

Cervical Cancer

HPV Vaccines to Prevent Cervical Cancer and other HPV-associated Diseases

John Schiller, Center for Cancer Research, NCI



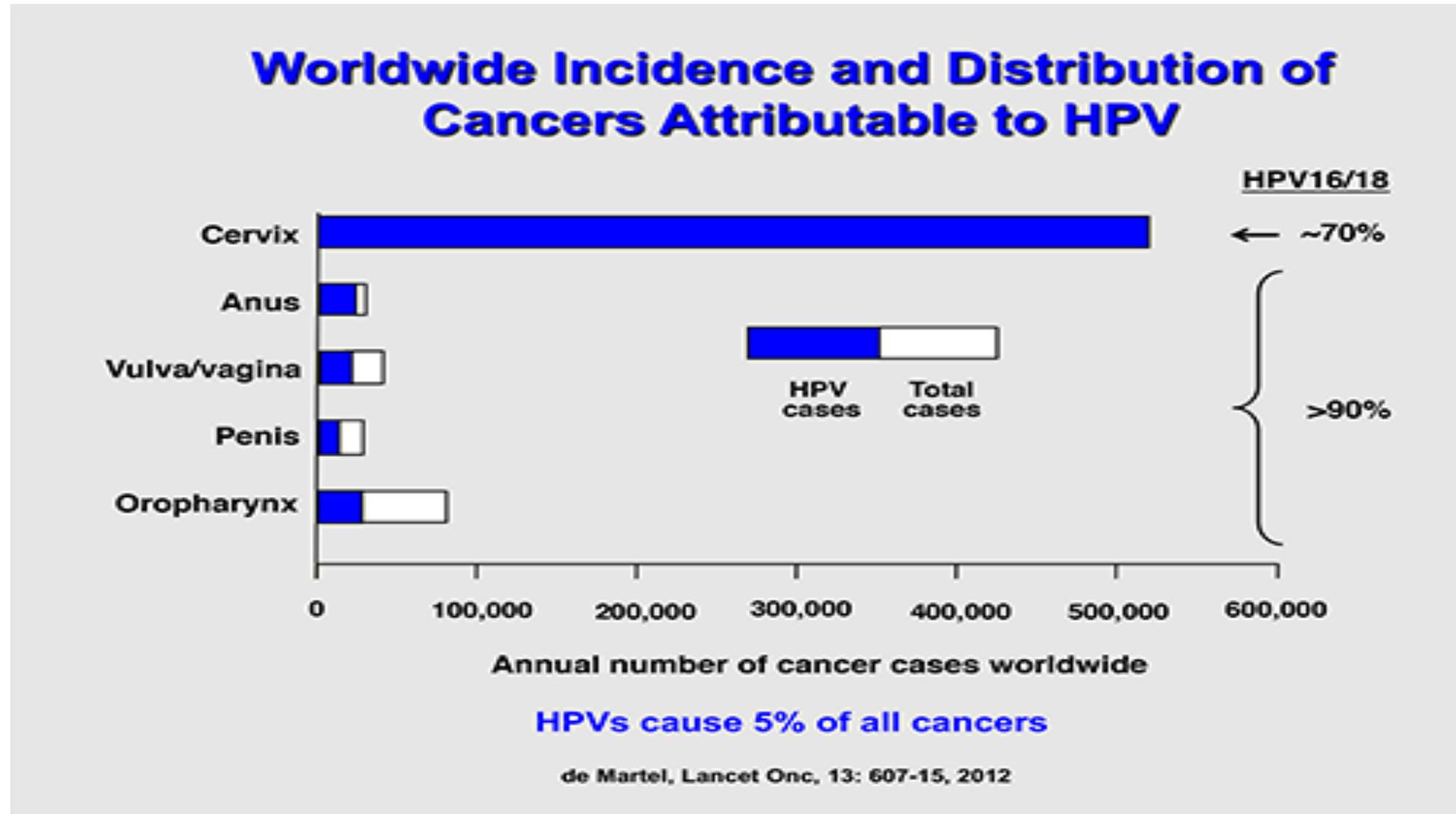
- HPV and Cancer
- Vaccine Efficacy/Effectiveness
- Key Implementation Issues
- Why they work so well

Annual Number of Cancer Cases Attributable To Specific Virus Infections

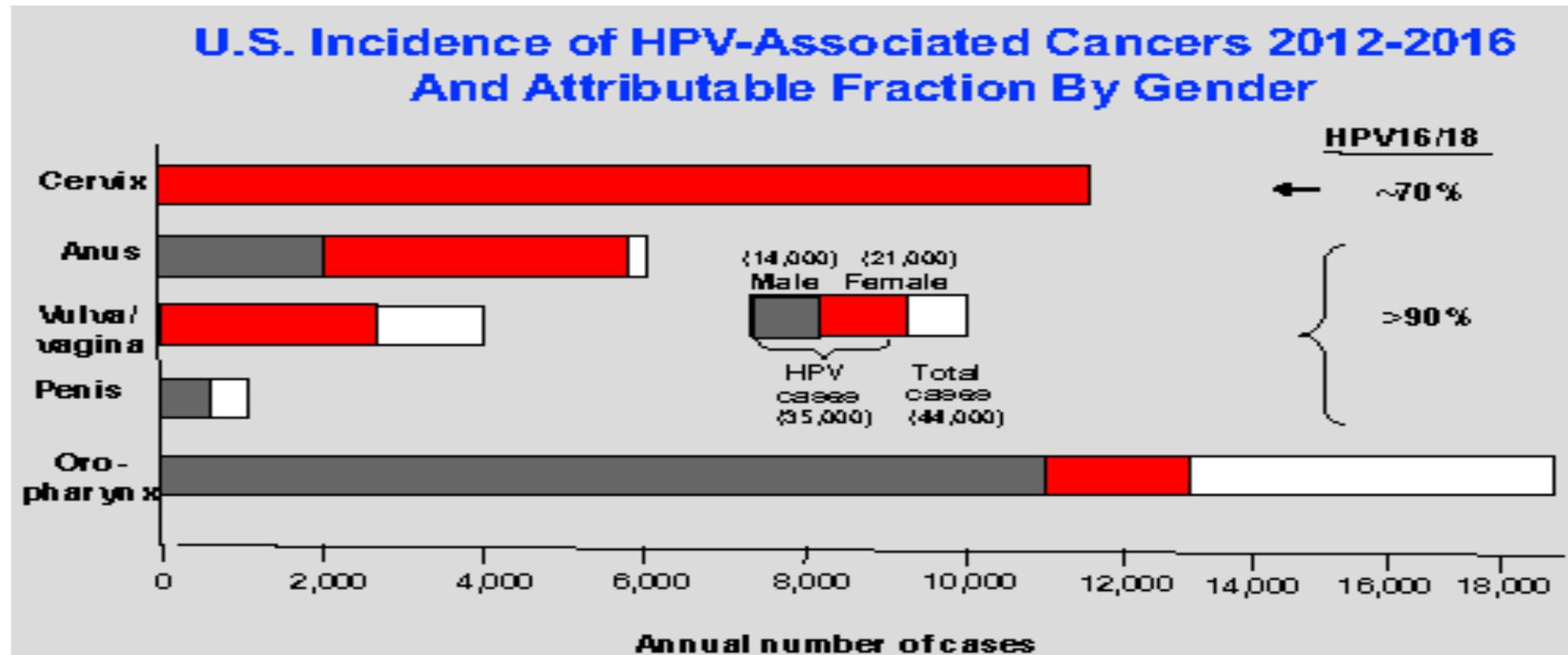
10% of All Cancers

Virus	Total	Females	Males
HPV	636 000	570 000	66 000
HBV	420 000	120 000	300 000
HCV	165 000	55 000	110 000
EBV	120 000	40 000	80 000
KSHV	43 000	15 000	29 000
HTLV	2 900	1 200	1 700

Cancers attributable to HPV



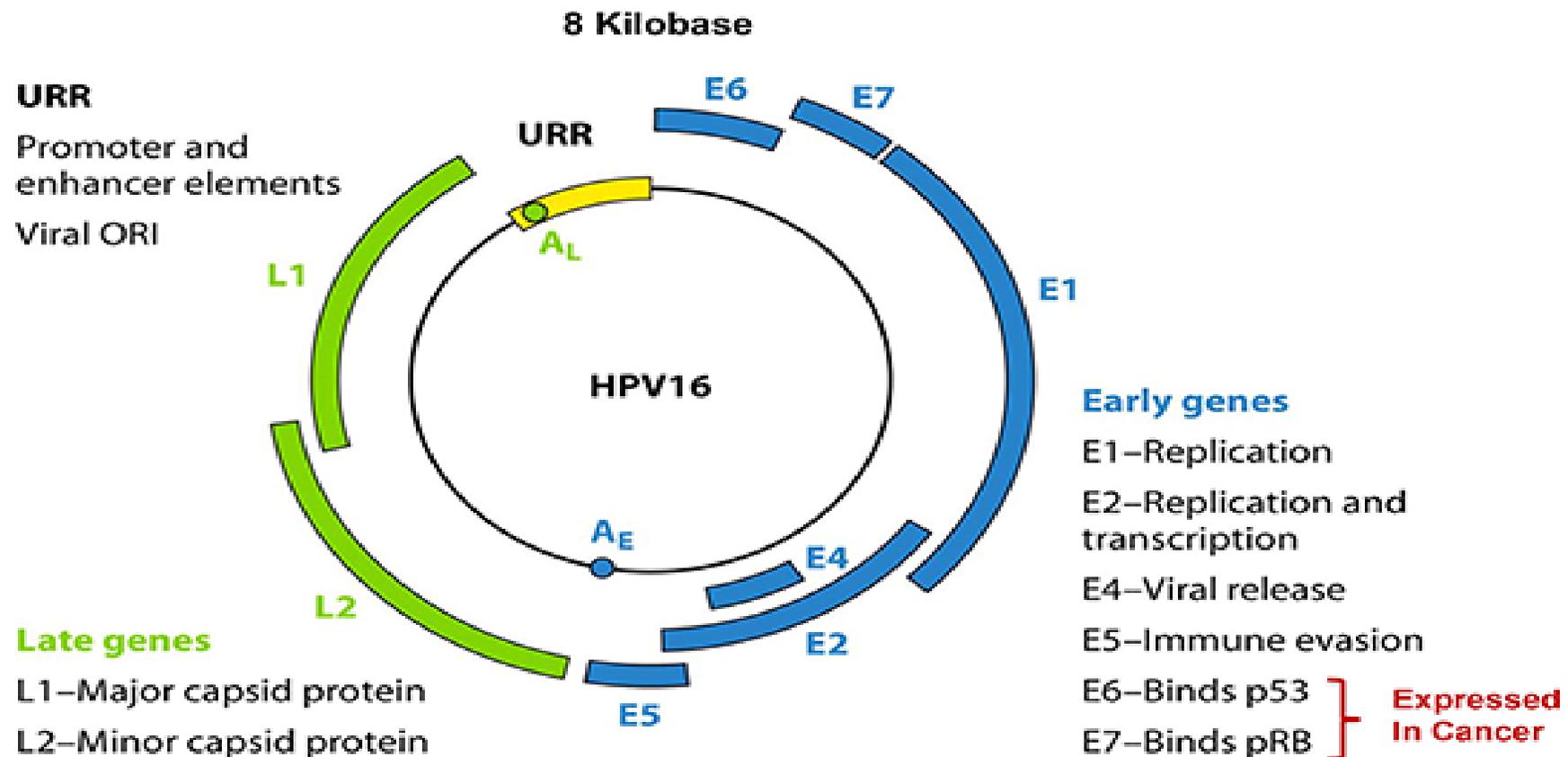
HPV incidence



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

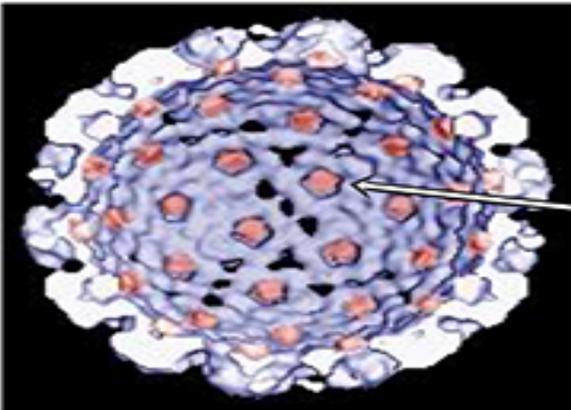
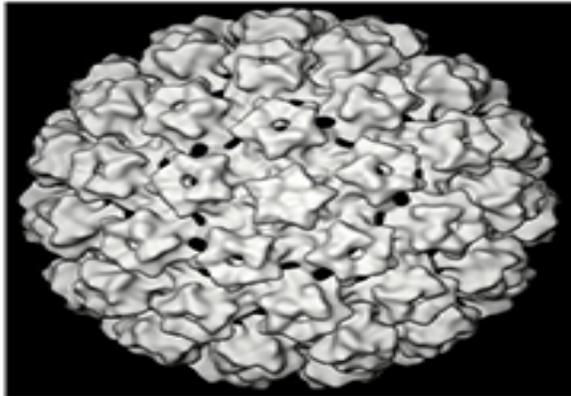
HIV genome

HPV16 Double Stranded Circular DNA Genome



Virion

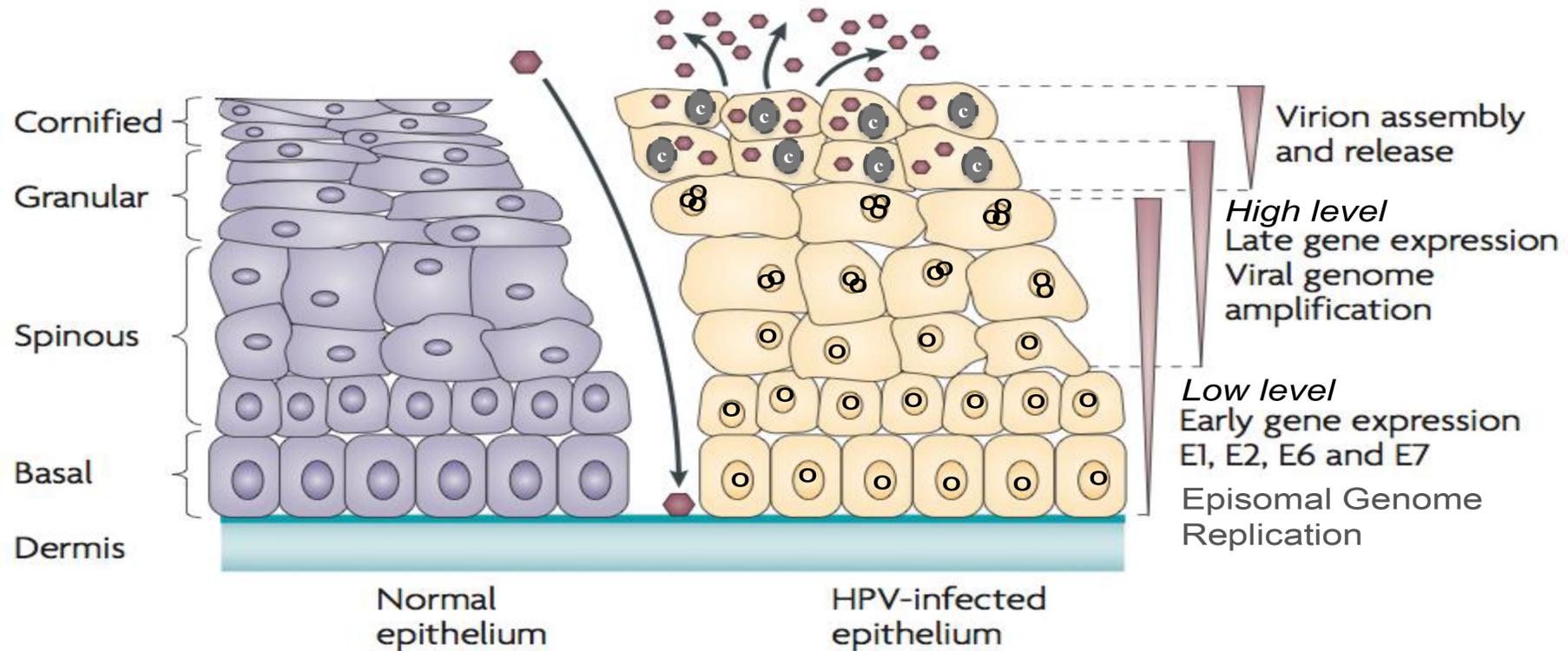
Papillomavirus Virion



- **Non-enveloped icosahedral shell formed by 72 pentamers of L1**
- **60 nanometer diameter**
- **A second capsid protein L2 is present at up to 72 copies**
- **8kb circular dsDNA genome (chromatinized)**

