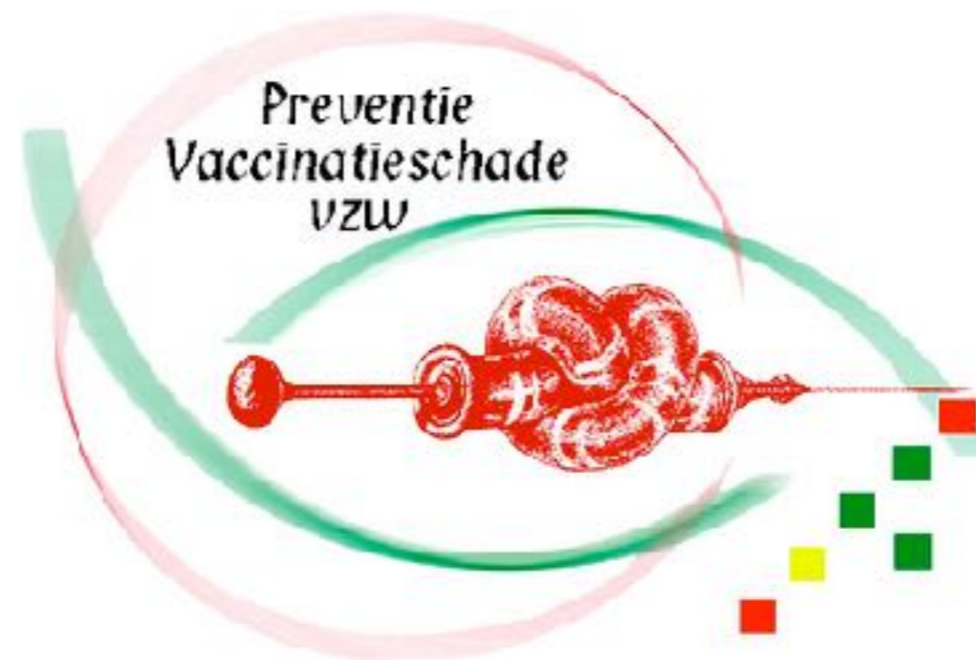


# HPV vaccinatie



Preventie vaccinatieschade vzw

dr. Kris Gaublomme

# Argumenten pro vaccinatie

- ❖ HPV (human papilloma virus) 16 of 18 is aanwezig in 70% van cervixkankers
- ❖ besmetting door seksueel contact: daarom vaccineren tijdens vroege puberteit
- ❖ snelle partnerwissel bij jeugd
- ❖ ook jongens (wegens ???)
- ❖ Andere indicaties: anale CA, keelCA, huidCA...

# De theorie

- ❖ 1° baarmoederhalskanker is het gevolg van HPV-infectie;
- ❖ 2° vaccinatie tegen HPV voorkomt deze infectie;
- ❖ 3° het voorkomen van HPV-infectie voorkomt baarmoederhalskanker.
- ❖ DUS: vaccineren = kankerpreventie

