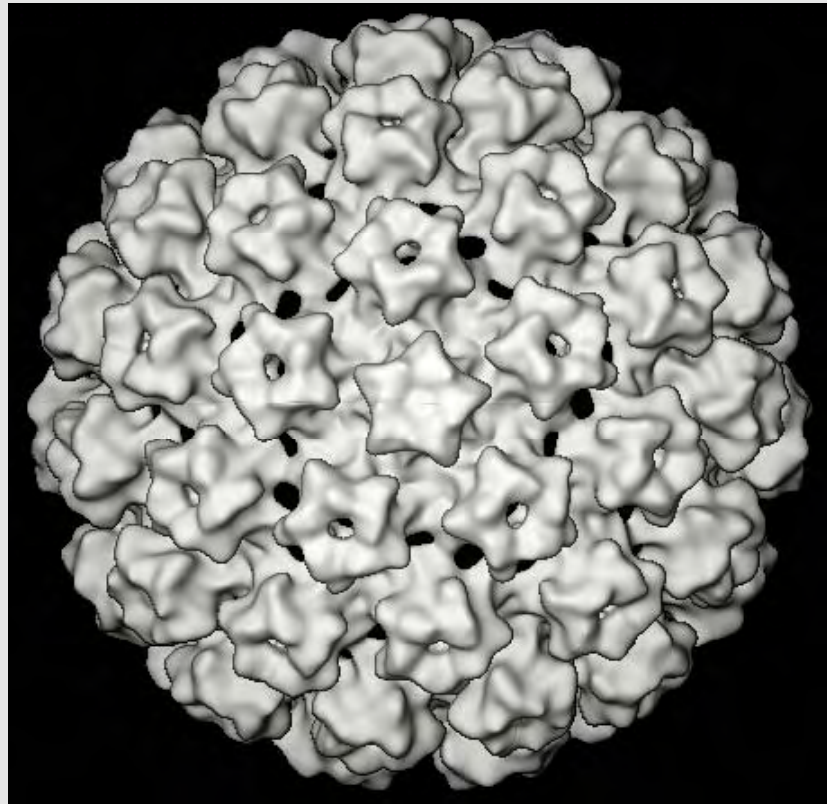


# An Update on HPV Vaccines

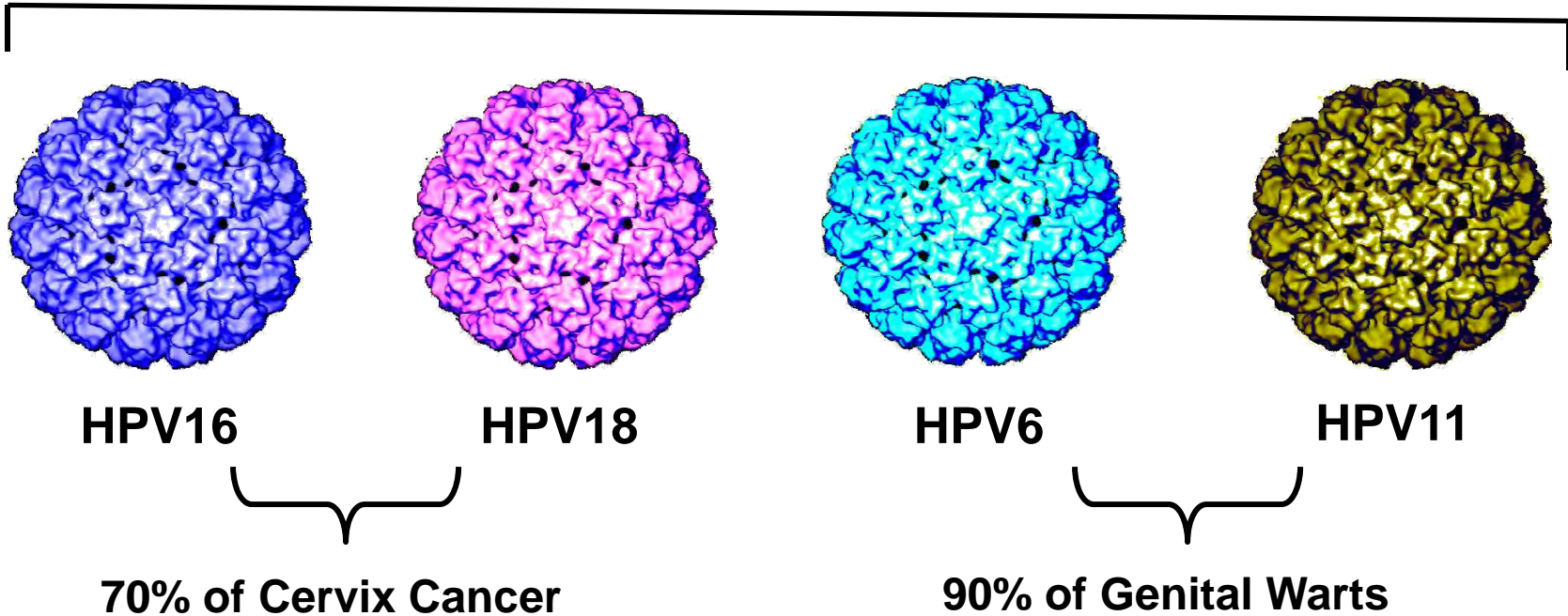
**John Schiller, National Cancer Institute, NIH, USA**



