BSc Global Health Session

The global challenge of HPV and scaling up vaccination

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Health Protection Agency, London

1st November 2012

Learning Objectives

- Type-specific HPV prevalence and disease burden worldwide
- Efficacy of current vaccines against vaccine & non-vaccine types
- Vaccine implementation and predicted impact on disease burden
- Mechanisms and definitions of vaccine-induced protection
- Need for and composition of next generation HPV vaccines

Papillomavirus infection and disease

Development of current HPV vaccines

HPV vaccine implementation and impact

Potential impact against non-vaccine types

Next generation vaccines

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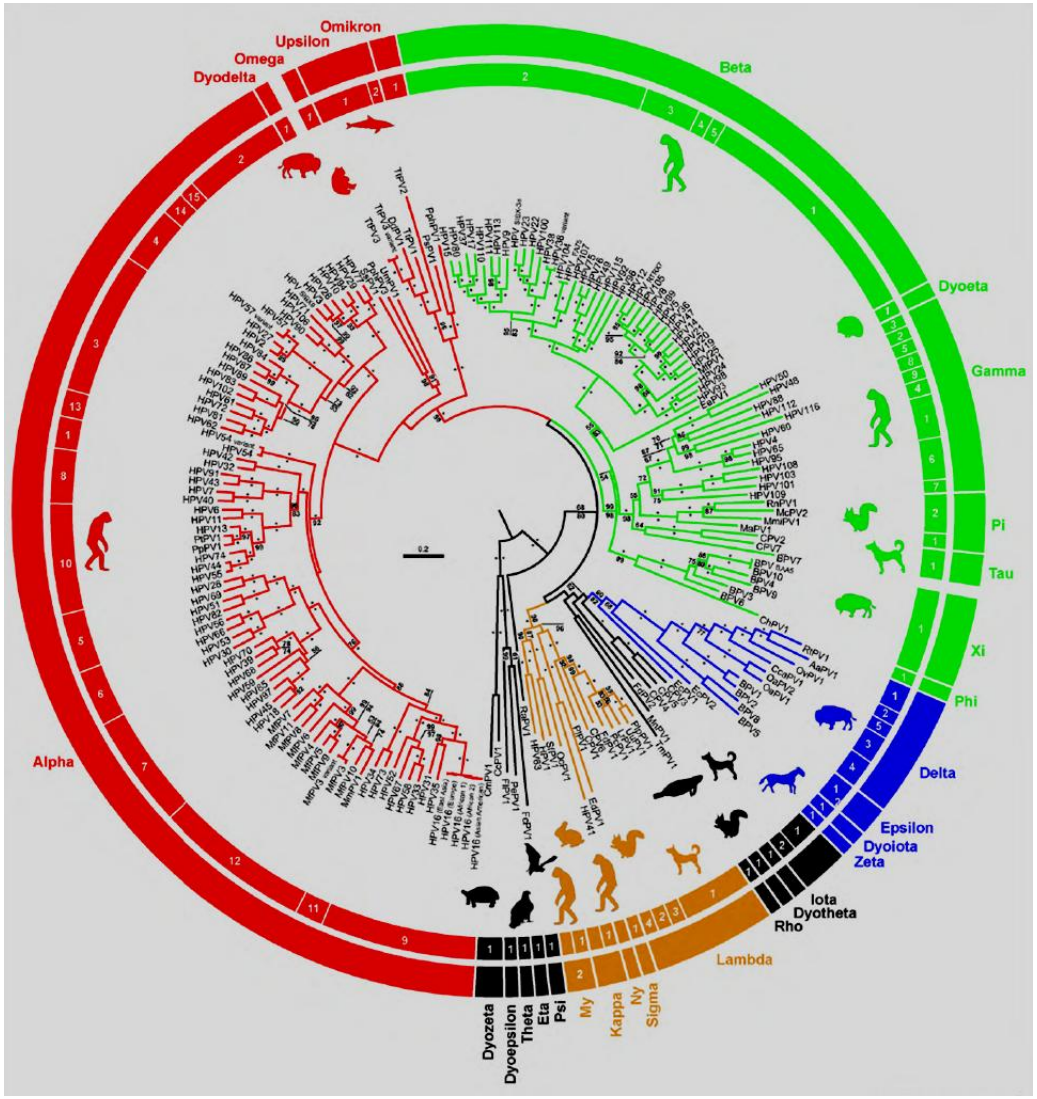
Next generation vaccines

Papillomavirus diversity



Humans, Apes/Monkeys

Cows, Deer

Dogs/Cats, Pumas/Lions

Horses, Bears

Hedgehogs, squirrels

Rabbits, bats, fowl

Turtles

Marine mammals

Bravo et al., 2010 Trends in Microbiology 18:432-8

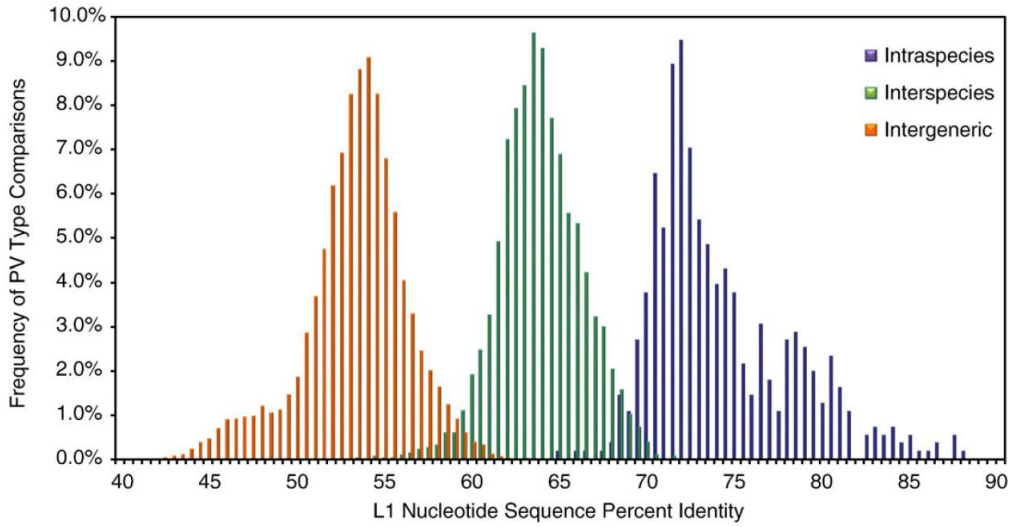
PV found in range of mammals, reptiles, avians

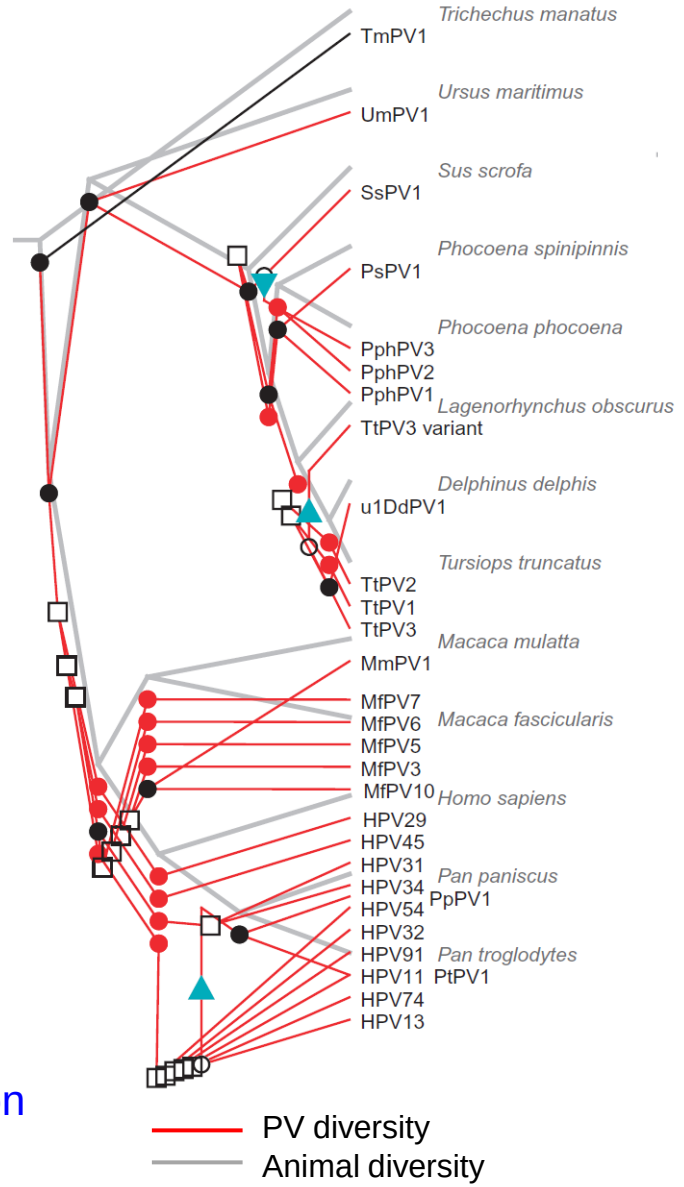
Lesion	Species	Reference
Cutaneous	Green sea turtle, Loggerhead sea turtle	Herbst 2009
	Francolin bird	Van Doorslaer 2009
	Diamond python	Lange 2011
Oral	Panther, Snow leopard, Bobcat, Asian Lion	Rector 2007
Genital	Short-beaked common dolphin, Killer whale, Harbour porpoise	Gottschling 2011

Rector et al., 2007 Genome Biology 8:R57
Herbst et al., 2009 Virology 383:131-35
Van Doorslaer et al., 2009 J. Virol. 83:8759-70
Lange et al., 2011 Virology Journal 8:436-40
Gottschling et al., 2011 Molecular Phylogenetics and Evolution 59:34-42

Papillomavirus diversity

Family: Papillomaviridae
Genus: e.g. Alpha-papillomavirus
Species: e.g. Alpha-papillomavirus 9
Type / Strain: e.g. HPV16

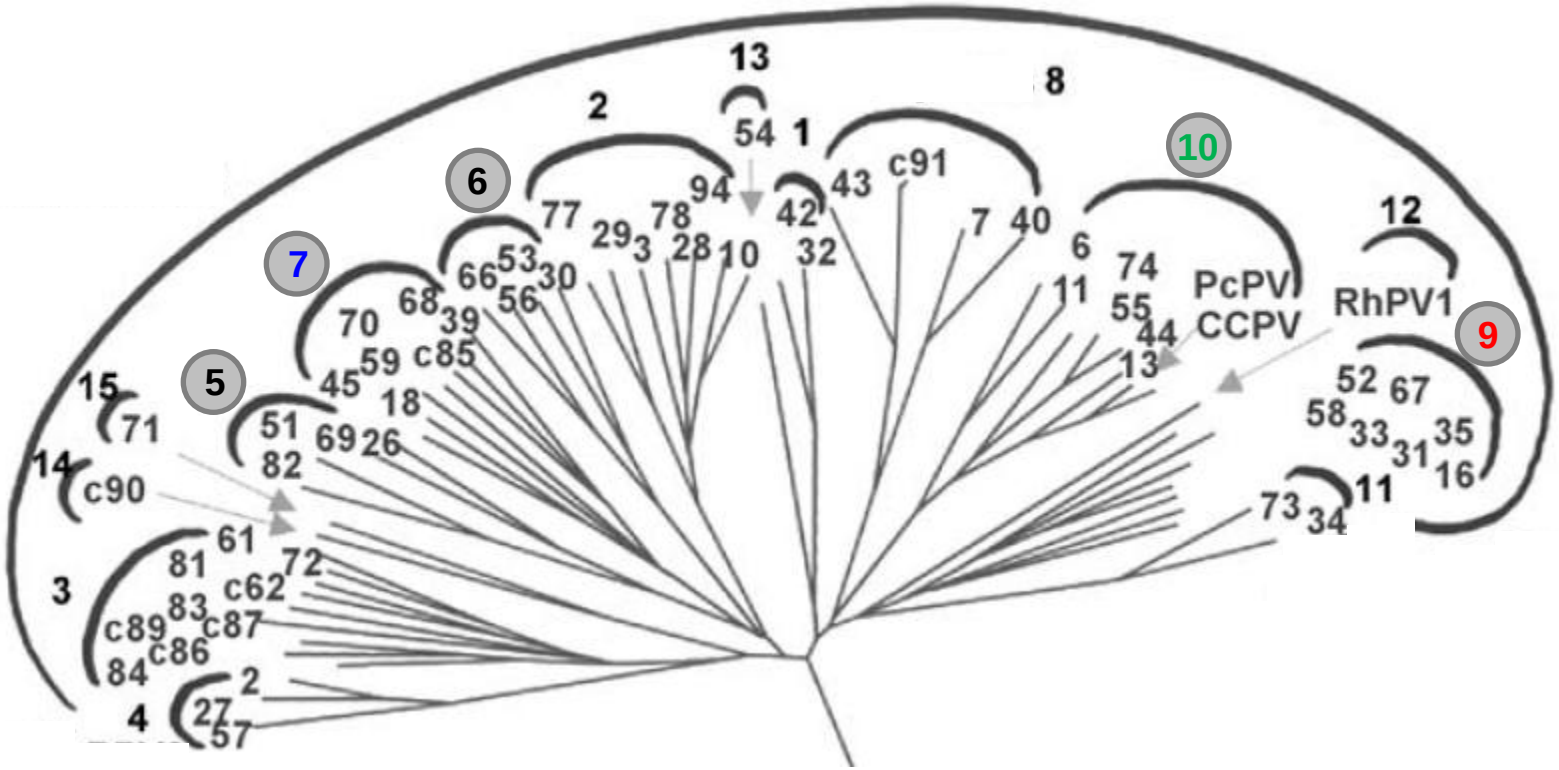




- Evolutionary rate ~$2x10^{-8}$ base substitutions / site / year
- Compared with HIV-1 ~$2x10^{-3}$
- Co-divergence (speciation) and inter-species transmission

Bernard et al., 2010 Virology 401:70–79
Gottschling et al., 2011 Mol. Biol. Evol. 28:2101–2113

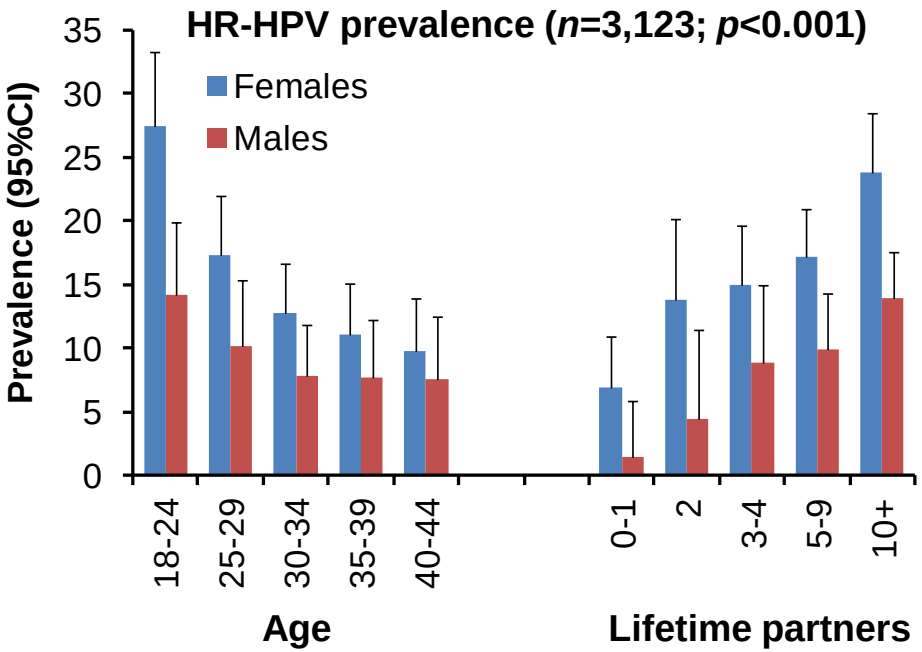
Alpha-Papillomavirus species and human disease



Cervical and other cancers (**HR**, High Risk)	**Alpha-7**:	HPV18, HPV39, HPV45, HPV59, HPV68
	Alpha-9:	HPV16, HPV31, HPV33, HPV35, HPV52, HPV58
	Alpha-5:	HPV51
	Alpha-6:	HPV56
Genital warts (**LR**, Low Risk)	**Alpha-10**:	HPV6, HPV11

de Villiers et al., 2004 Virology 324:17-27
Bouvard et al., 2009 Lancet Oncology 10:321-2

