

Overview of Cervical Cancer Vaccines

Cervical Cancer Vaccines: A Public Health Forum

Pikesville, MD

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Allan Hildesheim

Division of Cancer Epidemiology and Genetics

National Cancer Institute

BACKGROUND

HPV Genotypes

- Tissue tropism
 - Cutaneous vs. mucosal
- Cancer association
 - Oncogenic
 - Non-oncogenic
 - Unknown
- 15-18 HPV types recognized to be linked to cancer
- HPV-16/18 accounts for 70% of tumors

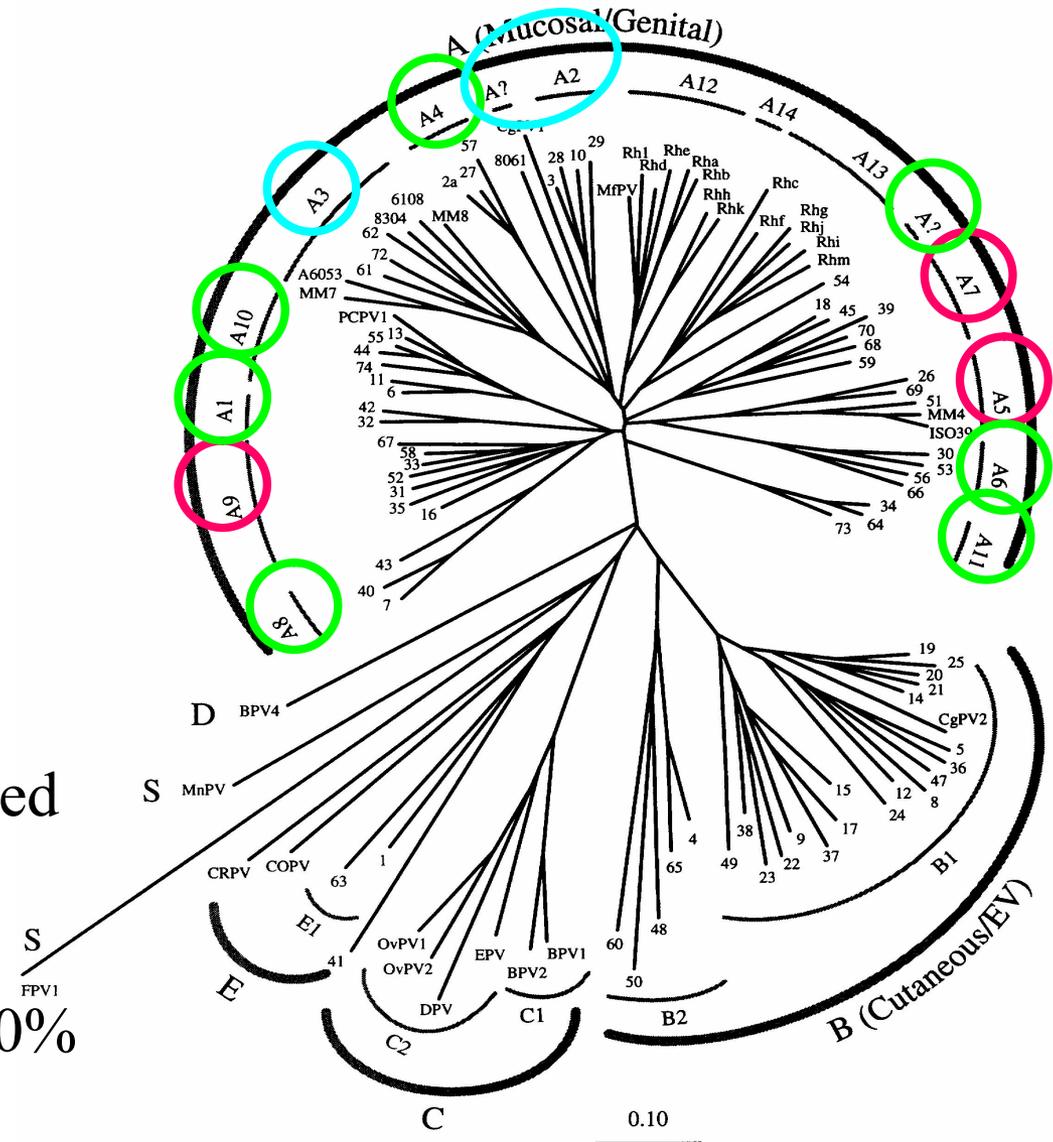
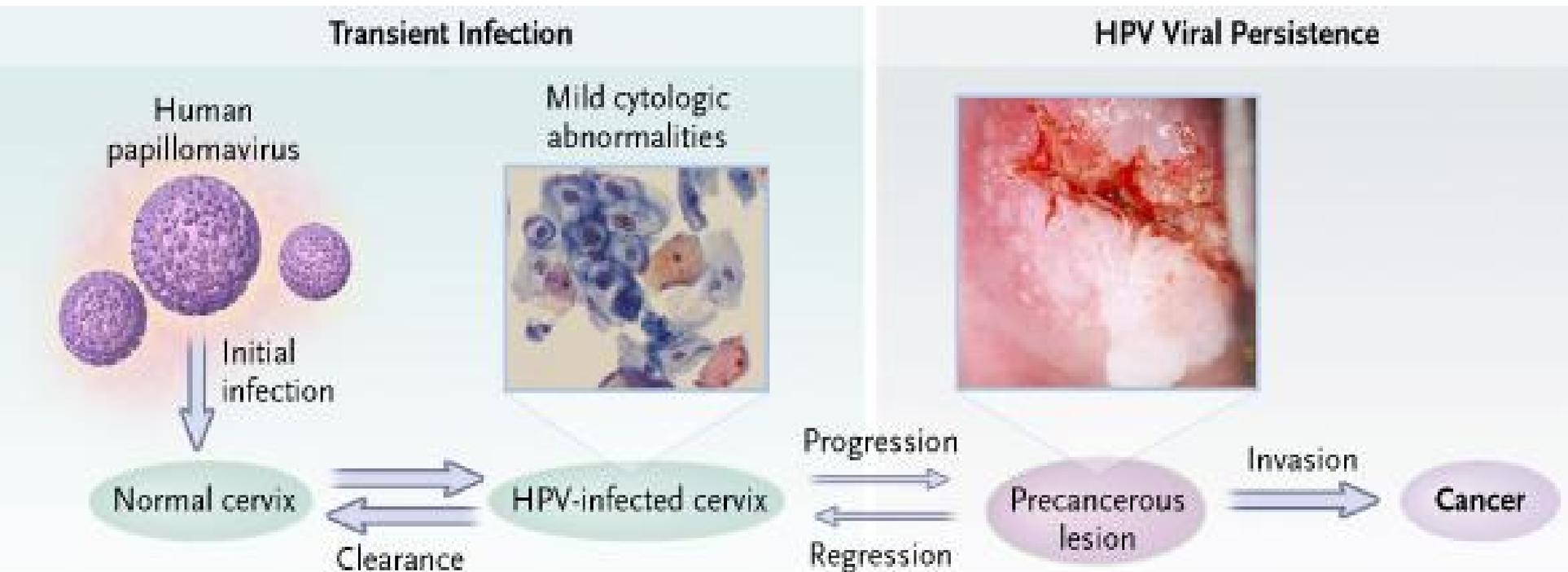
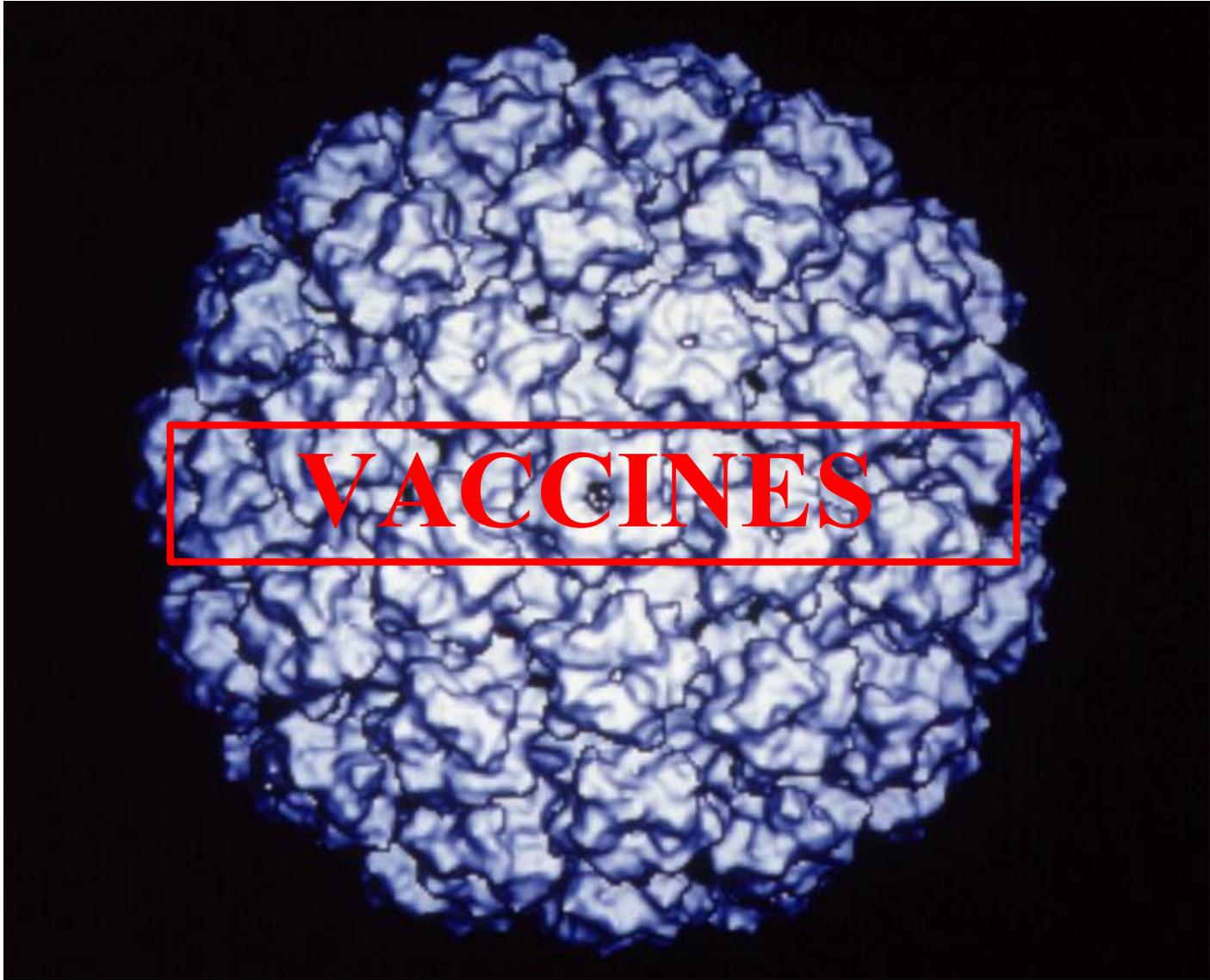


