

Innovations in Cervical Cancer Prevention:

How to Use HPV Vaccines & HPV Tests

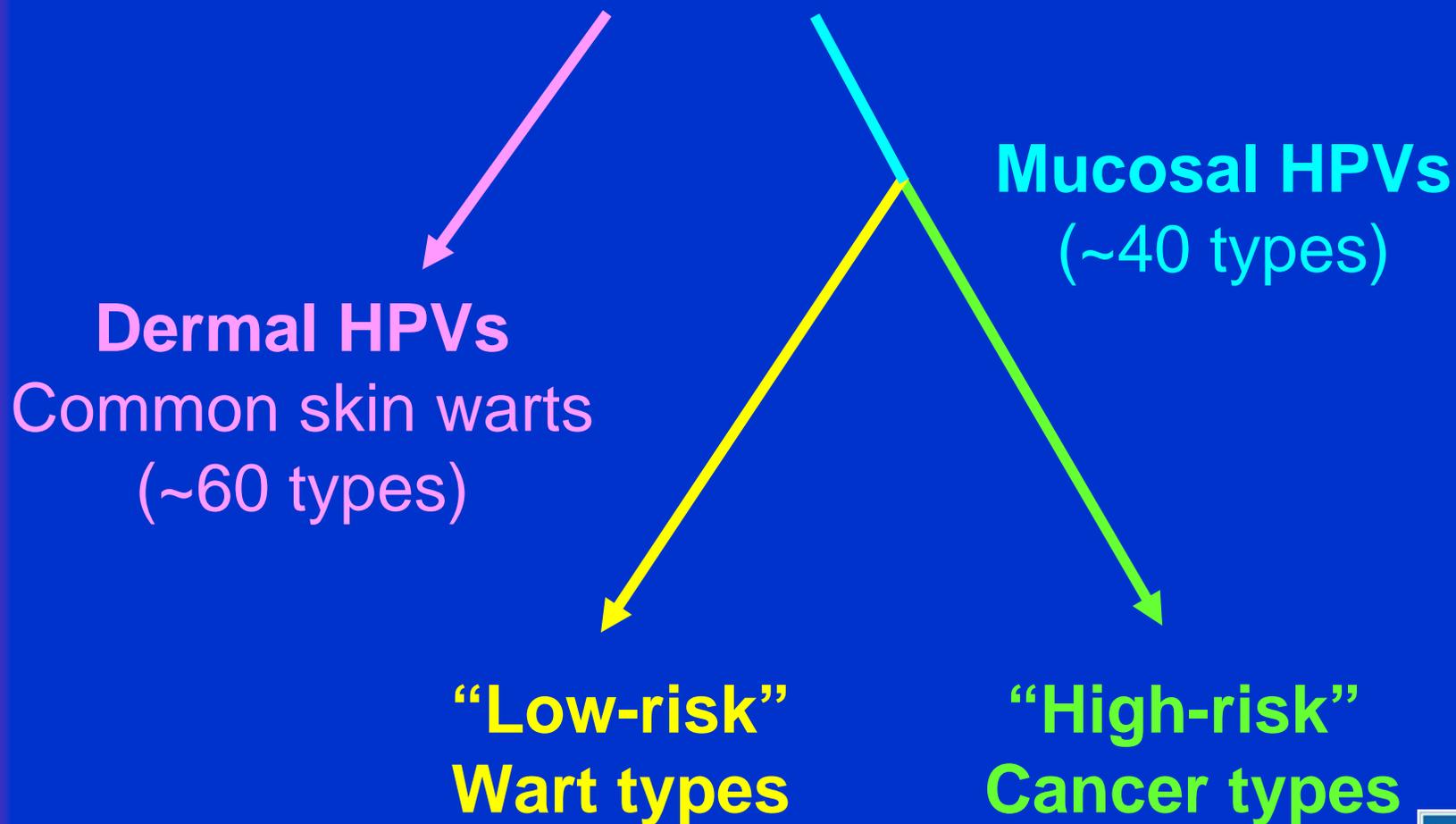
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Overview

- Types and epidemiology
- HPV and cervical disease
- HPV tests
- The new vaccine!

The HPV Family



Low Risk Mucosal HPVs

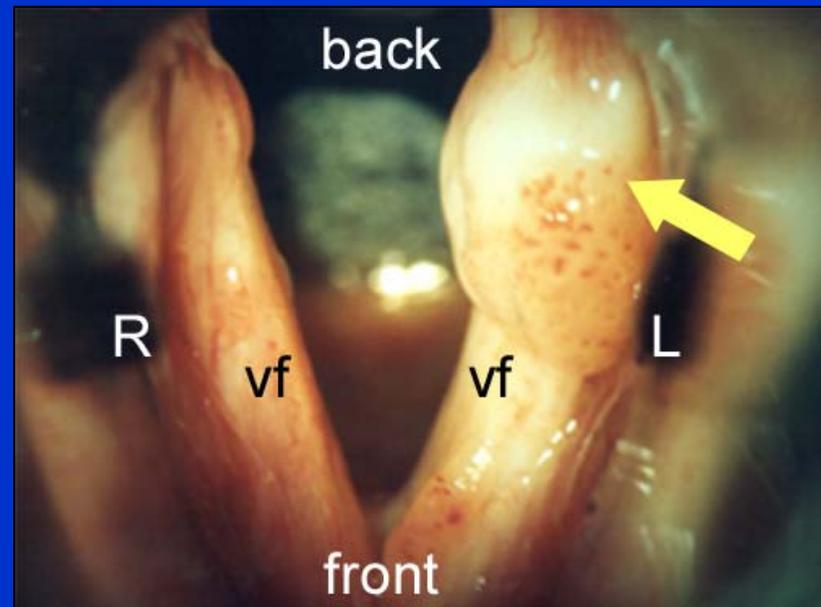
TYPES	<ul style="list-style-type: none">■ Most common: 6, 11■ Other: 40, 42, 43, 44, 54, 61, 70, 72, 81, 89
DISEASES	<ul style="list-style-type: none">■ Genital and oral warts■ Respiratory papillomatosis■ Low grade cervical Pap abnormalities

Anogenital Warts



Source: DOIA Website, 2000

Oral and Laryngeal HPV Lesions



Source: infocompu.com , Voiceproblem.org

High Risk Mucosal HPVs

TYPES

- Most common: 16, 18
- Other high risk: 31, 33, 35, 39, 45, 51, 52, 56, 58, 59,
- Likely HR: 26, 53, 66, 68, 73, 82

DISEASES

- Low and high grade cervical Pap abnormalities
- Cervical cancer
- Vulvar, vaginal, penile, and anal cancer
- Head and neck cancers

