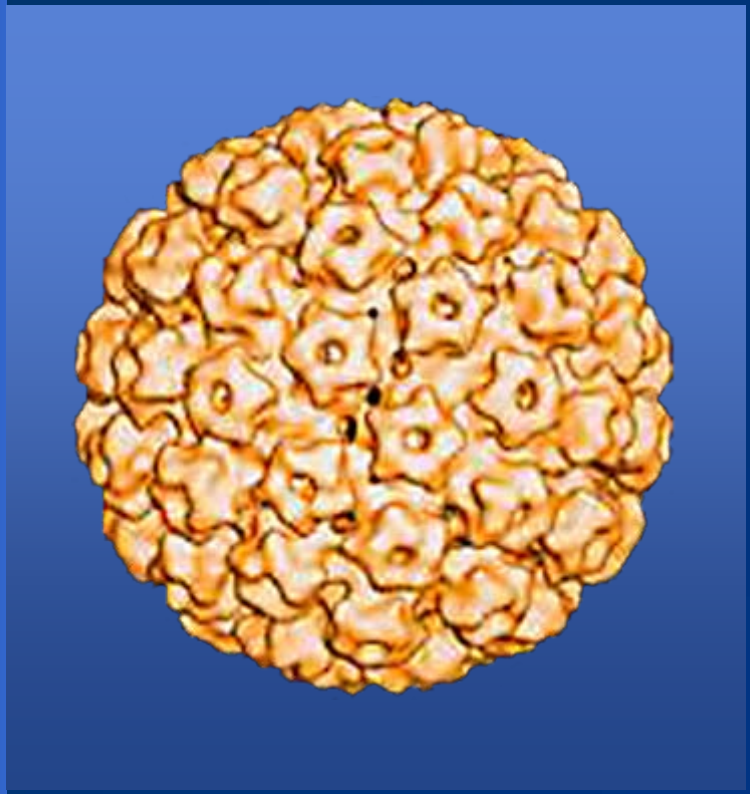
Cancer	% Associated With Certain HPV Types
Cervical*,[1]	>99%
Vaginal[2]	~50%
Vulvar[2]	~50%
Penile[2]	~50%
Anal[2]	~85%
Oropharyngeal[2,3]	~20%
Larynx and aerodigestive tract[2]	~10%

*Includes cancer and intraepithelial neoplasia

1. Walboomers JM, Jacobs MV, Manos MM, et al. *J Pathol*. 1999;189:12–19. 2. World Health Organization. Geneva, Switzerland: World Health Organization; 1999:1–22. 3. Herrero R, Castellsagué X, Pawlita M, et al. *J Natl Cancer Inst*. 2003;95:1772–1783.

HPV

Nonenveloped double-stranded DNA virus[1]

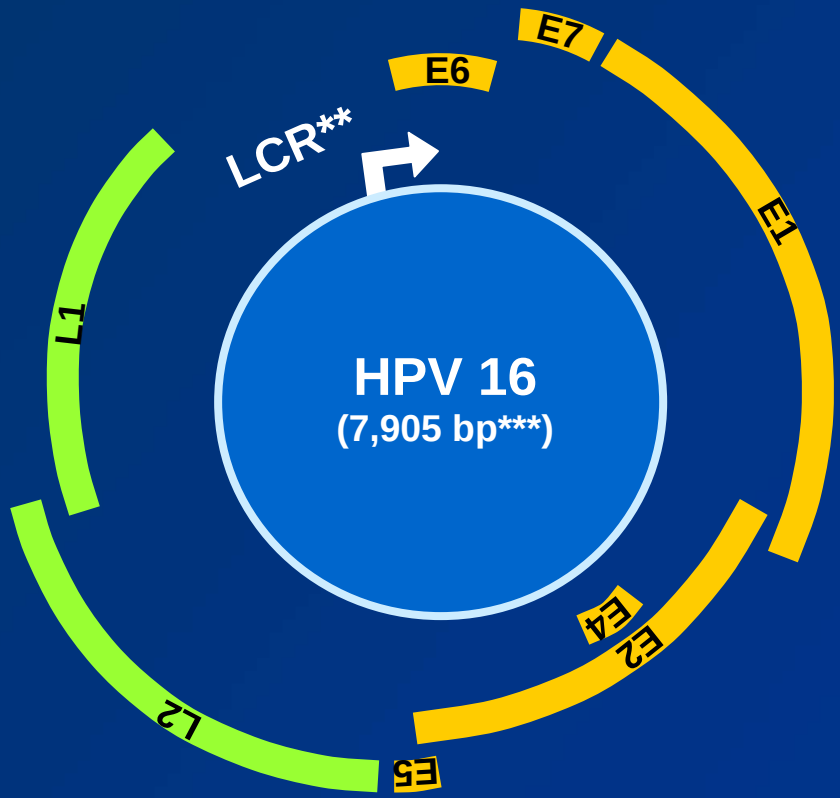


- **>100 types identified[2]**
- **~30–40 anogenital[2,3]**
  - **~15–20 oncogenic*[,2,3]**
    - **HPV 16 and HPV 18 types account for the majority of worldwide cervical cancers.[4]**
  - **Nononcogenic** types**
    - **HPV 6 and 11 are most often associated with external anogenital warts.[3]**

*High risk; ** Low risk

1. Howley PM, Lowy DR. In: Knipe DM, Howley PM, eds. Philadelphia, Pa: Lippincott-Raven; 2001:2197–2229.
2. Schiffman M, Castle PE. *Arch Pathol Lab Med*. 2003;127:930–934. 3. Wiley DJ, Douglas J, Beutner K, et al. *Clin Infect Dis*. 2002;35(suppl 2):S210–S224. 4. Muñoz N, Bosch FX, Castellsagué X, et al. *Int J Cancer*. 2004;111:278–285.

General Organization of a Papillomavirus Genome*,1

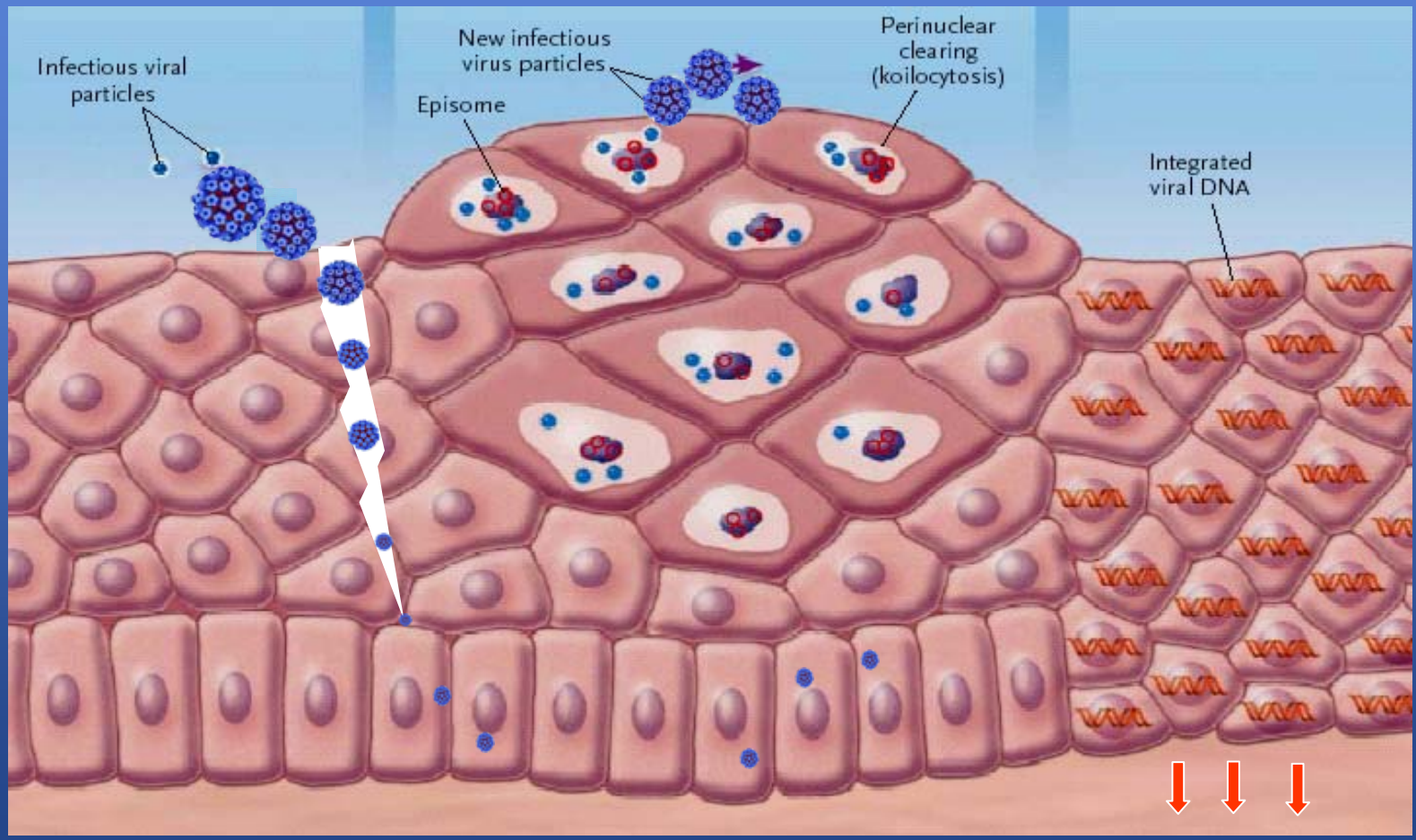


*Bars represent open reading frames.
**LCR = long control region
***bp = base pair

1. Adapted from Münger K, Baldwin A, Edwards KM, et al. *J Virol*. 2004;78:11451–11460.

Spectrum of Changes in Cervical Squamous Epithelium Caused by HPV Infection

Normal Cervix | **HPV Infection/ CIN* 1** | **CIN 2 / CIN 3 / Cervical Cancer**



*CIN = cervical intraepithelial neoplasia

Adapted from Goodman A, Wilbur DC. *N Engl J Med*. 2003;349:1555–1564.

Several Factors May Minimize/Prevent HPV Exposure to the Immune System

- No blood-borne phase of infection[1]
  - No viremia
- Limited and delayed expression of late viral capsid proteins[1,2]
- HPV does not lyse keratinocytes.[1]
  - No release of pro-inflammatory cytokines[1]
  - Little tissue destruction associated with HPV[3]
- E6 and E7 suppress interferon signaling necessary for cell-mediated immune response.[1]
- No activation of antigen-presenting cells (APCs)[1]

1. Tindle RW. *Nat Rev Cancer*. 2002;2:1–7. 2. Scott M, Nakagawa M, Moscicki A-B. *Clin Diagn Lab Immunol*. 2001;8:209–220. 3. Frazer IH. *Nature Rev Immunol*. 2004;4:46–54.

