

Primary and secondary prevention opportunities for HPV-driven head and neck cancer

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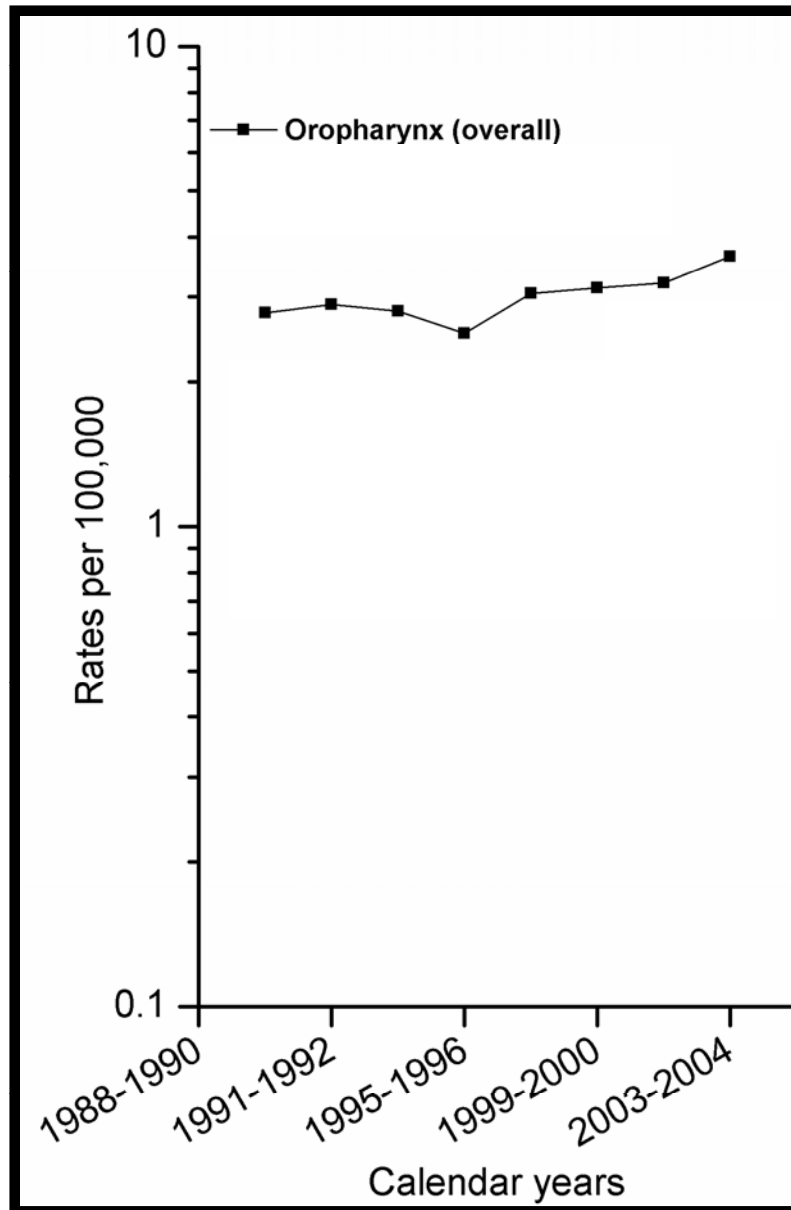
Overview

- 1. Should we even consider preventing this cancer?**
 - Trends in incidence over time

- 2. How can we prevent this cancer?**
 - Primary prevention via prophylactic HPV vaccination?
 - Secondary prevention via screening?

- 3. Areas for future research**

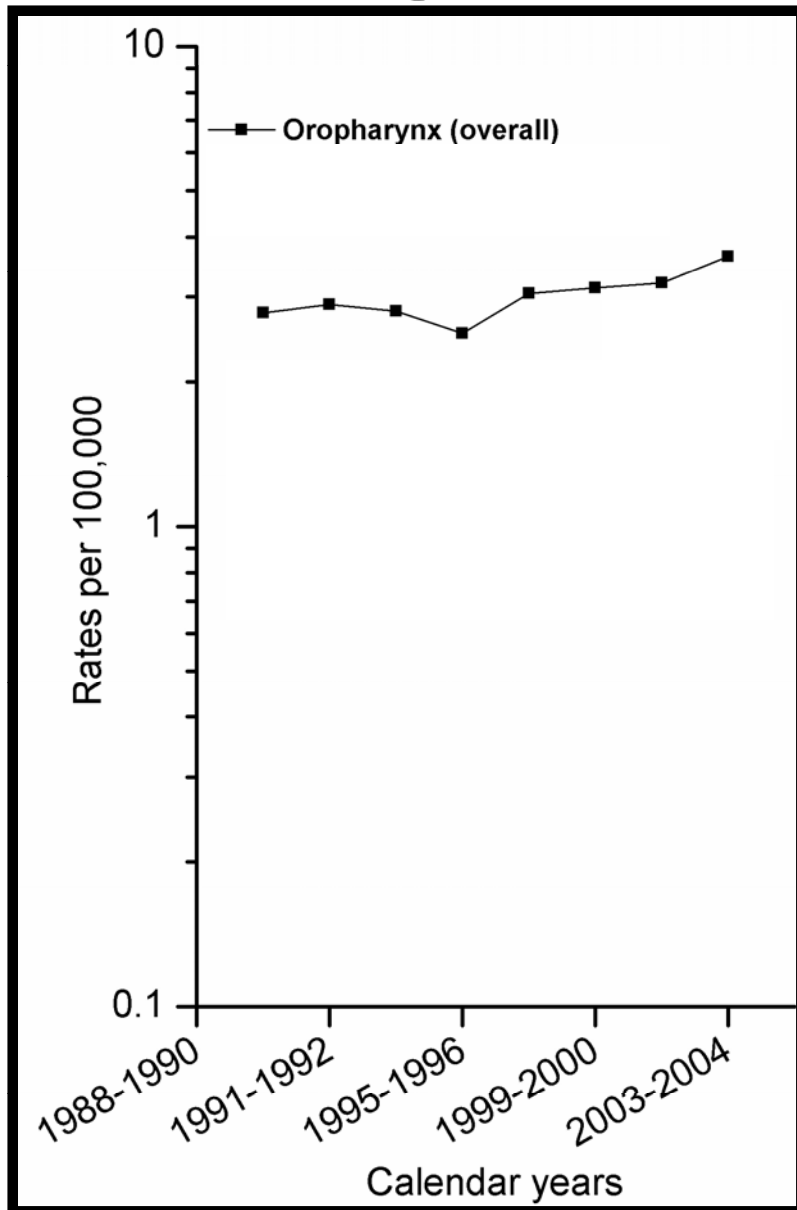
Incidence of OP cancer in the US



**Data from SEER9
1988-2004**

Chaturvedi AK et al, J Clin Oncology 2011.

Rising OP incidence in the US



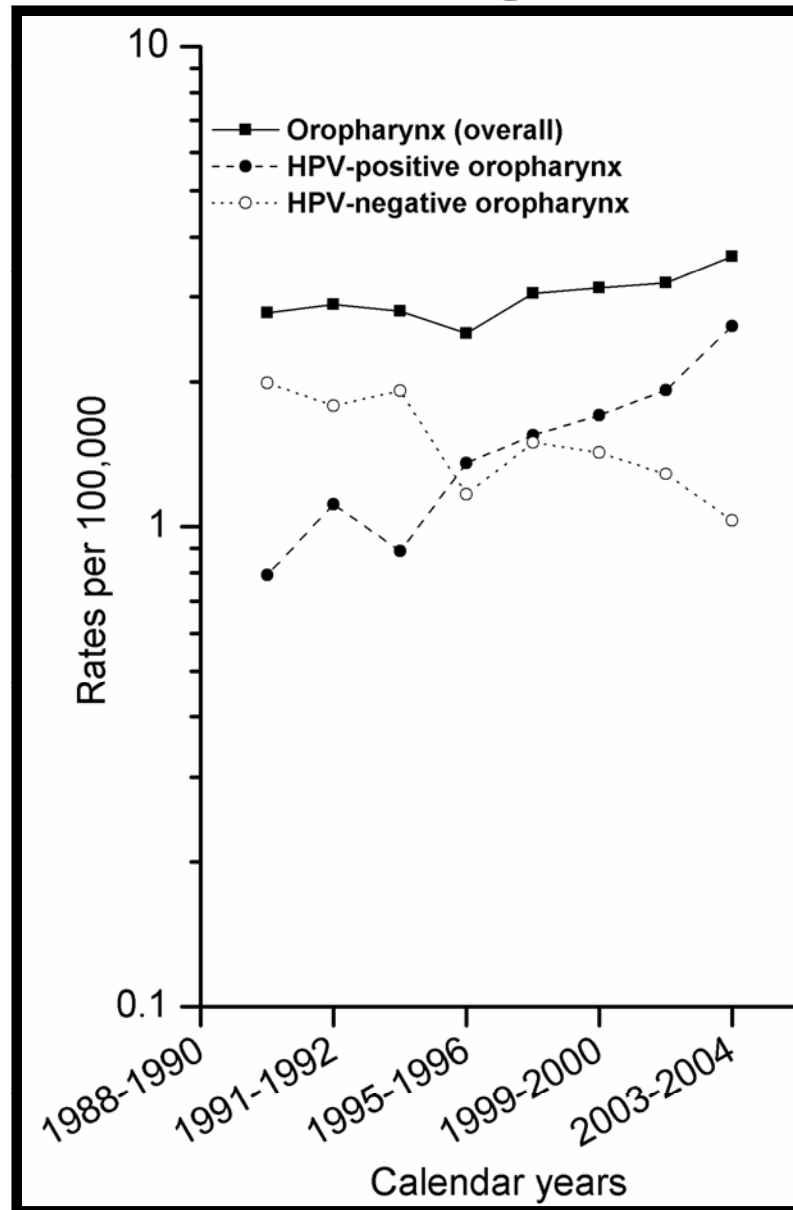
Similar trends:

