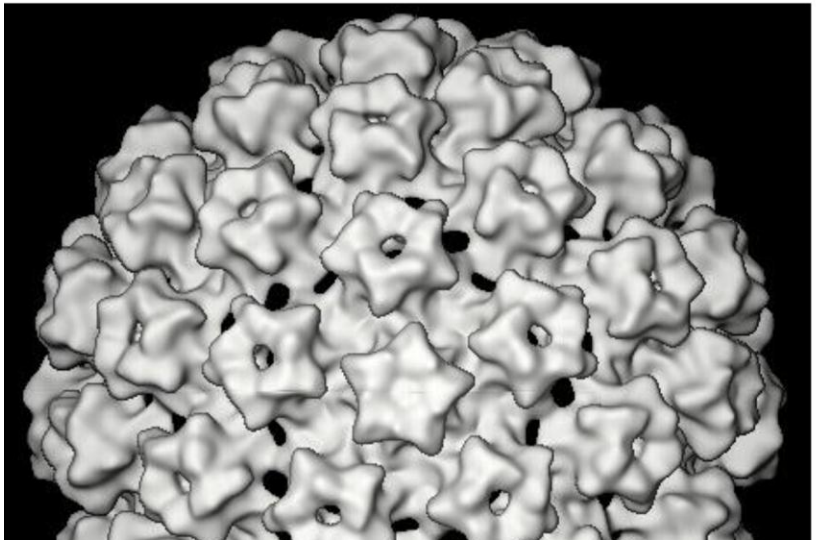
Vaccines to Prevent Ocogenic HPV Infections

Vaccines to Prevent Ocogenic HPV Infections

John Schiller, National Cancer Institute, NIH, USA



- **HPV and Cancer**
- **Prophylactic HPV Vaccine**
- **Implementation Issues**

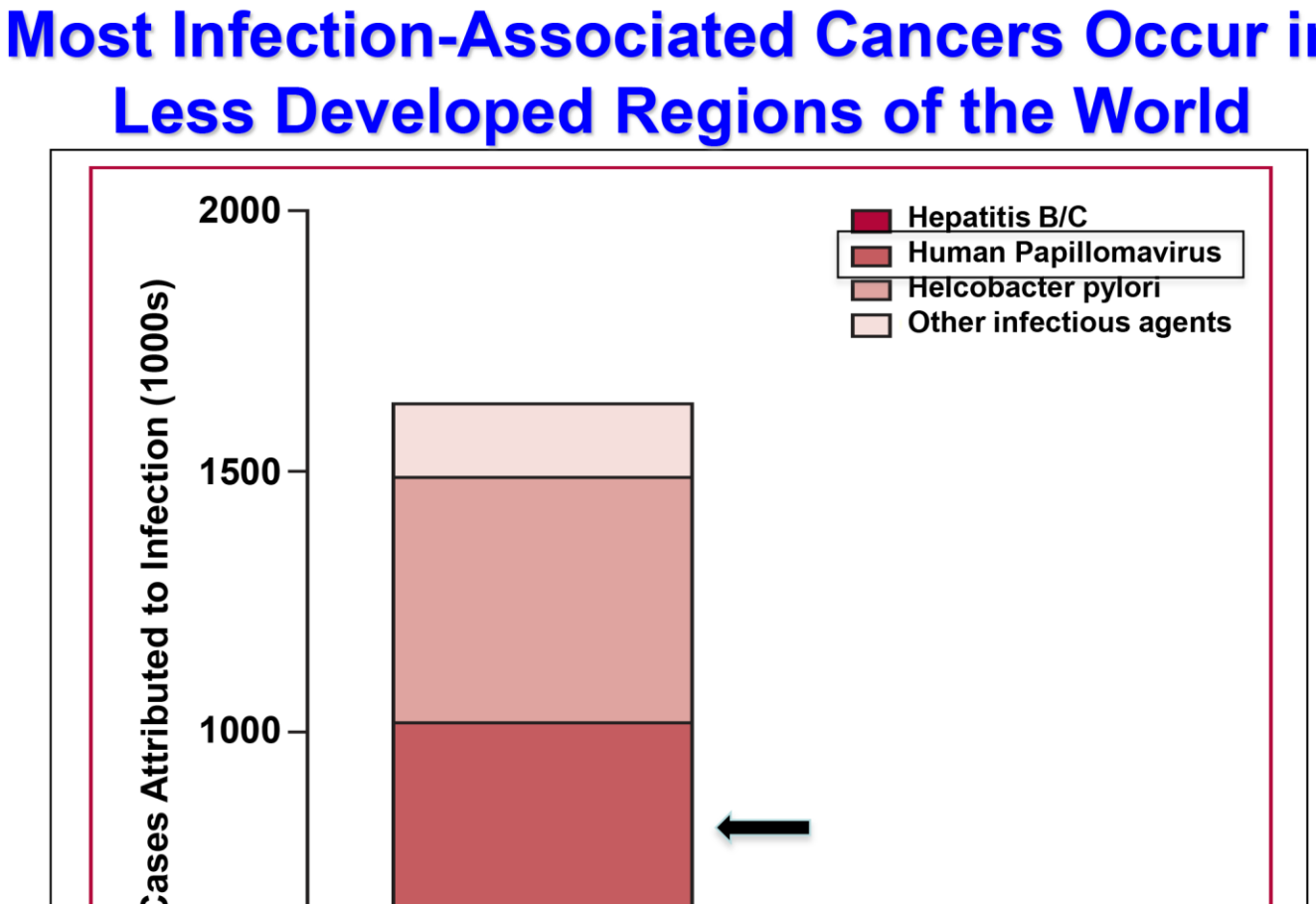
Infectious Agents are a major cause of cancer

ts Are a Major Cause of Cancer

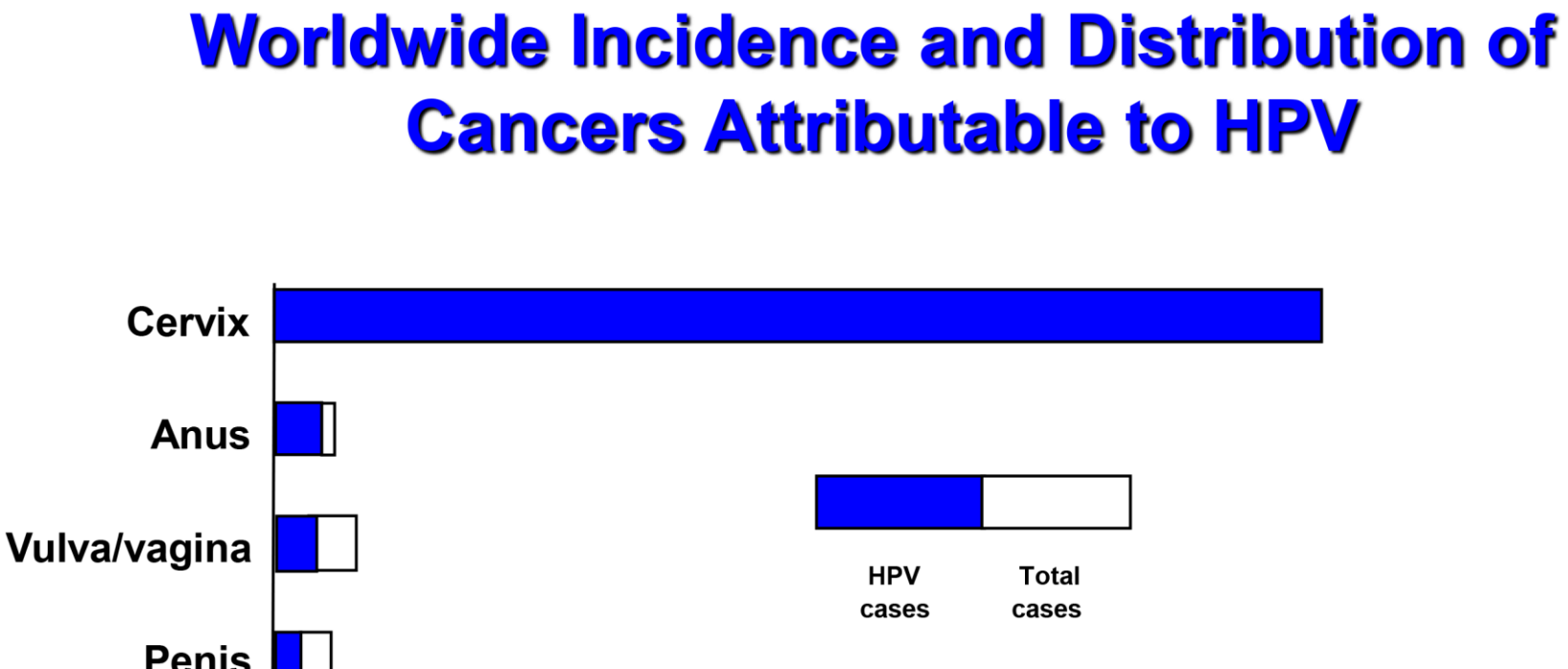
uman cancers are attributed to infection agents

nual dence	% of Infection Assoc. Cancers	Cancer Types
,000	32.5%	Gastric
,000	30.5%	Cervical, Anal, Penile, Oropharyngeal
,000	29.5%	Liver
,000	5.4%	Lymphoma, Nasopharyngeal
,000	2.1%	Kaposi's Sarcoma
000	0.3%	Bladder

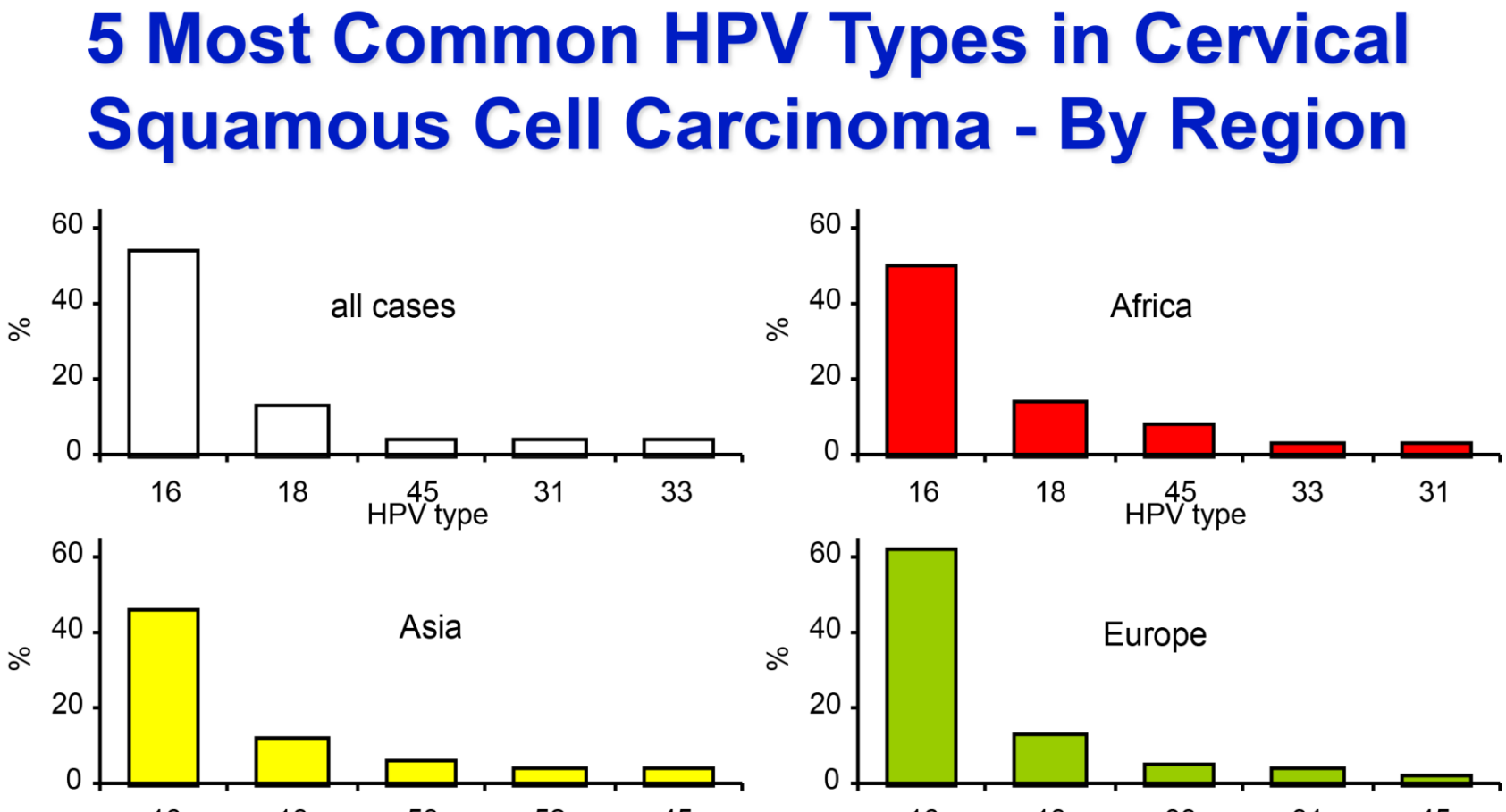
Most Infection-Associated Cancer Occur in Less Developed Regions of the World



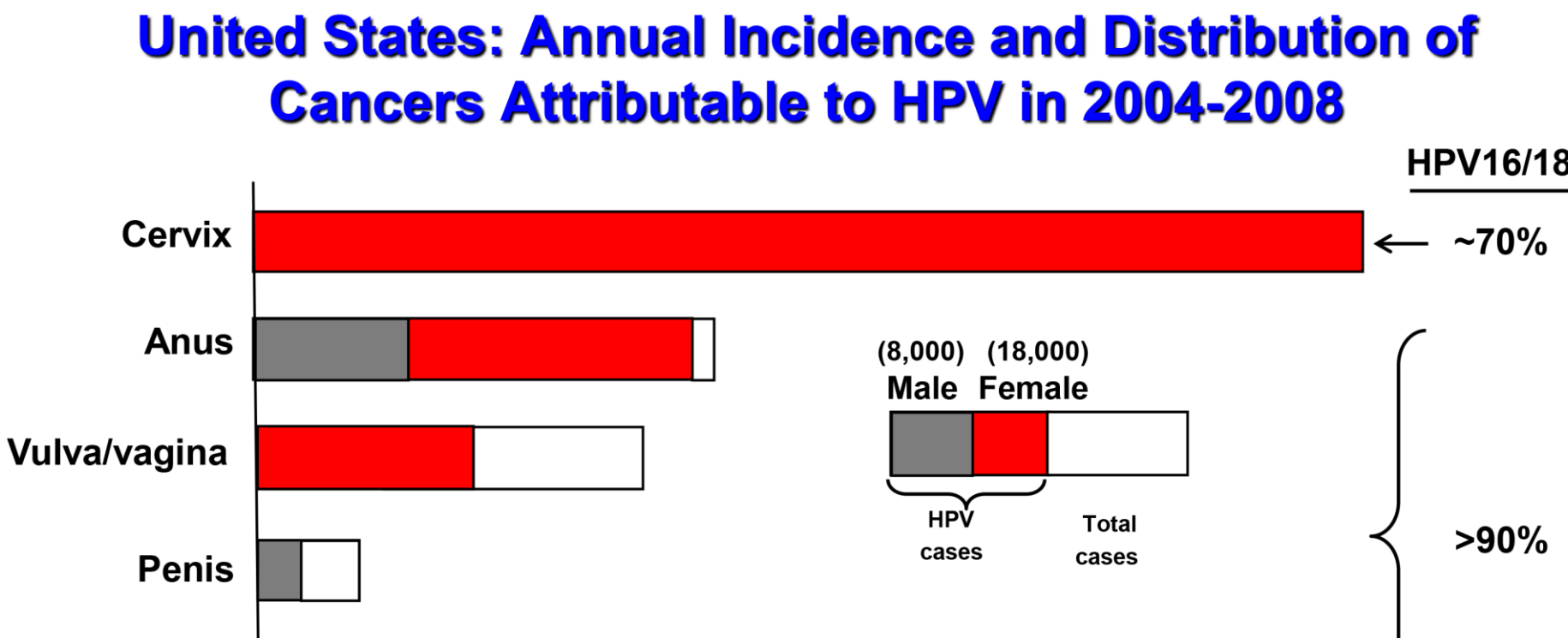
Worldwide Incidence and Distribution of Cancers Arributable to HPV



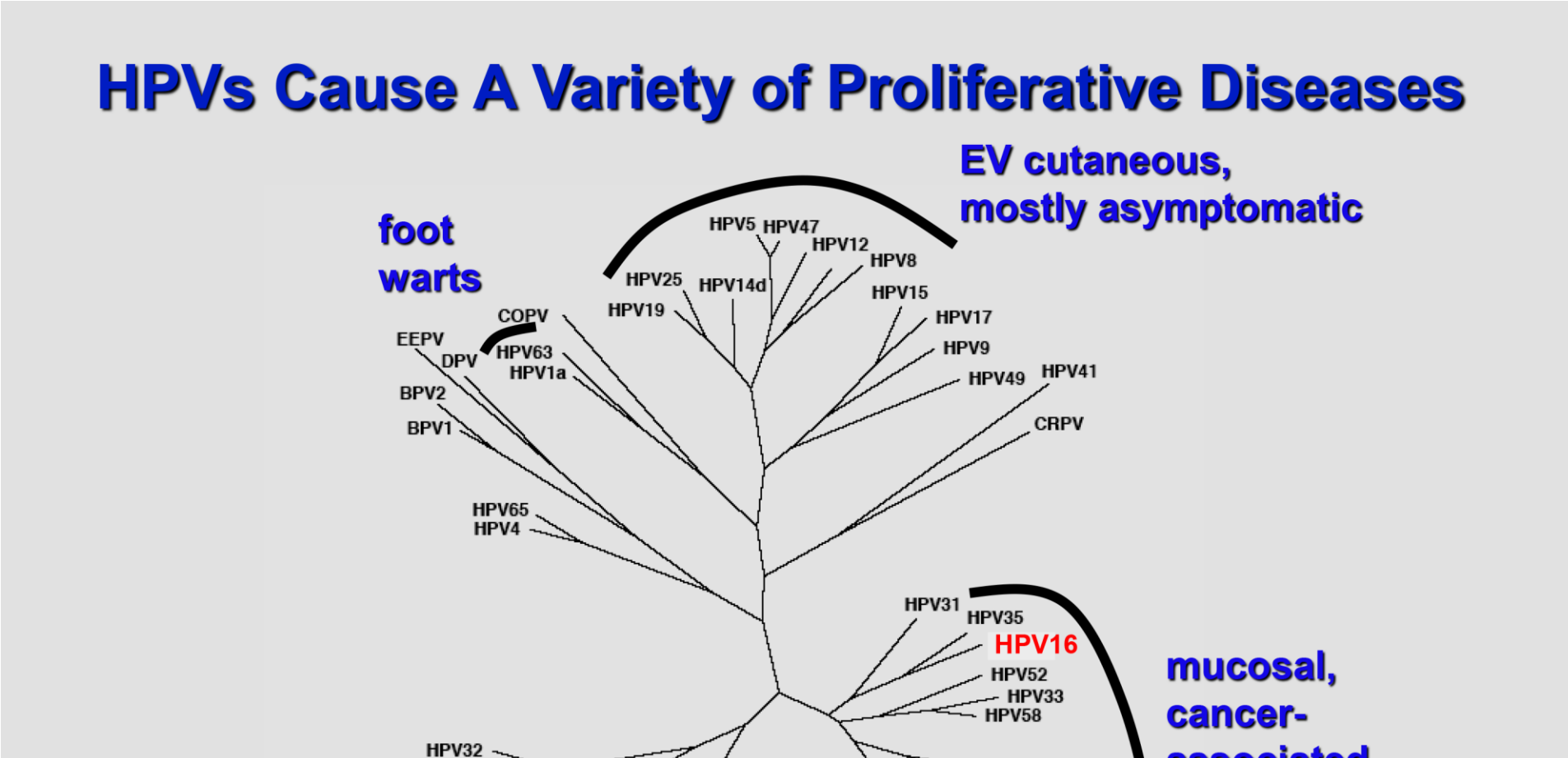
5 Most Common HPV Types in Cervical Squamous Cell Carcinoma-By Region



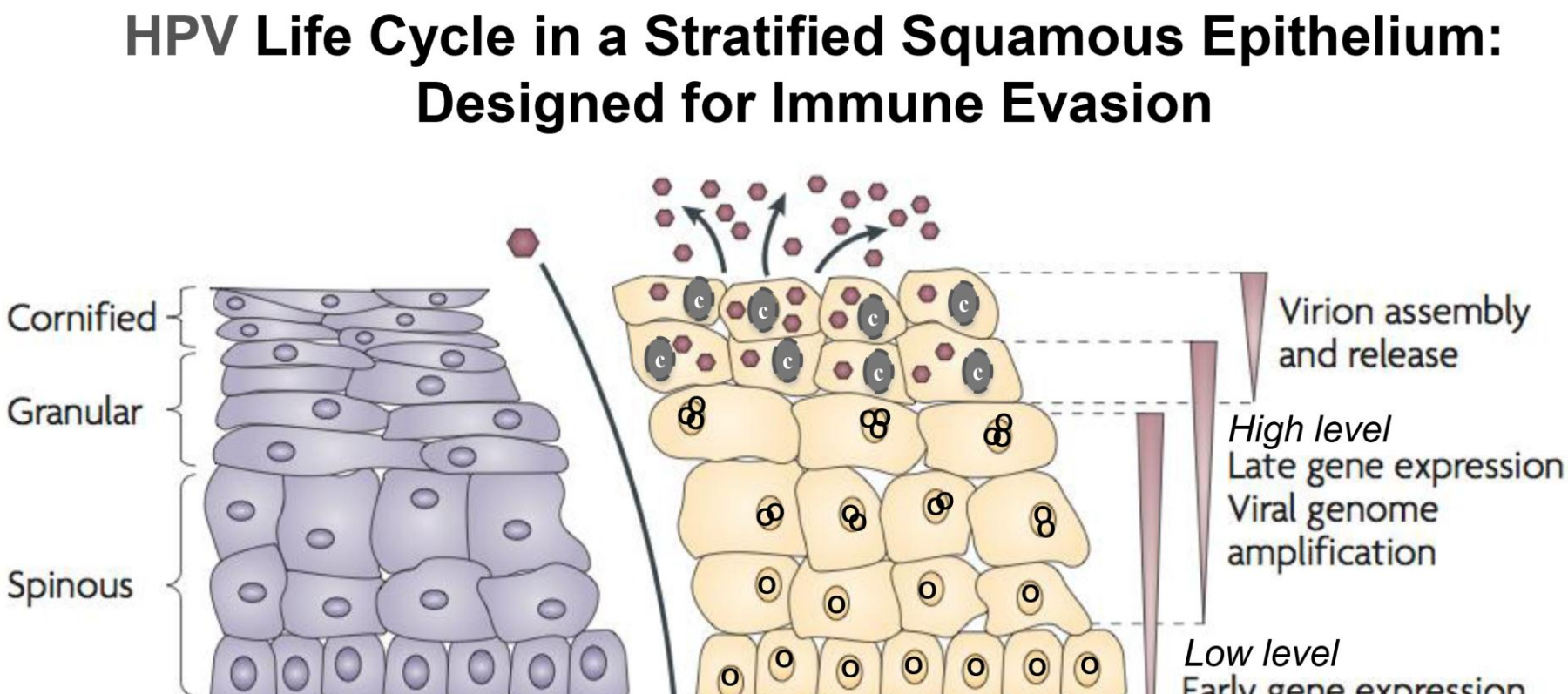
United States: Annual incidence and distribution of cancers attributable to HPV in 2004-2008