Figure 1. Neighbor joining phylogenetic tree of 106 PVs based on CPR region of L1.

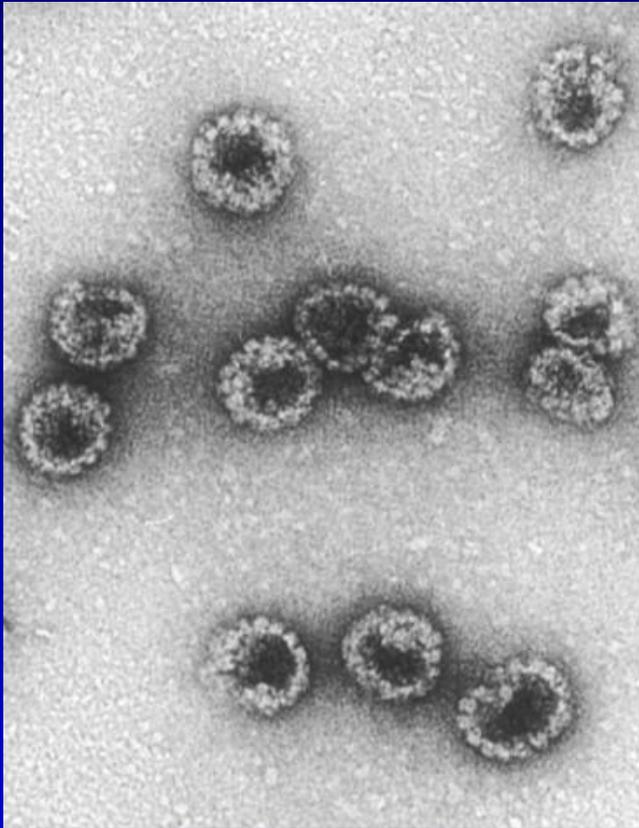
Where We Are Now: Critical Steps in Cervical Carcinogenesis





VACCINES

Current Prophylactic Vaccines are Based on Purified Papillomavirus-Like Particles (VLPs)



- Empty shells composed of the L1 major virion protein
- Generated in yeast or Baculovirus/insect cells
- Non-infectious and non-oncogenic

HPV VLP Vaccines

GlaxoSmithKline:

HPV16 } 70% of Cx Ca
HPV18 }

ASO4 Adjuvant
(Alum+MPL)
Made in insect cells

Merck:

HPV16 } 70% of Cx Ca
HPV18 }

HPV6 } 90% of Genital Warts
HPV11 }

Alum Adjuvant
Made in yeast

Proof of Principle HPV VLP Prophylactic Efficacy Trials *

Study:	Koutsky 2002	Harper 2004	Villa 2005	Mao 2006
VLP Types:	16	16,18	6,11,16,18	16
Adjuvant:	Alum	AS04	Alum	Alum
Sponsor:	Merck	GSK	Merck	Merck
Trial Sites:	US	US/CA/BR	US/EU/BR	US
Age:	16-23	15-25	16-23	16-23
No. (ATP):	1533	721	468	1505
Vacc. Schedule (Mos):	0, 2, 6	0, 1, 6	0, 2, 6	0, 2, 6
Follow-up (Yrs):	1.5	1.5	2.5	3.5
No. Persist. Infections: Cont/Vac % Efficacy	42/0 100%	7/0 100%	36/4** 90%	111/7*** 94%
No. CIN1+: Cont/Vac % Efficacy	9/0 100%	6/0 100%	3/0 100%	24/0 100%

*According to protocol (ATP) analysis for the types included in the vaccines

** 10 of 36 controls and 3 of 4 vaccinees were DNA positive only at the last visit

***19 of 111 controls and 7 of 7 vaccinees were DNA positive only at the last visit

US=United States, EU=European Union, BR=Brazil, CA=Canada, No.=number,

Persist=Persistent, Con/Vac=Controls/VLP vaccinees, CIN=Cervical Intraepithelial Neoplasia

Large Scale Efficacy Trials

<u>Sponsor</u>	<u>VLP Types</u>	<u>Trial Sites</u>	<u>Size</u>
Merck:	HPV 16/18/6/11	Multi-centric	>15,000
GSK:	HPV 16/18	Multi-centric	>15,000
NCI:	HPV 16/18	Costa Rica	7,500