- Canada¹
- Netherlands²
- Sweden³
- United Kingdom⁴
- Australia⁵

References:

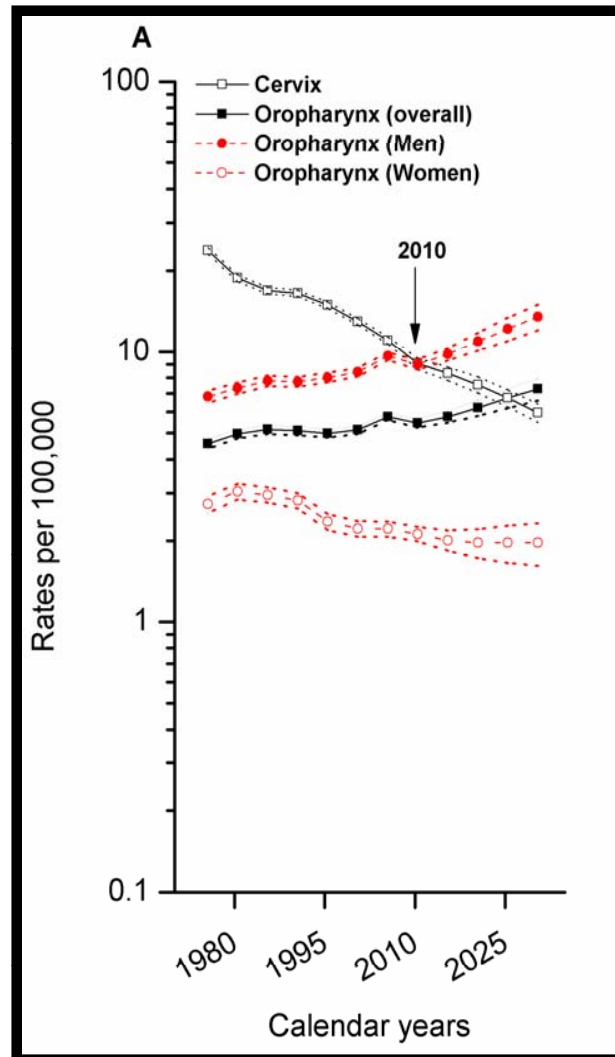
- ¹ Auluck A. Cancer 2010; 116:2635
- ² Braakhuis BJ. Oral Oncol 2009;45:e85
- ³ Hammarstedt L. Acta Otolaryng 2007; 127:988
- ⁴ Conway DI. Oral Oncol 2006; 42:586
- ⁵ Hong AM. Vaccine 2010;28:3269

HPV explains rising OP incidence



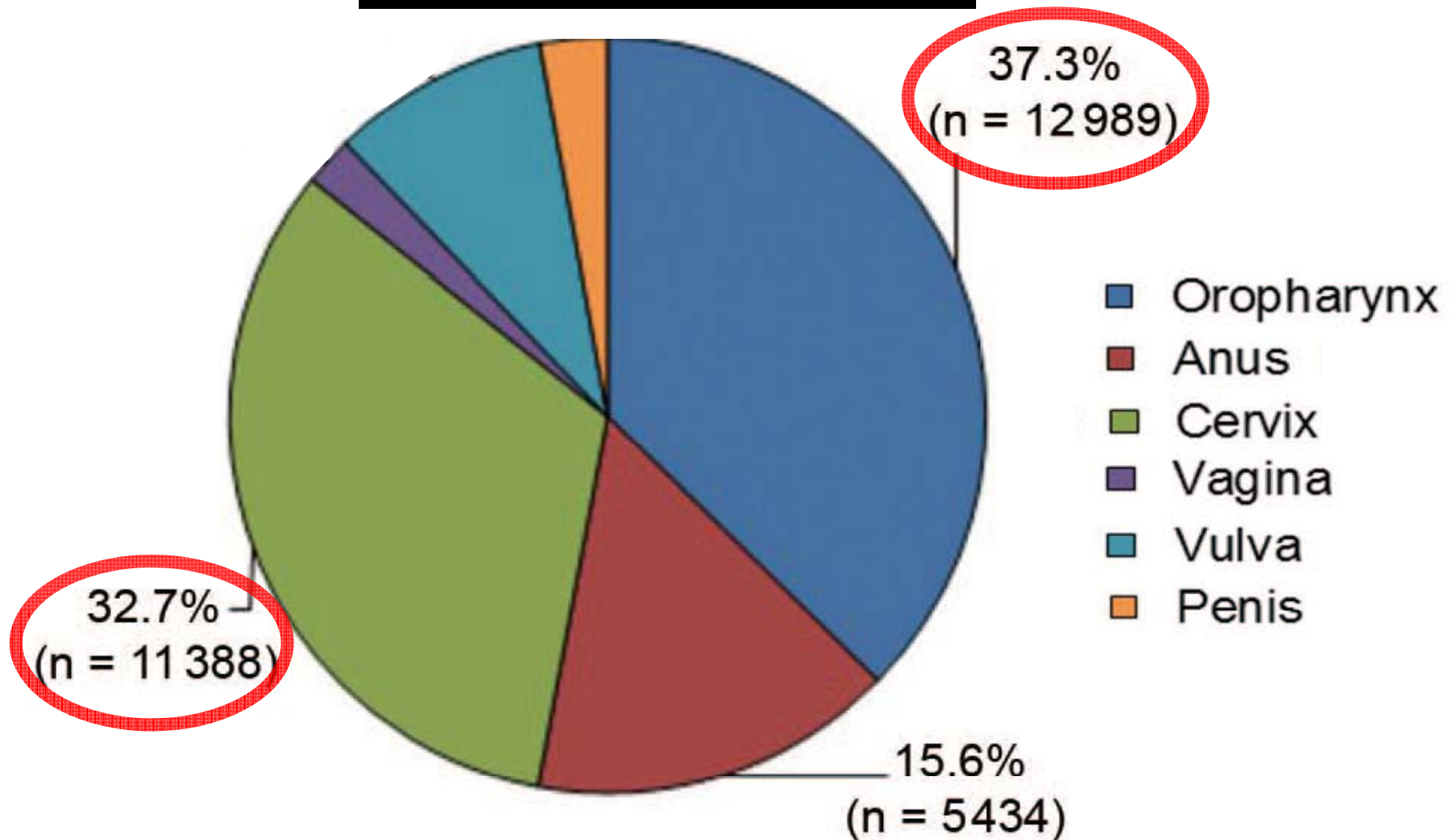
Chaturvedi AK et al, J Clin Oncology 2011.

Observed and projected incidence rates of OP and cervical cancers (US)

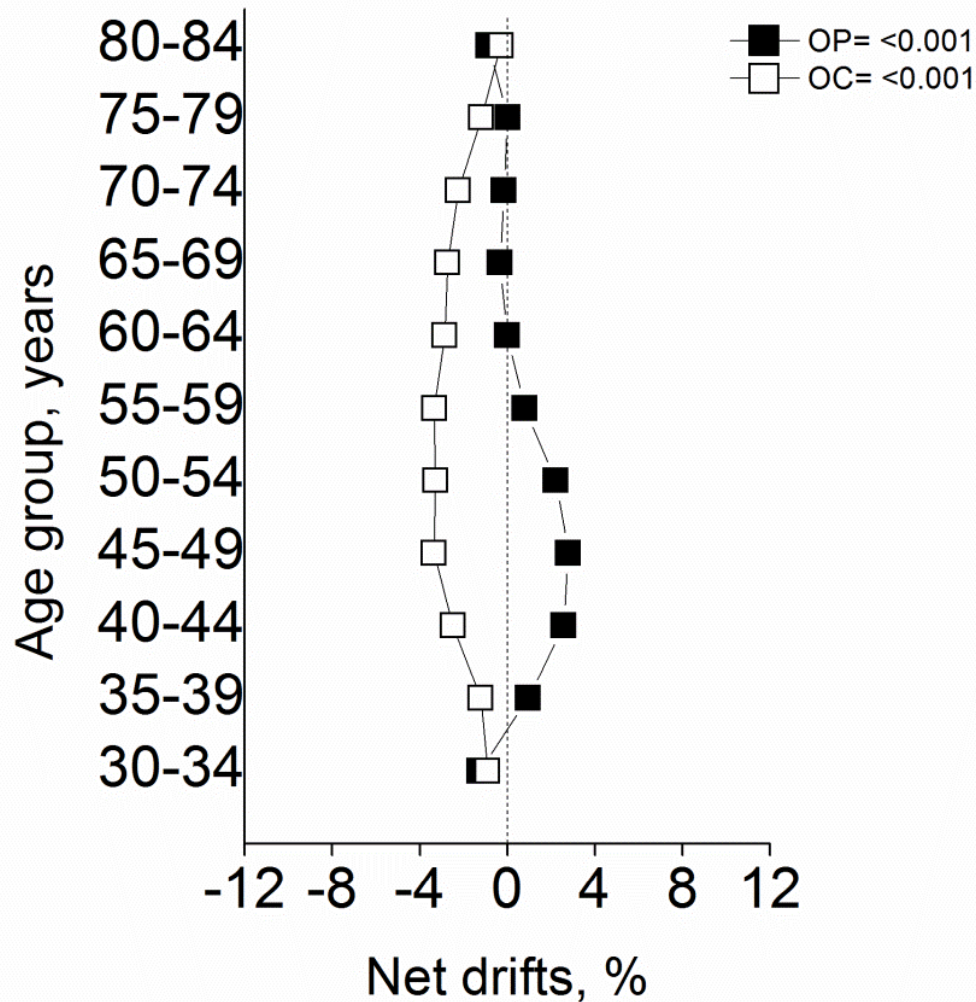


Chaturvedi AK et al, J Clin Oncology 2011.