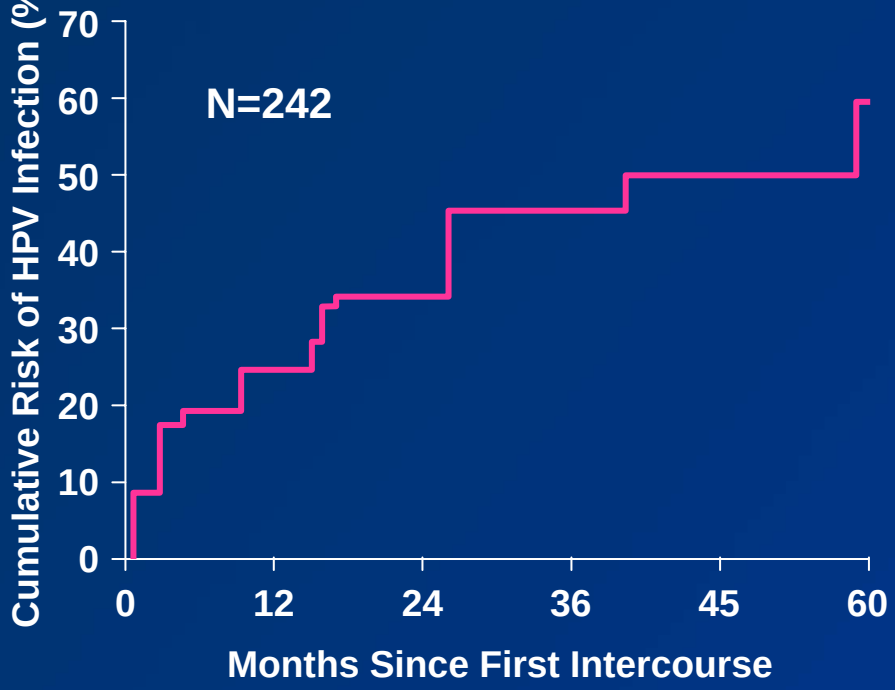
Detectable Serum Antibodies to HPV:
Limitations as Marker of Infection or Natural Immunity

- Antibody responses to HPV infection slow and weak[1]
  - **In a study of 588 women with HPV 16, 18, and 6 infections, median time to seroconversion was ~12 months after incident infection.**
  - **Did not occur in all women**
  - **Only 54%–69% seroconverted within 18 months of incident infection.**
- Antibody responses vary with HPV type.[1]
- Antibody levels are inconsistently found in cervical cancer patients.[2]

1. Carter JJ, Koutsky LA, Hughes JP, et al. *J Infect Dis*. 2000;181:1911–1999. 2. Carter JJ, Madeleine MM, Shera K, et al. *Cancer Res*. 2001;61:1934–1940.

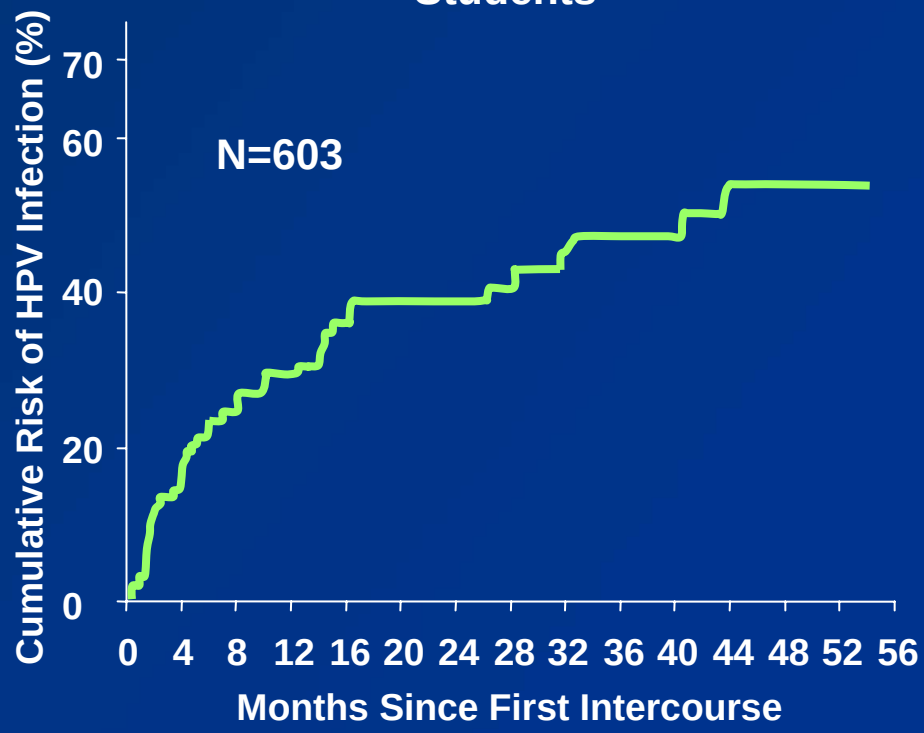
Risk of Acquiring HPV After First Intercourse

Cumulative Risk of Cervical HPV Infection in Female Adolescents With Only 1 Sexual Partner[1]



Adapted from Collins et al.[1]

Study of Female College Students[2]



Adapted from Winer et al.[2]

1. Collins S, Mazloomzadeh S, Winter H, et al. *BJOG*. 2002;109:96–98. 2. Winer RL, Lee S-K, Hughes JP, Adam DE, Kiviat NB, Koutsky LA. Genital human papillomavirus infection: Incidence and risk factors in a cohort of female university students. *Am J Epidemiol.* 2003;157:218–226, by permission of Oxford University Press.

HPV Clearance in Women

HPV 16 is more likely to persist than other types.[1]

Study (Country)	n	Mean Follow-up (Years)	Median Duration of Infection, Months		
			Type 16	Type 18	Type 6
Ho, 1998 (USA)[2]	608	2.2	11	12	6
Muñoz, 2004 (Colombia)[3]	1,610	4.1*	14	12	—
Richardson, 2003 (Canada)[4]	621	1.8	19	9	6
Woodman, 2001 (UK)[5]	1,075	2.4*	10	8	9**

*Median duration of follow-up
**Types 6 and 11

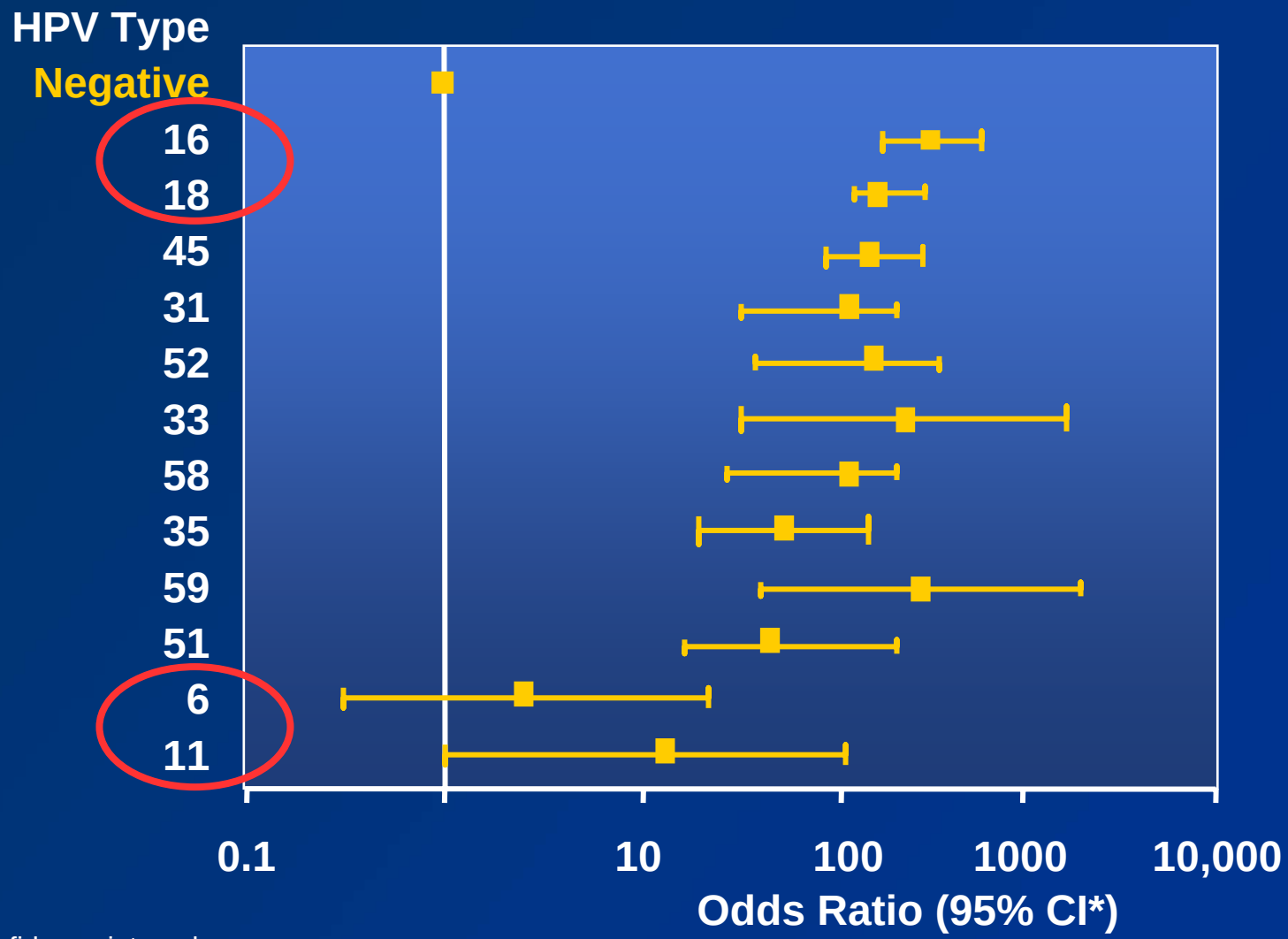
1. Londesborough P, Ho L, Terry G, Cuzick J, Wheeler C, Singer A. *Int J Cancer (Pred Oncol)*. 1996;69:364–368.
2. Ho GY, Bierman R, Beardsley L, Chang CJ, Burk RD. *N Engl J Med*. 1998;338:423–428. 3. Muñoz N, Méndez F, Posso H, et al. *J Infect Dis*. 2004;190:2077–2087. 4. Richardson H, Kelsall G, Tellier P, et al. *Cancer Epidemiol Biomarkers Prev*. 2003;12:485–490. 5. Woodman CB, Collins S, Winter H, et al. *Lancet*. 2001;357:1831–1836.

HPV Clearance

- In women 15–25 years of age, ~80% of HPV infections are transient.[1]
  - Gradual development of cell-mediated immune response presumed mechanism[2]
- In a study of 608 college women, 70% of new HPV infections cleared within 1 year and 91% within 2 years.[3]
  - Median duration of infection = 8 months[3]
  - Certain HPV types are more likely to persist (eg, HPV 16 and HPV 18)

1. Meijer CJLM, Helmerhorst TJM, Rozendaal L, van der Linden JC, Voorhorst FJ, Walboomers JMM. *Histopathology*. 1998;33:83–86. 2. Schiffman M, Kjaer SK. *J Natl Cancer Inst Monogr*. 2003;31:14–19. 3. Ho GYF, Bierman R, Beardsley L, Chang CJ, Burk RD. *N Engl J Med*. 1998;338:423–428.