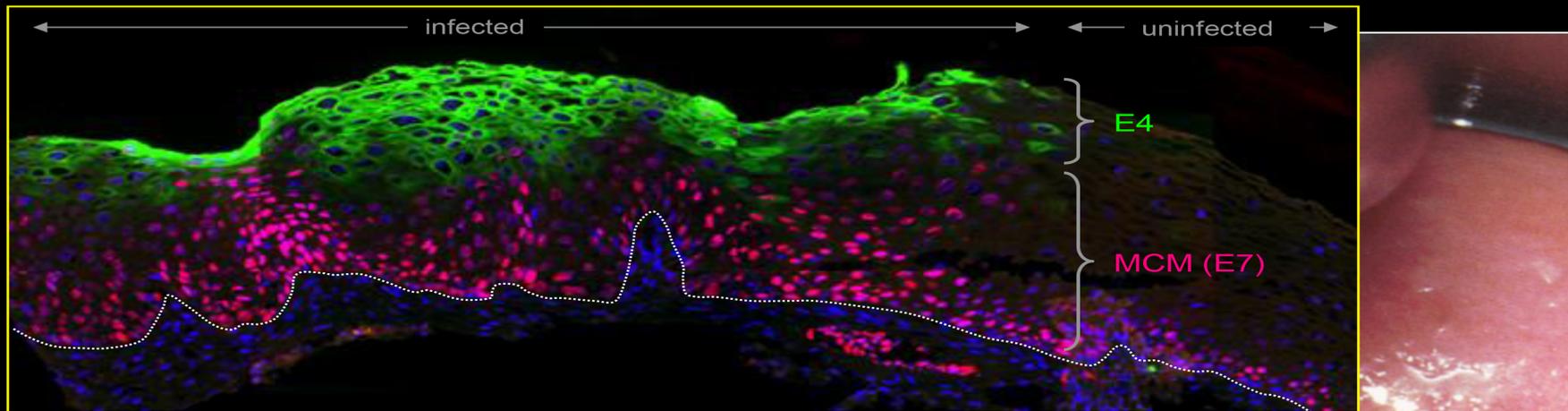
HPV life cycle

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



HPV infection

Productive HPV Infection: Hiding in Plain Site

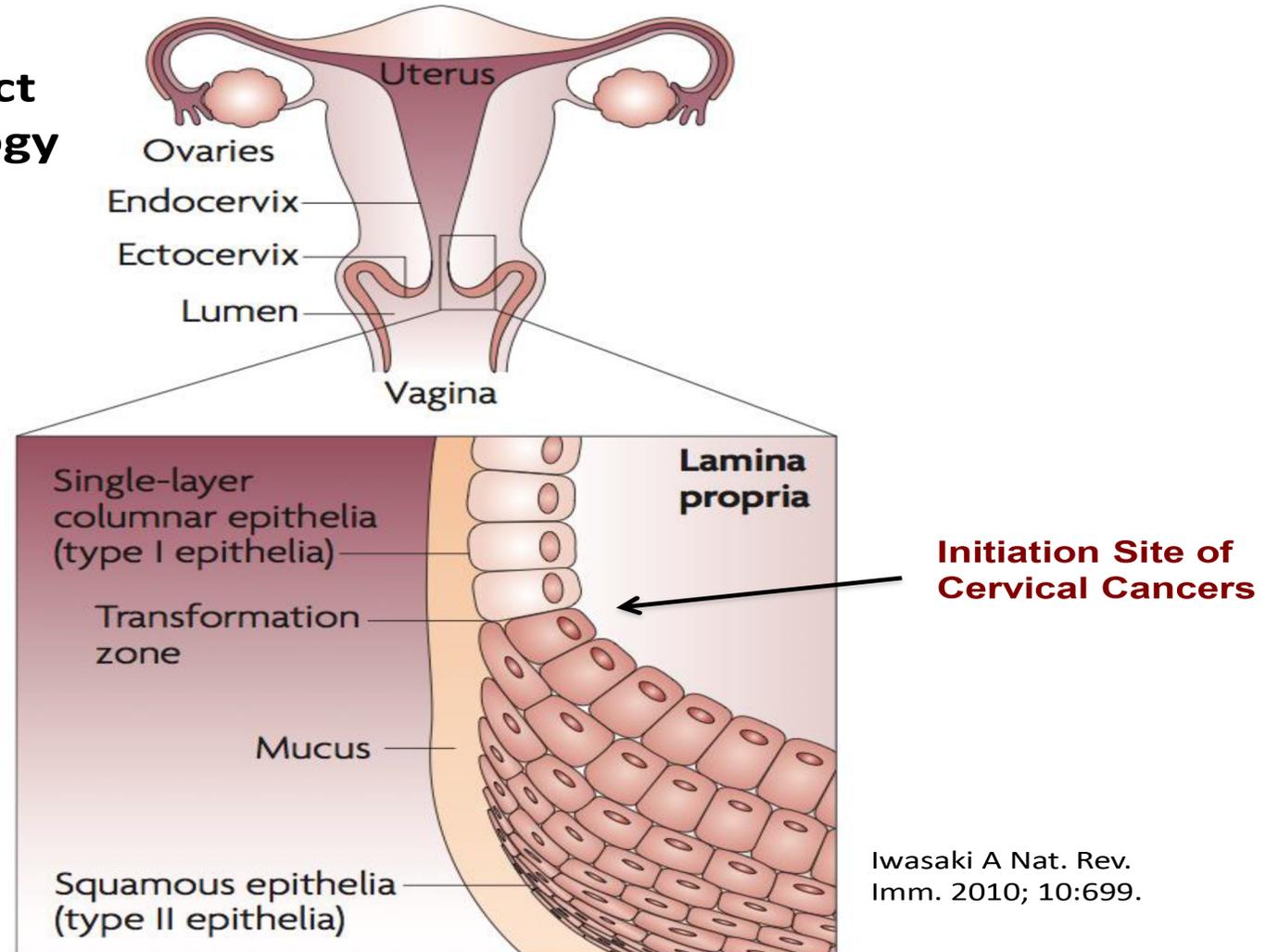


HPVs have evolved to exploit the limited immuno-surveillance of the upper layers of skin and mucosal membranes.



