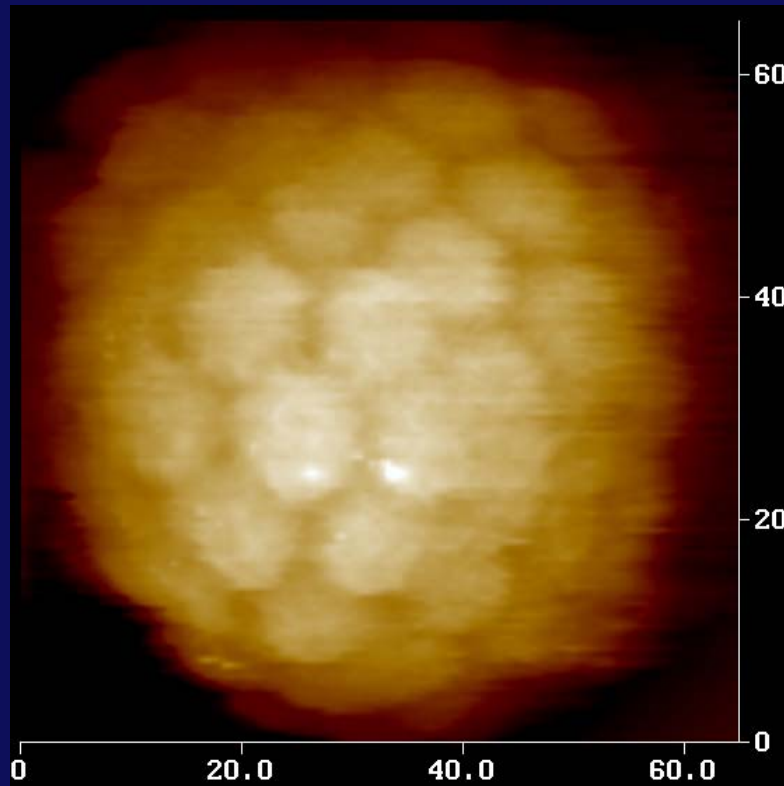




Human Papillomavirus Vaccines

Kevin A. Ault, MD

Introduction: HPV, Cancer and Vaccines



- Cervical cancer is usually caused by HPV
- Cervical cancer is a significant cause of death worldwide; 250,000 deaths reported per year
- Clinical trials of subunit vaccines show promise for preventing HPV infection and sequelae

HPV = human papillomavirus.

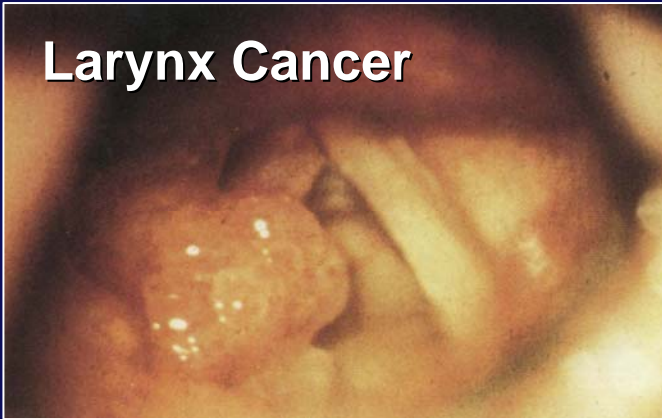
Image courtesy of Darron R. Brown, MD, Indiana University.

Infections and Cancers: Global Burden

Infection	Cancer	No. of Cases Worldwide	% Worldwide
<i>Helicobacter pylori</i>	Stomach	490,000	5.4
HPV	Cervix etc	550,000	6.1
Viral hepatitis	Liver	390,000	4.3
Totals		1.6 Million	17.7

HPV-Related Cancers

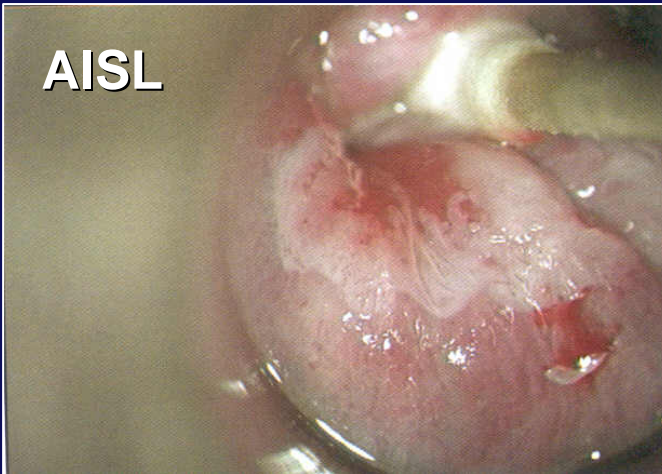
Larynx Cancer



Cervical Cancer



AISL



AISL = anal intraepithelial squamous lesion.

Images courtesy of Dr. John Lee, University of Iowa, and the American Society for Colposcopy and Cervical Pathology.

