

The Human Papilloma Viruses

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Classification of HPV induced diseases

Skin diseases

Benign

Malignant

Mucosal diseases

Benign

Malignant

Classification of HPV induced diseases

	Virus type	Associated disease
Skin diseases		
Benign	1, 2, 3, 4, 7, 10, 26, 27...	Warts
Malignant	5, 8	Epidemodysplasia verruciformis
Mucosal diseases		
Benign	6,11, 34, 40, 42, 43, 44, 53, 54, 57, 70, 72	Genital warts inc. condyloma acuminata Buschke-Loewenstein tumor Laryngeal papillomatosis
Malignant	16, 18, 31, 33, 35, 39 45, 51, 52, 56, 58, 59, 68, 73	Cervical dysplasias and carcinomas Other anogenital dysplasias and carcinomas
	31, 33, 45	Bowen's disease

Proportion of cancers etiologically associated to HPVs

Cervix	100%
Vagina	60%
Vulva	50%
Anus	50%
Penis	40%
Pharynx	30%

>70%
HPV 16/18

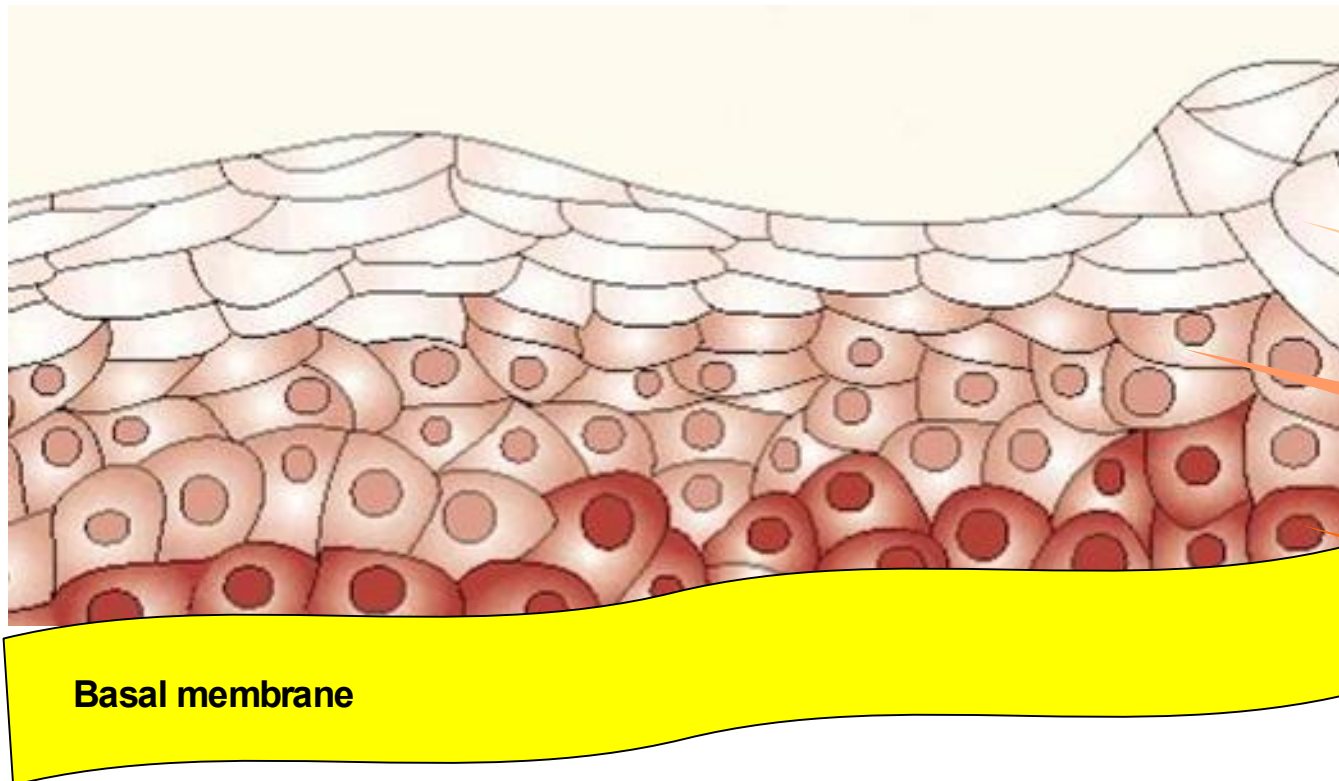
Burden of cervical HPV disease in Switzerland

- **Newly diagnosed cases of cervical cancer / year** **380**
- **Mortality from cervical cancer / year** **100**
- **Surgery for precancerous lesions / year** **~5000**

Human Papilloma Viruses

- **Family of Papovaviridae**
- **DNA**
- **Non inflammatory**
- **Tropism for epithelial cells**

A closer look at an epithelial layer



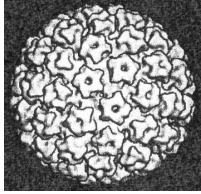
Dead cells

**Non dividing
living cells**

Dividing cells

Basal membrane

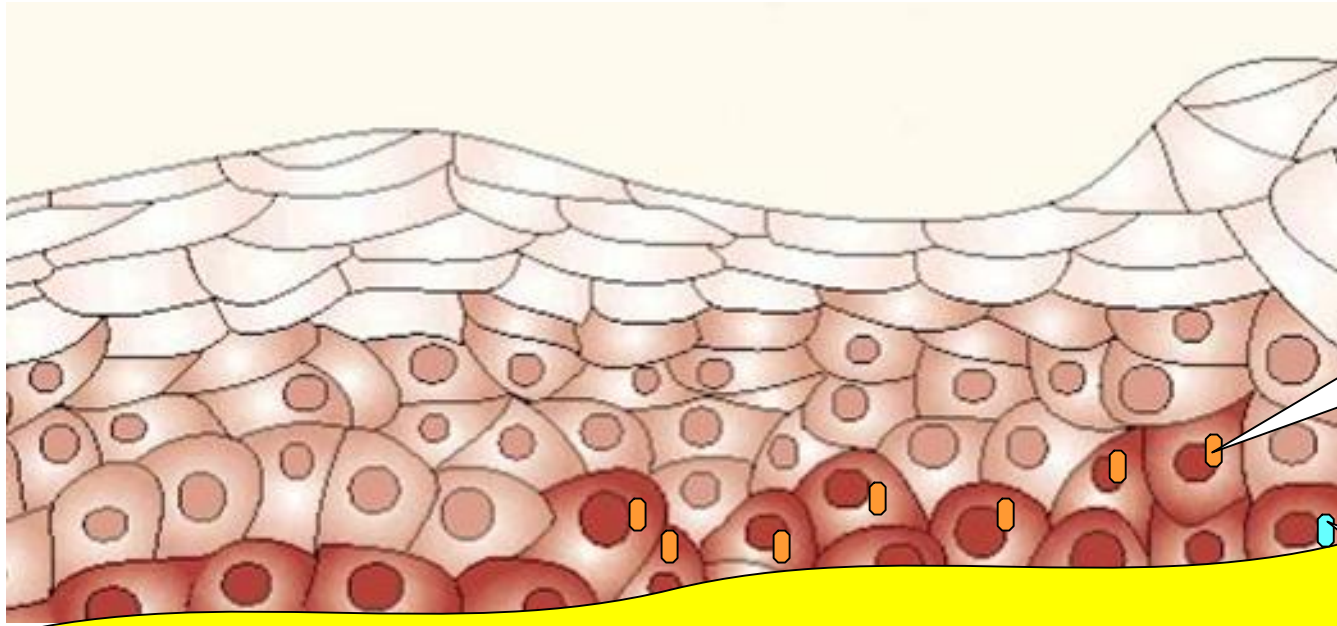
Virus needs to gain access to cells in the basal layer



