

Cervical Cancer

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

John Schiller, Center for Cancer Research, NCI



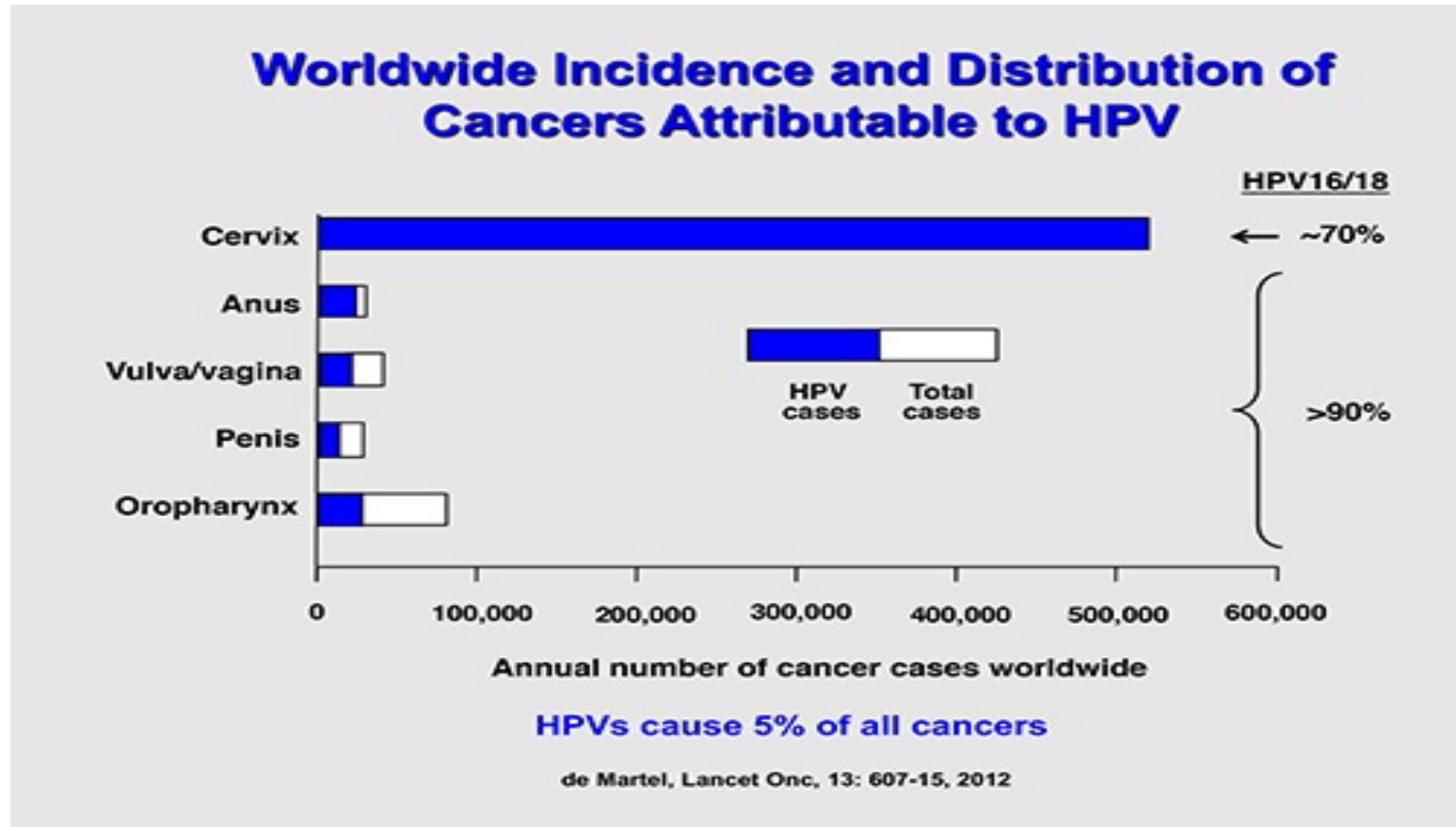
- HPV and Cancer
- Vaccine Efficacy/Effectiveness
- Key Implementation Issues
- Why they work so well

Annual Number of Cancer Cases Attributable To Specific Virus Infections

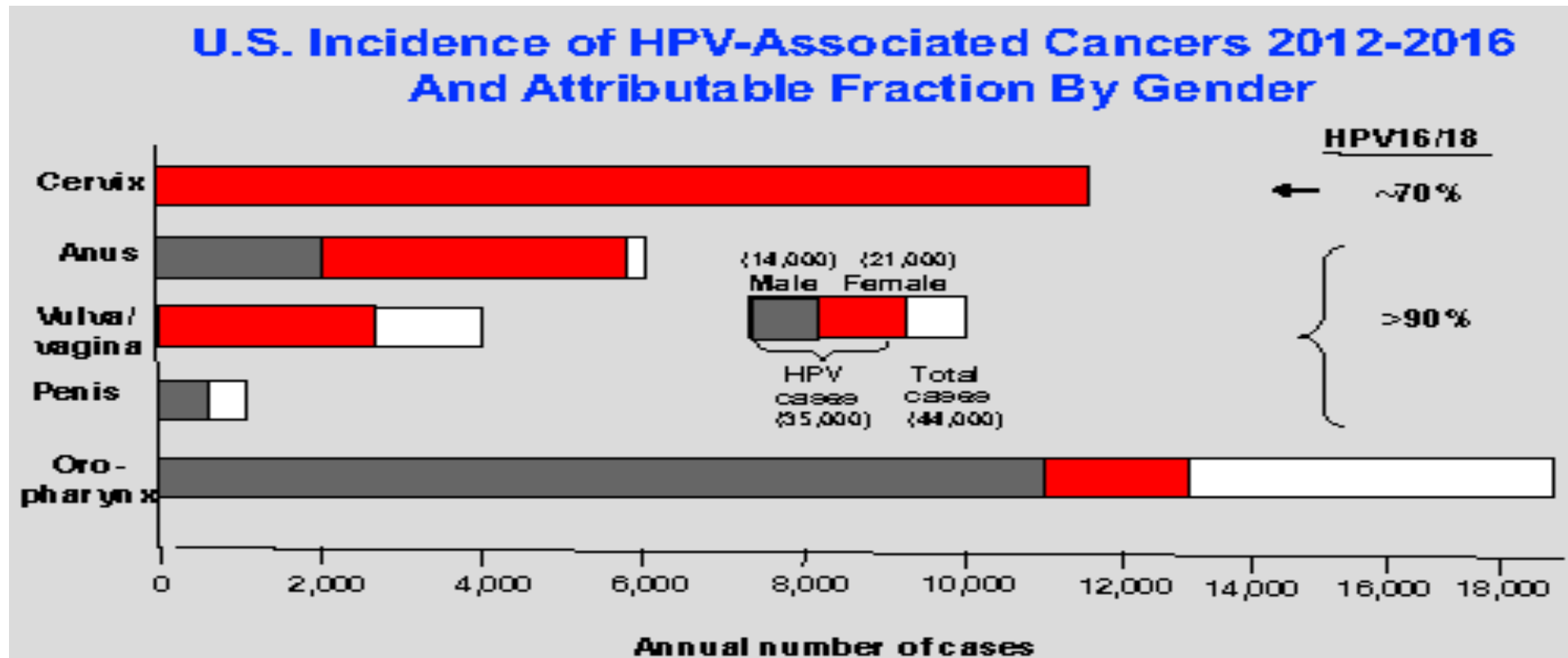
10% of All Cancers

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



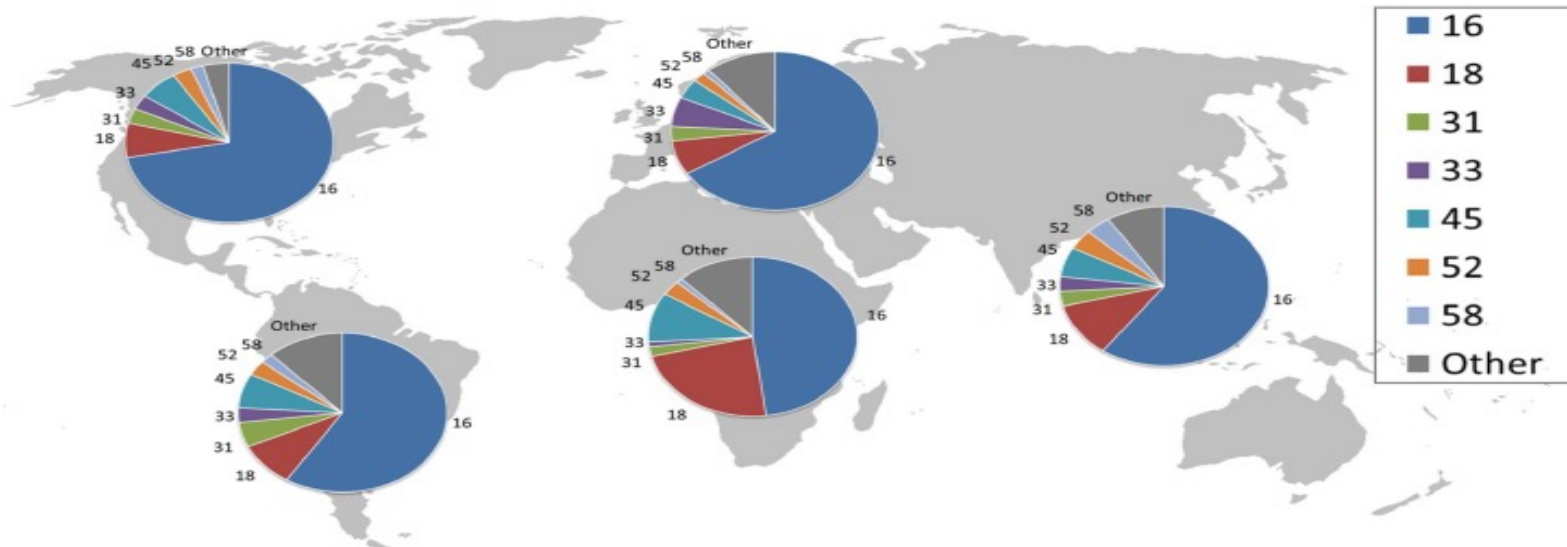
HPV incidence



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

World wide distributions of genotypes

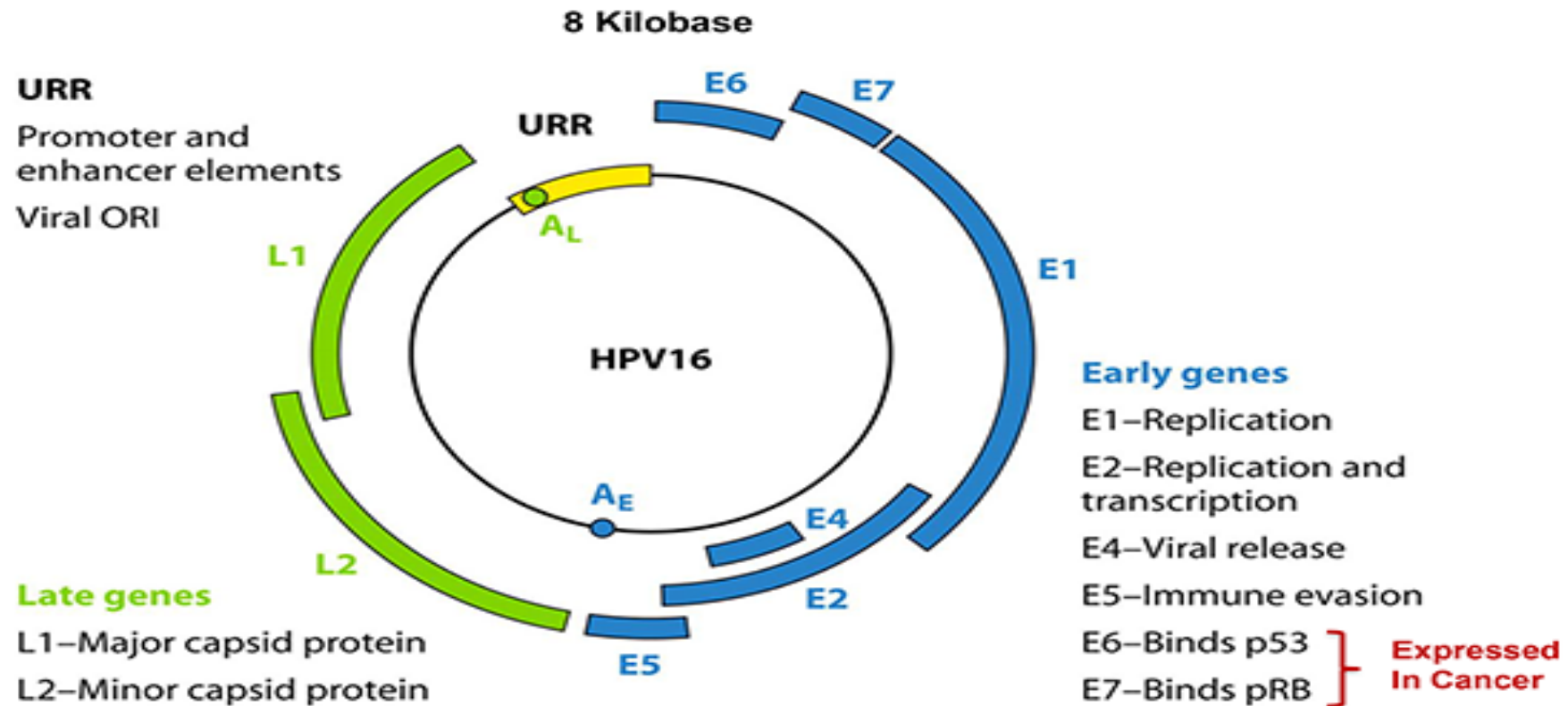
World Wide Distribution of Genotypes Detected in Cervical Cancer