HPV Infection in Squamous Epithelium

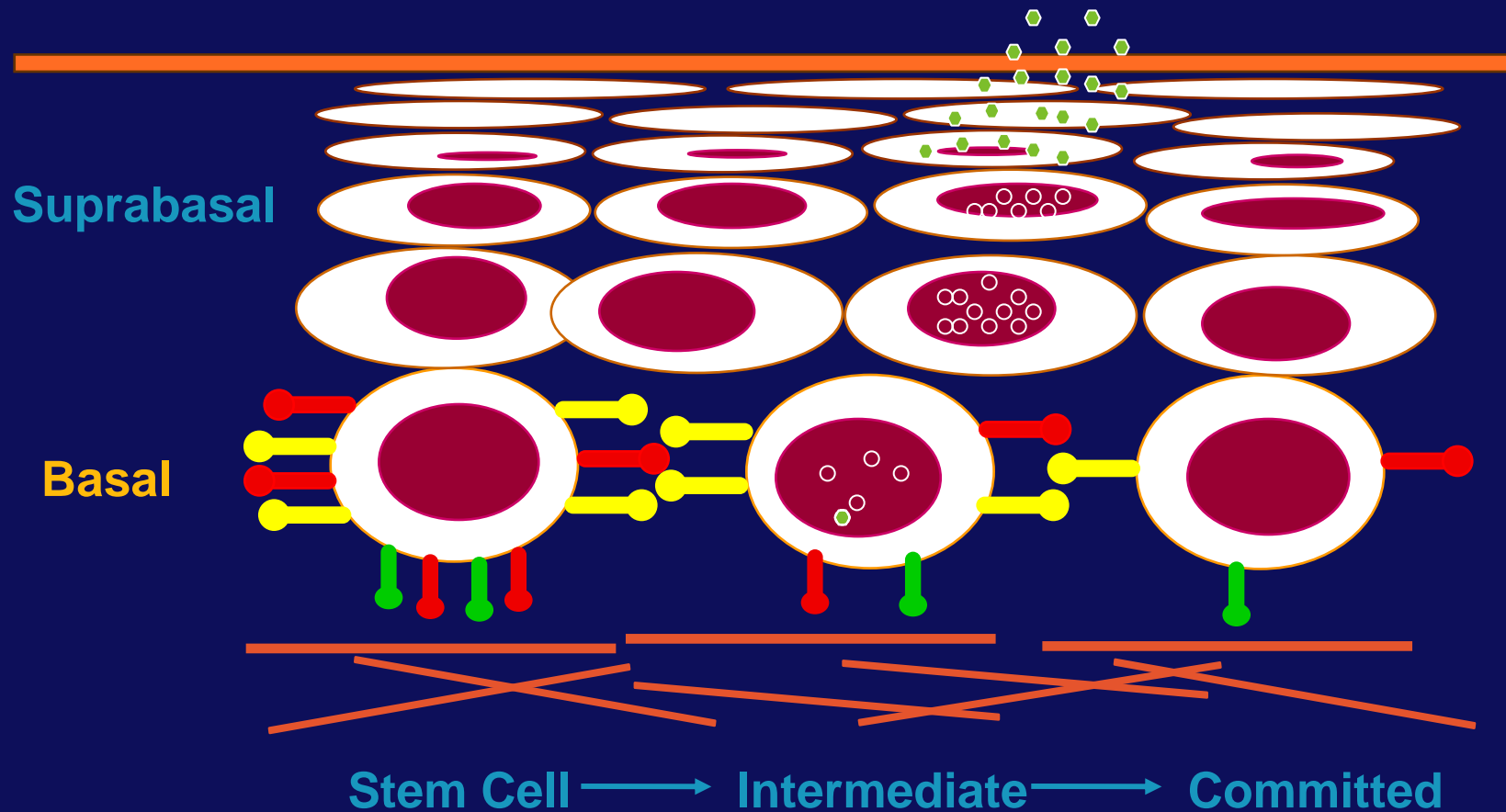
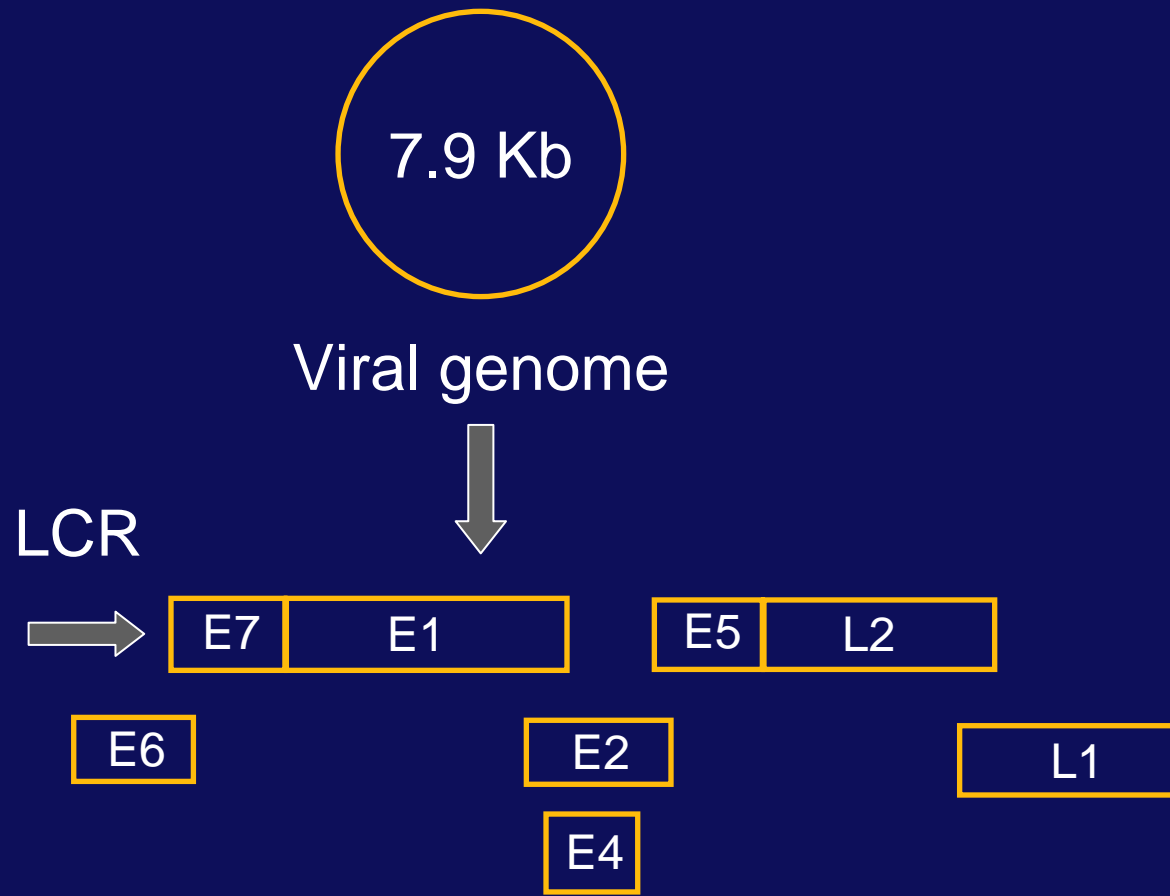


Image courtesy of Al J. Klingelutz, PhD, University of Iowa.

