# New prevention strategies vs Rotavirus and Human Papilloma Virus

26th October 2006

Société belge d'infectiologie et de microbiologie clinique
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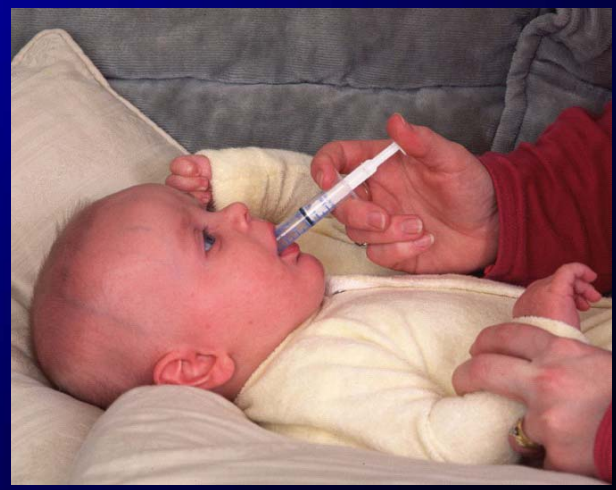
# Vaccination in the prevention of Rotavirus infection

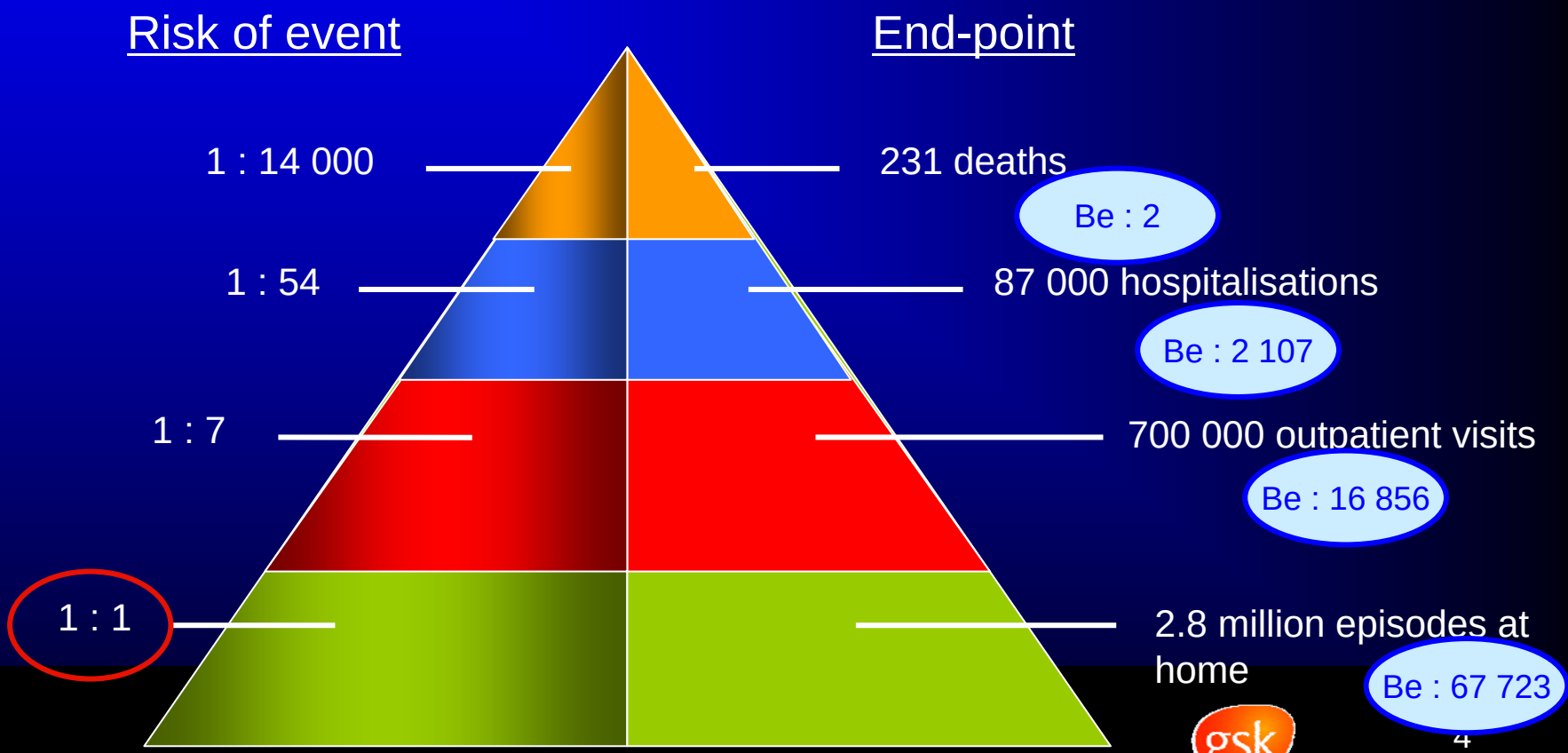


# Overview

- Features of natural infection with Rotavirus
- Vaccine development : choices and challenges
- Rotarix : clinical research results
- Conclusions

# Estimated European incidence of rotavirus gastroenteritis (25 EU countries)

An estimated 3.6 million rotavirus episodes per annum occur amongst the 23.6 million children under 5 years in the EU, making gastroenteritis caused by rotavirus the single most frequent vaccine-preventable illness among young children in the EU




Soriano-Gabarro M et al. Pediatr infect Dis J 2006 25(1):S7-S11. (N.B. These figures are estimated from a model)

# Transmission

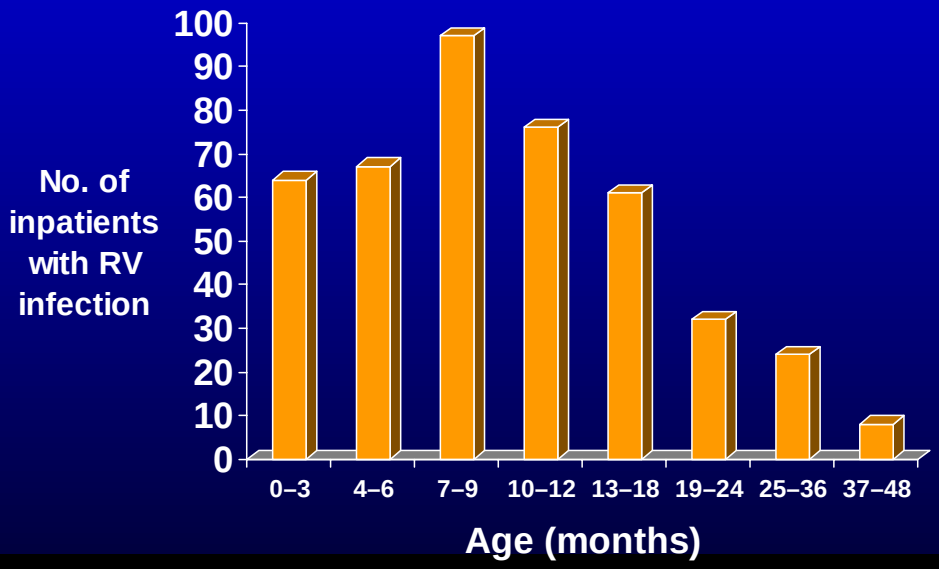
- Faecal-oral route predominant mode of transmission[1,2,3]
  - up to one trillion viral particles shed in faeces
  - shedding begins before symptoms and persists after illness
  - fomites on contaminated objects (e.g. toys) retain infectivity for several days
- Transmission still occurs despite improved sanitation[4]

[1] Fischer et al Vaccine2004; 22S:S49-S54,
[2]Dennehy Pediatr Infect Dis J, 2000;19:S103–5;
[3]Linhares and Bresee, Pan Am J Public Health 2000;8(5):305–330;
[4]Parashar et al, Emerg Infect Dis 1998:4(4):561–570; Photograph: Ross Whitaker/Getty Images

# Epidemiology

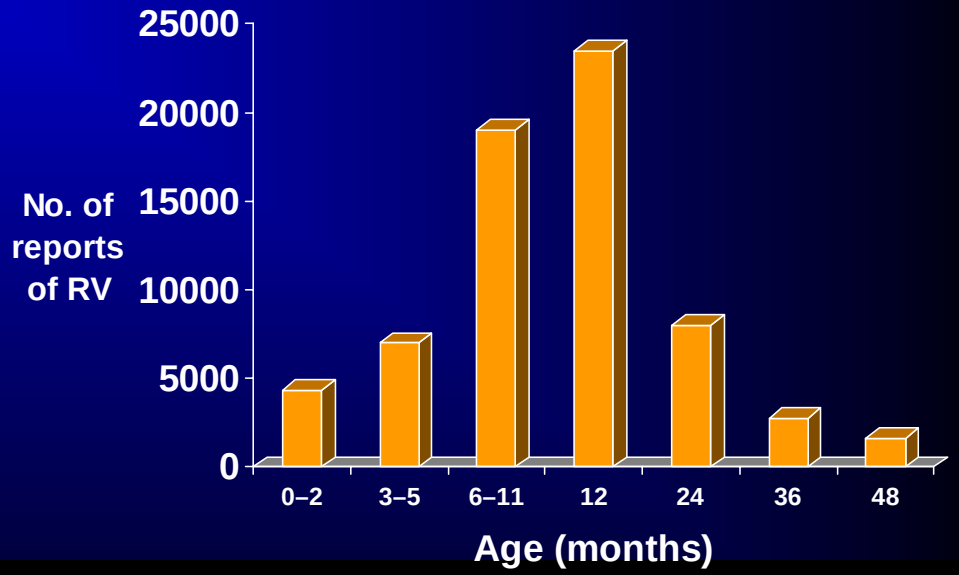
**Peak incidence of RV disease among children 6–24 months of age**

**US, Washington: January 1974–July 1982**




Brandt et al, J Clin Micro 1983 18 71–-78

**England and Wales: January 1990–December 1994**




Ryan et al, J Infect Dis 1996 174 S12–-S18



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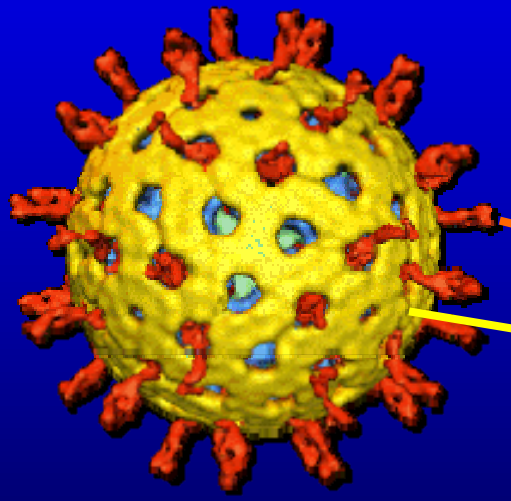
# The Virus



Reoviridae
Family

Group
(Seven )
- A
- B
- C, D, E, F, G

Sub-group
(Two )
- I
- II

VP6

Serotype

VP7

VP4

G
(1-14 )

P
(1-8)

G1P[8] G2P[4] G3P[8] G4P[8]

Modified from Parashar et al, Emerg Infect Dis 1998 4(4) 561–570

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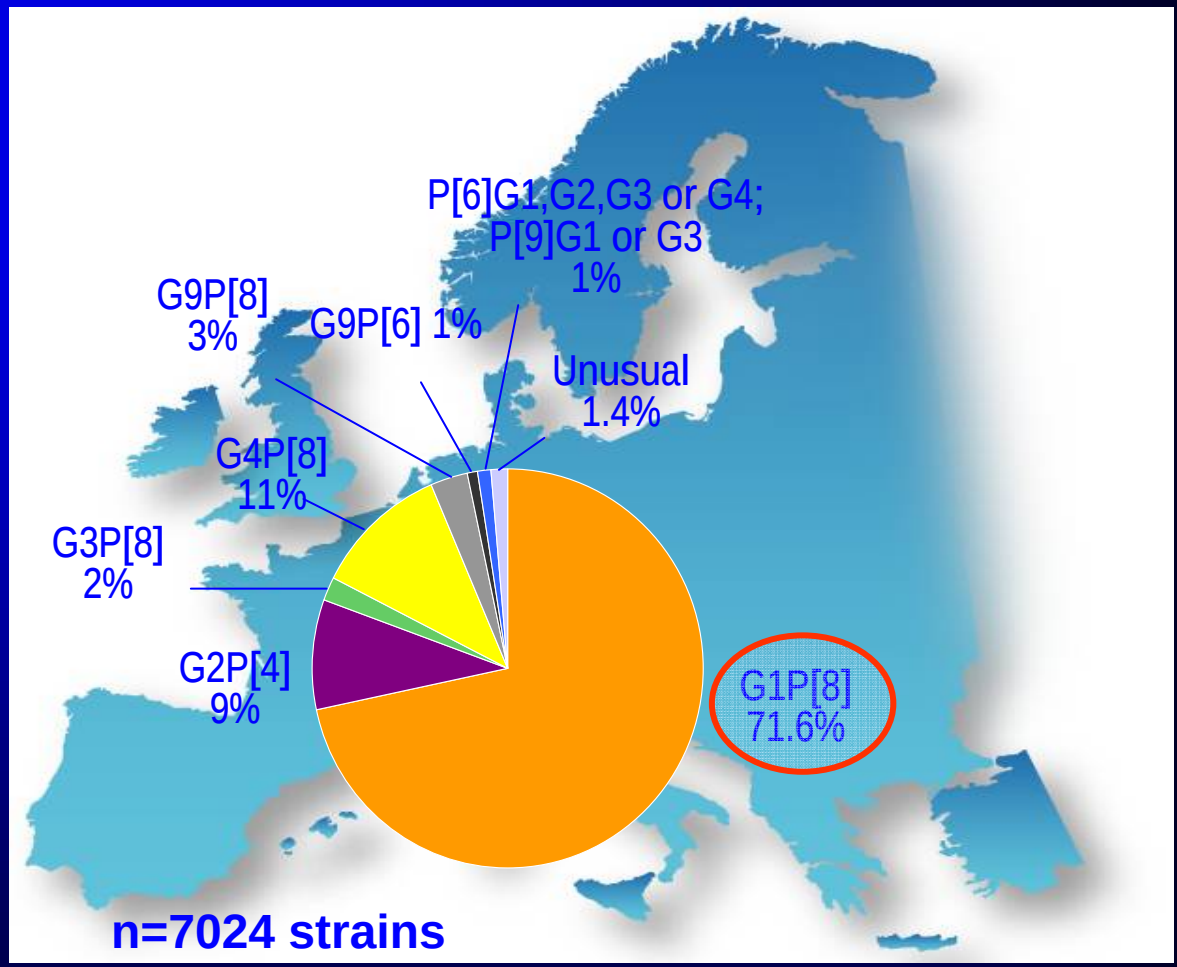
# European distribution of human group A rotaviruses

Four most common strains responsible for gastroenteritis (>93%):

- G1P[8]
- G2P[4]
- G3P[8]
- G4P[8]

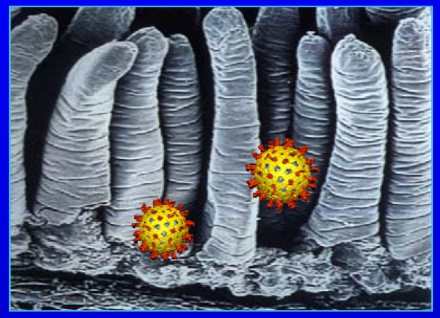
Emerging strain:

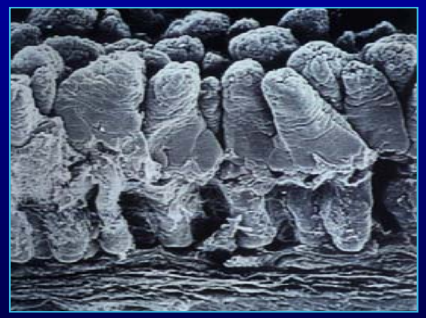
- G9P[8]




Santos N, Hoshino Y. Rev Med Virol 2005 Jan-Feb;15(1):29-56

# Pathogenesis





Rotaviruses adhere to the GI tract epithelia (jejunal mucosa)

↓

Atrophy of the villi of the gut

↓

Loss of absorptive area

↓

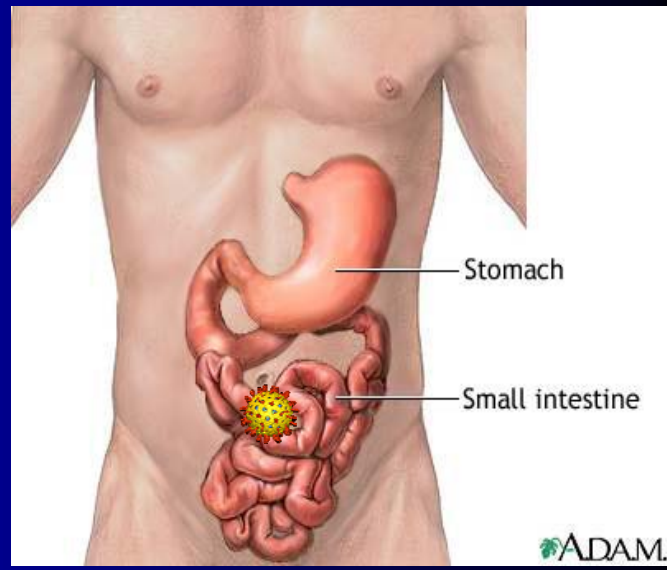
Flux of water and electrolytes

↓

NSP4 viral enterotoxin

↓

Enteric nervous system activation




**VOMITING AND DIARRHEA**

*Rotavirus infection in an animal model of infection. Photographs are from an experimentally infected calf. Reproduced with permission from Zuckerman et al, eds. *Principles and Practice of Clinical Virology*. 2nd ed. London: John Wiley & Sons; 1990:182. Micrographs courtesy of Dr. Graham Hall, Berkshire, UK.

