National Cancer Institute

The HPV Vaccine: From Bench to Bedside

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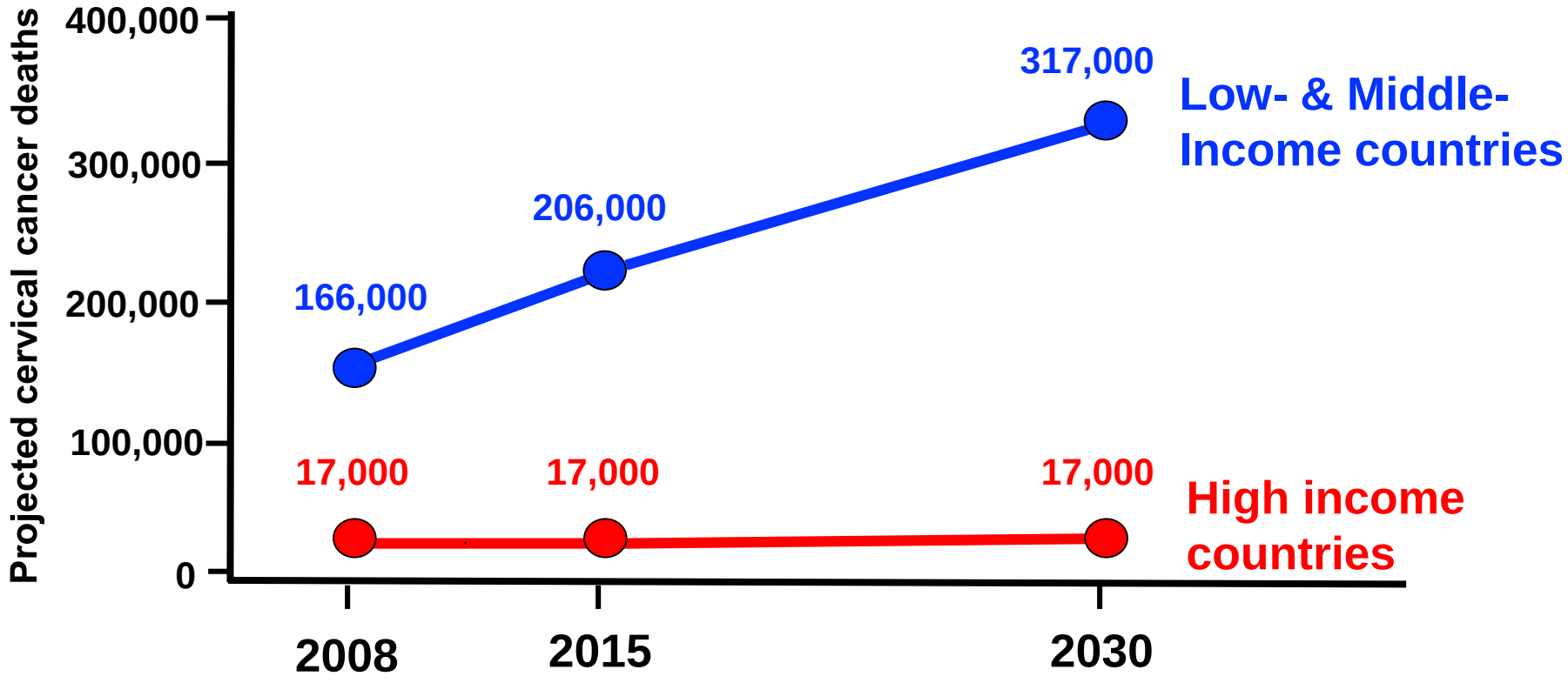
The views expressed are my own and do not necessarily reflect those of NCI/NIH

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health

Disclosures

- National Institutes of Health (NIH) has patents on papillomavirus L1 virus-like particle (VLP) vaccine technology. I am an inventor.
- NIH has licensed L1 VLP technology to Merck and GlaxoSmithKline, the two companies with commercial versions of the vaccine.
- ***I will discuss potential off-label uses of the EMA/FDA-approved vaccines: protecting against HPV-positive oropharyx cancer and fewer vaccine doses***
- Licensees of other NIH technologies of which I am an inventor: GlaxoSmithKline, Sanofi, Shanta Biotech, Cytos Biotech, Aura Biosciences, Etna Biotech, Acambis, PanVax

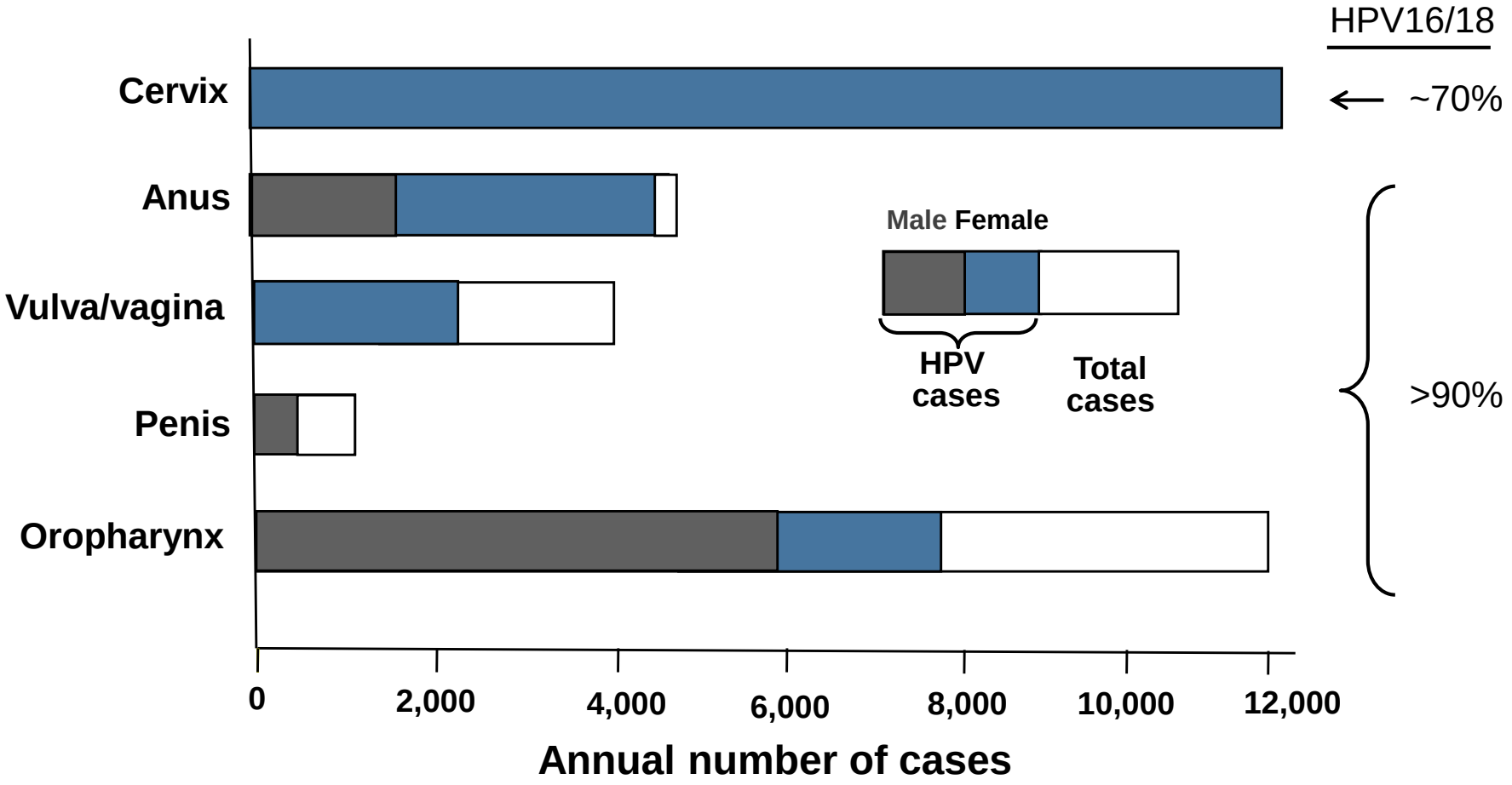
IARC's Globocan 2012 projection: Cervical cancer mortality rates continue to increase in Low- & Middle-income countries (LMIC's)



- In LMIC's, cervical cancer represents ~90% of HPV-associated cancer

Projections developed from Globocan 2012

USA: HPV-associated Non-cervical Cancers Affect Both Genders and are as Common as Cervical Cancer