Basal cells express a receptor for viral surface proteins

Penetration of the virus requires microscopical abrasions in the epithelium

Replication cycle of HPVs in dividing cells

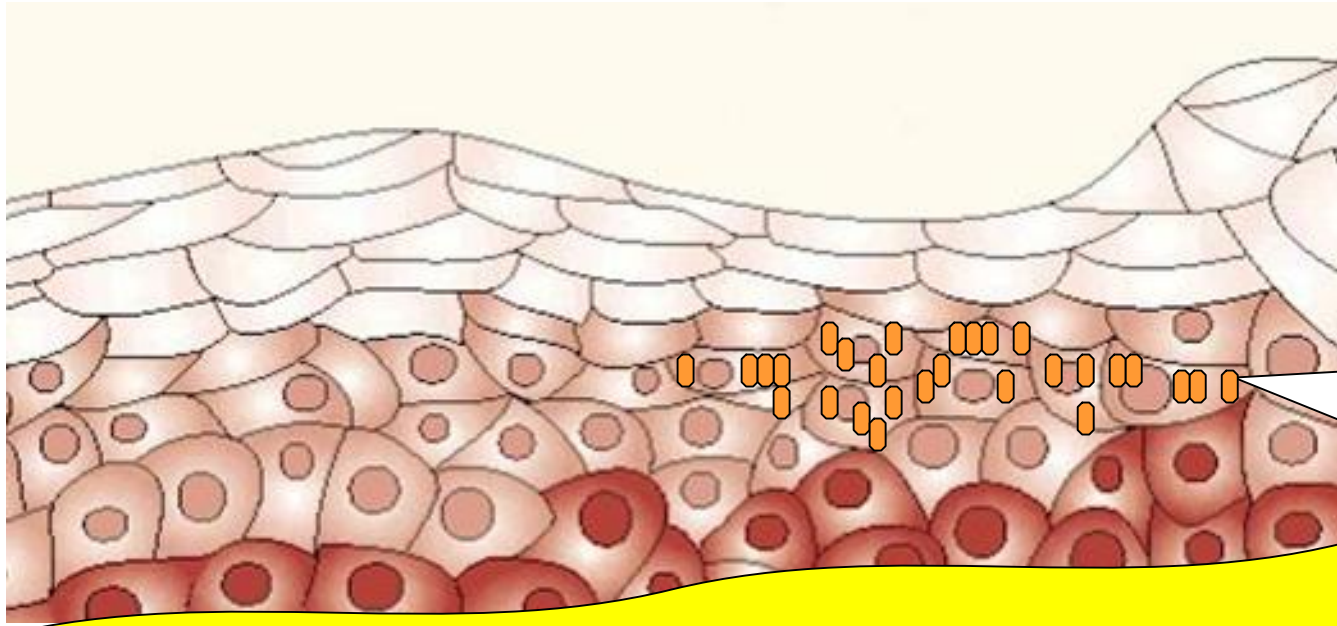


Cell and virus replicate together

~10 genomes at cell entry

Basal membrane

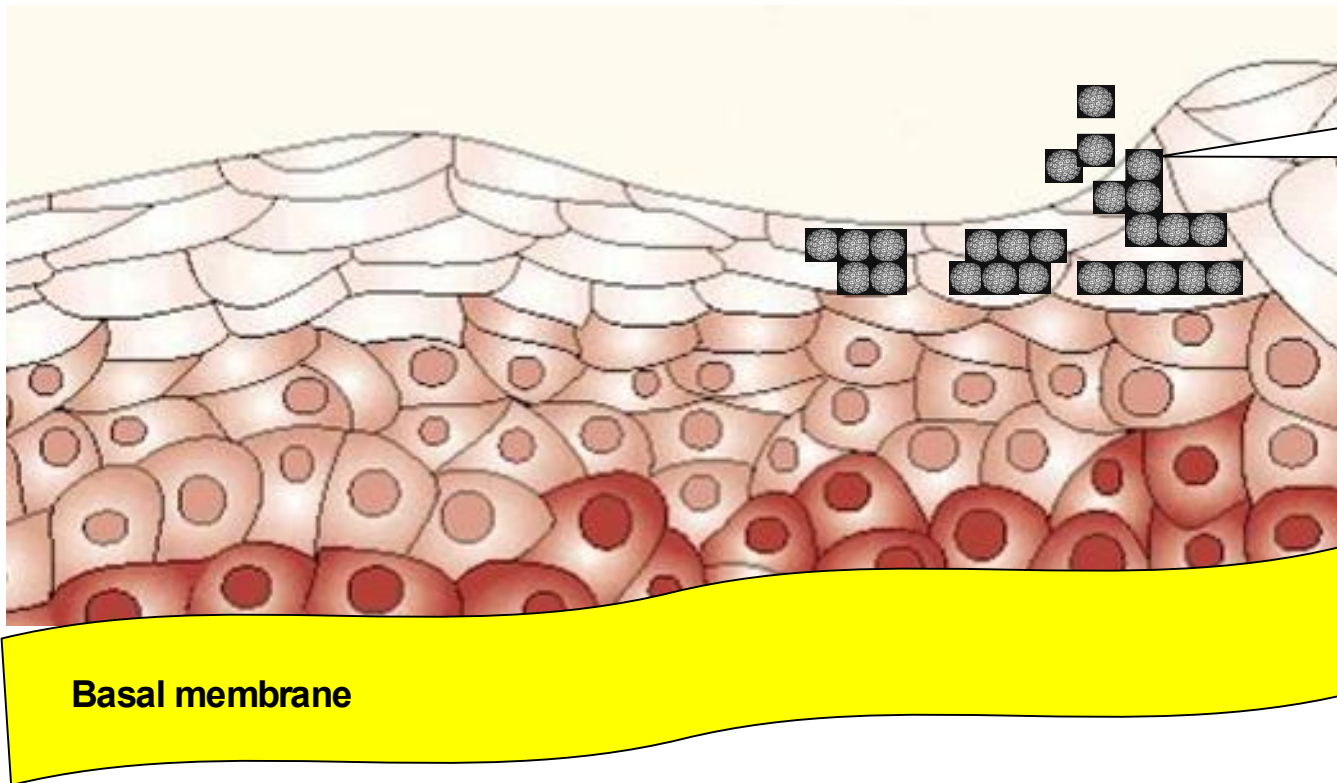
Replication cycle of HPVs in non dividing cells