Merck Phase III Trial Interim Results

- **Design**: double blind; placebo controlled; 12,000 18-25 yr old women followed 1.5 yrs
- **Tolerability**: Slightly more injection site pain than Alum; 0.2% drop out rate in each arm
- **Immunogenicity**: 99.5% Seroconversion; Titers 10-50 fold higher than natural infection

Merck Phase III Trial Interim Results:

Type-Specific Efficacy (FDA Filing – Dec 2005)

	Vaccine (N=6082) <u>Cases</u>	Placebo (N=6075) <u>Cases</u>	Efficacy (%)	95% <u>C.I.</u>
ATP CIN 2/3				
HPV 16/18	0	21	100	76-100
HPV 16	0	16	100	75-100
HPV 18	0	8	100	42-100
MITT CIN 2/3				
HPV 16/18	1	36	97	83-100
HPV 16	1	28	96	78-100
HPV 18	0	11	100	60-100

ATP = Outcomes after mo. 7, all three doses. HPV16/18 DNA and seronegative at 7 mo.
 MITT = Outcomes after mo 1., 1st dose. HPV16/18 DNA and seronegative at day 1.

U.S. FDA Approved Merck Vaccine on June 8, 2006

- **FDA Label: For girls and women 9-26.**
- **Recommendations for use are made by CDCP's ACIP (Advisory Committee on Immunization Practices)**
 - **They met in late June and recommended:**
 - **Vaccination of girls 11-12**
 - **As early as 9 years, if indicated**
 - **Catch-up vaccination for women 13-26**
 - **Most controversial aspect of recommendation**

GSK HPV16/18 vaccine

Sustained efficacy up to 4.5 years of a bivalent L1 virus-like particle vaccine against human papillomavirus types 16 and 18: follow-up from a randomised control trial

*Diane M Harper, Eduardo L Franco, Cosette M Wheeler, Anna-Barbara Moscicki, Barbara Romanowski, Cecilia M Roteli-Martins, David Jenkins, Anne Schuind, Sue Ann Costa Clemens, Gary Dubin, on behalf of the HPV Vaccine Study group**

Summary

Background Effective vaccination against HPV 16 and HPV 18 to prevent cervical cancer will require a high level of sustained protection against infection and precancerous lesions. Our aim was to assess the long-term efficacy, immunogenicity, and safety of a bivalent HPV-16/18 L1 virus-like particle AS04 vaccine against incident and persistent infection with HPV 16 and HPV 18 and their associated cytological and histological outcomes.

Methods We did a follow-up study of our multicentre, double-blind, randomised, placebo-controlled trial reported in 2004. We included women who originally received all three doses of bivalent HPV-16/18 virus-like particle AS04 vaccine (0.5 mL; n=393) or placebo (n=383). We assessed HPV DNA, using cervical samples, and did yearly cervical cytology assessments. We also studied the long-term immunogenicity and safety of the vaccine.

Findings More than 98% seropositivity was maintained for HPV-16/18 antibodies during the extended follow-up phase.

We noted significant vaccine efficacy against HPV-16 and HPV-18 endpoints: incident infection, 96.9% (95% CI 81.3–99.9); persistent infection: 6 month definition, 94.3 (63.2–99.9); 12 month definition, 100% (33.6–100). In a combined analysis of the initial efficacy and extended follow-up studies, vaccine efficacy of 100% (42.4–100) against cervical intraepithelial neoplasia (CIN) lesions associated with vaccine types. We noted broad protection against cytohistological outcomes beyond that anticipated for HPV 16/18 and protection against incident infection with HPV 45 and HPV 31. The vaccine has a good long-term safety profile.

Interpretation Up to 4.5 years, the HPV-16/18 L1 virus-like particle AS04 vaccine is highly immunogenic and safe, and induces a high degree of protection against HPV-16/18 infection and associated cervical lesions. There is also evidence of cross protection.

GSK HPV16/18 vaccine

4-year data on protection against incident HPV-16/18 infections

	Vaccine			Placebo			Vaccine efficacy, % (95% CI)	p
	Total women	Women reporting ≥1 HPV-16/18 event	Event rate (95% CI)*	Total women	Women reporting ≥1 HPV-16/18 event	Event rate (95% CI)*		
According-to-protocol analyses of extended follow-up phase (vaccine: n=350, placebo: n=344)								
HPV 16	311	1	0.2 (0.0-0.9)	280	21	4.0 (2.5-6.2)	95.8 (73.6-99.9)	<0.0001
HPV 18	310	0	0.0 (0.0-0.6)	291	11	2.0 (1.0-3.5)	100.0 (62.1-100)	0.0003
HPV 16/18	310	1	0.2 (0.0-0.9)	277	28	5.6 (3.7-8.1)	96.9 (81.3-99.9)	<0.0001
Intention-to-treat analyses of extended follow-up phase (vaccine: n=393, placebo: n=383)								
HPV 16	353	2	0.3 (0.0-1.1)	322	25	4.2 (2.7-6.2)	92.7 (70.9-99.2)	<0.0001
HPV 18	356	0	0.0 (0.0-0.5)	332	12	1.9 (1.0-3.3)	100.0 (65.6-100.0)	0.0001
HPV 16/18	352	2	0.3 (0.0-1.1)	313	31	5.5 (3.7-7.8)	94.4 (77.9-99.3)	<0.0001
According-to-protocol analyses of combined initial and follow-up phase (vaccine: n=473, placebo: n=470)								
HPV 16	414	1	0.1 (0.0-0.6)	385	40	4.5 (3.2-6.2)	97.7 (86.6-99.9)	<0.0001
HPV 18	414	2	0.2 (0.0-0.7)	385	17	1.9 (1.1-3.0)	88.9 (53.3-98.8)	0.0002
HPV 16/18	414	3	0.3 (0.1-0.9)	385	51	5.9 (4.4-7.7)	94.7 (83.5-98.9)	<0.0001
Intention-to-treat analyses of combined initial and follow-up phase (vaccine: n=560, placebo: n=553)								
HPV 16	481	7	0.5 (0.2-1.1)	470	55	4.4 (3.3-5.8)	88.0 (73.6-95.4)	<0.0001
HPV 18	481	3	0.2 (0.0-0.6)	470	29	2.3 (1.5-3.2)	90.0 (67.8-98.1)	<0.0001
HPV 16/18	481	9	0.7 (0.3-1.3)	470	73	6.0 (4.7-7.5)	88.5 (77.0-95.0)	<0.0001

*Per 100 person-years: number of cases divided by accrued person-time.

Table 4: Vaccine efficacy for incident HPV-16/18 infections, in cervical samples

GSK HPV16/18 vaccine

Preliminary evidence of cross-protection against some phylogenetically related HPV types

	Vaccine			Placebo			Vaccine efficacy (%) (95% CI)
	Total women	Women reporting ≥1 event of HPV 45, HPV 31, HPV 33, HPV 52, or HPV 58 and who did not report the same event in initial study	Event rate (95% CI)*	Total women	Women reporting ≥1 event of HPV 45, HPV 31, HPV 33, HPV 52, or HPV 58 and who did not report the same event in initial study	Event rate (95% CI)*	
HPV 45	528	1	0.1 (0.0 to 0.4)	518	17	1.2 (0.7 to 1.9)	94.2 (63.3 to 99.9)
HPV 31	528	14	0.9 (0.5 to 1.6)	516	30	2.1 (1.4 to 3.0)	54.5 (11.5 to 77.7)
HPV 33	529	12	0.8 (0.4 to 1.4)	519	13	0.9 (0.5 to 1.5)	8.6 (-117.3 to 61.9)
HPV 52	524	40	2.8 (2.0 to 3.8)	515	48	3.5 (2.6 to 4.6)	18.6 (-26.5 to 47.8)
HPV 58	529	14	0.9 (0.5 to 1.6)	517	16	1.1 (0.6 to 1.8)	14.0 (-87.9 to 61.1)

*Per 100 person-years: number of cases divided by accrued person-time.