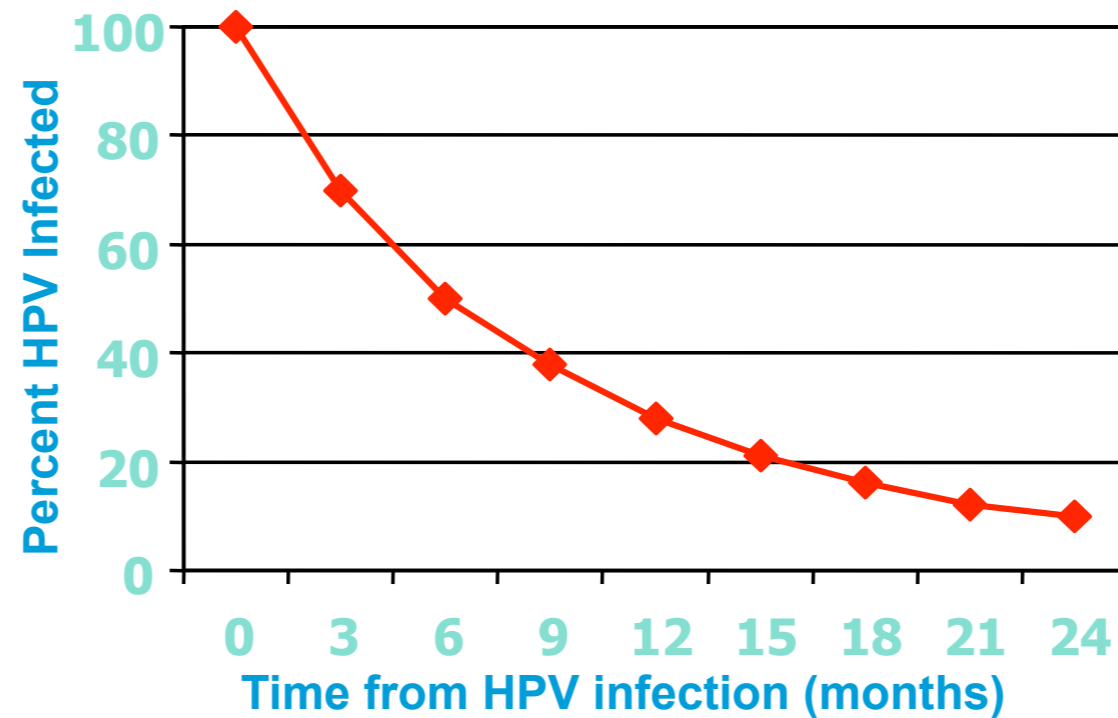
# De praktijk

- ❖ 1° Relatie HPV - baarmoederhalskanker
  - ★ 30% is niet HPV 16/18 gebonden
  - ★ aanwezigheid HPV = oorzaak ???
  - ★ gezonde dragers / draagsters: infectie ≠ ziekte !
  - ★ SPONTANE genezing in 90% der gevallen binnen 2 jaar

# Efficiëntie van vaccin



## Clearance of HPV Infections



*Adapted from Brown et al. JID 2005:191;182*

# De praktijk

- ❖ 2° *“Vaccinatie voorkomt HPV-infectie”*
- ★ nauwelijks gegevens bij - 15-jarigen; \*
- ★ vaccinatie bij geïnfecteerden geeft geen bescherming...
- ★ ...maar verhoogt zelfs het risico op CA met 44,6%;

# De praktijk

• The quadrivalent HPV vaccine was approved for use in young adolescents based on immunogenicity-bridging studies rather than efficacy studies.<sup>2</sup>

