

Cervical Cancer

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

John Schiller, Center for Cancer Research, NCI



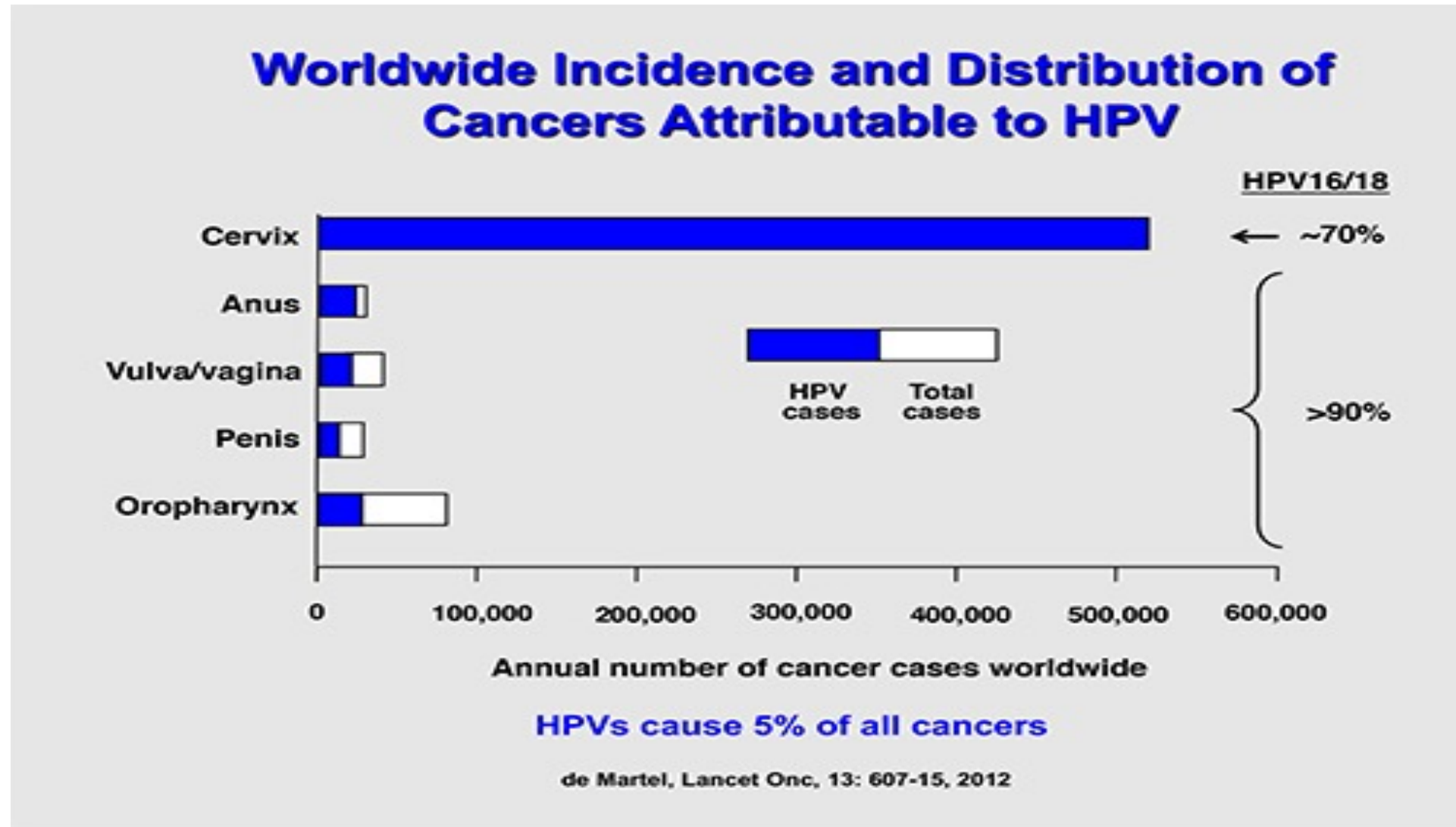
- HPV and Cancer
- Vaccine Efficacy/Effectiveness
- Key Implementation Issues
- Why they work so well

Annual Number of Cancer Cases Attributable To Specific Virus Infections

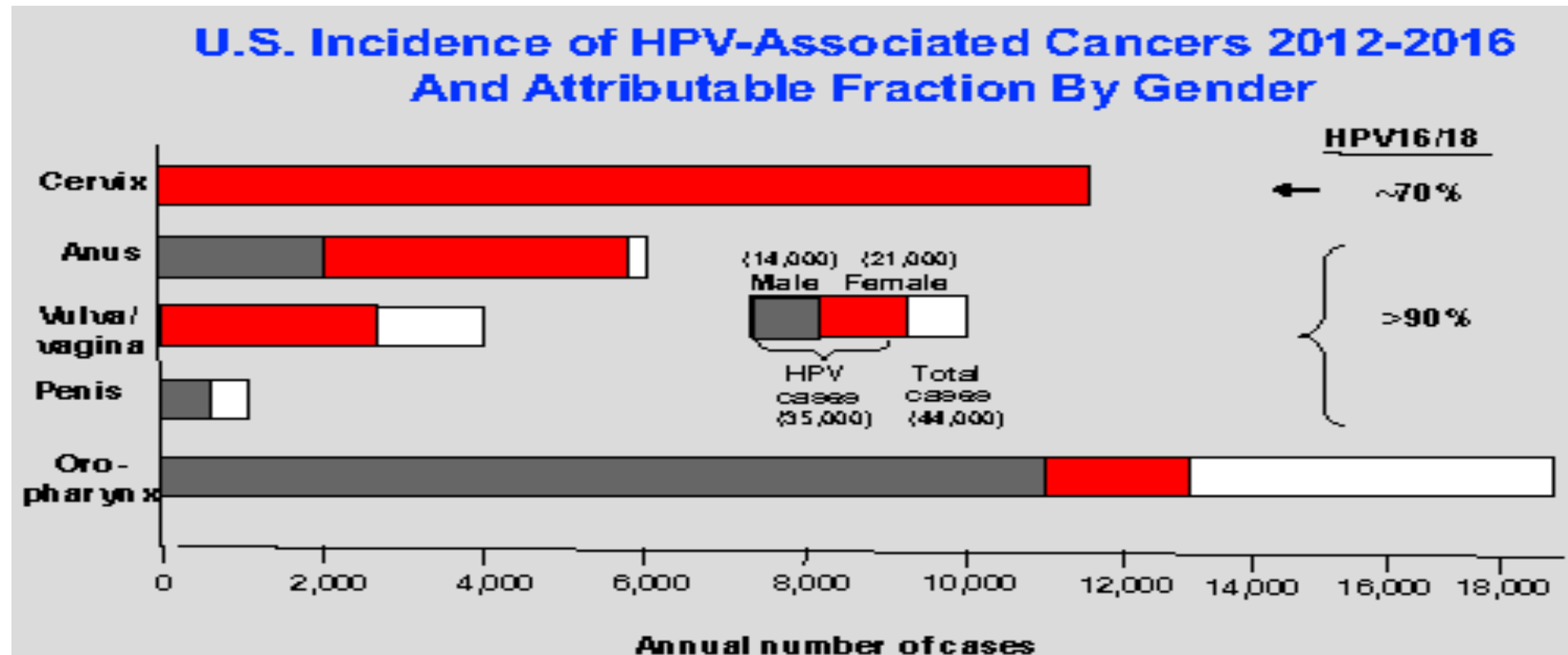
10% of All Cancers

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



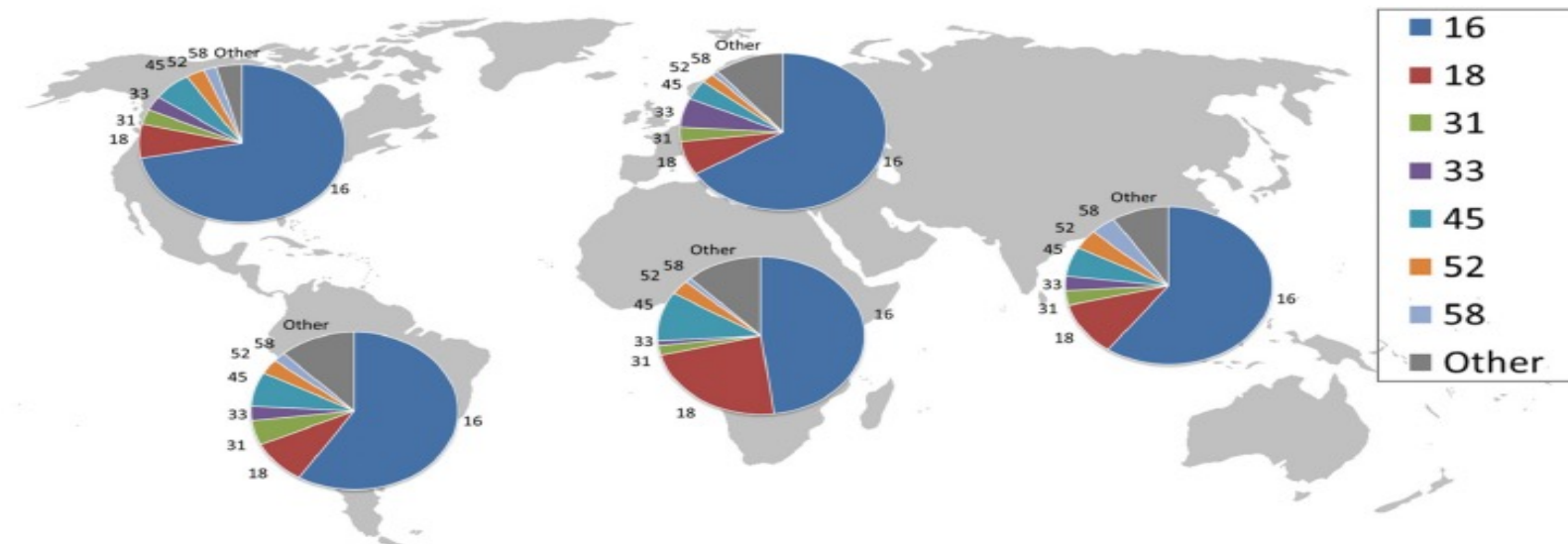
HPV incidence



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

World wide distributions of genotypes

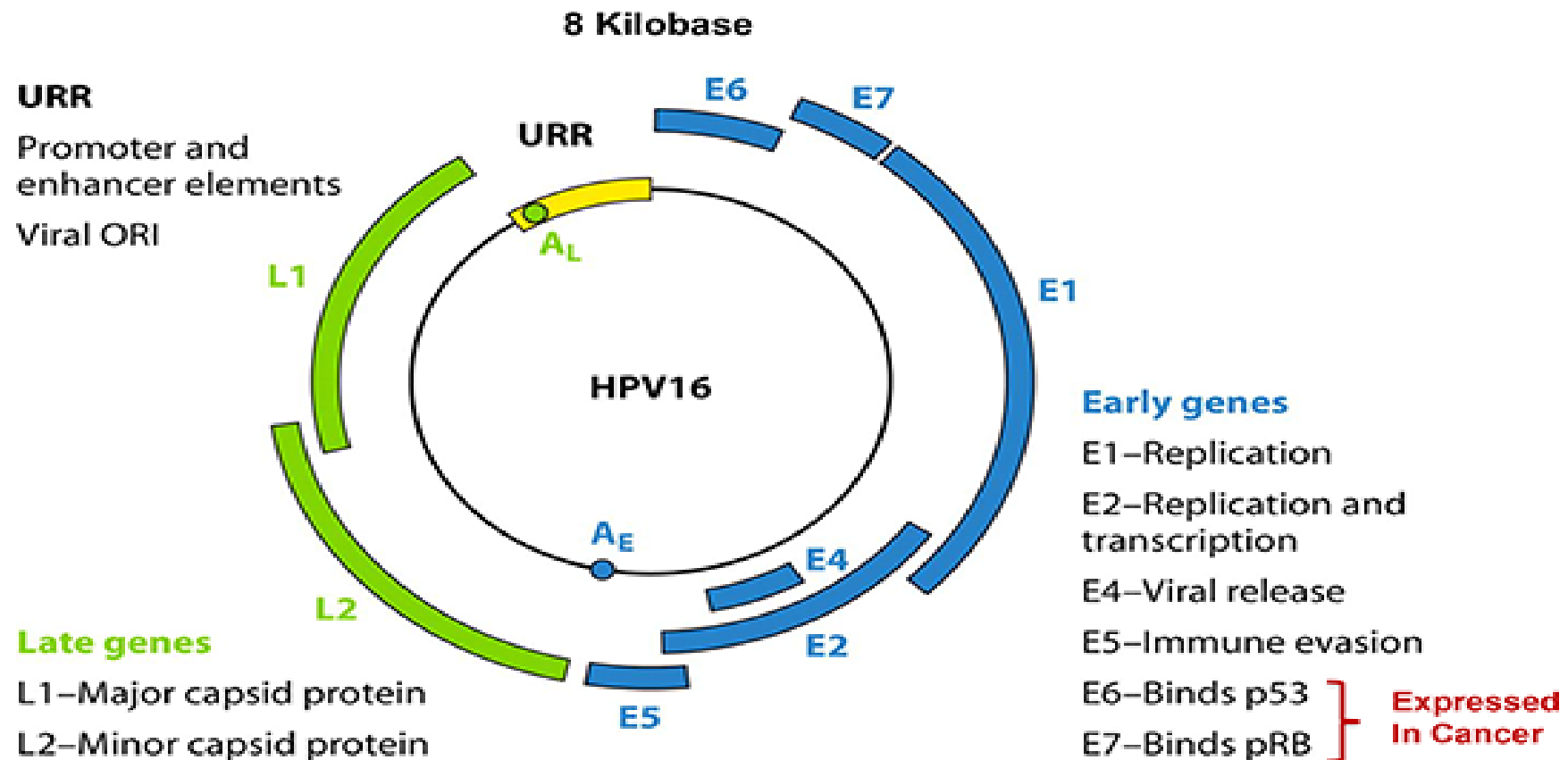
World Wide Distribution of Genotypes Detected in Cervical Cancer



HPV16 and HPV18 dominate everywhere

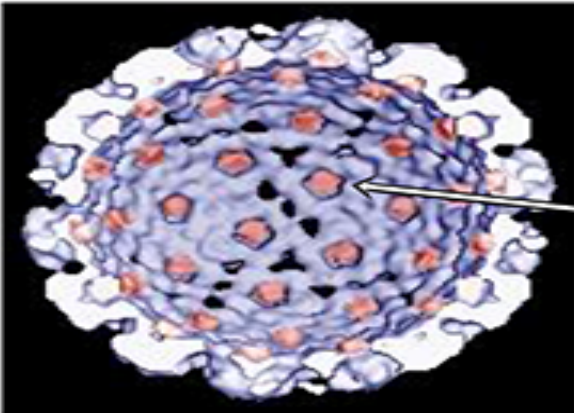
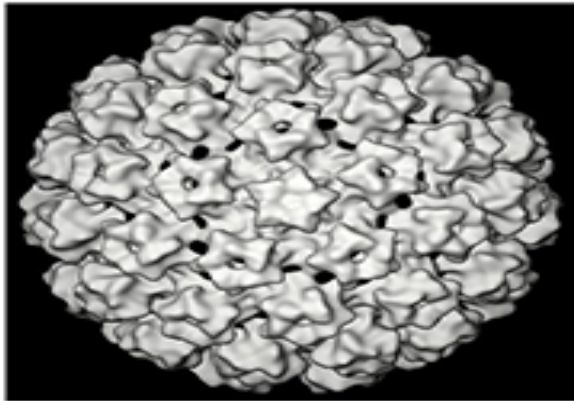
HIV genome