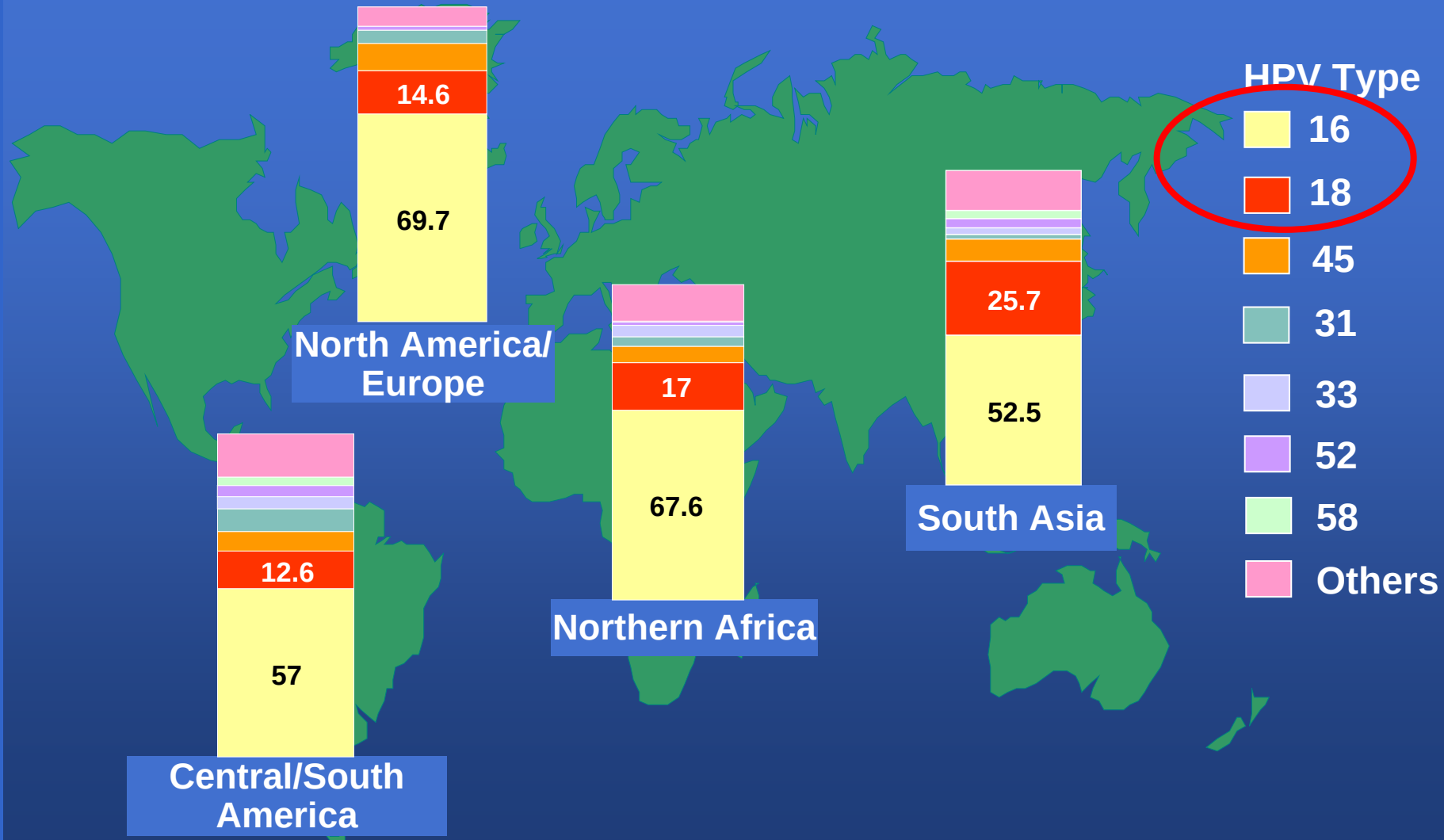
Risk of Invasive Cervical Cancer by HPV Type[1]



*CI = confidence interval

1. Muñoz N, Bosch FX, de Sanjosé S, et al. *N Engl J Med*. 2003;348:518–527.

Worldwide Prevalence of HPV Types in Cervical Cancer*,1



*A pooled analysis and multicenter case control study (N = 3607)

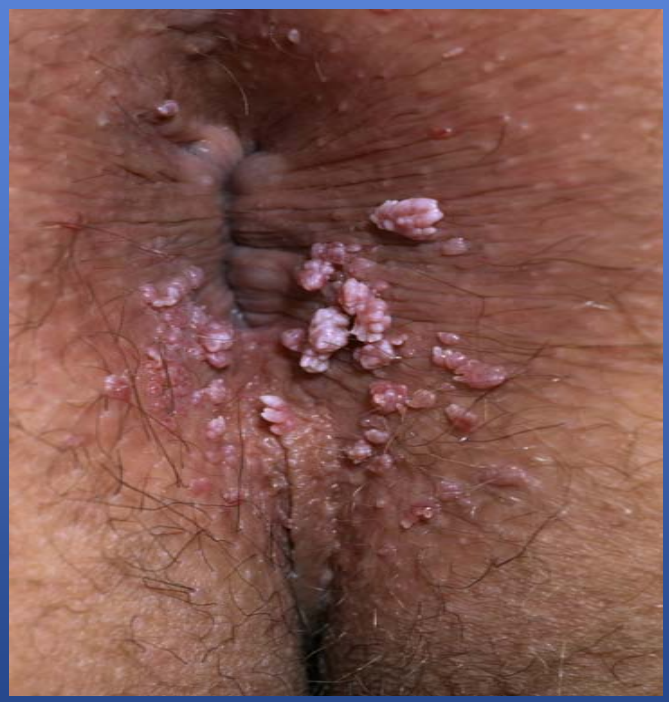
1. Muñoz N, Bosch FX, Castellsagué X, et al. *Int J Cancer*. 2004;111:278–285.

HPV Type Distribution, Cervical Cancer (n=263)

HPV type	TSGH				T1899		Overall	
	Squamous Cell Ca		Adeno or adenosquamous Ca					
High Risk								
16	100	51.0%	6	35.3%	9	64.3%	115	50.7%
18	16	8.2%	10	58.8%	1	7.1%	27	11.9%
58	19	9.7%	1	5.9%	3	21.4%	23	10.1%
33	19	9.7%	0	0.0%	0	0.0%	19	8.4%
52	6	3.1%	0	0.0%	1	7.1%	7	3.1%
31	4	2.0%	0	0.0%	0	0.0%	4	1.8%
45	3	1.5%	0	0.0%	0	0.0%	3	1.3%
35	2	1.0%	0	0.0%	0	0.0%	2	0.9%
59	2	1.0%	0	0.0%	0	0.0%	2	0.9%
68	2	1.0%	0	0.0%	0	0.0%	2	0.9%
39	1	0.5%	0	0.0%	0	0.0%	1	0.4%
Low Risk	1	0.5%	0	0.0%	0	0.0%	1	0.4%
Others								
MM4	2	1.0%	0	0.0%	0	0.0%	2	0.9%
New or unknown	5	2.6%	0	0.0%	0	0.0%	5	2.2%
Multiple	14	7.1%	0	0.0%	0	0.0%	14	6.2%
HPV Positive	196	86.7%	17	81.0%	14	87.5%	227	86.3%
HPV Negative	30	13.3%	4	19.0%	2	12.5%	36	13.7%

Source: Prevalence and Impacts of Cervical HPV Infections in Taiwan Tang-Yuan Chu, MD, PhD

HPV and Anogenital Warts



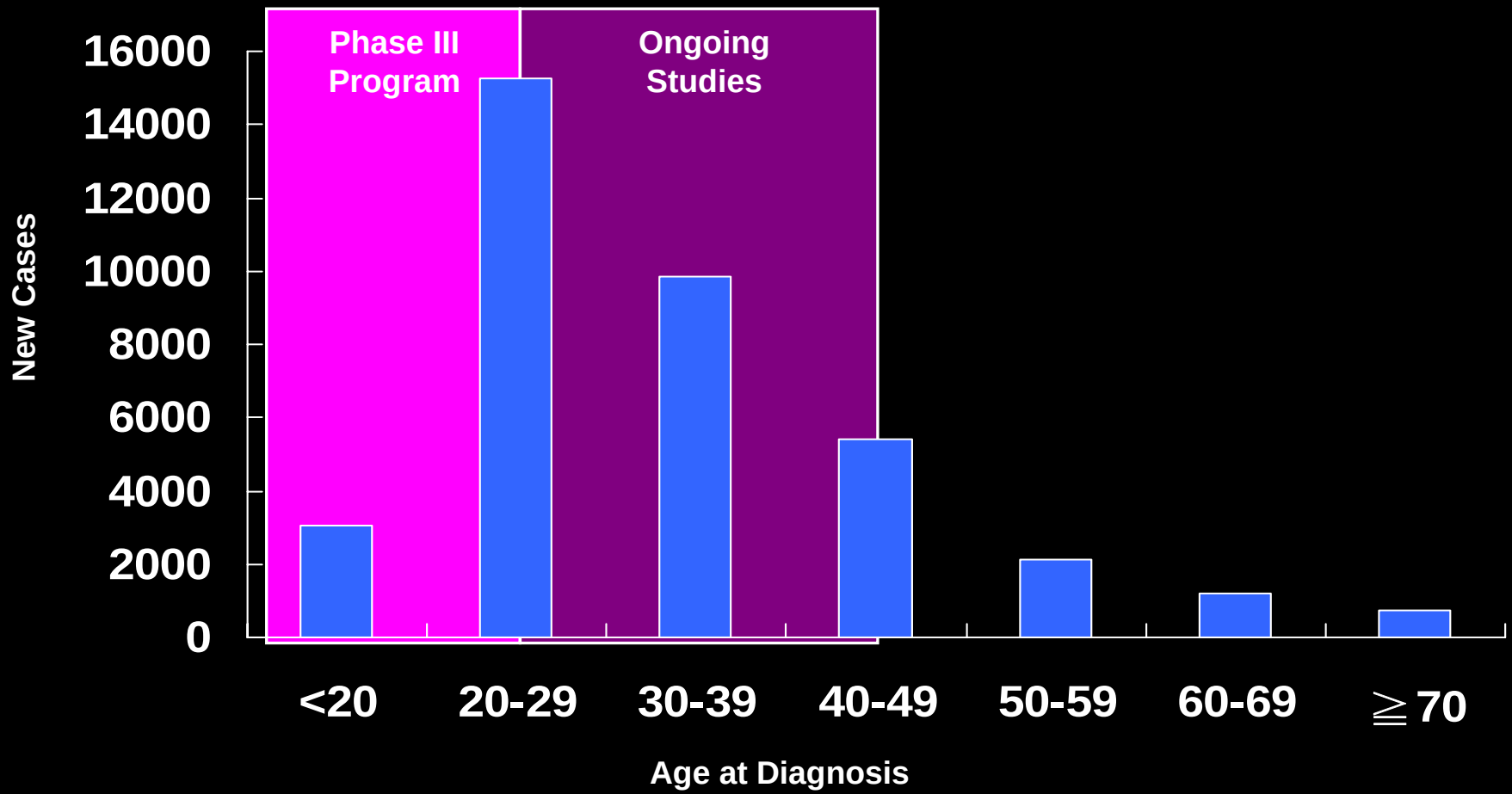
Perianal warts

- HPV 6 and 11 responsible for >90% of anogenital warts[1]
- Clinically apparent in ~1% of sexually active US adult population[2]
- Estimated lifetime risk of developing genital warts ~10%[3,4]

1. Jansen KU, Shaw AR. *Annu Rev Med*. 2004;55:319–331. 2. Koutsky L. *Am J Med*. 1997;102:3–8. 3. Franco EL, Villa LL, Richardson H, Rohan TE, Ferenczy A. In: Franco EL, Monsonego J, eds. Oxford, UK: Blackwell Science; 1997:14–22. 4. Tortolero-Luna G. *Hematol Oncol Clin North Am*. 1999;13:245–257, x.