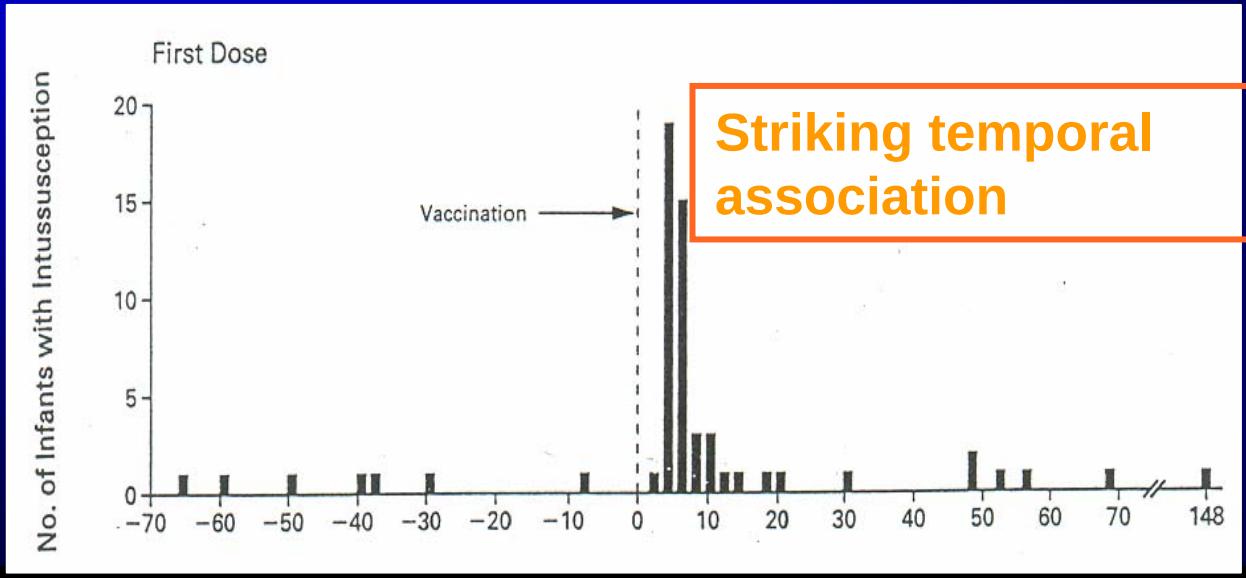
# Immunity after infection

- Natural rotavirus infection attenuates the severity of subsequent infections[1–3]
  - Infants become immune after 1–3 infections
  - Immunity leads to accelerated recovery from infection
  - Does not protect against re-infection or mild disease[5]
- Type of immunity
  - Systemic - mucosal
  - Humoral - cellular
- Serum IgA may be the best correlate of protection[4]

[1]Ward and Bernstein, J Infect Dis 1994 169 900–904; [2]Bernstein et al, J Infect Dis 1991 164 277–283; [3]Velazquez et al, N Eng J Med 1996 335 1022–1028; [4]Velazquez et al, J Infect Dis 2000 182 1602–1608; [5]Offit, Novartis Found Symp 2001 238 106–113

# Rota vaccines history

- Development of rotavirus vaccines began in 1970's
- First rotavirus vaccine licensed in the US in 1998:
  - **Rotashield®**
  - Rhesus-based tetravalent human reassortant vaccine (RRV-TV)
  - Withdrawn in 1999 due to causal link with **intussusception (IS)**




Murphy et al, N Engl J Med 2001 344 564–72.

# What is Intussusception?

- Bowel obstruction:
  - One segment of intestine folds inside the other
  - Intestine wall swells and bleeds
- Most common cause of intestinal obstruction in children less than 2 years old:
  - 90% unknown cause (idiopathic)
  - 10% related to intestinal mass
  - Male infants aged 3–9 months most at risk
  - Death rare if access to treatment prompt

Normal intestine

Start of Intussusception

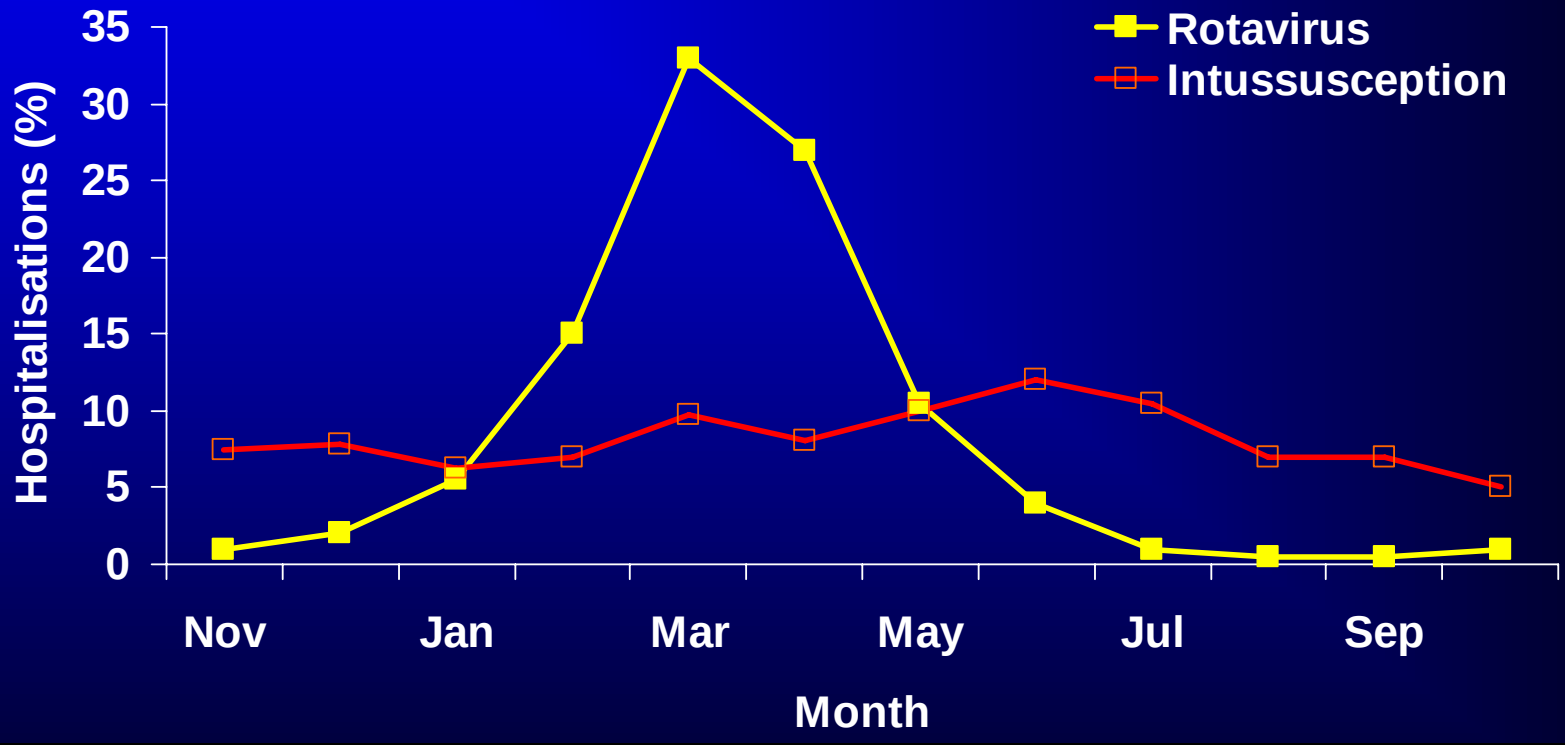
Intussusception



Kombo et al, Pediatrics 2001 108(2) E37; http://www.who.int/vaccines-documents/DocsPDF02/www640.pdf

# Rotavirus Seasonal Hospitalization and IS cases in New York State

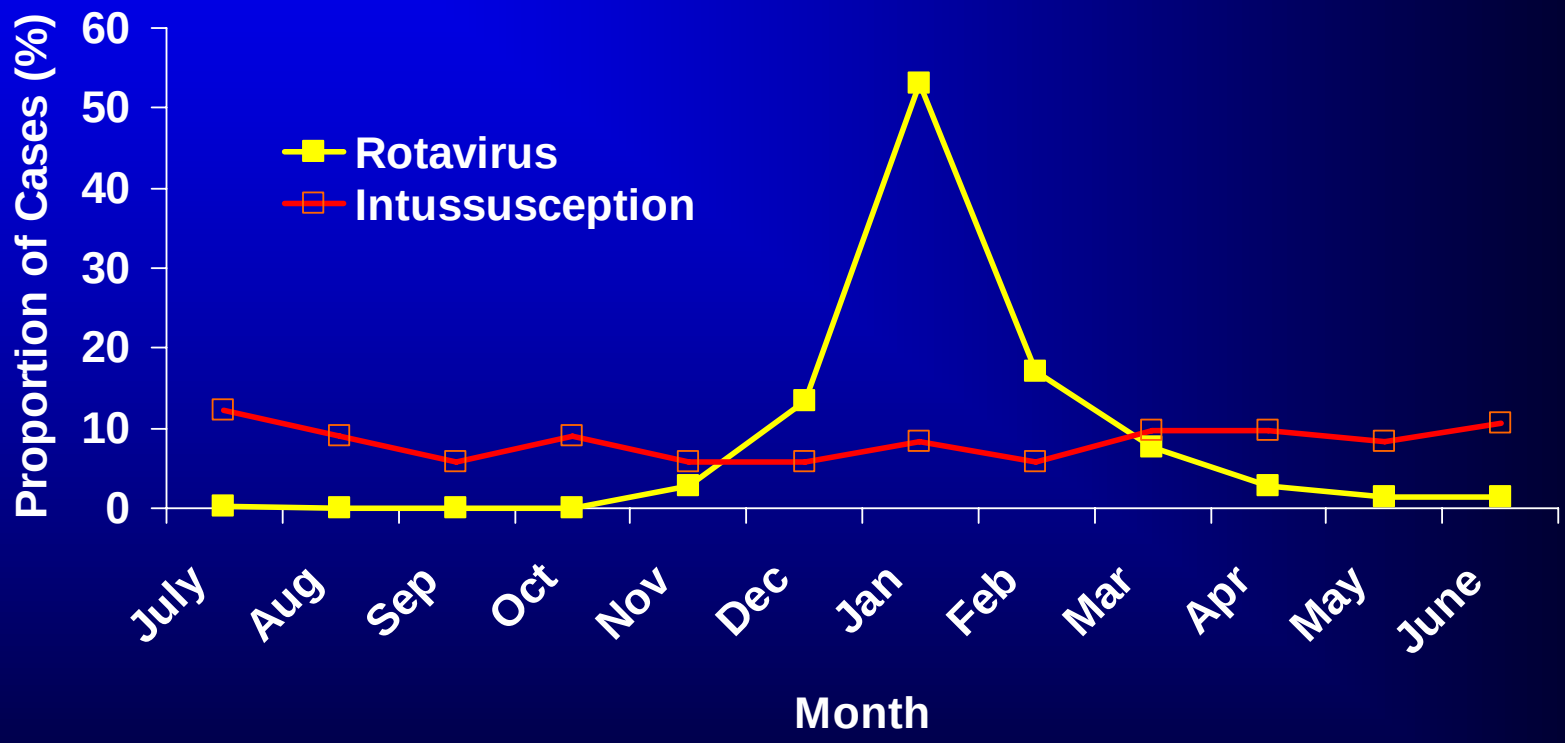
**Seasonal distribution of hospitalizations for rotavirus diarrhea and IS among children aged 3–23 months, during 1993–1995**




Rennels et al, Pediatr Infect Dis J 1998 17 924–925

# Rotavirus Seasonal Incidence and IS cases in US

**Seasonal distribution of rotavirus diarrhea and IS in children <3 years old**




Chang et al Pediatr Infect Dis J 2002 21 97–102 (Southern California Kaiser Permanente Health Care Plan)

# Vaccine development : choices and challenges

- Choice of the Rotavirus type
  - Inactivated or life attenuated virus
  - Human or animal/human

G1P8
(human –attenuated)

- Choice of the vaccine type
  - Oral or injection

Oral

- The safety challenge
  - Intussusception

N = 63 000 !

- Complexity of the vaccination schedule
  - Di – Te – Per – HiB – HB – Polio (2-3-4 M)
  - Prevenar (2-3-4 M)

Co-ad studies

# Content of vaccine

**89-12 strain G1P[8] isolated from stools of a 15-month old boy in Cincinnati** — P O

Passaged 26 times in Primary African Green Monkey Kidney (AGMK)

J Gamble Inst. Med. Research, Cincinnati — P 26

Further Passaged in Approved AGMK

AVANT DynCorporation — P 33

Further Passaged in Vero Cell Line & Cloning steps

GSK Bio — P 4O

Further passaged in Vero cell line

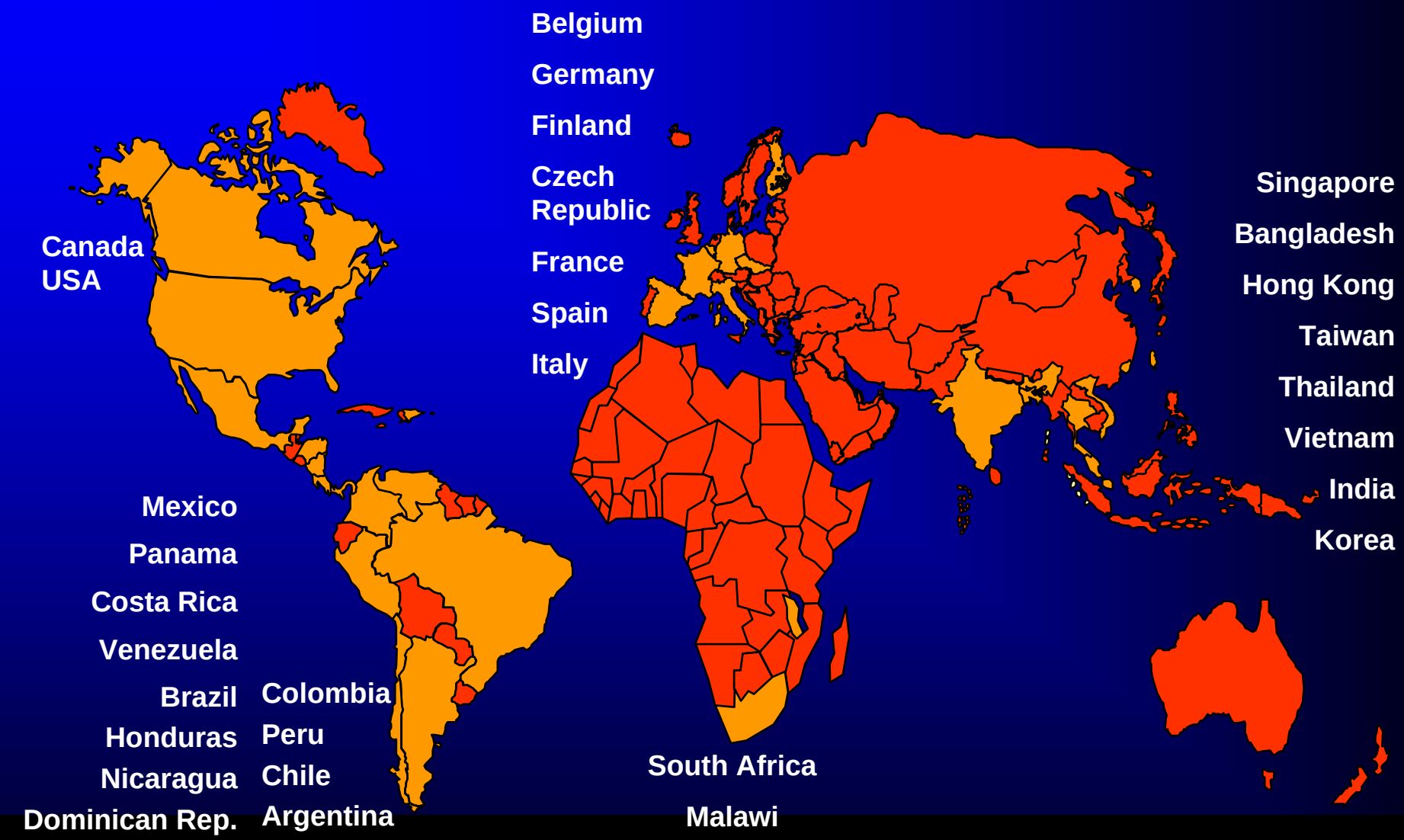
RIX4414 master seed — P 43

**RIX 4414 vaccine lot**

# Goals of rotavirus vaccination

- Provide early protection, comparable to that conferred by natural rotavirus infection
- Protect against moderate/severe RVGE
- Prevent hospitalisation due to RVGE
- Reduce morbidity and socioeconomic burden
- Reduce any RV infection independant of the severity !
- Reduce the global incidence of rotavirus mortality

# Rotarix: Phase I – II – III Studies




… a worldwide development

# Rota-023 - Safety Study Aims

- Placebo-controlled, randomized double blind study (63,000)
- Randomisation : 1 : 1

- Primary Endpoint
  - Safety of RIX4414 with respect to definite IS occurring within 0 - 30 days after each of two vaccine doses

- Secondary Endpoint
  - Safety of RIX4414 with respect to definite IS from Day 0 to 2-3 months post dose 2

Ref: Vesikari T et al ESPID 2005, Abstract 31

# Rotarix : no increased intussusception risk after vaccination

- Phase III trial involving over 60,000 subjects showed no increased risk of IS between Rotarix & placebo[1]

| Timing of IS | Rotarix n ~ 31,000 | Placebo n ~ 31,000 | Relative risk IS Rotarix vs Placebo (95% CI) |
|---|---|---|---|
| IS cases within 31-day window | 6 | 7 | 0.85 (0.30;2.42) |
| IS cases between dose 1 and 30-90 days post dose 2 | 9 | 16 | 0.56 (0.25;1.24) |