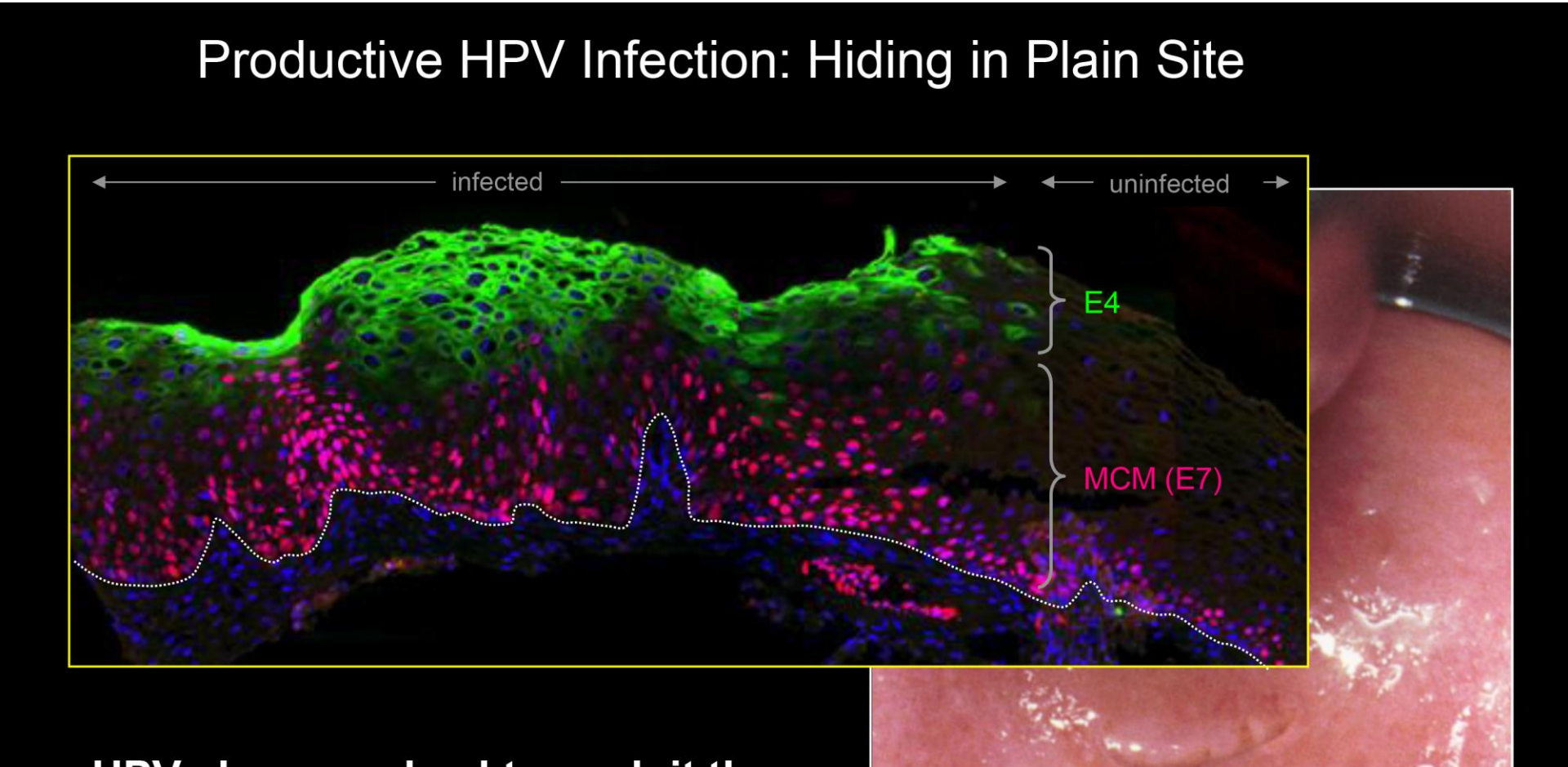
HPVs cause a variety of proliferative diseases



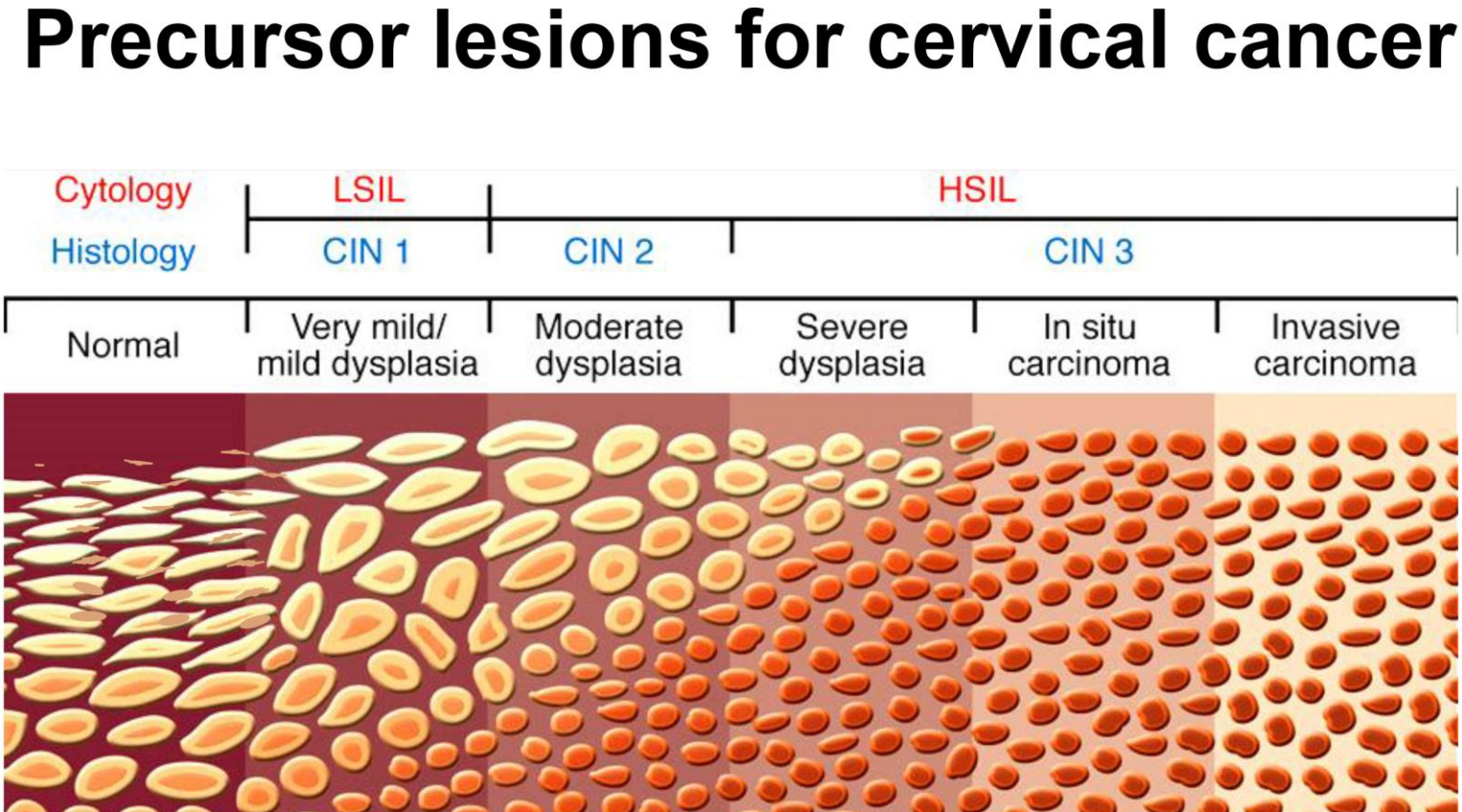
HPV Life Cycle in a Stratified Squamous Epithelium: Designed for Immune Evasion



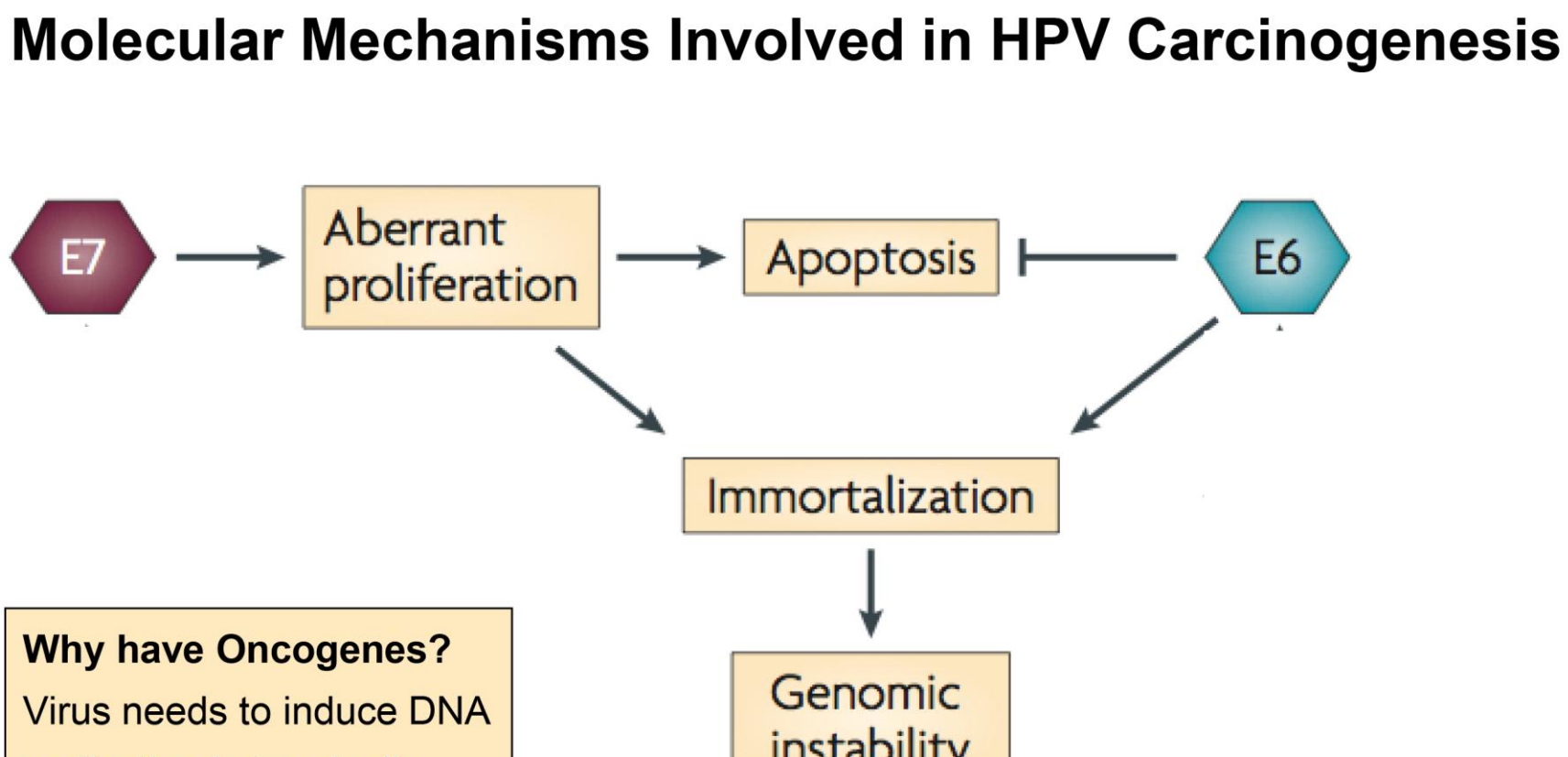
Productive HPV Infestion Hiding in Plain Site



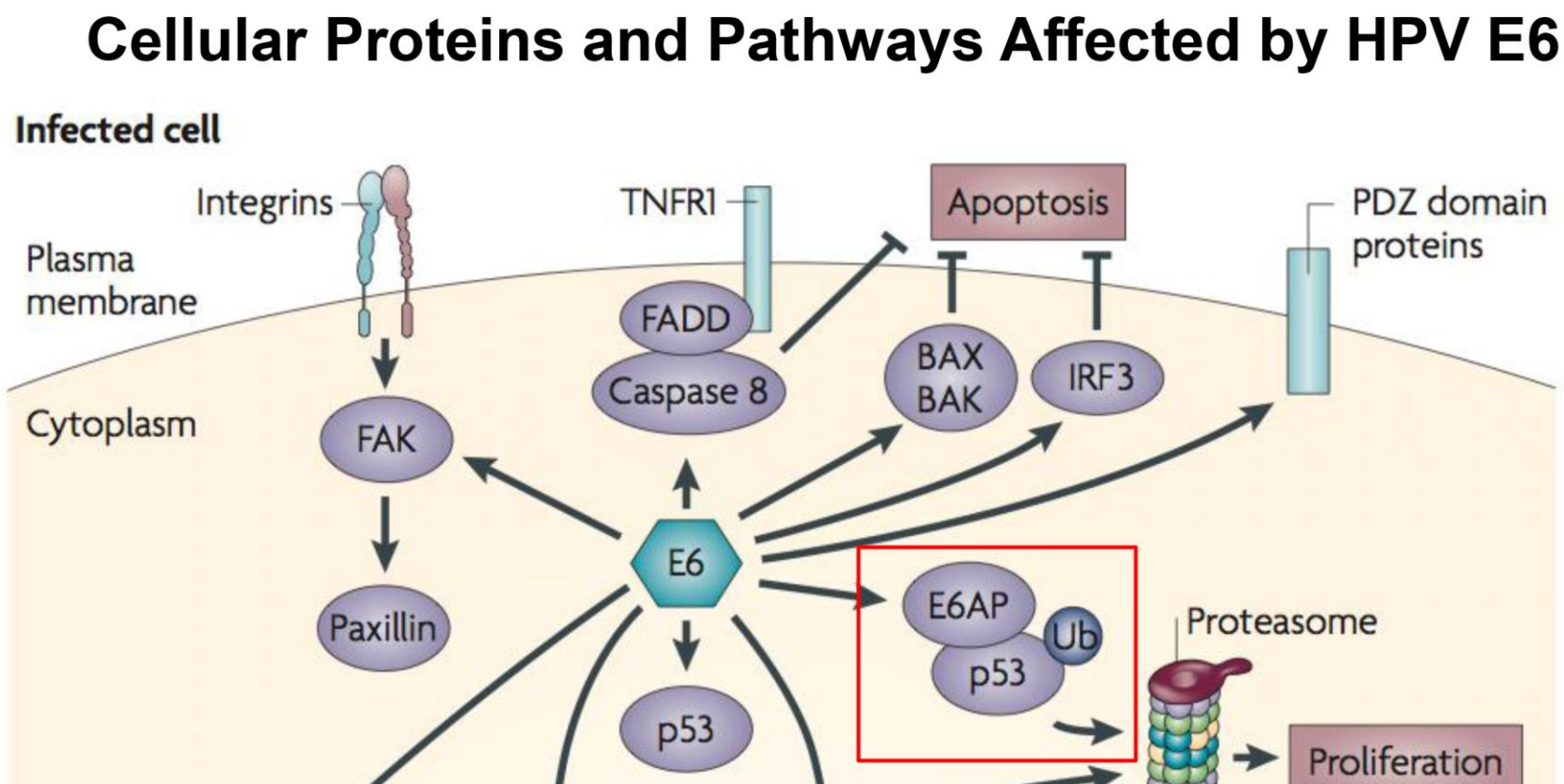
Precursor lesions for cervical cancer



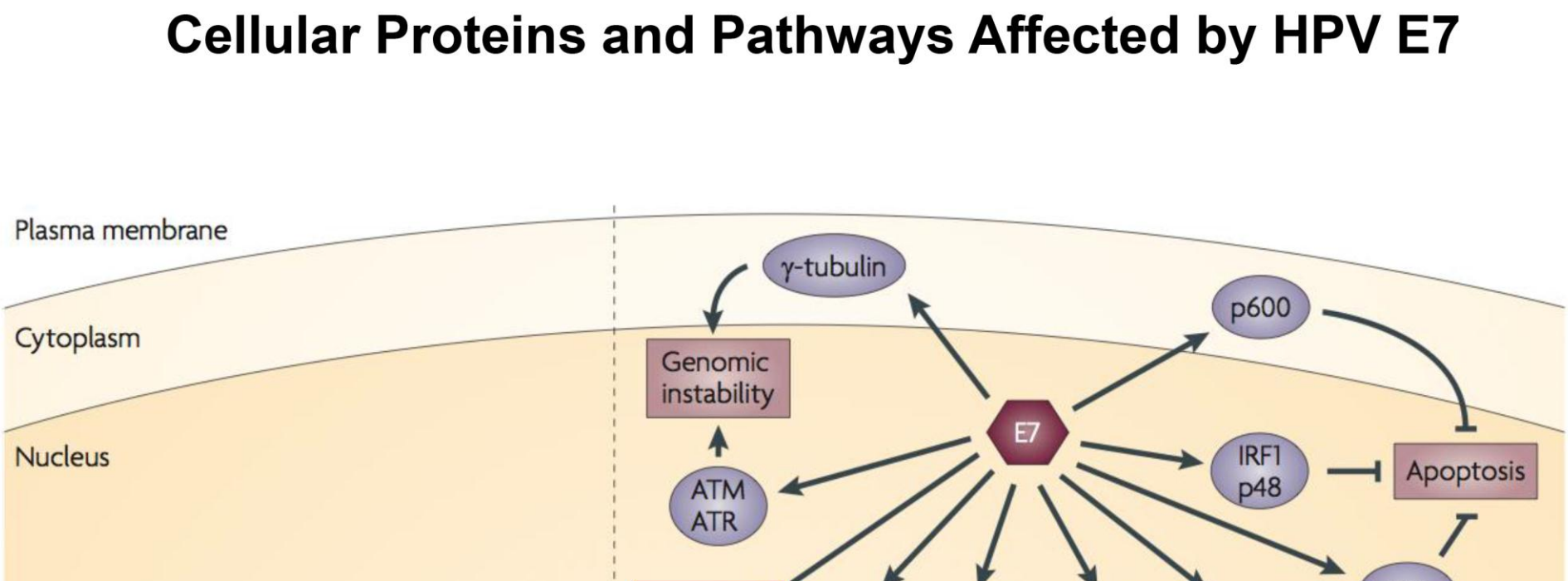
Molecular Mechanisms Involved in HPV Carcinogenesis



Cellular Proteins and Pathways affected by HPV E6

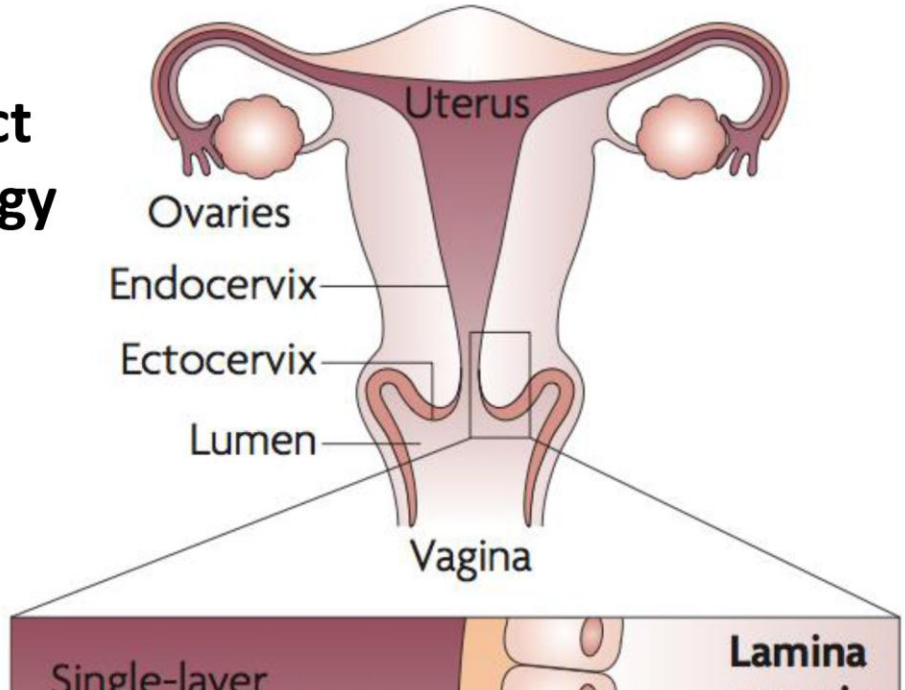


Cellular Proteins and Pathways Affected by HPV E7



Femaile Reproductive Tract Anatomy & Histology

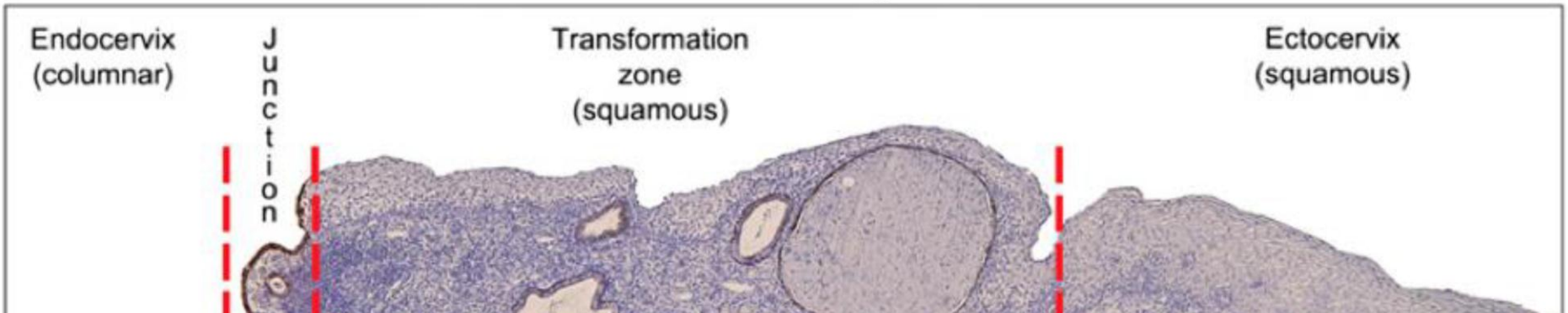
Female Reproductive Tract Anatomy & Histology



