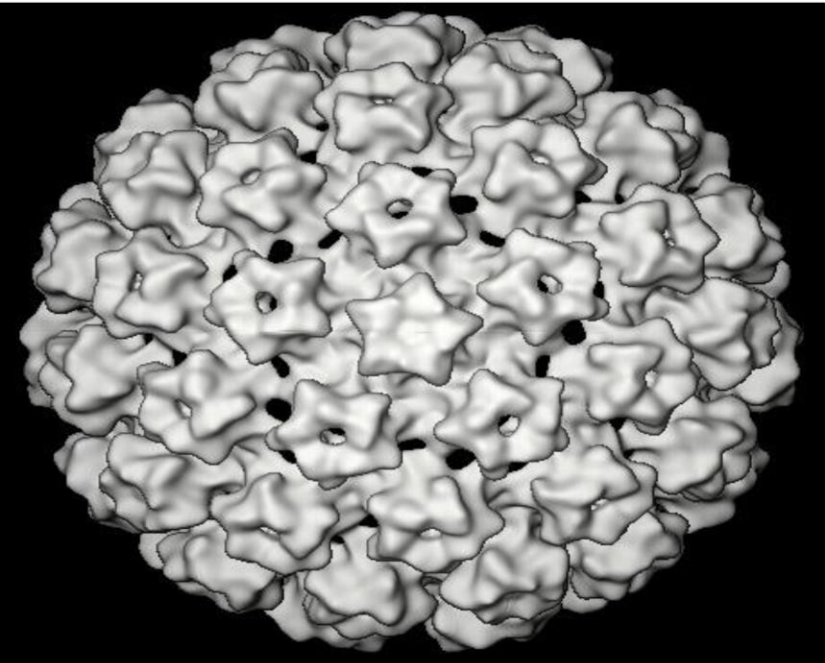


HPV infections

Vaccines to Prevent Orogenic HPV Infections

John Schiller, National Cancer Institute, NIH, USA



- HPV and Cancer
- Prophylactic HPV Vaccine
- Implementation Issues

Infectious agents

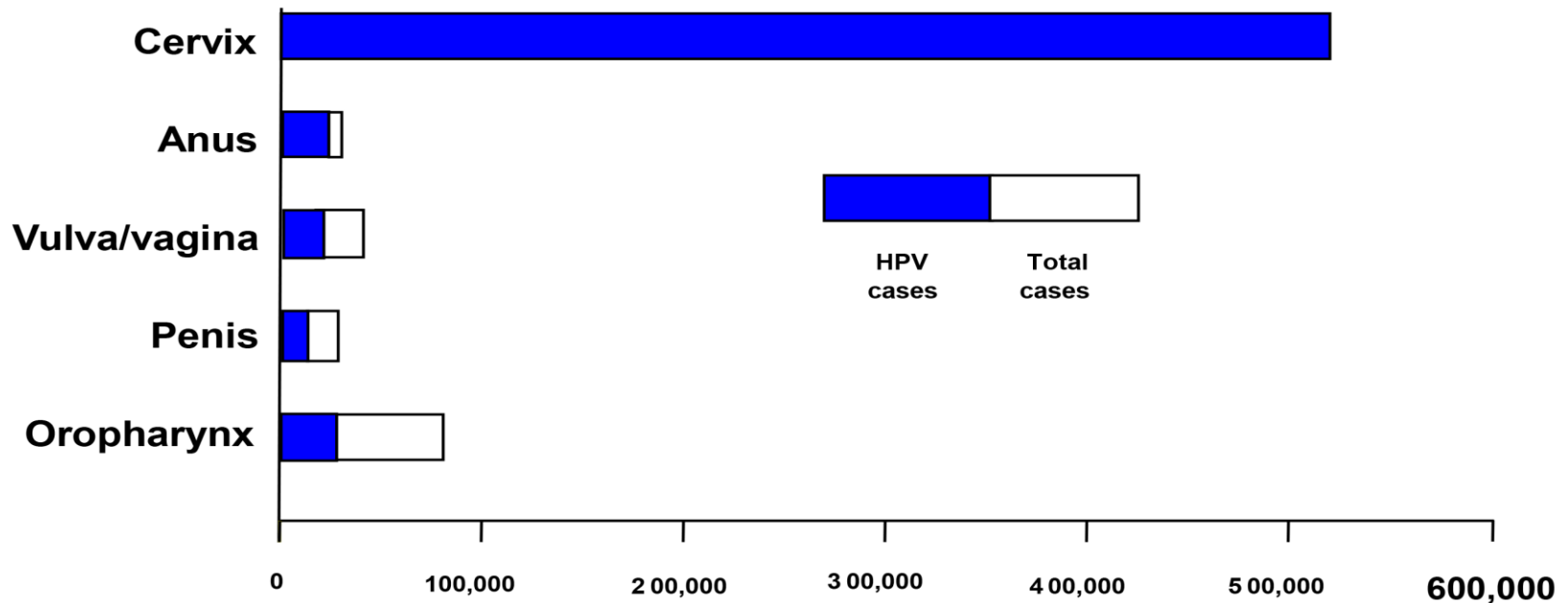
Infectious Agents Are a Major Cause of Cancer

An estimated 16% of human cancers are attributed to infection agents

Microbe	Annual Incidence	% of Infection Assoc. Cancers	Cancer Types
Helobacter pylori	660,000	32.5%	Gastric
Human Papillomavirus	610,000	30.5%	Cervical, Anal, Penile, Oropharyngeal
Hepatitis B and C Virus	600,000	29.5%	Liver
Epstein-Barr Virus	110,000	5.4%	Lymphoma, Nasopharyngeal
Kaposi's Sarcoma Virus	43,000	2.1%	Kaposi's Sarcoma
Schistosoma haematobium	6,000	0.3%	Bladder
Human T-cell Lymphotropic Virus-1	2,100	0.1%	Adult T cell Leukaemia
Opistharchis/Clonors chis	2,000	0.1%	Cholangiocarcinoma
TOTAL	2,000,000	100%	

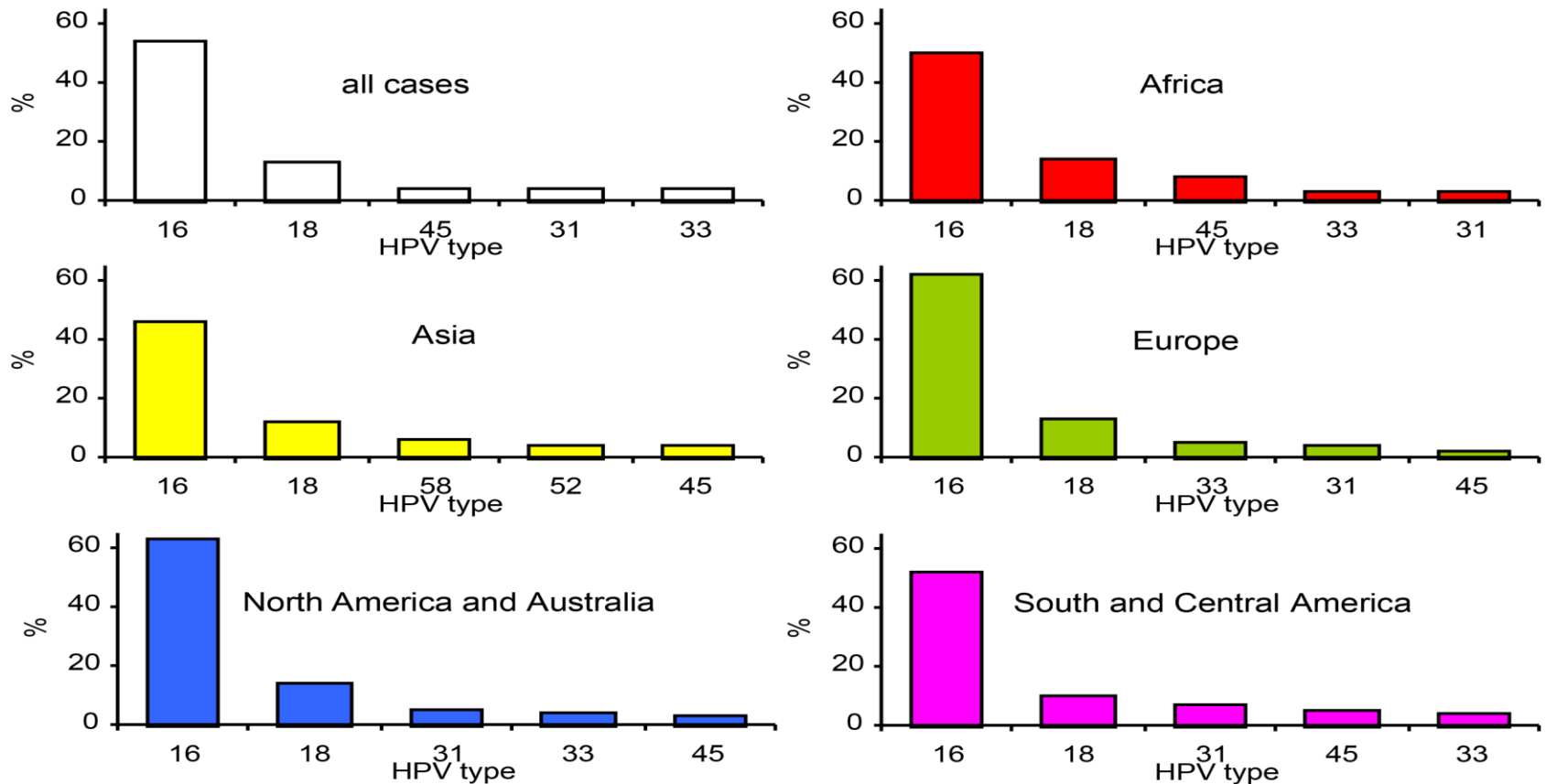
Cancers and HPV

Worldwide Incidence and Distribution of Cancers Attributable to HPV



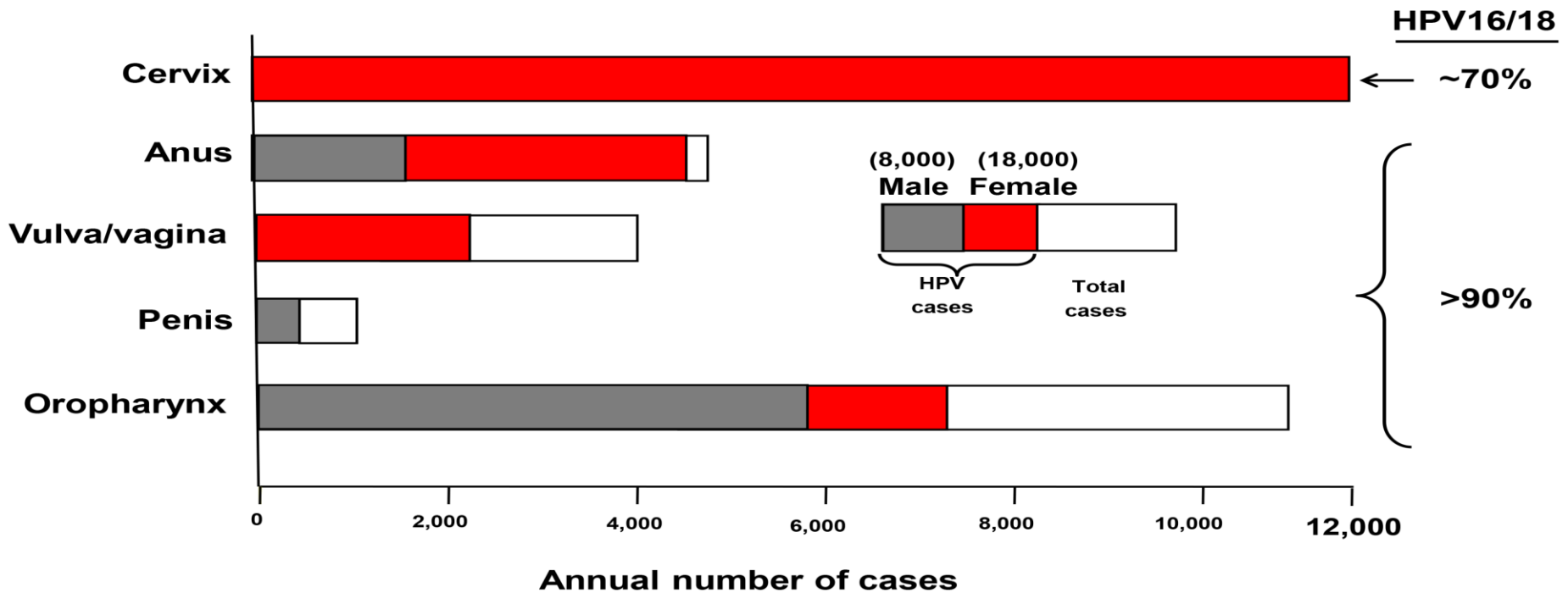
HPV types

5 Most Common HPV Types in Cervical Squamous Cell Carcinoma - By Region



HPV cancers

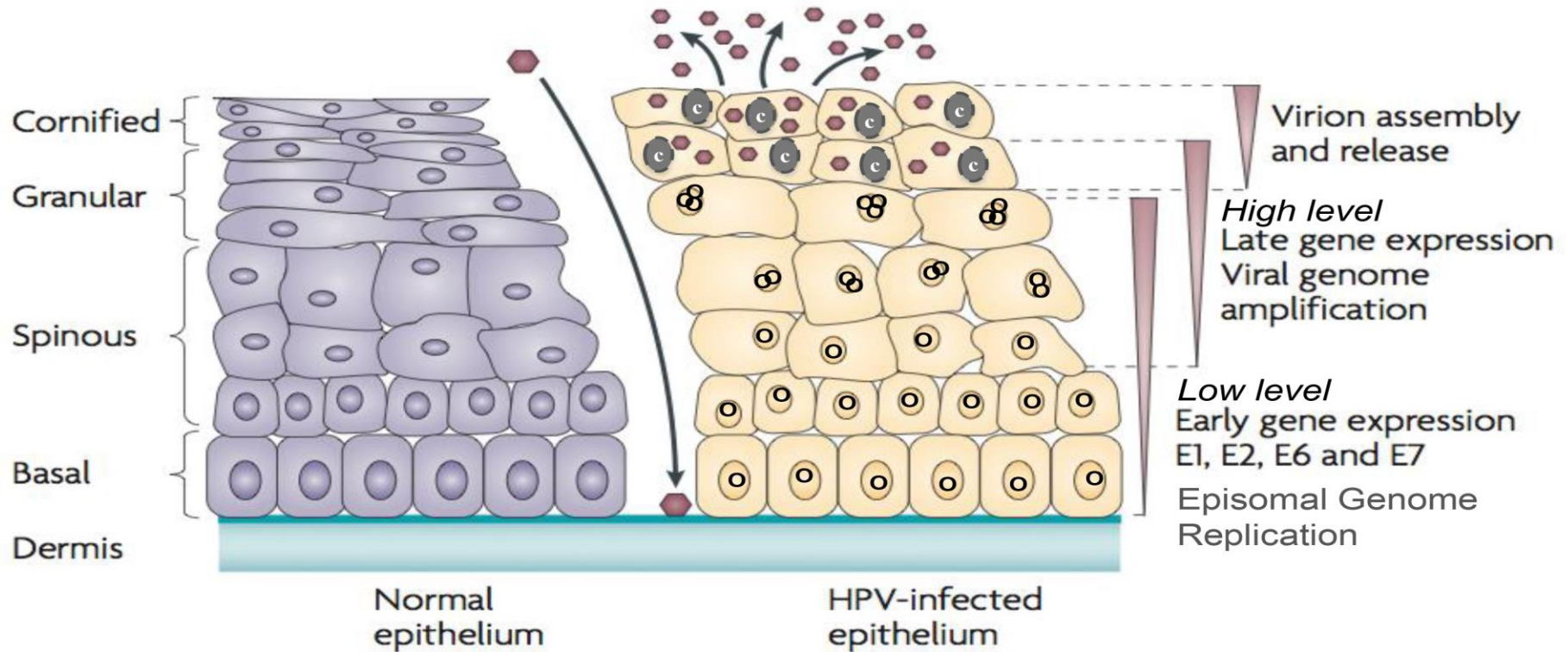
United States: Annual Incidence and Distribution of Cancers Attributable to HPV in 2004-2008



- Pap screening has reduced the incidence of cervical cancer by ~ 80%
- Incidence of HPV-positive oropharynx cancer 1988-2004 increased 225%