HPV Genome

HPV genomic organization

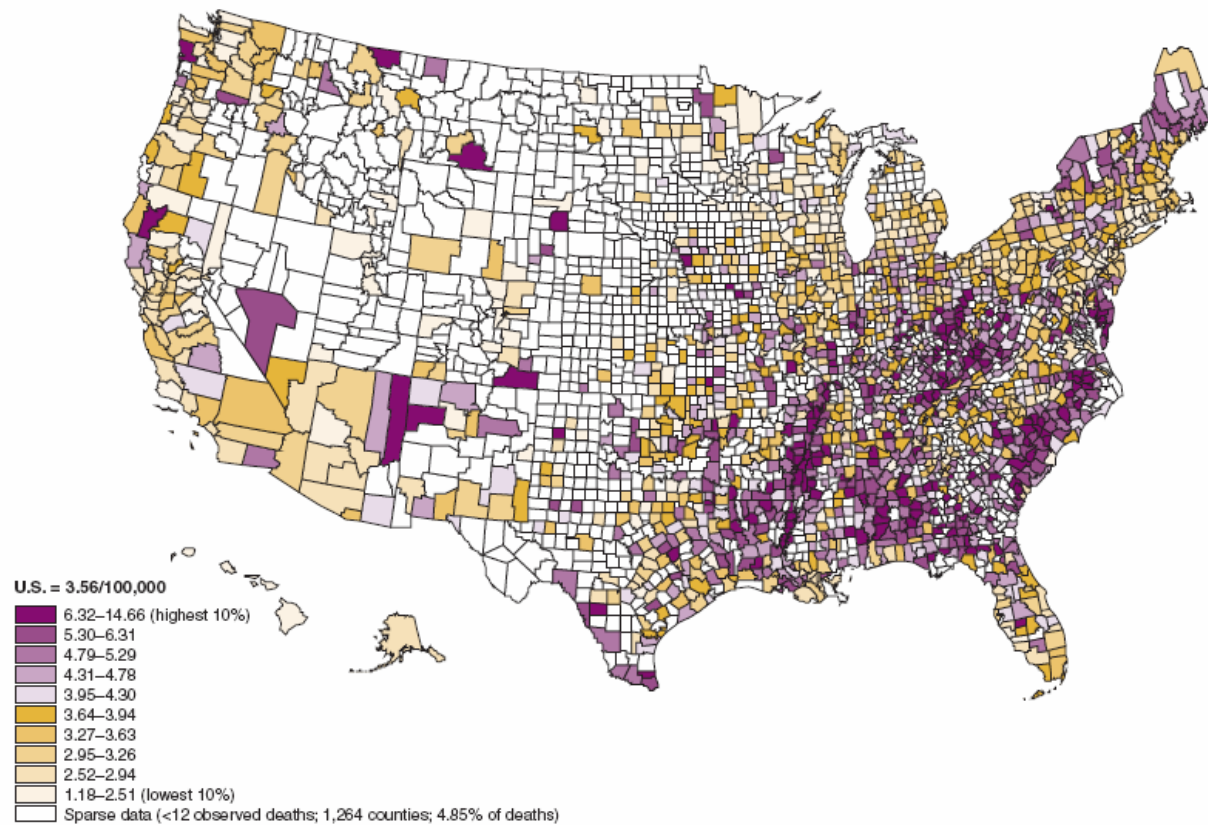


LCR = long control region.

Genome of HPV

- Divided into late and early genes
- L1 and L2 are capsid proteins
- E6 – binds and degrades p53
- E7 – binds and degrades members of the retinoblastoma family proteins
- Oncogenic-type gene products have greater activity than benign types of HPV