Incidence of HPV-associated cancers- USA



Rising OPC incidence occurs at younger ages in the U.S.



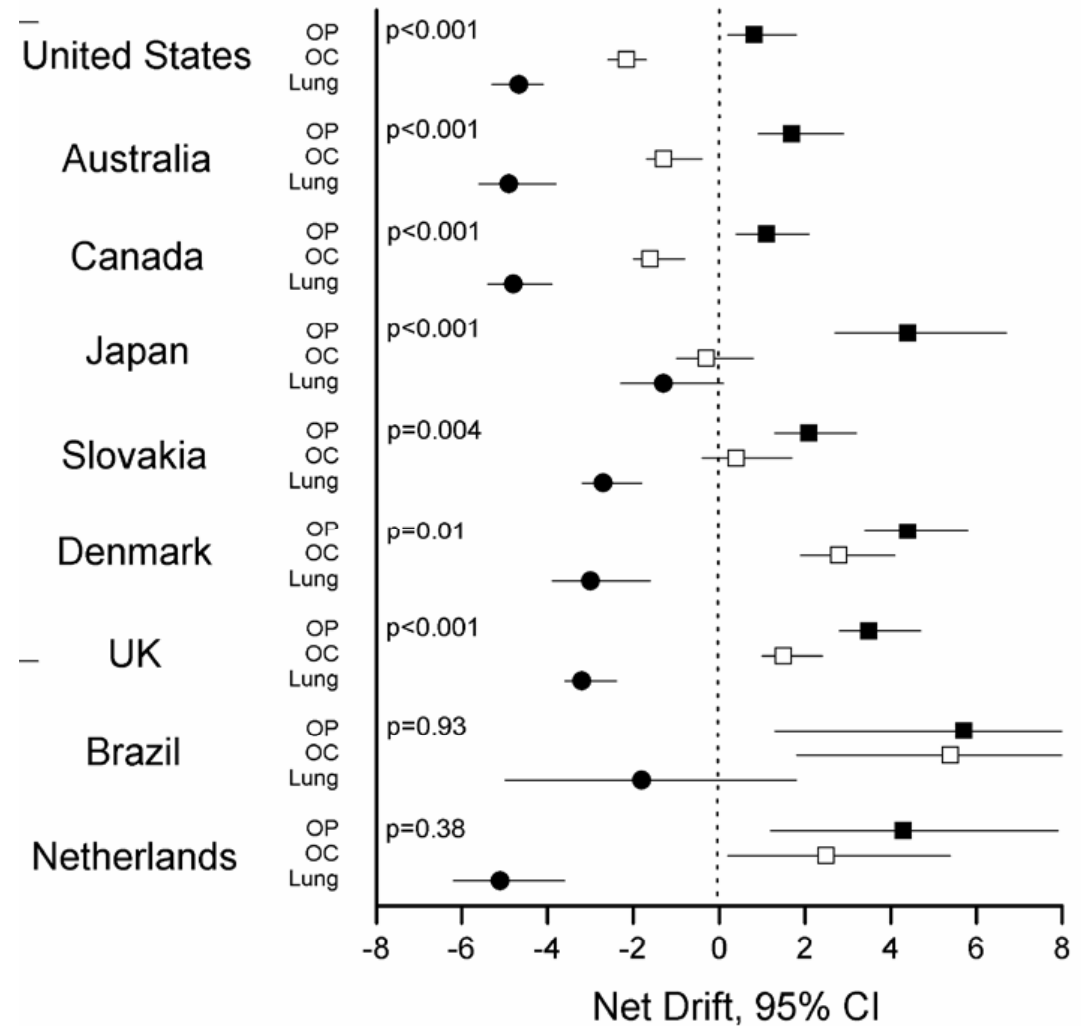
Slide courtesy of Anil Chaturvedi

U.S. incidence rates: summary

- **Increasing oropharyngeal cancer incidence**
 - Men
 - Younger ages
- **Decreasing incidence for oral cavity cancers**
 - Men and women
 - Younger ages
- **Oropharyngeal cancer incidence rates inconsistent with trends in smoking**
 - Supports the role of HPV infection

International trends among men 1983-2002

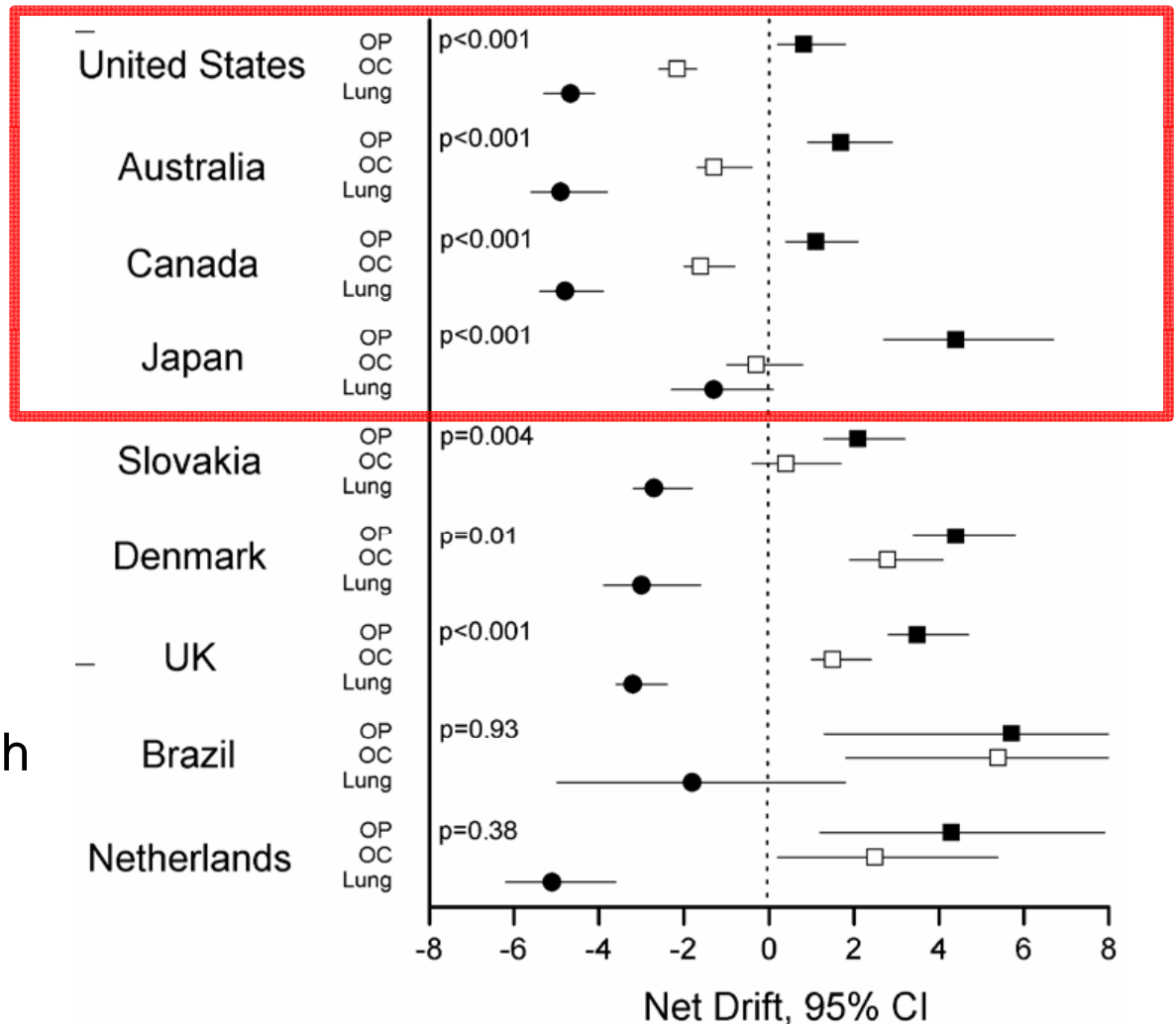
- Rising oropharyngeal cancer incidence in developed countries
- Decreasing incidence for oral cavity cancers and lung cancers
- Oropharynx cancer incidence inconsistent with trends in smoking



Chaturvedi AK et al, J Clin Oncology 2013.