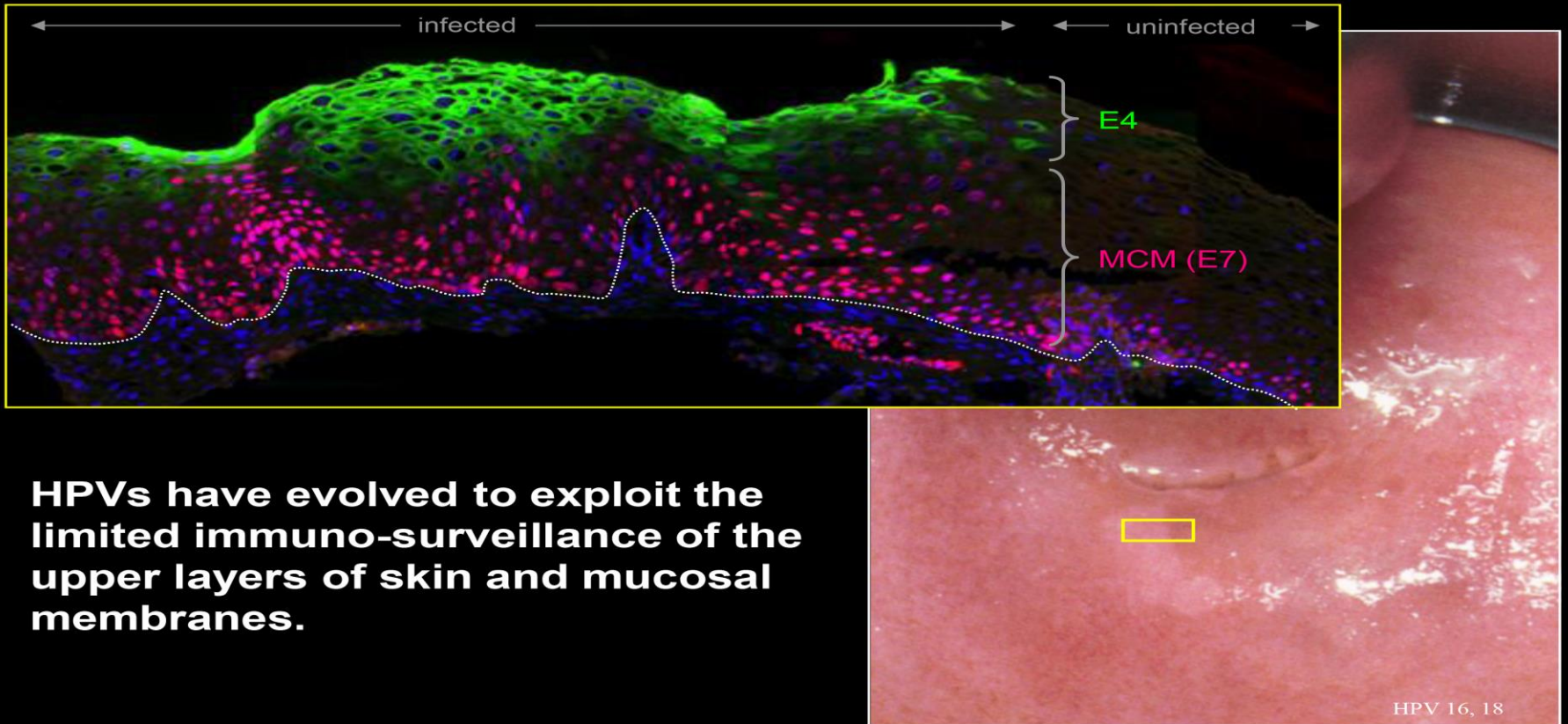
HPV life cycle

HPV Life Cycle in a Stratified Squamous Epithelium: Designed for Immune Evasion



HPV infection

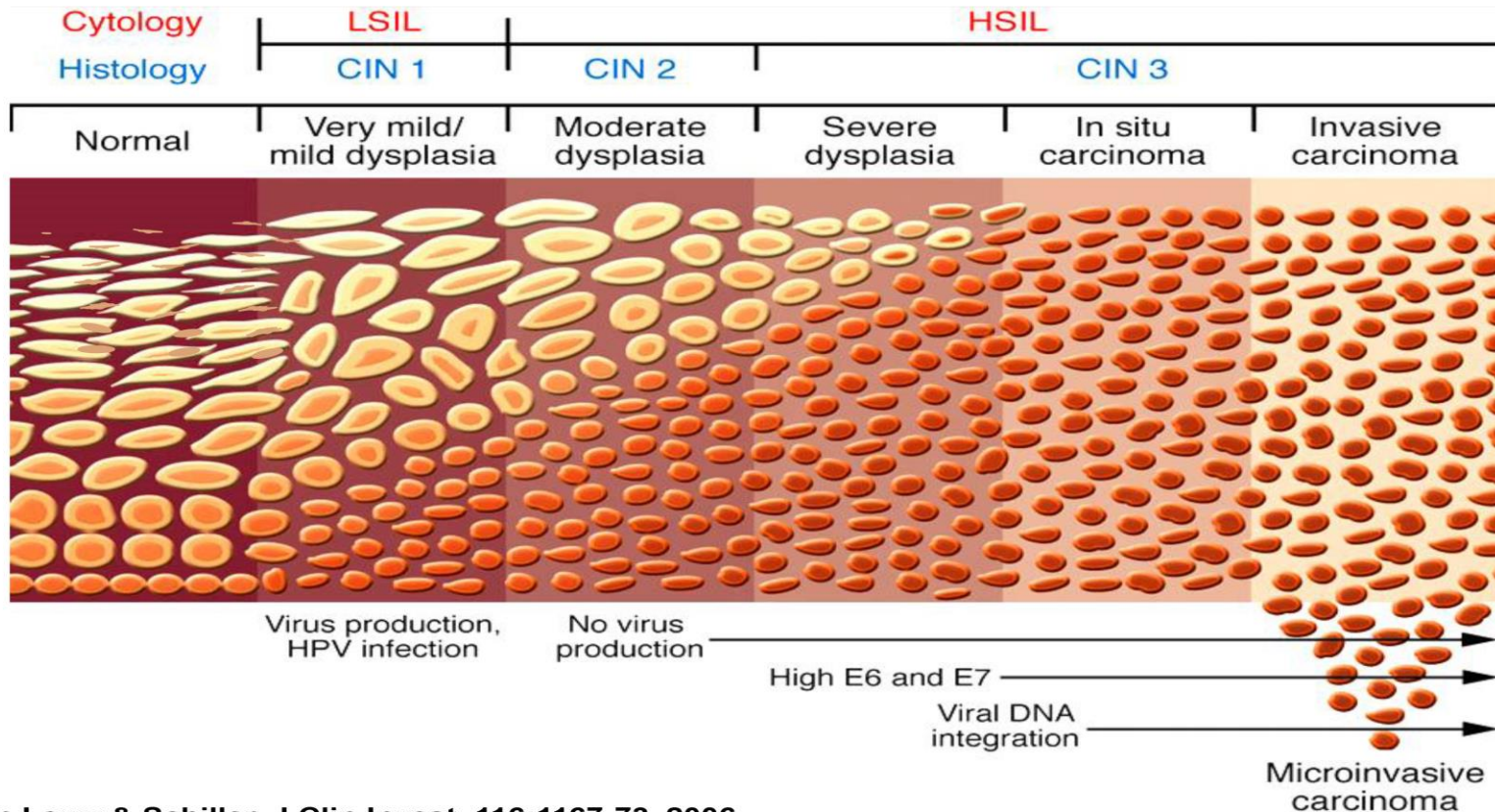
Productive HPV Infection: Hiding in Plain Site



HPVs have evolved to exploit the limited immuno-surveillance of the upper layers of skin and mucosal membranes.

