Séminaire de pathologie infectieuse
Namur, CHU, 27 septembre 2007

Nouveautés vaccinales

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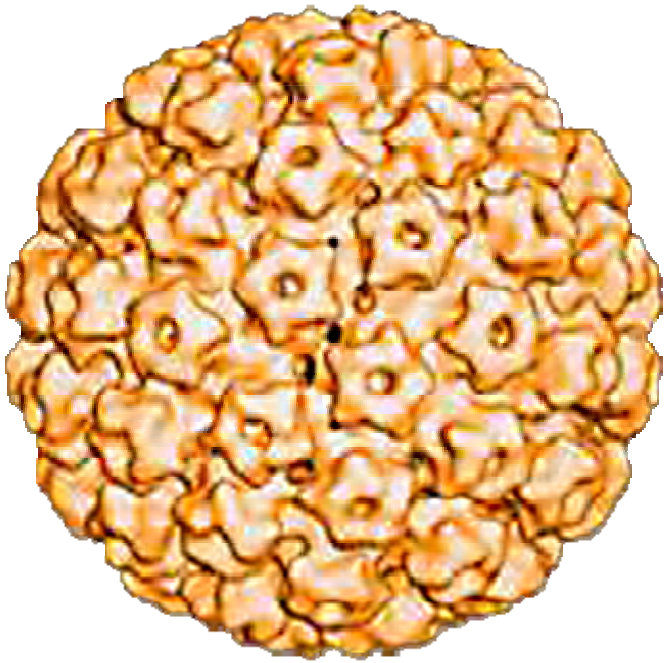
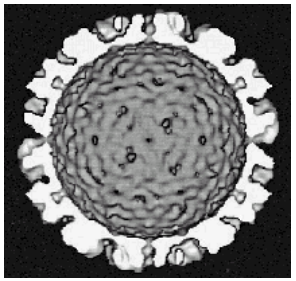
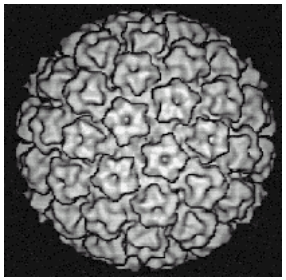
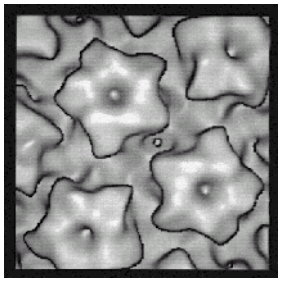
Human Papillomaviruses



- Circular double stranded DNA viruses
  - ➔ 7000 - 8000 base pairs
  - ➔ Non-enveloped capsid consisting of 72 pentavalent capsomeres
- Up to 200 different genotypes
- Classified according to:
  - ➔ Tropism: *Cutaneous or Mucosal*
    - ➔ ≈30–40 genotypes infect anogenital mucosa
  - ➔ Risk of neoplasia: *Low risk or High risk*
    - ➔ ≈20 genotypes cause cervical cancer







Syrjänen and Syrjänen. Papillomavirus infections in human pathology in Wiley & Sons, Chichester; 2000. p.11–46.

Clearly defined pathogenic HPV types and related diseases

Classification	Examples Types	Associated disease
Cutaneous		
Low Risk	1, 2, 3, 10, 27	Plantar and cutaneous warts
High Risk	5, 8	Epidermodysplasia verruciformis
Mucosal		
Low Risk	6, 11, 42, 43, 44, 55 (common types)	Condyloma acuminata Recurrent Respiratory (Laryngeal) Papillomatosis (JORRP) 6-11 = 90% of genital warts[2] Cervical lesions CIN 1 (4 to 25%)[3-5]
High Risk	16, 18, 31, 33, 45, 35, 39, 51, 52, 55, 56, 59, 66	Flat warts, Bowen's disease Cervical dysplasia and carcinoma 16-18 = 70% of cervical cancer[6] Carcinoma of penis, vulva, vagina, anus

1. Wieland et al. Papillomaviruses in human pathology: Epidemiology, pathogenesis and oncogenic role. In: Gross, Barasso Eds. Human papillomavirus infection: A clinical atlas. Ullstein-Mosby; 1997. p.1–18. 2. Von Krogh. *Eur J Dermatol.* 2001; 11:598–603 3. Clifford GM abstract 237 21st International Papillomavirus Conference 2004; 4. Feoli-Fonseca et al. *J Med Virol.* 2001;63:284–292; 5. Koutsky L *The American Journal of Medicine*;102,3-8, 1997; 6.Muñoz N. *N Engl J Med* (348) 2003: 518-27.

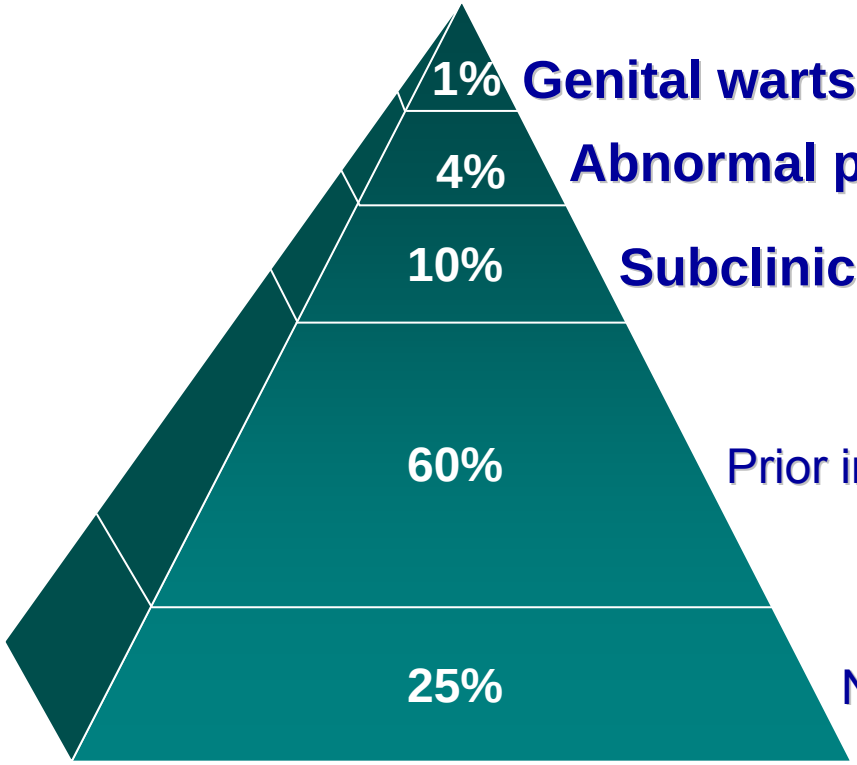
Mechanisms of HPV transmission and acquisition

- Sexual contact
  - Through sexual intercourse[1]
  - Genital–genital, manual–genital, oral–genital[2-4]
  - Genital HPV infection in virgins is rare, but may result from nonpenetrative sexual contact[2]
  - Condom use may help reduce the risk, but it is not fully protective[2]
- Nonsexual routes
  - Mother to newborn (vertical transmission; rare)[5]
  - Fomites (eg, undergarments, surgical gloves, biopsy forceps)[6,7]
    - Hypothesized but not well documented
- Very variable progression
  - Not possible to determine who will develop disease
  - 70 % of sexually active women will get a Papillomavirus infection during their lifetime*
  - May take many years to appear
  - Number of co-factors, identified and non-identified
  - Cervical Cancer: rare and late complication of HPV infection

1. Kjaer SK, Chackerian B, van den Brule AJC, et al. *Cancer Epidemiol Biomarkers Prev*. 2001;10:101–106. 2. Winer RL, Lee S-K, Hughes JP, Adam DE, Kiviat NB, Koutsky LA. *Am J Epidemiol*. 2003;157:218–226. 3. Fairley CK, Gay NJ, Forbes A, Abramson M, Garland SM. *Epidemiol Infect*. 1995;115:169–176. 4. Herrero R, Castellsague X, Pawlita M, et al. *J Natl Cancer Inst*. 2003;95:1772–1783. 5. Smith EM, Ritchie JM, Yankowitz J, et al. *Sex Transm Dis*. 2004;31:57–62. 6. Ferenczy A, Bergeron C, Richart RM. *Obstet Gynecol*. 1989;74:950–954. 7. Roden RBS, Lowy DR, Schiller JT. *J Infect Dis*. 1997;176:1076–1079. *Koutsky. *Am J Med* 1997;102:3–8.

70% of people will get a HPV infection during lifetime[1]

Estimated prevalence of genital PapillomaVirus infection in a US population of men and women aged 15-49 years[2,3]



Genital warts

Abnormal pap or colposcopy

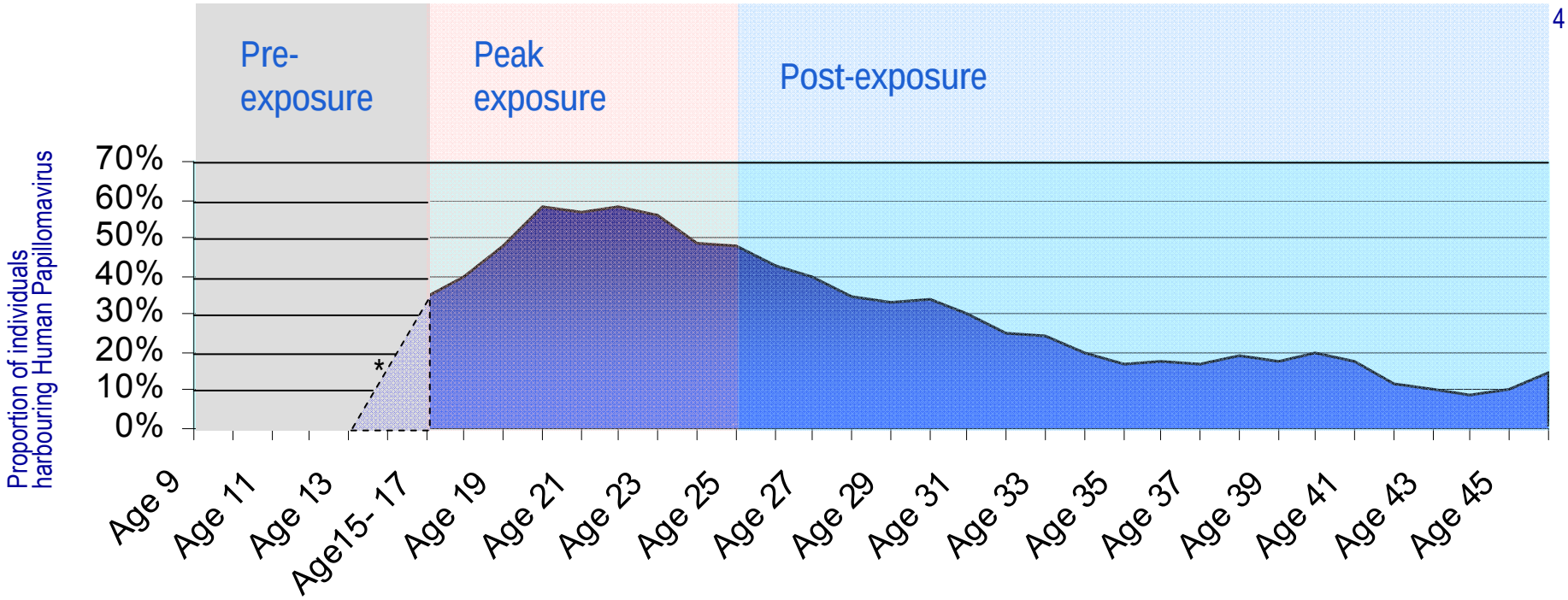
Subclinical infection, detected by DNA test

Prior infection, evidenced by antibodies

No prior/current infection

1. Bosch F.X. Natl Cancer Inst Monogr 2003 31: 3-13
2. Koutsky. *Am J Med* 1997;102:3–8.
3. Koutsky, et al. Epidemiol Review, 1988,10:122-163.

Highly prevalent HPV encountered in adolescence - early adulthood[1,2,3]

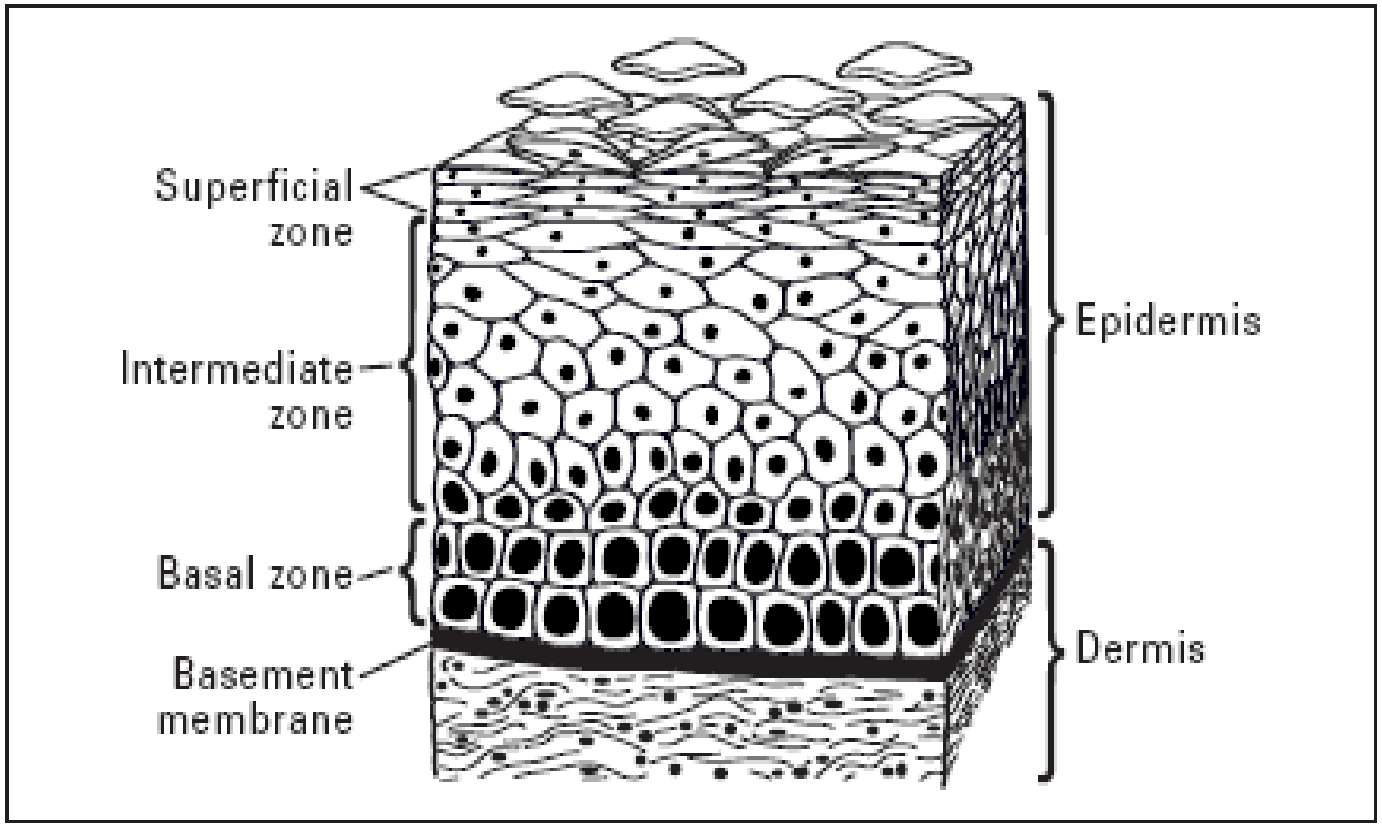


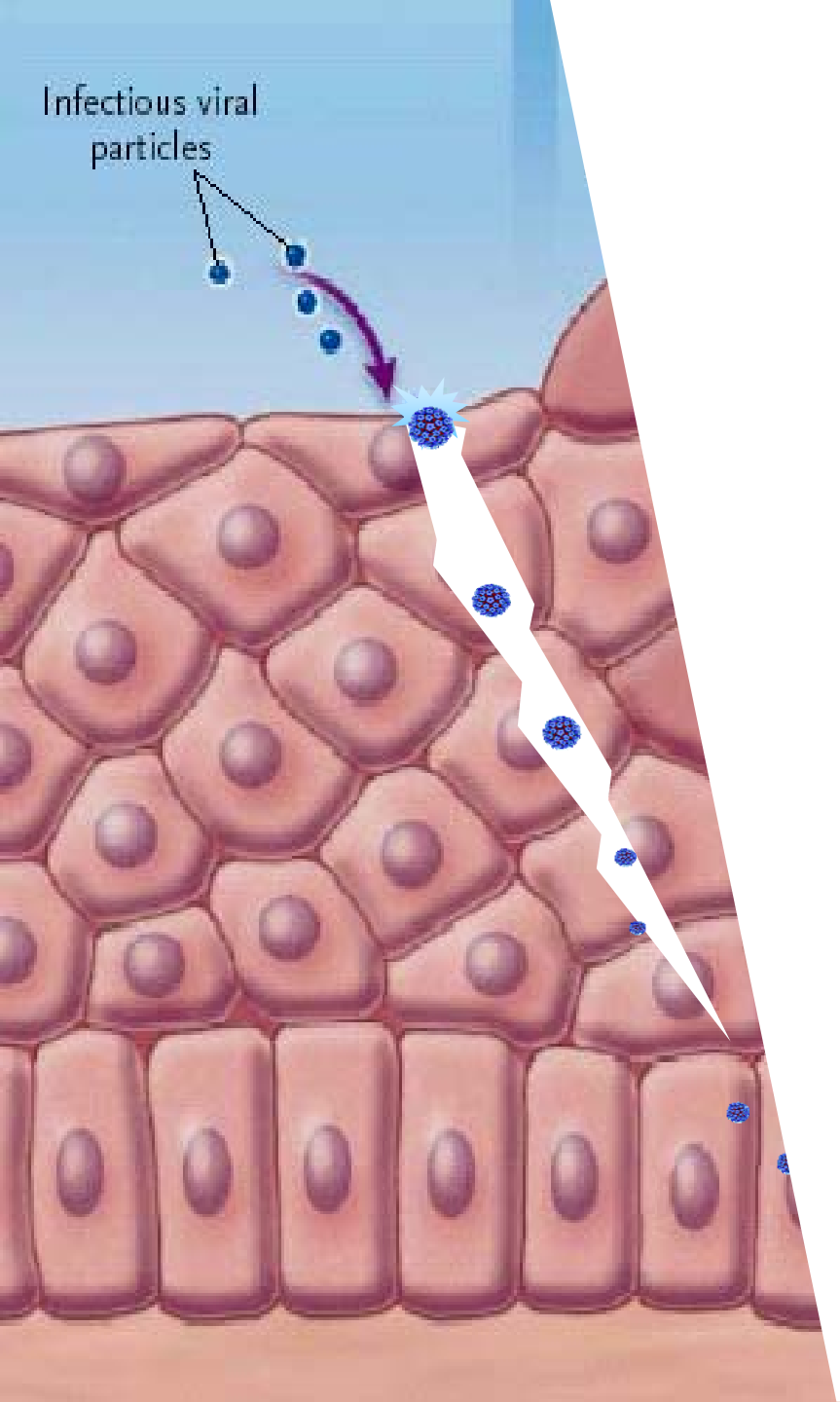
- An estimated 70% of sexually active people will be exposed to the virus at some point during their life[1,2,3]

[1] Koutsky LA. Am J Med 1997
[2] Koutsky LA et al. Epidemiology Rev 1988
[3] Syrjänen K et al. Sex Transm Dis 1990
[4] n=11,851 cervical smears of Danish women (15-93 yrs), Sanofi Pasteur MSD, data on file