Table 7: Vaccine efficacy against incident infection with HPV 45, HPV 31, HPV 52, HPV 33, and HPV 58 in cervical samples from intention-to-treat analyses

From Harper et al., Lancet, 2006

GSK Filled for Licensure in Europe in March 2006

- **Licensure expected as early as March 2007**
- **GSK has announced its plans to file for licensure in the US by the end of this year**
 - **If this occurs, licensure in the US could occur by Summer 2007**
- **Filing in other countries**



NCI/Costa Rica Community-Based HPV 16/18 Vaccine

Efficacy/Effectiveness Trial

Summary of Study Design

- Population: 7,466 women 18-25 in Costa Rica
- Design: 2 arm randomized trial (0,1,6 months)
 - Arm 1 – Hepatitis A Vaccine (Havrix)
 - Arm 2 – HPV 16/18 Vaccine (GSK Vaccine)
- Enrollment: June 2004 - December 2005
- Follow-up: 4 yrs @ yearly intervals (more frequently if clinically indicated)
- Cross-over: @ end or sooner if recommended by DSMB
- Outcomes: HPV 16/18-associated persistent infections, and cervical precursors (CIN2+)

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- What ages should be targeted for vaccination?
- Should men be vaccinated?
- How to combine vaccination with existent screening programs?

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- What ages should be targeted for vaccination?
 - **Known: Vaccine prophylactic**
 - **Known: HPV exposure and initial infection occurs in the first few months/years after initiation of sexual activity**

HPV PREVALENCE BY AGE

Guanacaste, Costa Rica

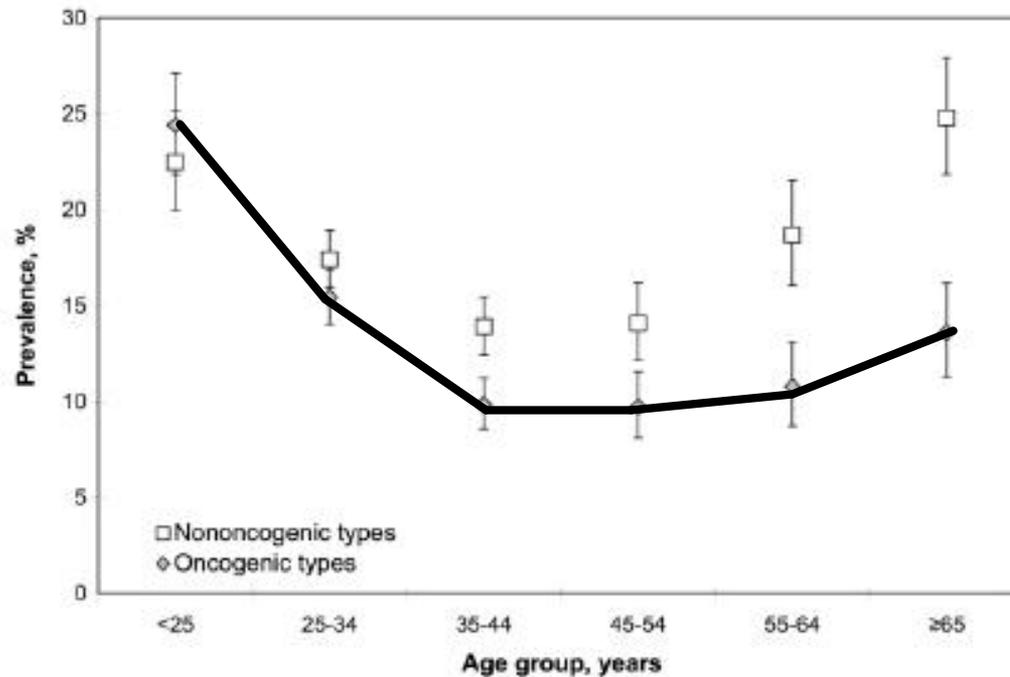


Figure 2. Prevalences of oncogenic human papillomavirus (HPV) types (16, 18, 26, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68, 73, and AE2 [82 subtype]) and nononcogenic HPV types (2, 6, 11, 13, 26, 32, 34, 40, 42–44, 53–55, 57, 61, 62, 64, 67–72, 74, AE10 [74 variant], 81–85, 89, and AE9), by age group. Bars indicate binomial exact 95% confidence intervals.

There are still many unanswered questions that make implementation of vaccination programs a difficult endeavor