Sexual transmission – ancient and modern

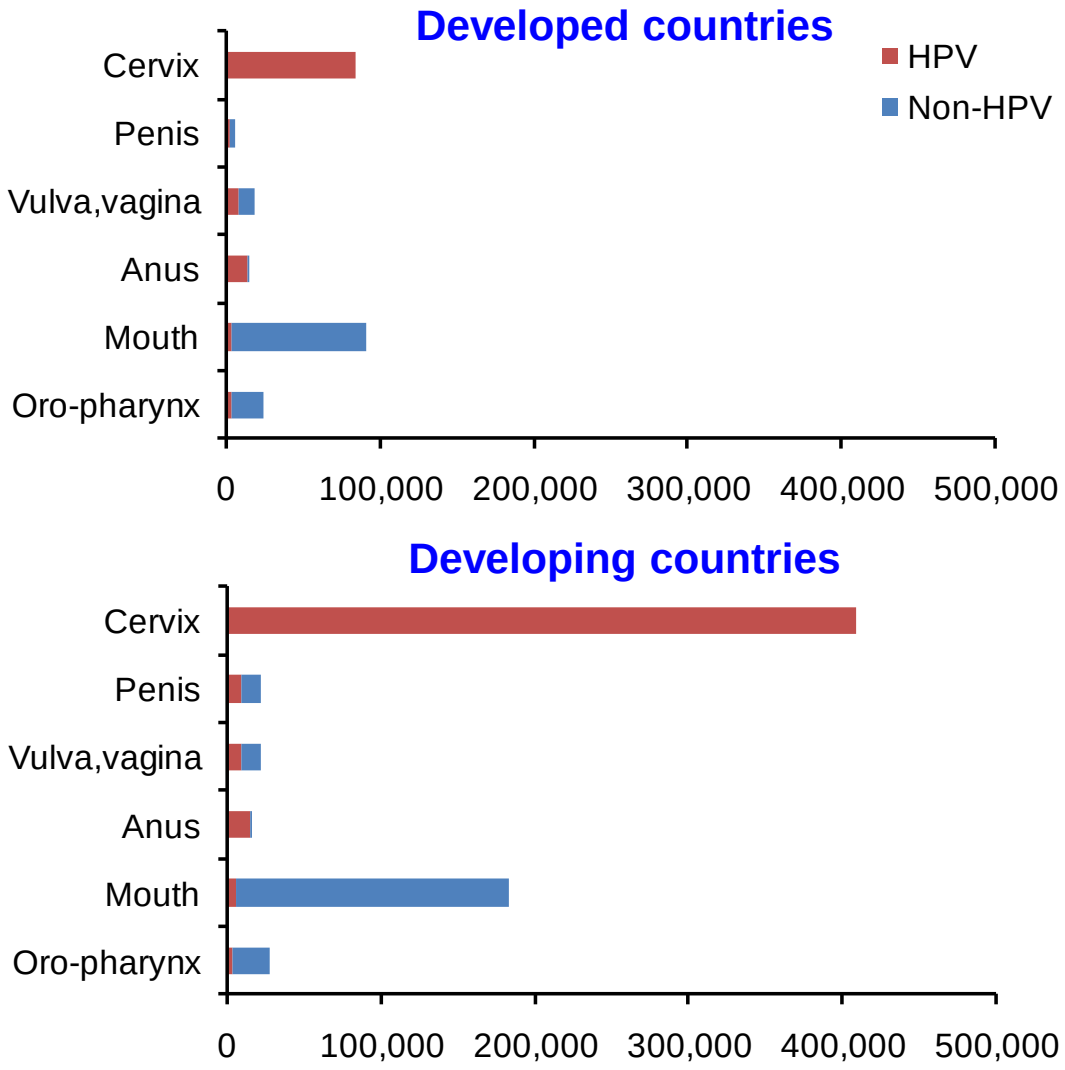


"herb Parthenium parviflorum for removing warts from the glans penis" Hippocrates, *ca*. 400 BCE

c.1st Romans attributed genital warts to promiscuity
c.19th Cervical cancer in prostitutes > nuns
c. 20th zur Hausen isolated HPV from warts and cervix cancer
c. 21st Vaccine introduced

Onon, 2011. Best Pract Res Clin Obstet Gynaecol 25:565–574
Johnson et al., 2012. Sex Transm Infect. 88:212-7.

Association of HPV with other cancers

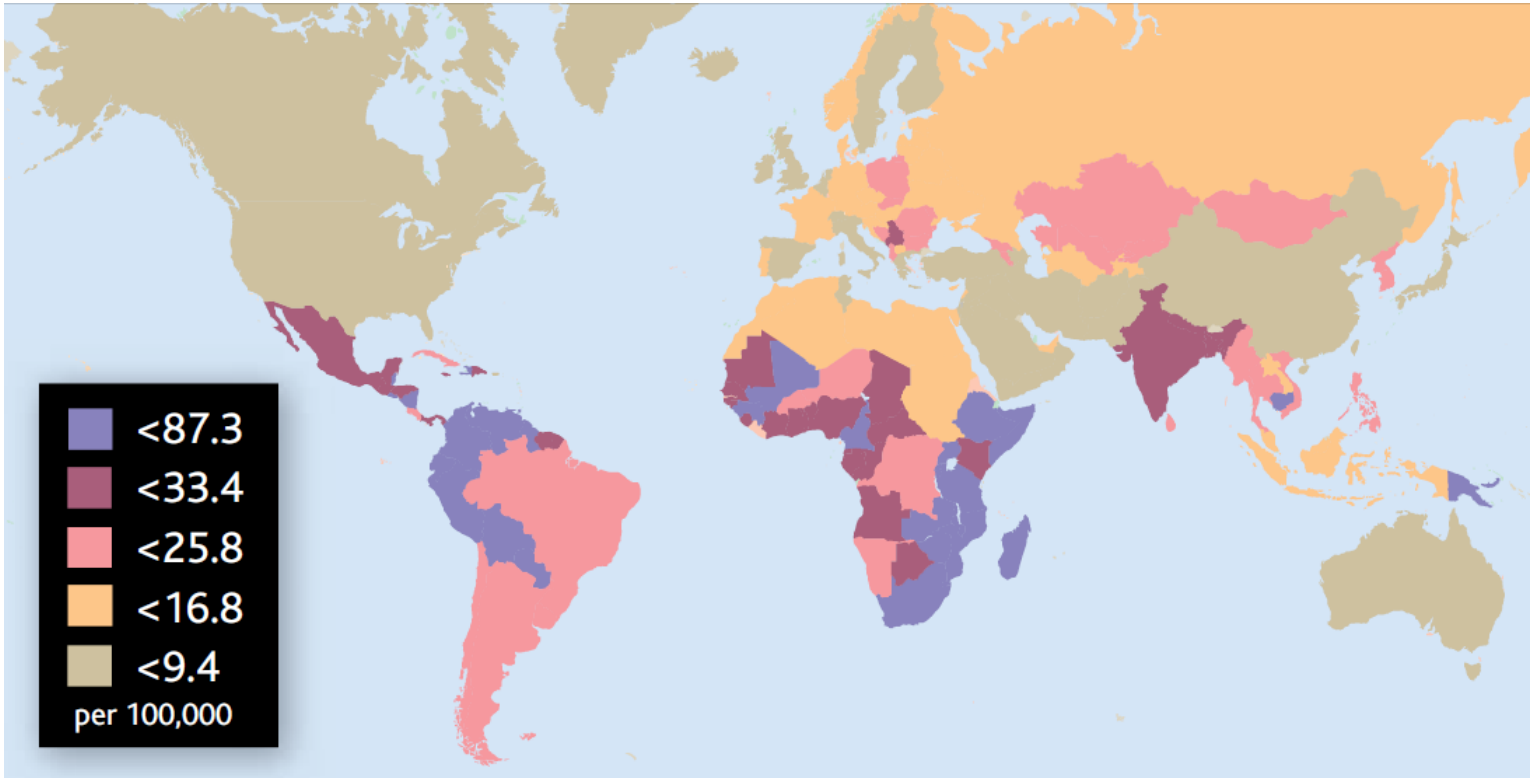


Site	%
Cervix	100
Penis	40
Vulva/Vagina	40
Anus	90
Mouth	3
Oro-pharynx	12

Parkin and Bray, 2006 Vaccine 24S3:11-25

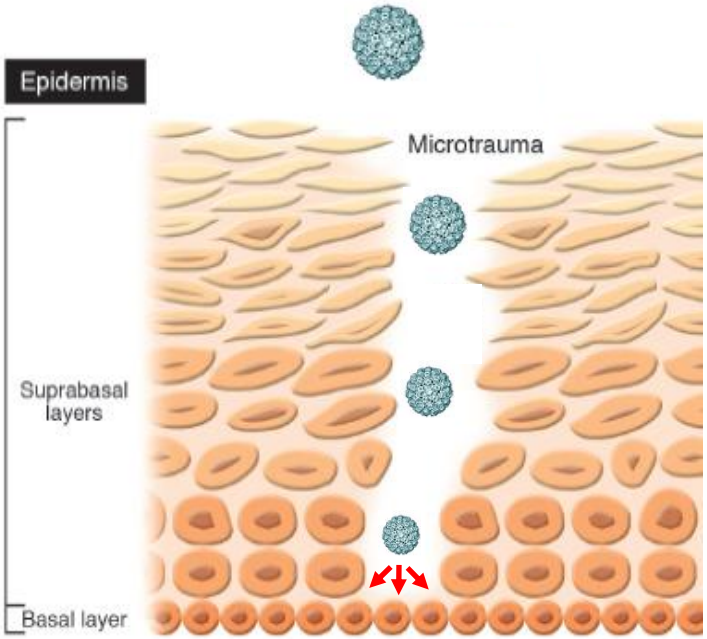
Most cancers of the cervix in developing countries

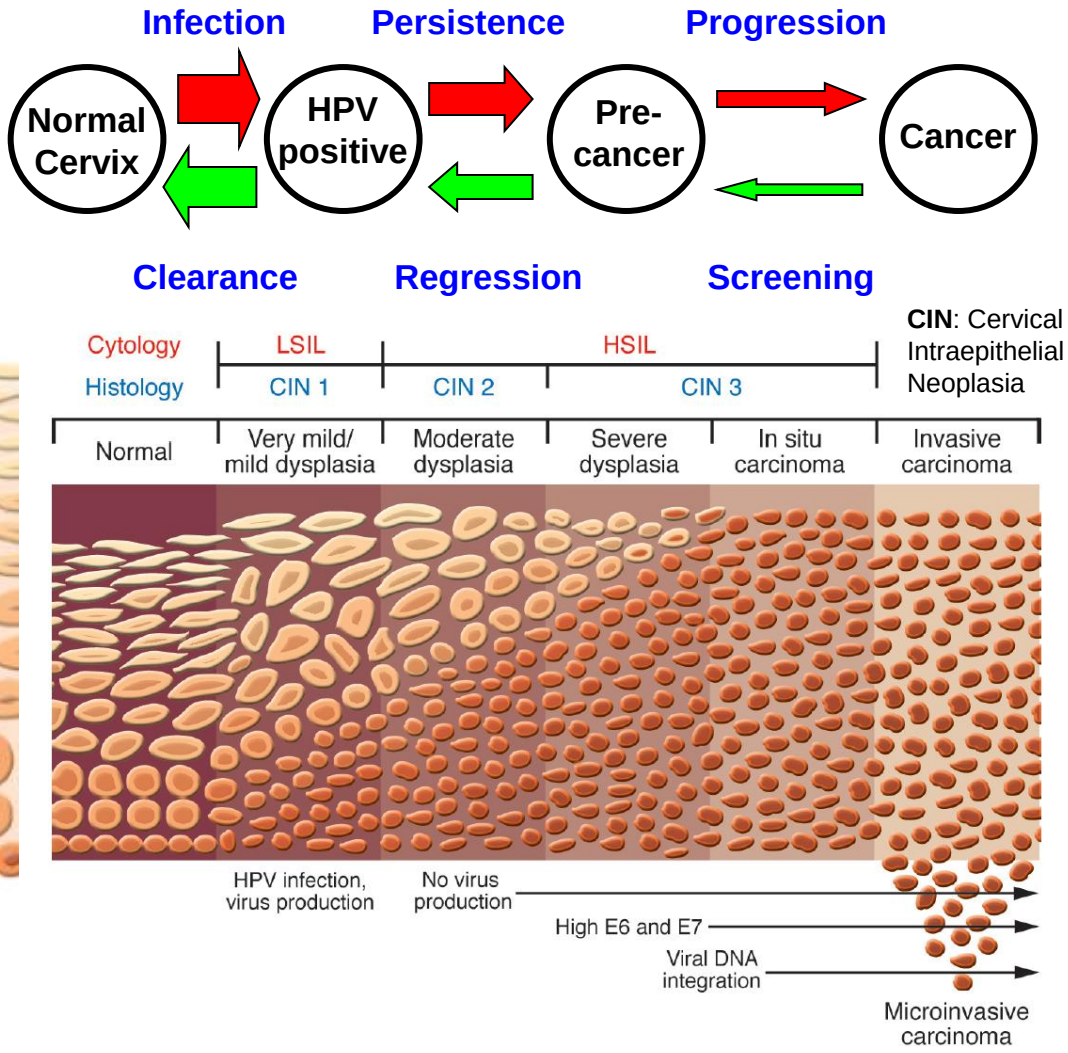
- Cervical cancer 3rd most common cancer in women worldwide
- 530,000 cases and 275,000 death per annum
- Lower rates due to screening or lack of reporting infrastructure



