Oncogenic Microbial Agents are Molecular Targets

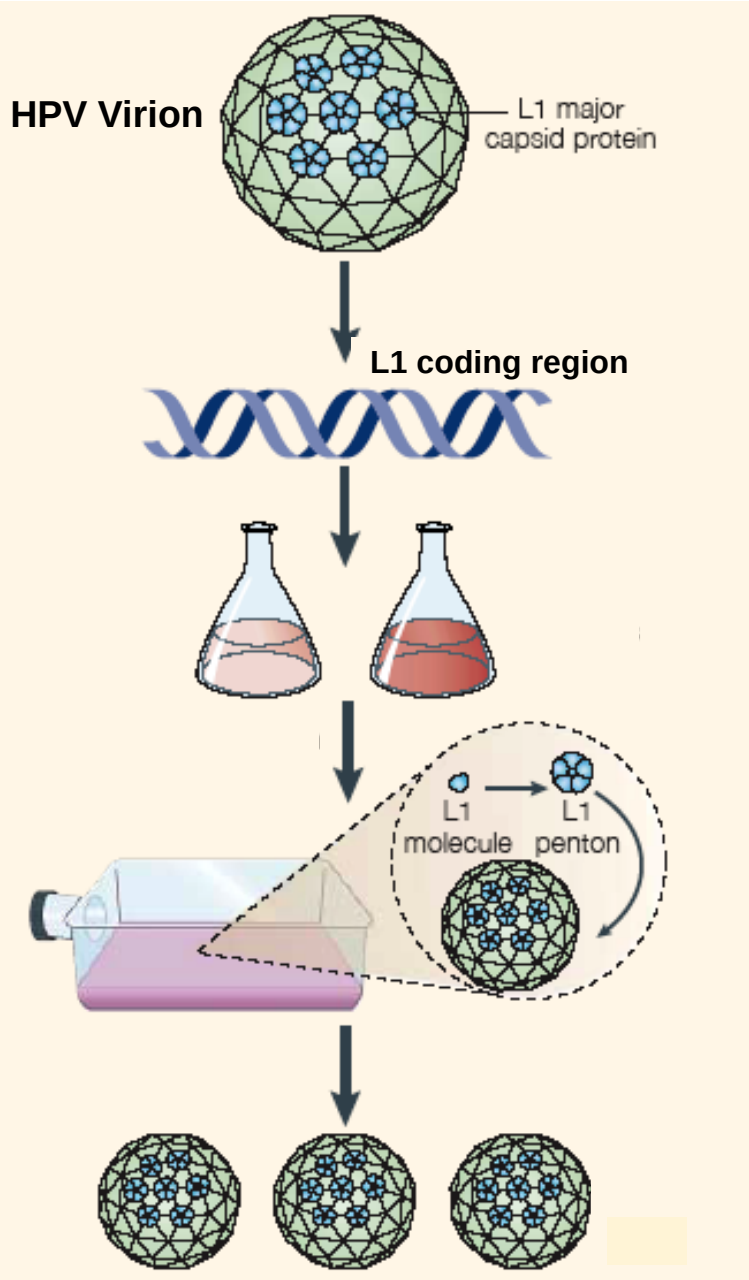
- **Genes and proteins of oncogenic microbial agents (such as HPV) are as much molecular targets as B-raf, EGFR, etc.**
- **Microbial targets (such as HBV, HCV, and HPV) have theoretical translational advantages over cell-encoded targets**
  - **They represent foreign genes and proteins; easier to develop specific interventions against them**
- **For a vaccine, HPV has an additional advantage**
  - **Most HPV infections are self-limited and confer resistance to re-infection; the vaccine simply needs to mimic the main immune response that restricts re-infection**

Our "Qualifications" for Vaccine Development

- Experience in vaccines - no
- Experience in immunology - no
- Experience in translational research - no
- Experience in papillomavirus structural proteins and virus structure - no
- Experience in basic papillomavirus biology - yes

