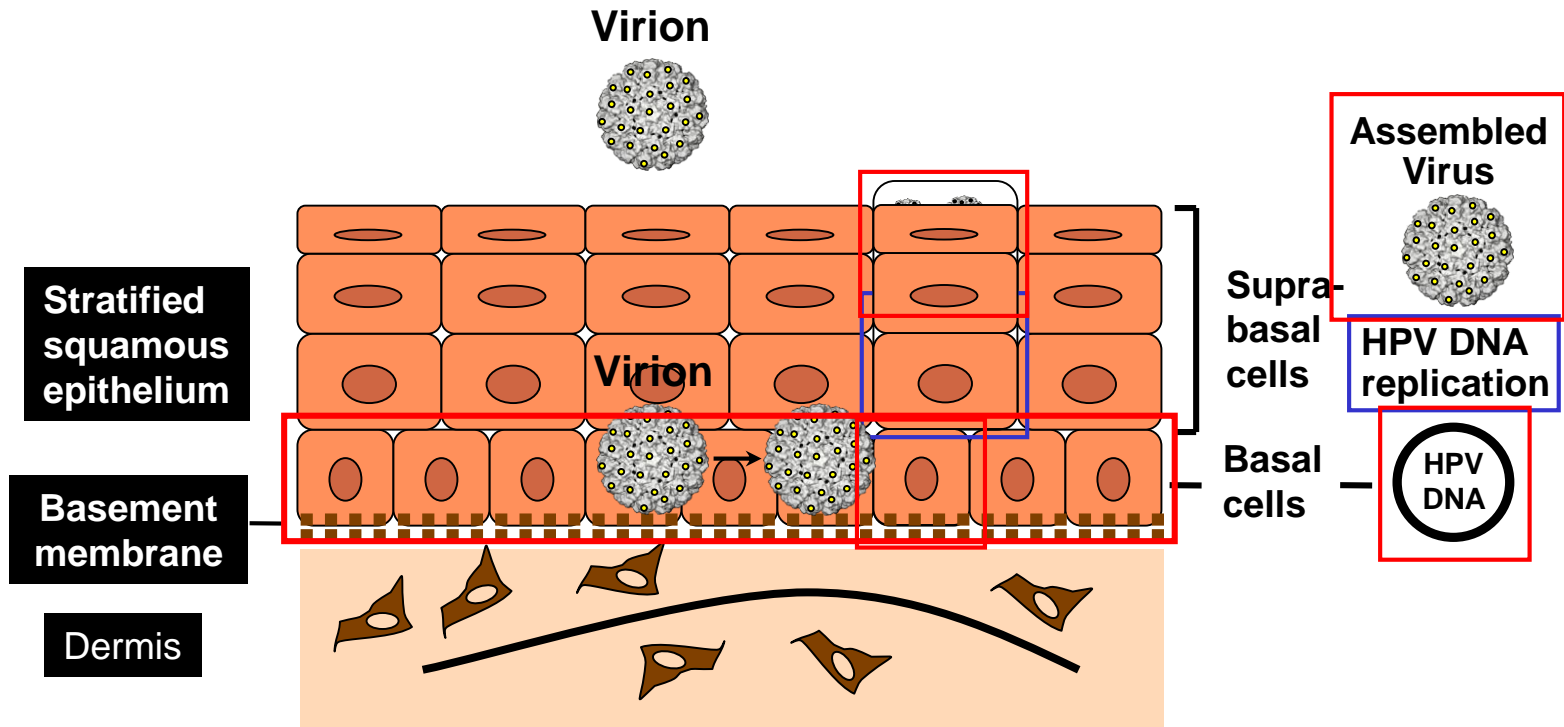