Cervical Intraepithelial Neoplasia



Source: Mosby STD Atlas, 1997, Geneva Foundation

Squamous Carcinoma



Source: Mosby STD Atlas, 1997; DOIA Website, 2000

Bowenoid Papulosis



M Mosby *STD Atlas, 1997*

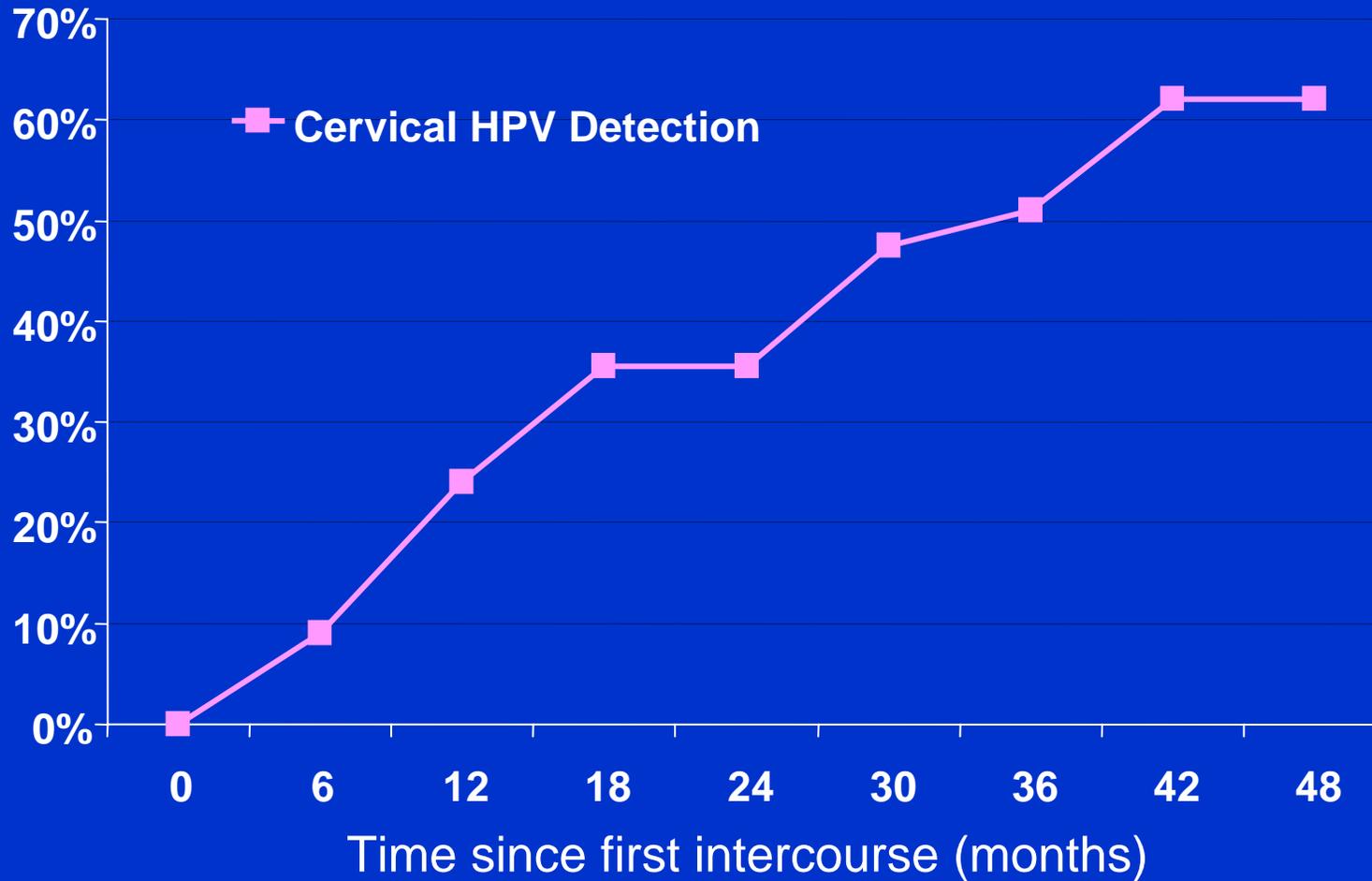
Genital HPV Infection in the U.S.

- 20 million people currently infected
- 6.2 million new infections annually
- Up to 80% of sexually active people acquire HPV at some point in their lives