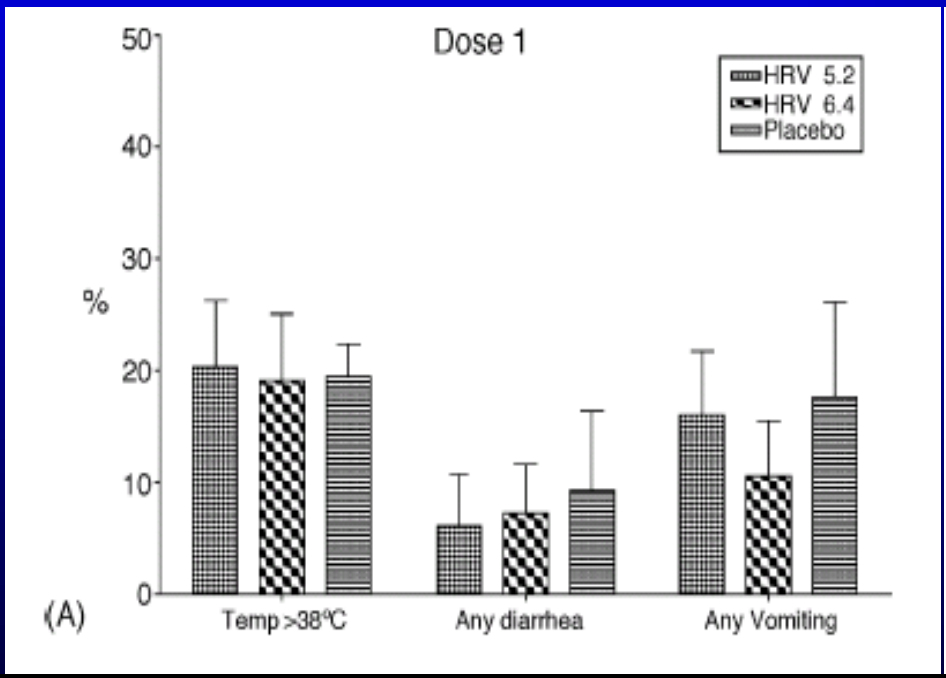
- Overall safety vaccine : similar to placebo

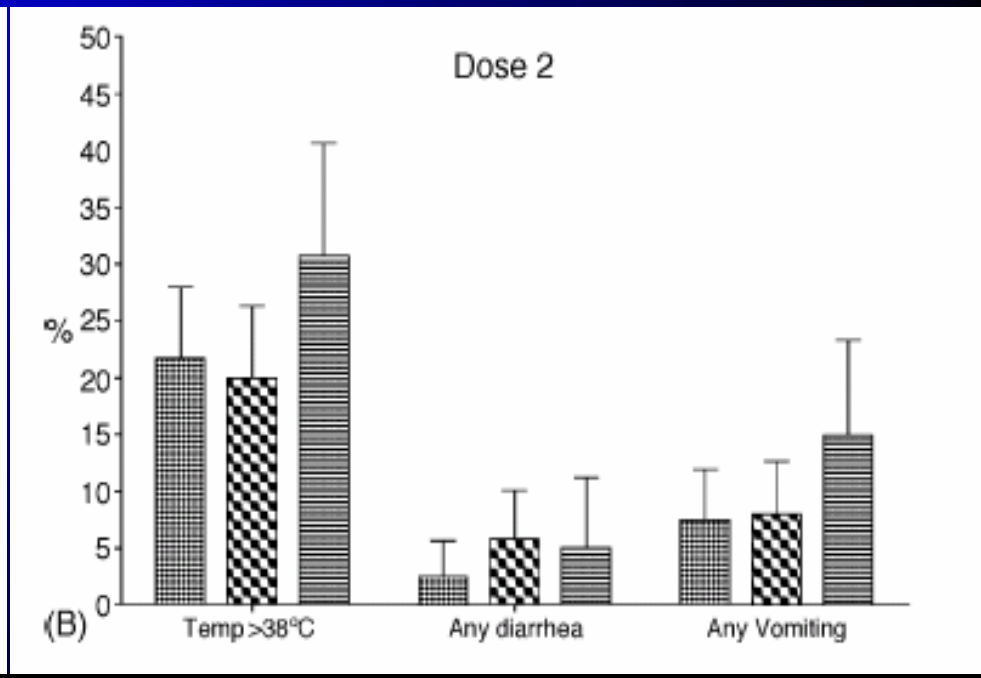


Ruiz-Palacios et al NEJM 2006 (354(1)) : 11-21

# Rotarix tolerance evaluation (US – Canada)

- Placebo controlled randomised (1 : 1) study (N = 529)
- Tolerance : similar to placebo



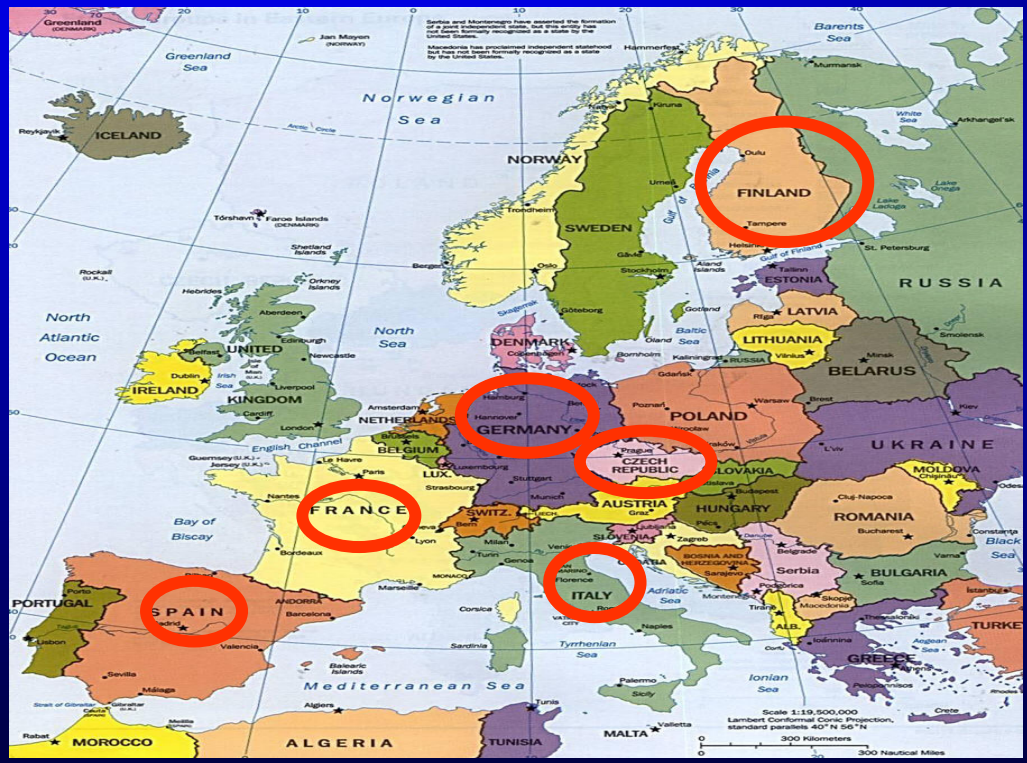




Dennehy PH et al. Vaccine, 2006,24,3780-3781

# Rotarix European efficacy study

**(ESPID 2006, T Vesikari et al.)**

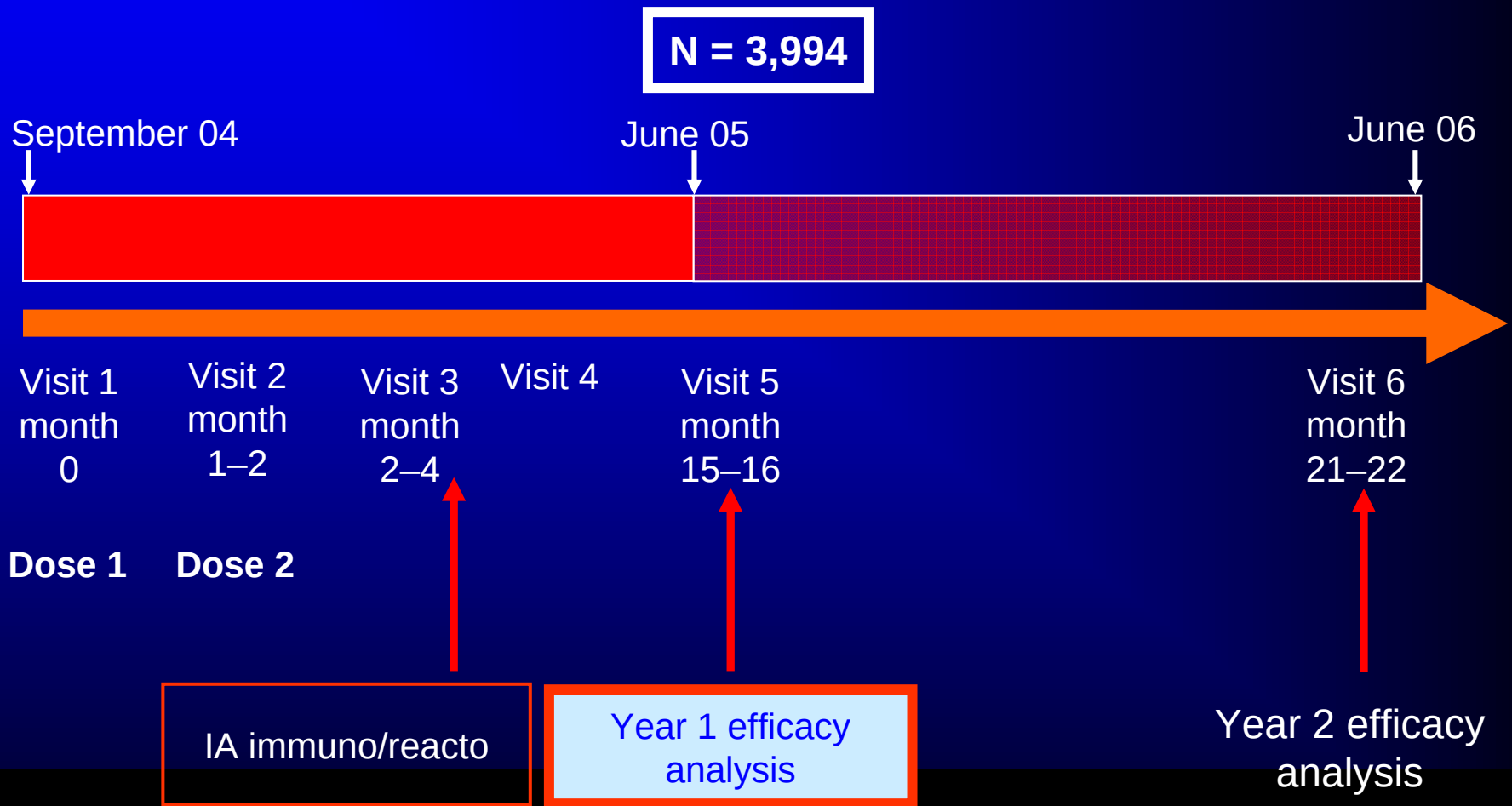
- Espid – May 2006




Total cohort N=3,994

Vesikari T et al. ESPID, May 3-5, 2006. Abstract 75 – oral presentation

# Rotarix European efficacy study (-036) (Vaccine : placebo 2:1 randomization)




Vesikari T et al. ESPID, May 3-5, 2006. Abstract 75 – oral presentation

# Efficacy results : European study (-036)

| | |
|---|---|
| Hospitalisation RV GE | 100 % |
| Severe RV GE | 95.8 % |
| Any RV GE | 87.1 % |
| RV GE medical interventions | 92 % |

Vesikari T et al. ESPID, May 3-5, 2006. Abstract 75 – oral presentation

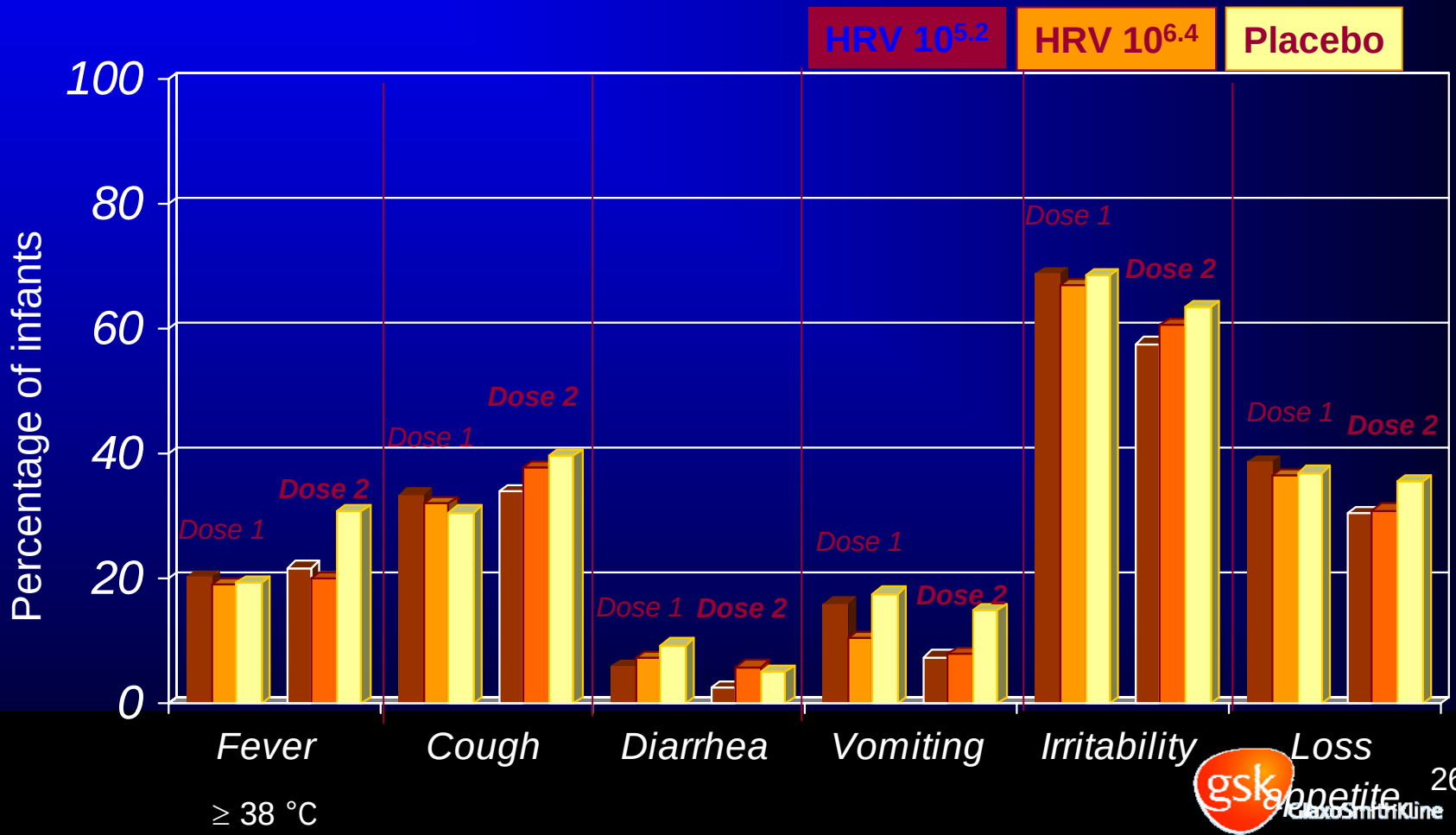
# Efficacy results : long term protection (2Y) Latina (-023)

| | |
|---|---|
| Hospitalisation RV GE | 83 % |
| Severe RV GE | 80.5 % |
| Hospitalisation Any GE | 39.3 % |

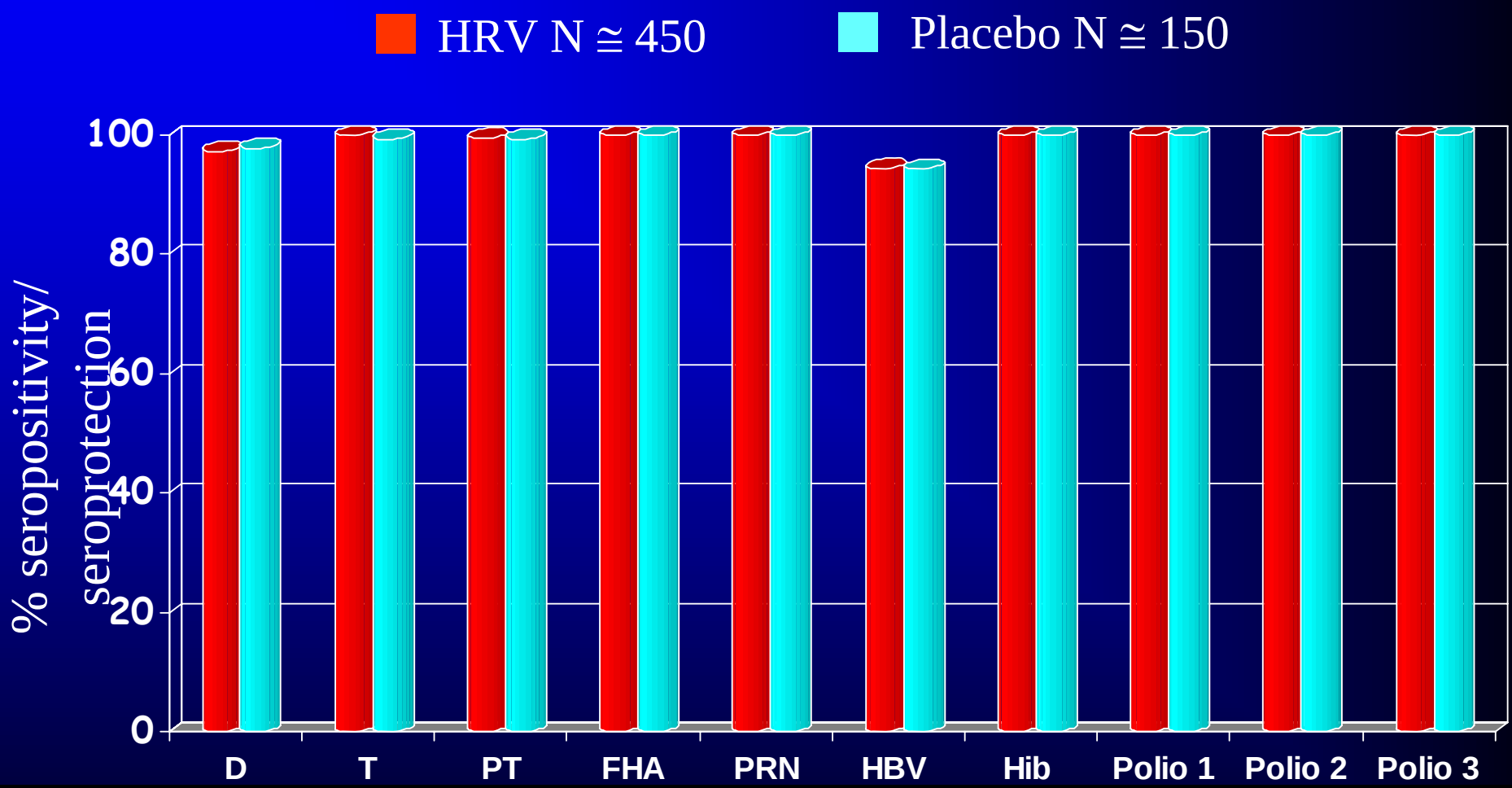
Velazquez et al. ICAAC Sep 2006.