Junction cells of Transformation Zone Express Unique Biomarkers

Junction Cells of Transformation Zone Express Unique Biomarkers

Keratin 7 staining



Transformation Zones in Other HPV Cancers

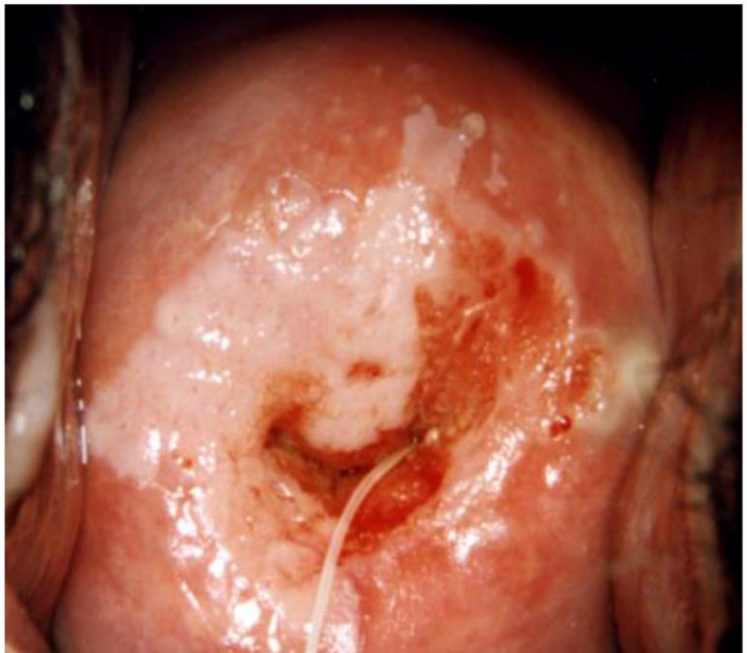
Transformation Zones in Other HPV Cancers

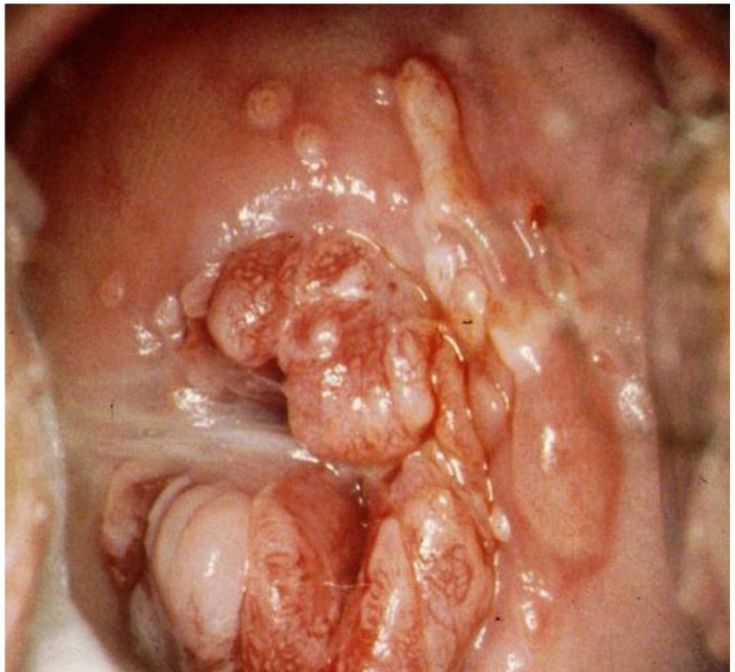
Anal cancer also occur at the transformation zone.

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

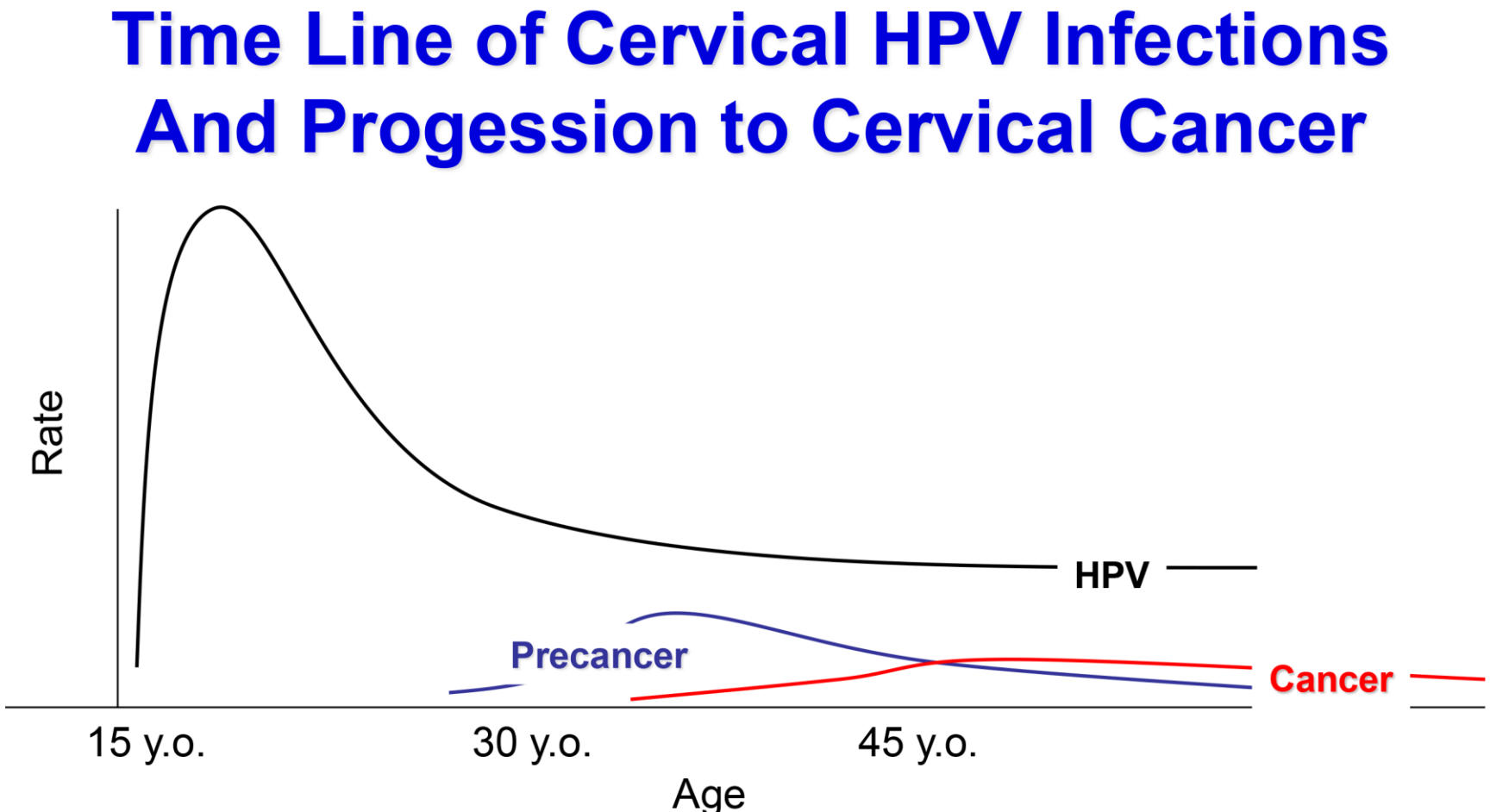
Cervical Cancers Develop at the Transition Zone Between Squamous and Columnar Epithelium

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





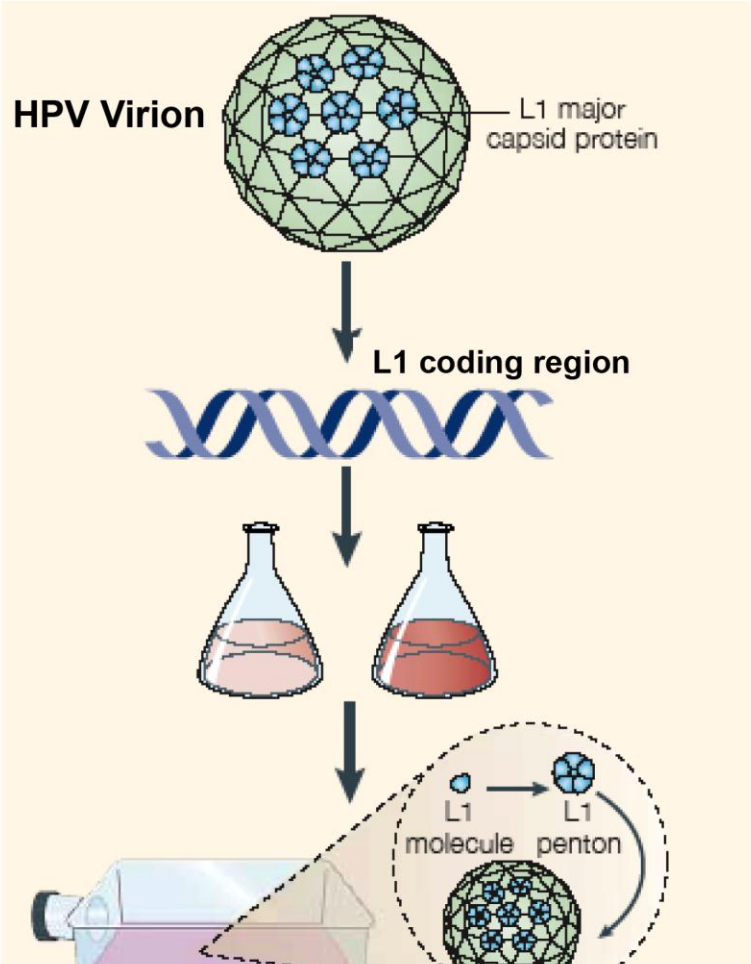
Time Line of Cervical HPV Infections and Progression to Cervical Cancer



Key To Developing HPV Prophylactic Vaccines

IM injection of virions, but not denatured forms of the major virion protein L1 or L1 peptides, induced protection from experimental infection in animal models. Generating an immunogen with conformationally correct L1 was critical.

Prophylactic HPV Vaccines Are L1 Virus Line Particles (VLPs)



Prophylactic HPV Vaccines Are L1 Virus Like Particles (VLPs)

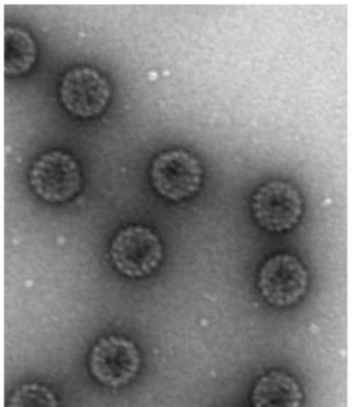
L1 Insertion into a Baculovirus Expression Vector

Production in Insect Cells

Spontaneous assembly of L1 into VLPs

Induce high titers

HPV16 L1 VLPs



Two Distinct HPV L1 VLP Vaccines have been Commercialized

Two Distinct HPV L1 VLP Vaccines Have Been Commercialized

Cervarix:
GlaxoSmithKline

HPV16
HPV18
} **70% of Cervical Ca**

ASO4 Adjuvant (Aluminum + MPL)*

Made in insect cells

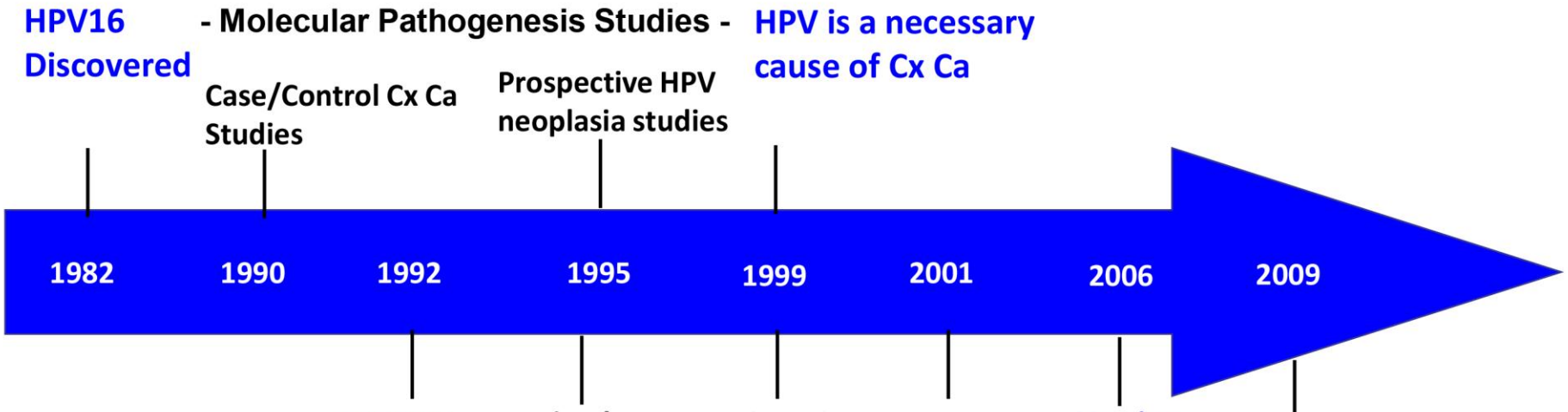
Gardasil:
Merck

HPV16
HPV18
} **70% of Cervical Ca**

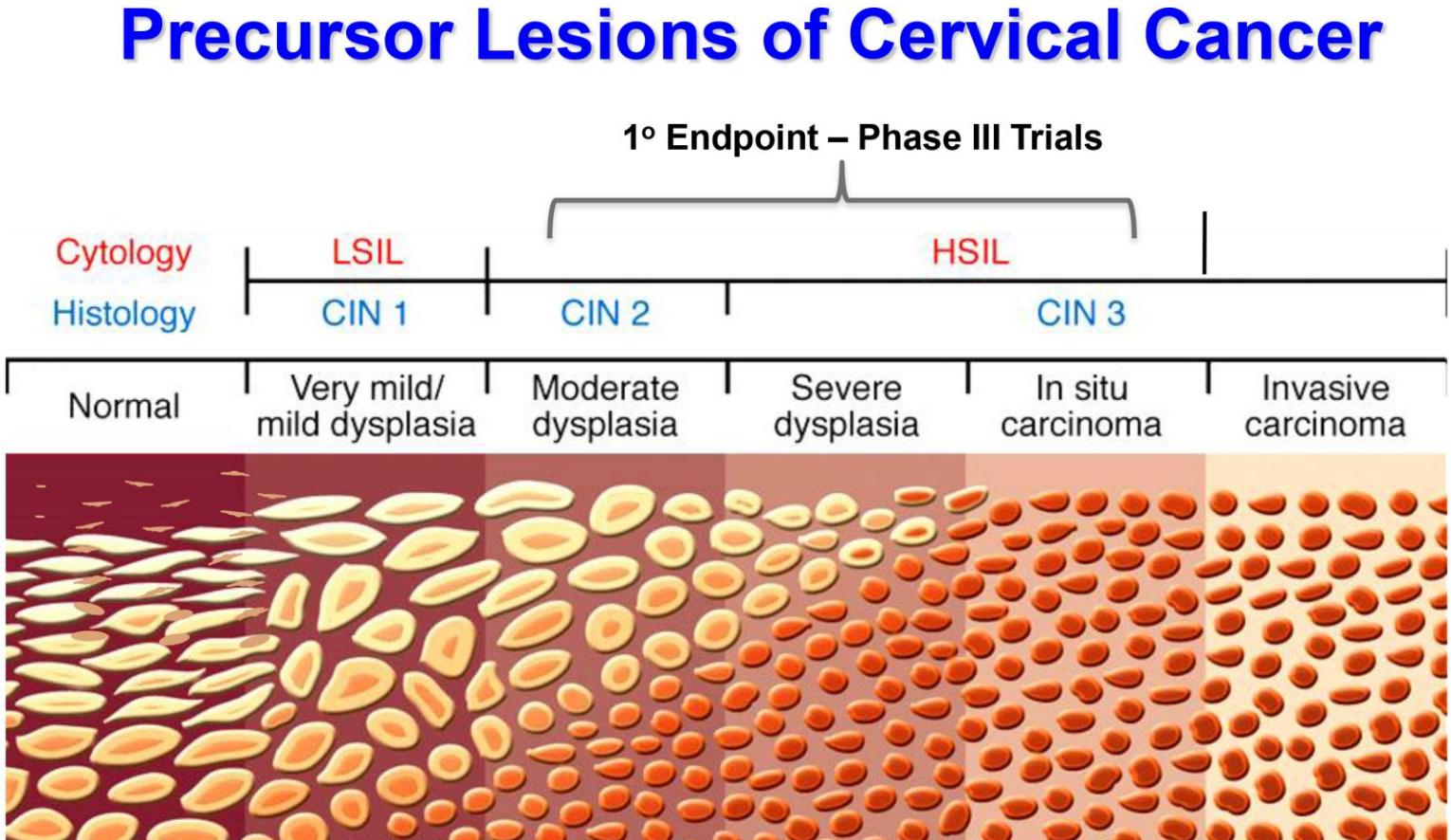
HPV6
HPV11
} **90% of Genital Warts**

Timeline of HPV Association with Cancer vs Vaccine Development

Timeline of HPV Association with Cancer vs Vaccine Development



Precursor Lesions of Cervical cancer



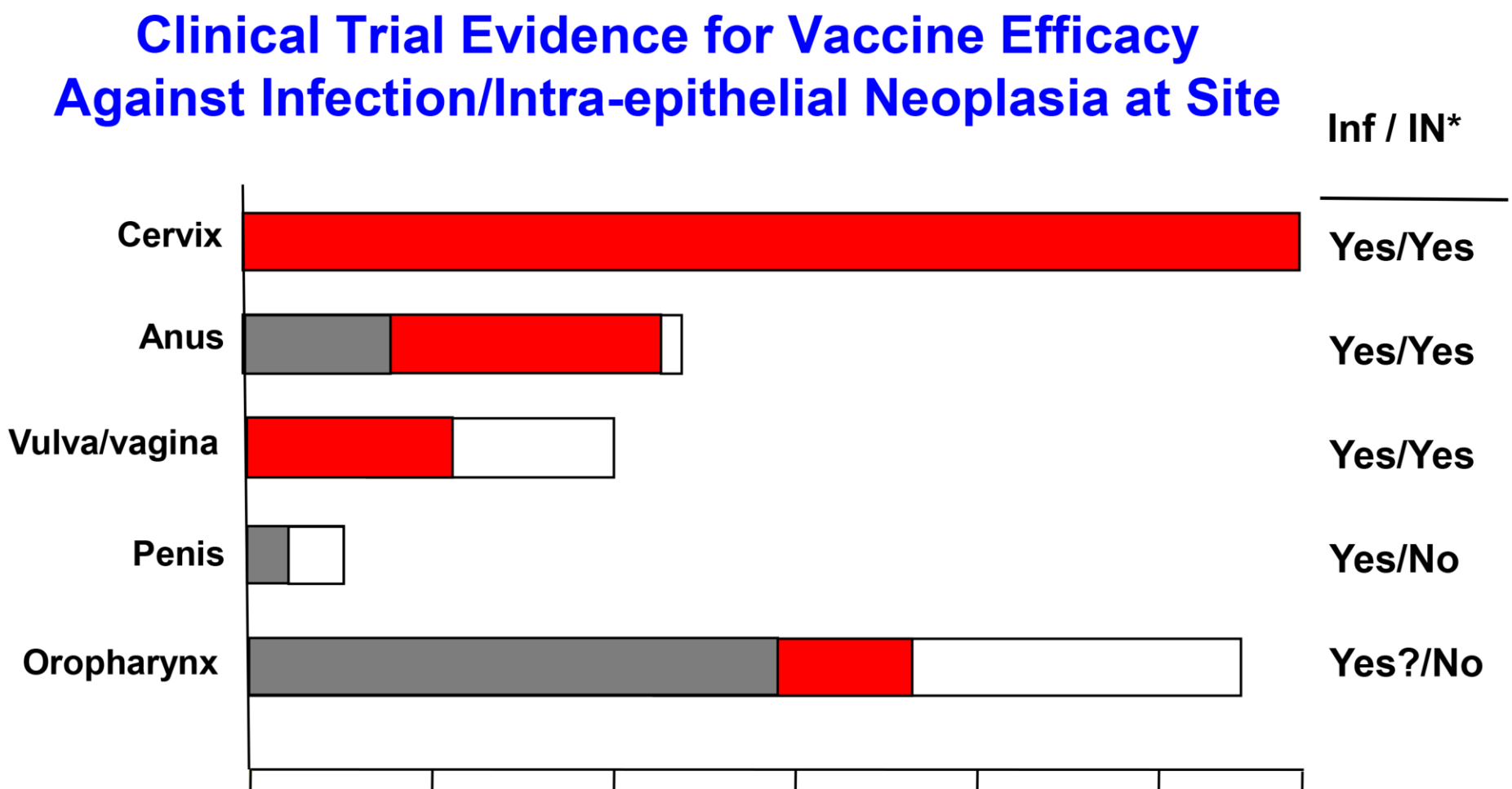
Efficacy of HPV VLP Vaccines Against Incident Disease by Vaccine-Targeted Types in Randomized Trials