Choosing an appropriate molecular target for a preventive HPV vaccine

- **Licensed vaccines against microbial agents are mainly preventive; induction of neutralizing antibodies is critical.**
- **HPVs contain viral oncogenes (E5, E6, E7). Implies you need a subunit vaccine lacking the oncogenes.**
- **Papillomaviruses encode two proteins that induce neutralizing antibodies, the capsid proteins L1 and L2.**
  - ***L1 contains the immunodominant neutralization epitopes. They are conformationally dependent.***
- ***OUR HYPOTHESIS: L1 can self-assemble to make empty particles having a conformation that induces high levels of neutralizing antibodies.***



Prophylactic HPV Vaccines Are L1 Virus Like Particles (VLPs)

L1 Insertion in Baculovirus Expression Vector

Production in Insect Cells

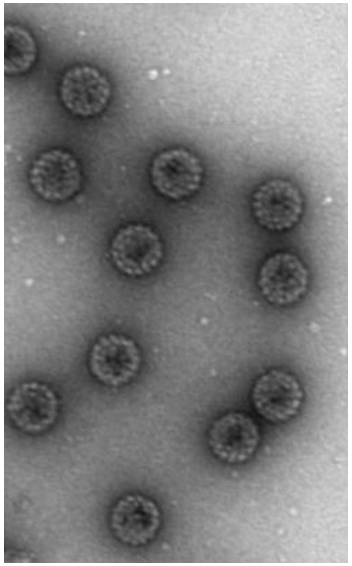
Spontaneous assembly of L1 into VLPs

Induce high titers of virion neutralizing antibodies

Shown initially for BPV-1, then for HPV16

Non-infectious, Non-oncogenic

HPV16 L1 VLPs



Reinhard Kirnbauer et al. PNAS 1992

JOURNAL OF VIROLOGY, Dec. 1993, p. 6929–6936
0022-538X/93/126929-08$02.00/0
Copyright © 1993, American Society for Microbiology
Vol. 67, No. 12

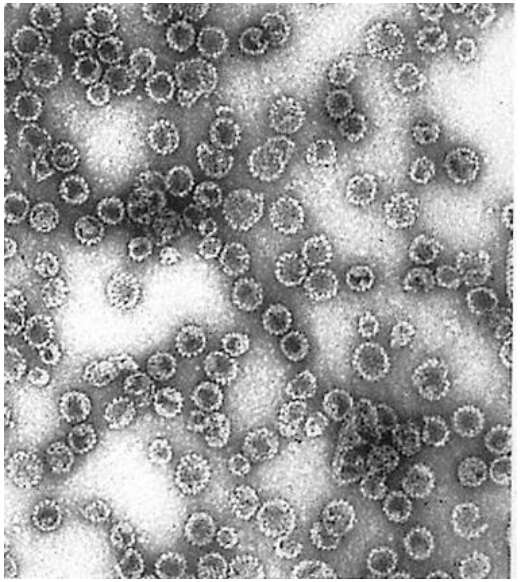
Efficient Self-Assembly of Human Papillomavirus Type 16 L1 and L1-L2 into Virus-Like Particles

REINHARD KIRNBAUER,[1] JANET TAUB,[1] HEATHER GREENSTONE,[1] RICHARD RODEN,[1] MATTHIAS DÜRST,[2] LUTZ GISSMANN,[2] DOUG R. LOWY,[1] AND JOHN T. SCHILLER[1]*

Laboratory of Cellular Oncology, National Cancer Institute, Bethesda, Maryland 20892,[1] and Deutsches Krebsforschungszentrum, 6900 Heidelberg, Germany[2]

