

Primary & Secondary Prevention of HPV-associated Cancers

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Disclosures

- The National Institutes of Health (NIH) has patents on papillomavirus L1 virus-like particle (VLP) vaccine technology. I am an inventor of this technology.
- The NIH has licensed the L1 VLP technology to Merck and GlaxoSmithKline, the two companies with commercial versions of the vaccine.
- ***I will discuss potential off-label uses of the FDA-approved vaccines (protecting against additional diseases and giving fewer doses)***
- Other NIH technologies on which I am an inventor have been licensed to GlaxoSmithKline, Sanofi, Shanta Biotech, Cytos Biotech, Aura Biosciences, Etna Biotech, Acambis, PanVax

Outline of Presentation

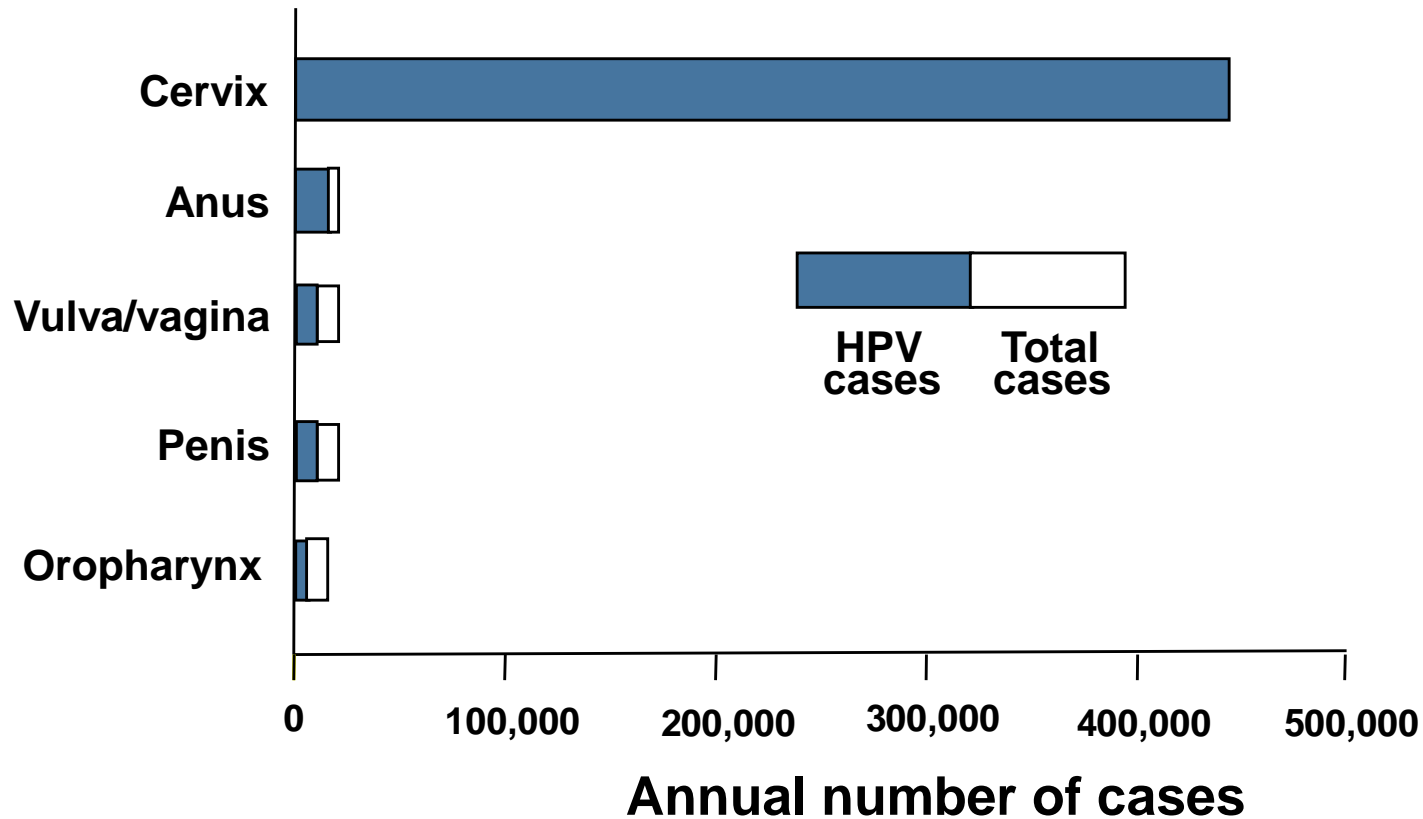
- HPV vaccination: to prevent HPV-associated cancers
- Primary HPV-based cervical cancer screening: to reduce incidence and mortality even further than screening by cytology
- Aspirin: a candidate intervention for colorectal cancer prevention

Implications of Identifying HPV as The Main Cause of Cervical Cancer

- **1983/4: Identification of HPV16/18; zur Hausen and colleagues - Nobel Prize 2008**
- **Natural history of HPV infection/pathogenesis of cervical cancer**
- **Identification of other HPV-associated cancers**

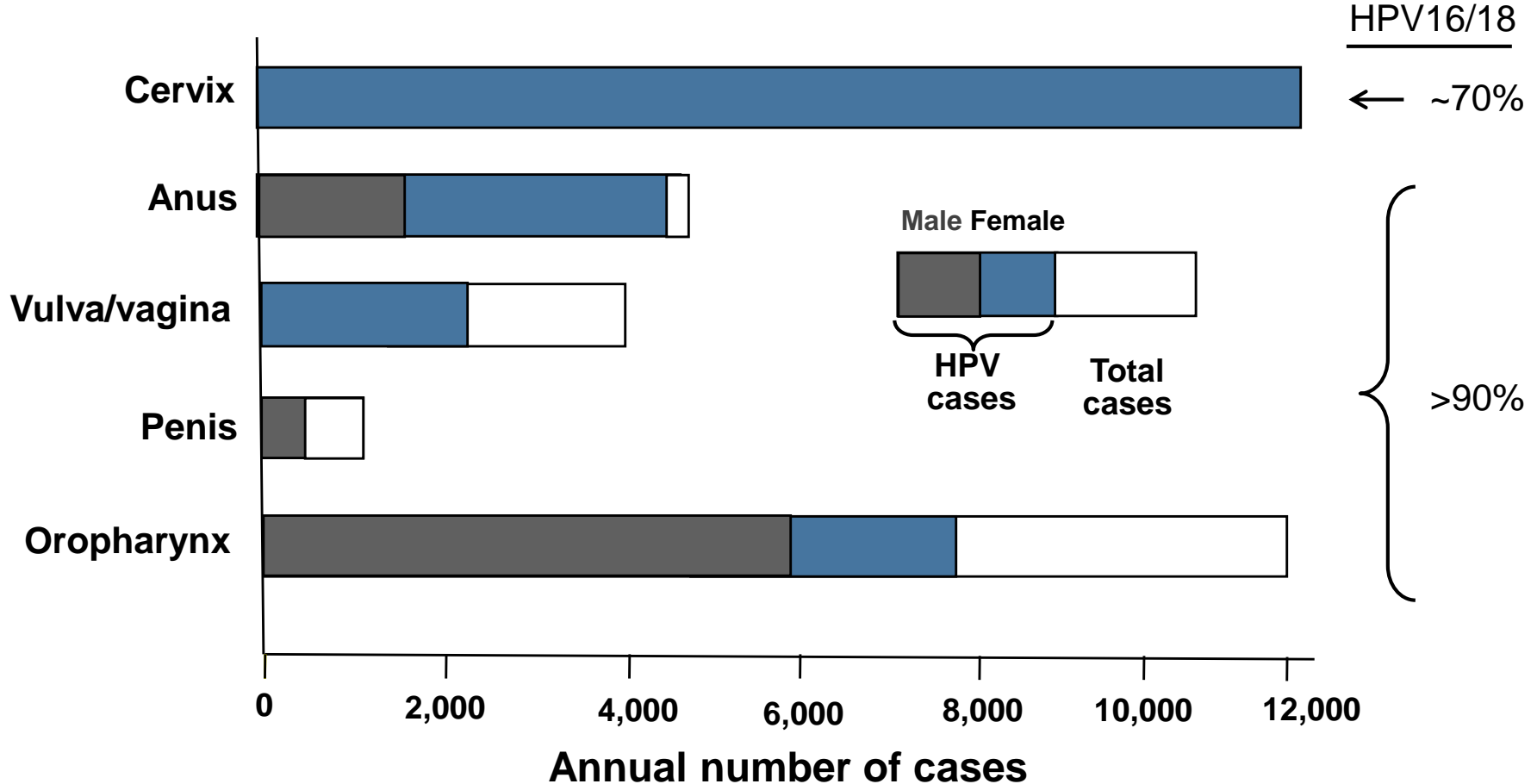
***Epidemiology of
HPV-associated
Cancer***