Cohen , 2005. Science 308: 618-21
Jemal et al., 2011 CA Cancer J Clin 61:69–90

HPV infection through disease - stages

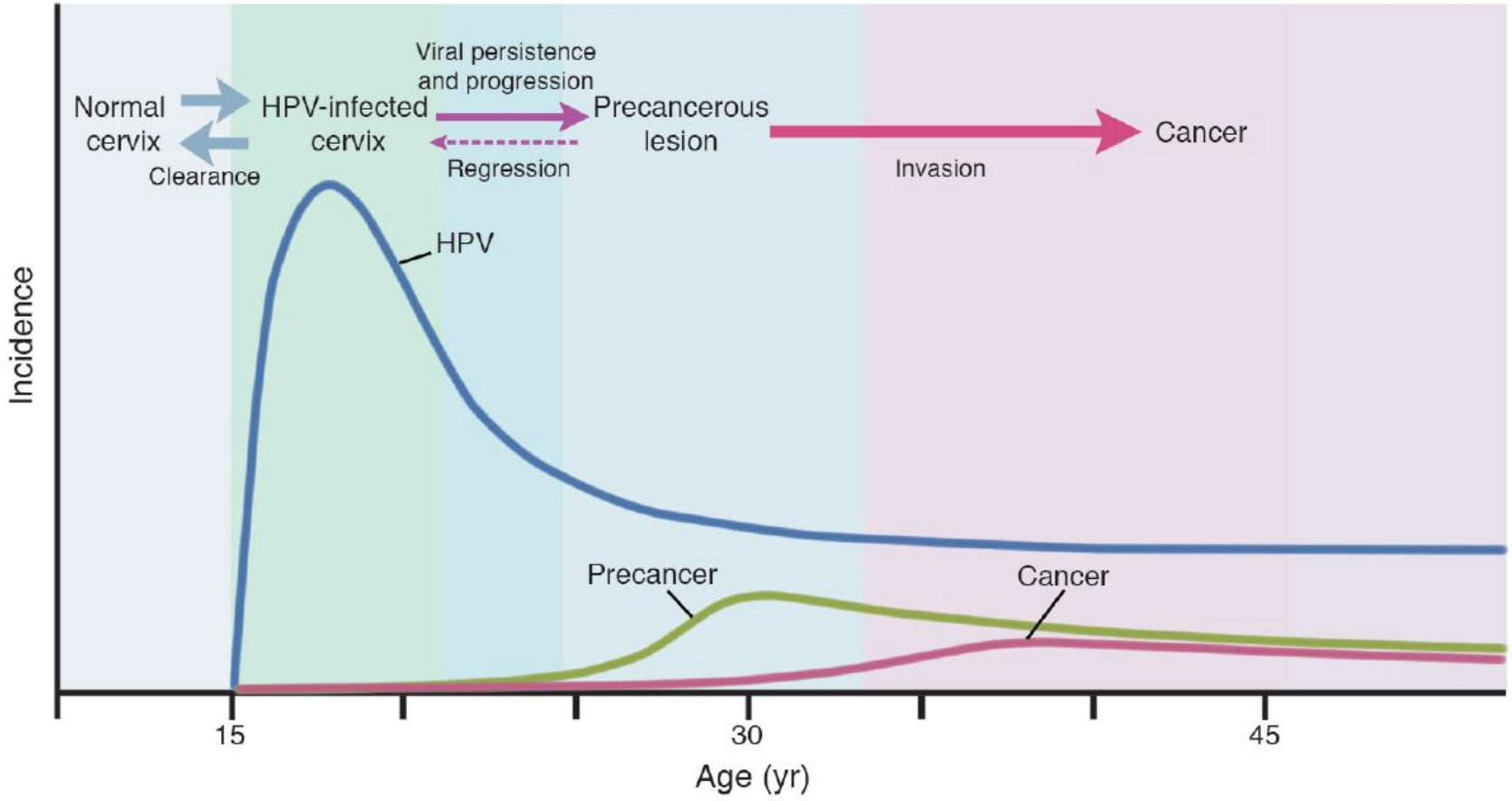




Lowry & Schiller, 2006 J Clin Invest,116:1167

HPV infection through disease - timelines

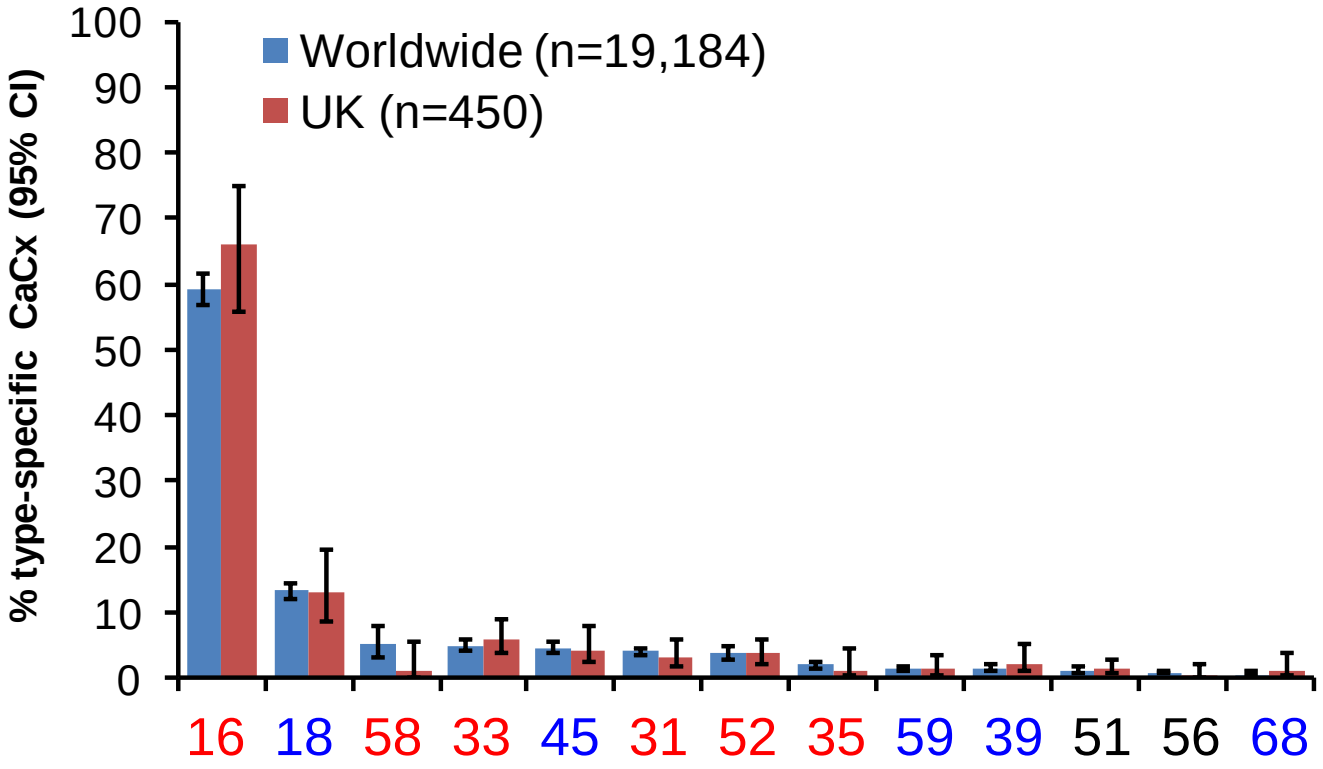
- Infection through disease takes many decades
- Trial endpoints include persistent infection and pre-cancerous lesions



Lowry & Schiller, 2006 J Clin Invest,116:1167

Worldwide type-specific cervical disease burden

- HPV16 and HPV18 associated with *ca*. 70% of cervical cancers
- *ca*. 98% associated with α7 (18-like) or α9 (16-like) HPV types

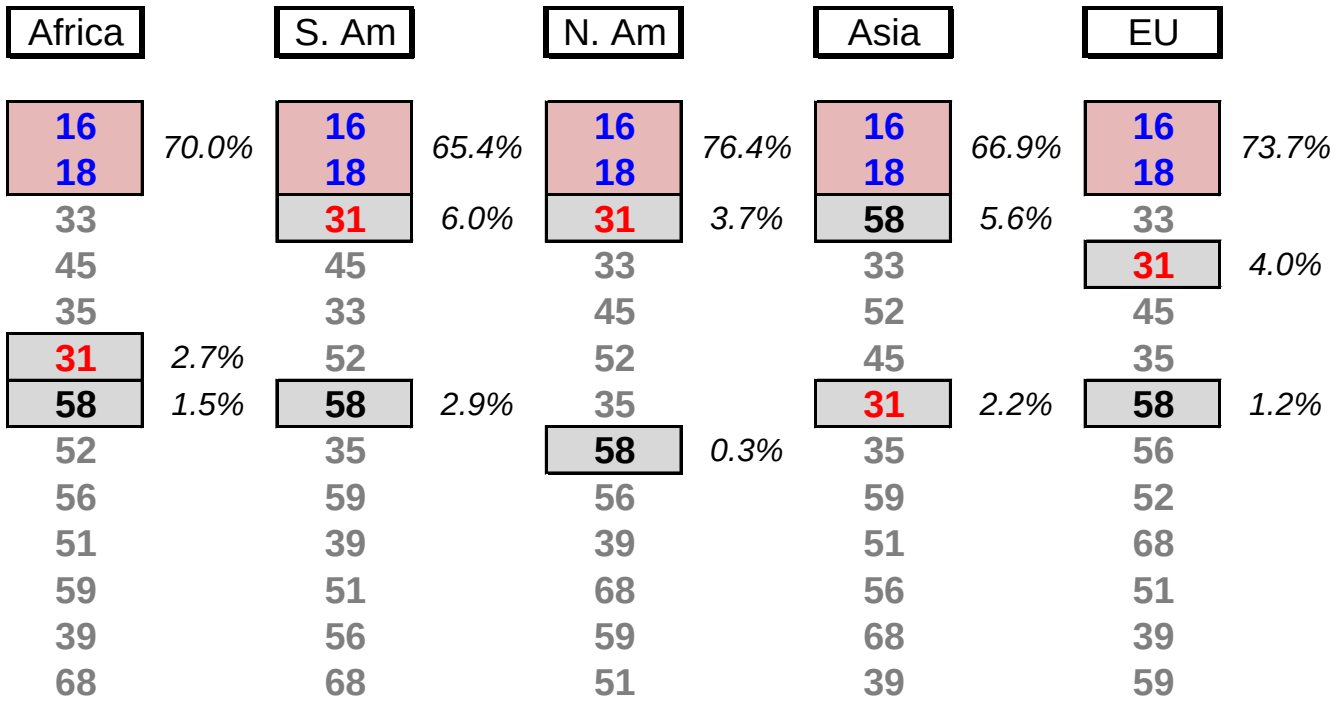


Alpha-7: HPV18, HPV39, HPV45, HPV59, HPV68
Alpha-9: HPV16, HPV31, HPV33, HPV35, HPV52, HPV58

Li et al., 2011. Int J Cancer 128:927–935
Howell-Jones et al., 2010. Br J Cancer 103:209 – 216

Worldwide type-specific disease prevalence

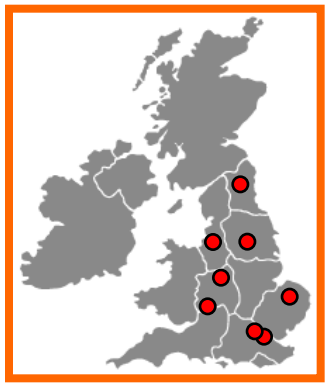
- Geographical differences in ranking but HPV16/18 most prevalent
- Differential sampling of regions means these can only be estimates

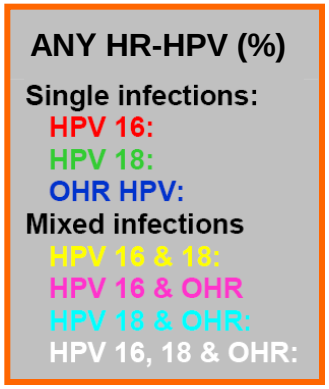


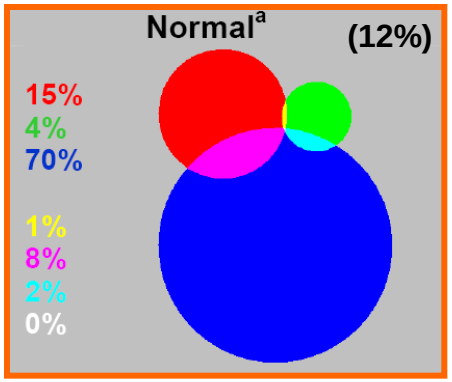
Alpha-7: HPV18, HPV39, HPV45, HPV59, HPV68
Alpha-9: HPV16, HPV31, HPV33, HPV35, HPV52, HPV58

Bosch et al., 2008 Vaccine 26S:K1–K16

Type-specific infection through disease



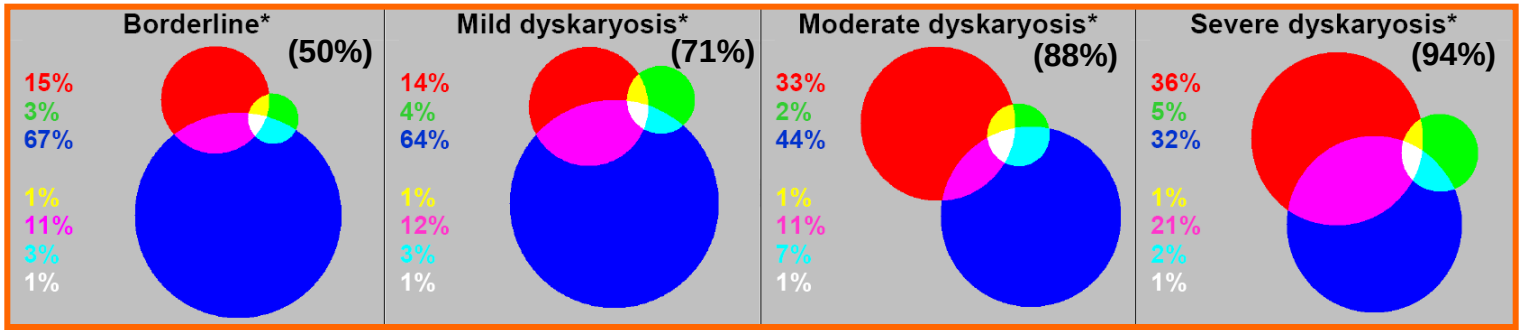


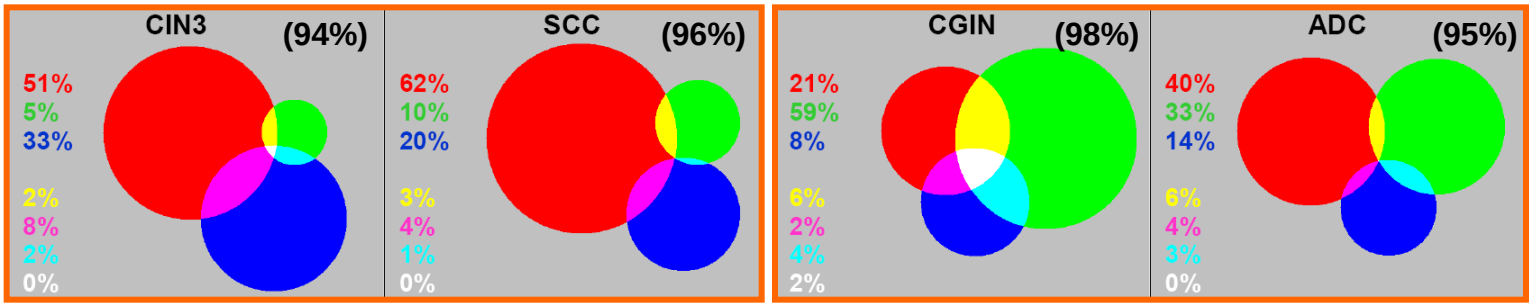


N=4,719 LBC
N=1,515 biopsies

8 English sites

Baseline (2008)

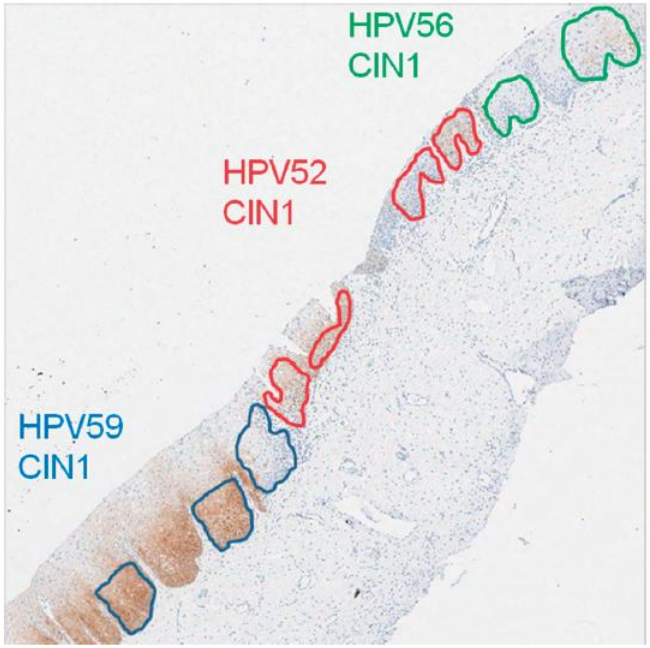




Howell-Jones et al., 2010 Br J Cancer 103, 209 – 216

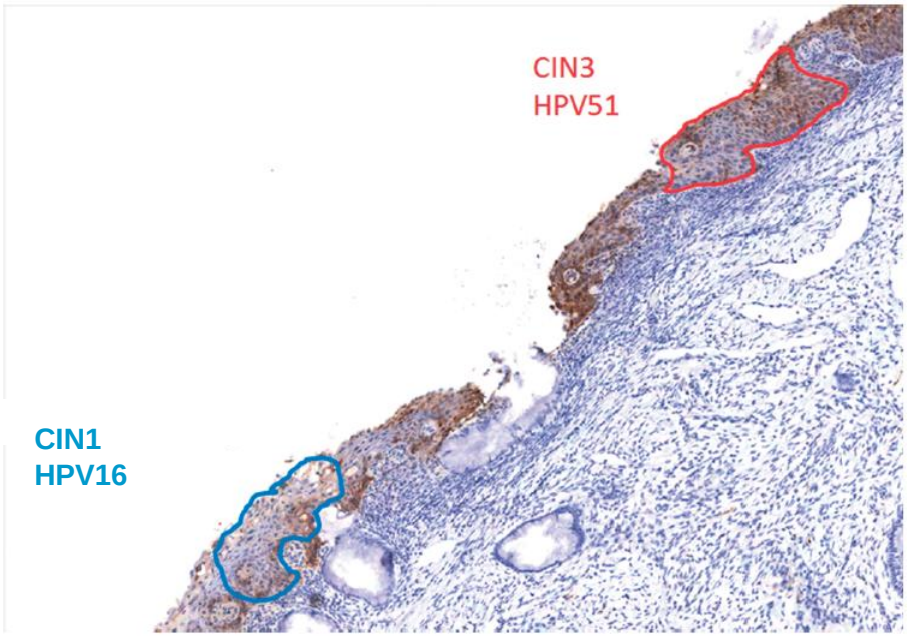
Multiple infections tend to be at independent sites