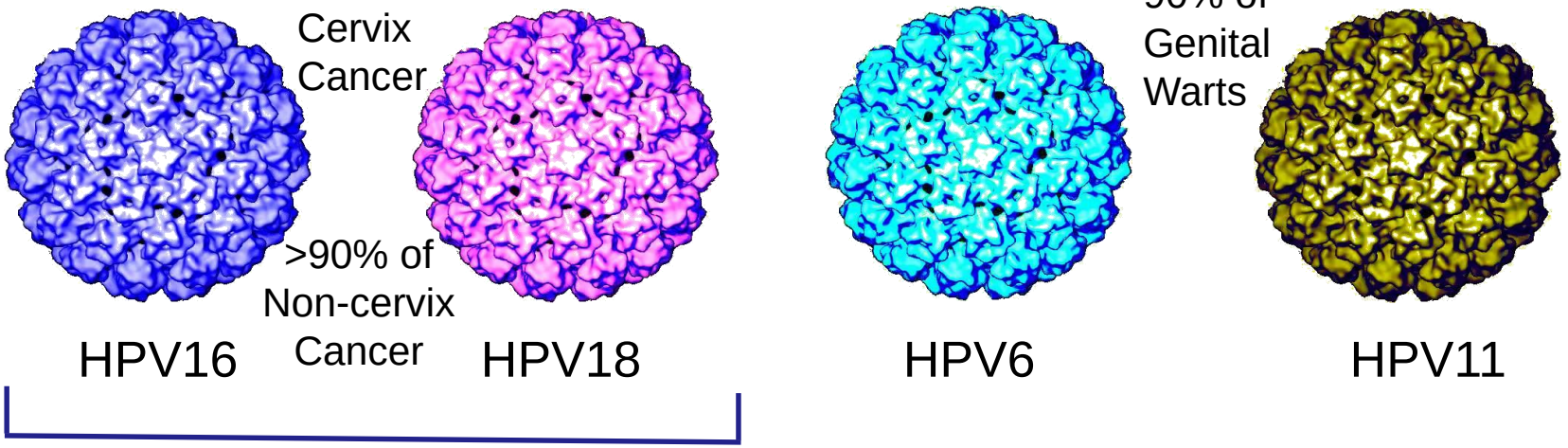
Received 14 June 1993/Accepted 18 August 1993

- HPV16 L1 from the HPV16 reference strain was a mutant. The critical mutation was Histidine at amino acid 202, while wild type HPV16 and other HPVs encode Aspartate at this residue.
- Wild type HPV16 L1, isolated from benign lesions, formed VLPs efficiently, in contrast to the HPV16 reference strain.



The Commercial Vaccines Are Composed of Multiple Types of HPV L1 VLPs

Gardasil (Merck)



Cervarix (GlaxoSmithKline)

Three intramuscular injections over 6 months

Summary of phase III HPV vaccine trials

- **In uninfected patients, HPV vaccination can confer close to 100% protection against incident persistent infection and disease attributable to the HPV vaccine types**
  - **HPV vaccination can also protect against non-cervical infection and disease, while screening is only for cervical cancer**
- **There is limited cross-protection against non-vaccine HPV types.**
- **HPV vaccination does not alter the natural history of prevalent infection, i.e., it is not therapeutic**

Goals of HPV Vaccination

- **To directly reduce the risk of infection and disease in vaccinees**
- **To indirectly reduce these risks by reducing the prevalence of the HPV vaccine types in the general population (herd/community immunity)**

Australia: Fall in Prevalence of HPV Vaccine Types after Initiating National Vaccine Program