Cervical Cancer accounts for >90% of HPV-associated cancer in Developing World



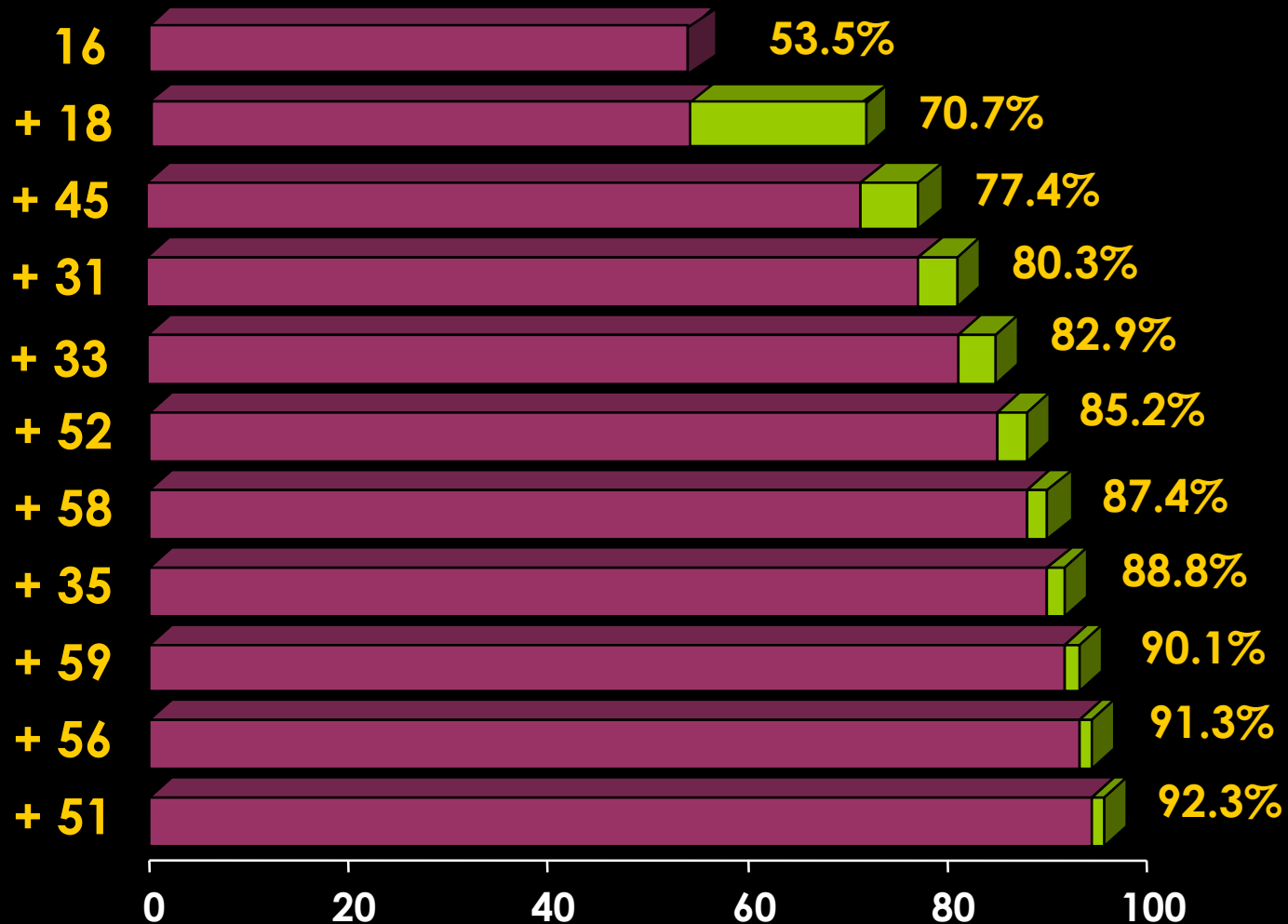
- ~85% of global cervical cancer occurs in developing world; ~88% of deaths
- ~1% of women in developing world will die of cervical cancer before they are 75 (Ferlay et al, Int J Cancer, 2015)

USA: HPV-associated Non-cervical Cancers Affect Both Genders and are as Common as Cervical Cancer

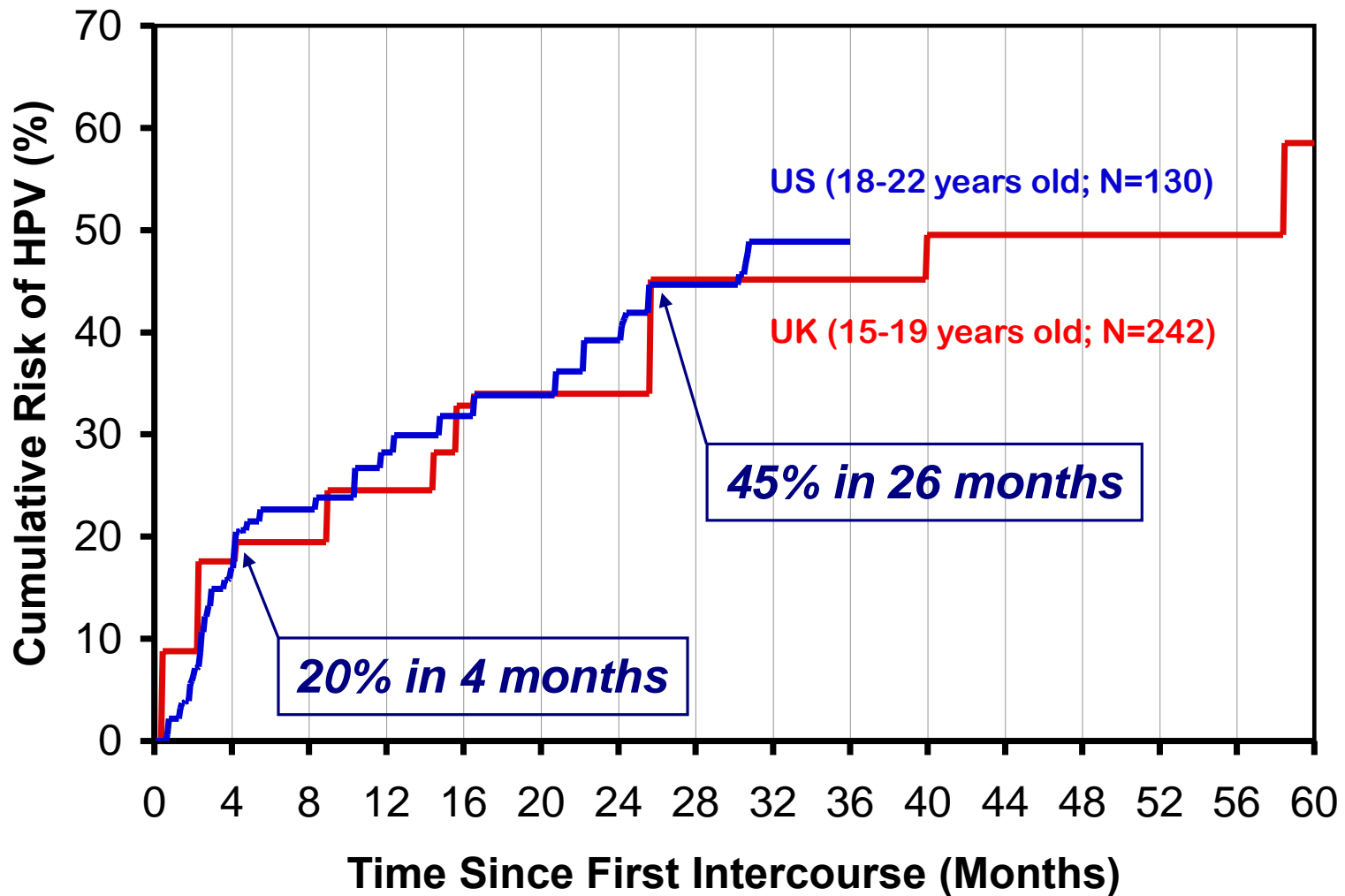


- Pap screening has reduced cervical cancer incidence by ~80%
- No approved screening tests for other HPV-associated cancers
- Incidence of HPV-positive oropharynx cancer 1988-2004 increased >3-fold

Cervical Cancer is Attributable to Multiple HPV Types; HPV16 Predominates



Rapid Acquisition of Genital HPV Infection in Young Women With Their First Sexual Partner



***The First Generation
HPV Vaccines***

Laboratory of Cellular Oncology, CCR, NCI

John Schiller

Patricia Day

Rhonda Kines

Cynthia Thompson

Hanna Seitz

Nicolas Cuburu

Susana Pang

Alessandra Handisurya

Carla Cerqueira

Chris Buck, Diana Pastrana - *LCO, CCR, NCI Bethesda*

**Aimee Kreimer, Allan Hildesheim, Mark Schiffman, Mahboobeh Safaeian, Ligia Pinto -
*DCEG, NCI, Bethesda***

Peter Choyke, Marcelino Bernardo - *Molecular Imaging, CCR, NCI, Bethesda*

Jeffrey Roberts – FDA, Rockville

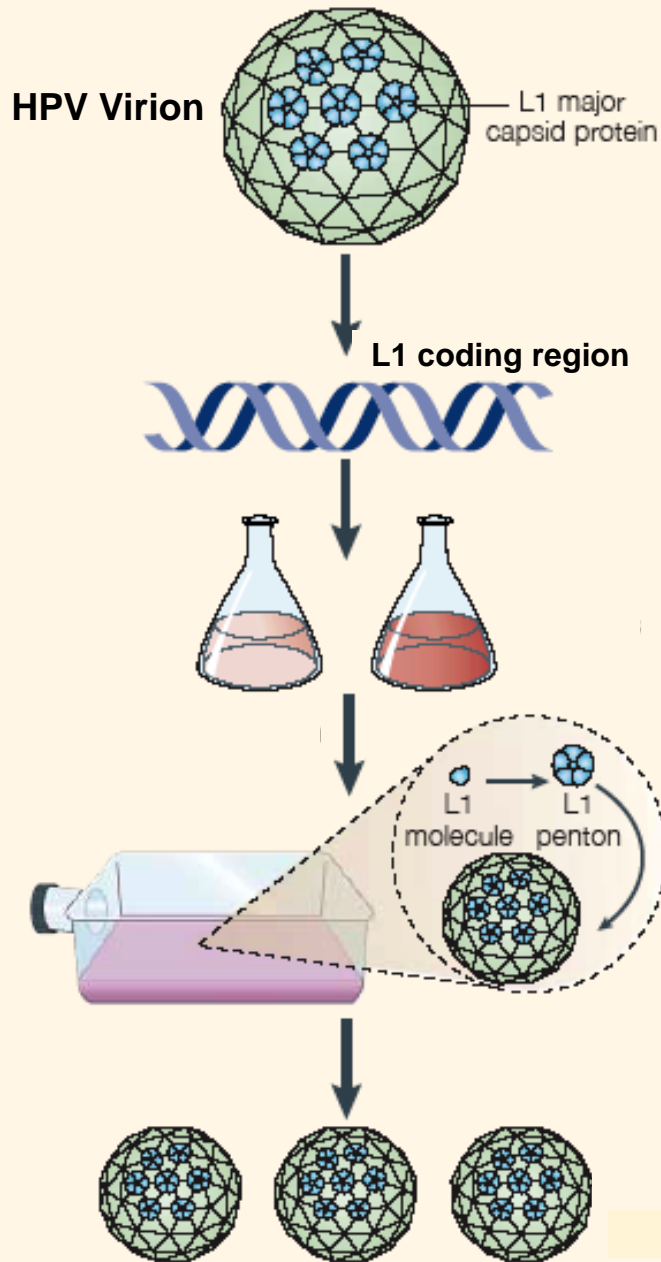
Rolando Herrero – *IARC, Lyon, France*

Bryce Chackerian - *University of New Mexico*

Reinhard Kirnbauer - *University of Vienna, Austria*

Choosing an appropriate molecular target for a preventive HPV vaccine

- **Licensed vaccines against microbial agents are mainly preventive; induction of neutralizing antibodies is critical.**
- **HPVs contain viral oncogenes (E5, E6, E7). Implies you need a subunit vaccine lacking the oncogenes.**
- **Papillomaviruses encode two proteins that induce neutralizing antibodies, the capsid proteins L1 and L2.**
 - ***L1 contains the immunodominant neutralization epitopes. They are conformationally dependent.***
- ***OUR HYPOTHESIS: L1 can self-assemble to make empty particles having a conformation that induces high levels of neutralizing antibodies.***