International trends among men 1983-2002

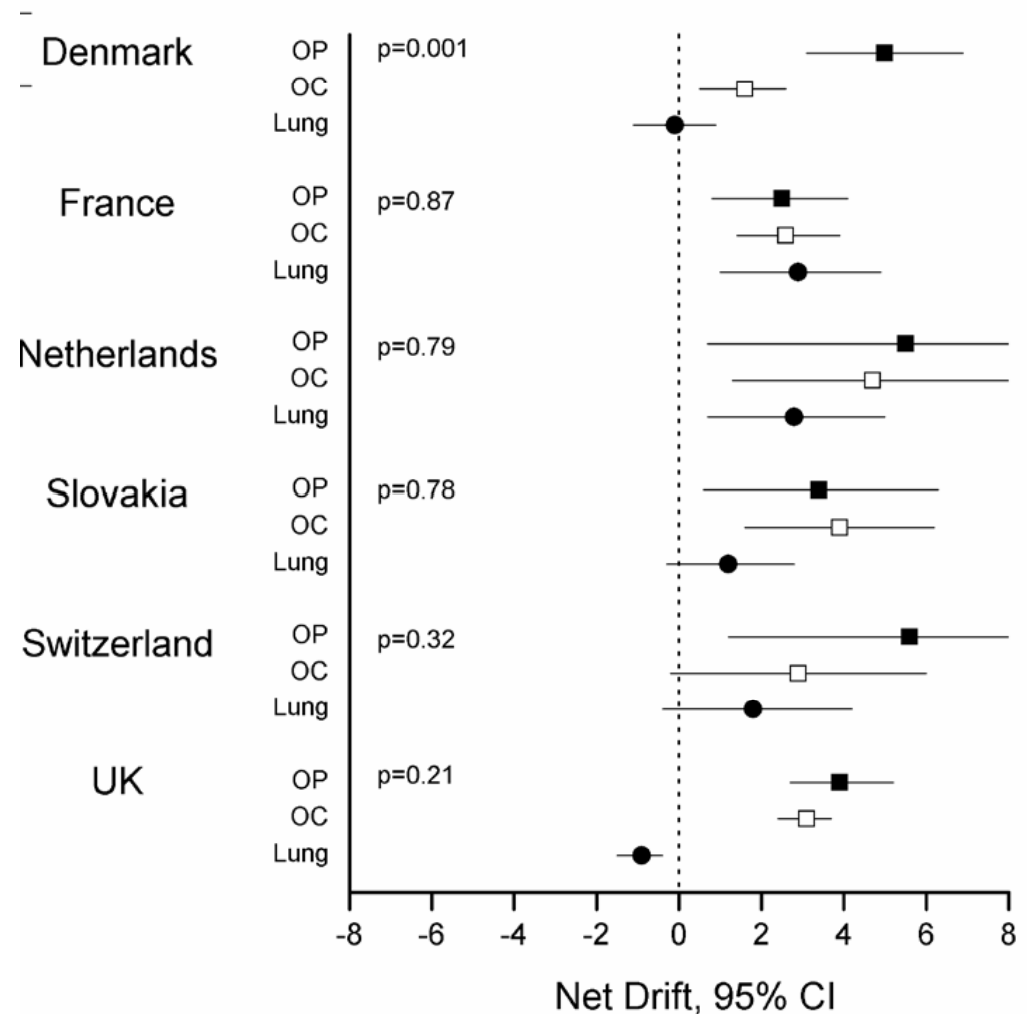
- Rising oropharyngeal cancer incidence in developed countries
- Decreasing incidence for oral cavity cancers and lung cancers
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Chaturvedi AK et al, J Clin Oncology 2013.

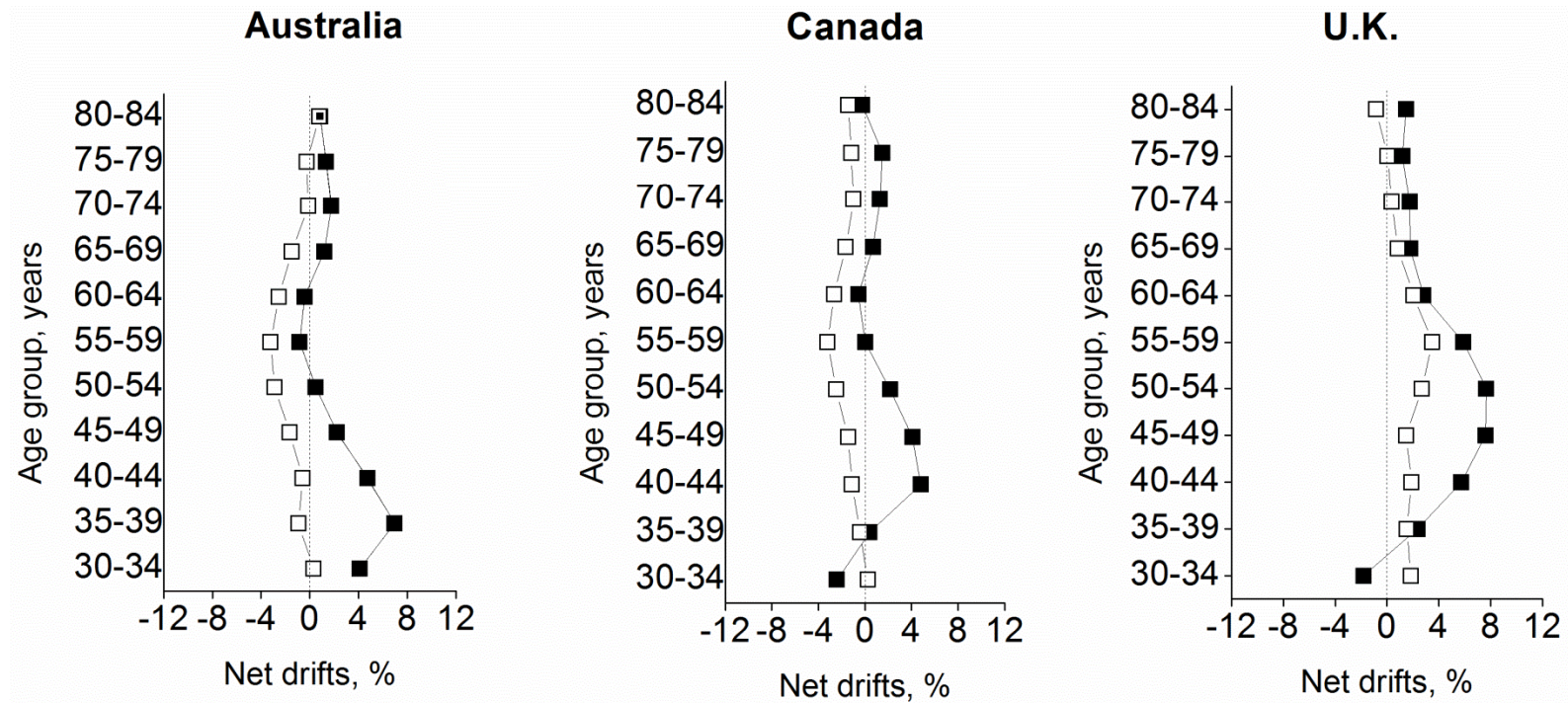
International trends among women 1983-2002

- Rising oropharyngeal cancer generally accompanied by rising incidence for oral cavity and lung cancers
- Oropharynx cancer incidence consistent with trends in smoking



Chaturvedi AK et al, J Clin Oncology 2013.

OPC trends by age in men



Rising OPC incidence predominantly at younger ages

Worldwide incidence trends:

summary

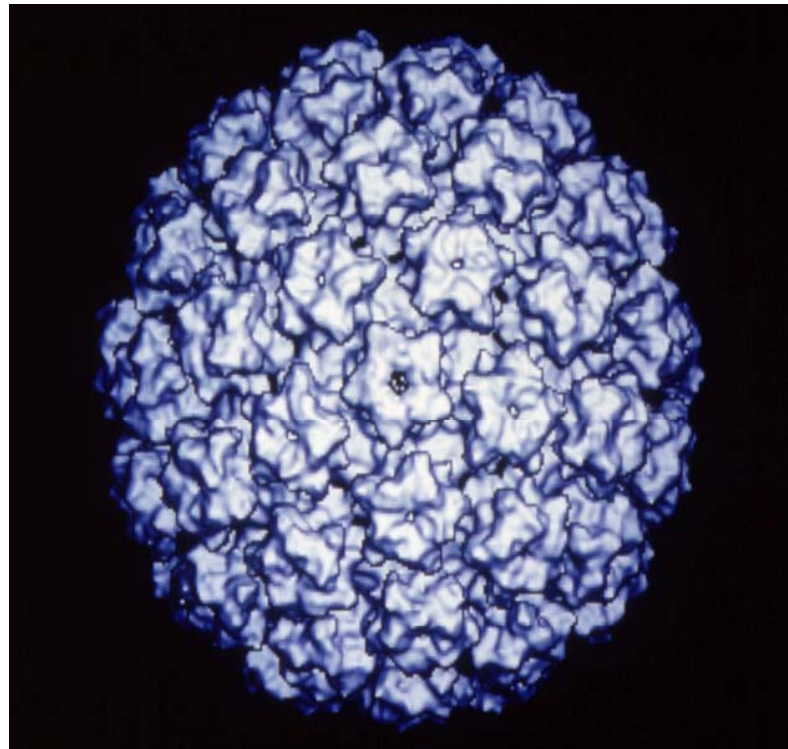
- **Increasing oropharynx cancer incidence during the past 20-30 years in the U.S. and other developed countries**
 - **Predominantly in men**
 - **Younger ages**
- **Oropharynx cancer incidence rates not consistent with incidence for other smoking-associated cancers (oral cavity and lung)**
- **Rising incidence because of HPV?**

Prevention methods for HPV-associated cancers

1. Primary- prophylactic HPV vaccination
2. Secondary- viral DNA or other viral determinants
 - HPV16 E6 serum antibodies

Primary prevention

Prophylactic HPV vaccination



Kirnbauer R, Booy F, Cheng N, Lowy DR, Schiller JT. Papillomavirus L1 major capsid protein self-assembles into virus-like particles that are highly immunogenic. Proc Natl Acad Sci 1992.