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

No gential HPV infection detected in at entry

End Point	Sex	Age	Vaccine	Efficacy

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



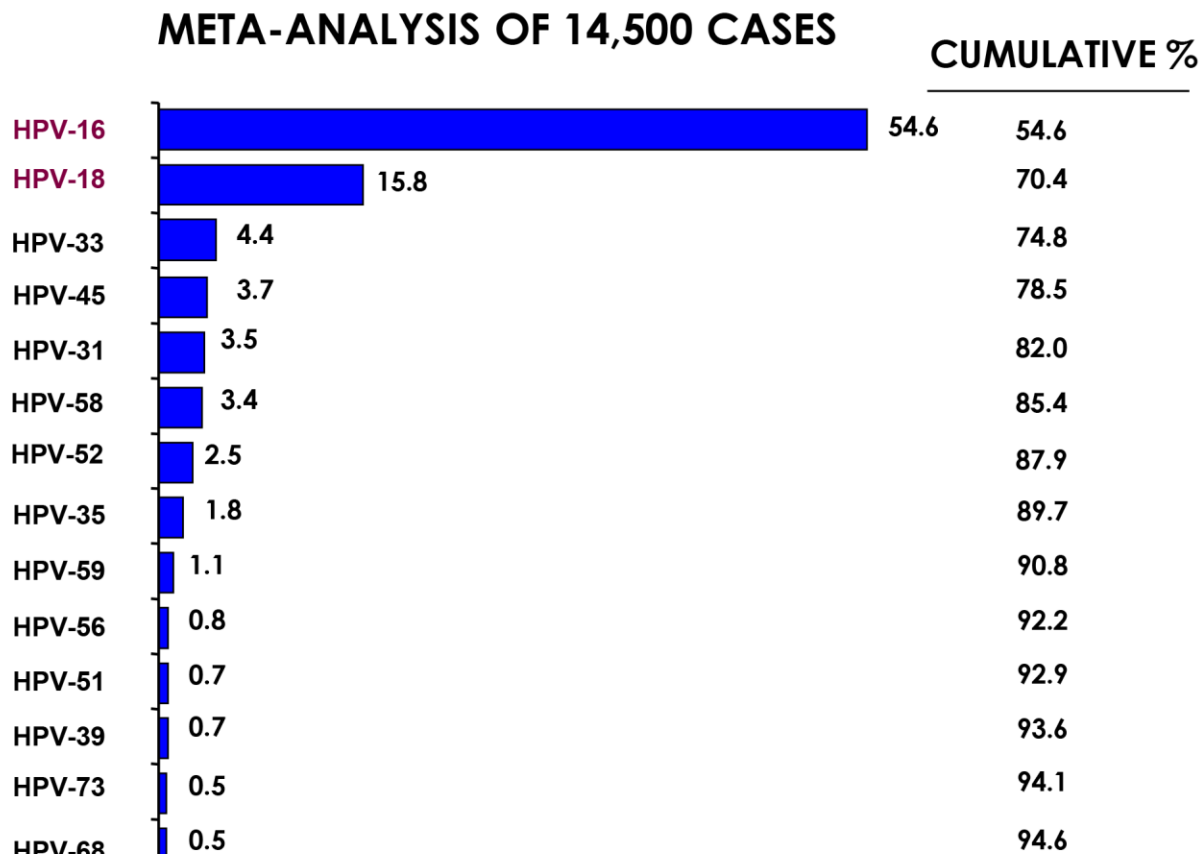
n’t prevent infection or disease caused by
the other HPV types that cause 30% of
cancer not caused by HPV16/18.

n’t induce regression of established HPV
ons or prevent progression of HPV-induced
s.

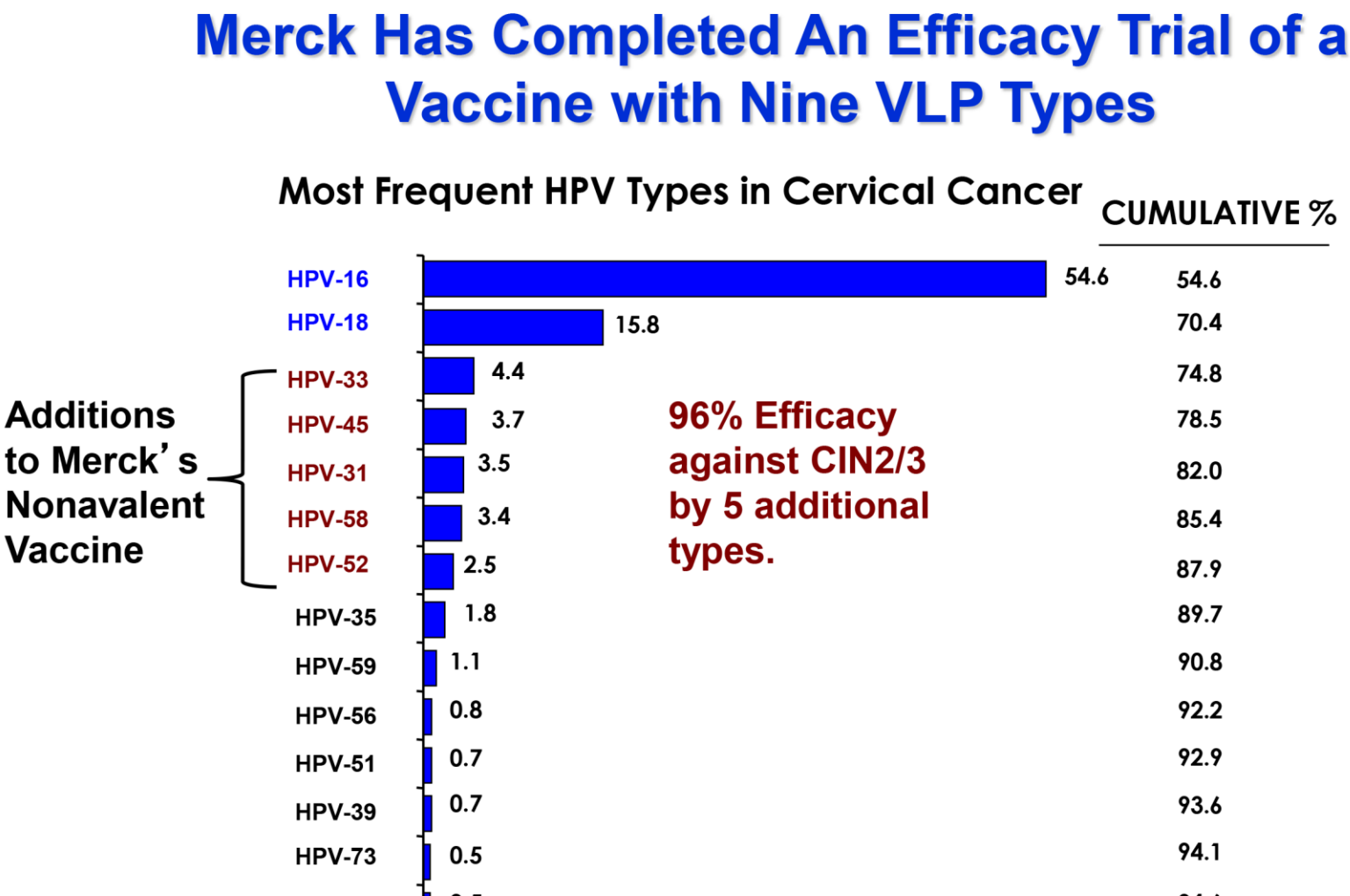
n’t

Percentages of Cervical Cancer Cases Attributed to the Most Frequent HPV Types in All

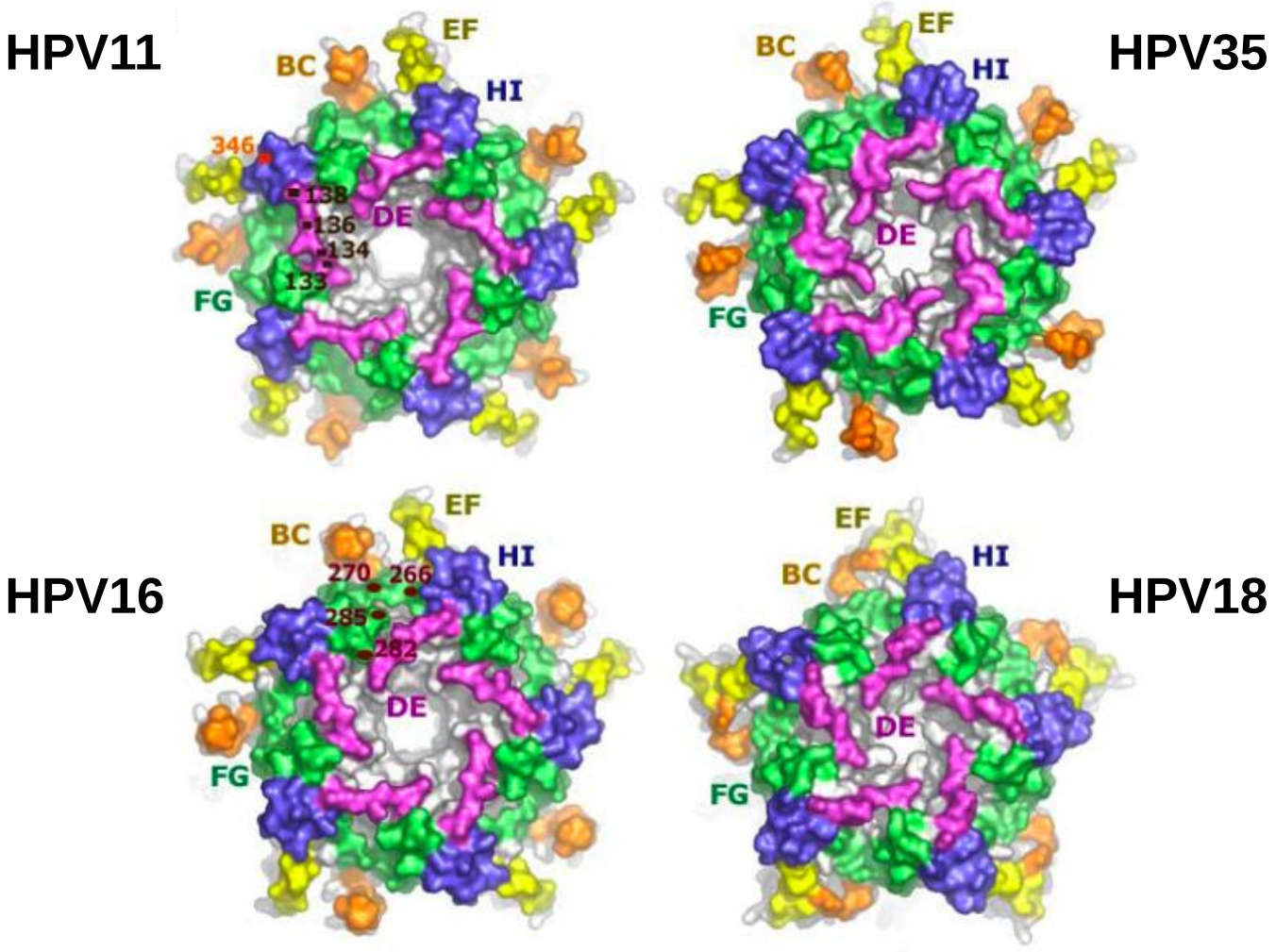
PERCENTAGES OF CERVICAL CANCER CASES ATTRIBUTED TO THE MOST FREQUENT HPV TYPES IN ALL WORLD REGIONS



Merck has Completed an Efficacy Trial of a Vaccine with Nine VLP Types



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



surface representation of L1 pentamers

Bishop *et al*., 2007

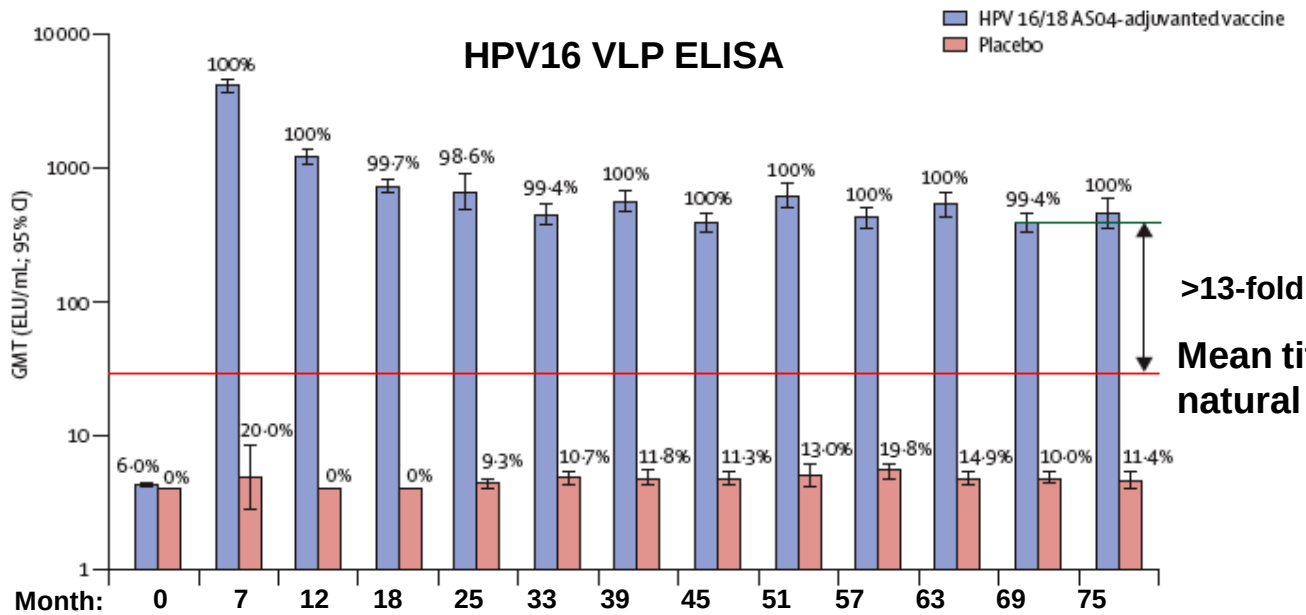
Consistency of Antibody Response to VLPs

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%

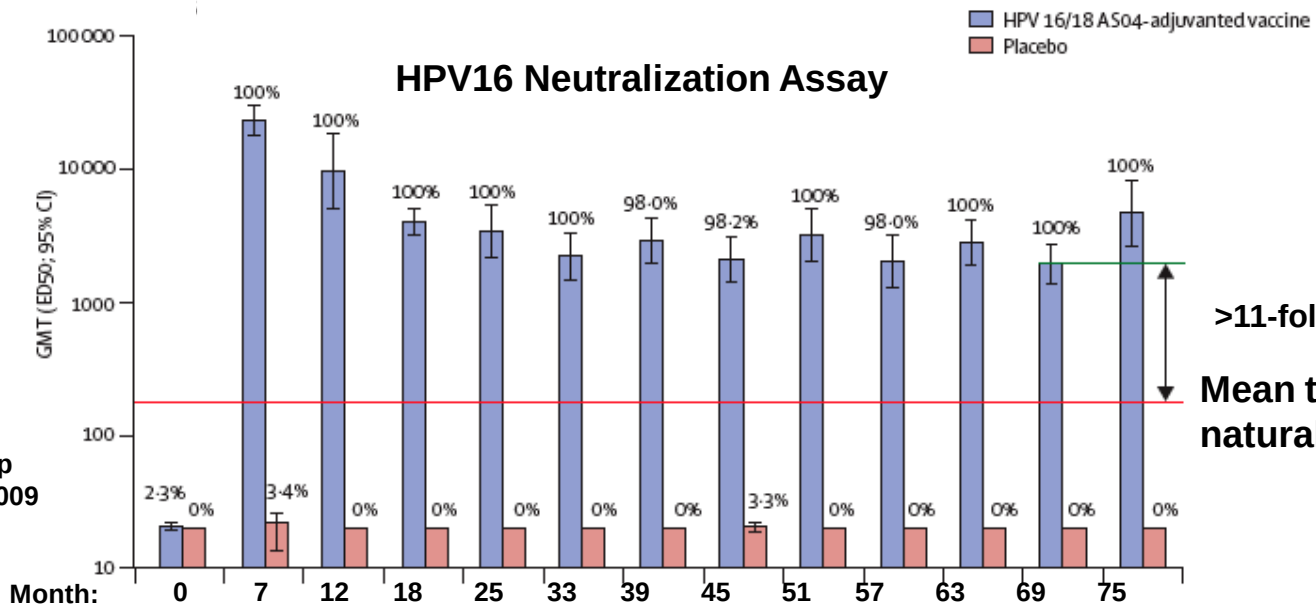
*4666 women vaccined 3 times by intramuscular injection

Durability of Antibody Response to Cervarix



>13-fold higher

Mean titer after natural infection



>11-fold higher

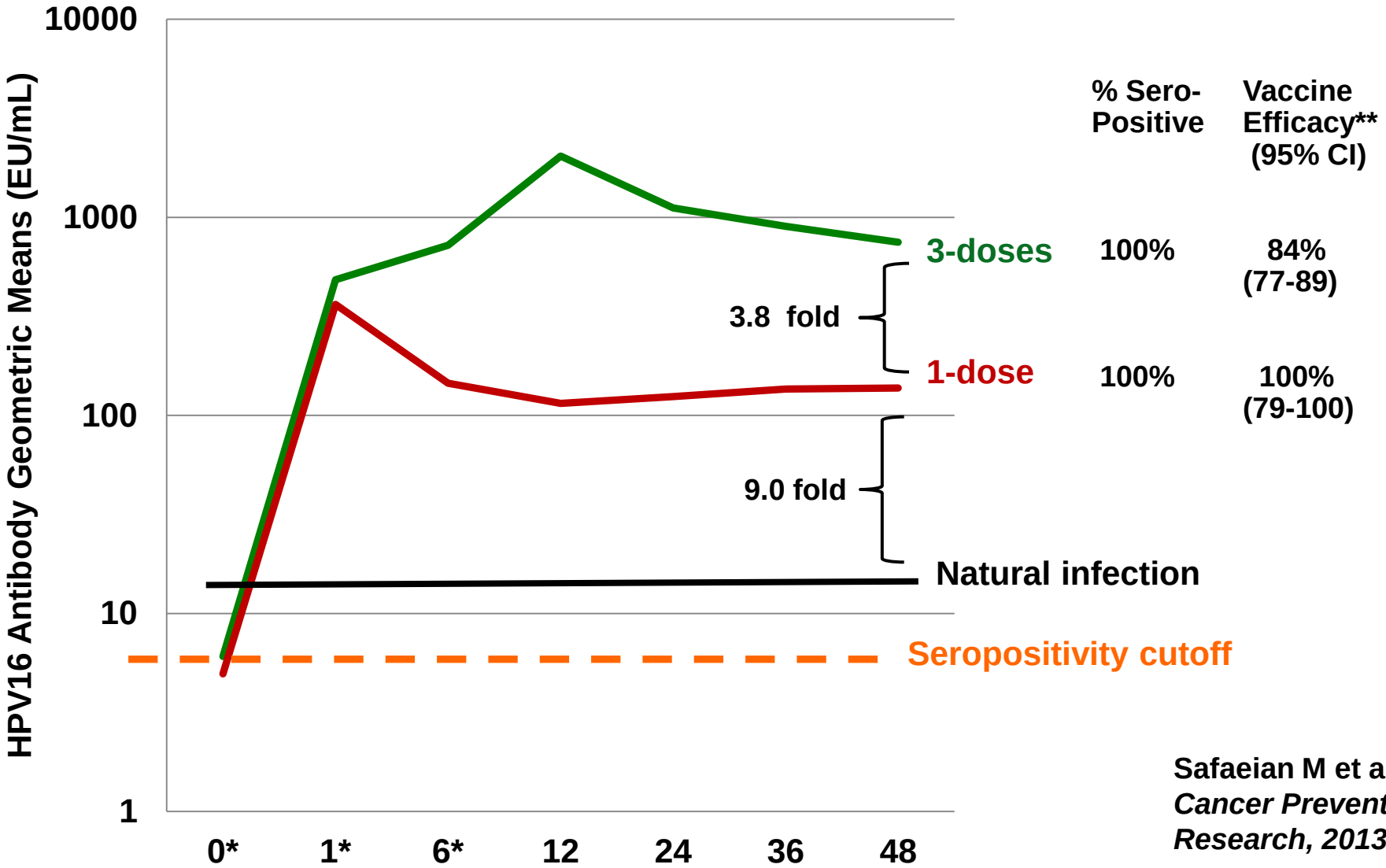
Mean titer after natural infection

The GSK Vaccine HPV-007 Study Group
Lancet 374:301-14, 2009

Duration of Protection

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

HPV VLP Vaccination Induces Consistent Ab Response and Protection Even After a Single Dose*



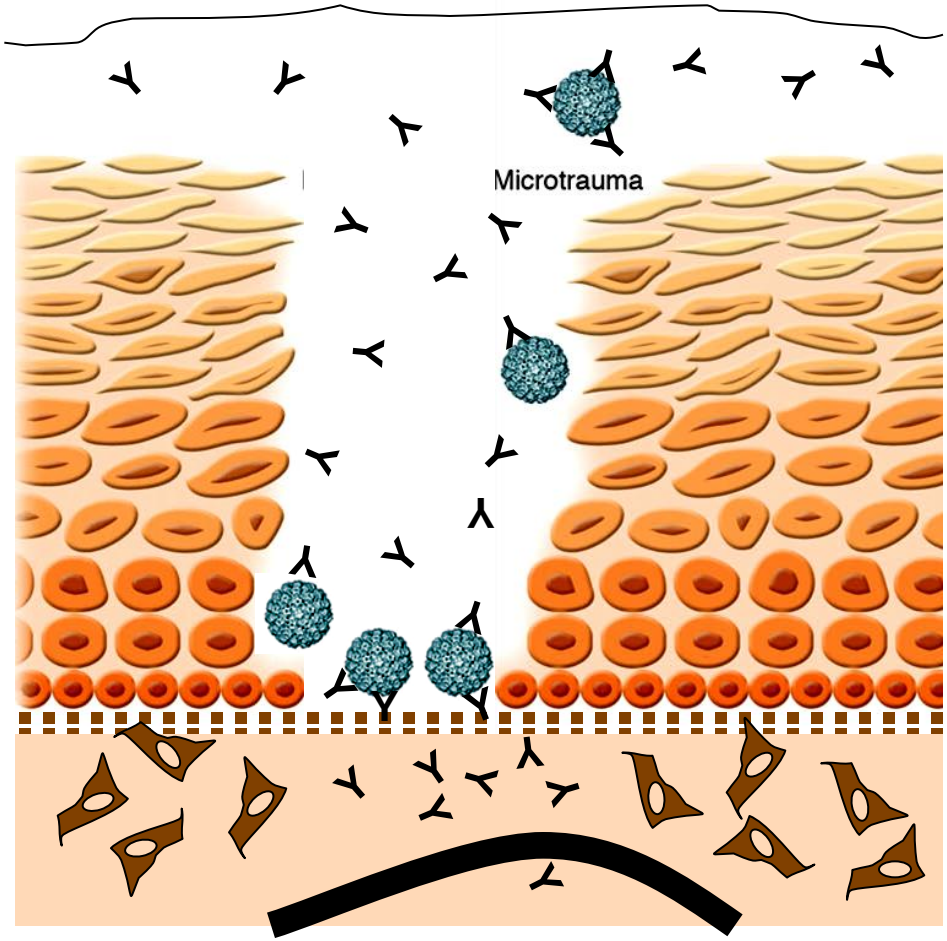
Safaeian M et al
Cancer Prevention Research, 2013

*Post hoc analysis from Costa Rica Trial of Cervarix
** Efficacy against persistent HPV16 infection

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

Transudated Abs in Mucus*

Exudated Abs at Sites of Trauma#



Cervical Mucus

Cervical Epidermis

Basement Membrane

Dermis

* 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*

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 8 years, after antibody levels have

HPV Vaccines Are Now Established Products

Licensed worldwide to the prevention of cervical cancer and in some cases other HPV induced neoplasia including anal cancer and genital warts.