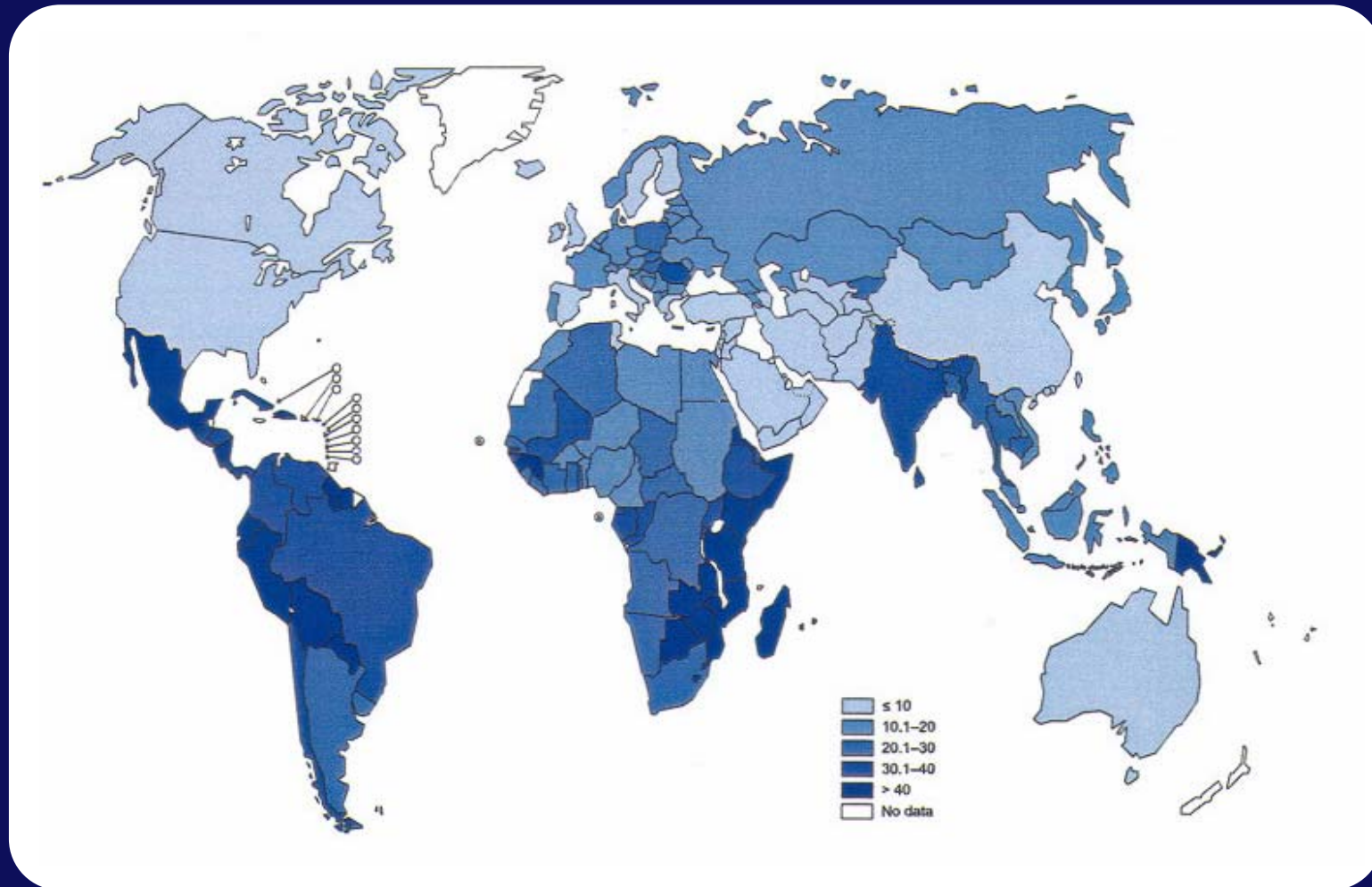
Cancer Mortality Rates by County



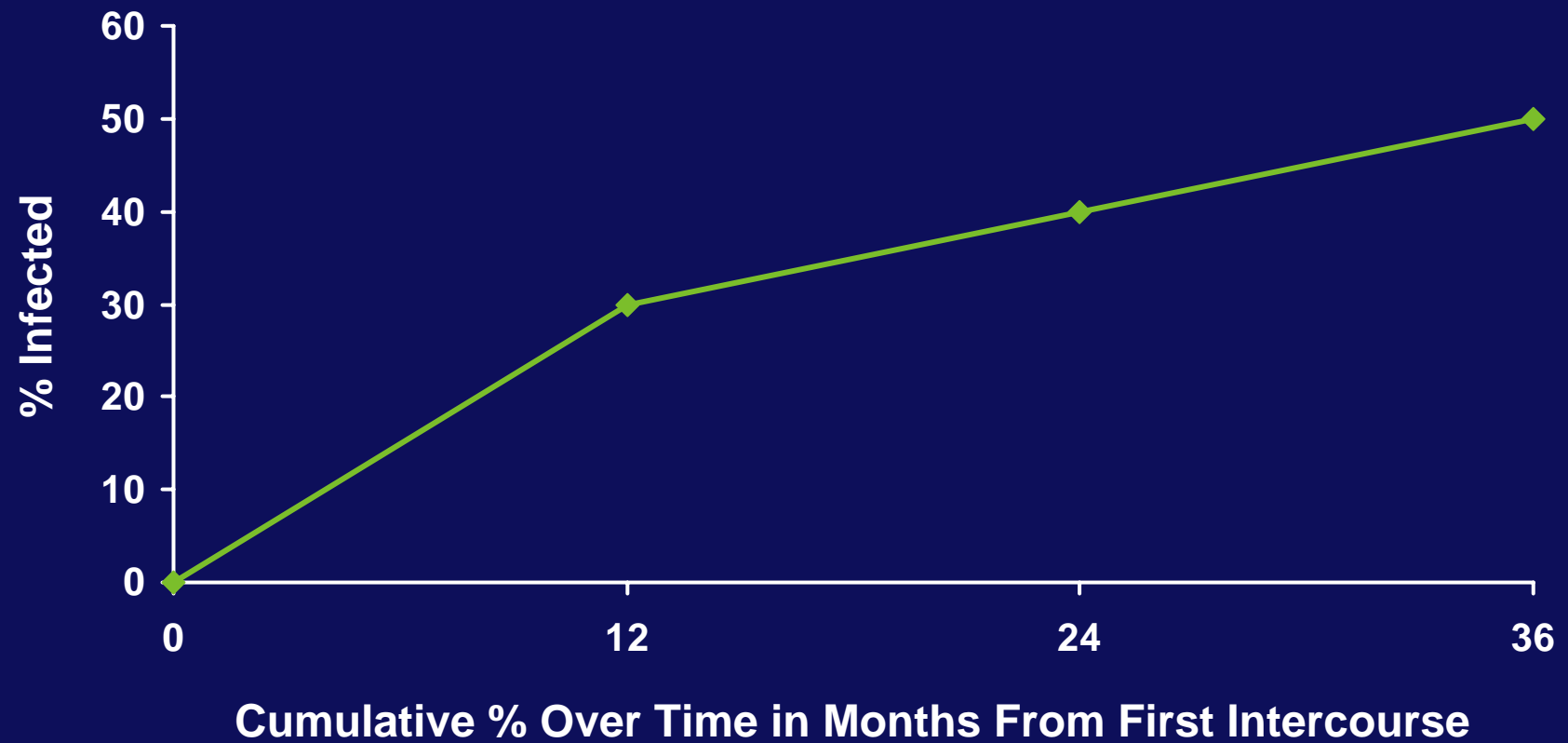
Age-adjusted 1970 US population. Cervix uteri: all races, females, 1970-1998.

Freeman HP, Wingrove BK. National Cancer Institute, Center to Reduce Cancer Health Disparities; May 2005.
NIH Pub. No. 05-5282.

Estimated Age-Standardized Incidence of Cervical Cancer per 100,000 Women in 2000



HPV Infection Among College-Aged Women



HPV VLP as a Potential Vaccine

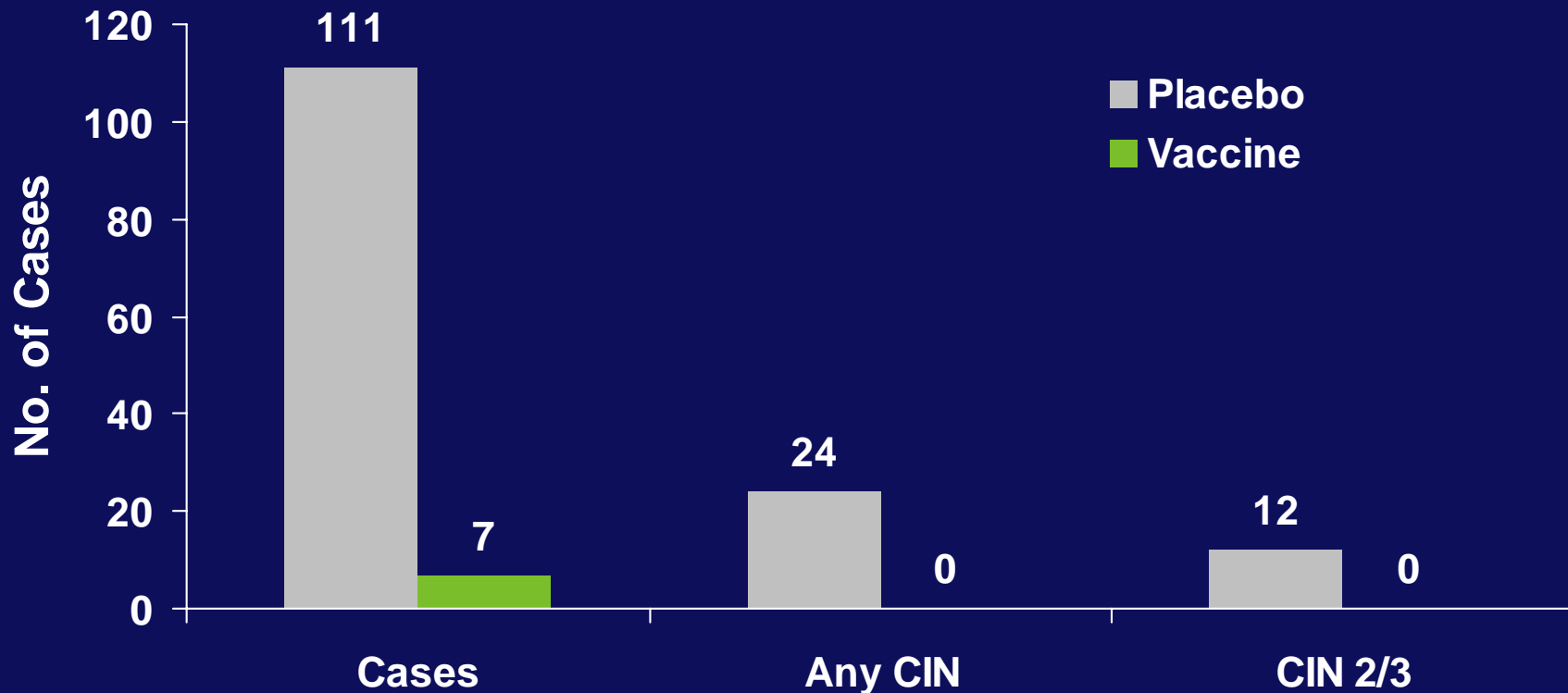
- VLP is the product of the HPV 16 L1 gene
- Capsid proteins self-assemble into “pseudovirions”
- A treatment of three injections over a 6-month period is known to be highly immunogenic and well tolerated
- Similar dosing scheme to that of hepatitis B
- Works in animal models