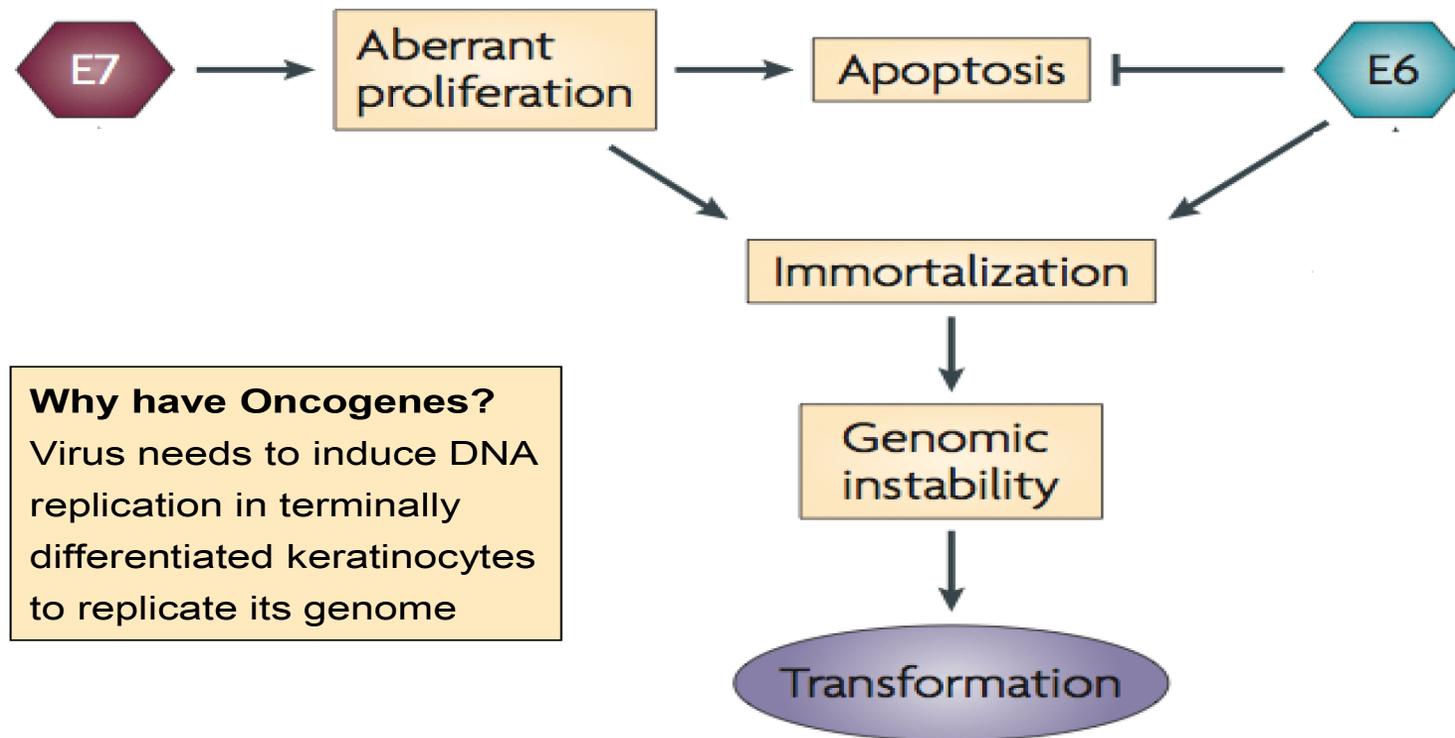
Cervical cancer

Female Reproductive Tract Anatomy & Histology



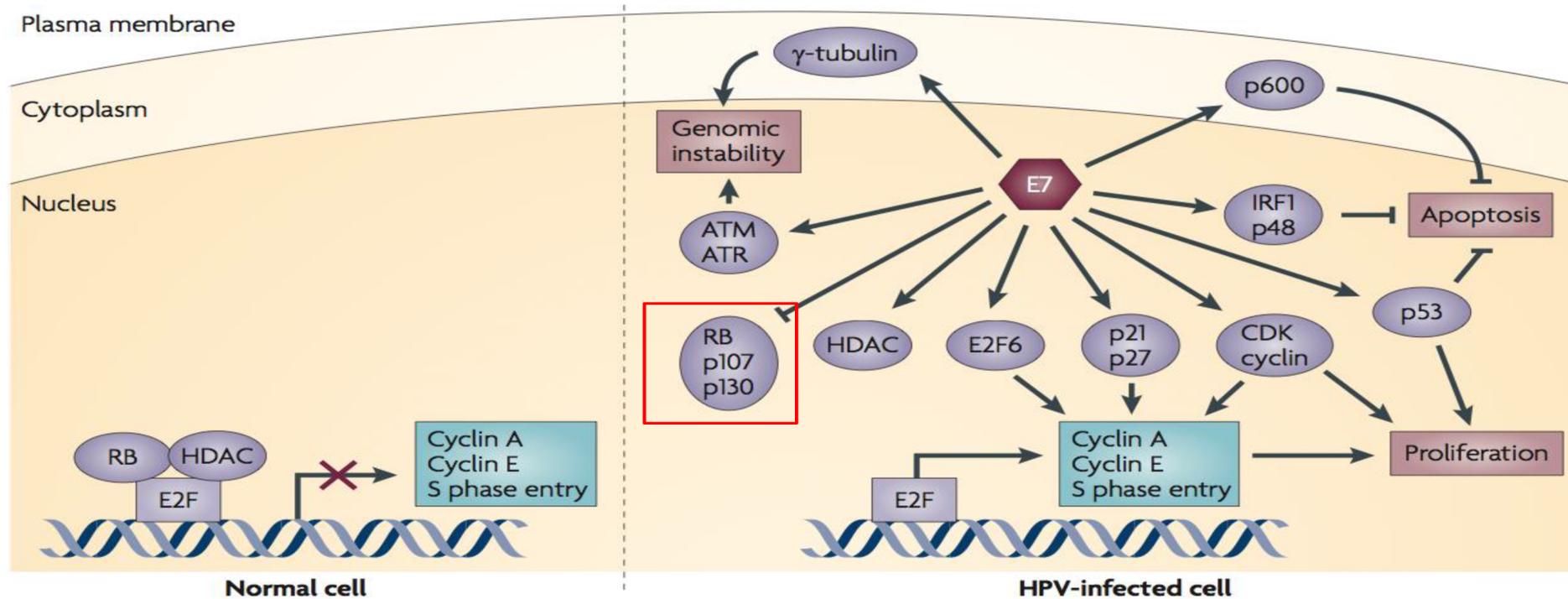
HPV carcinogenesis

Molecular Mechanisms Involved in HPV Carcinogenesis



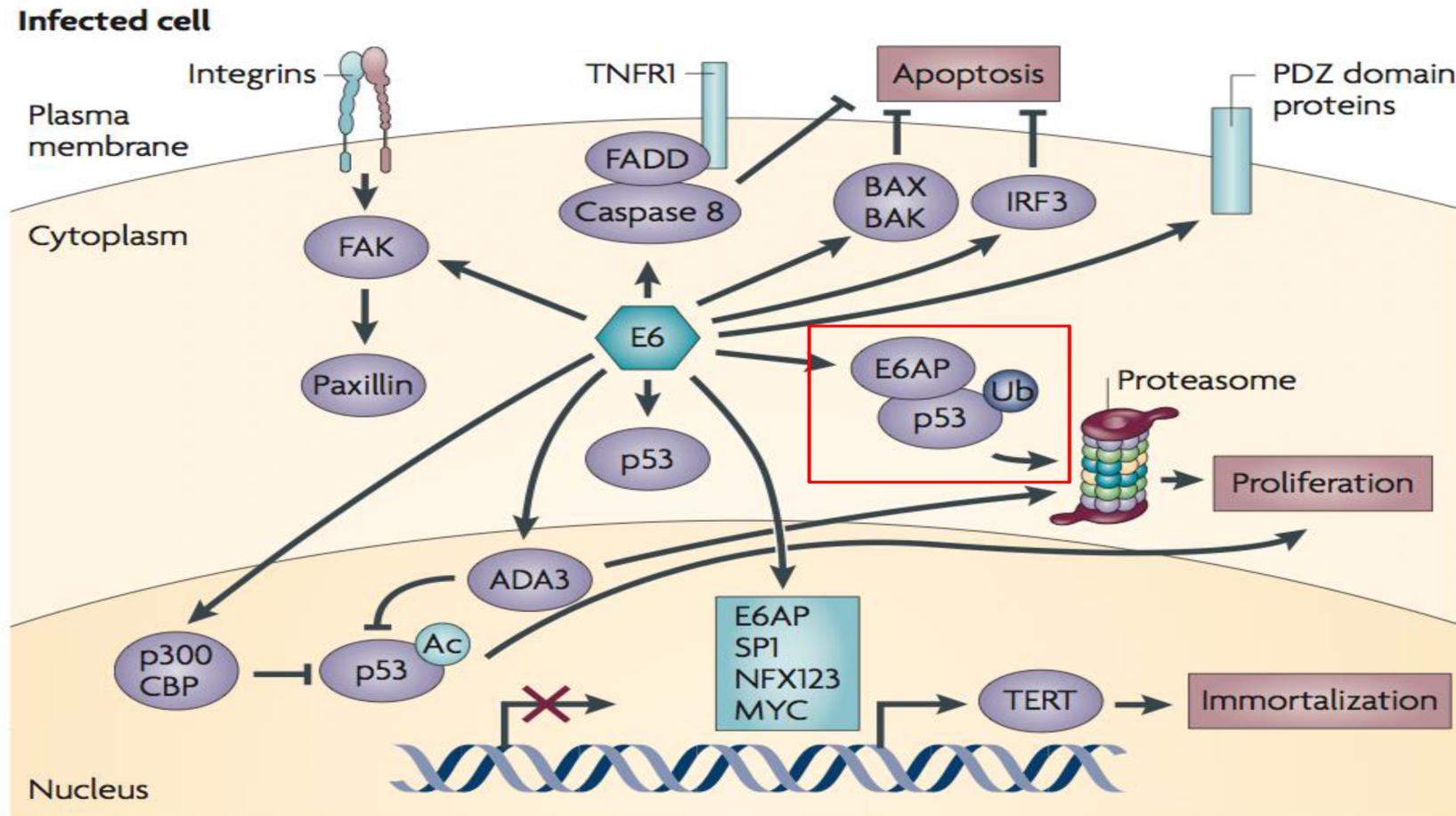
Cellular proteins

Cellular Proteins and Pathways Affected by HPV E7



HPV pathways

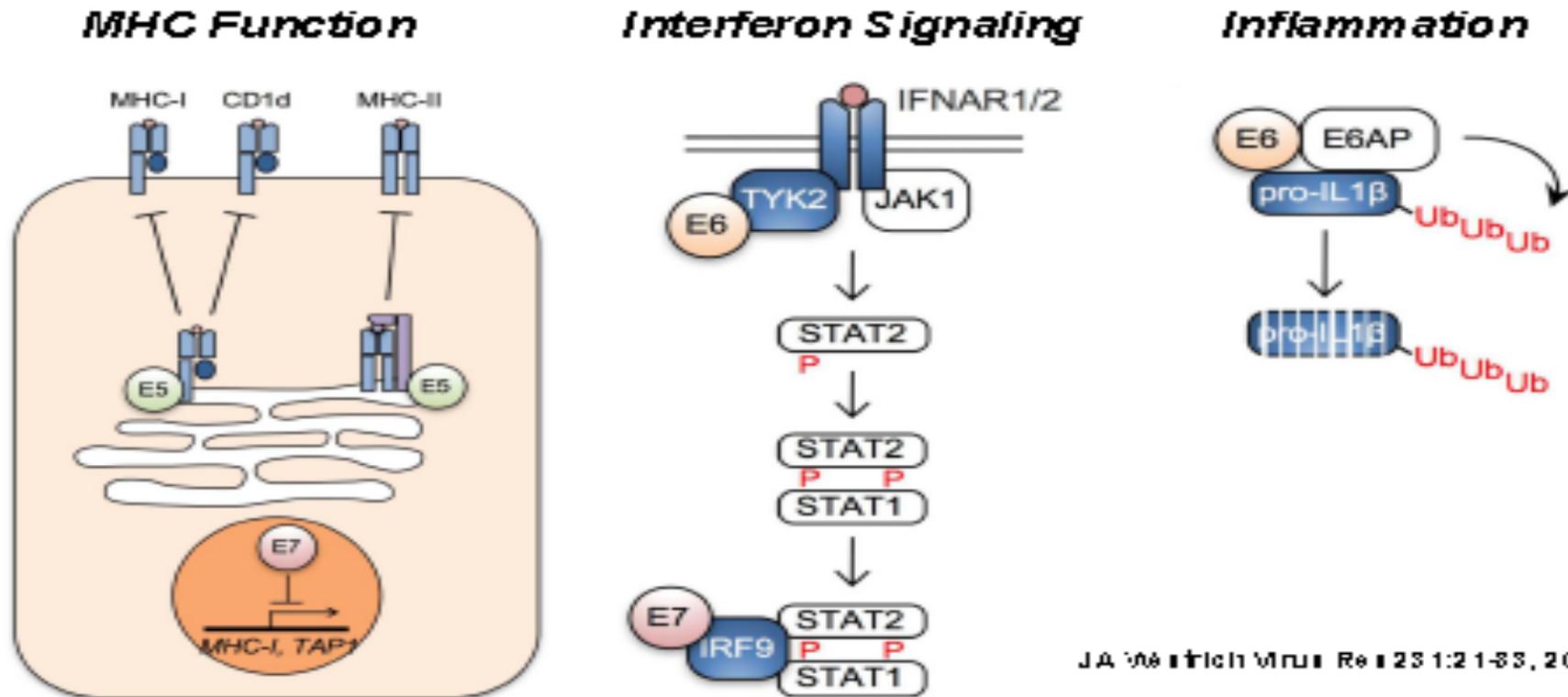
Cellular Proteins and Pathways Affected by HPV E6



HPV oncoproteins

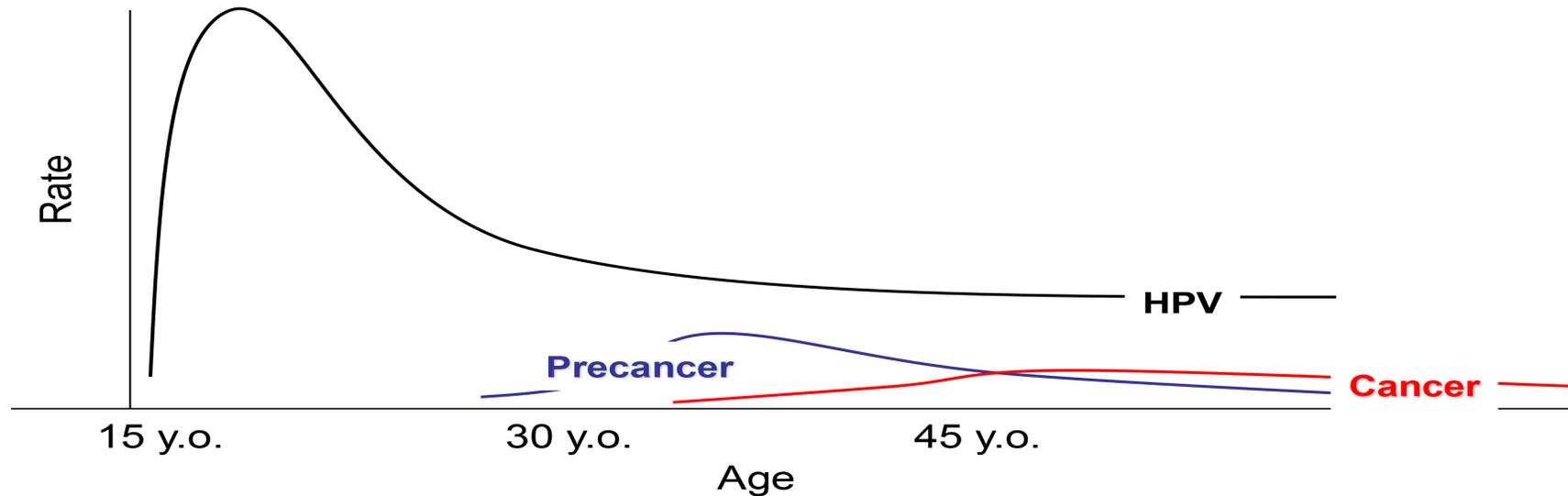
HPV Oncoproteins Also Inhibit Immune Responses

Promotes virus persistence



HPV infection time line

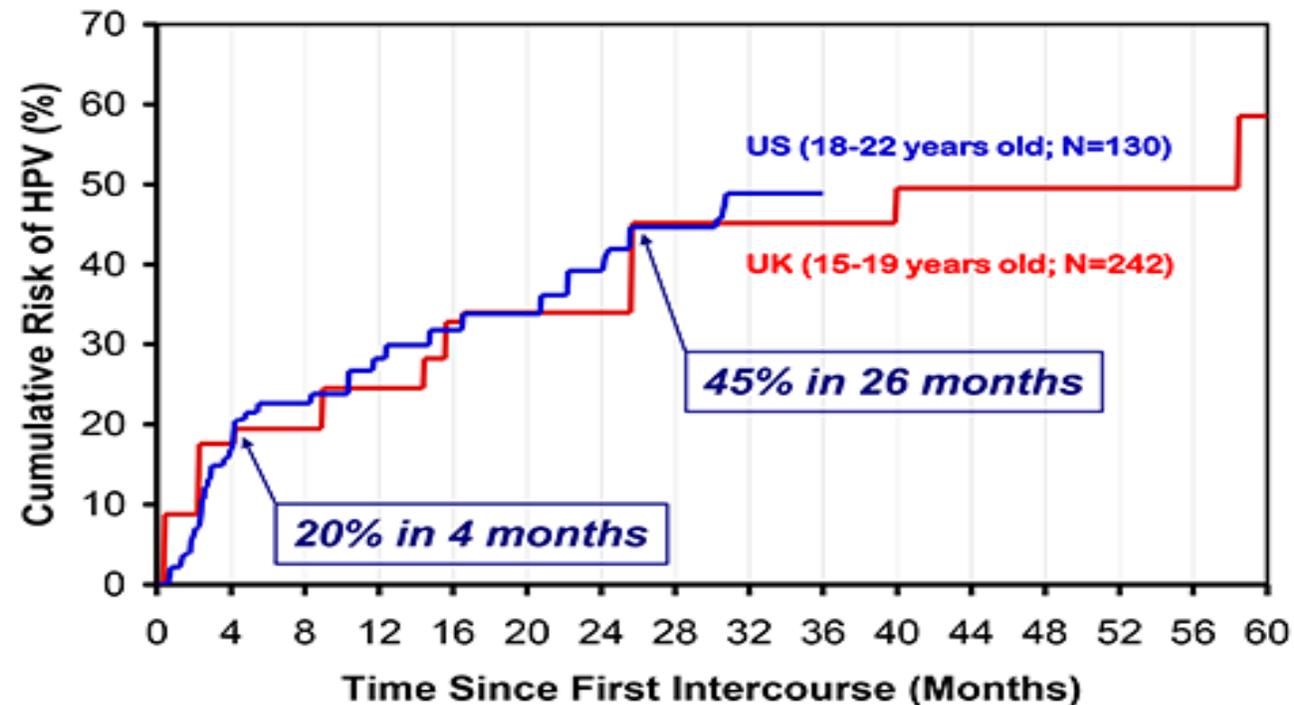
Time Line of Cervical HPV Infections And Progression to Cervical Cancer