FDA-approved HPV vaccines

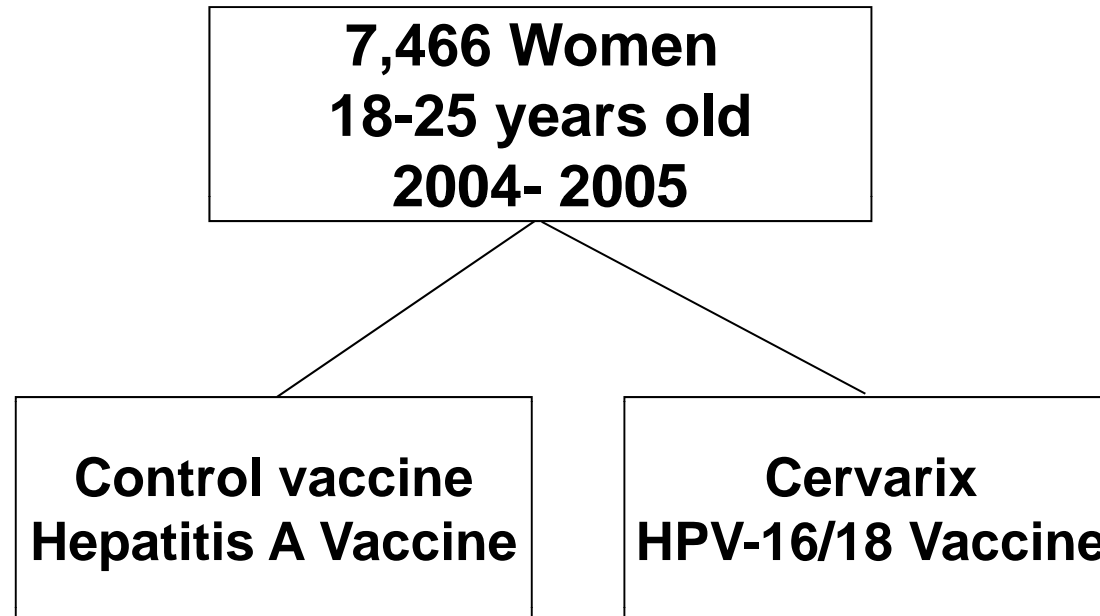
Manufacturer (Trade name)	Vaccine types	Cervical vaccine efficacy
Merck (Gardasil)	HPV16 and 18 HPV6 and 11 'quadrivalent'	>95%
GlaxoSmithKline (Cervarix)	HPV16 and 18 'bivalent'	>95%

Both vaccines were tested and approved using a 3-dose regimen

Efficacy at non-cervical sites

Cancer Site	Published vaccine efficacy against HPV16/18	
	<u>Merck</u>	<u>GlaxoSmithKline</u>
Anus	High	High
Vagina/Vulva	High	High
Penis	High	Not evaluated
Oropharynx	Not evaluated	High

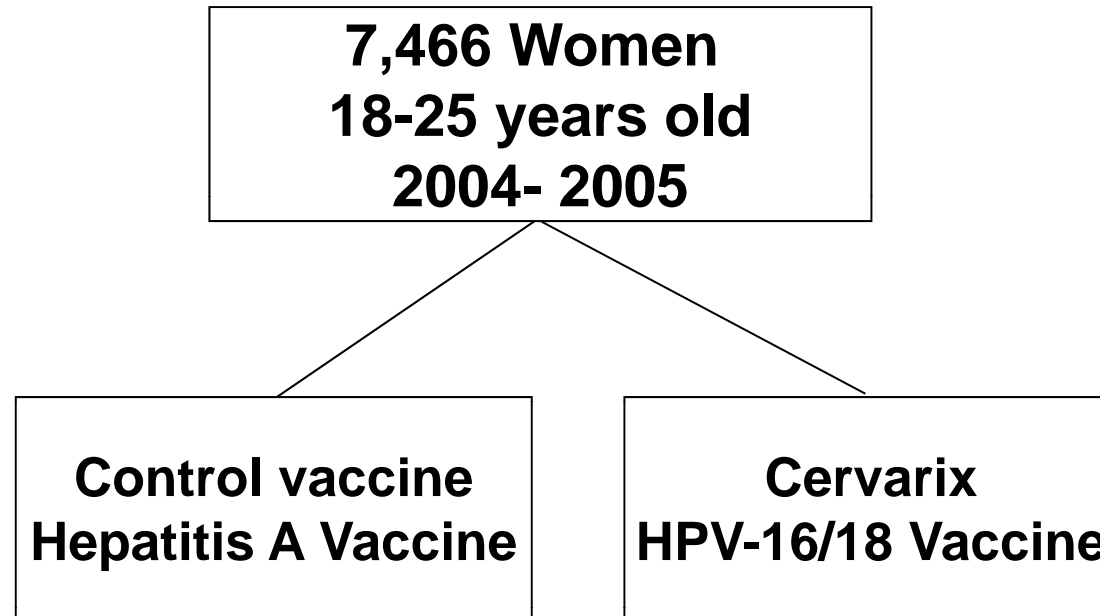
Costa Rica Vaccine Trial



Herrero R *et al* Cancer Discovery 2011;1:408
Herrero R *et al* Vaccine 2008;26:4795



Costa Rica Vaccine Trial



- Annual follow-up for 4 years
- Cervical samples collected at all visits
- Oral specimens collected at 4 year visit



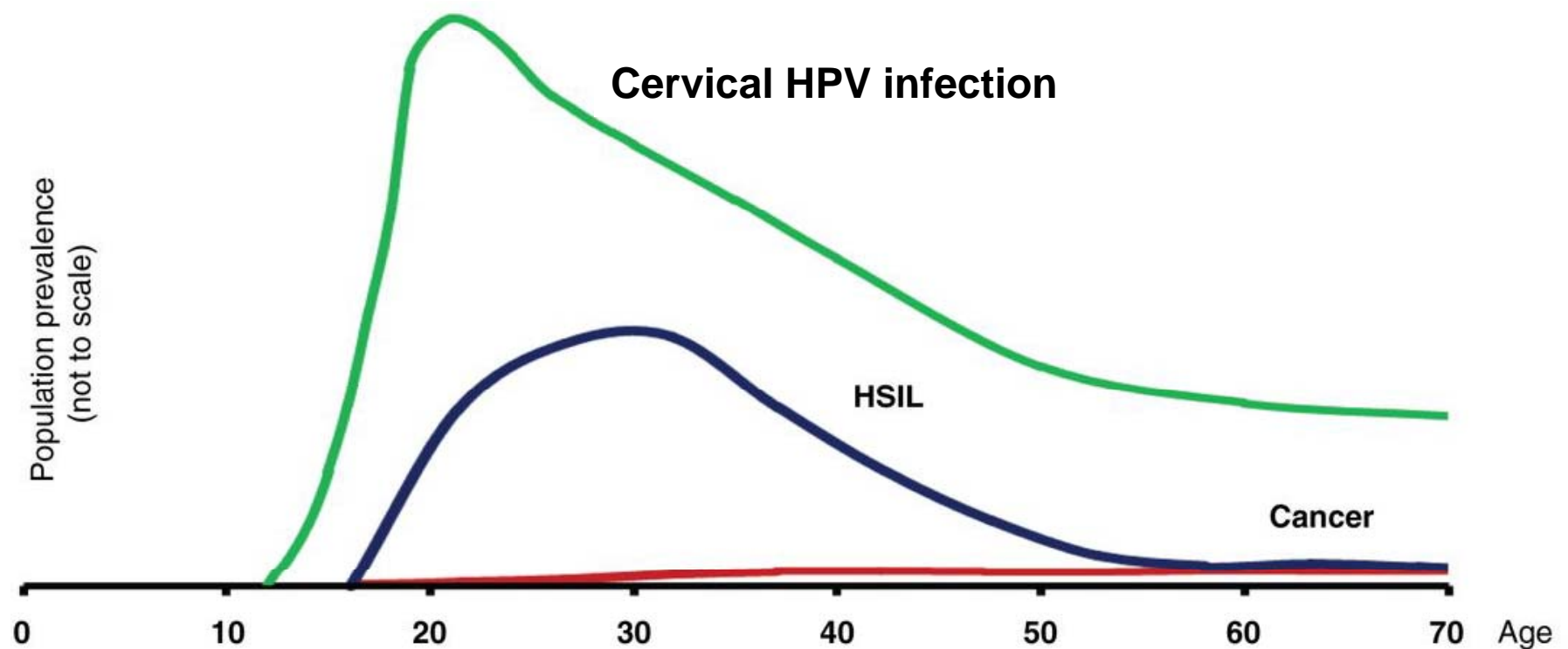
Vaccine efficacy against oral HPV 16/18 infections- 4 years of protection

Arm	# Women	# HPV16/18 Infections	HPV16/18 VE (95%CI)
HPV	2910	1	93% (63% to 100%)
Control	2924	15	