# Rotarix safety when co-administered

**Solicited symptoms reported within 15 days post-vaccination, DTPa-IPV, Hib , PnC co-administered (N= 529)**



# Immunogenicity of concomitant DTPa-IPV/Hib one month post-dose 3 (HBV given at 0, 1, 5 months)



# Conclusions

- Rotarix has shown excellent protective efficacy results
  - 100 % vs RV GE hospitalisation
  - 95.8 % vs severe RV GE
- Rotarix has a good safety profile
  - Safety similar to placebo
- Rotarix is a live attenuated human rotavirusvaccine to be given orally , in 2 doses :
  - As of the age of 6 w
  - Minimum 4 weeks interval between the 2 doses
  - Vaccination completed by age of 6M
- Rotarix can be given with the classically administered pediatric vaccines

# Cervical Cancer prevention : a new paradigm

# Overview

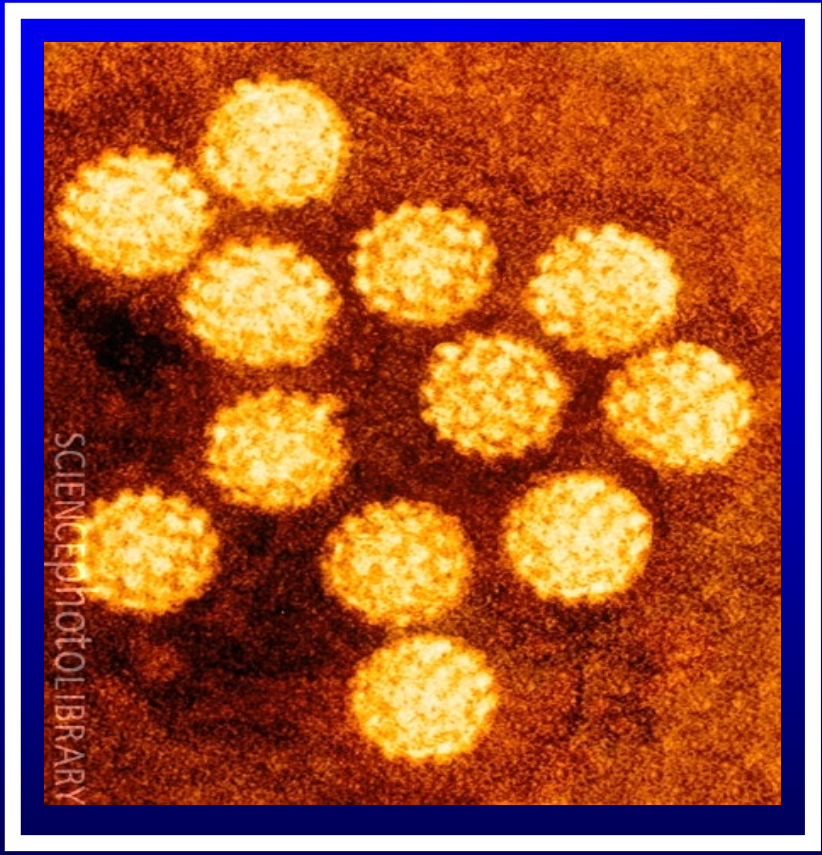
- Cervical cancer : a viral cause
- Epidemiology of Cervical cancer
- Development of HPV vaccine
- Cervical cancer prevention : present and future

# Cervical cancer - HPV : a long story !

- 1842 : absence of cervical cancer (CC) in nuns suggests role of sexual activity
- 1907 : experimental human transmission of cutaneous warts through cell free preparation
- 1974 : suggestion  of role of HPV in CC
- 1983 : isolation of HPV type 16 from cervical pre-cancerous lesions and CC
- 1985 : detection of specific active viral genes in CC
- 1999 : confirmation of the “100 %” association of HPV and CC *

* Walboomers & al : J. Path. 1999 : 12 - 19 (189)

# Human papillomavirus

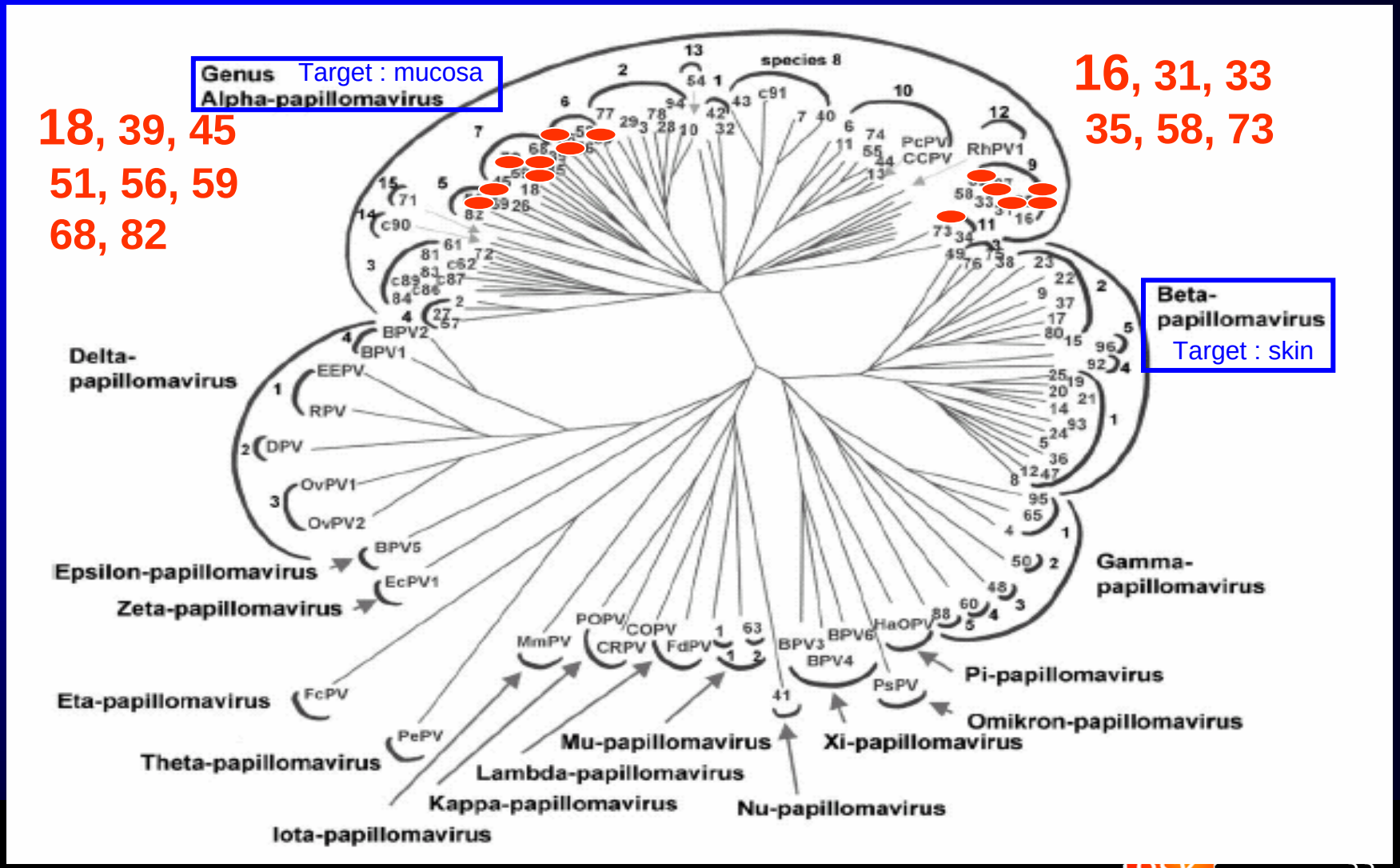



HPV capsids,
approximately 55 nm in diameter

- There are more than 200 types of HPV
- Small DNA-virus containing two strands of DNA within a spherical shell (capsid)
- +/- 30 types target genital mucosa
- 15 are “so called” high risk or oncogenic
- Low risk types cause benign genital warts

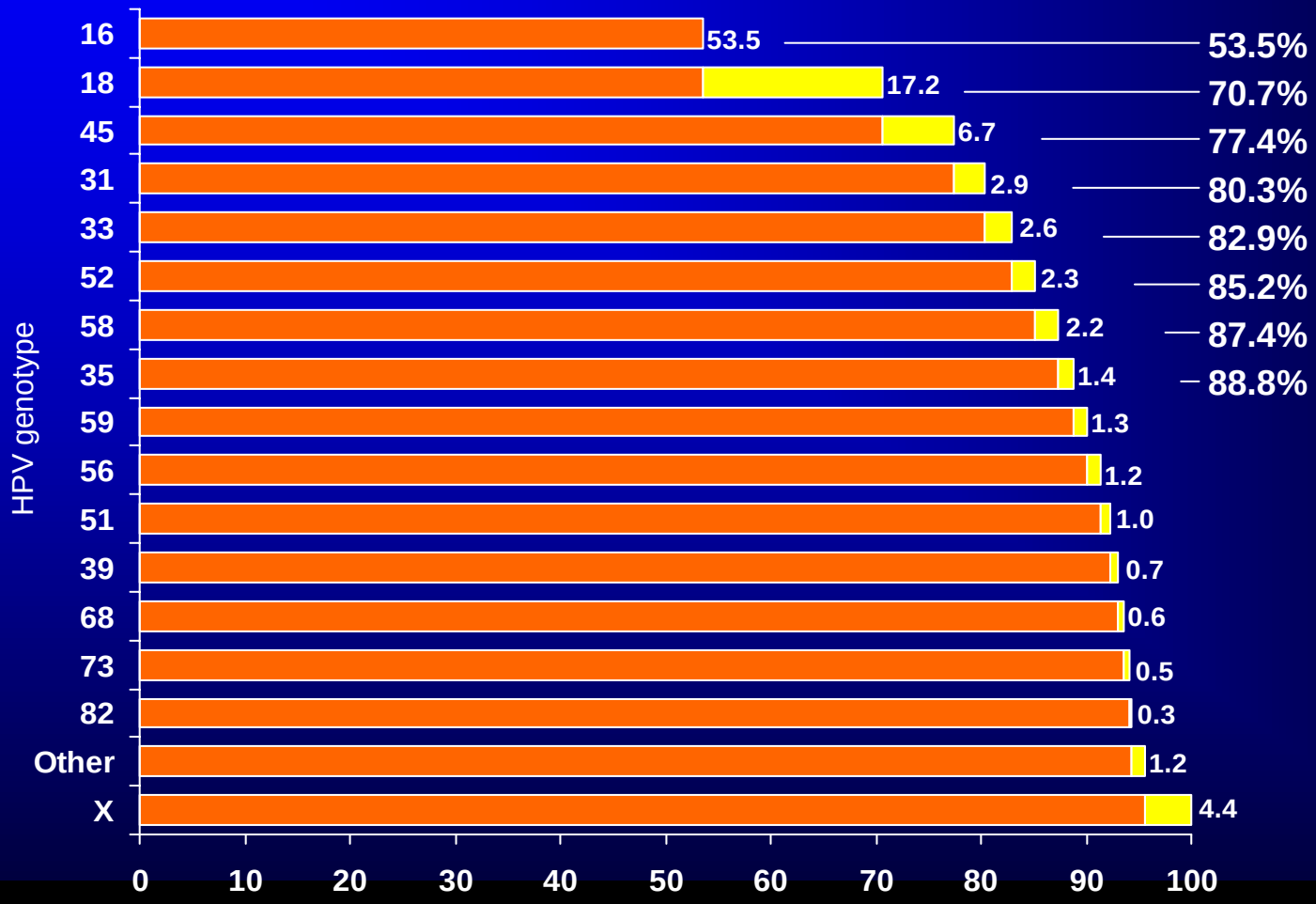
Image source: Dr Linda Stannard, UCT/Science Photo Library

# Papillomavirus – phylogenetics




de Villiers EM et al. Virology 2004; 324: 17–27.

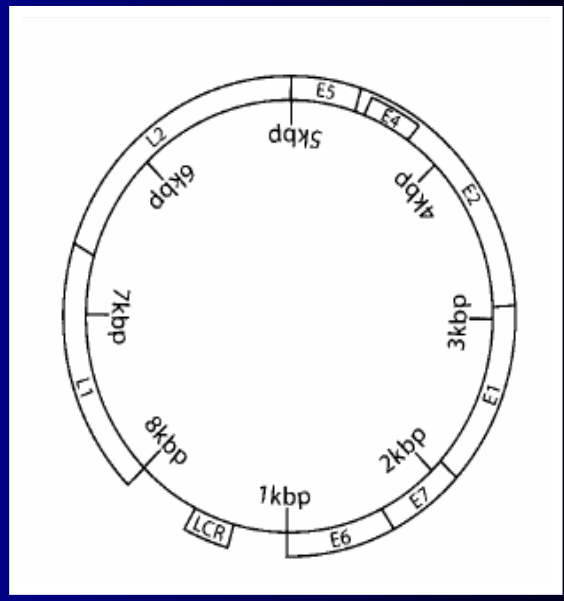
# HPV types in cervical cancer

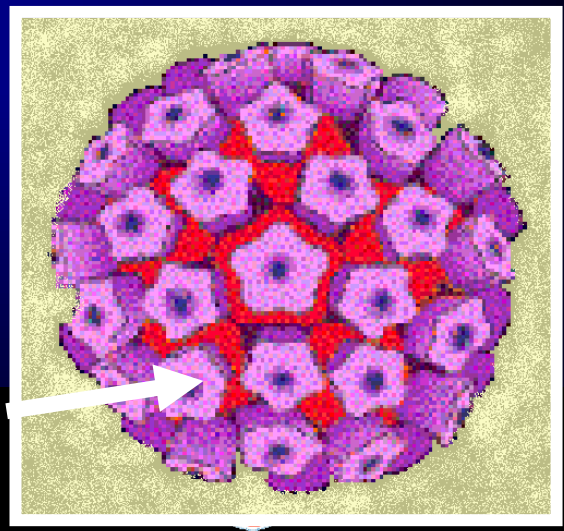



Munoz N et al. Int J Cancer 2004; 111: 278–85.

# Genetics and structure of HPV

- The HPV genome is a single molecule of double-stranded, circular DNA[1]
- **E6:** oncogene – inactivates p53 (tumour suppressor/DNA repair)
- **E7:** oncogene – binds to pRb (gene transcription inhibitor)
- **L1:** major viral capsid protein – immunogenic
- **L2:** minor viral capsid protein – immunogenic