- **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.**

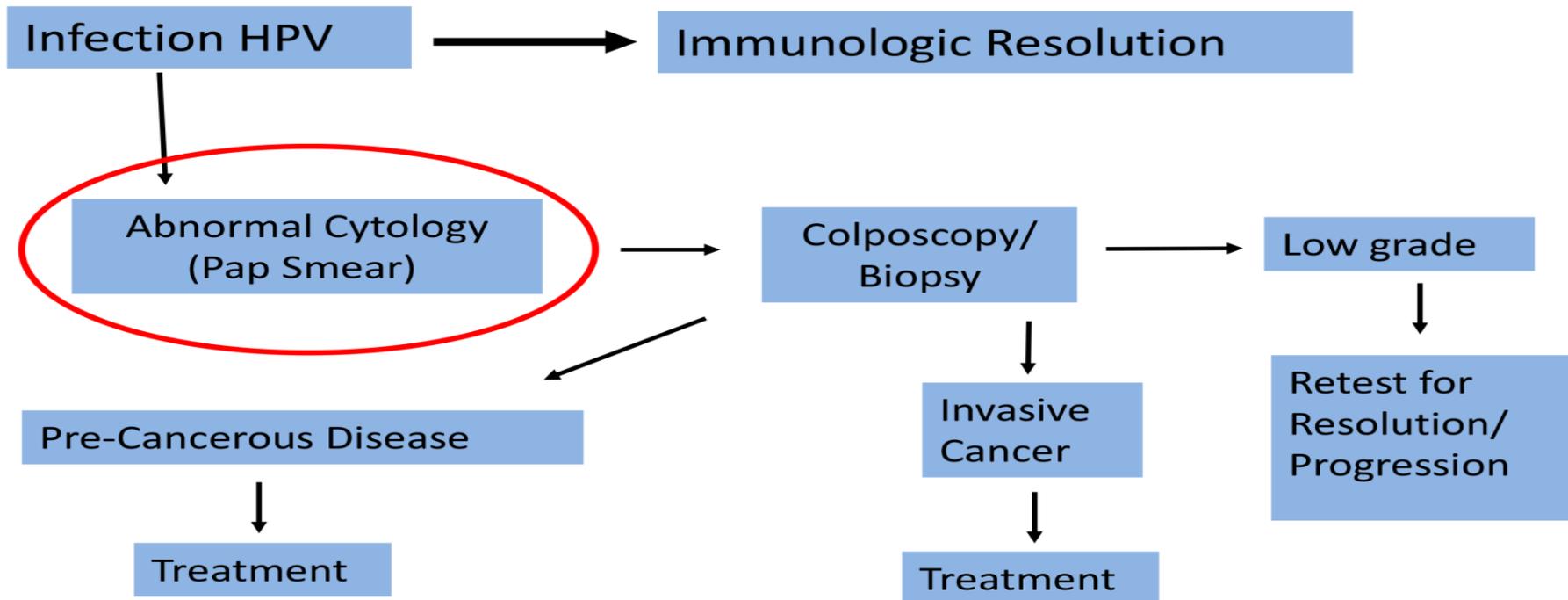
HPV infection

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



Pap screening

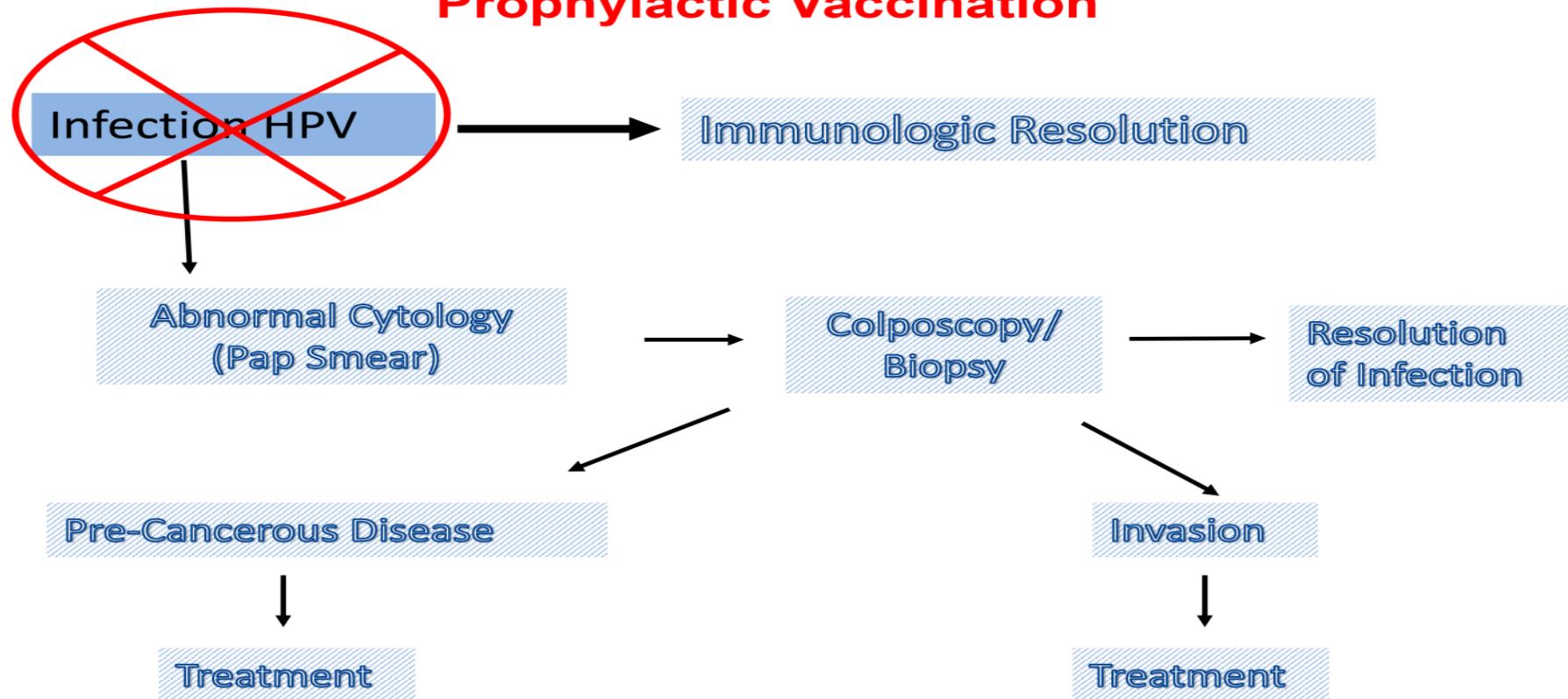
Current Pap Screening Is “Secondary” Prevention of Cervical Cancer



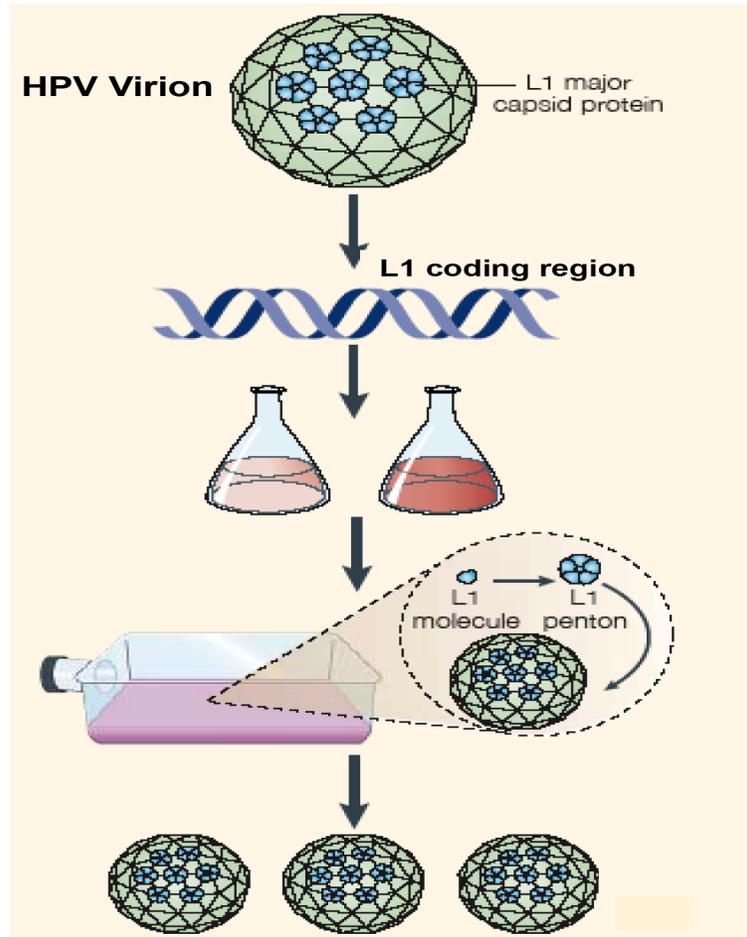
Primary prevention

The Future Is Primary Prevention

Prophylactic Vaccination



Virus like particles



Prophylactic HPV Vaccines Are L1 Virus Like Particles (VLPs)

L1 Insertion into a Baculovirus Expression Vector

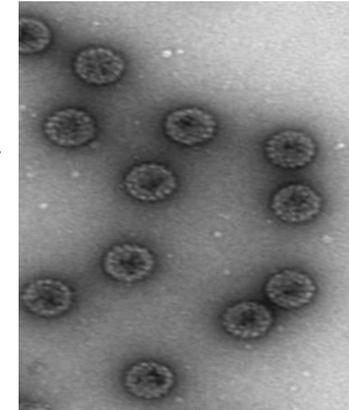
Production in Insect Cells

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

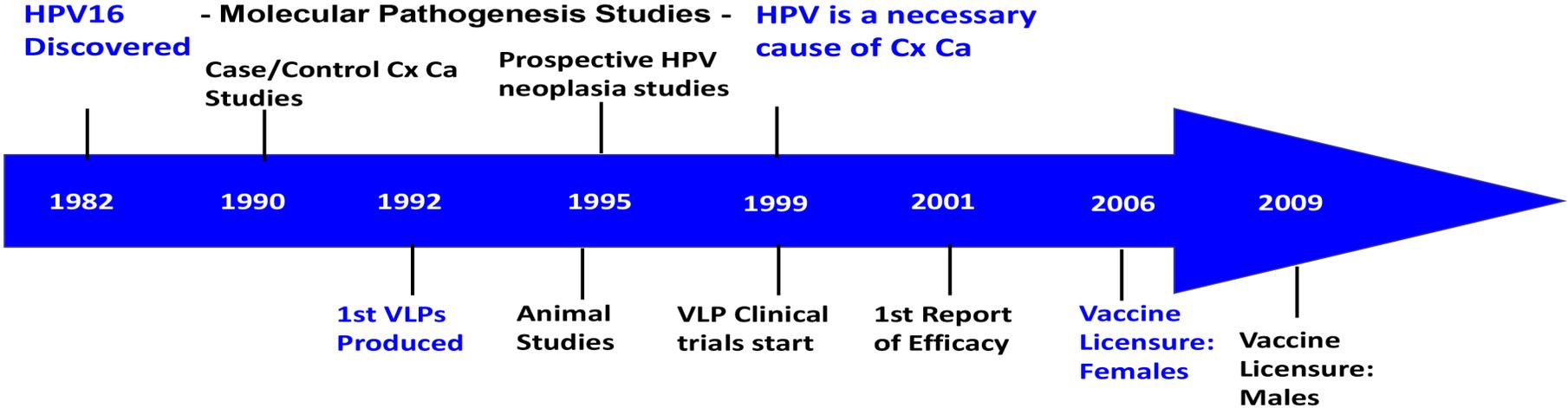
Name	Producer	VLP Types	Adjuvant	Production	Licensed
Cervarix	GSK	16,18	AS04*	Insect Cells	2007
Gardasil	Merck	16,18, 6,11	Alum	Yeast	2006
Gardasil-9	Merck	16,18,31, 33,45,52,58 6,11	Alum	Yeast	2014

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

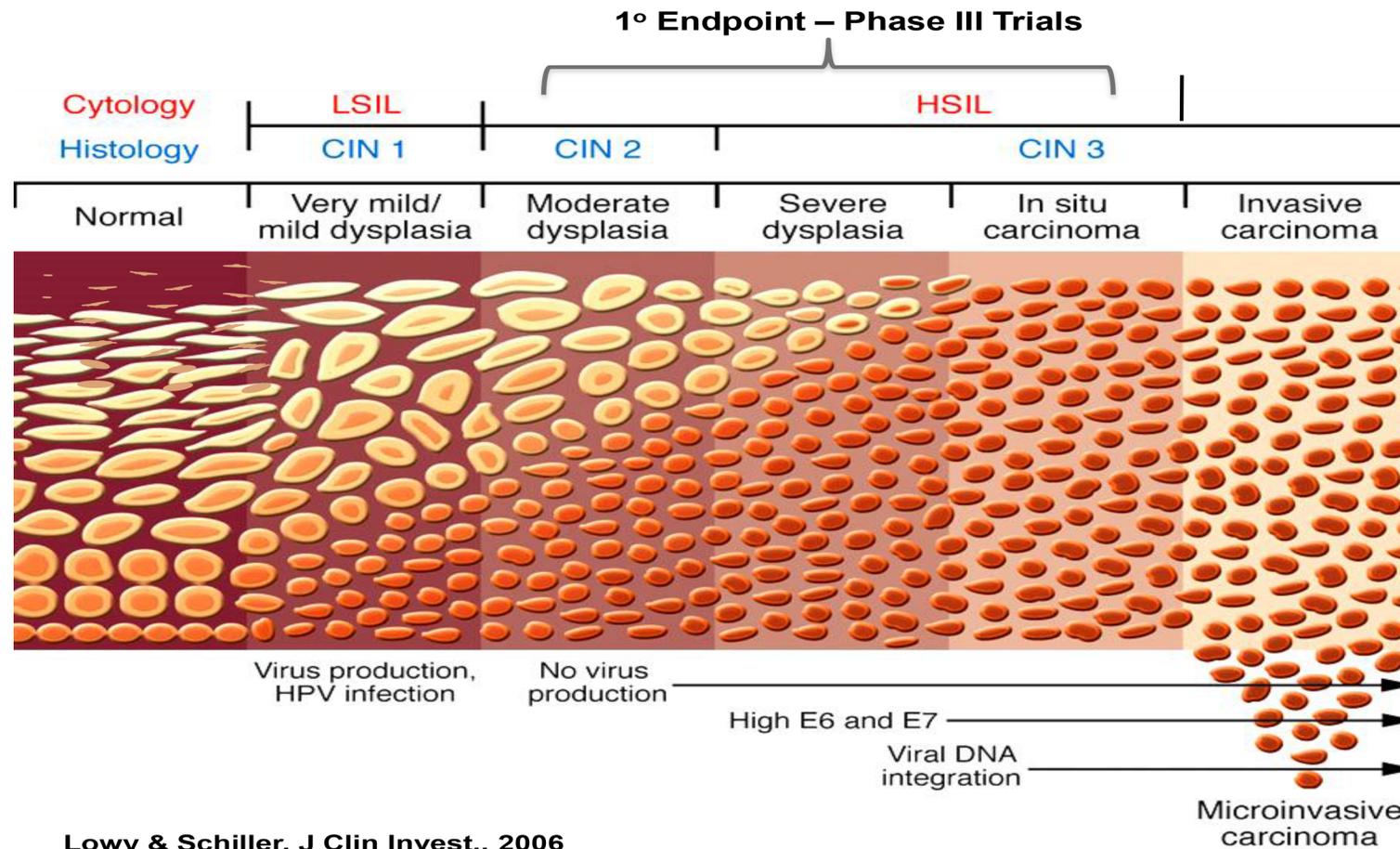
Timeline of HPV Association

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

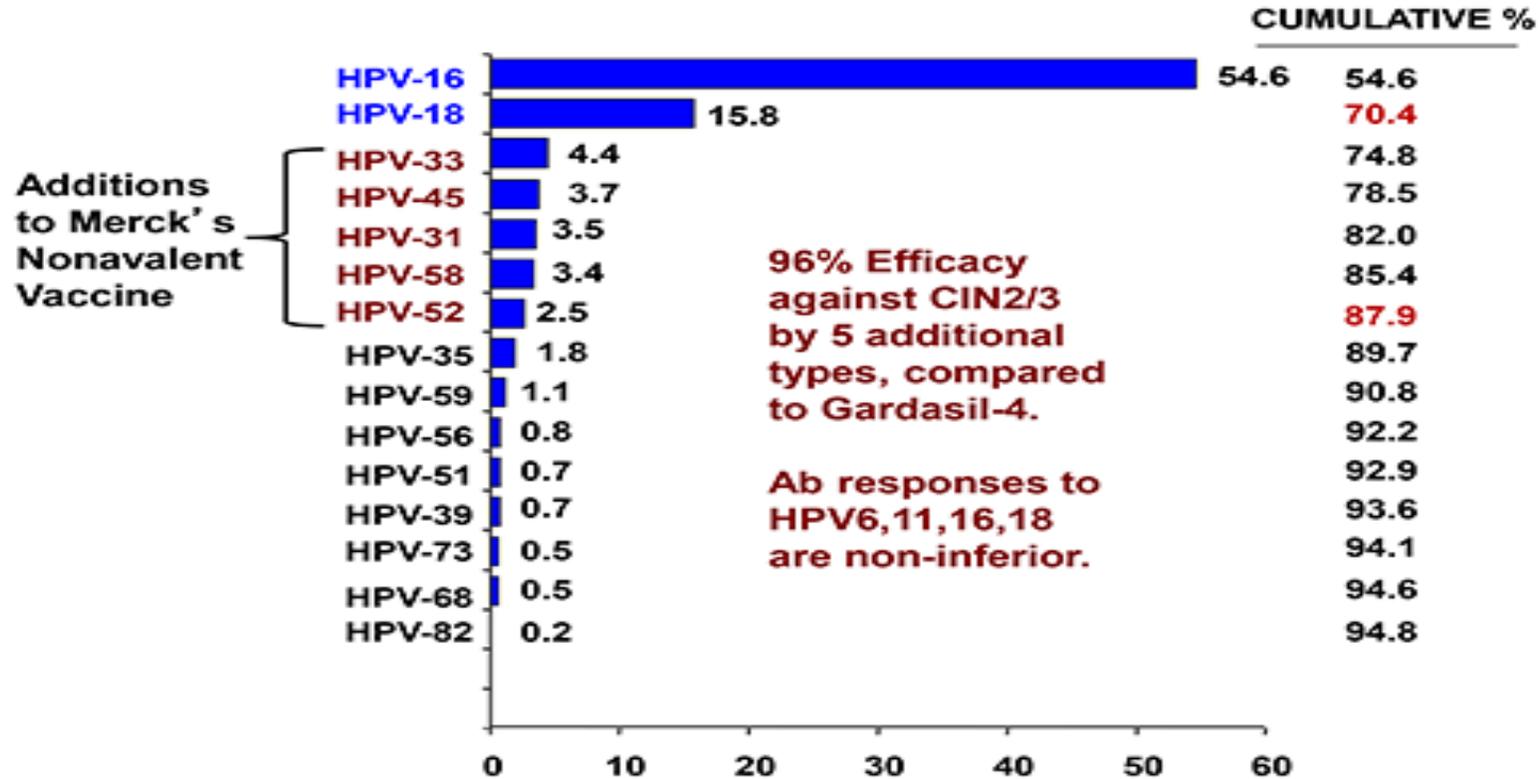
CIN III: Cervical Intraepithelial Neoplasia Grade 3