HPV16 and HPV18 dominate everywhere

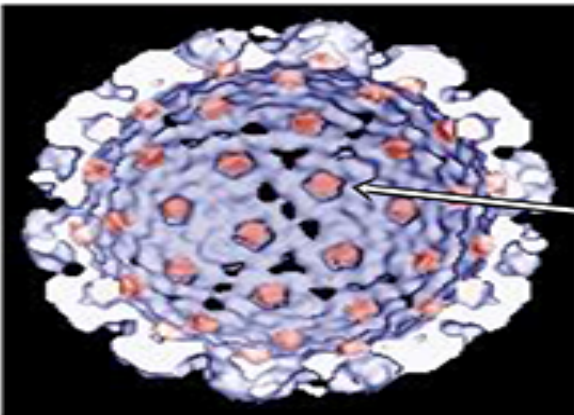
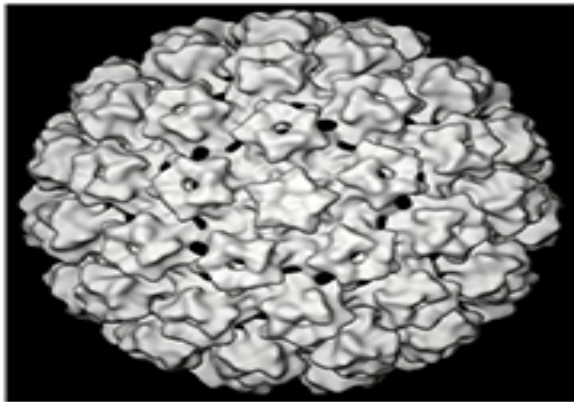
HIV genome