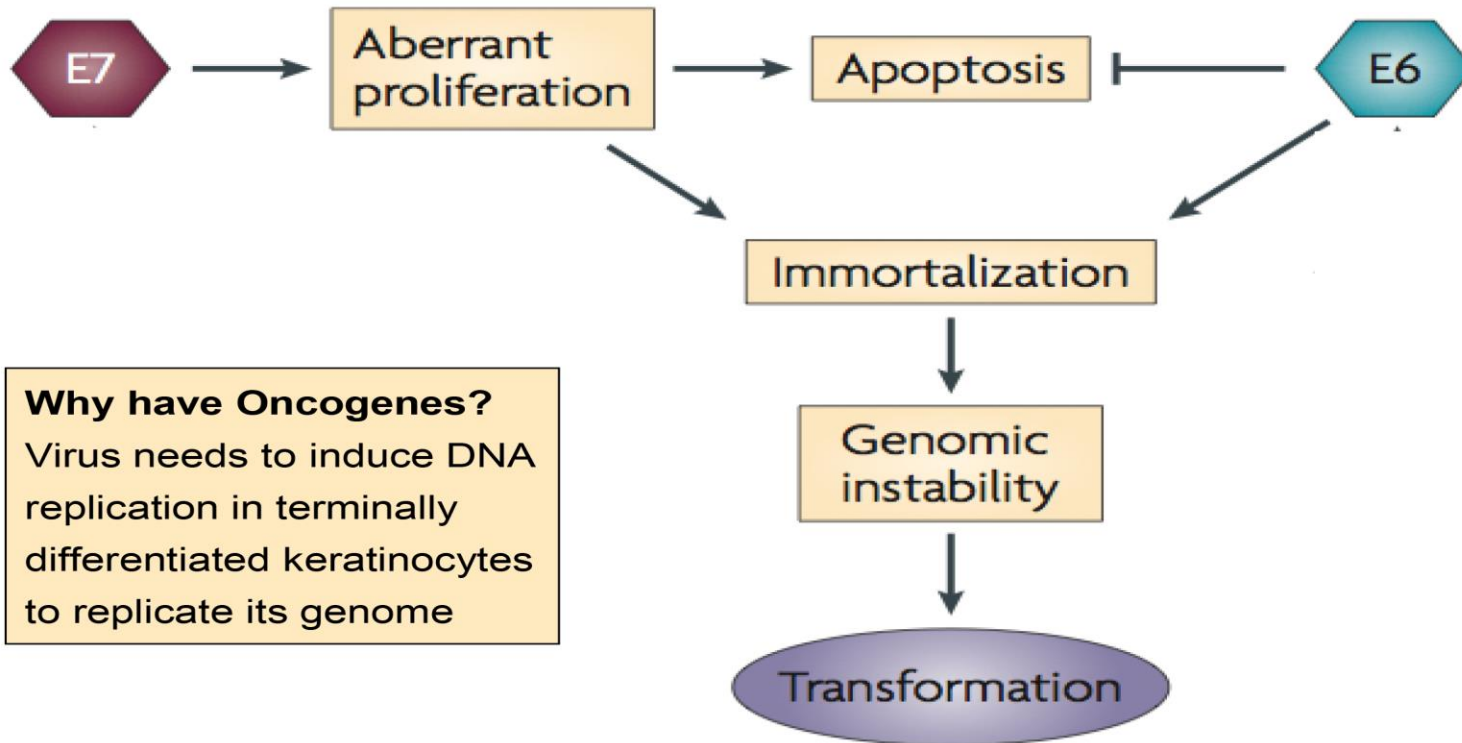
Precursor lesions

Precursor lesions for cervical cancer



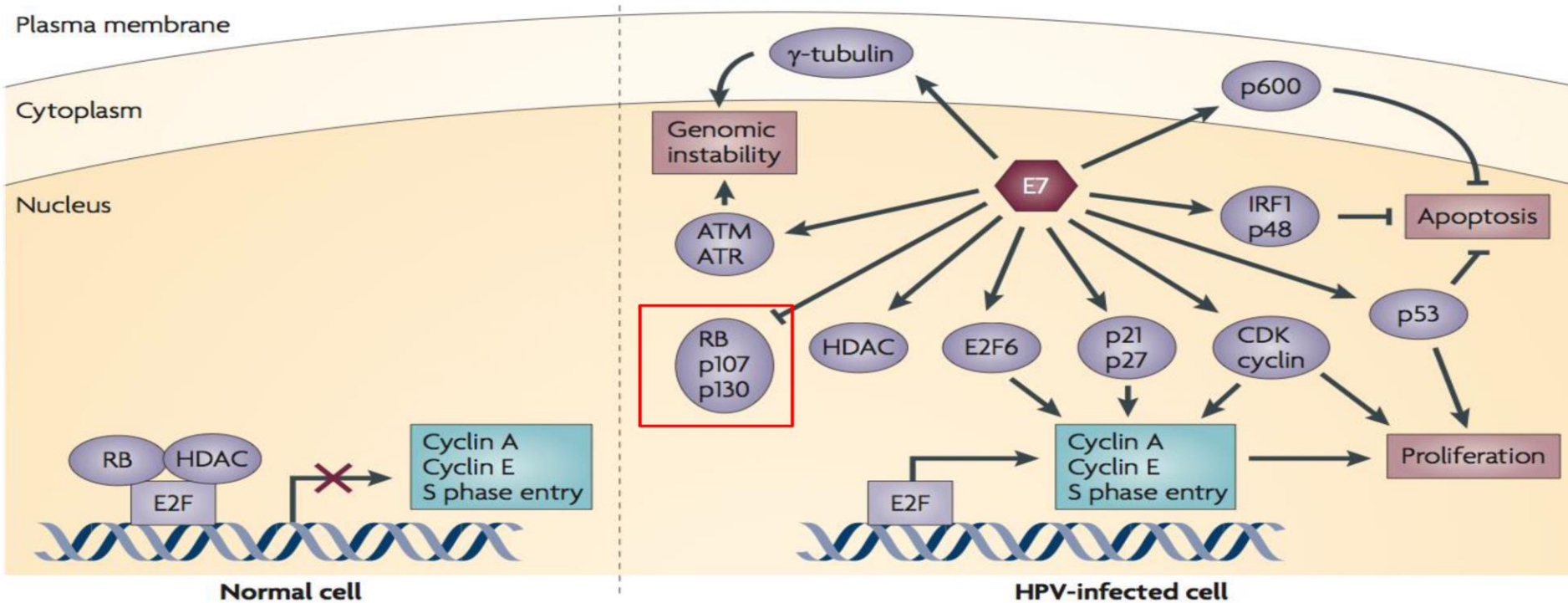
HPV carcinogenesis

Molecular Mechanisms Involved in HPV Carcinogenesis



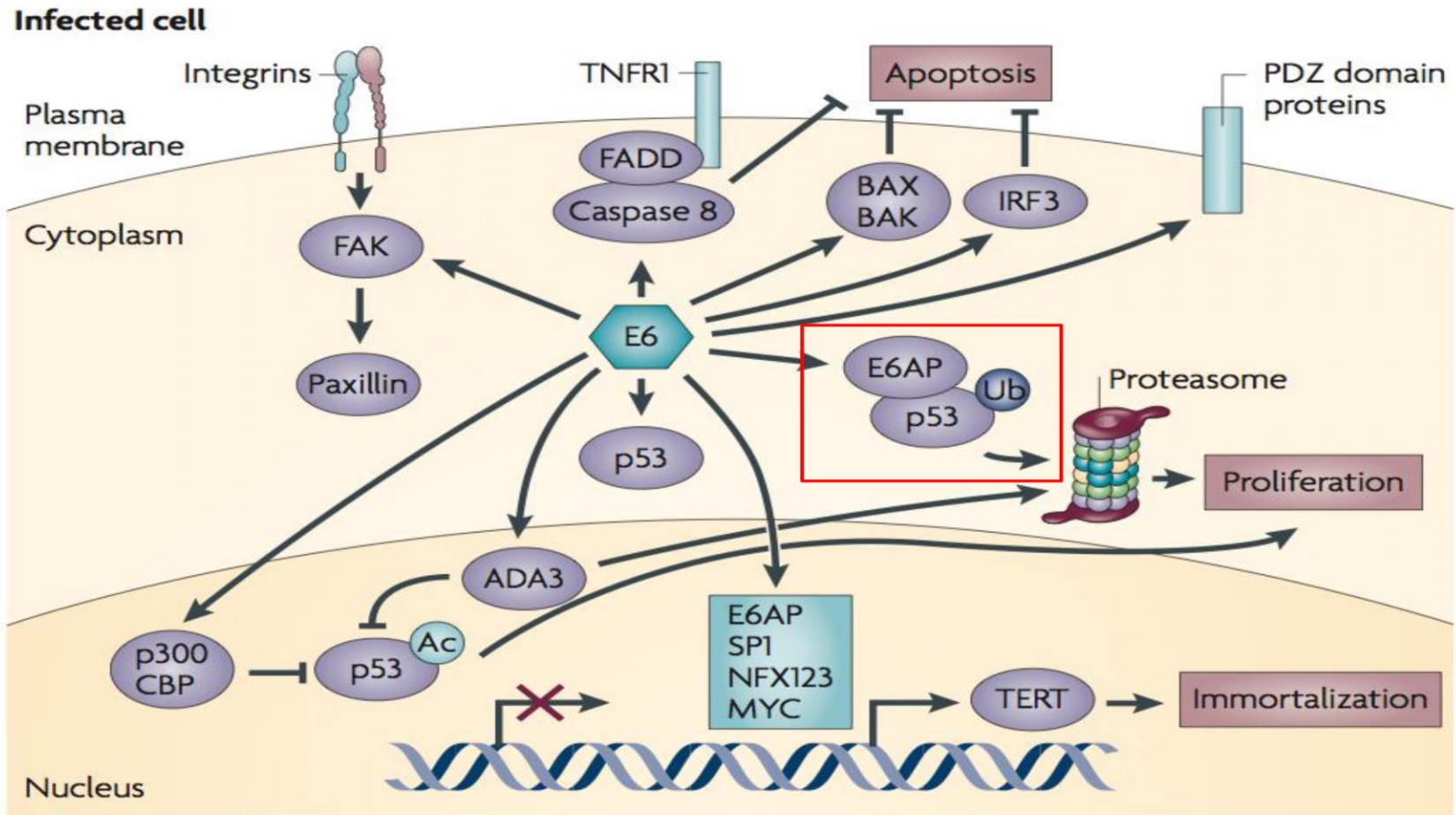
Cellular proteins

Cellular Proteins and Pathways Affected by HPV E7



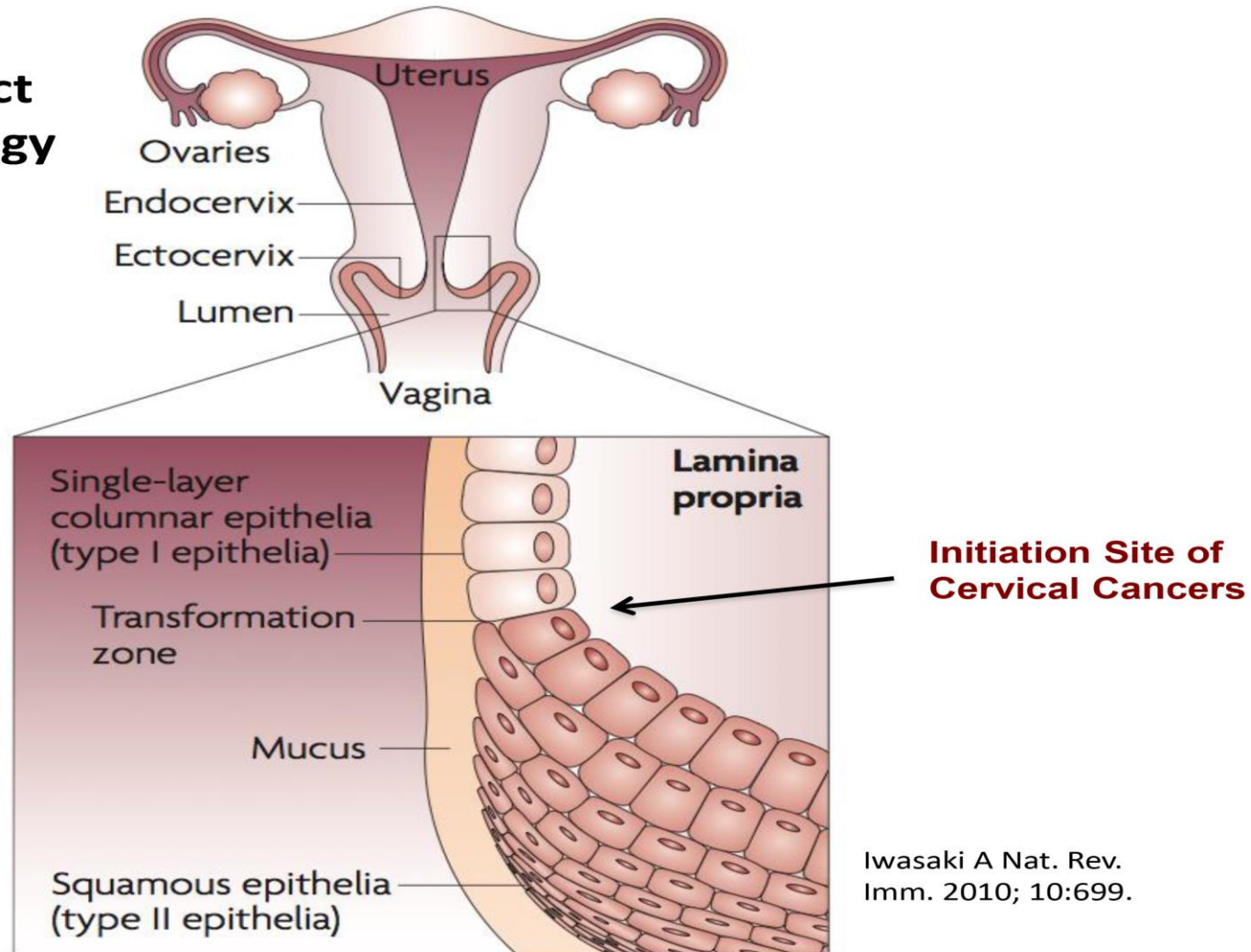
HPV pathways

Cellular Proteins and Pathways Affected by HPV E6



Cervical cancer

Female Reproductive Tract Anatomy & Histology



Transformation Zones in Other HPV Cancers

Anal cancer also occur at the transformation zone.

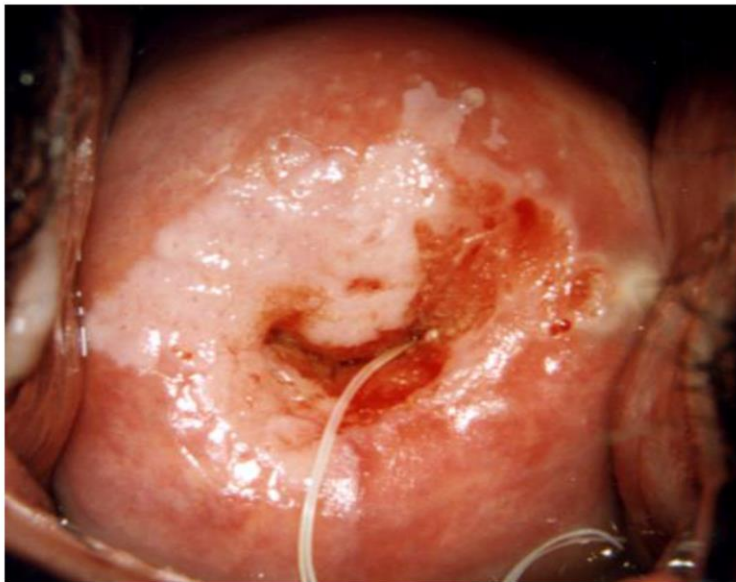
HPV Infections of the vulvar, vagina and penis are common.

Cancers at these site are relatively rare.

They lack a transformation zone.

Transition zone

Cervical Cancer Develop at the Transition Zone Between Squamous and Columnar Epithelium



High-grade Precursor



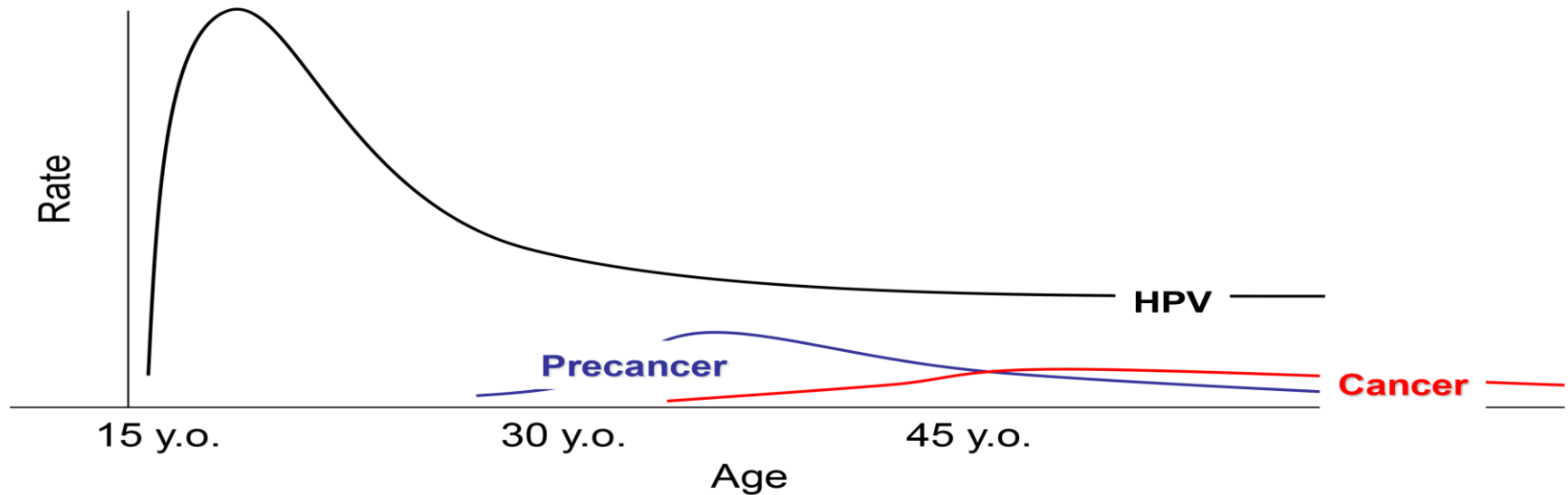
Invasive Cancer

Takes 10 years on average



HPV infection time line

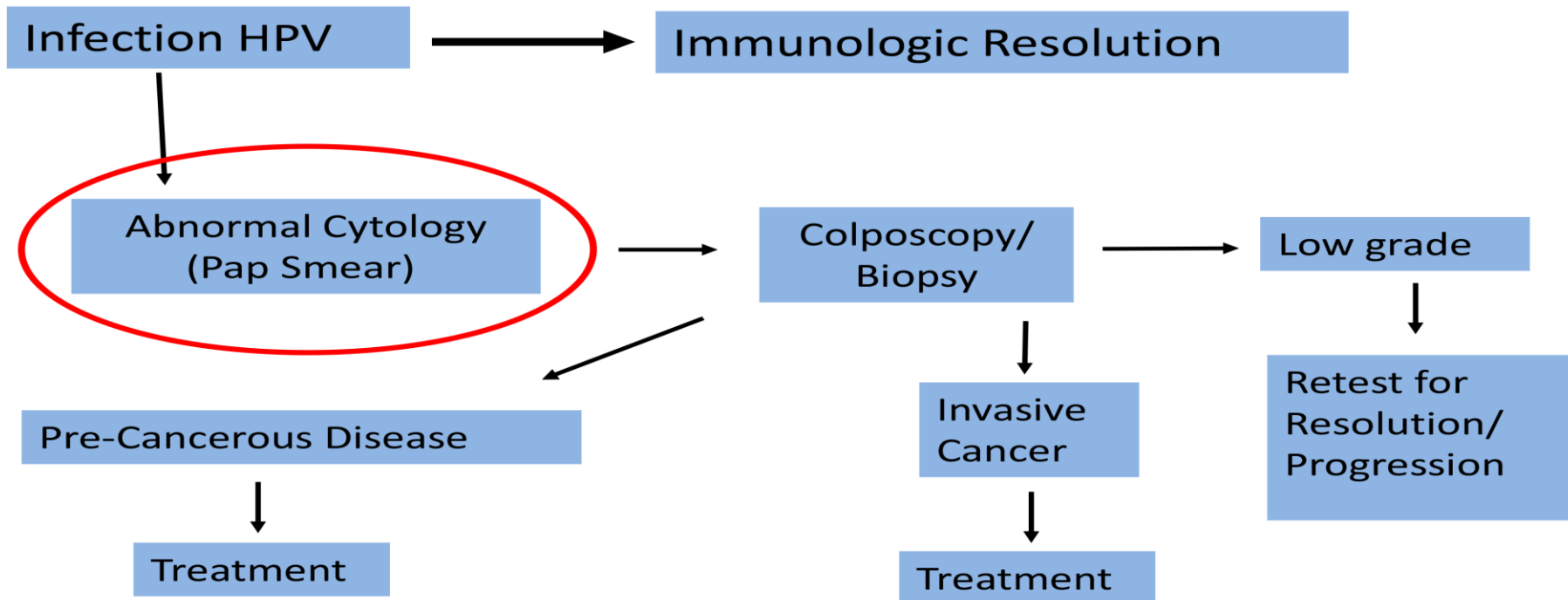
Time Line of Cervical HPV Infections And Progression to Cervical Cancer



- **Lifetime incidence of genital HPV infection >80% in U.S.**
- **Most infections clear spontaneously, eliminating cancer risk for that infection.**
- **Persistent infection with a high-risk HPV, especially HPV16 or 18, is the single most important risk factor for progression to precancer and cancer.**

Pap screening

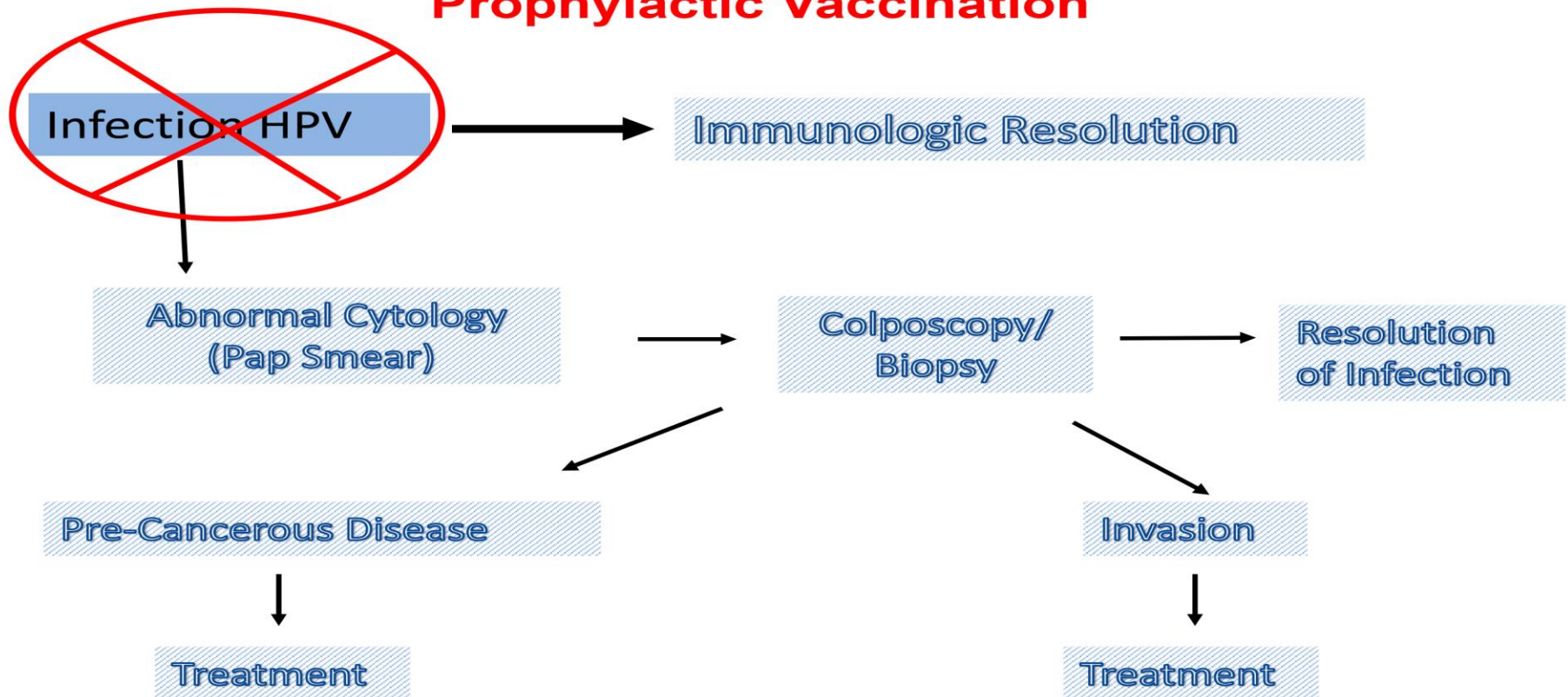
Current Pap Screening Is “Secondary” Prevention of Cervical Cancer



Primary prevention

The Future Is Primary Prevention

Prophylactic Vaccination

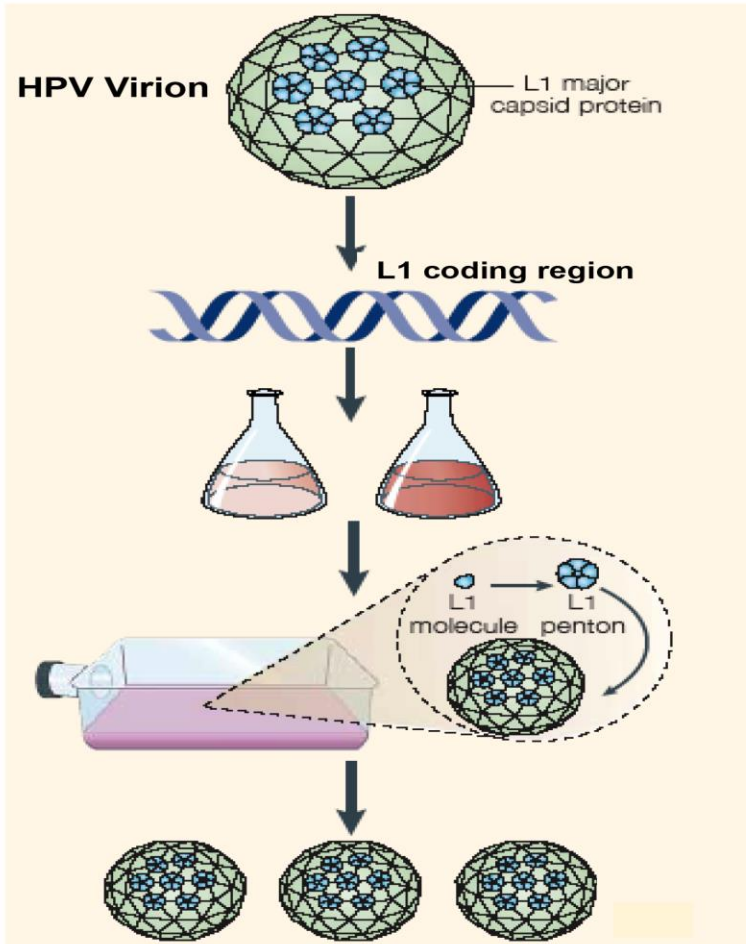


Prophylactic vaccines

Key To Developing HPV Prophylactic Vaccines ca. 1990

IM injection of Papillomavirus virions, which does not lead to virus replication, induced protection from experimental infection in animal models. Injection of denatured forms of the major virion protein L1 or L1 peptides didn't protect. Generating an immunogen with conformationally correct L1 was critical. But there was no scalable source of authentic virions for making an inactivated vaccine.