CIN1: HPV52, **HPV56** and **HPV59**



CIN: Cervical Intraepithelial Neoplasia

Mixed CIN1 and CIN3: **HPV16** and **HPV51**



$p16^{INK4a}$ (brown) upregulated by disruption of pRb-E2F complexes (which control cell cycling) by HPV E7

Quint et al., 2012 J Pathol 227:62-71

Papillomavirus infection and disease

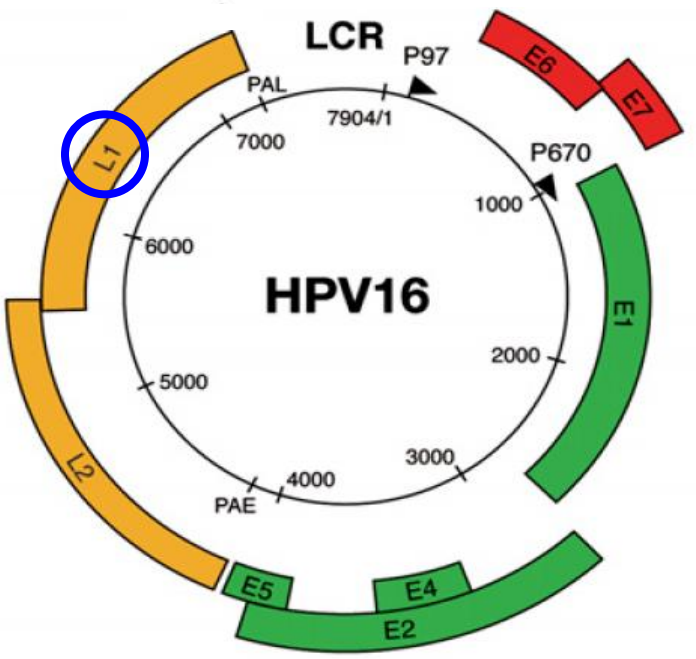
Development of current HPV vaccines

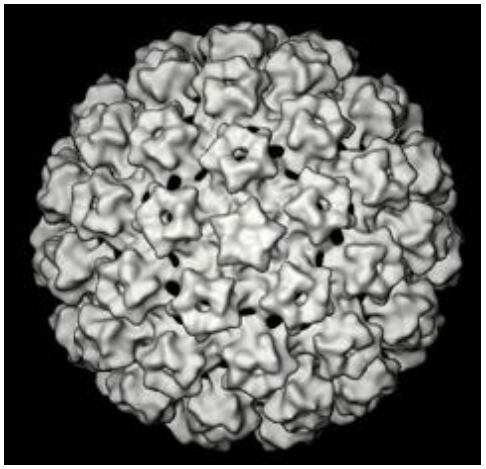
HPV vaccine implementation and impact

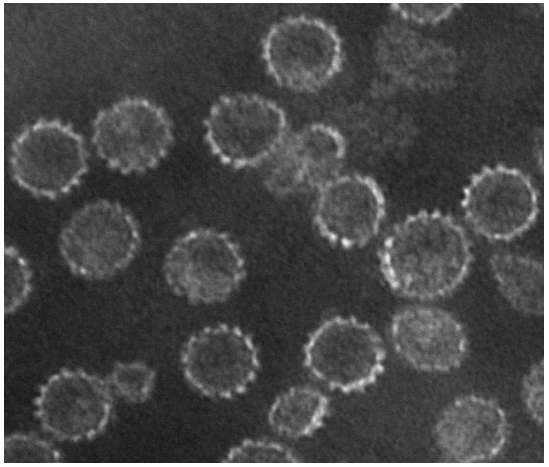
Potential impact against non-vaccine types

Next generation vaccines

HPV vaccines: structure







Structural genes, **Regulatory** genes and **Oncogenes** expressed from 8kb genome

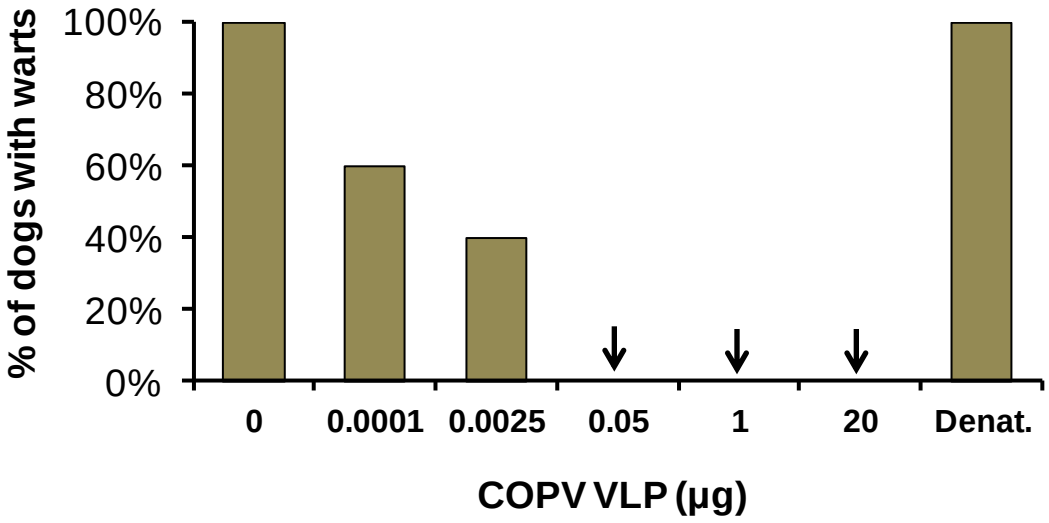
L1 self-assembles into a pentamer for which 72 pentamers make up L1 capsid

Basis of virus-like particle vaccine

Doorbar et al., 2006 Clinical Science 110:525
NCI (National Cancer Institute, US), 2008
HPV VLP EM, HPA

HPV vaccines: pre-clinical evidence

- Canine Oral PV VLP protects against COPV lesions
- Passive transfer of purified IgG protects naïve dogs from COPV challenge
- Protection mediated by antibodies to conformational epitopes
- Similar results obtained using Cotton-tail rabbit PV
- Immunization with HPV VLP in humans and animals elicit high titer Ab



Suzicj et al., 1995 PNAS 92:11553
Breitburd et al., 1995 J Virol 69:3959

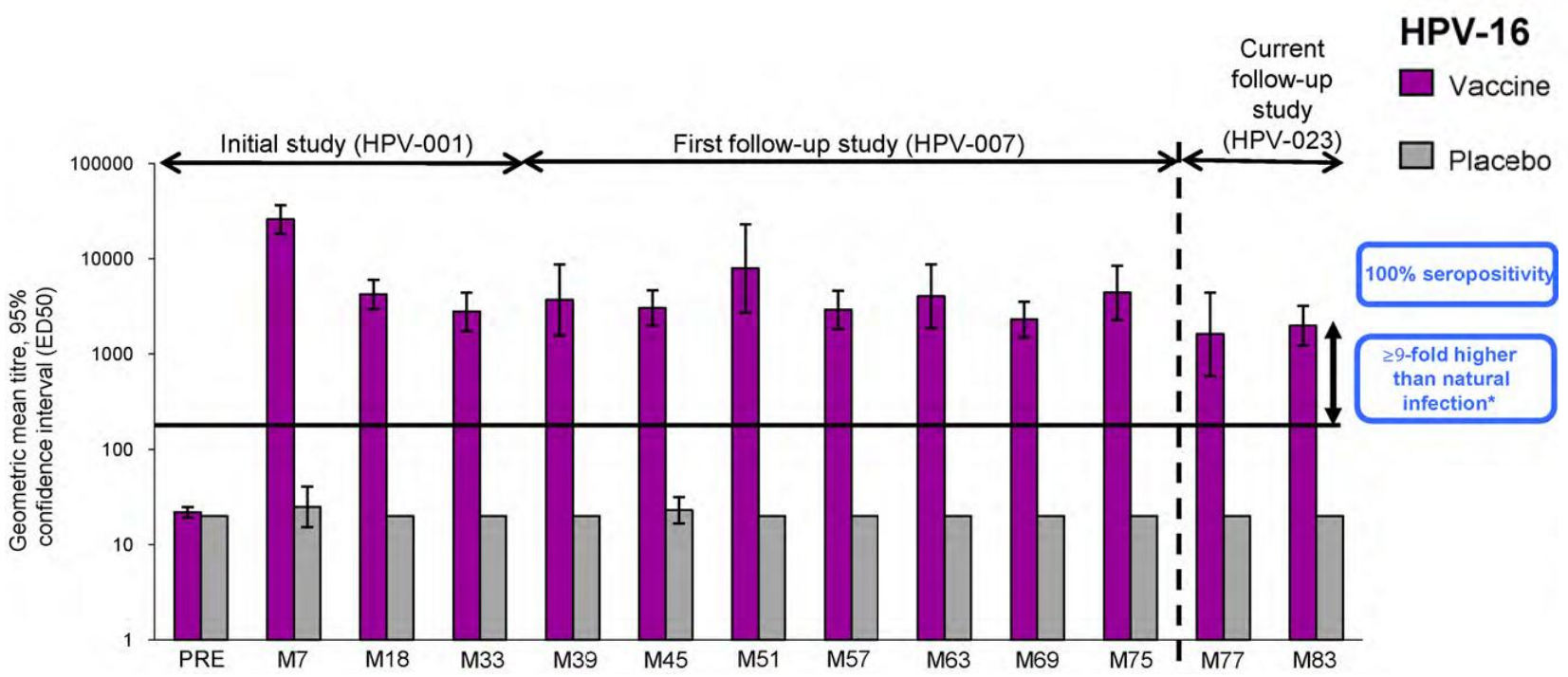
HPV vaccines: manufacturers

	Cervarix	Gardasil
Manufacturer	GSK	Merck / Sanofi
VLP	16/18	6/11/16/18
Source	Insect cells	Yeast cells
Adjuvant	Alum, MPL	Alum
Dose (µg)	20/20	20/40/40/20
Schedule (months)	0, 1, 6	0, 2, 6
Route	IM	IM

MPL, monophospholipid

HPV vaccines: immunogenicity to vaccine types

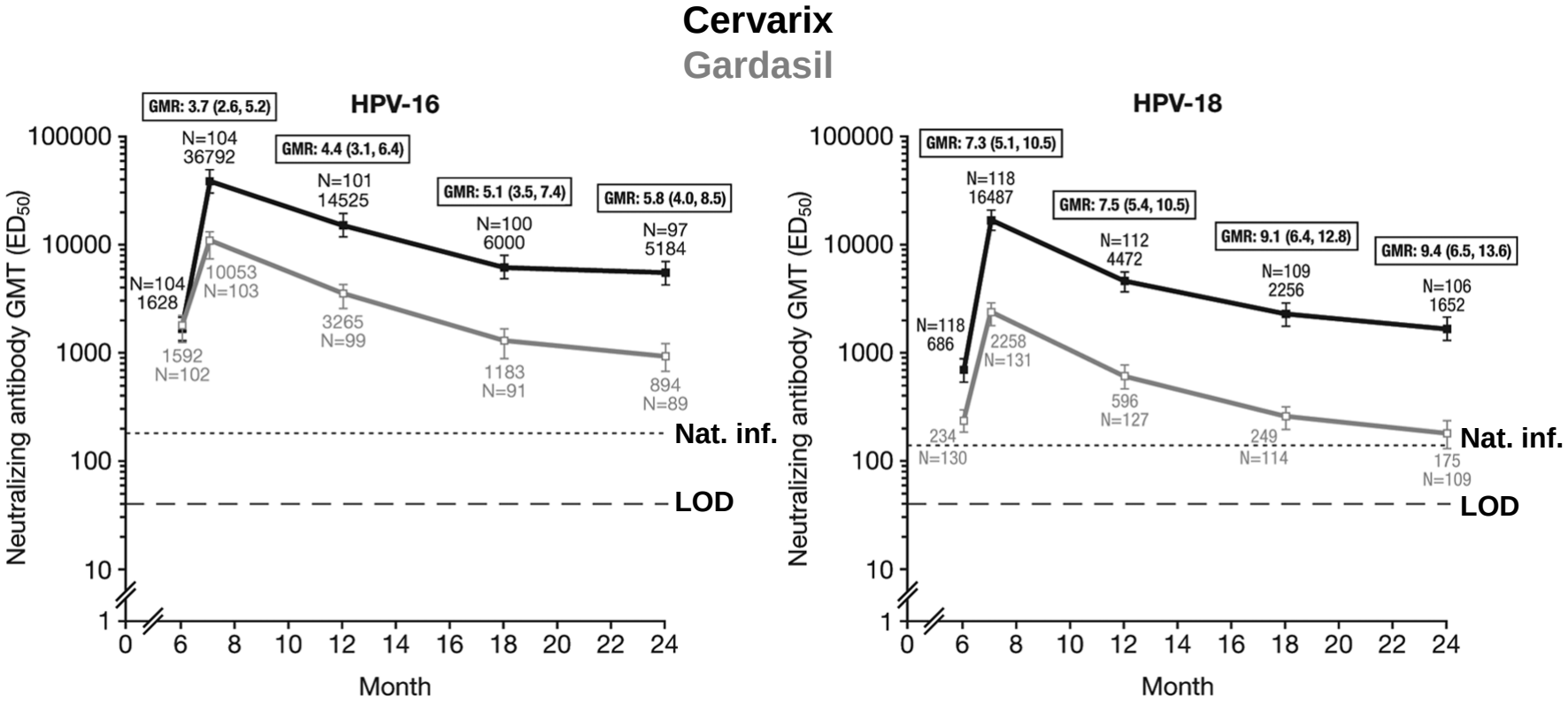
- Sustained antibody 10x level above natural infection to ≥7 years
- Assumed antibodies are effectors of vaccine-type protection in humans
- Unclear what antibody level correlates with protection
- Unclear whether booster is required over longer term



De Carvalho et al., Vaccine. 2010 28:6247-55.