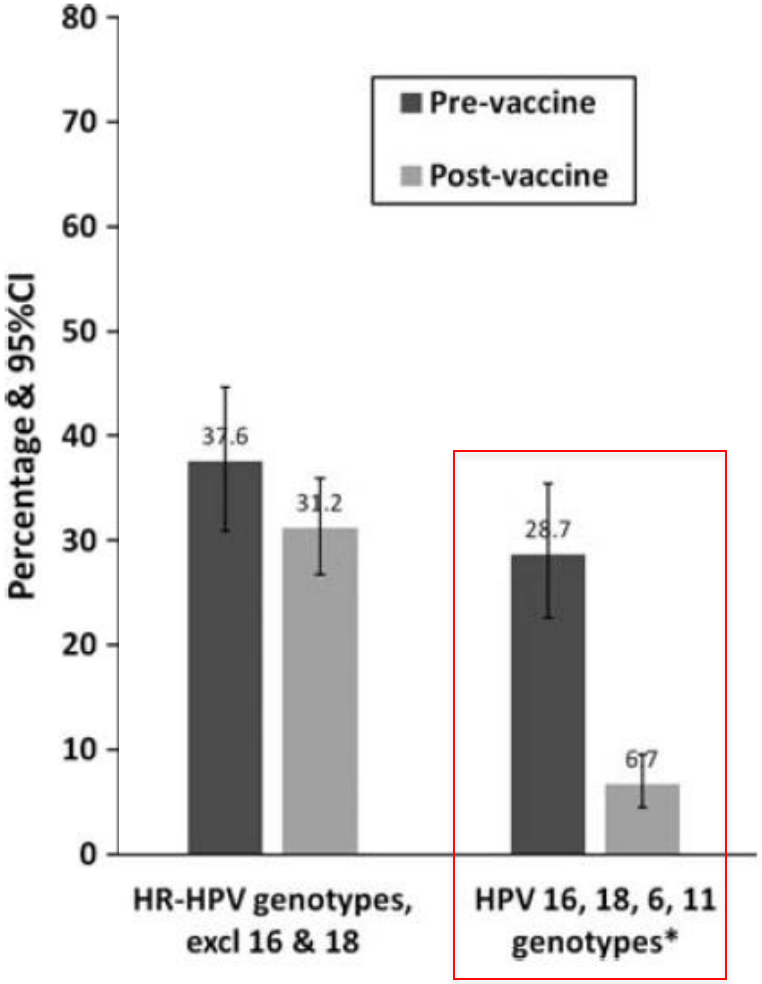
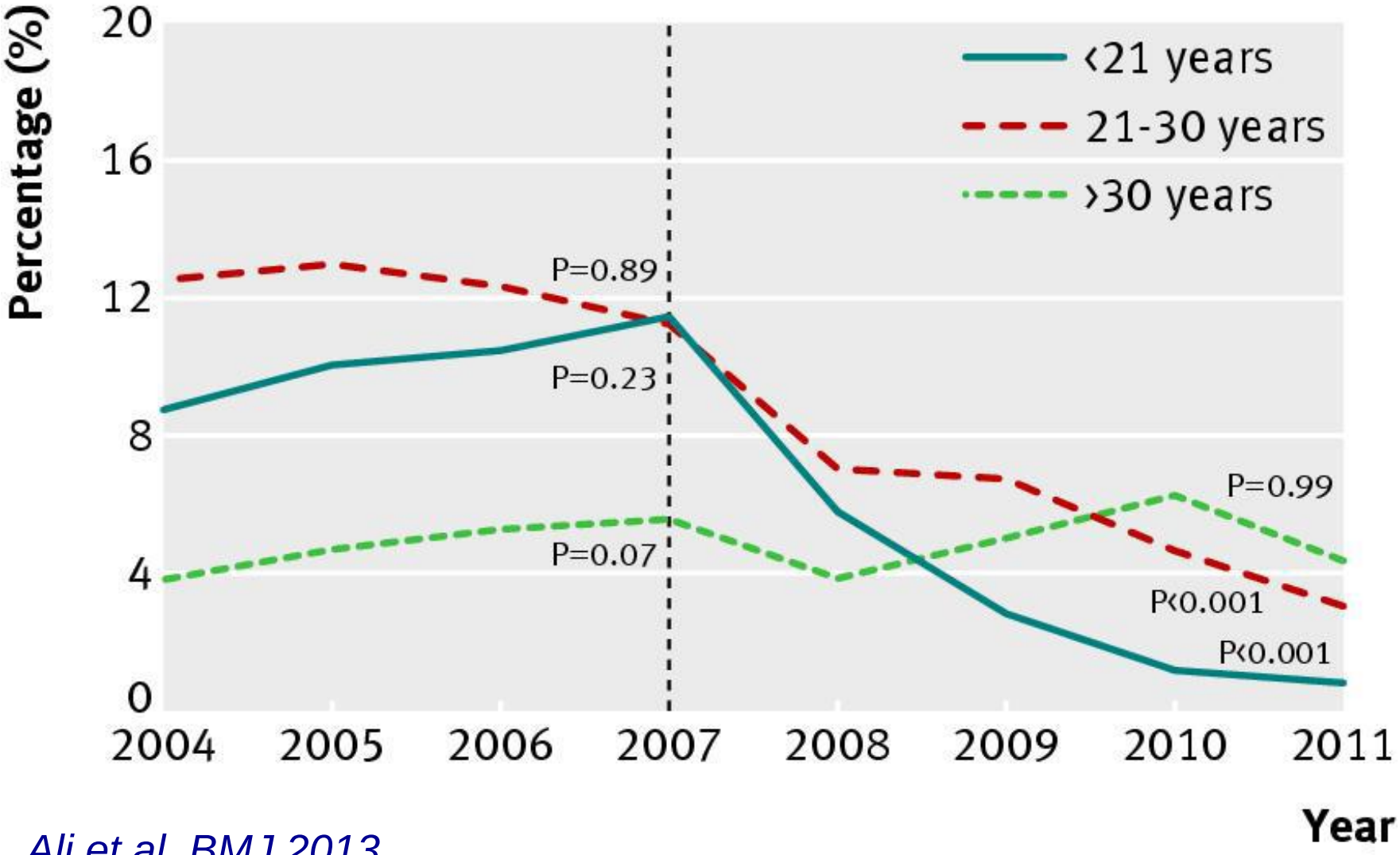