Virus like particles



Prophylactic HPV Vaccines Are L1 Virus Like Particles (VLPs)

L1 Insertion into a Baculovirus Expression Vector

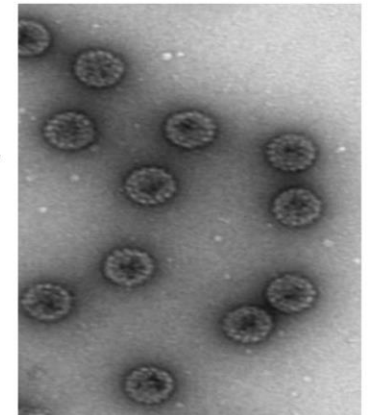
Production in Insect Cells

Spontaneous assembly of L1 into VLPs

Induce high titers of virion neutralizing antibodies

Non-infectious, Non-oncogenic

HPV16 L1 VLPs



Three vaccines

Three Distinct HPV L1 VLP Vaccines Have Been Commercialized

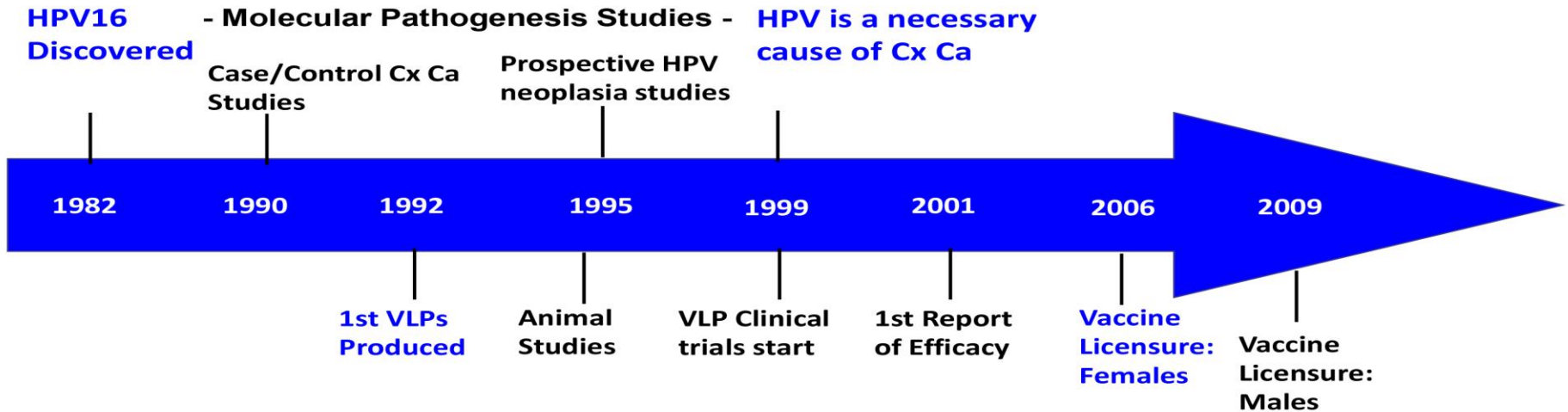
Name	Producer	VLP Types	Adjuvant	Production	Licensed
Cervarix	GSK	16,18	AS04*	Insect Cells	2007
Gardasil	Merck	16,18,6,11	Alum	Yeast	2006
Gardasil-9	Merck	16,18,31,33,45,52,58,6,11	Alum	Yeast	2014

IM Injections at 0, 1 or 2, and 6 months
1, 6 months for <15 yrs in EU, and now in U.S.

* MPL First TLR Agonist Adjuvant to be FDA Approved

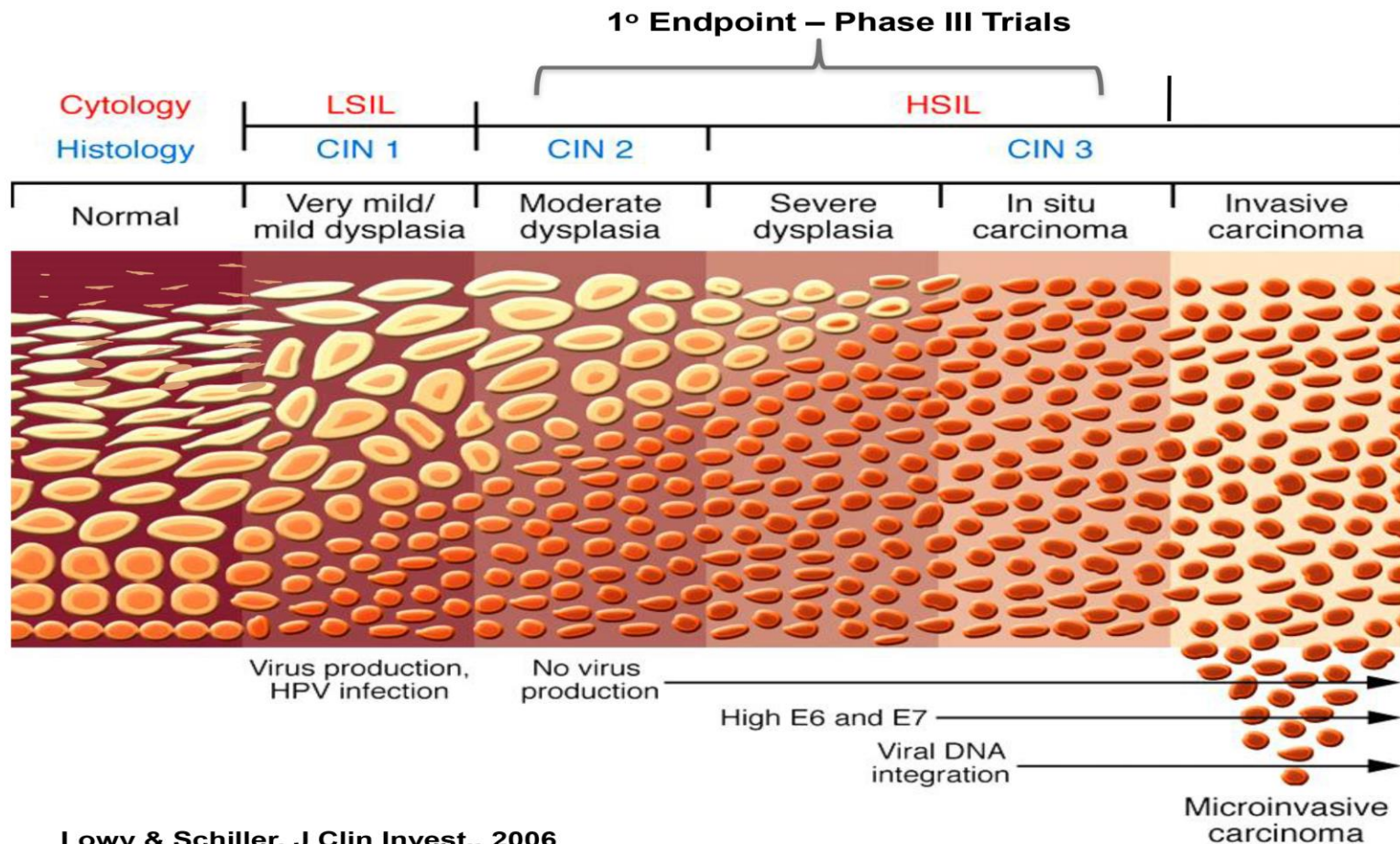
Timeline of HPV Association

Timeline of HPV Association with Cancer vs Vaccine Development



Precursor Lesions

Precursor Lesions of Cervical Cancer



Efficacy of HPV Vaccine

Efficacy of HPV VLP Vaccines Against Incident Disease By Vaccine-Targeted Types in Randomized Trials

No genital HPV infection detected in at entry

End Point	Sex	Age	Vaccine	Efficacy (95% CI)
CIN III	Female	15-25	Cervarix	100% (90.5-100)
CIN III	Female	15-26	Gardasil	100% (85.5-100)
Genital Warts	Female	15-26	Gardasil	96.4% (91.4-98.4)
AIN	Male	16-26	Gardasil	77.5% (39.6-93.3)
Genital Warts	Male	16-26	Gardasil	89.4% (65.5-97.9)

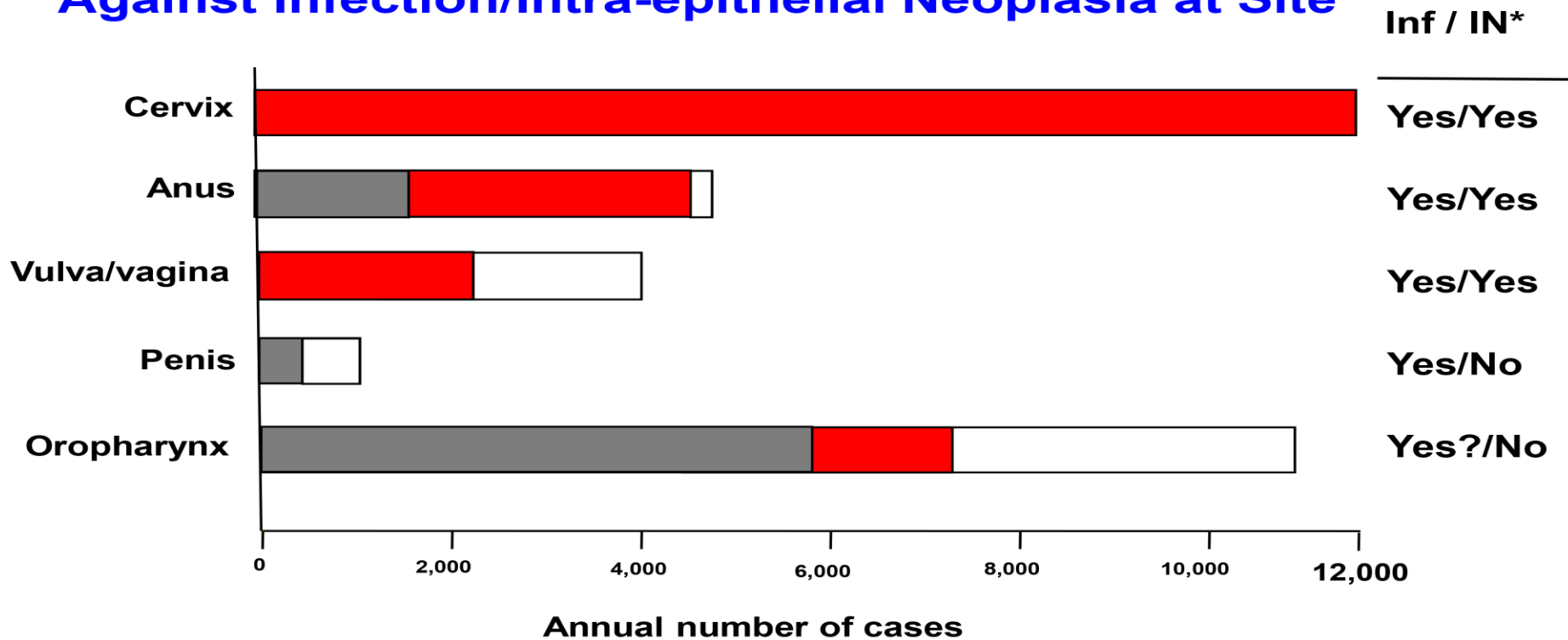
Data from Lehtinen Lancet Oncol 2011; Munoz JNCI 2010; Palefsky NEJM 2011; Giuliano NEJM 2011

CIN III: Cervical Intraepithelial Neoplasia Grade 3

AIN: Anal Intraepithelial Neoplasia of any grade

Clinical Trial Evidence

Clinical Trial Evidence for Vaccine Efficacy Against Infection/Intra-epithelial Neoplasia at Site



* Against Vaccine Targeted Types

What the HPV Vaccines Don't Do

**They don't prevent infection or disease caused
by**

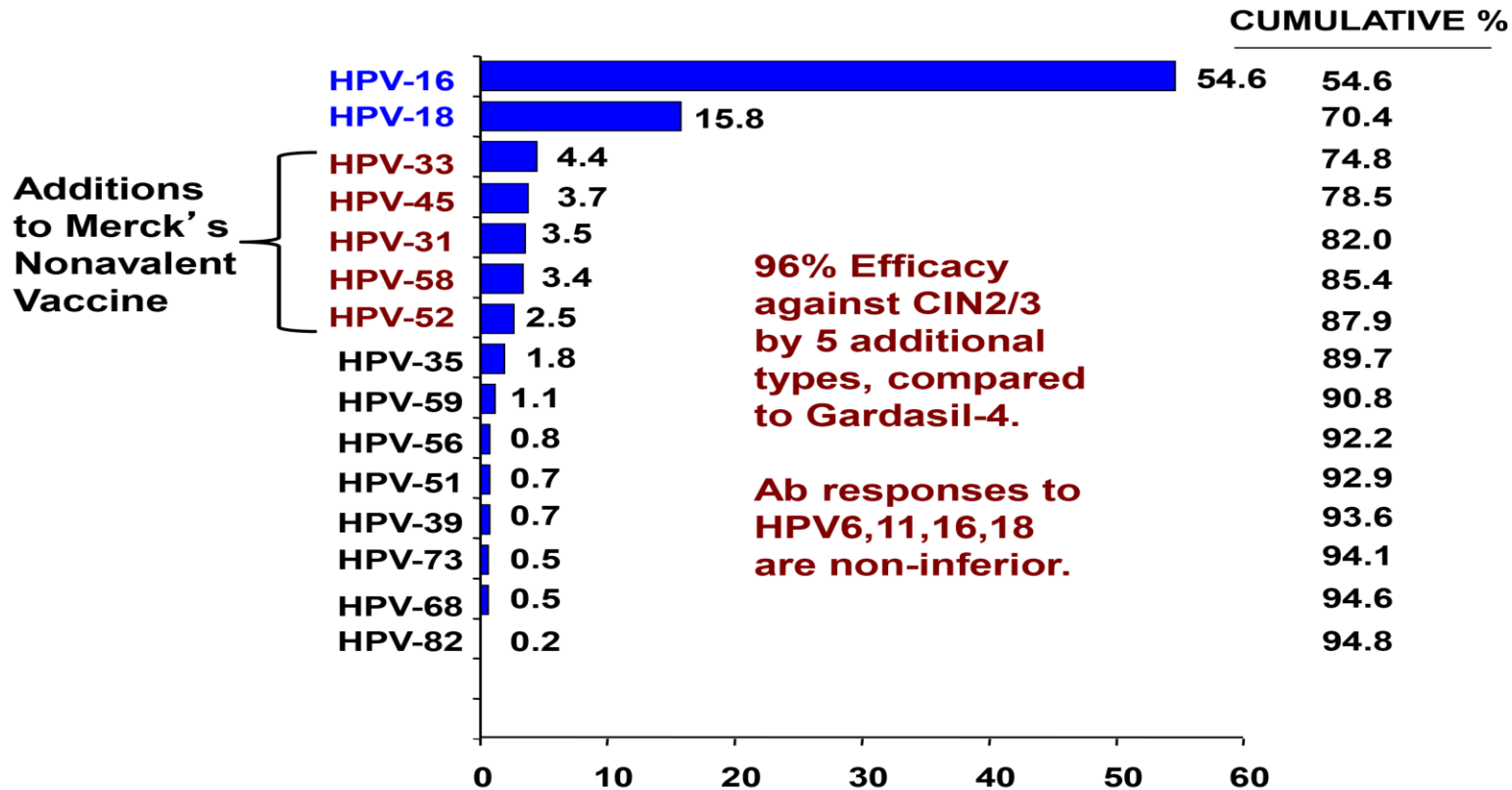
**most of the other HPV types that cause 30% of
cervical cancer not caused by HPV16/18.**

**They don't induce regression of established HPV
infections or prevent progression of HPV-induced
lesions.**

Gardasil-9

Merck's Gardasil-9

Most Frequent HPV Types in Cervical Cancer



Protection from Initial Infection

Protection From Initial Infection

- **Most Vaccinees never tested positive for HPV infection as measured by sensitive PCR Assays.**
- **“Breakthrough” infection tended to appear early in the trials suggesting that most were emergence of prevalent infection.**
- **Results imply that sterilizing immunity normally generated.**