W. Cates, STD 1999; Weinstock, Persp Sexual Repro Health 2004

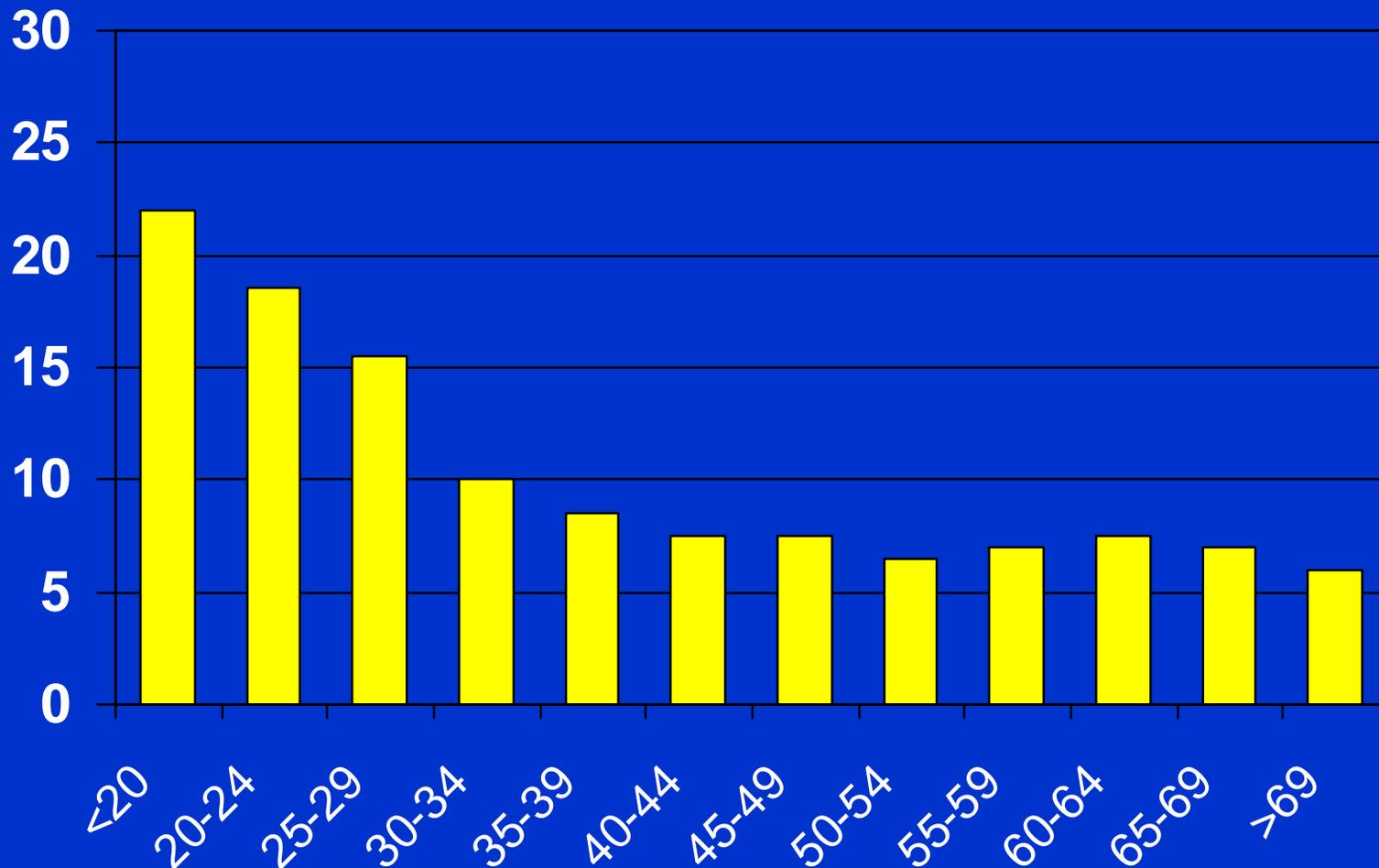


Incidence of Cervical HPV Detection in Women from the Time of Sexual Debut



Collins et al. Br J Obstet Gynecol 2002;109:96

Age-Specific HPV Prevalence among Women with Normal Cytology

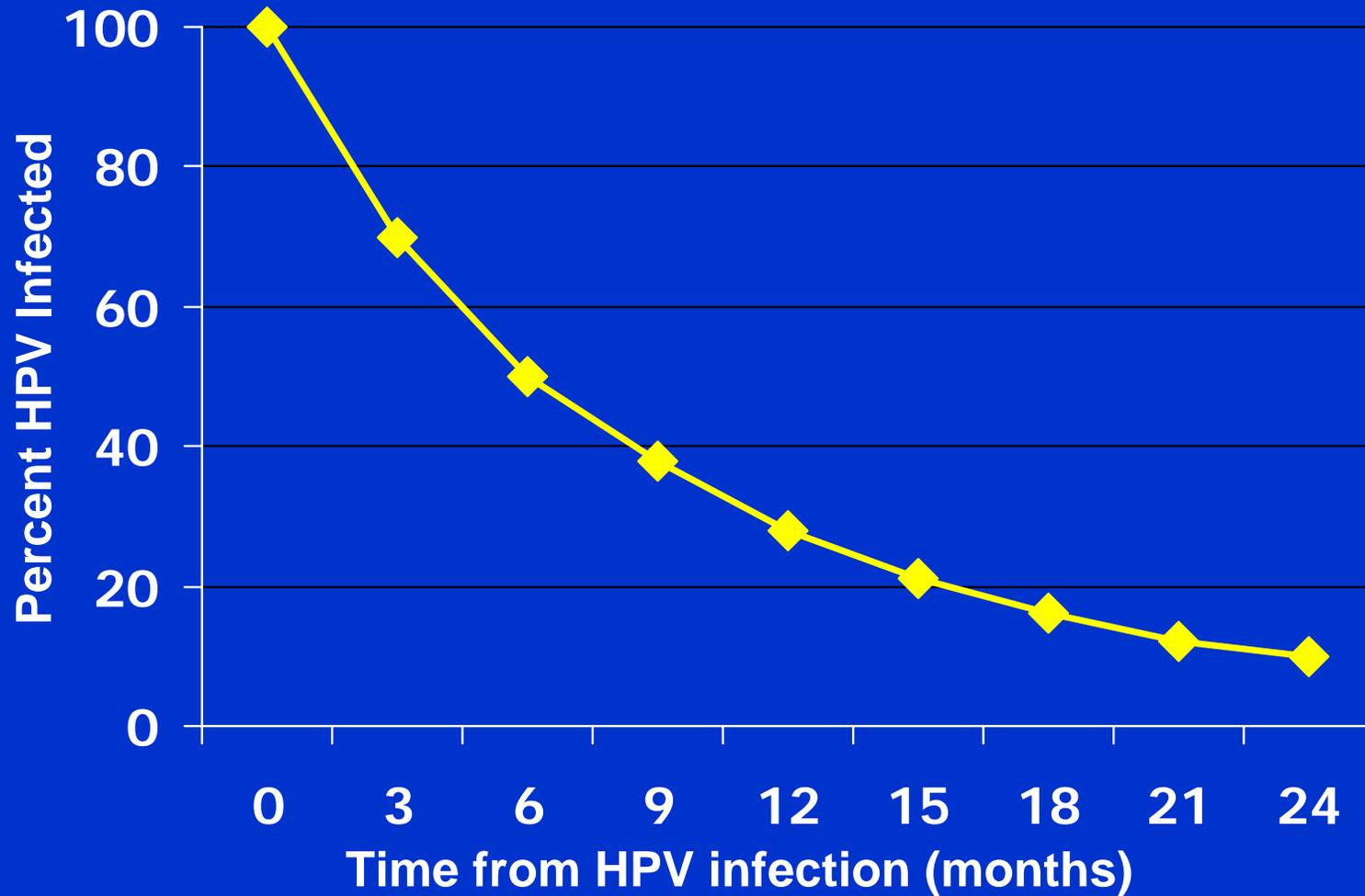


Adapted from: Wright et al. 2006 Vaccine 24S3: 254



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Clearance of HPV Infections Over 2 Years



Adapted from Brown et al. JID 2005;191;182

Risk Factors for Incident HPV Infection: New Findings Related to Condoms

Risk Factors	Adj. HR (95% CI)
Frequency of condom use	
< 5%	1.0
5 – 49%	1.0 (0.5-1.8)
50 – 99%	0.5 (0.3-0.9)
100%	0.3 (0.1-0.6)
No. of new sex partner	
0	1.0
1	4.8 (2.4-9.7)
More than 1	6.9 (2.9-16.0)
No. previous partners of sex partners	
1+ or unknown	1.0
None	0.0 (0-0.2)