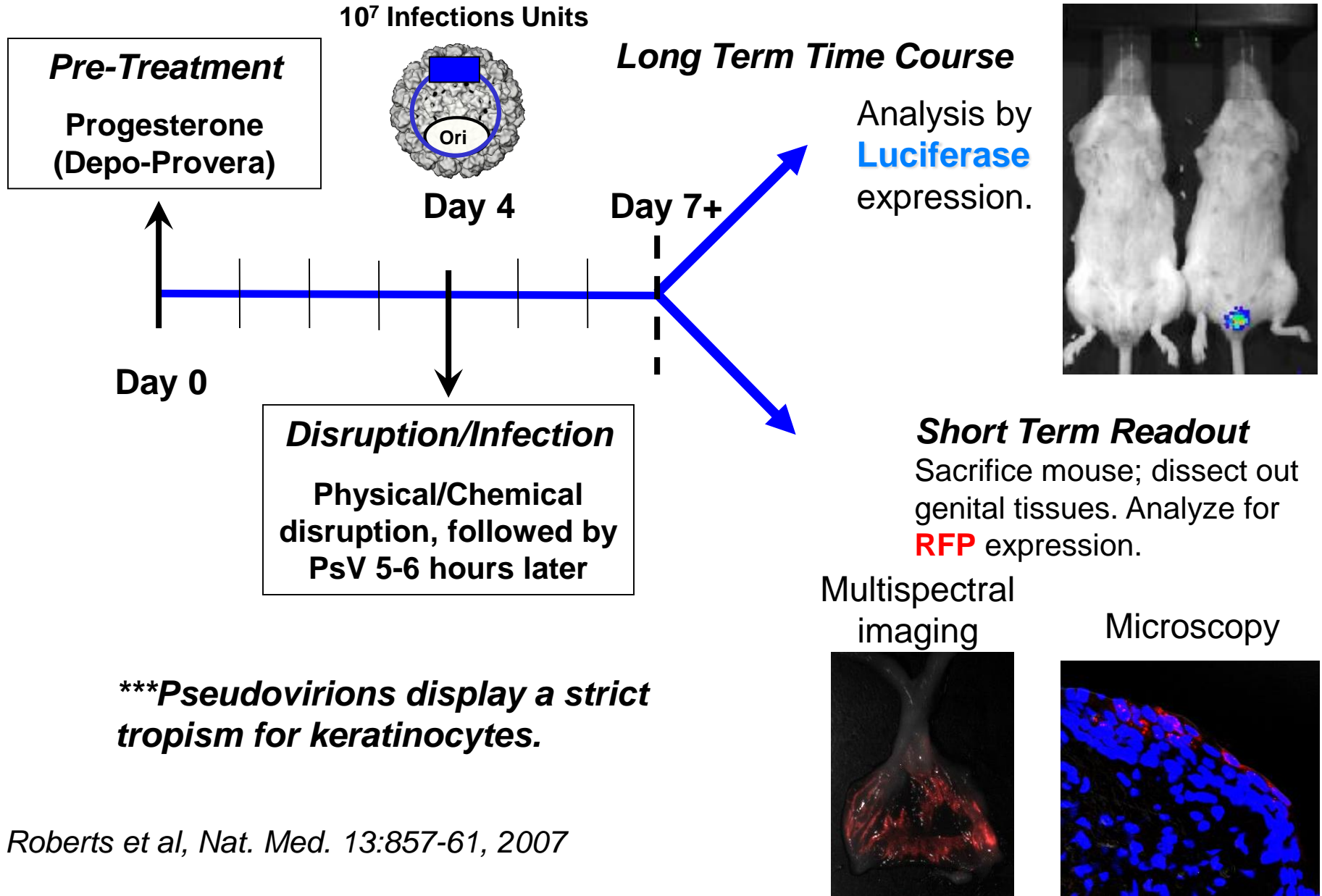