HPV and cervical mucosa – Normal Epithelium

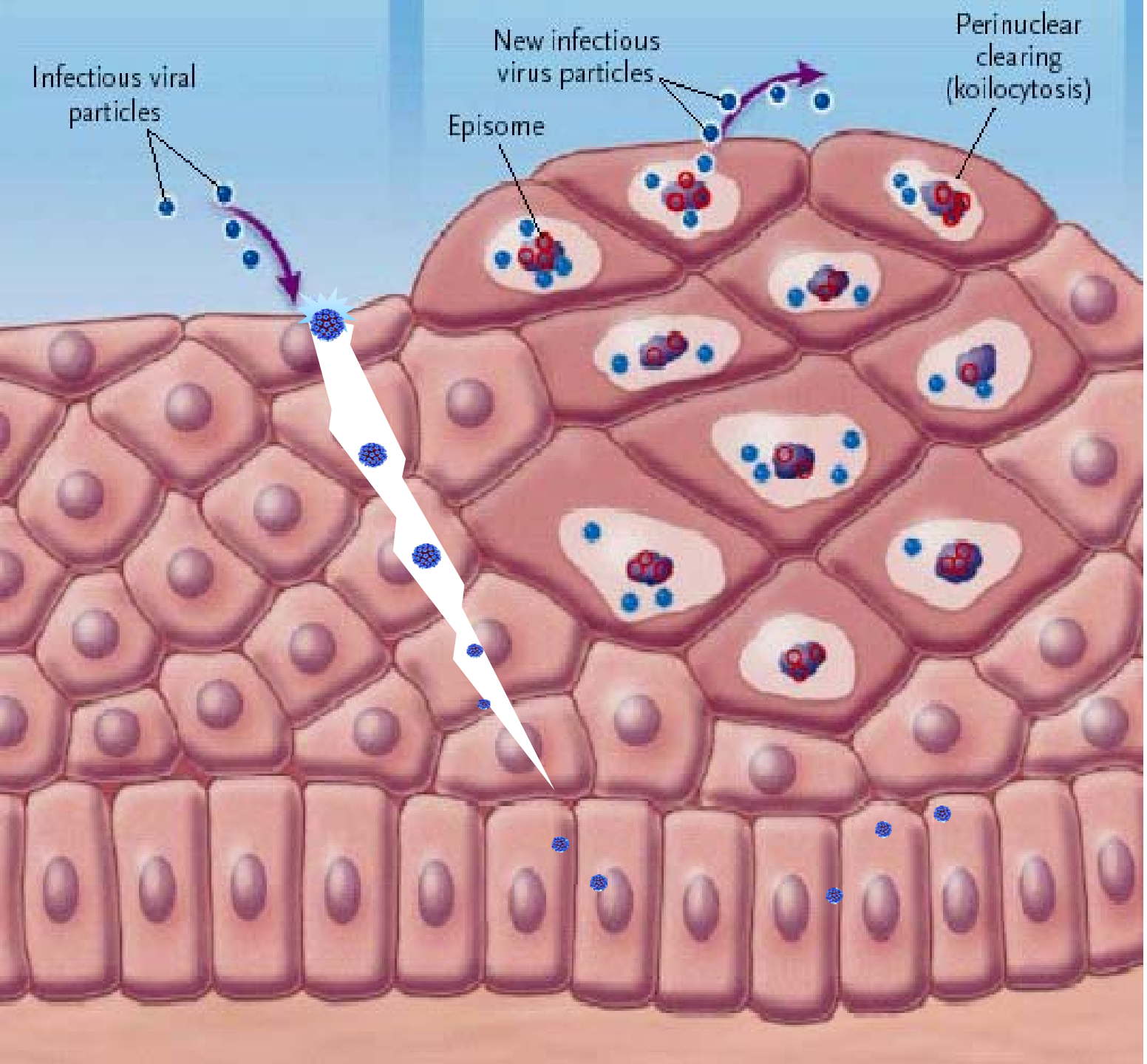
Schematic Representation of Normal Stratified Squamous Epithelium





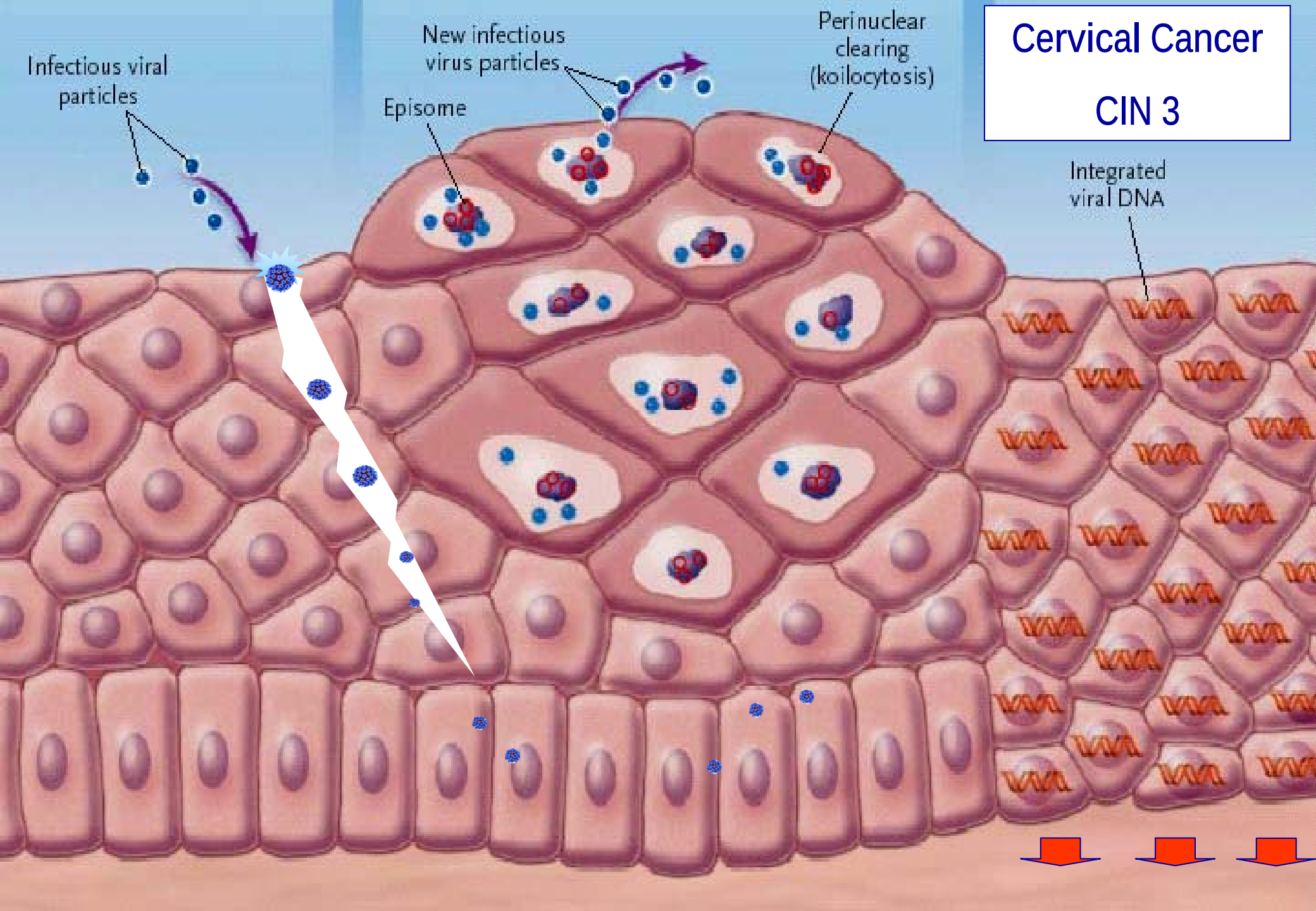
Normal Cervix

HPV enters through a break in the epithelium

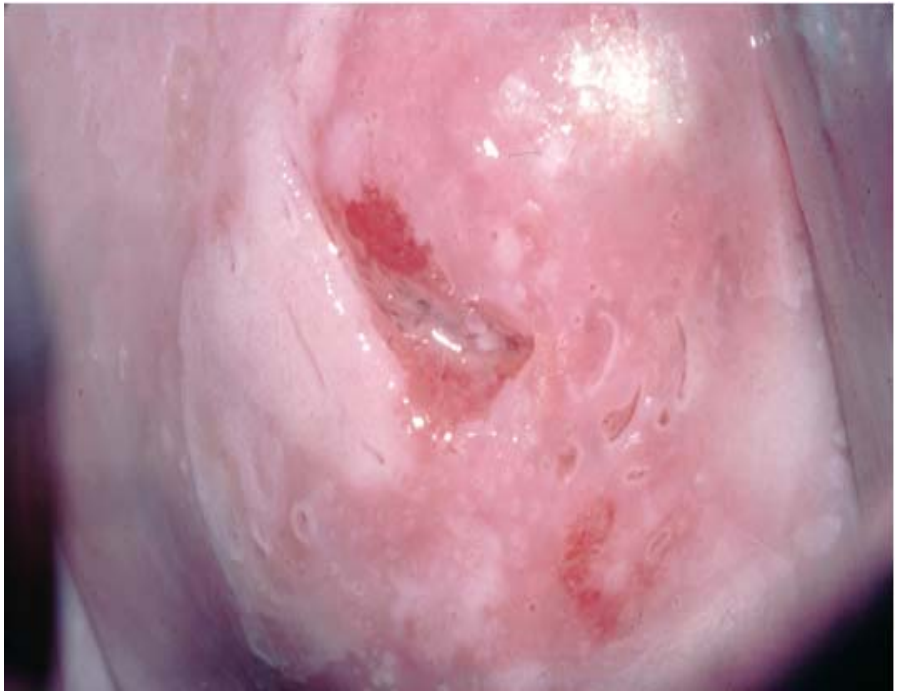


HPV infection

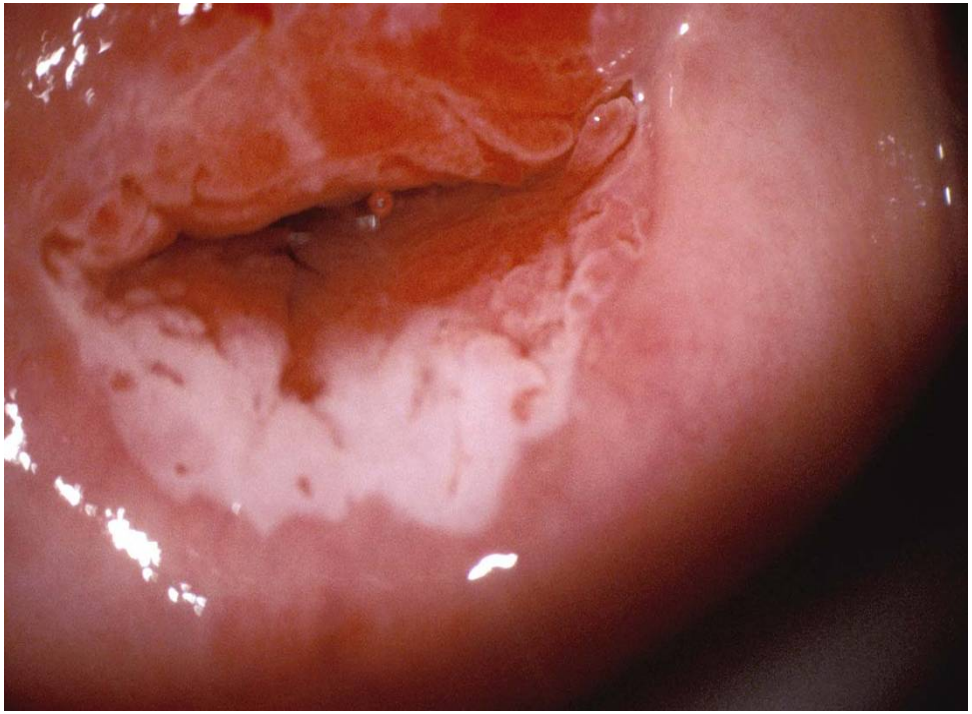
CIN 1


Infectious viral particles
New infectious virus particles
Episome
Perinuclear clearing (koilocytosis)
Integrated viral DNA
Cervical Cancer
CIN 3

CIN 1 – 2/3



CIN 1
Image courtesy of the family of
Dr Renso Barrasso (deceased)



CIN 3
Image courtesy of Prof J Monsonego

Cervical cancer – Definition

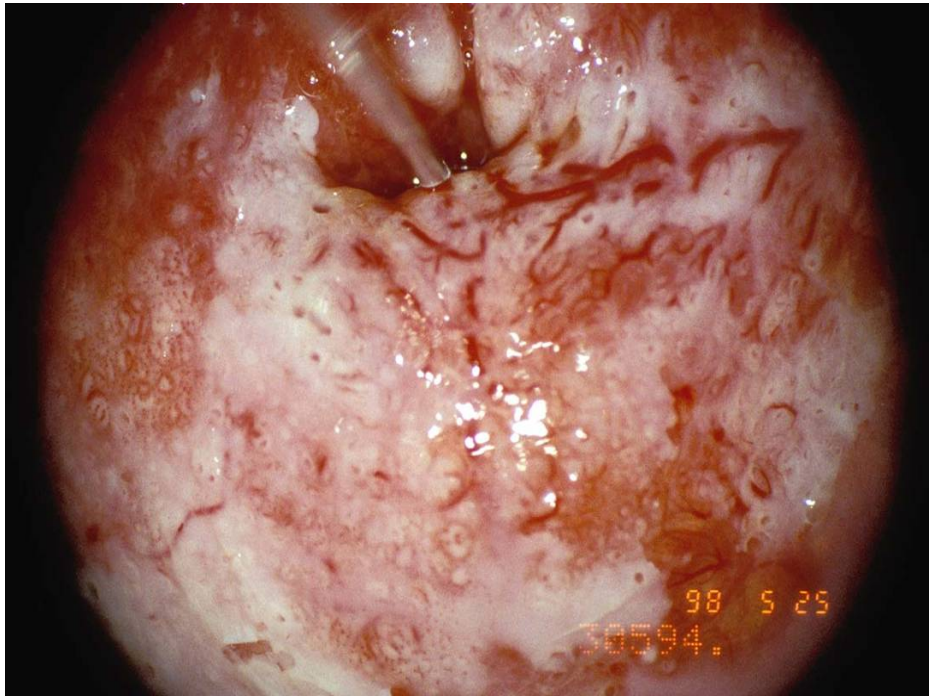
Cervical cancer results from malignant transformation of the cells which make up the lining of the uterine cervix

Malignant change most often occurs at the transformation zone

Malignant changes to the cells lining the uterine cervix produce:

Squamous epithelium
- Squamous cell carcinoma (SCC)

Columnar epithelium
- Adenocarcinoma
- Adenosquamous carcinoma



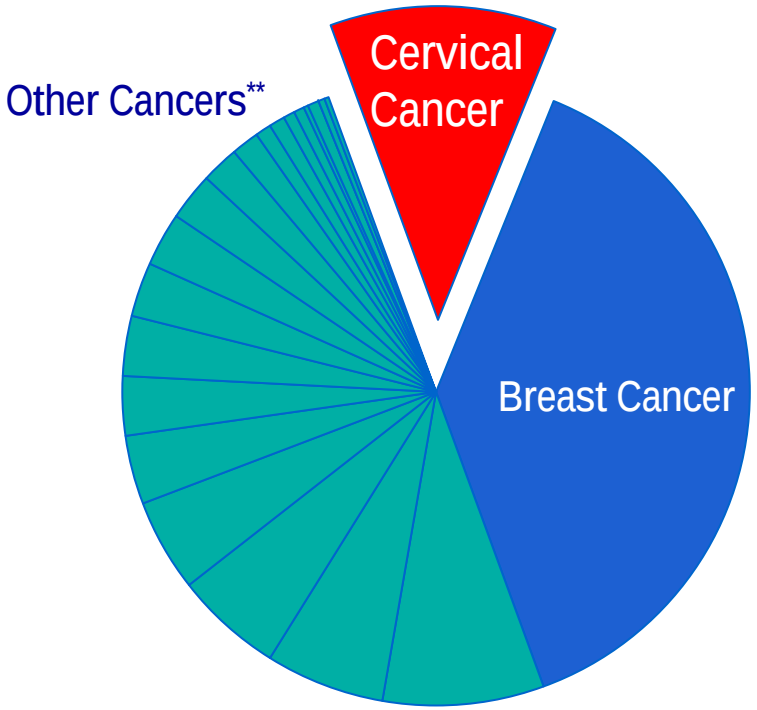
Place du cancer du col dans le monde

- 500.000 cancers par an

  $\Rightarrow$ 250.000 morts/an

- Lié à des virus hautement prévalents dans la majorité des populations sexuellements actives dans le monde

Cervical cancer is the second most common cause of death from cancer among young women in Europe*



Female cancers (age 15–44 yrs) in the European Union (2002)[1]

High mortality despite screening for early detection

- 33,500 women diagnosed with Cervical Cancer each year in Europe*,[1]
- 15,000 die (~45%)[1] equivalent of 40/day or nearly 2/hour

* European Union (25 member states) plus Iceland, Norway and Switzerland

** Skin melanoma (7.5), Ovary (5.4), Thyroid (4.9), Colon/Rectum (4.4), Non-Hodgkin lymphoma (3.2), Hodgkin lymphoma (2.7), Lung (2.6), Corpus uteri (2.5), Brain-CNS (2.4), Leukaemia (2.3), Stomach (1.7), Kidney (1.3), Oral Cavity (0.7), Bladder (0.7), Pancreas (0.6), Liver (0.4), Other Pharynx (0.4), Multiple Myeloma (0.3), Larynx (0.2), Nasopharynx (0.2), Oesophagus (0.2)

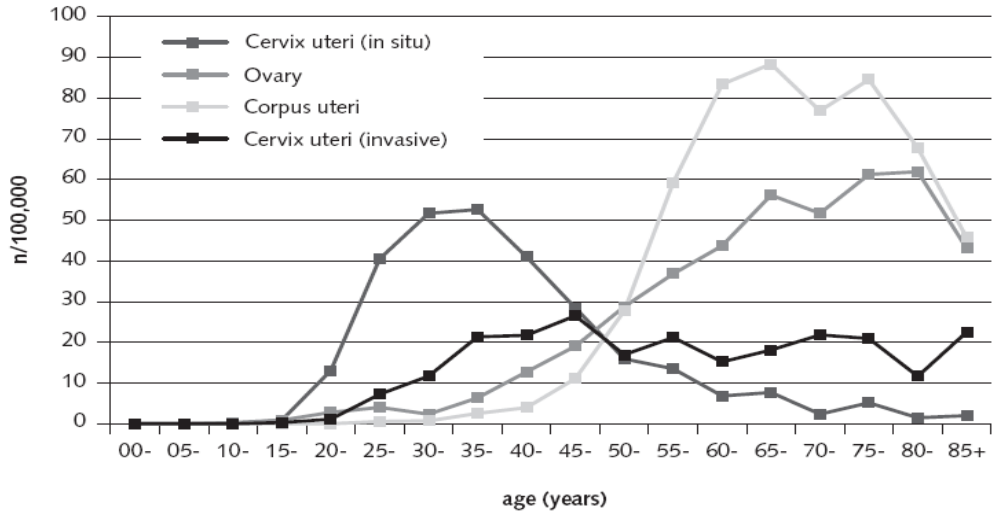
sanofi pasteur MSD
vaccines for life

[1] Ferlay et al, Globocan 2002: IARC Cancer Base No.5. Version 2.0 ARC Press, 2004
[2] Insinga et al. Am J Obstet Gynecol 2004

Cervical Cancer Incidence – Belgium

- Globocan 2002 – Belgium : 667 cases invasive cancer – 326 deaths
  (http://www-dep.iarc.fr)

Cervix uteri (invasive and in situ), corpus uteri and ovary: age-specific incidence in 2000-2001



E. Van Eycken, N. De Wever, Cancer Incidence and Survival in Flanders, 2000-2001. Flemish Cancer Registry Network, VLK, Brussels, 2006