HPV16 Double Stranded Circular DNA Genome



Virion

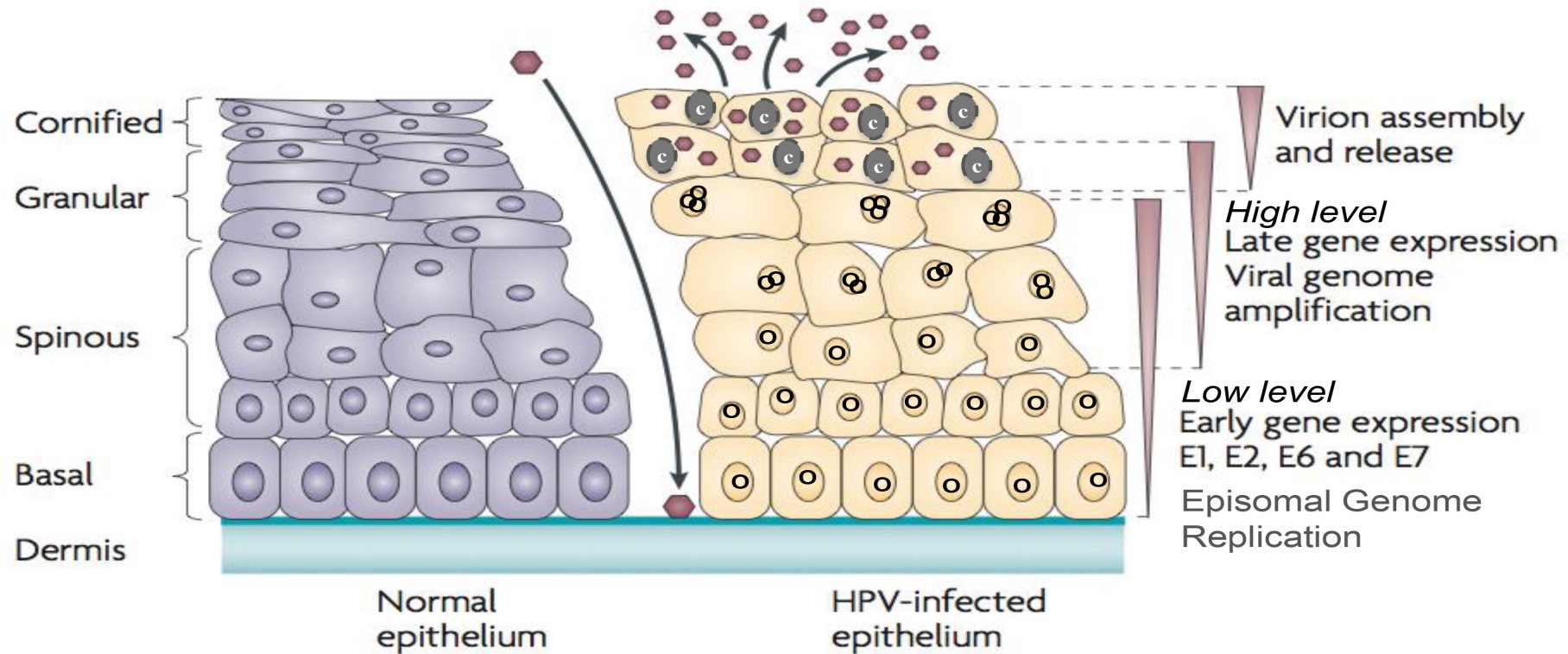
Papillomavirus Virion



- **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)**

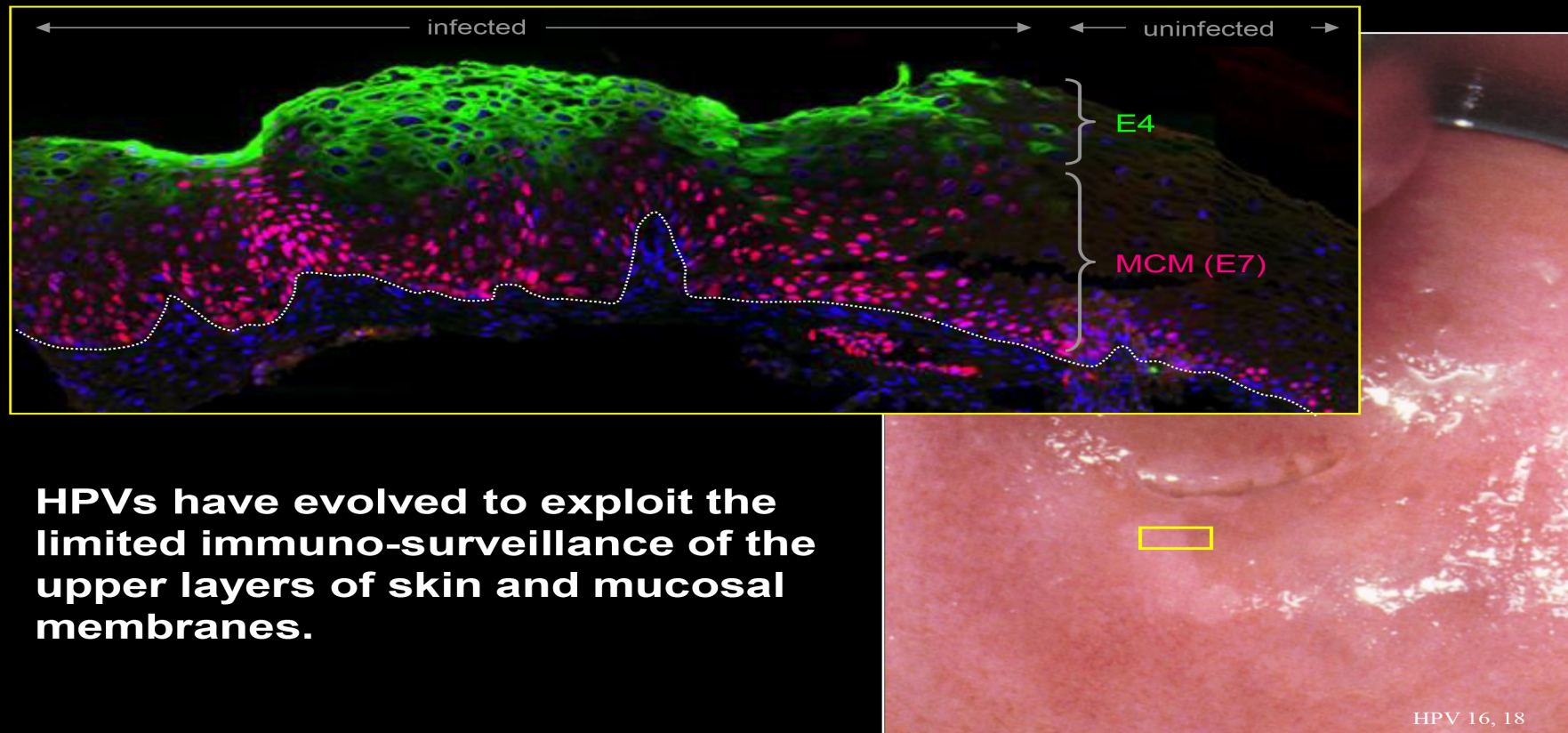
HPV life cycle

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



HPV infection

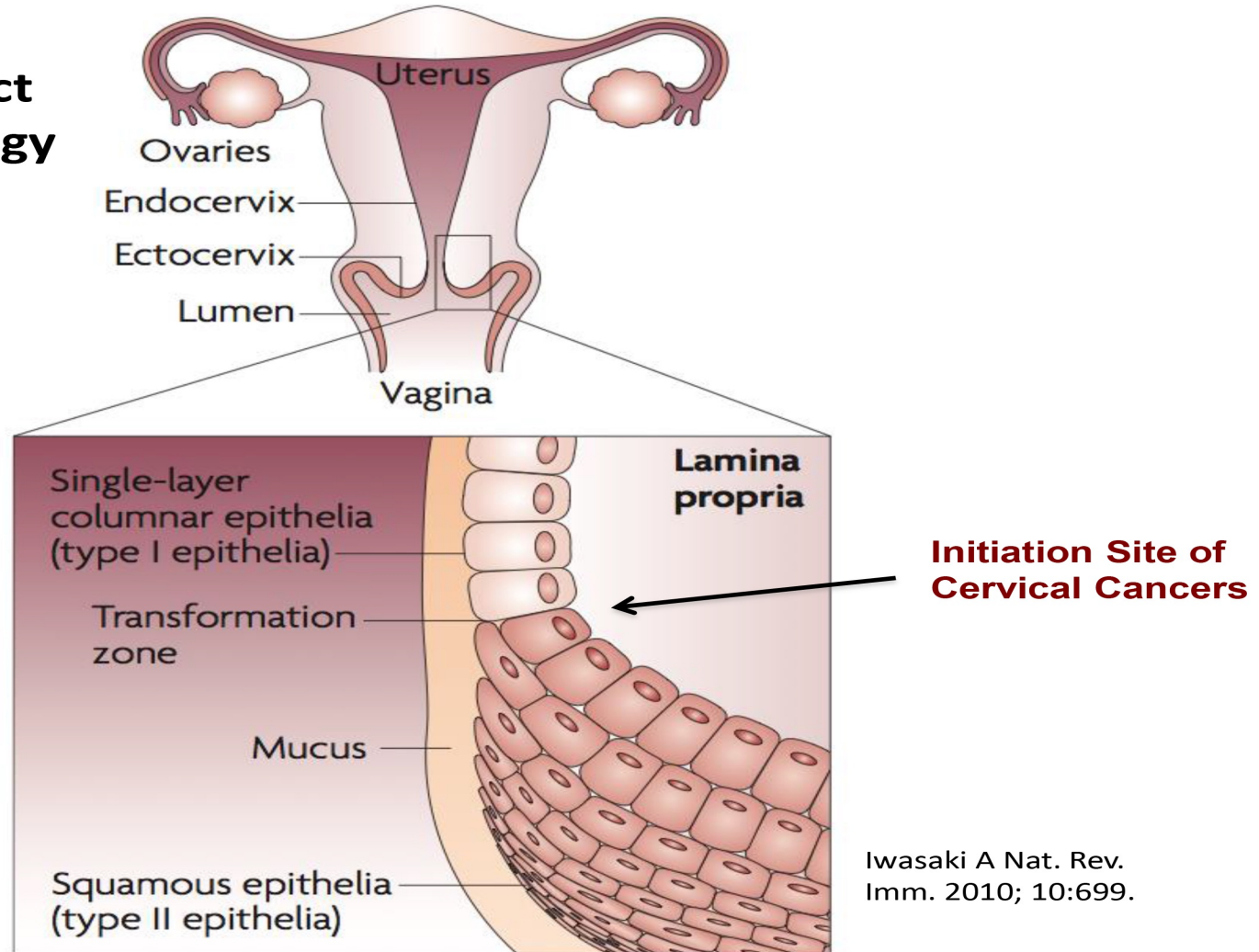
Productive HPV Infection: Hiding in Plain Site