VLP = virus-like particles.

HPV VLP as a Potential Vaccine (CONT'D)

- Multiple phase I studies
- Phase II/III studies vary in size from hundreds to tens of thousands of subjects
- Efficacy studies usually involve adolescent and college-aged female participants
- Exclusion – number of partners, abnormal cytology
- End points – infection, persistence, or disease
- Must be HPV-naive for inclusion in per-protocol analysis

HPV 16 VLP as a Potential Vaccine: 4-Year Results

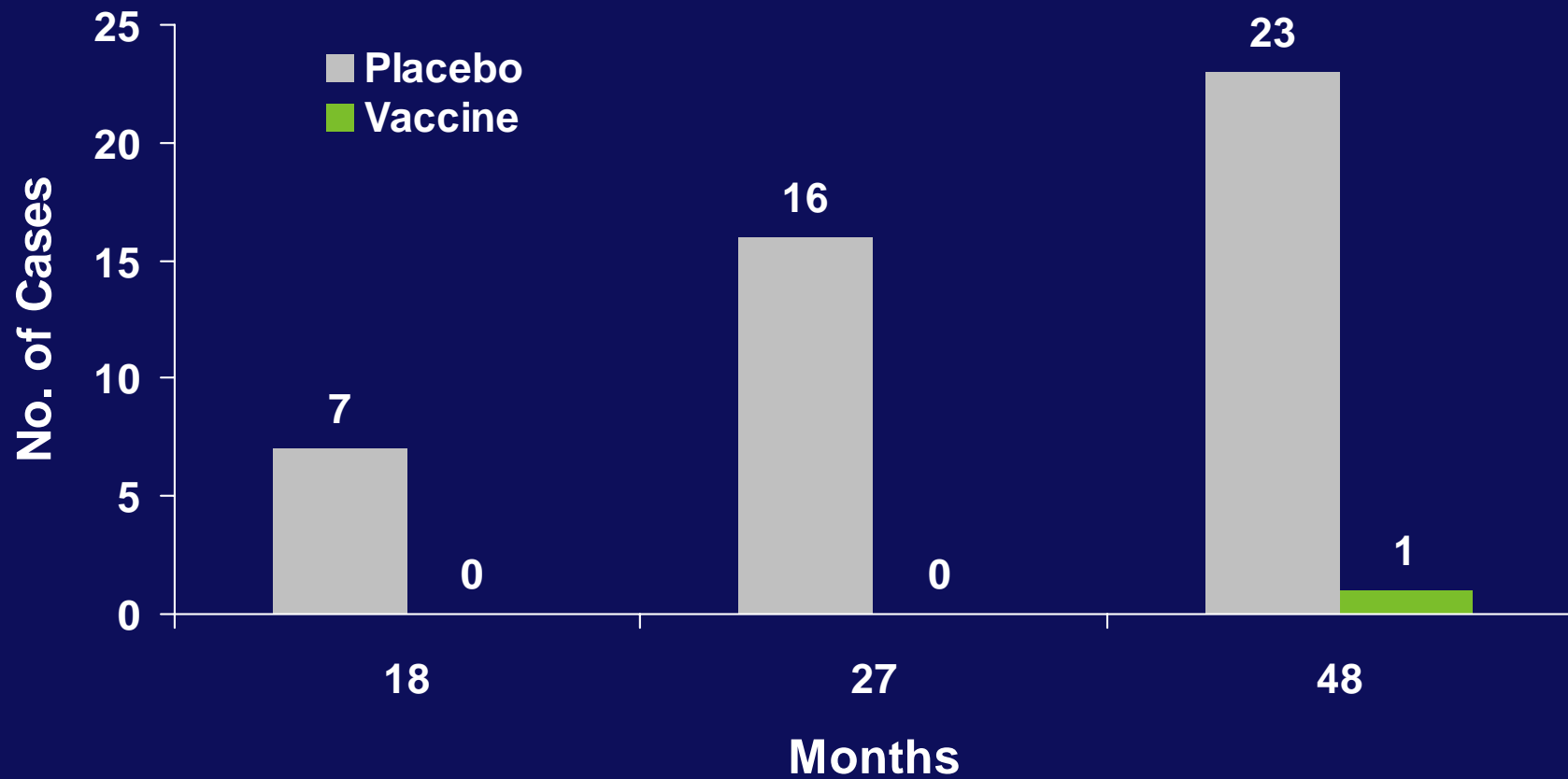


N = 2391; 94% effective.

CIN = cervical intraepithelial neoplasia.

Ferris D, et al. Presented at: Society of Gynecologic Oncologists 36th Annual Meeting; 2005; Miami, Fla. Abstract 8; Mao C, et al. Presented at: 44th Interscience Conference on Antimicrobial Agents and Chemotherapy; 2004; Washington, DC. Abstract 3741.