Worldwide Sales:

Gardasil – 100 million doses since 2006

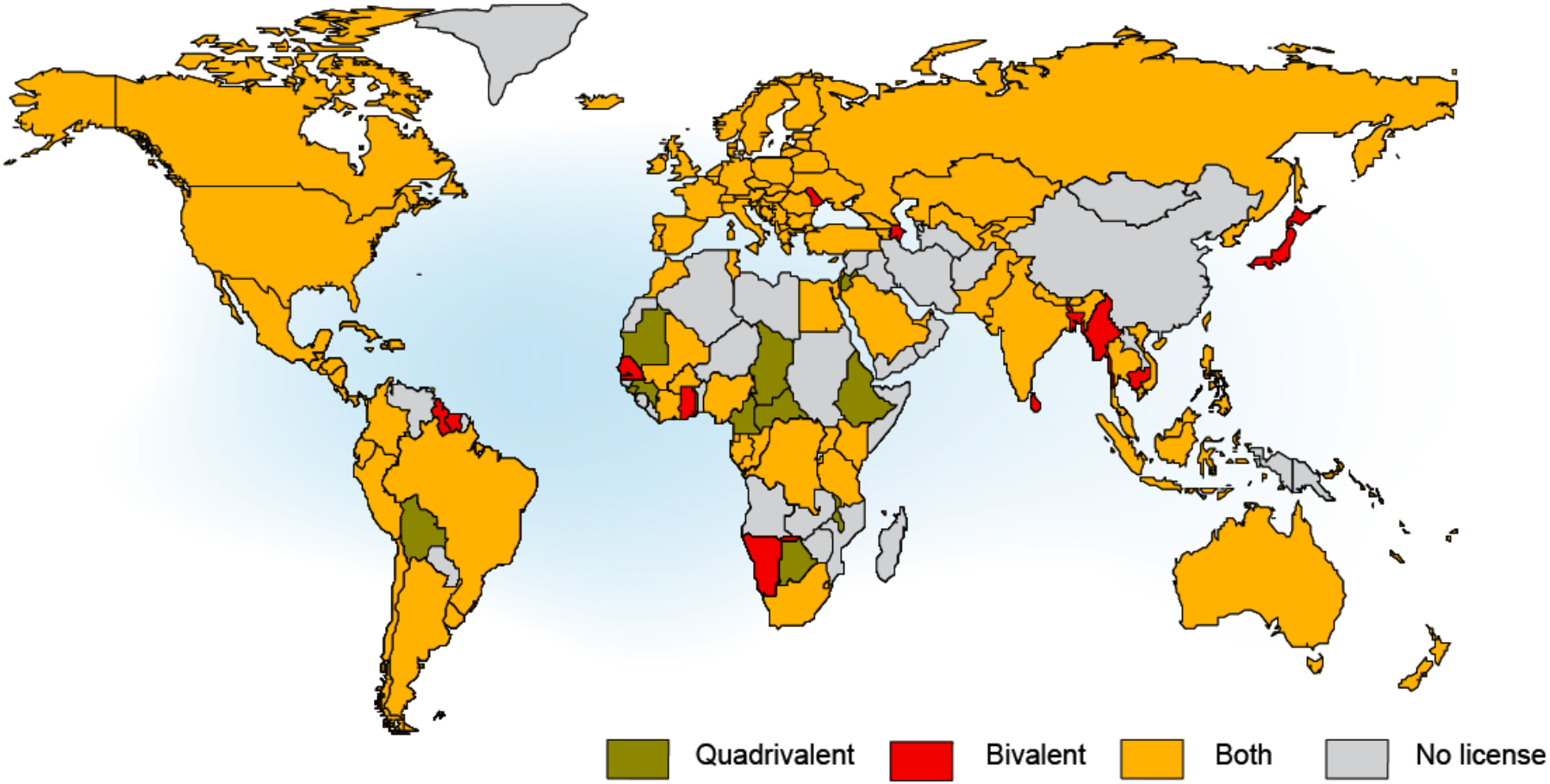
Cervarix – 25 million doses since 2007 (2009 in US)

FDA approval of Gardasil for genital warts in men – 2009

for anal cancer in both sexes - 2010

Global HPV Vaccine Licensure Status

March 2010



Weekly Epi Report 84: 117-32, 2009

Less Than 3 Dose Vaccination Programs

Two doses at 0 and 6 moths approved for young adolescents in:

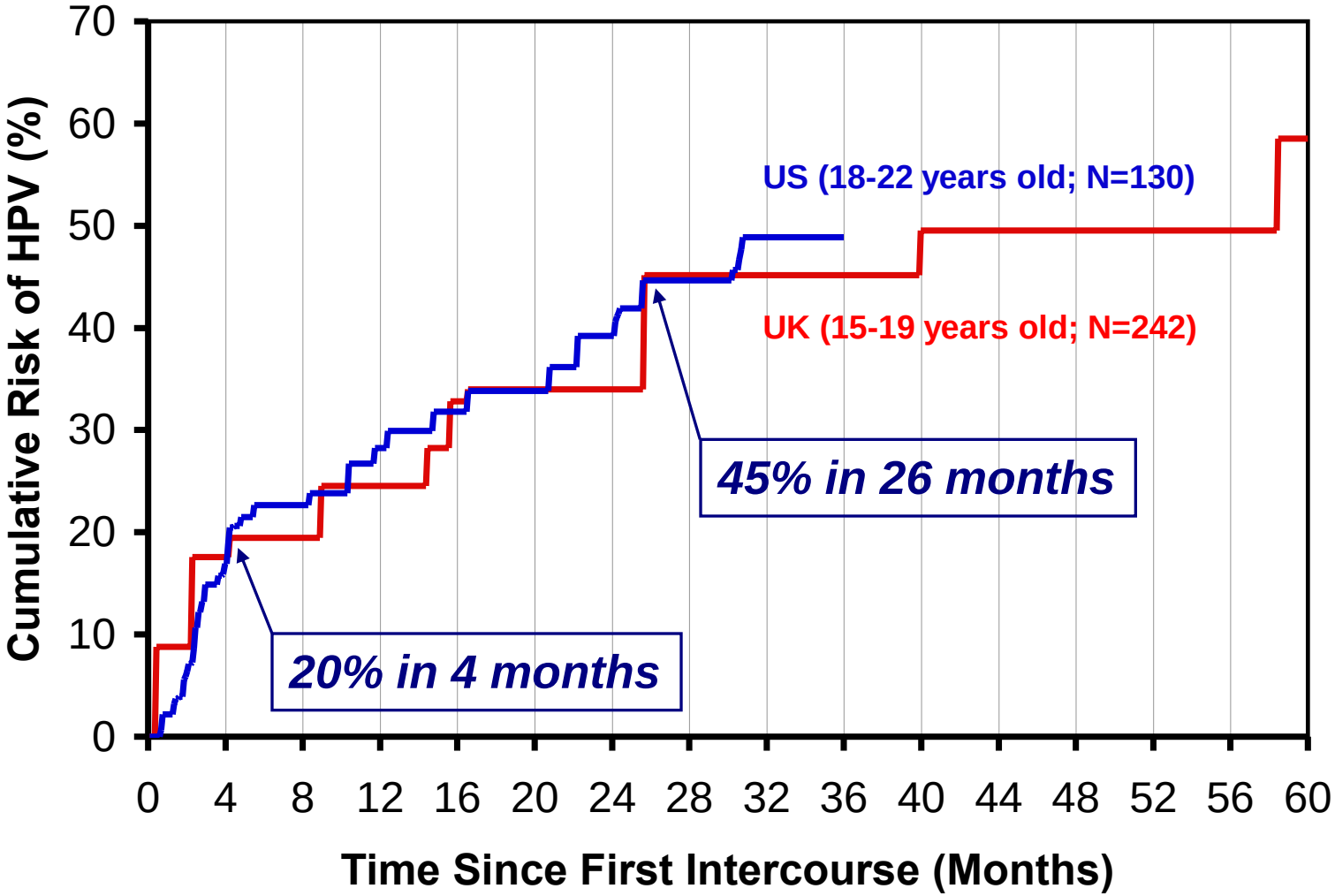
- **EU – EMA approval in 2014 for 9-13 yr olds**
- **Switzerland**
- **Mexico**
- **Quebec**

Based on immunobridging: two doses in young adolescents generates antibody titers that are non-inferior to three doses in 15-26 year olds in which efficacy was established.

Outstanding Implementation Issues

- Who to vaccine: Girls > Boys = young women > men
- Delivery of three IM doses to early adolescents
- Effects of vaccine on Cervical Ca screening recommendations and compliance
- Delivery to ecomomically disadvanced individuals

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



UK data adapted from *Collins et al, BJOG 109: 96-98, 2002* US data adapted from *Winer et al, J Inf Dis 197:279-282, 2008*

October 2011

CDC Advisory committee recommends that boys ages 11-12 be routinely vaccinated with Gardasil, with catch up through age 26. Previous recommendation was "permissive".

Why the change in recommendation?

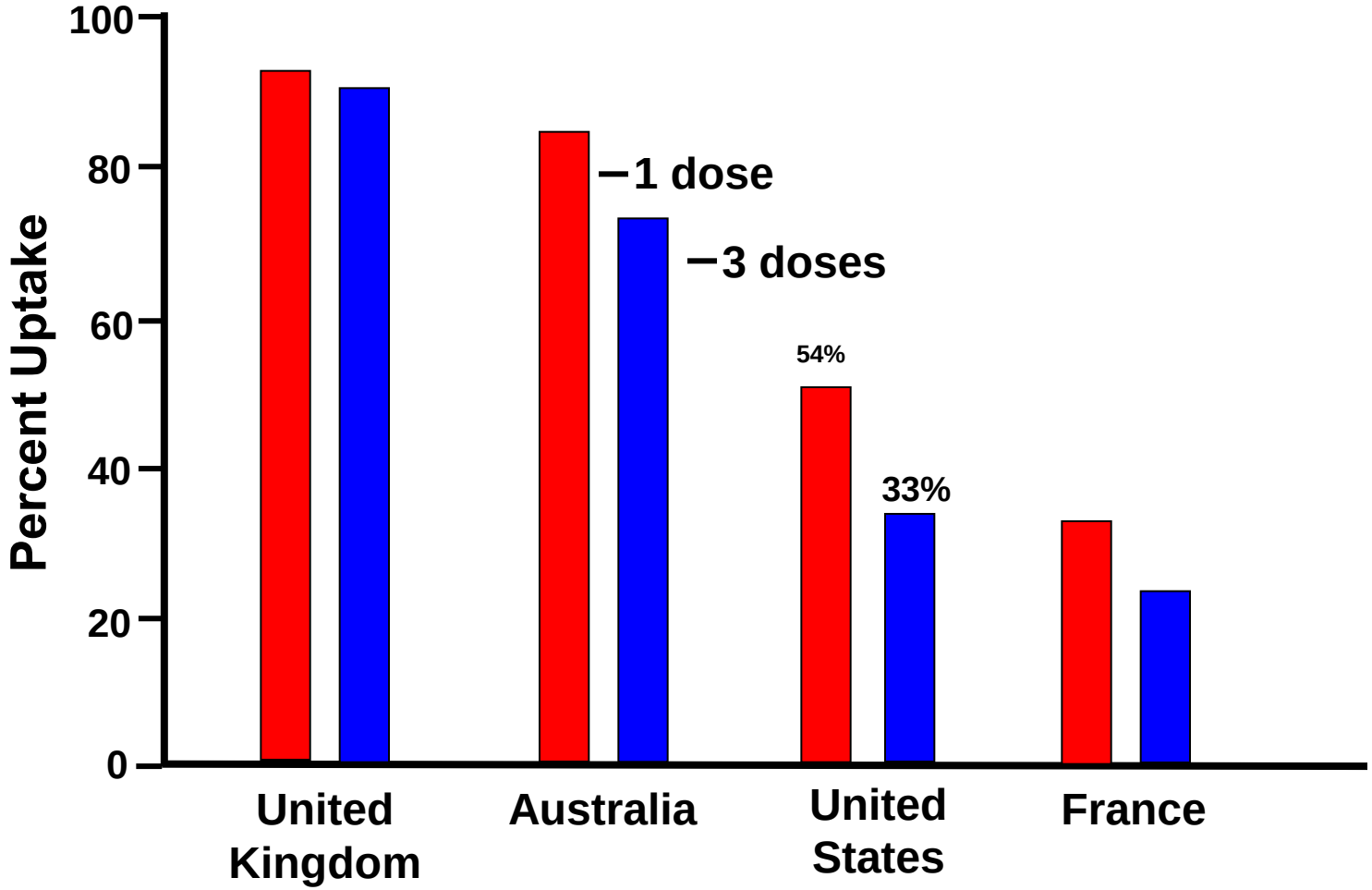
1.Poor uptake rates in girls

2.Indication for prevention of anal cancer

Outstanding Implementation Issues

- Who to vaccine: Girls >> Boys = young women > men
- Delivery of three IM doses to early adolescents
- Effects of vaccine on Cervical Ca screening recommendations and compliance
- Delivery to ecomomically disadvanced individuals

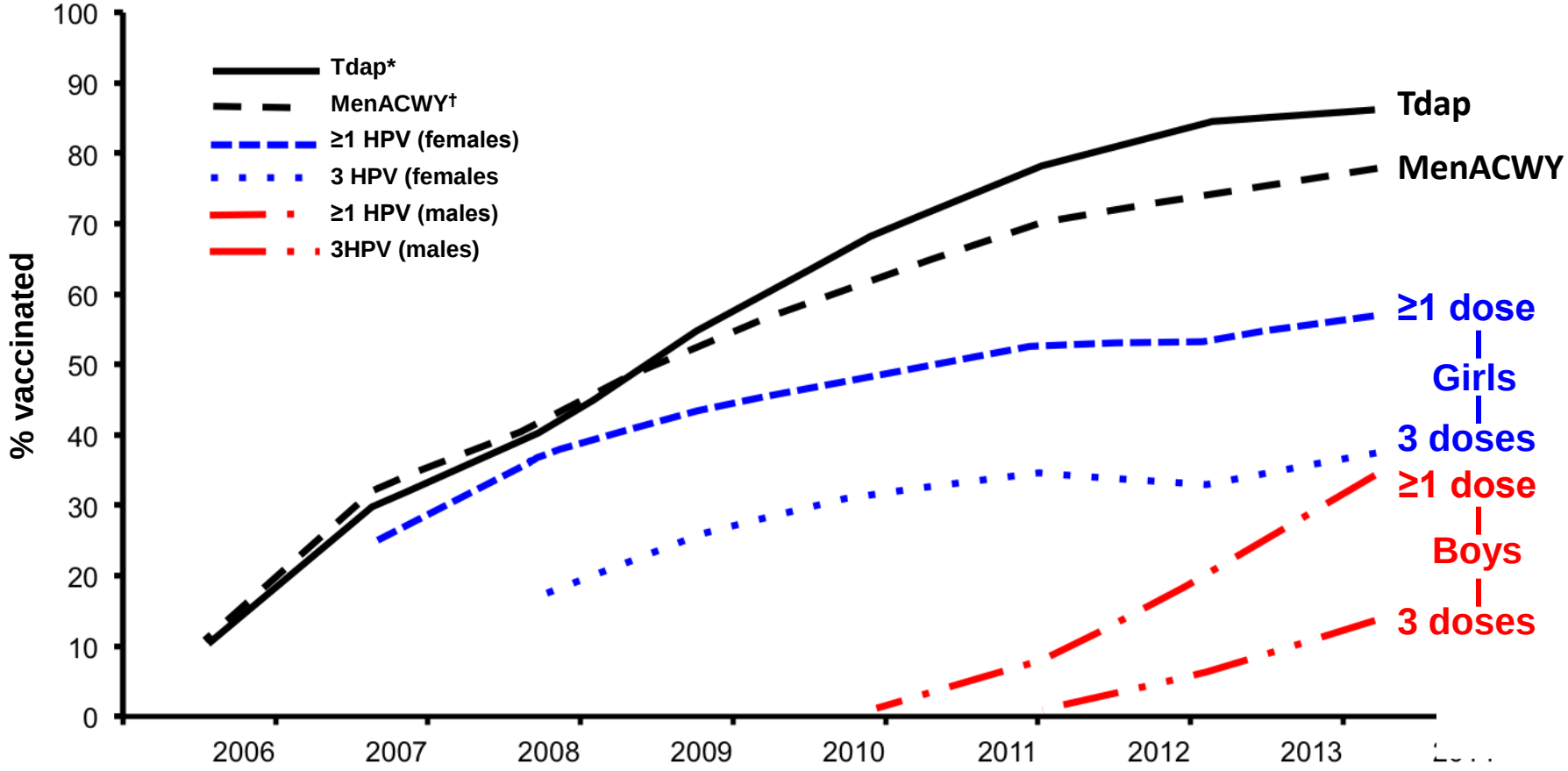
Variable Uptake of HPV Vaccine
(2012 data for girls)



Delivery: School | School | Clinic | Clinic

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

MMWR Vol 63, #29, July 25, 2014

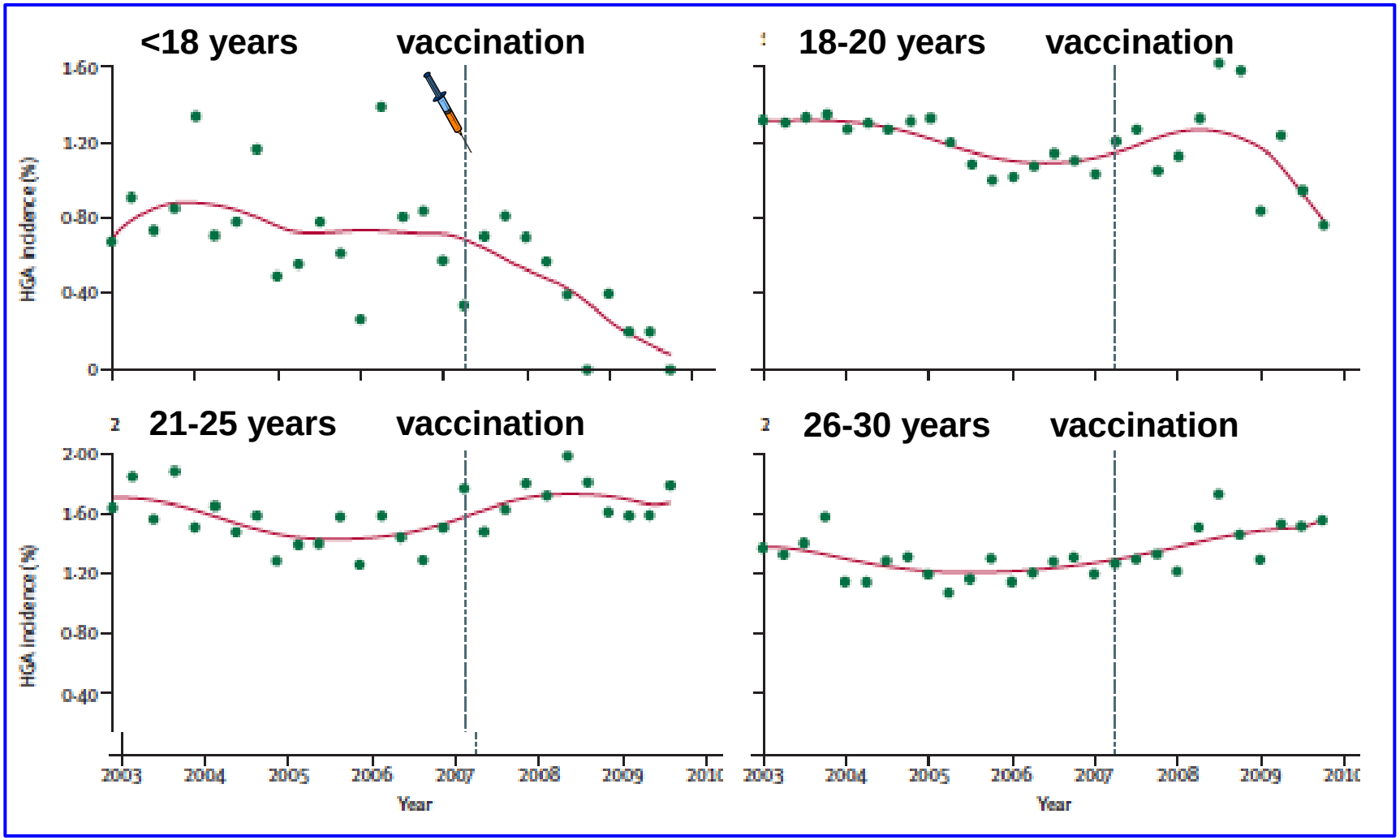


Abbreviations: Tdap = tetanus, diphtheria, acellular pertussis vaccine; MenACWY = meningococcal conjugate vaccine; HPV-1 = human papillomavirus vaccine, ≥1 dose; HPV-3 = human papillomavirus, ≥3 doses.