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

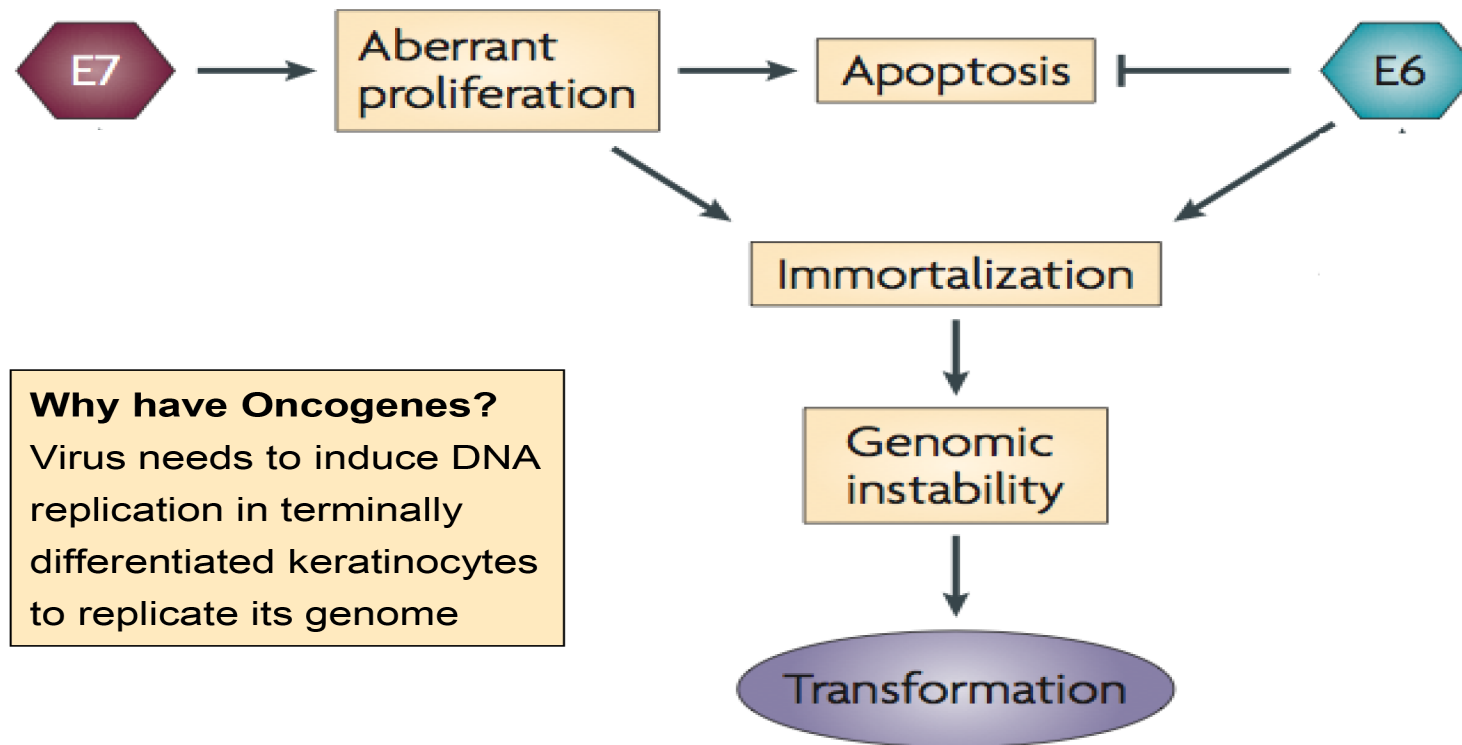
Cervical cancer

Female Reproductive Tract Anatomy & Histology



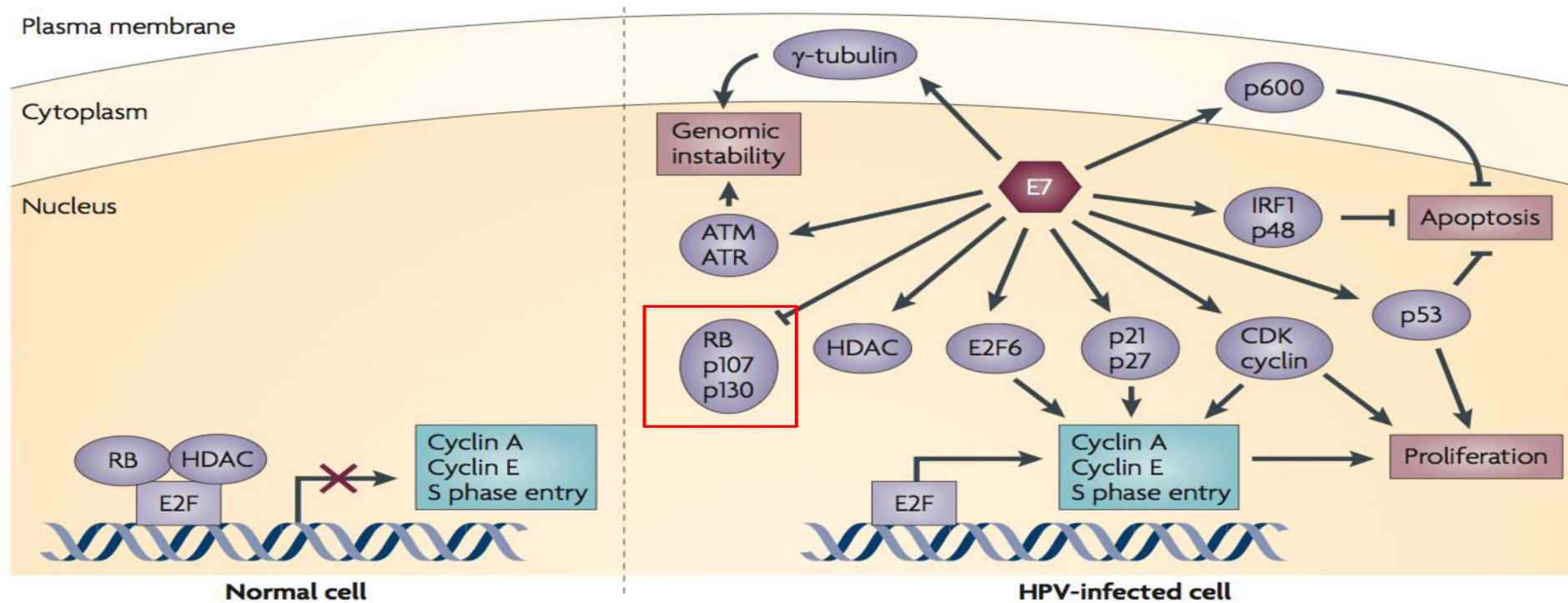
HPV carcinogenesis

Molecular Mechanisms Involved in HPV Carcinogenesis



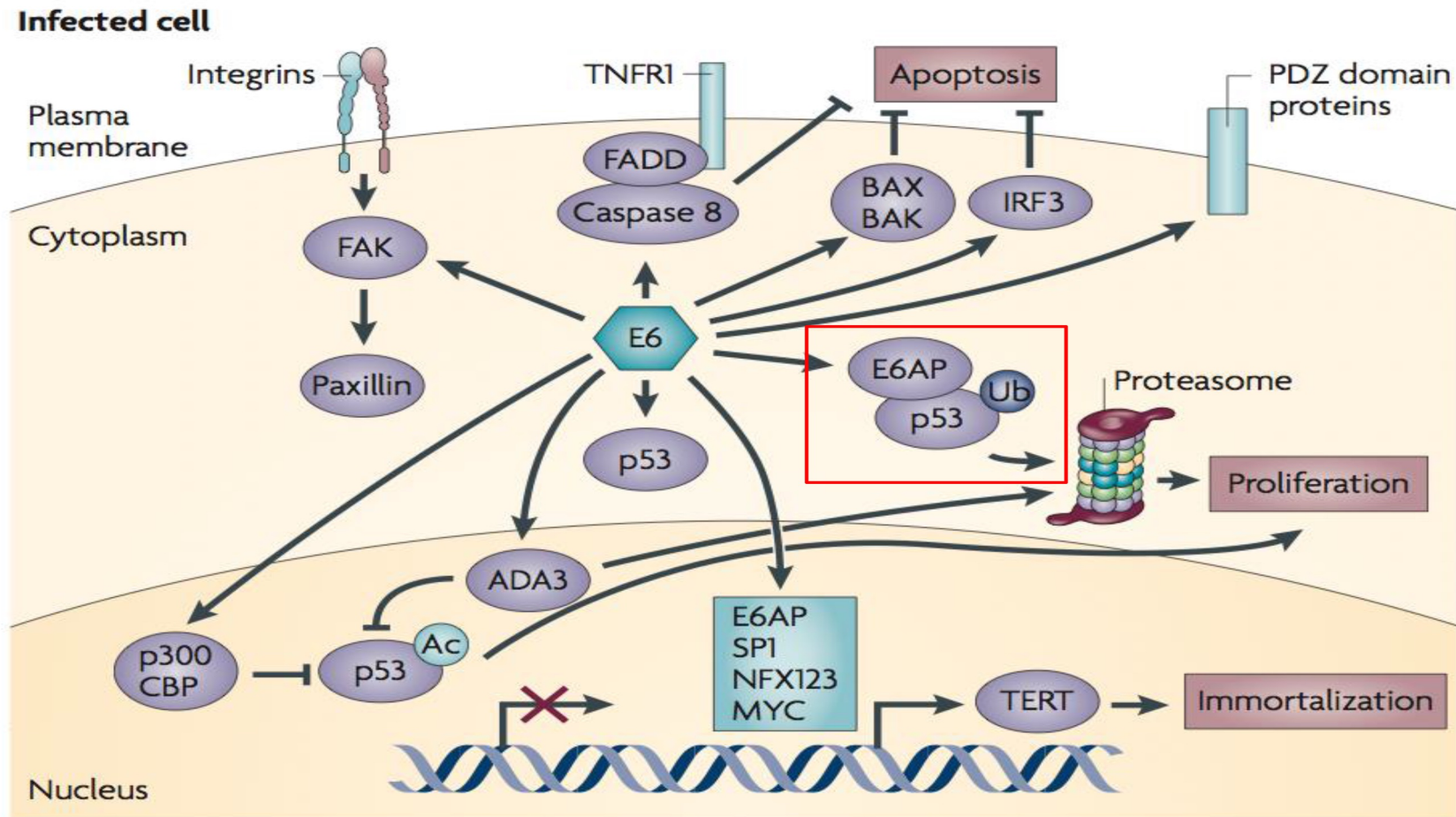
Cellular proteins

Cellular Proteins and Pathways Affected by HPV E7



HPV pathways

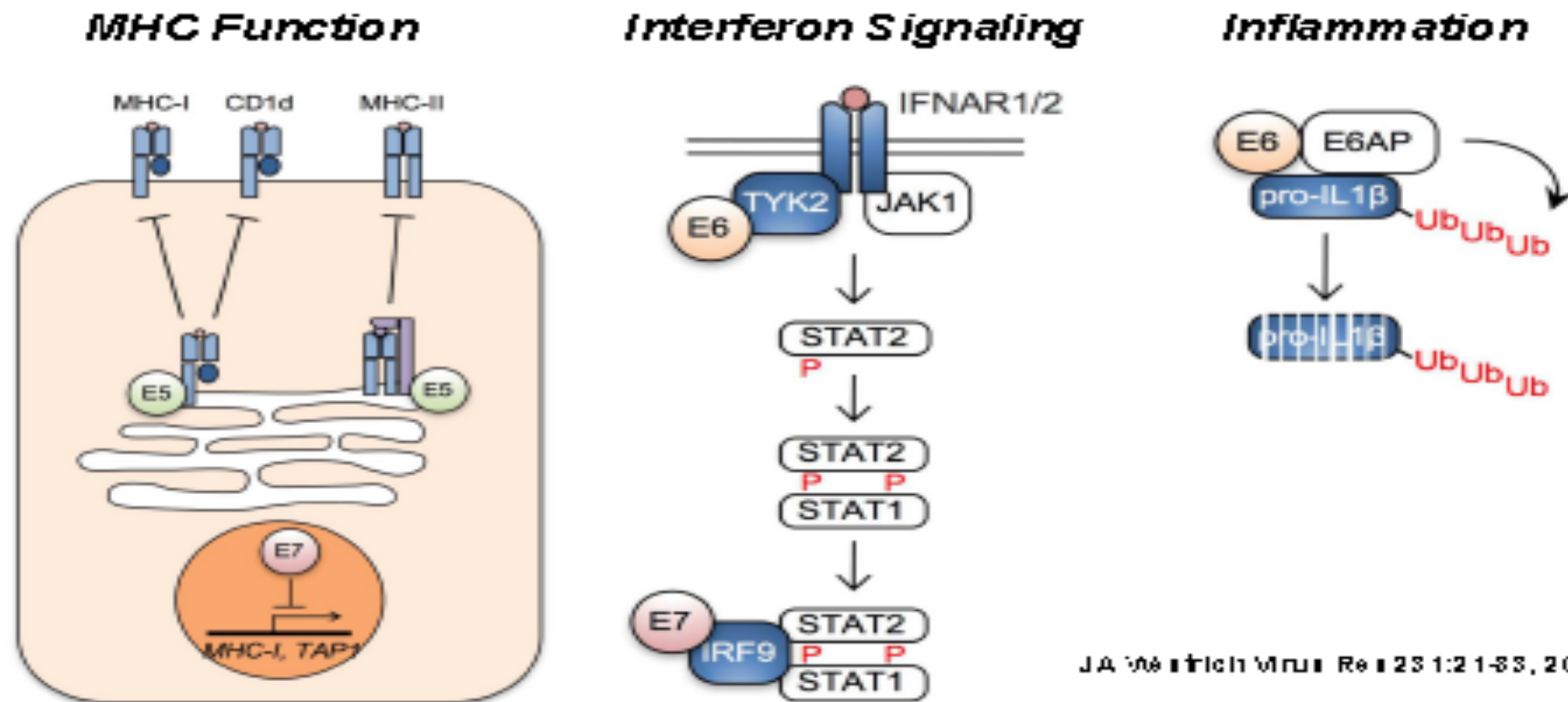
Cellular Proteins and Pathways Affected by HPV E6



HPV oncoproteins

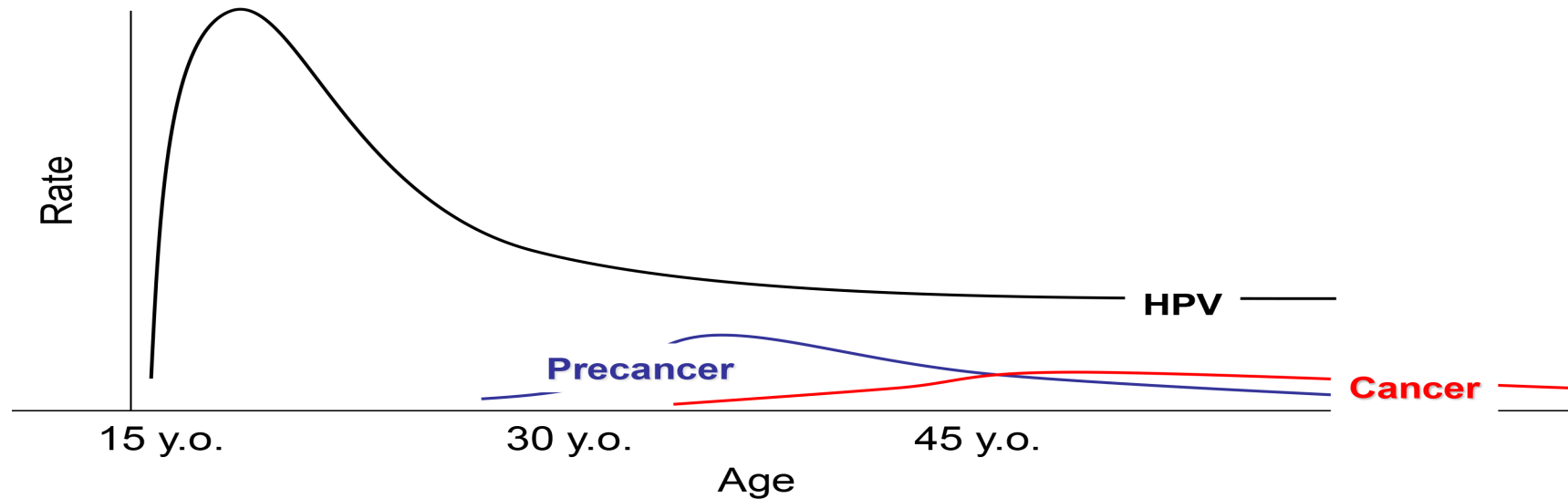
HPV Oncoproteins Also Inhibit Immune Responses

Promotes virus persistence



HPV infection time line

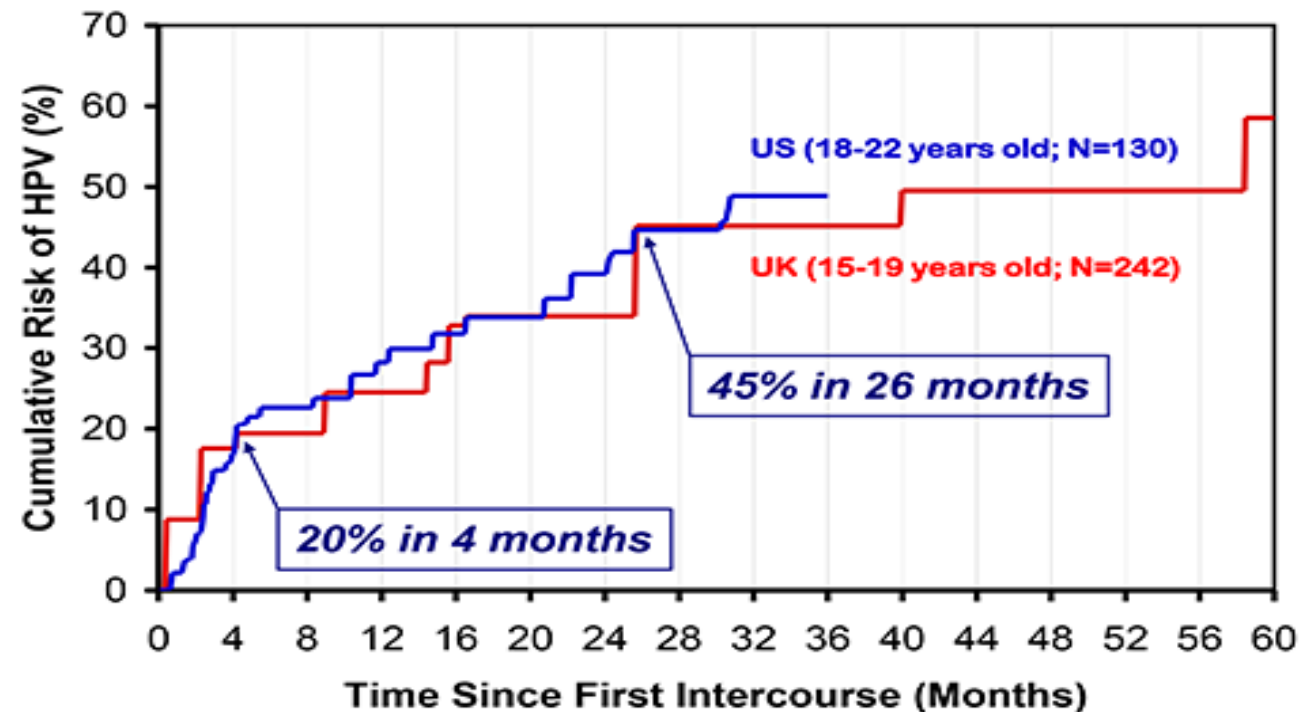
Time Line of Cervical HPV Infections And Progression to Cervical Cancer