AIN: Anal Intraepithelial Neoplasia of any grade

Gardasil-9

Merck's Gardasil-9 Was FDA Approved Dec. 2014

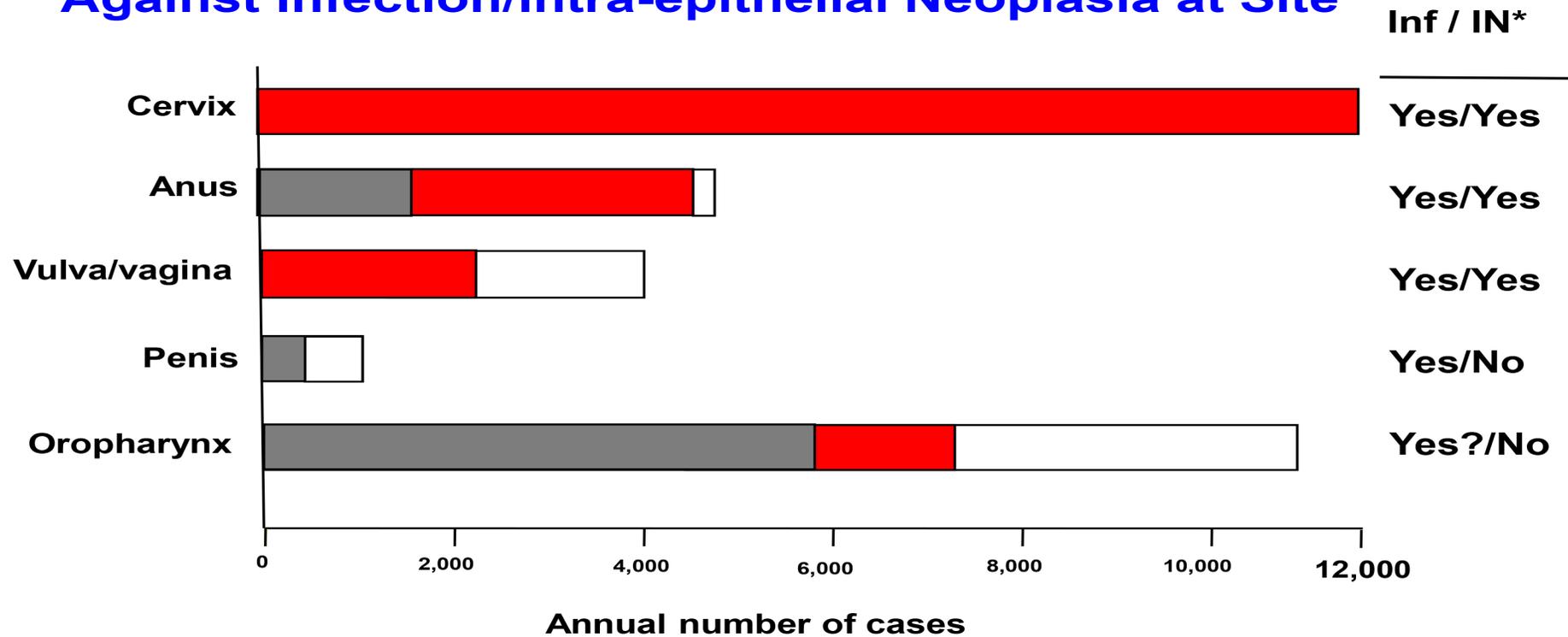
Most Frequent HPV Types in Cervical Cancer



Now available in the U.S.

Clinical Trial Evidence

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



* Against Vaccine Targeted Types

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.**

HPC vaccine

What the HPV Vaccines Don't Do

- **They don't prevent infection or disease caused by most of the other HPV types that cause cervical cancer.**
- **They don't induce regression of established HPV infections or prevent progression of HPV-induced lesions.**

HPV VLP vaccine

HPV VLP Vaccines Have an Excellent Safety Record

- Low grade and transient injection site reactions, particularly pain, are common.
- Systemic reactions, when they occur, are mild and self-limiting.
- Syncope (fainting) is sometimes observed (needle related).

Serious Adverse Events Following HPV Vaccination

Study	Vaccine	% Vaccine	% Control	Relative Risk (95% CI)
Future I	Gardasil	1.8%	1.7%	1.07 (0.71-1.60)
Future II	Gardasil	0.7%	0.9%	0.83 (0.56-1.24)
PATRICIA	Cervarix	7.5%	7.5%	1.00 (0.91-1.11)

No patterns of serious adverse events following immunization in trials or post-licensure surveillance that would suggest a causal relation to the vaccine.

HPV vaccines

HPV Vaccines Are Now Established Products

- **Commercially available for more than 10 years.**
- **Licensed in over 100 countries.**
- **Over 300 million doses given globally.**
- **Increasing evidence of effectiveness in national immunization programs.**

Vaccine effectiveness

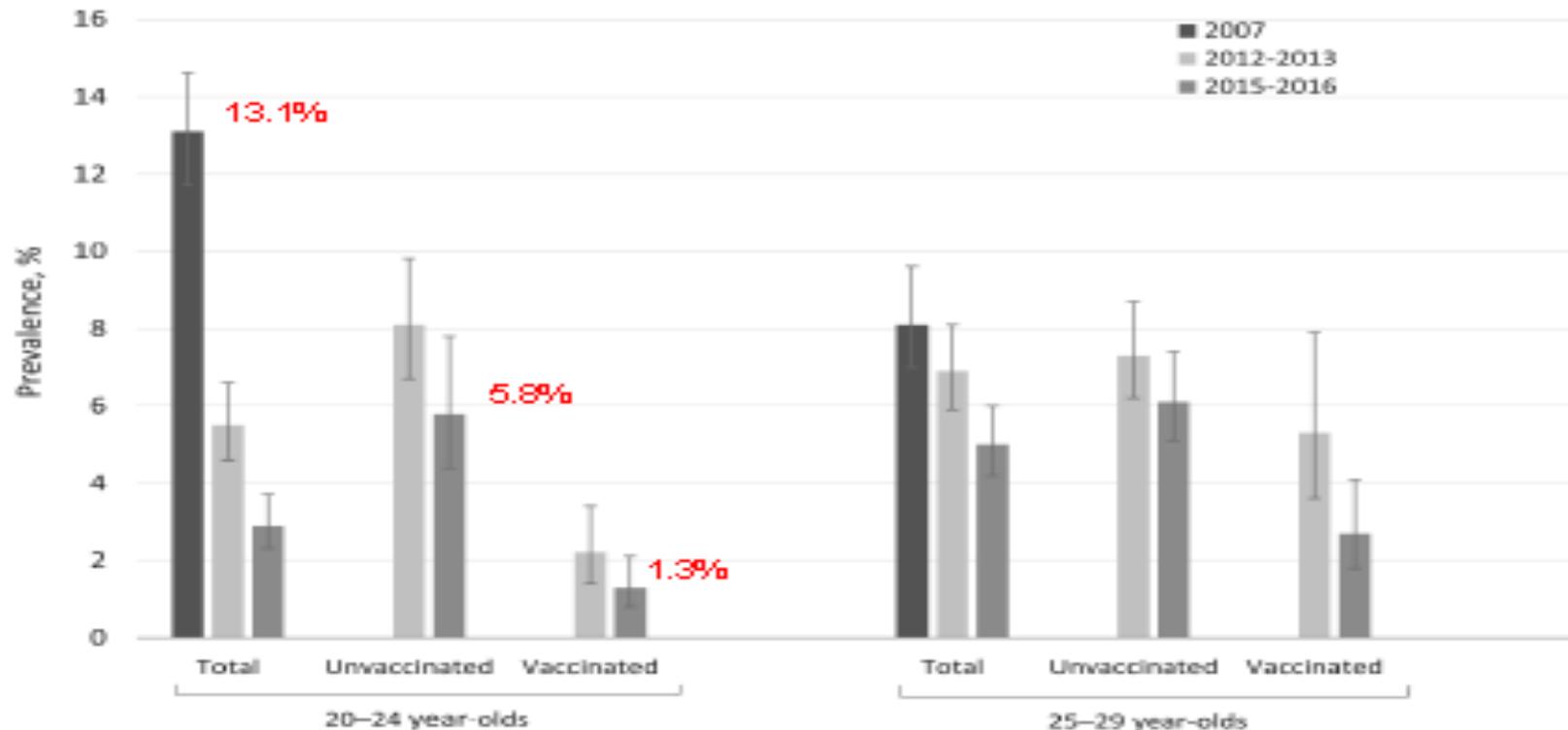
Vaccine Effectiveness: Evidence From National Immunization Programs

Country	Type-Specific Infection		Genital Warts		Cervical Lesions
	Female	Male	Female	Male	Female
Australia	+	+	+	+	+
Britain	+		+		+
USA	+	+	+		+
Canada			+		+
Denmark			+	+	+
Sweden			+	+	+
France	+				
Spain			+		
Italy			+	+	
Israel			+	+	

HPV prevalence

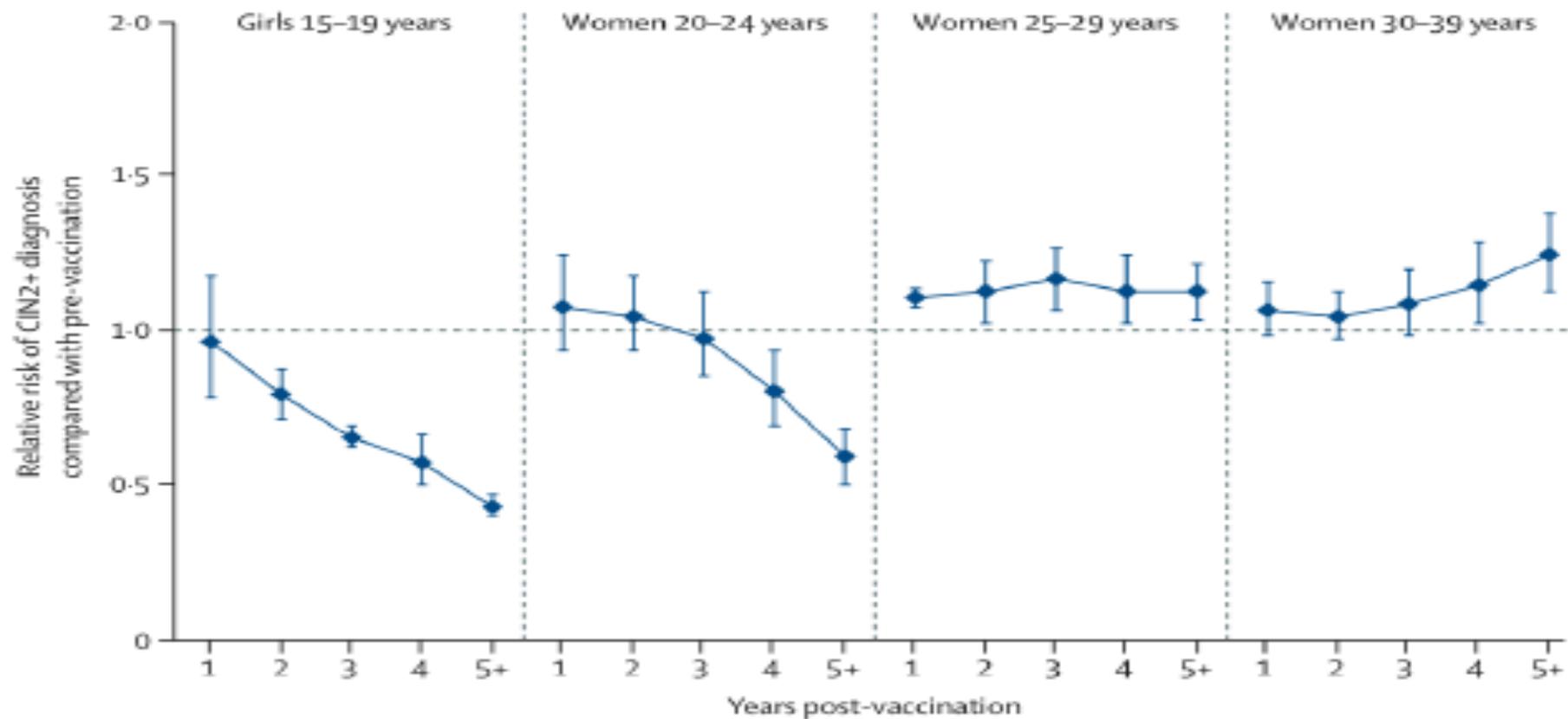
Vaccine Type HPV Prevalence in U.S. Women Receiving at Least One Vaccine Dose

L.E. Markowitz et al. / Vaccine 37 (2019) 3918–3924



Cin2+ changes

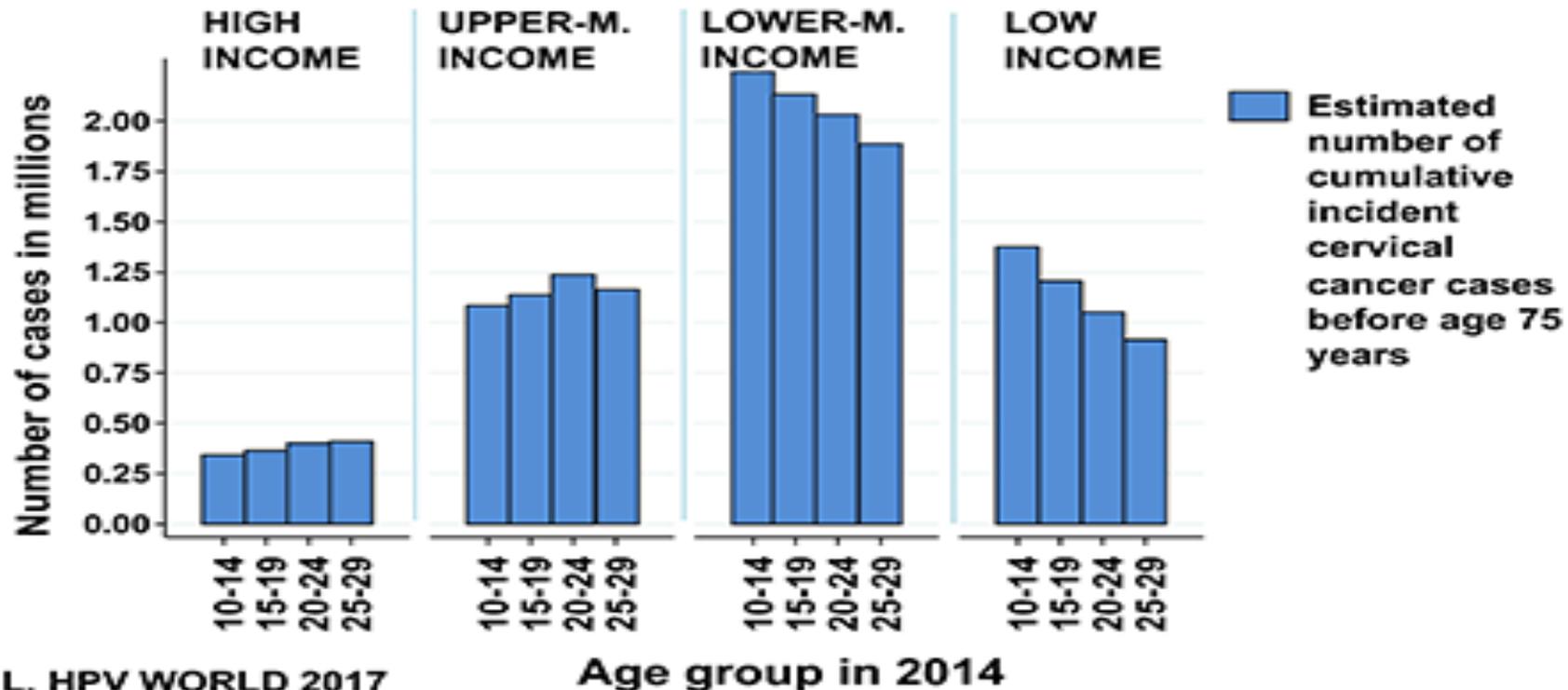
Changes in CIN2+ in Screened Females After Vaccine Introduction In Countries with At Least 50% Coverage