HPV16 Double Stranded Circular DNA Genome



Virion

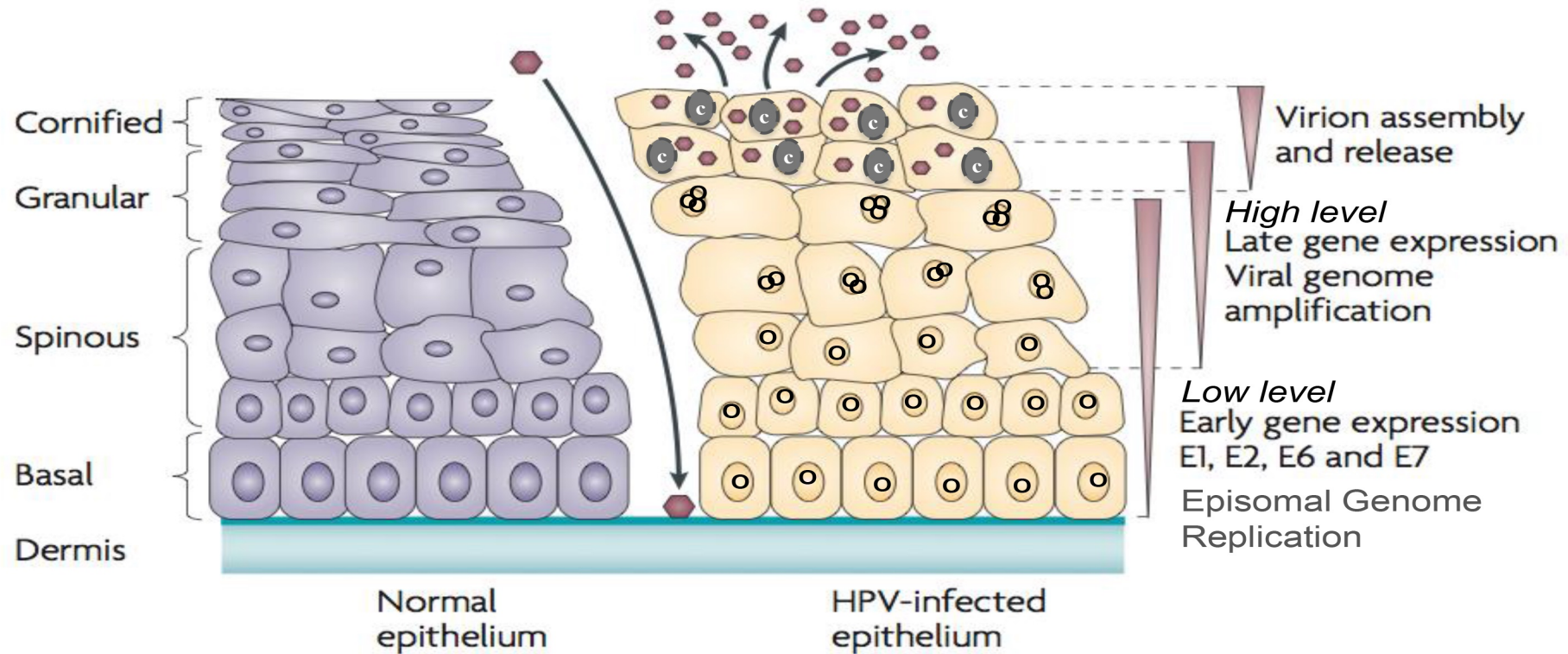
Papillomavirus Virion



- **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)**

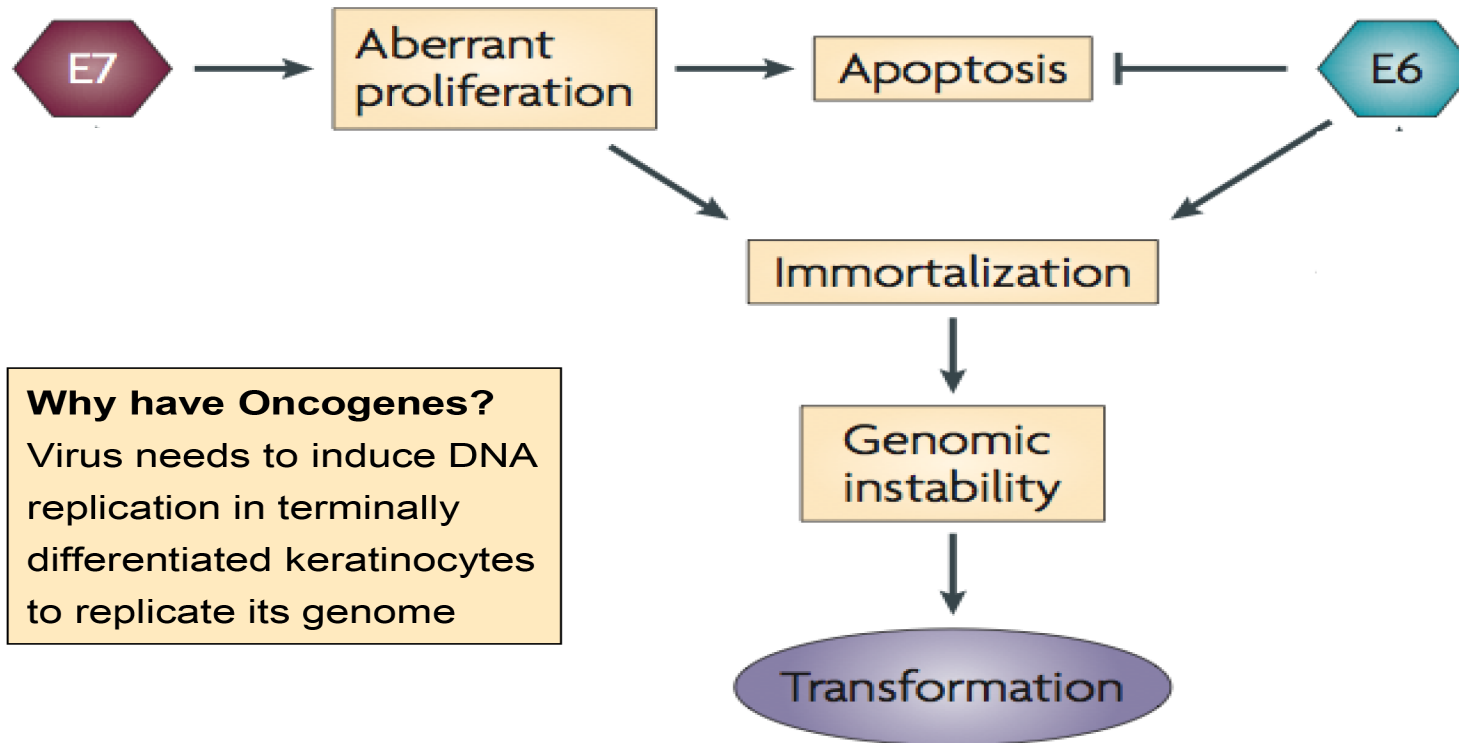
HPV life cycle

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



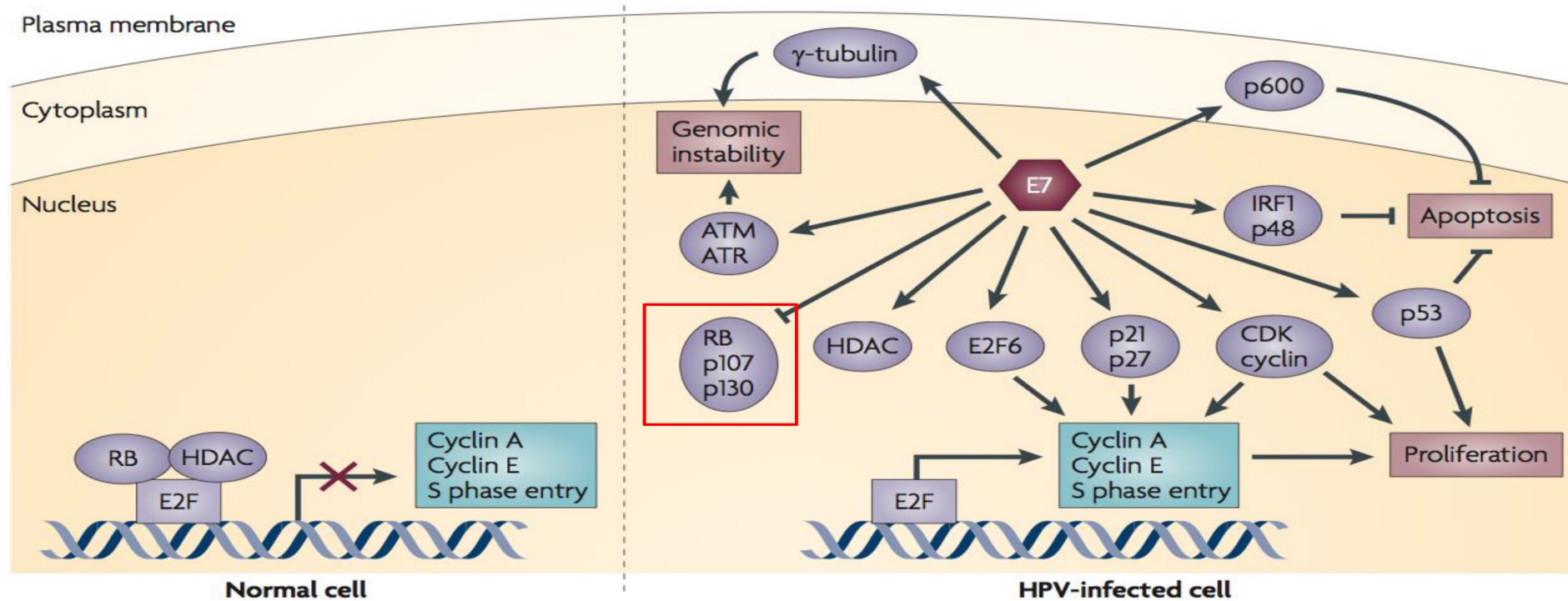
HPV carcinogenesis

Molecular Mechanisms Involved in HPV Carcinogenesis



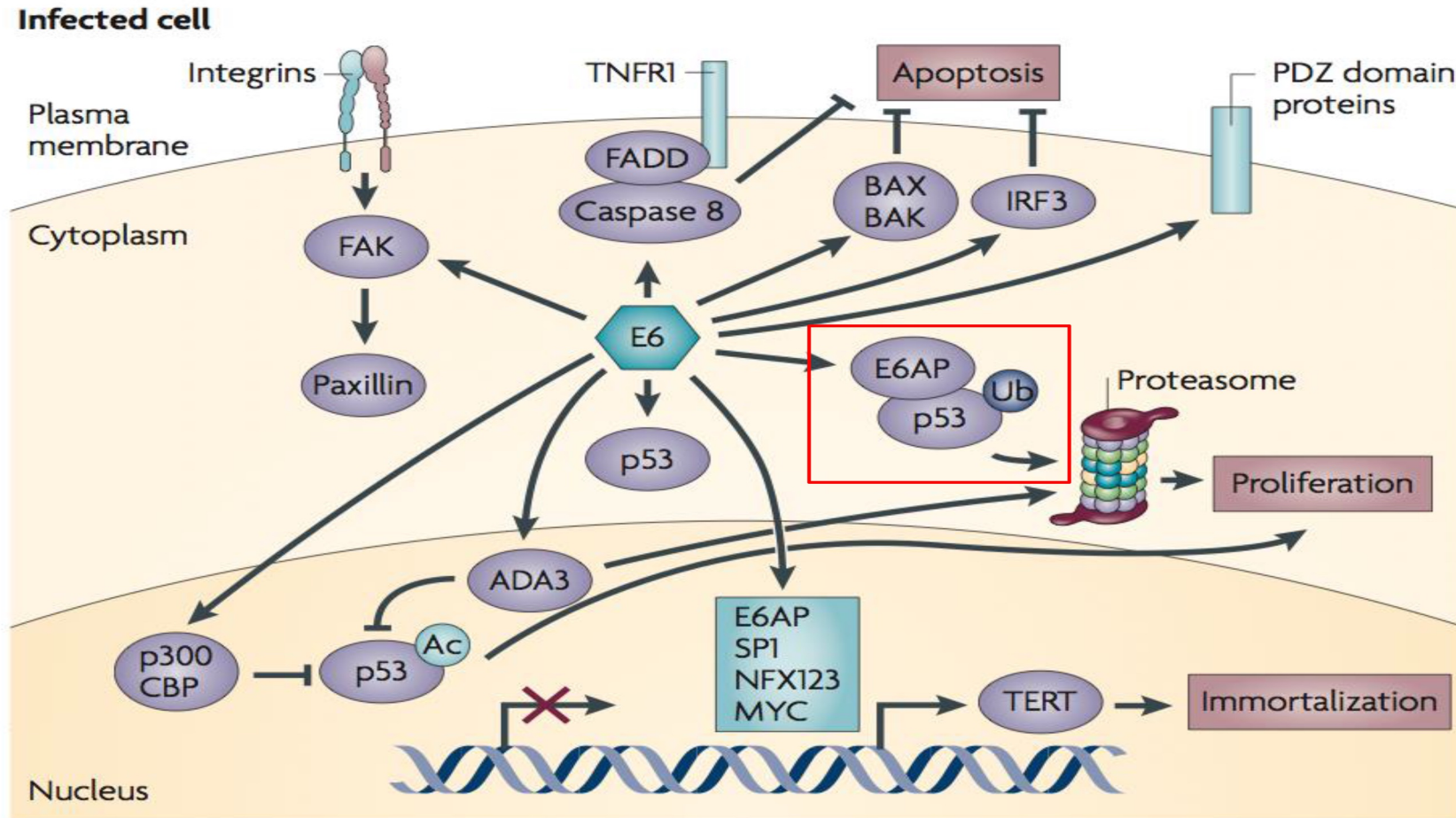
Cellular proteins

Cellular Proteins and Pathways Affected by HPV E7



HPV pathways

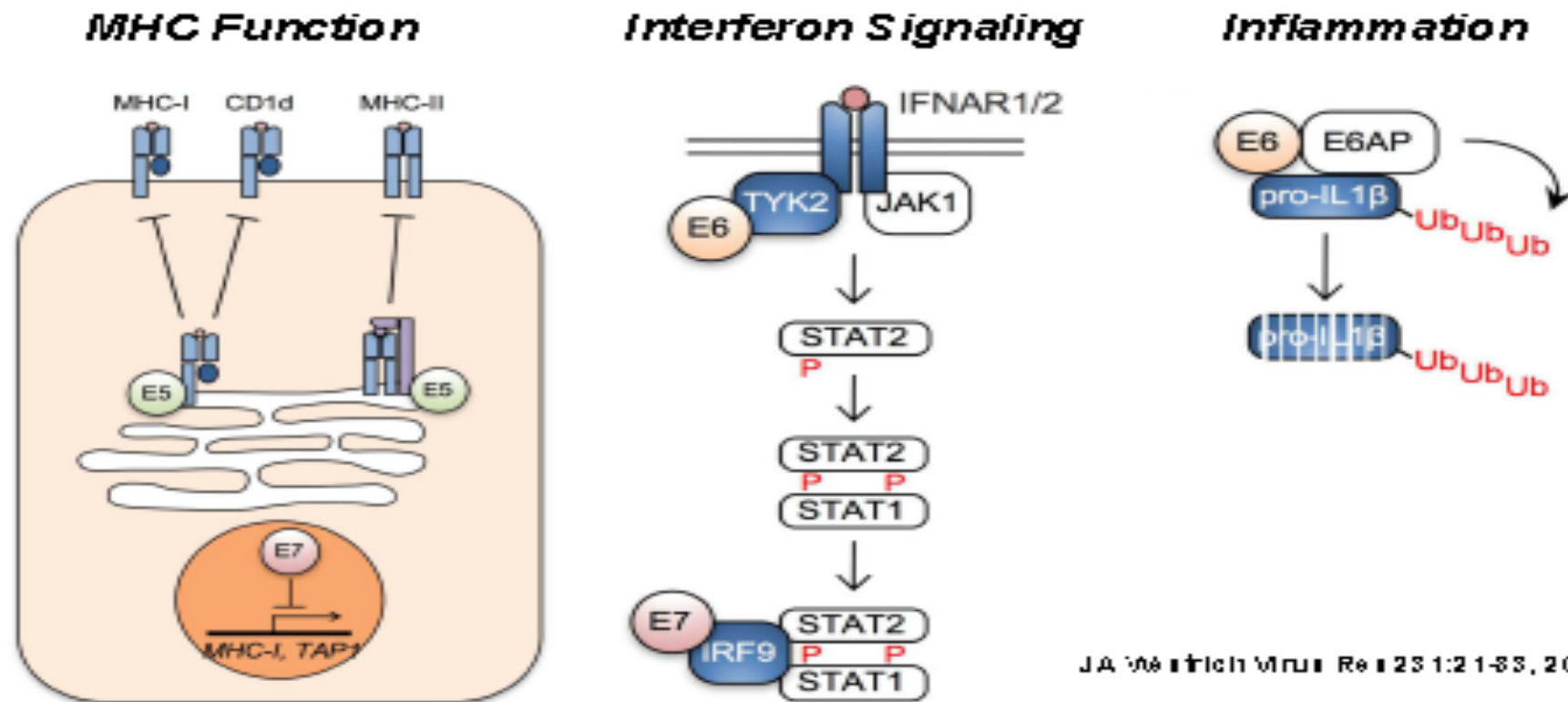
Cellular Proteins and Pathways Affected by HPV E6



HPV oncoproteins

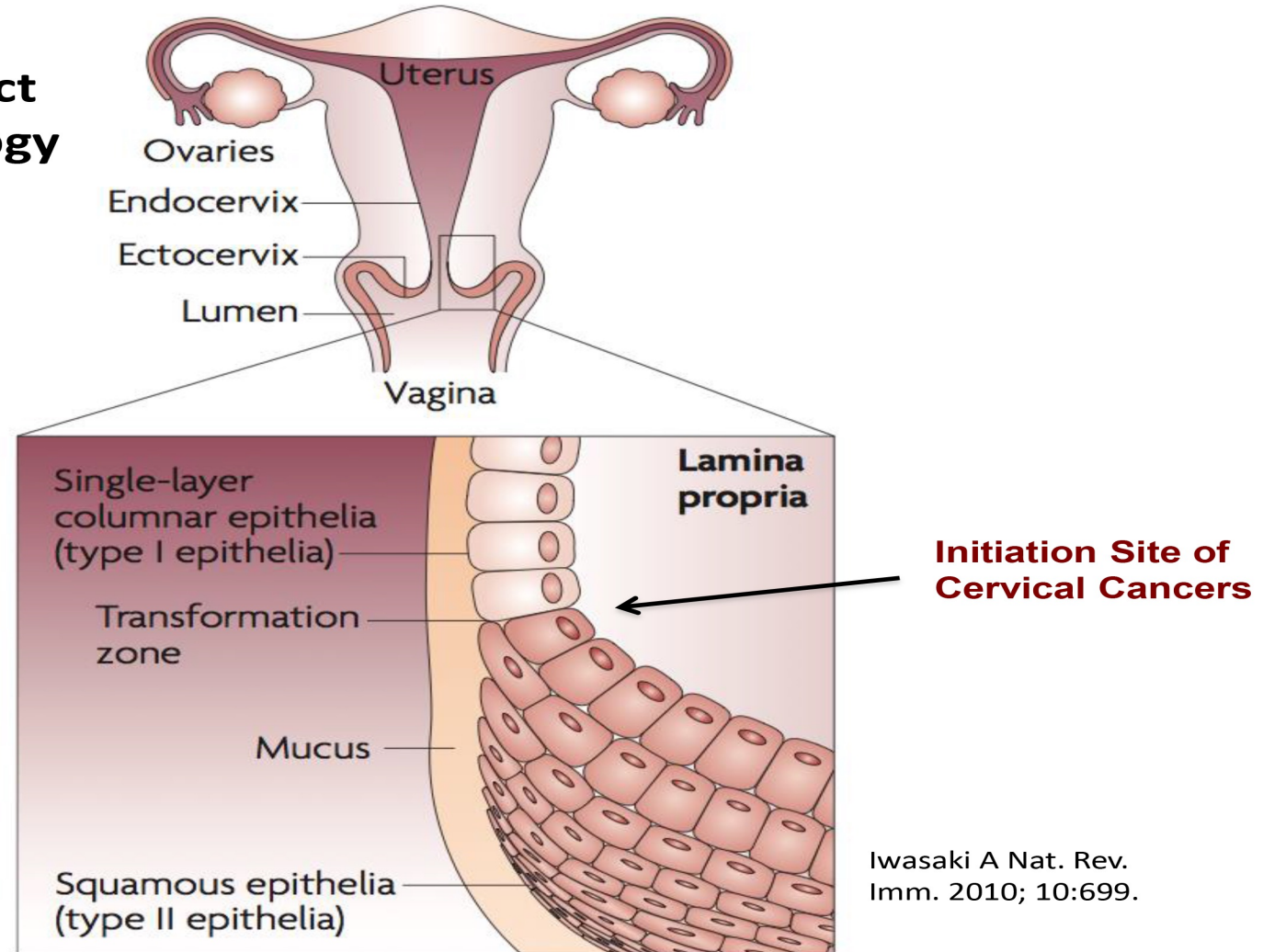
HPV Oncoproteins Also Inhibit Immune Responses