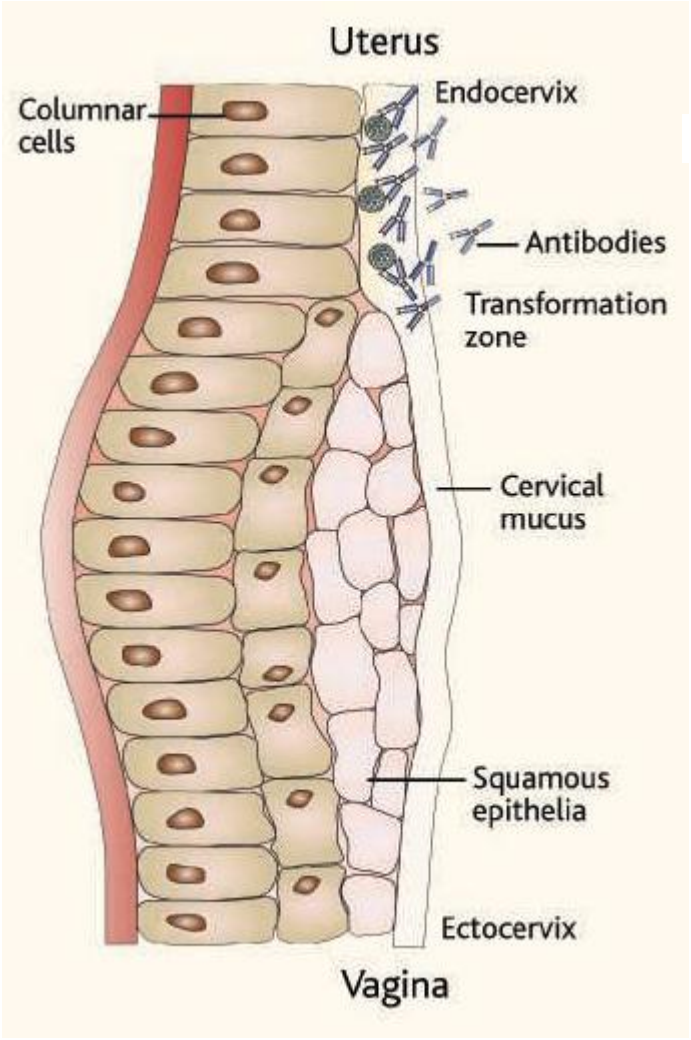
HPV vaccines: Cervarix® vs. Gardasil®

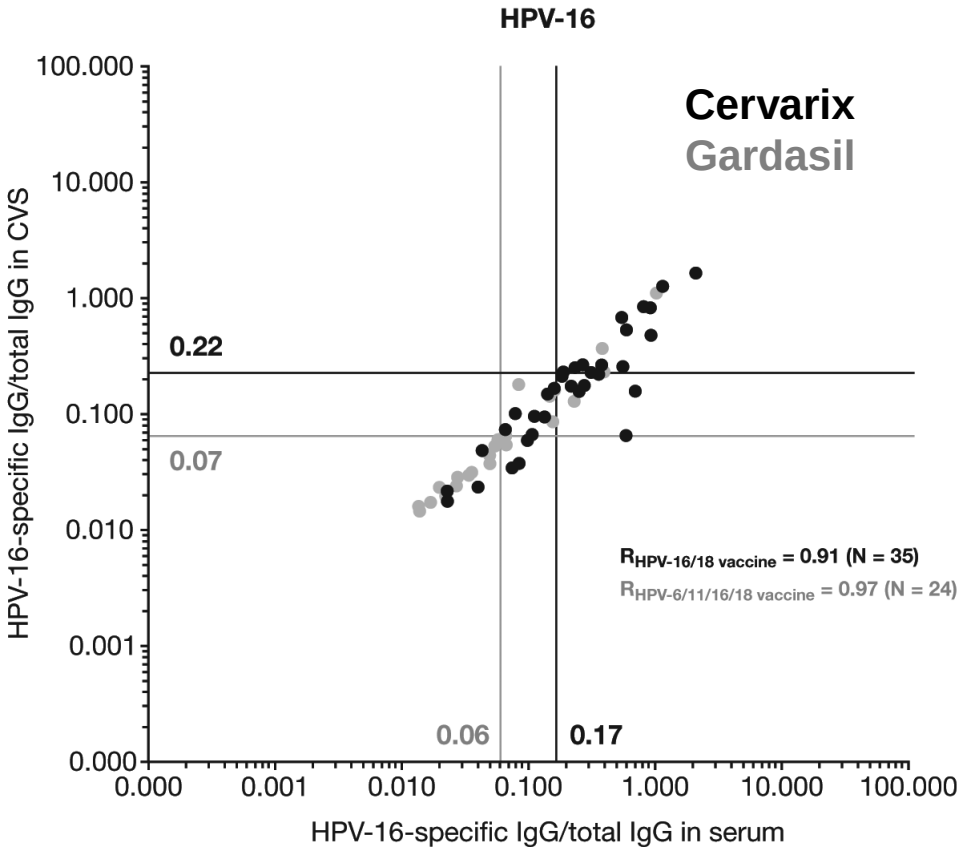
- Cervarix 3-5 fold higher antibody titers compared to Gardasil
- HPV16 response 3-5 fold higher antibody titers than for HPV18



Einstein et al., 2011 Human Vaccines 7: 1343-58

HPV vaccine antibody detected at genital mucosa





CVS: Cervicovaginal secretions

Einstein et al., 2011 Human Vaccines 7: 1343-58
Cohen, 2005. Science 308: 618-21

High vaccine type (HPV16/18) efficacy

	Endpoint	Vaccine	Control	Efficacy
Cervarix	CIN1	5 / 5466	141 / 5452	97% (91.6 – 98.9)
	CIN2	1 / 5466	97 / 5452	99% (94.2 – 100)
	CIN3	0 / 5466	27 / 5452	100% (85.5 – 100)
	AIS	0 / 5466	6 / 5452	100% (15.5 – 100)
Gardasil	CIN2	0 / 7864	71 / 7865	98% (93.3 – 99.8)
	CIN3	2 / 7864	63 / 7865	97% (88.1 – 99.6)
	AIS	0 / 7864	7 / 7865	100% (30.9 – 100)
	VIN/VAIN2+	0 / 7900	23 / 7902	100% (82.6 – 100)

CIN: Cervical Intraepithelial Neoplasia; **AIS**: Adenocarcinoma in situ
VIN: vulvar intraepithelial neoplasia; **VAIN**: vaginal intraepithelial neoplasia

Lehtinen et al., 2012 Lanect Oncology 13:89-99
Kjaer et al., 2009 Cancer Prev Res 2:868-878

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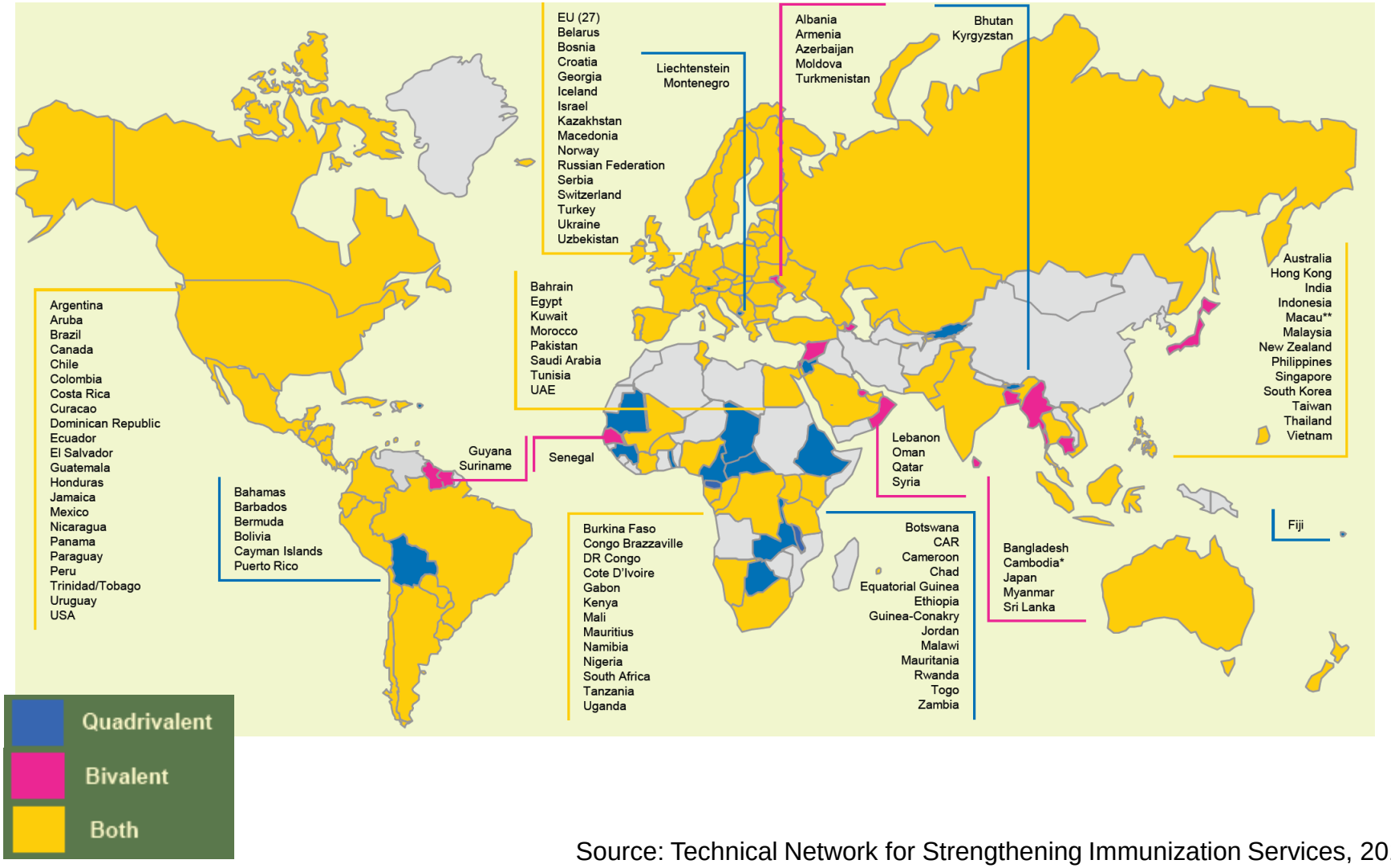
Vaccine implementation: Worldwide licensure (2011)



Source: Technical Network for Strengthening Immunization Services, 2011

Vaccine implementation: Cost

- Cost is a major hurdle to HPV vaccine programme implementation
- Negotiation with major players over several years has brought costs down

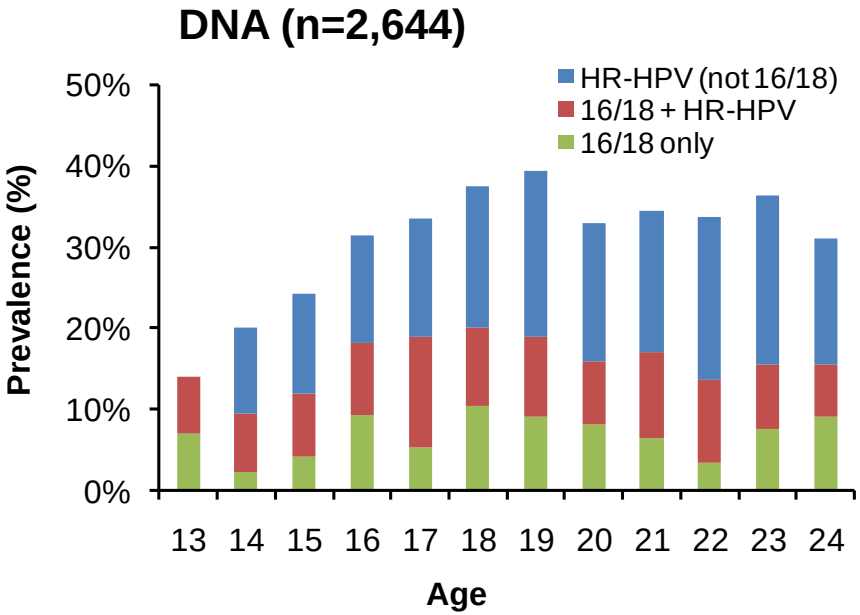
Vaccine	Source	Price (per dose)
HPV	Industrialized countries	$100 – 233
	Developing countries	$30 – 110
	PAHO	$14
	GAVI	$5
MMR	UNICEF	$1
DTP		20¢
BCG		10¢

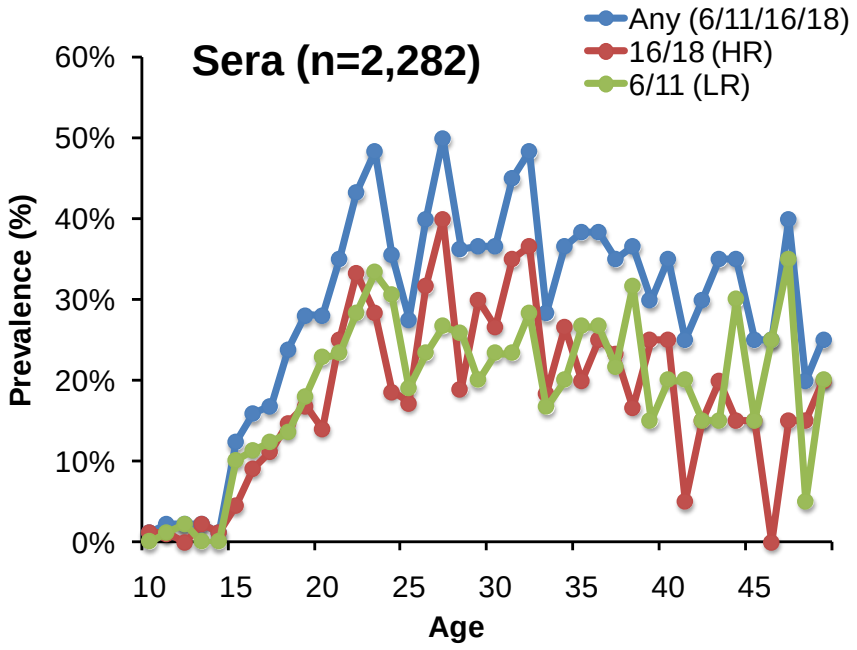
PAHO: *Pan American Health Organization*
GAVI: *Global Alliance for Vaccines and Immunisation* - WHO, World Bank, UNICEF, Gates Foundation, industry
MMR: Measles, Mumps, Rubella vaccine
DTP: Diphtheria, Pertussis (whooping cough) and Tetanus vaccine
BCG: Bacillus Calmette–Guérin (Bovine TB) vaccine

Source: GAVI Alliance, 2012
UNICEF, 2012

Pre-vaccine HPV prevalence (England)

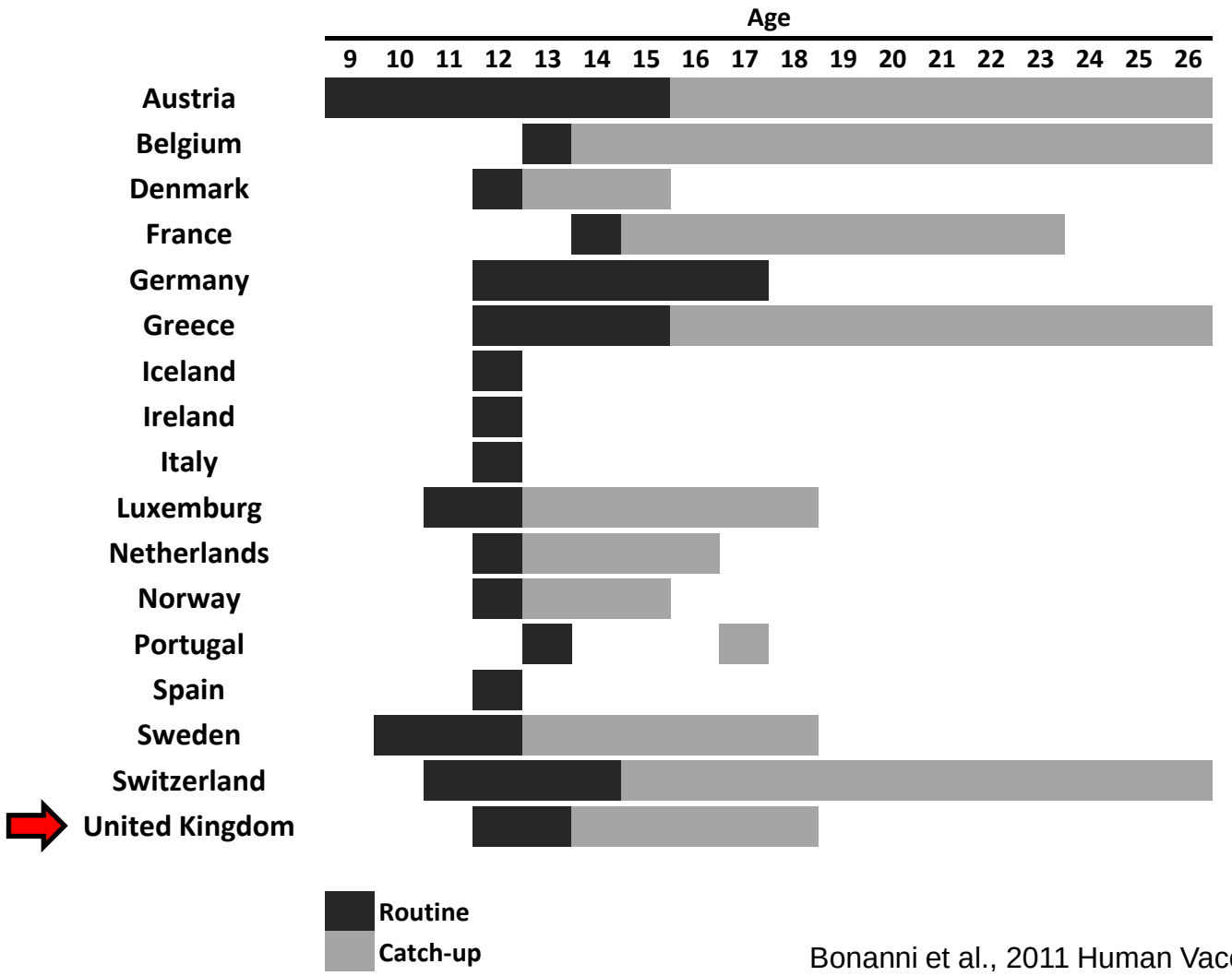
- Baseline to confirm appropriate ages & compare with post-vaccine data
- Cervarix® vaccine introduced Sept 2008; Gardasil® used from Sept 2012