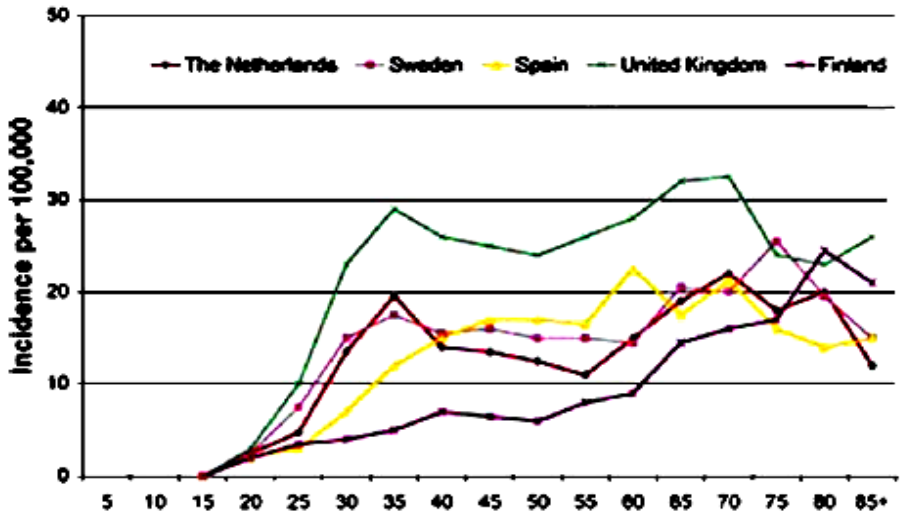
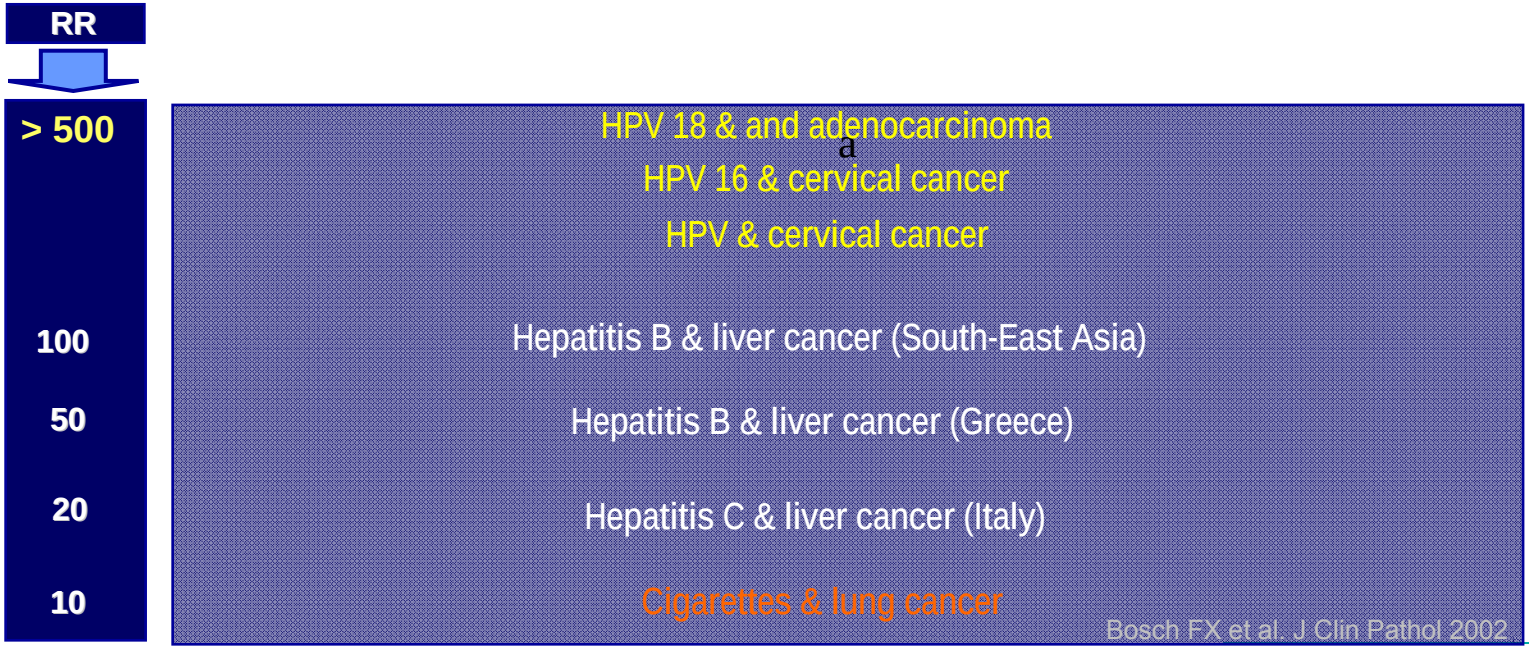


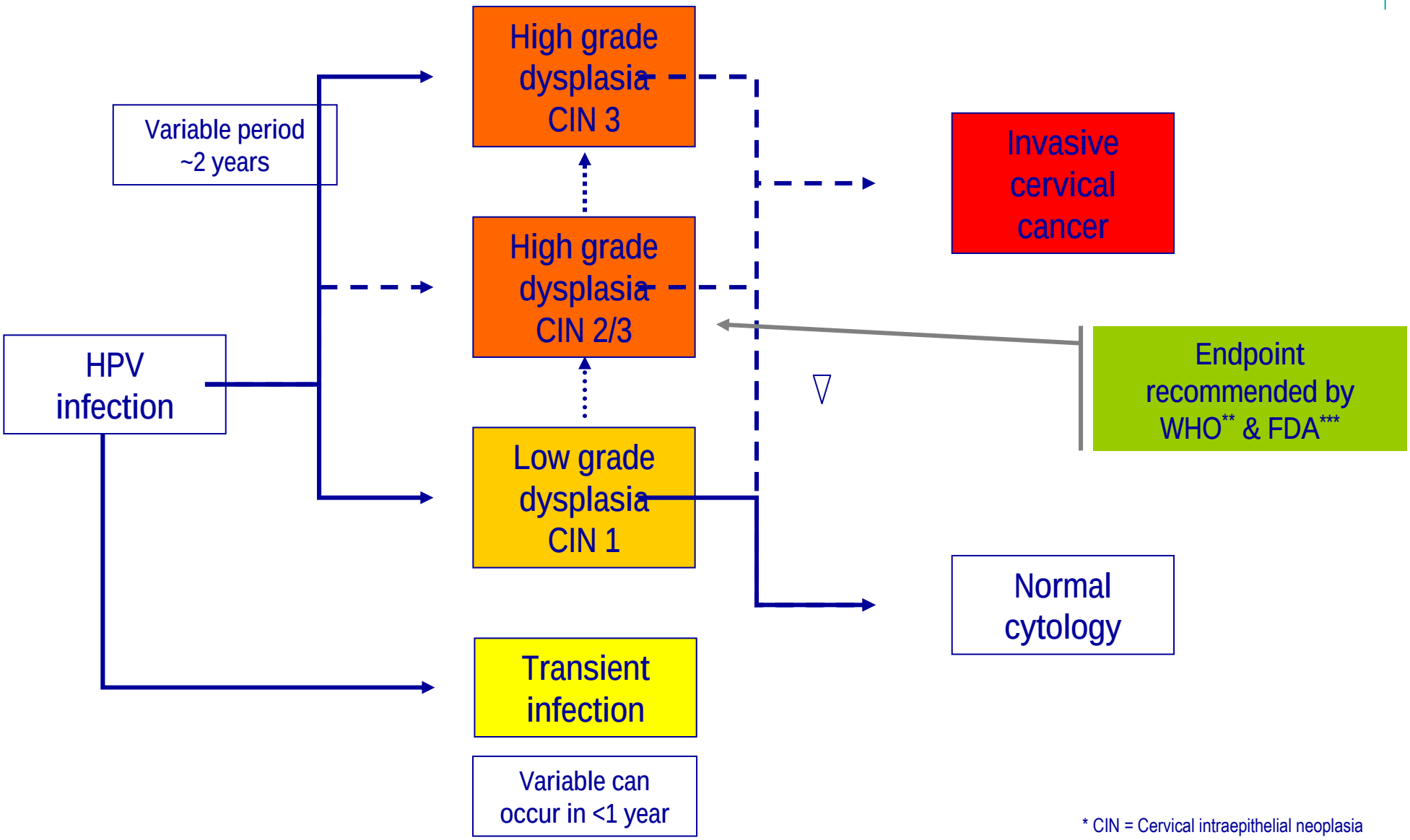
Fig. 2. Age-specific incidence rates of cervical cancer in five European countries. (With permission from: Bosch FX, de Sanjosé S. Chapter 1: Human Papillomaviurs and Cervical Cancer-Burden and Assessment of Causality. J Natl Cancer Inst Monogr 2003,31:3–14).

HPV : Necessary cause for cervical cancer

- Papillomavirus is necessary to develop cervical cancer
  - ➔ Virtually 100% attributable to Papillomavirus
    - Primary research Bosch (JNCI 1995): prevalence 93 % HPV DNA (>1000 biopsies from 22 countries)
    - Re-analysis Walboomers (J Pathol 1999): HPV DNA in 99.7 %
    - Delvenne (Vaccine 2001) HPV causes cancer in organotypic culture models
  - ➔ Environmental and other co-factors
- HPV Infection and Cancer Risk



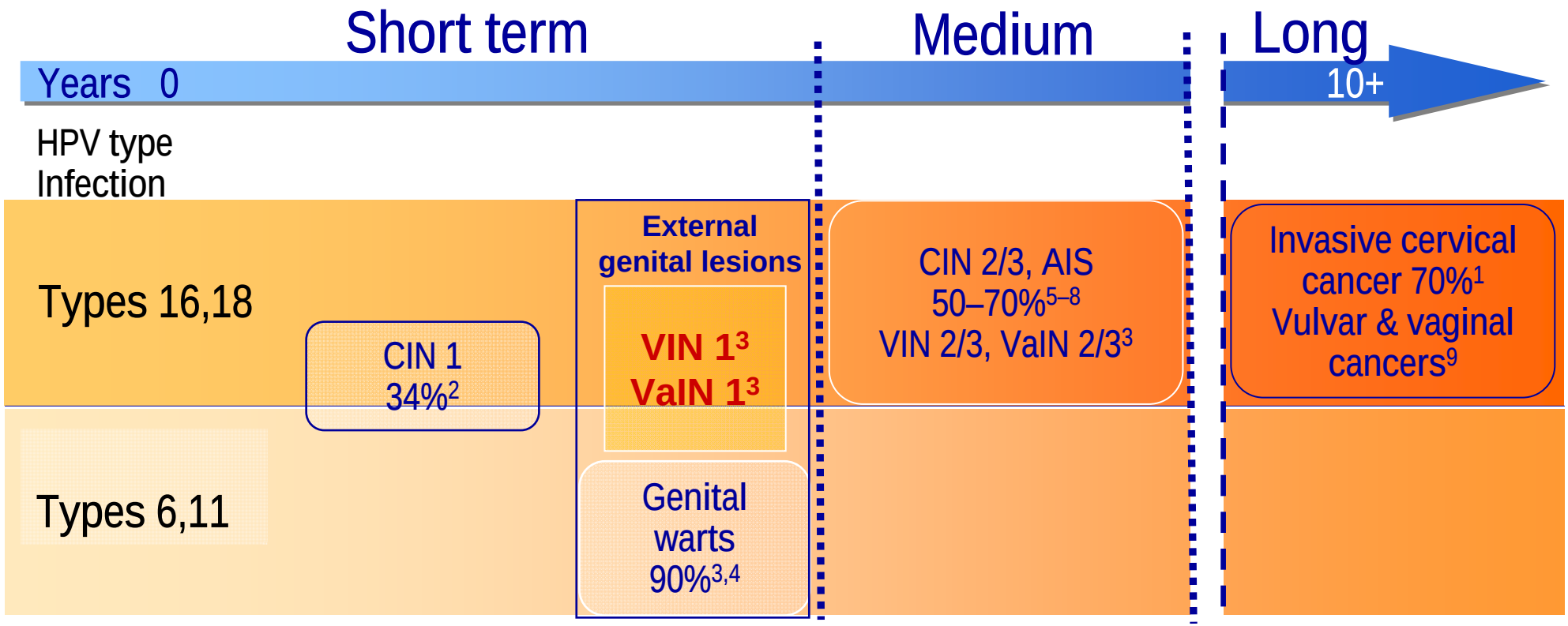
CIN - Current model of genital carcinogenic HPV on disease progression



Winer RL, Kiviat NB, Hughes JP et al. Development and duration of human papillomavirus lesions, after initial infection. *J Infect Dis* 2005;191:731–738.

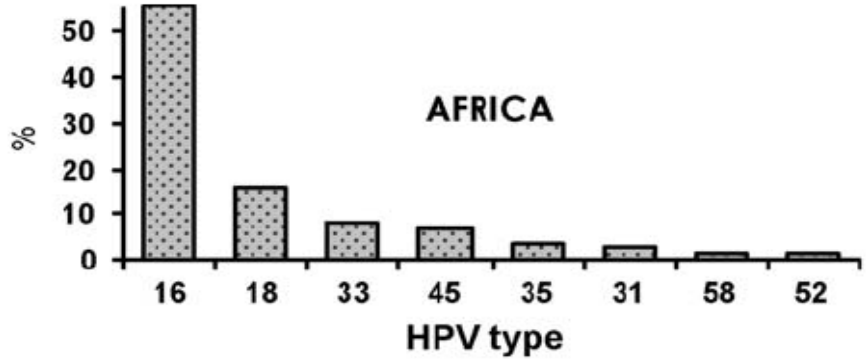
* CIN = Cervical intraepithelial neoplasia
** Food and Drug Administration US
*** World Health Organisation

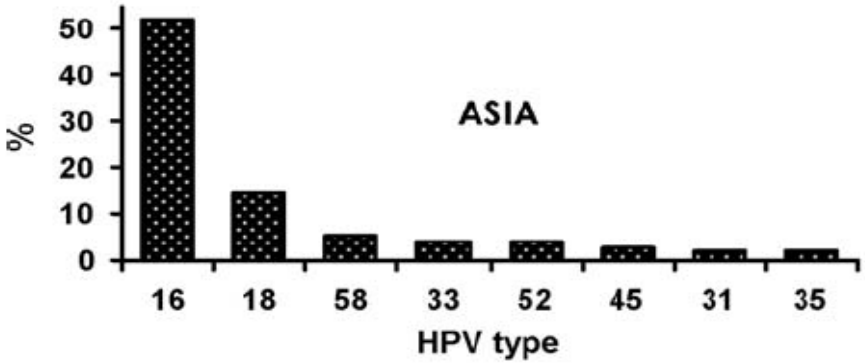
Human Papillomavirus types 6,11,16,18 are the 4 most common types affecting person's health

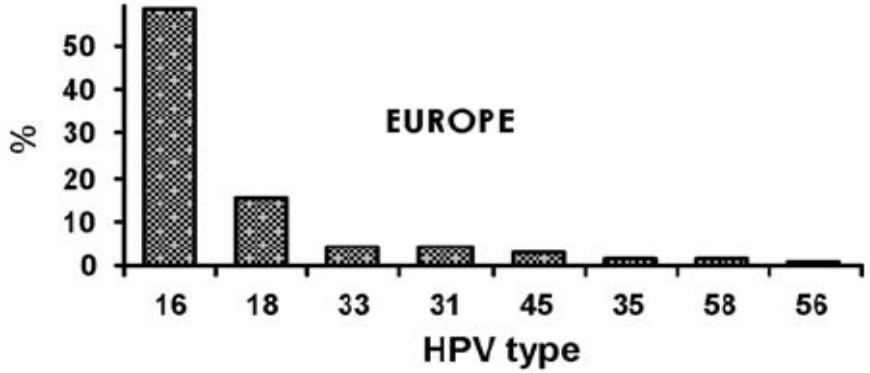


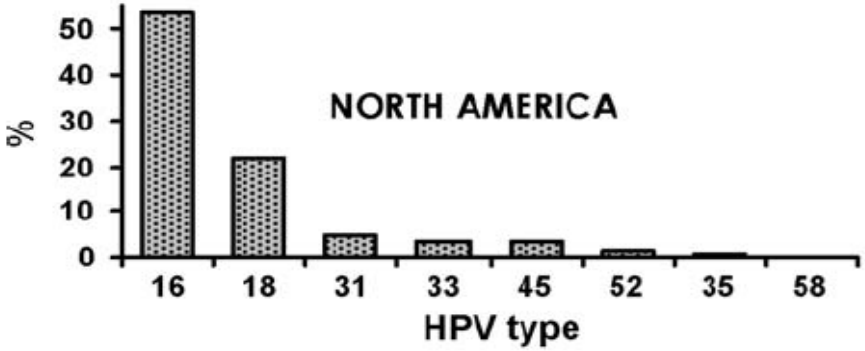
1. Munoz N, Bosch FX, de Sanjose S et al. Epidemiologic classification of human papillomavirus types associated with cervical cancer. *N Engl J Med* 2003;348:518–527. 2. Clifford GM, Rana RK, Franceschi S et al. Human papillomavirus genotype distribution in low-grade cervical lesions: Comparison by geographic region with cervical cancer. *Cancer Epidemiol Biomarkers Prev* 2005;14:1157–1164. 3. Wieland U and Pfister H. Papillomaviruses in human pathology: Epidemiology, pathogenesis and oncogenic role. In: Gross, Barrasso eds. Human Papilloma Virus Infection: A clinical atlas. Ullstein Mosby; 1997. p1–18. 4. Von Krogh G. Management of anogenital warts (condyloma acuminata). *Eur J Dermatol* 2001;11:598–603. 5. Sotlar K, Diemer D, Dethleffs A et al. Detection and typing of human papillomavirus by E6 nested multiplex PCR. *J Clin Microbiol* 2004;42:3176–3184. 6. Clifford GM, Smith JS, Aguado T et al. Comparison of HPV type distribution in high-grade cervical lesions and cervical cancer: A meta analysis. *Br J Cancer* 2003;89:101–105. 7. Liaw KL, Glass AJ, Manos MM et al. Detection of human papillomavirus DNA in cytologically normal women and subsequent cervical squamous intraepithelial lesions. *J Natl Cancer Inst* 1999;91:954–960. 8. Voglino G, Poso F, Privitera S et al. [The role of human papillomavirus in cyto-histological practice: Distribution and prevalence of high-risk strains (16, 18, 31, 33 and 35) in intraepithelial lesions and neoplasia of the uterine cervix.] *Pathologica* 2000;92:516–523. 9. Carter JJ, Madeleine MM, Shera K et al. Human papillomavirus 16 and 18 L1 serology compared across anogenital cancer sites. *Cancer Res* 2001;61:1934–1940. 10. Pagliusi SR and Aguado MT. Efficacy and other milestones for human papillomavirus vaccine introduction. *Vaccine* 2004;23:569–578.

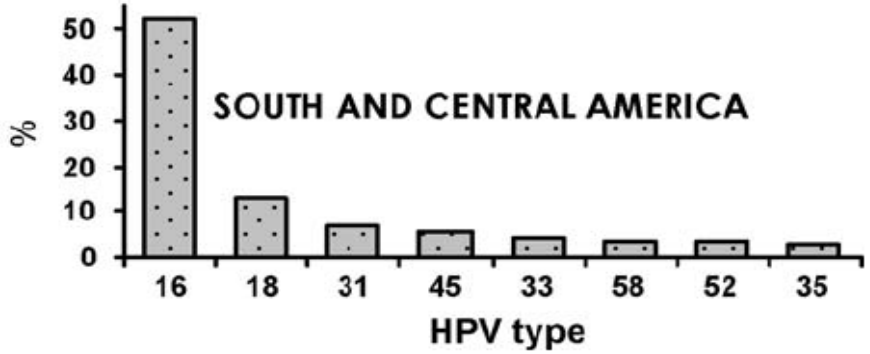
Distribution HPV - Invasive Cervical cancer





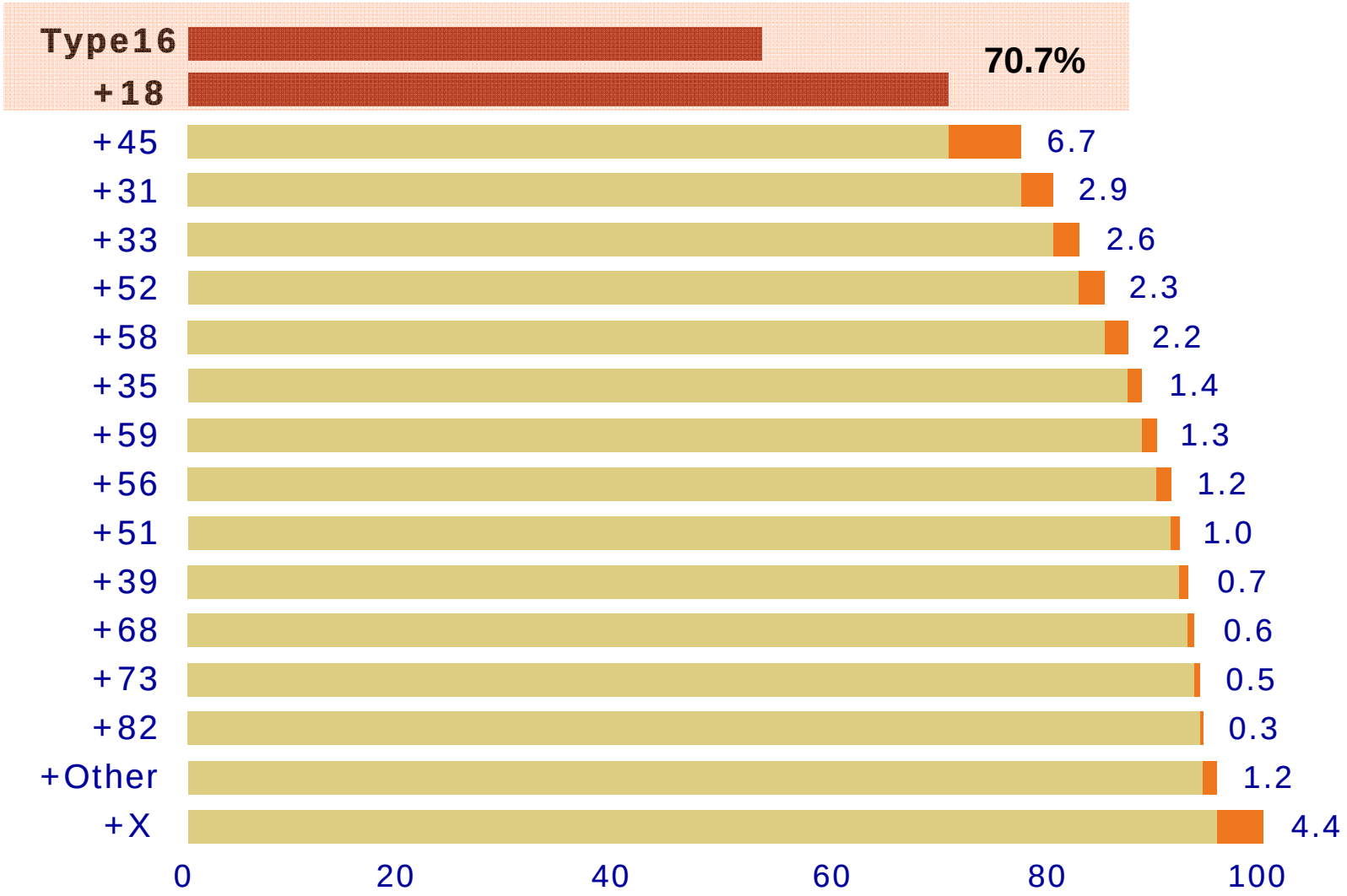






Clifford G et al. Vaccine 2006

Human Papillomavirus in Cervical Cancer - Worldwide



Munoz N et al. Int J Cancer 2004

High variability screening Europe

	Recommendation		% regularly screened	Cervical cancer Mortality/ 100,000[4] (0-64 yrs)	Cervical cancer Incidence/ 100,000[4] (0-64 yrs)
	Age range (years)	Interval (years)			
Belgium[1]	25–64	3	59	2.2	8.4
Denmark[2]	23–59	3	75	3.3	11.4
England[2]	25–64	3 to 5	83	2.2	7.7
Finland[2]	30–60	5	93	1.2	3.6
France[2]	25–65	3	69	2.0	8.7
Germany[2]	20–85	1	50	2.6	10.1
Italy[2]	25–64	3	53 -74	1.5	7.4
Netherlands[2]	30–60	5	77	1.5	6.7
Spain[2, 3]	20–64	3 to 5	49.6	1.6	6.9
Sweden[2]	23–60	3	83	2.2	7.4