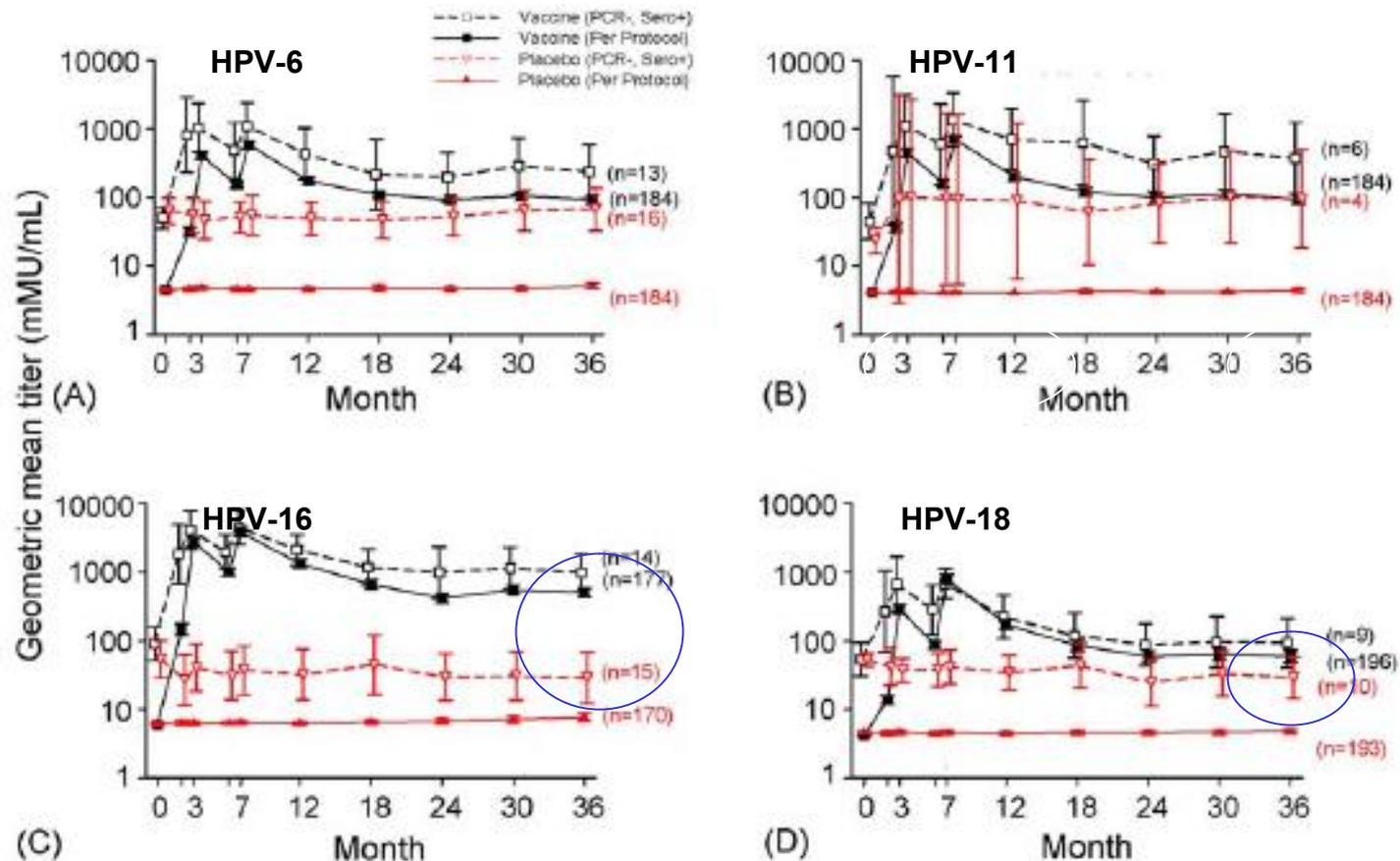
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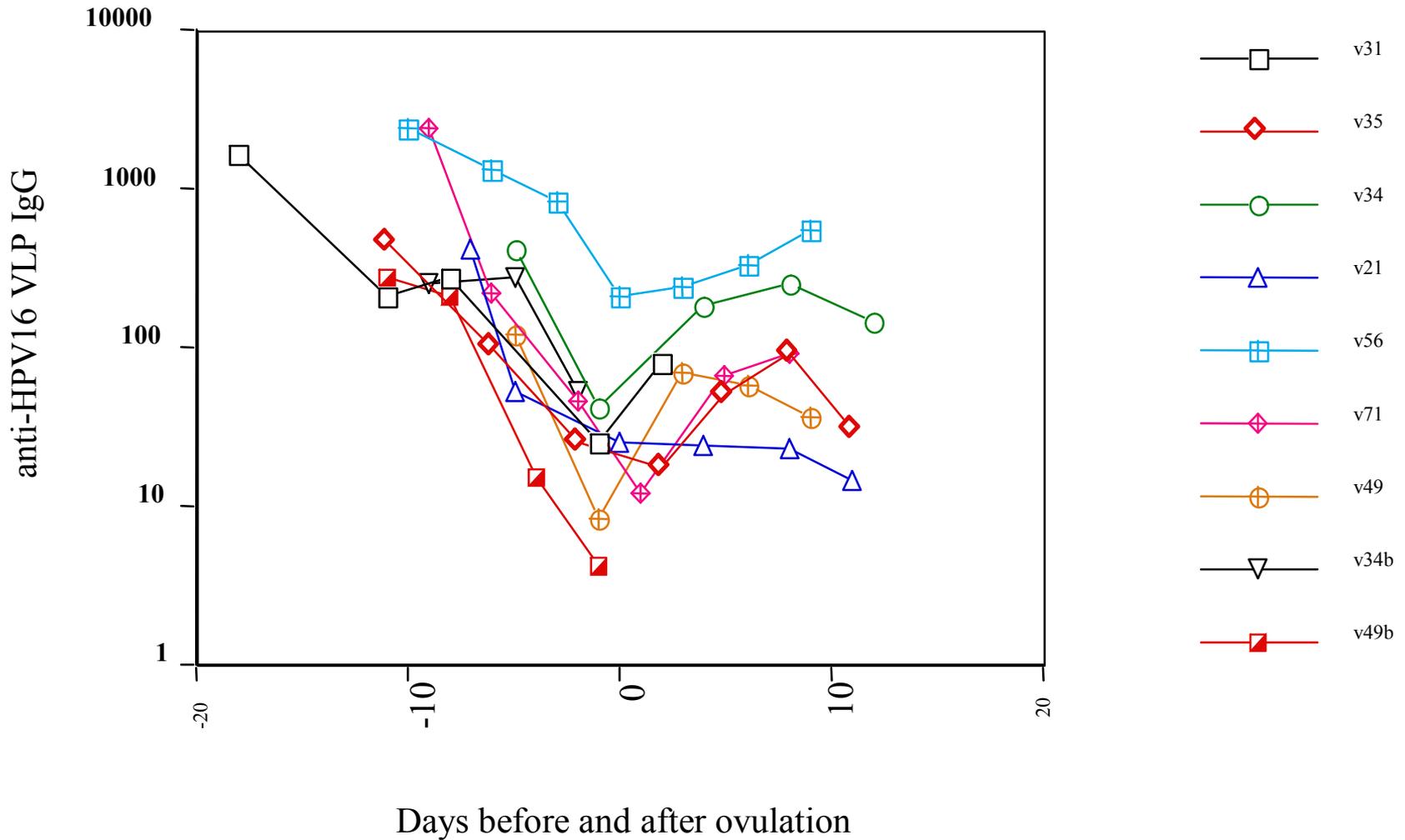
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 - Therefore, should target young girls/women prior to initiation of sexual activity
- Problem #1: Length of protection unknown - unclear if targeting young children is a viable option

Although HPV-16 antibody titers are maintained over time, it is unclear whether the same is true for other HPV types

L.L. Villa et al. / Vaccine 24 (2006) 5571–5583



Titers of anti-HPV16 VLP IgG in cervical secretions during ovulatory cycles



There are still many unanswered questions that make implementation of vaccination programs a difficult endeavor

- What ages should be targeted for vaccination?
 - Known: Vaccine prophylactic
 - Known: HPV exposure and initial infection occurs in the first few months/years after initiation of sexual activity
 - Therefore, should target young girls/women prior to initiation of sexual activity
 - Problem #1: Length of protection unknown - unclear if targeting young children is a viable option
 - Problem #2: Unclear if vaccination of women after initiation of sexual activity is warranted

Merck Phase III Trial Results:

Combined* Analysis of Efficacy Against CIN2+ MITT3 Analysis **

(18May06 FDA VRBPAC Meeting)

<u>Endpoint</u>	Vaccine (N=9075) <u>Cases</u>	Placebo (N=9075) <u>Cases</u>	Efficacy (%)	95% <u>C.I.</u>
CIN2+ containing HPV-6/11/16/18	118	186	36%	19-50
CIN2+ containing Any HPV	287	328	12%	0-25

* Combines across three trials that evaluated the HPV-6/11/16/18 vaccine.

** MITT3 includes all participants who received at least one vaccine regardless of entry HPV serostatus or PCR results, provided they had documentation of follow-up at least once after the one month visit

**There are still many unanswered questions
that make implementation of vaccination
programs a difficult endeavor**

- **Should men be vaccinated?**
 - **Known: Vaccine not approved for use in males**
 - **Known: Trials in men are underway**
 - **Known: Male genitalia is not bathed in neutralizing antibodies generated by vaccination**
 - **Problem #3: Unclear whether male vaccination will protect men and/or reduce transmission to their partners**