Winer, NEJM 2006 354:2645-54





HPV and Cervical Disease

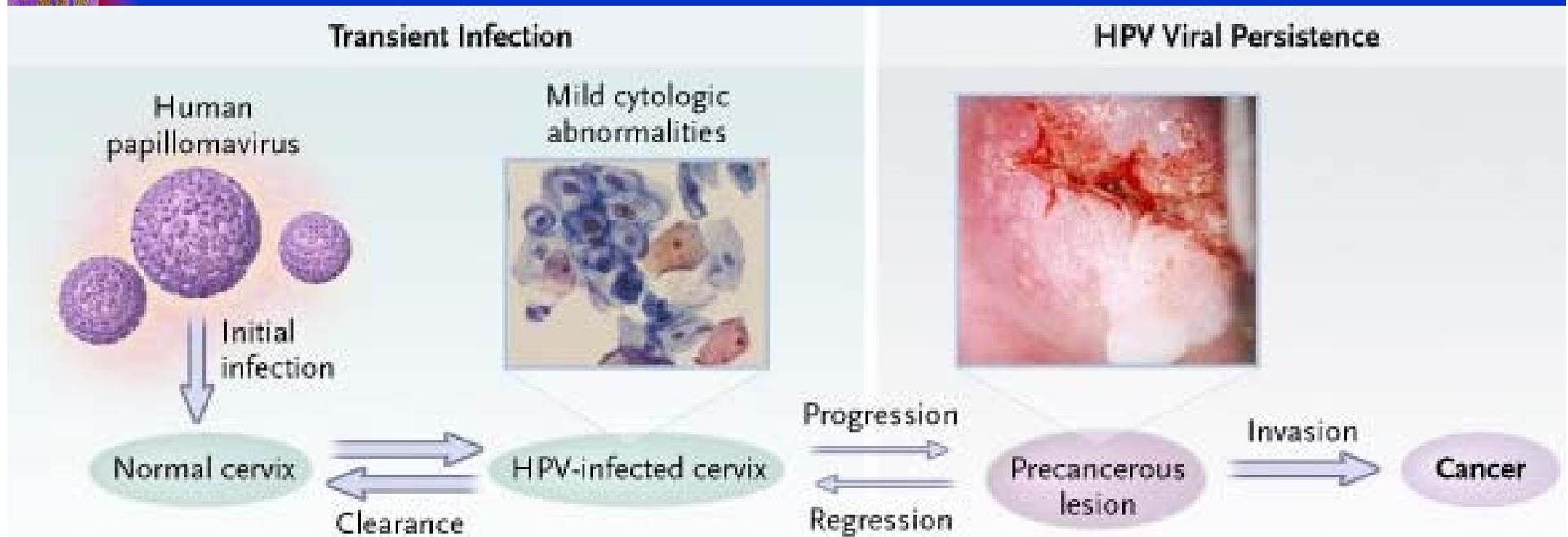
Cervical Cancer in the U.S.

- Projected 11,150 new cases and 3,670 deaths in 2007
- Significant racial and ethnic disparities
- Preventable with screening and early treatment
- Nearly 100% caused by HPV
- 70% caused by HPV types 16 and 18