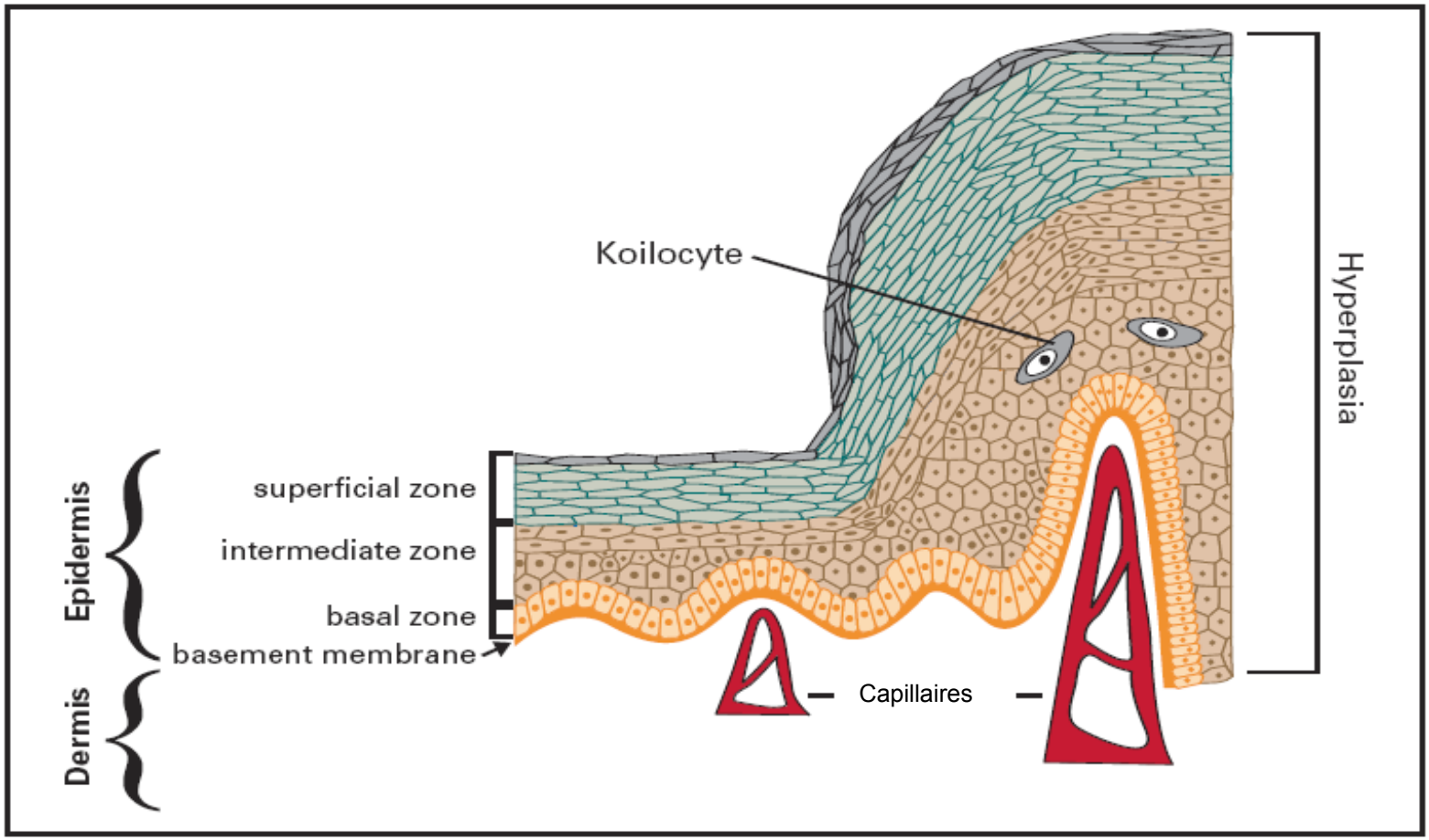
Globocan 2002
BELGIUM
incidence 667cases
mortality 326 cases

Maximum impact of screening limited:

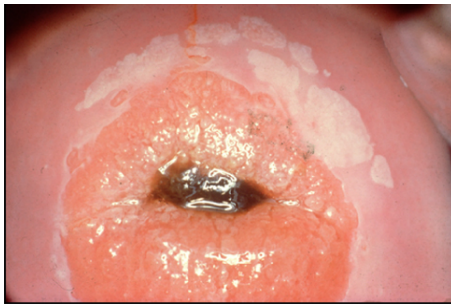
- Never reach 100% coverage
- Need high compliance throughout adulthood
- Hi sensitivity = lo specificity and vice versa

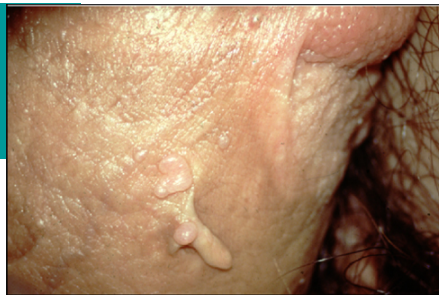
1.van Ballegooijen et al. *Eur J Cancer.* 2000;36:2177–2183.
2. Anttila et al. *Br J Cancer.* 2004;91:935–941.
3. Luengo Matos et al. *Aten Primaria.* 2004;33:229–236.
4. Ferlay et al, editors. Globocan 2002:IARC Press, 2004
5. Arbyn M Eur J Cancer 2000, KCE report 2006

Genital warts – Epidermal changes



Progression from Papillomavirus Infection to Genital Warts





Within 20 months*

Initial HPV infection (mainly types 6, 11)

Continuing infection

CIN 1 LSIL

Genital warts

Cleared HPV infection

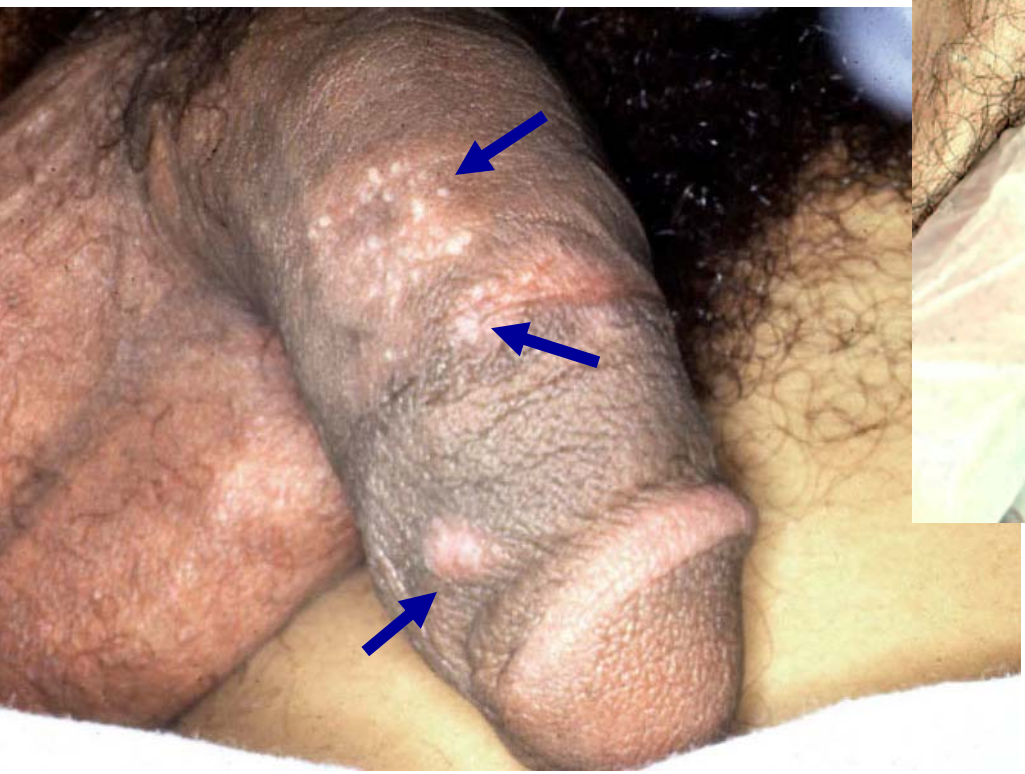
High incidence (1% adults 15–49 years)*

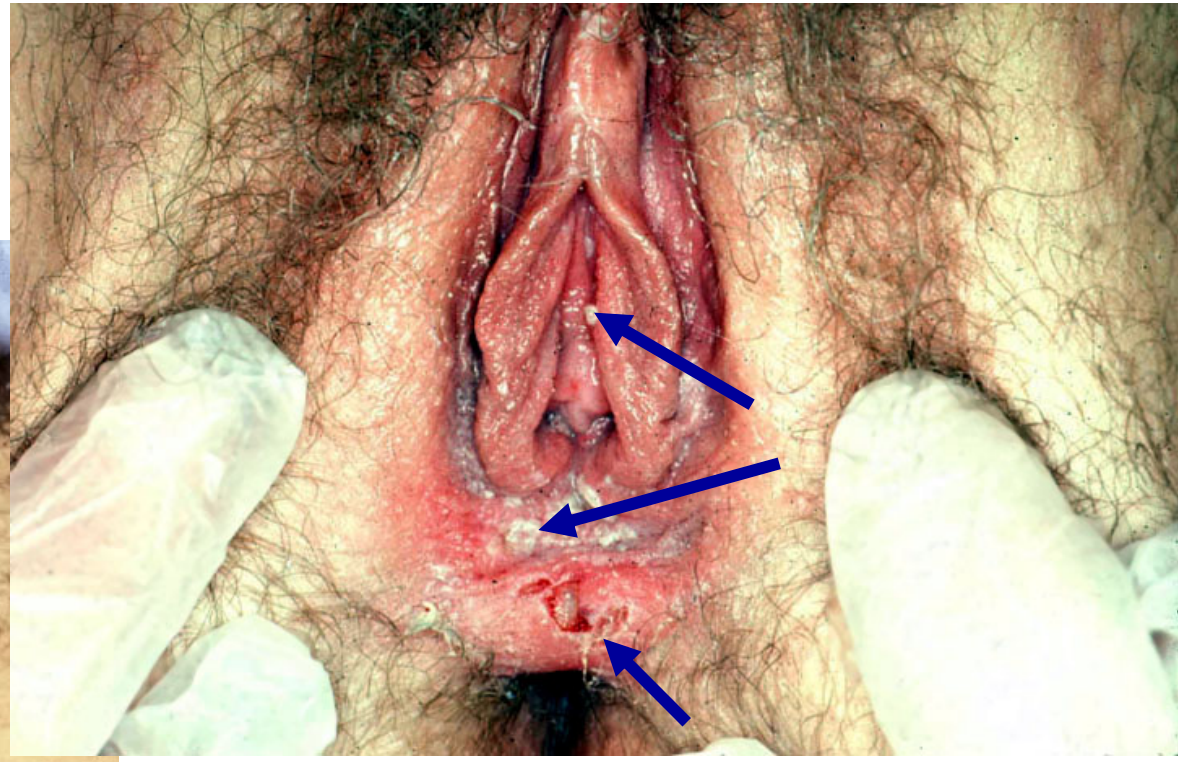
Distress, anxiety
Difficult to treat

Wart-causing HPV types found in up to 25% of LSIL/CIN**

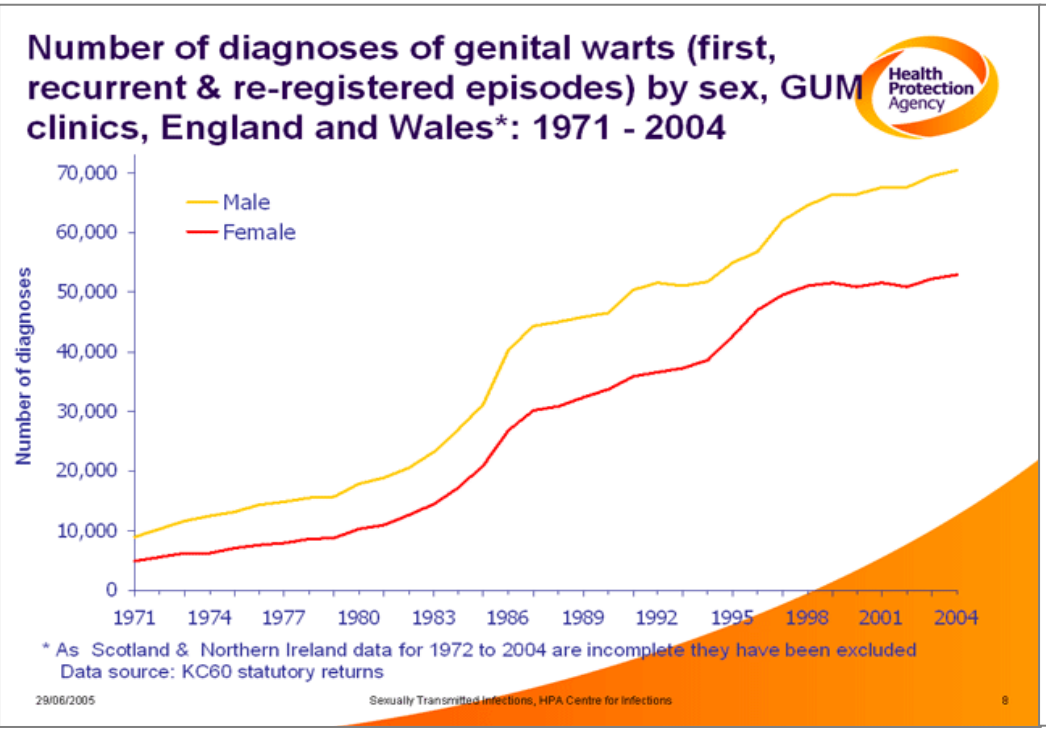
Koutsky. *Am J Med.* 1997;102:3–8. Feoli-Fonseca et al. *J Med Virol.* 2001;63:284–292.

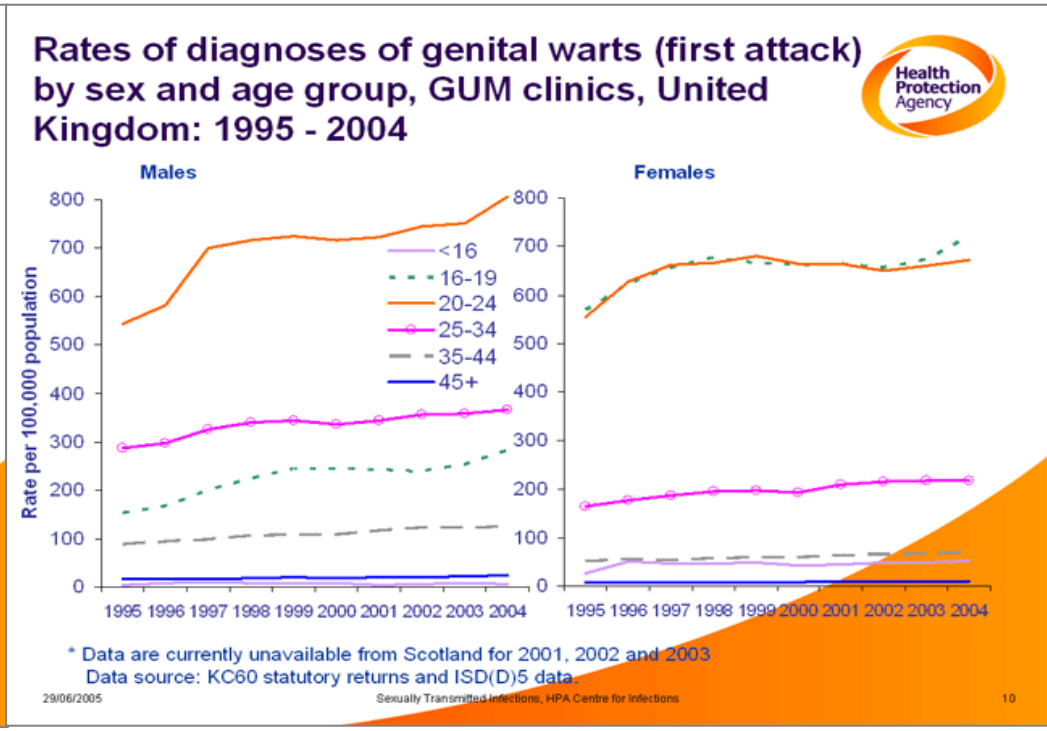
Genital Warts - examples





Rising Incidence of genital warts





Male incidence x 8
Female incidence x 11

30 % of diagnoses among females under 20 years
Highesr rates in males in age group 20-24 years

http://www.hpa.org.uk/infections/topics_az/hiv_and_sti/sti-warts/epidemiology/epidemiology.htm# - as accessed 6-11-2006

Genital warts – Treatment options

Treatment options for genital warts, with associated clearance and recurrence rates

Treatment		Clearance rate (%)		Recurrence rate (%)
Method	Type	End of first treatment course	After 3 months	
Cryotherapy[1]	Ablative	63–88	63–92	0–39
Electrocautery[1]	Ablative	93–94	78–91	24
Imiquimod[2]	Immune response modifier (IRM)	50–62	50–62	13–19
Interferon[1]	IRM			
Intralesional		19–62	36–62	0–33
Systemic		7–51	18–21	0–23
Topical		6–90	33	6
Laser therapy[1]	Ablative	27–89	39–86	<7–45
LEEP[1]	Surgical	<90		
Podophyllin[1]	Cytotoxic	32–79	22–73	11–65
Podophyllotoxin[1]	Cytotoxic	42–88	34–77	10–91
Surgery/scissor excision[1]	Surgical	89–93	36	0–29
Trichloroacetic acid[1]	Ablative	50–81	70	36

1. Beutner KR and Wiley DJ. Recurrent external genital warts: A literature review. *Papillomavirus Rep* 1997;8:69-74. 2. Clinical Effectiveness Group (Association for Genitourinary Medicine and the Medical Society for the Study of Venereal Diseases. National guideline for the management of anogenital warts (http://www.bashh.org/guidelines/2002/hpv_0302b.pdf last accessed on 18.08.06)

Genital cancers related to HPV – Concluding comments

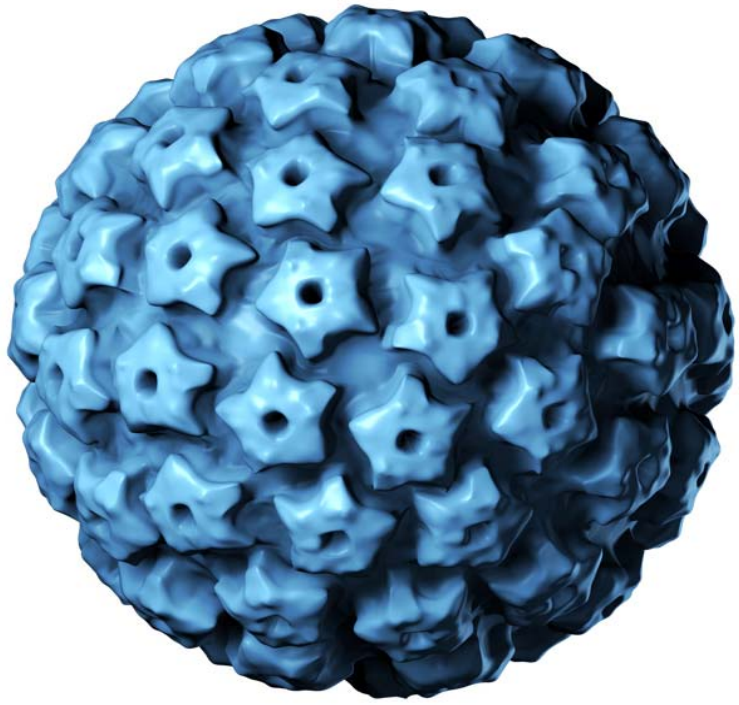
In addition to causing cervical cancer and CIN, human papillomavirus infection is also associated with cancers of the vulva and vagina, VIN and VaIN[1]

The predominant HPV types associated with these diseases are HPV 6 11, 16 and 18[1]

Data on the incidence of vulvar and vaginal cancers are not readily available for Europe

Each year hundreds of women die from cancer of the vagina and vulva in the US

If the disease is diagnosed early the patient has a better prognosis,[2] however, the treatment options available can have considerable emotional and physical consequences



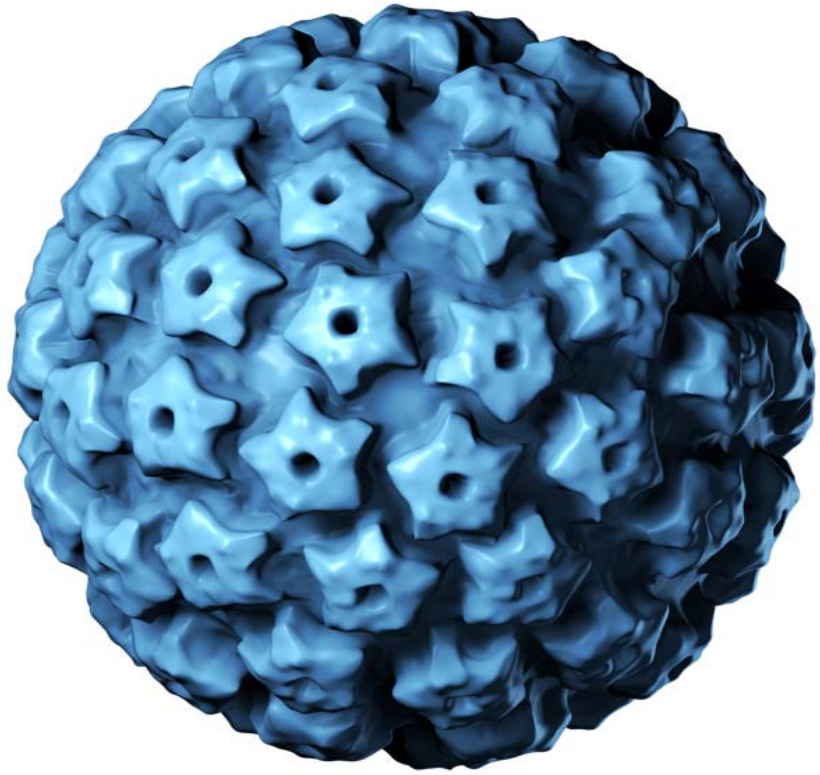
1. Wieland U, Pfister H. Papillomaviruses in human pathology: Epidemiology, pathogenesis and oncogenic role. In: Gross, Barrasso Eds. Human papilloma virus infection: A clinical atlas. Ullstein Mosby; 1997. p1–18. 2. www.cancer.gov/cancertopics/pdq/treatment (last accessed on 17.02.06).