- **Pap screening has reduced cervical cancer incidence by ~80%**
- **No approved screening tests for other HPV-associated cancers**
- **Incidence of HPV-positive oropharynx cancer 1988-2004 increased >3-fold**

MMWR, 2012; Chaturvedi et al, J Clin Oncol, 2011; Gillison, Chaturvedi, and Lowy., 2008

First Generation HPV Vaccines

Many Collaborators: If you want to go quickly, go alone; If you want to go far, go together

Laboratory of Cellular Oncology, CCR, NCI

John Schiller

Patricia Day
Rhonda Kines
Cynthia Thompson
Tara Berman

Nicolas Cuburu
Susana Pang
Alessandra Handisurya
Carla Cerqueira

Chris Buck, Diana Pastrana - ***LCO, CCR, NCI Bethesda***

Aimee Kreimer, Allan Hildesheim, Mark Schiffman, Mahboobeh Safaeian, Ligia Pinto - ***DCEG, NCI, Bethesda***

Peter Choyke, Marcelino Bernardo - ***Molecular Imaging, CCR, NCI, Bethesda***

Jeffrey Roberts – FDA, Rockville

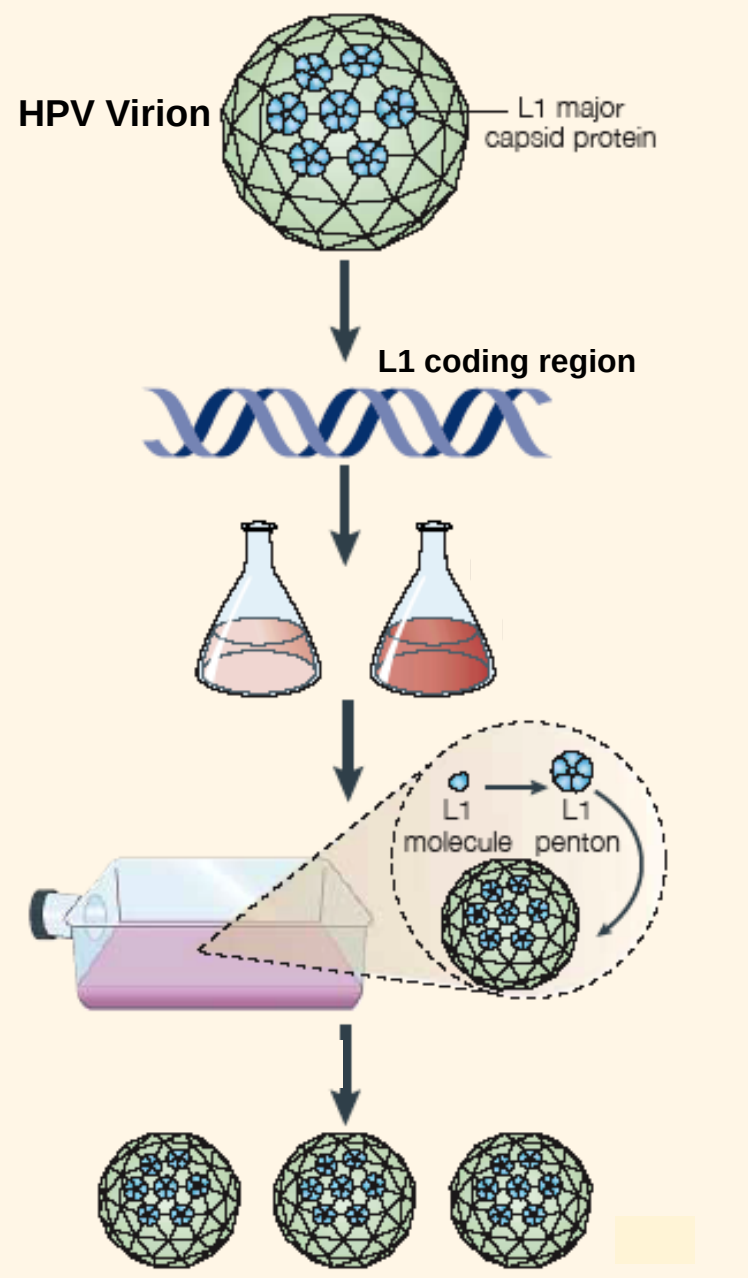
Rolando Herrero – ***IARC, Lyon, France***

Bryce Chackerian - ***University of New Mexico***

Reinhard Kirnbauer - ***University of Vienna, Austria***

Choosing an appropriate molecular target for a preventive HPV vaccine

- **Licensed vaccines: mainly preventive, induce neutralizing antibodies**
- **HPVs contain viral oncogenes (E5, E6, E7); need subunit vaccine lacking oncogenes.**
- **Two HPV proteins can induce neutralizing antibodies: capsid proteins L1 and L2.**
  - ***L1 contains the most immunogenic neutralization epitopes; conformational***
- ***OUR HYPOTHESIS: L1 self-assembles, makes empty particles with correct conformation, induce high levels of neutralizing antibodies.***



Prophylactic HPV Vaccines Are L1 Virus-Like Particles (VLPs)

Insert L1 in Baculovirus expression vector

Produce L1 in insect cells

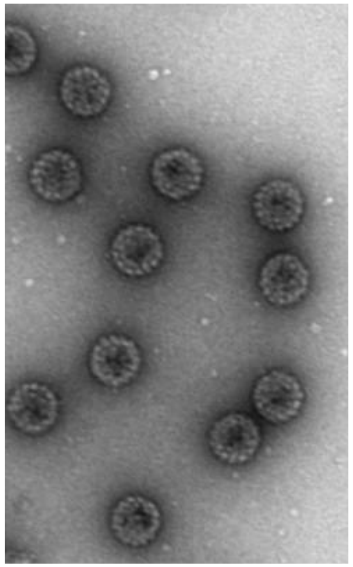
L1 spontaneously assembles into VLPs

L1 VLP vaccination Induces high titers of neutralizing antibodies

Shown first for BPV-1, then for HPV16

Non-infectious, Non-oncogenic

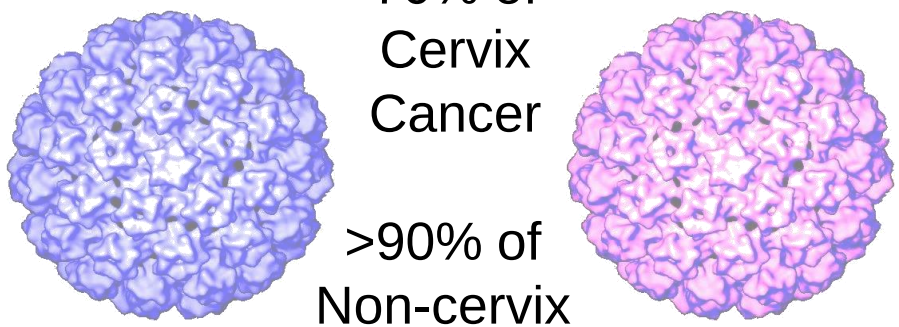
HPV16 L1 VLPs



Reinhard Kirnbauer et al. PNAS 1992; J Virol 1993

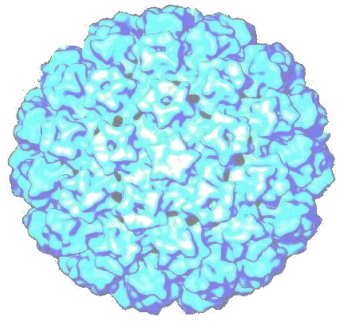
First generation HPV vaccines: Composed of Multiple Types of HPV L1 VLPs

Gardasil (quadrivalent, Merck)

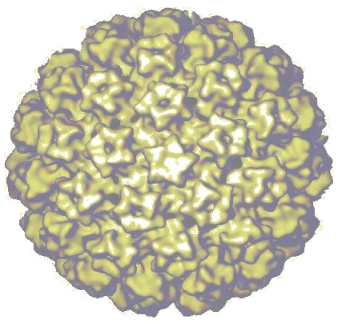


70% of Cervix Cancer

>90% of Non-cervix Cancer



90% of Genital Warts



HPV16 HPV18 HPV6 HPV11

Cervarix (bivalent, GlaxoSmithKline)

Three intramuscular injections over 6 months

Vaccine 29 (2011) 8279–8284

Contents lists available at SciVerse ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Monitoring the safety of quadrivalent human papillomavirus vaccine: Findings from the Vaccine Safety Datalink☆