Prophylactic HPV Vaccines Are L1 Virus Like Particles (VLPs)

L1 Insertion in Baculovirus Expression Vector

Production in Insect Cells

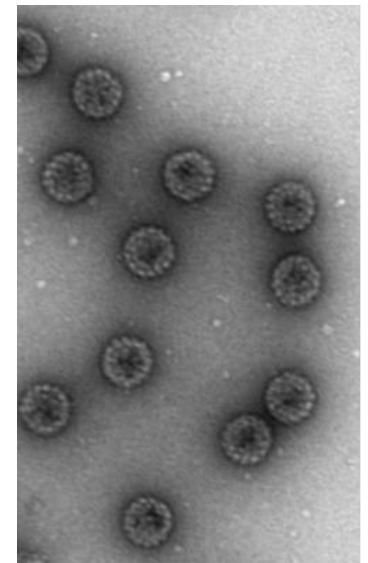
Spontaneous assembly of L1 into VLPs

Induce high titers of virion neutralizing antibodies

Shown initially for BPV-1, then for HPV16

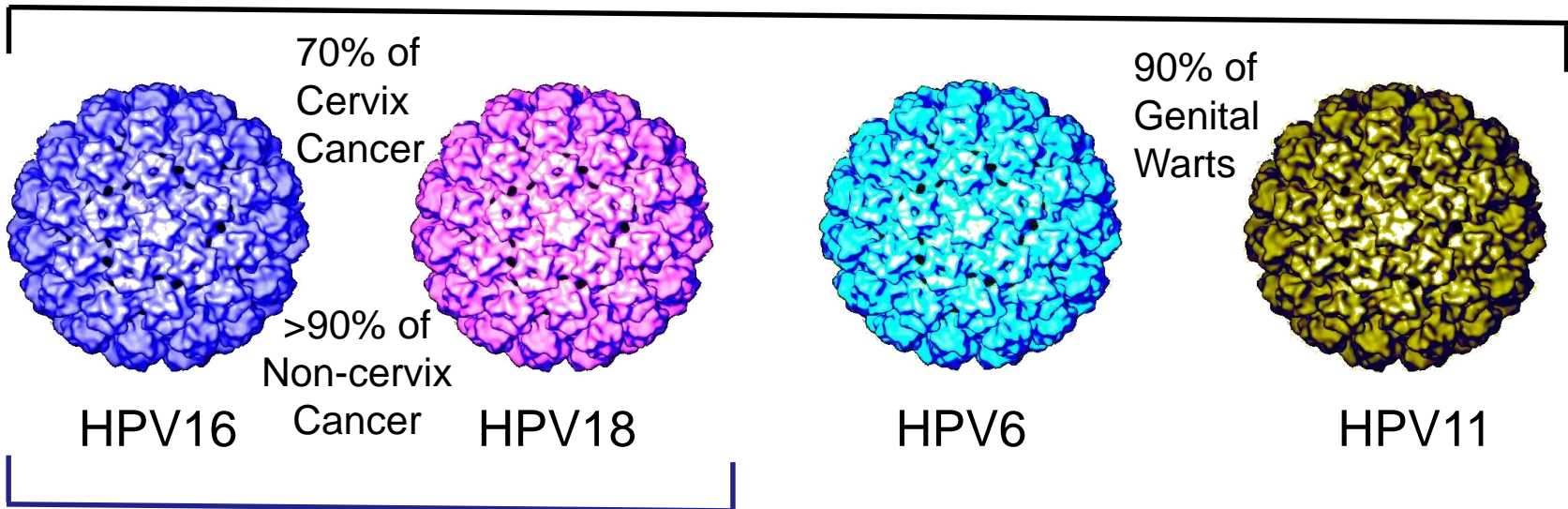
Non-infectious, Non-oncogenic

HPV16 L1 VLPs



The Commercial Vaccines Are Composed of Multiple Types of HPV L1 VLPs

Gardasil (Merck)



Cervarix (GlaxoSmithKline)

Three intramuscular injections over 6 months

Summary of phase III HPV vaccine trials

- In uninfected patients, HPV vaccination can confer close to 100% protection against incident persistent infection and disease attributable to the HPV vaccine types
 - HPV vaccination can also protect against non-cervical infection and disease, while screening is only for cervical cancer
- There is limited cross-protection against non-vaccine HPV types
- Cross-protection is greater with the bivalent vaccine than with the quadrivalent vaccine, perhaps because the bivalent vaccine is more immunogenic than the quadrivalent vaccine
- HPV vaccination does not alter the natural history of prevalent infection, i.e., it is not therapeutic



Monitoring the safety of quadrivalent human papillomavirus vaccine: Findings from the Vaccine Safety Datalink[☆]

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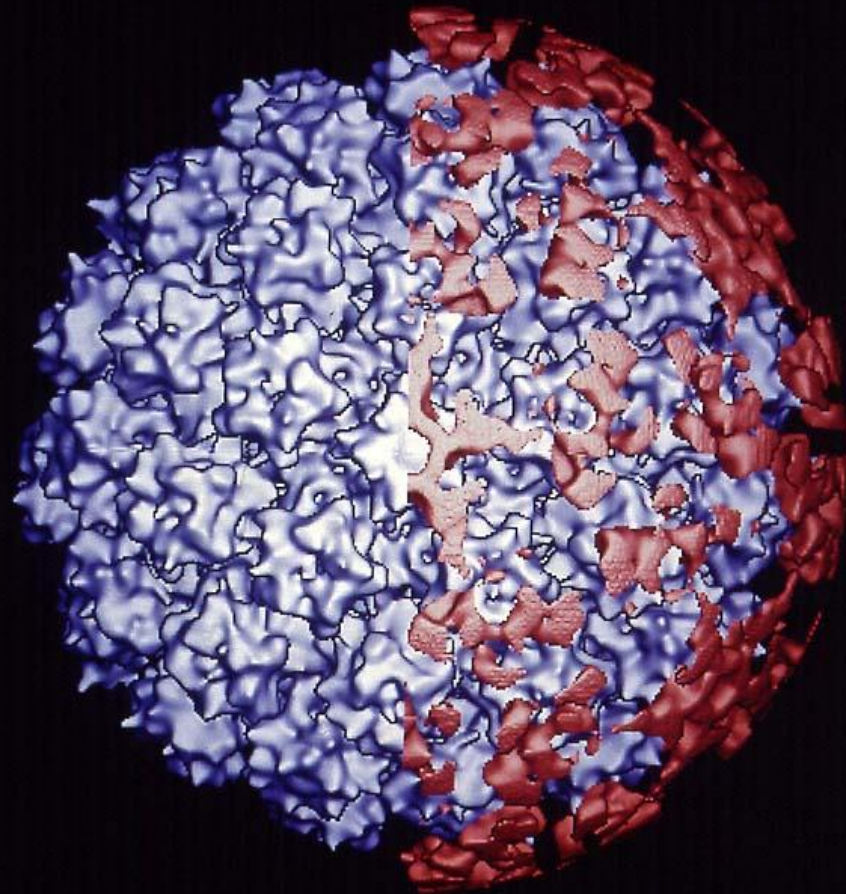
^e Institute for Health Research, Kaiser Permanente Colorado, Denver, CO, USA

- Prospective post-licensure assessment of 600,558 doses (Gardasil) from 7 managed care organizations
- ***No vaccine-related increased risk to prespecified outcomes:*** Guillan-Barré syndrome, stroke, venous thromboembolism, appendicitis, seizure, allergic reactions
 - Prespecified outcomes were derived from CDC analysis from VAERS (Vaccine Adverse Events Reporting System): Slade et al, JAMA 2009
 - Similar conclusions in Denmark from 997,585 girls, of whom 296,826 received 696,240 doses (Gardasil): Arnheim-Dahlstrom et al., BMJ, 2013
 - Rate of anaphylaxis (1 case, 26 y.o.) similar to other vaccines
 - Rate of fainting similar to that of other adolescent vaccines

High Efficacy of VLP Vaccine

- **The repetitive structure of the VLP immunogen is intrinsically immunogenic**
- **Tissue-associated neutralizing antibodies are exudated at potential sites of infection**
 - **Antibody levels at these sites reflect their level in serum, rather than their lower level in the non-disrupted genital tract**
- **HPV is highly susceptible to neutralizing antibodies**