Figure 1. Differences in human papillomavirus (HPV) genoprevalence between prevaccine and postvaccine populations. *$P < .05$ for difference in percentages between groups. Abbreviations: CI, confidence interval; excl, excluding; HR-HPV, high-risk HPV.

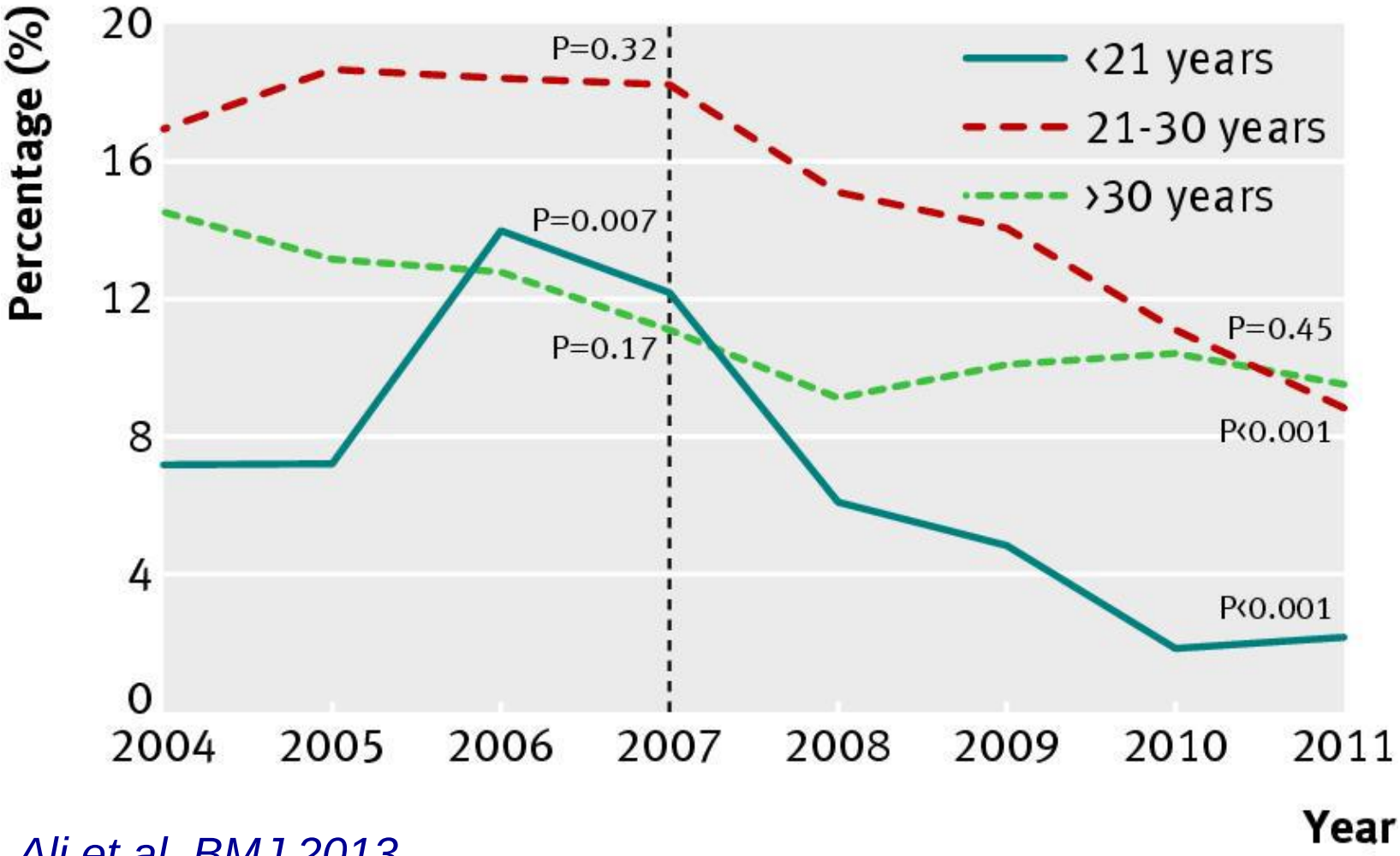
Tabrizi et al, J Infect Dis 206: 1645-51, 2012