***Following microtrauma, HPV's bind to the basement membrane, infect basal cells, and replicate in suprabasal cells***



# HPV Genital Challenge Model Protocol

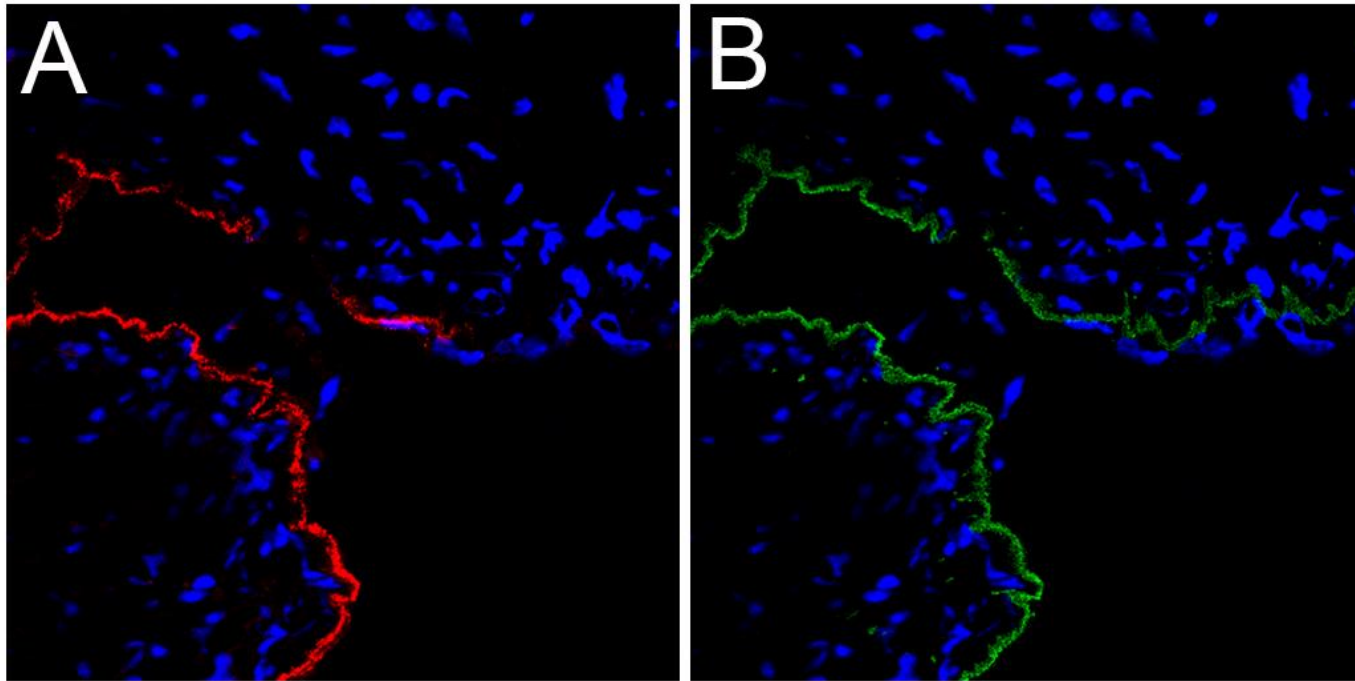


**\*\*\*Pseudovirions display a strict tropism for keratinocytes.