*Neutralizing L1 Antibodies (in red)
Bound to Papillomavirus Particle*

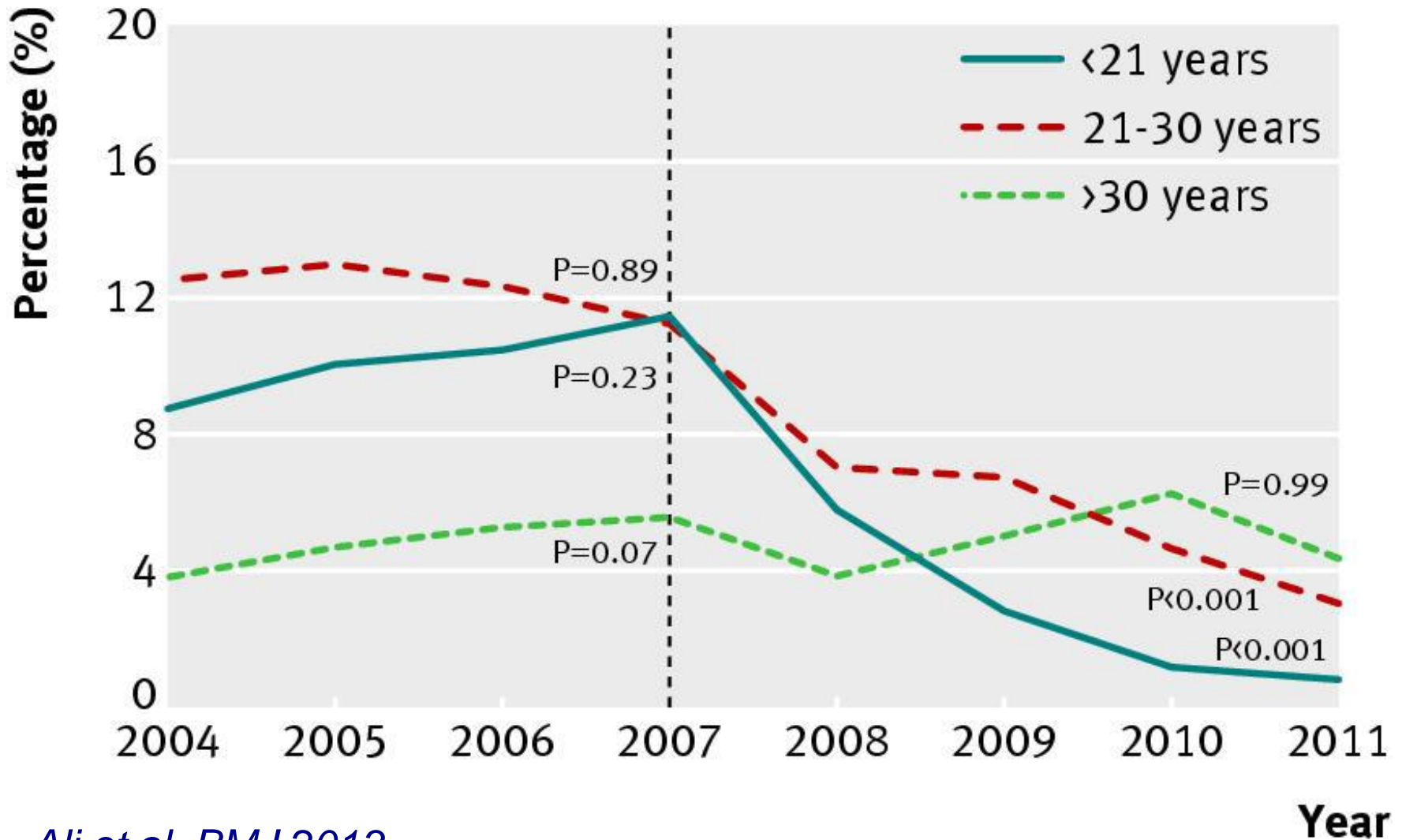


***Initial Population-
wide Impact of HPV
Vaccination***

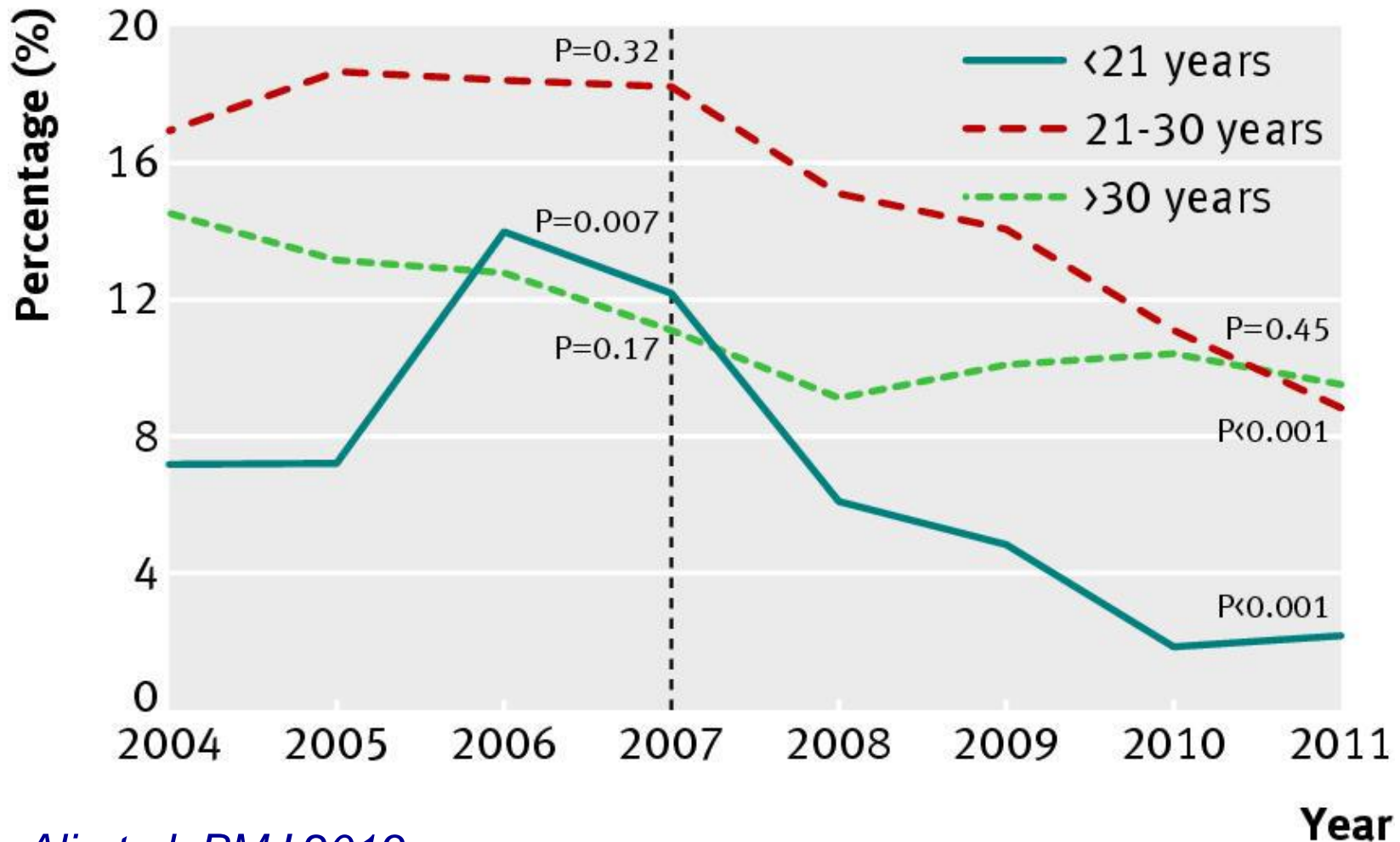
Goals of HPV Vaccination

- **To directly reduce the risk of infection and disease in vaccinees**
- **To indirectly reduce these risks by reducing the prevalence of the HPV vaccine types in the general population (herd/community immunity)**

Age-dependent Decrease in Genital Warts in Australian Women After HPV Vaccine Implementation in 2007



Herd Immunity: Decreased Incidence of Genital Warts in Heterosexual Australian Men Following Female HPV Vaccine Implementation in 2007



Ali et al, BMJ 2013

Australia: Fall in Prevalence of HPV Vaccine Types after Initiating National Vaccine Program