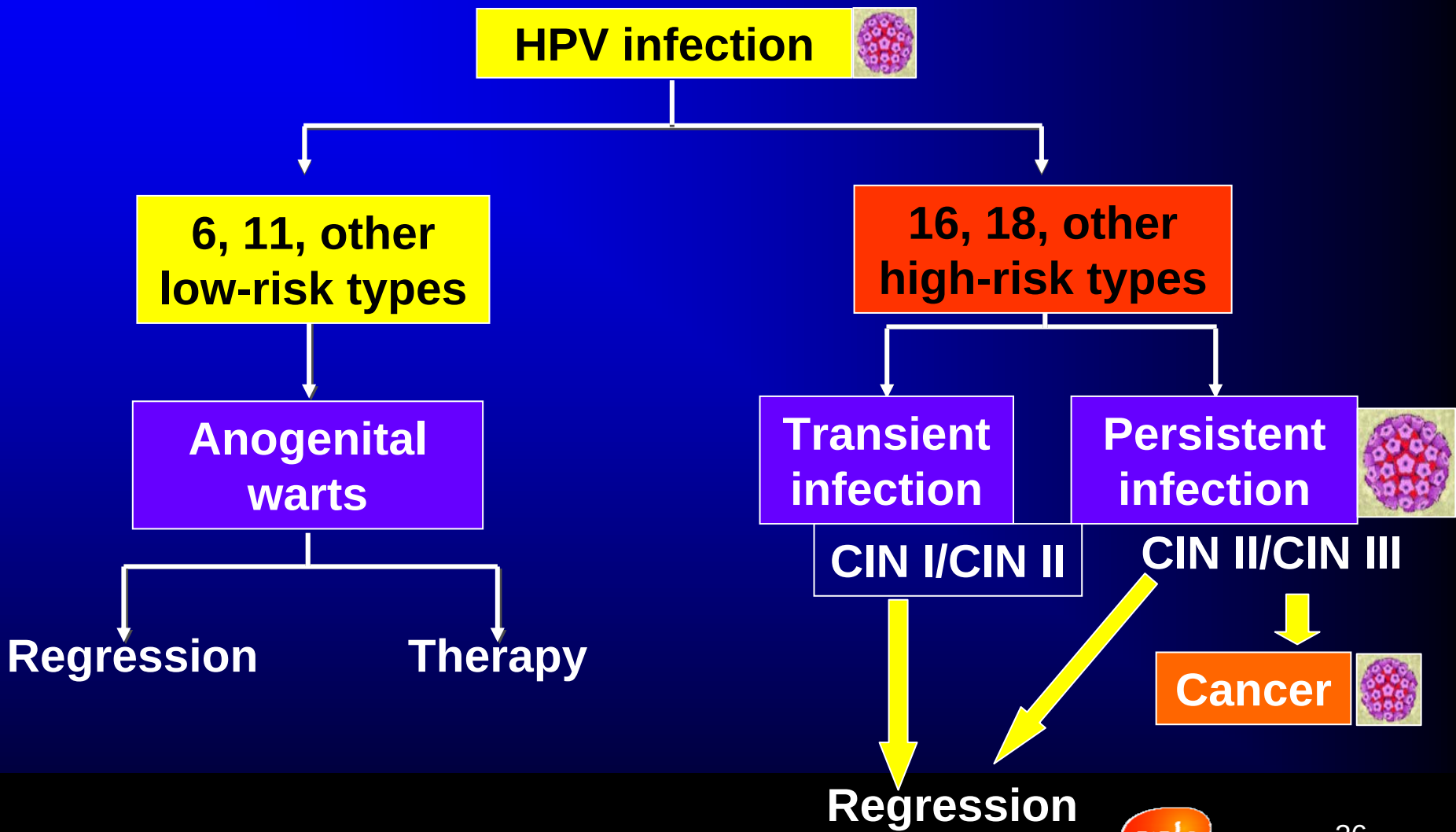


L1 pentamer

1. Burd EM. Clin Microbiol Rev 2003; 16: 1–17.

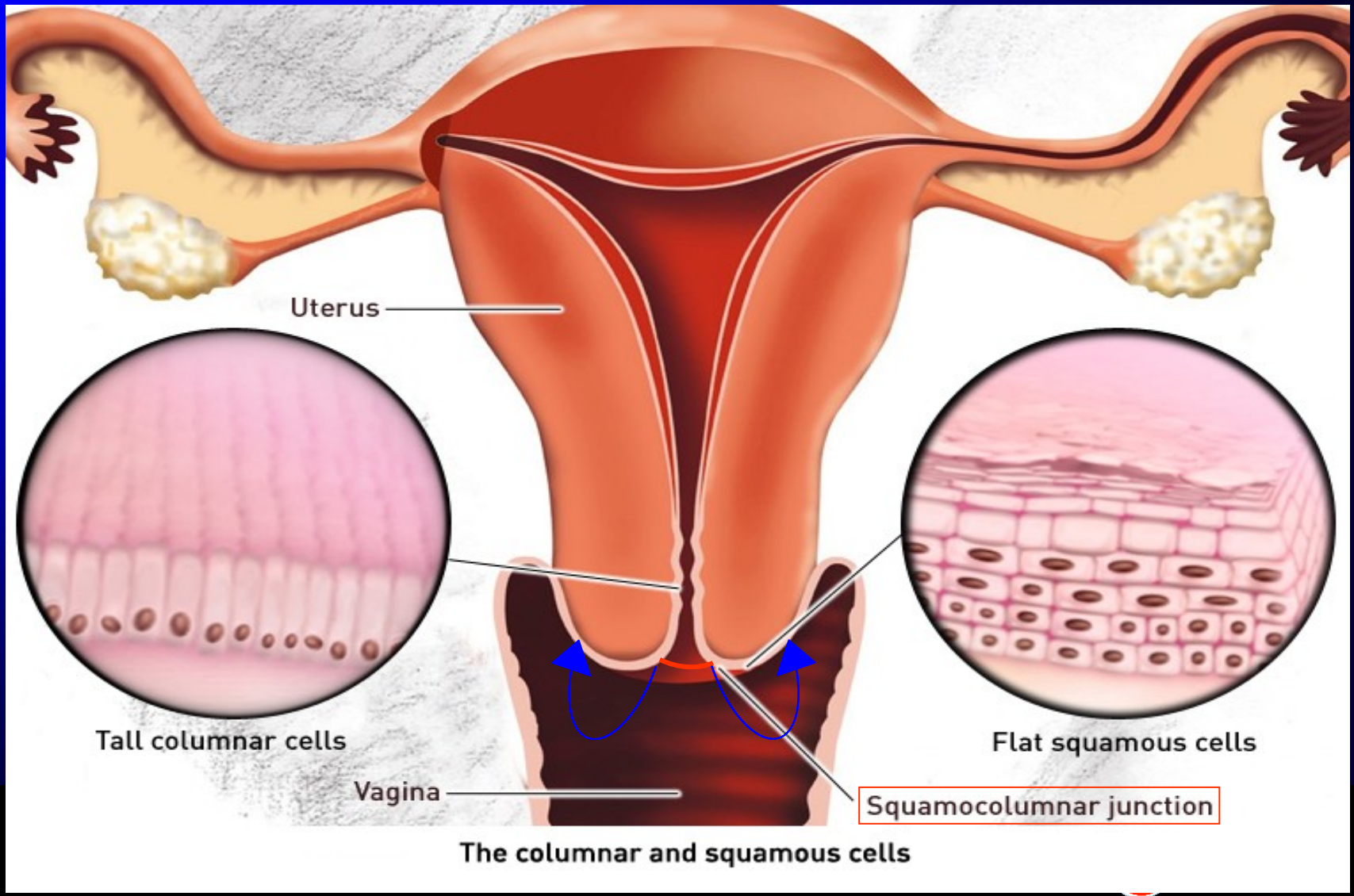
# Natural history of HPV infection



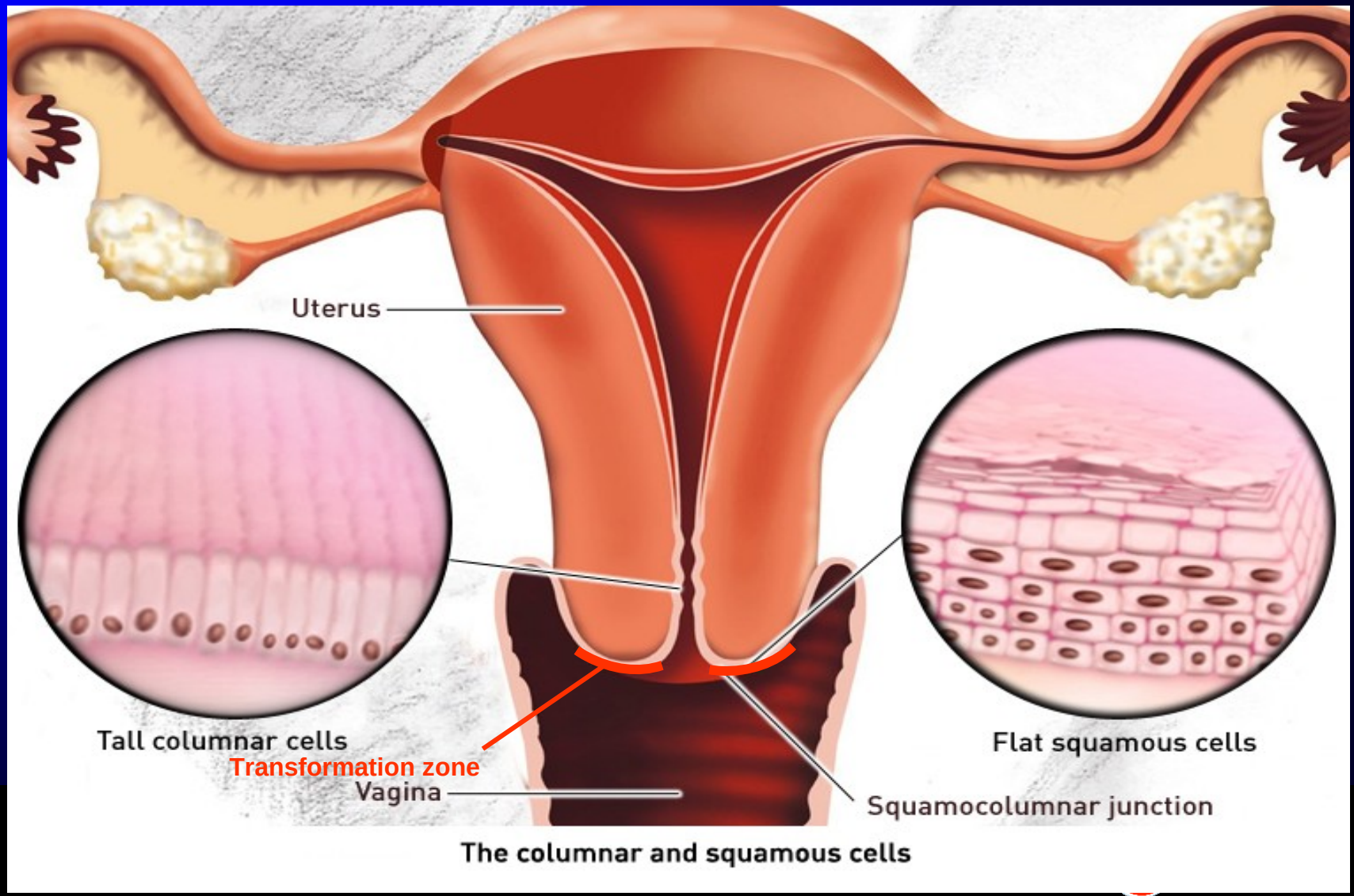

CIN = cervical intraepithelial neoplasia

# Cytology of the cervix

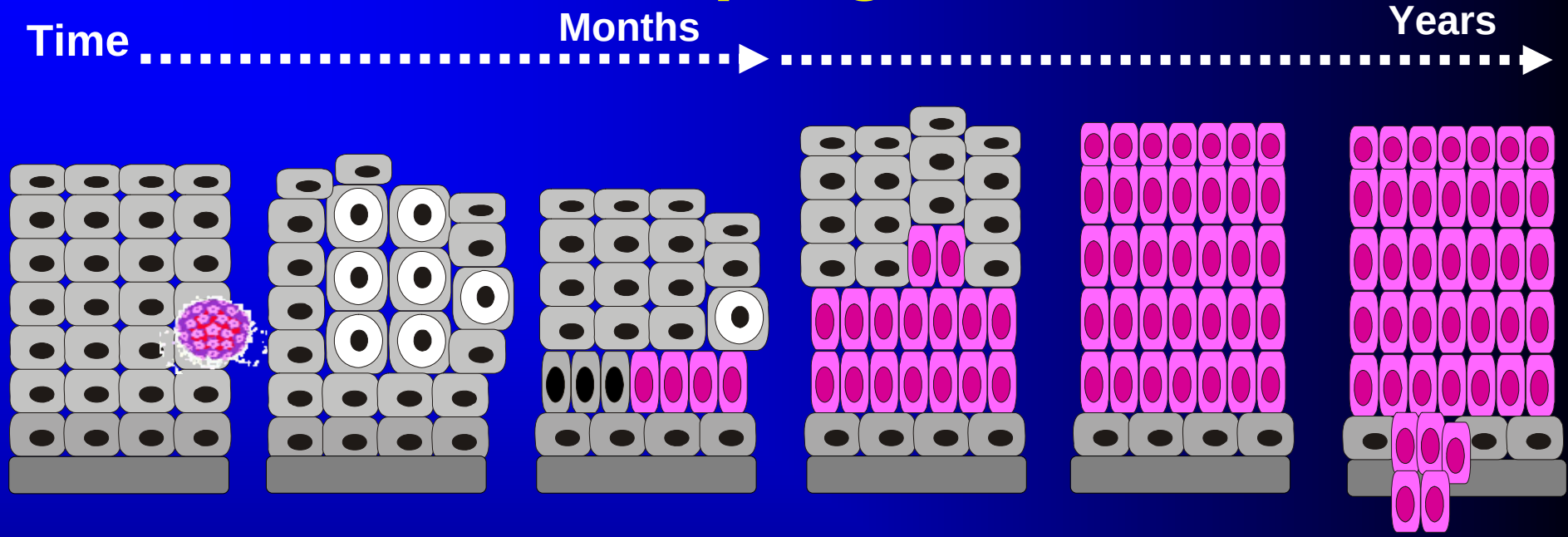
## squamocolumnar junction



# Cytology of the cervix
## transformation zone



# Disease progression




Persistent HPV infection

CIN = Cervical intraepithelial neoplasia

# Protective immunological mechanisms

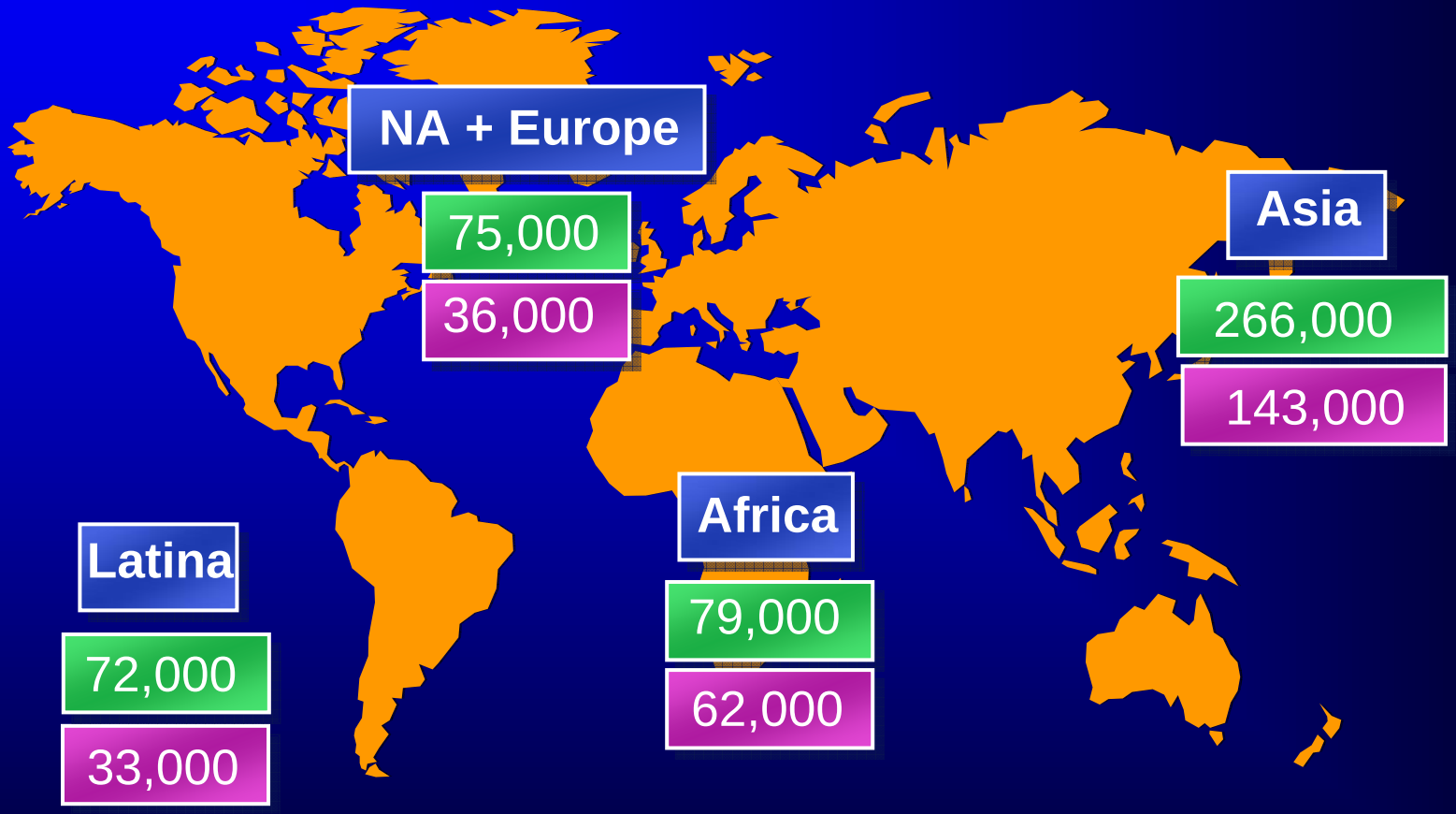
- Natural exposure to viruses usually results in :
  - cell-mediated responses and/or
  - production of specific antibodies
- But : oncogenic HPV types down-regulate production of cytokines essential for immune response[1,2]
- Prior infection with an oncogenic HPV type does not automatically induce immunity against subsequent infection or reduce the risk of a HPV infection becoming persistent[3-5]
  - The level of protection offered by natural exposure is variable
- After natural infection serum Ig  can develop vs VLP1

[1]De Jong A et al. Cancer Research 2004:64:5449–55;
[2]Stanley M. Vaccine 2006;24S1:S1/16–22;
[3]Viscidi RP et al. Cancer Epidemiology, Biomarkers & Prevention 2004; 13: 324–7;
[4]Thomas KK et al. J Infect Dis 2000; 182: 1097-102;
[5]Mayrand M-H et al.J Clin Microb 2000; 38(9): 3388-93.

# Overview

- Cervical cancer : a viral cause
- Epidemiology of Cervical cancer
- Development of HPV vaccine
- Cervical cancer prevention : present and future

# Medical need – epidemiology



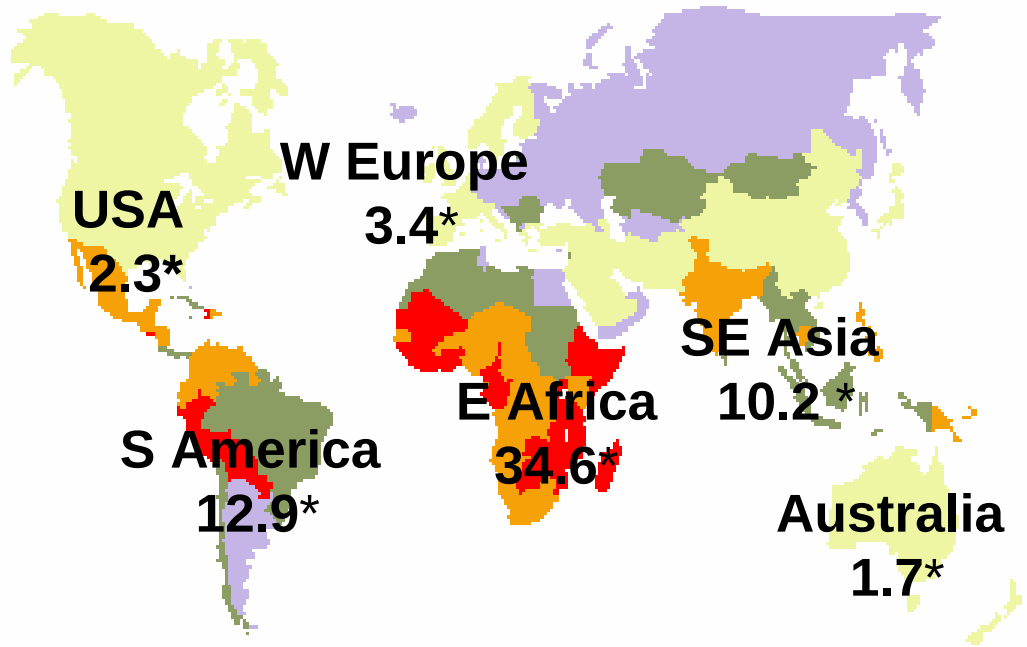

New cases per year: ~ 500,000

Deaths per year: ~ 270,000



Ferlay J et al. Globocan 2002. IARC 2004.