Immune mediators

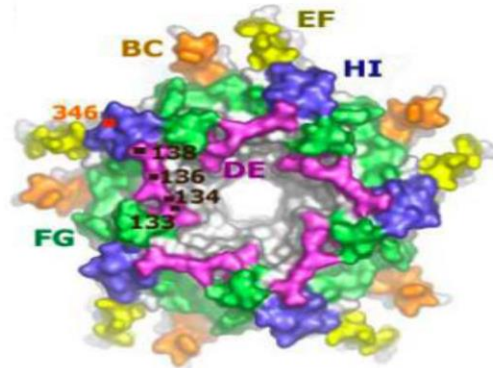
Why Antibodies Are Likely to be the Immune Mediators of Protection

- **High levels of virus-neutralizing antibodies are routinely generated by VLP vaccination.**
- **Cross-protection in clinical trials mirrors antibody-mediated cross-neutralization in vitro.**
- **Protection can be passively transferred in serum from vaccinated to naïve individuals in animal challenge models.**
- **Cell mediated effectors generally function only after infection has occurred and sterilizing immunity is observed.**
- **L1 is not detectably expressed in basal epithelial cells.**

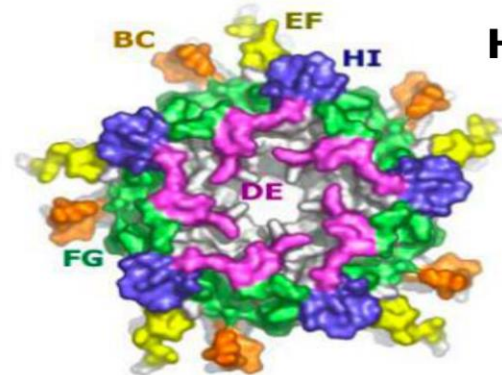
L1 Surface Loops

Neutralizing Abs Recognize Multiple Conformation-Dependent and Type-Specific Epitopes on L1 Surface Loops

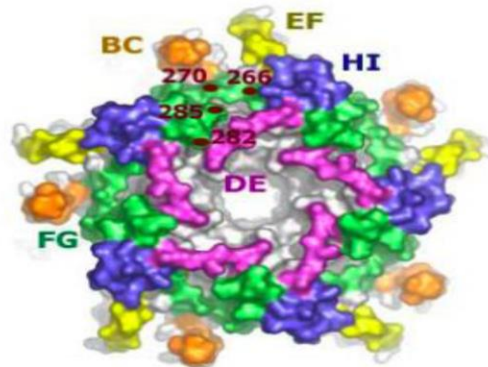
HPV11



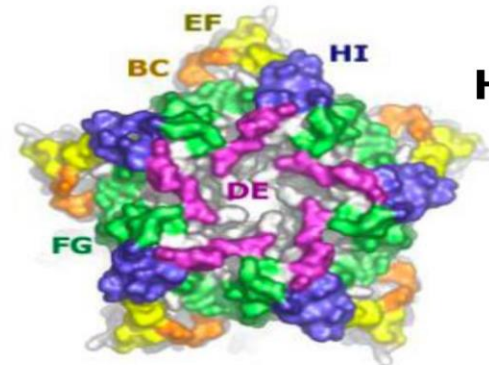
HPV35



HPV16



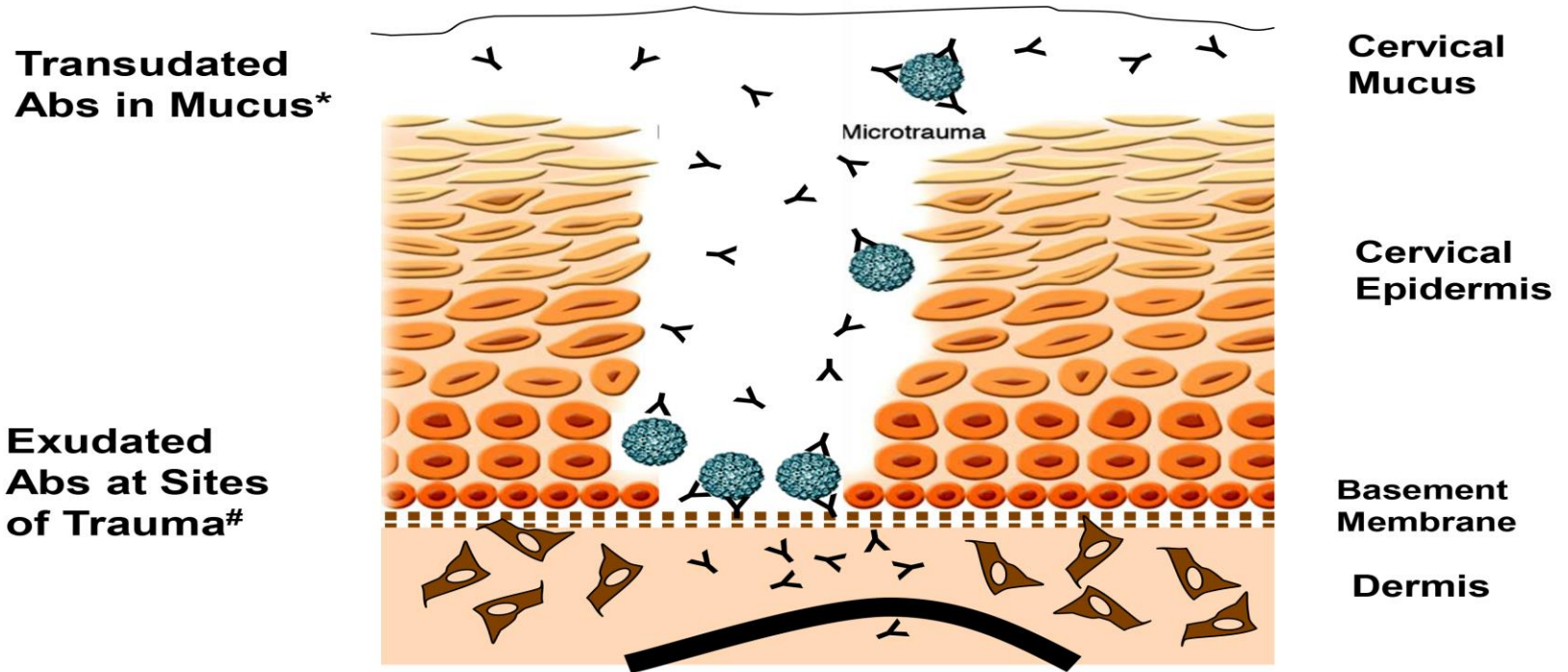
HPV18



surface representation of L1 pentamers

VLP Vaccine

How Could IM Injection of a VLP Vaccine Induce a Protective Ab Response at the Cervix?



* VLP-specific IgG in women's cervical mucus after IM vaccination: *Nardelli et al. JNCI, 2003*

In a mouse model, trauma is required for cervicovaginal infection and virions specifically bind to basement membrane after trauma: *Roberts et al., Nat Med, 2007*

Antibody response

Consistency of Antibody Response to VLPs

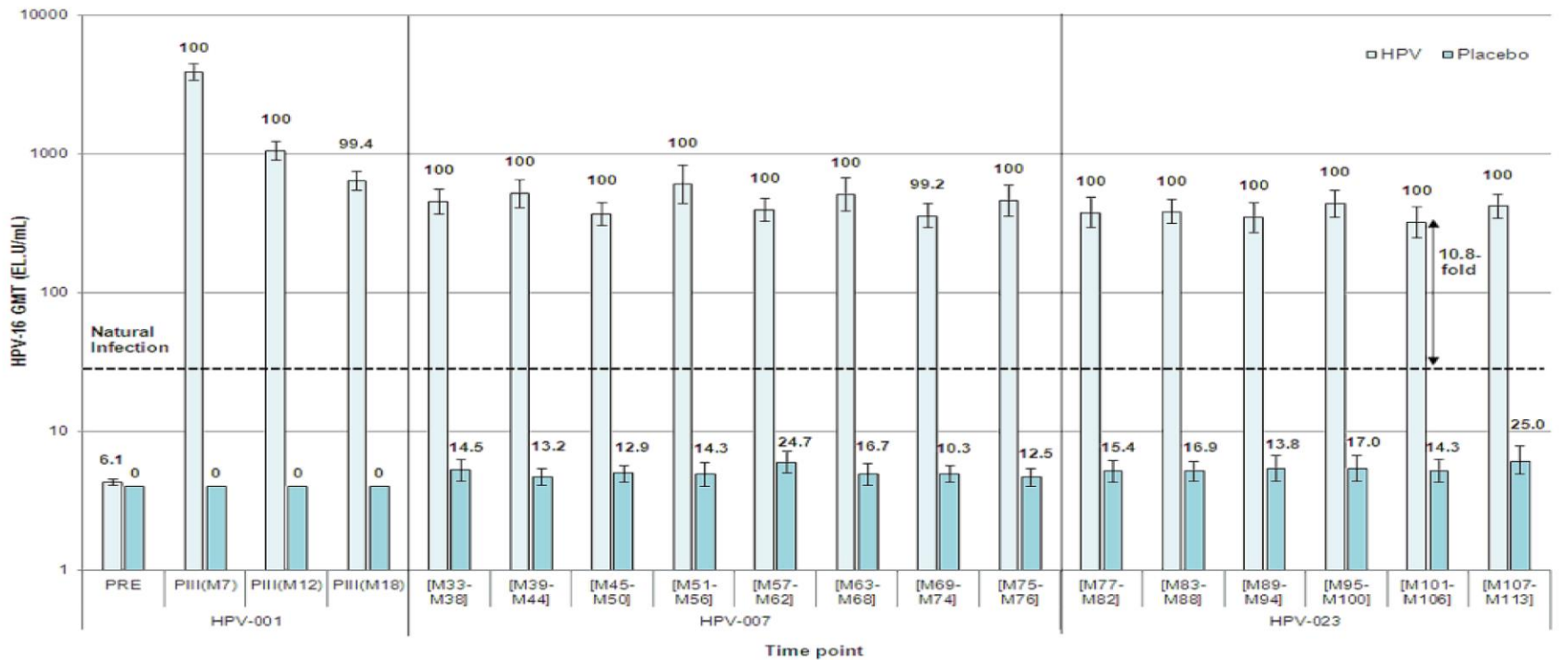
Percent of Women Serocoverting to Individual HPV VLPs in Merck Quadravalent VLP Vaccine Gardasil*

HPV6	99.8%
HPV11	99.8%
HPV16	99.8%
HPV18	99.5%

*4666 women vaccinated 3 times by intramuscular injection

Antibody response to Cervarix

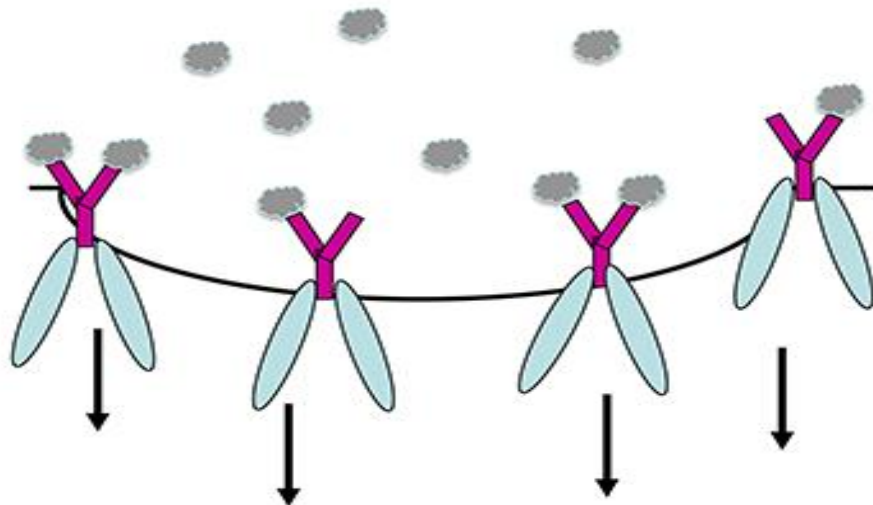
Durability of Antibody Response to 3 Doses of Cervarix: 9.4 yrs



Repetitive protein arrays

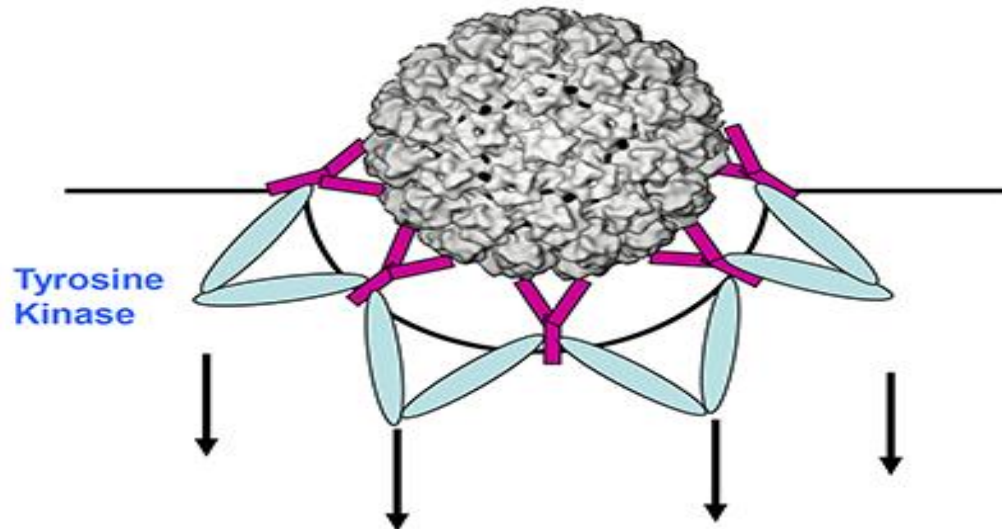
B Cells Recognize Dense Repetitive Protein Arrays as Dangerous Microbial Structures

Monomeric BCR/ Protein Complexes



Weak Activation Signals
Low Level Antibodies
Short duration

Oligomerization of BCR/Protein Signaling Complexes



Strong Survival/Proliferation Signals
High Level Antibodies
Long Duration

The B Cell Receptor is an antigen-specific pattern recognition receptor.

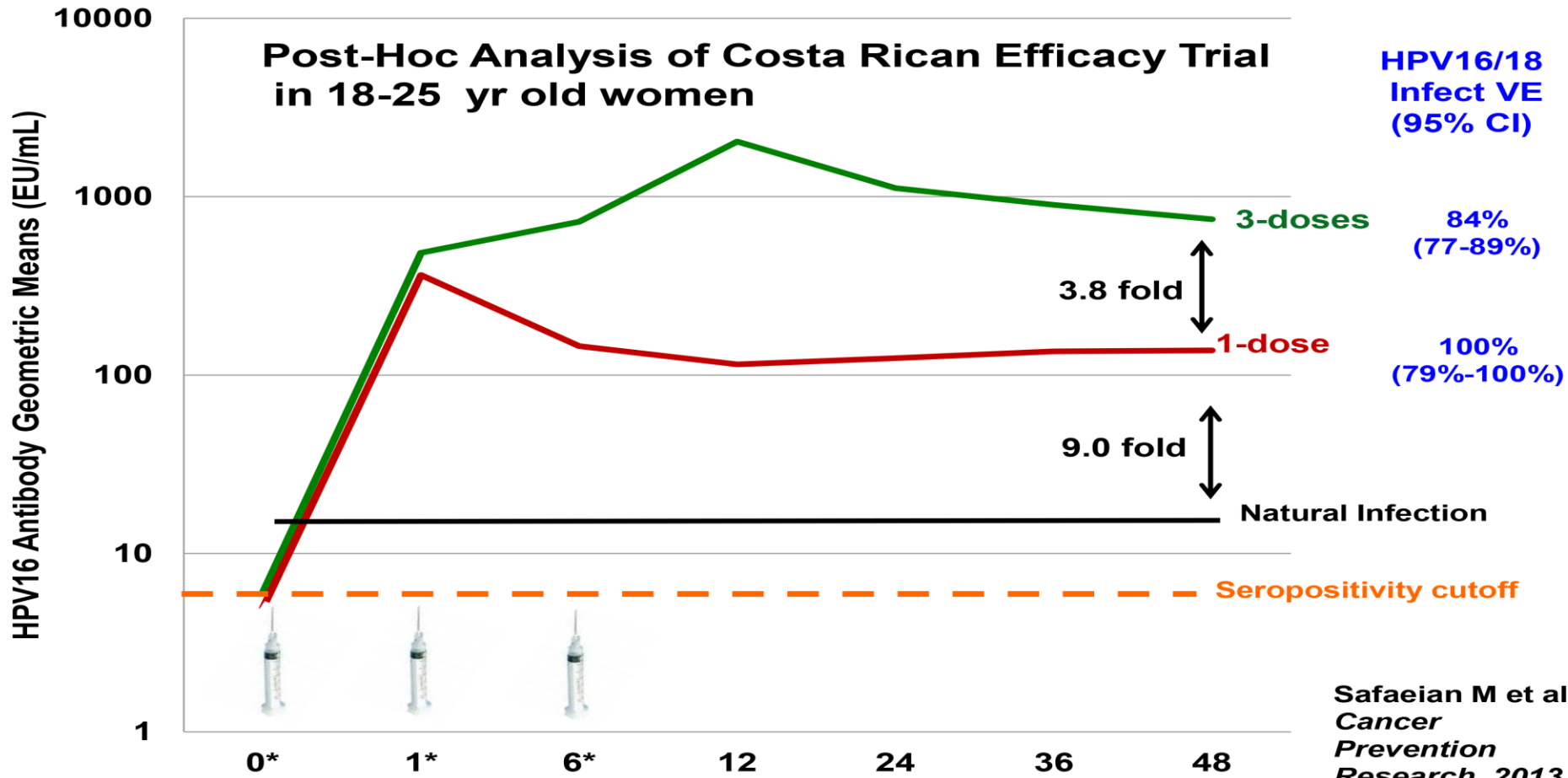
Duration of Protection

Duration of Protection

Strong Protection through the ten years since the studies began. No evidence for increase numbers of breakthrough infections.