**

# *HPV16 Binds the Basement Membrane*

**HPV-16**

**Laminin-5**

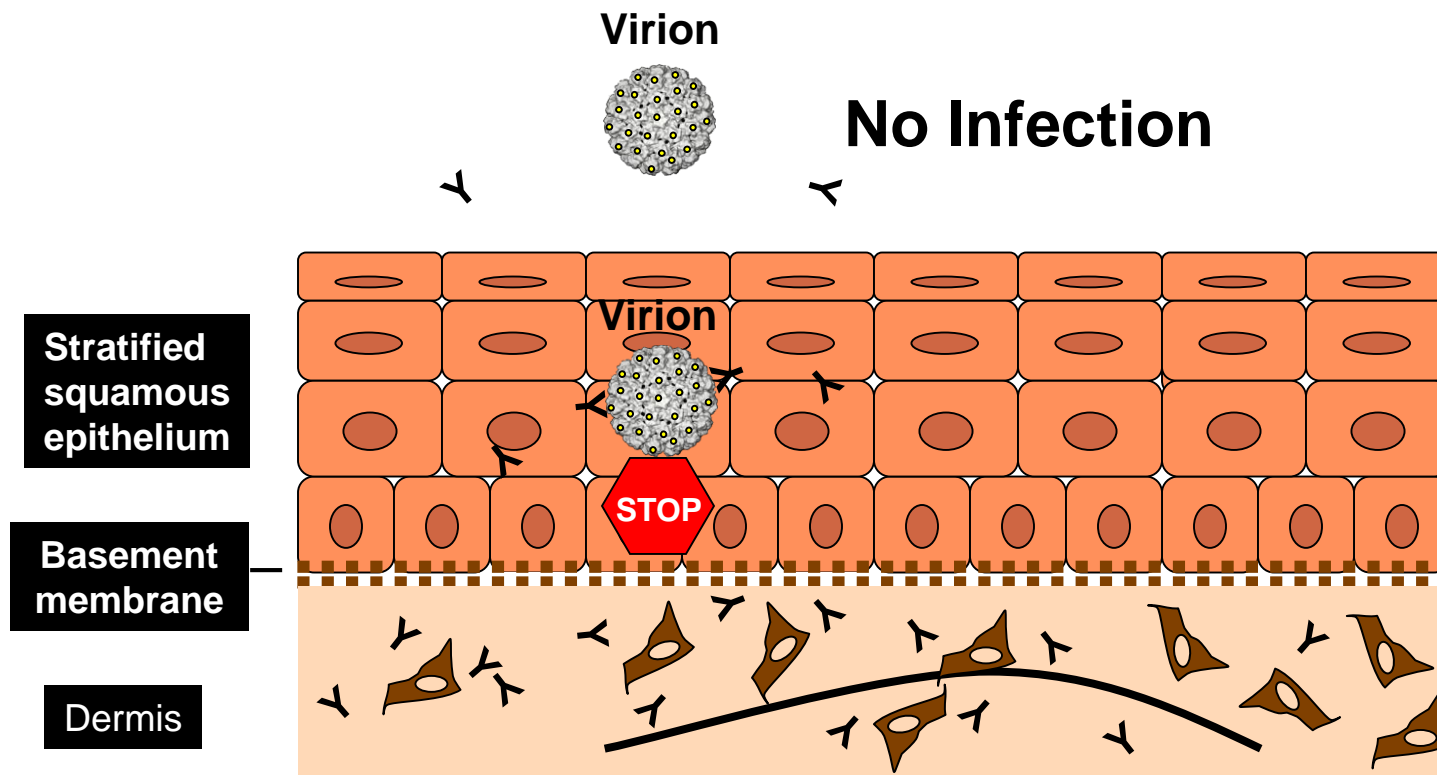


**Mouse vaginal tract: 2 hours after exposure to HPV16  
(8 hours after exposure to nonoxynol-9)**

# ***Mechanisms of HPV infection and Vaccine-induced protection***

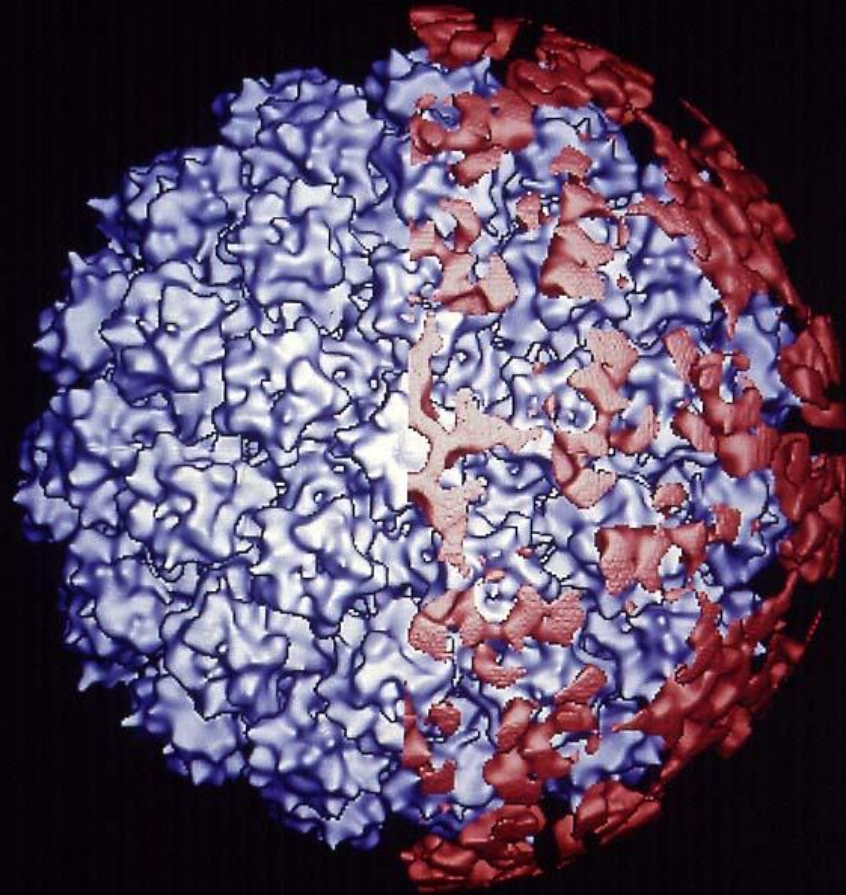
- **Question:**
  - **How does systemic immunization with a sub-unit vaccine prevent a local mucosal or local skin infection?**
- **A two-part answer:**
  - **(1) Local wounding is required for HPV infection**
  - **(2) Infection is prevented by exudation of systemic protective antibodies at these potential sites of infection**