Source: ACS www.cancer.org

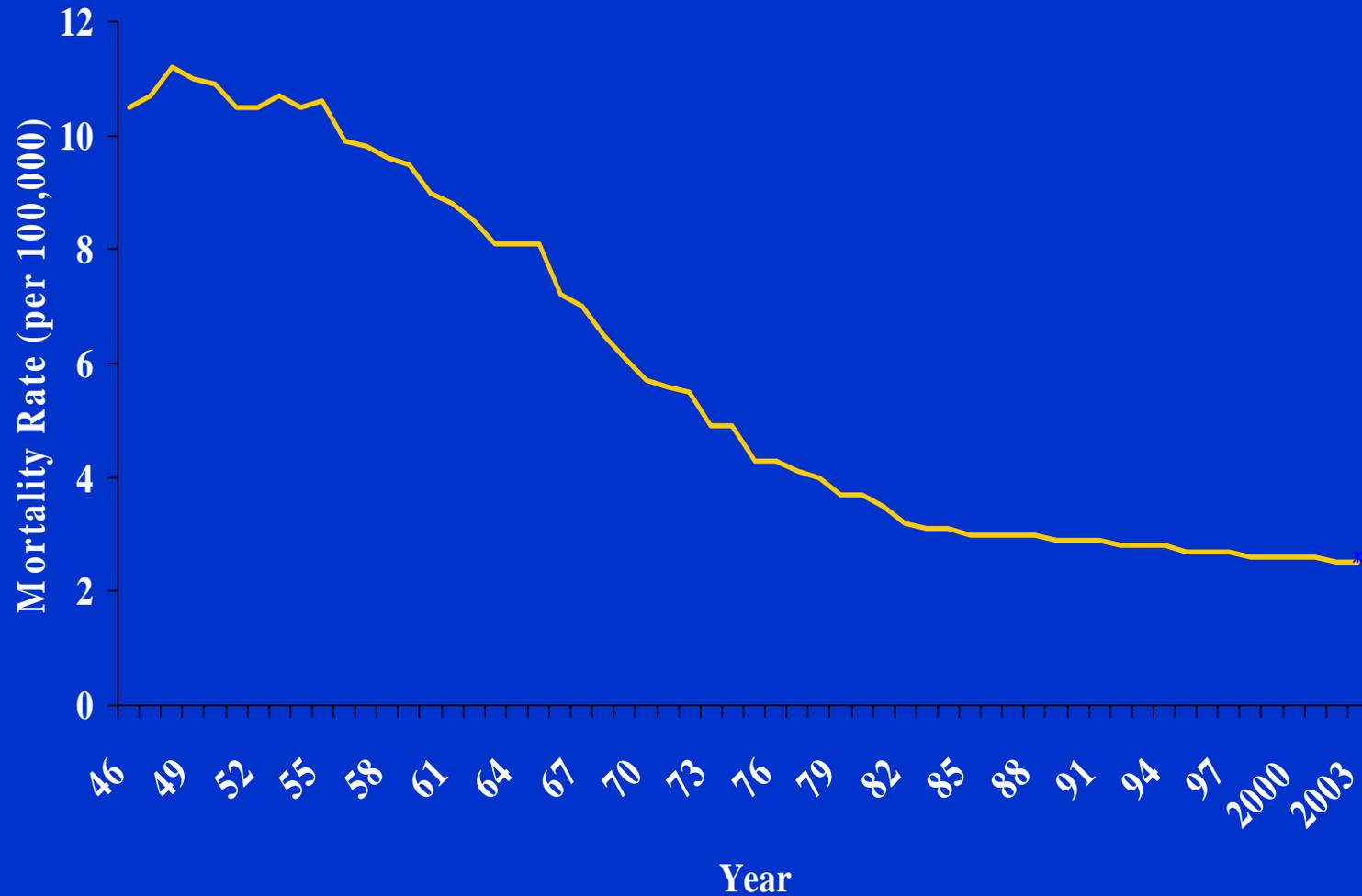


Stages of Cancer Progression



Wright & Schiffman, NEJM 2003

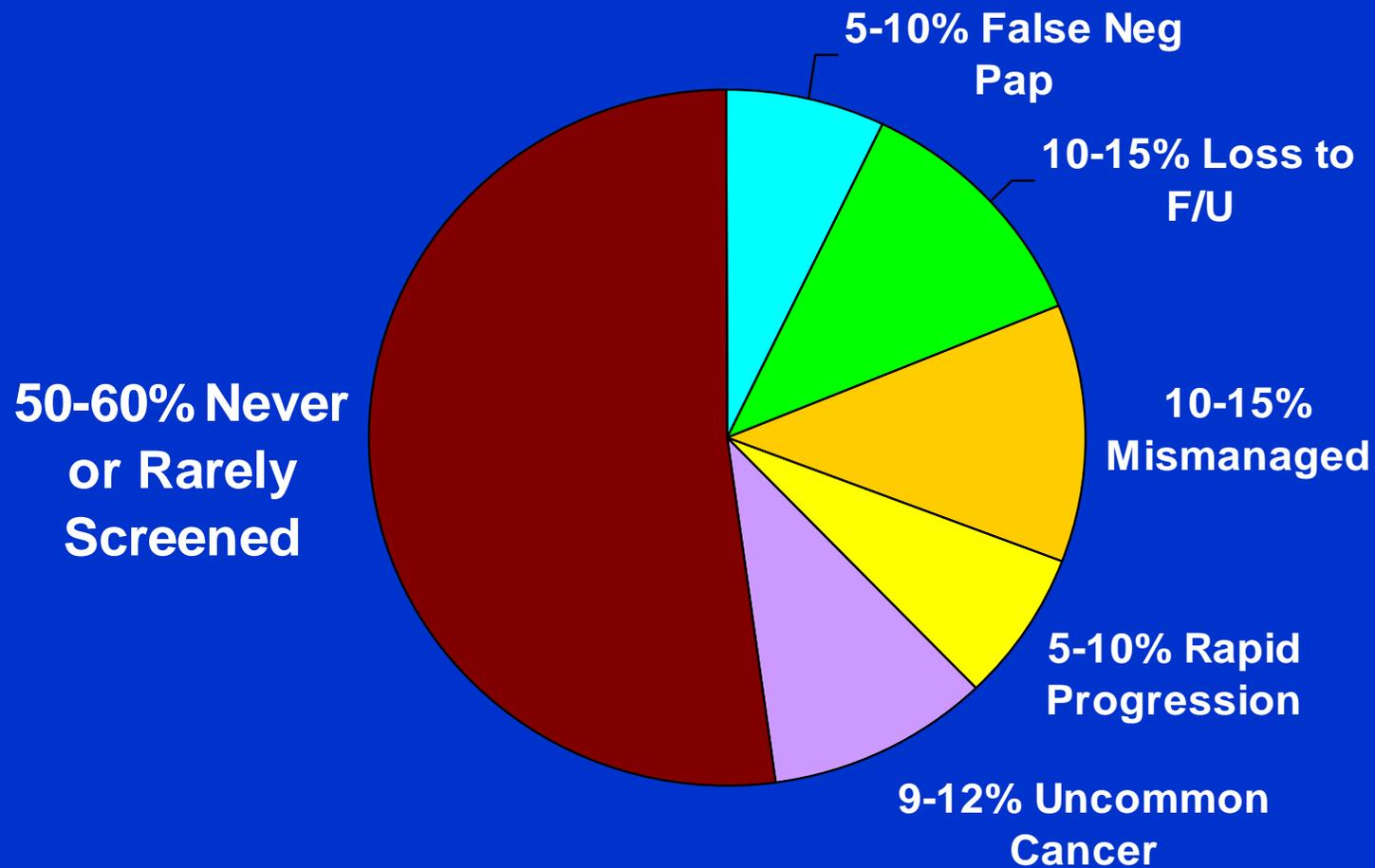
Cervical Cancer Mortality Rates, U.S., 1946-2003



Source: NCI SEER data: www.seer.cancer.gov



Factors Contributing to Cervical Cancer Diagnosis



Pap Screening Guidelines

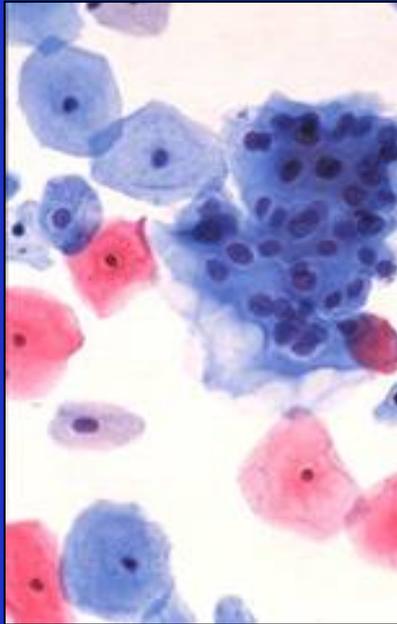
- Start: 3 years after onset of vaginal intercourse, no later than age 21
- Annually until age 30 (every 2 years if using liquid cytology)
- At age 30, women with 3 consecutive satisfactory normal Paps can be screened every 2-3 years
- Stop: Age 70 or older with 3 or more consecutive satisfactory normal Paps and no abnormal Pap within the past 10 years

* Some exceptions apply: DES, HIV

ACS, 2002



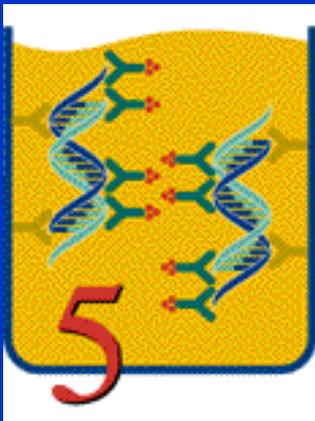
Liquid Based Cytology



- Virtually all of sample collected
- Even distribution of cells
- Easier for cytologists to read
- ? Increased sensitivity for SIL
- Specimen available for HPV and other STD tests
- Decreased specificity
- Increased cost

HPV DNA Test

RNA probe cocktails to the most common cancer-associated HPV types:



16, 18,
31, 33, 35, 39, 45,
51, 52, 56, 58, 59, & 68

Digene Hybrid Capture II

Clinical Indications for HPV DNA Testing

FDA-cleared for:

- Triage of ASCUS
- Adjunct screening in women age 30 and over

Supported by research:

- 12-month f/u of LSIL in adolescents
- Follow-up management of:
 - ◆ No CIN on colpo
 - ◆ Biopsy-proven CIN I
 - ◆ Post treatment CIN II & III

NO ROLE for HPV DNA Testing

- ✘ Screening in women under 30
- ✘ Diagnosis of genital warts
- ✘ Testing in males
- ✘ Triage of ASC-H, LSIL or higher grade lesions
- ✘ Evaluation of sexually active female prior to vaccination
- ✘ Patients diagnosed with non-HPV STD
- ✘ Partners of patients with warts or non-HPV STD