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

† HPV vaccination recommendations were published in March 2007.

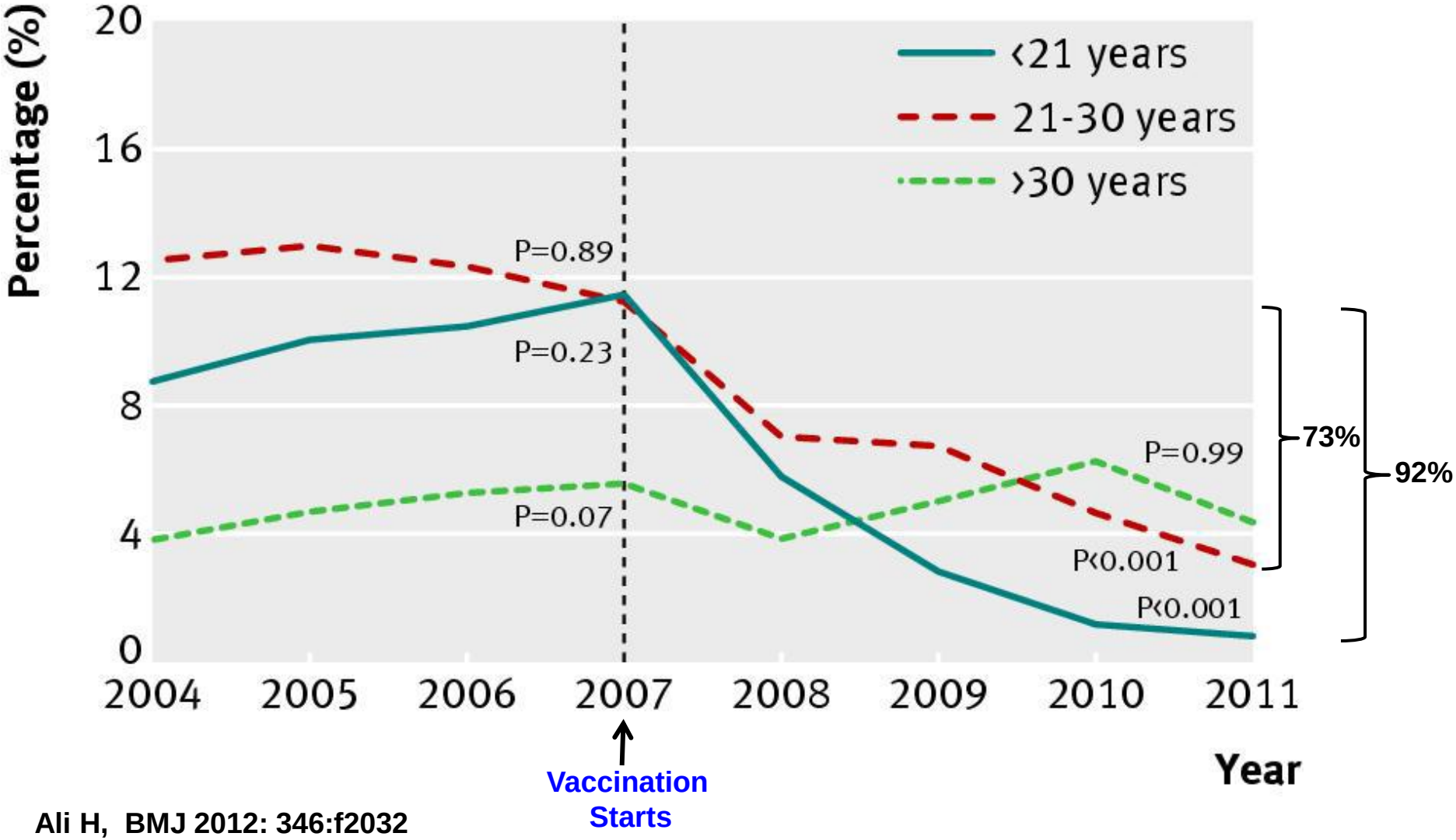
Reduction in CIN2+ Cervical Dysplasia: Gardasil in Australia



Brotherton et al, Lancet 377: 2085-92, 2011

Genital Wart Time Trends in Australia 2004-2011

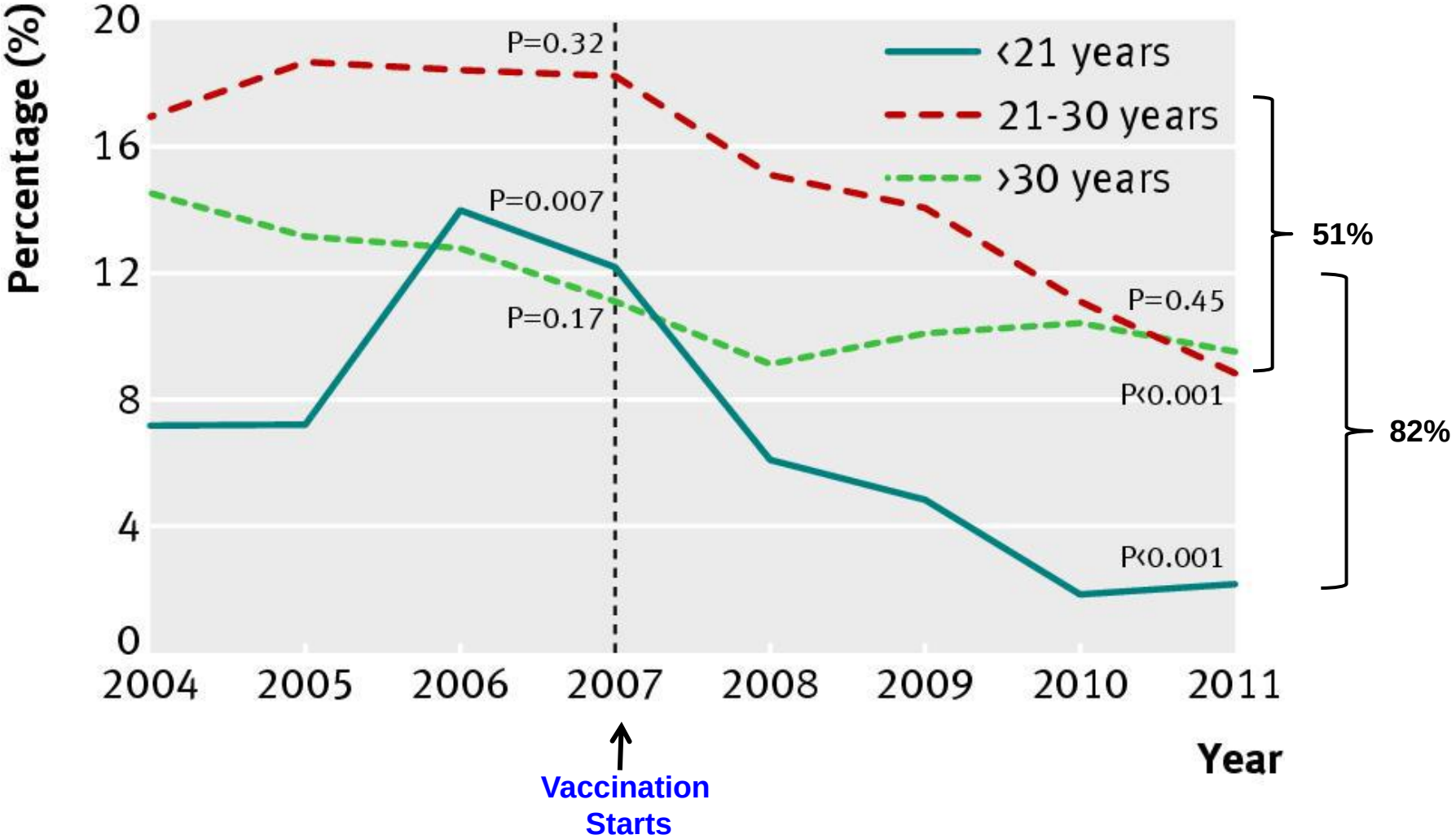
Women



Ali H, BMJ 2012: 346:f2032

Genital Wart Time Trends in Australia 2004-2011

Heterosexual Men



Ali H, BMJ 2012: 346:f2032

Evidence of Herd Immunity

Outstanding Implementation Issues

- Who to vaccine: 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 ecomomically disadvanced inviduals

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 ~20% of cervical cancers.
- Need to convince vaccinated women to comply with existing screening programs.

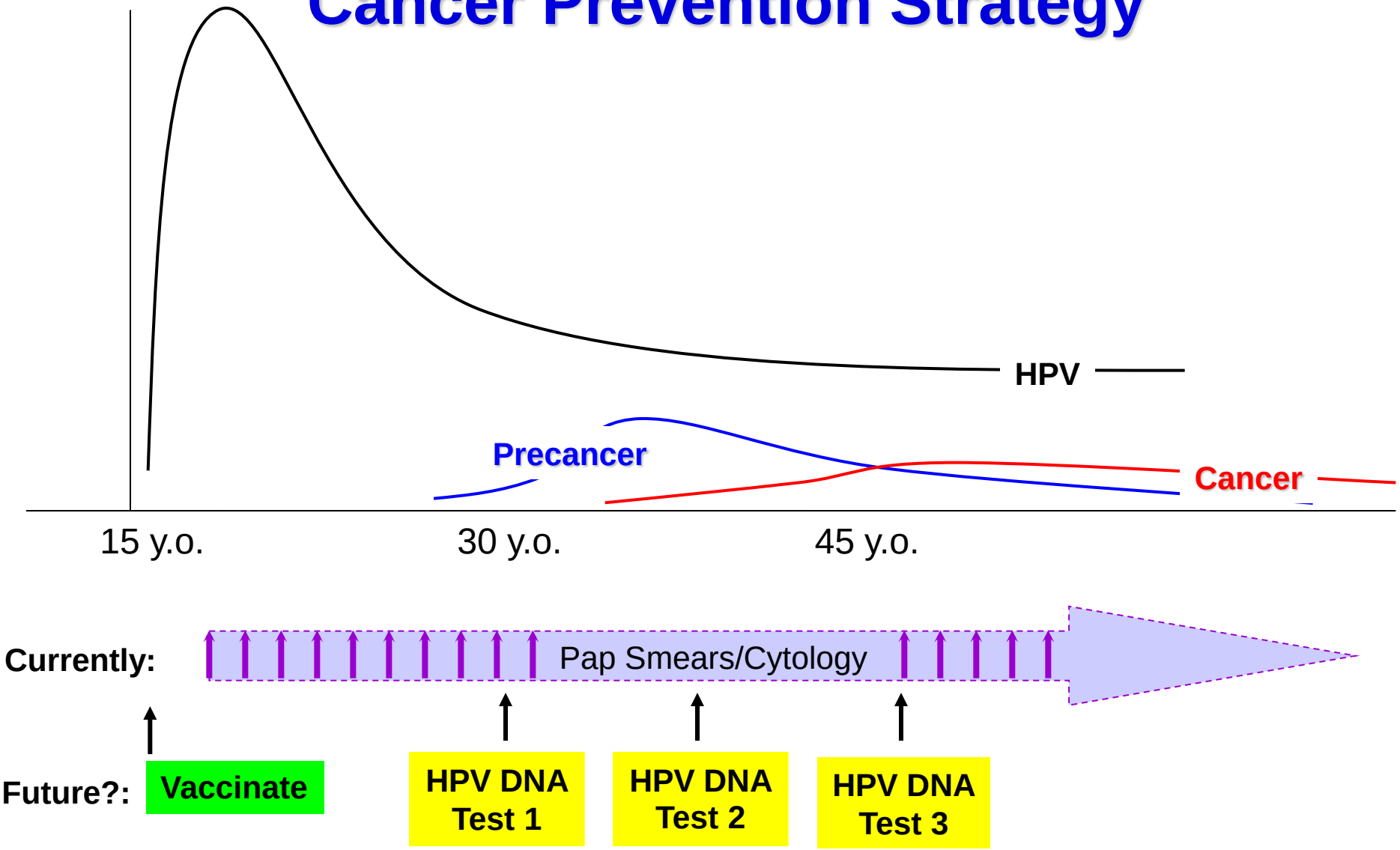
Screening Accounts For Most of the Direct Costs of HPV Interventions in the U.S.

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%
Genital Warts	0.3	3.6%
RRP	0.2	2.1%

Chession et al. Vaccine, Epub Aug 3, 2012

A Shift to an HPV-Based Cervical Cancer Prevention Strategy



Thanks to Mark Schiffman and Phil Castle, NCI

Outstanding Implementation Issues

- Who to vaccine: Girls >> Boys > Older women > older men
- Delivery of three IM doses to early adolescents (or are two doses enough?)
- Effects of vaccine on Cervical Ca screening recommendations and compliance
- Delivery to ecomomically disadvanced individuals – 85% of of cervical cancer occur in developing countries.

Delivery to Ecomomically Disadvanced Individuals

- Both companies are committed to sale to GAVI at less than $5 per dose.
- Vaccine manufacture in emerging countries.
- Deliver fewer than three doses.
- 2nd generation vaccines that could be manufactured and/or delivered at lower cost.

On the Horizon

- Merck's nonavalent vaccine: VLPs of 5 more HR types
- L2 vaccines: broad protection w/ a monovalent vaccine
- Manufacture of HPV vaccines in emerging countries
- Therapeutic vaccines to treat persistent infection and pre-malignant intra-epithelial neoplasia

Vaccines Against Microbes Causing Cancer?

Microbe	Yearly Incidence	Prophylactic Vaccine	Cancer Types
Helobacter pylori	660,000	NO	Gastric
Human Papillomavirus	610,000	YES	Cervical, Anal, Penile, Oropharyngeal
Hepatitis B Virus	340,000	YES	Liver
Hepatiis C Virus	200,000	NO	
Epstein-Barr Virus	110,000	NO	Lymphoma, Nasopharyngeal
Kaposi's Sarcoma Virus	43,000	NO	Kaposi's Sarcoma
Schistosoma haematobium	6,000	NO	Bladder
Human T-cell Lymphatropic Virus-1	2,100	NO	Adult T cell Leukaemia
Opistharchis/Clonorschis	2,000	NO	Cholangiocarcinoma

Key Collaborators

Doug Lowy

Past Members of the Lab:

Richard Roden	Diana Pastrana
Chris Buck	Reinhard Kirnbauer
Jeff Roberts	Rhonda Kines

Present Members of the Lab

Patricia Day	Cindy Thompson
Carla Cequeira	Susana Pang
Nicolas Cuburu	Alessandra Handisurya

Outside

Allan Hildesheim, Aimee Kreimer, Mahboobeh Safaeian:
DCEG, NCI

Denise Nardelli: Universitaire Vaudois – Lausanne

Protection from Initial Infection

Protection From Initial Infection

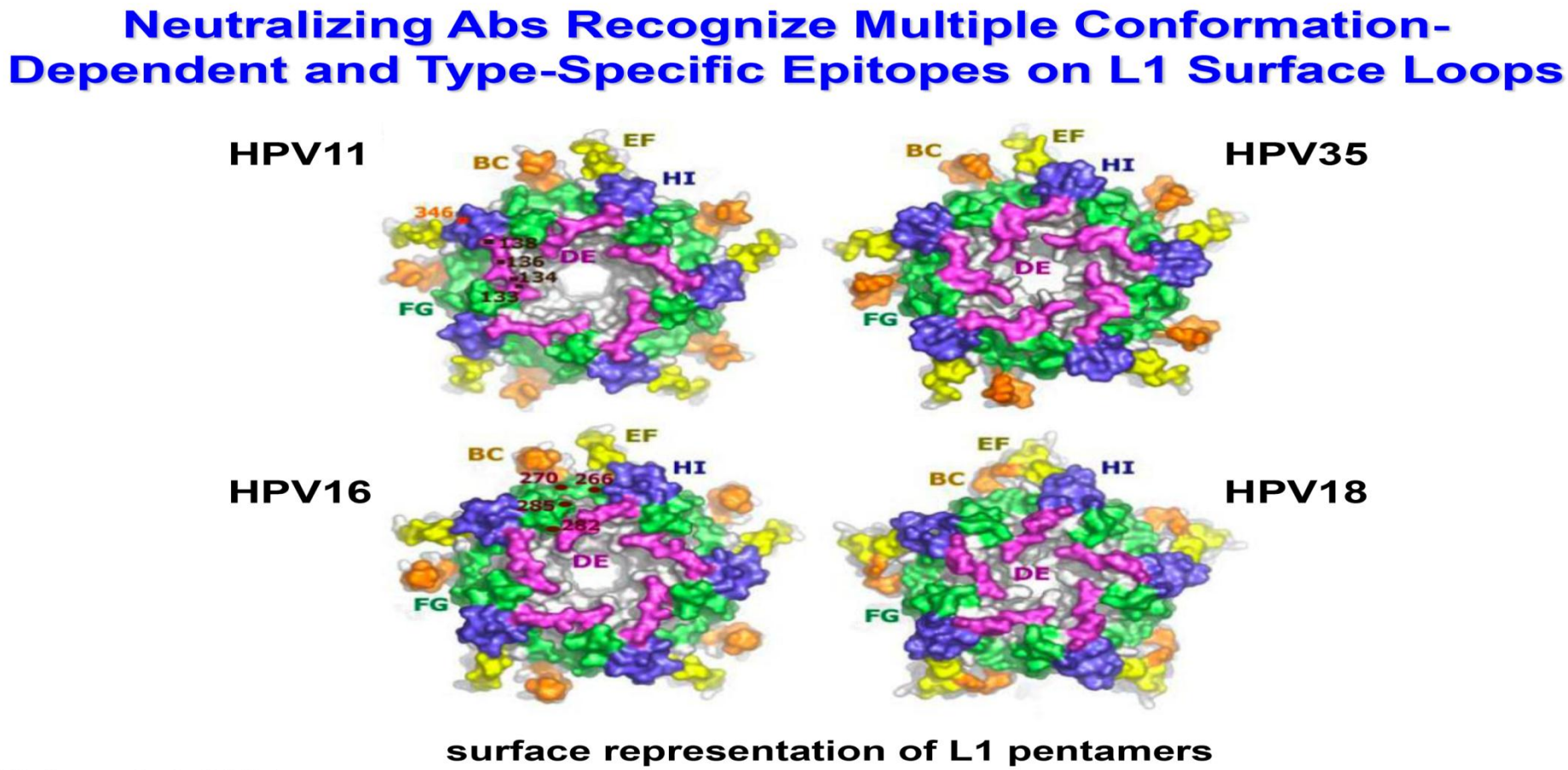
- Most Vaccinees never tested positive for HPV infection as measured by sensitive PCR Assays.
- "Breakthrough" infection tended to appear early in the trials suggesting that most were emergence of prevalent infection.
- Results imply that sterilizing immunity normally generated.

Why Antibodies are likely to be the Immune Mediators of Protection

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.