- **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.**

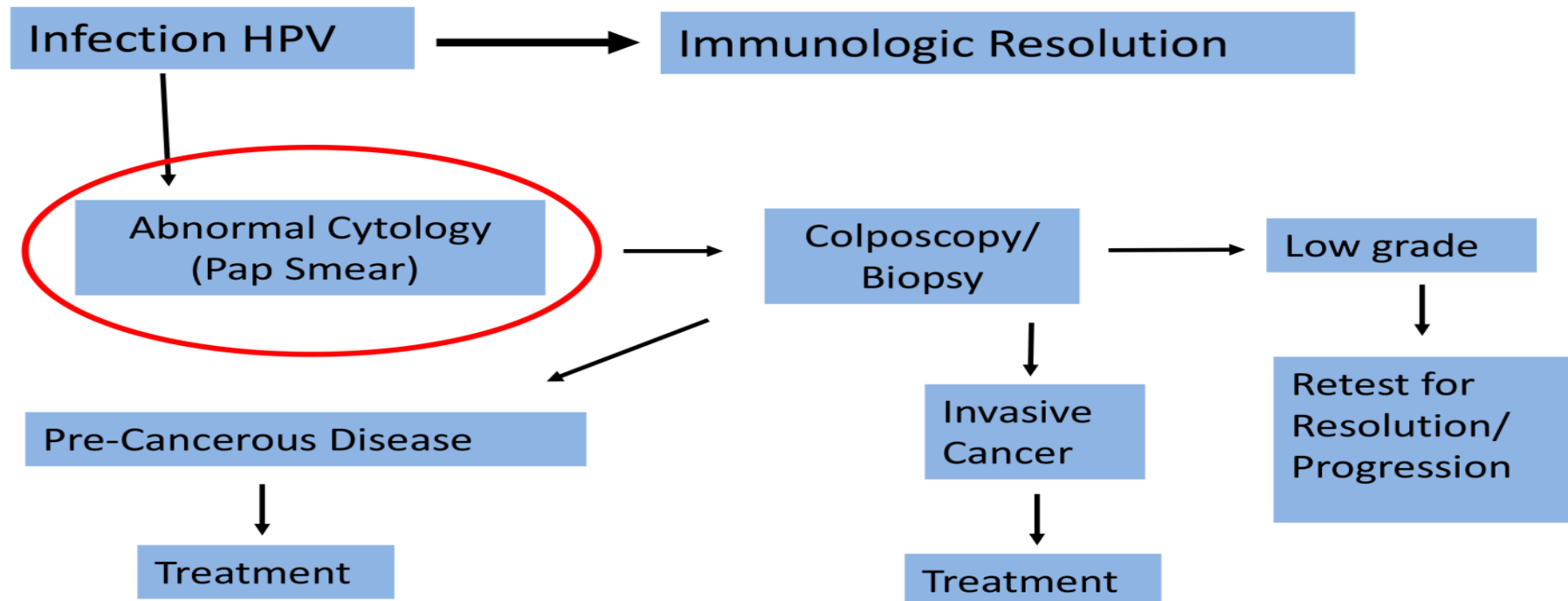
HPV infection

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



Pap screening

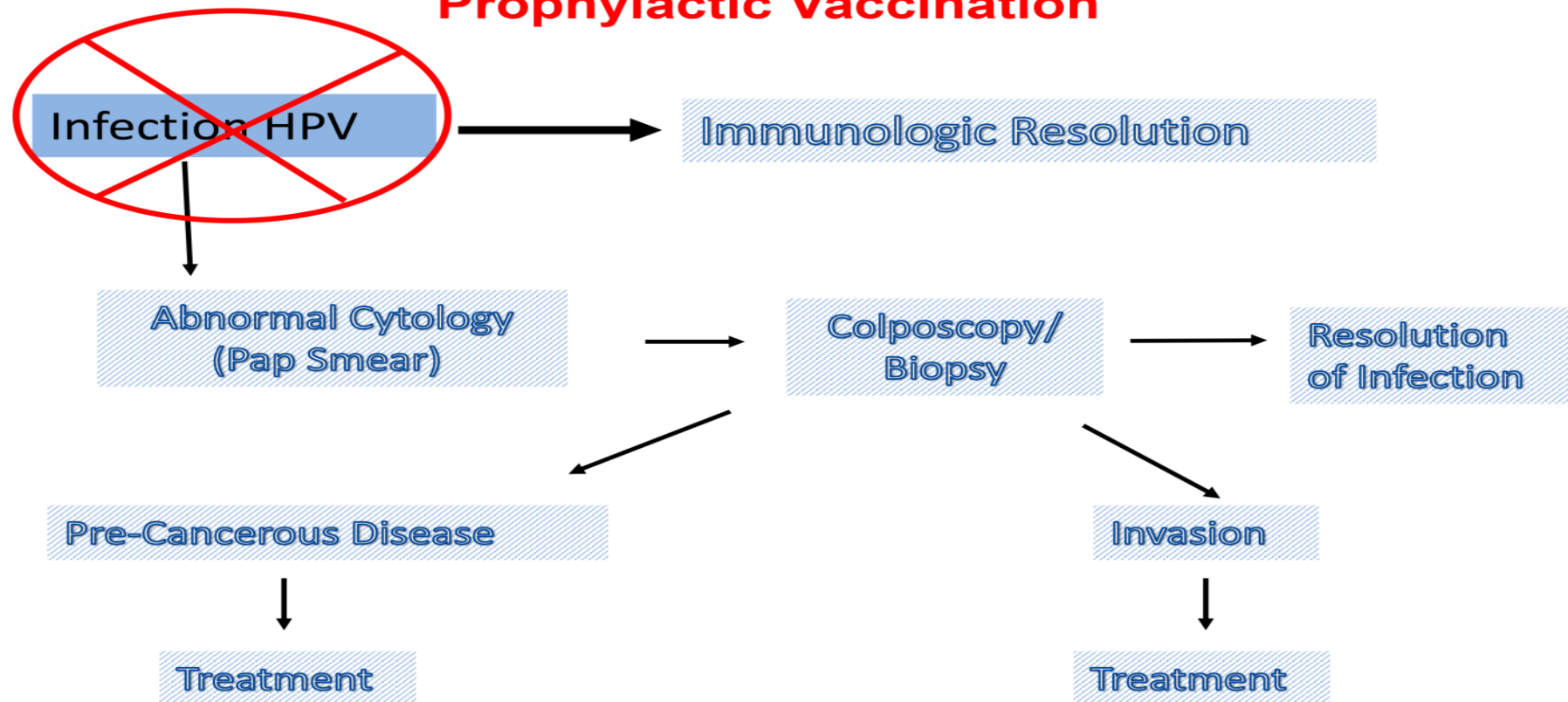
Current Pap Screening Is “Secondary” Prevention of Cervical Cancer



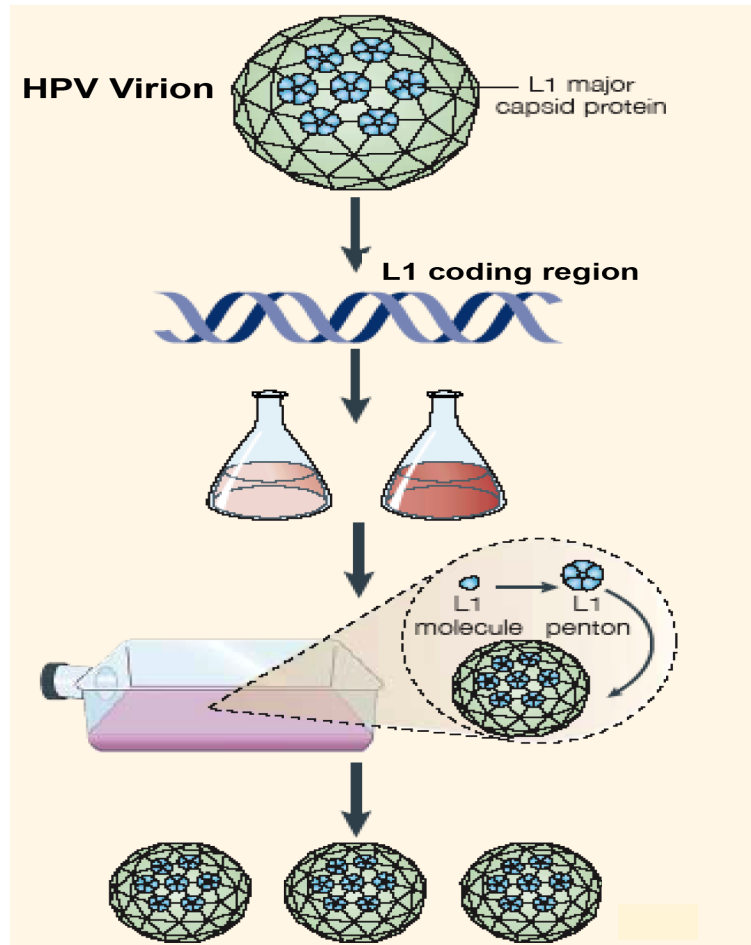
Primary prevention

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

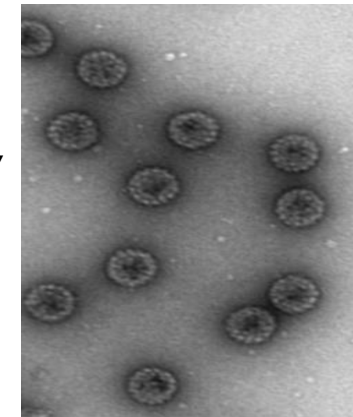
Production in Insect Cells

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

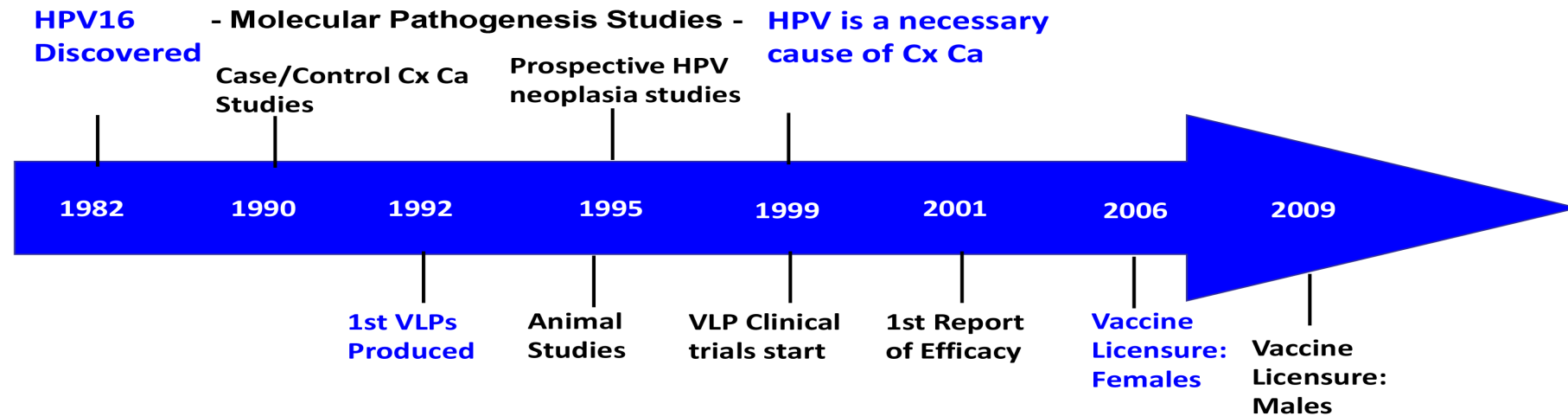
Name	Producer	VLP Types	Adjuvant	Production	Licensed
Cervarix	GSK	16,18	AS04*	Insect Cells	2007
Gardasil	Merck	16,18, 6,11	Alum	Yeast	2006
Gardasil-9	Merck	16,18,31, 33,45,52,58 6,11	Alum	Yeast	2014

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



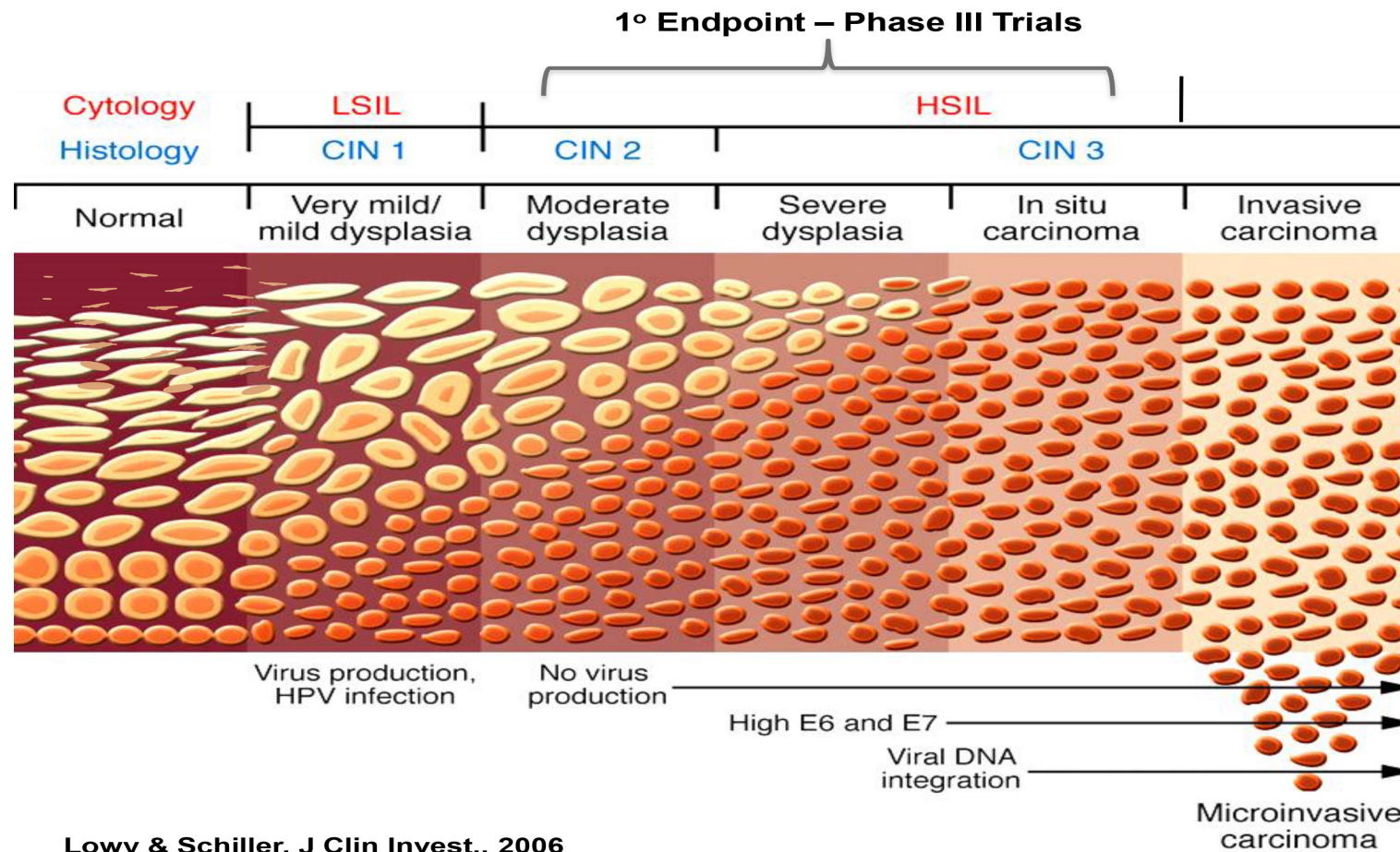
COVID timeline

The Time Line for Developing COVID Vaccines Was Much Shorter!