**Virus amplifies to ~1000
genomes per cell
High expression of early (E)
antigens**

Basal membrane

Replication cycle of HPVs in dead cells

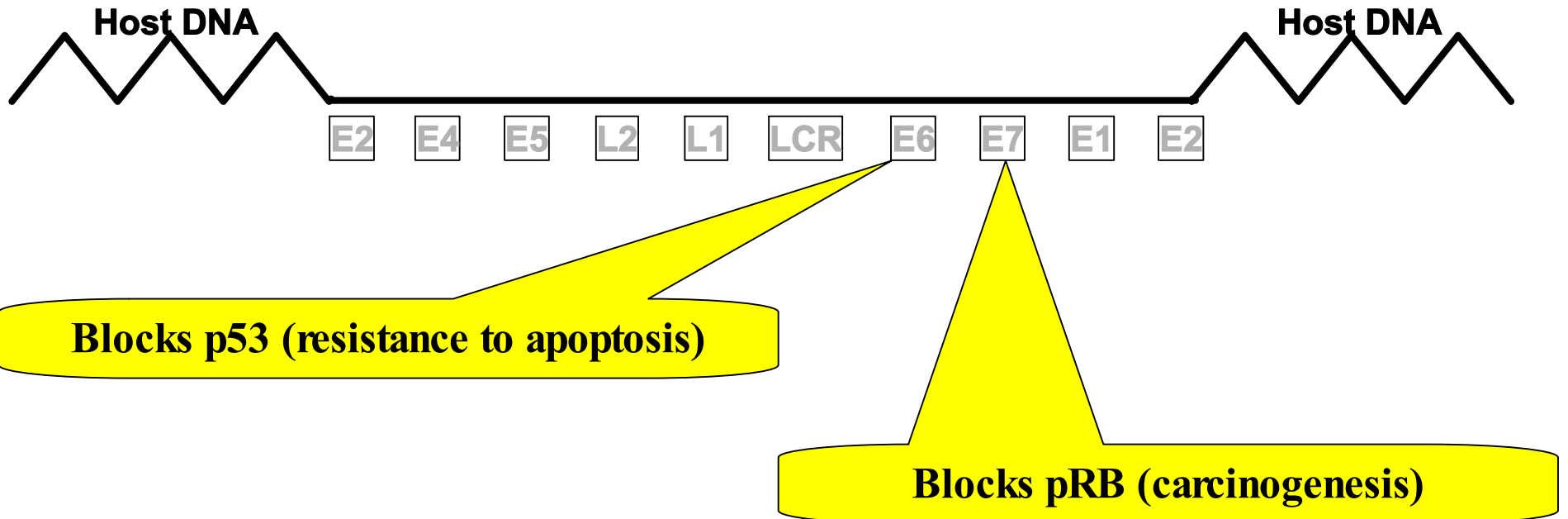


Virions assembled & released
from ruptured cells

The viral genome

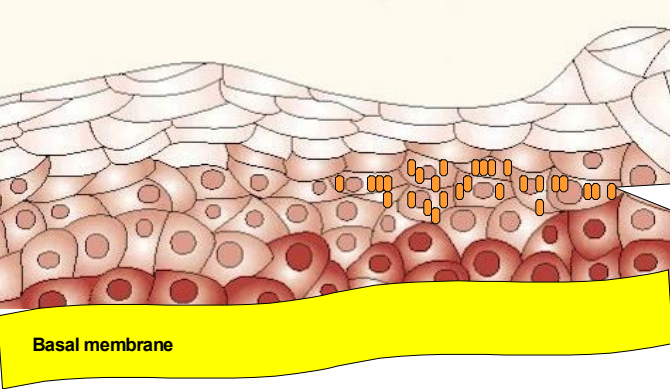


Integration into host genome



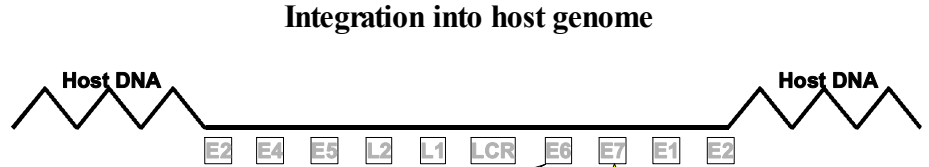
Impact of HPVs on epithelial layers

Replication cycle of HPVs in non dividing cells



Virus amplifies to ~1000 genomes per cell
High expression of early (E) antigens

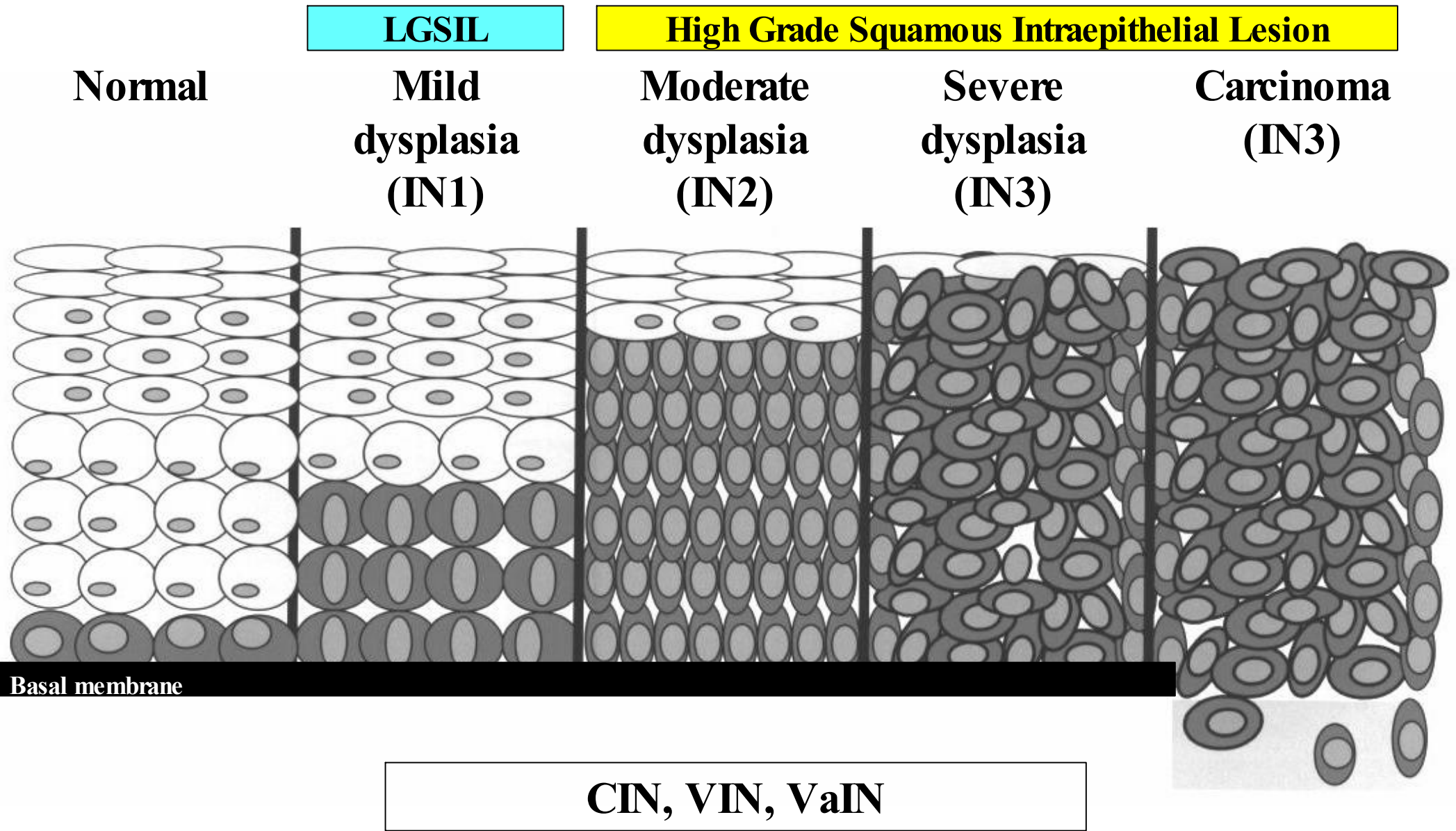
The viral genome



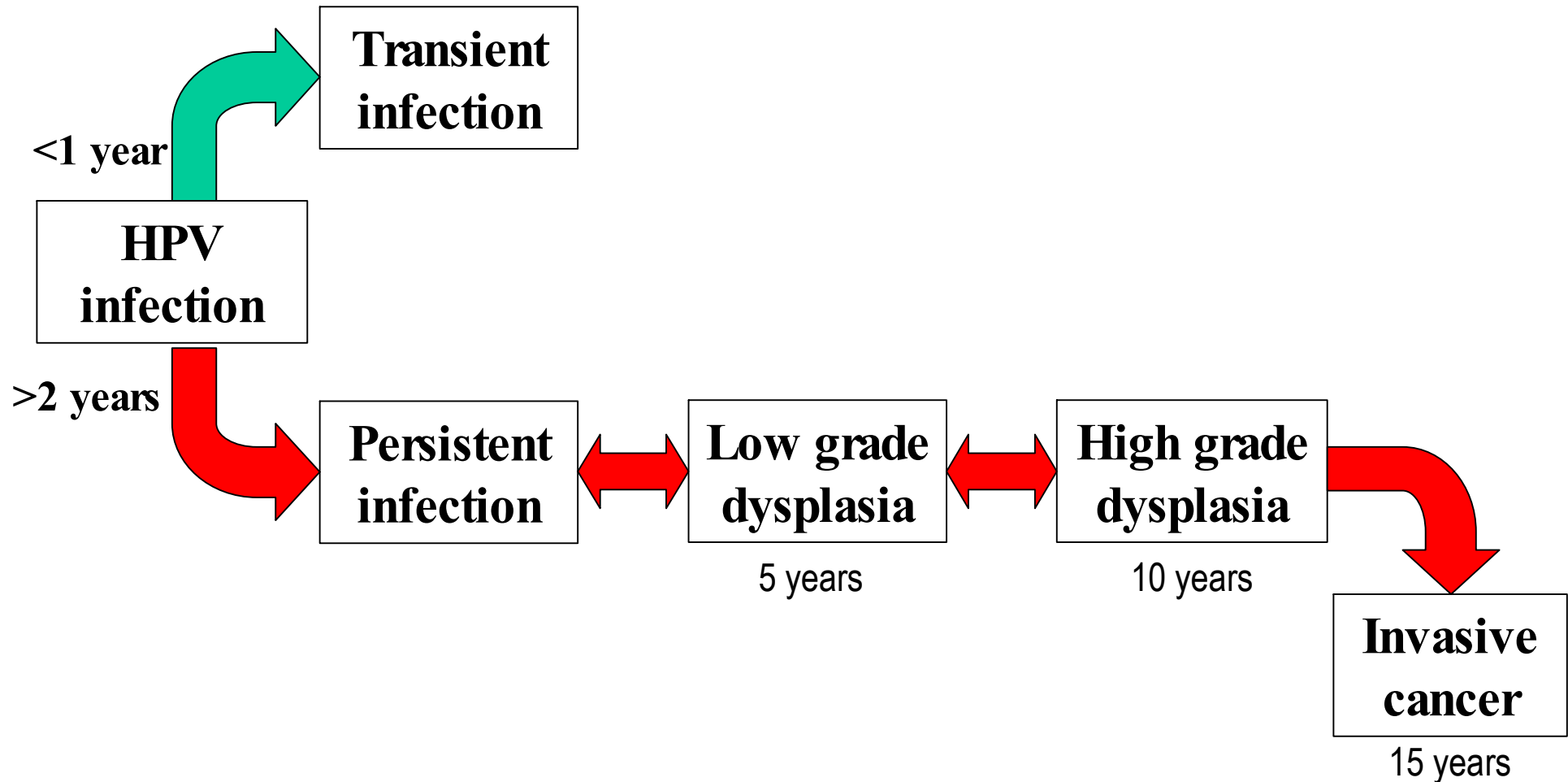
Blocks p53 (resistance to apoptosis)
Risk of persistent infection

Blocks pRB (carcinogenesis)
Risk of malignant proliferation

Staging of the impact of HPVs on epithelial layers

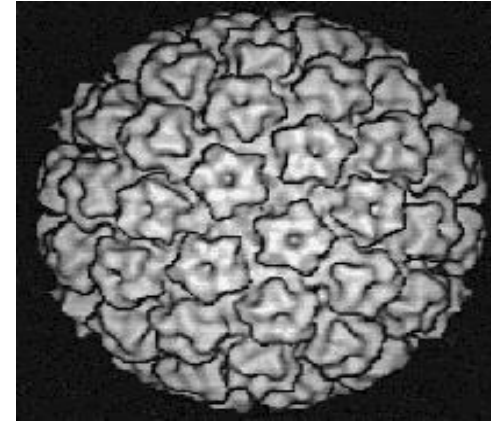


An HPV infection needs to be persistent in order to become potentially carcinogenic



A closer look at the virus

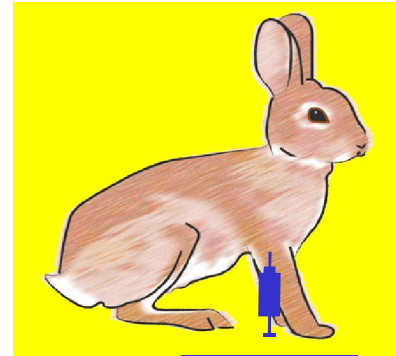
Outer surface made of 72 pentamers of **L1 protein**
(and L2)



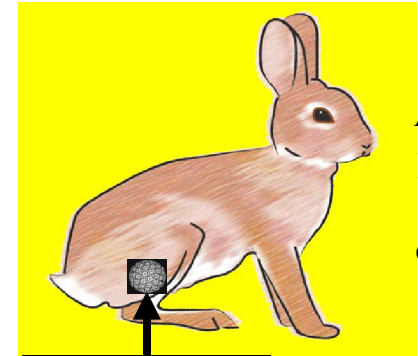
L1 protein weak immunogen as such but strong one when adjuvanted

Anti L1 antibody is neutralizing in animal models

Active immunization



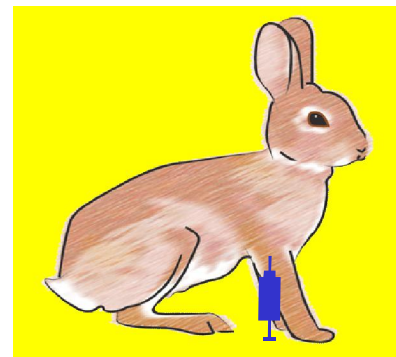
1.
Vaccination



2.
Viral challenge

Animal is protected from challenge

Passive immunization



Vaccination

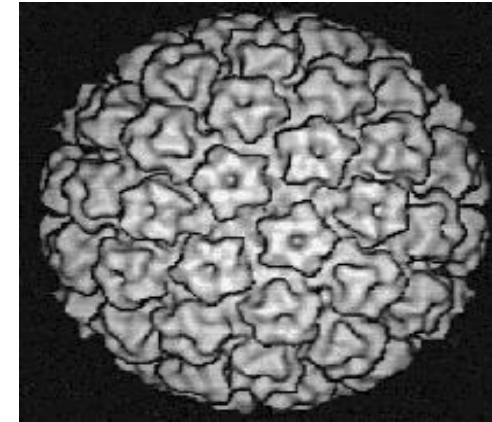
Animal's serum is neutralizing the virus *in vitro*