# HPV Vaccines Contain Multiple Virus-Like Particle (VLP) Types

## Gardasil - Merck

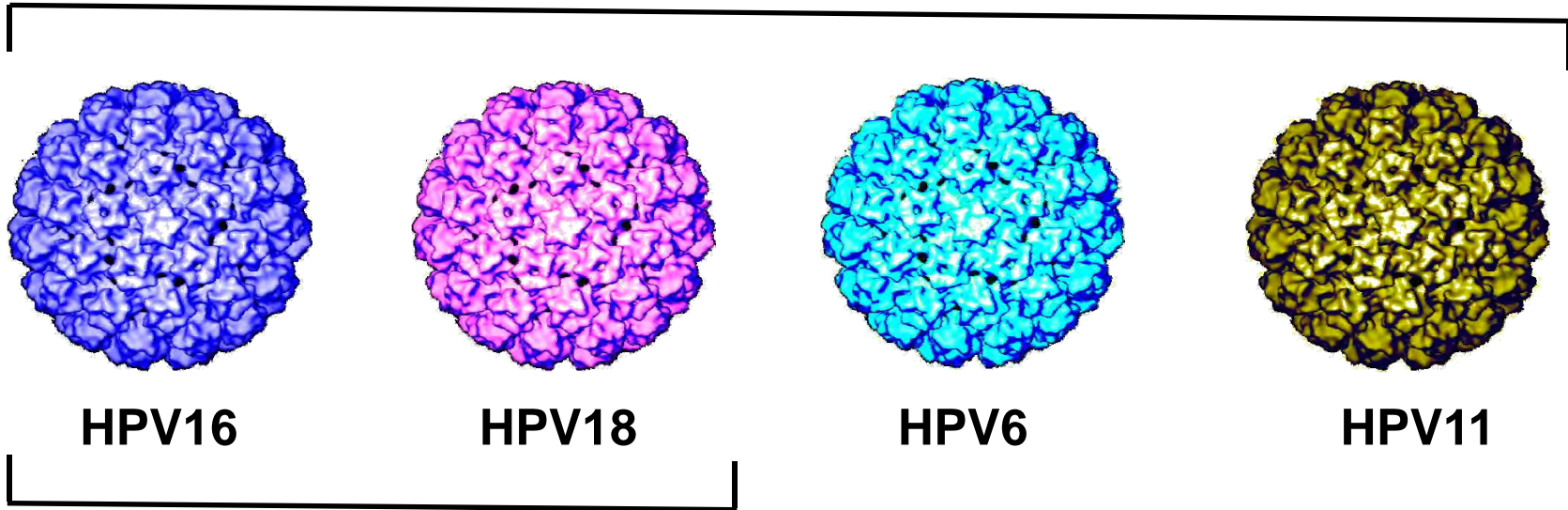
w/ standard aluminum-based adjuvant



Three Intramuscular injections over 6 months

# HPV Vaccines Contain Multiple VLP Types

**Gardasil - Merck**  
w/ standard aluminum adjuvant



**Cervarix - GlaxoSmithKline**  
w/ aluminum plus novel component adjuvant

**Three Intramuscular injections over 6 months**

# **HPV VLP Vaccine Clinical Trials: Young Women Ages 15-26**

## **Positives**

- **High efficacy against the strains specifically targeted by the vaccines. Prevent almost 100% of cervical HPV endpoints from incident infection to high grade cervical precancer. Potentially reduce cervical cancer risk by 70-85%.**
- **Gardasil is almost 100% protective against genital warts.**
- **Excellent safety record: modest local pain the most common side effect. No serious adverse events have been causally linked to the vaccines.**