Non-vaccine scenario

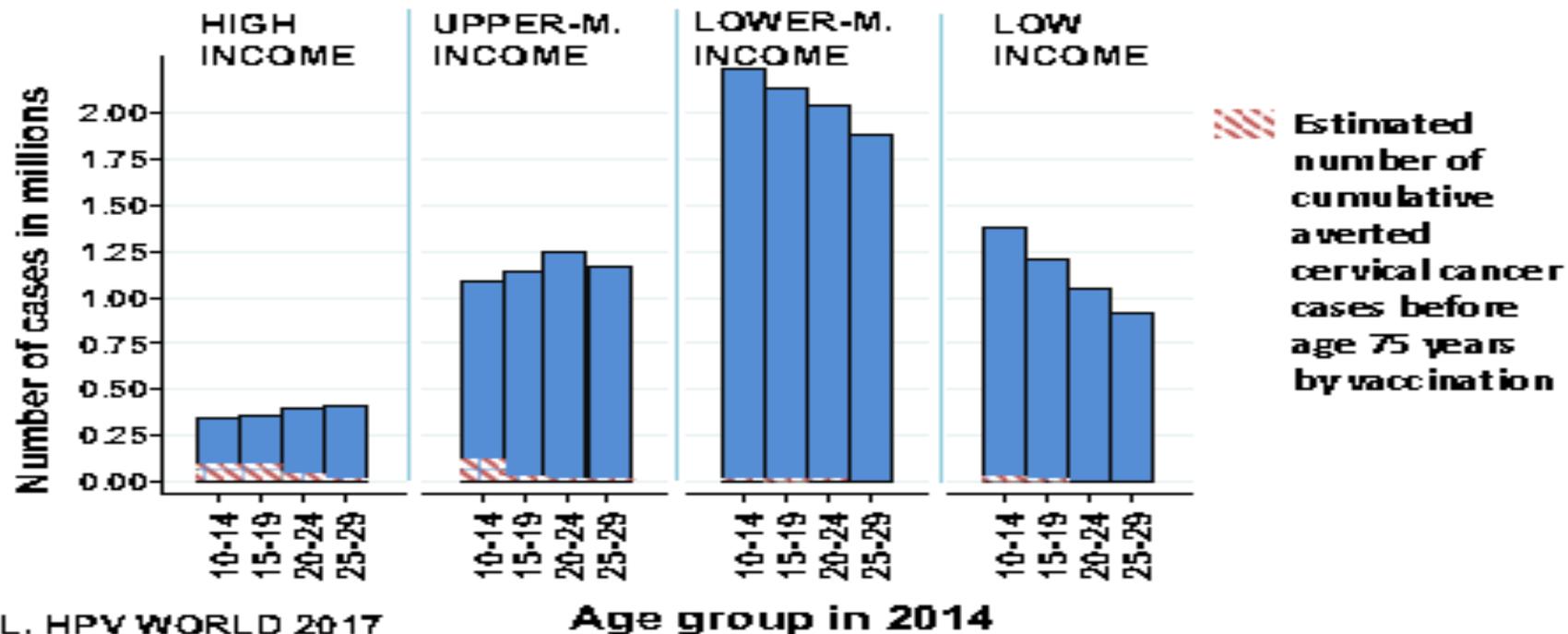
Non-Vaccine Scenario: 19 Million Cases and 10 Million Deaths From Cervical Cancer

Worldwide projection for the next 65 years



Cancer averted by HPV vaccination

**Cancers Averted by HPV Vaccination:
365,000 cases and 150,000 deaths**
Worldwide projection for the next 65 years



HPV vaccination

HPV Vaccination of U.S. Girls and Boys: Aged 13-17 in 2019

	<u>Complete series*</u>	<u>At least one dose</u>
Girls:	57%	73%
Boys:	52%	70%

* 2 doses if <15 yrs old; 3 doses if >15 yrs old

\$5 per dose

Increasing Uptake, Particularly in Low Resource Settings

- **Both companies are committed to sale to GAVI at less than \$5 per dose.**
- **Vaccine manufacture in emerging countries. Cecolin, an HPV16/18 VLP vaccine just licensed in China.**
- **Address vaccination hesitancy by education programs aimed families and health care providers.**
- **Transition to single dose vaccination programs.**

Vaccine manufacture

Increasing Uptake, Particularly in Low Resource Settings

- **Both companies are committed to sale to GAVI at less than \$5 per dose.**
- **Vaccine manufacture in emerging countries. Cecolin, an HPV16/18 VLP vaccine just licensed in China.**
- **Address vaccination hesitancy by education programs aimed families and health care providers.**
- **Transition to single dose vaccination programs.**

Vaccine development in China

PROPHYLACTIC HPV VACCINES IN DEVELOPMENT - CHINA

Company	Vaccine	Expression system	IND	PI	PII	PIII	BLA	MKT
1	GSK	HPV-2 (16, 18)	Vaccines					
2	Merck	HPV-4 (6, 11, 16, 18)						
3	Merck	HPV-9 (6, 11, 16, 18, 21, 20, 45, 52, 58)						
4	Innovo	HPV-2 (16, 18)	Cell					
5	Sarum	HPV-2 (16, 18)						
6	ChIBG/CDIBP	HPV-4 (6, 11, 16, 18)						
7	Innovo	HPV-2 (6, 11)	Cell					
8	Kangle-abH	HPV-2 (16, 18, 58)						
9	Bova	HPV-4 (6, 11, 16, 18)						
10	Bova	HPV-9 (6, 11, 16, 18, 21, 20, 45, 52, 58)						
11	Sarum	HPV-9 (6, 11, 16, 18, 21, 20, 45, 52, 58)						
12	Innovo	HPV-9 (6, 11, 16, 18, 21, 20, 45, 52, 58)						
13	ChIBG/CDIBP	HPV-4 (6, 16, 52, 58)						
14	Kangle-abH	HPV-9 (6, 11, 16, 18, 21, 20, 45, 52, 58)						
15	Jiangsu Ruithe	HPV-9 (6, 11, 16, 18, 21, 20, 45, 52, 58)						
16	ChIBG/CDIBP	HPV-11 (6, 11, 16, 18, 21, 20, 45, 52, 58, 59, 62)						
17	Huaning	HPV-14 (6, 11, 16, 18, 21, 20, 26, 29, 45, 51, 52, 56, 59, 62)						

 Early stage
  Late stage

Data source: NMPA data, china.com.cn.gov, updated in April 2019

From: Peter Dull BMS F

Gecolin: the first "generic" HPV vaccine. Licensed only in China.

Address vaccination hesitancy

Increasing Uptake, Particularly in Low Resource Settings

- **Both companies are committed to sale to GAVI at less than \$5 per dose.**
- **Vaccine manufacture in emerging countries. Cecolin, an HPV16/18 VLP vaccine just licensed in China.**
- **Address vaccination hesitancy by education programs aimed families and health care providers.**
- **Transition to single dose vaccination programs.**

Single dose

Increasing Uptake, Particularly in Low Resource Settings

- **Both companies are committed to sale to GAVI at less than \$5 per dose.**
- **Vaccine manufacture in emerging countries. Cecolin, an HPV16/18 VLP vaccine just licensed in China.**
- **Address vaccination hesitancy by education programs aimed families and health care providers.**
- **Transition to single dose vaccination programs.**

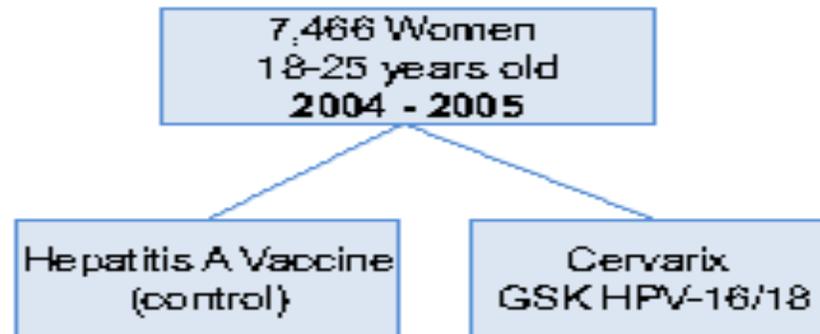
Single dose

Why do we think a single dose might sufficient?

Costa Rica vaccine trial

NCI Costa Rica Vaccine Trial (CVT) Publicly-Funded Trial Launched Prior to Licensure

NCI PI: Alan Hildesheim
C.R. PI: Rolando Herrero



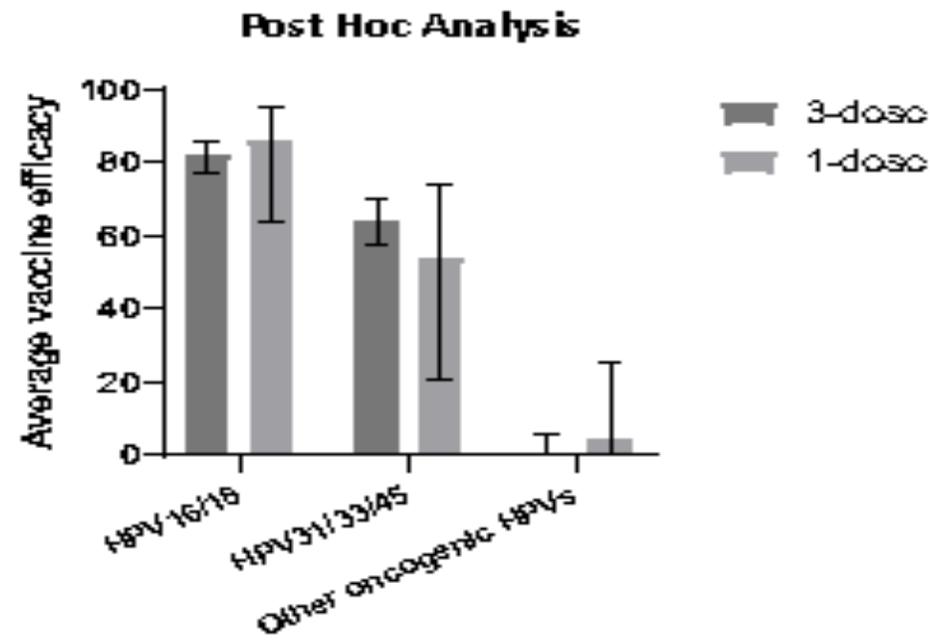
20% received <3 doses

- Annual follow-up for 4 years, then long term follow-up
- Cervical samples collected at all visits



Cervarix trial

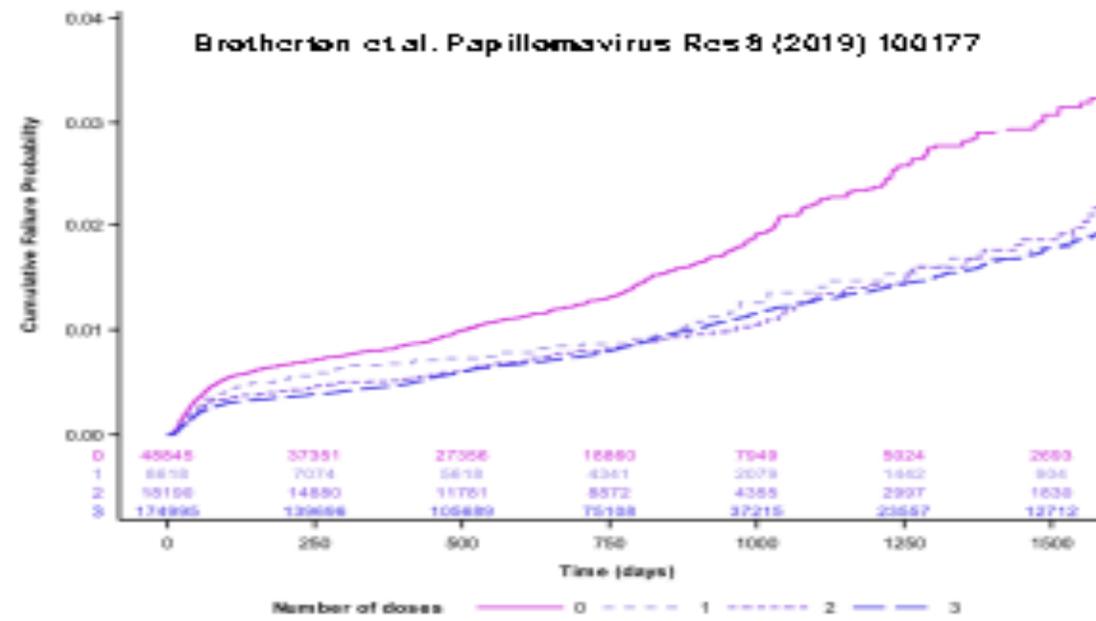
Costa Rica Vaccine Trial of Cervarix: Average Vaccine Efficacy Against Incident HPV Infection for Years 2–11



Tsang S et al, JNCI (2020)

Gardasil Australian trial

Failure Probability for CIN2+/AIS in Screened Australian Women Eligible for Gardasil When <15 Year Old by Doses Received



Single dose

Is It Time to Adopt Single Dose HPV Vaccination Programs?

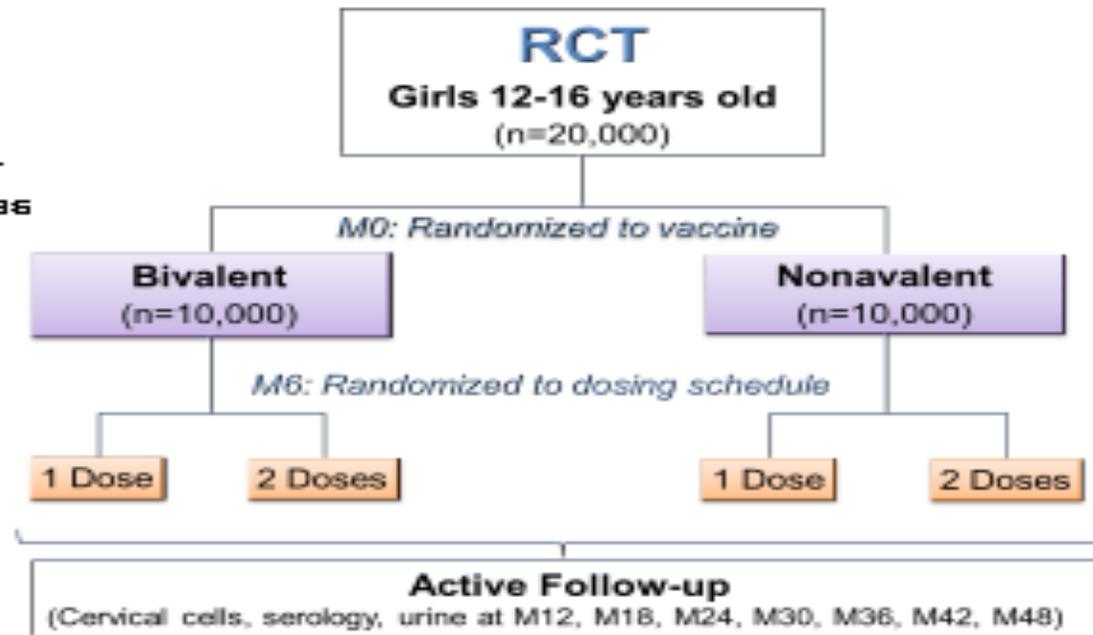
These post-hoc findings provide insufficient evidence to generally promote implementation of single dose HPV vaccination programs.