Current vaccine implementation

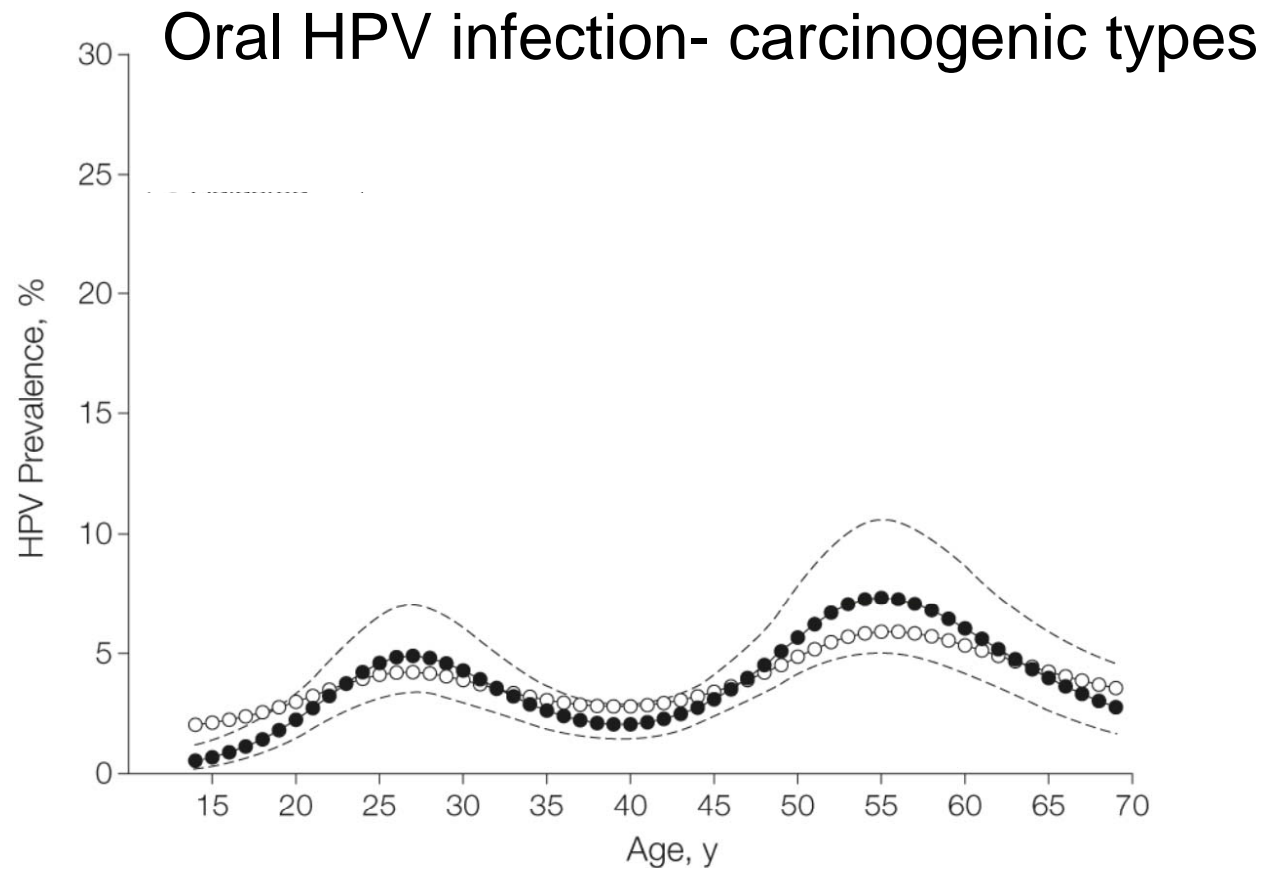
- Does the natural history of oral HPV infection differ from that of cervical?
 - Relevant for vaccine administration
 - Prophylactic vaccine- needs to protect against bolus of incident infection

How long does the vaccine need to work?



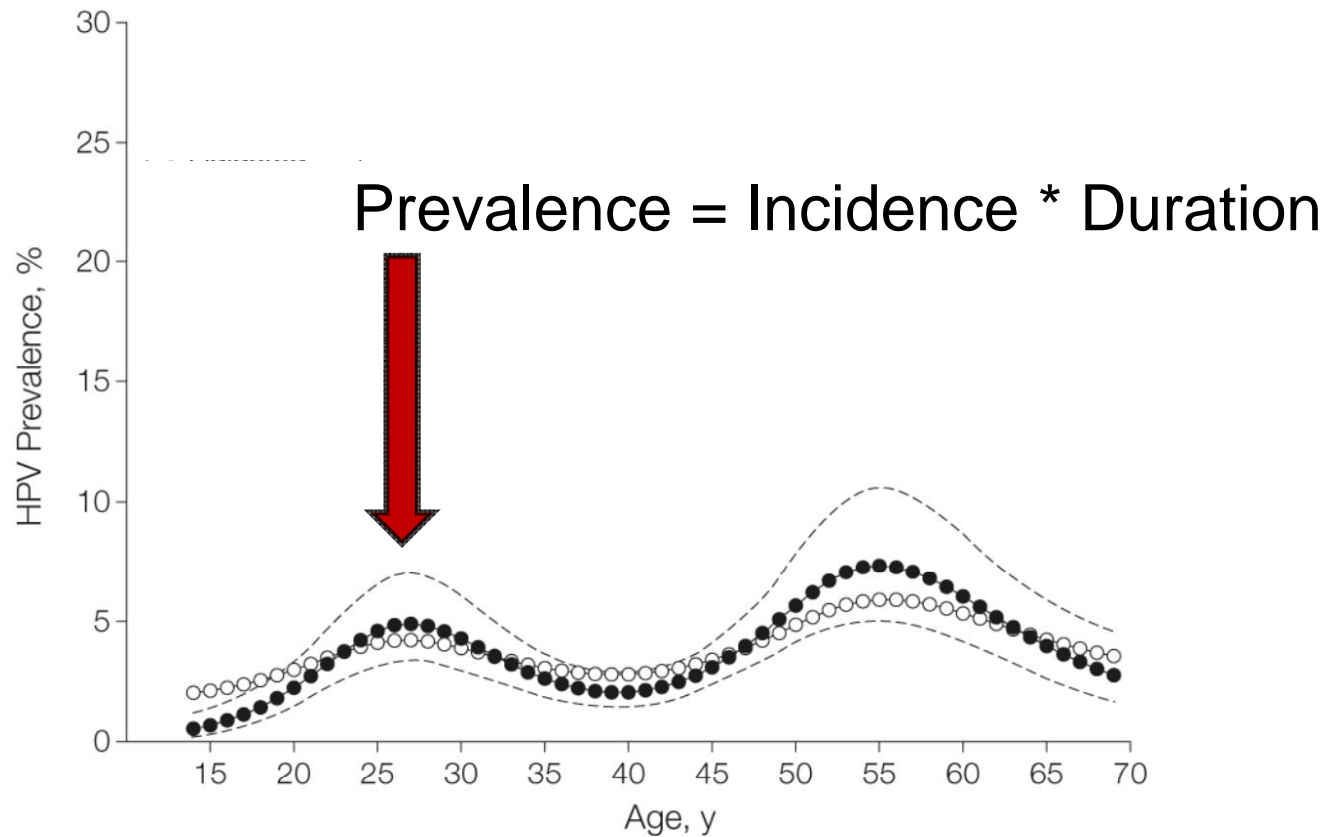
Schiffman M et al. CEBP 2013.

How long does the vaccine need to work?



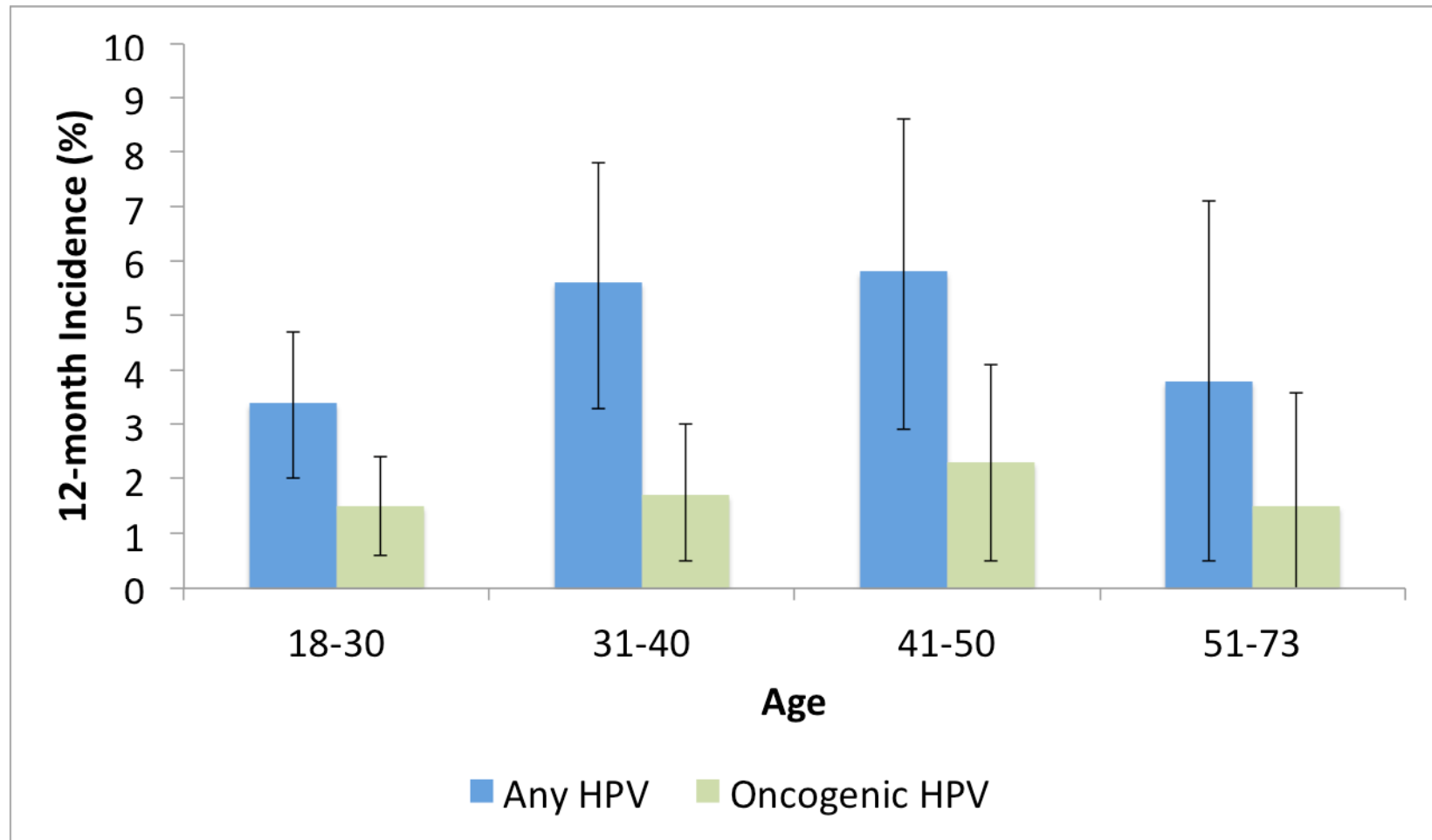
Gillison ML et al. JAMA 2012.

Age-specific prevalence of oral HPV infection



Gillison ML et al. JAMA 2012.