# **HPV VLP Vaccine Clinical Trials: Young Women Age 15-26**

## **Limitations**

- **Protection is strain restricted, although some protection against non-vaccine strains detected, especially for Cervarix.**
- **Duration of protection is unknown, but strong protection, at 6 years, after VLP antibody levels have reached a plateau, is very encouraging.**
- **The vaccines do not act therapeutically to induce regression of established infections.**

# **Regulatory Approval of HPV VLP Vaccines**

**Merck's Gardasil was approved in 2006 in the E.U., U.S. and 100+ other countries.**

**GSK's Cervarix was approved in 2007 in the E.U., Australia, and 50+ other countries. U.S. decisions is pending.**

## **Gardasil Approval Specifics**

- **US FDA approved for 9-26 yr old females in June '06**
- **European Union and Australia approved for:**
  - 9-26 yr old females**
  - 9-15 yr old boys**

**Approval in 9-15 yr old girls and boys is based on immunogenicity bridging studies not efficacy, i.e. the antibody responses are non-inferior.**

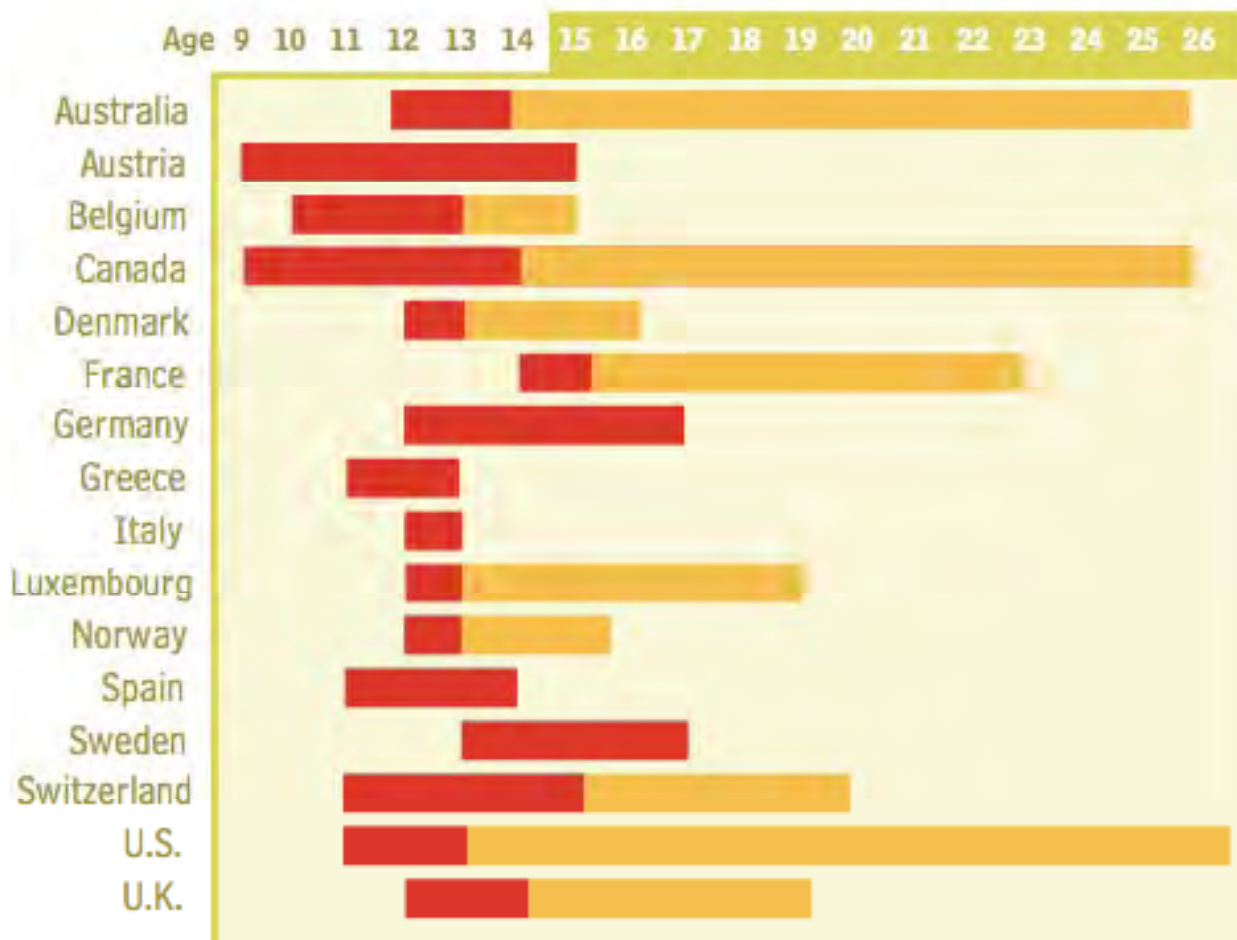
# **Cervarix Approval Specifics**

**Australia: 9-45 yr old females**

**E.U.: 10-25 yr old females**

**Approval in 9-15 yr old girls and 26-45 yr old women is based on immunogenicity bridging studies not efficacy.**

# Recommendations for HPV Vaccination as of October 2007



Age group included in most phase III vaccination trials  
 Main age  
 Catch up

From: Tom Wright, HPV Today, February 2008

# **Gardasil Efficacy In Other Groups: Summary of Recent Meeting Reports**

## **Analyses in Naïve Subjects Receiving 3 Doses**

### **\*Women aged 24-45:**

**92% reduction in incident HPV6/11/16/18 cervical dysplasia/genital warts**

### **#Males aged 16-26:**

**85% reduction in incident 6 mo. persistent infection caused  
by HPV6/11/16/18**

### **#Males aged 16-23:**

**90% reduction in incident of external warts caused by HPV6/11/16/18**

**\* Eurogin, Nov. 2008, Nice France**

**# 25th IPV Conference, May 2009, Malmo Sweden**

**Licensure for young boys and older women is expected in many developed countries. However, the cost/benefit ratio may be too high to support public funding for vaccination of these groups.**

## **Recent Meeting Reports: Immunogenicity**

### **Two vs Three doses of Gardasil:**

**Two doses in 9-13 year old girls at 0 and 6 mo.  
generated equivalent antibody responses as three doses  