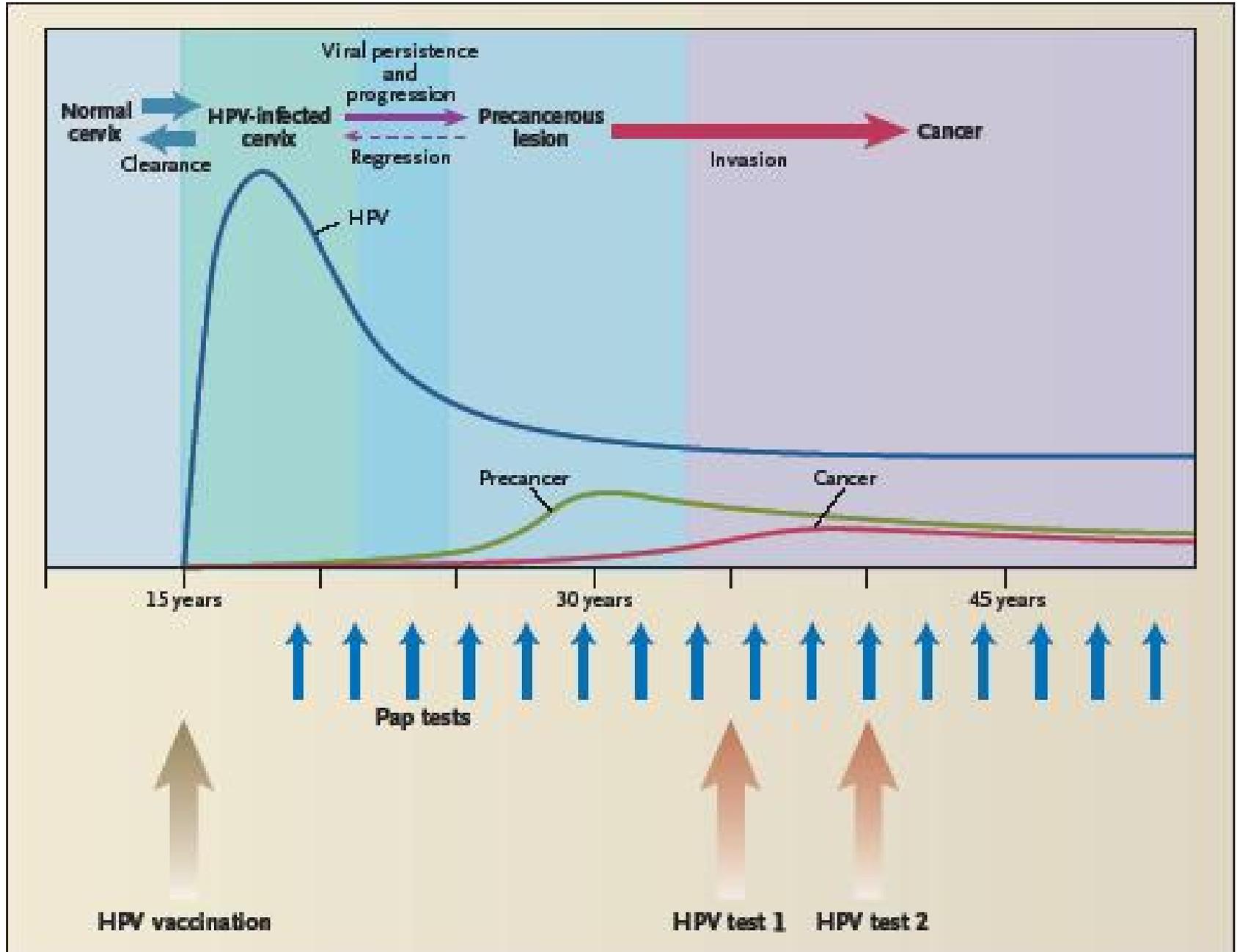
**There are still many unanswered questions
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- How to combine vaccination with existent screening programs?
 - **Known – vaccination will not eliminate need for screening since current vaccines protect against a subset of the 15-18 HPV types that can cause cancer and do not protect those who already have persistent infection or precancer lesions.**

There are still many unanswered questions that make implementation of vaccination programs a difficult endeavor

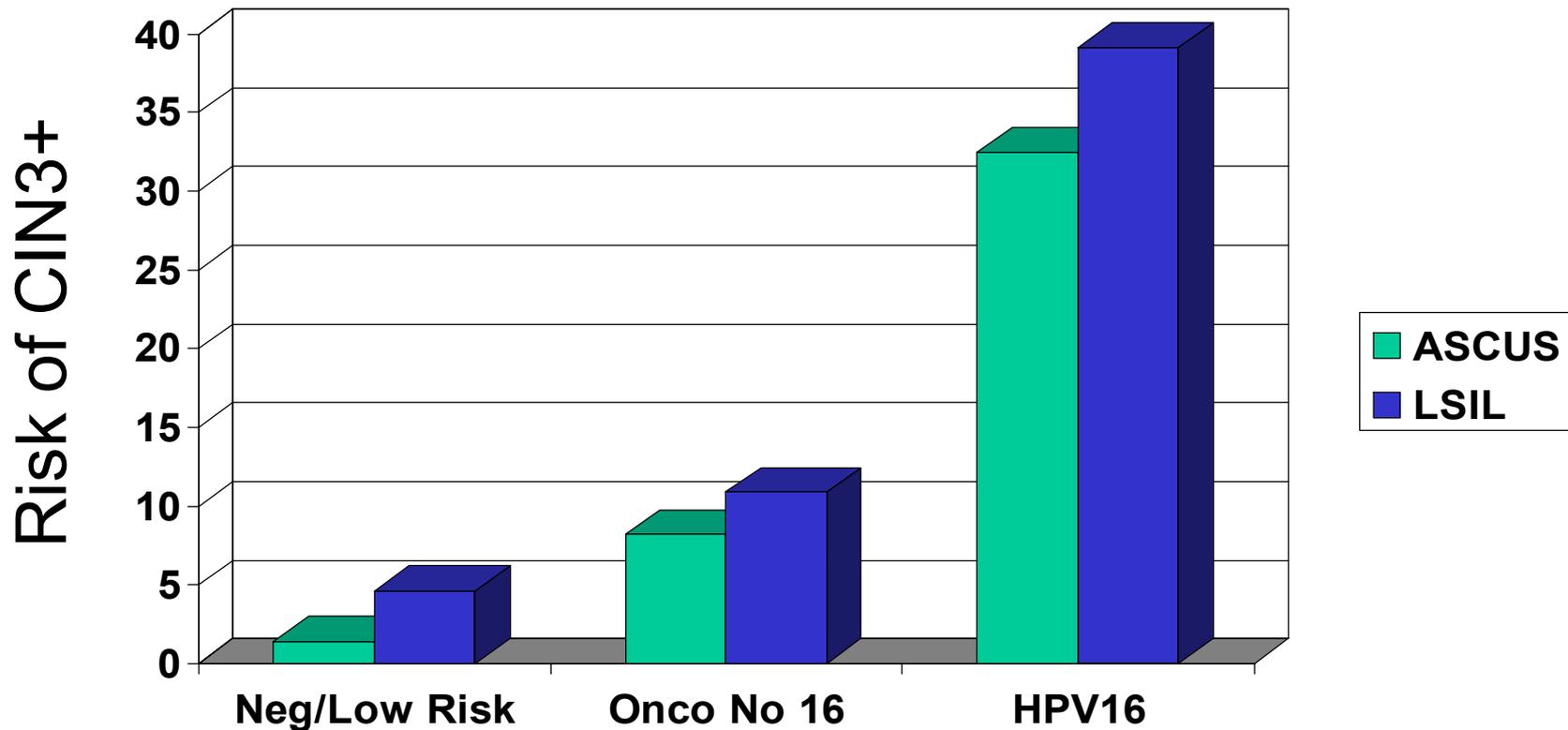
- How to combine vaccination with existent screening programs?
 - Known – vaccination will not eliminate need for screening since current vaccines protect against a subset of the 15-18 HPV types that can cause cancer and do not protect those who already have persistent infection or precancer lesions.
 - **Problem #4: How to avoid drop in cervical cancer screening compliance among vaccinated women?**
 - **Problem #5: How to ensure that vaccination programs reach populations that historically have not benefited from screening programs?**
 - **Problem #6: How to add vaccination to our “prevention portfolio” in a cost-effective manner?**