Animal's serum is neutralizing the virus *in vivo*

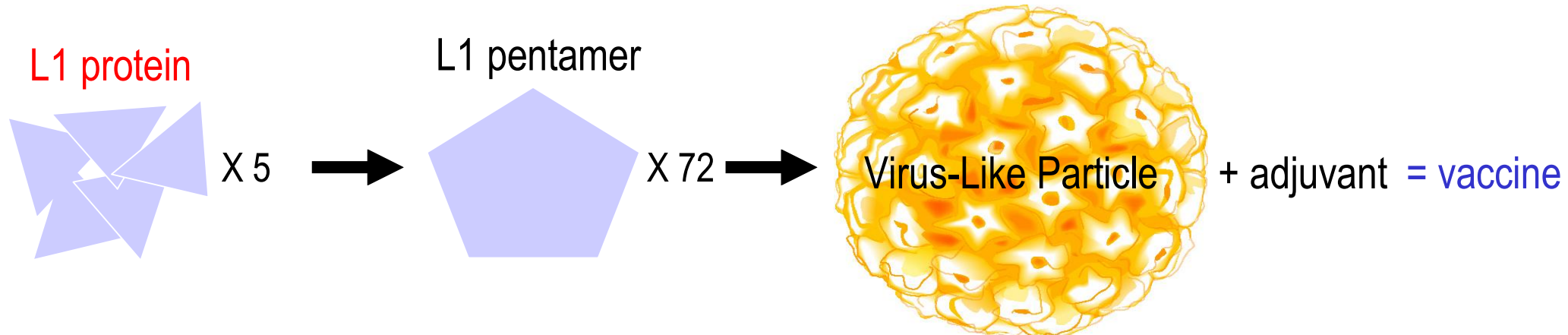


A closer look at the virus helps to figure up the vaccine

Outer surface made of 72 pentamers of **L1 protein** (and L2)