in 16-26 year old women at 0, 2, and 6 mo.  
Will the antibody responses last as long?**

### **Cervarix vs Gardasil:**

**Serum antibody responses were higher for Cervarix:  
2.3-4.8 fold higher for HPV16  
6.8-9.1 fold higher for HPV18  
Will this result in longer duration of protection?**

# Who Should Be Vaccinated?

**It depends on your resources!**

**In descending order of importance:**

- **10-14 year old girls - the ultimate target group since they have not yet been exposed to these sexually transmitted viruses. Antibody respond to the vaccine better than in young women.**
- **Sexually active women - since many may not yet been exposed to at least one of the vaccine types; may reduce transmission - increase herd immunity. But, the number of “older women” who haven’t been exposed to HPV16/18 and would develop cancer if they were decreases with age.**
- **Adolescent boys and men - only 8% of HPV cancer in men; may be small impact on herd immunity if coverage of women high; most models suggest male vaccination would not be cost effective**

# Can High Coverage Rates Be Achieved?

## School-Based Vaccination Programs Work: The UK Experience

Region	Age	School-Based?	Coverage
Scotland	12-13	Yes	90%
England	12-13	Yes	80%
Scotland	17-18	Yes	90%
England	17-18	No	30%

Henry Kitchener, IPV Conference, May 2009, Malmo Sweden

- **80% coverage in Australia 12-18 yr old - School Based**
- **25% coverage (at least one dose) in U.S. 13-17 yr old - disorganized**

**It's critical to vaccinate girls who won't get screened later in life!**

# **2nd Generation HPV Vaccines: Addressing the Implementation Limitations**

- **Nine Valent VLP - Merck**
- **L1 recombinant Ty21a *Salmonella typhi* -  
Indian Immunologicals**
- **L1 recombinant Measles - Berna vaccine strain  
Zydus-Cadila**
- **L2 Vaccine - Shanta, Acambis**

**But don't wait for these vaccines before vaccinating your girls:  
they many years away and won't be therapeutic.**

**Thanks for your attention!**

# Cervarix: Final Phase III Efficacy in Young Women

18,664 women 15-25 yrs old followed for 3 years post vaccination

<b>Cohort</b>	<b>Endpoint</b>	<b>Vaccine Efficacy (96.1% C.I.)</b>
ATP	16/18 CIN2+	92.9 (79.9, 98.3)
ATP: multi-type causation	16/18 CIN2+	98.1 (88.4, 100)
Total Vaccine Cohort	Any CIN2+	30.4 (16.4, 42.1)
TVC - naive	Any CIN2+	70.2 (54.7, 80.9)
TVC - naive	Any CIN3	87.0