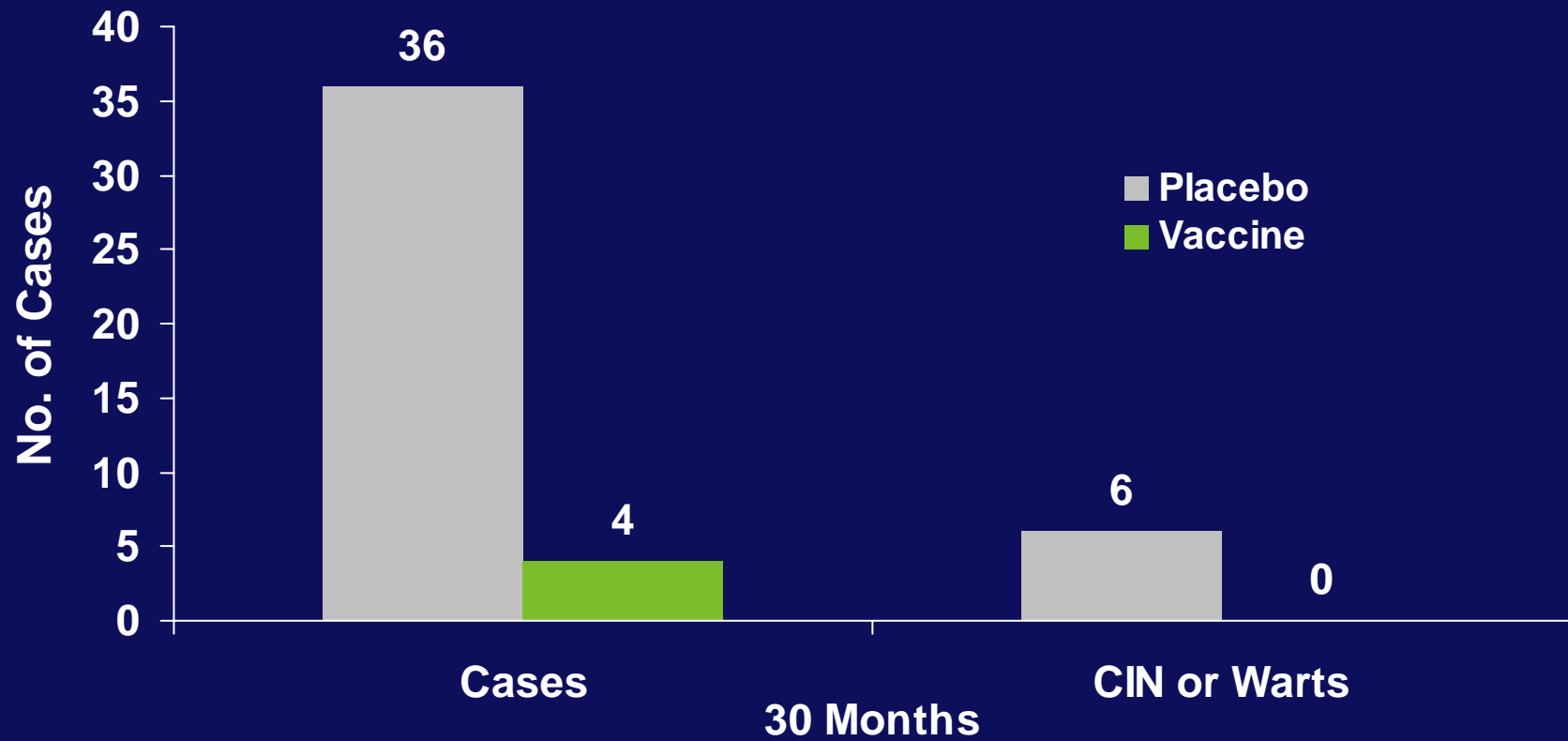
Bivalent HPV 16/18 Vaccine



N = 1113; 97% effective.

Harper DM, et al. *Lancet*. 2004;364:1757-1765; Harper DM, et al. *Lancet*. 2006;367:1247-1255.

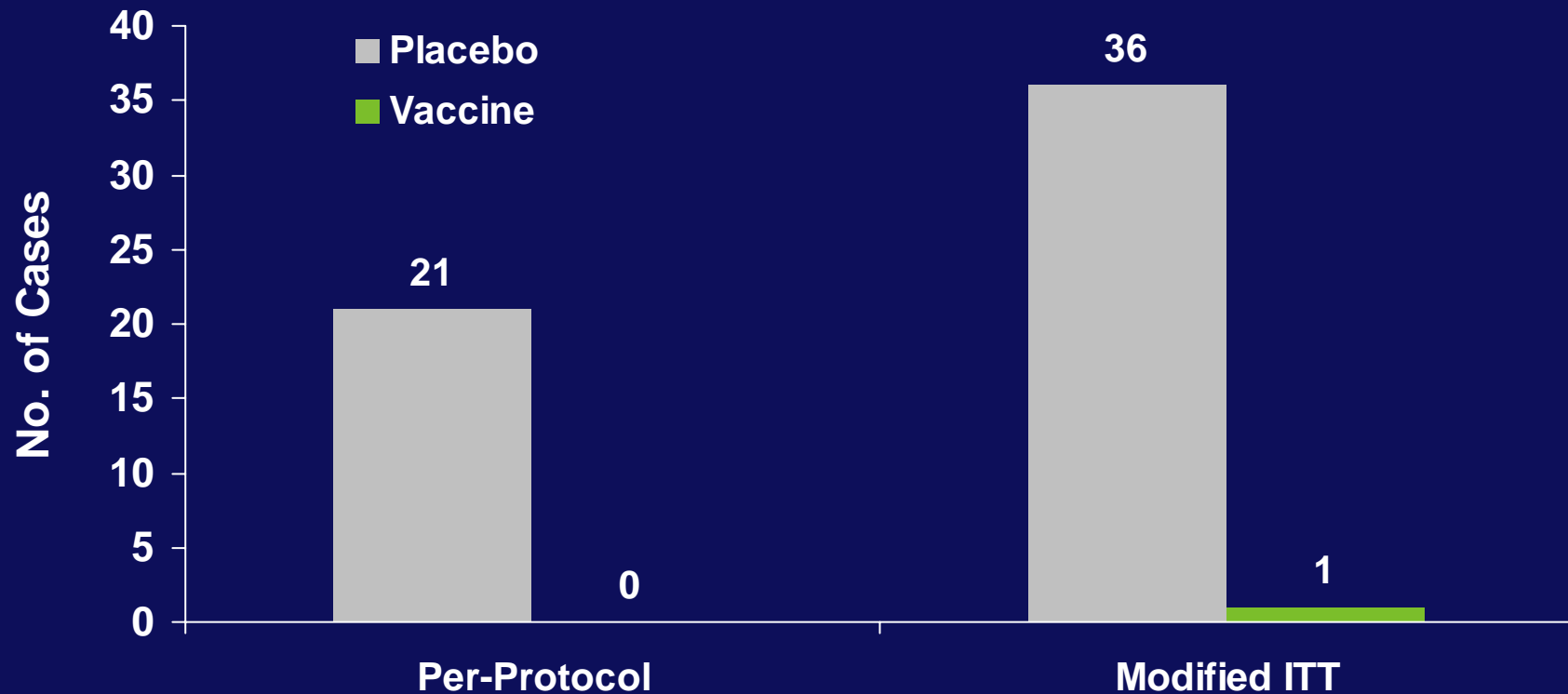
Quadrivalent HPV 6/11/16/18 Vaccine



N = 552; 90% effective.