Early adoption in low resource settings with a contingency plan to boost if needed might be justified.

Clinical protocol

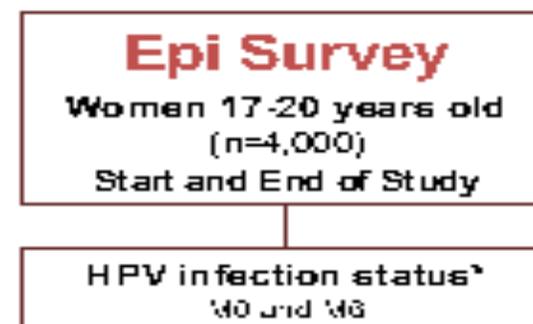
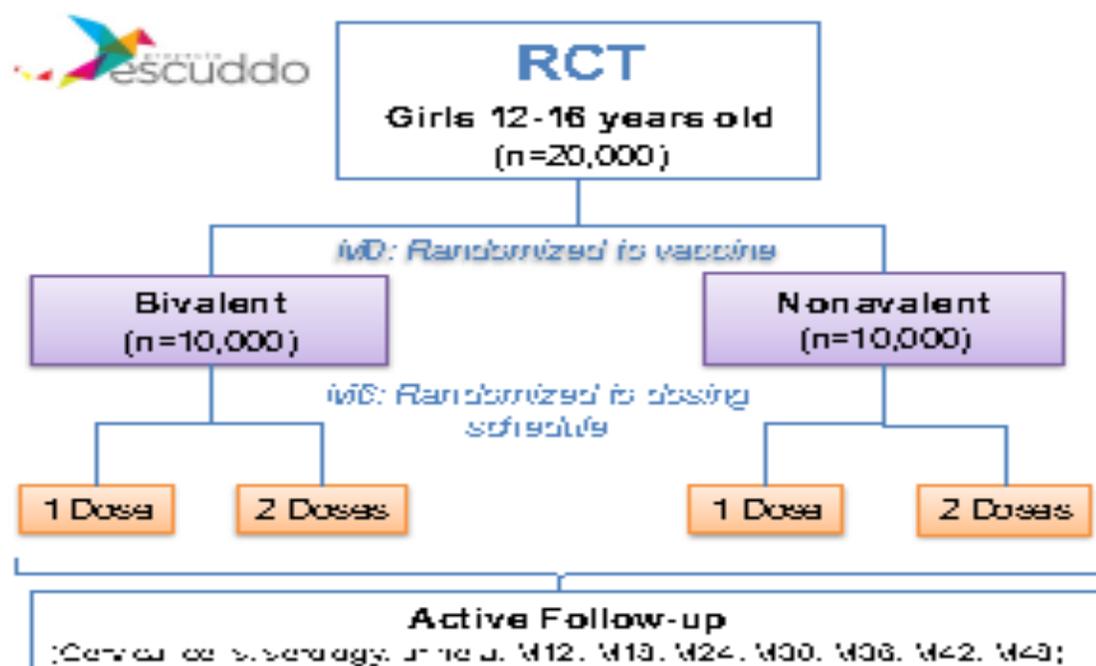
Evaluate non-inferiority of one versus two doses in the prevention of new cervical HPV16/18 infections that persist 6+ months


NGI PI: Aimee Kreimer
C.R. PI: Carolina Porras



Clinical protocol

Evaluate one dose of HPV vaccination compared to zero doses



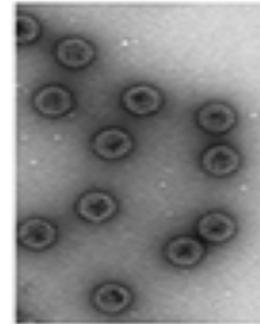
*Receive HPV vaccine after assessment of HPV infection status

Results in 2025-26

Why do HPV VLP vaccines work so well?

Why Do HPV VLP Vaccines Work So Well?

- The vaccines are exceptionally good at inducing neutralizing antibodies.
- Infection mechanism make HPVs exceptionally susceptible to neutralizing antibodies.
- HPVs have DNA genomes so can't evolve rapidly to evade nAb responses.



HPV16 L1 VLPs

Provides plausibility for HPV VLPs as the first subunit vaccine to induce long term protection after a single dose

Antibody responses to VLPs

Consistency of Antibody Response to VLPs

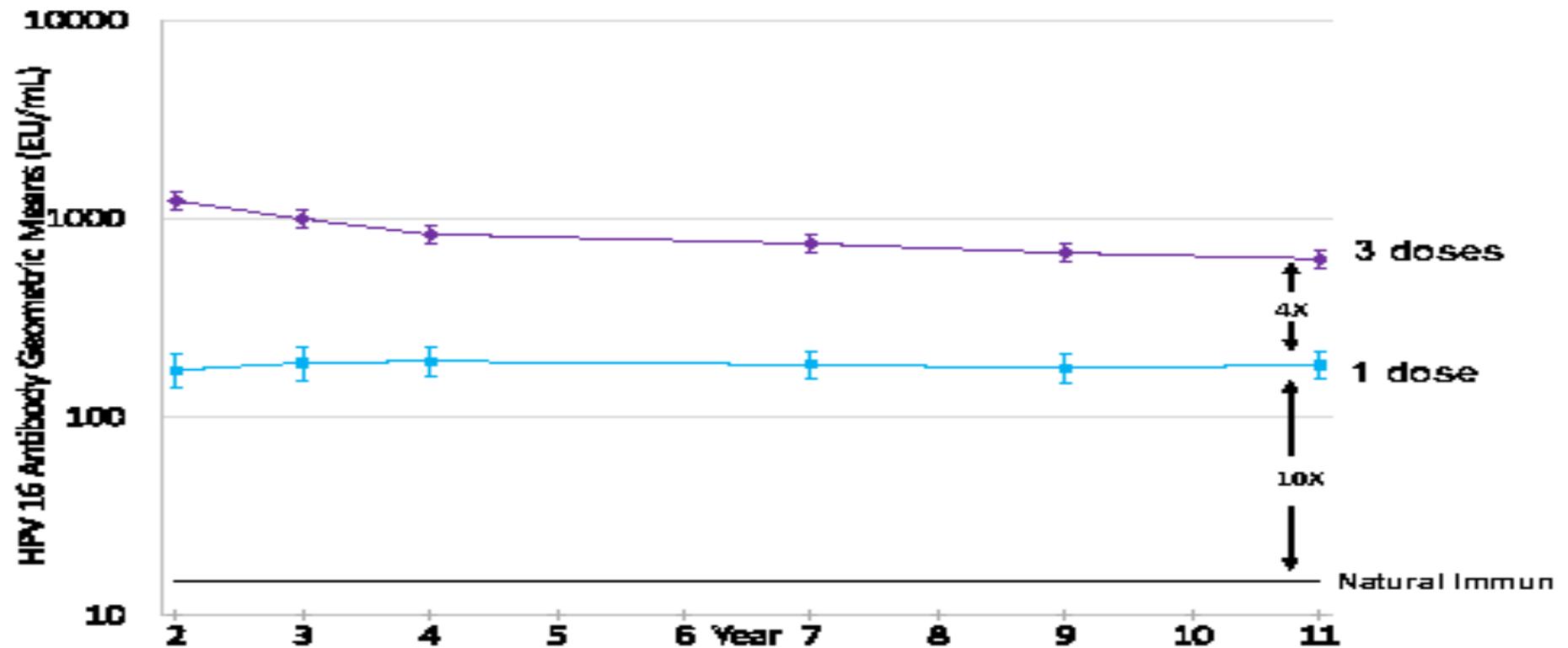
Percent of Women Serocoverting to Individual HPV VLPs in Merck VLP Vaccine Gardasil*

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

*4666 women vaccinated 3 times by intramuscular injection

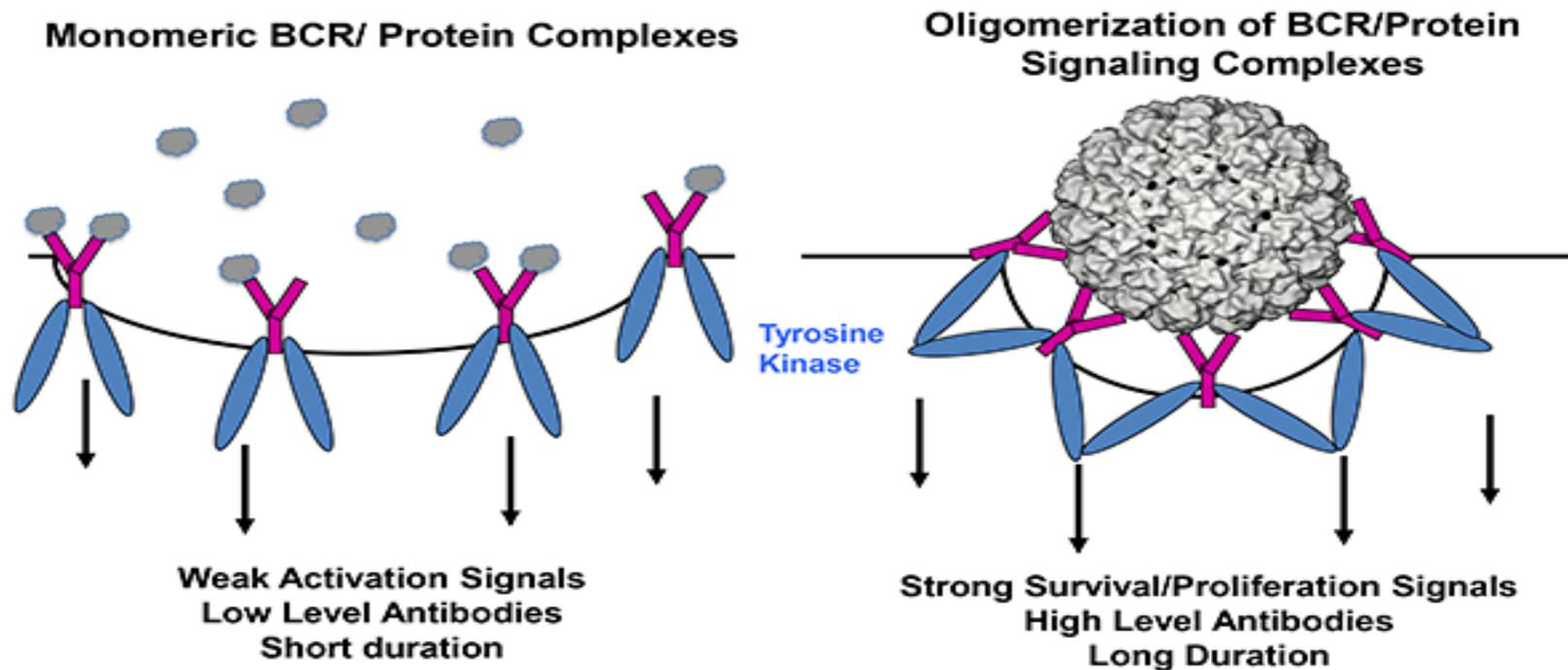
Stable HPV16 serum antibodies

CVT: Stable HPV16 serum antibodies for 11 years
Results similar for HPV18



B cells recognize dense repetitive protein arrays

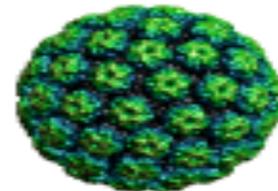
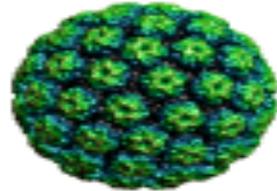
B Cells Recognize Dense Repetitive Protein Arrays as Dangerous Microbial Structures



Repetitive Ag structure guides the decision to invest in long term Ab production.

Repetitive antigen display

VLPs Have Highly Repetitive Antigen Display



B cells specifically recognize particulate antigens with epitope spacing of 50-100Å as foreign.

This epitope spacing is commonly found on microbial surfaces, e.g. virus major capsid protein or bacterial pili.

Protein complexes with this spacing rarely occur in vertebrate animals.

So BCRs have evolved as antigen specific pattern recognition receptors.

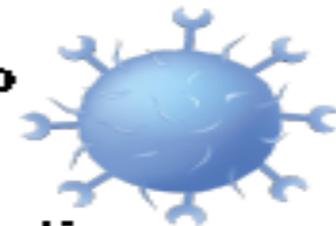
[Bachmann et al. Science 1993; 262: 1448](#)

VLP advantage

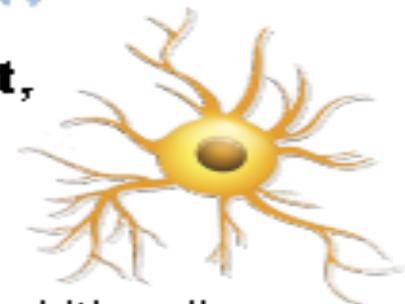
Additional Advantages of VLPs

- They have the right particle size for efficient trafficking to lymph nodes
- They are readily phagocytized and so induce strong T-helper responses
- Their poly-valency leads to stable binding of natural low-avidity IgM and Complement, which promotes their acquisition by follicular dendritic cells*

Lymph nodes



T-cell



Dendritic cell

Lessons for COVID-19 vaccines

Lessons For COVID-19 Vaccines?

Virus-like display of antigen, e.g. RBD, is the strategy most likely to consistently induce high titers of long-lasting antibodies.