Julianne Gee[a,*], Allison Naleway[b], Irene Shui[c], James Baggs[a], Ruihua Yin[c], Rong Li[c], Martin Kulldorff[c], Edwin Lewis[d], Bruce Fireman[d], Matthew F. Daley[e], Nicola P. Klein[d], Eric S. Weintraub[a]

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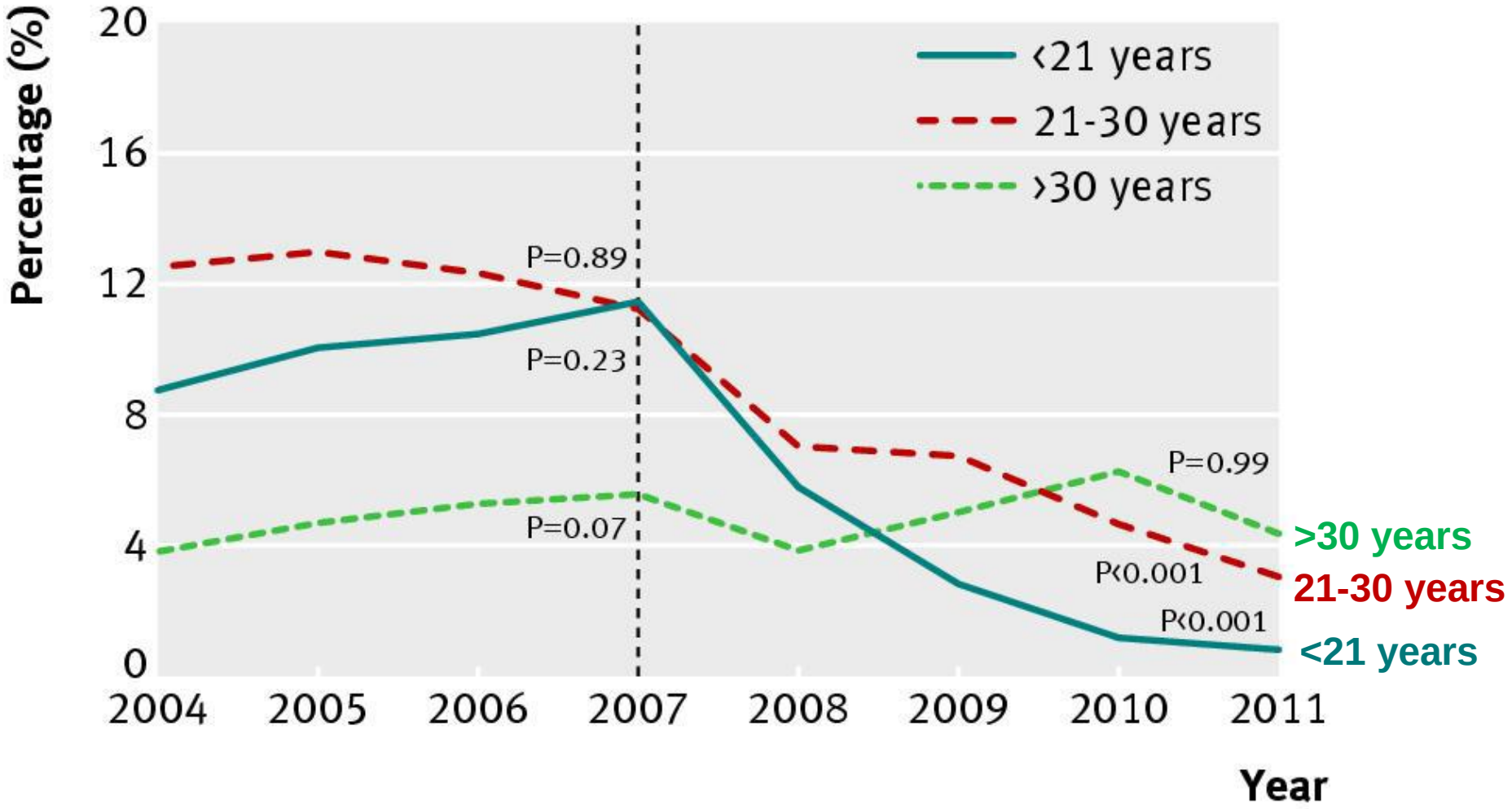
- Prospective post-licensure assessment of 600,558 doses (Gardasil) from 7 managed care organizations
- ***No excessive vaccine-related increased risk to prespecified outcomes:*** Guillan-Barré syndrome, stroke, venous thromboembolism, appendicitis, seizure, *allergic reactions*
  - Prespecified outcomes were derived from CDC analysis from VAERS (Vaccine Adverse Events Reporting System): Slade et al, JAMA 2009
  - Similar conclusions in Denmark from 997,585 girls, of whom 296,826 received 696,240 doses (Gardasil): Arnheim-Dahlstrom et al., BMJ, 2013
  - ***Rate of anaphylaxis (1 case, 26 y.o.) similar to other vaccines***
  - Rate of fainting similar to that of other adolescent vaccines

Short-term Population-wide Impact of HPV Vaccination

Goals of HPV Vaccination

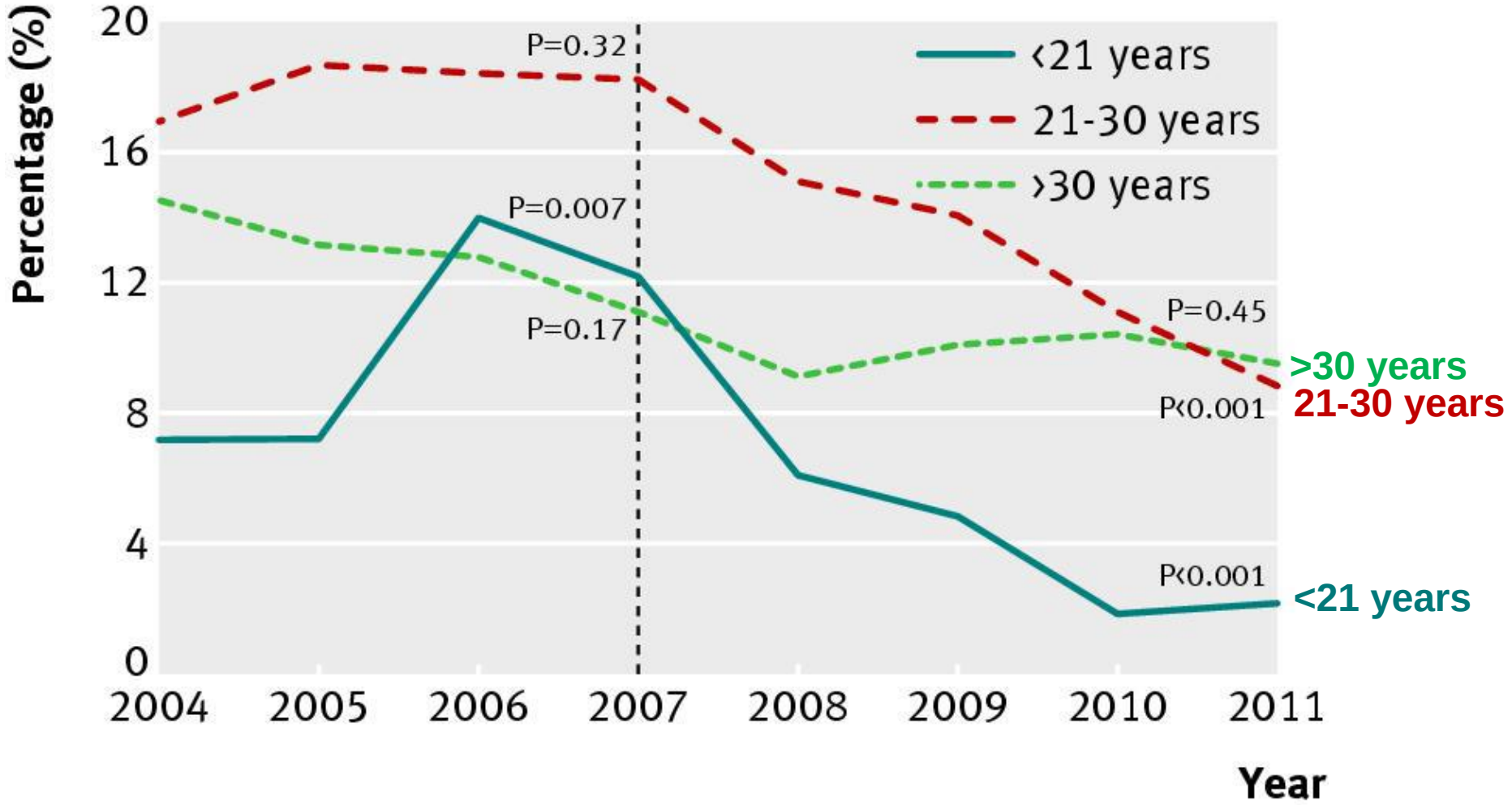
- **Directly reduce risk of infection and disease in vaccinees**
- **Indirectly reduce risk by reducing prevalence of “HPV vaccine types” in general population (herd immunity)**