Howell-Jones et al., 2012. Vaccine 30:3867–3875
Desai et al., 2011. Sex Trans Dis 38:622

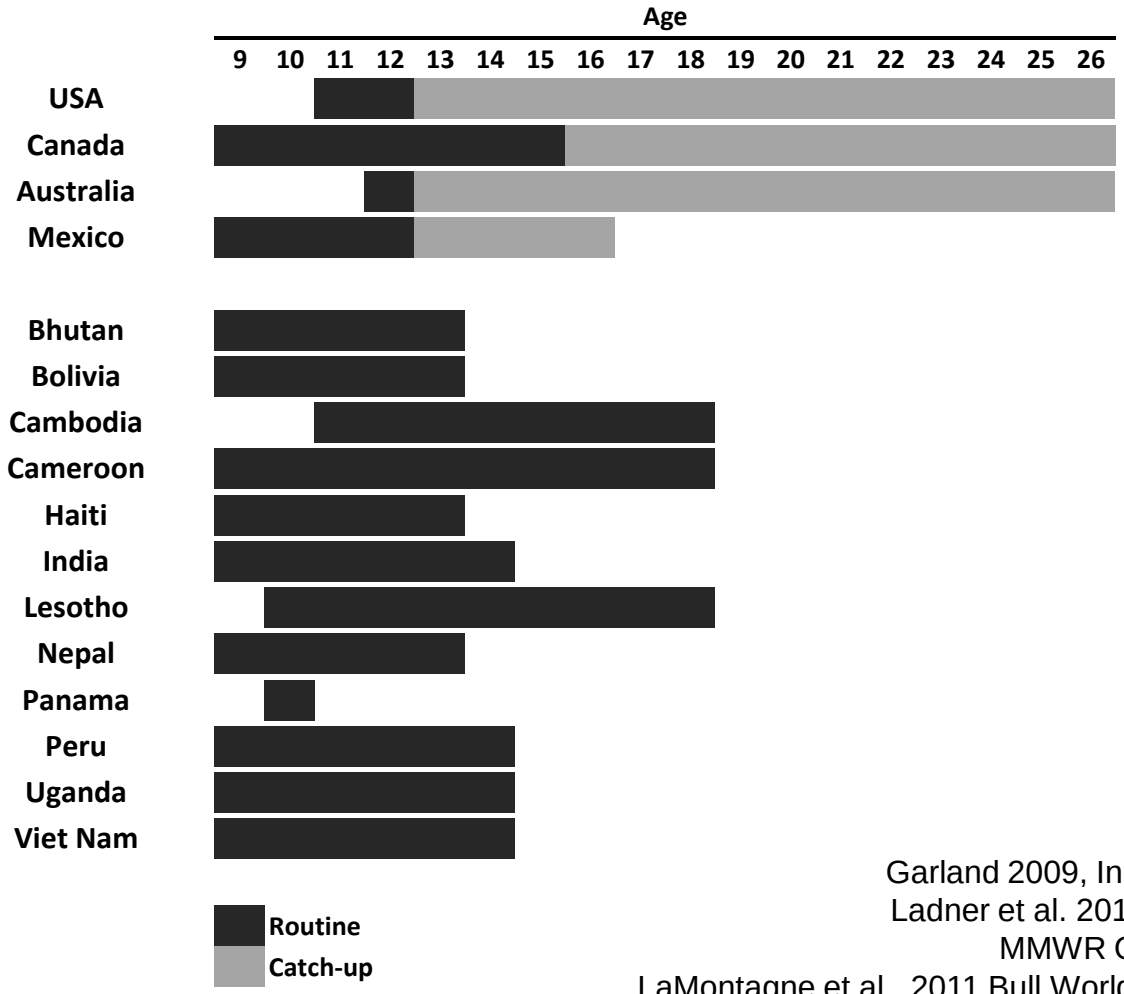
Vaccine implementation: Europe



Bonanni et al., 2011 Human Vaccines 7: S128-135

Vaccine implementation: Worldwide

- Mixed delivery effectiveness
- Developing countries limited to sites rather than national programmes



Garland 2009, Indian J Med Res 130:311-321
Ladner et al. 2012 BMC Public Health 12:370
MMWR October 14, 2011 Vol. 60 (40)
LaMontagne et al., 2011 Bull World Health Organ 89:821–830B

Vaccine implementation: Feasibility studies

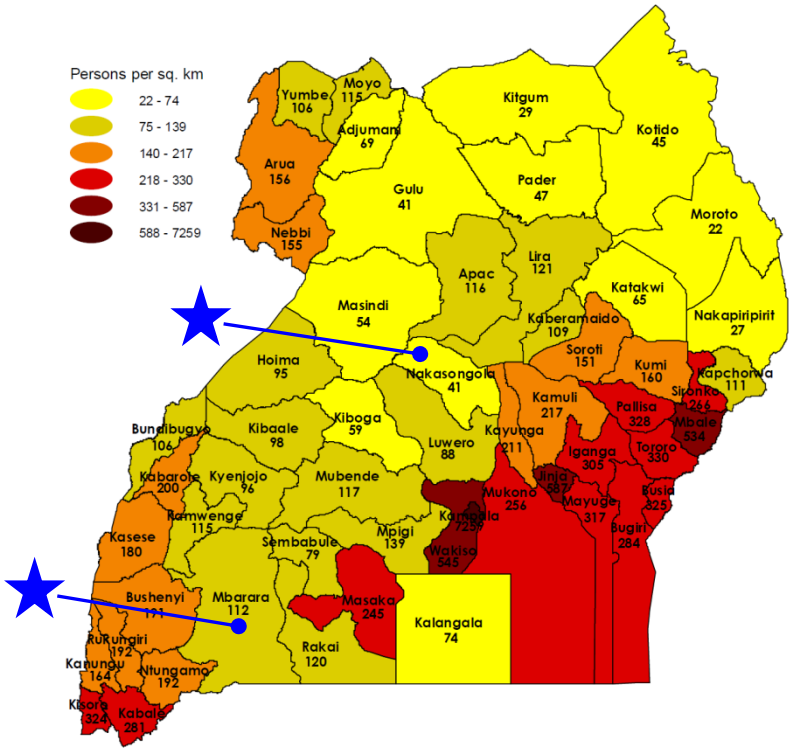
- 7,269 girls aged *ca*. 10 -14 years old participated in feasibility studies
- Mixed delivery mechanisms but generally good coverage

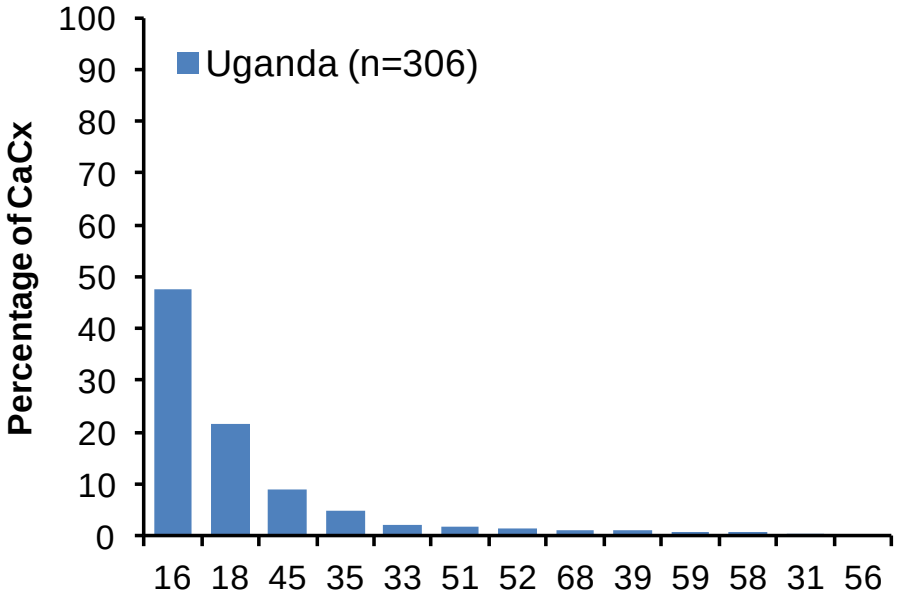
	Schools (n)	Health centres (n)	Coverage (%)
Peru	264	161	83%
Uganda	417	69	53 - 91%
Viet Nam	38	72	83%
India	537	672	77-88%

LaMontagne et al., 2011 Bull World Health Organ 89:821–830B

Vaccine implementation: e.g. Uganda

- 2 rural districts trialled during 2009-10 (★)
- Uganda announces initiation of vaccine programme Q3 2012
- Gardasil targeting 140,000 9-13 years in 12 of 111 districts over 2 years
- 2002 census est. 187,500 girls 10-14 years old in Uganda

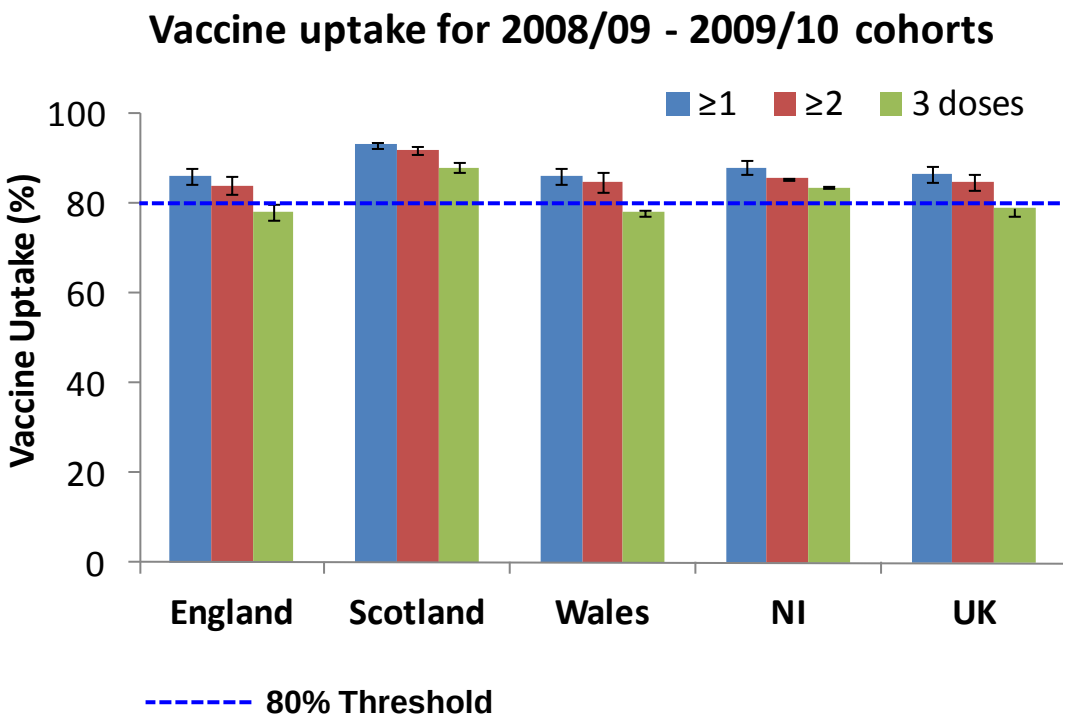




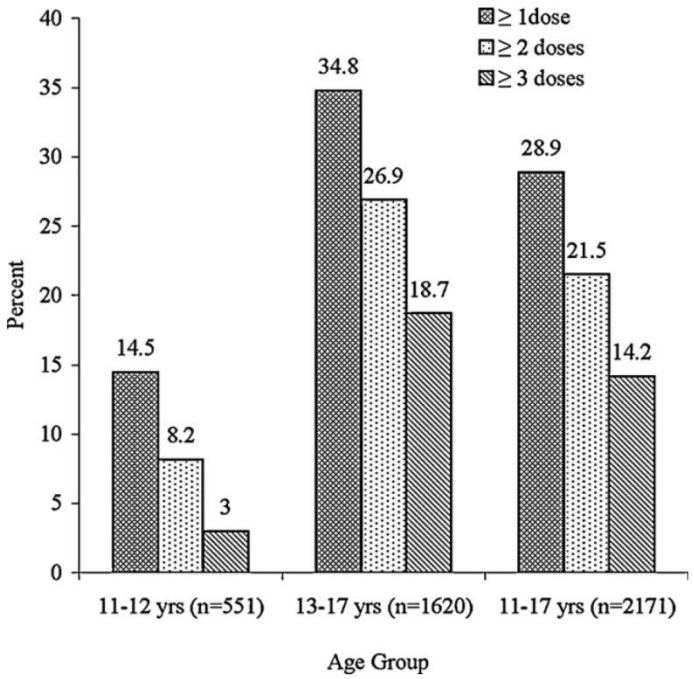
Odida et al. 2010 Infectious Agents and Cancer 5:15
Gullard 2012 BMJ 345:e6055
2002 Uganda Population and Housing Census

HPV vaccine coverage

United Kingdom



United States



UK Dept Health 2010
Laz et al., 2012 Vaccine 30:3534-40

Implementation issues: Worldwide

- Adolescent girls (school-based programmes), attendance issues
- Knowledge base low, acceptance issues, health education
- Infrastructure to maintain cold chain
- Improve and maintain coverage rates
- Post-vaccine surveillance, impact monitoring
- 2 dose schedule will reduce costs and thus may extend coverage

Post vaccine surveillance (Australia)

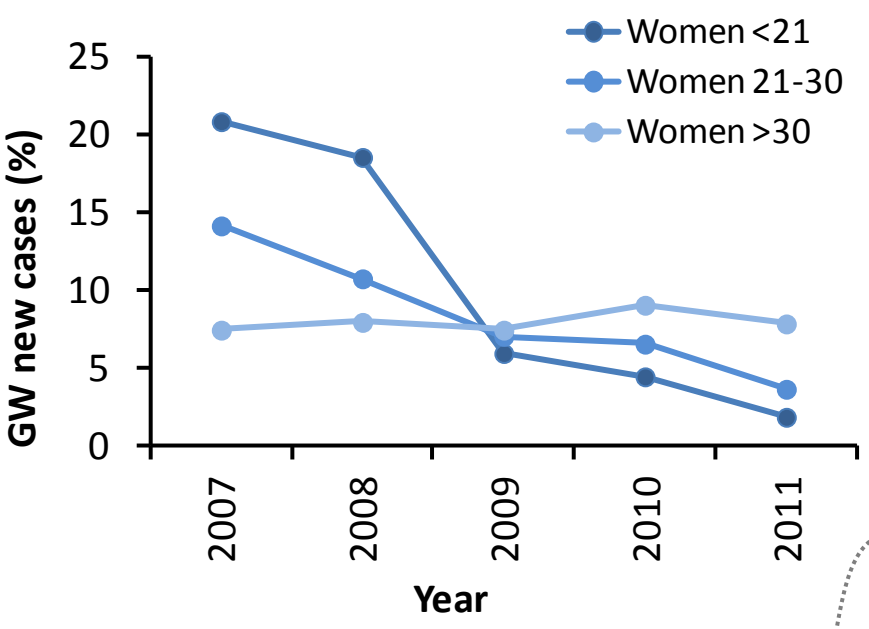
- Gardasil vaccine from 2007 (12-27 yr women) vs CIN2+