Dobson, JAMA, May 1, 2013—Vol 309, No. 17 1793

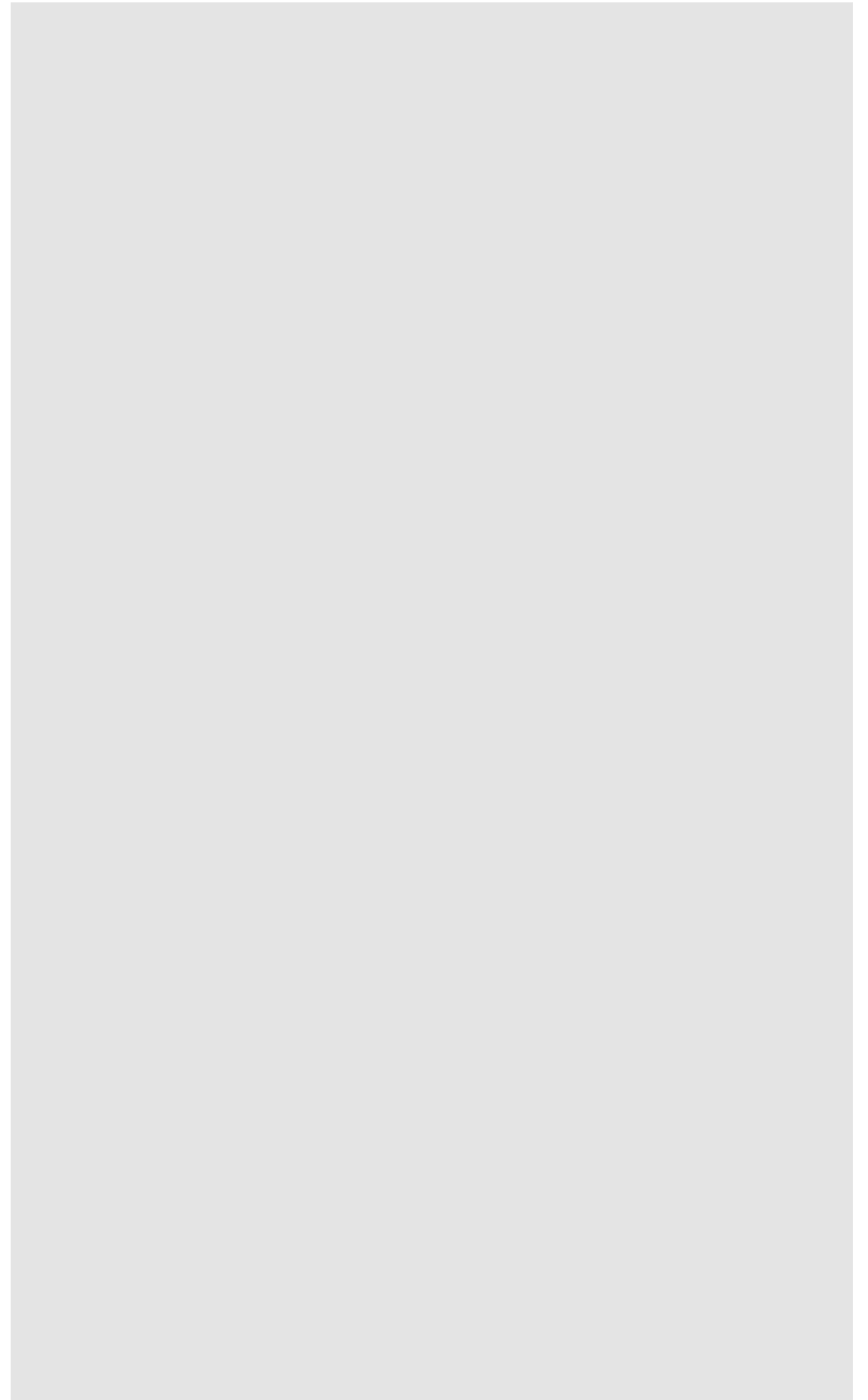
# De praktijk

- ❖ 3° “preventie van HPV-infectie voorkomt baarmoederhalskanker”.
- ★ geen bewijzen; geen studies op lange termijn;
- ★ 1+1=1: vaccinatie + uitstrijkjes biedt geen voordeel t.o.v. uitstrijkjes alleen;
- ★ CA door chromosoombreuk, niet door HPV?
- ★ “70% daling kankers na vaccinatie” pas na 60 jaar merkbaar;
- ★ teruggang door vaccinatie trager dan door spontane teruggang en screening (4% per jaar; 91,4% / 60J).



have been developed. That is the good news. The bad news is that the overall effect of the vaccines on cervical cancer remains unknown. As Kim and Goldie<sup>1</sup> point out in this issue of the *Journal*, the real impact of HPV vaccination on cervical cancer will not be observable for decades.