Promotes virus persistence



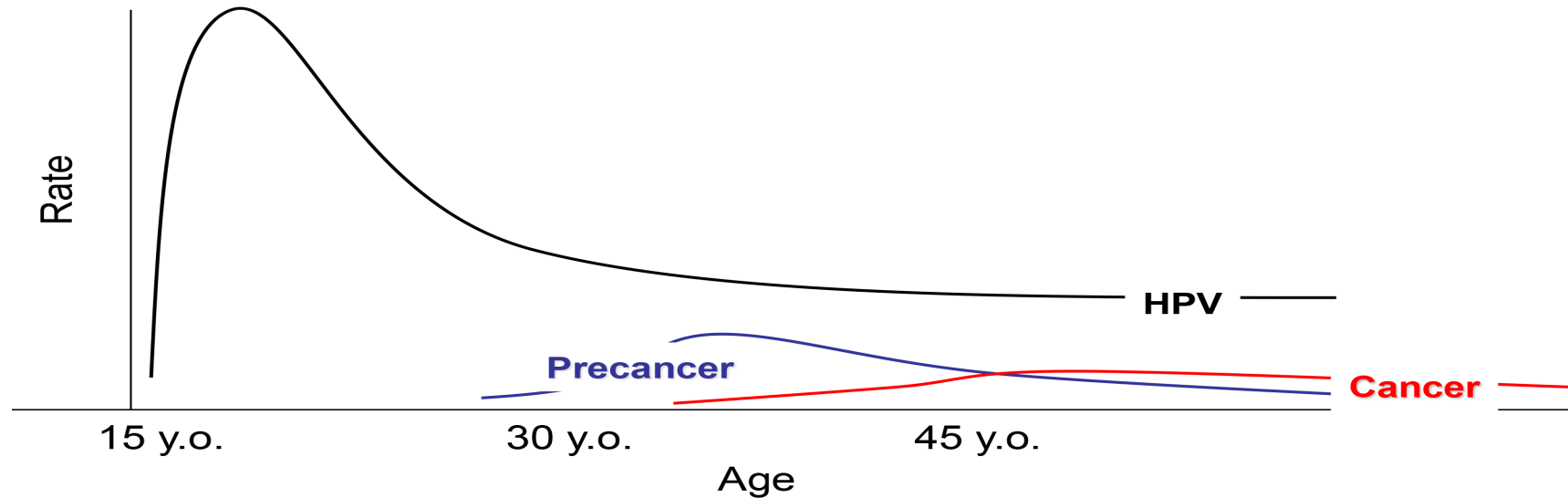
Cervical cancer

Female Reproductive Tract Anatomy & Histology



HPV infection time line

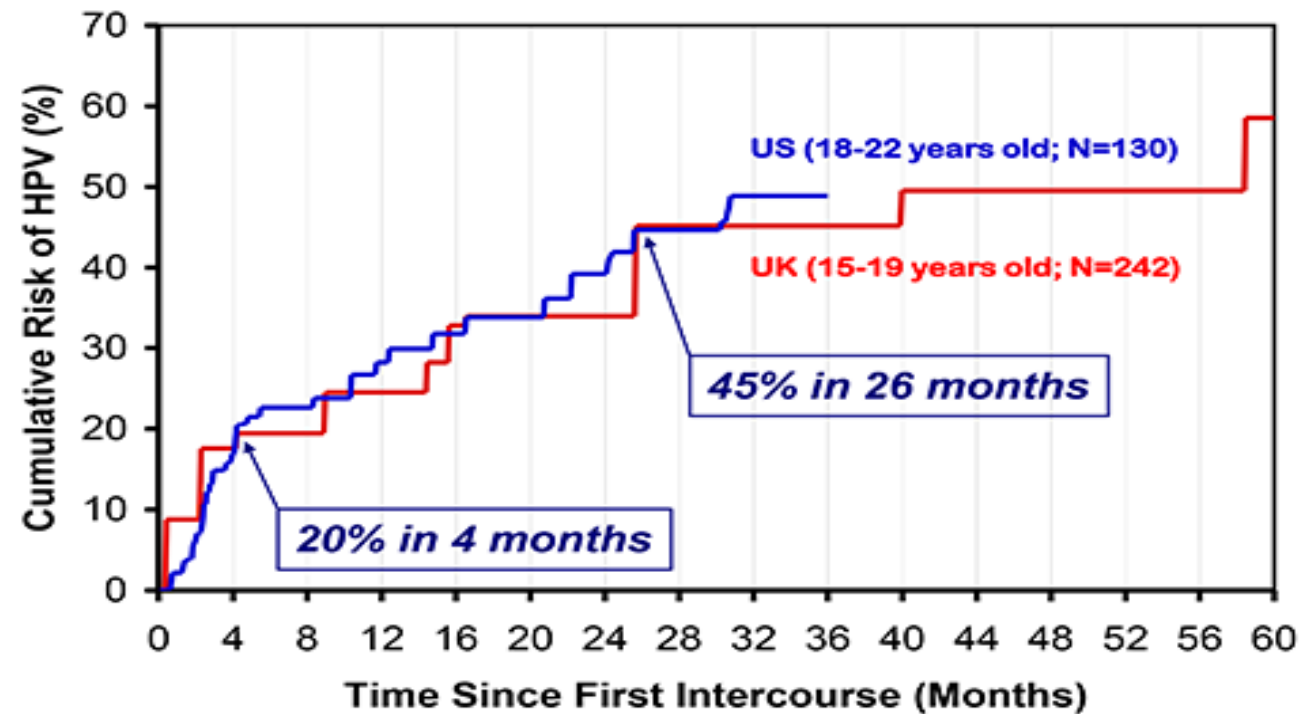
Time Line of Cervical HPV Infections And Progression to Cervical Cancer



- **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.**

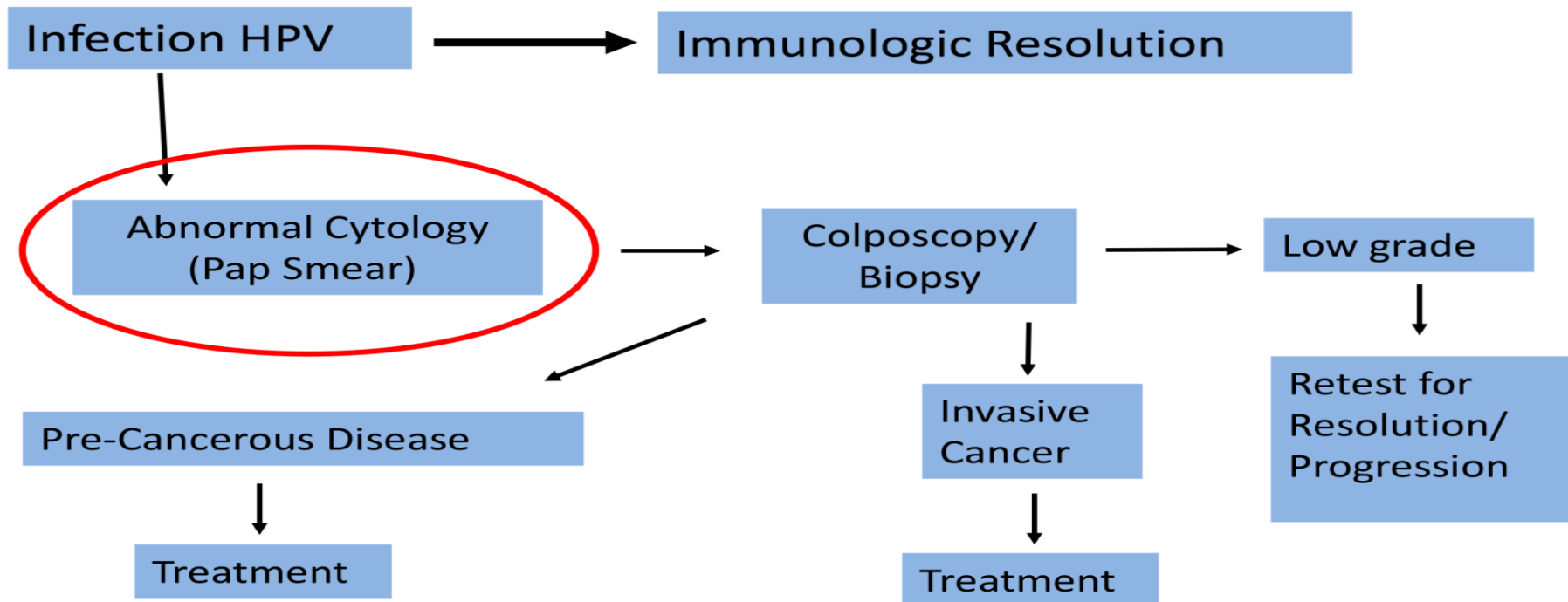
HPV infection

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



Pap screening

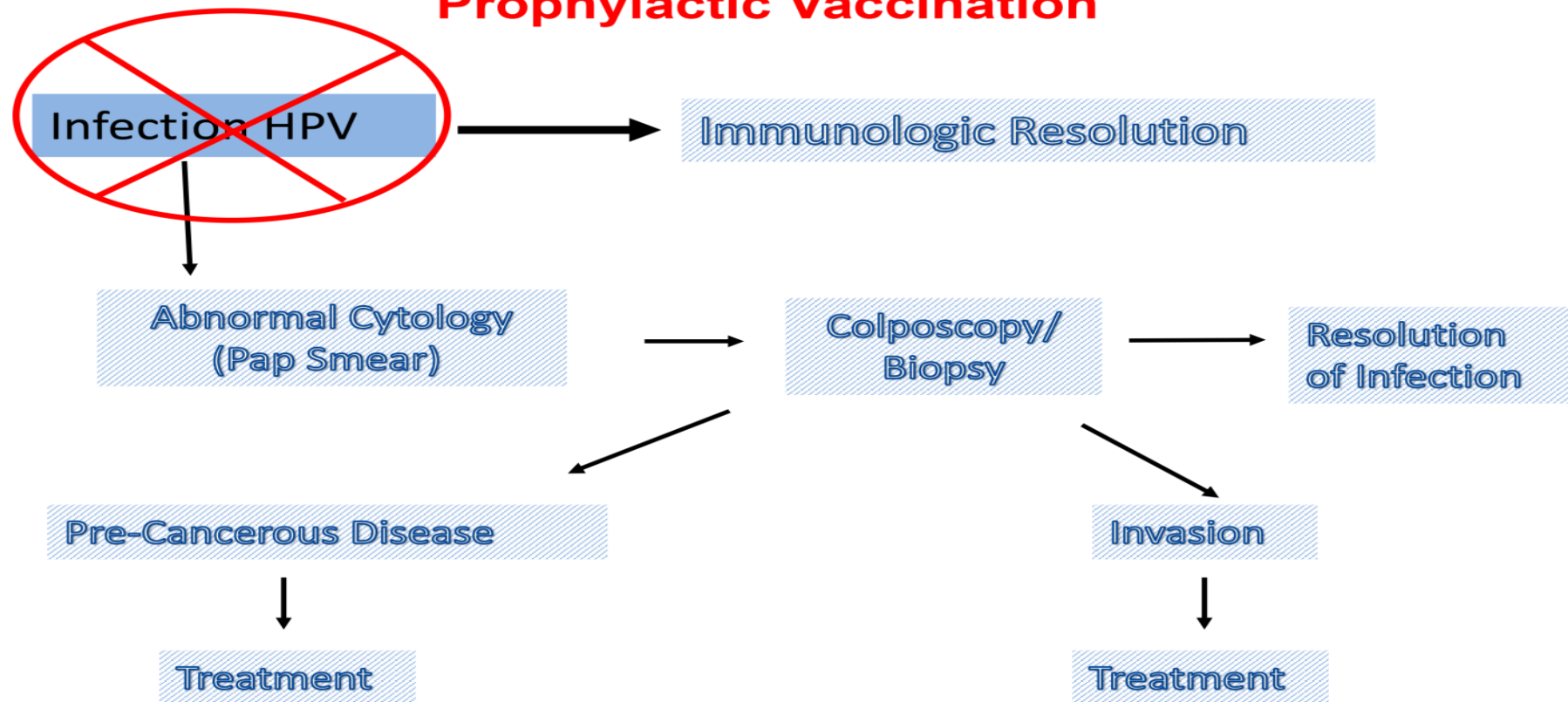
Current Pap Screening Is “Secondary” Prevention of Cervical Cancer