Studies Conducted in Age Ranges at Risk for HPV Disease

Number of Cases with Genital Warts Diagnosed by Gynecologists and Urologists in 2003 in Taiwan



Database:2003 academic National health Insurance Research Database

GARDASIL® Clinical Data Update

MSD

Expected Indication GARDASIL®: Label at Launch

Char-acteristics

- Quadrivalent vaccine (HPV types 6, 11, 16, 18)
  - Yeast-derived, recombinant L1 VLP on aluminum adjuvant
  - Refrigerator stable (2-8° C), and 36 month expiry

Draft Indications

Indicated for the prevention of cancer, precancerous or dysplastic lesions, genital warts, and infection caused by human papillomavirus (HPV) types targeted by the vaccine

For prevention of the following:

- Cervical, vulvar, vaginal cancer (HPV 16, 18)
- AIS and CIN 2 and 3 (HPV 16, 18)
- CIN 1 (HPV 6,11,16,18)
- Genital warts (condyloma acuminata) (HPV 6,11)
- VIN 1,2,3 and VaIN 1,2, 3 (HPV 6,11,16,18)
- HPV infection (HPV 6,11,16,18)

Dosage & Admin-istration

- 3-dose regimen: 0, 2, 6 months
- Recommended for children and adolescents 9 through 17 years of age and women 18 through 26 years of age
- Safety and immunogenicity were determined in boys aged 9-15 years

1x Vial Carton

10x Syringe Carton for Syringe without Safety Device

Rationale for a Quadrivalent HPV (Types 6, 11, 16, and 18) L1 VLP Vaccine

Type	Women	Men
6/11	▪ >90% of genital warts[2] ▪ 90% of RRP Lesions ▪ ~10% of low-grade cervical lesions[3]	▪ >90% of genital warts[2] ▪ 90% of RRP Lesions ▪ Transmission to women[9]
16/18	▪ ~25% of low-grade cervical lesions[3] ▪ ~50% of high-grade cervical lesions[4] ▪ ~70% of cervical cancer[3,5,6] ▪ ~70% of other genital cancers[7,8]	▪ ~60% of anal cancer[10] ▪ Transmission to women[9]

Assembly of HPV Virus Like Particles

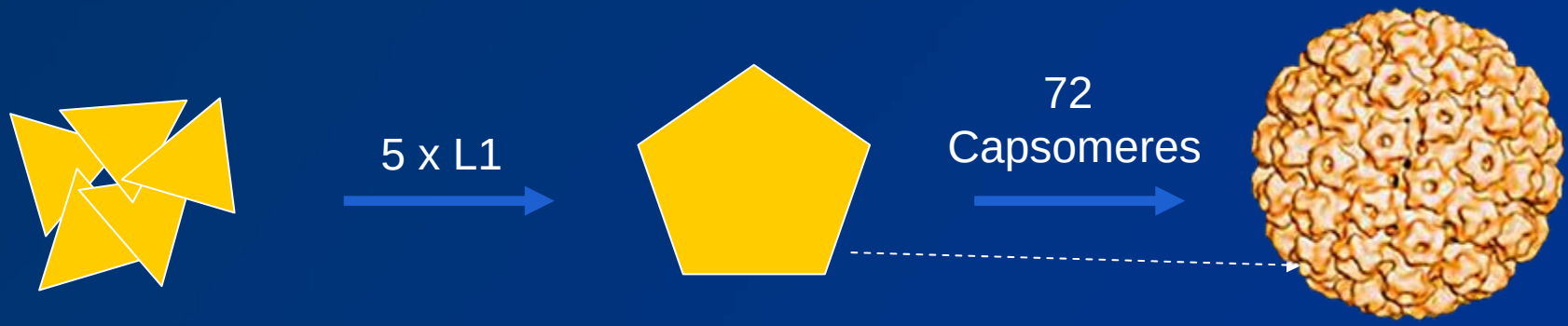
L1 Protein
(55–57 kD)

5 x L1

L1 Capsomere
(~280 kD)

72
Capsomeres

VLP
(~20,000 kD)

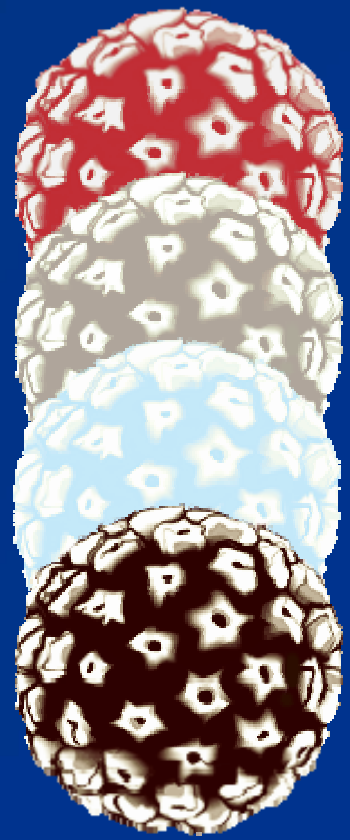


* VLP = Virus-like particle.

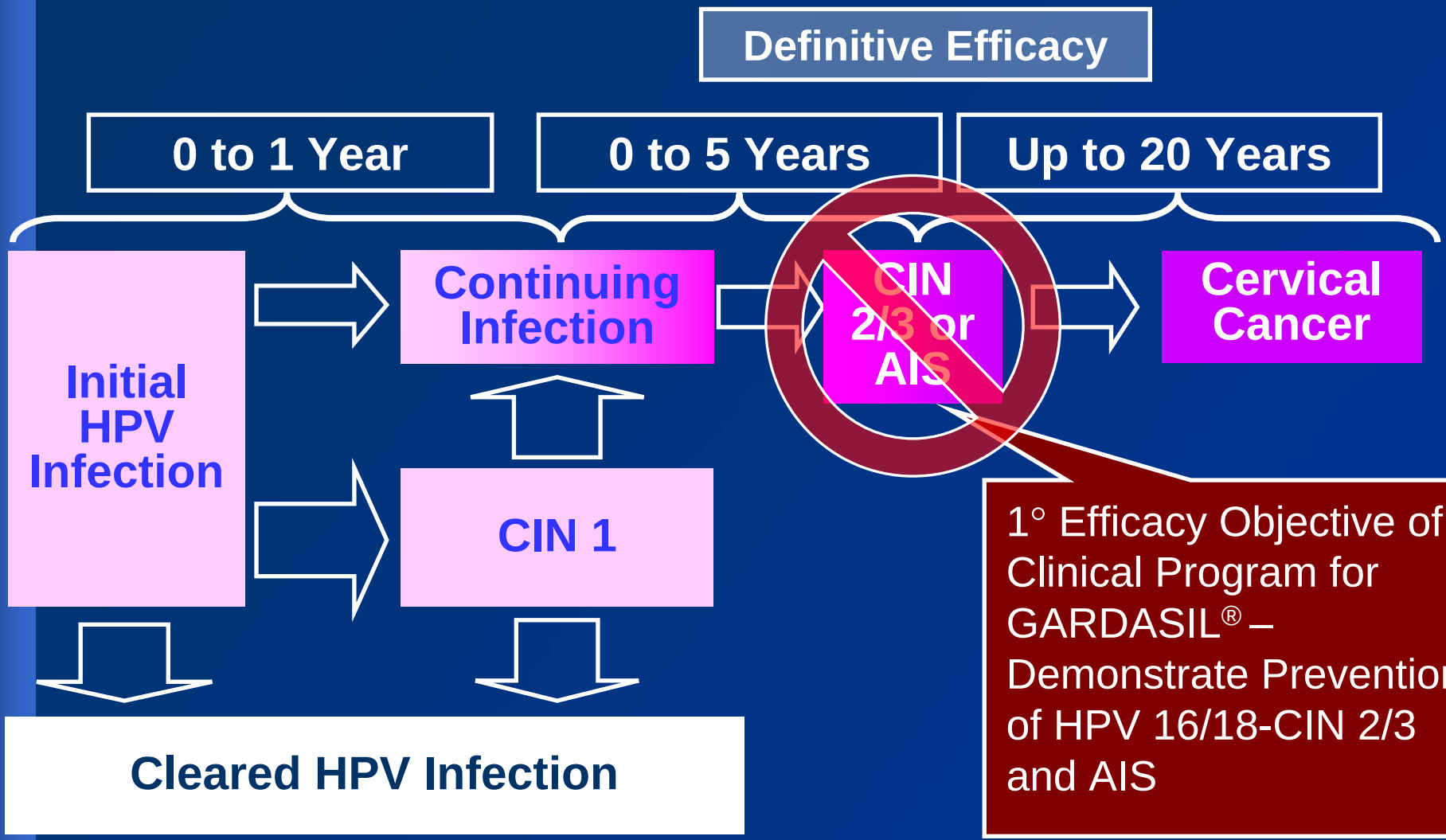
1. Kirnbauer R, Booy F, Cheng N, Lowy DR, Schiller JT. *Proc Natl Acad Sci USA.* 1992;89:12180–12184. 2. Syrjänen KJ, Syrjänen SM. Chichester, United Kingdom: John Wiley & Sons, Inc; 2000:11–51.