Other HPV-related diseases – Concluding comments

In addition to causing cervical cancer,[1, 2] human papillomaviruses are also associated with many other malignant (cancerous) and benign (non cancerous) lesions including:

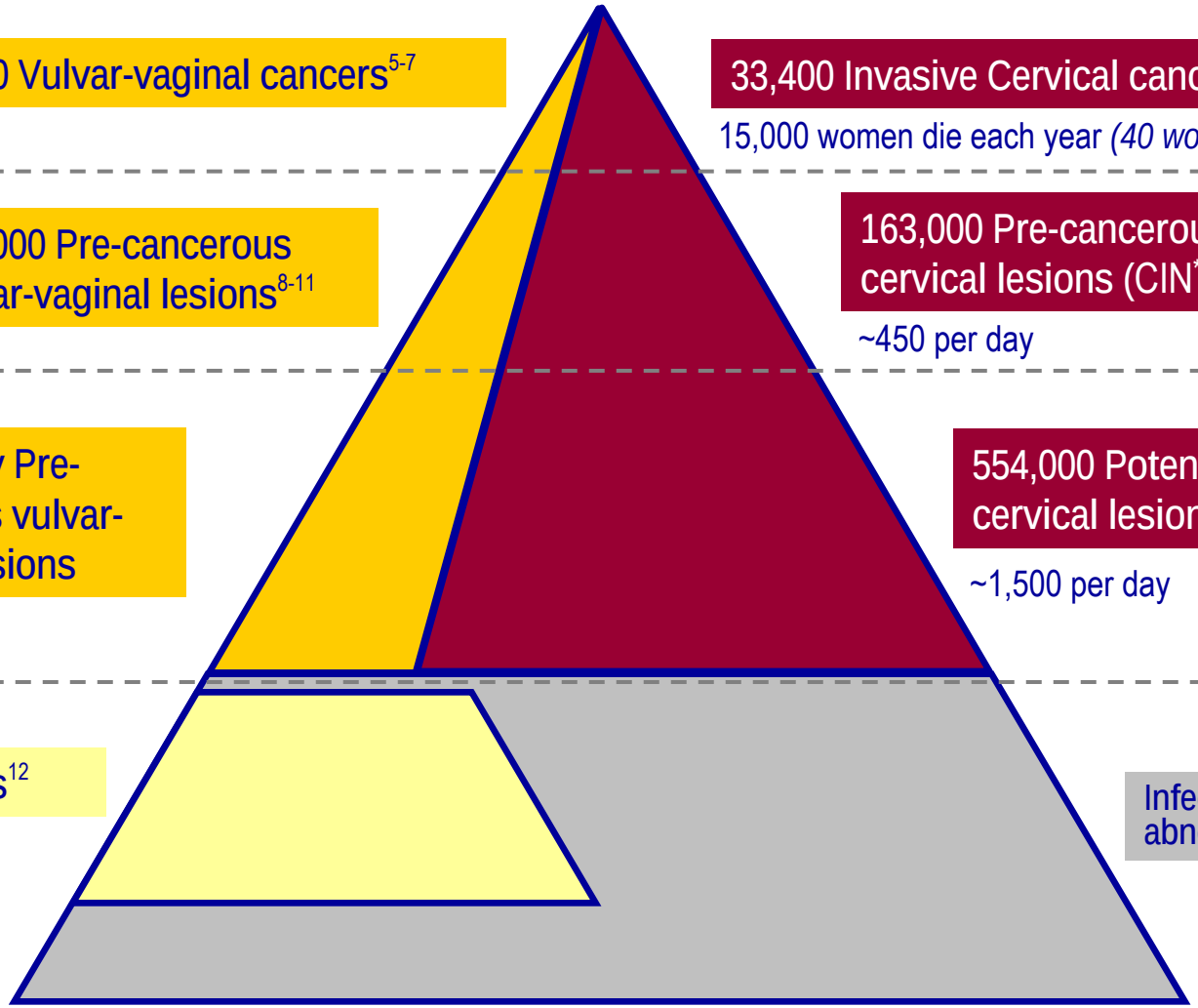
- Anal cancer and anal intraepithelial neoplasia (AIN)[3]
- Penile cancer and penile intraepithelial neoplasia (PIN)[3]
- Juvenile onset recurrent respiratory papillomatosis (JORRP)[4]
- Some cases of more rare cancers such as oesophageal cancer and conjunctival cancer[3]

Each year there are too many deaths from these human papillomavirus-related diseases[5]



1. Munoz N. Human papillomavirus and cancer: The epidemiological evidence. *J Clin Virol* 2000;19:1–5. 2. Walboomers JM, Jacobs MV, Manos MM et al. Human papillomavirus is a necessary cause of invasive cervical cancer. *J Pathol* 1999;189:12–19. 3. Wieland U, Pfister H. Papillomaviruses in human pathology: Epidemiology, pathogenesis and oncogenic role. In: Gross, Barrasso Eds. Human papilloma virus infection: A clinical atlas. Ullstein Mosby; 1997. p1–18. 4. Kosko JR and Derkay CS. Role of cesarean section in prevention of recurrent respiratory papillomas – Is there one? *Int J Pediatr Otorhinolaryngol* 1996;35:31–38. 5. Jemal A, Murray T, Ward E et al. Cancer statistics, 2005. *CA Cancer J Clin* 2005;55:10–30.

Human Papillomavirus diseases start before and go beyond Cervical Cancer (estimated numbers of cases in women / year in Europe*)



~2,000 Vulvar-vaginal cancers[5-7]

33,400 Invasive Cervical cancer[1]

15,000 women die each year *(40 women/day or ~2/hour)*[2]

~30,000 Pre-cancerous vulvar-vaginal lesions[8-11]

163,000 Pre-cancerous cervical lesions (CIN**2/3)[2,3]

~450 per day

Potentially Pre-cancerous vulvar-vaginal lesions

554,000 Potentially pre-cancerous cervical lesions (CIN**1)[2,4]

~1,500 per day

250,000 Genital warts[12]

Infection without detectable abnormalities

JORRP (rare)***[13-15]

* 25 EU member states + Iceland, Norway & Switzerland ** CIN = Cervical intraepithelial neoplasia *** Juvenile recurrent respiratory papillomatosis

[1] Ferlay et al, eds. Globocan 2002. IARC Cancer Base No. 5. Version 2.0. IARC Press, 2004
[2] Insinga et al. *Am J Obstet Gynecol* 2004
[3] Clifford et al. *Br J Cancer* 2003
[4] Clifford et al. *Cancer Epidemiol Biomarkers Prev* 2005
[5] Parkin et al. Cancer incidence in five continents (CIS) Vol VIII
[6] Daling et al. *Gynecol Oncol* 2002
[7] Madeleine et al. J Natl Cancer Inst 1997
[8] Dodge et al. Gynecol Oncol 2001
[9] van Beurden et al. Cancer 1995
[10] Hording et al. *Gynecol Oncol* 1995
[11] Jones et al. *Eur J Gynaecol Oncol* 2001
[12] UK Health Protection Agency. CDR Weekly. 2003
[13] Gissmann et al. J Virol 1982
[14] Mounts et al. Proc Natl Acad Sci USA 1982
5] Abramson AL et al. Laryngoscope 1987

Types 6,11,16,18 cause the vast majority of genital HPV diseases

Disease	Cases/year in Europe*		Estimated proportion 6,11,16,18 related disease among HPV disease
	16,18	6,11	
Cervical Cancer	~ 25,000[1,2]		~ 75%
Pre-Cancerous Cervical Lesions	~ 112,000[2-4]		~ 70%
Pot. Pre-cancerous Cervical Lesions	~ 200,000[3,5]	~ 80,000[3,5]	~ 35-50%
Vulvar-Vaginal Cancer	~ 1,900[6-8]	yet to be determined	~ 95%
Pre-Cancerous Vulvar-Vaginal Lesions	~ 24,000[7,9–12]	~ 1,500[13]	~ 80%
Genital warts		>225,000[14–16]	~ 90%

* 25 EU member states plus Iceland, Norway and Switzerland ** CIN = Cervical Intraepithelial Neoplasia

[1] Ferlay et al, eds. Globocan 2002. IARC Cancer Base No. 5. Version 2.0. IARC Press, 2004; [2] Clifford et al. *Br J Cancer* 2003; [3] Insinga et al. *Am J Obstet Gynecol* 2004; [4] Sotlar et al. *J Clin Microbiol* 2004; [5] Clifford et al. Cancer Epidemiol Biomarkers Prev 2005; [6] Parkin et al. Cancer incidence in five continents (CI5). Volume VIII; [7] Daling et al. *Gynecol Oncol* 2002; [8] Madeleine et al. *J Natl Cancer Inst* 1997; [9] Dodge et al. *Gynecol Oncol* 2001; [10] Hording et al. Gynecol Oncol 1995; [11] van Beurden et al. Cancer 1995; [12] Jones et al. Eur J Gynaecol Oncol 2001; [13] Madeleine et al. J Natl Cancer Inst 1997; [14] UK Health Protection Agency. CDR Weekly 2003; [15] Von Krogh. Eur J Dermatol 2001; [16] Wieland et al. In Gross, Barrasso eds. Human papillomavirus infection: A clinical atlas. Ullstein Mosby. 1997

European Union endorsed the breakthrough in the prevention of Cervical Cancer on 20 sept 2006

Fast approval of Gardasil® (9 months of review)

Strong indications for Gardasil®[1]

- Prevention of Cervical Cancer
- Prevention of Pre-cancerous Cervical Lesions *(CIN*2/3)*
- Prevention of Pre-cancerous Vulvar Lesions *(VIN**2/3)*
- Prevention of Genital Warts

caused by Human Papillomavirus types 6,11,16,18

Additional properties

- Efficacious against Potentially Pre-canc. Cervical Lesions *(CIN*1)*
- Reduction of Pre-cancerous Vaginal Lesions *(VaIN***2/3)*

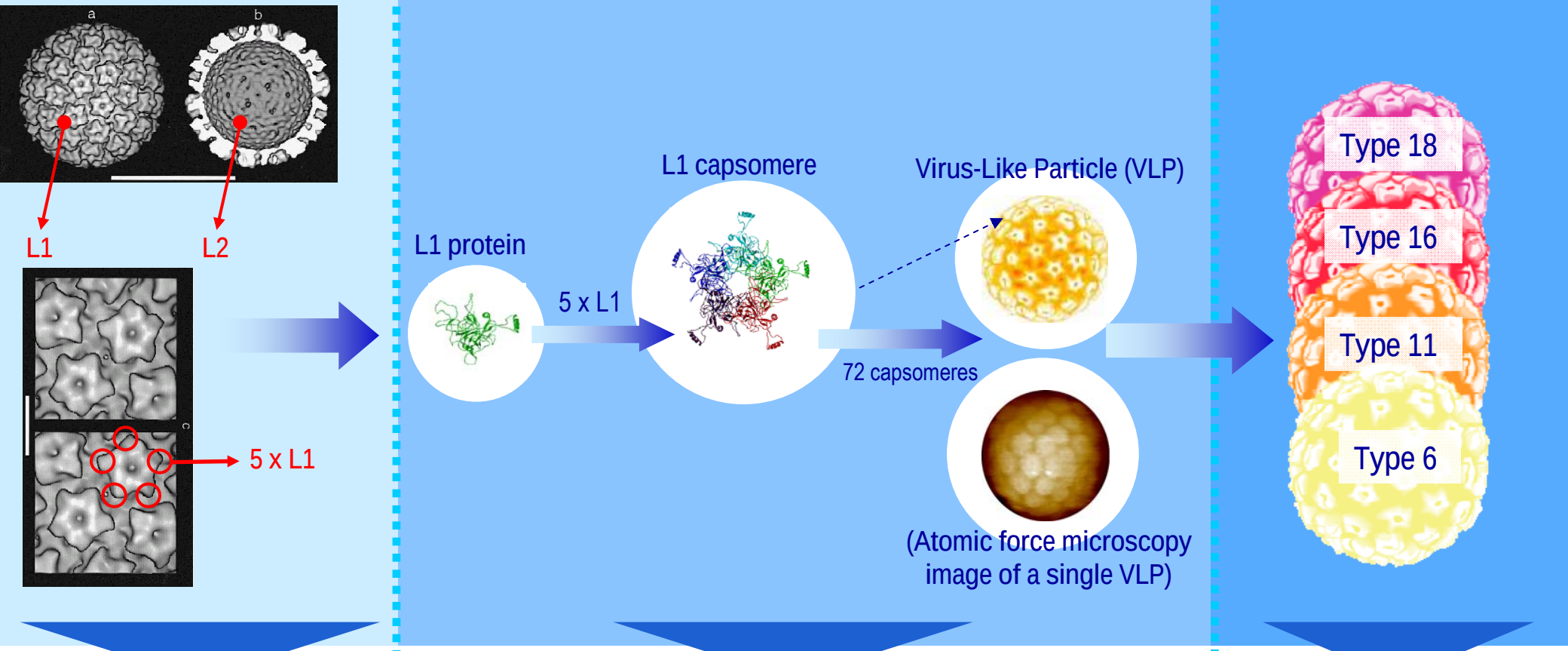
[1] Indication of Gardasil in the European Union: Prevention of high-grade cervical dysplasia (CIN 2/3), cervical carcinoma, high-grade vulvar dysplastic lesions (VIN 2/3), and external genital warts (condyloma acuminata) causally related to Human Papillomavirus (HPV) types 6, 11, 16 and 18. Section 4.1 (Therapeutic Indications) of Summary of Product Characteristics, SPC

* Cervical intraepithelial neoplasia

** Vulvar intraepithelial neoplasia

*** Vaginal intraepithelial neoplasia

Gardasil® Human Papillomavirus Vaccine (types 6,11,16,18)
Production



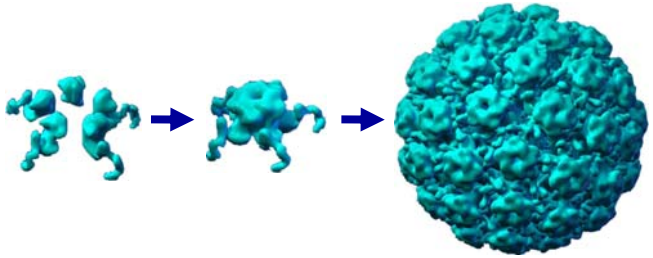
HPV virus :
L1 = external protein
L2 = internal protein

Production in yeast
(HPV L1 gene integrated in genome)
Saccharomyces cerevisiae

GARDASIL®
0.5 ml
injected in 3 doses
0, 2, 6 months

Gardasil® combines innovation and experience to optimally balance efficacy, safety and supply

Innovation through a new principle in vaccination



Assembly of the L1 virus protein leading to the Virus-Like Particles (VLP) contained in Gardasil®

- Virus-Like Particles (VLP)* mimic the virus and induce strong and persistent immune response
- AAHS** adjuvant further focuses the response and directs it to produce specific antibodies
- Clinically proven strong induction of immune memory[1]

Experience drawn from millions of doses of well accepted vaccines

- Vaccines with AAHS adjuvant have proven high efficacy and good safety profile

Up to 100% sustained efficacy – good safety profile – generally well tolerated in large clinical trials[2,3]

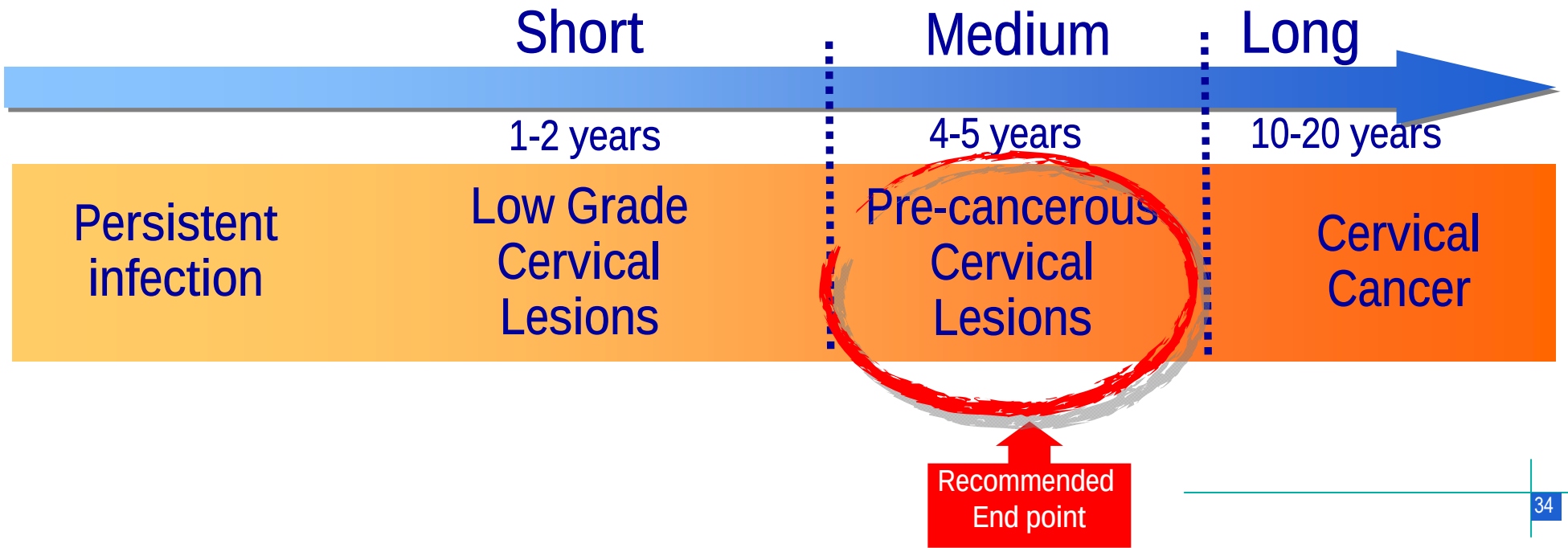
* Empty shells made of viral protein but without any genetic material of the virus. They closely resemble the Human Papillomavirus but cannot cause disease.