- **Key antigens for inducing neutralizing antibodies had been identified for other coronaviruses.**
- **Rapid vaccine develop platforms, e.g mRNA and viral vectors, were available.**
- **COVID 19 was plugged into existing pipelines.**
- **Massive public and private financial support.**
- **Pivotal trials for licensure relatively short.**

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)

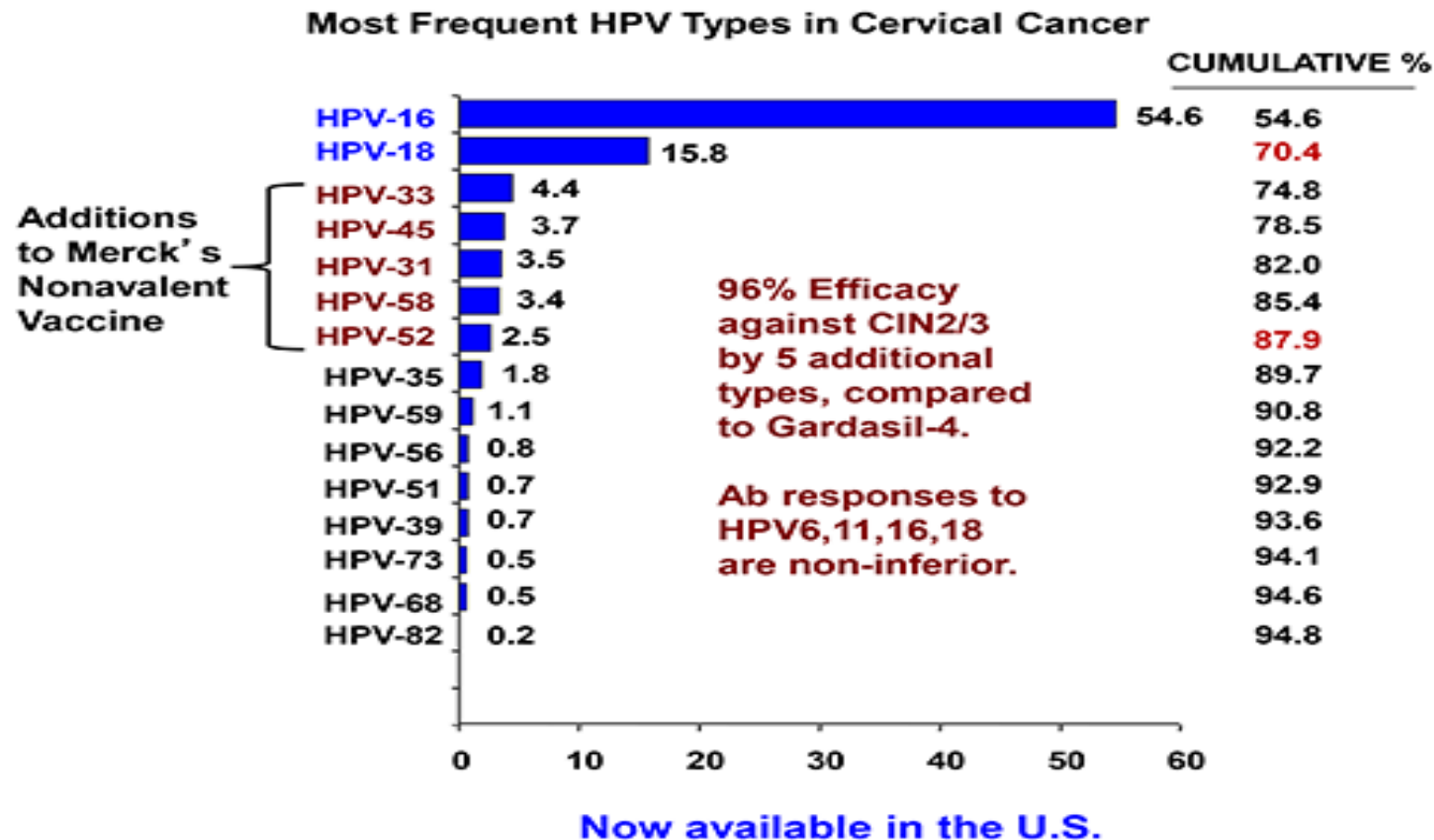
Data from Lehtinen Lancet Oncol 2011; Munoz JNCI 2010; Palefsky NEJM 2011; Giuliano NEJM 2011

CIN III: Cervical Intraepithelial Neoplasia Grade 3

AIN: Anal Intraepithelial Neoplasia of any grade

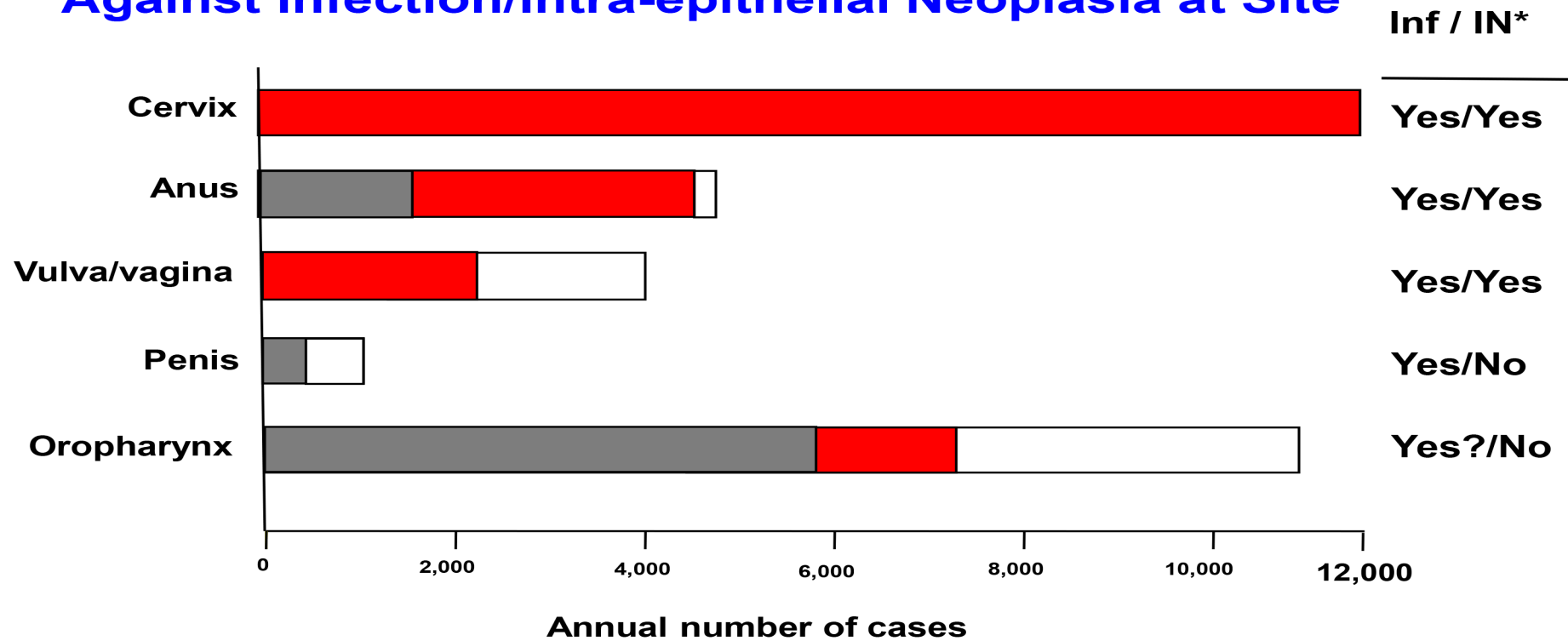
Gardasil-9

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



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.**

HPV vaccineGlobal HPV 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 vaccines

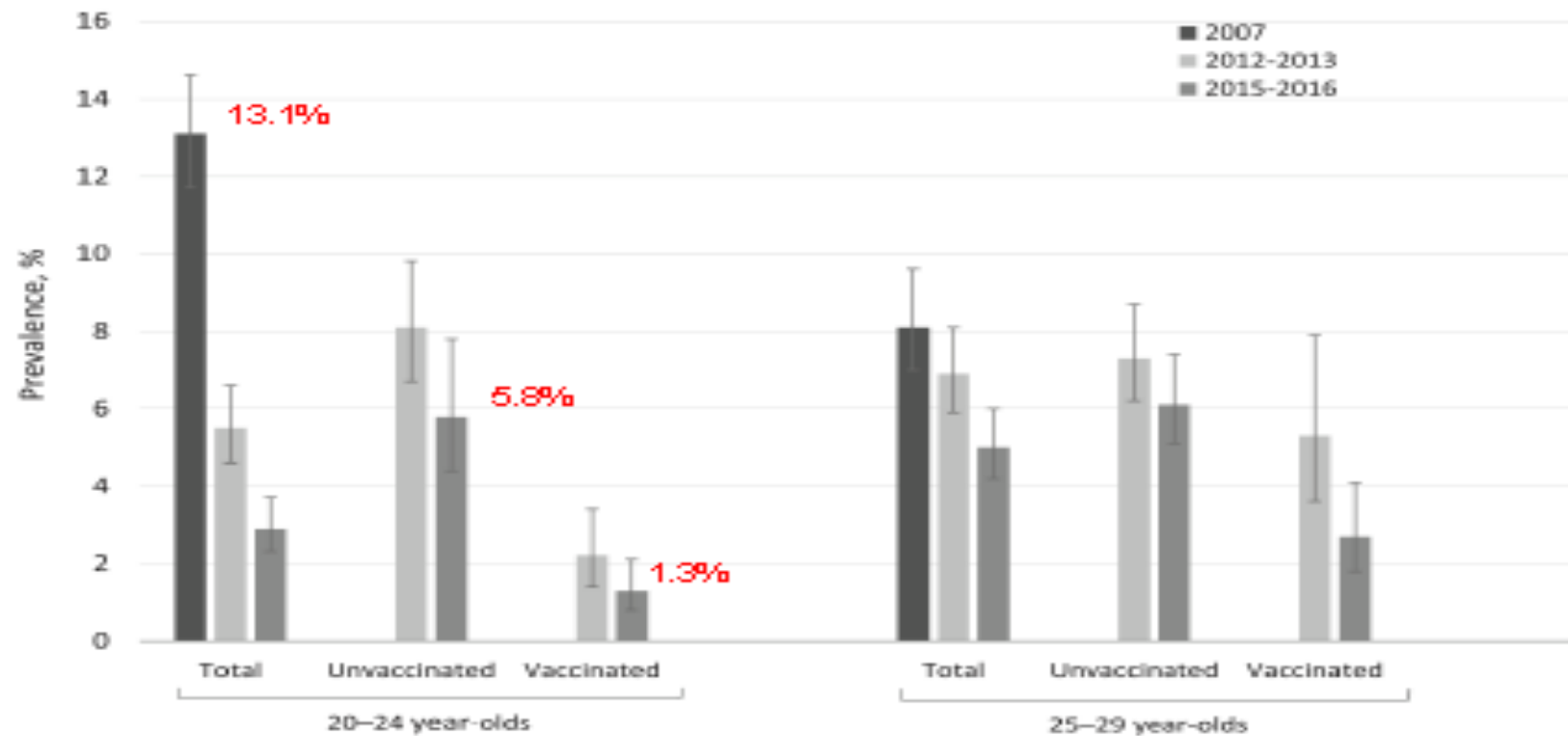
HPV Vaccines Are Now Established Products

- **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.**

HPV prevalence

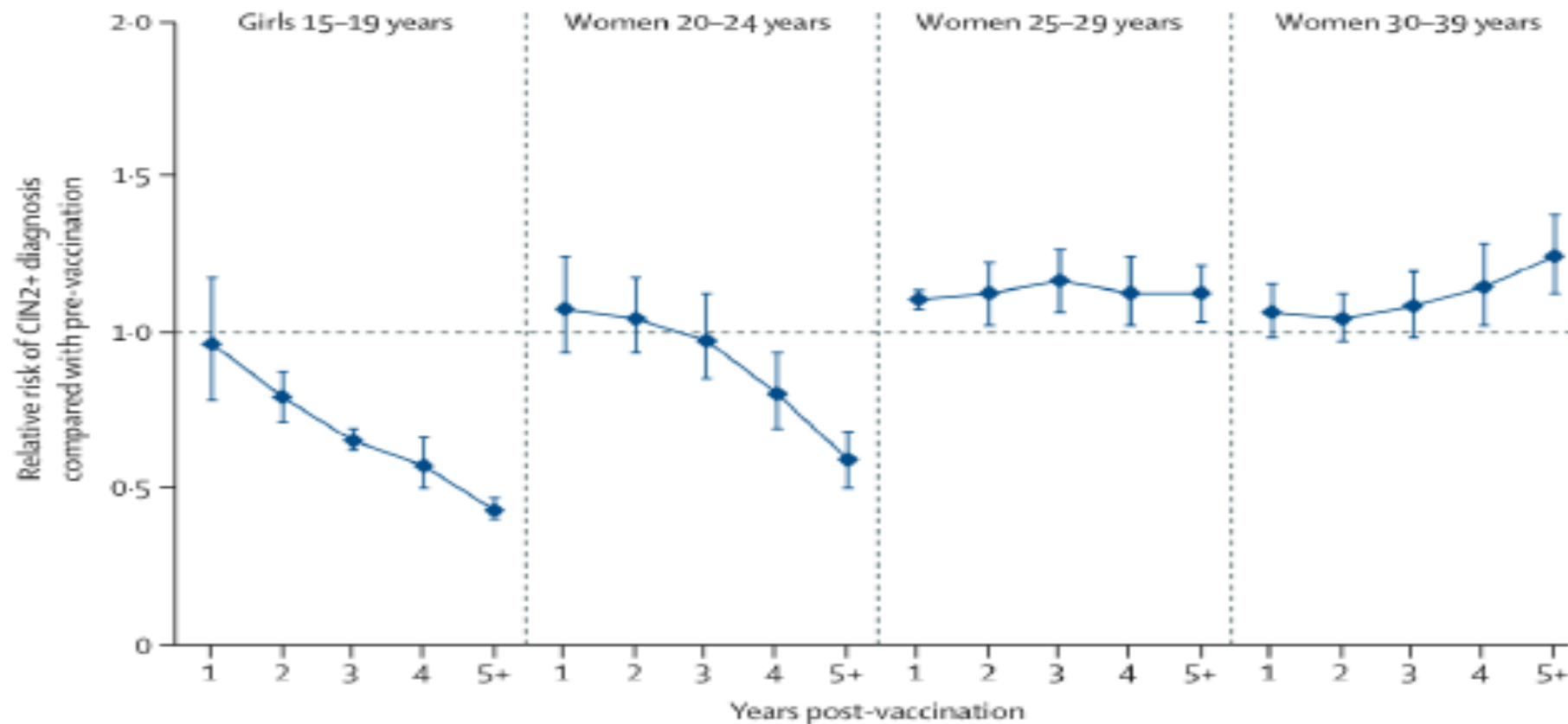
Vaccine Type HPV Prevalence in U.S. Women Receiving at Least One Vaccine Dose