Immunologic Basis for GARDASIL®

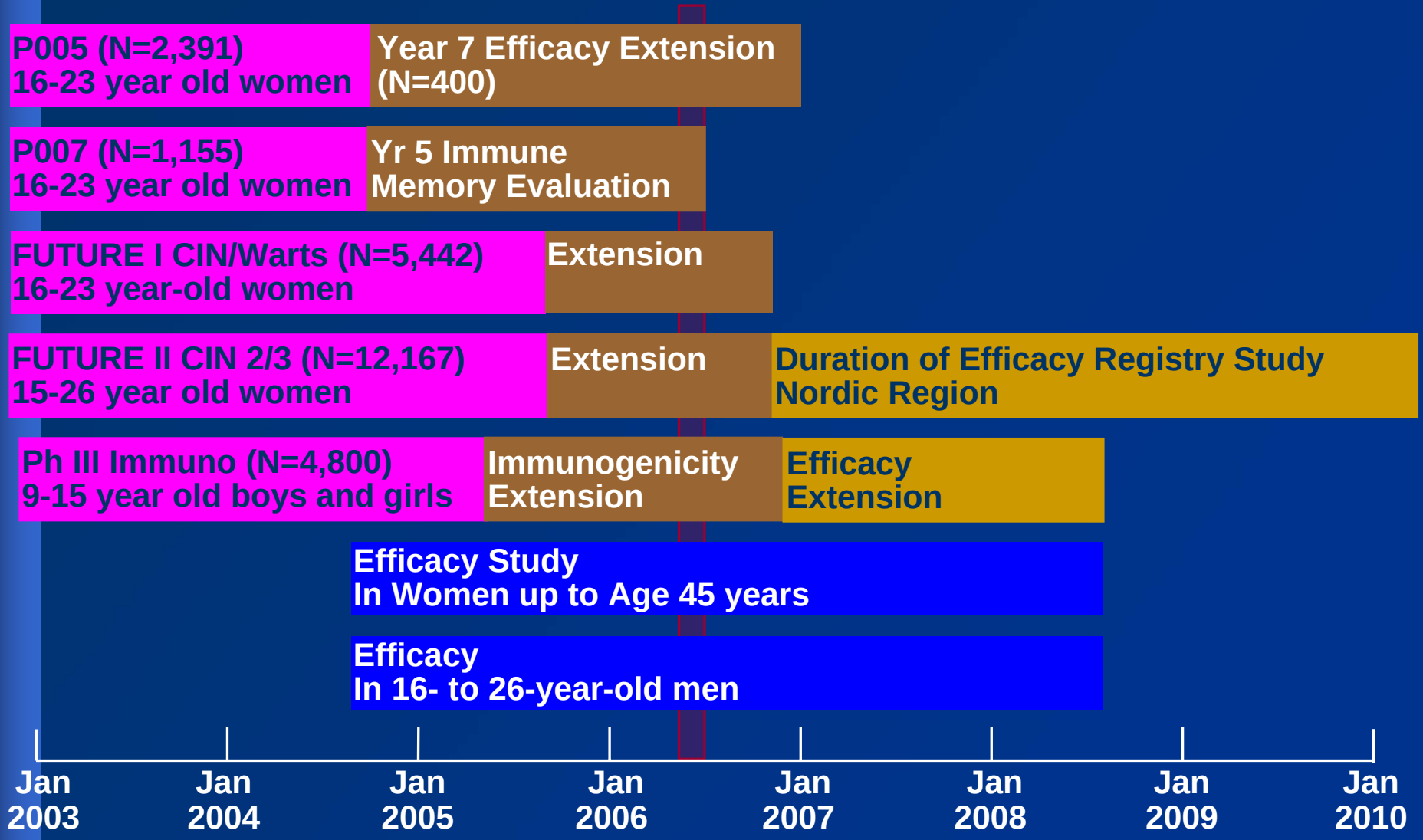
- L1 HPV major capsid protein self-assembles into virus-like particles (VLPs)
- In animal models of papillomavirus infection using species-specific VLPs
  - Vaccination results in protection from infection and disease
  - Efficacy associated with development of neutralizing antibodies
  - Transfer of serum from vaccinated to unvaccinated animals transfers protective efficacy



CIN 2/3 and AIS — Established Surrogate Markers for Cervical Cancer

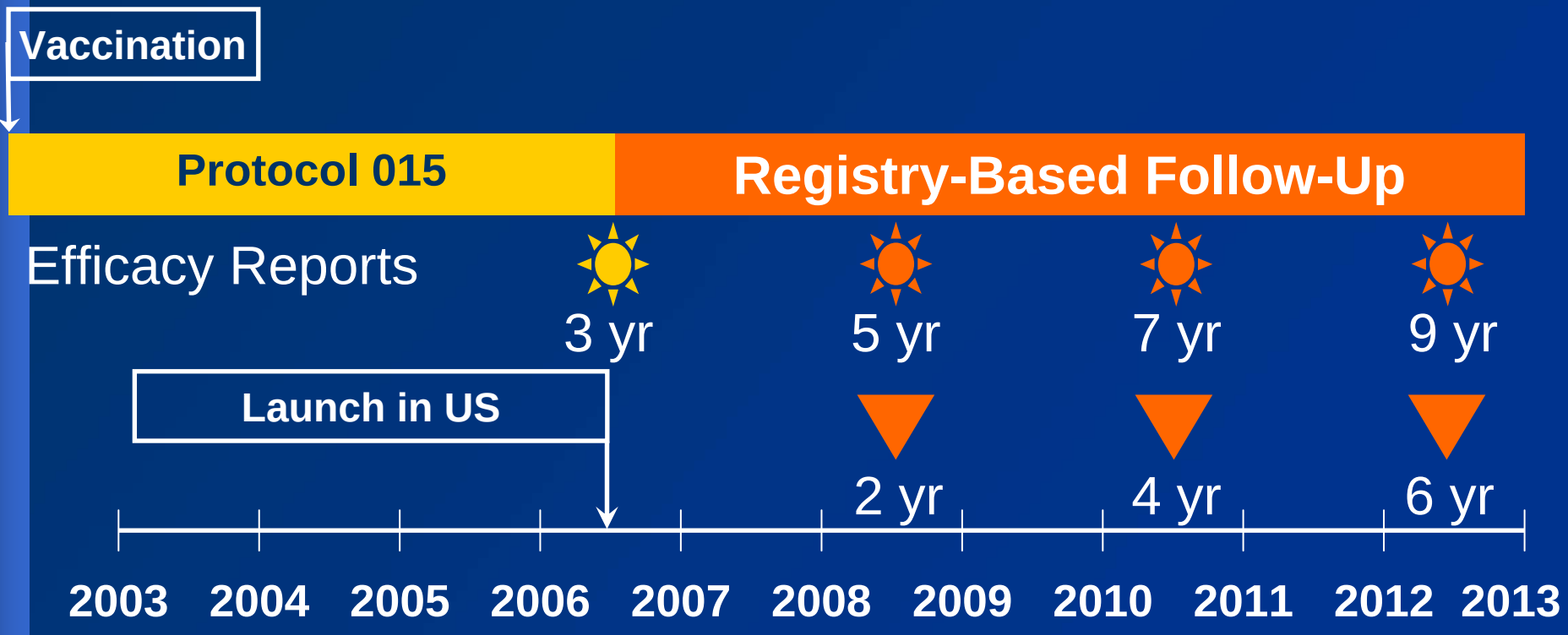


Clinical Program for GARDASIL® (2003 and Later)



Sentinel Cohort to Evaluate Duration of Efficacy

- The Nordic Region requires reporting of Pap test and biopsy results by national ID number to centralized registries
- In 5800 CIN 2/3 study subjects enrolled in the region, these registries will be used to define long-term duration of efficacy



HPV 16 Vaccine Proof-of-Principle Efficacy Study

HPV 16 Vaccine Proof-of-Principle Efficacy Study[a]: Final Results

Per-protocol efficacy cohort[b]
Median 40 months after completion of vaccination regimen

End Point[c]	Number of HPV 16 Vaccine Cases (n=755)	Number of Placebo Cases (n=750)	Vaccine Efficacy (%)	95% Confidence Interval	*P* Value
Persistent HPV 16 infection + CIN[d]	7	111	94	88–98	<0.0001
HPV 16$^+$ on ≥2 visits ≥4 mo apart	0	68	100	95–100	
HPV 16$^+$ on last recorded visit	7	19	67	17–88	
HPV 16-related CIN[c] 1	0	12	100	71–100	
HPV 16-related CIN[c] 2/3	0	14	100	65–100	
HPV 16-related CIN[c] 2	0	7	100	33–100	
HPV 16-related CIN[c] 3	0	6	100	18–100	

[a]Double-blind, placebo-controlled study.
[b]HPV L1 VLP Vaccine 40 mcg (N=1193); Placebo (N=1198).
[c]Subjects are counted once within each category. Subjects may appear in more than one category.
[d]CIN = cervical intraepithelial neoplasia
Ault et al. Am College of O&G. San Francisco CA, May 7-11, 2005. Poster 2759.

Human HPV (Types 6, 11, 16, 18) L1 VLP Vaccine Phase II Dose-Ranging Immunogenicity and Efficacy Study[1]

1. Villa LL, Costa RL, Petta CA, et al. *Lancet Oncol*. 2005;6:271–278.

Human HPV (Types 6, 11, 16, 18) L1 VLP Vaccine Phase II Dose-Ranging Immunogenicity and Efficacy Study: Efficacy Phase[1]

Per-protocol efficacy cohort: Clinical outcomes

End Point	Number of Vaccine Cases (n=276)	Number of Placebo Cases (n=275)	Vaccine Efficacy (%)	95% Confidence Interval	*P* Value
HPV 6/11/16/18 Infect*, CIN**, or GW***	4	36	90	71–97	$<10^{-3}$
Infection	4	35	89		
Disease	**0**	**6**	**100**		**0.0151**
Genital warts	**0**	**3**	**100**		**NA**
CIN	**0**	**3**	**100**		**NA**

- Vaccine cases:
  - HPV 16: 3 cases single positive at the last visit on record
  - HPV 18: 1 case persistent HPV 18 infection detected at months 12 and 18 only

*Infect = Persistent HPV 6, 11, 16, or 18 infection: Detection of relevant HPV in cervical samples obtained on >2 consecutive visits ≥4 months apart or detection of HPV 6, 11, 16, or 18 at the last visit on record without confirmed persistence
**CIN = cervical intraepithelial neoplasia
***GW = genital warts
NA = Number of events too small for meaningful efficacy estimates.
1. Villa LL, Costa RL, Petta CA, et al. *Lancet Oncol*. 2005;6:271–278.

Human HPV (Types 6, 11, 16, 18) L1 VLP Vaccine Phase III Efficacy Trials (FUTURE I & II)

(FUTURE I)

Females United to Unilaterally Reduce Endo-Ectocervical Disease

Clinical Protocol (FUTURE I)

- 5455 women (16-23 yrs) randomized to vaccine/ placebo at day 1, and months 2 and 6.
- Pap tests taken at regular intervals.
- Colposcopy referral was algorithm-based. Biopsies were HPV typed. Histology slides were read by a blinded pathology panel.
- Primary endpoints were HPV 6/11/16/18-related

  (a) cervical intraepithelial neoplasia (CIN 1-3), adenocarcinoma *in situ*, and cervical cancer;

  (b) EGL (genital warts, vulvar/vaginal intraepithelial neoplasia or cancer).
- Analyses were per protocol (PP) (received 3 doses, had no major protocol violations, were sero (-) at day 1 and DNA (-) day 1 to month 7 to the respective HPV type) and modified intention to treat (MITT) (received $\geq$1 dose and were (-) to the respective HPV type at day 1).
- Follow-up began at month 7 and day 30 in the PP and MITT analyses, respectively.

Sattler C et al. 2005 ICAAC Conference, Washington DC, December 16-19, 2005. Poster.

Primary Efficacy Results (FUTURE I)

	Quadravalent HPV Vaccine			Placebo			Efficacy (%)	CI**
	n	cases	Rate*	n	cases	Rate*		
PP								
CIN or Worse	2240	0	0	2258	37	1.0	100***	87-100
genital warts, vulvar/ vaginal neoplasia	2261	0	0	2279	40	1.0	100***	88-100
MITT†								
CIN or Worse	2557	2	< 0.1	2573	57	1.0	97	87-100
genital warts, vulvar/ vaginal neoplasia	2620	3	0.1	2628	59	1.1	95	84-99

*Cases/Subject years at risk*100 **97.5% CI for PP, 95% for MITT ***P<0.001, †Received ≥1 dose and were (-) to the respective HPV type at day 1

Sattler C et al. 2005 ICAAC Conference, Washington DC, December 16-19, 2005. Poster.