Villa LL, et al. *Lancet Oncol.* 2005;6:271-278.

Quadrivalent HPV: Initial Phase III Results for CIN 2/3

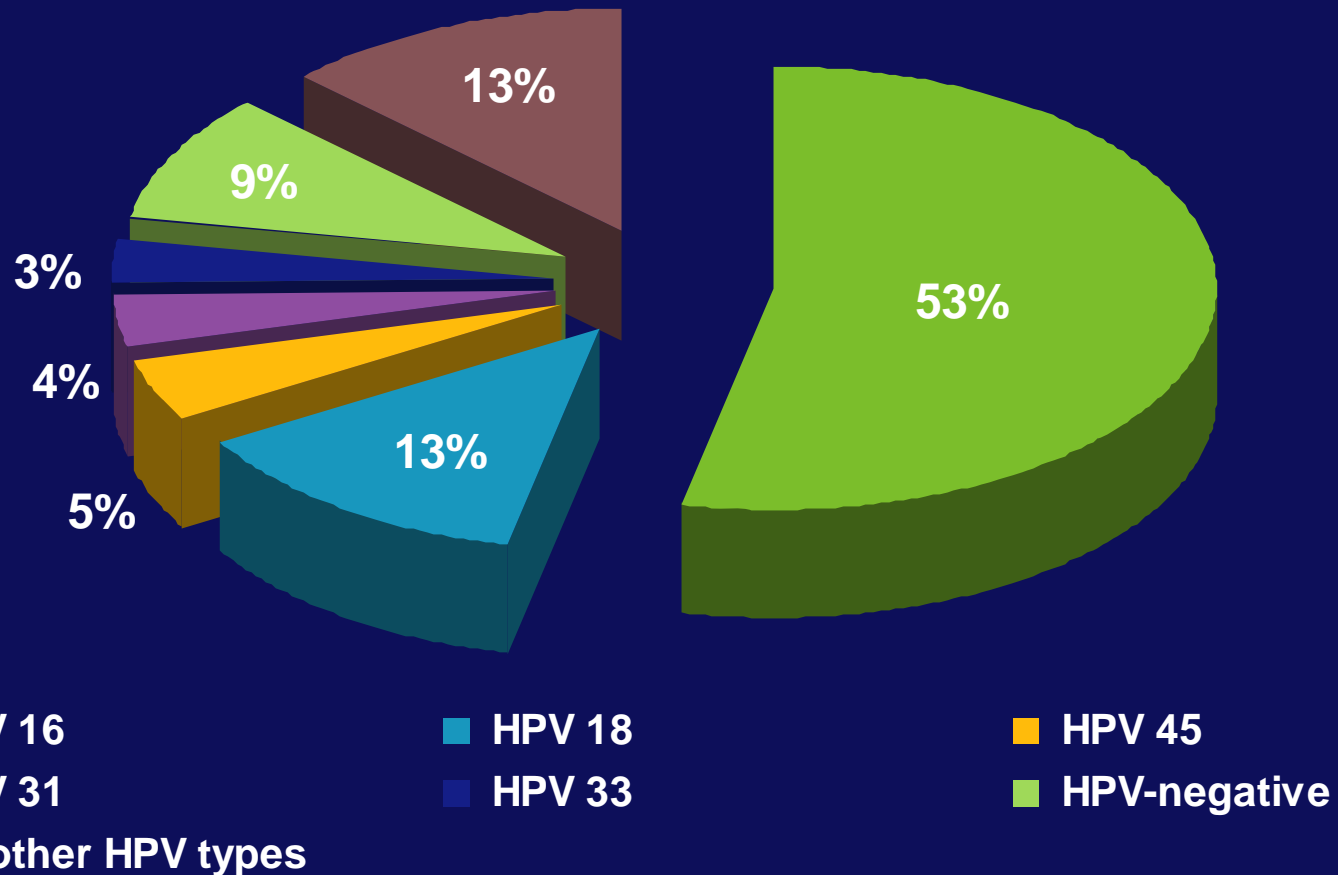


N = 12,167.

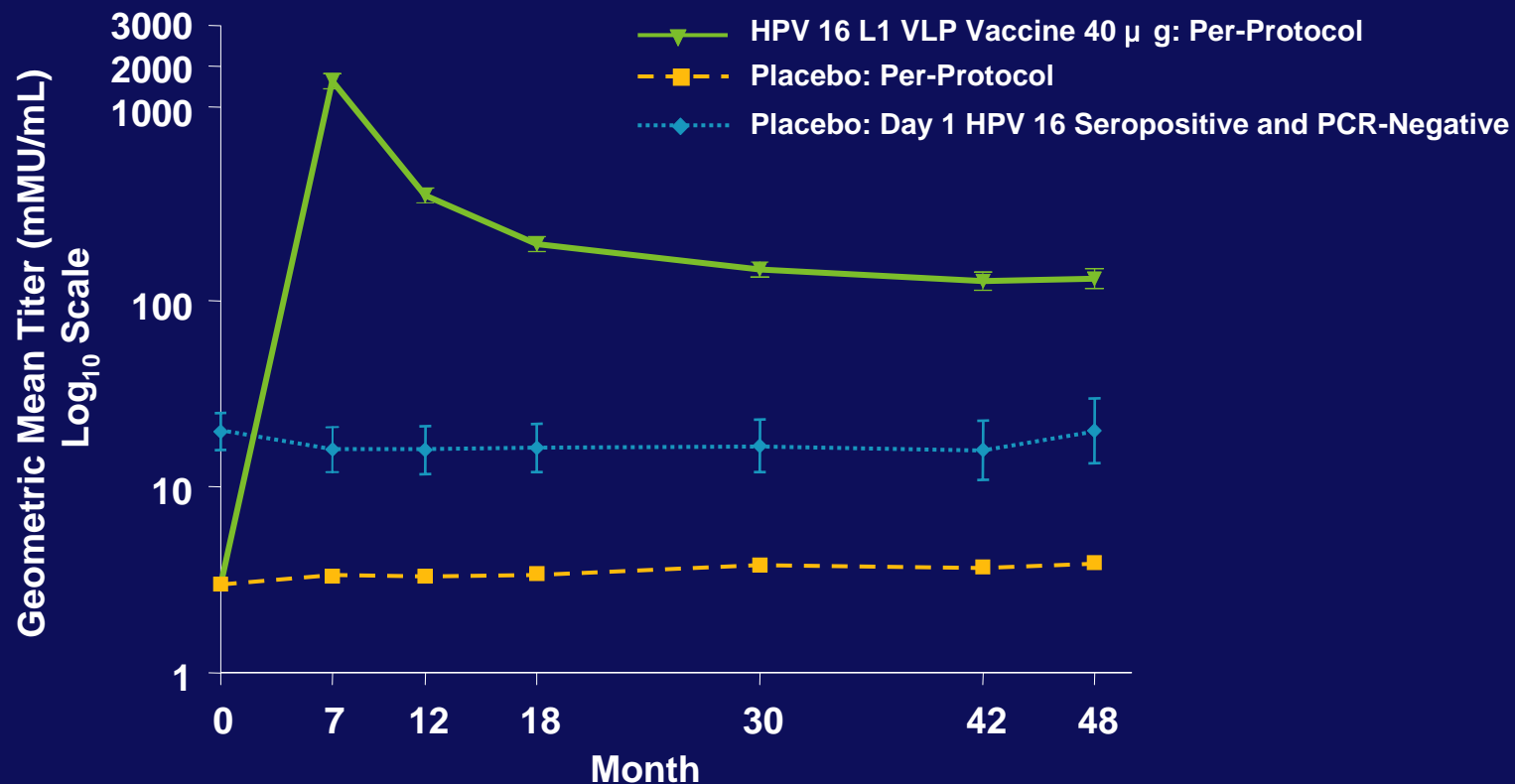
ITT = intent-to-treat.