Virologic aspects

Virologic Aspects Contributing to Efficacy

In vivo Murine Model of Vaginal HPV Infection

The remarkably slow process of infection makes HPVs exceptionally susceptible to inhibition by antibodies

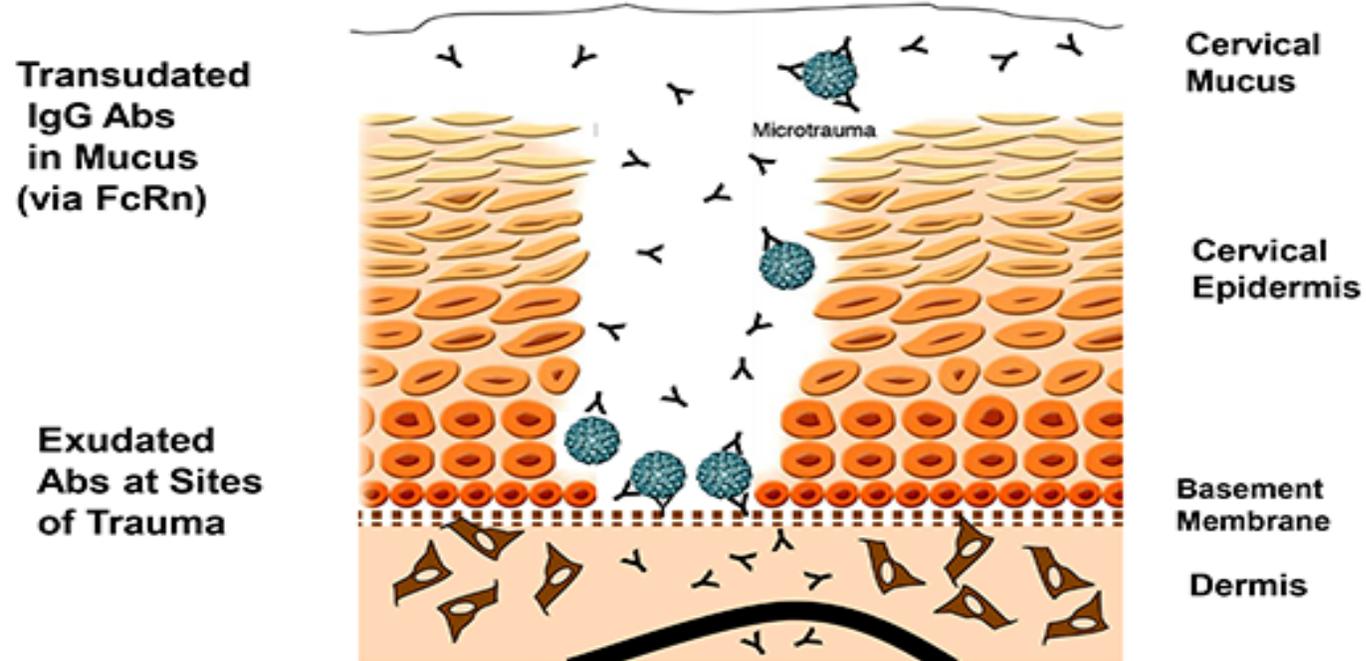


HSPG = Heparan Sulfate Proteoglycan

Rhonda Kines et al. PNAS 2009; 106:20458-63

Cervix Ab response

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: but 10-100X less than in serum - *Nardelli et al. JNCI, 2003*
- Cervicovaginal HPV infection in a mouse model requires epithelial trauma: *Roberts et al., Nat Med, 2007*

Antibody titers and protection

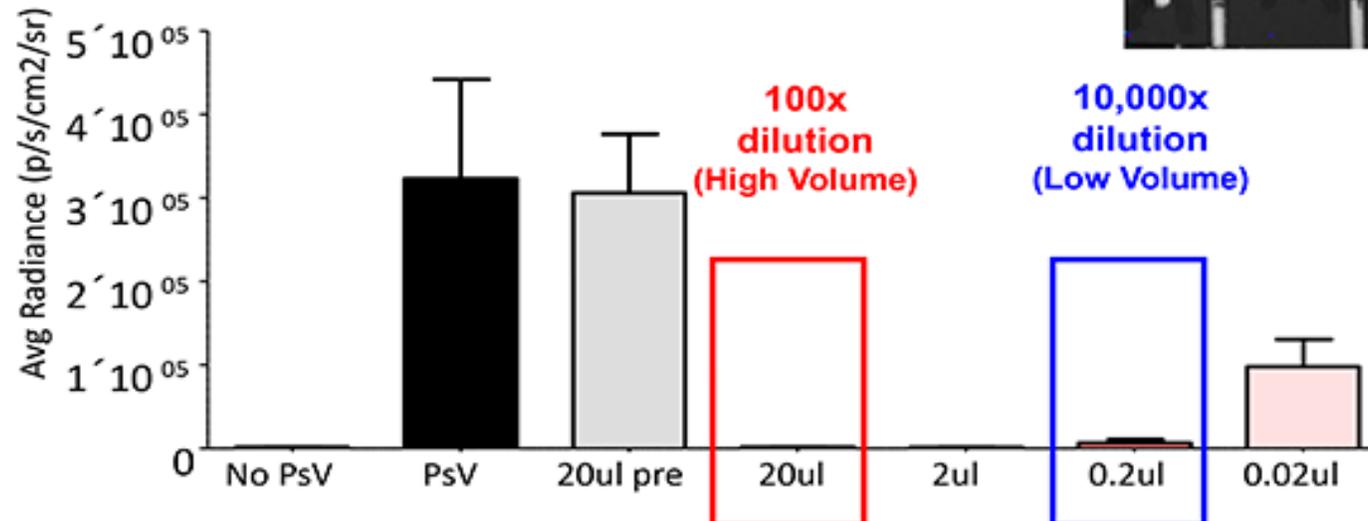
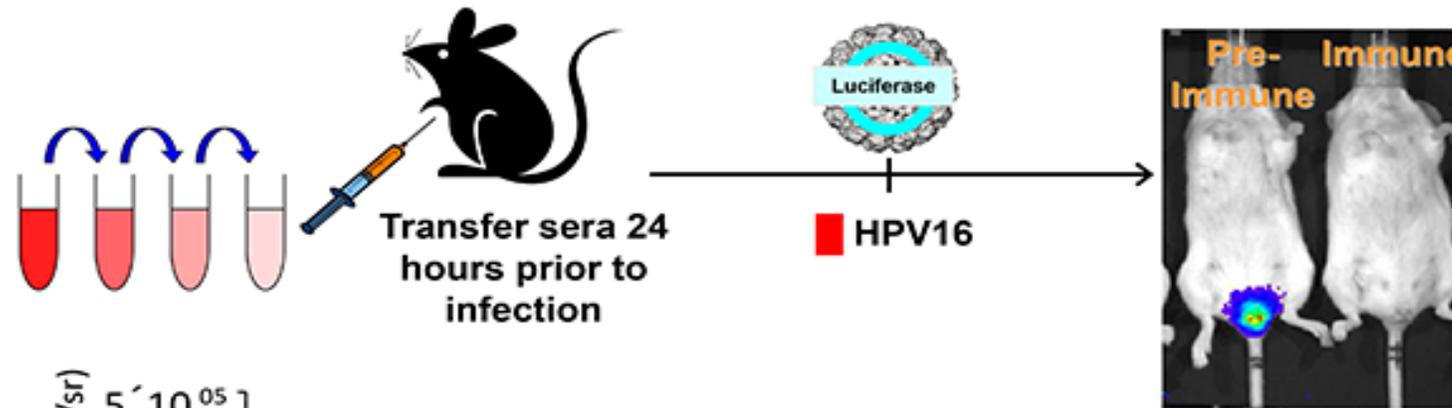
Antibody Titers and Protection

Are the plateau titers after vaccination near the minimum needed for protection?

Will the 4-fold difference between Ab titers after three vs one dose influence long-term protection?

Passive transfer

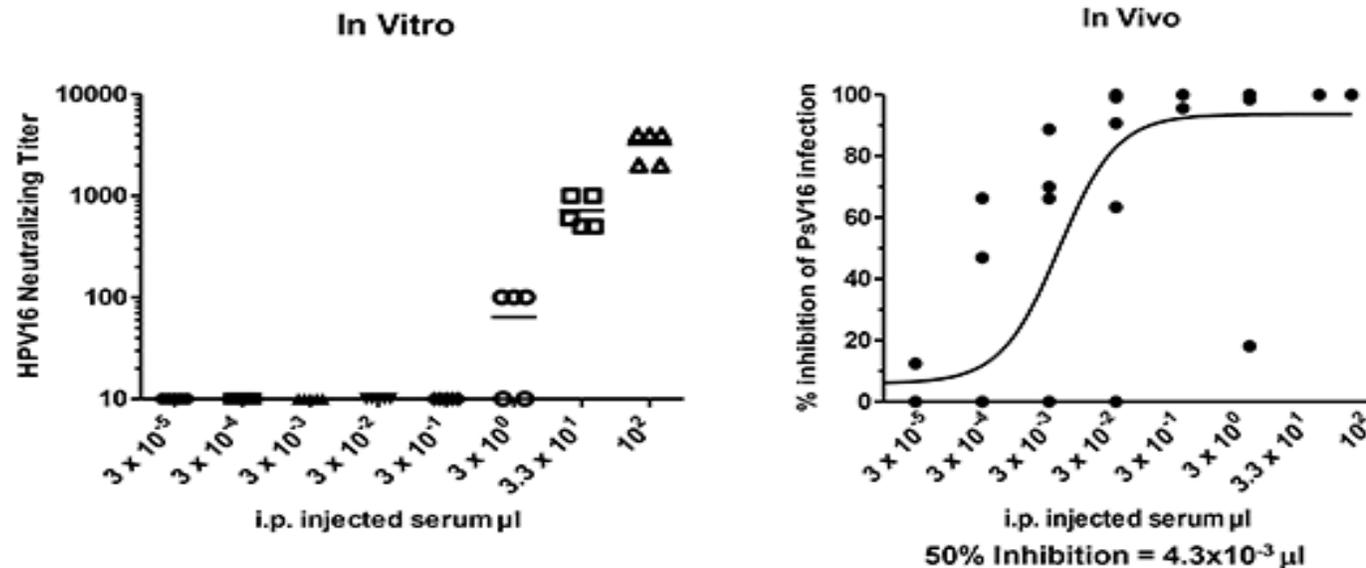
Passive Transfer of Rabbit Polyclonal Anti-16L1 VLP Sera



* Challenged with HPV16. See no protection from infection when challenged with HPV45

Gardasil sera protection

In vitro vs In Vivo Protection of Gardasil Sera Against HPV16 Pseudovirus Infection



Protection detected with 500-fold less sera in vivo than in vitro!

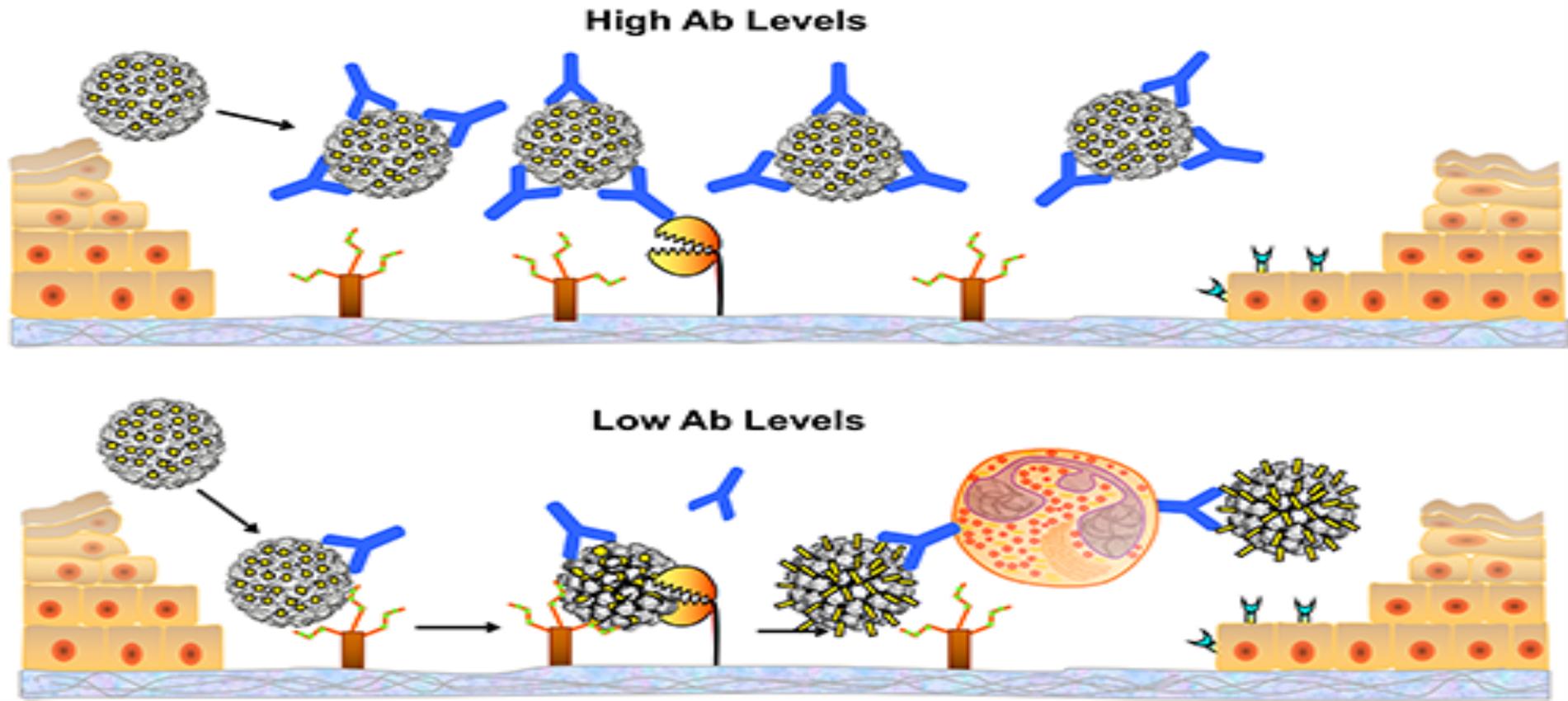
The in vitro assay is missing some potent mechanism of infection inhibition.

Longet et al, J Virol 2011

Mechanisms of in vivo infection

Mechanisms of In Vivo Infection Inhibition by VLP Abs

Day et al, Cell Host Microbe 2010; 8:260-70



Conclusions

Conclusions

- **The HPV VLP vaccines are very effective at preventing incident infection and disease by the vaccine types.**
- **Because the VLPs are exceptionally potent induces of neutralizing antibodies and the virus is exceptionally susceptible to inhibition by antibodies.**
- **The vaccines have great potential for reducing the burden of HPV-induced cancer worldwide.**
- **The primary challenge now is to see that the vaccines reach the individuals most in need of them.**
- **Demonstrating sustained efficacy of a single dose in a RCT could transform implementation programs.**

Cervical cancer tools

We Have the Essential Tools to Eliminate Cervical Cancer

- **The knowledge that virtually all cervical cancer are caused by oncogenic HPV infection.**
- **Vaccines for primary prevention of HPV infection.**
- **Screening for secondary prevention by diagnosis and treatment of precancerous lesions.**

Worldwide, cervical cancer remains a leading cause of cancer deaths in women.

Cervical cancer elimination

A Call for the Global Elimination of Cervical Cancer



World Health
Organization

Dr Tedros Adhanom Ghebreyesus
Director-General

Cervical Cancer: An NCD We Can Overcome
Intercontinental Hotel, Geneva
19 May 2018

“Cervical cancer is one of the most preventable and treatable forms of cancer.”

”Prevention and early treatment are also highly cost-effective.”

“HPV vaccines are truly wonderful inventions. If only we had vaccines against every form of cancer.”

“Our challenge is to ensure that all girls globally are vaccinated against HPV and that every women over 30 is screened and treated for pre-cancerous lesions.”

Key Collaborators

Key Collaborators

Present Members of the Lab:

Doug Lowy

Patricia Day

Nicolas Cuburu

Cindy Thompson

Susana Pang

Carla Cequeira

Tara Berman

Lukas Bialkowski

Alex Bell

Past Members of the Lab:

Richard Roden

Chris Buck

Jeff Roberts

Bryce Chackerian

Diana Pastrana

Reinhard Kirnbauer

Rhonda Kines

Rina Kim

DCEG: Allan Hildesheim, Aimee Kreimer, Mahboobeh Safaeian, Mark Schiffman, Sholom Wacholder, Josh Sampson

IARC: Rolando Herrero

Universitaire Vaudois, Lausanne: Denise Nardelli

Aura Biosciences: Eli de los Pinos, Rhonda Kines, Steve Monk