** Amorphous Aluminium Hydroxyphosphate Sulfate, 225 µg of Aluminium

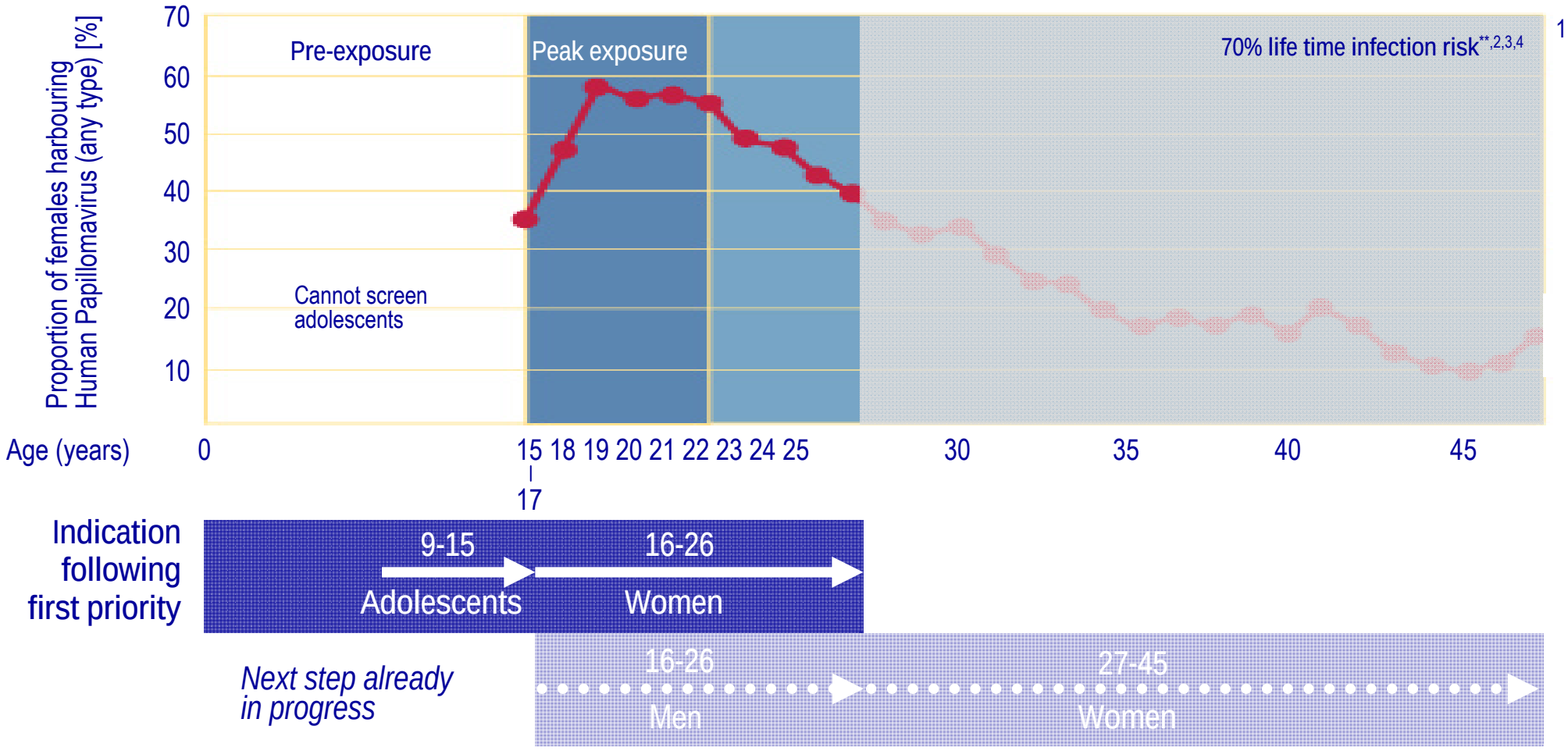
[1] Villa LL et al. oral presentation, ICID, 15th-18th June 2006, Lisbon, Portugal
[2] Skjeldestad FE et al. abstract, IDSA, 7 October 2005. San Francisco, USA
[3] Ferris D et al. Abstract, ICAAC, 16–19 September 2005, Washington DC, USA

Gardasil® Human Papillomavirus Vaccine (types 6,11,16,18) Study Endpoints

- Need for an appropriate efficacy end-point (event that is counted as a case of the disease) to evaluate the difference between vaccinees and placebo recipients
  - ➔ Unethical and impossible to use invasive Cervical Cancer as an endpoint
  - ➔ FDA/EMEA and WHO agree that pre-cancerous Cervical Lesions are the preferred endpoint
- CIN 3 and AIS are classified as Stage 0 cervical cancers according to FIGO (International Federation of Obstetrics and Gynaecology).



Stepwise development of Gardasil® to meet public health priorities



[1] Cervical smears of Danish women aged 15-93 (n=11,865) collected in 2005, Krüger Kjaer S et al. EUROGIN. 23-26 April 2006. Paris, France

[2] Koutsky LA. Am J Med 1997

[3] Koutsky LA et al. Epidemiology Rev 1988

[4] Syrjänen K et al. Sex Transm Dis 1990

* United States' Centers for Diseases Control and Prevention's Advisory Committee on Immunization Practices

** for sexually active people

HPV 16 Vaccine Proof-of-Principle 4 Year Follow-up Results

Per-Protocol Efficacy Cohort
Median 48 Months After Completion of the Vaccination Regimen

Endpoint	Placebo Cases	HPV 16 Vaccine Cases	Vaccine Efficacy	95% Confidence Interval
Confirmed persistant infection	92	0	100%	96-100
CIN 1	14	0	100%	71-100
CIN 2/3	12	0	100%	65-100

Mao et al. Obstet Gynecol 2006; 107: 18-27

High efficacy against Cervical Cancer and other HPV diseases before and beyond Cervical Cancer in studies with ~25,000 women

Disease related to types 6,11,16,18 (primary endpoint)	Gardasil® per protocol efficacy analysis
Cervical Cancer (CIN*2/3 and AIS**)	100% 95% CI [93,100][1]
Pre-cancerous (CIN*2/3) & Potentially pre-cancerous cervical lesions (CIN*1)	100% 97.5% CI [87,100][2,†]
Pre-cancerous vulvar lesions Pre-cancerous vaginal lesions	100% 95% CI [41.4,100][2] No cases in vaccine group[§]
Genital warts	100% 95% CI [78.5,100][2‡]

In women exposed to one or more vaccine virus types, Gardasil® was still up to 100% efficacious against disease caused by the remaining types to which the women had not been exposed[3]

* Cervical Intraepithelial Neoplasia ** Adenoma Carcinoma in Situ

[1] Ault K, Abstract, European Cancer Conference (ECCO) November 2nd, 2005, Paris France
[2] Sanofi Pasteur MSD, data on file, 2005
[3] Ferris, D. Abstract, EUROGIN meeting, Paris, France, 26 April 2006

† 95,2% (95% CI [87.2,98.7]) in the combined analysis of several clinical studies
‡ 98.9%(95% CI [93.7,100]) in the combined analysis of several clinical studies
§ Current observation of 0 cases in the vaccine group vs. 5 cases in the placebo group suggesting 100% efficacy, not yet statistically significant

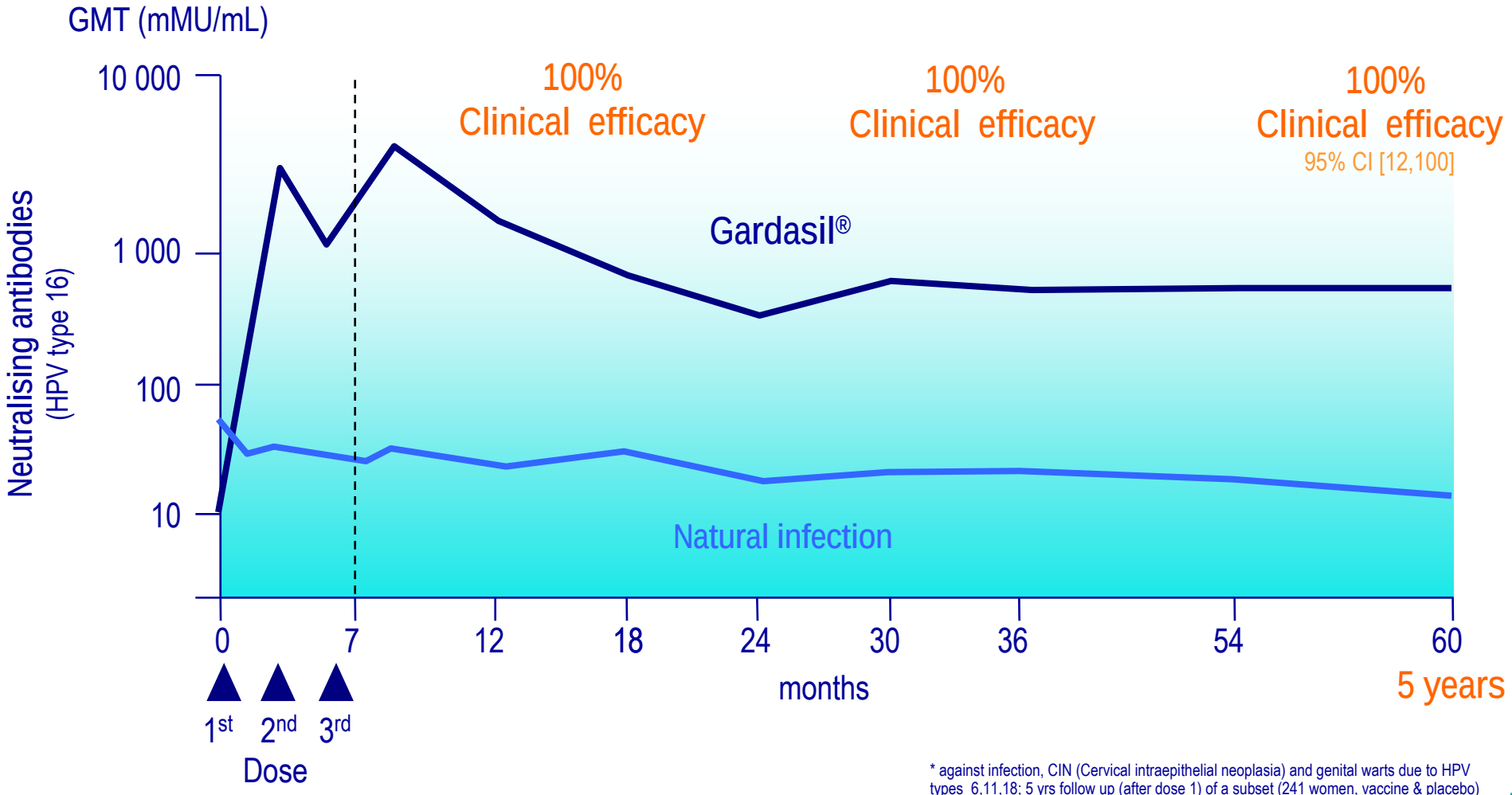
Protection induite par vaccin

- Par production Ac
  - ➔ IgG : à des taux > 100 fois les taux sur infection naturelle
    chez toutes les vaccinées
    → pas utilité contrôler ces taux
  - ➔ IgM et A : taux et durée moindres
- Immunité cellulaire : rôle (important) probable
  cf. pas de protection par infection naturelle
  ou : rôle taux Ac ++ ?
  Durée de la protection: au moins 5 ans

- ! Screening reste nécessaire !

Gardasil®: 5 year results confirm high and sustained efficacy

Antibody titre and clinical efficacy of Gardasil® over time



* against infection, CIN (Cervical intraepithelial neoplasia) and genital warts due to HPV types 6,11,18; 5 yrs follow up (after dose 1) of a subset (241 women, vaccine & placebo) from a phase II efficacy study

Villa LL – Costa RL – Br J Cancer 2006
Sanofi Pasteur MSD, data on file, 2006

Quid de la protection des femmes déjà infectées?

- Gardasil :
  - ➔ HPV+/Ac+ : pas de protection démontrée
  - ➔ HPV+/Ac - : trend, avec 27 % protection < CIN1/3 et adénoC
  - ➔ HPV-/Ac+ : effet booster, avec↑ Ac de 12 à 26 X à J 60

- Si HPV+/Ac+ pour un des sérotypes :

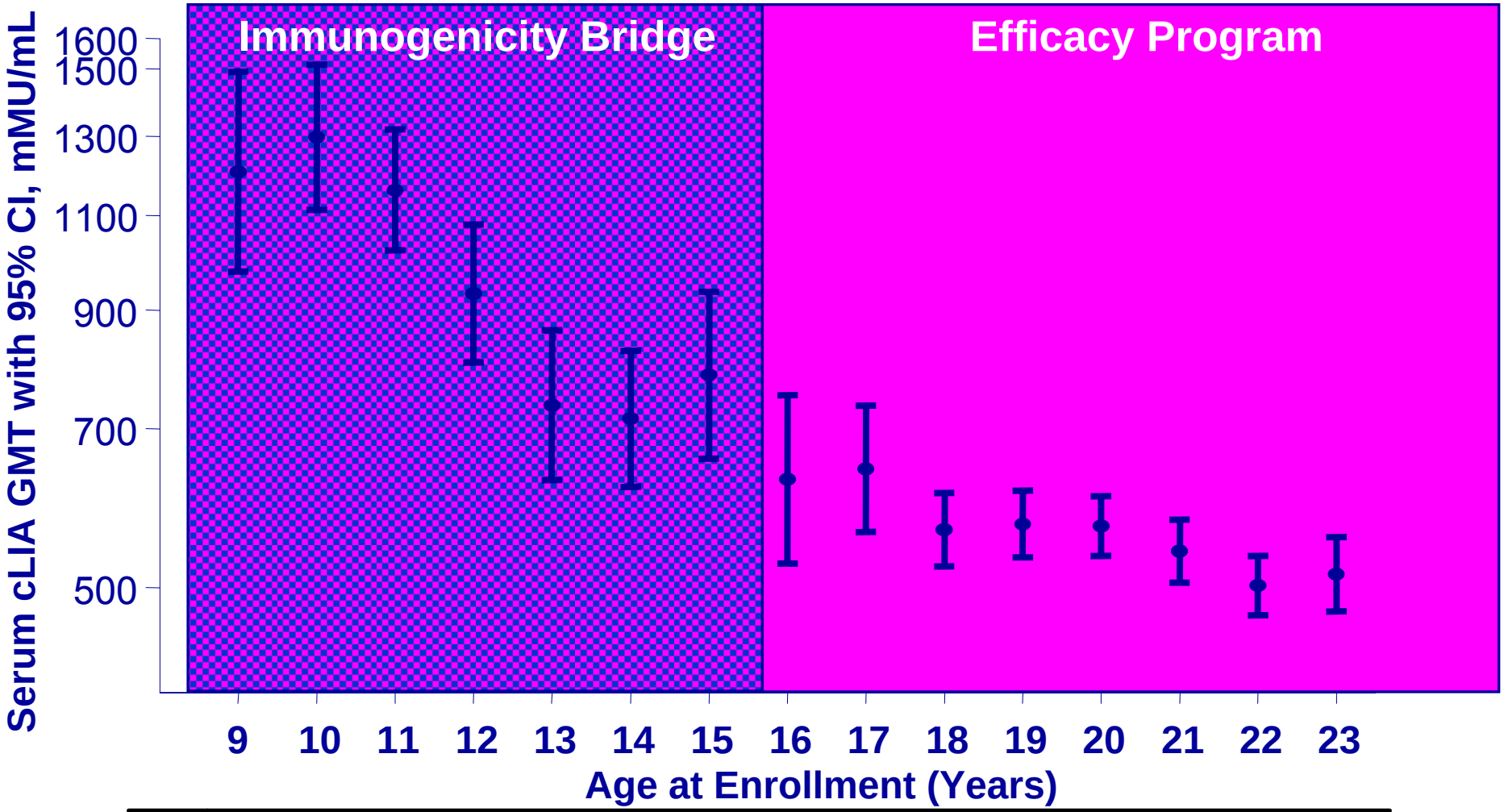
  n'empêche pas immunogénicité pour autres sérotypes vaccinaux

In clinical with ~25,000 women, Gardasil® has shown a very good safety profile and was very well tolerated

- The most commonly reported adverse events were injection site reactions and fever

- Fever >38.9°C (oral temperature) within 5 days post-vaccination visit was reported in 1.5% of the GARDASIL® -vaccinated population (n=6,040) compared to 1.1% in the placebo group (n=3,981)

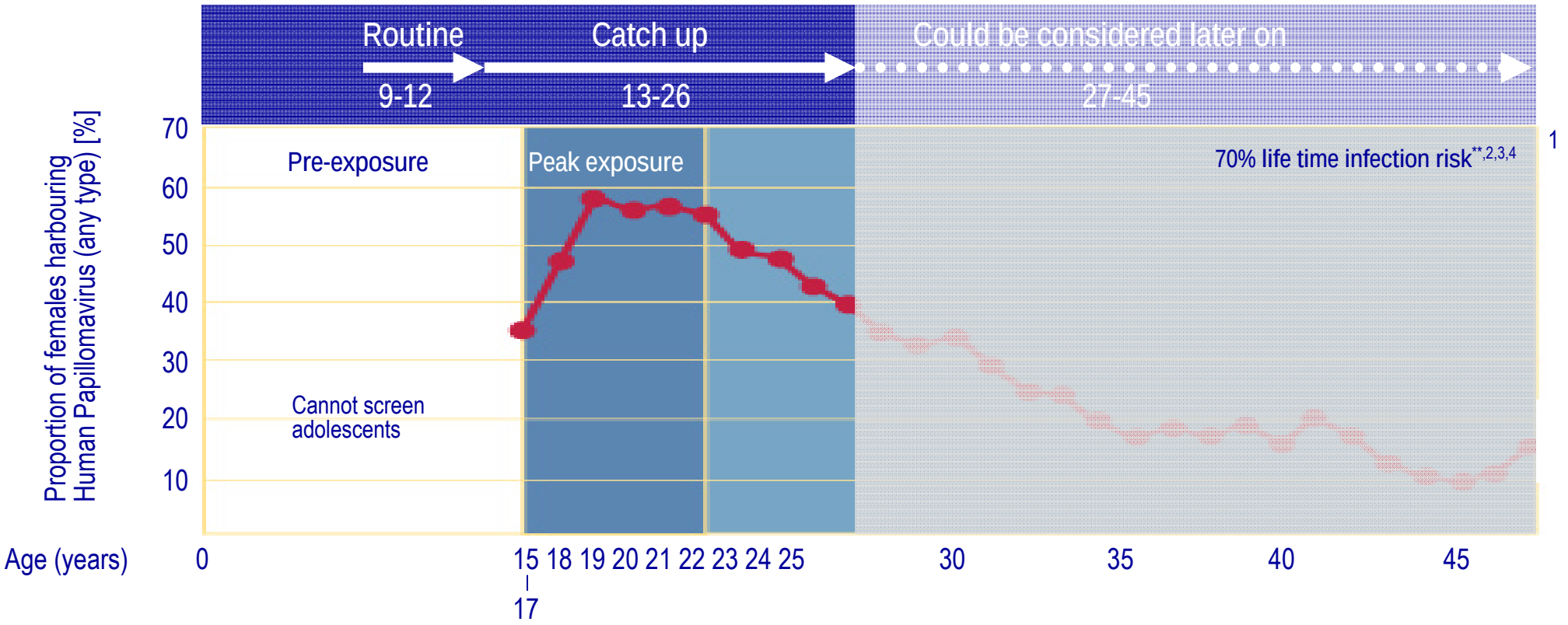
Children - adolescents higher immune response than adults



	Number of Subjects Evaluable (n)														
Age	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
n	68	129	166	141	166	148	109	85	137	440	511	624	576	564	400

Nolan T et al. 2005, Block et al. Pediatrics 2006

Human Papillomavirus vaccination should start with those who would benefit most *(comparable to the US CDC's ACIP* recommendation + recent VVOG*** guidelines)*



[1] Cervical smears of Danish women aged 15-93 (n=11,865) collected in 2005, Krüger Kjaer S et al. EUROGIN. 23-26 April 2006. Paris, France

[2] Koutsky LA. Am J Med 1997

[3] Koutsky LA et al. Epidemiology Rev 1988

[4] Syrjänen K et al. Sex Transm Dis 1990

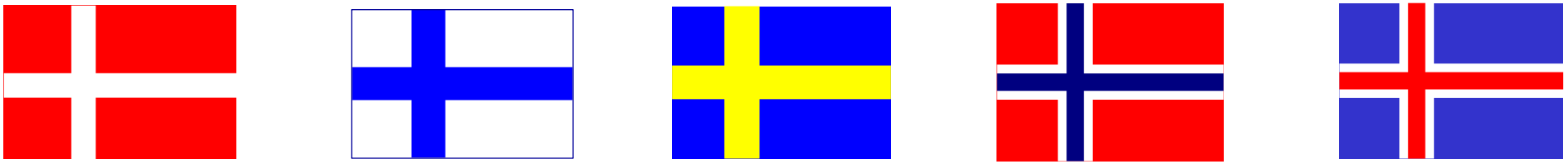
* United States' Centers for Diseases Control and Prevention's Advisory Committee on Immunization Practices