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



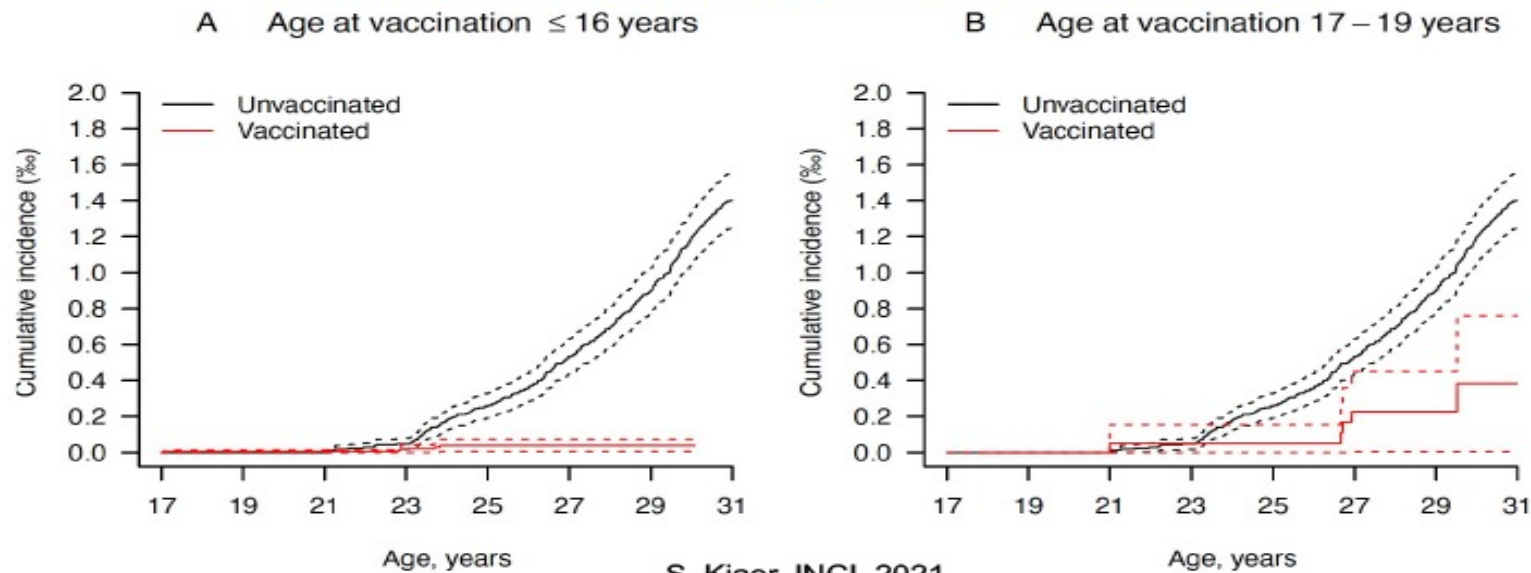
Cin2+ changes

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



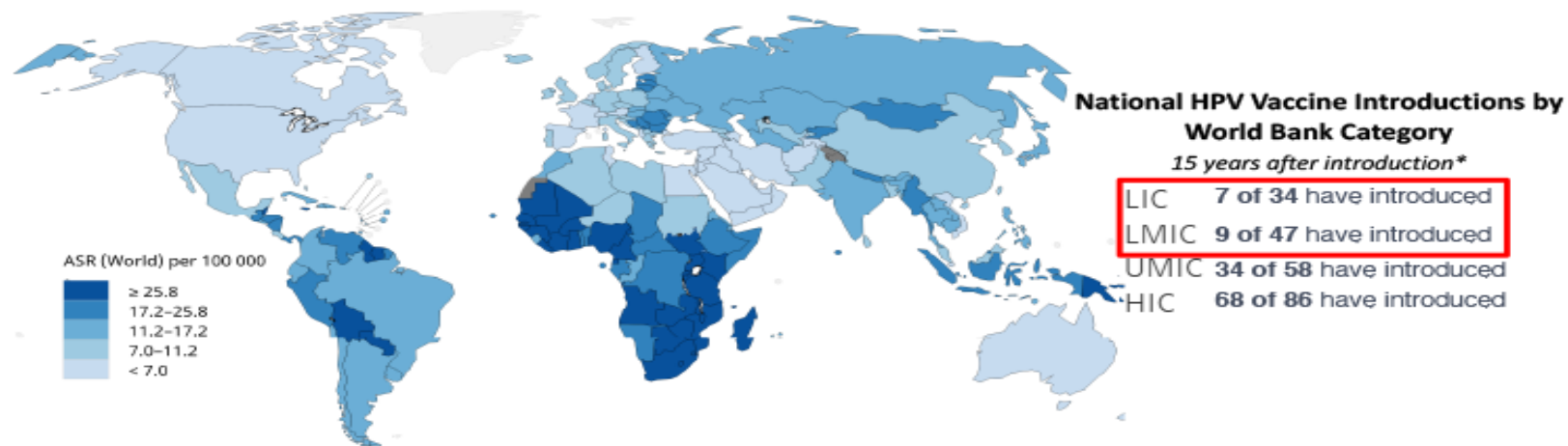
Cervical cancer incidence by age

Decreased Cervical Cancer Incidence in Danish Women By Age When They Received the HPV Vaccine



Global cervical cancer incidence

Global Cervical Cancer Incidence *“A Story of Inequality”*



Worldwide coverage peaked at 15% in 2019

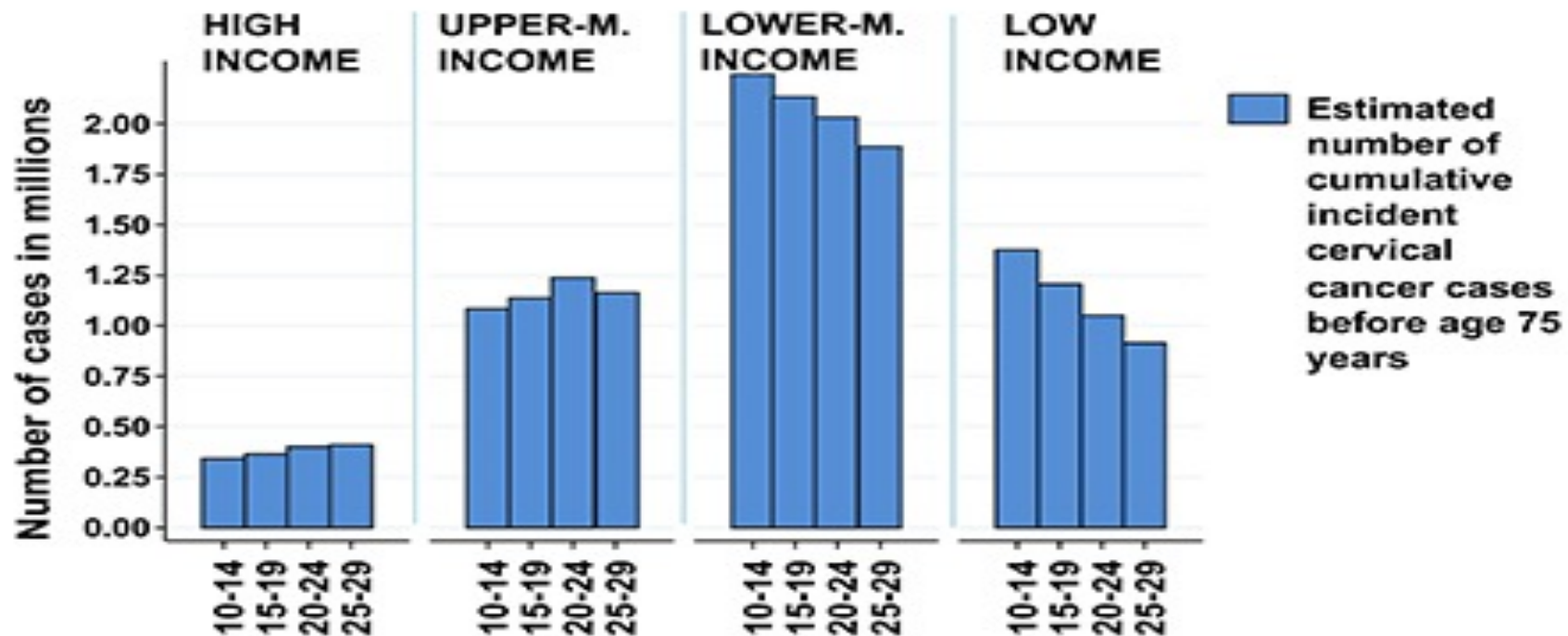
Vaccine coverage in 10-20 yr females <3% in LMICs vs 34% in HICs.

**Introduction not always synonymous with nationwide-implementation*

Non-vaccine scenario

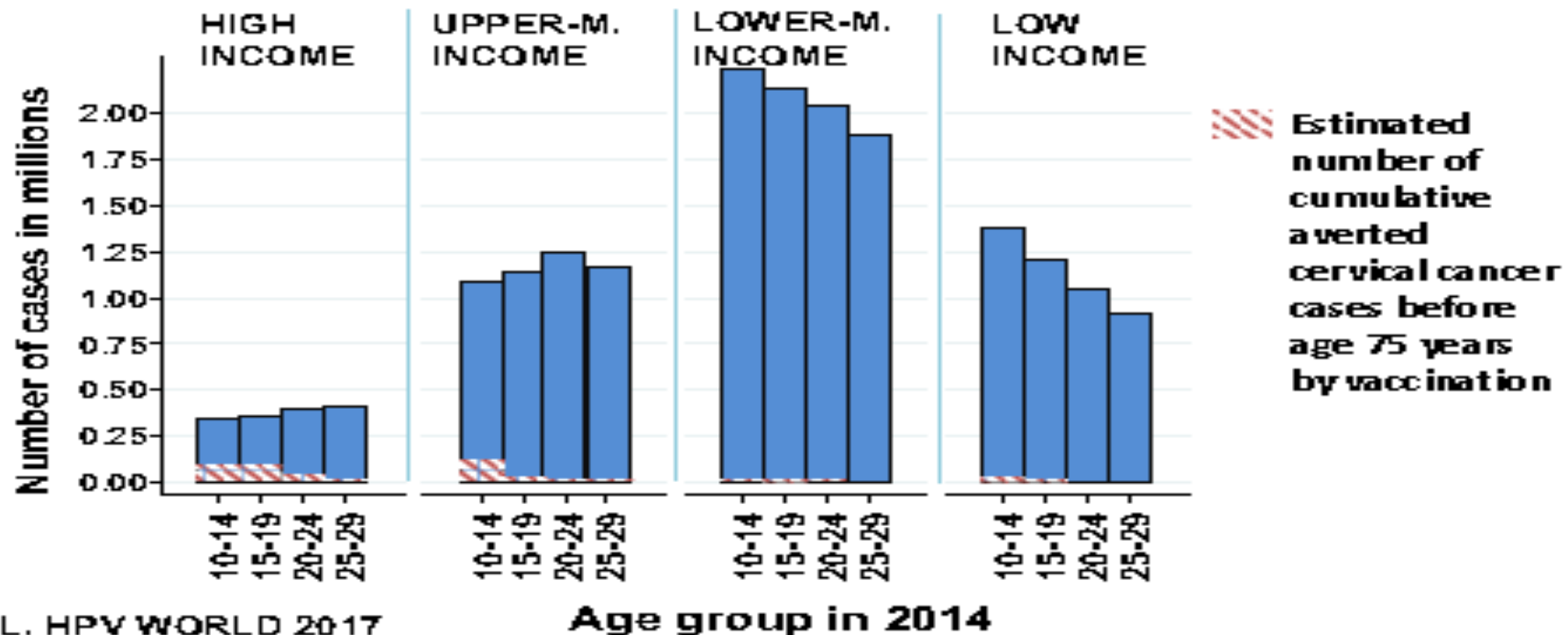
Non-Vaccine Scenario: 19 Million Cases and 10 Million Deaths From Cervical Cancer

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 → 2020

	<u>Complete series*</u>	<u>At least one dose</u>
Girls:	57% → 61%	73% → 77%
Boys:	52% → 56%	70% → 73%

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

Surprisingly little COVID 19 effect!

\$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

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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)	inactivated						
2	Wondr	HPV-4 (6, 11, 16, 18)	recom (S. cerevisiae)						
3	Wondr	HPV-9 (6, 11, 16, 18, 21, 20, 45, 52, 58)	recom (S. cerevisiae)						
4	Innovo	HPV-2 (16, 18)	ECOL						
5	Sanofi	HPV-2 (16, 18)	recom (P. pastoris)						
6	ChIBG/COIBP	HPV-4 (6, 11, 16, 18)	recom (H. polymorpha)						
7	Innovo	HPV-2 (6, 11)	ECOL						
8	Kangleweibin	HPV-2 (16, 18, 58)	ECOL						
9	Boya	HPV-4 (6, 11, 16, 18)	recom (H. polymorpha)						
10	Boya	HPV-9 (6, 11, 16, 18, 21, 20, 45, 52, 58)	recom (H. polymorpha)						
11	Sanofi	HPV-9 (6, 11, 16, 18, 21, 20, 45, 52, 58)	recom (P. pastoris)						
12	Innovo	HPV-9 (6, 11, 16, 18, 21, 20, 45, 52, 58)	ECOL						
13	ChIBG/COIBP	HPV-4 (6, 16, 52, 58)	recom (P. pastoris)						
14	Kangleweibin	HPV-9 (6, 11, 16, 18, 21, 20, 45, 52, 58)	ECOL						
15	Longou Ruithe	HPV-9 (6, 11, 16, 18, 21, 20, 45, 52, 58)	recom (H. polymorpha)						
16	ChIBG/COIBP	HPV-11 (6, 11, 16, 18, 21, 20, 45, 52, 58, 59, 62)	recom (H. polymorpha)						
17	Huanglei	HPV-14 (6, 11, 16, 18, 21, 20, 26, 29, 45, 51, 52, 56, 59, 62)	inactivated						



Early stage



Late stage

Data source: NMPA data, clinicaltrials.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.**
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- **Transition to single dose vaccination programs.**

Single dose

Increasing Uptake, Particularly in Low Resource Settings

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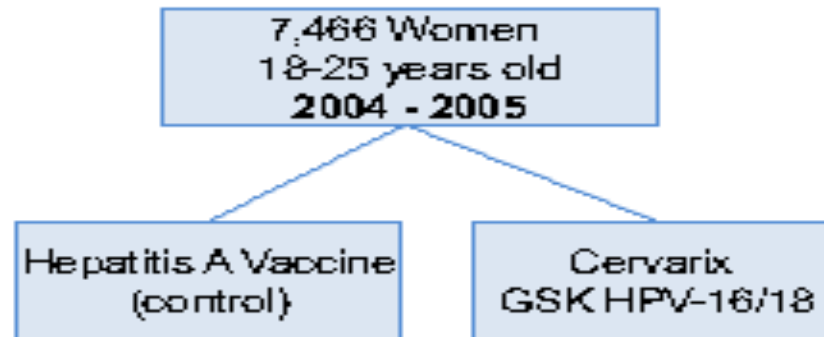
Single dose