Durable Serum Abs

One Dose of Cervarix Induces Durable Serum Abs



7 Year Follow Up of CVT*

For 1 dose recipients:

- No breakthrough infections**
- Continued stability of Ab titers.**

Antibody ratios

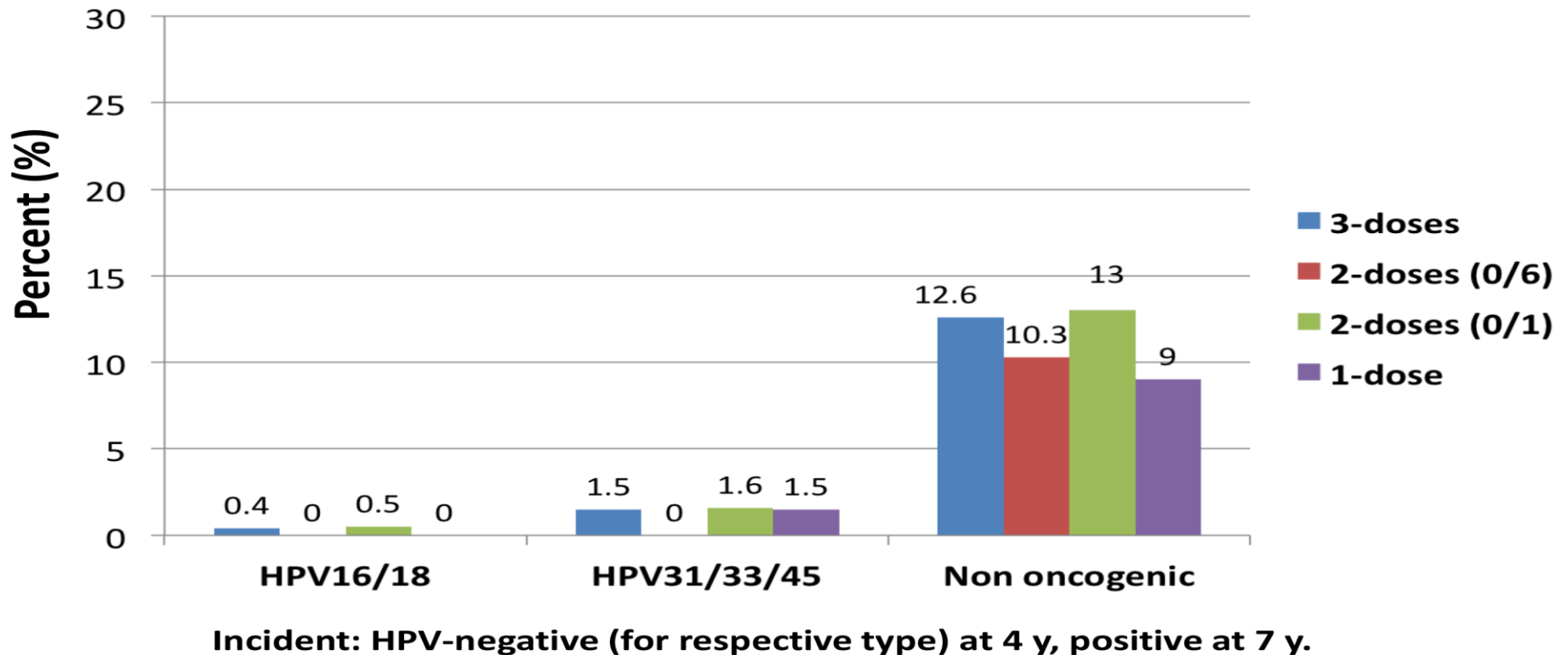
Antibody GM Ratios (95% CI): 1 dose vs 3 doses

No. of doses	HPV16 GM Ratio (95% CI)	HPV18 GM Ratio (95% CI)
4 years		
3	Referent	Referent
1	0.27 (0.22-0.33)	0.33 (0.26 – 0.41)
7 years		
3	Referent	Referent
1	0.29 (0.23 – 0.35)	0.41 (0.33 – 0.50)

One dose to three dose GMT ratios are similar at yr 4 and yr 7.

Incident Infections

Incident Infections Yrs 4-7



Single dose efficacy

NCI-Sponsored* Single Dose Efficacy Trial

- **4 Arms RCT: 1 vs 2 dose Cervarix
1 vs 2 dose Gardasil-9**
- **5000 13-16 yr old Costa Rican females per arm.**
- **4 year primary trial; long term follow up.**
- **Primary Endpoint: 6 mo. Persistent infection by the types in the vaccine.**
- **Pilot phase has begun.**

* With support from the Gates Foundation

VLP vaccine

Conclusions: HPV VLP Vaccine Efficacy

- **VLP vaccines are highly effective at protection against a spectrum of anogenital HPV endpoints from incident infection to high grade precancer.**
- **Gardasil is also highly protective against genital warts in women and men.**
- **Protection is type-restricted, consistent with protection being antibody mediated.**
- **Duration of protection is unknown, but strong protection at 10 years, after antibody levels have reached a plateau, is very encouraging**

Who to Vaccinate

Girls >> Boys = young women > men

- **Depends on your resources and screening program.**
- **Girls 1st because cervical cancer dominates worldwide.**
- **Decreased effect with age because chance of previous exposure goes up and chance of new exposure goes down.**
- **Male cancers more prominent with good Cx Ca screening.**

Who to vaccinate

Who to Vaccinate

Girls >> Boys = young women > men

- **Depends on your resources and screening program.**
- **Girls 1st because cervical cancer dominates worldwide.**
- **Decreased effect with age because chance of previous exposure goes up and chance of new exposure goes down.**
- **Male cancers more prominent with good Cx Ca screening.**
- **U.S. recommendations: Routine 11-12 yr olds.
Females: 9-26. Males 9-21 (MSMs 9-26).**

Vaccinating boys

Arguments For Vaccinating Boys

- **Primary protection from male cancers**
- **Secondary protection of women**
- **Protection of MSMs**
- **Gender Equity**
- **More rapid induction of herd immunity**
- **Politics**

Arguments Against

- **Not cost effective if high coverage in girls**
- **Competing demand for public health resources**

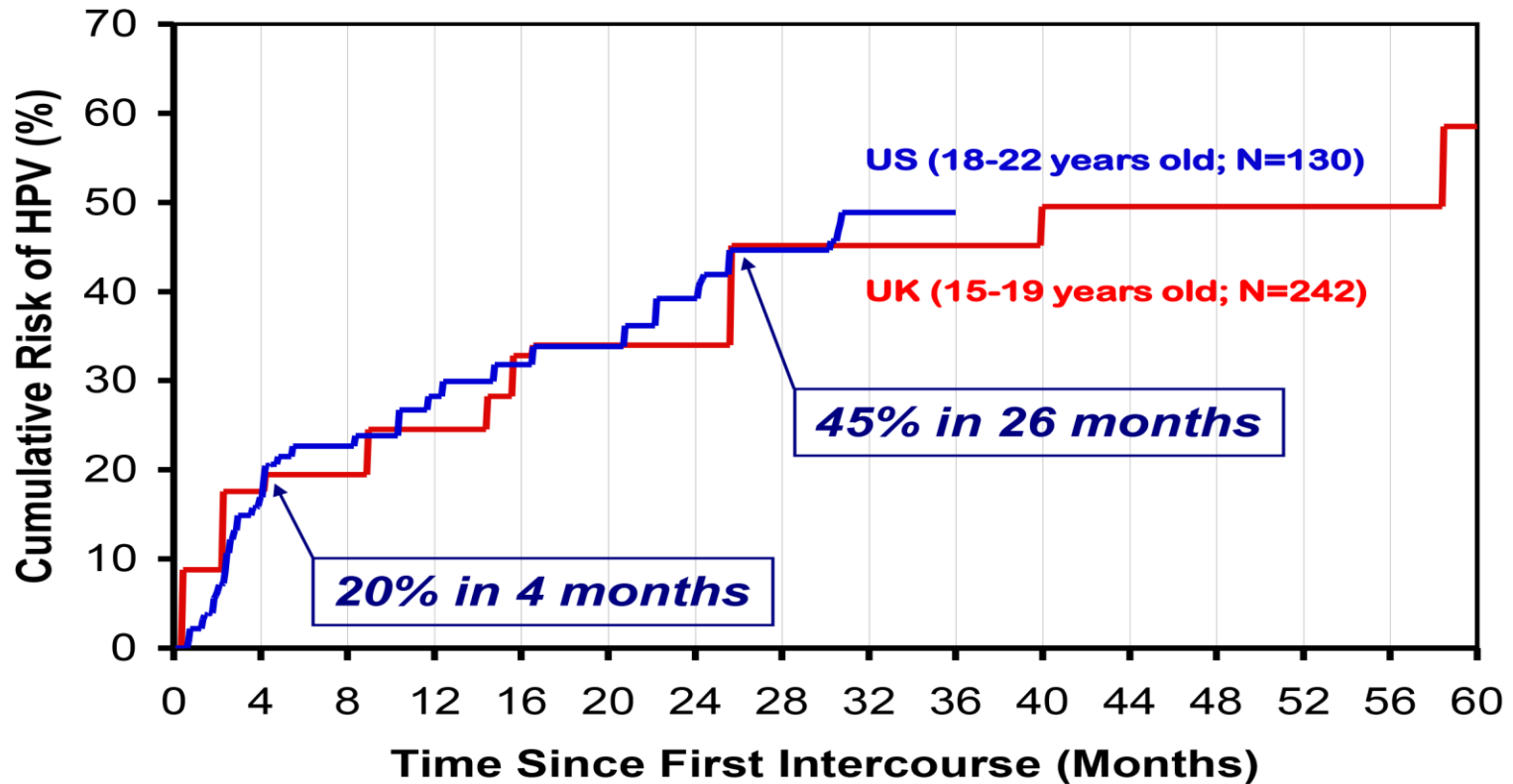
Implementation issues

Outstanding Implementation Issues

- **Who to vaccinate: Girls >> Boys = young women > men**
- **Delivery of two or three IM doses to early adolescents**
- **Effects of vaccine on Cervical Ca screening recommendations and compliance**
- **Delivery to economically disadvantaged individuals**

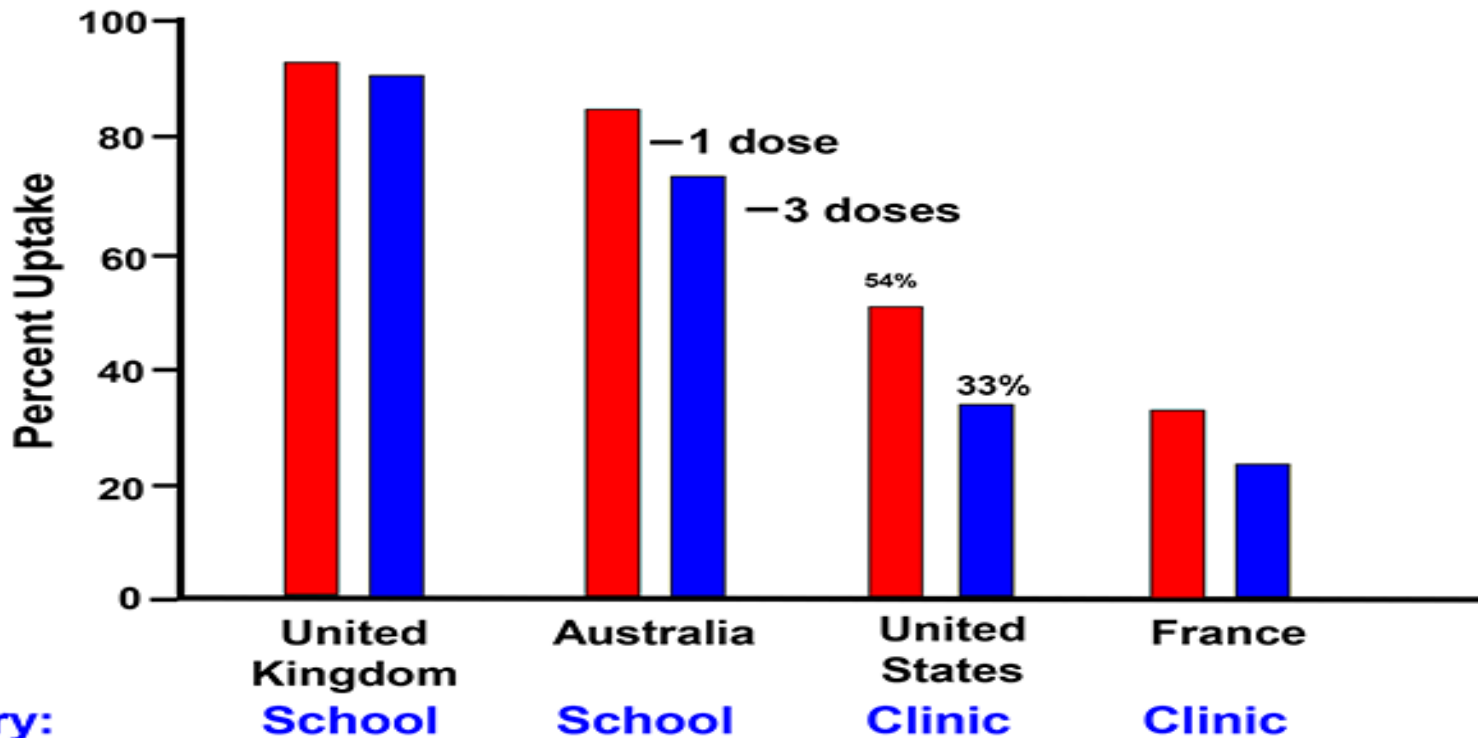
Genital HPV infection

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



Vaccine uptake

Variable Uptake of HPV Vaccine (2012 data for girls)

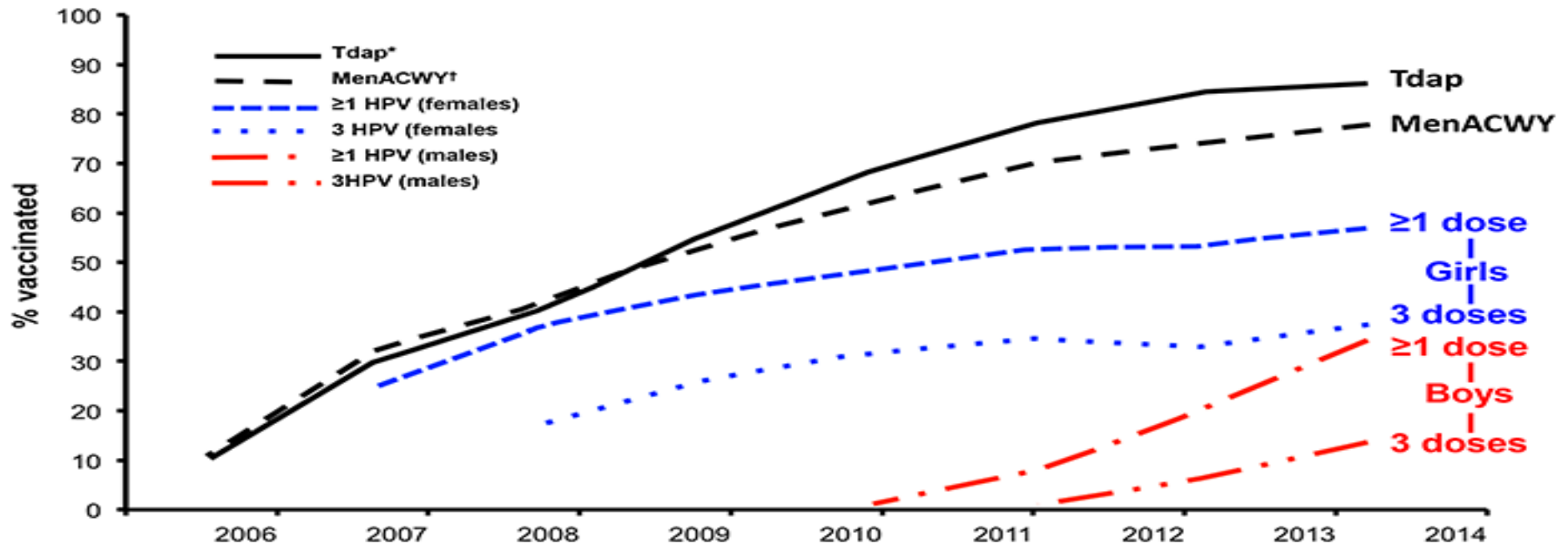


Delivery:

U.S. vaccination rates

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

MMWR Vol 63, #29, July 25, 2014



Abbreviations: Tdap = tetanus, diphtheria, acellular pertussis vaccine; MenACWY = meningococcal conjugate vaccine; HPV-1 = human papillomavirus vaccine, ≥ 1 dose; HPV-3 = human papillomavirus, ≥ 3 doses.