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



Bishop *et al.*, 2007

Consistency of Antibody Response to VLPs

Consistency of Antibody Response to VLPs

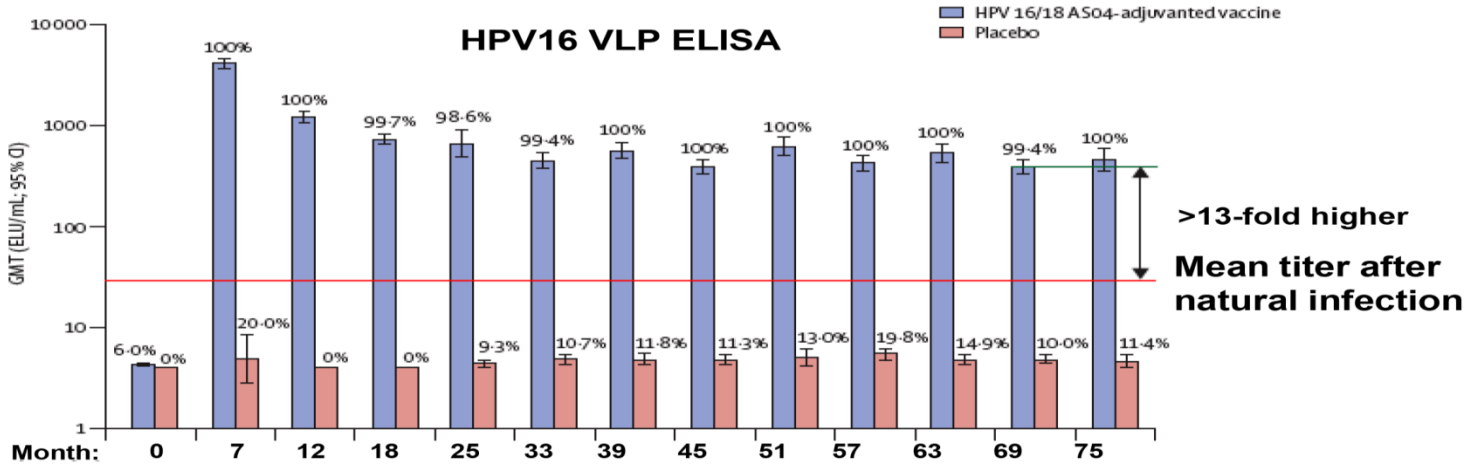
Percent of Women Serocoverting to Individual HPV VLPs in Merck Quadravalent VLP Vaccine Gardasil*

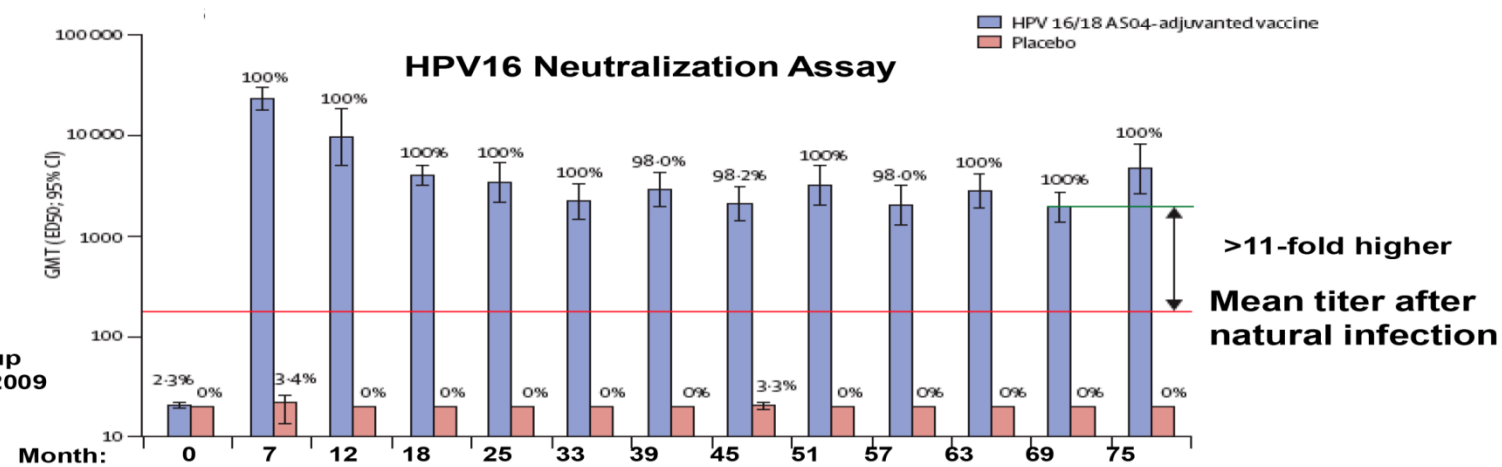
HPV6	99.8%
HPV11	99.8%
HPV16	99.8%
HPV18	99.5%

*4666 women vaccined 3 times by intramuscular injection

Durability of Antibody Response to Cervarix

Durability of Antibody Response to Cervarix





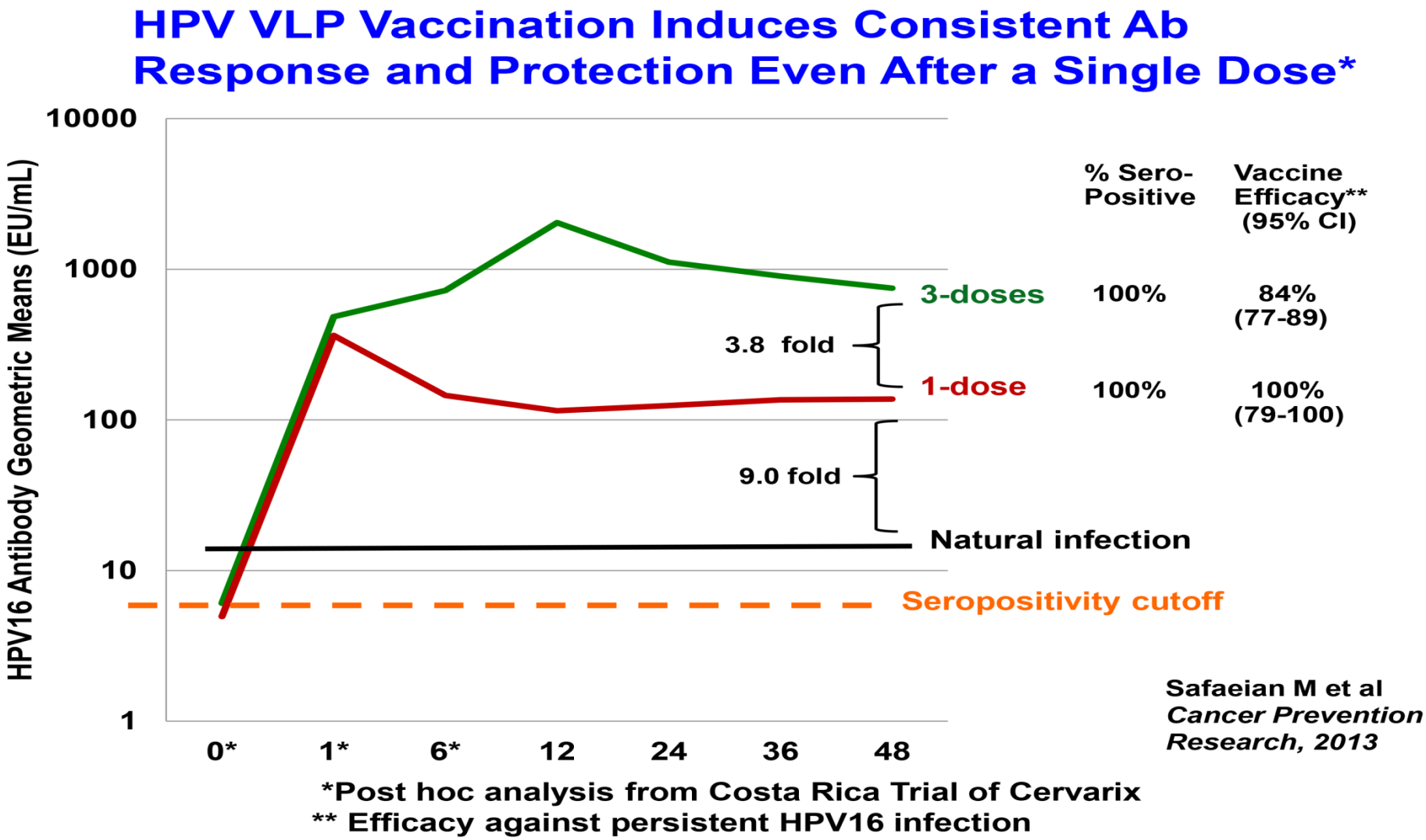
The GSK Vaccine HPV-007 Study Group Lancet 374:301-14, 2009

Duration of Protection

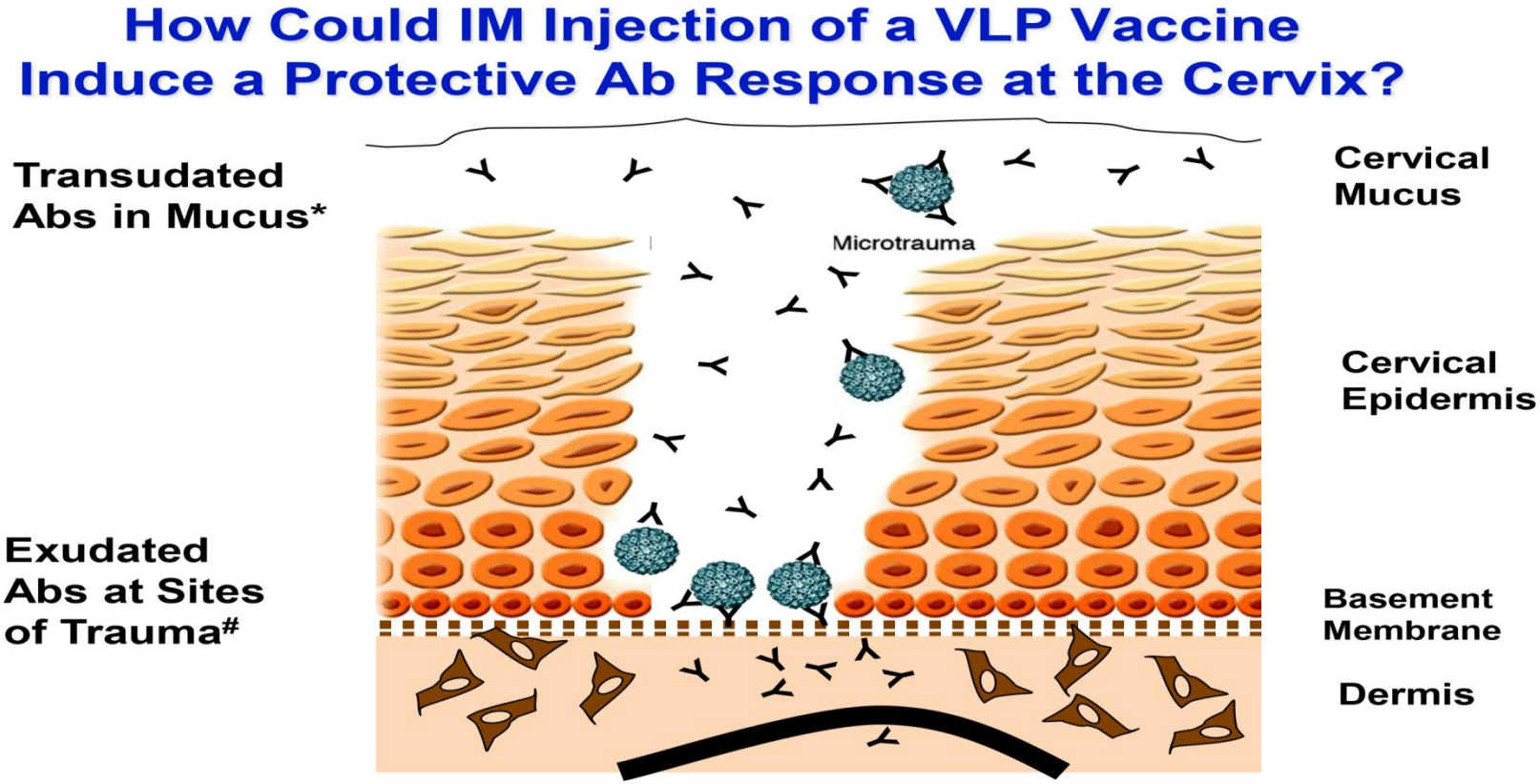
Duration of Protection

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

HPV LVP Vaccination Induces Consistent Ab Response and Protection Even After a Single Dose



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*

HPV VLP Vaccine Efficacy

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 8 years, after antibody levels have

HPV Vaccines are now established products

HPV Vaccines Are Now Established Products

Licensed worldwide to the prevention of cervical cancer and in some cases other HPV induced neoplasia including anal cancer and genital warts.

Worldwide Sales:

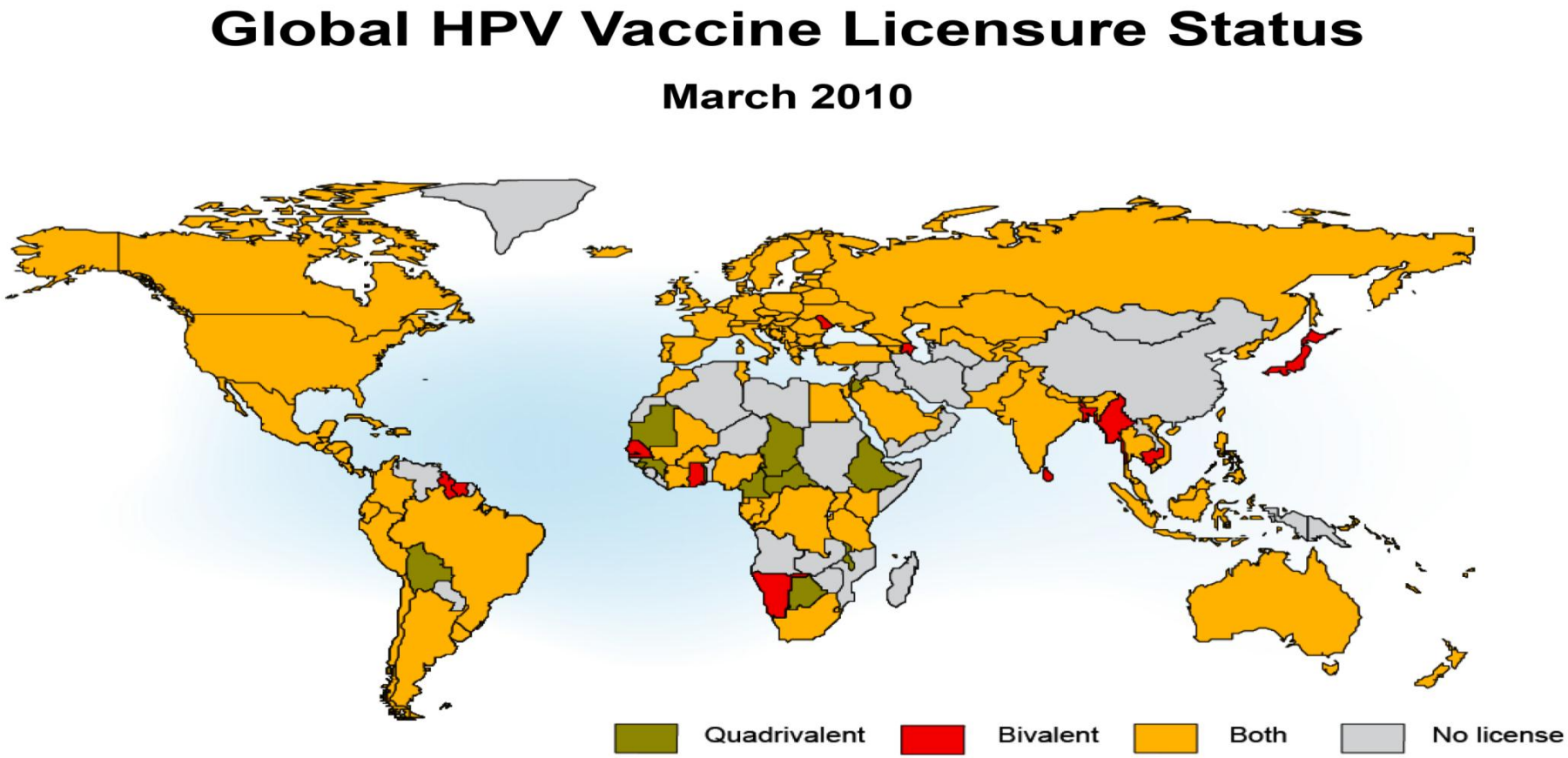
Gardasil – 100 million doses since 2006

Cervarix – 25 million doses since 2007 (2009 in US)

FDA approval of Gardasil for genital warts in men – 2009

for anal cancer in both sexes - 2010

Global HPV Vaccine Licensure Status



Weekly Epi Report 84: 117-32, 2009

Less Than 3 Dose Vaccination Programs

Less Than 3 Dose Vaccination Programs

Two doses at 0 and 6 moths approved for young adolescents in:

- **EU – EMA approval in 2014 for 9-13 yr olds**
- **Switzerland**
- **Mexico**
- **Quebec**

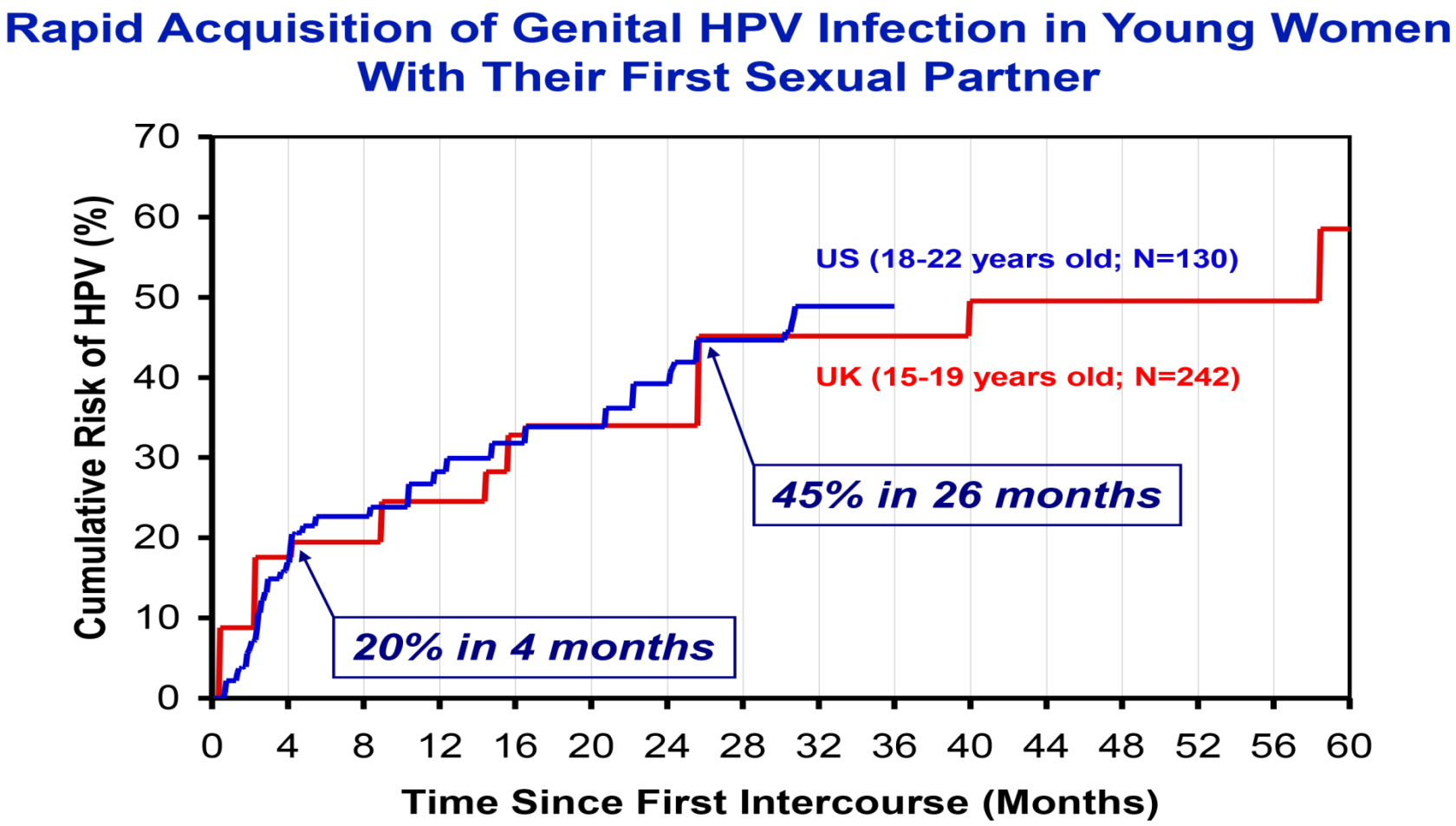
Based on immunobridging: two doses in young adolescents generates antibody titers that are non-inferior to three doses in 15-26 year olds in which efficacy was established.

Outstanding Implementation Issues

Outstanding Implementation Issues

- Who to vaccine: Girls > Boys = young women > men
- Delivery of three IM doses to early adolescents
- Effects of vaccine on Cervical Ca screening recommendations and compliance
- Delivery to ecomomically disadvanced individuals

Rapid Acquisition of Genital HPV Infection in Young Women with their first Sexual Partner



UK data adapted from *Collins et al, BJOG 109: 96-98, 2002* US data adapted from *Winer et al, J Inf Dis 197:279-282, 2008*

Change in Recommendation

October 2011

CDC Advisory committee recommends that boys ages 11-12 be routinely vaccinated with Gardasil, with catch up through age 26. Previous recommendation was "permissive".

Why the change in recommendation?