Integration of HPV Vaccination and Screening



HPV Testing Can Clarify Equivocal Paps

HPV+ ASCUS = LSIL for Risk of CIN3



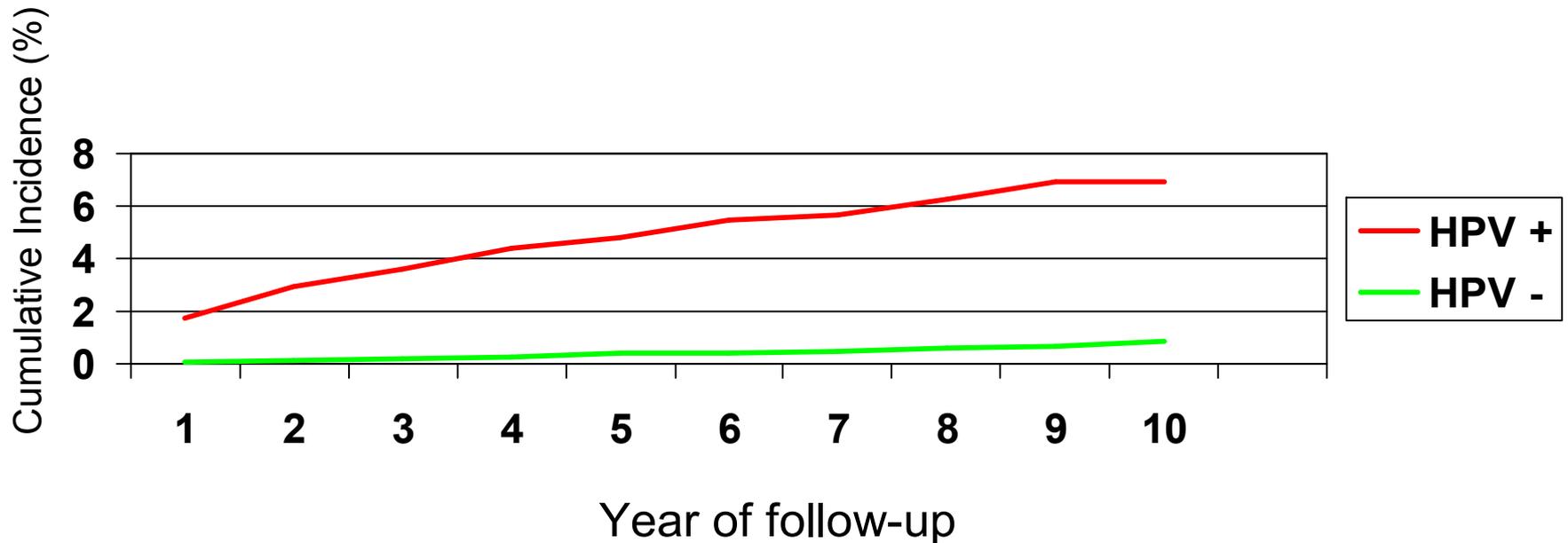
Maybe HPV Can be Used as a Primary Screen?

Accuracy of HPV testing vs. Pap smear for detection of CIN 3+
Guanacaste, Costa Rica

Strategy	Sensitivity	Specificity
HPV DNA testing	85.3%	88.2%
Smear (\geqASCUS)	63.0%	93.7%

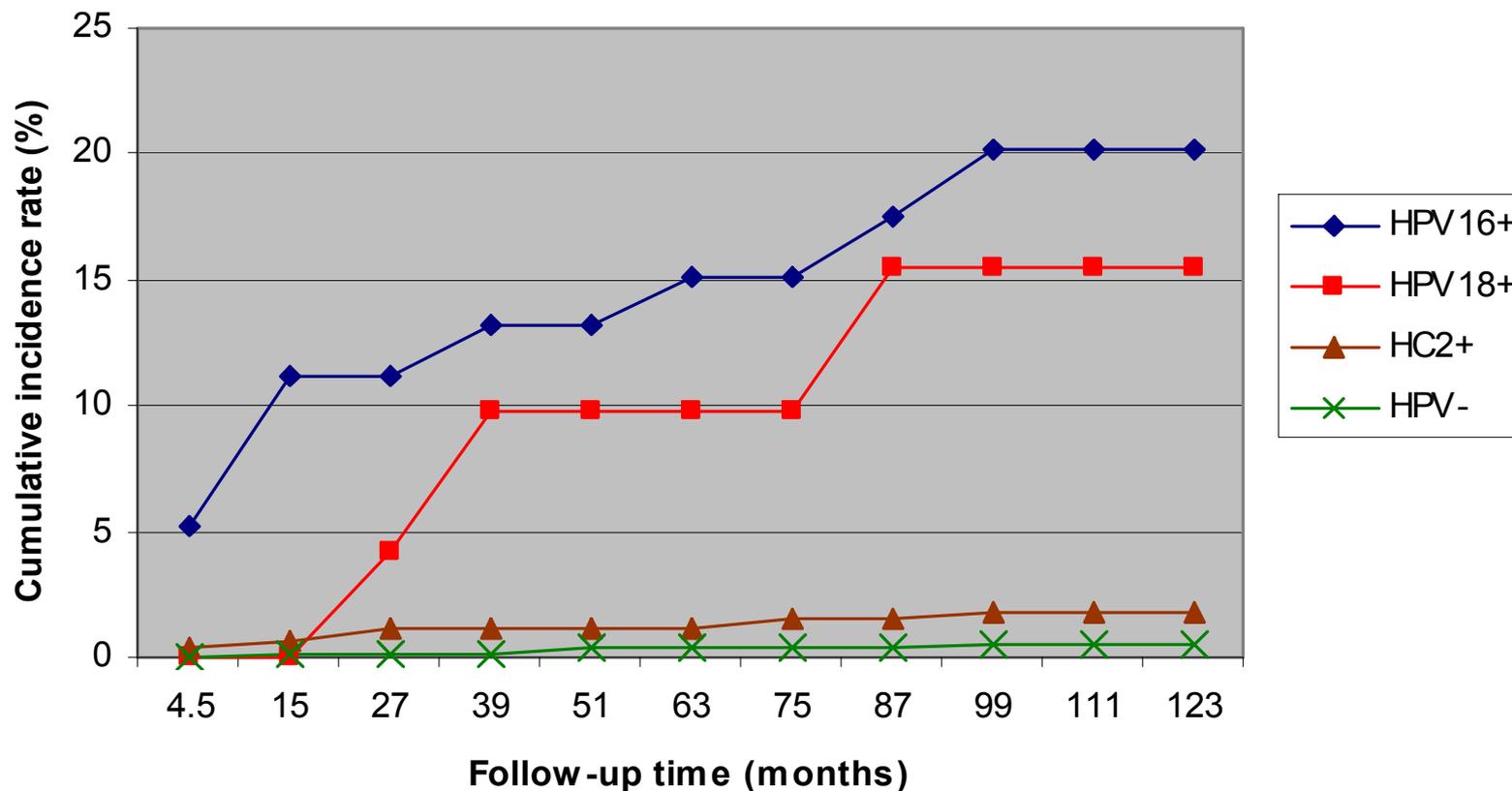
CIN 3 within 2 years or invasive cancer within 7 years of a single baseline test among 9,000 screened women.