* Tdap and MenACWY vaccination recommendations were published in March and October 2006, respectively.

† HPV vaccination recommendations were published in March 2007.

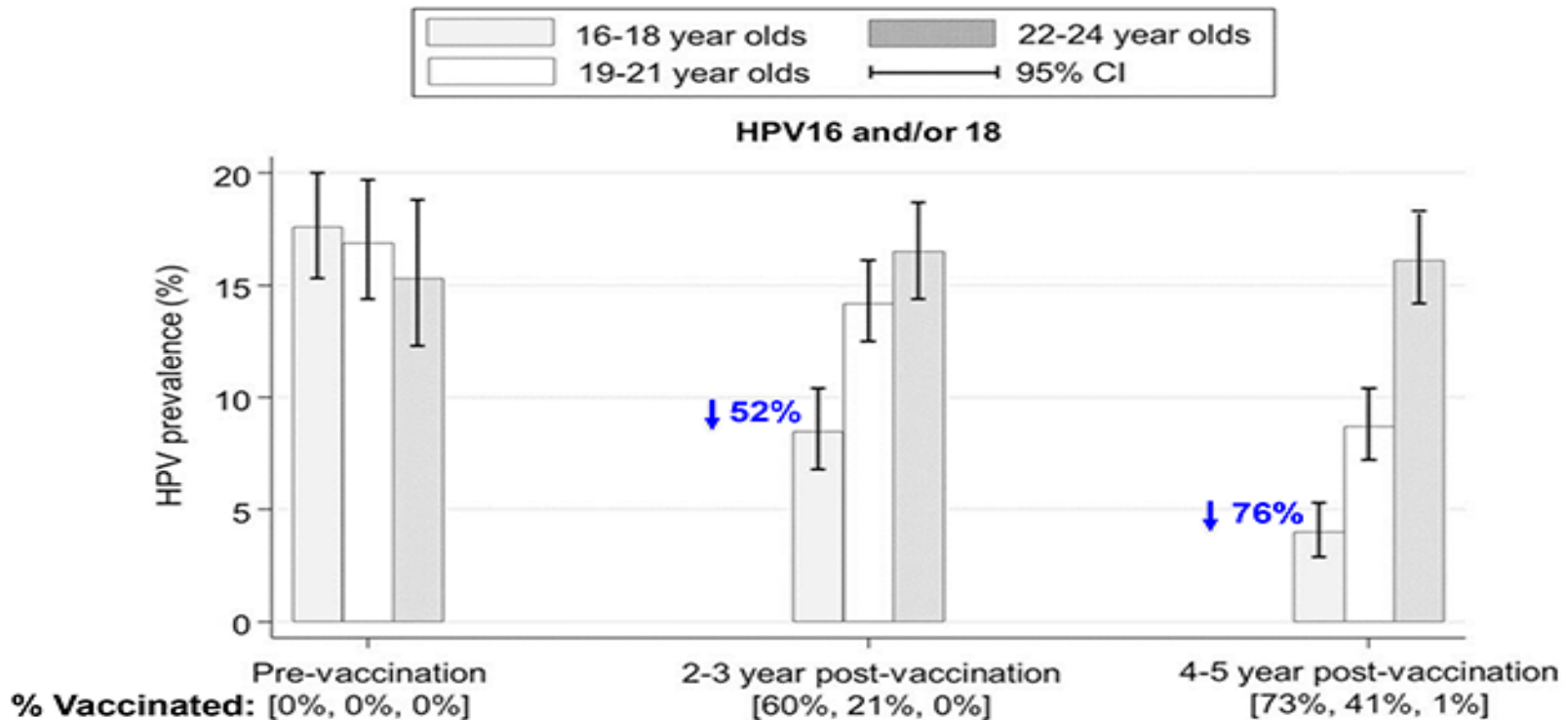
HPV vaccine in US

Why Low Uptake of HPV Vaccine in US?

- **Medical uncertainties at time of FDA approval (June 2006); e.g., safety, duration of protection. Subsequent evidence of vaccine safety and duration of protection; seems to have had little impact on vaccine uptake.**
- **Continuing “provider hesitancy”: lack of strong vaccine recommendation from health care workers is a major factor.**
- **“Push-back” from efforts to make vaccine mandatory in 2007.**
- **Concerns about vaccination promoting sexual disinhibition – not supported by published studies.**
- **Best argument for vaccinating early may be that immune response is better before puberty.**

HPV types by age

Prevaccination and Postvaccination Prevalence of HPV Types By Age: Cervarix in England.

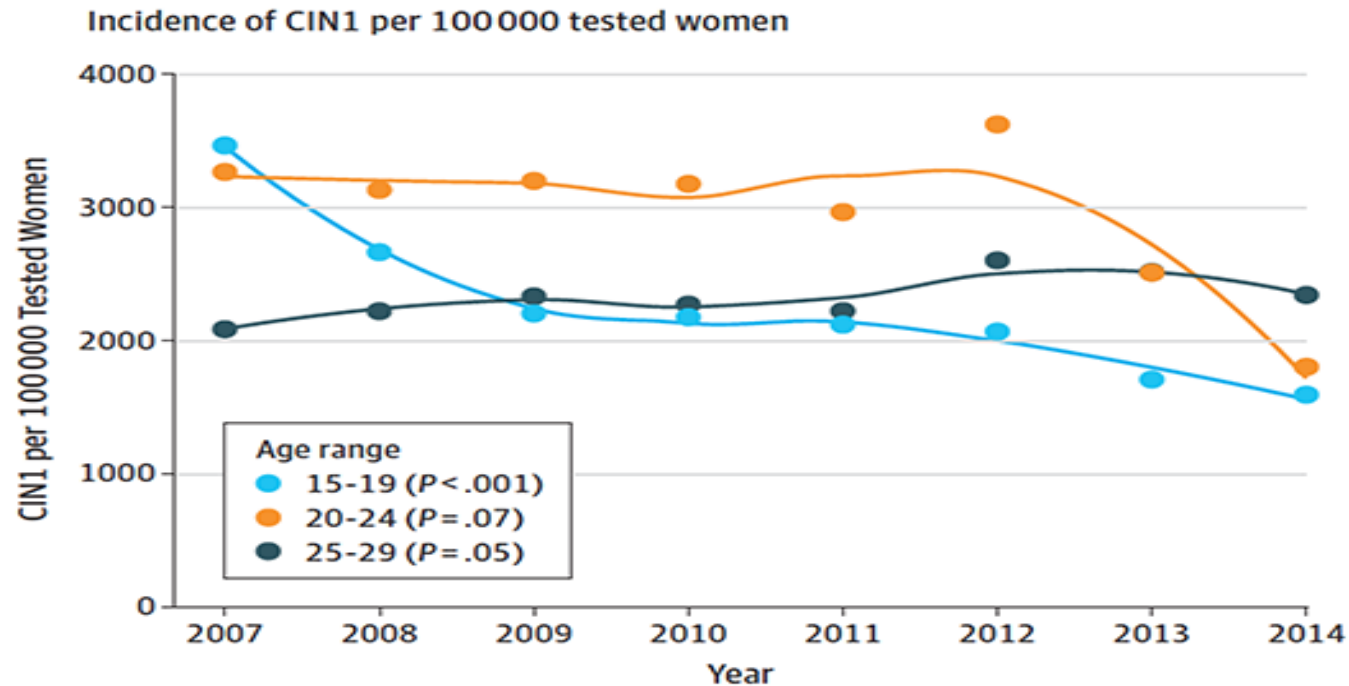


In young women attending Chlamydia screening

CIN-1

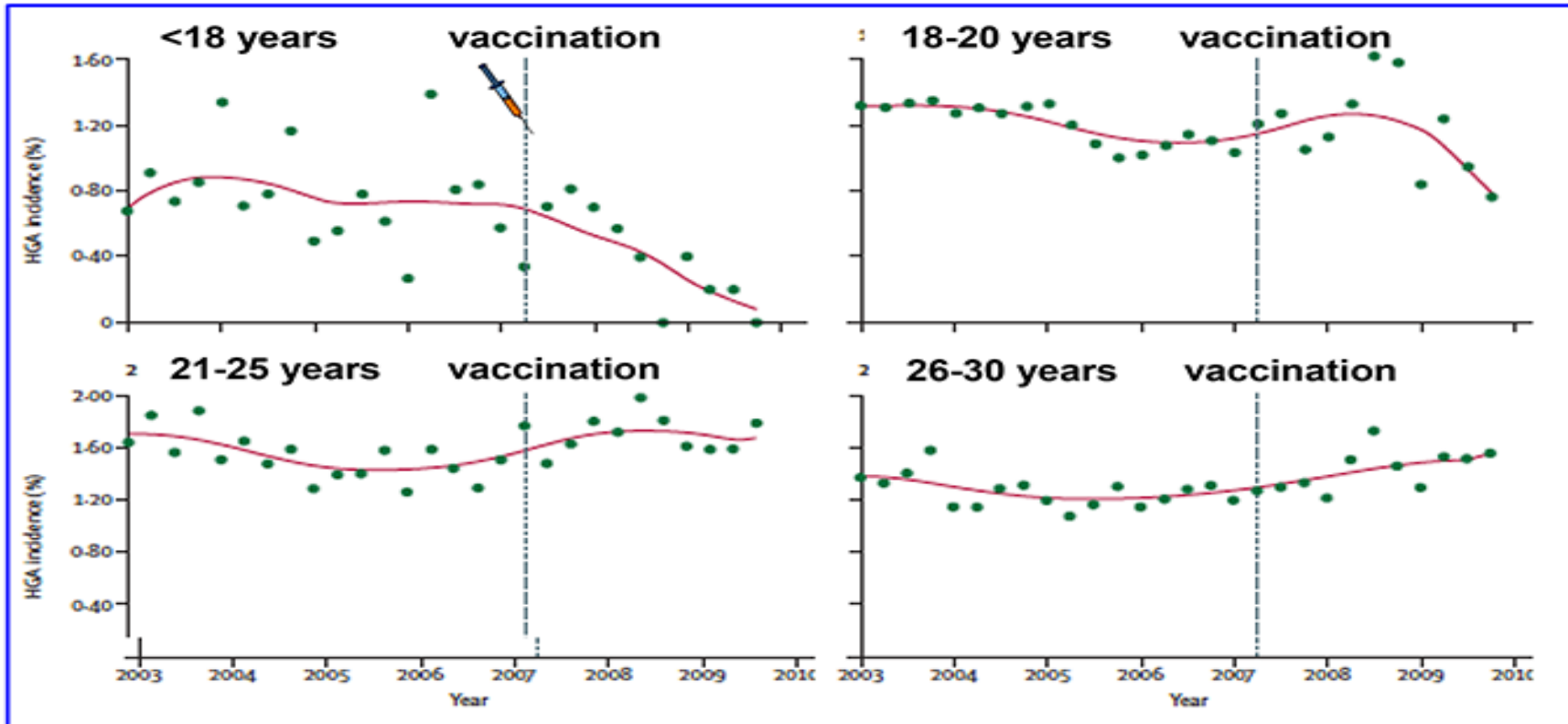
Reduction in CIN in New Mexico

Population-Based Incidence Rates – CIN 1



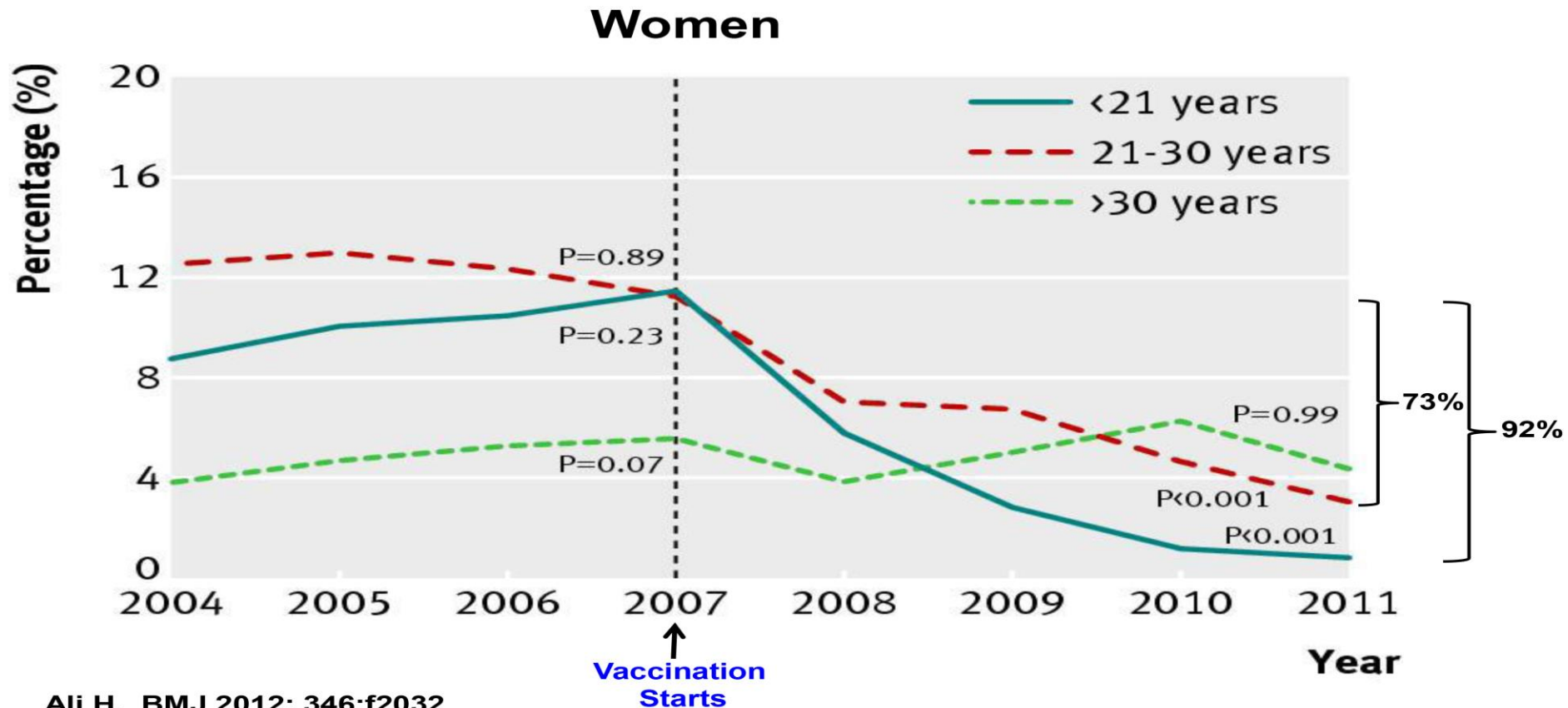
CIN2+

Reduction in CIN2+ Cervical Dysplasia: Gardasil in Australia



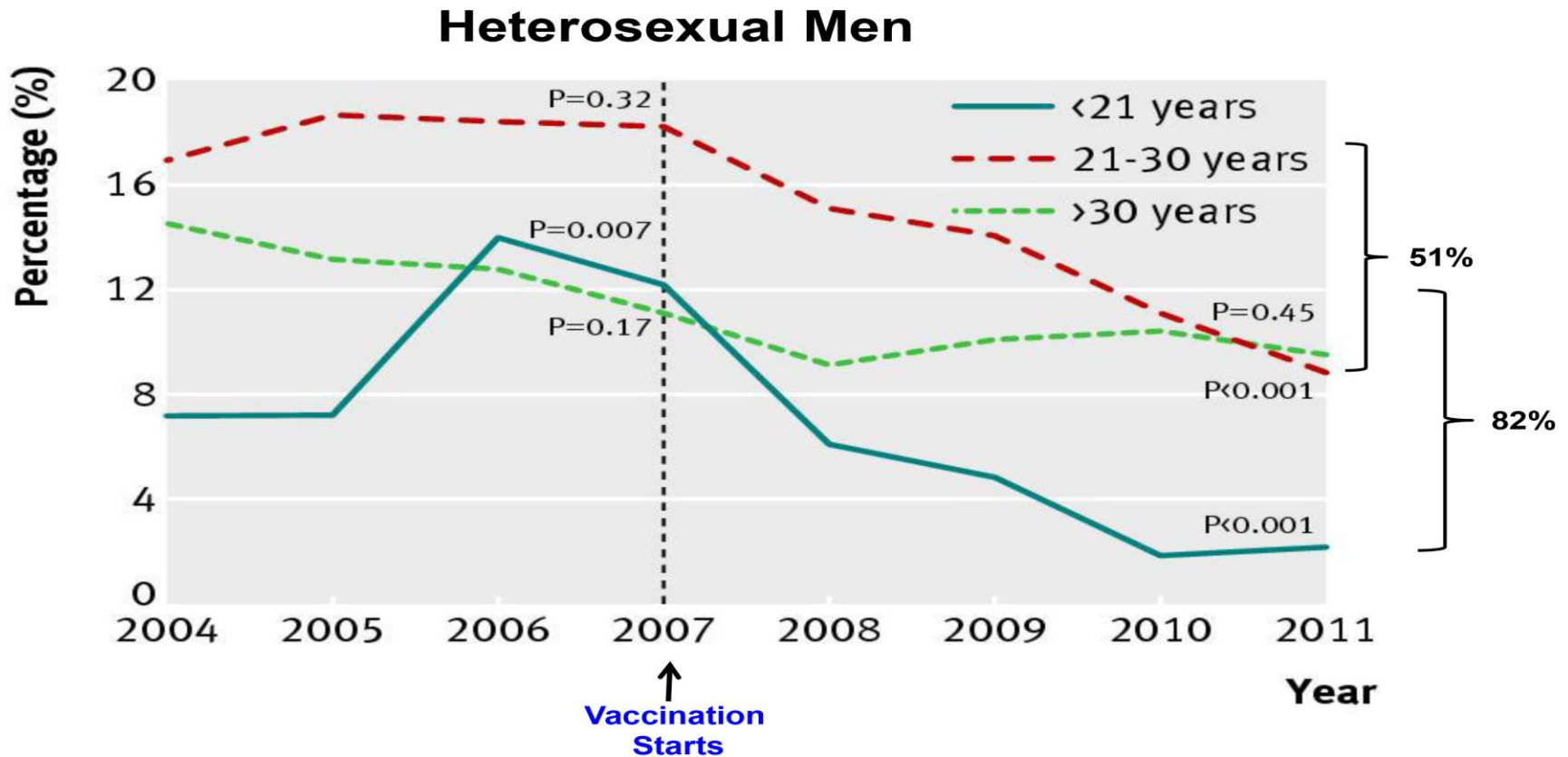
Genital Warts

Genital Wart Time Trends in Australia 2004-2011



Genital Warts in Men

Genital Wart Time Trends in Australia 2004-2011



Implementation Issues

Outstanding Implementation Issues

- **Who to vaccinate: Girls >> Boys > Older women > older men**
- **Delivery of three IM doses to early adolescents**
- **Effects of vaccine on Cervical Ca screening recommendations and compliance.**
- **Delivery to economically disadvantaged individuals**