# Region-specific mortality rates

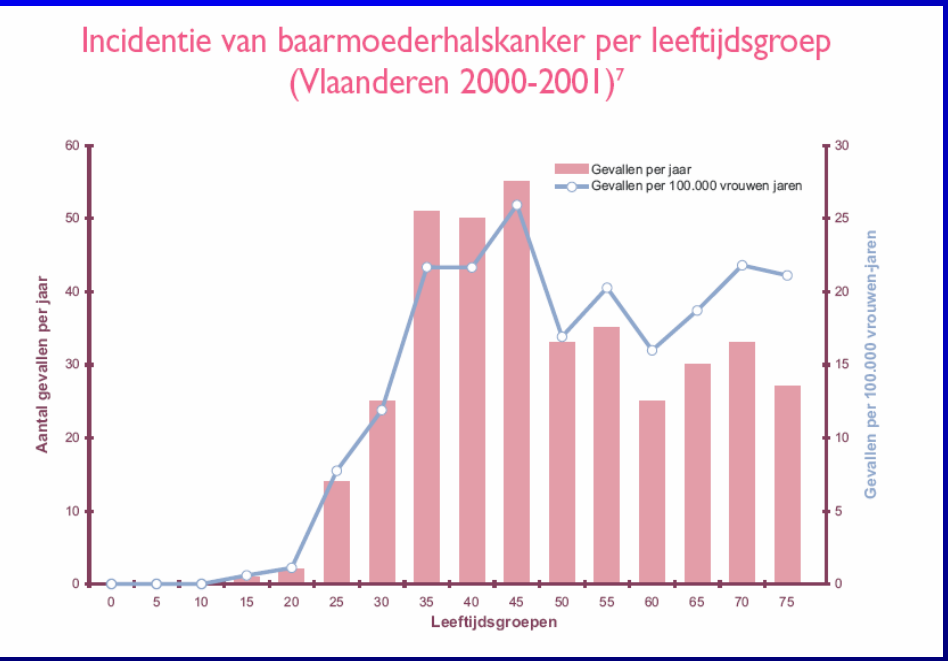


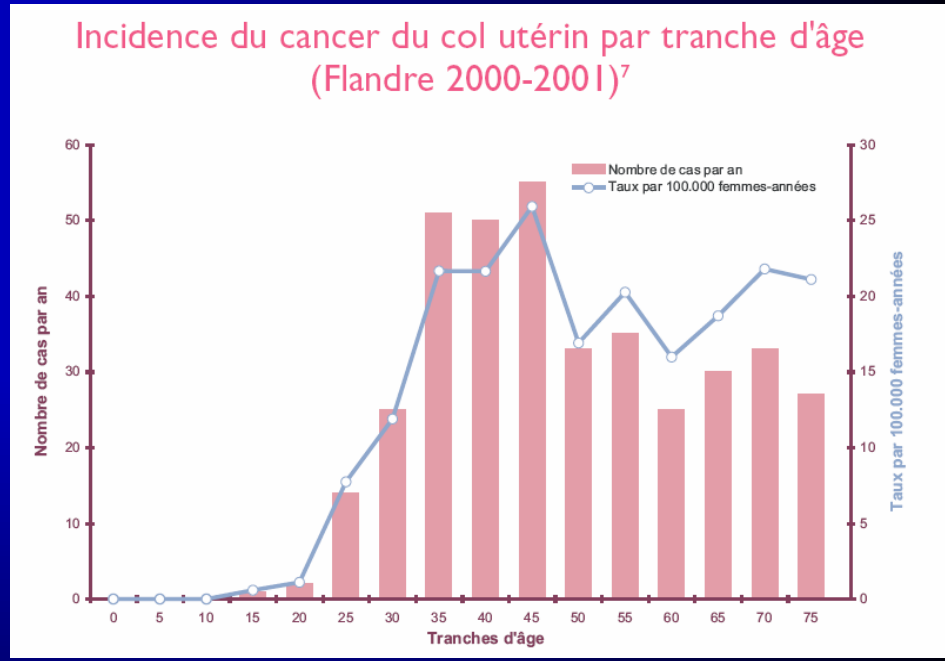

*Rate per 100,000 population (all ages).

Ferlay J et al. Globocan 2002. IARC 2004.

# CC incidence / mortality in Be

## Flanders




## Belgium (data 2002)

- 667 new cases per year
- 326 deaths

Ferlay J et al. Globocan 2002. IARC 2004.

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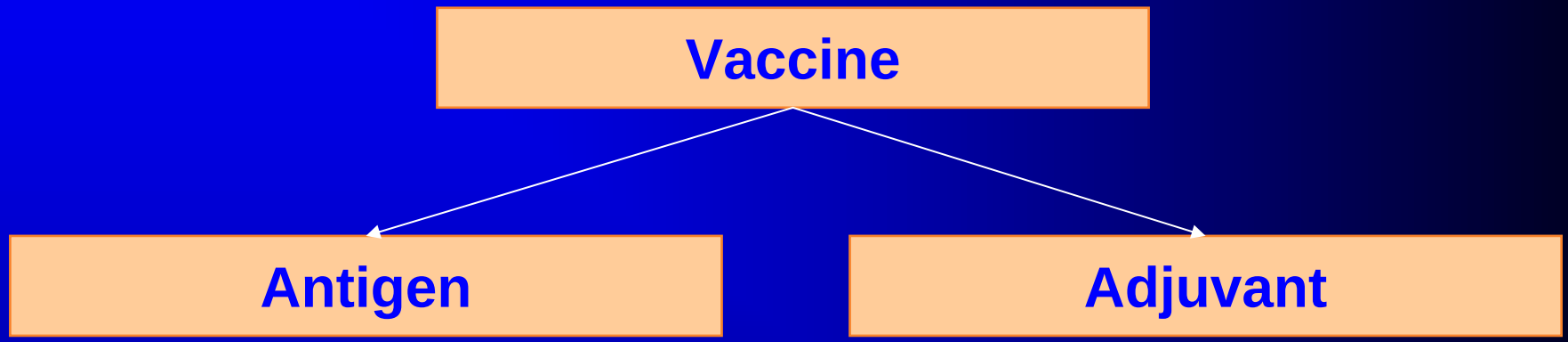
- Cervical cancer prevention : present and future

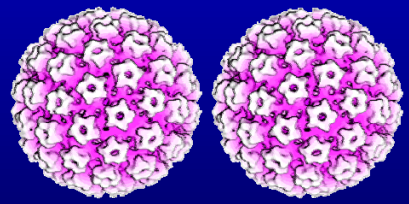
# Composition of most vaccines



# GSK's HPV 16/18 Candidate Vaccine

**GSK's HPV 16/18 Candidate Vaccine**

**Antigen**
**20 µg HPV 16 L1 VLP**
**20 µg HPV 18 L1 VLP**



HPV16-L1 VLP | HPV18-L1 VLP

- Recombinant L1 protein
- Self-assemble into virus-like particles
- Resemble intact viruses
- Non-infectious

**Adjuvant System 04 (AS04)**

**Immunostimulant**
**50 µg MPL**

**Monophosphoryl Lipid A**

**and**

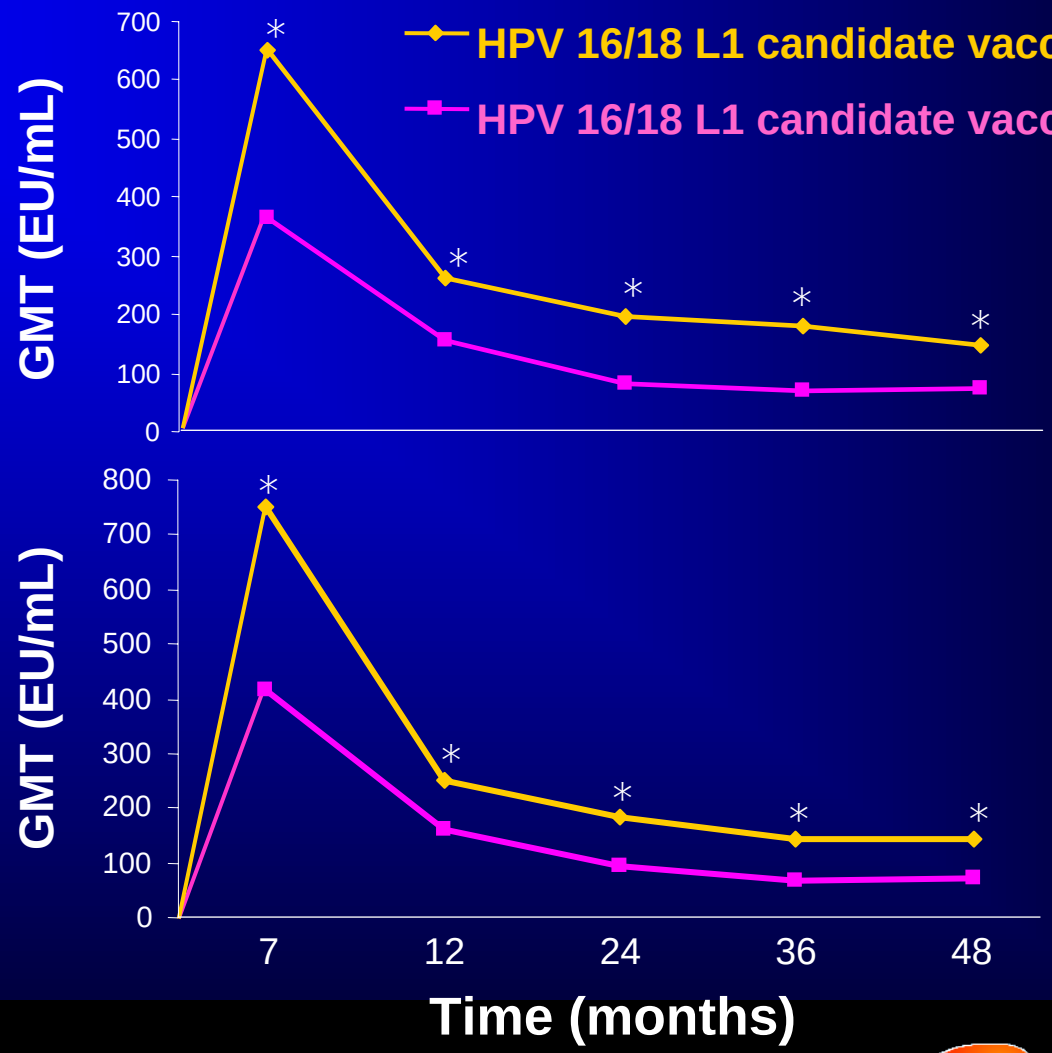
**Carrier**
**500 µg Al(OH)3**

# AS04 : a new adjuvant ?

- Included in Fendrix® : licensed
  - Hep B vaccine for renal dialysis patients

- In total : +/- 28 000 subjects received +/- 43 000 doses ASO4 containing vaccines up till now

# AS04 induces high and persistent neutralising antibody levels




**3 doses of vaccine administered at 0, 1 and 6 months**

**Statistically significant ($p<0.05$)**



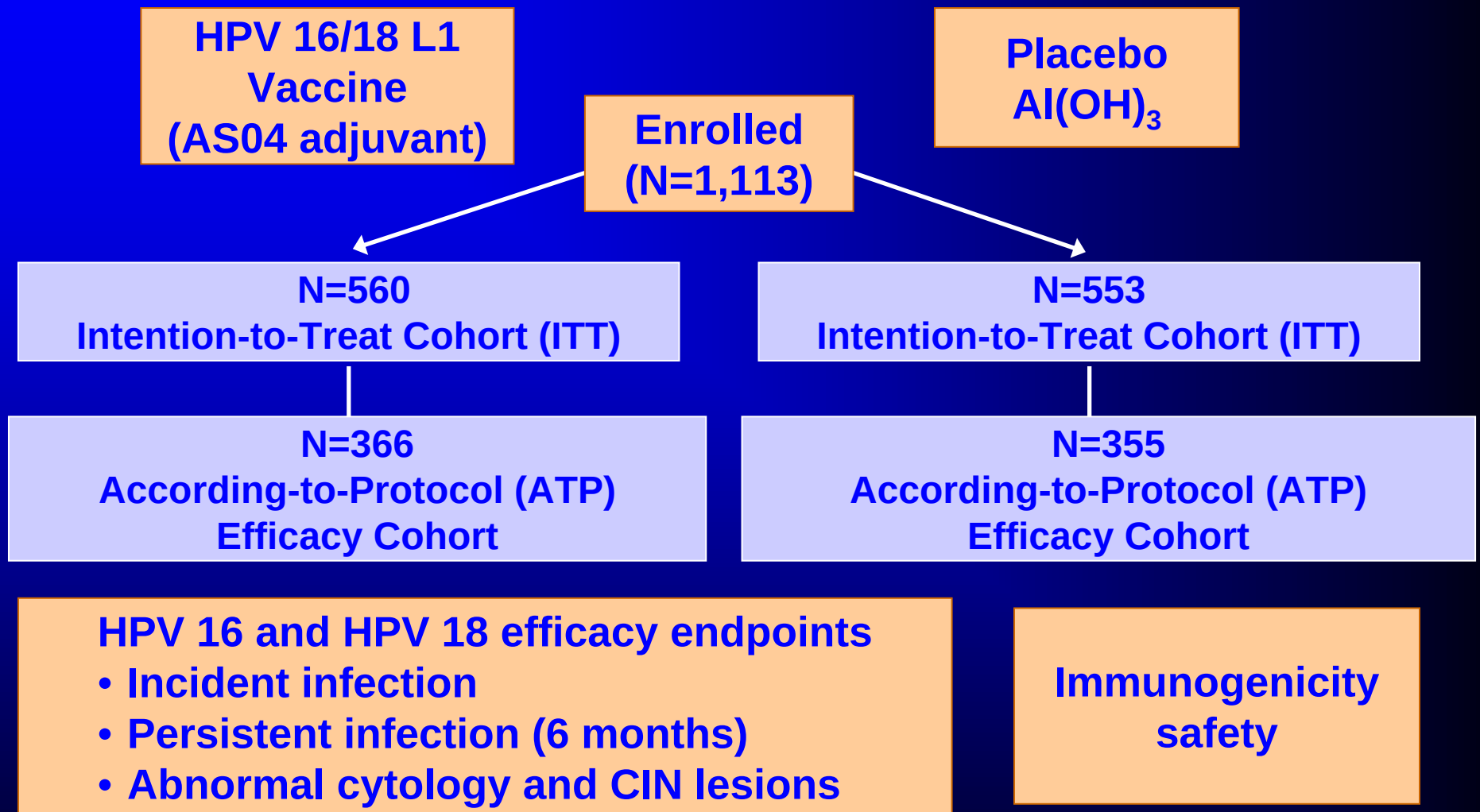
Giannini SL et al. Vaccine 2006; 24: 5937-49.

# HPV 001 initial HPV efficacy study

- Double-blind, randomised, controlled trial
- Brazil, Canada and USA
- Women 15–25 years of age with ≤6 lifetime partners
  - Seronegative for HPV 16/18
  - DNA negative for high-risk types
- Vaccination schedule: 0, 1 and 6 months
- Follow-up: 18 months (extension phase up to 27 months)

Harper DM et al. *Lancet* 2004;364:1757–65.

# HPV 001 study design




Harper DM et al. *Lancet* 2004;364:1757–65.

# GSK studies HPV 001 and HPV 007: Sustained protection up to 4.5 years

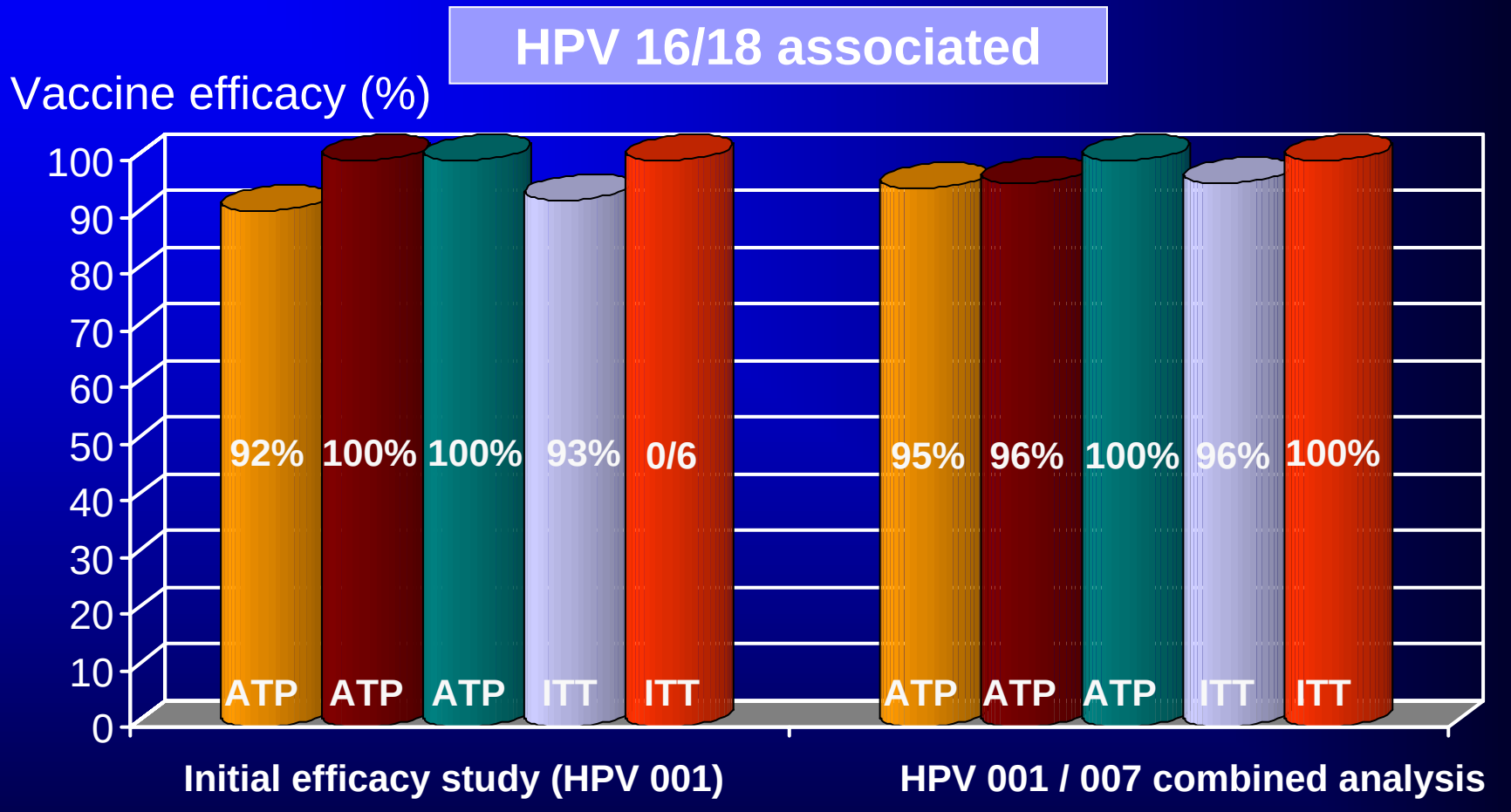





Figure based on Harper DM et al. Lancet 2004; 364:1757–65.