Age-dependent decrease in genital warts in Australian women after HPV Vaccine Implementation in 2007



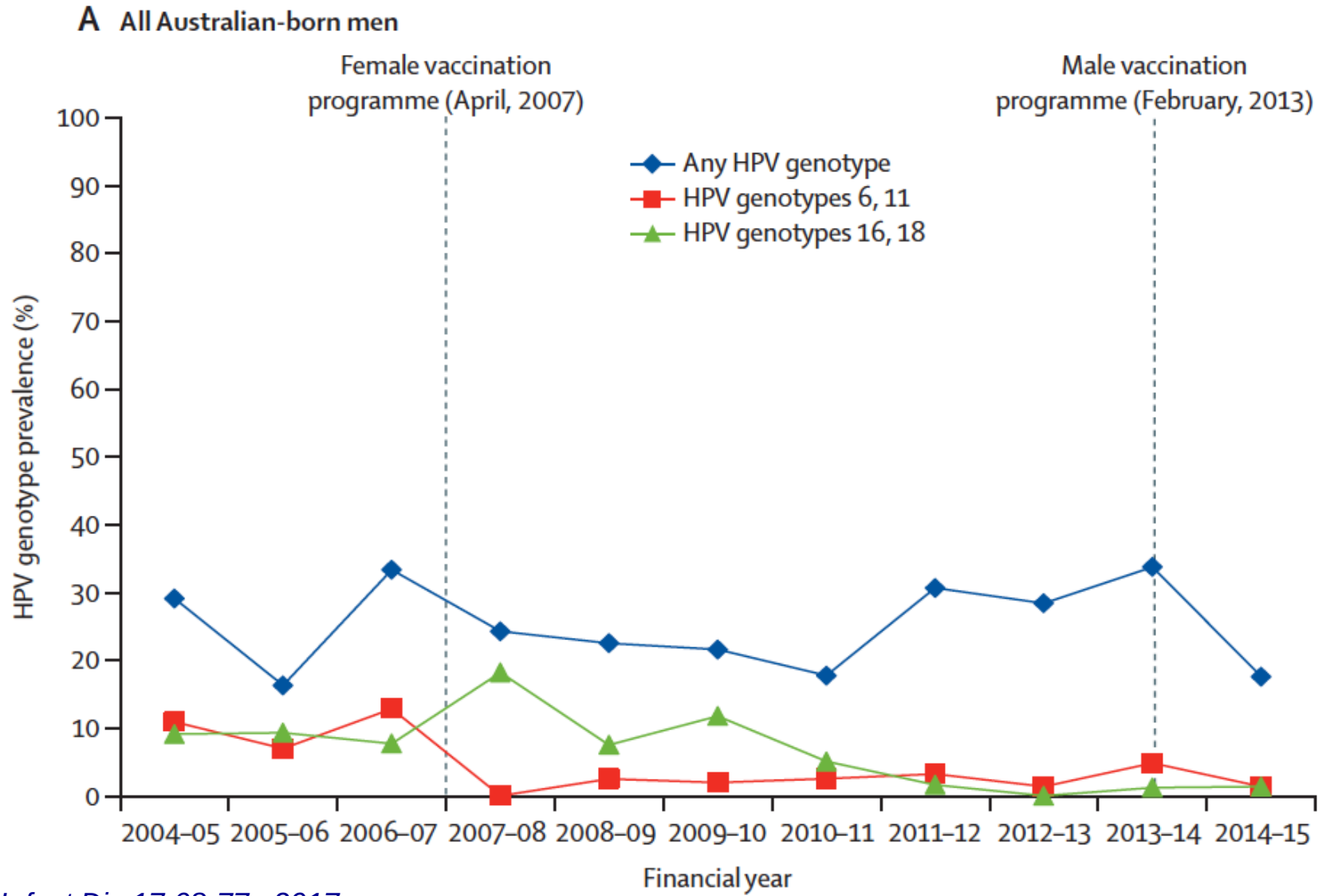
Ali et al, BMJ 2013

Herd Immunity: Decreased incidence of genital warts in heterosexual Australian men following female HPV vaccine implementation in 2007



Ali et al, BMJ 2013

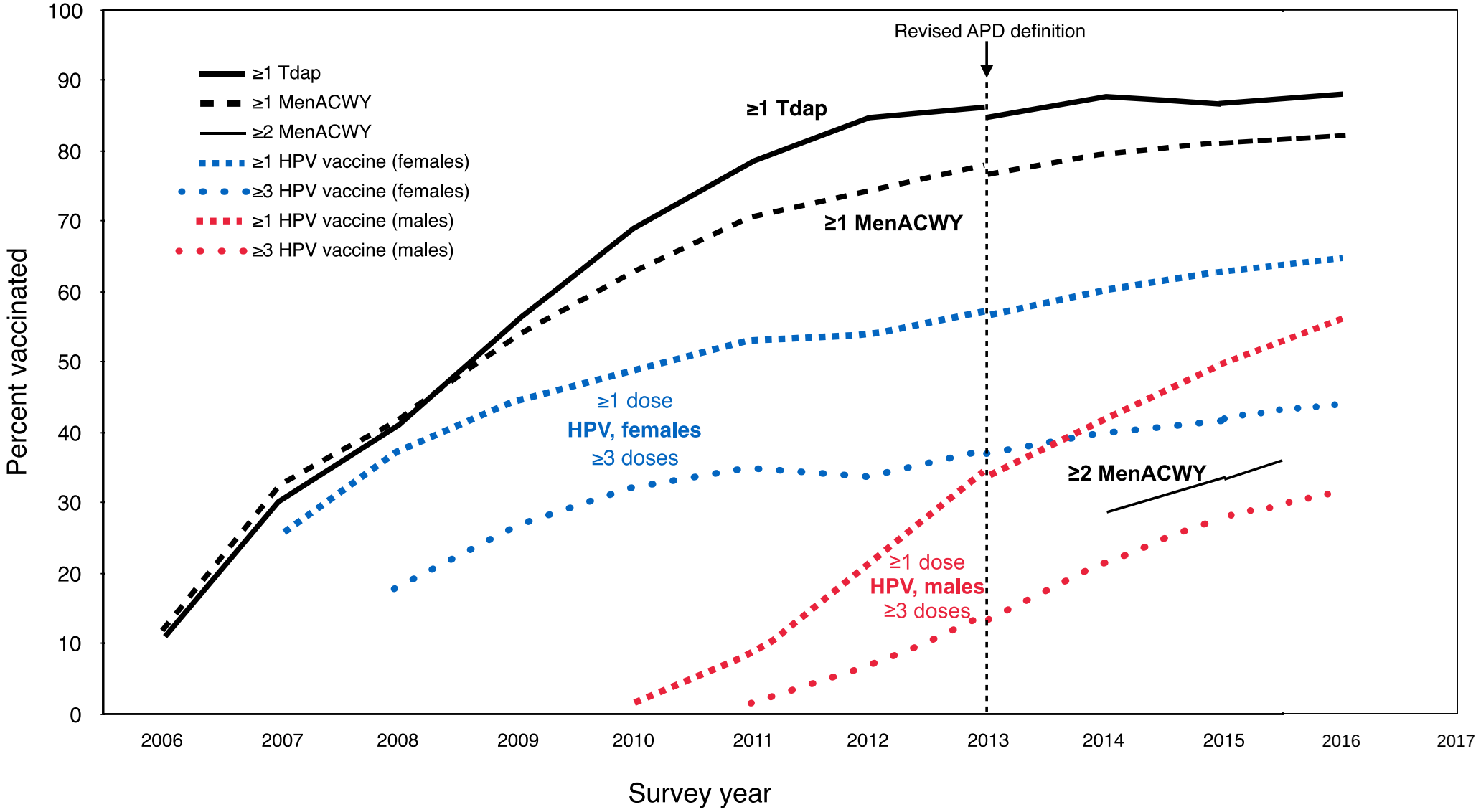
Herd immunity: Decreased prevalence of HPV6/11/16/18 in heterosexual Australian men following female HPV vaccine implementation in 2007