Age-dependent Decrease in Genital Warts in Australian Women After HPV Vaccine Implementation in 2007



Ali et al, BMJ 2013

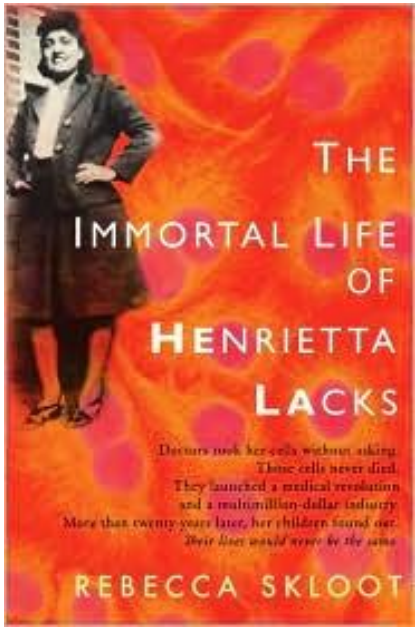
Herd Immunity: Decreased Incidence of Genital Warts in Heterosexual Australian Men Following Female HPV Vaccine Implementation in 2007



Ali et al, BMJ 2013

Henrietta Lacks (HeLa cells) had Cervical Adenocarcinoma

- **Pap smear screening has been more effective in reducing the incidence of squamous cell carcinoma than adenocarcinoma**
- **~ 90% of adenocarcinoma of the cervix is caused by HPV16 or HPV18**
- **Henrietta Lacks had cervical adenocarcinoma not detected by cytology**
- **Her cancer should now be preventable by HPV vaccination or HPV-based screening**



High Efficacy of VLP Vaccine

- **The repetitive structure of the VLP immunogen is intrinsically immunogenic**
- **Tissue-associated neutralizing antibodies are exudated at potential sites of infection**
  - **Antibody levels at these sites reflect their level in serum, rather than their lower level in the non-disrupted genital tract**
- **HPV is highly susceptible to neutralizing antibodies**

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**