Incidence of oncogenic oral HPV infections: the *HIM Study*



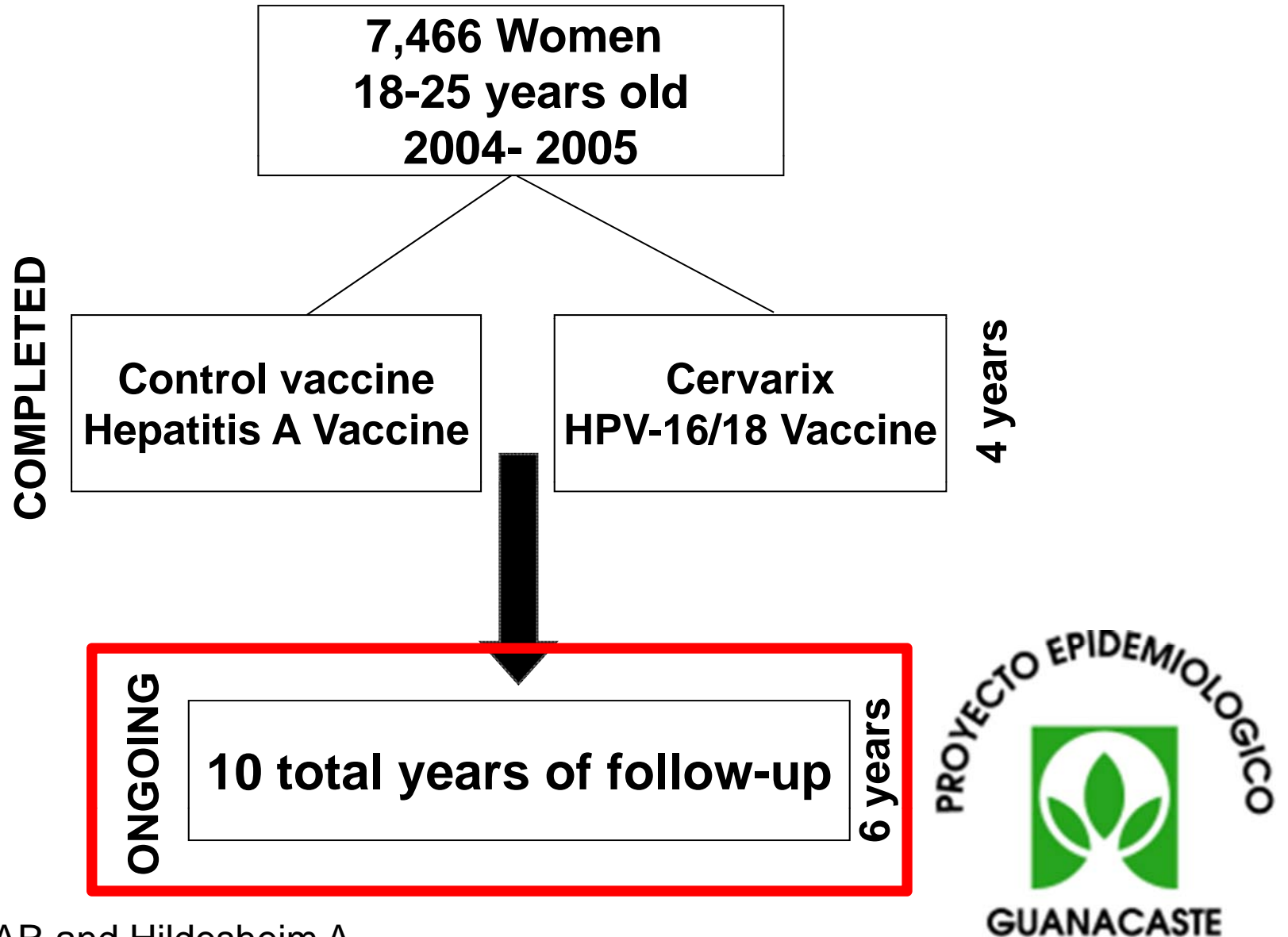
Kreimer AR et al. Lancet 2013.