*** Vlaamse Vereniging Obstetrie Gynaecologie

** for sexually active people

Long Term Follow-Up Study Through Nordic Registries

Denmark Finland Sweden Norway Iceland



Phase III Study Registry-Based Follow-Up

Study population

3.5 yr 6 yr 8 yr 10 yr

New subjects

2 yr 4 yr 6 yr

2003 2004 2005 2006 2007 2008 2009 2010 2011 2012 2013

Cervarix (GSK)

- Vaccin bivalent 16-18, sur culture cellulaire d'insecte
- Adjuvant différent :
  - ➔ Sanofi: Hydroxyde d'aluminium
  - ➔ GSK: idem +ASO4
- Revendique taux Ac plus élevé/plus longtemps,

  MAIS techniques ELISA différentes …

⇒ étude comparative des 2 vaccins va commencer

< immunogénicité sur 18-26 ans (+ autres sous groupes)

Cervarix

- Protection croisée (sur PCR des sérotypes) après 6 mois montrée pour type 45 (95 %) et 31 (54 %) et 52

  Données en attente chez Sanofi

- Effficacité sur prévention infection persistante et prévention des lésions précancéreuses provoquées par 16 et 18 : 100 %

  (si on prend en compte virus dans lésion et échantillons antérieurs)

  ou 90% si

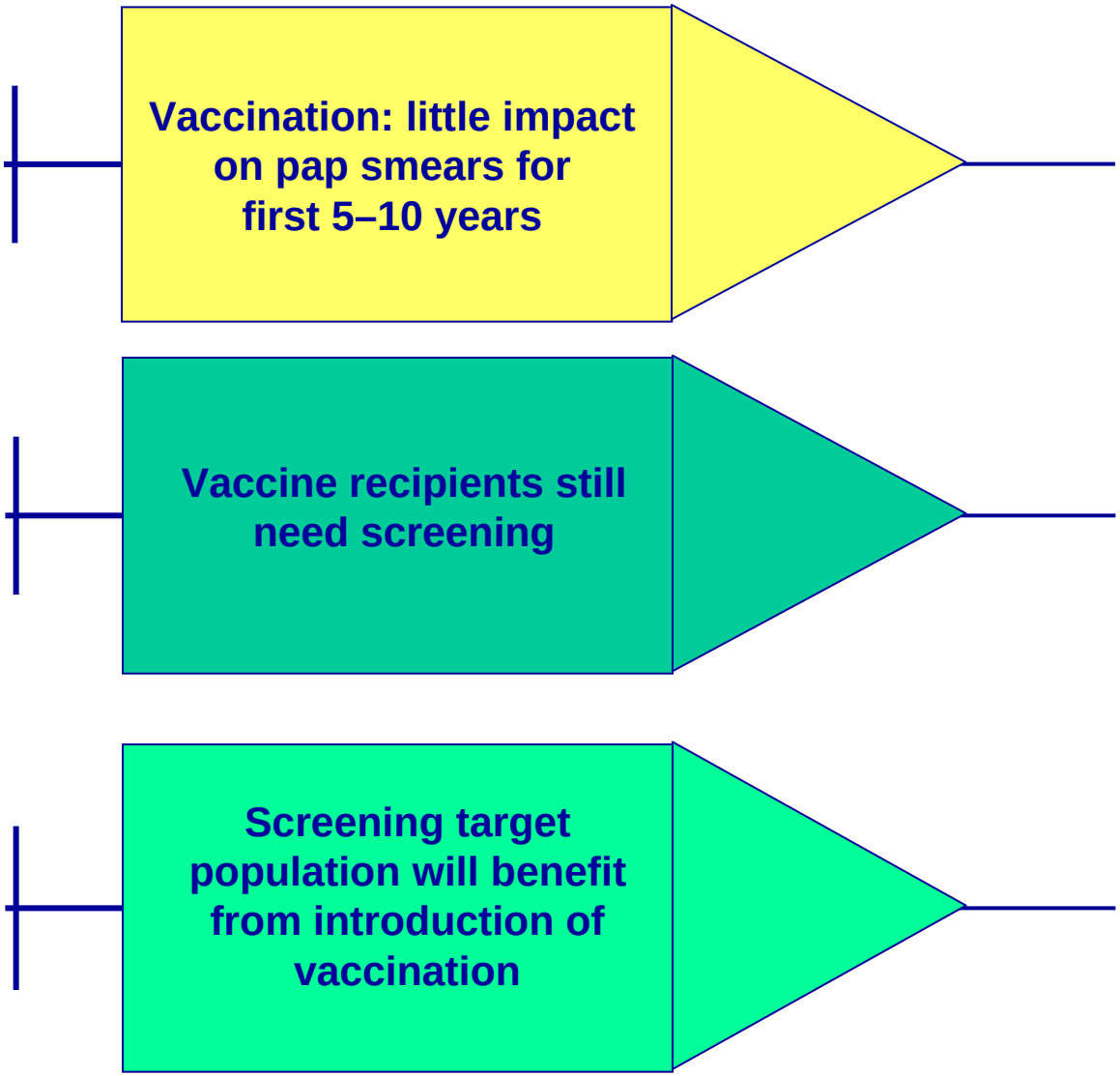
  sur >18.000 femmes de 15 à 25 ans de 14 pays de 4 continents

  Lancet juin 2007

  NB:Recul de plus de 5 ans ausssi quant au maintien efficacité

  Meilleure immunogénicité chez 10-14 ans aussi (taux x2)

Papillomavirus vaccination and screening:
A strong interaction in the future



- Long natural history of disease
- Vaccines targeted to cover 70% oncogenic HPV infections
- Screening = opportunity for vaccination
- Increased HPV-cancer awareness ➔ ↑ screening
- Screening not 100% effective (coverage, sensitivity)

Risque « virologique »?

- Shift possible vers sérotypes cancérigènes non vaccinaux

  MAIS : 16 et 18 induisent le plus haut risque de dysplasie

  (suivi de 10 ans)

- ! Screening reste nécessaire !

Rotavirus

Prévention de la gastroentérite à rotavirus des petits enfants

Rotavirus

- Agents les plus fréquents de gastroentérite aigue(GE) de par le monde
  chez nourrisson et jeune enfant
- Chaque année : 125.105 cas et 500.000 décès (> 80 % dans PVD)
- Chez nous : léthalité très faible mais cause 15-50 % des GE
  → 1ère cause hospit et 2ème consultation chez les < 5 ans

- Rotavirus : virus ARN avec triple enveloppe protéique
  réassortiment assurant diversité++ des virus circulant
  MAIS 4 génotypes prédominants (> 90 % des hospit.)
  G1, G2, G3, G4, et émergeance du G9 récente

Epidémiologie

- Incidence sous estimée

  ? 15.200/100.000 enfants de < 5 ans en Europe

  Mortalité 1/54.000

- ! Aspect infection nosocomiale USA : ¼ des diagnostics !

  cf. étude européenne : 90% GE nosoco sont virales

  transmission par personnel à partir environnement (dose infectante faible/ excrétion virale++)

- Belgique : 6-7.000 hospit/an

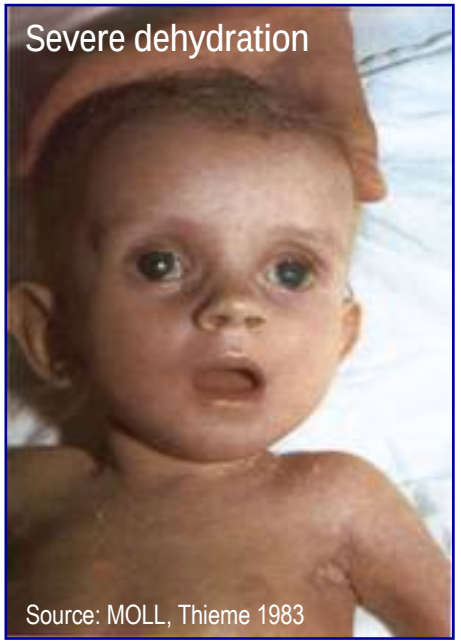
Epidemiologie

- Essentiellement entre 6 et 24 mois
  - 95% infectés > 1 fois à l'âge de 5 ans
  - avant 3 mois: asymptomatique car Ac maternels / allaitement / immaturité intestinale
  - infection symptomatique très rares après 5 ans car immunité s'accroît à chaque épisode

- Avec impact essentiellement sur qualité de vie des enfants / parents

Paediatric Rotavirus Gastroenteritis can lead to severe consequences

- Hits when infants are particularly vulnerable (6-24 months)[1]
- No known risk factors[1]
- Unpredictable evolution of symptoms & severity[1,2,3]
  - ➔ Overnight, a seemingly mild PRG can become life-threatening
- >20 diarrhoea or vomiting episodes in 24 h not uncommon[3]
- Severe dehydration may require hospitalisation

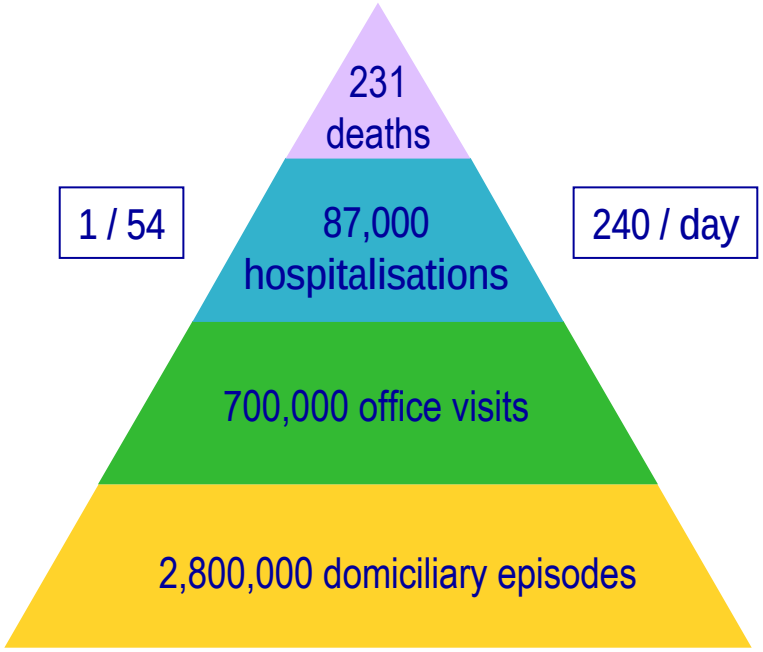


[1] Raebel MS, Ou BS, Pharmacotherapy,1999
[2] Clark HF, Offit PA.Ped Ann 2004
[3] Matson D.O. In: Long SS Ed. Principles and Practice of Paediatric Infectious Diseases 2003

Rotavirus is a leading cause of infant hospitalisation[1,2]

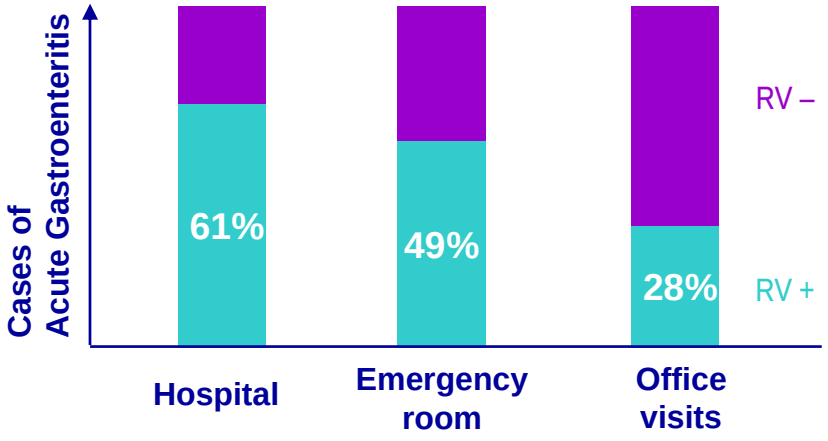
Virtually all children will be infected at least once by the age of 2 to 3[3,4]

In Europe* per year in children <5 yrs[5]



* European Union (25)

Rotavirus represents 50-60% of emergency room visits & hospitalisations for paediatric gastroenteritis[6]



REVEAL study 2004/2005, Epidemiology in seven European regions*

[1] Moulin F et al. Arch Pediatr 2002
[2] Johansen K et al. Acta Paediatr 1999
[3] Clark et al, in Plotkin & Orentstein eds. Vaccines, 2004
[4] Offit and Clark, 2000, in Principles & Practise of Infectious Disease, 2000
[5] Soriano-Gabarro M et al. Paediatr Infect Dis J 2006
[6] Giaquinto C et al. Oral presentation, ESPID congress, May 3-5, 2006, Basel

** in Belgium, England, France, Germany, Italy, Spain, Sweden

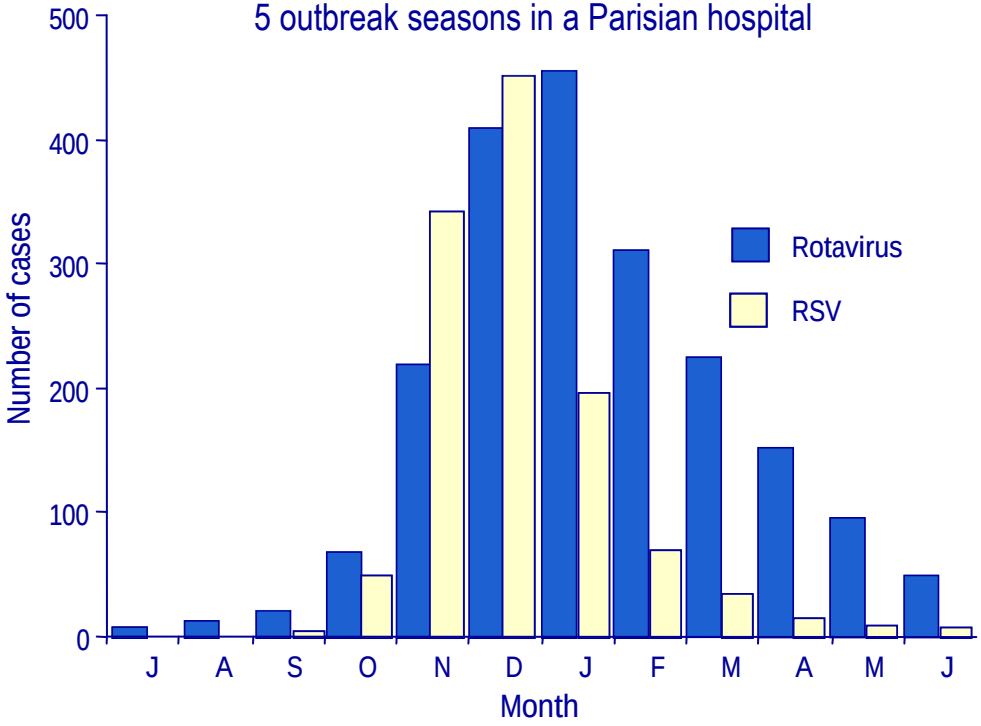
RV+ = Rotavirus positive

RV- = Rotavirus negative

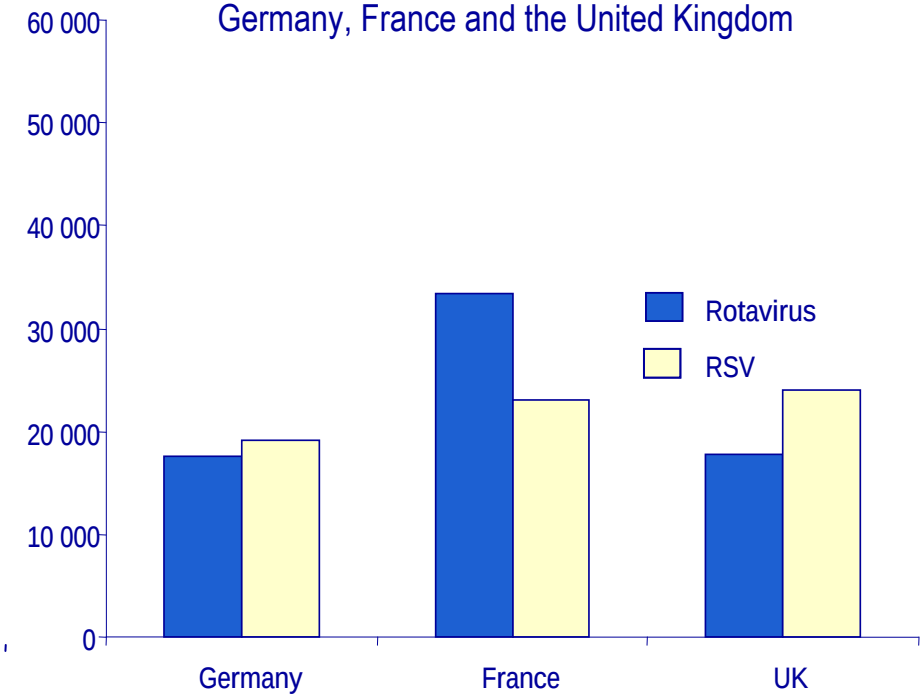
Paediatric Rotavirus Gastroenteritis (PRG) peaks in winter and leads to similar numbers of hospitalisation as RSV*

PRG can overload hospitals at a time when they are already busy with RSV infections & bronchiolitis

Monthly distribution of RSV and rotavirus during 5 outbreak seasons in a Parisian hospital



Number of hospitalisations per year in Germany, France and the United Kingdom

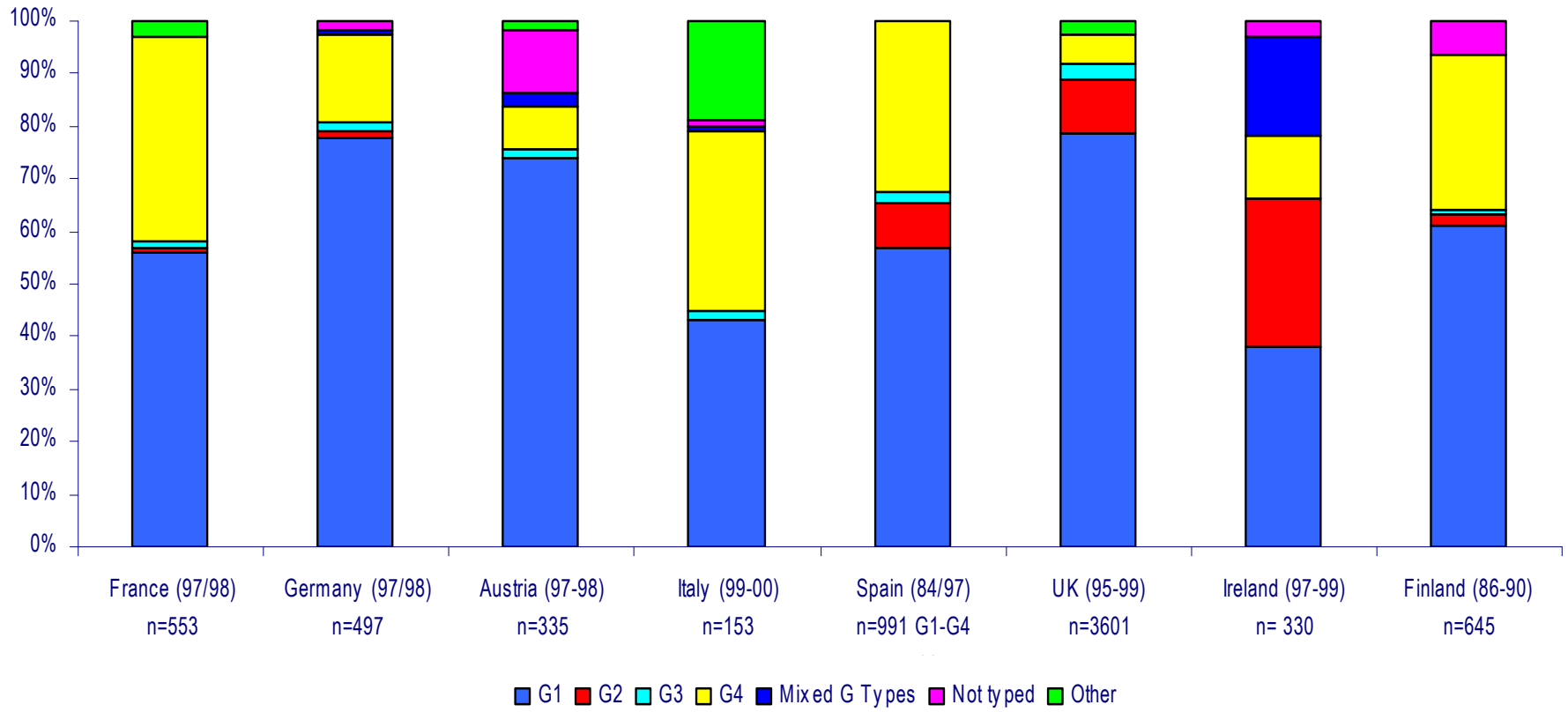


Granry et al. *Conférences d'actualisation* 2001; Weigl et al. *Epidemiol Infect* 2002; Ryan et al. *JID* 1996
Muller-Pebody et al. *Epidemiol Infect* 2002; Gendrel et al. *Arch Pediatr* 1999;
Le Roux P et al. Arch Pediatr 2004; Moulin F et al. BEH,1999;
http://www.grog.org/cgi-files/db.cgi?action=bulletin_vrs;
who.int/vaccines-diseases/diseases/rotavirusdisease.shtml;
Sanofi Pasteur MSD, REVEAL**, final report 2006
** *Rotavirus gastroenteritis Epidemiology and Viral types in Europe Accounting for Losses in Public Health & Society, prospective multicentre, observational study in 7 EU regions, Oct 2004 to Sept 2005*