Koutsky L, et al. Presented at: Infectious Diseases Society of America 43rd Annual Meeting; October 7, 2005; San Francisco, Calif. Abstract LB-8a.

HPV Types That Cause Cervical Cancer: A Worldwide Survey



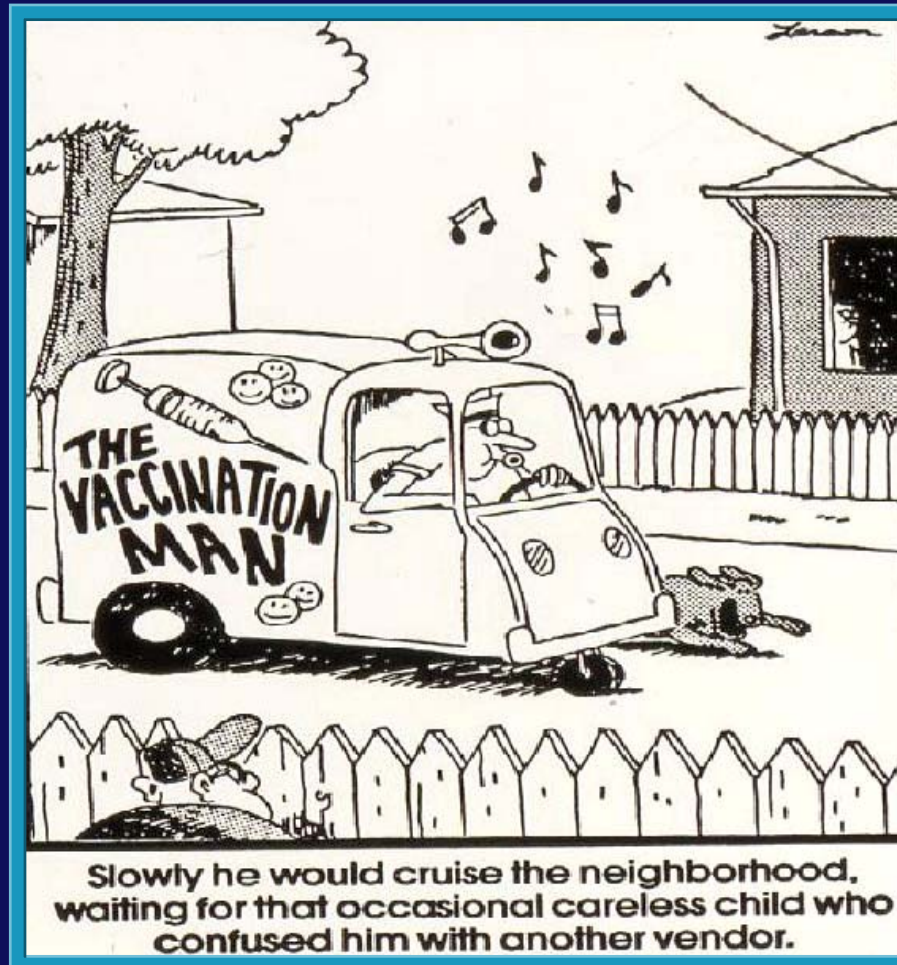
Antibody Responses to HPV L1 VLP Vaccine



No. of Subjects	0	7	12	18	30	42	48
HPV 16 L1 VLP Vaccine 40 µg: Per-Protocol	684	684	663	649	609	533	481
Placebo: Per-Protocol	680	680	661	638	604	532	489
Placebo: Day 1 HPV 16 Seropositive and PCR-Negative	131	105	99	97	89	78	72

Ault KA, et al. Presented at: American Society of Clinical Oncology Annual Meeting; 2005; Orlando, Fla. Abstract 5024.

This Strategy Is Unlikely to Work....



HPV Vaccines: Current State of Research

- Promising efficacy trials and phase III results to be published, FDA/ACIP decisions are pending
- Multivalent vaccines are used in later-phase clinical trials in adolescents and adults
- Duration of protection? – Modeling suggests antibodies persist for years to a decade but we do not know immune correlates of protection
- Cross protection? Type replacement? Herd immunity?

ACIP = Advisory Committee on Immunization Practices; FDA = Food and Drug Administration.

Lowy DR, Schiller JT. *J Clin Invest.* 2006;116:1167-1173; Steinbrook R. *N Engl J Med.* 2006;354:1109-1112.

HPV and Cancer: Past, Present and Future



- 1930 – Cervical cancer is the no. 1 cancer mortality among women in the United States
- 1941 – Papanicolaou publishes his paper in the *American Journal of Obstetrics and Gynecology*
- 2004 – 13,000 cases in the United States; 500,000 worldwide
- 2006 – Cervical cancer vaccine