L1 protein weak immunogen as such but strong one when adjuvanted



Vaccine products

Gardasil®

Quadrivalent L1 VLP

16, 18, 6, 11

Sanofi Pasteur MSD

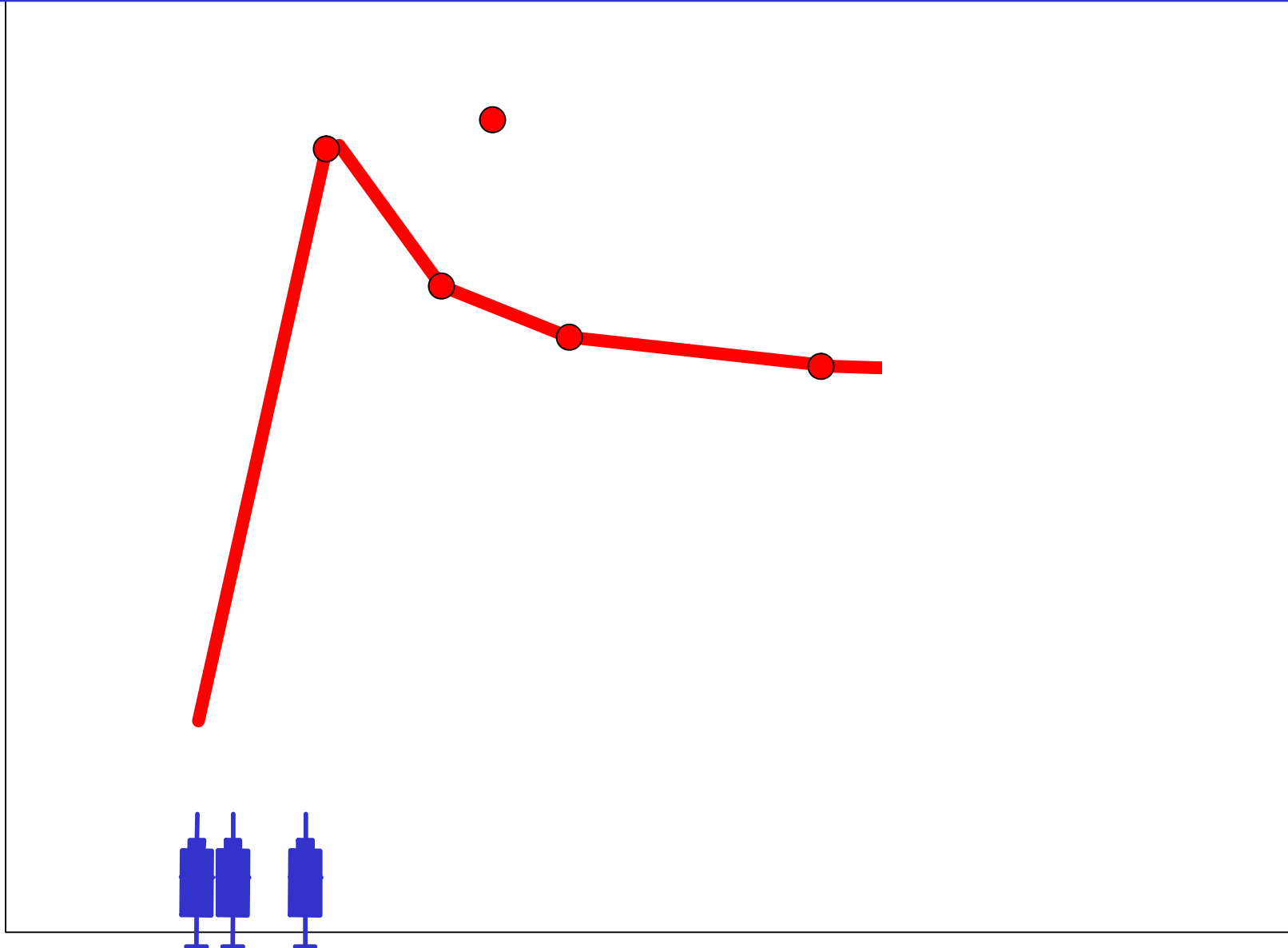
Cervarix®

Bivalent L1 VLP

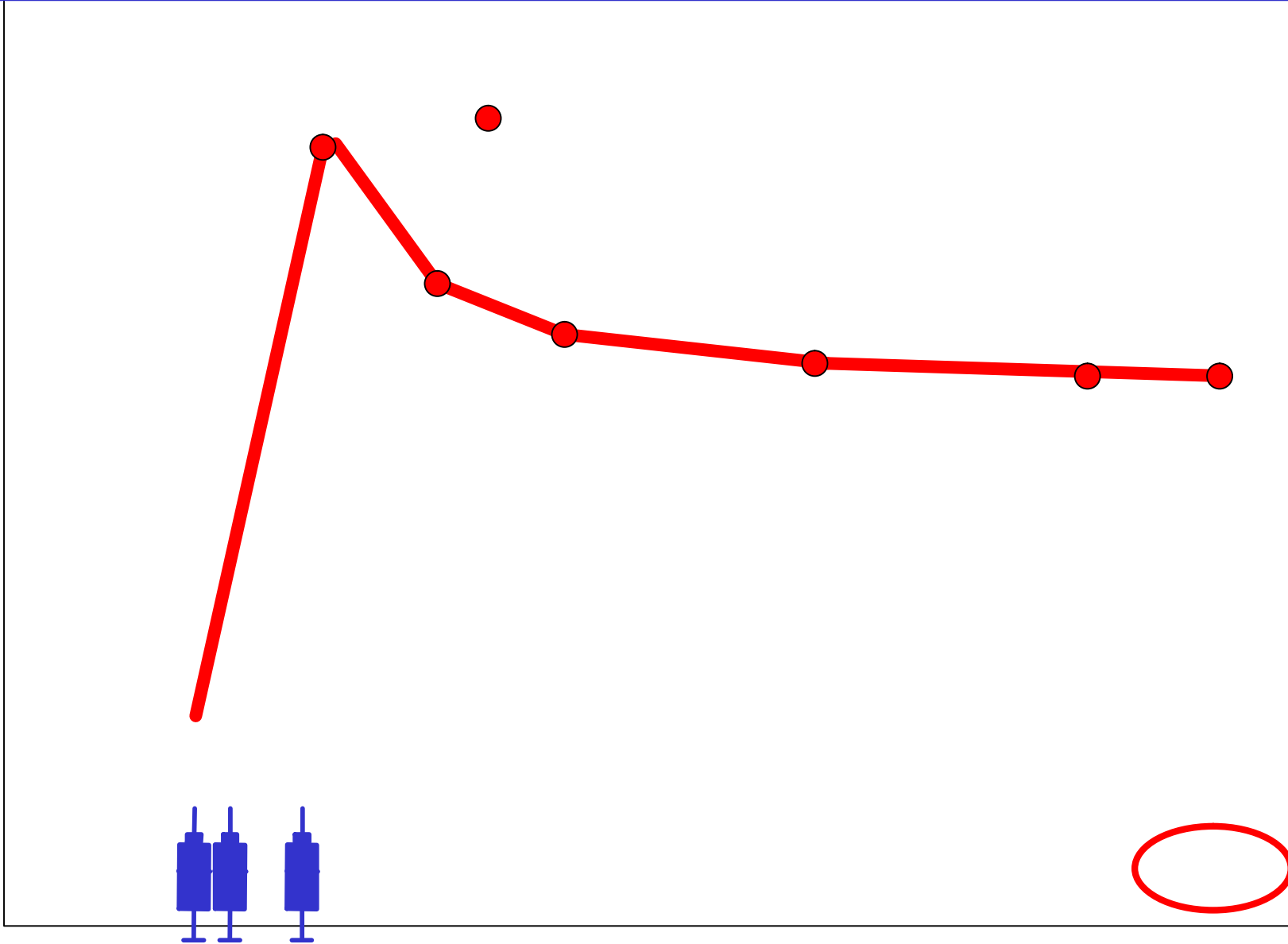
16, 18

GlaxoSmithKline

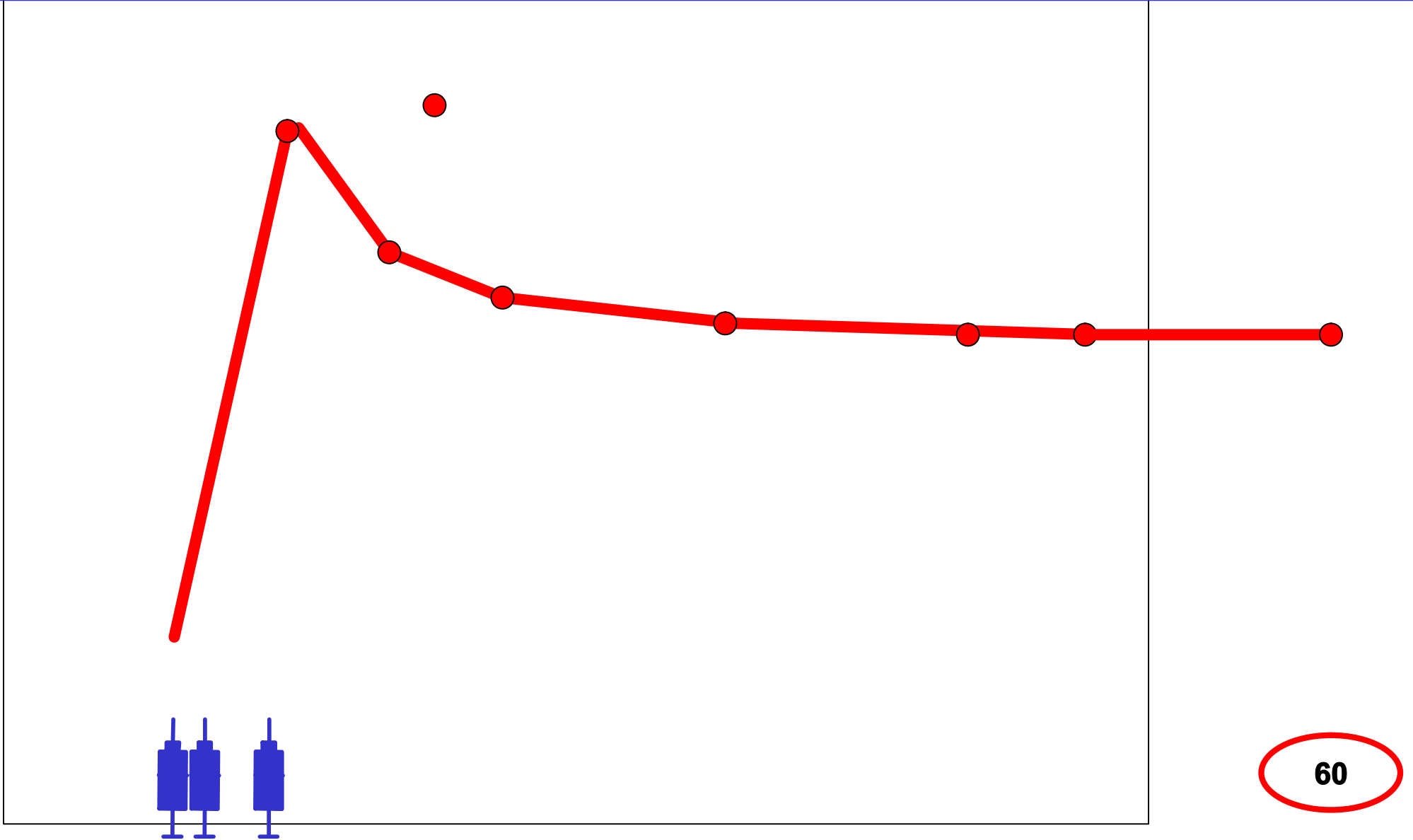
Immune response to vaccination (HPV 16)



Longevity of immune response to vaccination (HPV 16)

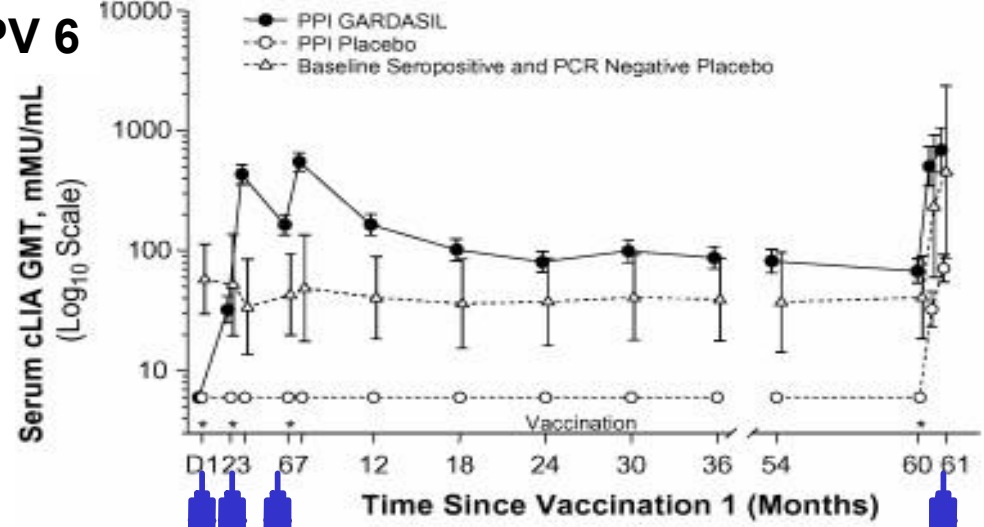


Longevity of immune response to vaccination (HPV 16)

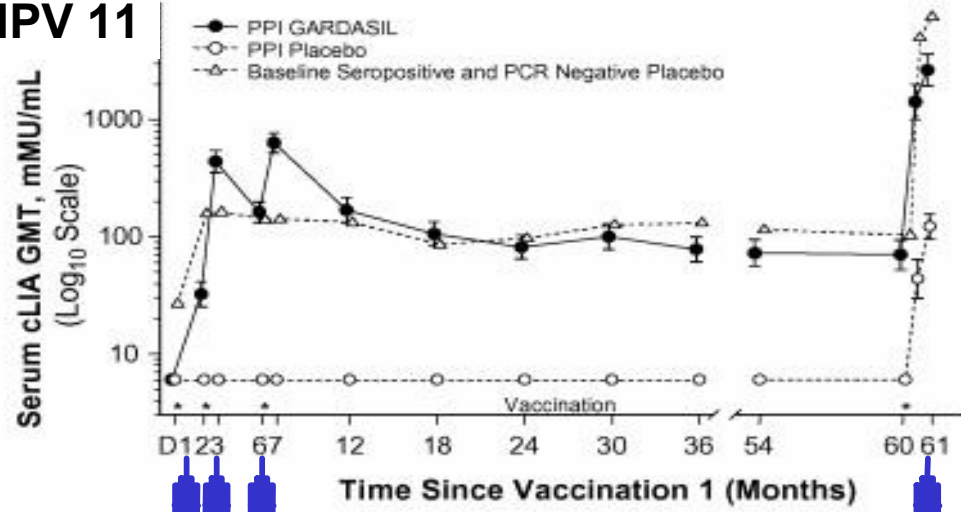


Immune response to boosting (1 dose)