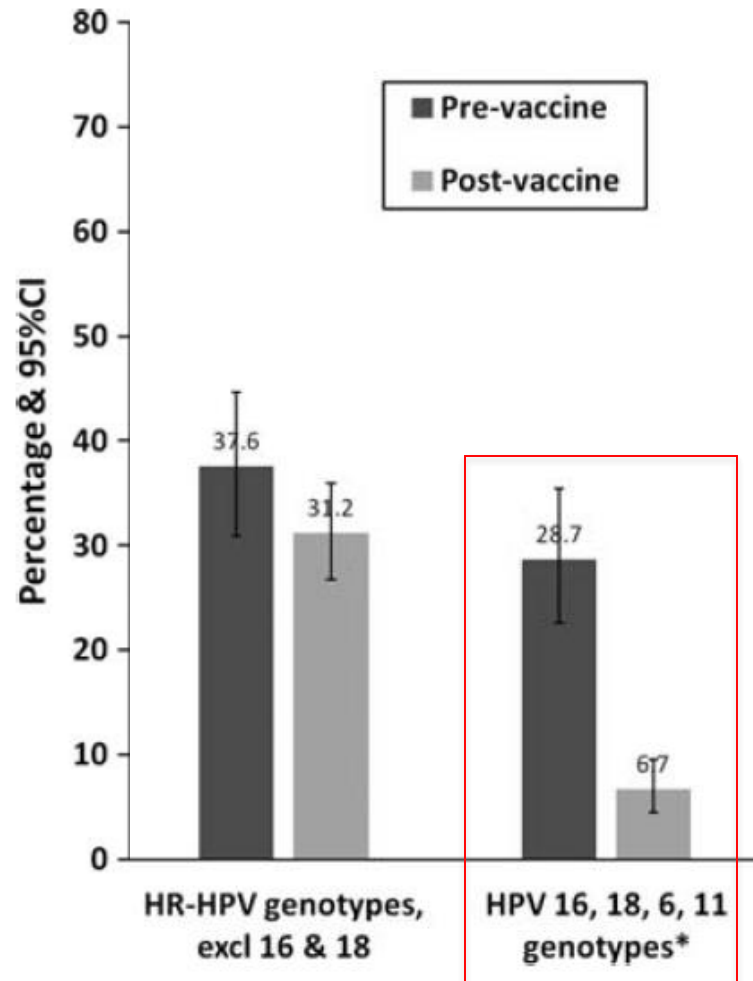
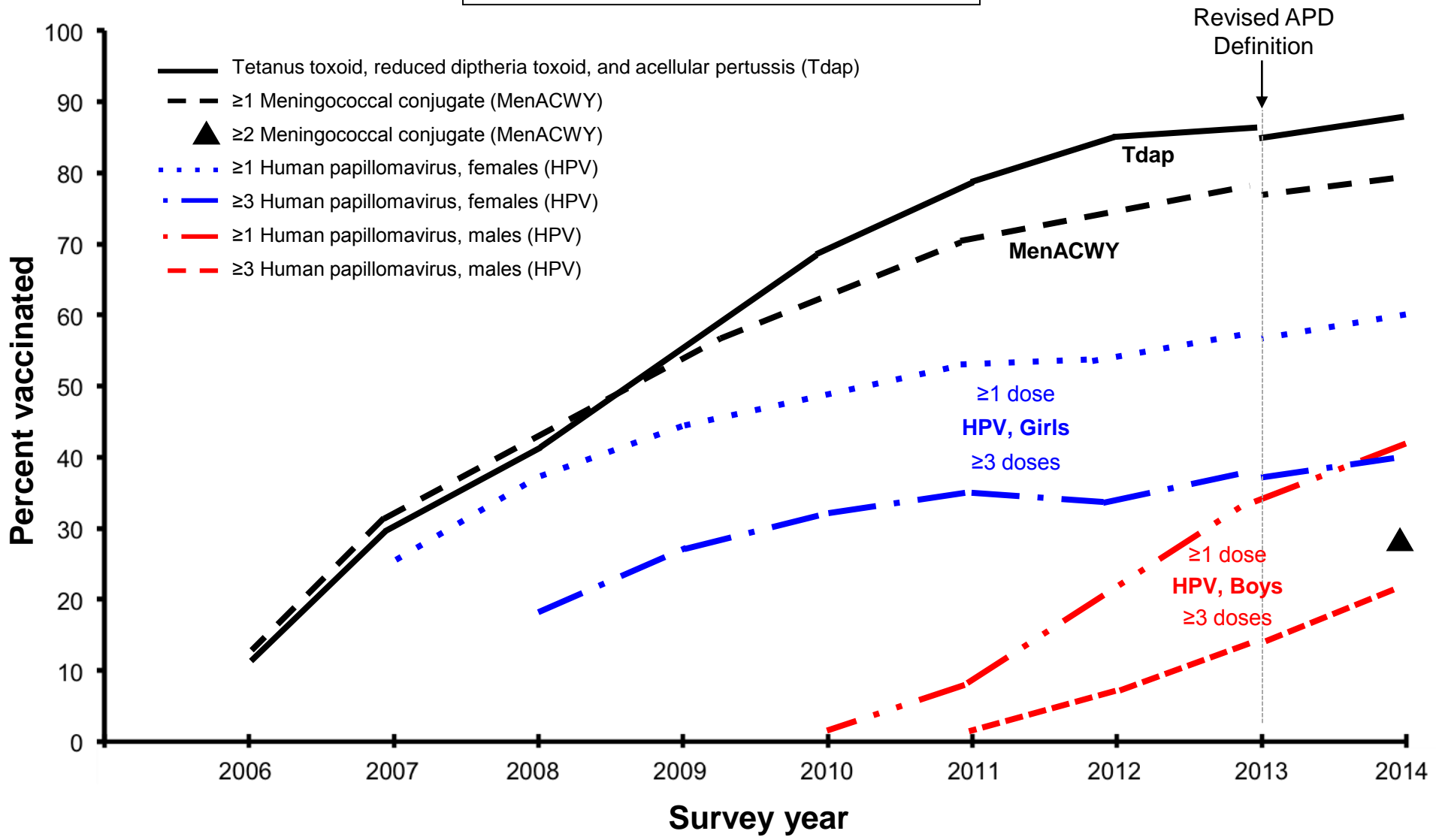


Figure 1. Differences in human papillomavirus (HPV) genoprevalence between prevaccine and postvaccine populations. * $P < .05$ for difference in percentages between groups. Abbreviations: CI, confidence interval; excl, excluding; HR-HPV, high-risk HPV.

***Limited HPV
Vaccine Uptake in
the United States***

Trends in U.S. Vaccination Rates: Ages 13-17 Years

MMWR Vol. 64, #29, July 31, 2015



Parents' Top 5 Reasons for not vaccinating their Children with the HPV Vaccine (CDC, 2013)

Parents of girls		
Reason	%	(95% CI)
Lack of knowledge	15.5	(13.0–18.5)
Not needed or necessary	14.7	(12.5–17.3)
Safety concern/Side effects	14.2	(11.8–16.8)
Not recommended	13.0	(10.8–15.5)
Not sexually active	11.3	(9.1–13.9)

Parents of boys		
Reason	%	(95% CI)
Not recommended	22.8	(20.6–25.0)
Not needed or necessary	17.9	(15.9–20.1)
Lack of knowledge	15.5	(13.7–17.6)
Not sexually active	7.7	(6.4–9.2)
Safety concern/Side effects	6.9	(5.6–8.5)

Stokley et al, MMWR 63:620-4, July 25, 2014

2014 HPV and Meningococcal Vaccination Rates for 13-17 year olds

	HPV vaccine (1 dose)		Meningococcal vaccine
	Girls	Boys	
United States	60%	42%	79%
Below poverty	67%	52%	79%
At or above poverty	58%	39%	79%
Maryland	58%	47%	86%

From MMWR July 31, 2015

***For Adolescents,
Two Vaccine Doses
may be Sufficient***

Two vaccine doses: The future is now (except in the US)

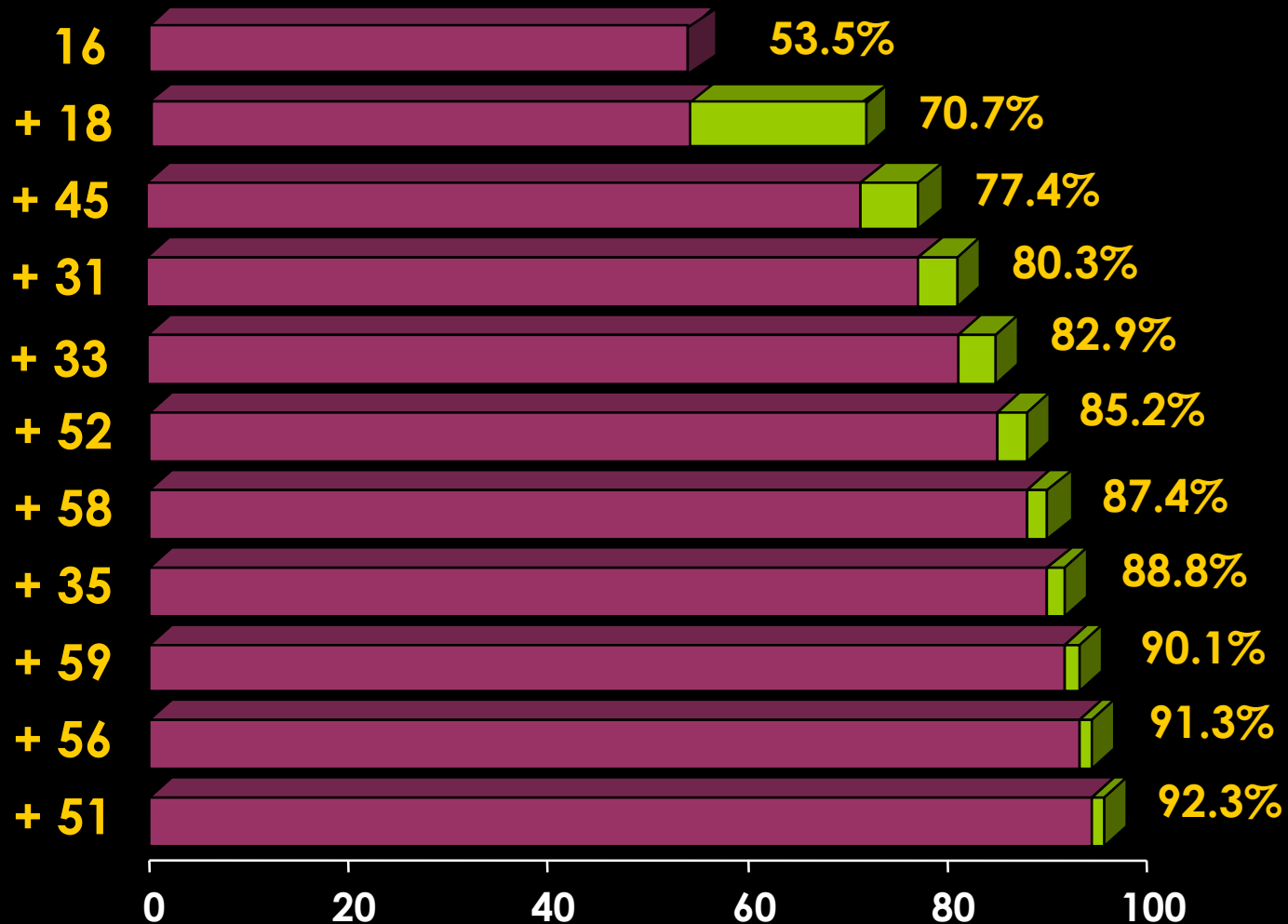
- Immune response in girls and boys <15 years old is stronger than in older teenagers
- In young adolescents, 2 doses separated by 6 months produce an immune response similar to those in the responses in the efficacy trials
- ***European Medicines Agency approval and World Health Organization Strategic Advisory Group of Experts recommendation for 2 doses for HPV vaccines:***
 - ***Bivalent (GSK) girls 9-14***
 - ***Quadrivalent (Merck) girls & boys 9-13***