Harper DM et al. Lancet 2006;367:1247–55.

# GSK studies 001 & 007 up to 4.5 years: First evidence of cross protection vs types 45 & 31

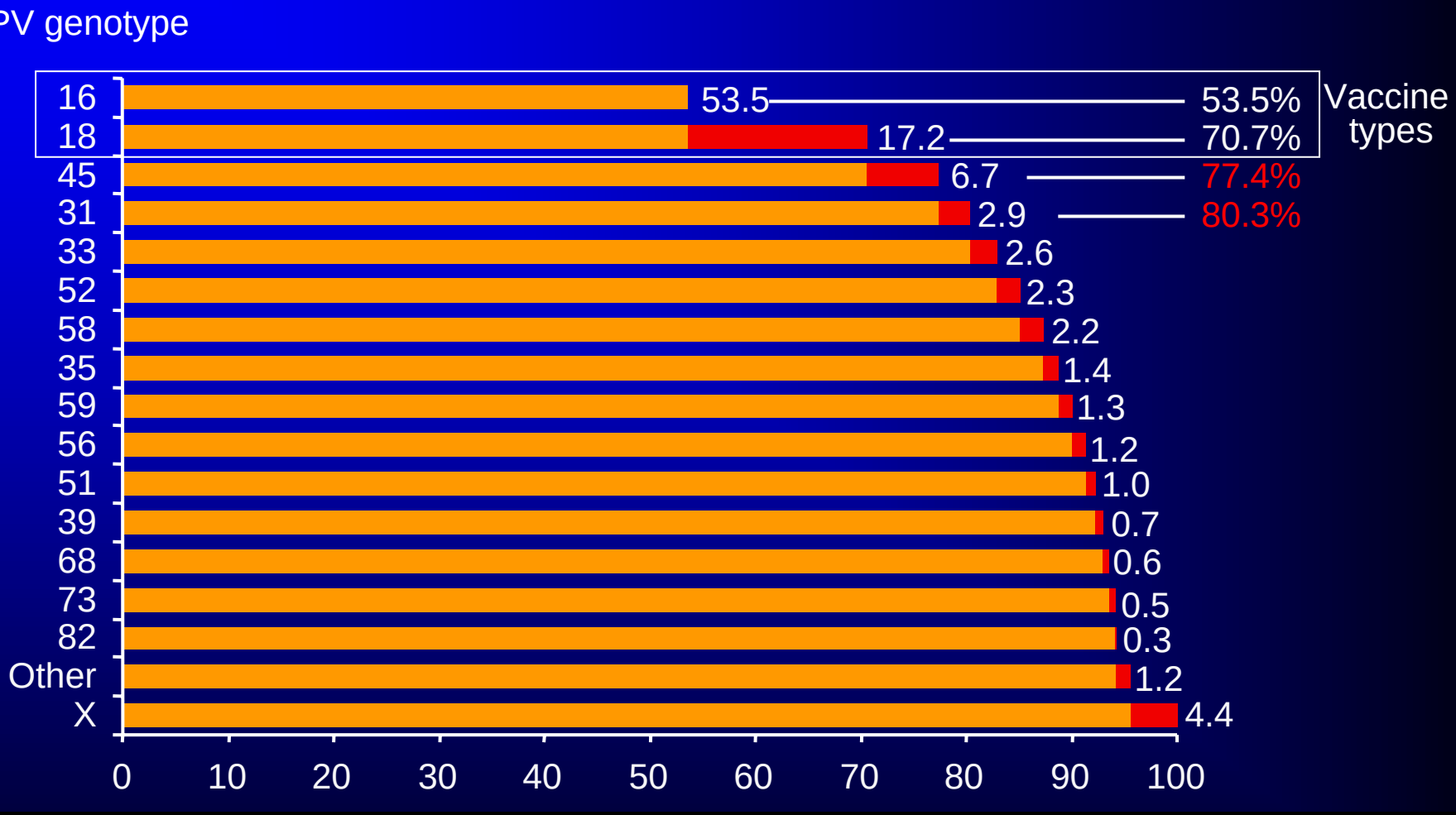
Incident infection with most common oncogenic types beyond 16 & 18

| HPV Type | Vaccine | | | Placebo | | | Vaccine Efficacy (%) (95% CI) |
|---|---|---|---|---|---|---|---|
| | | | Event rate (rate per 100) (95% CI) | | | Event rate (rate per 100) (95% CI) | |
| | N | n | Rate | N | n | Rate | |
| HPV-45 | 528 | 1 | 0.1 (0.0-0.4) | 518 | 17 | 1.2 (0.7-1.9) | 94.2 (63.3-99.9) |
| HPV-31 | 528 | 14 | 0.9 (0.5-1.6) | 516 | 30 | 2.1 (1.4-3.0) | 54.5 (11.5-77.7) |
| HPV-33 | 529 | 12 | 0.8 (0.4-1.4) | 519 | 13 | 0.9 (0.5-1.5) | 8.6 (-117.3-61.9) |
| HPV-52 | 524 | 40 | 2.8 (2.0-3.8) | 515 | 48 | 3.5 (2.6-4.6) | 18.6 (-26.5-47.8) |
| HPV-58 | 529 | 14 | 0.9 (0.5-1.6) | 517 | 16 | 1.1 (0.6-1.8) | 14.0 (-87.9-61.1) |

**Study not powered to evaluate cross protection against all individual types**

Harper *et al.* Lancet 2006; 367: 1247-55
Combined initial efficacy and extended follow up studies

# HPV types in cervical cancer




Muñoz N et al. Int J Cancer 2004; 111: 278–85

# GSK study HPV-007: Safety profile during extended follow up

| | Vaccine N (%) | Placebo N (%) |
|---|---|---|
| Adverse events | | |
| Women with at least 1 adverse event reported | 54 (15.4%) | 81 (23.5%) |
| Adverse events reported | 65 | 98 |
| New Onset Chronic Disease (NOCD)* | | |
| Women with at least 1 NOCD event reported | 10 (2.9%) | 18 (5.2%) |
| NOCD events reported | 10 | 19 |
| Serious adverse events | | |
| Women with at least 1 SAE reported | 16 (4.6%) | 19 (5.5%) |
| SAEs reported | 21 | 19 |

Harper et al. Lancet 2006; 367: 1247-55
ATP Safety analysis

*Including auto immune diseases

# Vaccination of older women ?

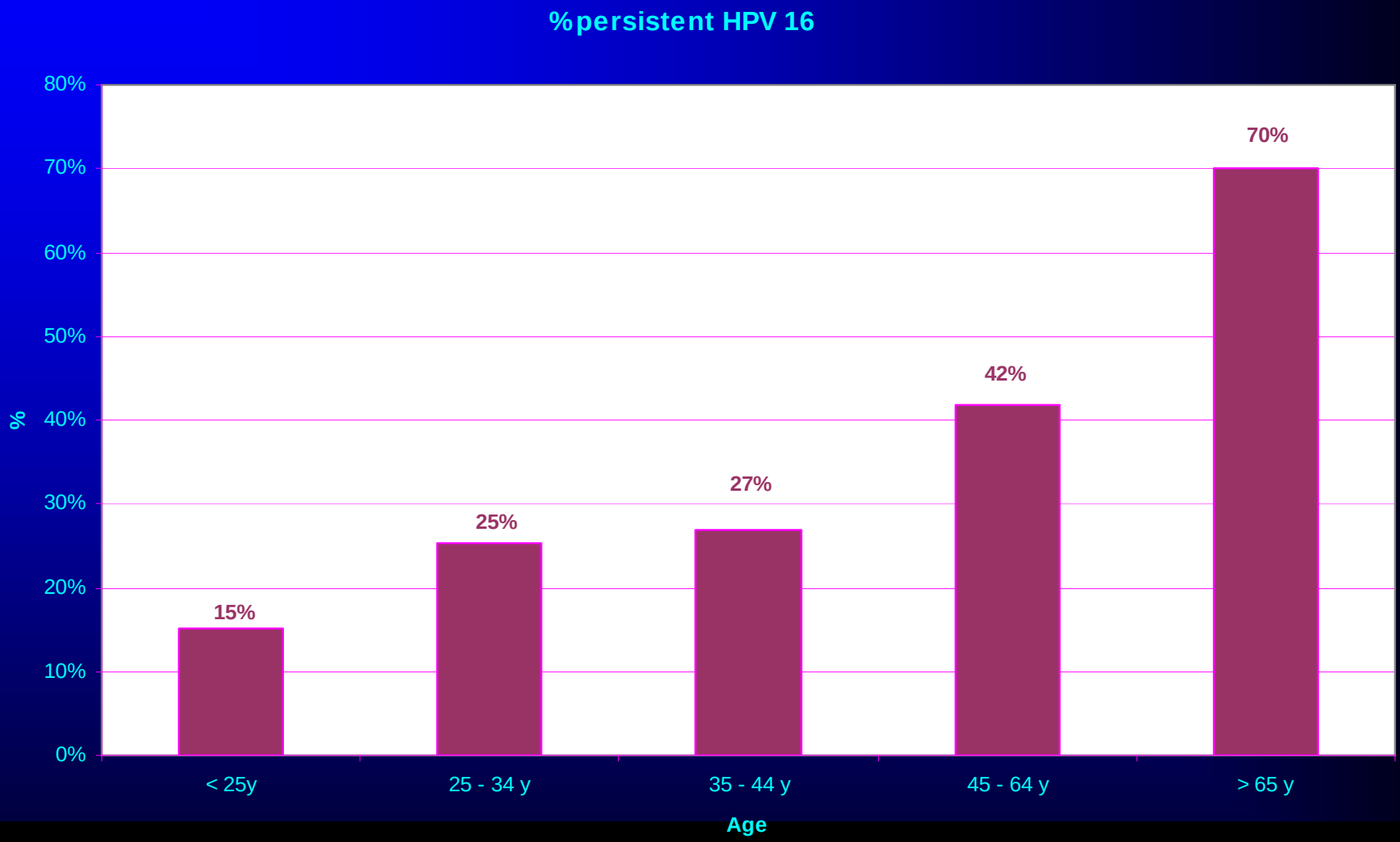
# HPV acquisition and clearance rates over 3 years

| Age (baseline) | Women initially HPV- | | Women initially HPV+ | | Acquisition rate (%) | Clearance rate (%) |
|---|---|---|---|---|---|---|
| | HPV- | HPV+ | HPV- | HPV+ | | |
| 21 | 56 | 10 | 17 | 3 | 15.2 (8.4–25.7) | 85.0 (64.0–94.8) |
| 31 | 73 | 12 | 10 | 3 | 14.1 (8.3–23.1) | 76.9 (49.7–91.8) |
| 41 | 72 | 11 | 14 | 3 | 13.3 (7.6–22.0) | 82.4 (59.0–85.4) |
| 51 | 262 | 71 | 29 | 10 | 21.3 (17.3–26.0) | 74.4 (58.9–85.4) |
| Total | 463 | 104 | 70 | 19 | 18.3 (15.4–21.7) | 78.7 (69.0–85.9) |



Grainge MJ et al. Emerg Infect Dis 2005;11:1680–5.

# Risk of persistant infection by age




Adapted from Castle P et al, JID 2005;191: 1808 -16

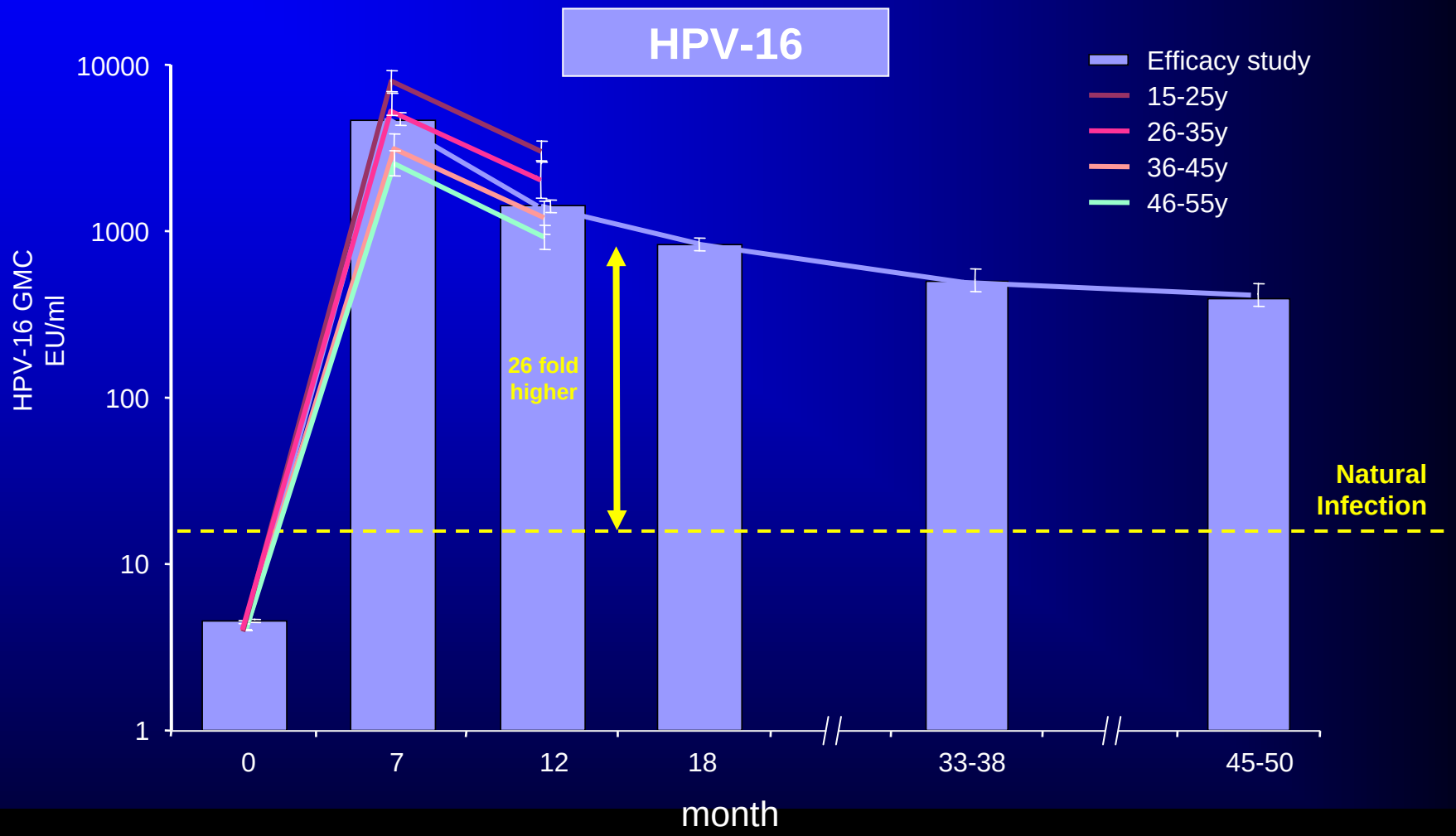
# GSK study HPV-014: Immunogenicity in Women 15-55 years of age

- Open, age-stratified trial in Germany and Poland (N=666)
- Study objectives
  - **Primary objective:** To demonstrate non-inferiority of seroconversion rates to the HPV-16/18 vaccine
    - **26-45** (26-35 and 36-45) **years** (N=220) compared to **15-25 years** (N=220)
  - **Secondary objective:** To demonstrate non-inferiority of seroconversion rates to the HPV-16/18 vaccine
    - **46-55 years** (N=220) compared to **15-25 years**
- 3 doses of HPV-16/18 vaccine at months 0, 1 and 6
- Study will continue up to 48 months; results presented are up to 12 months



Schwarz et al. ASCO 2006 : Abstract 1008

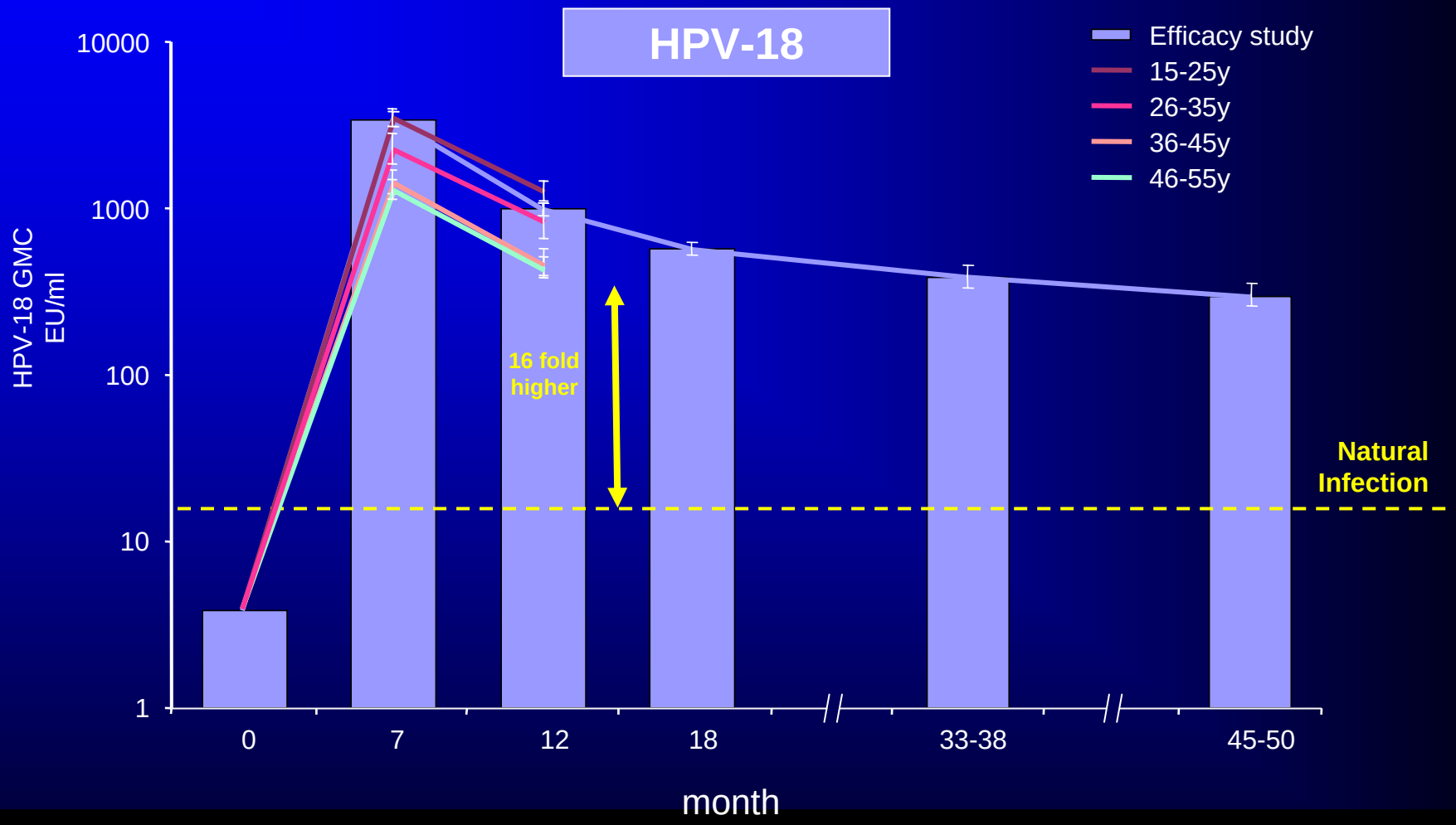
# HPV-16 antibody levels observed in efficacy study