* Respiratory Syncitial Virus

There are several different rotavirus types that circulate in unpredictable proportions: from country to country…

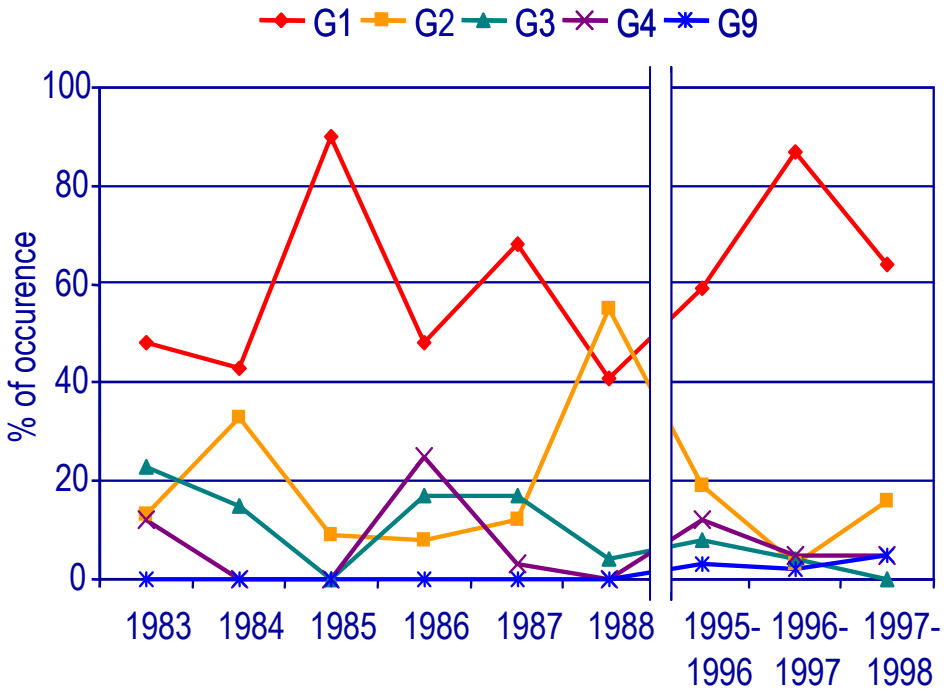
Geographic distribution of rotavirus serotypes collected in selected European countries



France: Bon F et al, J Clin Microbiol, 2000; Germany: Ehlken B et al, Acta Paediatr, 2002
Austria: Frühwirth M et al, J Clin Microbiol, 2000; Italy: Arista S, Europ J Epidemiol, 2003
Spain: Cilla G et al, Epidemiol Infect, 2000; UK: Iturriza-Gomara et al, J Virol, 2001
Ireland: O'Halloran et al. J Clin Microbiol, 2000; Finland: Maunula L et al, Arch Virol, 1995

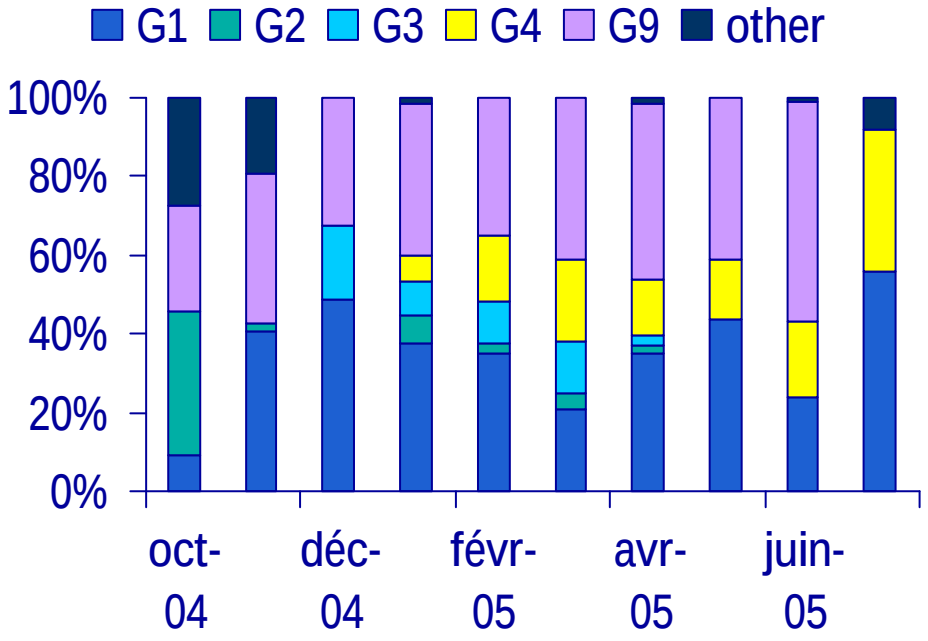
...from year to year ...and even from month to month

Temporal fluctuation of the prevalence of rotavirus G serotypes in the United Kingdom (1983-1988,1995-1998)



Santos N, Hoshino Y,Rev Med Virol, 2005

Proportion of G-serotypes (%) per month in the seven REVEAL* study areas

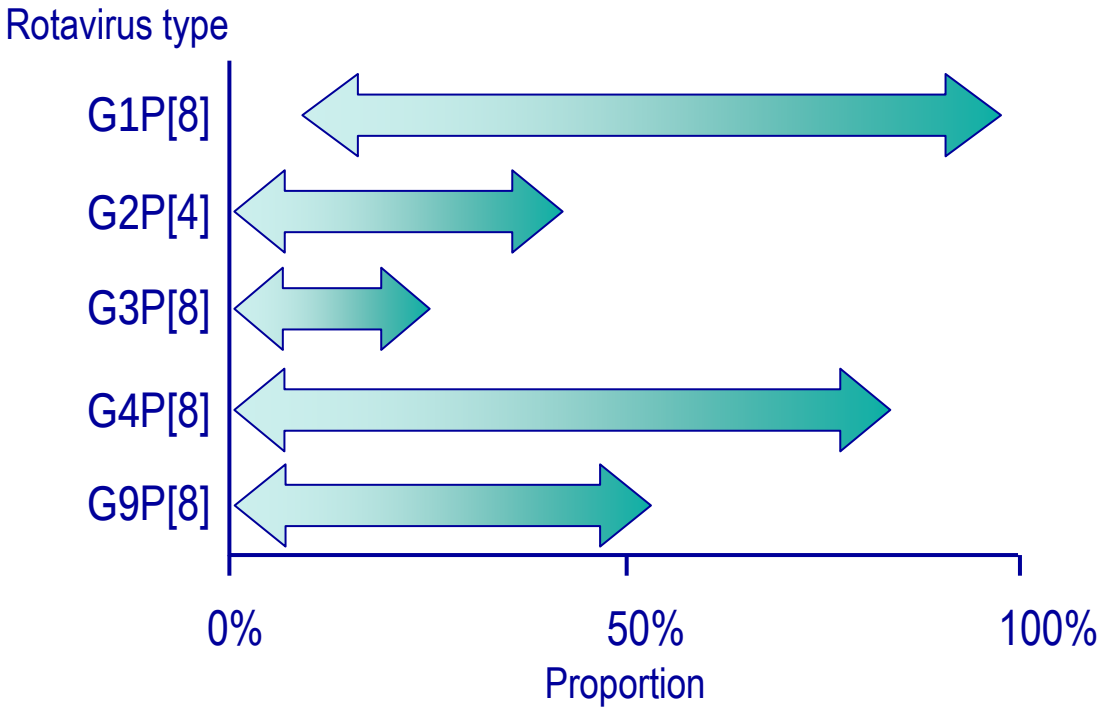


* Rotavirus gastroenteritis Epidemiology and Viral types in Europe Accounting for Losses in Public Health & Society

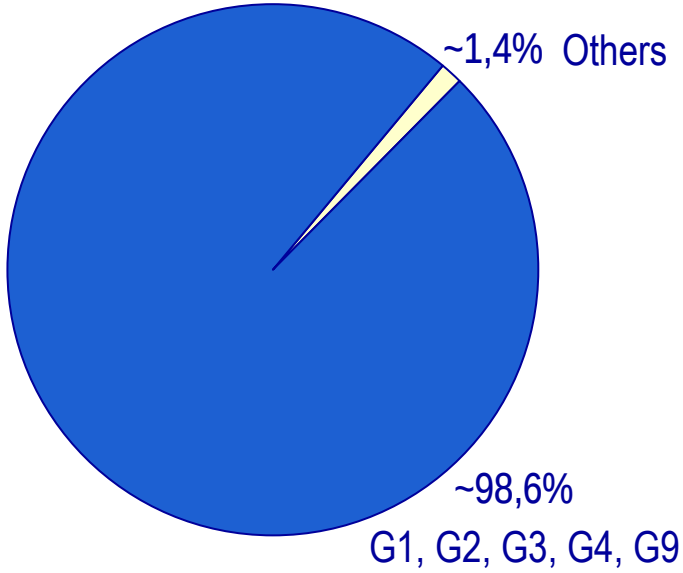
P van Damme, Oral presentation,7th International Rotavirus Symposium, Lisbon, 12th June 2006 REVEAL Prospective multicentre, observational study in 7 EU regions, Oct 2004 to Sept 2005

It is unpredictable which rotavirus type will infect a given child at a given time in a given region…

Variation in the distribution of rotavirus types in Europe[1]



Proportion of rotavirus serotypes (in %) as
- collected in several European countries[2]
- observed in the 7 REVEAL* study areas[3]



… but 5 rotavirus types are responsible for ~98% of rotavirus disease

[1] Desselberger U et al. Pediatr Infect Dis J 2006
[2] between 1983-2002 (n=7024 strains), Santos N, Hoshino, Rev Med Virol, 2005
[3] between October 2004 and September 2005, P van Damme, Oral presentation, 7th International Rotavirus Symposium, Lisbon, 12th June 2006 REVEAL Prospective multicentre, observational study in 7 EU regions, October 2004 to September 2005

* Rotavirus gastroenteritis Epidemiology and Viral types in Europe Accounting for Losses in Public Health & Society

Efficacité des vaccins

- Première génération (fin années ’70)

  souche non humaine, par voie orale : résultats faibles / variables

  vaccin tétravalent (1998) : RotaShield

  OK, mais retiré après 1 an car risque faible/démontré d’invagination intestinale : 1/38-58.000, ↑↑ si après 6 mois d’âge…

- Deuxième génération (2006)

  Rota Teq : pentavalent réassortant

  Rotarix : monovalent humain

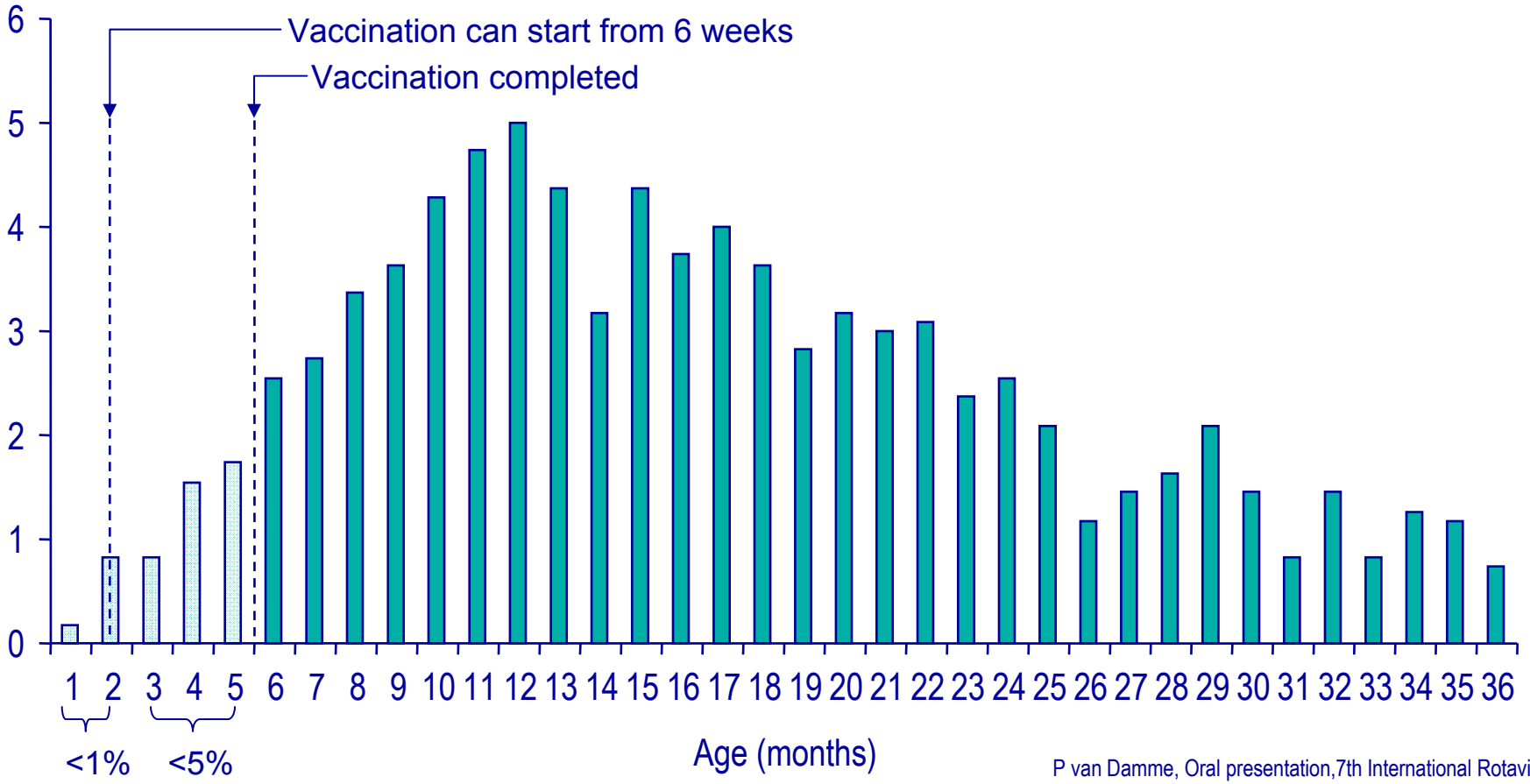
Rota Teq

- Vaccin pentavalent basé sur G1, G2, G3, G4, G6
- Vivant atténué par voie orale, sur réassortant virus bovin / virus humain
- Trois doses à 4 sem. intervalle, entre 6 ème et 26 ème sem.
- Efficacité : globale 74 %
  sur formes sévères : 98 %
- Pas augmentation risque invagination

- Pas interférence avec vaccin hexavalent

RotaTeq® vaccination starts early and is completed before peak infection

Proportion of cases of Paediatric Rotavirus Gastroenteritis (%) per month of age



P van Damme, Oral presentation,7th International Rotavirus Symposium, Lisbon, 12th June 2006 REVEAL Prospective multicentre, observational study in 7 EU regions, October 2004 to September 2005

RotaTeq®'s indication covers the 5 predominant disease-causing rotavirus

Composition	5-type (pentavalent) G1, G2, G3, G4, P1
Indication[1]	Covering the 5 predominant disease-causing rotavirus types
Efficacy[2,3]	High & consistent
Safety / tolerability[2]	Good safety profile & well tolerated
Use	Oral Fully liquid, ready-to-use  3 doses, ≥ 4 weeks apart

⇨ from the age of 6 weeks

⇨ G1, G2, G3, G4 & G9

⇨ 98%* - 100%** prevention of severe disease§

⇨ 96%† - 100%†† reduction of hospitalisation$

Efficacy & Safety studied in 70,000 infants[2]

➔One of the largest studies in vaccine history (REST#)

➔Stringent protocol with high quality level

[1] EU license, 27th June 2006
[2] Vesikari T et al. N Engl J Med 2006
[3] Block SL et al. CDC, 2005

* 95% CI [88.3, 100]
** 95% CI [35,100]
† 95% CI [90.5,98,2]
†† 95% CI [67.4,100]

§ due to the serotypes G1, G2, G3, G4
$ due to the serotypes G1, G2, G3, G4, G9

Rotavirus Efficacy and Safety Trial

Rotarix

- Basé sur souche G1
- Vivant atténué; 2 doses à > 4 semaines, entre 6ème et 24ème sem.
- Pic excrétion virale à J7, sans maladie dans contacts

- Plusieurs études montrent :
  - > 70% contre toutes formes
  - > 85% contre formes sévères et +/- 90% contre formes nécessistant hospitalisation
  - Protection croisée contre G3, G4, G9
  - Pas d'augmentation invagination
- Etude RDB en cours dans 6 pays européens;
  résultats préliminaires : >96 % protection sur formes sévères

Cout des infections à Rotavirus

- Dans une étude d'un des producteurs de vaccin :
  - ➔ coût pour l'Europe : 91.000.000 euros / an en hospitalisation
- Etudes coût/efficacité indépendantes en attente

Zona

Prévention du réveil localisé d'une infection à Herpès zoster

Zona

- Plus de 50% ont plus de 60 ans
- Complication la plus fréquente: neuropathie post zostérienne

  dont la fréquence augmente avec âge

  qui peut durer des années

  pas (bien) prévenu par trait. antiviral (au contraire sympt. aigus)

- Lié à diminution immunité cellulaire spécifique avec âge
- Zona suscite booster naturel: rares récidives si immunocompétents

Zostavax (Sanofi Pasteur)

- Vaccin vivant atténué; 14 fois plus puissant que vaccin Varicelle

  Etude RDB sur 38.500 patients de > 60 ans (NEJM 2005)

  Sur suivi médian de 3,1 ans:

  - Zona: 315 versus 642 (-51%)
  - Névralgies post zoster: 27 versus 80 (-66%)

- Effets secondaires plus fréquents dans groupe vaccin, mais mineurs à modérés

  Pas en Belgique avant 2ème moitié de 2008

Vaccin méningo conjugué A/C/Y/W135

- Cf. vaccin conjugué C

  vaccination large dans nombreux pays européens, dont Belgique.

  →diminution drastique du nombre de cas / modif. épidémiologiques.
  (49% cas en 2001, 10% en 2005)

- Cf. vaccin polysaccharidique A/C/Y/W135:

  inadéquat chez nous car:

  -seul C réellement présent

  -protection limitée dans temps (3 ans) et âge (> 2 ans) cf.polysacch.
  impliquant revaccination/ diminution (significative?) taux Ac induit

  Employé (presque) uniquement,en Europe, pour vaccination :
  voyageurs dans ceinture des méningites / pélerins Hajj-Omrah

Menactra (Sanofi Pasteur)

- Vaccin conjugué quadrivalent (conjuguaison à toxoide diphtérique)
- Induit immunité long cours (plus de 8 ans au moins)
- Evite portage
- Recommandé en routine depuis 2005 aux USA par ACIP,
  pour 11-12 ans, puis 11-18 ans,
  ainsi que de 19 à 55 ans si risque accru.
  (cf.depuis '97-2000: 1/3 cas sont Y et 1/3 C)
- Associé à syndrôme de Guillain Barré (risque?)
- Intérêt en Belgique?

  Souches Y et W135 : 2 et 4% du total, stables en nombre absolu

  (↑en nombre relatif)

Vaccin antipneumococcique conjugué 10 ou 13 valents

Cf. activité du vaccin 7 valents clairement montrée:

-diminution des infections invasives de enfant ET des adultes (protection de groupe)

-diminution des souches R aux AB

MAIS: - shift vers souches NON vaccinales

-adéquation insuffisante pour épidémio adulte

- Les deux nouveaux vaccins (GSK et Wyeth):

-étendent souches couvertes pour enfants

- couvrent de 75 à 85% des souches invasives de l'adulte

Phases 3 en cours/programmées

Et le futur plus lointain….

- Vaccin S.pyogenes
- Vaccin S.aureus,P.aeruginosa,C.difficile…
- Vaccins CMV,EBV,….(HIV…)

  Désillusion récente pour HCV…
- Vaccin P.falciparum: existe (Malarix), à améliorer

  < % protection, groupes d'âge,..
- Vaccin M.tuberculosis(autre que BCG…)
- MAIS aussi vaccins avec « nouveaux « adjuvants/techniques(ADN,..)

  à application muqueuse (le 1er: Influenza)

  thérapeutiquess (HIV,…)

  oncologiques