(FUTURE II)

Females United to Unilaterally Reduce Endo-Ectocervical Disease

Combined Phase II/Phase III Efficacy Studies of Human HPV (Types 6, 11, 16, 18) L1 VLP Vaccine: Statistical Plan

- Primary efficacy evaluation in PP population
  - received 3 vaccinations within 1 year
  - no major protocol violations
  - HPV 16/18 sero(-) at day 1 and HPV 16/18 DNA(-) day 1 to month 7
  - Cases were counted starting after month 7.
- Supportive analysis in prespecified MITT population
  - received $\geq$1 vaccination
  - HPV 16/18 sero(-) and HPV 16/18 DNA(-) at day 1
  - Cases were counted starting 30 days after day 1.
- The combined analysis of the 4 studies was prespecified in 2001.
  - In the HPV 16 vaccine study, only HPV 16-related cases were considered.
  - The primary end point was the combined incidence of HPV 16/18-related CIN 2/3, AIS, or cancer.
  - Primary hypothesis tested at the $\alpha = 0.05$ (two-sided) level.

PP = per-protocol
MITT = modified intention-to-treat

Infectious Disease Society of America (IDSA) Meeting, October 5-9, 2005, in San Francisco, California

Primary Efficacy Results (FUTURE II)

Per-protocol population, 2 yr follow-up

	Vaccine (N=6082)		Placebo (N=6075)				
HPV 16/18-related CIN 2/3 or AIS	n	Cases	n	Cases	Efficacy (%)	CI	*P* Value
Per-protocol	5301	0	5258	21	100	(76–100)*	<0.001

Per-protocol = received 3 doses of vaccine; no major protocol violations; HPV 16/18 sero(-) at day 1 and HPV 16/18 DNA(-) from day 1 to month 7; cases counted starting after month 7, the follow-up was 2 years after the first vaccination.

*97.96% CI is provided based on a multiplicity adjustment to preserve the overall 1-sided type I error rate of 0.025.

FUTURE = Females United to Unilaterally Reduce Endo/Ectocervical Disease
CIN = cervical intraepithelial neoplasia
AIS = adenocarcinoma in situ

Infectious Disease Society of America (IDSA) Meeting, October 5-9, 2005, San Francisco, California

Secondary Efficacy Results (FUTURE II)

Pre-specified modified Intention To Treat (MITT) Population
Average Duration of Follow-up: 2 Years After the First Vaccination

	Vaccine (N=6082)		Placebo (N=6075)				
HPV 16/18-related CIN 2/3 or AIS	n	Cases	n	Cases	Efficacy (%)	CI	*P* Value
MITT	5736	1	5766	36	97	(83–100)	<0.001

MITT = received ≥1 vaccination; HPV 16/18 sero(-) and HPV 16/18 DNA(-) at day 1; cases were counted starting 30 days after first vaccination.

FUTURE = Females United to Unilaterally Reduce Endo/Ectocervical Disease
CIN = cervical intraepithelial neoplasia
AIS = adenocarcinoma in situ

Infectious Disease Society of America (IDSA) Meeting, October 5-9, 2005, in San Francisco, California

Combined Phase II / Phase III Efficacy Studies of Human HPV (Types 6, 11, 16, 18) L1 VLP Vaccine

Combined Phase II/Phase III Studies of Human HPV (Types 6, 11, 16, 18) L1 VLP Vaccine: Primary Efficacy Analysis

Per-protocol population
Median duration of follow-up = 4, 3, and 2 years depending on studies

	Vaccine		Placebo		Efficacy (%)	95% CI	*P* Value
	n	Cases	n	Cases			
PP							
HPV 16/18-related CIN 2/3 or AIS	8487	0	8460	53	100	(93–100)	< 0.001
CIN 2	8487	0	8460	36	100	(89–100)	
CIN 3 or AIS	8487	0	8460	32	100	(88–100)	

PP = received 3 vaccinations within 1 year; no major protocol violations; HPV 16/18 sero(-) at day 1 and HPV 16/18 DNA(-) day 1 to month 7; cases counted starting after month 7.
CIN = cervical intraepithelial neoplasia; AIS = adenocarcinoma in situ.

Infectious Disease Society of America (IDSA) Meeting, October 5-9, 2005, in San Francisco, California

Combined Phase II/Phase III Studies of Human HPV (Types 6, 11, 16, 18) L1 VLP Vaccine: Secondary Efficacy Analysis*

Pre-specified Modified Intention-to-Treat (MITT) population
Median duration of follow-up = 4, 3, and 2 years depending on studies

	Vaccine		Placebo		Efficacy (%)	95% CI	*P* Value
	n	Cases	n	Cases			
MITT HPV 16/18-related CIN 2/3 or AIS	9342	1	9400	81	99	(93–100)	< 0.001
CIN 2	9342	1	9400	55	98	(89–100)	
CIN 3 or AIS	9342	0	9400	52	100	(93–100)	

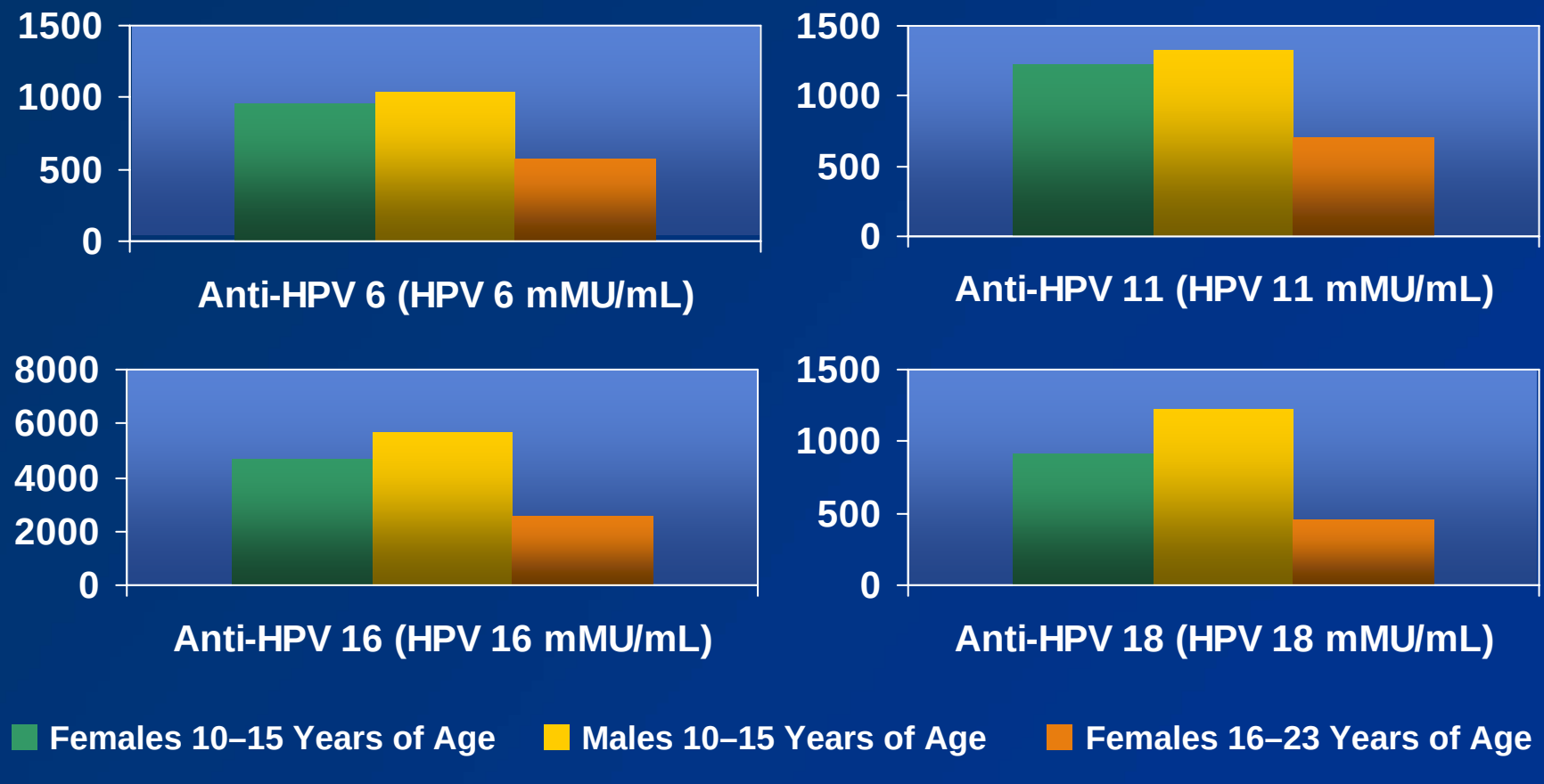
MITT = received ≥1 vaccination; HPV 16/18 sero(-) and HPV 16/18 DNA(-) at day 1; cases were counted starting 30 days after first vaccination.
CIN = cervical intraepithelial neoplasia
AIS = adenocarcinoma in situ

Infectious Disease Society of America (IDSA) Meeting, October 5-9, 2005, in San Francisco, California

Human HPV (Types 6, 11, 16, 18) L1 VLP Vaccine

Adolescent Immunogenicity Substudy

Human HPV (Types 6, 11, 16, 18) L1 VLP Vaccine Phase III Adolescent Immunogenicity Substudy: Anti-HPV GMTs* at Month 7



*GMT = geometric mean titers

Presented at: European Society for Paediatric Infectious Diseases (ESPID). Valencia, Spain; May 18–20, 2005

Safety of Human HPV (Types 6, 11, 16, 18) L1 VLP Vaccine

Pregnancy Outcomes for Human HPV (Types 6, 11, 16, 18) L1 VLP Vaccine

Subjects who received at least 1 dose of vaccine

	Protocol 005		Protocol 007		Protocol 016
	HPV Vaccine (n=1191)	Placebo (n=1196)	HPV Vaccine (n=863)	Placebo (n=292)	HPV Vaccine (n=509)
Pregnancies, n	**34**	**34**	**14**	**4**	**11**
Unknown outcomes	4	4	3	0	3
Known outcomes	30	30	11	4	8
In pregnant women with known outcomes, n					
Full term: no complications to mother and child	15	6	3	3	6
Full term: complication to mother	2	1	0	0	0
Prematurity	0	0	1*	0	0
Spontaneous or induced abortion	6	5	3	0	1
Elective termination	7	18	4	1	1

*Twin infants born premature with respiratory distress syndrome

Overseas Indications

TGA/Australia (6/22)	FDA/United States of America (6/8)
GARDASIL is indicated in females aged 9-26 years for the prevention of cervical, vulvar and vaginal cancer, precancerous or dysplastic lesions, genital warts and infection caused by HPV 6, 11, 16 and 18 (which are included in the vaccine). GARDASIL is indicated in **males aged 9-15 years** for the prevention of infection caused by HPV 6, 11, 16 and 18 (which are included in the vaccine).	GARDASIL is indicated in girls and women 9-26 years of age for the prevention of the following diseases caused by HPV types 6, 11, 16, and 18: Cervical cancer Genital warts (condyloma acuminata) and the following precancerous or dysplastic lesions: Cervical AIS, CIN 2/3, VIN 2/3 VaIN 2/3, CIN 1

US CDC's ACIP Recommendation for Gardasil®

June 29th, 2006

http://www.cdc.gov/od/oc/media/pressrel/r060629.htm

Recommendation

- Three doses of Gardasil® should be routinely given to girls when they are 11 or 12 years old.
- The vaccination series can be started as early as nine years old at the discretion of the physician or health care provider.
- The recommendation also includes girls and women 13-26 years old because they will benefit from getting the vaccine.
- The vaccine should be administered before onset of sexual activity (i.e., before women are exposed to the viruses), but females who are sexually active should still be vaccinated.