HPV Infection at Baseline Predicts Subsequent Precancer and Cancer

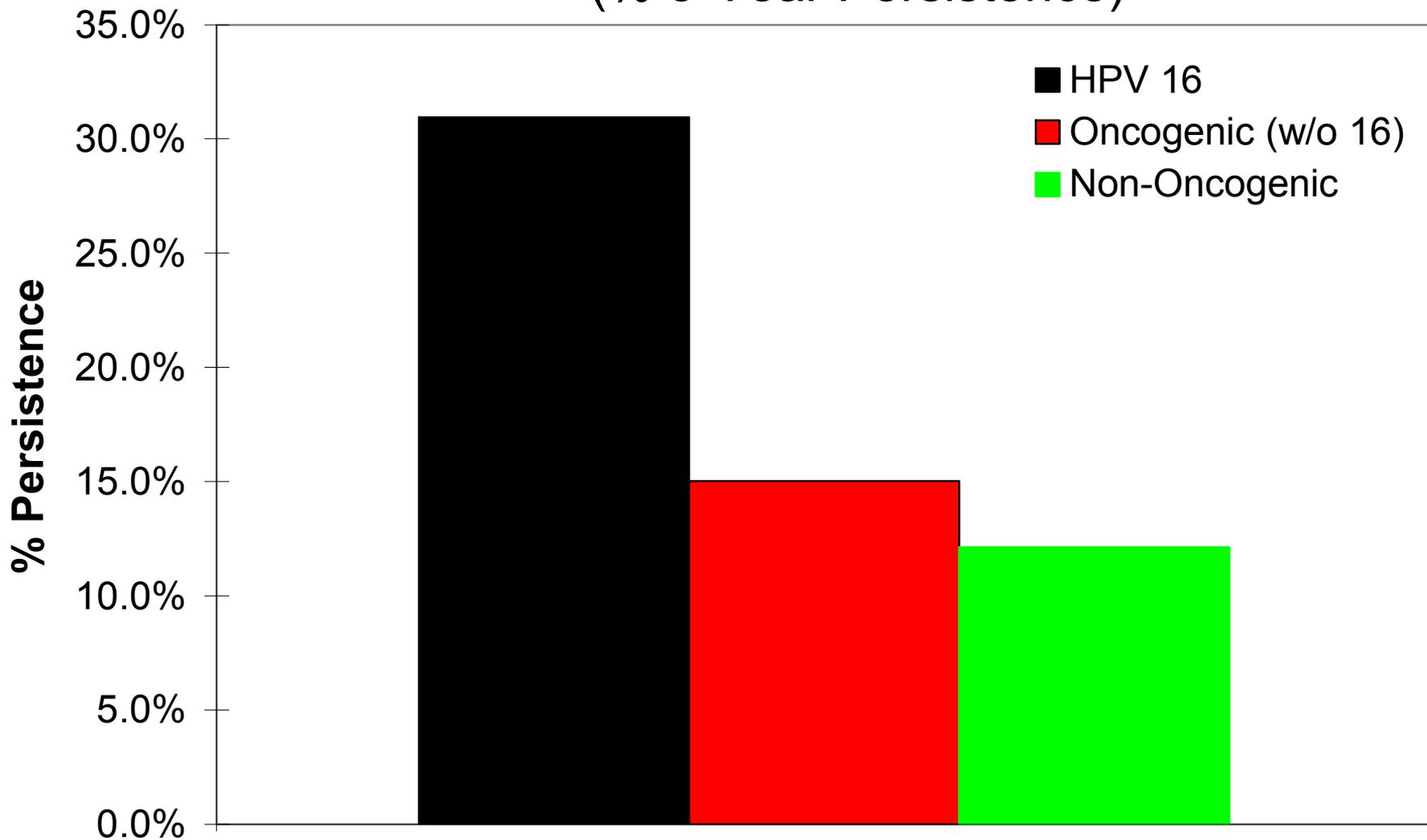


Prospective Evidence (Portland) that HPV16 is the Most Important Type

Cumulative incidence of cervical cancer/precancer in women 30+ over a 10-year period



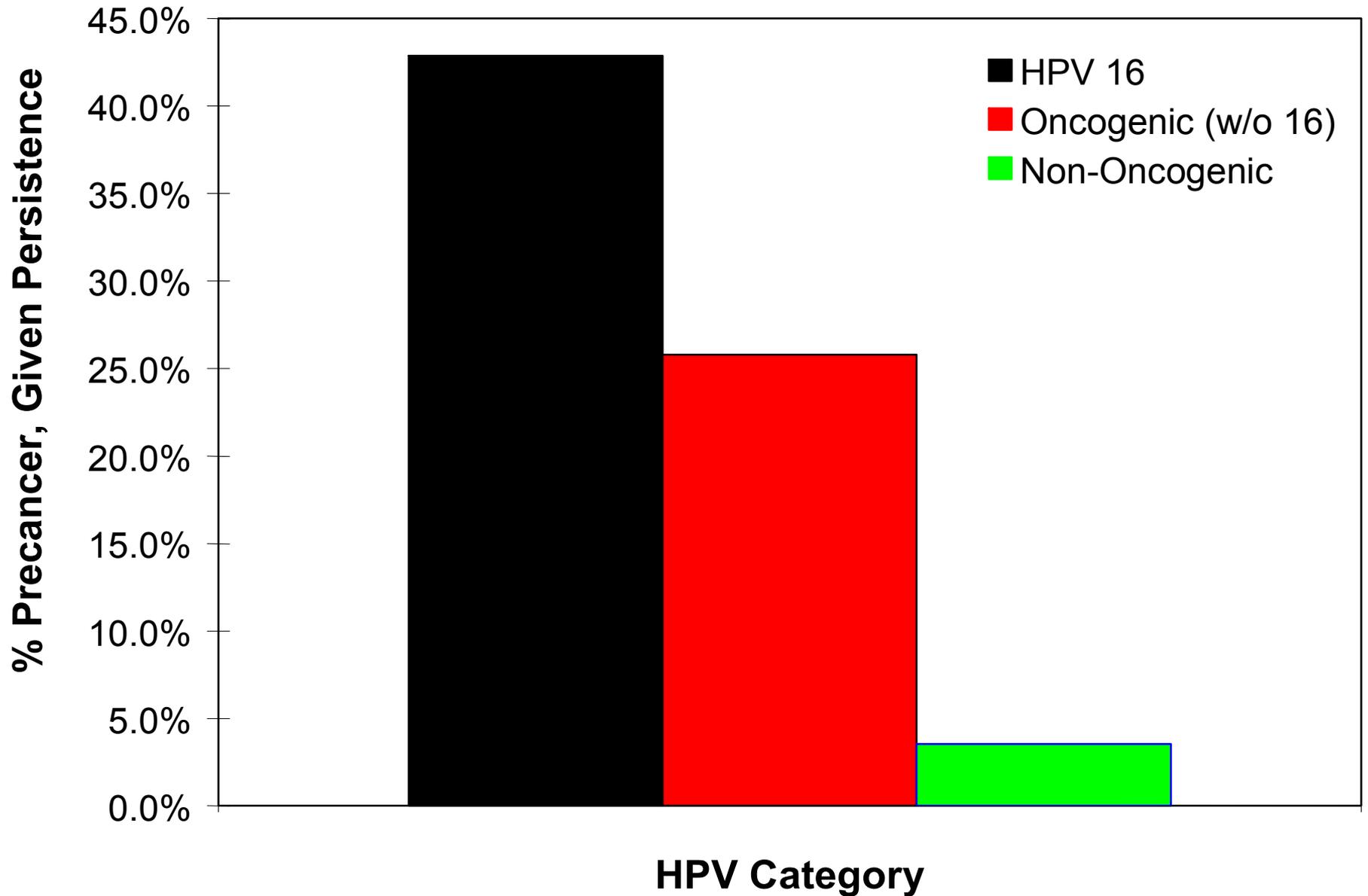
HPV16 Persists Longer Than Any Other Type (% 5-Year Persistence)



HPV Category

Schiffman, Virology 2005

Persistent HPV16 Infection Poses Very High Risk of Precancer



Integration of HPV Vaccination and Screening