Paavonen et al., 25th IPV Conference, May 2009, Malmo Sweden

# Outstanding Implementation Issues

- **High Cost of the Vaccine: Gardasil is \$120 per dose**
- **What ages to start vaccinating**
- **What age is too old for catch up vaccination**
- **Acceptance of an STI vs Cervical Cancer vaccine (but >30 million doses of Gardasil sold)**
- **Delivery of 3 IM doses to early adolescents**
- **Effects of vaccine on Cervical Ca screening recommendations and compliance**

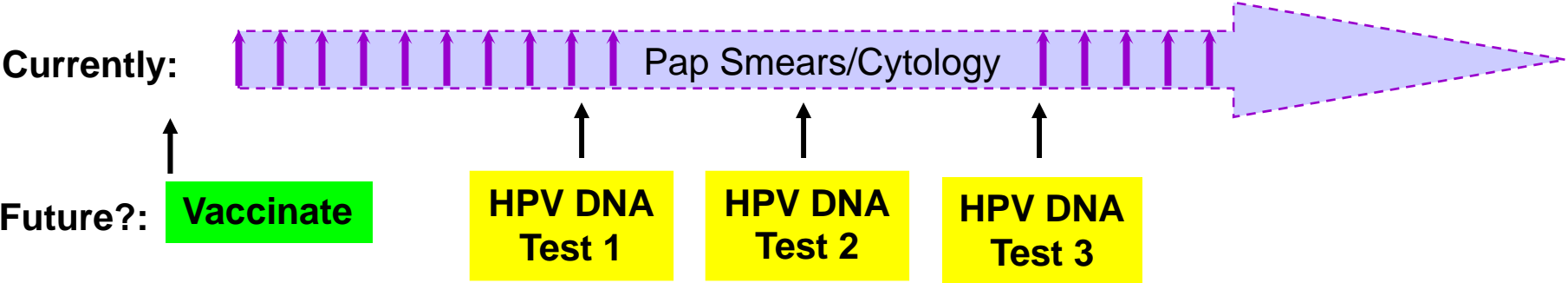
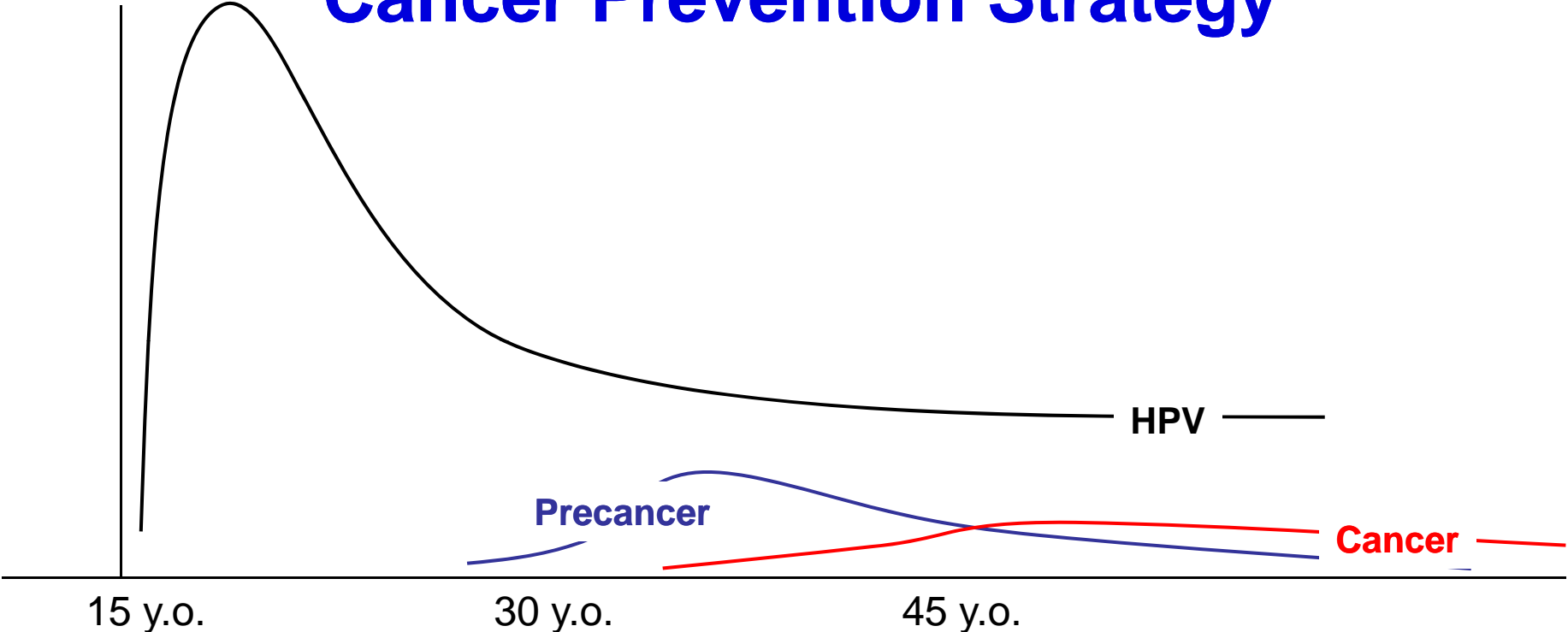
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# **We Can't Give Up Screening**