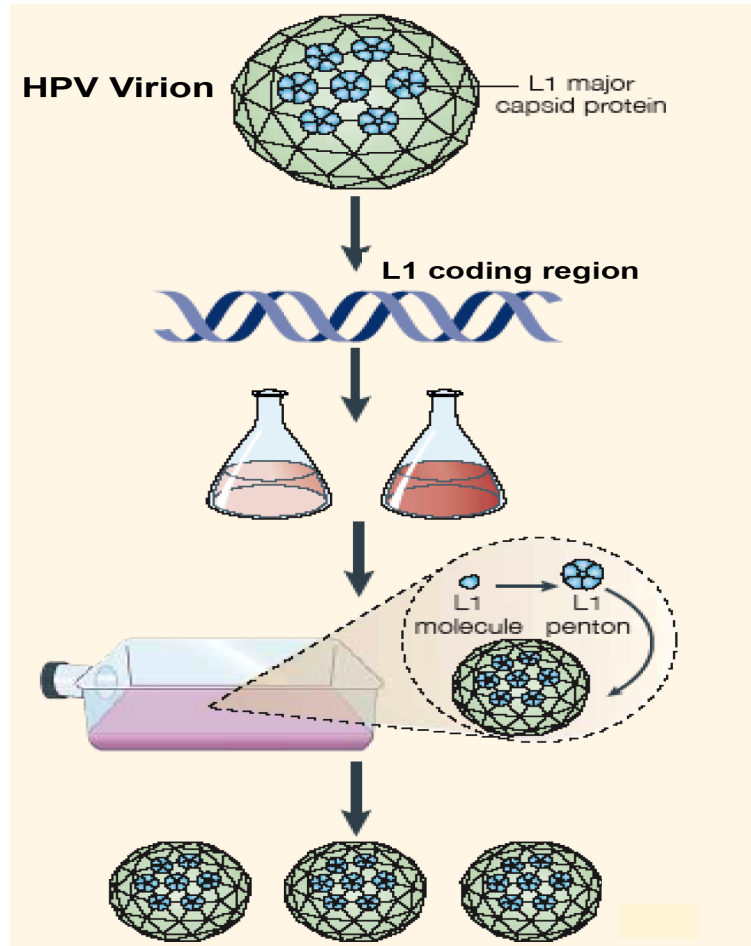
Primary prevention

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

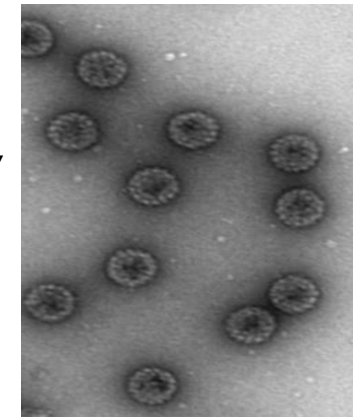
Production in Insect Cells

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

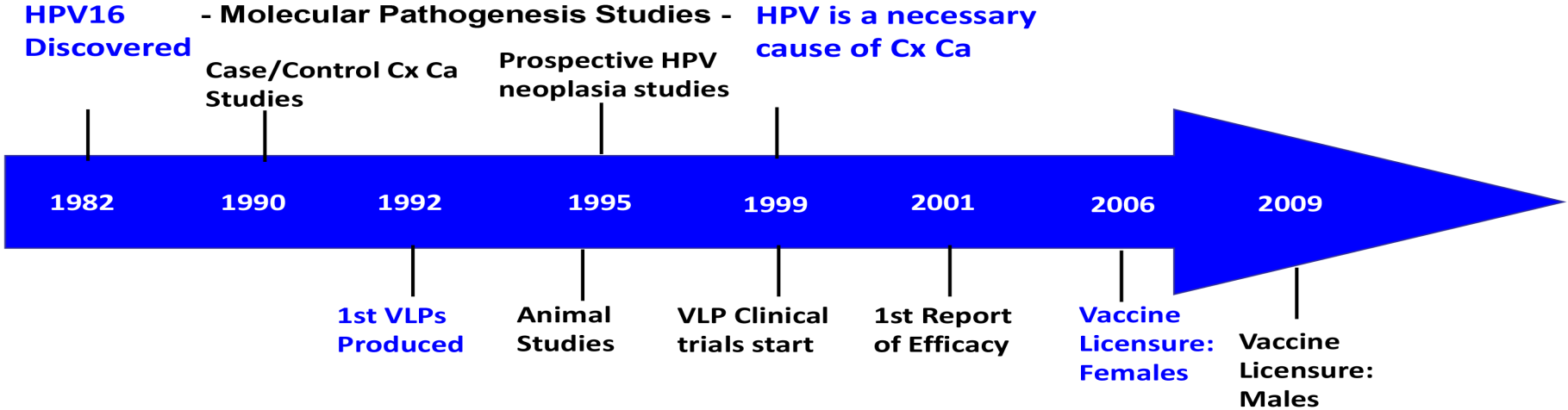
Name	Producer	VLP Types	Adjuvant	Production	Licensed
Cervarix	GSK	16,18	AS04*	Insect Cells	2007
Gardasil	Merck	16,18, 6,11	Alum	Yeast	2006
Gardasil-9	Merck	16,18,31, 33,45,52,58 6,11	Alum	Yeast	2014

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



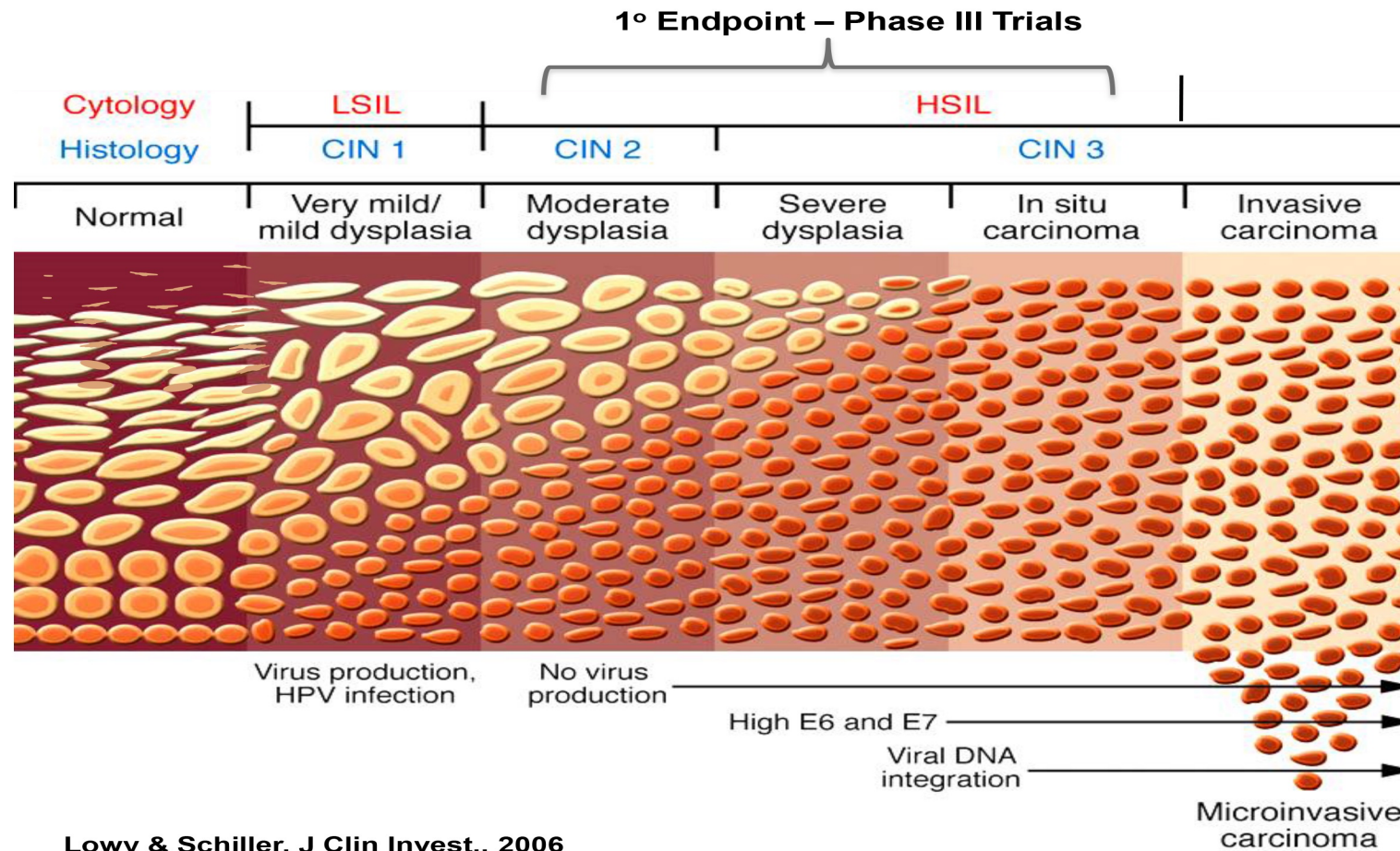
COVID timeline

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



Vaccine Efficacy

Summary of Vaccine Efficacy in Randomized Clinical Trials

Trials in women ages 15-26.

Primary analyses in those negative for vaccine types at enrollment.

Protection against vaccine targeted types:

- **95-100% against cervical precancers**
- **95% against genital warts**
- **No indication of waning immunity for > decade**

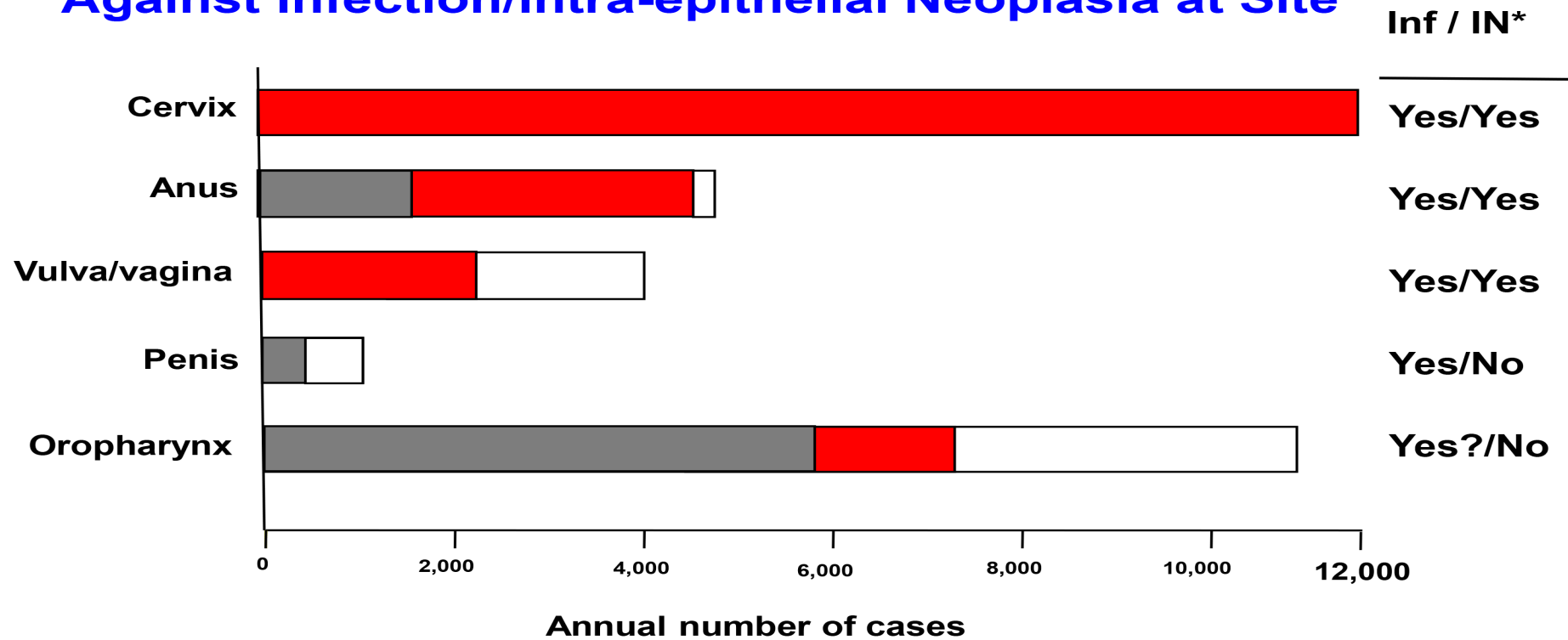
Infection protection

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, presumably by inducing antibodies that prevent infection.**
- **Apparently not the case for COVID 19!**

Clinical Trial Evidence

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



* Against Vaccine Targeted Types

HPC vaccine Global 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.**

National immunization programs

How well do the vaccines work in national immunization programs?