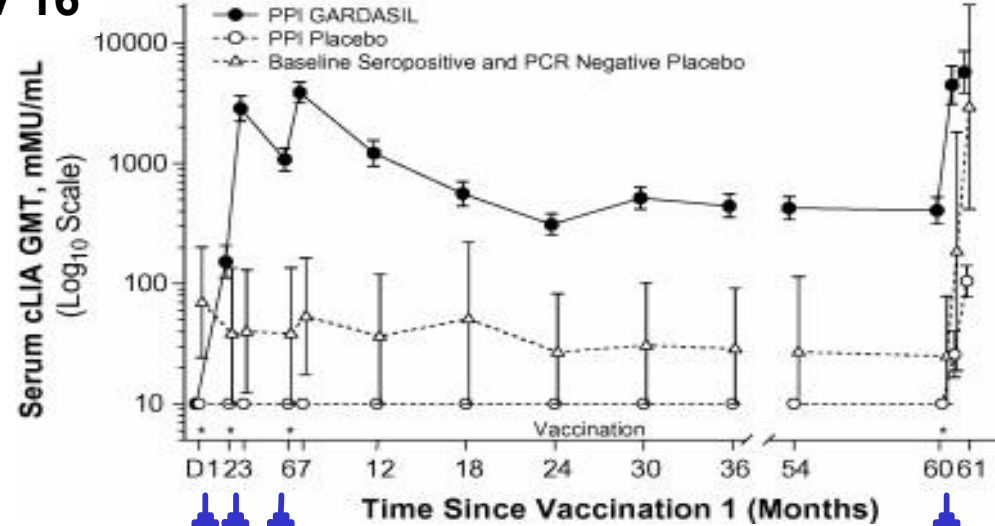
HPV 6



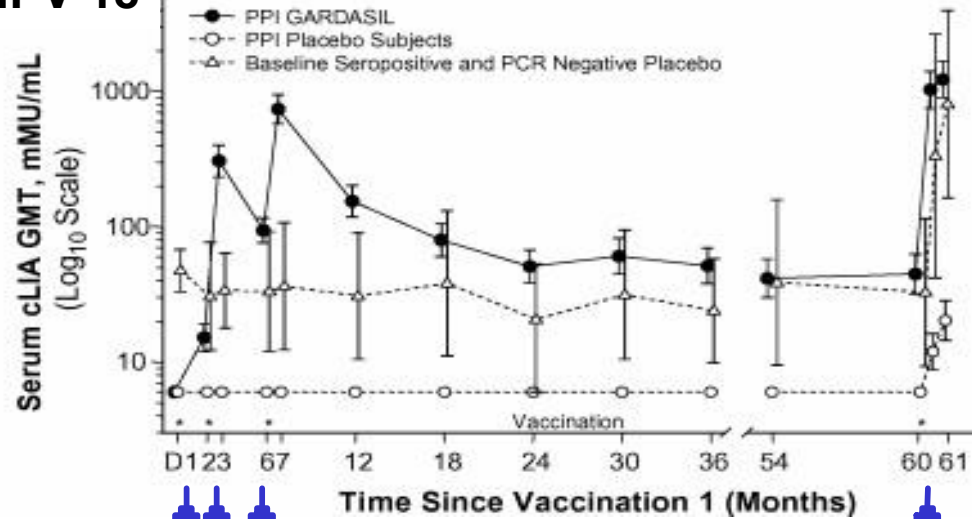
HPV 11



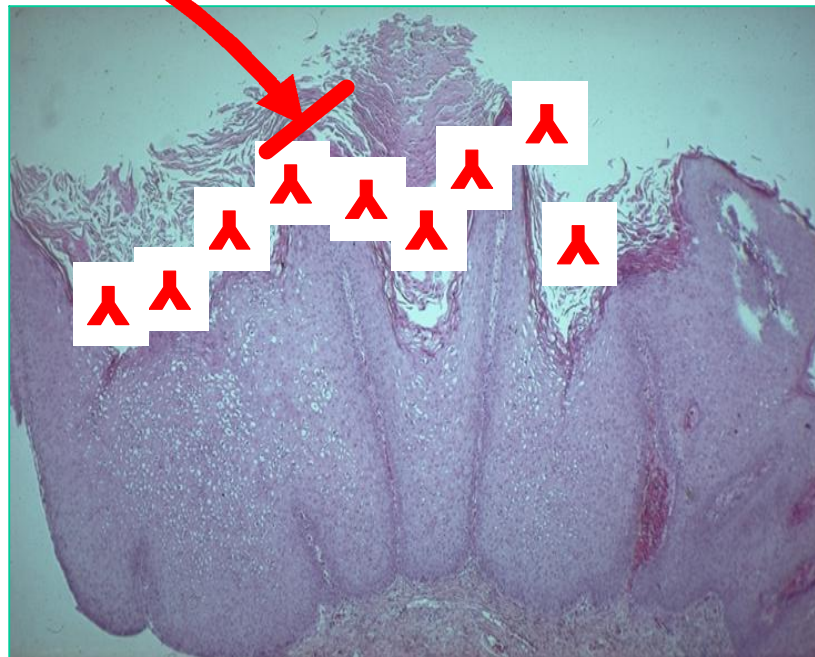
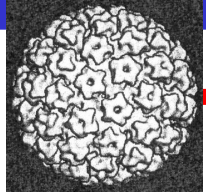
HPV 16



HPV 18



Antibody needs to be present at the site of first contact of virus with epithelial layer



Protection is mediated by neutralising antibody transudating from serum to genital mucous

Protective efficacy from cervical lesions induced by HPV 16/18. Analysis at 3 years

- **Entire group ~12'000 women 15-23 years**
- **RCT**
- **4-valent vaccine or placebo**
- **3 doses at time 0, 2 months & 6 months**
- **Endpoints: Cervical lesions (CINs -cervical intraepithelial neoplasias-)**

Per protocol analysis

10'000 women: all in ideal setting (group A)

- **Normal cytology & negative serology at inclusion**
- **Normal cytology at the end of immunization process**

Protection from lesions of any severity 98%

Protection from CIN 3 lesions 97%

Not quite *per protocol* analysis

11'000 women: group A + those infected during vaccination process (group B)

- **Normal cytology & negative serology at inclusion**
- **Abnormal cytology at the end of immunization process**

Protection from lesions of any severity 95%

Protection from CIN 3 lesions 95%

Intent to treat analysis

12'000 women: group A + group B + those with protocol violations (group C)

- **No cytology & no serology at inclusion**
- **Less than 3 doses**

Protection from lesions of any severity 44%

Protection from CIN 3 lesions 45%

Pragmatic view on protection data from cervical disease

➤ Women in ideal setting (group A)

Any cervical lesion	98%
CIN 3 lesion	97%

Protection to be expected when vaccinating young girls in a systematic way

➤ Group A + women infected during vaccination process (group B)

Any cervical lesion	95%
CIN 3 lesion	95%

Protection to be expected when vaccinating adolescent girls in a systematic way

➤ Group A + group B + women with protocol violations (group C)

Any cervical lesion	44%
CIN 3 lesion	45%

Protection to be expected when vaccinating young women

Protective efficacy from genital lesions (other than cervical) induced by HPV 16/18. Analysis at 3 years

- **Entire group ~5'000 women 16-24 years**
- **RCT**
- **4-valent vaccine or placebo**
- **3 doses at time 0, 2 months & 6 months**
- **Endpoints:**
 - **Vaginal intraepithelial neoplasias (VaIN)**
 - **Vulvar intraepithelial neoplasias (VIN)**
 - **Genital warts (including condyloma)**

Per protocol analysis

Women in ideal setting

- **Normal cytology & negative serology at inclusion**
- **Normal cytology at the end of immunization process**

Protection from VaIN & VIN 2/3 100%

Protection from genital warts 100%

Intent to treat analysis

Women in non ideal setting

- **Infection during vaccination process**
- **Protocol violations**

Protection from VaIN & Vin 2/3 **62%**

Protection from genital warts **76%**

Pragmatic view on protection data from genital disease (other than cervical)

➤ Women in ideal setting

VaIN 2/3 VIN 2/3 100%

Genital warts 100%

**Protection to be expected when vaccinating
young girls in a systematic way**

➤ Women in *non ideal* setting

VaIN 2/3 VIN 2/3 62%

Genital warts 76%

**Protection to be expected when vaccinating
young women**

Evidence of cross protection

- **Group ~18'000 women 15-25 years**
- **RCT**
- **2-valent vaccine or placebo**
- **3 doses at time 0, 1 months & 6 months**
- **Endpoints: Cervical lesions (CINs -cervical intraepithelial neoplasias-)**

**Protection from cervical lesions of any severity
induced by non vaccine types**

27%

Cross protection: heterogeneous and inconstant

2-valent vaccine

HPV type	Time point in follow up	Vaccine efficacy
HPV 45*	Short term ¹	94%
	Longer term ²	62%
HPV 31**	Short term ¹	55%
	Longer term ²	11%
HPV 33	Short term ¹	9%
	Longer term ²	45%
HPV 52	Short term ¹	19%
	Longer term ²	47%

*Crossreaction with type 18

**Crossreaction with type 16

Swiss recommendations

Exclusively in females

- **Baseline vaccination:** 11-14 y
- **Catch up vaccination:** 15-19 y
- **Selective vaccination:** 20-26 y

Schedule

3 doses:

Gardasil

0, 2, 6 months

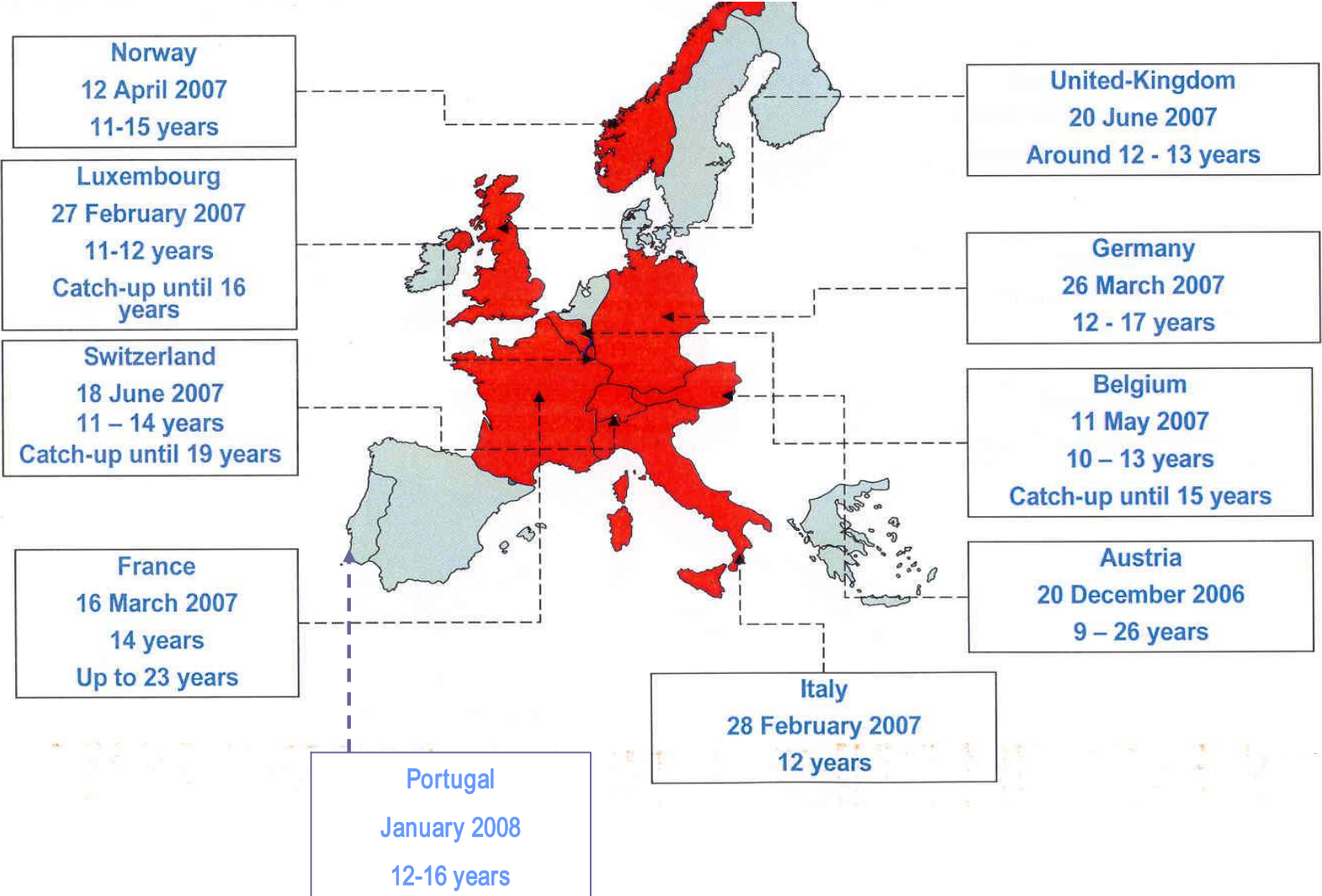
Cervarix

0, 1, 6 months

Maintenance

Not definitely determined.....possibly

Official country recommendations in Europe



Undesirable effects

	Gardasil®			Cervarix®	
	Vaccine	Plac. (AI)	Plac. (saline)	Vaccine	Plac. (AI+MPL)
Local effects	N = 5088	N = 3470	N = 320	N = 531	N = 538
Pain	84%	75%	49%	93%	87%
Swelling	25%	16%	7%	34%	21%
Redness	25%	18%	12%	36%	24%
Severe pain	3%	1%	0.6%		
Important swelling	2%	0.6%	0%		
Important redness	0.9%	0.4%	0%		
Sytemic effects	N = 5088	N = 3790		N = 531	N = 538
Headache				62%	61%
Fatigue				58%	54%
Prurigo				25%	20%
Fever	13%	11%		17%	14%
Nausea	7%	7%			
Vertigo	4%	4%			
Muscle ache	2%	2%			
Joint pains	1%	1%			
Sleep disturbance	1%	1%			
Death	0.08%*	0.07%			

Very safe and pretty reactogenic, Cervarix® more so than Gardasil®!

**Who is to perform
HPV vaccination?**

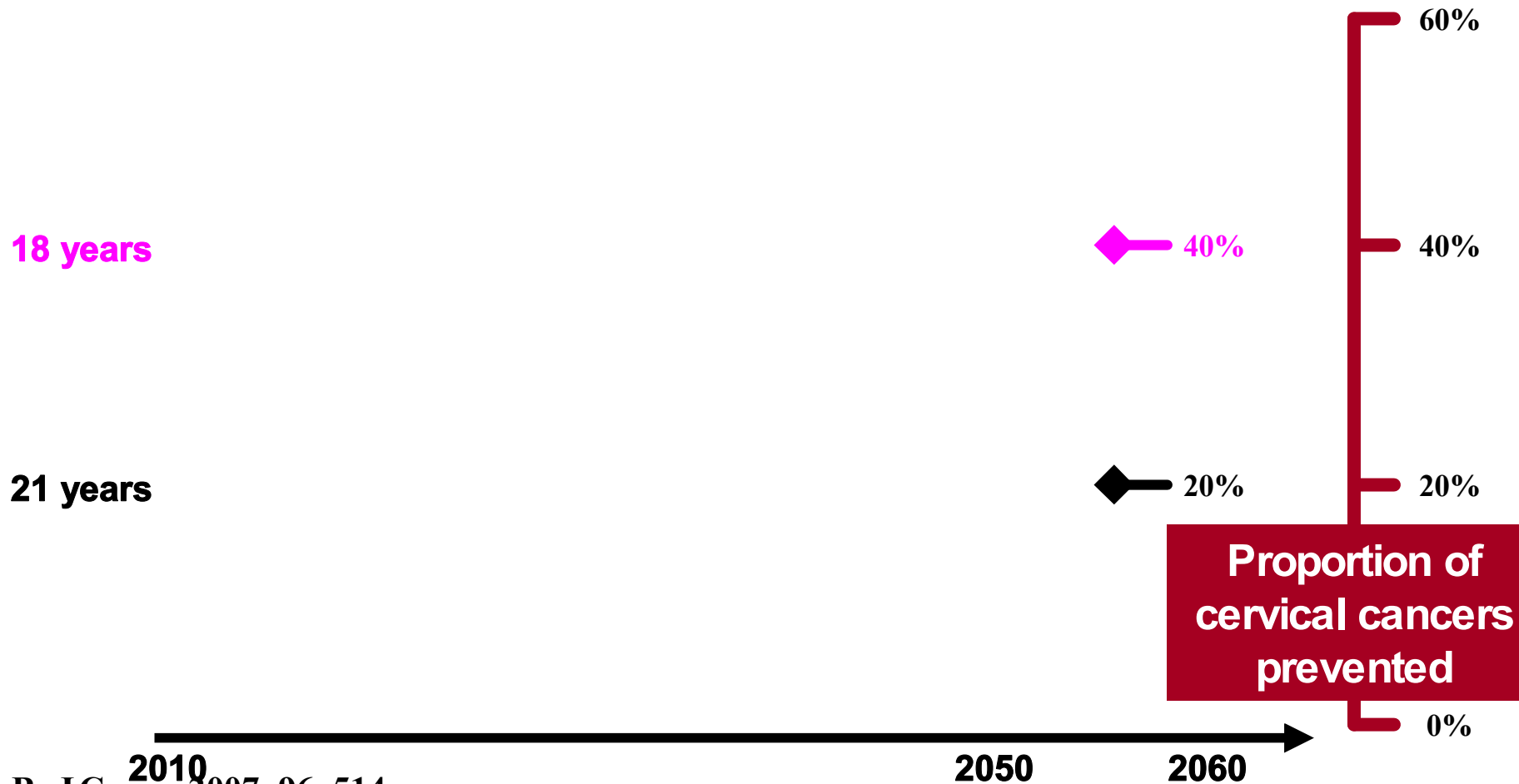
Gynecologists?

Pediatricians?

Public health system?

2008: if gynecologists start to vaccinate women at the age of.....

Finish modelization



2008: if school health systems start to vaccinate female students at the age of.....