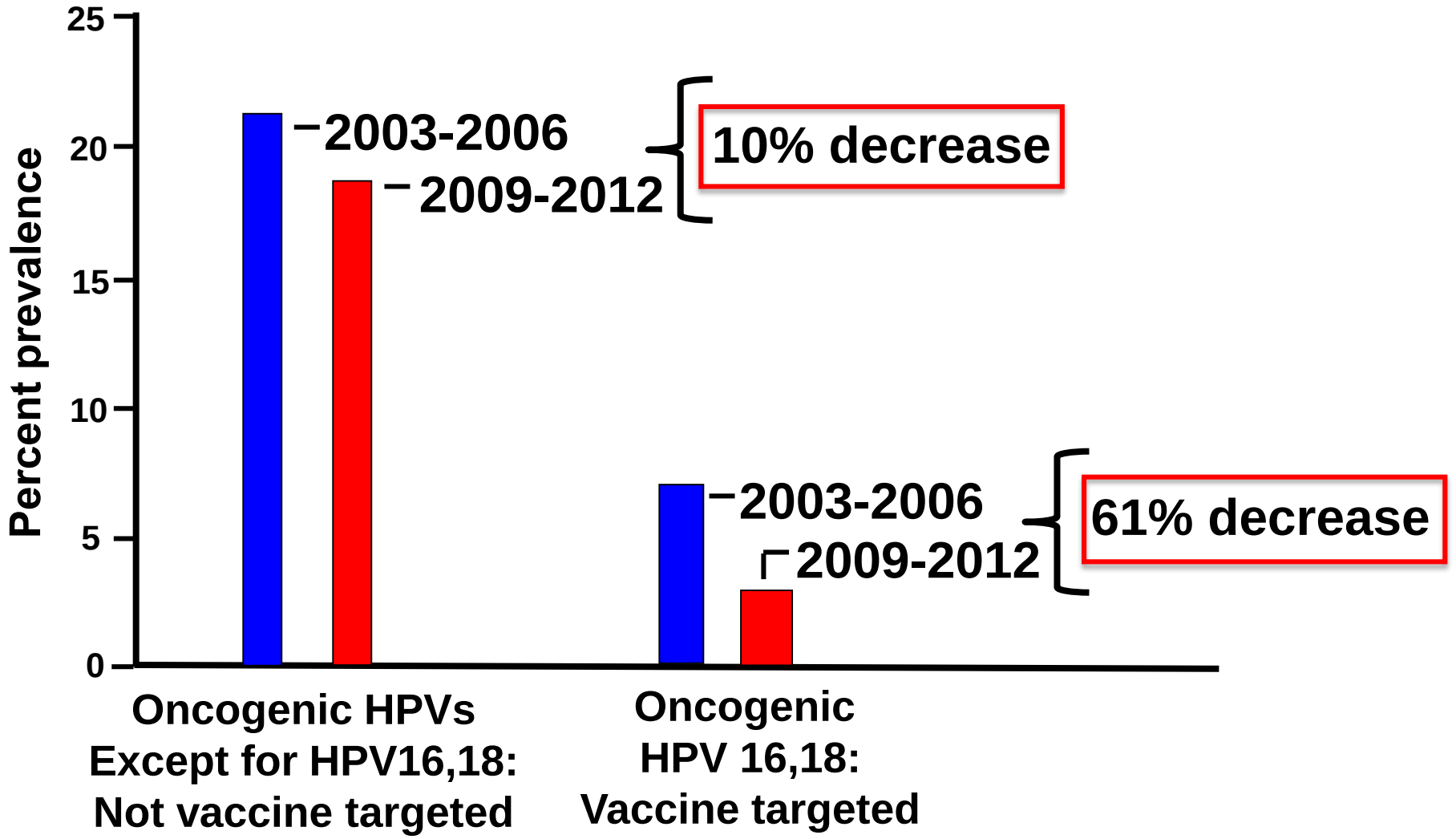
Chow et al, Lancet Infect Dis 17:68-77, 2017

Trends in U.S. Vaccination Rates: Ages 13-17 Years

MMWR Vol. 66, #33, August 25, 2017



Decreased prevalence of HPV16/18 in the US despite limited HPV vaccine uptake: 14-19 year old girls (51% received 1 or more doses)



Adapted from Markowitz et al, Pediatrics 2016

Parents' Top 5 Reasons for not vaccinating their Children with the HPV Vaccine (CDC, 2013)

Parents of girls		
Reason	**%**	**(95% CI)**
Lack of knowledge	15.5	(13.0–18.5)
Not needed or necessary	14.7	(12.5–17.3)
Safety concern/Side effects	14.2	(11.8–16.8)
Not recommended	13.0	(10.8–15.5)
Not sexually active	11.3	(9.1–13.9)

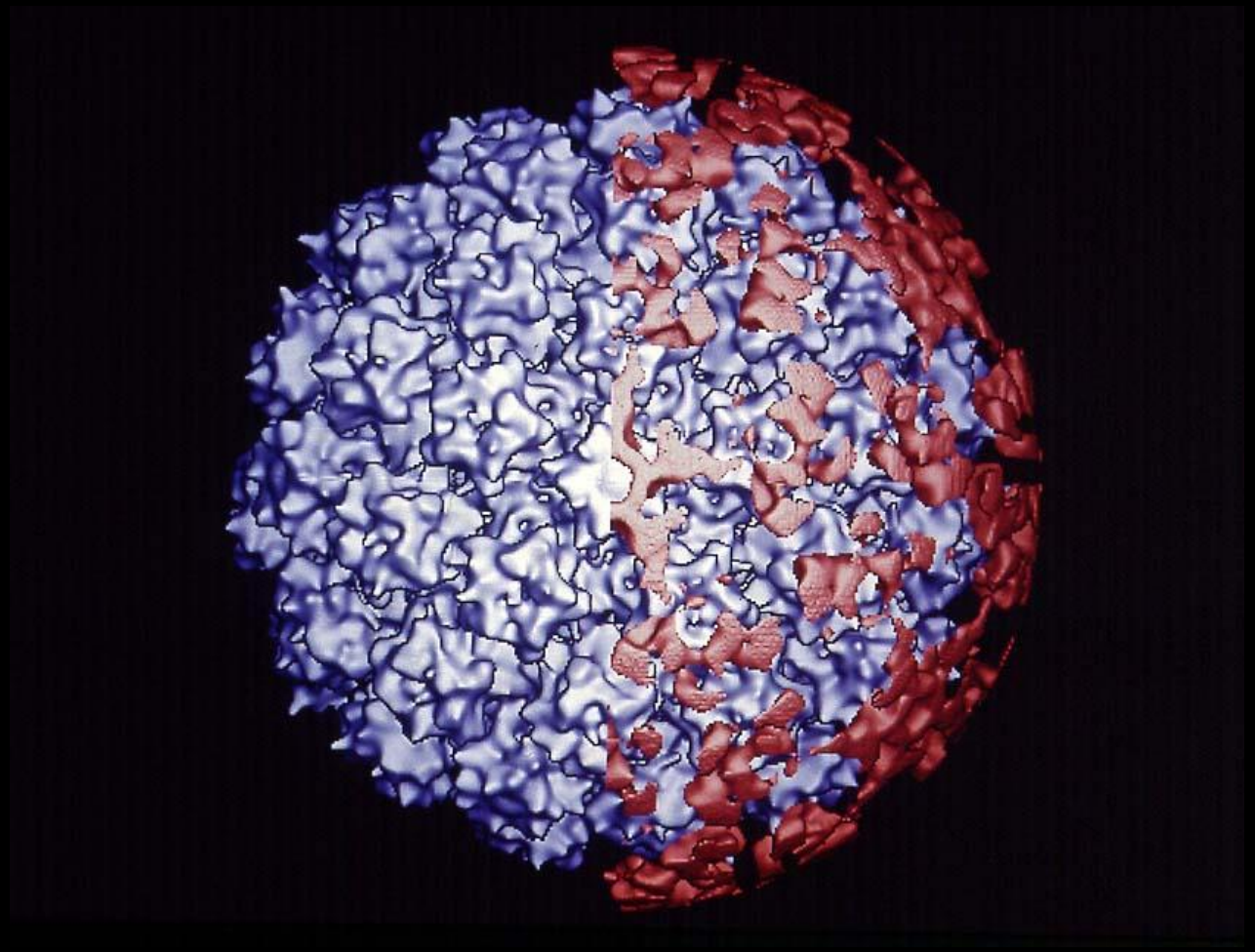
Parents of boys		
Reason	**%**	**(95% CI)**
Not recommended	22.8	(20.6–25.0)
Not needed or necessary	17.9	(15.9–20.1)
Lack of knowledge	15.5	(13.7–17.6)
Not sexually active	7.7	(6.4–9.2)
Safety concern/Side effects	6.9	(5.6–8.5)