Gardasil targeted infections

Reduction in the Gardasil-Targeted Type Infections in the US

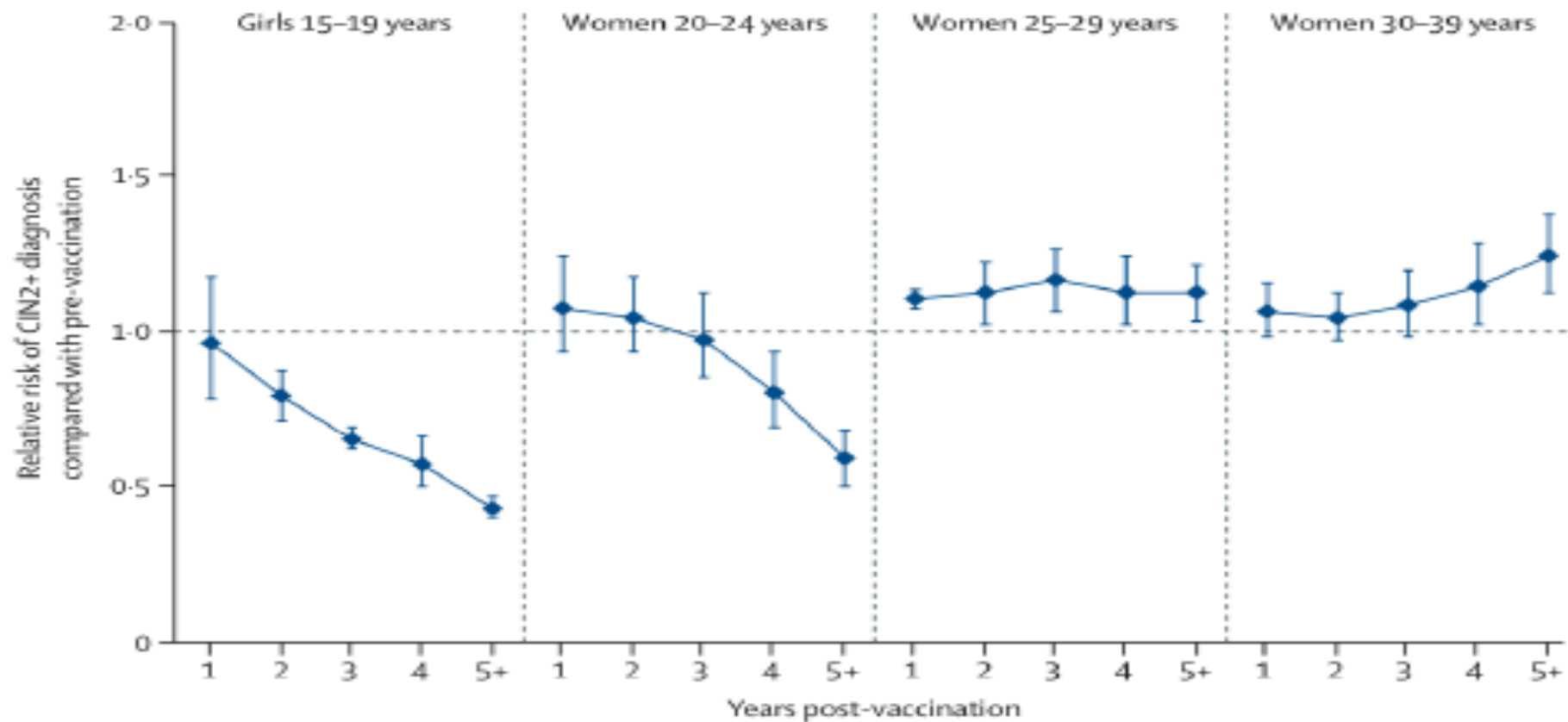
Precent reduction in the prevalence of the four Gardasil-targeted types from pre-vaccination (2003-6) to vaccination period (2015-18) in sexually experienced females

Age	Vaccinated	Unvaccinated
14-19	97%	87%*
20-24	86%	65%*

***Evidence of strong herd protection**

Cin2+ changes

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

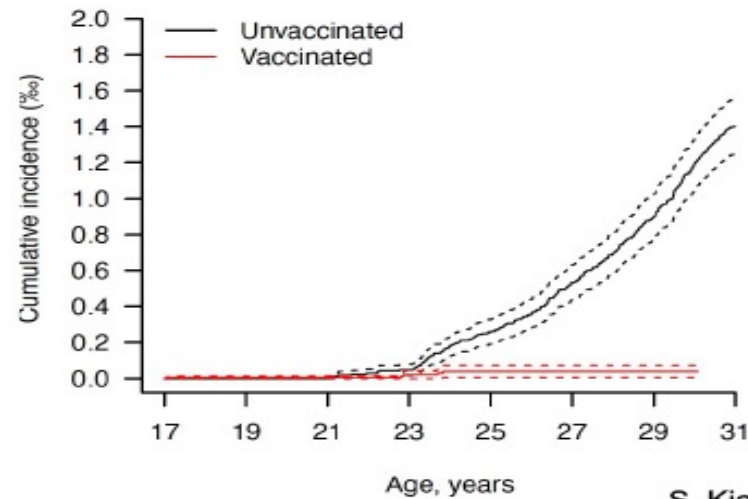


Cervical cancer incidence by age

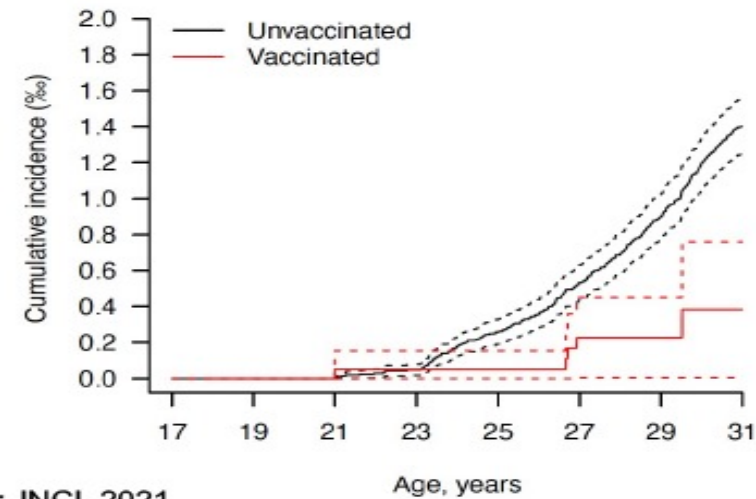
Decreased Cervical Cancer Incidence in Danish Women By Age When They Received the HPV Vaccine

A Age at vaccination ≤ 16 years

B Age at vaccination 17 – 19 years

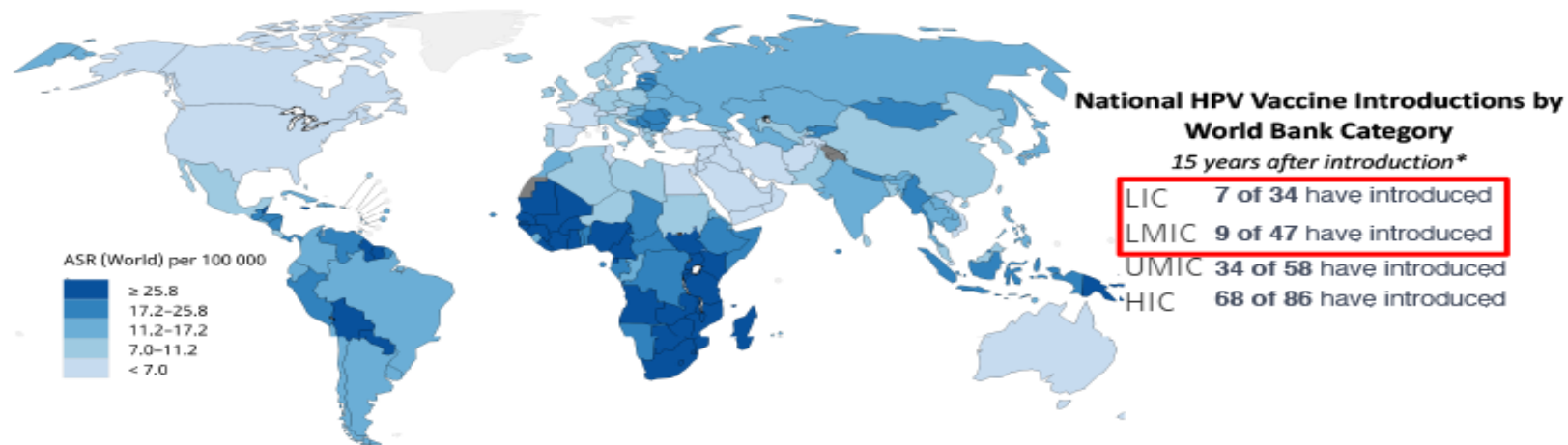


S. Kjaer JNCI, 2021



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*

Uptake

Uptake is the Key to Impact

Increasing Uptake, Particularly in Low Resource Settings



Both companies are committed to selling to GAVI at less than \$5 per dose



Vaccine manufacture in emerging countries



Address vaccination hesitancy through education programs aimed at families and health care providers



Transition to single dose vaccination

Single dose

Why do we think a single dose might be sufficient?

There are currently no single dose subunit vaccines.

Single dose efficacy

Summary of Clinical Trial Finds Supporting Single Dose Efficacy

- **NCI Costa Rica:** In post hoc analyses, no difference in efficacy against infection after 1, 2, or 3 doses of **Cervarix** after **11 years**¹.
- **IARC India trial:** In post hoc analyses, no difference in efficacy against infection after 1, 2, or 3 doses of **Gardasil** after **10 years**².
- **KEN-SHE Kenya trial:** In randomized control trial of 15-20 yo females, **97% protection** against persistent HPV16/18 infections for **3 years** after a single dose **Cervarix** or **Gardasil 9**³.

¹Kreimer A JNCI 2020. ²Basu P Lancet Onc 2021. ³Barnabas R 2022, DOI [10.21203/rs.3.rs-1090565/v1](https://doi.org/10.21203/rs.3.rs-1090565/v1)

Costa Rica vaccine

Costa Rica HPV Vaccine RCT: Compare Efficacy of One Dose vs. Two Doses of Gardasil 9 and Cervarix



Allan Hildesheim



Aimée R. Kreimer



Rolando Herrero

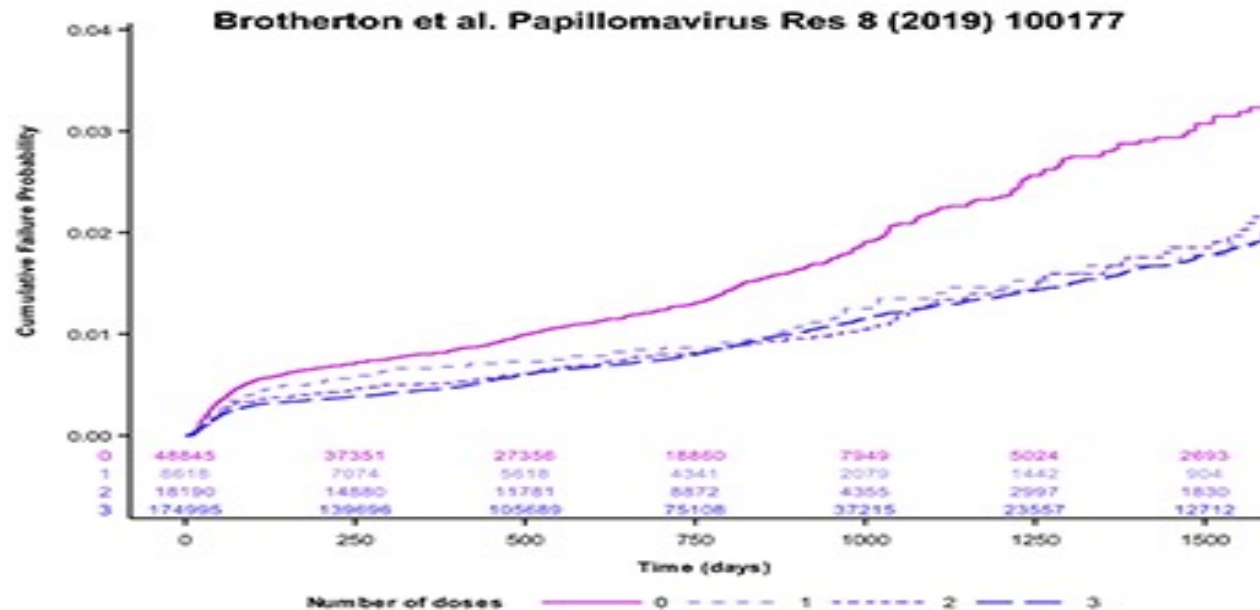
- **6 month persistent infection endpoint**
- **Fully enrolled 20,000 12-16 year old girls**
- **5 year trial, read out in 2025**
- **Goal: Convince public health officials to adopt one dose programs.**

Trial supported by Bill & Melinda Gates Foundation and by NCI

National vaccination program

Evidence From National Vaccination Programs

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



Landmark 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.