***A Second Generation
Vaccine: Protecting
against a Larger
number of HPV
Types***

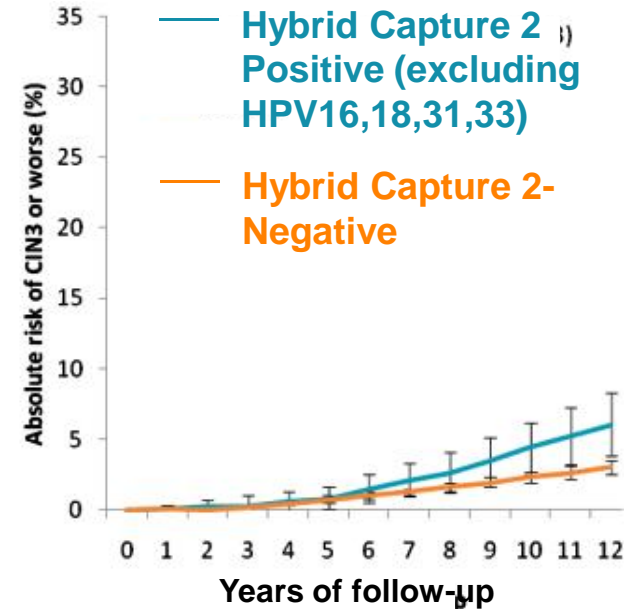
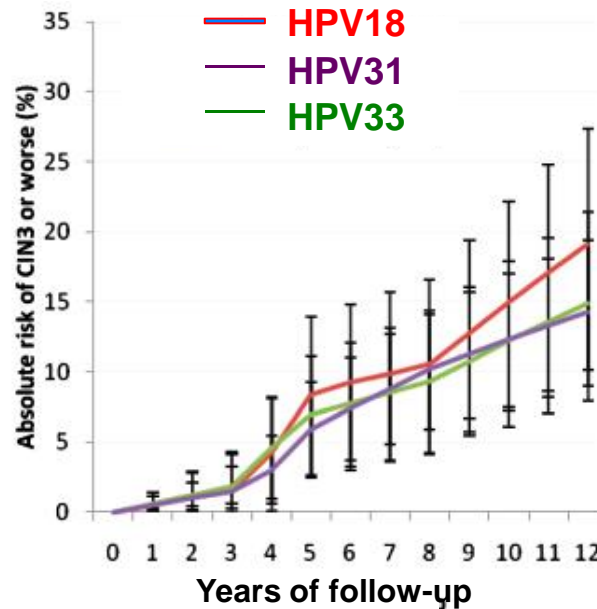
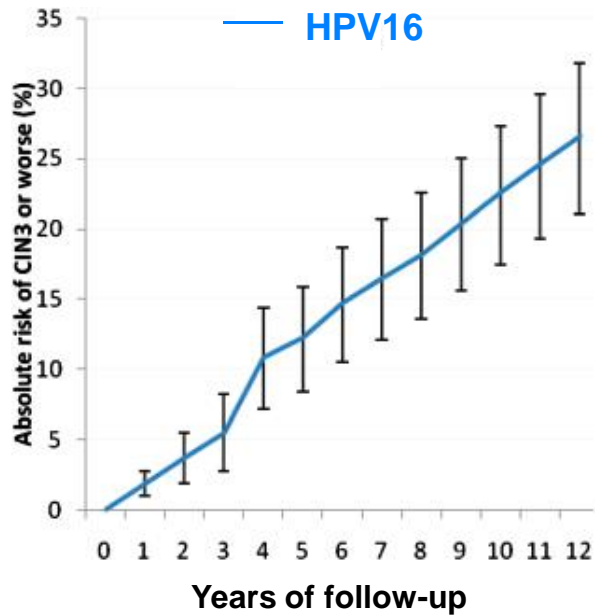
A 9-valent VLP vaccine: adding 5 oncogenic HPV types to the quadrivalent vaccine

- A randomized controlled trial that compared the efficacy of the quadrivalent vaccine to the 9-valent vaccine
- ***CIN2+ vaccine efficacy against the 5 additional HPV types was 96%: 1 case in the 9-valent group vs. 27 cases in quadrivalent group***
 - Joura et al, A 9-valent HPV vaccine against infection and epithelial neoplasia in women. New Eng J Med 372: 711-23, 2015
- FDA approval, December, 2014
- ACIP recommendation, February, 2015
- Two dose non-inferiority immunogenicity trial in young adolescents in progress

Potential Reduction in Cervical Cancer from the Addition of Multiple HPV Types to L1 VLP Vaccine



HPV Type Affects the Rate of Development of CIN3 or worse in women with normal cytological findings at baseline: The Danish Cohort Study



A single HPV test predicts 10-fold increased risk of CIN3 for >10 years

From Kjaer et al, J Natl Cancer Inst 102: 1478-88, 2010

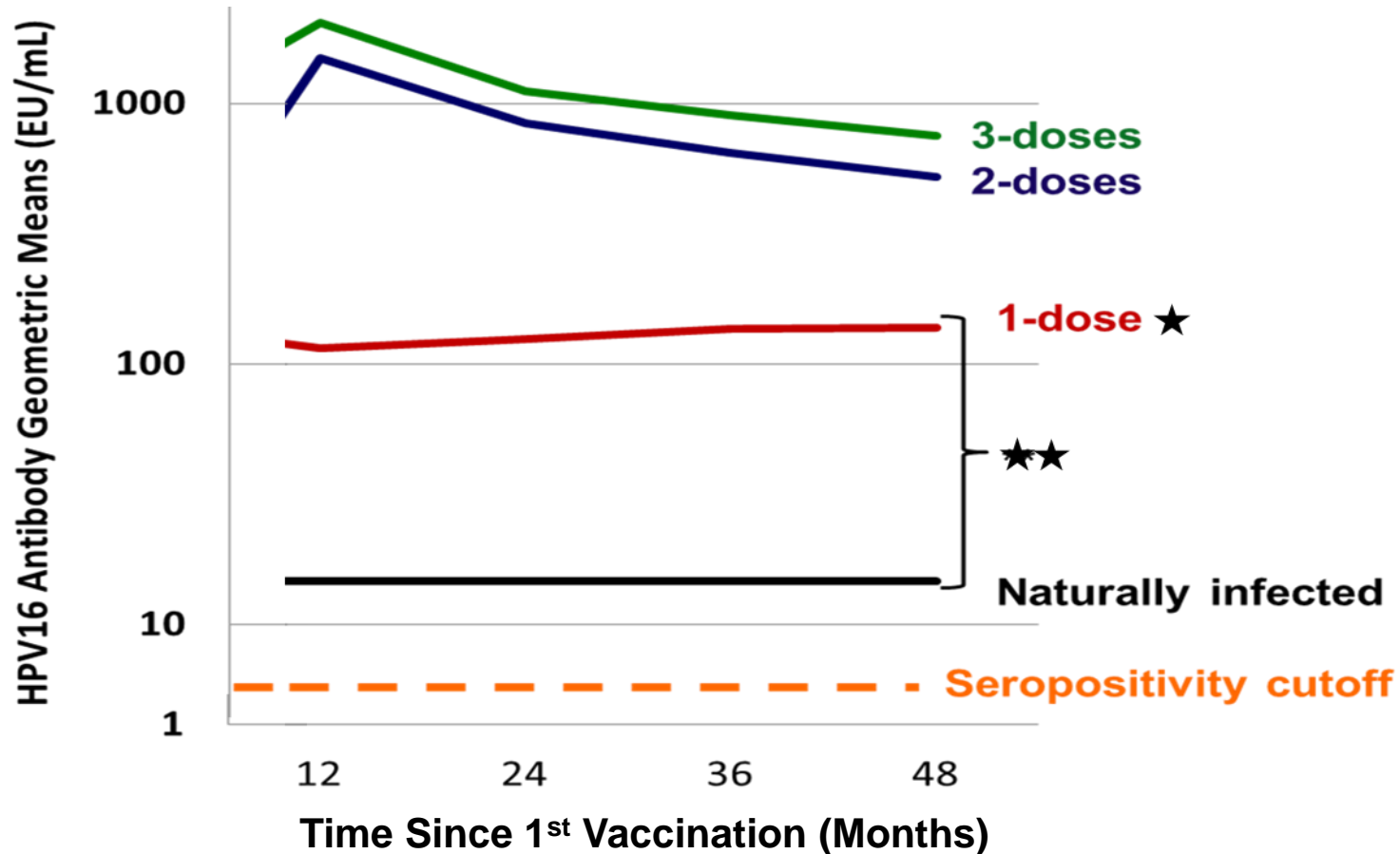
***Ongoing Research:
Could One Vaccine
Dose be Sufficient?***

One or two vaccine doses (Cervarix, GSK) can induce 4 years of protection against persistent (6 months) HPV infection with HPV16/18

Number of doses	Vaccine arm	Number of women	Number of events	Rate per 100 women	HPV vaccine efficacy % (95% CI)
3 doses	Control	3010	229	7.6%	84 (77-88)
	HPV	2957	37	1.3%	
2 doses	Control	380	24	6.3%	81 (63-94)
	HPV	422	5	1.2%	
1 dose	Control	188	15	8.0%	100 (79-100)
	HPV	196	0	0.0%	

- ***Similar results in GSK PATRICIA trial: Kreimer et al, Lancet Oncol 16:775-86, 2015***
- ***It is unknown whether these results can be extrapolated to Gardasil***
Kreimer et al, JNCI 103: 1444-51, 2011

Stable Serum Antibody Levels from a Single HPV Vaccine Dose



* 4-fold difference between 1 and 3 dose plateau titers

** ~10-fold difference between 1 dose and natural infection plateau titers

Stable antibody titers after 1 dose

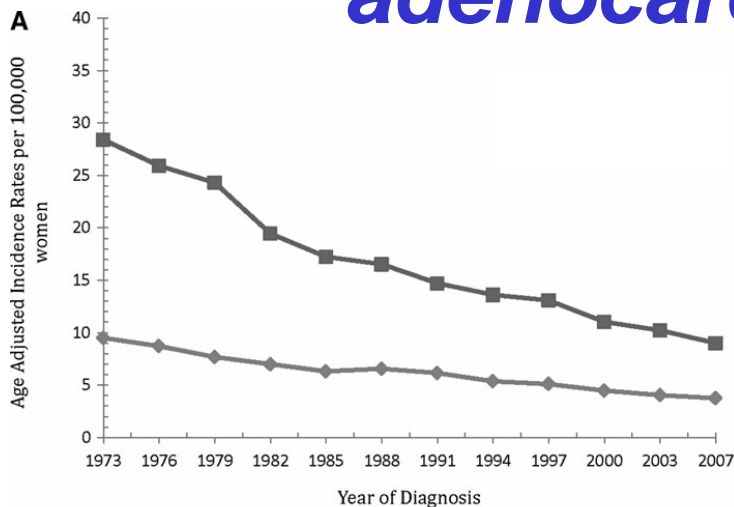
- **There is no precedent for 1 dose of a protein-based sub-unit vaccine to induce stable antibody titers for several years**
- **May be attributable to two factors**
 - **VLPs are highly immunogenic**
 - **The AS04 adjuvant is a TLR4 agonist**
- **A possible randomized controlled trial to rigorously test the efficacy of 1 dose**
 - **Test two commercial vaccines: one with alum, one with AS04**