Harper et al. Lancet 2006; 367: 1247-55

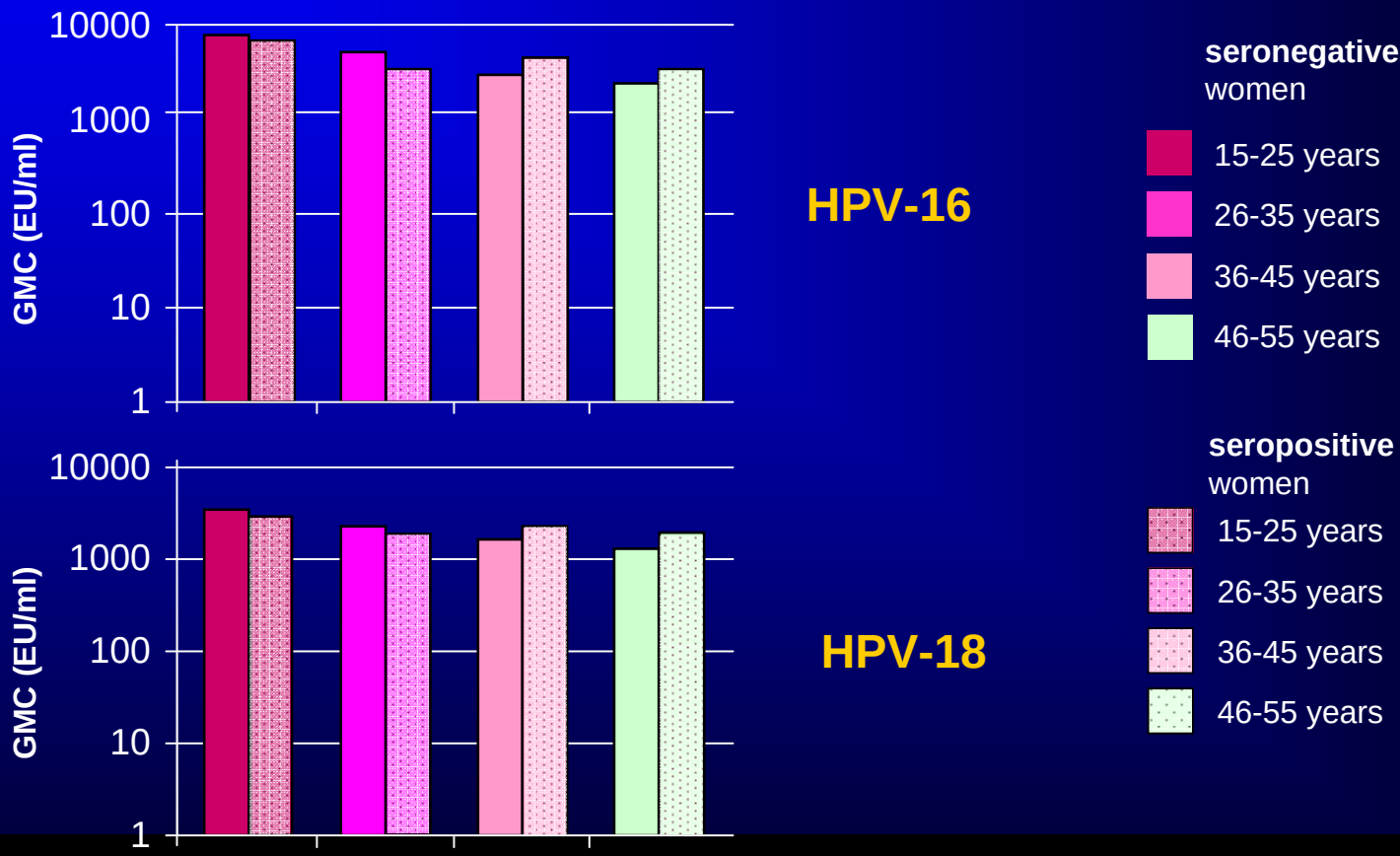
Schwarz et al. ASCO 2006 : Abstract 1008

# Antibody levels in all ages comparable to those observed in efficacy study



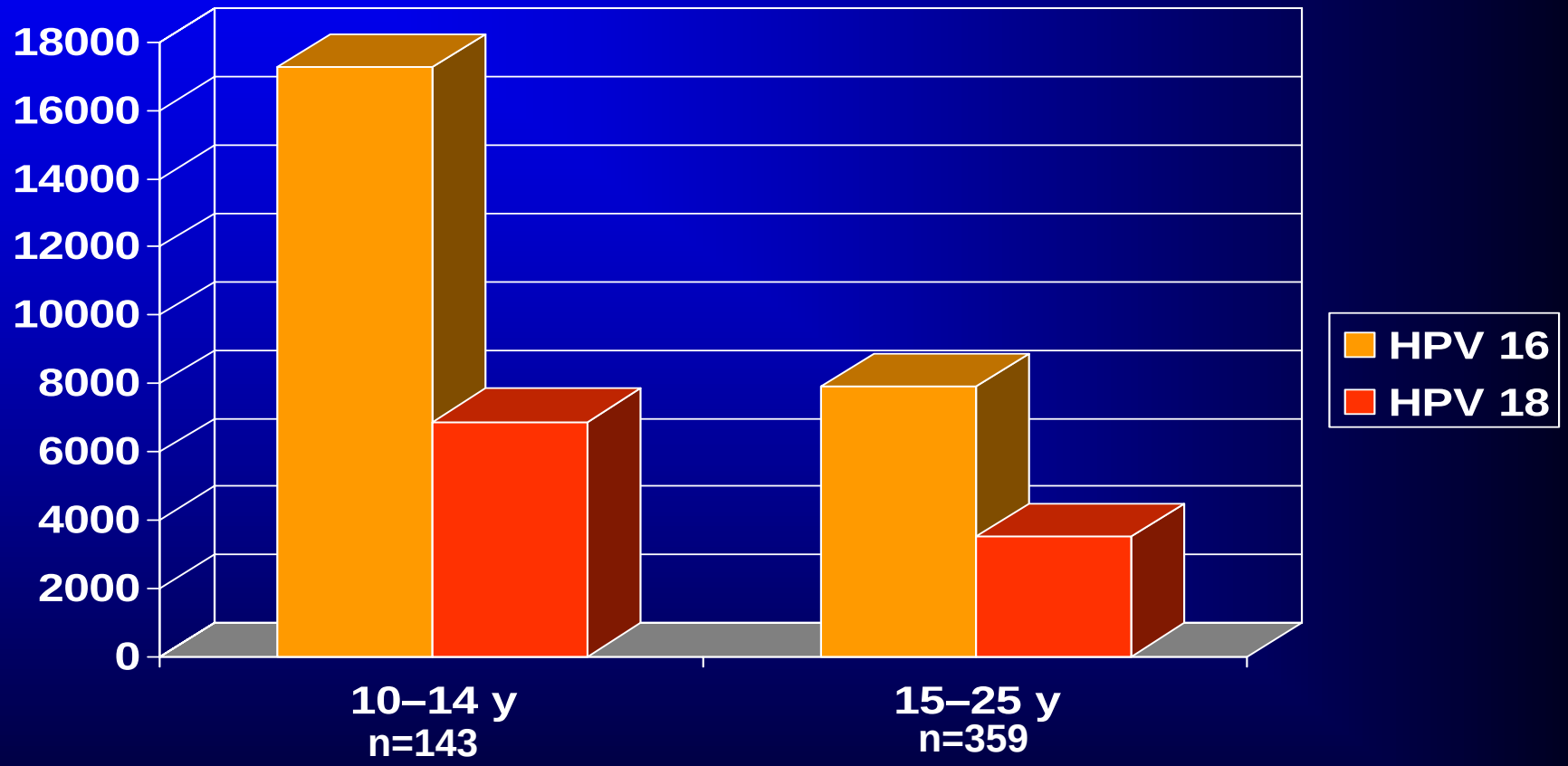

Schwarz et al. ASCO 2006 : Abstract 1008
Harper et al. Lancet 2006; 367: 1247-55

# GSK study HPV-014: Antibody concentrations in initially seronegative and seropositive women




Schwarz et al. ASCO 2006 : Abstract 1008

# Immuno-bridging study in adolescents 10-14y vs 15-25y of age (HPV 012)




Dubin G et al. ICAAC 2005.

# Overview

- Cervical cancer : a viral cause
- Epidemiology of Cervical cancer
- Development of HPV vaccine
- Cervical cancer prevention : present and future

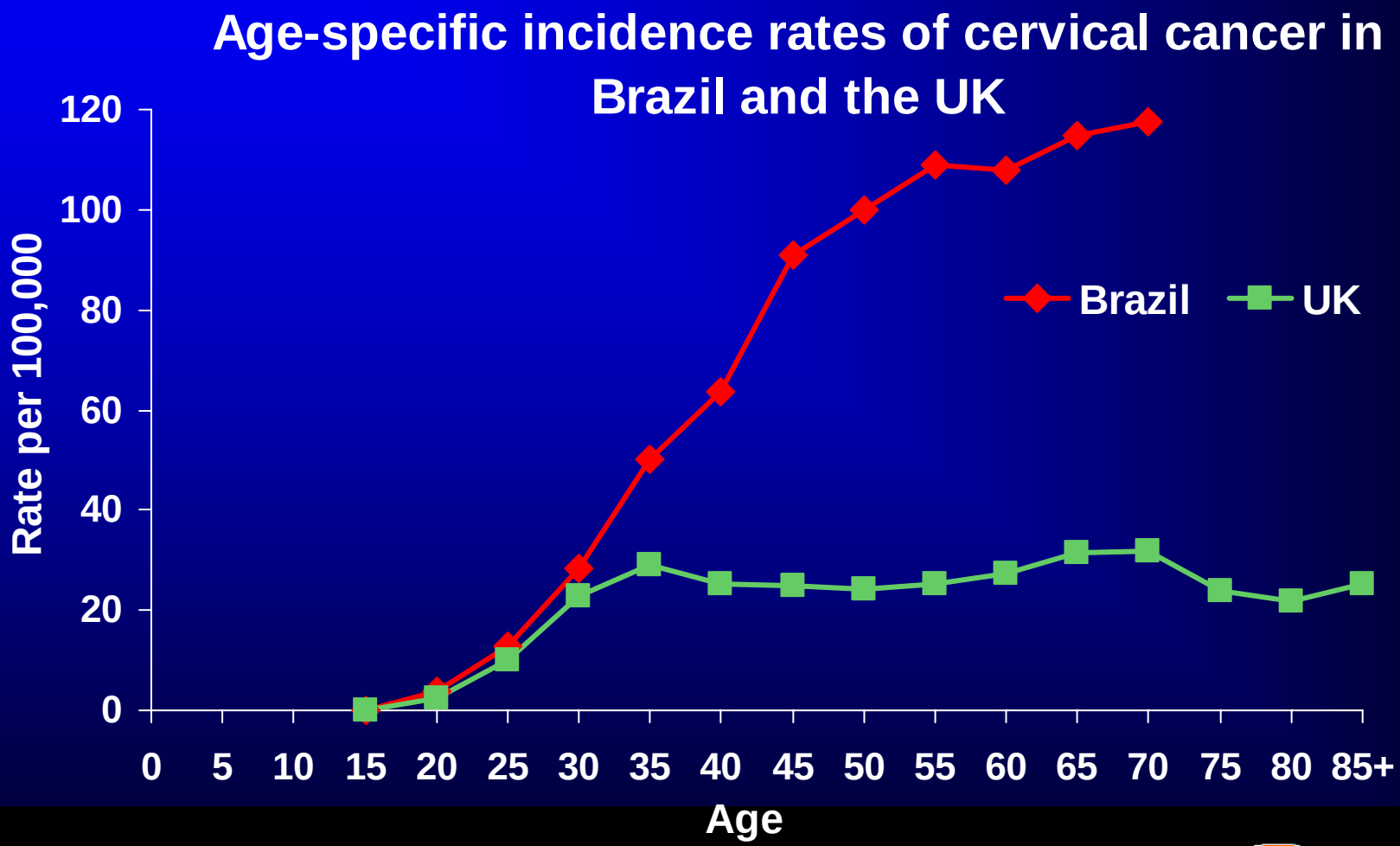
# Actual CC-screening

- Recommendations in terms of frequency and follow-up differ from country to country

- Be :
  - Start : 25 Y
  - Every 3 Y
  - Until : 60 Y if no new sex partner and nl test at 60

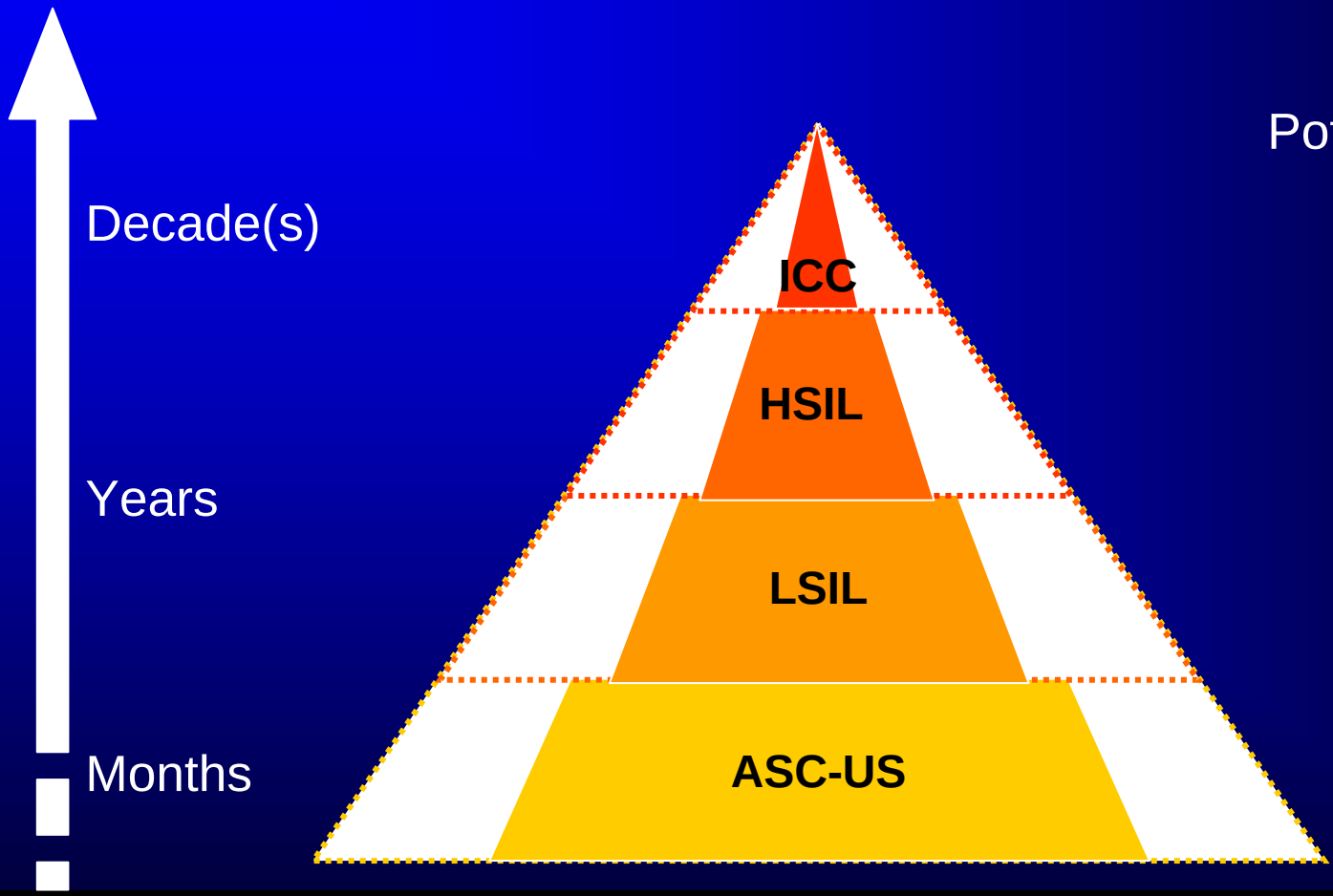
- Standard
  - Cytology is the standard for screening :
    - Classic cytology
    - Liquid based
  - HPV-testing used in case of abnormal cytology for further triage

# Impact of screening on CC :
## Age-specific incidence : Brazil vs UK




Ferlay J et al. Globocan 2002. IARC 2004.

# Potential impact of the HPV 16/18 candidate vaccine




**ASC-US: Atypical squamous cells of undetermined significance;**
**L/HSIL: Low/high grade squamous intraepithelial lesion; ICC: Invasive cervical cancer**

GlaxoSmithKline

# Future CC prevention strategies

**ACIP recommendation (www.CDC.gov. : 29-6-2006)**

- Vaccinate girls 11-12 Y
- Catch-up vaccination for 13-26 Y recommended
- Screening remains the same

**Considerations**

- Vaccination of older women :
  - HPV – acquisition rate remains high in older women
- CC Screening algorhythm :
  - frequency
  - HPV-test or cytology as screening tool

# Thank You !