WHO decision

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Single dose programs

Countries Introducing Single Dose Programs

26 countries have formally adopted single dose HPV vaccination, including:

**United Kingdom
Australia
India
Nigeria**

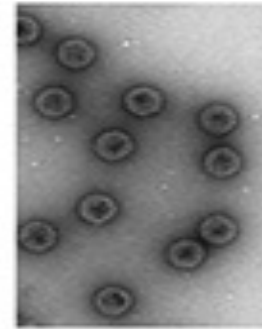
**Ireland
Mexico
Bangladesh
Malawi**

Thanks to Paul Bloem, WHO

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

Sero-conversion

Consistency of Sero-Conversion to VLPs

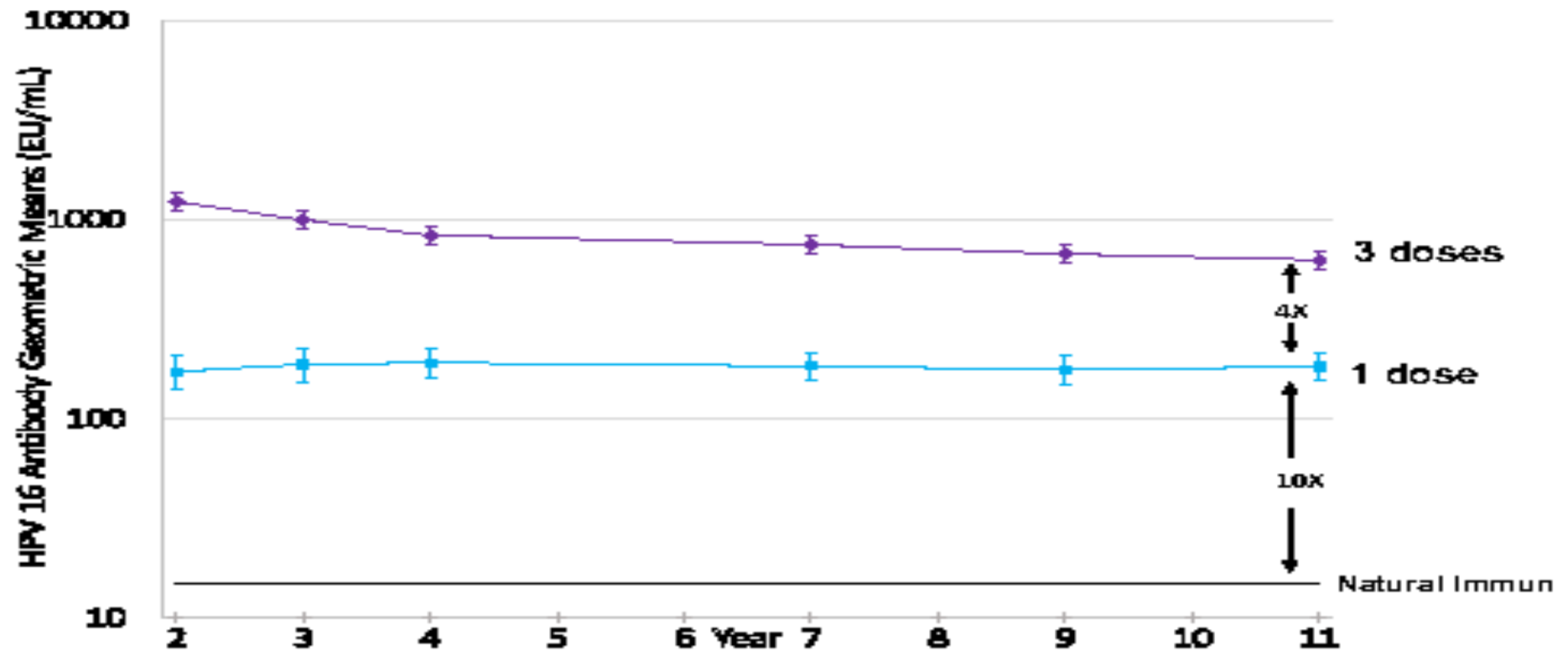
Percent of Girls Seroconverting to Cervirix or Gardasil-9*

# Doses	Cervarix		Gardasil-9	
	HPV16	HPV18	HPV16	HPV18
One	99.3%	98.6%	100%	98.5%
Two	100%	100%	100%	100%
Three	99.3%	99.3%	100%	100%

- One Months after last dose in Tanzanian girls ages 9-14
- Measured in a VLP ELISA

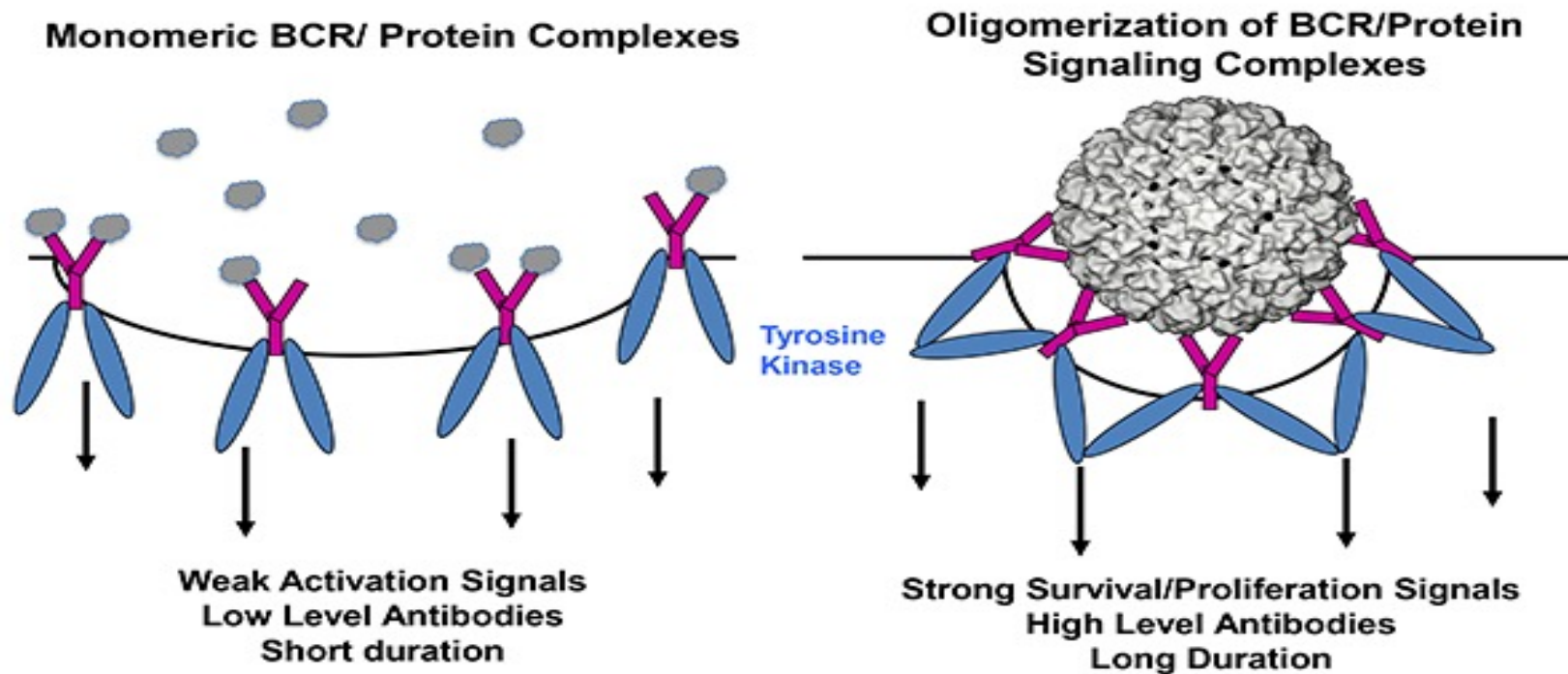
Stable HPV16 serum antibodies

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



B cells recognize dense repetitive protein arrays

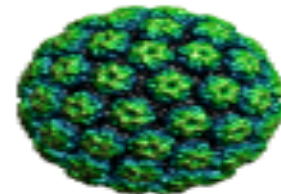
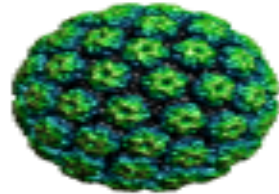
B Cells Recognize Dense Repetitive Protein Arrays as Dangerous Microbial Structures



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.

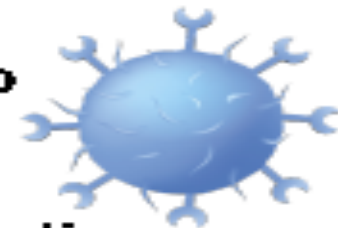
[Bachmann et al. Science 1993; 262: 1448](#)