Stokley et al, MMWR 63:620-4, July 25, 2014

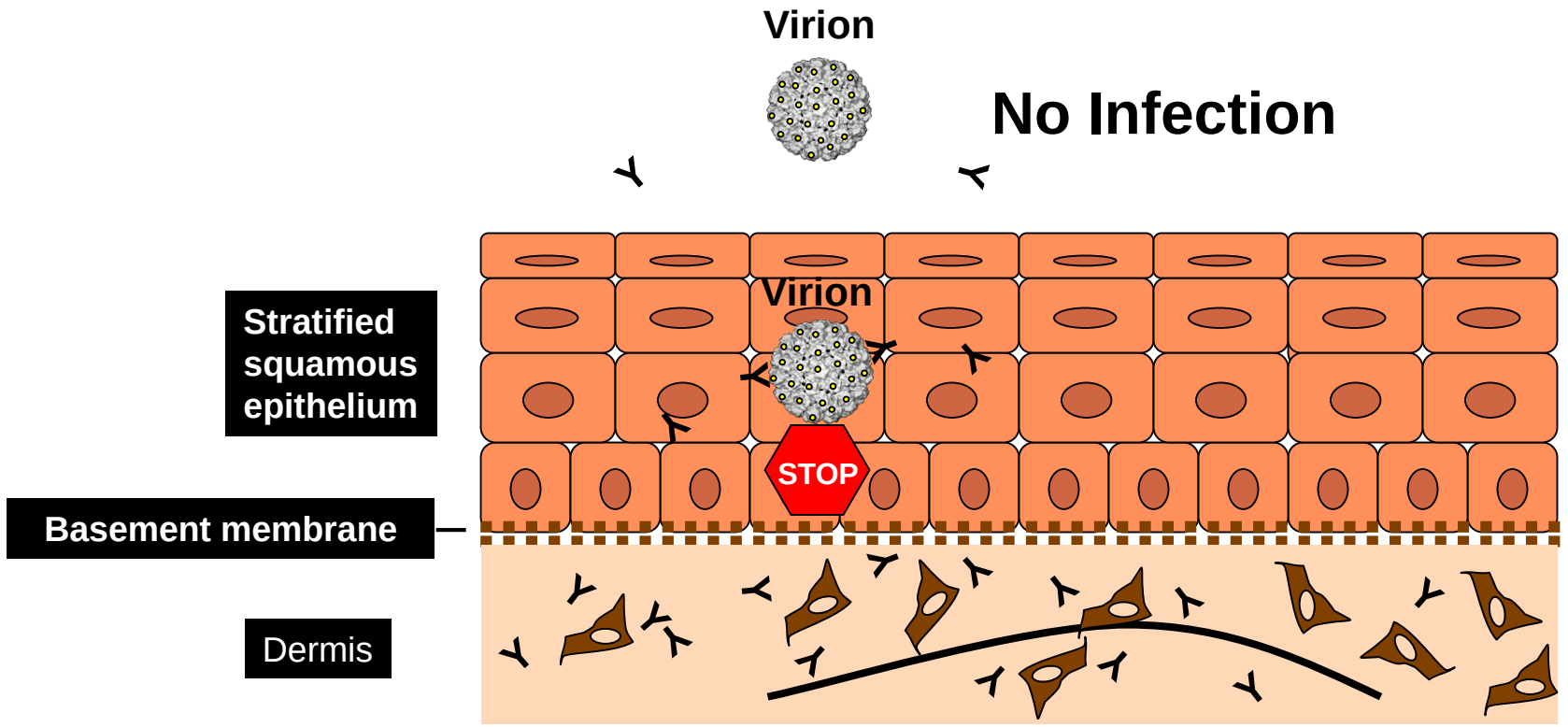
High Efficacy of VLP Vaccine

- **Repetitive structure of VLP intrinsically immunogenic**
- **Tissue-associated neutralizing antibodies exudated at potential sites of infection**
  - **Levels of exudated antibodies high, similar to serum levels, not lower levels of non-disrupted genital tract**
- **HPV highly susceptible to neutralizing antibodies**

Neutralizing L1 Antibodies (in red) Bound to Papillomavirus Particle



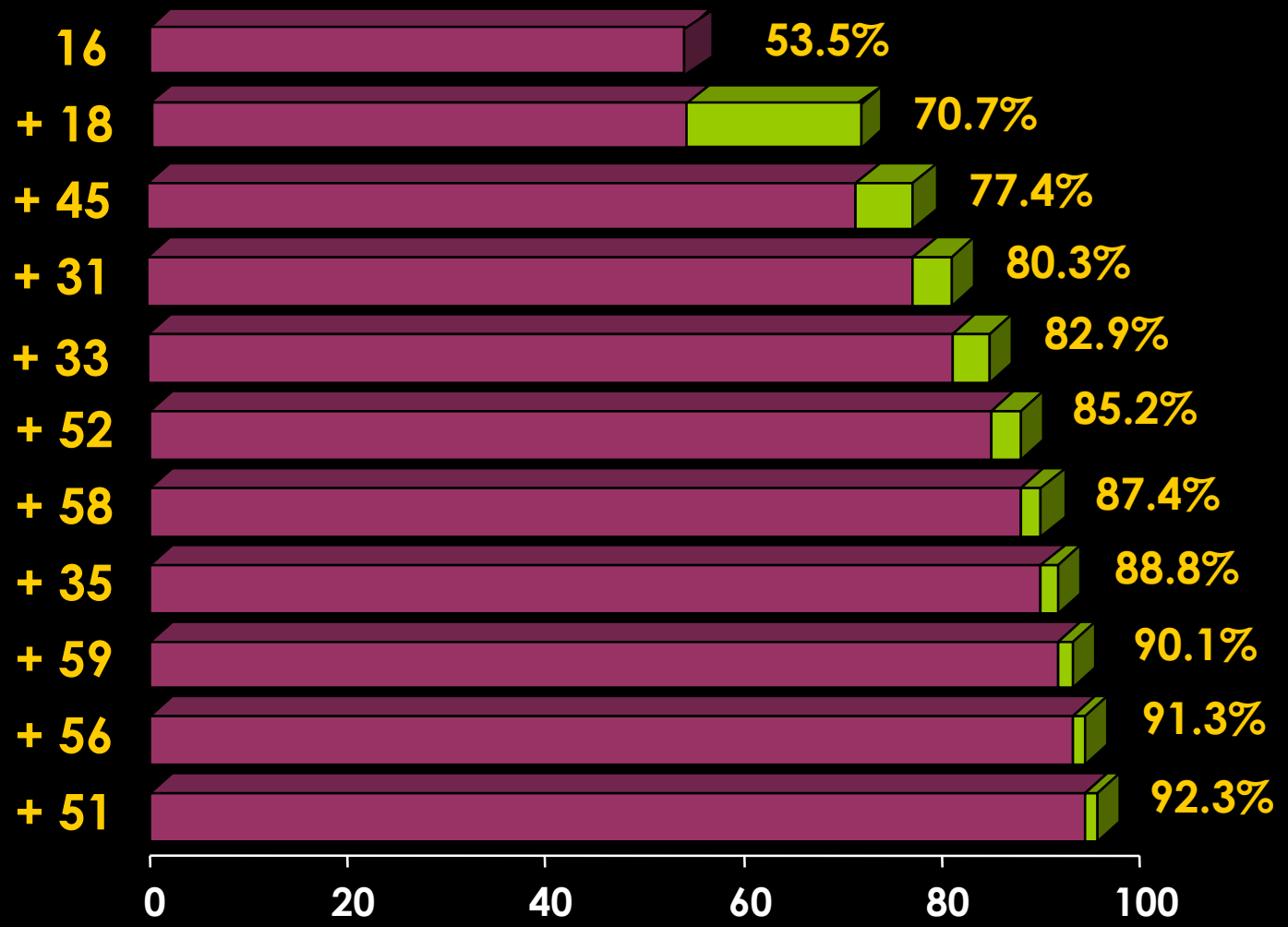
High titer antibodies induced by HPV vaccination prevent basement membrane binding