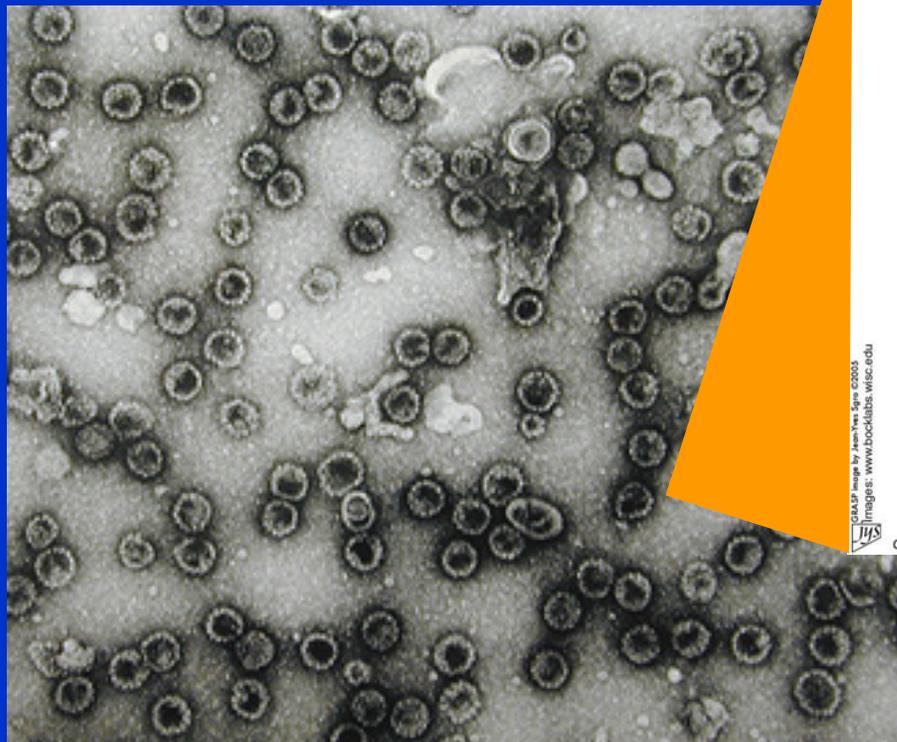




HPV Vaccine

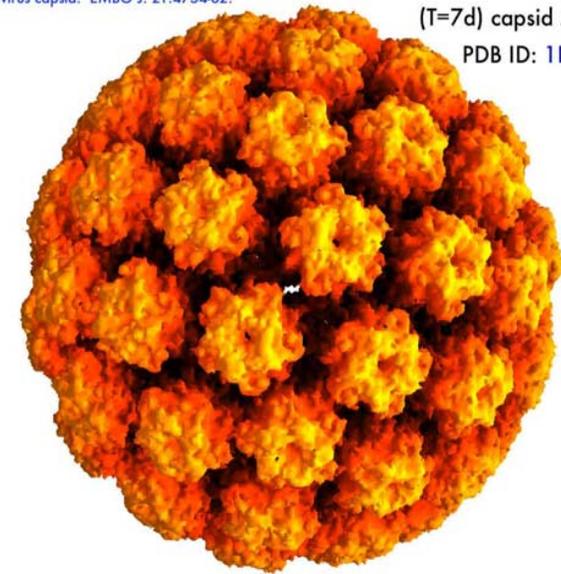
HPV Virus-Like Particles (VLPs)

L1 major capsid protein synthesized in yeast or insect cells assembles into structures resembling whole virus:



Modis Y, Trus BL, Harrison SC (2002). Atomic model of the papillomavirus capsid. EMBO J. 21:4754-62.

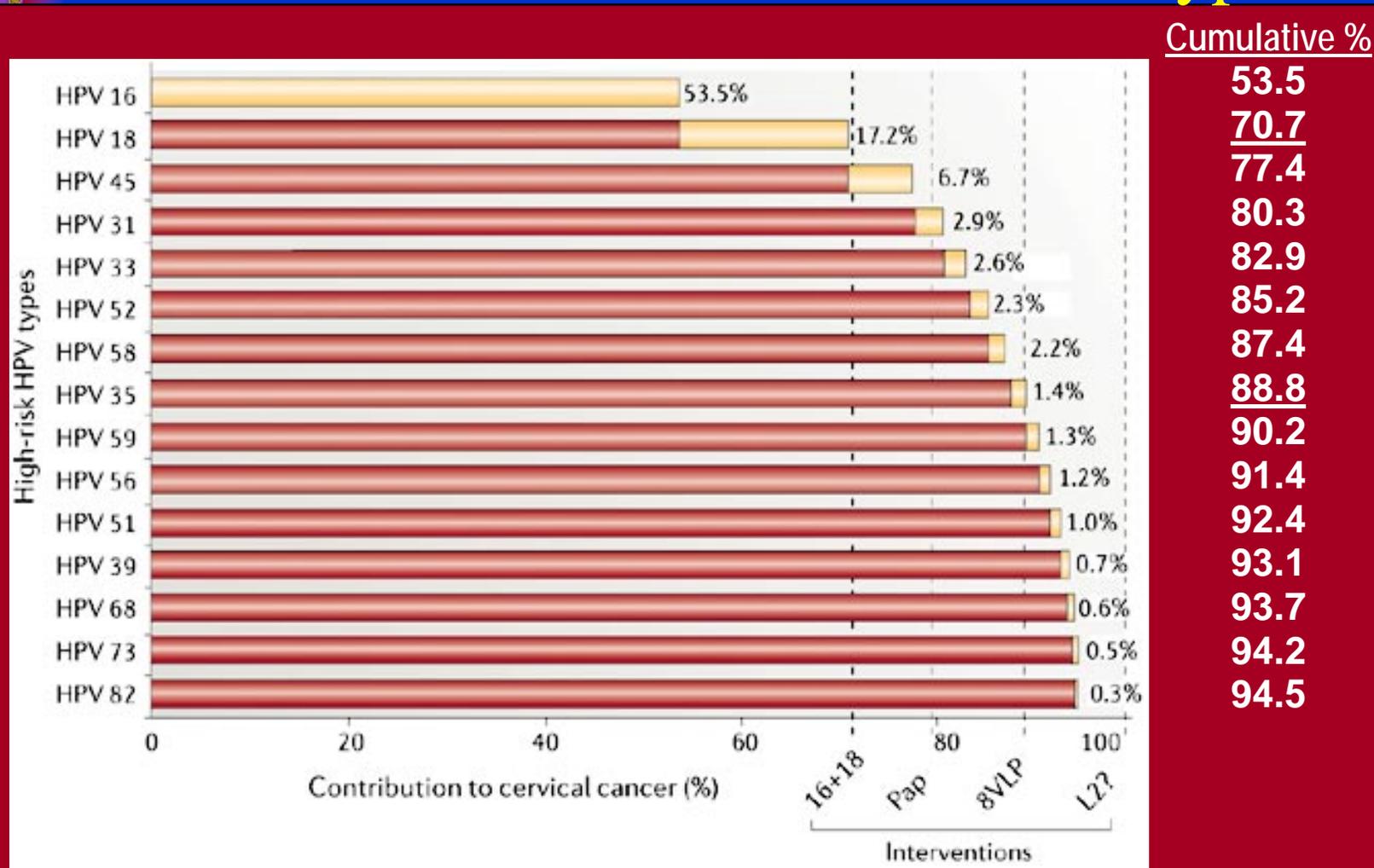
Human Papillomavirus 16 L1
(T=7d) capsid Model
PDB ID: 1LOT