- **The vaccine won't help women with established infections/lesions.**
- **If type restricted, the current VLP vaccines could not prevent ~20% of cervical cancers.**
- **Need to convince vaccinated women to comply with existing screening programs.**

# A Shift to an HPV-Based Cervical Cancer Prevention Strategy

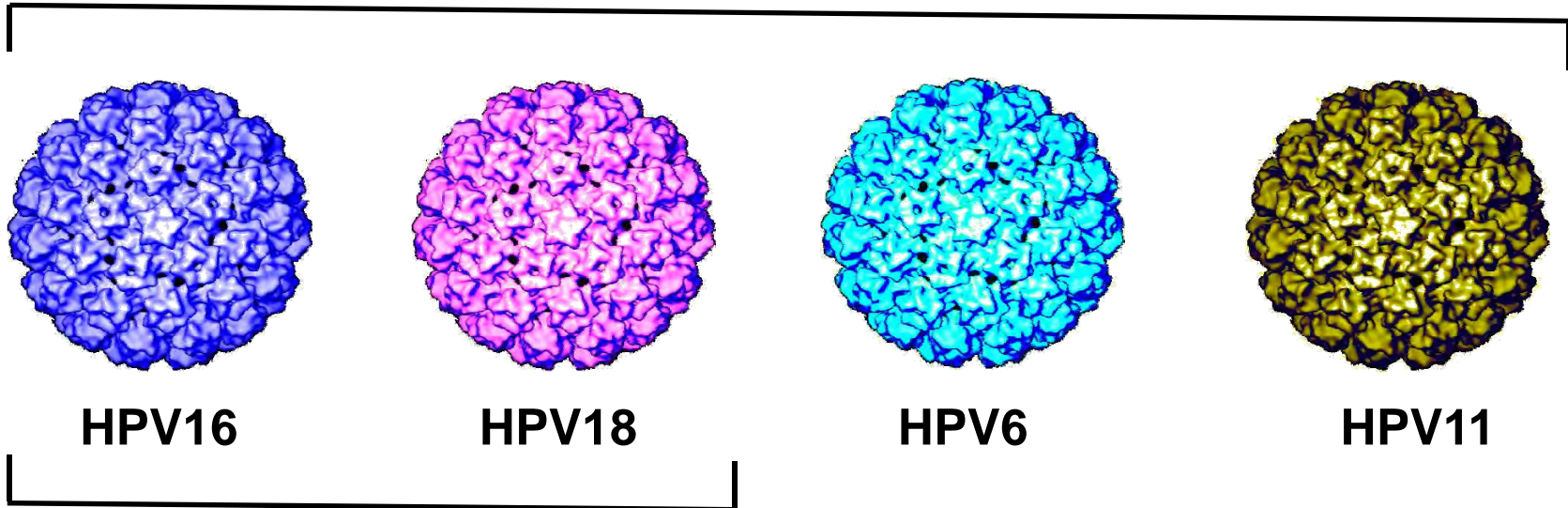


Thanks to Mark Schiffman and Phil Castle, NCI

# HPV Vaccines Contain Multiple VLP Types

## Gardasil (Merck)

w/ aluminum hydroxyphosphate sulfate



## Cervarix (GlaxoSmithKline)

w/ aluminum hydroxide + MPL (AS04)

Three Intramuscular injections over 6 months