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



Protection after 1,2, or 3 doses of Cervarix

Protection After 1, 2 or 3 Doses of Cervarix Through 11 Years, Costa Rica Vaccine Trial

Post-hoc analysis of RCT: women vaccinated at age 18–25 years randomized to receive 3 doses of 2vHPV or control but not all completed series

Doses	Number	Prevalent 16/18 HPV % (95% CI)	Vaccine efficacy % (95% CI)
3 doses	1365	2.0 (1.3–2.8)	80.0% (70.7–87.0)
2 doses	62	1.6 (0.1–7.7)	83.8% (19.5–99.2)
1 dose	112	1.8 (0.3–5.8)	82.1% (40.2–97.0)
Control	1783	10.0 (8.7–11.4)	Reference

Protection after 1,2 or 3 doses of Gardasil-4

Protection After 1, 2 or 3 Doses of Gardasil-4 Through 10 years, India IARC Trial

Doses	Number	Incident 16/18 HPV % (95% CI)	Persistent 16/18 HPV % (95% CI)	VE against persistent infection % (95% CI)
3 doses	1649	3.0 (2.3-3.8)	0.1 (0.0 – 0.4)	91.2% (75.3 – 98.7)
2 doses (0, 6 months)	1685	2.6 (2.0-3.3)	0.1 (0.0 – 0.4)	94.5% (82.4 – 99.8)
1 dose	2454	3.1 (2.6-3.8)	0.0 (0.0 – 0.3)	94.2% (83.7 – 99.1)
Control	1268	9.7 (8.2-11.3)	2.7 (1.9 – 3.7)	Reference

Post-hoc analysis; women vaccinated at age 10-18 years, randomized to receive 3 or 2 4vHPV doses

Unvaccinated women age-matched to married vaccinated participants recruited as controls

Persistent infection defined as the same HPV type detected in consecutive samples at least 10 months apart

VE adjusted for background HPV infection frequency, time between date of marriage and first cervical specimen collection, and number of cervical specimens per participant

Basu et al, Lancet Oncology Oct 2021 with updated data presented to SAGE WG

Confidential; unpublished data

Single dose trial

KEN-SHE Single Dose Trial

- Randomized trial of 1 dose of 9vHPV or 2vHPV or meningococcal vaccine
 - 2250 Kenyan women aged 15–20 years; 1-5 lifetime partners; HIV negative
- 1458 girls evaluated for efficacy at **month 18** in mITT HPV 16/18 cohort

Study arm	Number	Incident persistent HPV 16/18	Incidence/ 100 PY	VE % (95% CI)
Gardasil-9	496	1	0.17	97.5% (81.7–99.7)
Cervarix	489	1	0.17	97.5% (81.6– 99.7)
MCV	473	36	6.83	Reference

Enrollment between December 2018 and June 2021

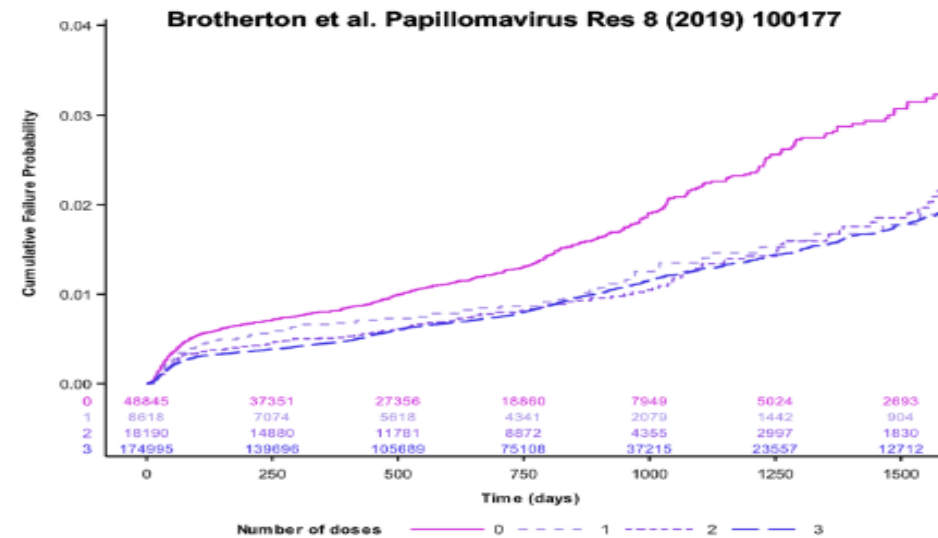
mITT, modified intention to treat: HPV 16/18 HPV DNA negative (external genital and cervical swabs) at enrollment and month 3 (self-collected vaginal swab) and HPV antibody negative at enrollment

Barnabas R, et al., 2022, DOI [10.21203/rs.3.rs-1090565/v1](https://doi.org/10.21203/rs.3.rs-1090565/v1)

National vaccination programs

Evidence From National Vaccination Programs

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



WHO decision

An April, 2022 Landmark Decision by the WHO



One-dose Human Papillomavirus (HPV) vaccine offers solid protection against cervical cancer

SAGE recommends updating dose schedules for HPV as follows:

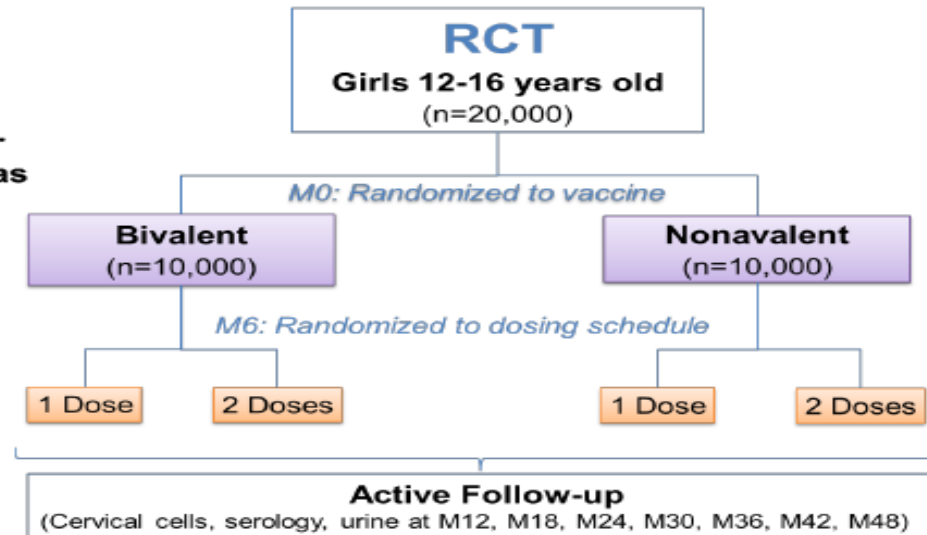
- **one or two-dose schedule** for the primary target of girls aged **9-14**
- **one or two-dose schedule** for young women aged **15-20**
- Two doses with a 6-month interval for women **older than 21**.

Immunocompromised individuals, including those with HIV, should receive three doses if feasible, and if not at least two doses. There is limited evidence regarding the efficacy of a single dose in this group.

One versus two doses

Formal Evaluation of One vs Two doses In Preventing New Cervical HPV16/18 Infections That Persist 6+ Months

 **proyecto
escudo**
NCI PI: Aimee Kreimer
C.R. PI: Carolina Porras

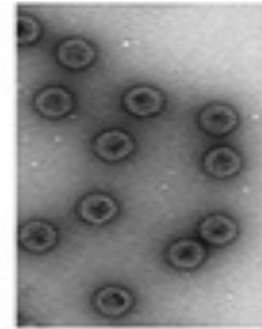


Goal: Convince skeptical public health officials to adopt one dose programs.

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***

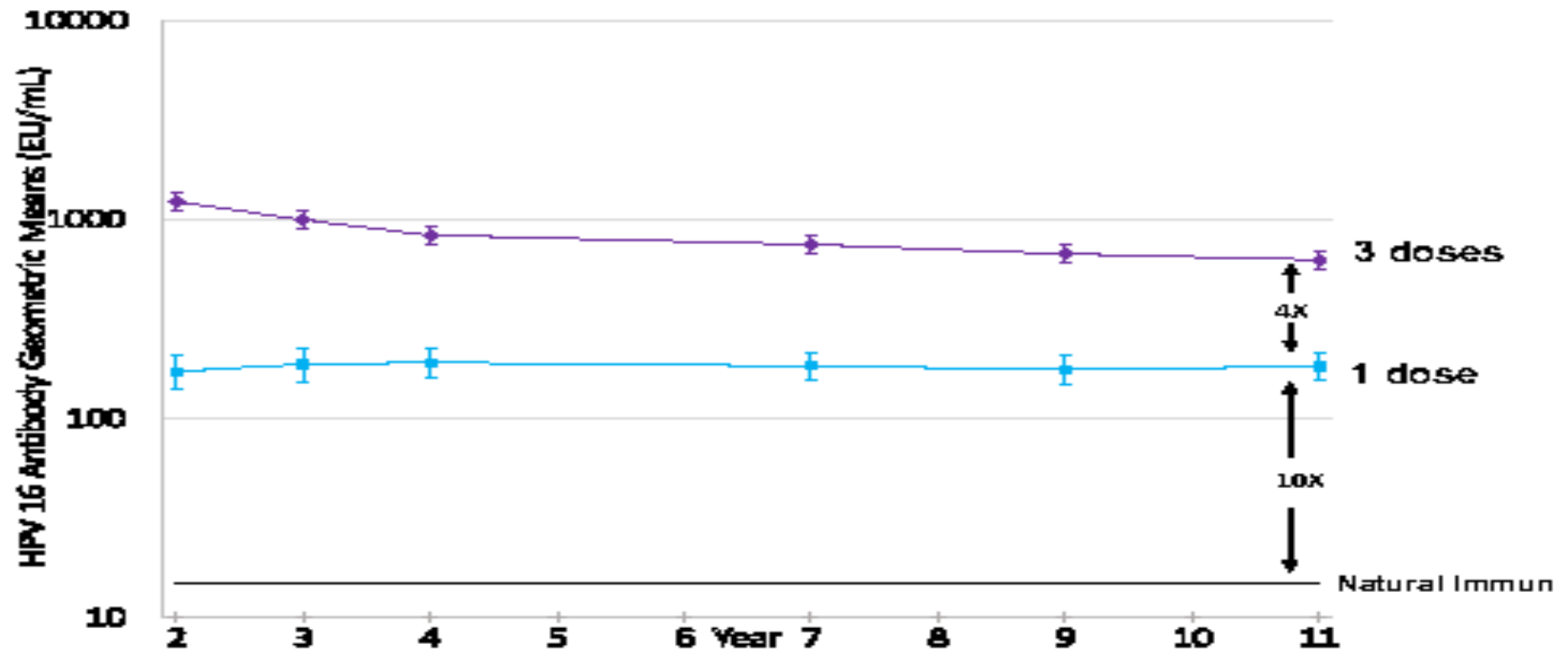
HPV6	99.8%
HPV11	99.8%
HPV16	99.8%
HPV18	99.5%

***4666 women vaccinated 3 times by intramuscular injection**

Stable HPV16 serum antibodies

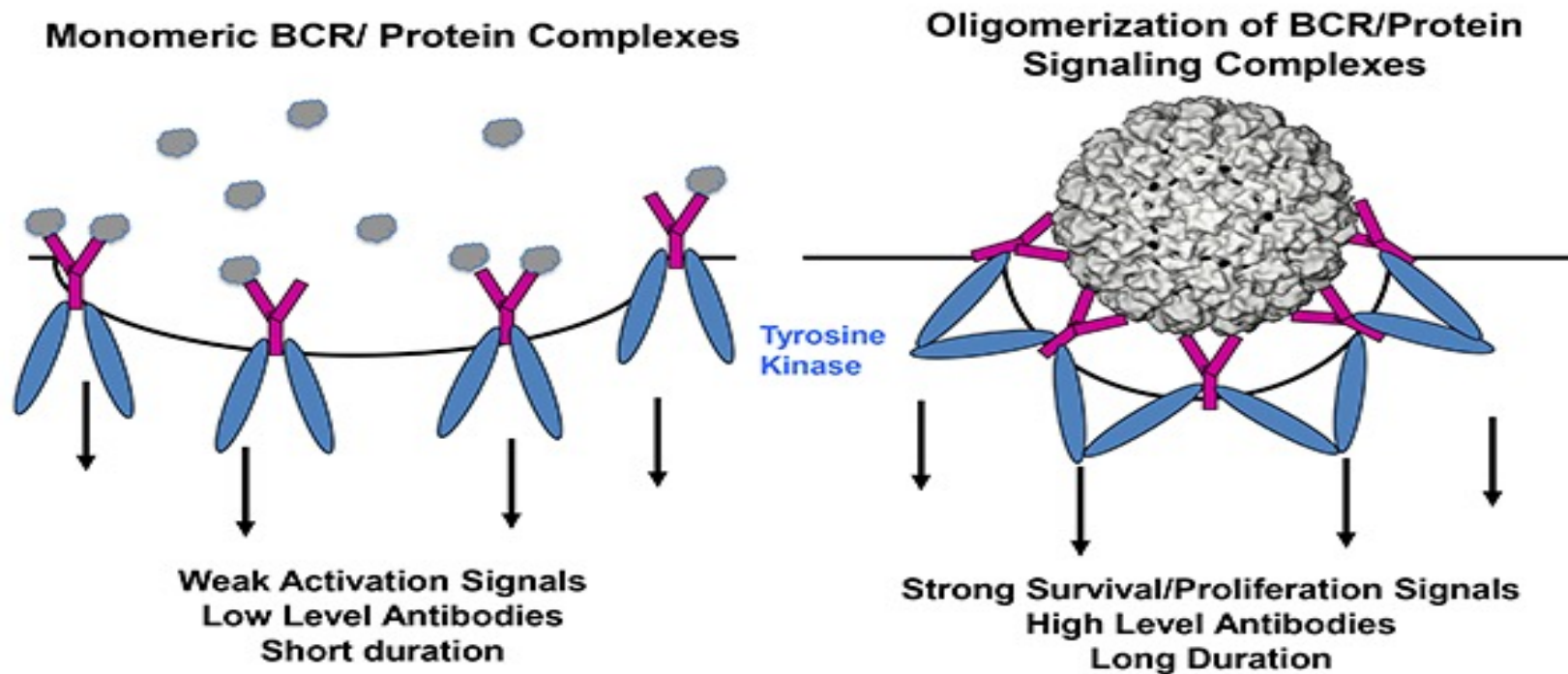
CVT: Stable HPV16 serum antibodies for 11 years

Results similar for HPV18



B cells recognize dense repetitive protein arrays

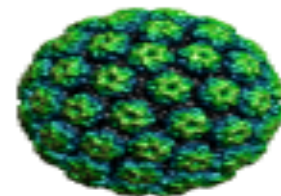
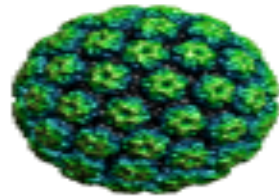
B Cells Recognize Dense Repetitive Protein Arrays as Dangerous Microbial Structures



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.