CBASP image by Jean-Yves Snyé ©2003
Images: www.dockleibs.wisc.edu

Coordinates from: PDB: www.rcsb.org/pdb/ VIPER: mmtsb.scripps.edu/viper/

Percent of Worldwide Cervical Cancer Cases Attributed to Different HPV Types



Roden & Wu, *Nature Reviews Cancer* 6, 753–763 (Oct 2006)

Current HPV Vaccines

	Quadrivalent	Bivalent
Manufacturer	Merck	GSK
Product	Gardasil ®	Cervarix ®
VLP types	6, 11, 16, 18	16, 18
Antigen source	Yeast	Baculovirus
Adjuvant	Alum	ASO4
Timing	0, 2, 6 months	0, 1, 6 months
Target groups	Females 9-26 No data in males	Females 10-45
FDA clearance	June 2006	Expected 2008

NEJM 2002;347:1645; *Lancet* 2004;364:1757;
Lancet Oncol 2005;6:271



Quadrivalent Vaccine Efficacy Trial Design

- Inclusion criteria:
 - Females 16-26 years old
 - ≤ 4 lifetime sexual partners
- Baseline testing:
 - Serologic status to HPV 6/11/16/18
 - Viral DNA test
 - Pap smear
- Follow-up: 5 years
- Endpoints (clinical outcomes):
 - Histopathology
 - HPV DNA type in biopsy
 - External genital warts

Quadrivalent Vaccine Efficacy Trial Analysis

- Efficacy studies
 - Per protocol analysis
 - Intention to treat (ITT): “general population” analysis, vaccine types
 - ITT, outcomes caused by vaccine and non-vaccine types
- Immunogenicity bridging studies

Quadrivalent HPV Vaccine Efficacy

CLINICAL ENDPOINT	Per Protocol	ITT HPV 16/18-related	ITT All HPV-related
CIN 2/3 or AIS	99%	44%	18%
VIN 2/3 or VaIN 2/3	100%	71%	49%
HPV 6/11/16/18-related genital warts	99%	68.5%	not reported

CIN = Cervical Intraepithelial Neoplasia
VIN = Vulvar Intraepithelial Neoplasia

AIS = Adenocarcinoma in situ
VaIN = Vaginal Intraepithelial Neoplasia

*Future II Study Group. Lancet June 2007
E. Jaura et al. Lancet May 2007
Merck package insert 2006*



Bivalent HPV Vaccine Efficacy

HPV 16/18-Related Infections and Cervical Lesions

Endpoint	Vaccine (n=414)	Placebo (n=385)	Efficacy	95% CI
Incident HPV 16/18 Infections	1	28	96.9%	(81.3, 99.9)
Persistent HPV 16/18 Infection (12 month)	0	9	100%	(52.2, 100)
HPV16/18 related CIN 1+	0	8	100%	(42.4%, 100%)
HPV 16/18 related CIN 2/3+	0	5	100%	(-7.7%, 100%)

CIN 1+ = CIN1, CIN2, CIN3, adenocarcinoma in situ, invasive carcinoma

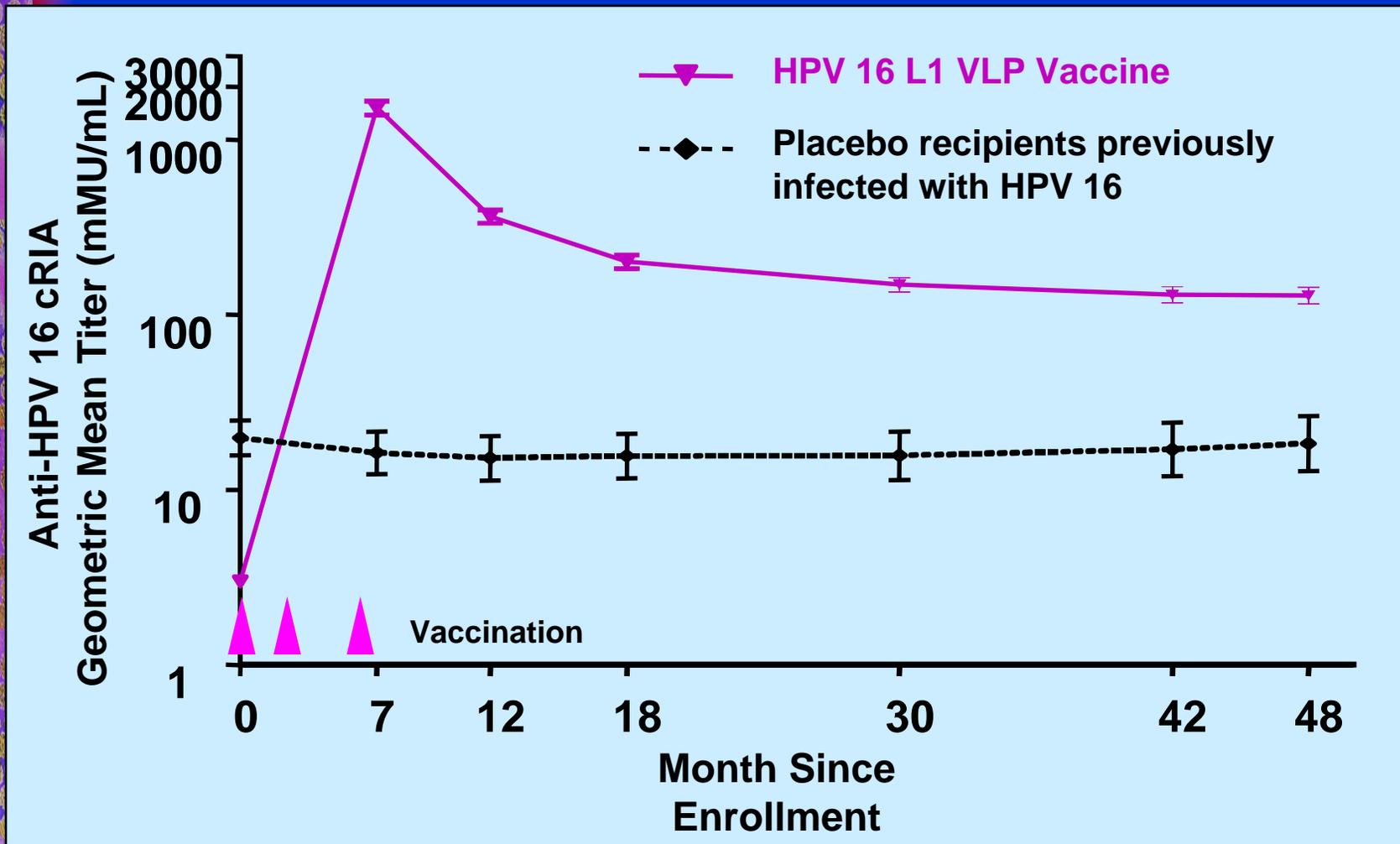
CIN 2+ = CIN2, CIN3, adenocarcinoma in situ, invasive carcinoma