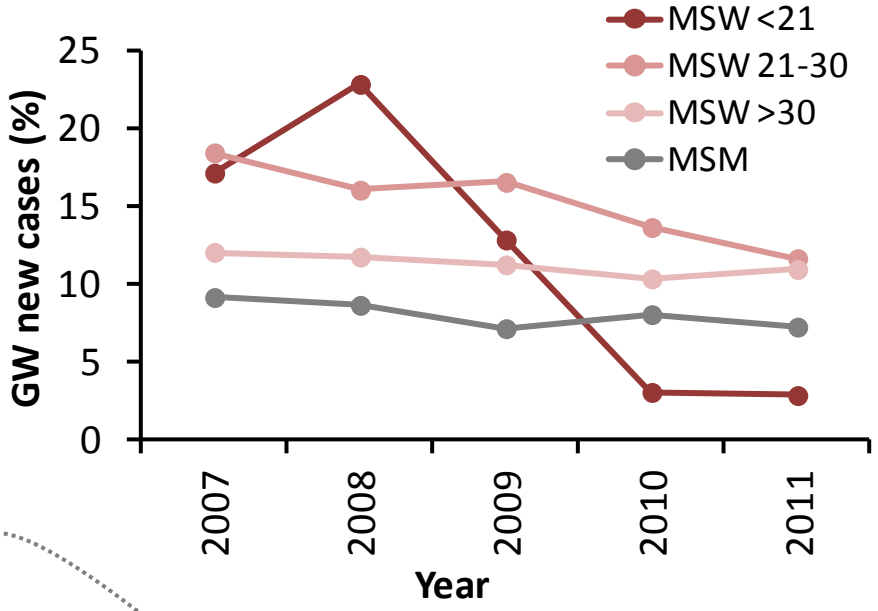
HGA: High Grade Cervical Abnormalities

Brotherton et al., 2011 Lancet 377: 2085–92

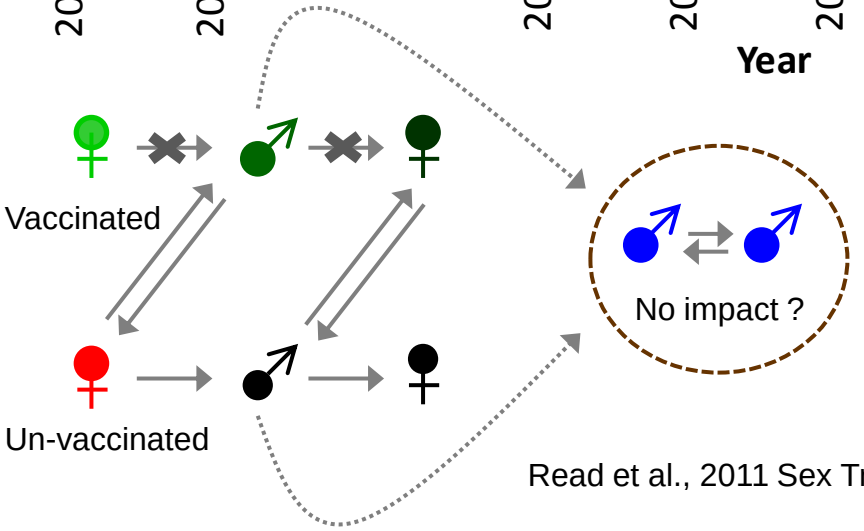
Post vaccine surveillance (Australia)

- Gardasil vaccine from 2007 (12-27 yr women) vs genital warts (GW)





Men (and women) likely to benefit from herd immunity but also likely to be under constant challenge from unvaccinated women and men. MSM unlikely to benefit.



Read et al., 2011 Sex Transm Infect 87:544

Papillomavirus infection and disease

Development of current HPV vaccines

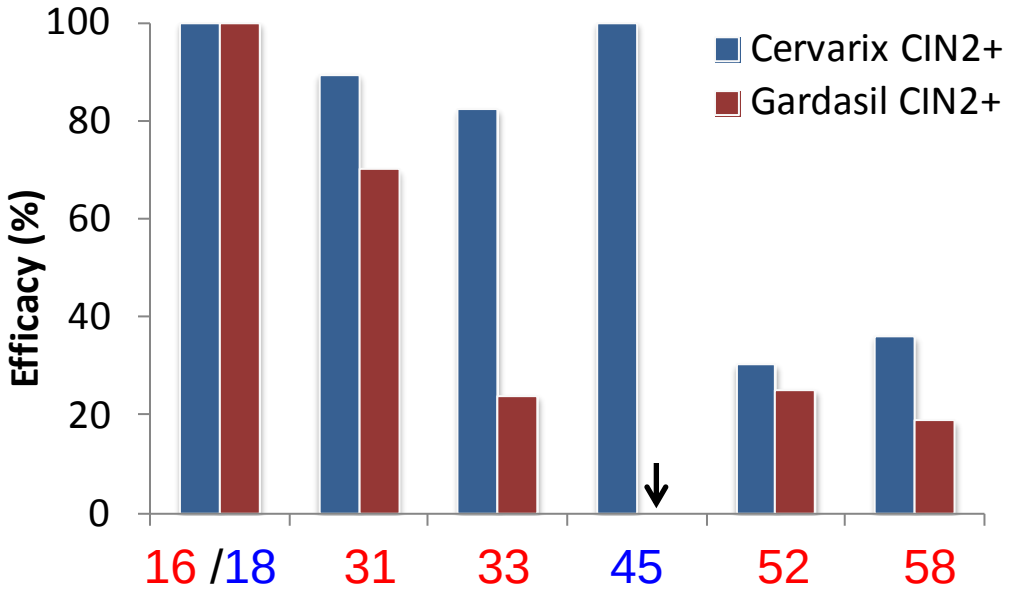
HPV vaccine implementation and impact

Potential impact against non-vaccine types

Next generation vaccines

Efficacy to related non-vaccine types

- Some degree of efficacy against related non-vaccine types
- Possible vaccine differences in efficacy against some non-vaccine types
- **HPV31, 33, 45**: associated with a further *ca*. 10% of cervical cancers

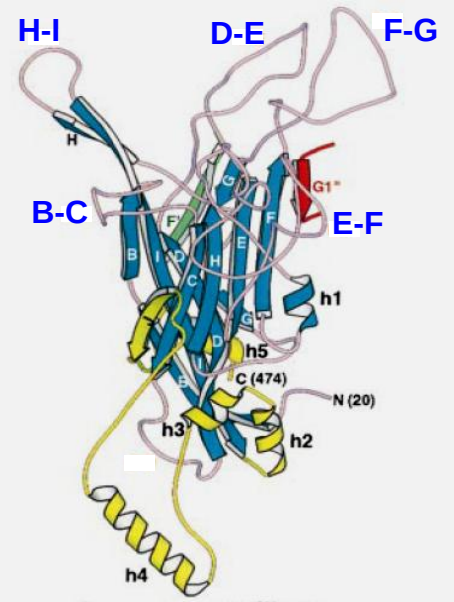


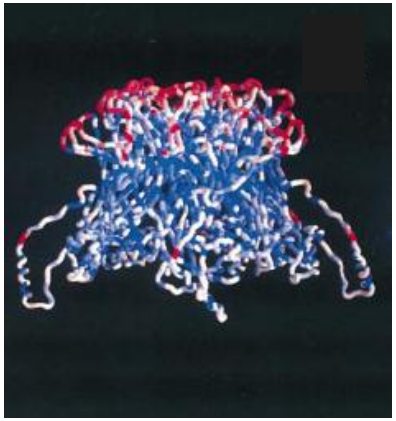
Alpha-7: HPV18, HPV39, HPV45, HPV59, HPV68
Alpha-9: HPV16, HPV31, HPV33, HPV35, HPV52, HPV58

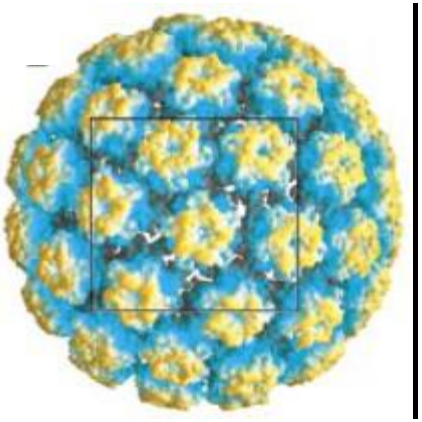
Brown et al., 2009 J Infect Dis. 199:926-35
Wheeler et al., 2012 Lancet Oncol. 13:100-10

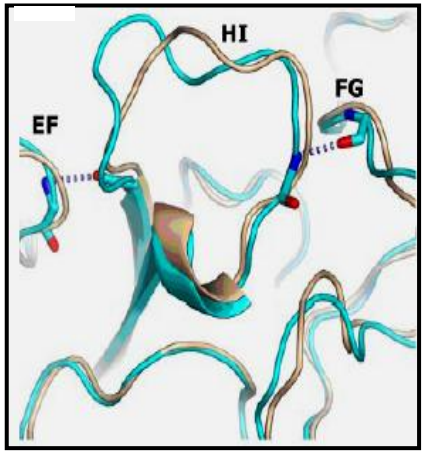
L1 structural impact on antibody recognition

- Antibody response highly type-specific, no cross-neutralizing MAbs exist
- Anecdotal cross-reactivity data following VLP immunization of animals









L1 major capsid protein contains variable loops BC, DE, EF, FG, HI

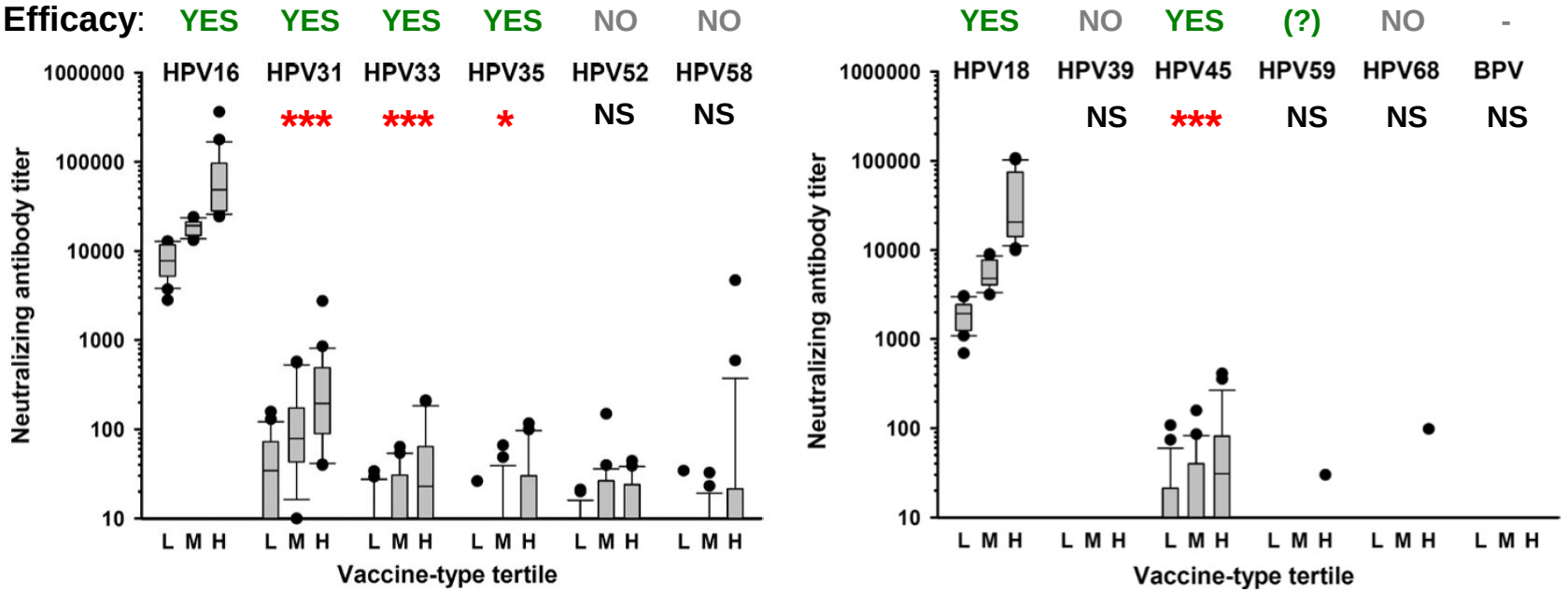
Surface exposed variable loops are target for **type-specific** antibodies

Differences between HPV types reflected in loop structure

Chen et al., 2000 Mol Cell 5:557
Bishop et al., 2007 J Biol Chem 282:31803

Cervarix immunogenicity to non-vaccine types

- Antibodies generated to non-vaccine types ≤1% of vaccine-type titer
- Another study (Kemp 2011, NCI) similar data using HPV31/45/52/58
- At least coincident with vaccine efficacy data



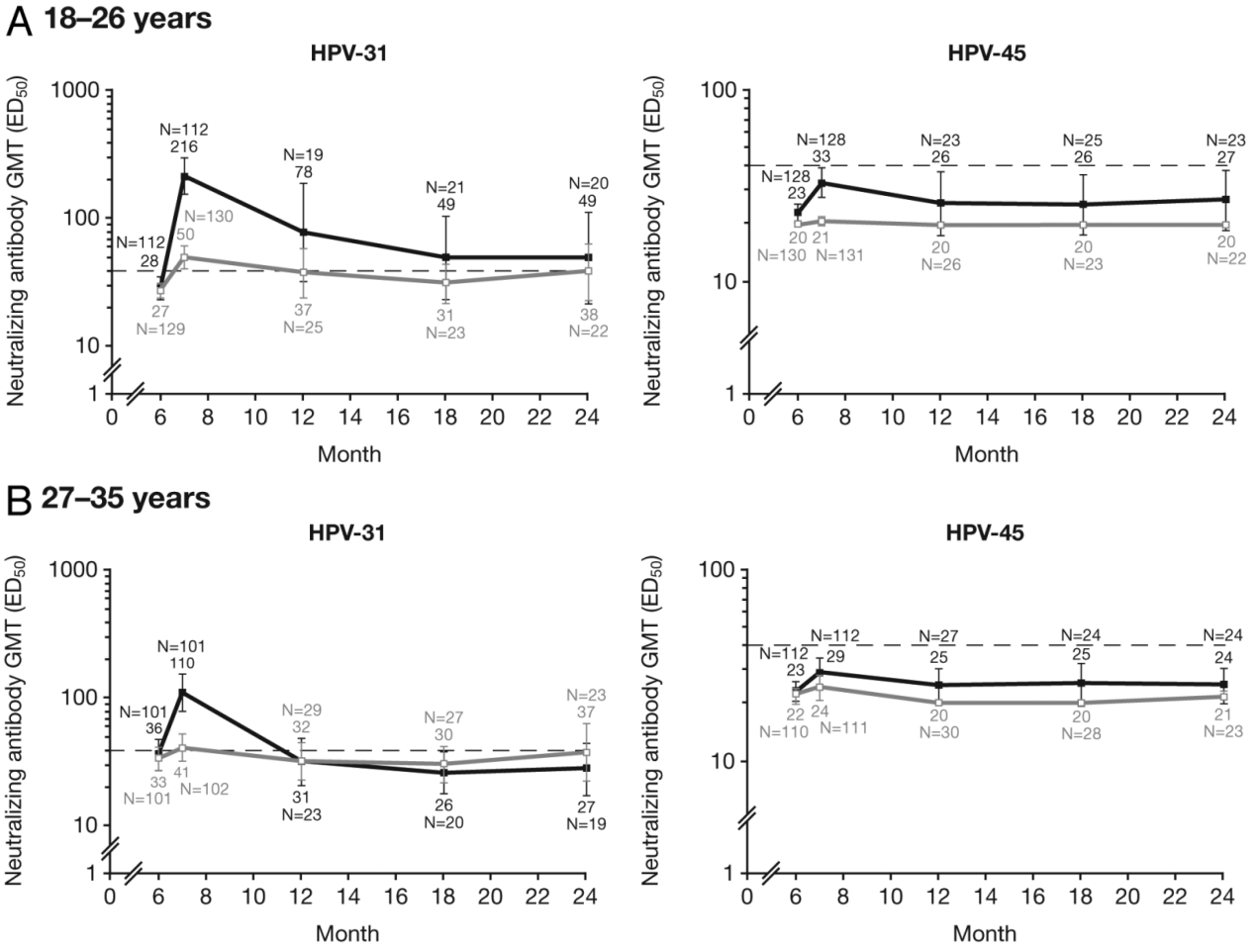
NS p>0.05; * p<0.05; ** p<0.01; *** p<0.001

L M H: Low, Middle, High vaccine type tertiles
NCI: National Cancer Institute, US (originators of VLP, PsV)

Draper et al., 2011 Vaccine 29:8585-8590
Kemp et al., 2011 Vaccine 29:2011-14
Wheeler et al., 2012 Lancet Oncology 13:100-110