***HPV Testing in
Cervical Cancer
Screening***

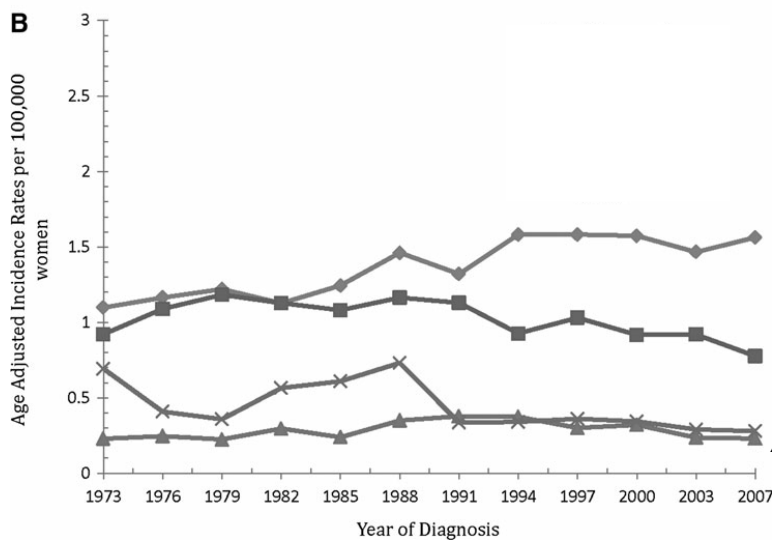
Cervical Cancer Screening: From Pattern Recognition to Molecular Diagnosis

- **Pap smear screening and other cytology-based methods are based on “pattern recognition”**
- **They have reduced cervical cancer incidence and mortality (~80% in the USA)**
- **HPV-based screening is etiology-based. It is more sensitive and has higher positive predictive value**
- **2014: Primary cervical cancer screening by HPV-based testing approved by FDA starting at age 25 (Cobas HPV test, Roche Molecular Systems)**

Cervical cancer rates (USA): Decreasing squamous cell cancer, stable adenocarcinoma

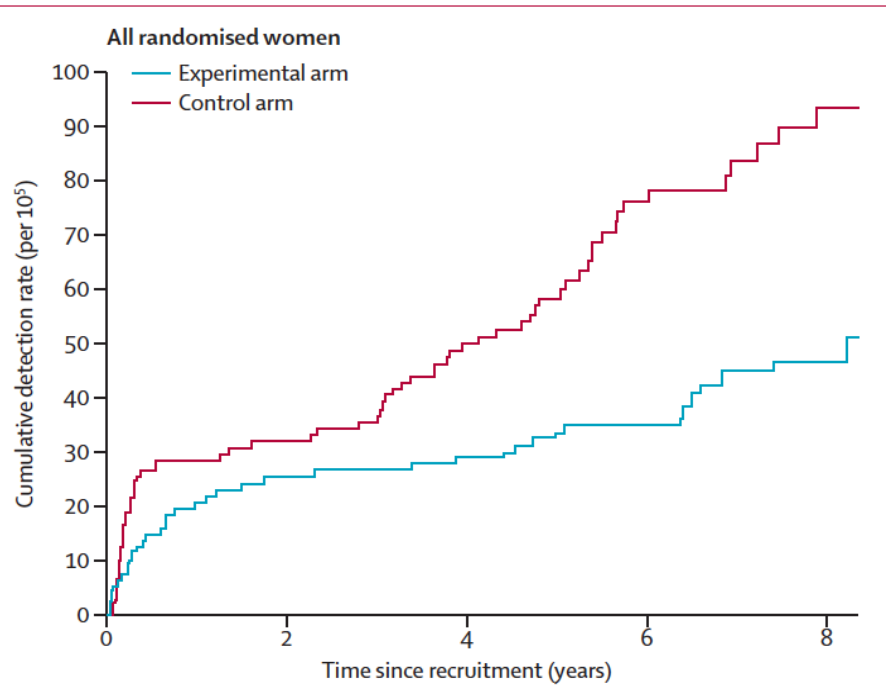


Squamous cell: blacks
Squamous cell: whites



Adenocarcinoma: whites
Adenocarcinoma: blacks
Adenosquamous: blacks & whites

HPV testing can prevent more cervical cancers, especially adenocarcinomas, than cytology



Pooled rate ratio*
(95% CI)

Morphology

Squamous-cell carcinoma

0.78 (0.49–1.25)

Adenocarcinoma

0.31 (0.14–0.69)

Adenocarcinoma vs
squamous-cell carcinoma

0.34 (0.12–0.90)

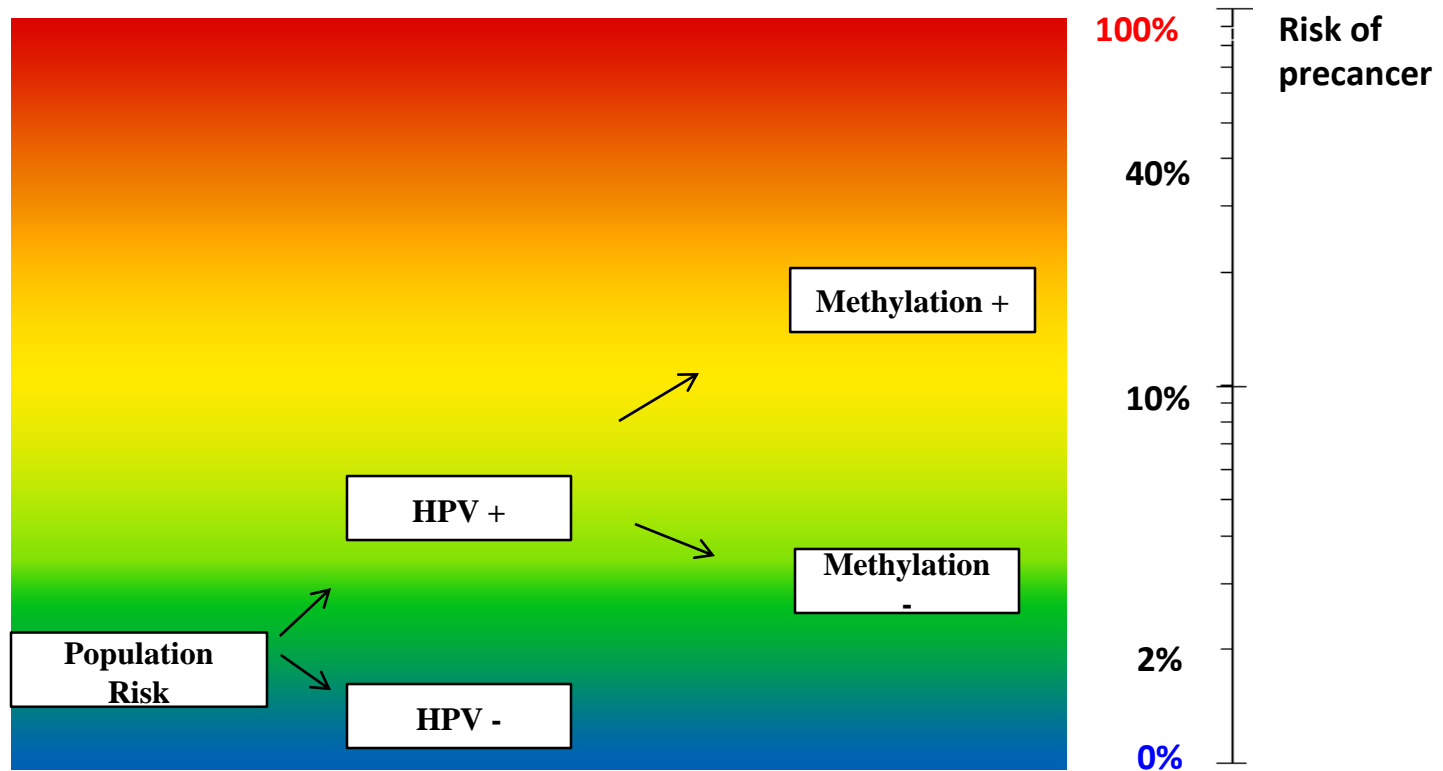
*Ratio of incidence with HPV testing
vs. incidence with cytology

**Pooled cervical cancer incidence from 4 randomized controlled trials of
cytology (control arm) vs. HPV testing (experimental arm)**

HPV testing: Ancillary molecular testing to increase specificity (CIN2/3+)

- Pap HPV testing has high sensitivity but sub-optimal specificity (CIN2/3+)
- Candidate ancillary molecular testing based on HPV-induced pathogenesis
- HPV induces p16^{INK4A} and Ki-67 expression
- Progression to CIN3+ is associated with methylation of silenced HPV genes