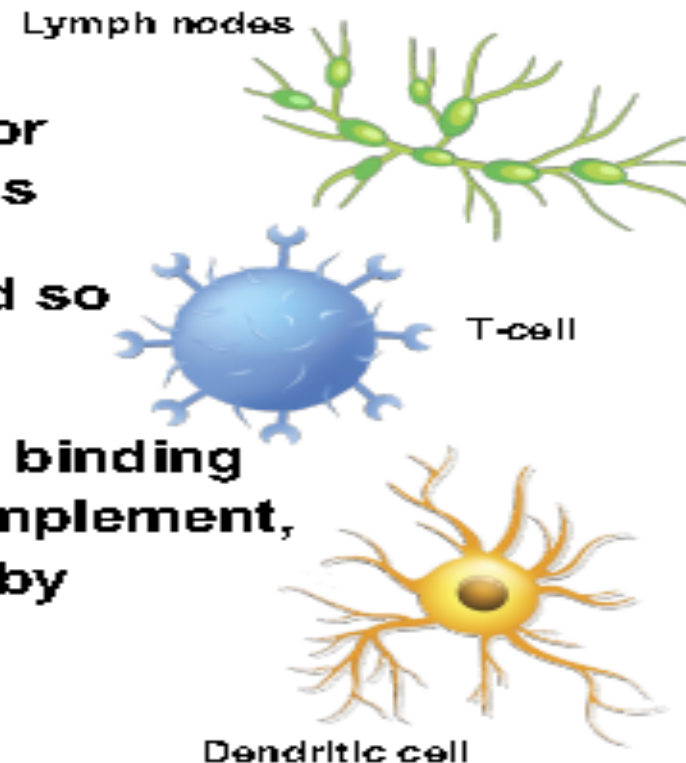
So BCRs have evolved as antigen specific pattern recognition receptors.

[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*



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

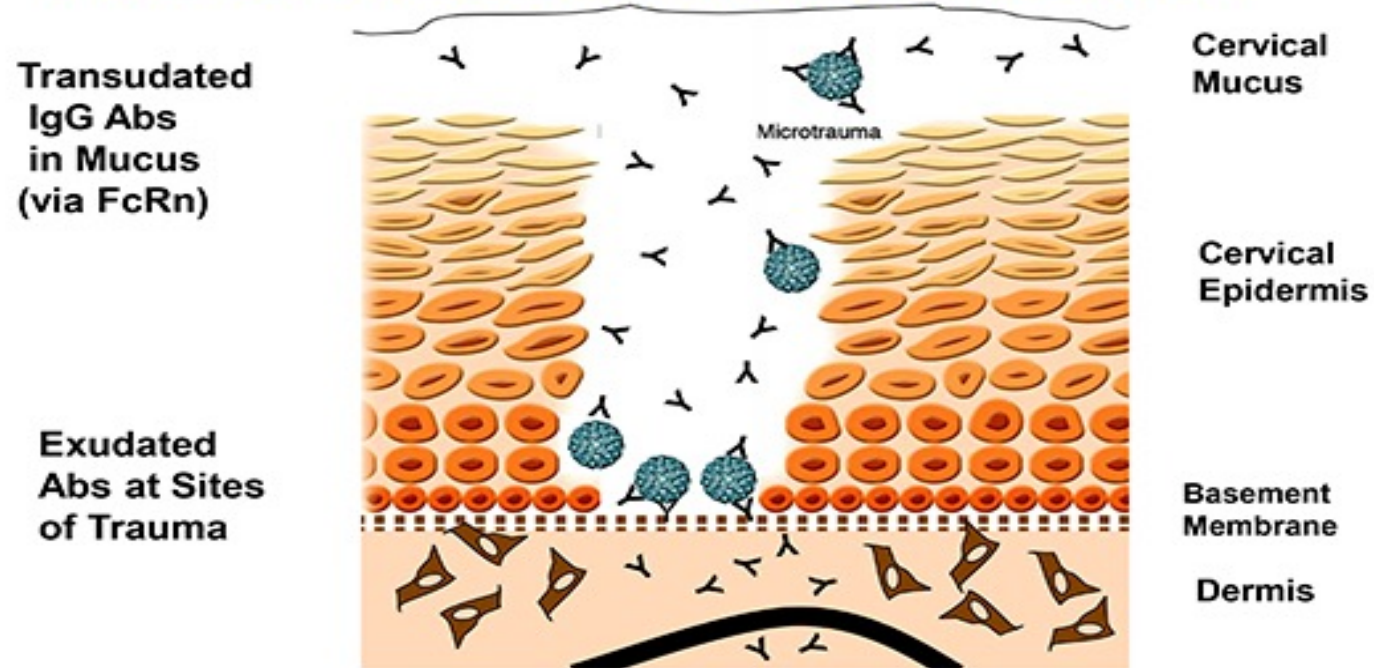


HSPG = Heparan Sulfate Proteoglycan

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

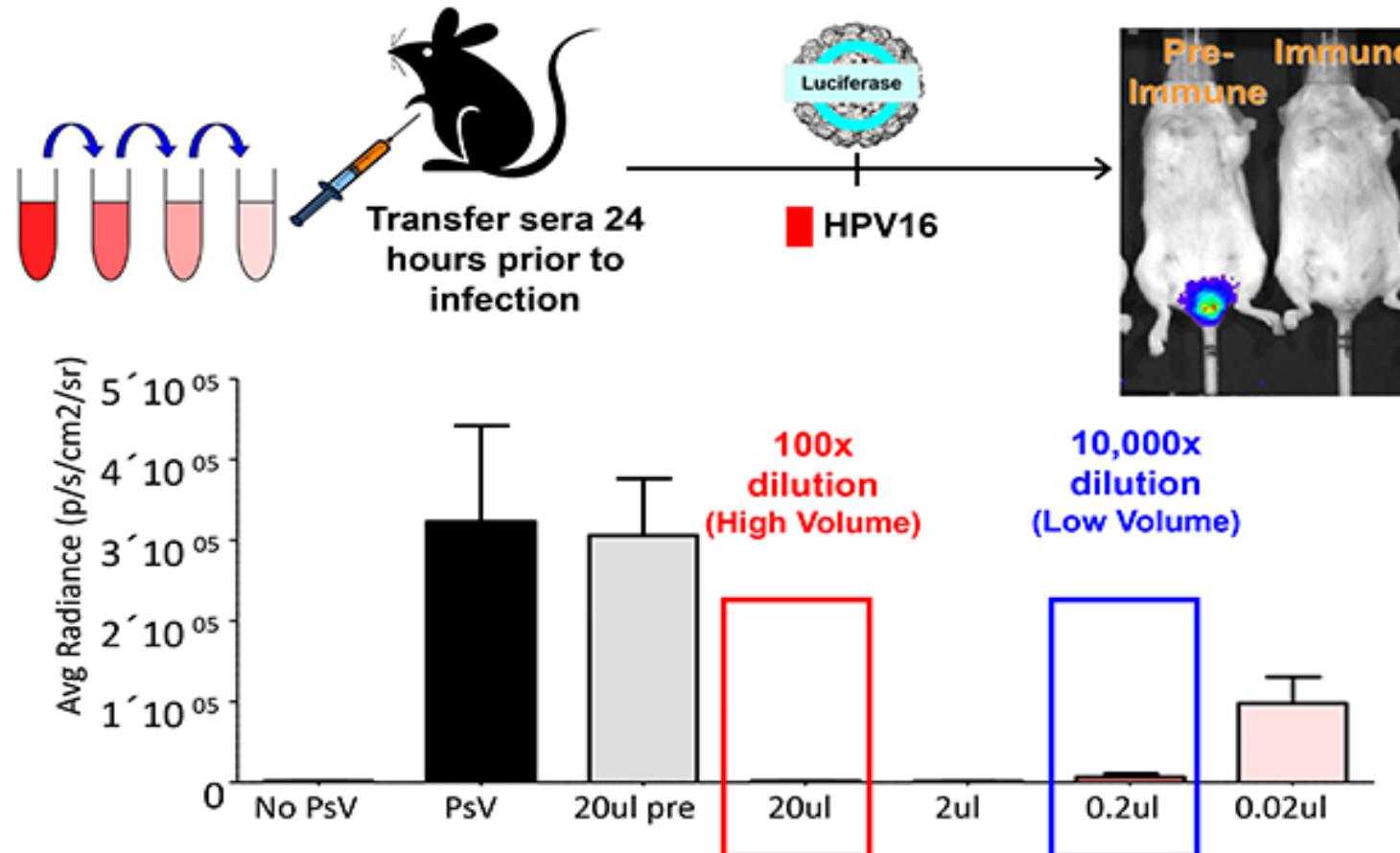
Antibody Titers and Protection

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

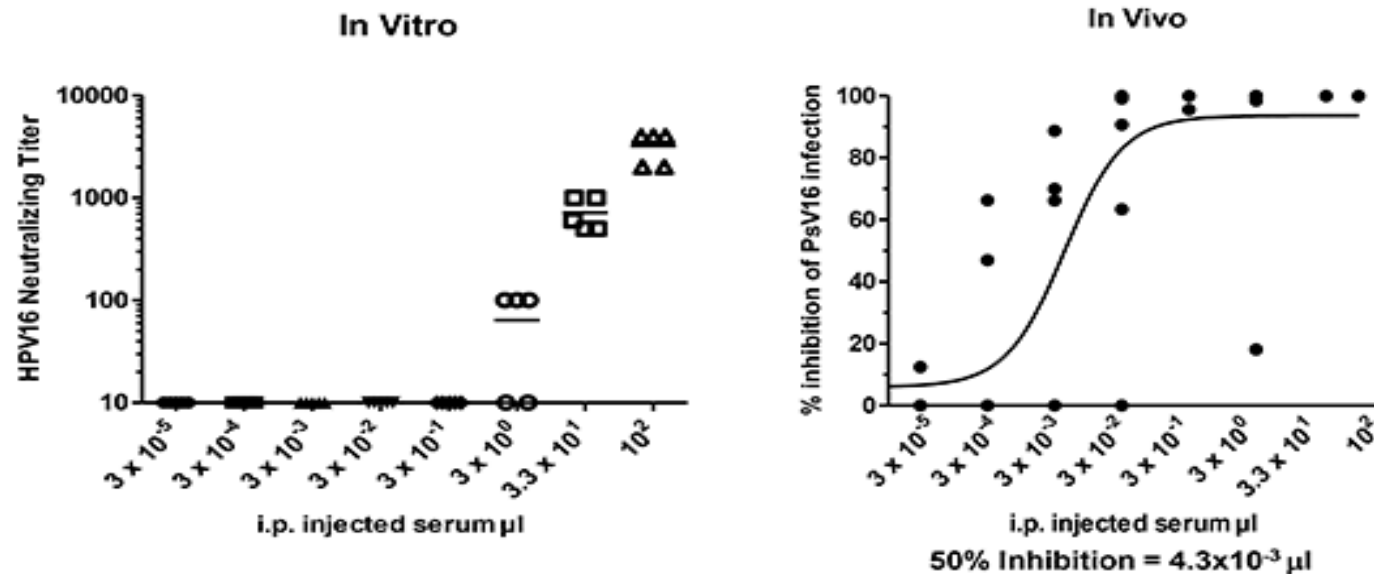
Passive Transfer of Rabbit Polyclonal Anti-16L1 VLP Sera



* 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

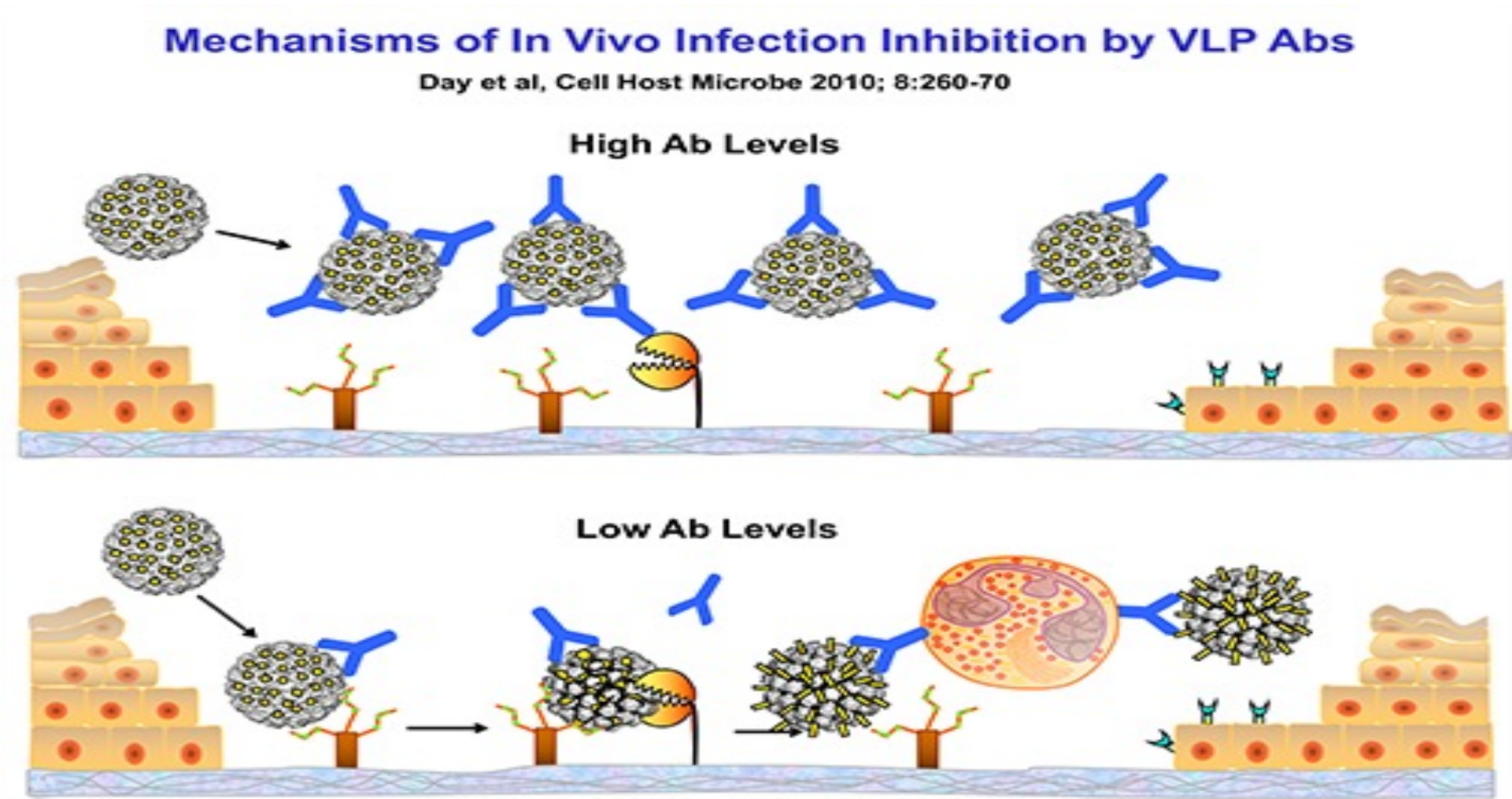


Protection detected with 500-fold less sera in vivo than in vitro!

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

Longet et al, J Virol 2011

Mechanisms of in vivo infection



Lessons for COVID-19 vaccines

Lessons For COVID-19 Vaccines?

Inducing sterilizing immunity will be much more difficult:

- **Covid directly infects the apical surface of upper respiratory tract epithelium.**
- **There is not extensive transudation of systemic IgG in the upper respiratory tract (although there is in the lung).**

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.**
- **Adoption of single dose vaccination could dramatically increase global uptake.**

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.

Global elimination of cervical cancer

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.”

“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

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