Duration of vaccine protection at different anatomic sites

	Non-cervical sites	Cervix
Years of follow-up	4	>8

Long-term follow-up studies are required

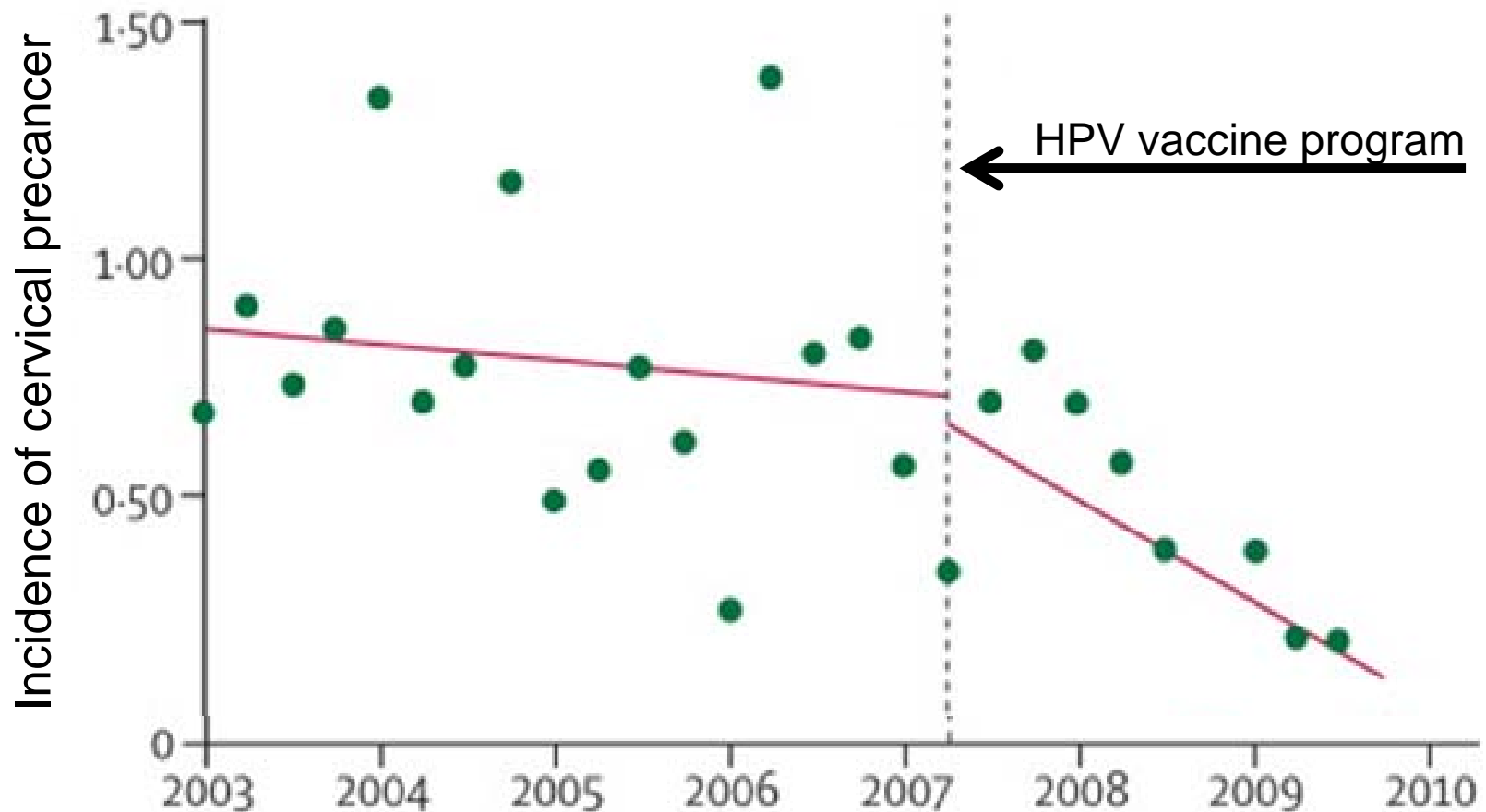
CVT Long-term follow-up



PIs: Kreimer AR and Hildesheim A

Population-level impact on cervical precancer

Australia: uptake ~80% for all 3 doses

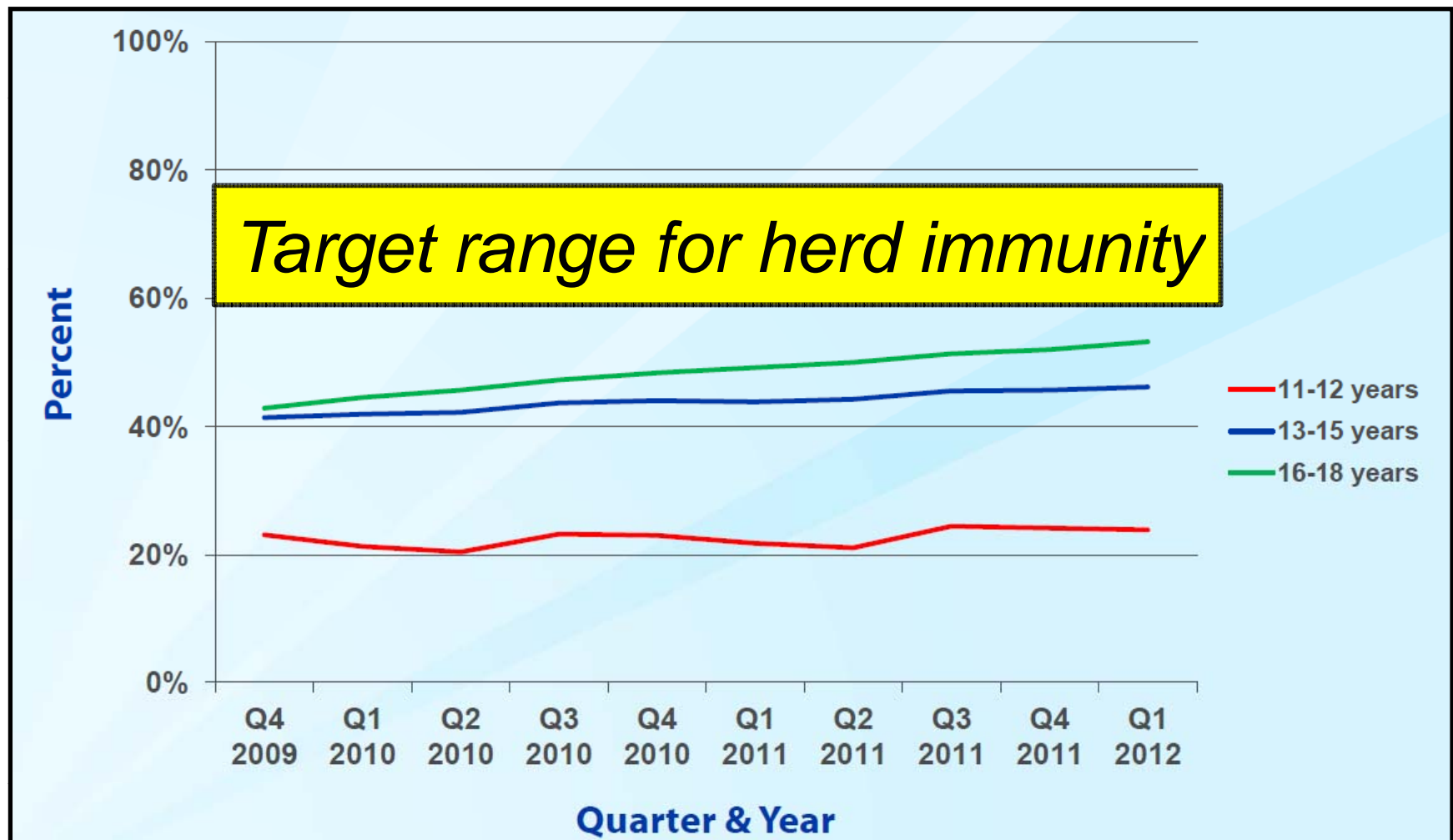


HPV-vaccine uptake among females (1st dose), USA



Website: <http://www.cdc.gov/vaccines/acip/meetings/downloads/slides-jun-2012/02-HPV-Cullen.pdf>

HPV-vaccine uptake among females (1st dose), USA



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Secondary prevention will remain necessary

1. Inadequate rates of vaccine uptake
 - USA: females (20 to 40%) and males (<5%)
2. Current generations at risk for cancer will not be protected by vaccination
 - at least the next several decades

Potential for screening HPV-driven oropharyngeal cancer?

- Case-control studies: HPV16 E6 antibody positivity associated with current diagnosis of HPV16-positive oropharyngeal cancer
 - L1 antibodies- markers of exposure
 - E6 antibodies- more likely to mark disease

Potential for screening HPV-driven oropharyngeal cancer?

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 - E6 antibodies- more likely to mark disease
- **Can HPV16 E6 serum antibodies predict risk of HPV-driven oropharynx cancer?**

European Prospective Investigation into Cancer and Nutrition (EPIC)

- 400,000 participants gave a blood sample
- Evaluated HPV serologic biomarkers in head and neck cancer cases and controls
- Blood draw to cancer diagnosis: 6.5 years (0.1 to 14 years)



Nature Reviews | Cancer

HPV16 E6: OPC marker?

	Controls (n= 1599)	Oral cavity (n= 180)	Larynx (n= 247)	Oropharynx (n= 135)
N (%)	9 (0.6%)	2 (1.1%)	3 (1.2%)	47 (34.8%)
adjOR		1.3 (0.3-6.9)	3.8 (0.8-18)	274 (110-681)

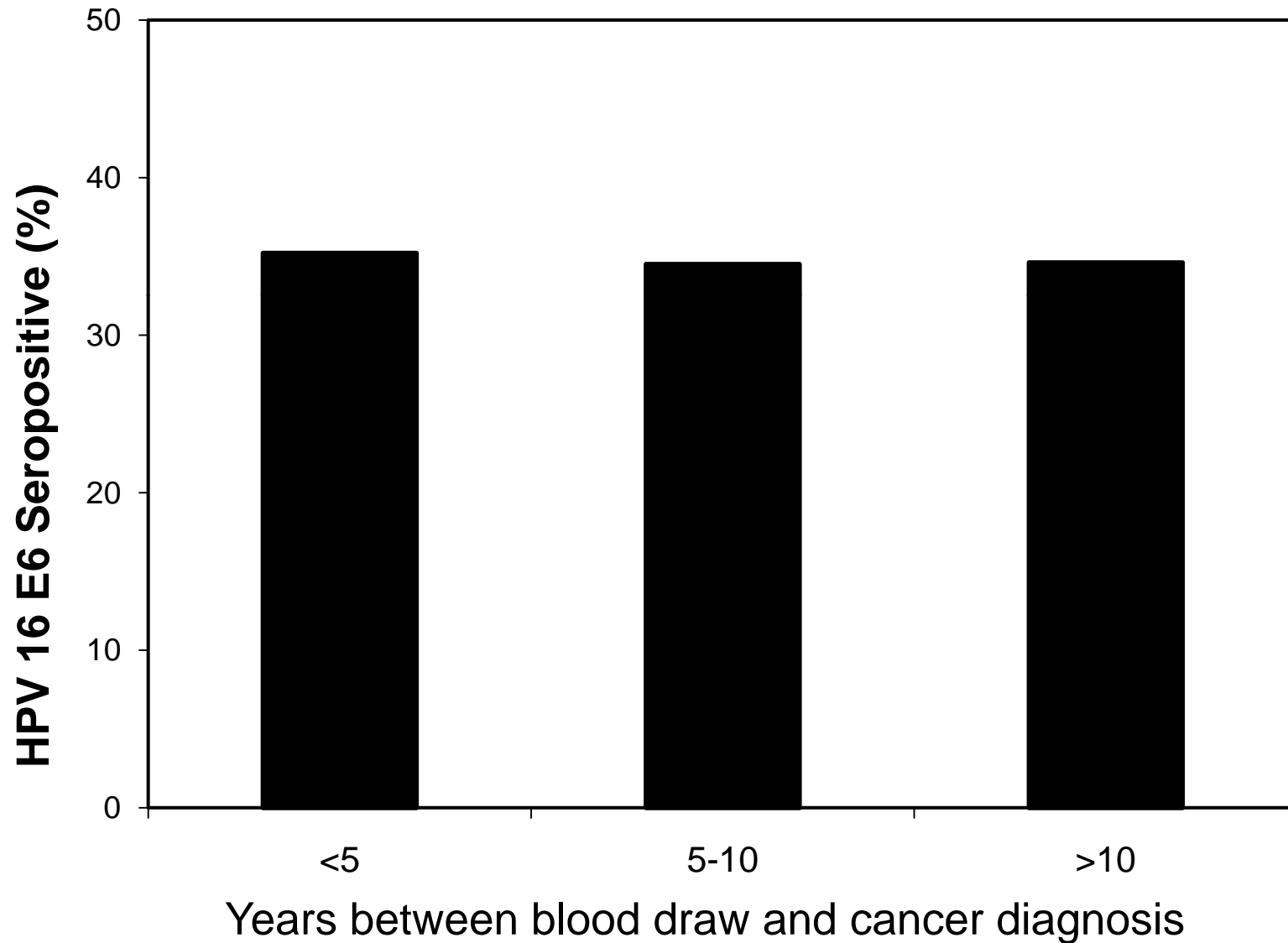
Kreimer AR et al, J Clin Oncology 2013.

HPV16 E6: OPC marker?

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Kreimer AR et al, J Clin Oncology 2013.

HPV16 E6 seropositivity among oropharyngeal cancer cases



Current investigations

1. Will our findings replicate in other cohorts?
2. What is the sensitivity of this marker?
3. HPV-driven oropharyngeal cancer, or anogenital cancers as well?
4. How long does an oral HPV16 infection need to persist before HPV16 E6 antibodies are made?

Checklist: Oropharyngeal Cancer **Screening**

- Test that detects cancer before symptoms
- Identifiable precancerous state
- Effective treatment
- Evidence of reduced incidence/mortality
- Benefits outweigh risks and costs

What would screening for OP cancer look like in the US?

Cancer Outcome	5yr cancer risk per 100K	Sensitivity	Specificity	# needed to screen per cancer case detected	# needed to screen positive per case detected
OP	32.6	63%	99.8%	4862	11
Cervix	68.5				
Cytology		58%	92%	2519	202
HPV		98%	91%	1491	135

Kreimer AR et al. J Clin Oncology In Press.

Primary Prevention

1. Demonstrated high vaccine efficacy against oral HPV infections
 - Potential to prevent all HPV-driven cancers
2. Wide coverage required
 - Remains inadequate in most regions
3. Additional data needed
 - Duration of protection, efficacy of fewer doses, L2 vaccine, etc.

Secondary Prevention

- Additional data are needed
 - What is the sensitivity of HPV16 E6 marker?
 - Will it predict HPV-driven cancers at other anatomic sites?
 - Is there a precursor lesion?
 - What diagnostics should be used to identify precancer?
 - How should a precancer be treated?
 - Will treatment work to reduce incidence of cancer?
 - Who should be screened?

Collaborators

NCI

- Allan Hildesheim (IIB)
- Hormuzd Katki (BB)
- Doug Lowy (CCR)
- Ligia Pinto (IIB-SAIC)
- Mahboobeh Safaeian (IIB)
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