Haug, C.; NEJM, 2008; 359:861



# Bedenkingen

- ❖ aanwezigheid = oorzaak ?
- ❖ één enkele oorzaak ??
- ❖ Belang van immuunstatus ?
- ❖ lichte chronische letsels genezen praktisch altijd spontaan
- ❖ matig ernstige letsels (CIN II) genezen in 78% spontaan
- ❖ ernstige letsels (CIN III) genezen ook nog voor een deel spontaan

# Voorwaarden voor kankerontwikkeling

- ❖ < 200 ≠ stammen
- ❖ slechts 40 kunnen genitale slijmvliezen infecteren
- ❖ slechts 18 kunnen kanker veroorzaken
- ❖ meestal enkel dysplasie
- ❖ zelfs bij infectie met HPV-16 infectie nog < 5% risico op CA
- ❖ latentietijd van 15 jaar
- ❖ risico loopt op met de leeftijd (quid beschermingsduur vaccin ?)
  - ★ 20 - 30 j lichte precancereuse letsels
  - ★ 30 - 40 j ernstige letsels
  - ★ 40 - 60 j invasieve CA

# Risicofactoren

- ❖ vroegtijdig seksueel contact;
- ❖ promiscuïteit (veel wisselende partners);
- ❖ veel zwangerschappen;
- ❖ andere seksueel overdraagbare aandoeningen (SOA's);
- ❖ slechte socio-economische omstandigheden;
- ❖ roken;
- ❖ langdurige orale contraceptie:
  - ★ < 5 jaar x 3, < 10 jaar x 10 (The Lancet, eind maart 2004).
  - ★ < 5 jaar x 2 ( WGO )
- ❖ een verzwakt immuunsysteem (iatrogeen?)
- ❖ verhoogd risico bij vaccinatie na HPV-infectie !!
- ❖ geografische spreiding: < 80% in ontwikkelingslanden

# Efficiëntie van vaccin

- ❖ combinatie niet efficiënter dan uitstrijkjes alleen
- ❖ herhaling nodig om de ?? jaar;
- ❖ geen bescherming tegen andere HPV-stammen
- ❖ versnelling mutaties, antigene shift =>
  - ★ vermindering van natuurlijke immuniteit;
- ❖ geen remmende invloed op andere virussen / bacteriën
- ❖ ontbrekende stammen in het vaccin: 11 en 58

<b>cytologie*</b>	L-SIL zie verslag cytopathologie
<b>Concentratie DNA*</b>	89,02 ng/μl
<b>HPV type 16 E7</b>	289 copies/cel
<b>HPV type 18 E7</b>	0 copies/cel
<b>HPV type 31 E6</b>	0 copies/cel
<b>HPV type 33 E6</b>	0 copies/cel
<b>HPV type 35 E6</b>	0 copies/cel
<b>HPV type 39 E7</b>	0 copies/cel
<b>HPV type 45 E7</b>	0 copies/cel
<b>HPV type 51 E7</b>	0 copies/cel
<b>HPV type 52 E7</b>	0 copies/cel
<b>HPV type 56 E7</b>	0 copies/cel
<b>HPV type 58 E7</b>	0 copies/cel
<b>HPV type 59 E7</b>	0 copies/cel
<b>HPV type 66 E6</b>	0 copies/cel
<b>HPV type 68 E7</b>	0 copies/cel
<b>HPV type 6 E6</b>	0 copies/cel
<b>HPV type 11 E6</b>	0 copies/cel
<b>HPV type 53 E6</b>	>99999 copies/cel (+ )
<b>HPV type 67 L1</b>	0 copies/cel
<b>BESLUIT HPV-TYPERING*</b>	Aanwezigheid van meerdere types HPV.