# VLP Vaccination Induces High Titer Antibodies that Prevent Basement Membrane Binding



Based on Patricia Day et al, *Cell Host Microbe* 16: 260-70, 2010

*Neutralizing L1 Antibodies (in red)  
Bound to Papillomavirus Particle*



# ***Two vaccine doses: The future is now (except in the US)***

- Immune response in girls and boys <15 years old is stronger than in older teenagers
- In young adolescents, 2 doses separated by 6 months produce an immune response similar to those in the responses in the efficacy trials
- ***European Medicines Agency approval and World Health Organization Strategic Advisory Group of Experts recommendation for 2 doses for HPV vaccines:***
  - ***Bivalent (GSK) girls 9-14***
  - ***Quadrivalent (Merck) girls & boys 9-13***

***One or two vaccine doses (Cervarix, GSK) can induce 4 years of protection against persistent (6 months) HPV infection with HPV16/18***

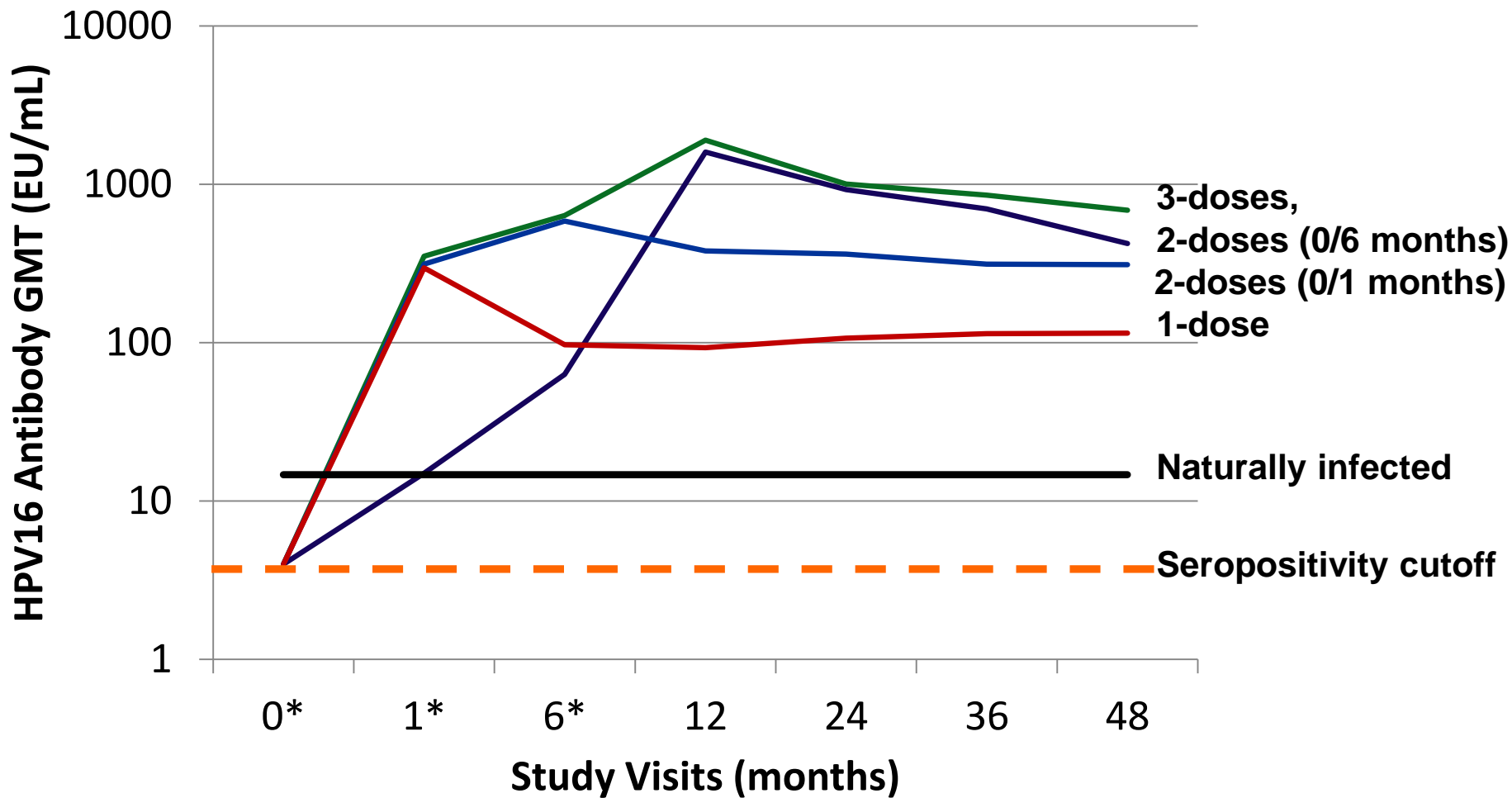
Number of doses	Vaccine arm	Number of women	Number of events	Rate per 100 women	HPV vaccine efficacy % (95% CI)
3 doses	Control	3010	229	7.6%	84 (77-88)
	HPV	2957	37	1.3%	
2 doses	Control	380	24	6.3%	81 (63-94)
	HPV	422	5	1.2%	
1 dose	Control	188	15	8.0%	100 (79-100)
	HPV	196	0	0.0%	

- ***Similar protection was seen against 12 month persistent infection***
- ***It is unknown whether these results can be extrapolated to Gardasil***