Harper et al, Lancet, 2006



Antibody Titers over Time

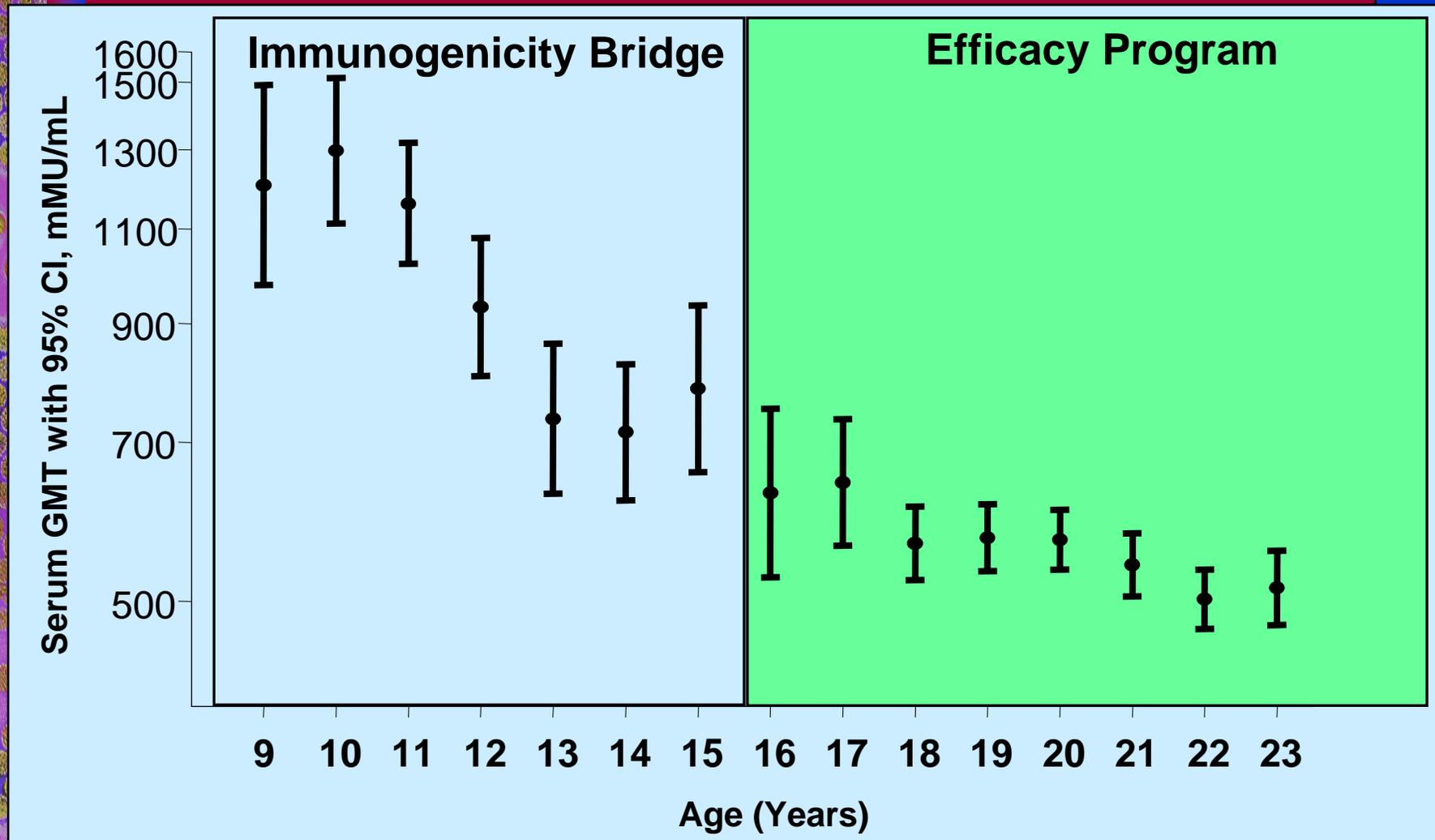
Anti-HPV 16 GMTs Through 3.5 Years



Mao et al, Ob Gyn, 2006

Antibody Titers by Age at Vaccination

Anti-HPV 6 GMTs (Quadrivalent HPV vaccine)



Merck, unpublished data, ACIP presentation by Eliav Barr, February 2006

Vaccine-Related Experiences

INJECTION SITE 1-5 D POST DOSE	Vaccine	Placebo (Alum)	Placebo (Saline)
Pain	83.9%	75.4%	48.6%
Swelling	25.4%	15.8%	7.3%
Erythema	24.6%	18.4%	12.1%
Pruritus	3.1%	2.8%	0.6%
SYSTEMIC 1-15 D POST DOSE	Vaccine	Placebo	
Fever	10.3%	8.6%	

→ Precaution re: Syncope – observe for 15 minutes

Data from Merck



All-Cause Systemic Adverse Experiences $\geq 1\%$ frequency, 1-15 days post-vaccine

Adverse Experience	Vaccine	Placebo
Pyrexia	13.0	11.2
Nausea	6.7	6.6
Nasopharyngitis	6.4	6.4
Dizziness	4.0	3.7
Diarrhea	3.6	3.5
Vomiting	2.4	1.9
Myalgia	2.0	2.0
Cough	2.0	1.5
Toothache	1.5	1.4
URI	1.5	1.5
Malaise	1.4	1.2
Arthralgia	1.2	0.9
Insomnia	1.2	0.9
Nasal congestion	1.1	0.9

Data from Merck



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HPV Vaccines: Other Key Findings

- Duration of protection at least 5 years; need for booster unknown
- Both vaccines provide cross protection
- No therapeutic value: no reduction in disease in women already infected with vaccine type(s)
- Research on efficacy in males in progress
- No role for HPV testing in vaccine program

Potential Annual Impact of Quadrivalent HPV Vaccine in the U.S.

HPV-related Disease	Annual Incidence	% HPV 16/18	Vaccine Preventable
Cervical cancer	11,000	~70%	7,700
Vulvar, vaginal, penile, anal cancer	5,700	~50%	2,850
Head & neck cancer	39,000	~10%	3,900
CIN 1	200,000	~30%	60,000
CIN 2/3, AIS	200,000	~50%	100,000
Resp papillomatosis	1,000	~90%	900
Genital warts	375,000	~90%	337,500

Adapted from Chesson 2004, SEER data



ACIP Recommendations (1)

- Routine vaccination of females ages 11-12 (as young as age 9)
- Catch-up vaccination for females 13-26
- Can be given despite history of abnormal Pap, HPV, warts
- No change in cervical cancer screening recommendations

ACIP Recommendations (2)

- Not recommended in pregnancy
- Contraindications:
 - Allergy to yeast or other vaccine component
 - Severe illness
- VAERS: www.vaers.hhs.gov or 800-822-7967
- Merck Pregnancy registry: 800-986-8999



Online HPV Resources

- Centers for Disease Control:

www.cdc.gov/std/hpv

- American Cancer Society:

www.cancer.org

- American Society for Colposcopy and Cervical Pathology: www.asccp.org