Gardasil 9: stam 6-16-18-31-33-45-52  
 Afwezig: stam 11, 58  
 Ongewenst: stam 20

# Efficiëntie van vaccin

Geen versnelde clearance bij besmette vrouwen (Hildesheim)

% Clearance		
	Gevaccineerd (3d)	Niet-gevaccineerd
6 m	33,4	31,6
12 m	48,8	49,8

# Efficiëntie van vaccin

Hildesheim,  
2007

**Table 2.** Viral Clearance and Vaccine Efficacy for Viral Clearance for HPV-16 and HPV-18 by Study Group at 6 Months and 12 Months of Follow-up

Follow-up Time, mo	No. Cleared/Total Infections (%) <sup>a</sup>		Vaccine Efficacy for Viral Clearance, % (95% CI)
	HPV Vaccine Group	Control Group	
HPV-16			
6	47/172 (27.3)	61/222 (27.5)	-0.2 (-13.2 to 11.3)
12	54/123 (43.9)	73/159 (45.9)	-3.7 (-28.2 to 16.1)
HPV-18			
6	35/76 (46.1)	34/76 (44.7)	2.4 (-30.5 to 27.0)
12	32/54 (59.3)	37/61 (60.7)	-3.5 (-62.0 to 33.8)
HPV-16/18 <sup>b</sup>			
6	82/248 (33.4)	95/298 (31.6)	2.5 (-9.8 to 13.5)
12	86/177 (48.8)	110/220 (49.8)	-2.0 (-24.3 to 16.3)
HPV-16/18 (restricted to women who received all vaccine doses) <sup>c</sup>			
6	81/241 (33.8)	93/288 (32.0)	2.6 (-10.1 to 13.8)
12	69/149 (46.5)	98/196 (50.0)	-7.0 (-31.7 to 13.0)
HPV-16/18 (restricted to women with single infections at entry)			
6	23/82 (28.0)	24/97 (24.7)	4.4 (-14.1 to 19.9)
12	28/63 (44.4)	37/79 (46.8)	-4.5 (-41.4 to 22.8)

Abbreviations: CI, confidence interval; HPV, human papillomavirus.

<sup>a</sup>Percentages calculated using generalized estimating equations method and may therefore vary from crude percentages.

<sup>b</sup>HPV-16/18 is defined as HPV-16 and/or HPV-18.

<sup>c</sup>All doses are defined as 2 doses at the 6-month follow-up and 3 doses at the 12-month follow-up.



# Efficiëntie van vaccin

“It is therefore crucial to give the vaccine to naïve individuals. During their review of Gardasil by the FDA, the efficacy of the vaccine was also evaluated on individuals who were exposed to the oncogenic HPV strains before vaccination since individuals who are non-naïve will also receive the vaccination. A concern was raised for disease enhancement (increase in CIN 2/3, cervical adenocarcinoma in situ or worse) in this subgroup. In these individuals, the efficacy was -25.8% (95% CI: -76.4, 10.1%).

Thus, vaccination with Gardasil of non-naïve individuals who had HPV 16/18 oncogenes before vaccination showed a higher level of premalignant cell changes than did placebo.

The increase in premalignant cell changes in non-naïve individuals, as suggested by the FDA, is consistent with the knowledge that **vaccination can cause reactivation of both target and non-target viruses**.

For individuals exposed to Gardasil, evidence of a selective and significant reactivation of the oncogenic non-target HPV types 52 and 56 was reported in the genital tract for all women.”