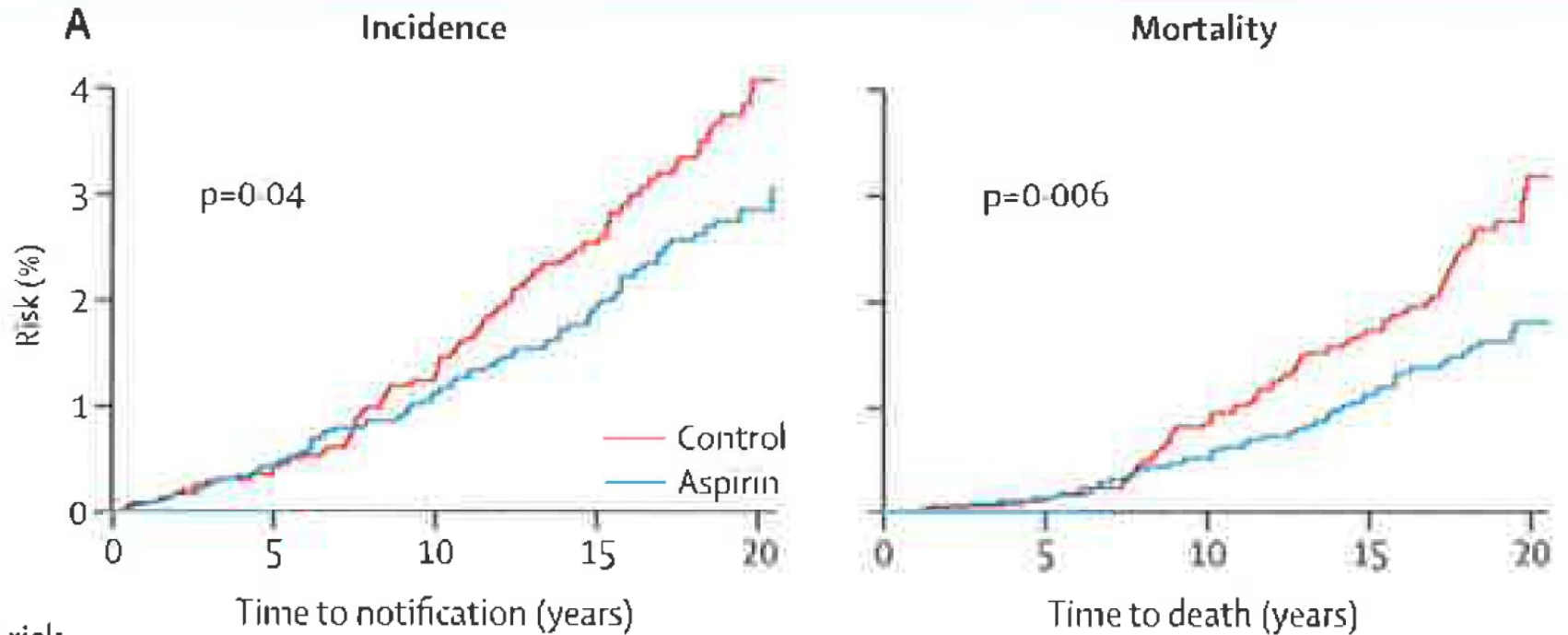
HPV Methylation for Triage of HPV-positive women



- HPV methylation can achieve risk stratification that alters clinical management
- Methylation testing can be done from the HPV DNA sample, is applicable for self-sampling

***Aspirin: a candidate
intervention for
preventing
colorectal cancer***

Long term use of low dose aspirin can reduce the risk of colorectal cancer



Number at risk

Control	4043	3645	3149	2545	806	4043	3653	3164	2566	814
Aspirin	4030	3618	3095	2552	779	4030	3629	3114	2575	785

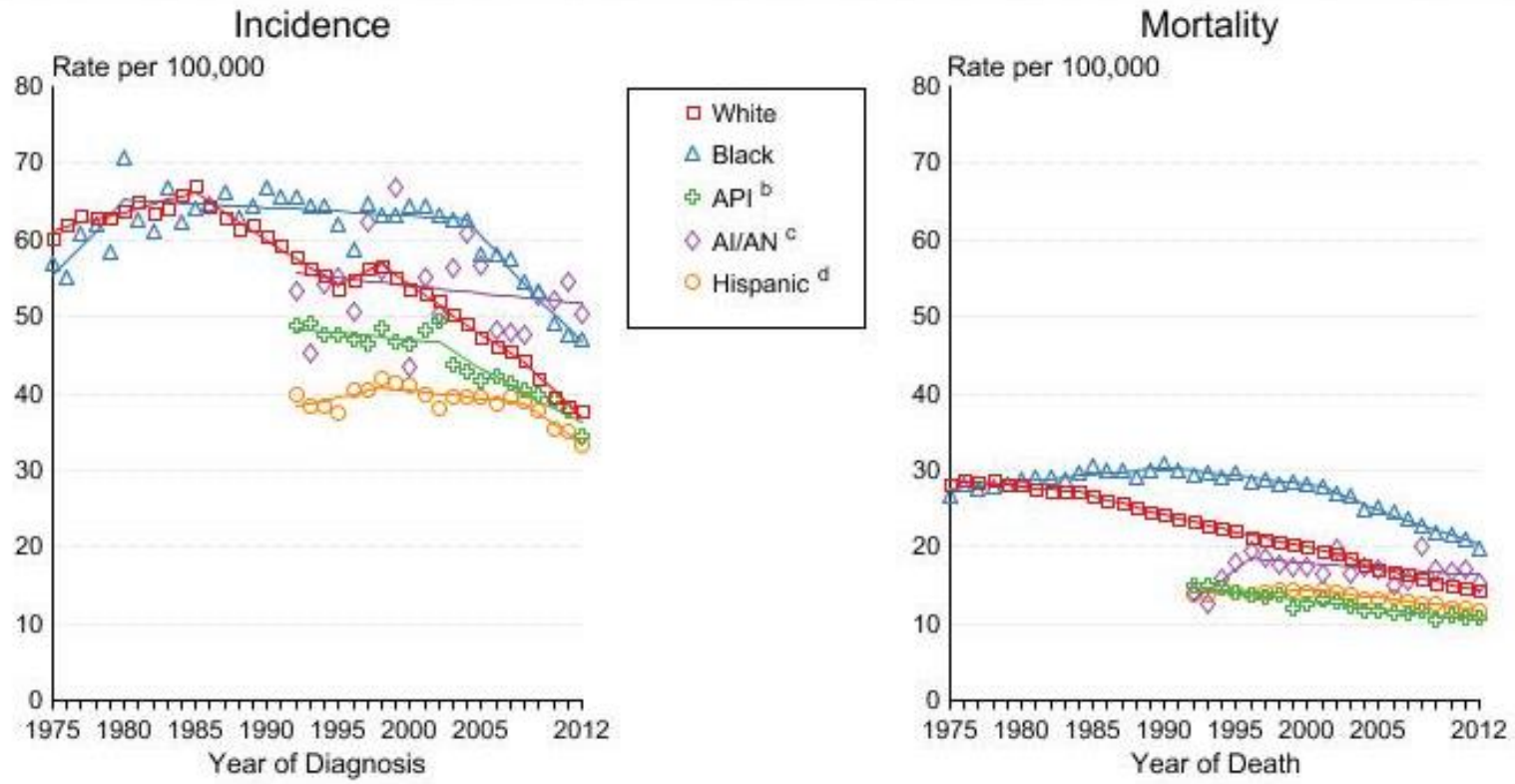
Rothwell et al, Lancet, 2010

USPSTF: Draft recommendation for aspirin to prevent colorectal cancer

- Use of aspirin for preventing colorectal cancer is tied to its use for preventing cardiovascular disease
- “The USPSTF recommends low-dose aspirin use for the primary prevention of cardiovascular disease (CVD) and colorectal cancer in adults ages 50 to 59 years who have a 10% or greater 10-year CVD risk, are not at increased risk for bleeding, have a life expectancy of at least 10 years, and are willing to take low-dose aspirin daily for at least 10 years.” September, 2015

SEER Incidence and US Death Rates^a Cancer of the Colon and Rectum, Both Sexes

Joinpoint Analyses for Whites and Blacks from 1975-2012
and for Asian/Pacific Islanders, American Indians/Alaska Natives and Hispanics from 1992-2012



Source: Incidence data for whites and blacks are from the SEER 9 areas (San Francisco, Connecticut, Detroit, Hawaii, Iowa, New Mexico, Seattle, Utah, Atlanta). Incidence data for Asian/Pacific Islanders, American Indians/Alaska Natives and Hispanics are from the SEER 13 Areas (SEER 9 Areas, San Jose-Monterey, Los Angeles, Alaska Native Registry and Rural Georgia). Mortality data are from US Mortality Files, National Center for Health Statistics, CDC.

- ^a Rates are age-adjusted to the 2000 US Std Population (19 age groups - Census P25-1103). Regression lines are calculated using the Joinpoint Regression Program Version 4.2.0, April 2015, National Cancer Institute. Joinpoint analyses for Whites and Blacks during the 1975-2012 period allow a maximum of 5 joinpoints. Analyses for other ethnic groups during the period 1992-2012 allow a maximum of 3 joinpoints.
- ^b API = Asian/Pacific Islander.
- ^c AI/AN = American Indian/Alaska Native. Rates for American Indian/Alaska Native are based on the CHSDA(Contract Health Service Delivery Area) counties.
- ^d Hispanic is not mutually exclusive from whites, blacks, Asian/Pacific Islanders, and American Indians/Alaska Natives. Incidence data for Hispanics are based on NHIA and exclude cases from the Alaska Native Registry. Mortality data for Hispanics exclude cases from New Hampshire and Oklahoma.

Aspirin to Prevent Cardiovascular Disease and Colorectal Cancer

- The final USPSTF recommendations are likely to be similar to its draft recommendations
- Increasing aspirin use among eligible individuals could prevent both cardiovascular disease and colorectal cancer
- Aspirin use for reducing risk of cardiovascular disease is lower among African Americans; increasing its use among African Americans could be an opportunity to reduce this health disparity

Summary and Conclusions (1)

- Identification of HPV as a necessary cause of virtually all cervical cancers has led to two etiology-based interventions: HPV vaccination & HPV-based screening
- HPV vaccination should dramatically reduce the incidence and mortality attributable to HPV-associated cancers, not just cervical cancer
- The high immunogenicity of the vaccine means long-term protection can be induced with fewer than 3 doses
- Second generation HPV vaccines with activity against a broader range of HPV types can achieve the greatest reduction in HPV-associated disease

Summary and Conclusions (2)

- HPV-based screening can reduce cervical cancer incidence even more effectively than cytology-based screening
- Development of ancillary tests (e.g., viral DNA methylation) may increase the specificity of HPV testing
- High vaccine uptake may enable raising the age at which cervical cancer screening is begun
- If the use of aspirin for preventing colorectal cancer becomes standard of care, it will provide a companion approach to screening for preventing colorectal cancer