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

Second generation vaccine: Protecting against more HPV types

Further reduction in cervical cancer by adding more HPV Types to L1 VLP Vaccine



Adapted from Munoz et al, Int J Cancer 111: 278-85, 2004

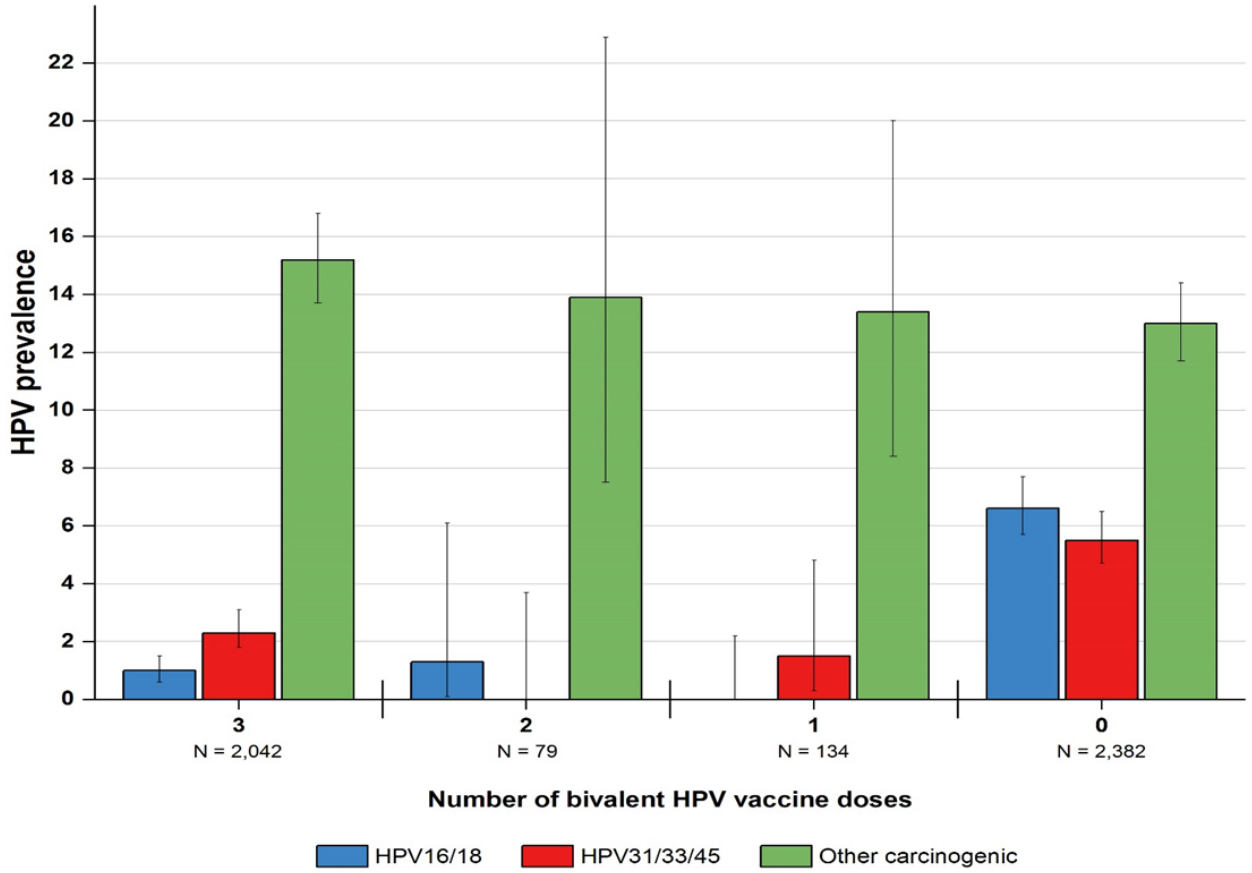
Might a single HPV vaccine dose confer years of protection?

A challenge: Projected limited impact on worldwide cervical cancer from current global HPV vaccination rates

- Only ~3% of eligible women in Low- and Middle-income countries (LMICs) have been vaccinated
  - ~33% of eligible women in industrialized world have been vaccinated
- Women in LMICs account for ~90% of worldwide cervical cancer mortality; ~8% of worldwide female cancer mortality
- **Widespread global uptake of HPV vaccine may require decreased costs & simplified logistics**
- **Possible solutions: Producing biosimilar vaccines and protecting vaccinees with a single dose**

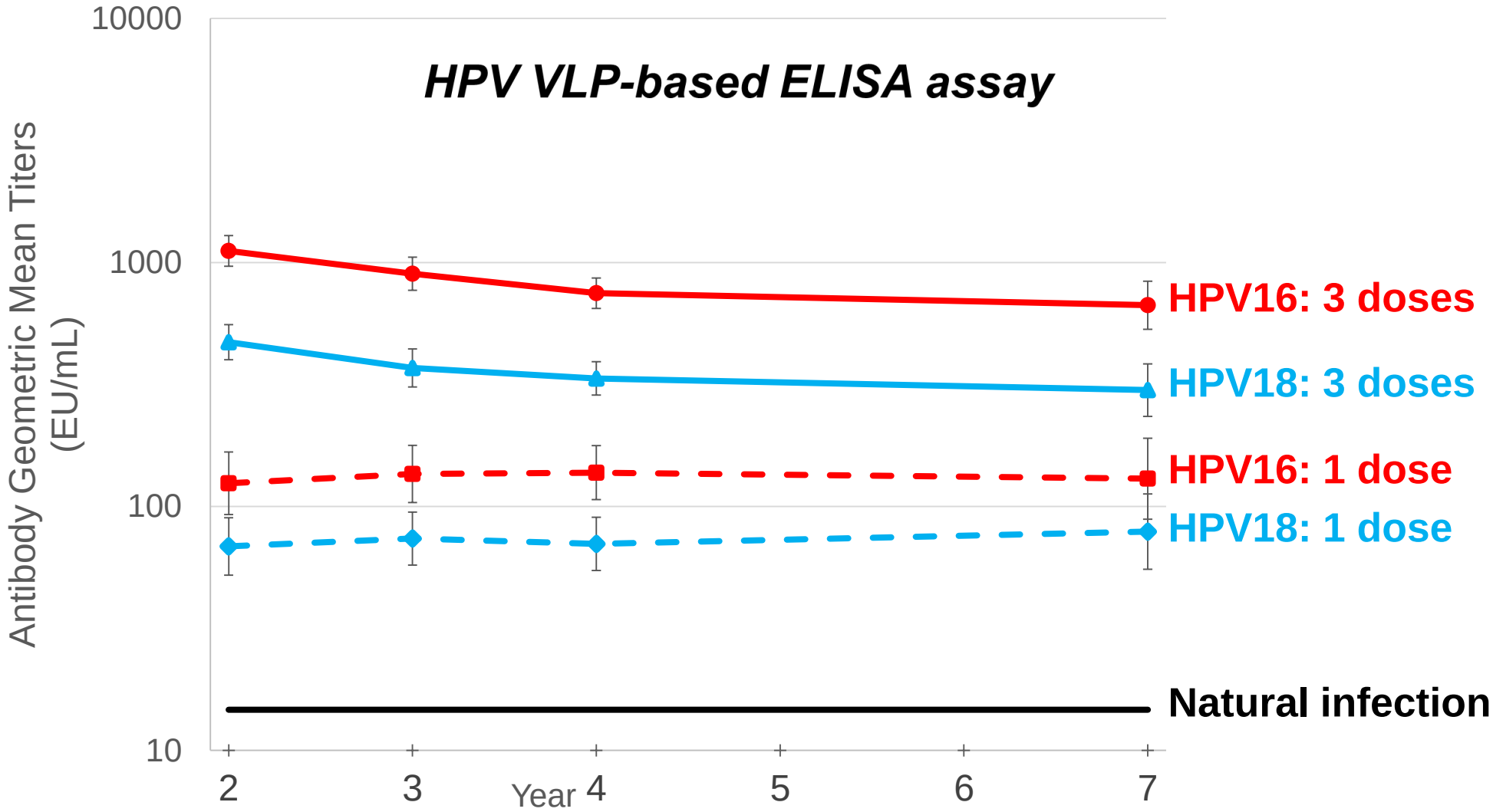
1, 2, or 3 doses of bivalent vaccine confer at least 7 years of protection against incident HPV 16/18 infection: Post-hoc analysis