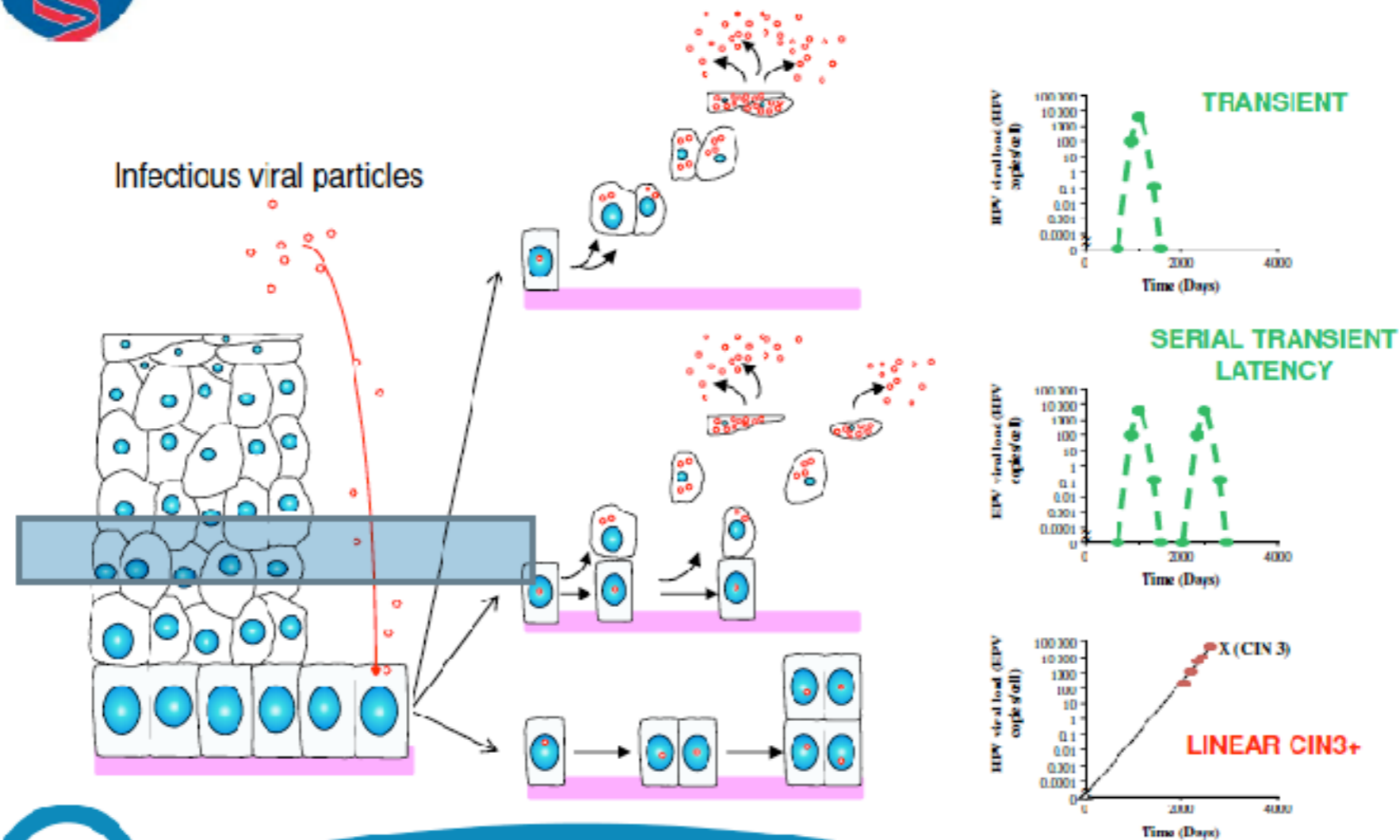
# Infecties na vaccinatie

- Walter R, Hartmann K, Fleisch F, Reinhart WH, Kuhn M. Reactivation of herpesvirus infections after vaccinations. *Lancet* 1999;353(9155):810.
- Bayas JM, González-Álvarez R, Guinovart C. Herpes zoster after yellow fever vaccination. *J Travel Med.* 2007;14(1):65-6.
- Rothova A, de Groot JD, Mudrikova T. Reactivation of acute retinal necrosis after flu H1N1 vaccination. *Br J Ophthalmol.* 2011;95(2):291
- Hwang CW Jr, Steigleman WA, Saucedo-Sanchez E, Tuli SS. Reactivation of herpes zoster keratitis in an adult after varicella zostervaccination. *Cornea.* 2013 Apr;32(4):508-9.
- Hassman LM, DiLoreto Jr DA. Immunologic factors may play a role in herpes simplex virus 1 reactivation in the brain and retina after influenza vaccination. *IDCases.* 2016 Sep 22;6:47-51.
- Jastrzebski A, Brownstein S, Ziai S, Saleh S, Lam K, Jackson WB. Reactivation of herpes zoster keratitis with corneal perforation after zoster vaccination. *Cornea.* 2017 Jun;36(6):740-2.
- Lieberman A, Curtis L. HSV2 reactivation and myelitis following influenza vaccination. *Hum Vaccin Immunother.* 2017 Mar 4;13(3):572-3.