*Kreimer et al, JNCI 103: 1444-1450, 2011*



# HPV16 GMTs among seronegatives



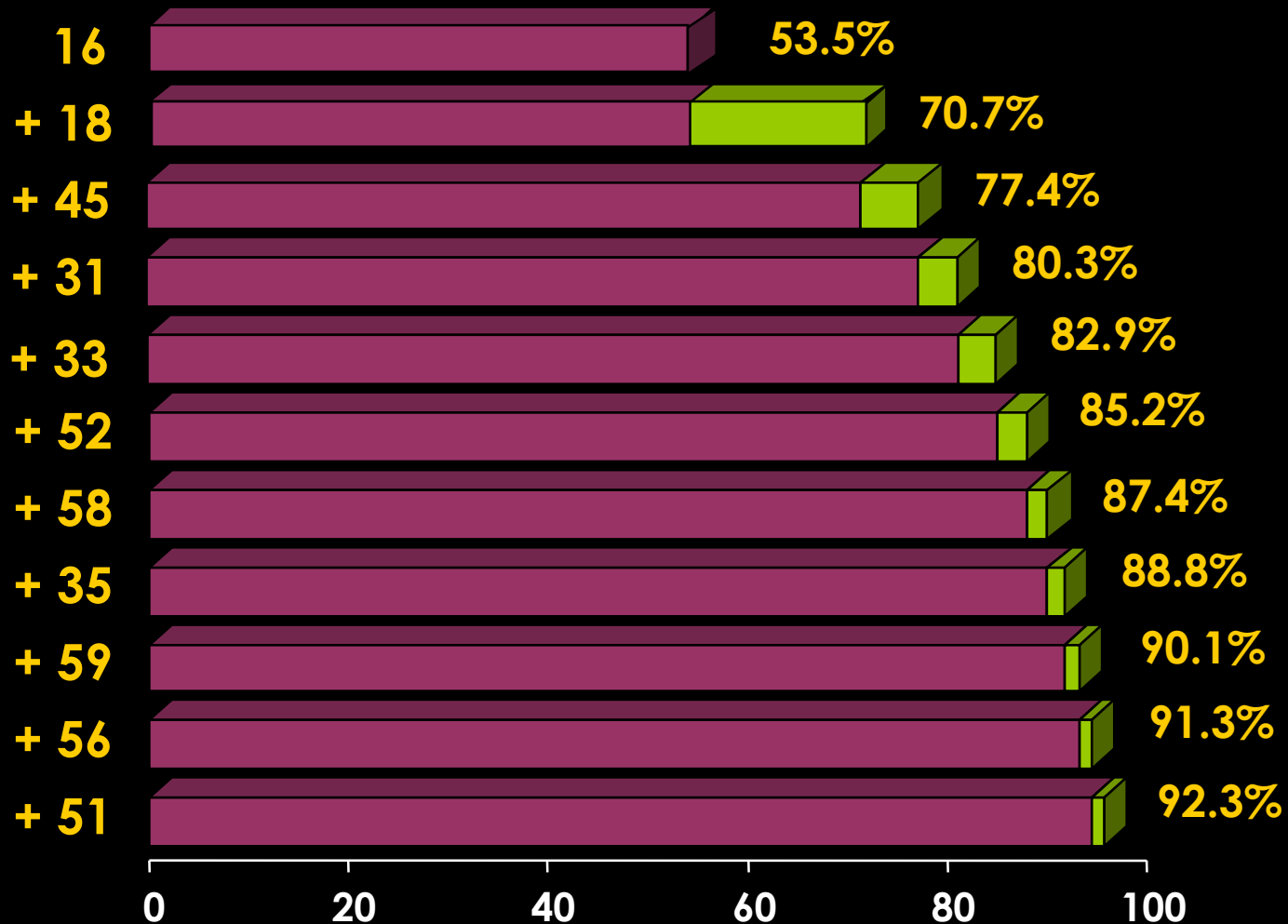
# ***Stable antibody titers after 1 dose***

- **There is no precedent for 1 dose of a protein-based sub-unit vaccine to induce stable antibody titers for several years**
- **May be attributable to two factors**
  - **VLPs are highly immunogenic**
  - **AS04 is a TLR4 agonist**
- **A possible randomized controlled trial to rigorously test the efficacy of 1 dose**
  - **Test two commercial vaccines: one with alum, one with AS04**