12 y

15 y

18 y

21 y

75%

70%

40%

20%

80%

60%

40%

20%

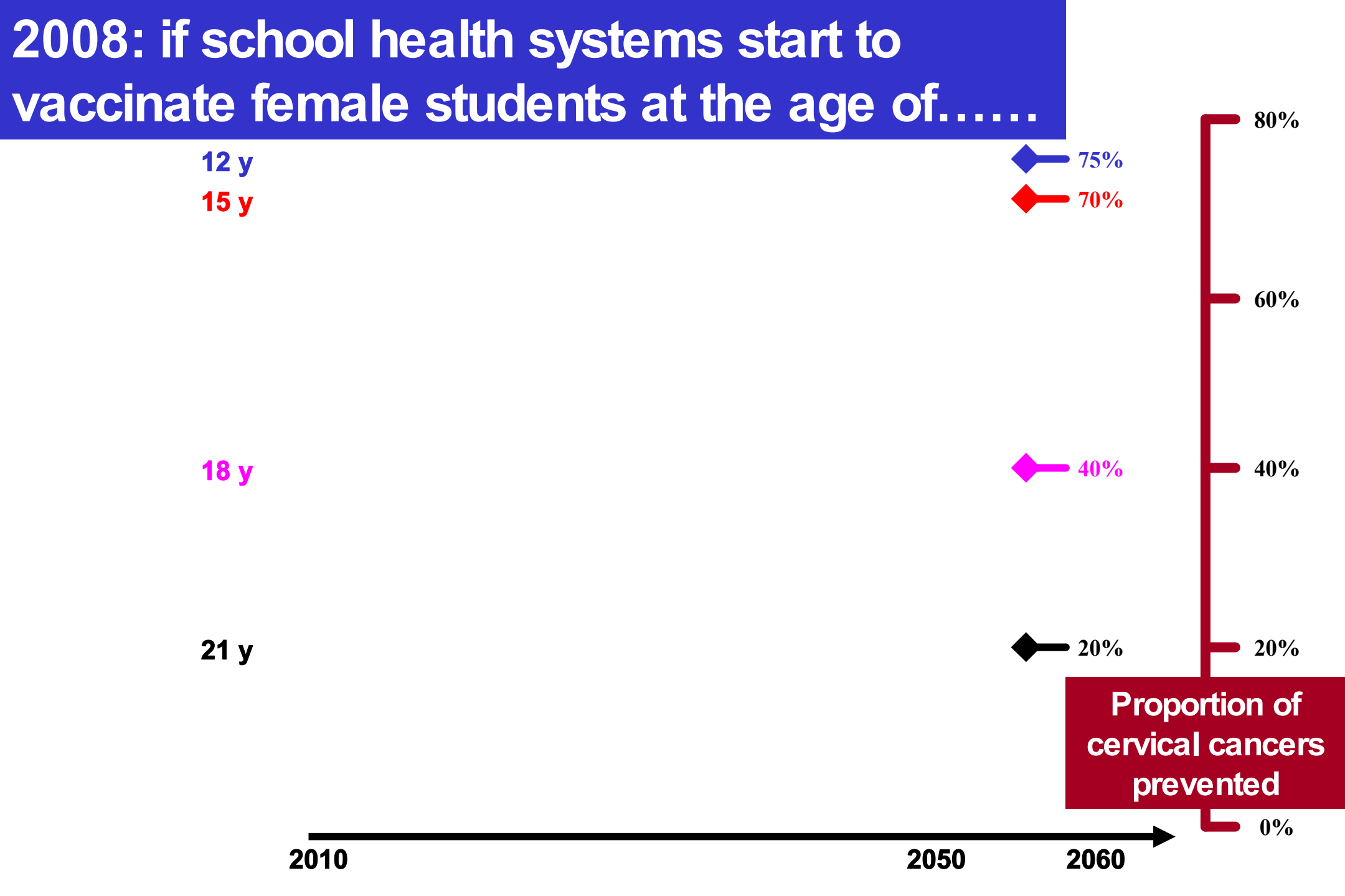
0%

2010

2050

2060

Proportion of cervical cancers prevented

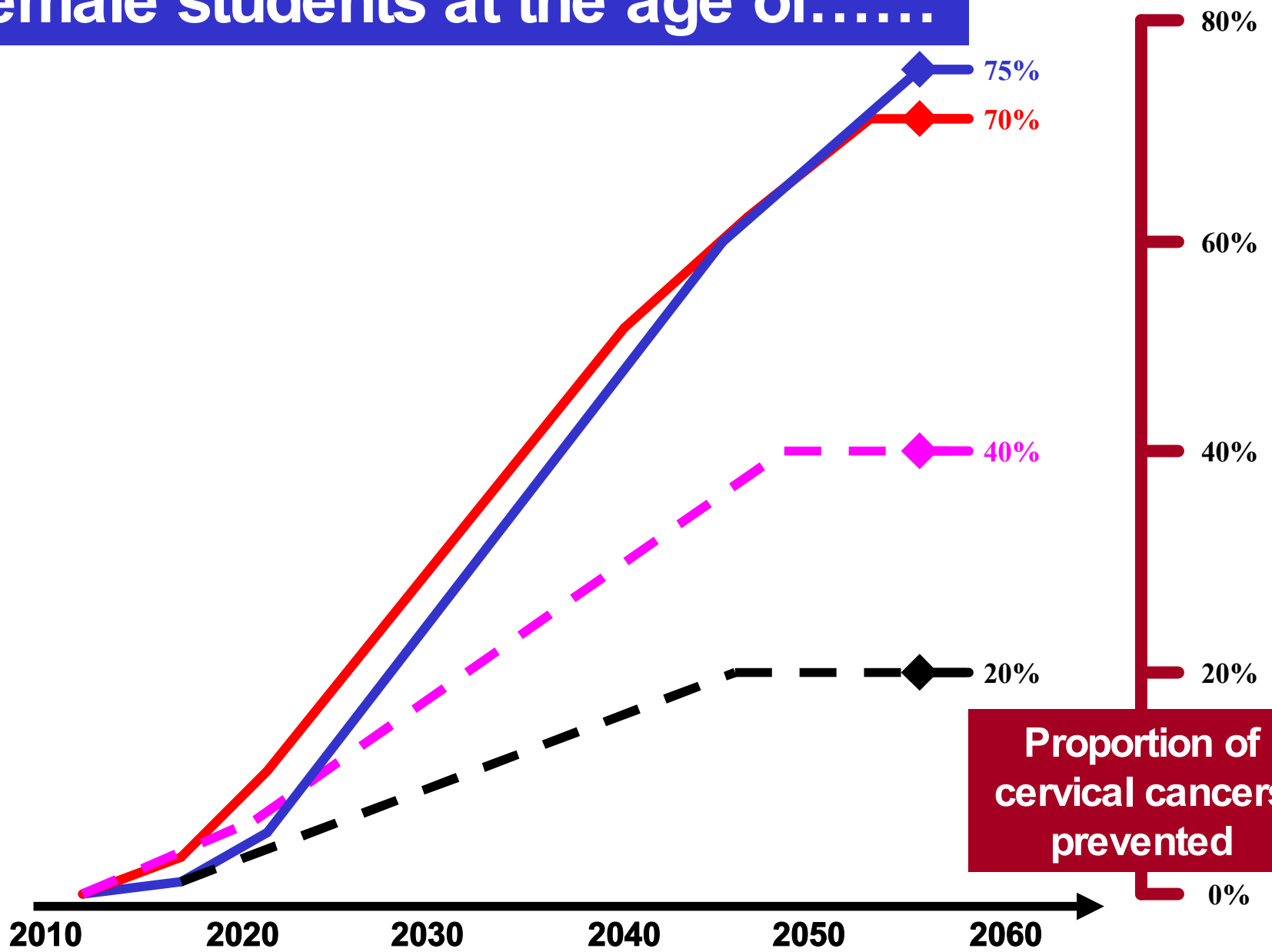


2008: if school health systems start to vaccinate female students at the age of.....

12 y
15 y

18 y

21 y

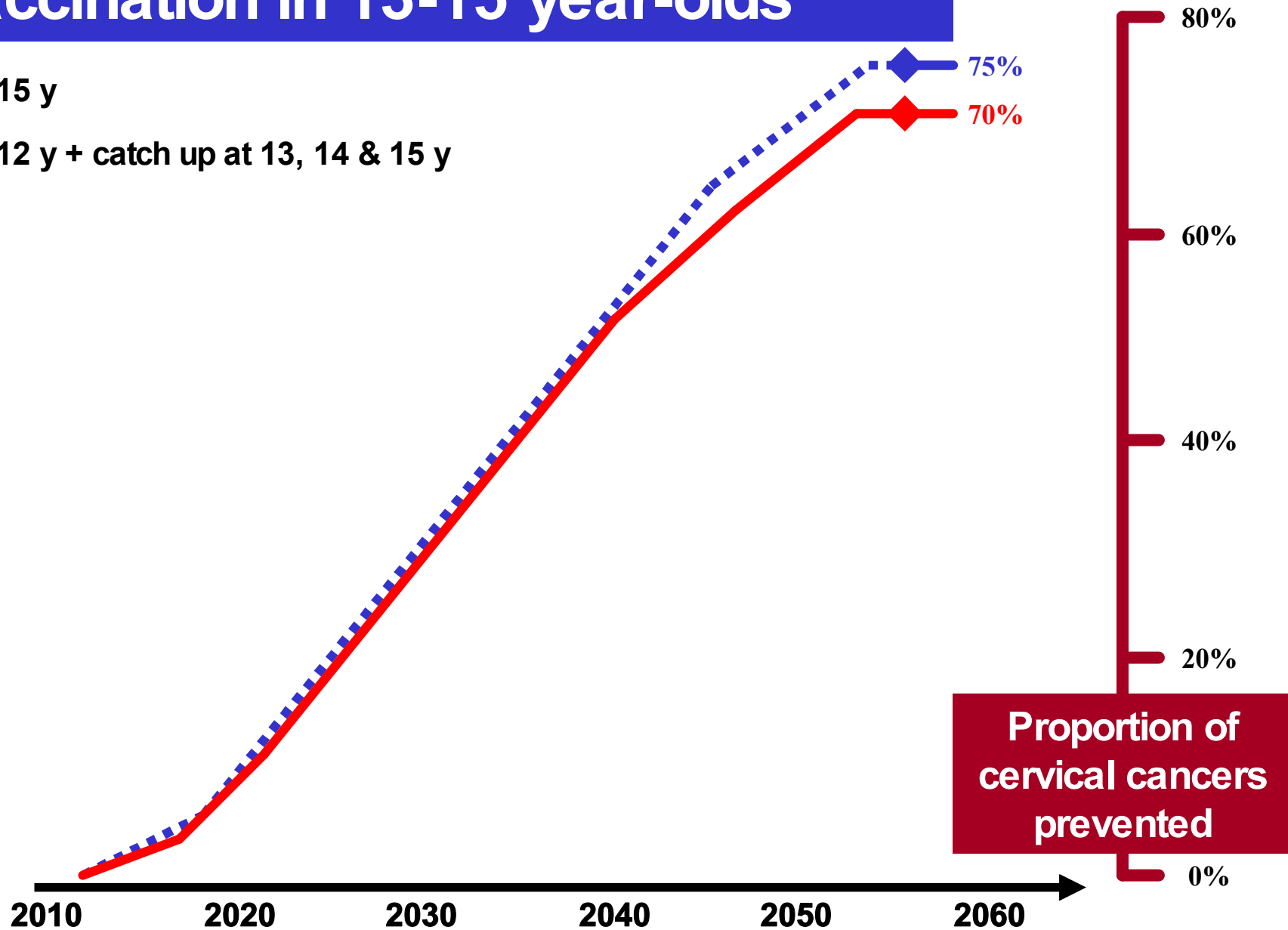


Proportion of cervical cancers prevented

2008: if school health systems perform catch up vaccination in 13-15 year-olds

— Vaccination at 15 y

- - - Vaccination at 12 y + catch up at 13, 14 & 15 y



Proportion of cervical cancers prevented

Vaccination program planned in Canton Vaud

In school year 2008-2009:

- Vaccination in 8th graders (14 years)
- Catch up in 9th graders and older (up to 19 y)

In school year 2009-2010:

- Regular vaccination in 7th graders (13 years)
- Catch up in 8th graders

From the school year 2010-2011 on:

- Regular vaccination in 7th graders