Safaeian et al, J Natl Cancer Inst, published August 28, 2017



- *Similar shorter term results in GSK PATRICIA trial: Kreimer et al, Lancet Oncol 2015*
- *Similar shorter term Gardasil results in IARC India trial, Sandaranarayanan et al, Lancet Oncol 2016*

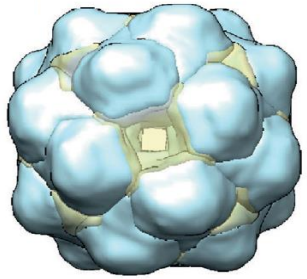
Stable HPV16/18 serum antibodies after bivalent HPV vaccination: Costa Rica Vaccine Trial



Safaeian M et al, JNCI, published August 28, 2017

Stable antibody titers have not been seen with other particle-based vaccines: Possible explanations

- **No precedent for stable antibody titers in a protein-based subunit vaccine**
- Hepatitis B virus (HBV) vaccine observations:
  - One dose induces a poor antibody response
  - Antibody titers continue to wane after 3 doses



Zhao, Trend Biotech 2013

- Possible explanations:
  - HBV vaccine yeast-produced particles: may have too few repeats, may be floating too loosely in the lipid bilayer, may not always make the correct cross-links in yeast (8 cysteines are located in a key antigenic region)
  - HPV vaccine VLPs may resemble an attenuated live-virus vaccine

Randomized controlled efficacy trial in Costa Rica to test efficacy of 1 dose vs. 2 doses (NCI & Gates Foundation)

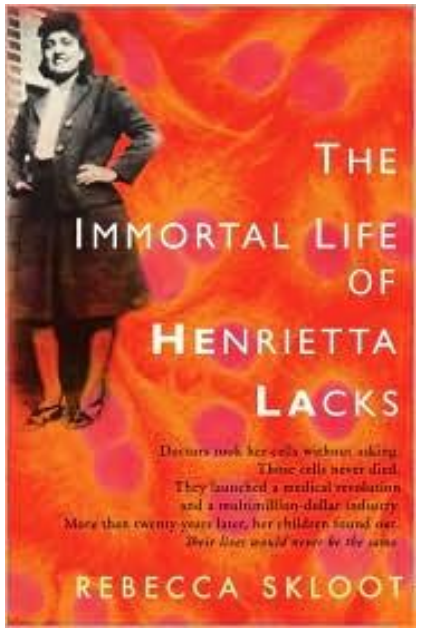
- **A 4-arm non-inferiority trial in 12-16 year old girls:** compare protection from 1 dose and 2 doses of bivalent vaccine (Cervarix, GSK) and 9-valent vaccine (Gardasil9, Merck)
  - Unethical to have a placebo arm; measure current HPV prevalence in young women in same area
- **Main hypothesis:** Protection induced by 1 dose is not inferior to 2 doses
- **Second hypothesis:** Protection will be similar for 1 dose of either vaccine (evaluates possible role of adjuvant; Merck uses alum, GSK uses AS04)
- **For more information:**
  - For 1 dose trial concept, see Kreimer et al, J Natl Cancer Inst, 2015; Kreimer et al, Vaccine, in press
  - See clinicaltrials.gov: Identifier NCT03180034

Potential impact of demonstrating 1 dose can confer strong protection

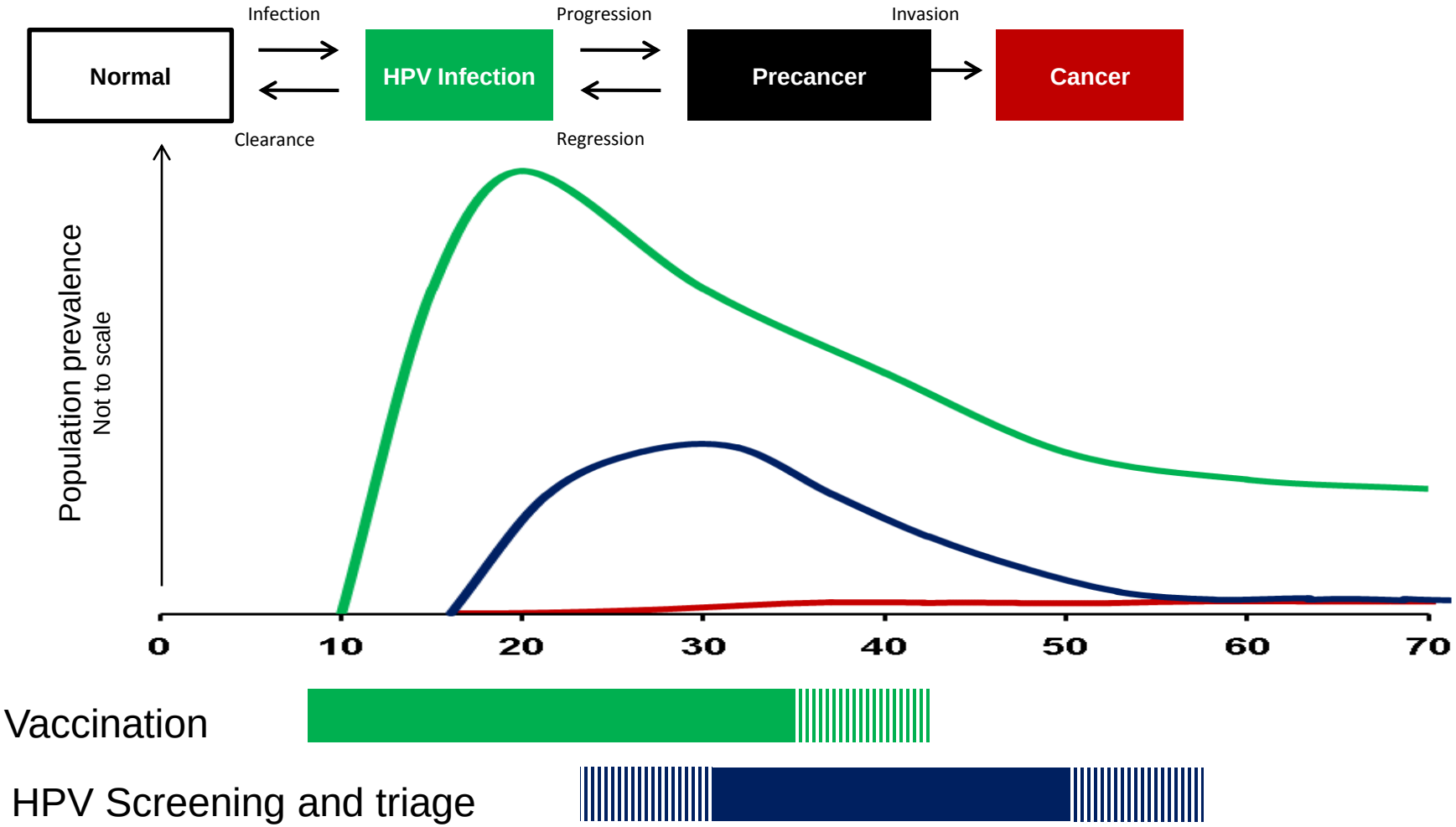
- Could establish a new minimum serum antibody titer needed for high level protection
- Could provide a strong rationale for considering a repetitive structure for future vaccines against other agents
- Could change standard of care in US & globally
  - Could save US > $300 million each year in vaccine costs
- Could make it feasible to control the worldwide public health problem of cervical cancer and other HPV-associated cancers

Henrietta Lacks (HeLa cells) had Cervical Adenocarcinoma

- **Pap smear screening: more sensitive for squamous cell carcinoma than adenocarcinoma**
- **~ 90% of cervical adenocarcinoma caused by HPV16 or HPV18**
- **Henrietta Lacks: HPV 18 cervical adenocarcinoma not detected by cytology**
- **Her cancer should now be preventable by HPV vaccination or by HPV-based screening**



A longer-term goal: "Rapid" reduction in worldwide cervical cancer by Vaccinating multiple birth cohorts of younger women & screening older women



Bosch et al, HPV Faster, Nature Rev Clin Oncol, 2016; modified by Mark Schiffman

Summary and Conclusions

- Basic research led to identification of HPV as the cause of several cancers and to development of the HPV vaccine
- The HPV vaccine is highly effective in preventing new infection and disease caused by the HPV types targeted by the vaccine
  - The HPV vaccine can induce strong herd immunity
- Control of HPV-associated cancer as a worldwide public health problem may soon be feasible