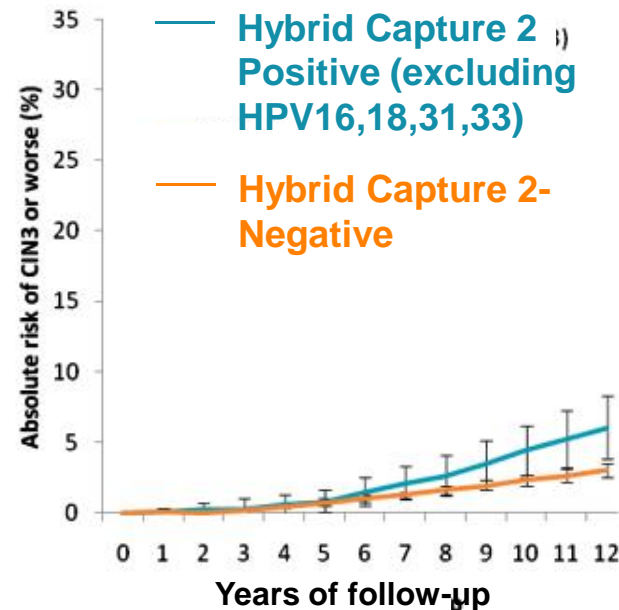
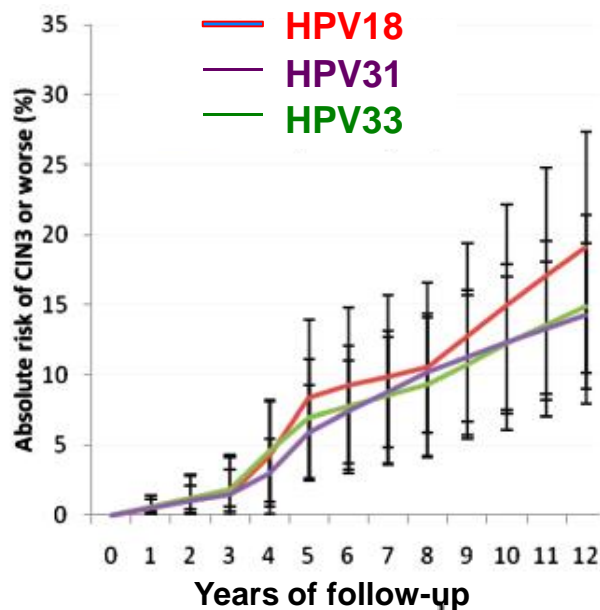
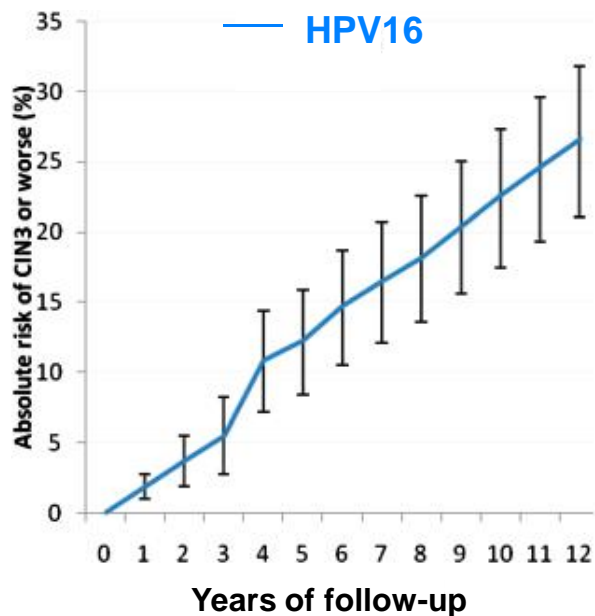
# ***Clinical trial of Merck's Nonavalent (9-valent) vaccine V503***

- In addition to the HPV types in quadrivalent vaccine (HPV6,11,16,18), V503 contains 5 additional oncogenic HPV types (HPV31,33,45,52,58)
- The control group received the quadrivalent vaccine; primary endpoint was CIN2+ against the 5 new HPV types (immunological non-inferiority against the other 4 types)
- ***CIN2+ vaccine efficacy against the 5 HPV types was 96%: 1 case in V503 group vs. 27 cases in quadrivalent group***
- More information: see Merck press release Nov 4, 2013

# Potential Reduction in Cervical Cancer from the Addition of Multiple HPV Types to L1 VLP Vaccine



# HPV Type Affects the Rate of Development of CIN3 or worse in women with normal cytological findings at baseline: The Danish Cohort Study



**A single HPV test predicts 10-fold increased risk of CIN3 for >10 years**

*From Kjaer et al, J Natl Cancer Inst 102: 1478-88, 2010*

# *Summary and Conclusions*

- Precision medicine (i.e., mechanism-based) can be a useful approach for cancer prevention and screening
- The HPV virus-like particle (VLP) vaccine is an example of precision medicine in cancer prevention. HPV-based screening is an example of precision medicine in cancer screening
- The high immunogenicity of the vaccine means long-term protection can be induced with fewer than 3 doses
- Second generation HPV vaccines with activity against a broader range of HPV types will be required to achieve the greatest reduction in HPV-associated disease

***Thank you!***

***lowyd@mail.nih.gov***