HPV Vaccine Questions and Answers

- http://www.cdc.gov/std/hpv/STDFact-HPV-vaccine.htm#hpvvac27

How effective is this vaccine?

- The vaccine has mainly been studied in young women who had not been exposed to any of the four vaccine HPV types. These studies found the vaccine to be 100% effective in preventing cervical precancers caused by the vaccine HPV types. These studies also found it to be almost 100% effective in preventing precancers of the vulva and vagina, and genital warts that are caused by the vaccine HPV types. The vaccine was less effective in young women who had already been exposed to a vaccine HPV type. This vaccine does not treat existing HPV, genital warts, precancers or cancers.

Will sexually active females benefit from the vaccine?

- Females who are sexually active may also benefit from the vaccine. But they may get less benefit from the vaccine since they may have already acquired one or more vaccine HPV type(s). Still, they would get protection against the vaccine HPV types they have not yet acquired. Few young women are infected with all four vaccine HPV types. Currently, there is no test available to tell whether a girl/woman has had any or all of the four vaccine HPV types.

Is the HPV vaccine safe?

- The FDA has approved the HPV vaccine as safe and effective. This vaccine has been tested in over 11,000 females (ages 9-26 years) in many countries around the world. These studies have shown no serious side effects. The most common side effect is soreness at the injection site.

How long does vaccine protection last? Will a booster shot be needed?

- The length of vaccine protection (immunity) is usually not known when a vaccine is first introduced. So far, studies have followed women for five years and found that they are protected. More research is being done to find out how long protection will last, and if a booster vaccine is needed years later.

Should girls/women be screened before getting vaccinated?

- No. Girls/women should not get an HPV test or Pap test to determine if they should get the vaccine. An HPV test or a Pap test can tell that a woman may have HPV, but these tests cannot tell the specific HPV type(s) that a woman has. Even girls/women with one vaccine HPV type could get protection against the other vaccine HPV types they have not yet acquired.

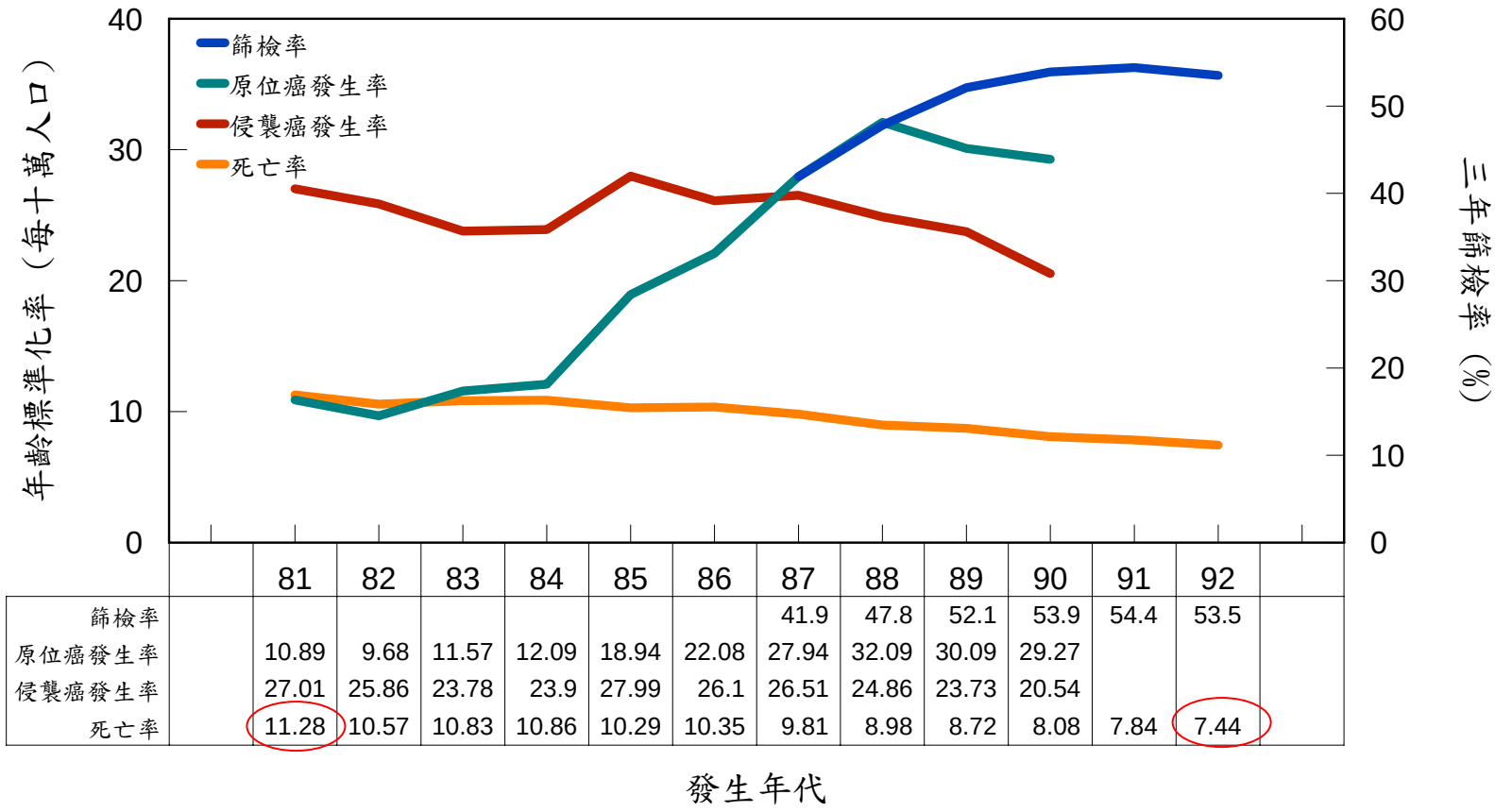
Should pregnant women be vaccinated?

- The vaccine is *not* recommended for pregnant women. There has been limited research looking at vaccine safety for pregnant women and their developing fetus. So far, studies suggest that the vaccine has not caused health problems during pregnancy, nor has it caused health problems for the infant-- but more research is still needed. For now, pregnant women should complete their pregnancy before getting the vaccine. If a woman finds out she is pregnant after she has started getting the vaccine series, she should complete her pregnancy before finishing the three-dose series.

Will girls/women be protected against HPV and related diseases, even if they don't get all three doses?

- It is not yet known how much protection girls/women would get from receiving only one or two doses of the vaccine. For this reason, it is very important that girls/women get *all three doses* of the vaccine.

子宮頸癌前病變及子宮侵襲癌



	81	82	83	84	85	86	87	88	89	90	91	92
篩檢率							41.9	47.8	52.1	53.9	54.4	53.5
原位癌發生率	10.89	9.68	11.57	12.09	18.94	22.08	27.94	32.09	30.09	29.27		
侵襲癌發生率	27.01	25.86	23.78	23.9	27.99	26.1	26.51	24.86	23.73	20.54		
死亡率	11.28	10.57	10.83	10.86	10.29	10.35	9.81	8.98	8.72	8.08	7.84	7.44

註：年齡標準化率係使用2000年世界標準人口為標準人口

子宮頸癌篩檢率與發生率及死亡率之長期趨勢，民國81-92年

Thanks for Your Attention!

Target group

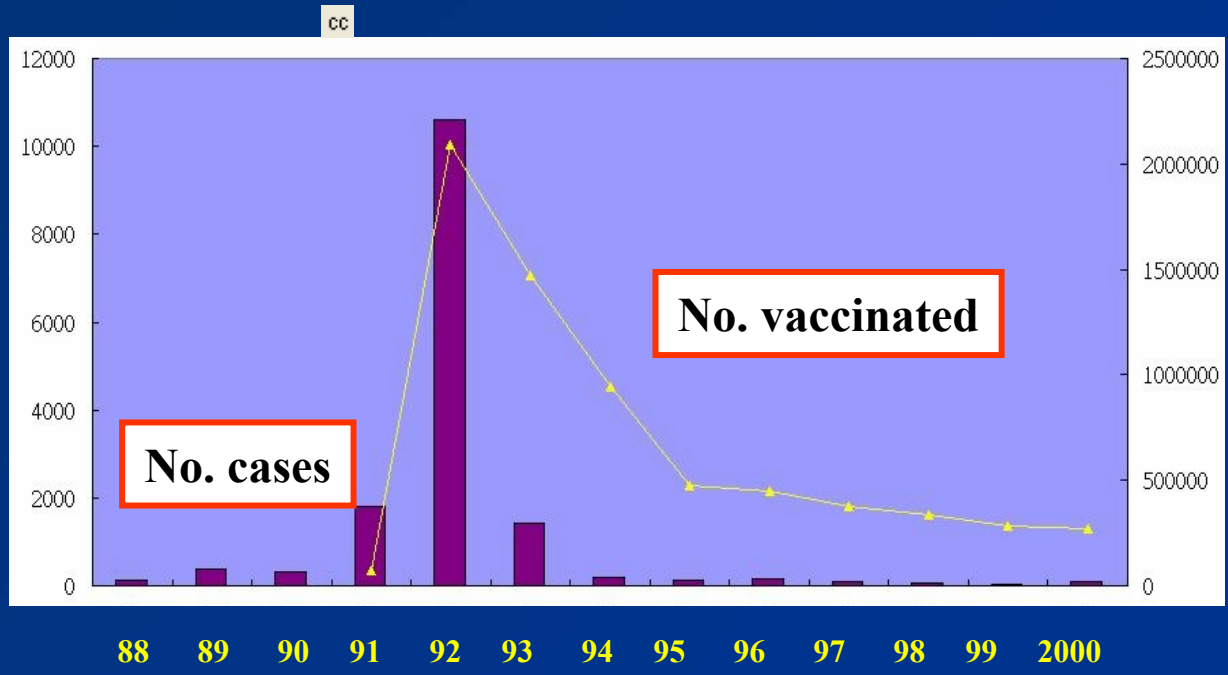
Females or males + females

- Males at risk for HPV infection and disease
  - Genital warts, anal cancer
  - Transmit HPV to women
- Fewer HPV infection studies in men