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

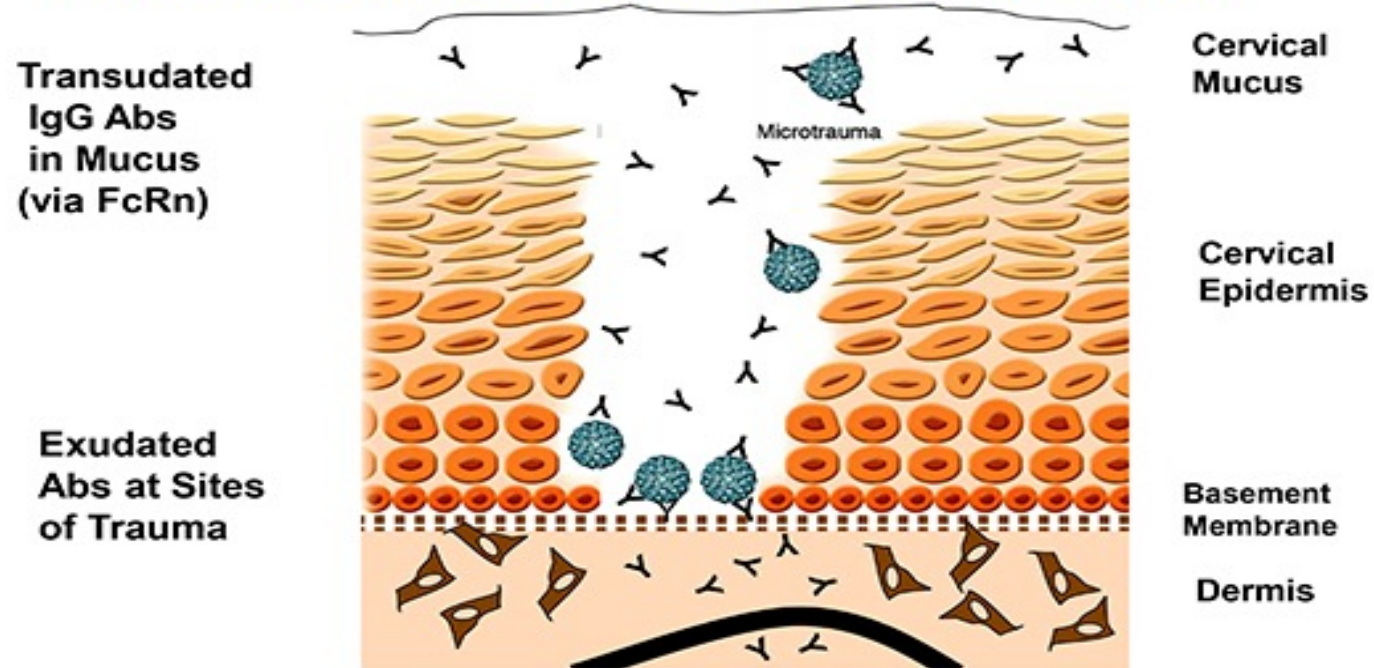


HSPG = Heparan Sulfate Proteoglycan

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

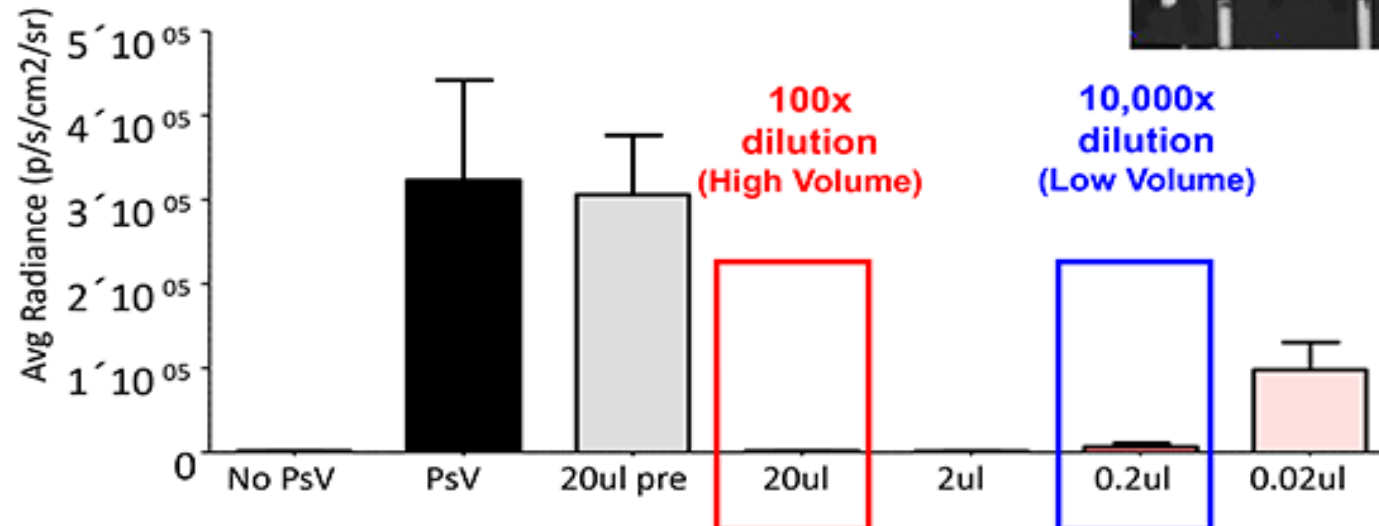
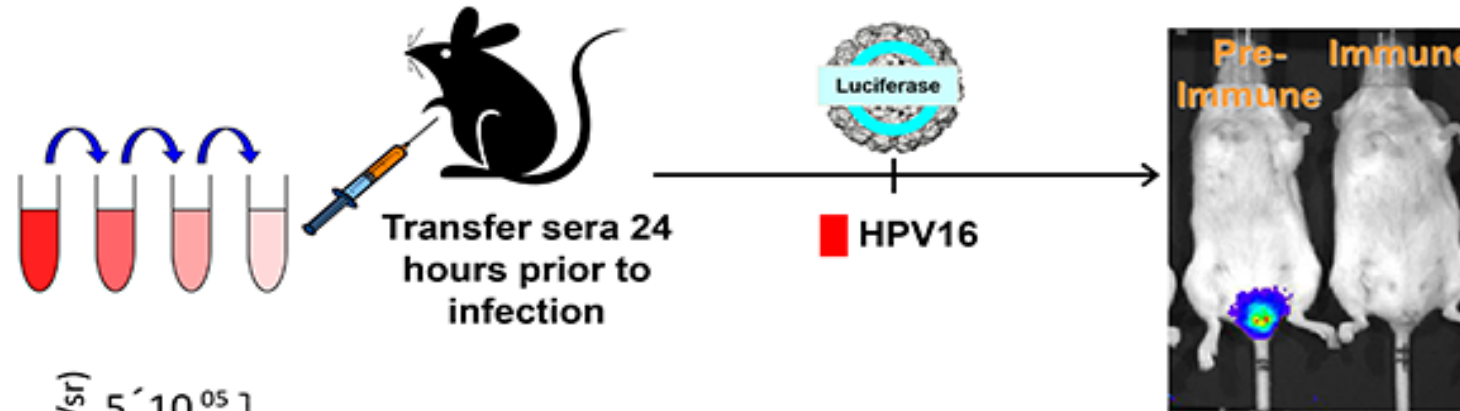
Antibody Titers and Protection

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

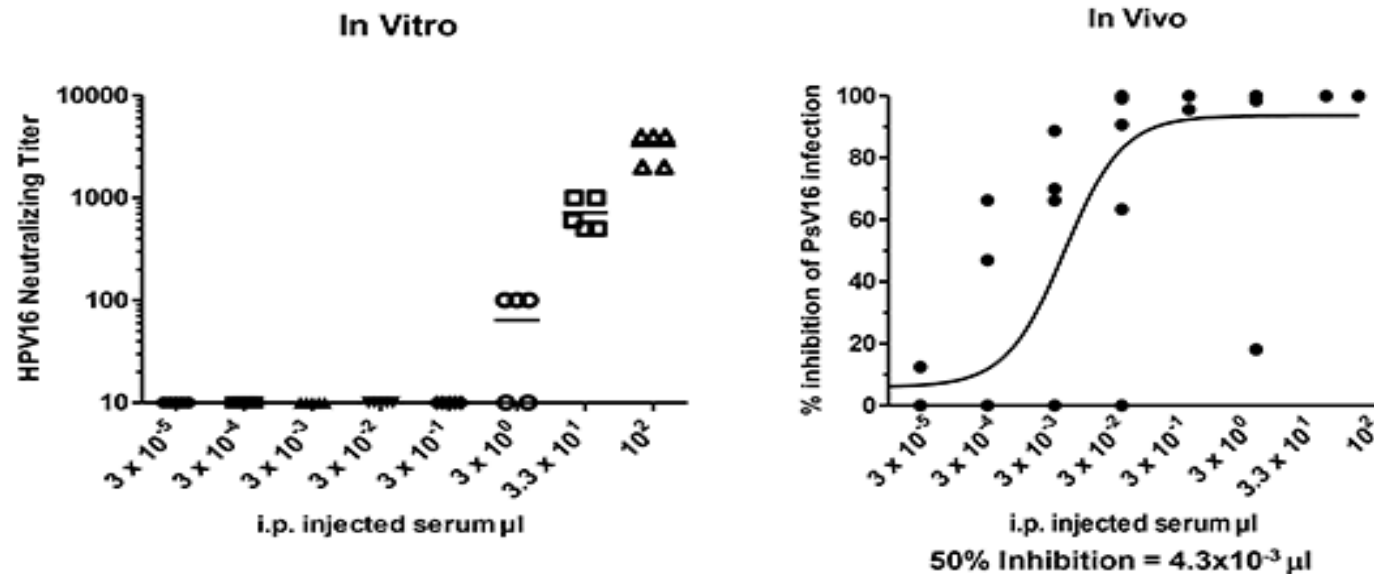
Passive Transfer of Rabbit Polyclonal Anti-16L1 VLP Sera



* 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!

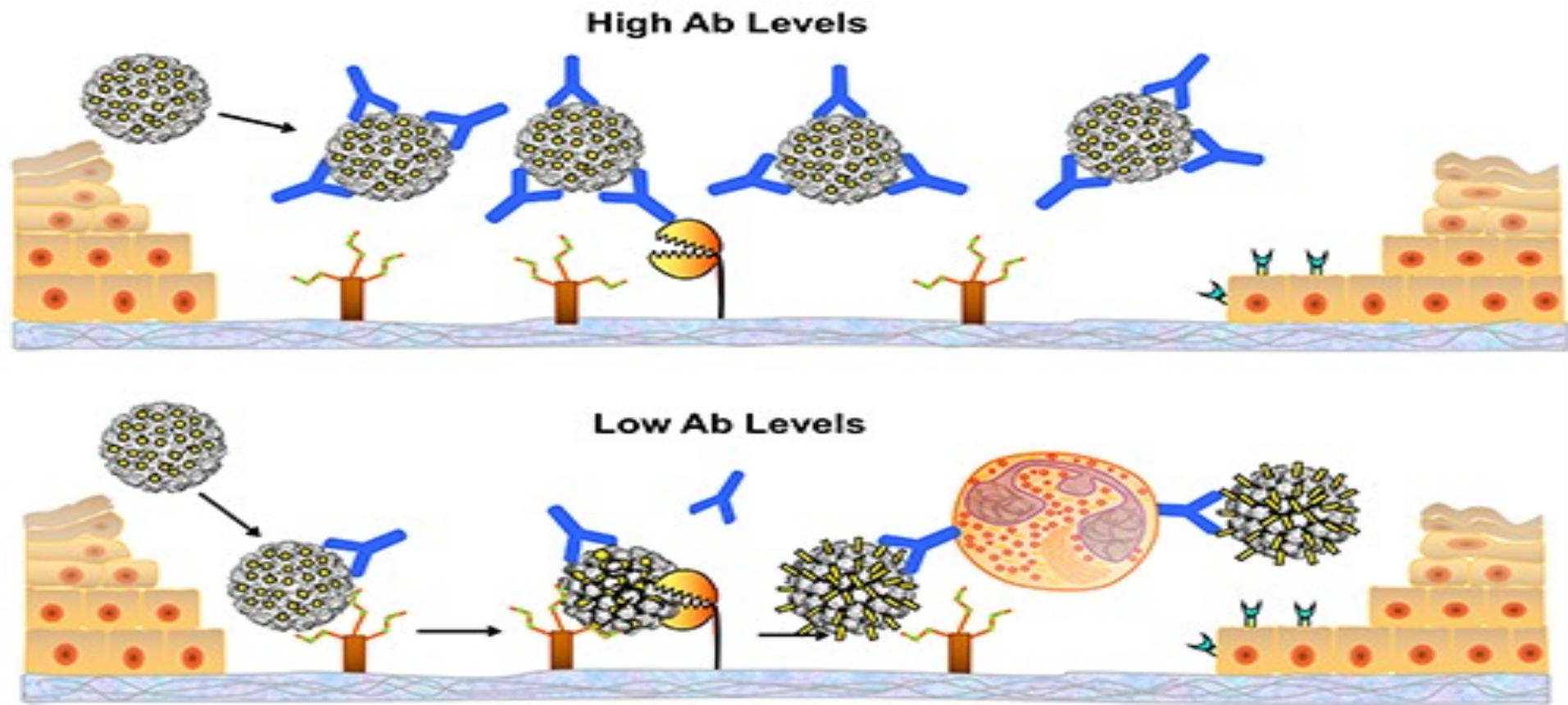
The in vitro assay is missing some potent mechanism of infection inhibition.

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



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 remarkably effective at preventing incident infection and disease by the vaccine types. They have become the benchmarks for viral subunit vaccines.**
- **The VLPs are exceptionally potent inducers of neutralizing Abs, and the virus is exceptionally susceptible to the Abs.**
- **The vaccines have great potential for saving millions of lives from HPV-induced cancers worldwide.**
- **The primary challenge now is to see that the vaccines reach the individuals most in need of them.**
- **Wide spread adoption of single dose vaccination could dramatically increase global uptake.**

Tools to eliminate cervical cancer

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.”

Collaborators

Key Collaborators

Present Members of the Lab:

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Lukas Bialkowski

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Patricia Day

Nathan Fons

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Chris Buck

Jeff Roberts

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