We can't give up screening

We Can't Give Up Screening

- **The vaccine won't help women with established infections/lesions.**
- **Since type restricted, the current VLP vaccines are not expected to prevent ~10-30% of cervical cancers.**
- **Need to convince vaccinated women to comply with recommended screening programs.**

HPV Interventions

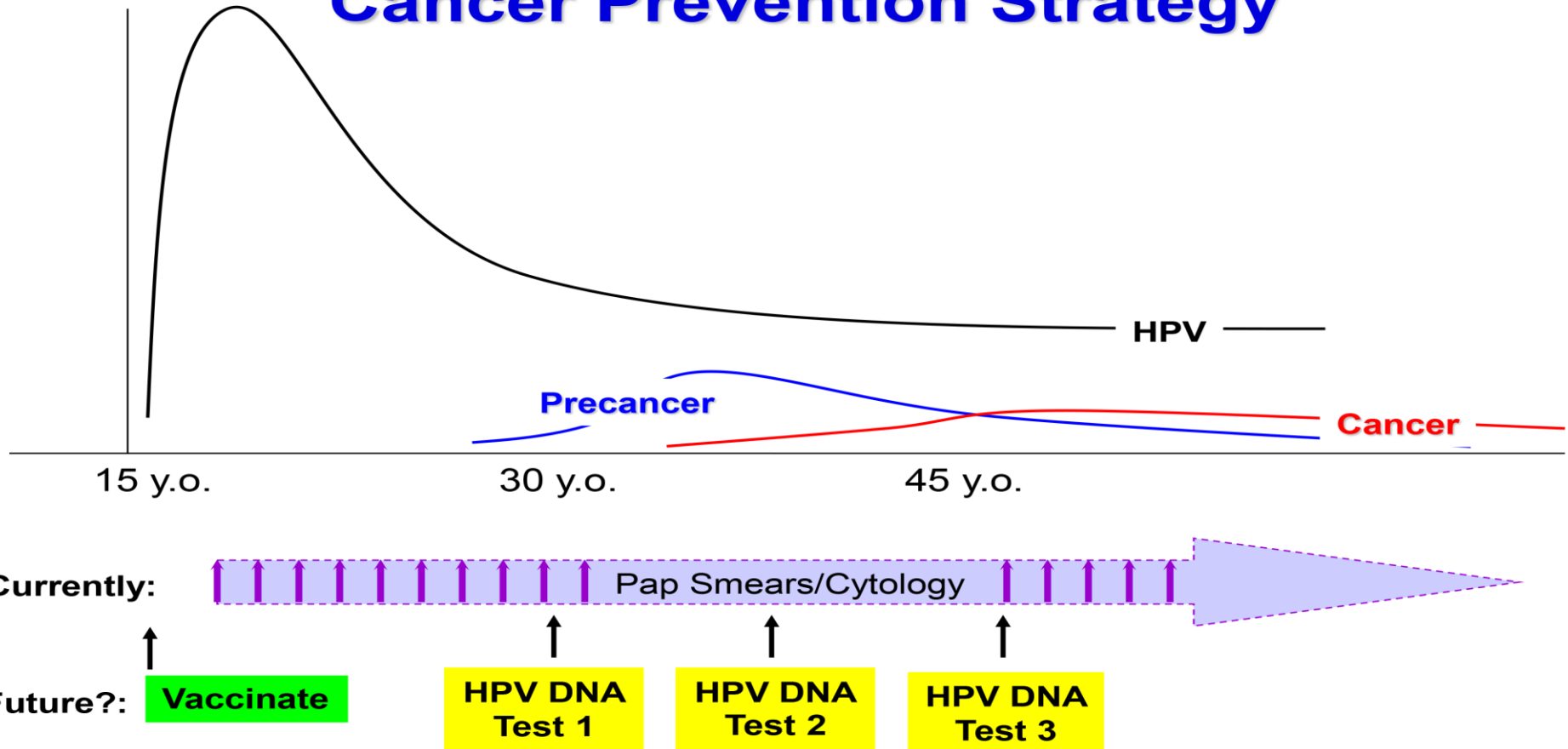
Screening Accounts For Most of the Direct Costs of HPV Interventions in the U.S.

Annual direct medical cost burden of preventing and treating HPV-associated diseases

Intervention	Cost- Billion \$	% of Total
Total	8.0	100%
Cx Ca Screening	6.6	82.3%
Cancer Tx	1.0	12.0%
Cx Ca Tx	0.4	5.0%
Oropharyn Ca Tx	0.3	3.6%

Cervical Cancer Prevention

A Shift to an HPV-Based Cervical Cancer Prevention Strategy



Thanks to Mark Schiffman and Phil Castle, NCI

Public HPV Vaccinations

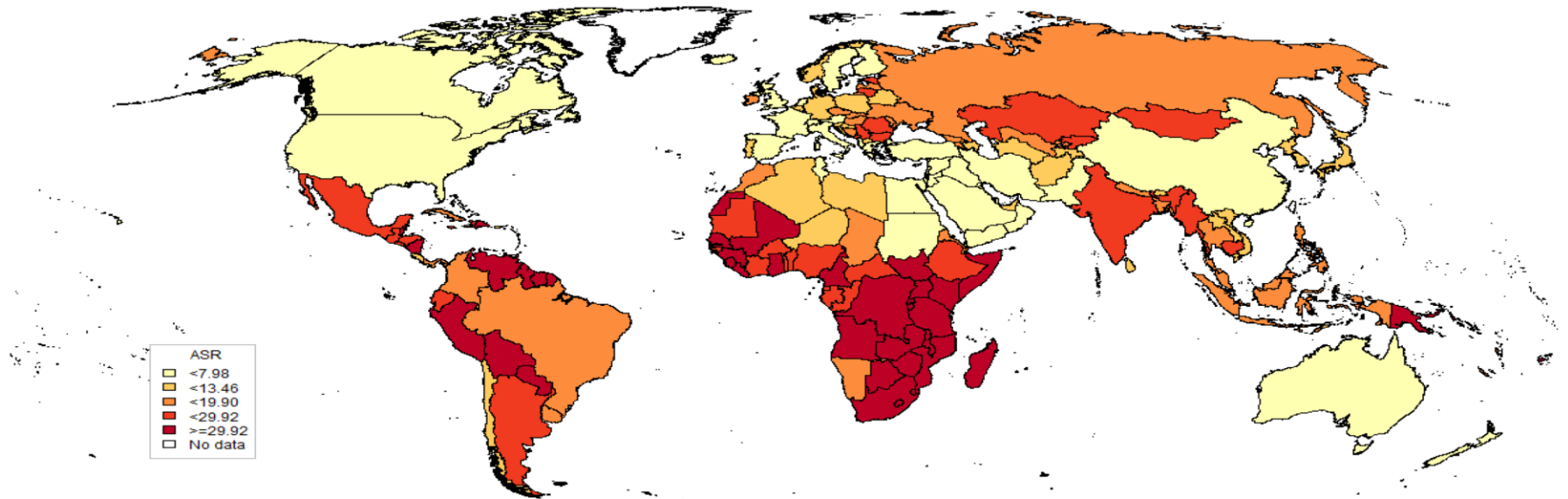
Countries That Have Introduced Publically Funded National HPV Vaccination Programs



Bruni et al. Lancet Global Health 2016; 4:3453-63

Cervical Cancer Cases

Age-standardized incidence rates of cervical cancer in World (estimations for 2012)

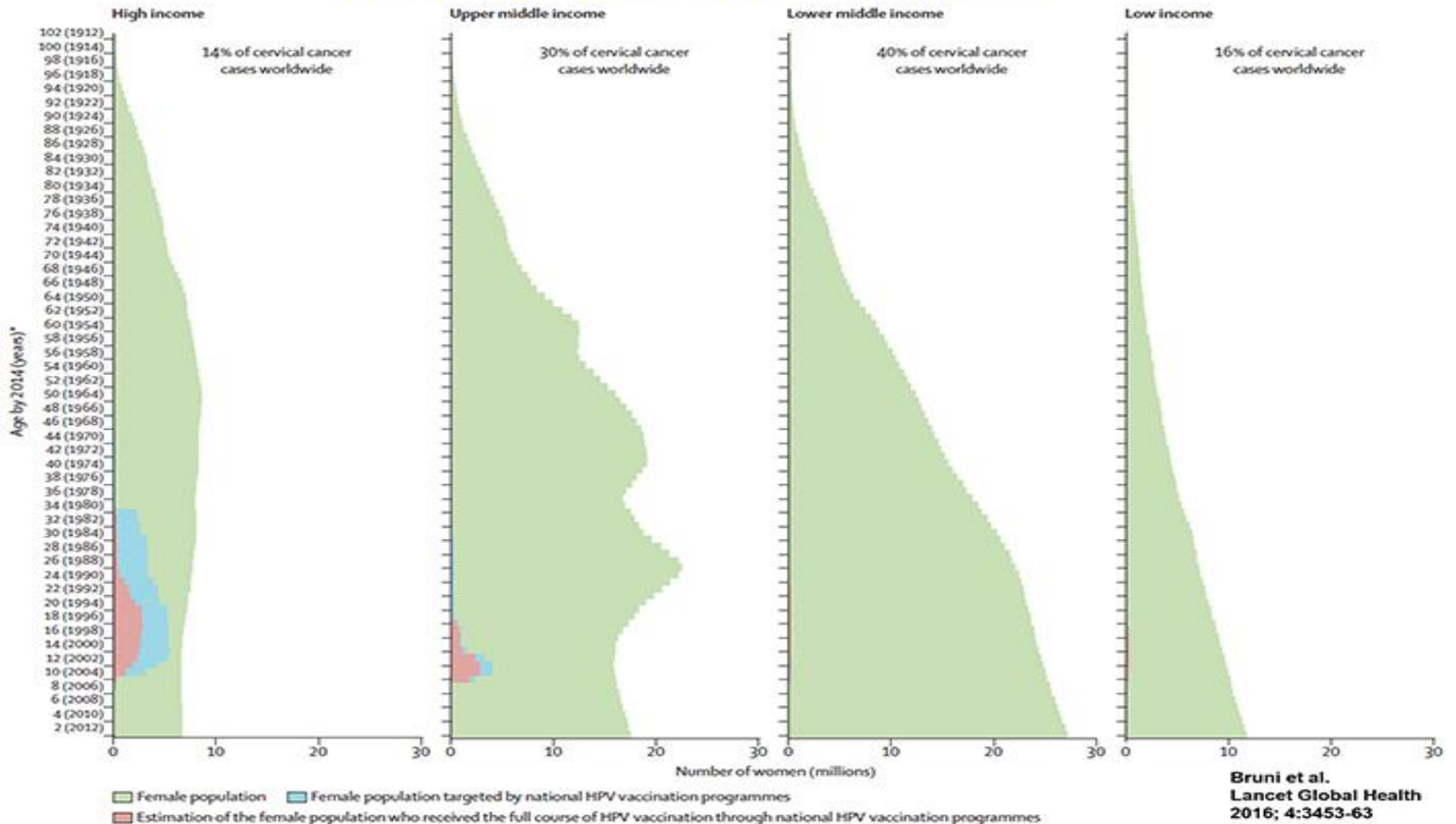


527,624 new cervical cancer cases are diagnosed annually in World (estimations for 2012).

Ferlay et al. 2013

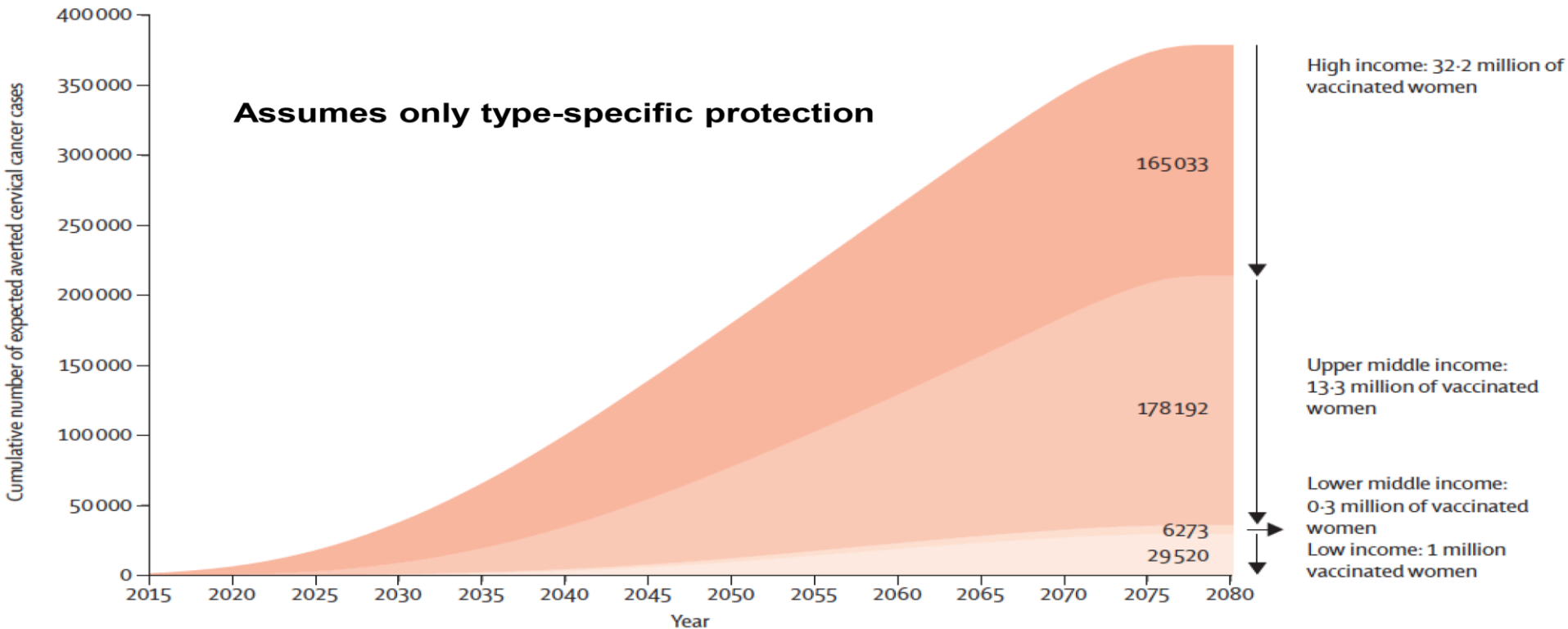
Worldwide HPV vaccine

Worldwide HPV Vaccine Uptake In Females



Cervical cancer prevention

Projection of Cervical Cancer Cases Prevented in Women Fully Vaccinated 2006-2014



We have already prevented 400,000 future cases of cervical cancer

Increasing Delivery

Increasing Delivery to Economically Disadvantaged Individuals

- **Both companies are committed to tiered pricing**
- **GAVI financing vaccine for poorest countries at \$5/dose**
- **Vaccine manufacture in emerging countries:**
 - **The HBV vaccine example.**
 - **A number of companies are moving forward with HPV vaccine development, e.g. E. coli based VLP production by Inovax in Xiamen, China.**
- **Administer less than three doses**

Key Collaborators

Key Collaborators

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Past Members of the Lab:

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Diana Pastrana

Chris Buck

Reinhard Kirnbauer

Jeff Roberts

Rhonda Kines

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Carla Cequeira

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