Taiwan

1986: rubella vaccine for 15 y/o girls

1992: universal vaccination



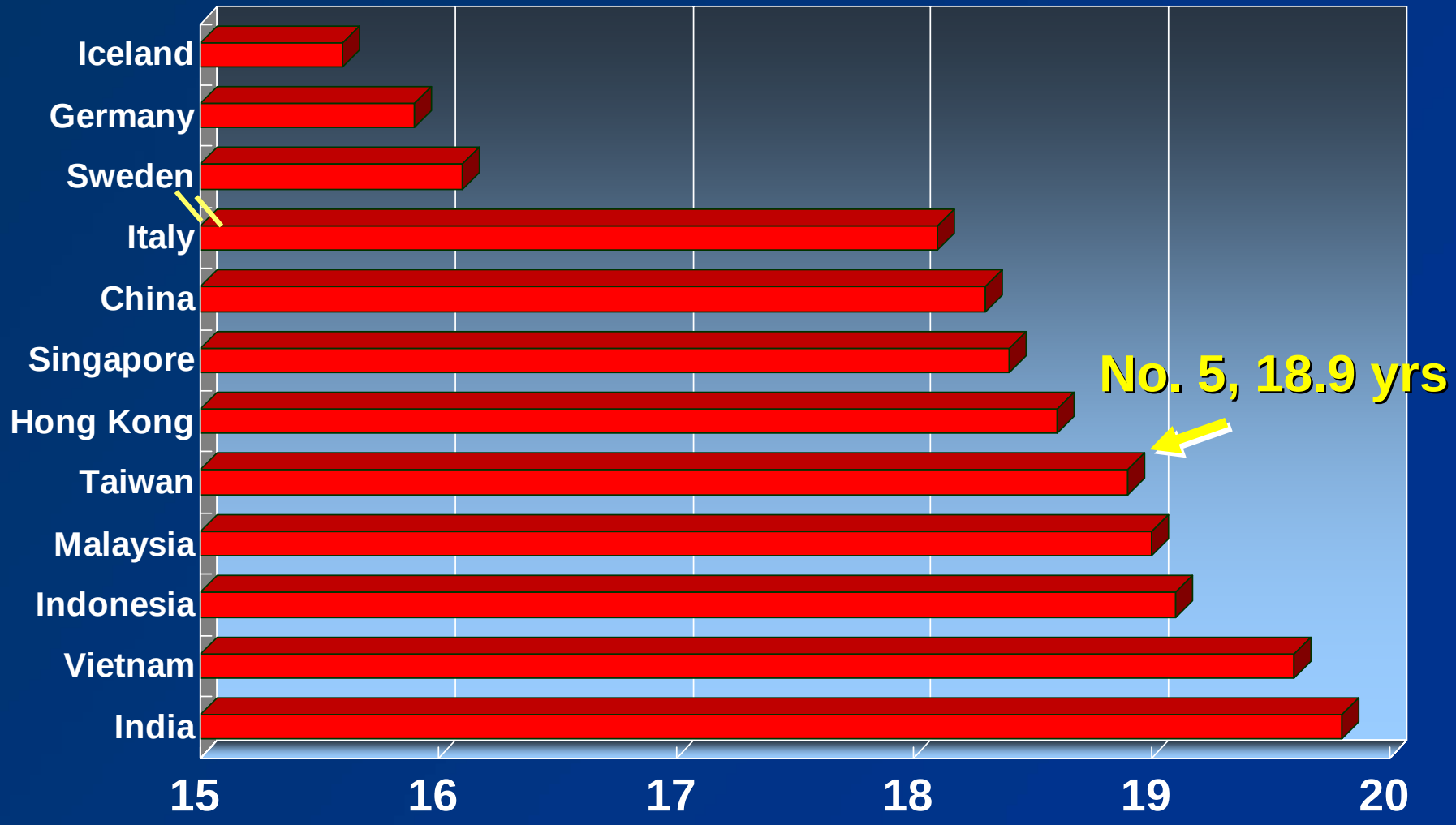
Source: P.I. Lee NTUH

CDC, Taiwan

Age of first sex

Durex report, 2005 (41 countries)

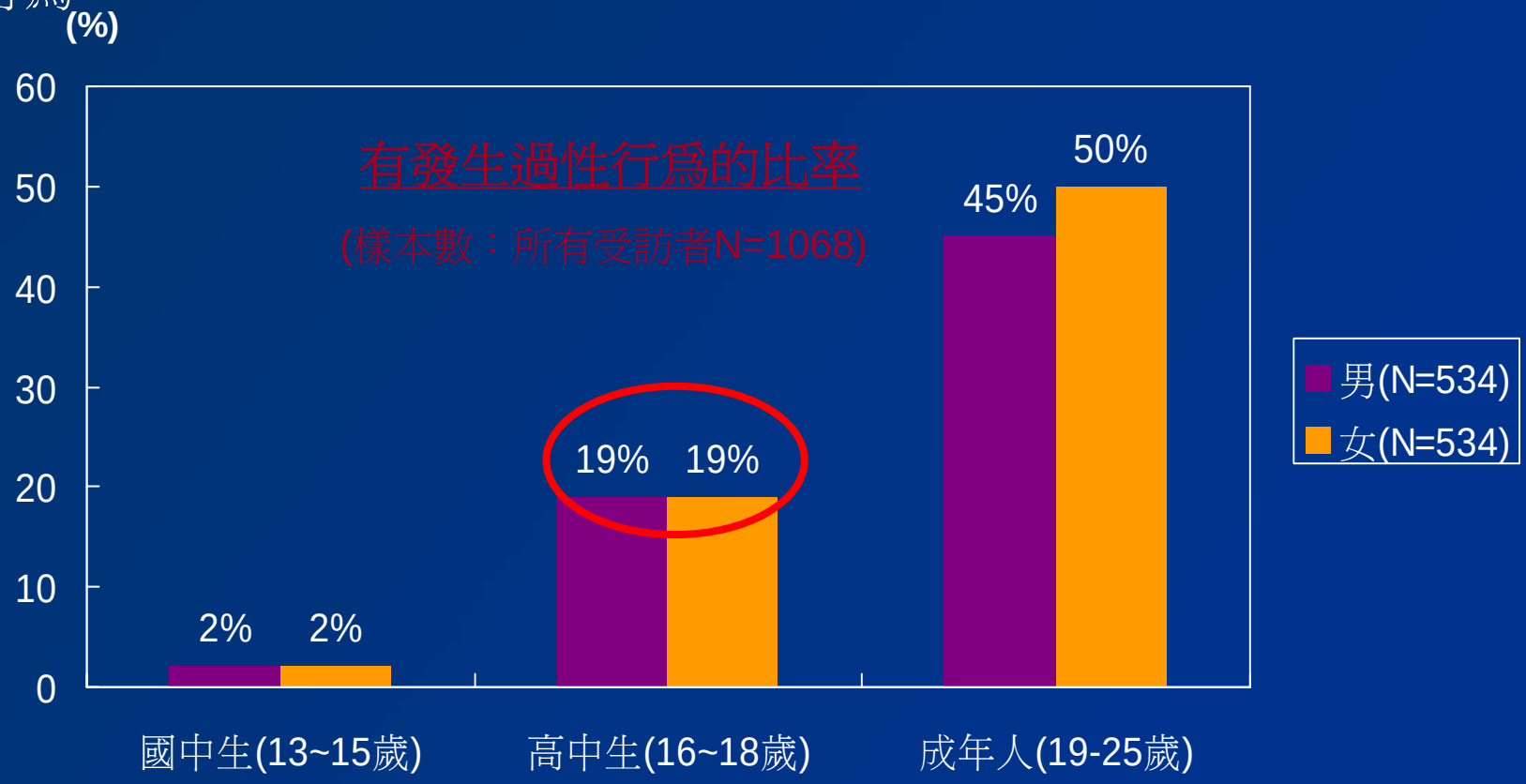
Average: 17.3 yrs



現在高中生每5人即有1人有性經驗

- 在1068位年輕人中，有33%已發生過性行為。

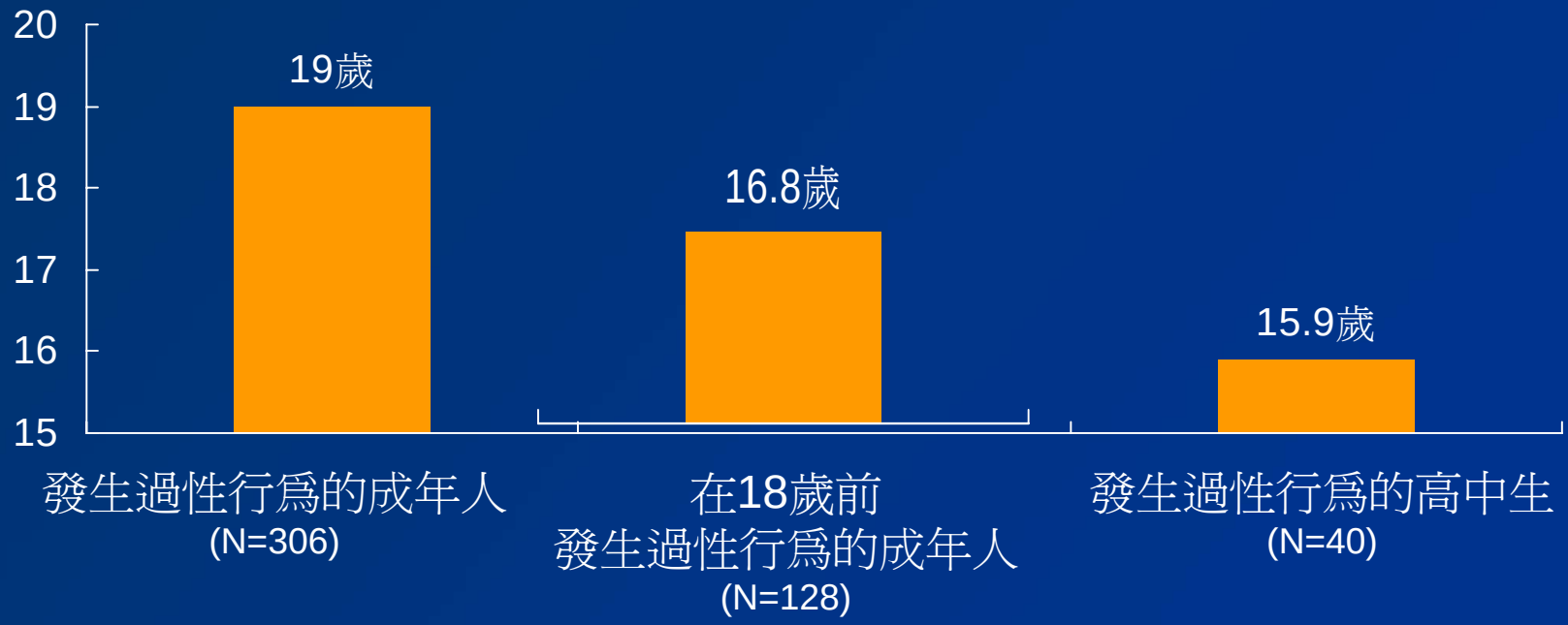
13-15歲的國中生中有2%表示曾經有過性行為經驗，16-18歲則有19%有過性行為。



資料來源:Q11.請問您自己是否以有過性行為的經驗

新世代年輕人性生態關鍵報告

- **第一次性行爲的年齡呈下降趨勢**
- 在18歲前發生過性行爲的成年人中，第一次性行爲平均在16.8歲，但16-18歲高中生的第一次平均爲15.9歲，早了將近一歲。



Source: 2006 7年級生性生態關鍵報告暨子宮頸癌疫苗最新進度報告 TNS 模範市場研究顧問公司/ 台灣婦產科身心醫學會

Efficacy in Women With Evidence of Current or Previous Infection With Vaccine HPV Types

Does Gardasil® Alter The Course of HPV Infection?

	Seronegative	Seropositive
PCR(-)	Prophylactic efficacy in HPV-naïve women: ≥95% reduction in incidence of HPV 6/11/16/18-related disease	Prevention of recurrence of infection : 100% reduction in incidence of HPV 6/11/16/18-related disease
PCR(+)	Post-exposure prophylaxis in women with early infection: 28%reduction in progression to CIN 2/3	Treatment of chronic HPV infection: No vaccine efficacy

With the exception of prophylactic efficacy, all efficacy findings represent trends only