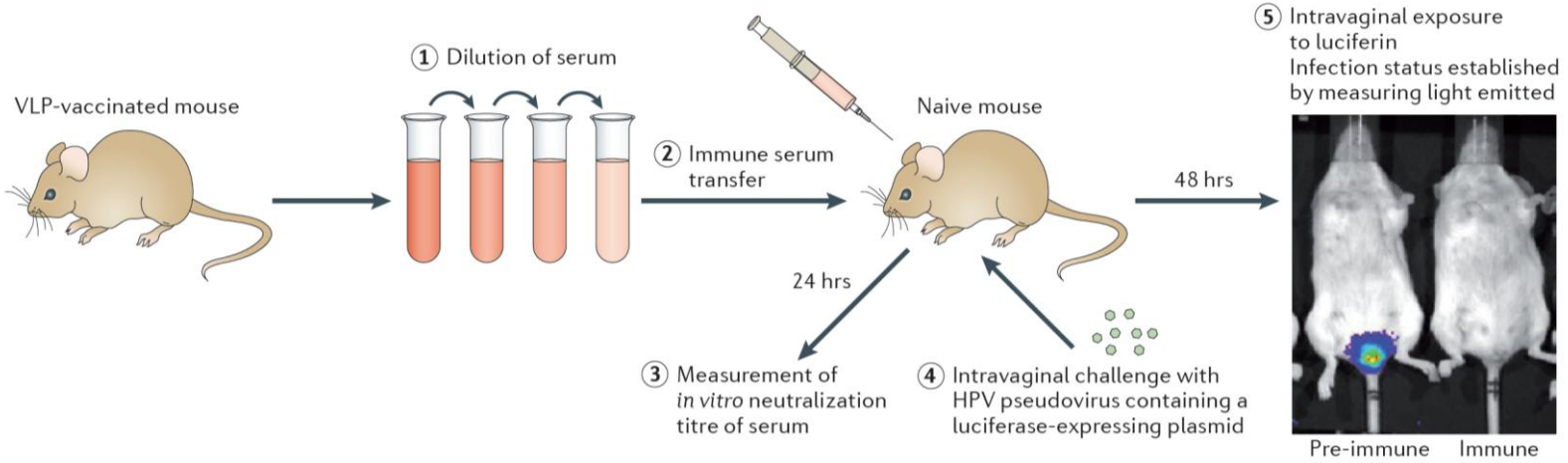
Cervarix > Gardasil cross-recognition

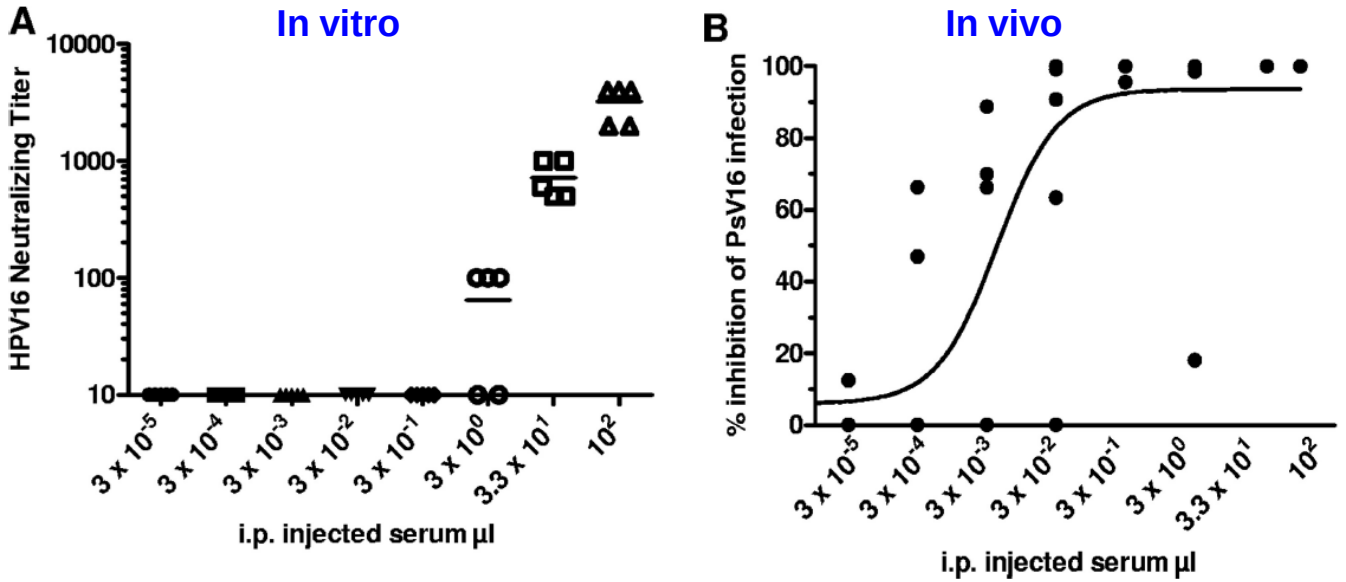
- For both HPV31 and HPV45 but at or below LOD; age dependent
- Are cross-neutralizing antibodies sufficient and track efficacy differences?



Einstein et al., 2011 Human Vaccines 7: 1359-73

Murine model suggests low Ab levels protect





Longet et al., 2011 J Virol 85:13253
Schiller and Lowy 2012 Nat Rev Micro 10:681-692

Worldwide type-specific disease prevalence

- Non-vaccine types HPV31, 33, 45 comprise 10 – 17% additional cancers

Africa		S. Am		N. Am		Asia		EU	
16	*70.0%*	**16**	*65.4%*	**16**	*76.4%*	**16**	*66.9%*	**16**	*73.7%*
18		**18**		**18**		**18**		**18**	
33	*7.6%*	**31**	*6.0%*	**31**	*3.7%*	58	*5.6%*	**33**	*4.4%*
45	*6.6%*	**45**	*5.0%*	**33**	*3.5%*	**33**	*3.9%*	**31**	*4.0%*
35		**33**	*3.7%*	**45**	*3.3%*	52		**45**	*2.9%*
31	*2.7%*	52		52		**45**	*2.5%*	35	
58		58		35		**31**	*2.2%*	58	
52		35		58		35		56	
56		59		56		59		52	
51		39		39		51		68	
59		51		68		56		51	
39		56		59		68		39	
68		68		51		39		59	

Alpha-7: HPV18, HPV39, HPV45, HPV59, HPV68
Alpha-9: HPV16, HPV31, HPV33, HPV35, HPV52, HPV58

Bosch et al., 2008 Vaccine 26S:K1–K16

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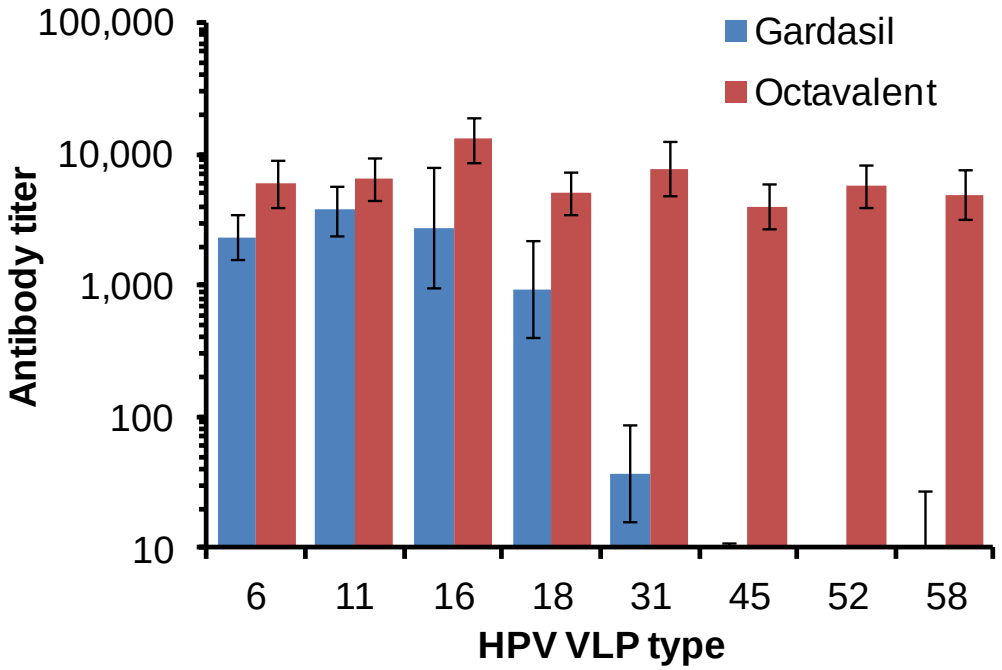
Next generation vaccines

Multivalent VLP vaccines

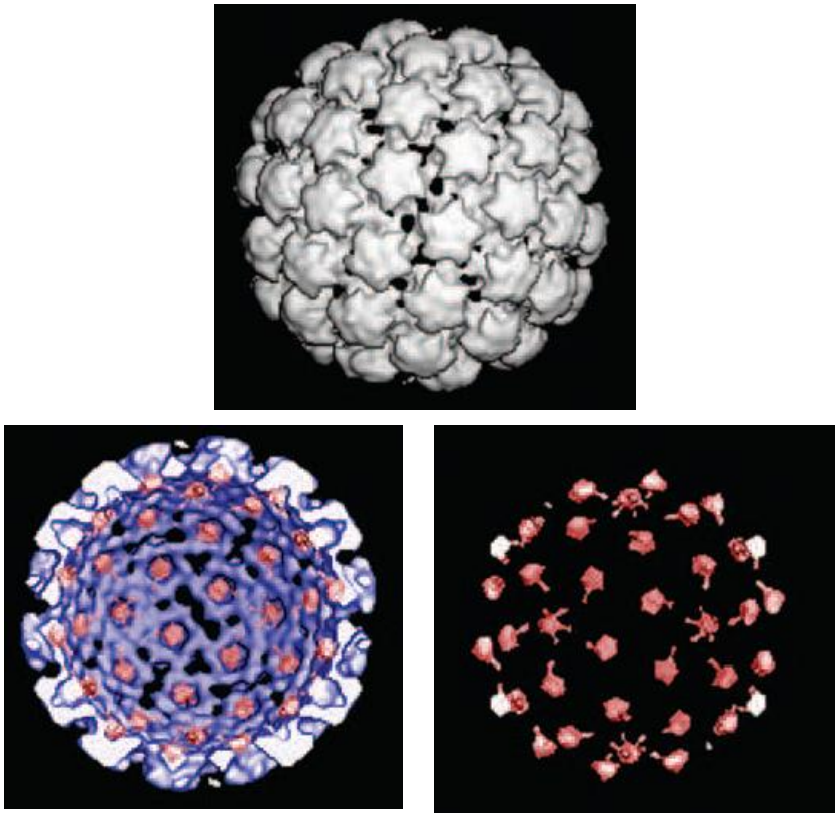
- Multivalent L1 VLP-based vaccines in the pipeline
- Merck study (NCT00851643), n=150 Phase I trial

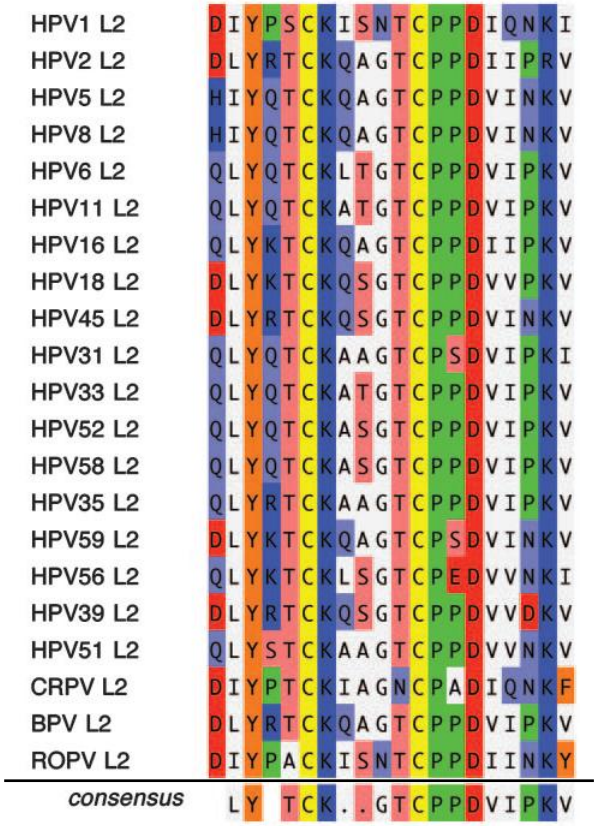


ClinicalTrials.Gov: NCT00851643

L2-based vaccines: pre-clinical development

- L2 protein embedded within each capsomer
- Highly conserved among HPV types

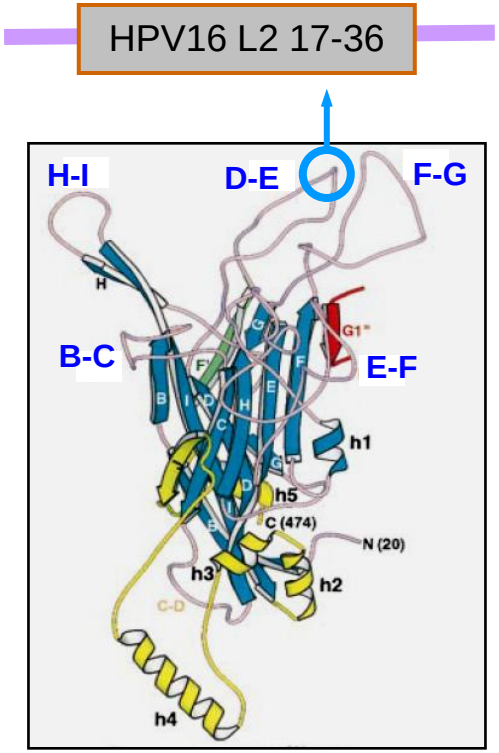


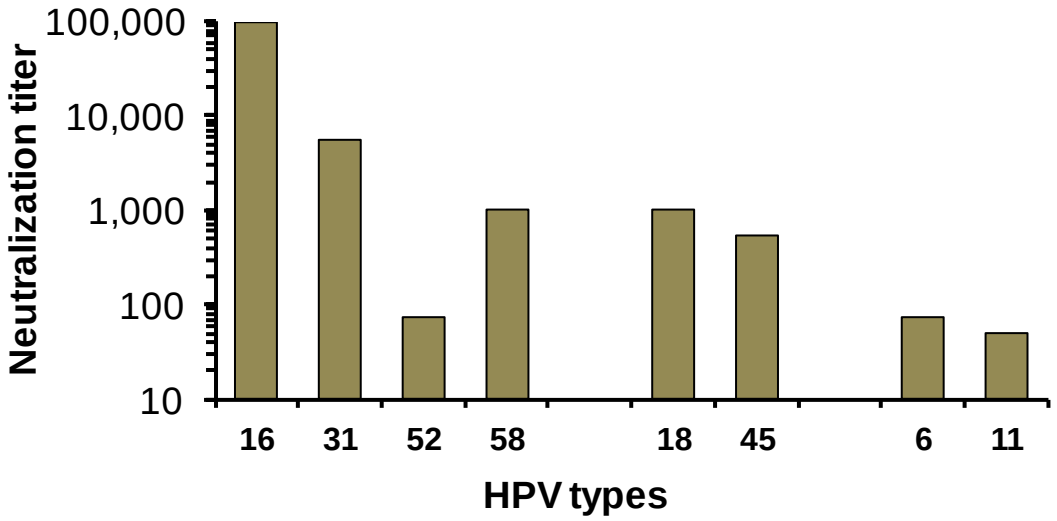


Buck et al., 2008 J Virol 82:5190
Gambhira et al., 2007 J Virol 81:11585

L2-based vaccines: pre-clinical development

- NZW rabbits immunized with chimeric HPV16 VLP elicits broad response
- Other strategies include using multi-type concatenated peptides
- L2 antibodies shown to be protective in CVC model
- Expected to be simpler and cheaper to produce





Schellenbacher et al., 2009 J Virol 83:10085

Known unknowns

- What will be the impact on vaccine-type disease in real world settings?
- What will be extent of herd immunity?
- Should boys and MSM be targeted by vaccine programmes?
- Will type-replacement occur where other HR-HPV types fill niche?
- What will be extent of cross-protection?
- What is longevity of vaccine and non-vaccine type protection?
- What will be long term worldwide impact on cervical cancer rates?
- What are the correlates of vaccine-induced protection?
- What are consequences of switching to a 2-dose schedule?
- Are there natural variants that will escape vaccine pressure?
- What form will the next generation vaccine(s) take?