1.Poor uptake rates in girls

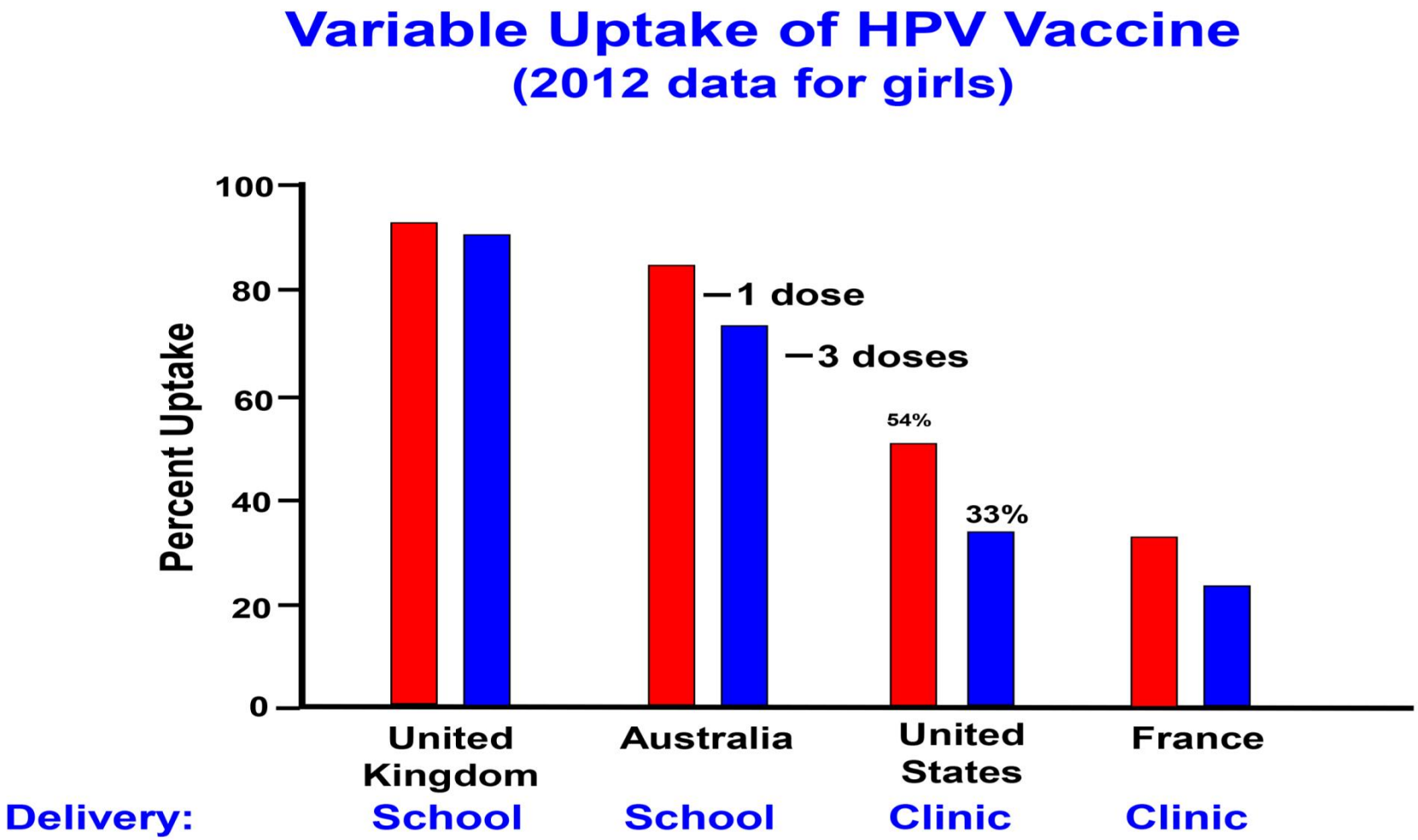
2.Indication for prevention of anal cancer

Outstanding Implementation Issues

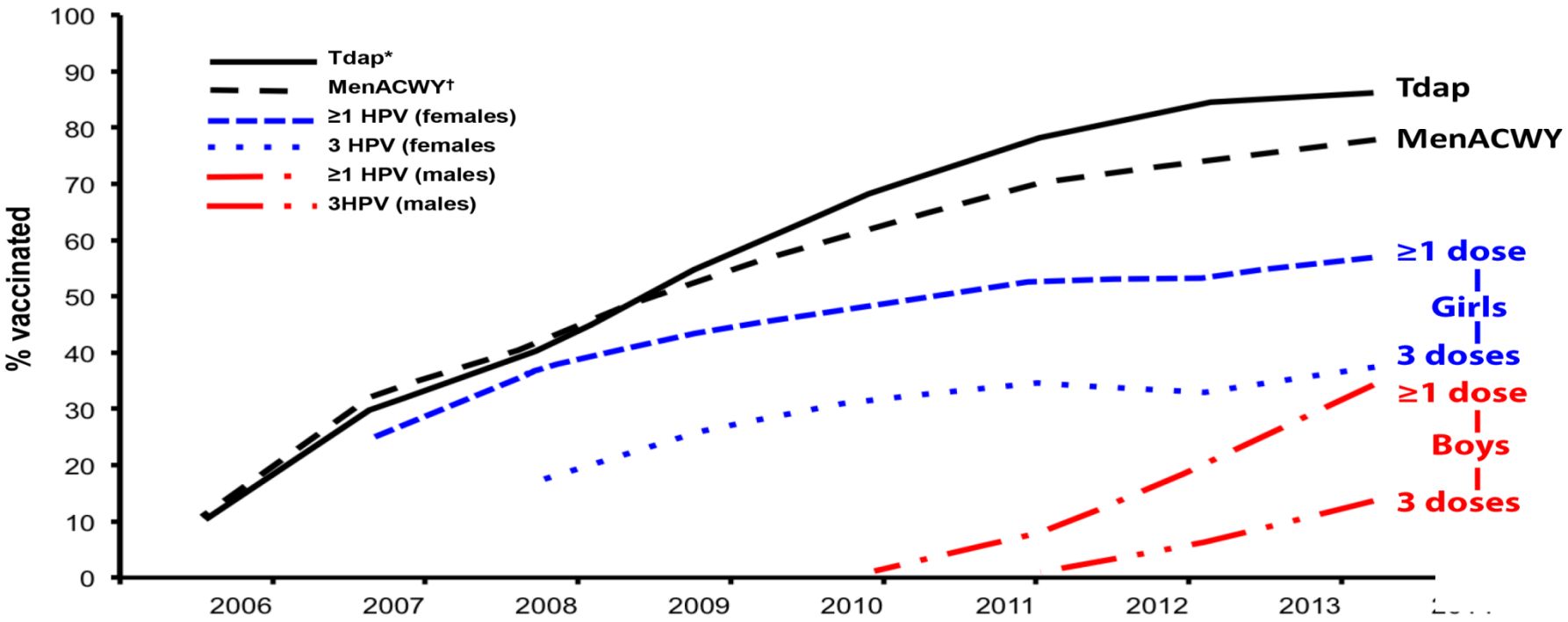
Outstanding Implementation Issues

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

Variable Uptake of HPV Vaccine

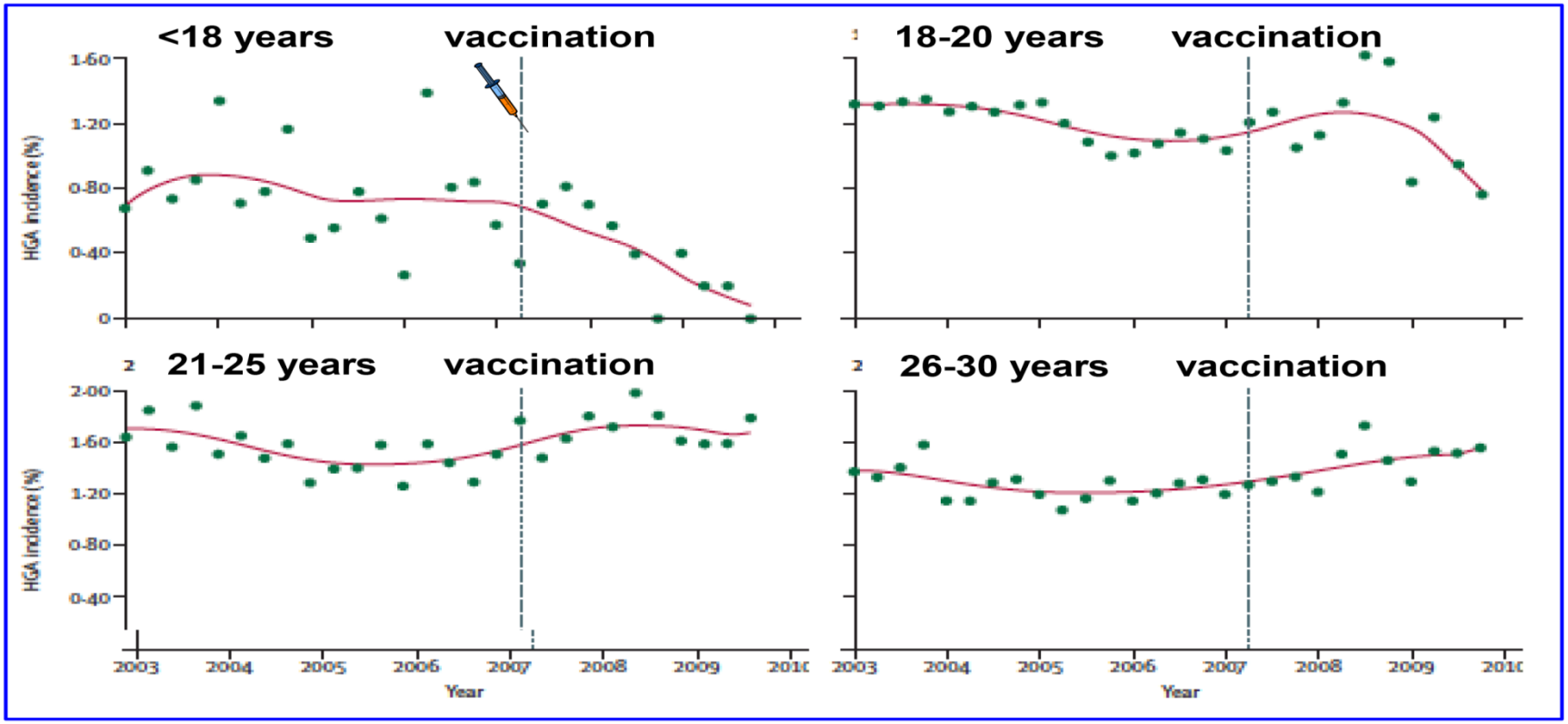


Trends in U.S. Vaccination Rates



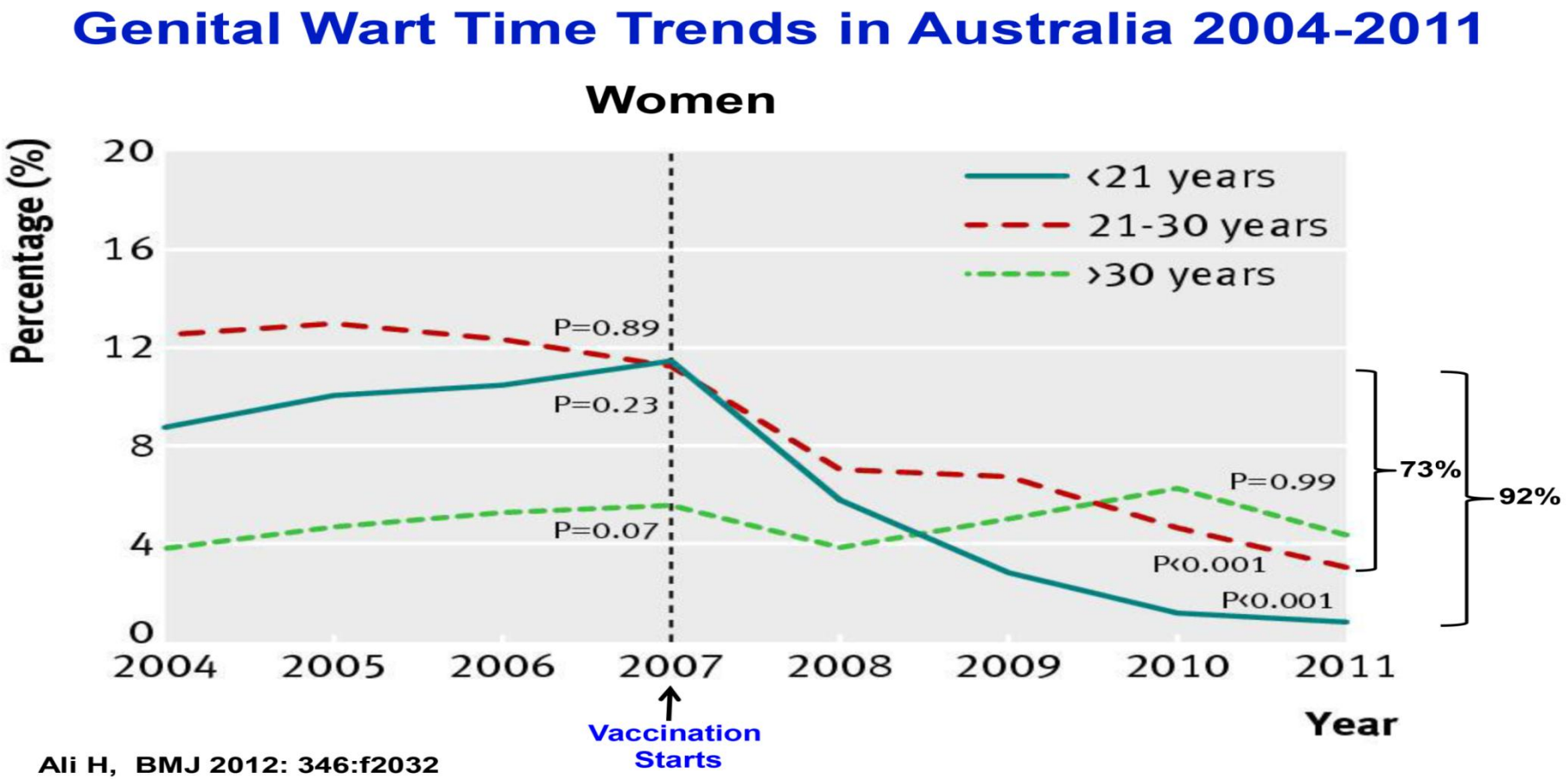
Abbreviations: Tdap = tetanus, diphtheria, acellular pertussis vaccine; MenACWY = meningococcal conjugate vaccine; HPV-1 = human papillomavirus vaccine, ≥1 dose; HPV-3 = human papillomavirus, ≥3 doses.
* Tdap and MenACWY vaccination recommendations were published in March and October 2006, respectively.
† HPV vaccination recommendations were published in March 2007.

Reduction in CIN2+ Cervical Cysplasia: Gerdasil in australia



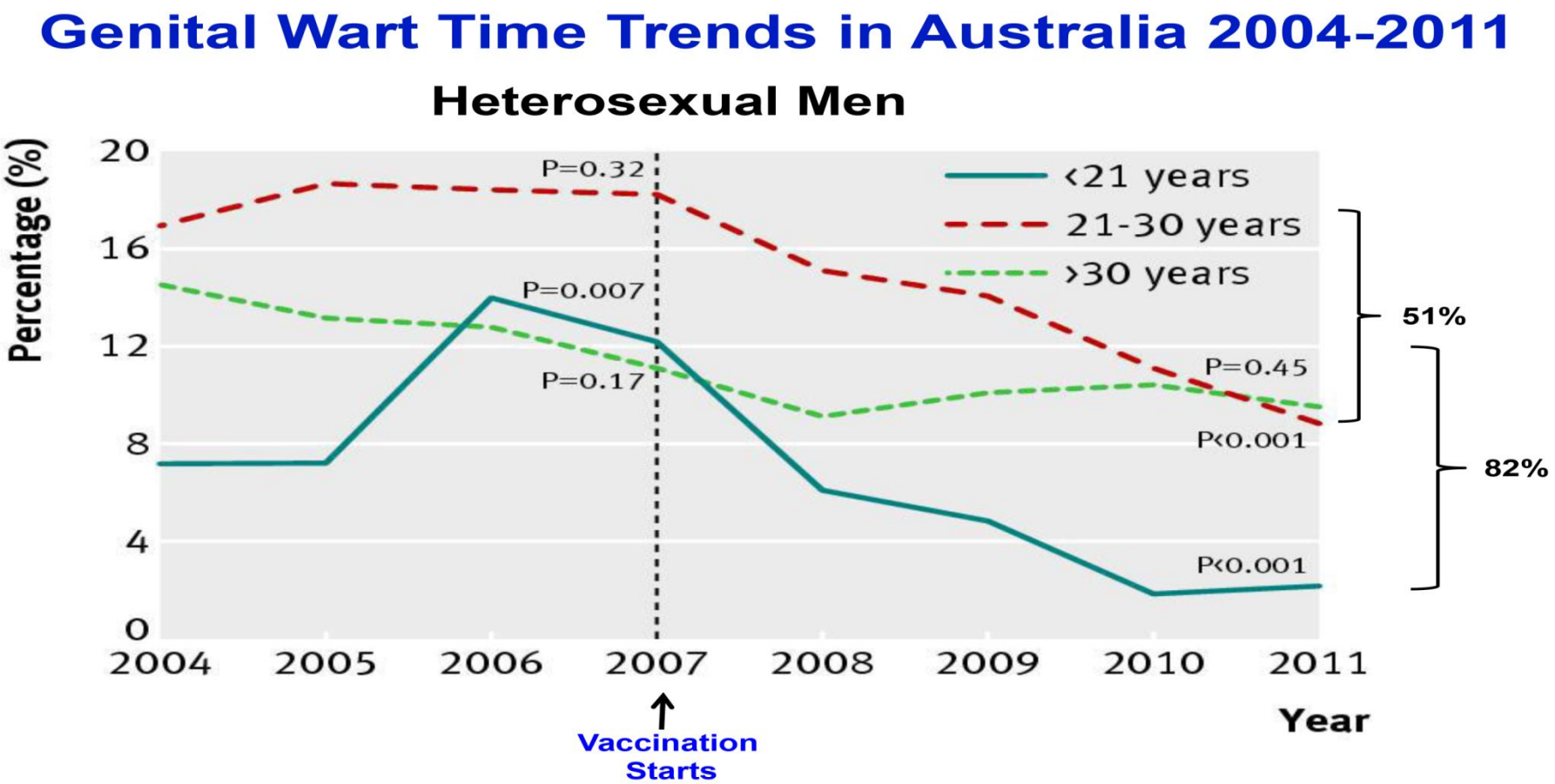
Brotherton et al, Lancet 377: 2085-92, 2011

Genital Wart Time Trends in Australia 2004-2011



Ali H, BMJ 2012: 346:f2032

Genital Wart Time Trends in Australia 2004-2011



Ali H, BMJ 2012: 346:f2032

Outstanding Implementation Issues

Outstanding Implementation Issues

- Who to vaccine: 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 ecomomically disadvanced inviduals

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 ~20% of cervical cancers.
- Need to convince vaccinated women to comply with existing screening programs.

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

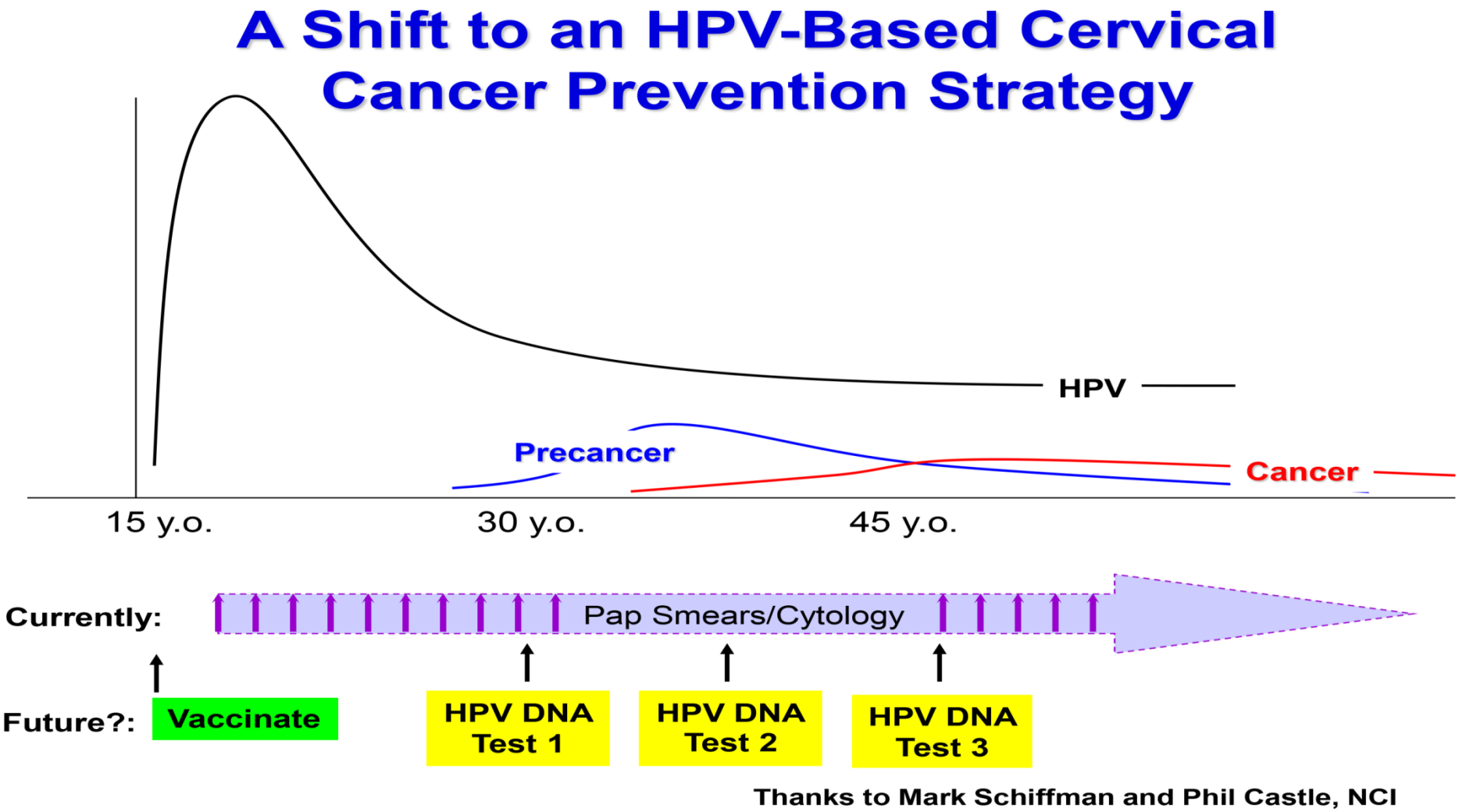
Screening Accounts For Most of the Direct Costs of HPV Interventions in the U.S.

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%
Genital Warts	0.3	3.6%
RRP	0.2	2.1%

Chession et al. Vaccine, Epub Aug 3, 2012

A Shift to an HPV-Based Cervical Cancer Prevention Strategy



Outstanding Implementation Issues

Outstanding Implementation Issues

- Who to vaccine: Girls >> Boys > Older women > older men
- Delivery of three IM doses to early adolescents (or are two doses enough?)
- Effects of vaccine on Cervical Ca screening recommendations and compliance
- Delivery to ecomomically disadvanced individuals – 85% of of cervical cancer occur in developing countries.

Delivery to Economically Disadvantaged Individuals

Delivery to Ecomomically Disadvanced Individuals

- Both companies are committed to sale to GAVI at less than $5 per dose.
- Vaccine manufacture in emerging countries.
- Deliver fewer than three doses.
- 2nd generation vaccines that could be manufactured and/or delivered at lower cost.

On the Horizon

On the Horizon

- Merck's nonavalent vaccine: VLPs of 5 more HR types
- L2 vaccines: broad protection w/ a monovalent vaccine
- Manufacture of HPV vaccines in emerging countries
- Therapeutic vaccines to treat persistent infection and pre-malignant intra-epithelial neoplasia

Vaccines Against Microbes Causing Cancer

Vaccines Against Microbes Causing Cancer?

Microbe	Yearly Incidence	Prophylactic Vaccine	Cancer Types
Helobacter pylori	660,000	NO	Gastric
Human Papillomavirus	610,000	YES	Cervical, Anal, Penile, Oropharyngeal
Hepatitis B Virus	340,000	YES	Liver
Hepatiis C Virus	200,000	NO	
Epstein-Barr Virus	110,000	NO	Lymphoma, Nasopharyngeal
Kaposi's Sarcoma Virus	43,000	NO	Kaposi's Sarcoma
Schistosoma haematobium	6,000	NO	Bladder
Human T-cell Lymphatropic Virus-1	2,100	NO	Adult T cell Leukaemia
Opistharchis/Clonorschis	2,000	NO	Cholangiocarcinoma

Key Collaborators

Key Collaborators

Doug Lowy

Past Members of the Lab:

Richard Roden	Diana Pastrana
Chris Buck	Reinhard Kirnbauer
Jeff Roberts	Rhonda Kines

Present Members of the Lab

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Carla Cequeira	Susana Pang
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