# Efficiëntie van vaccin



## Categorization of infection according to basal cell division

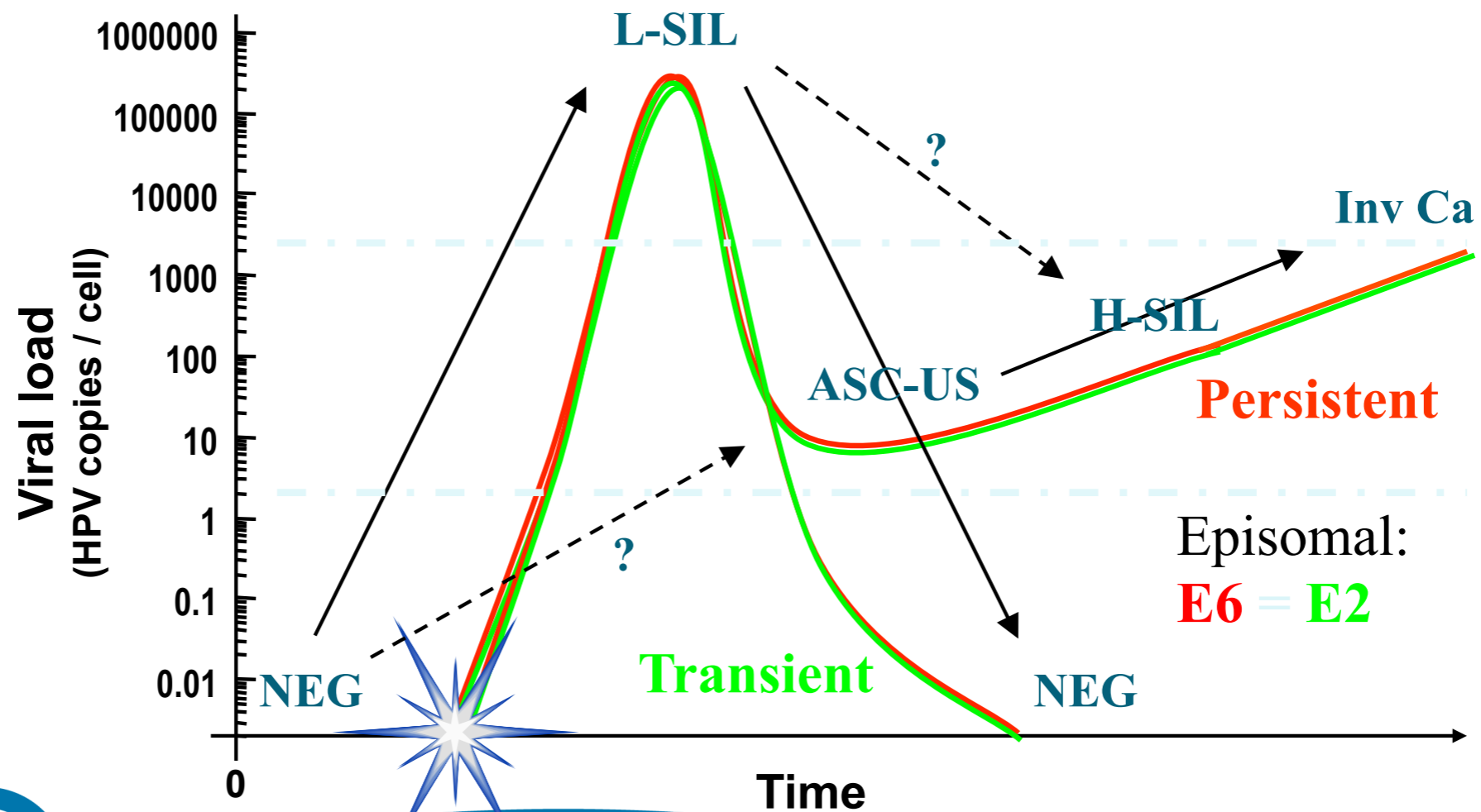


# Efficiëntie van vaccin



## Verloop HPV infection

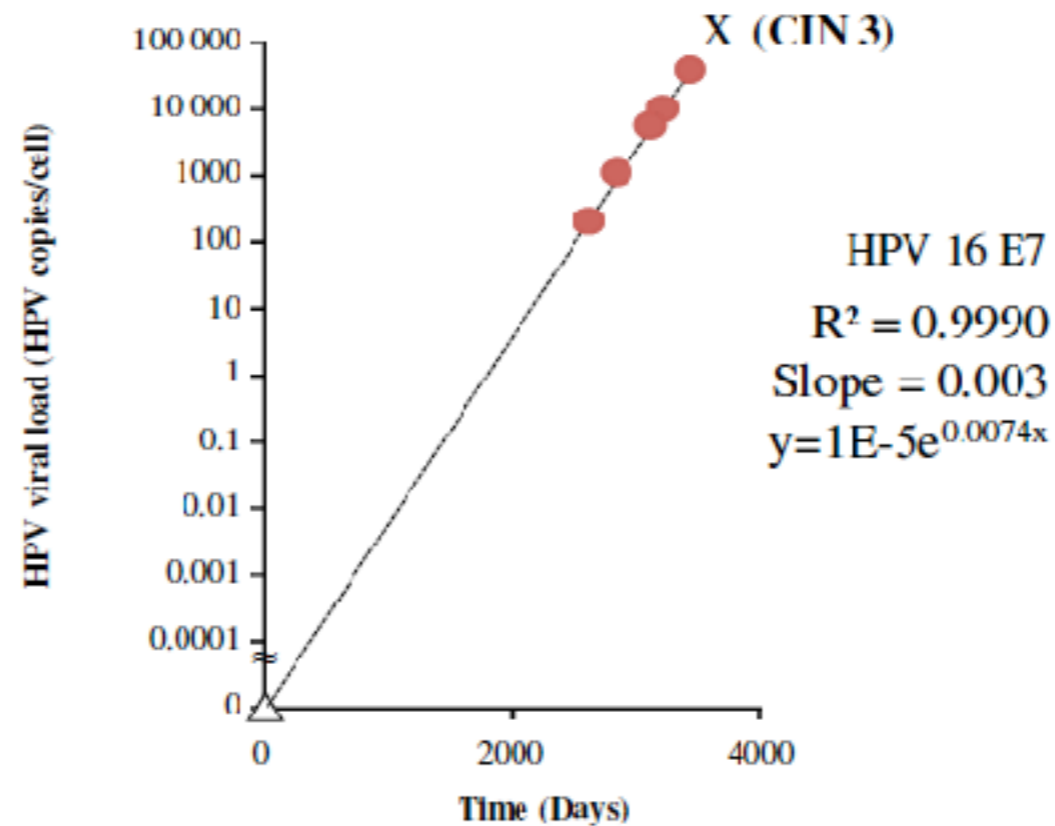
SIL = Squamous Intraepithelial Lesion



# Efficiëntie van vaccin



## Evolution of the Viral Load (HPV Copies/Cell) Over Time (in Days) in Cases Developing CIN3+



Circles = viral load measurements. Triangle represents the calculated starting point of the linear increase leading to CIN3+ with viral load of 0.00001 HPV copies/cell. The dotted line represents the least squares line. X = detection of CIN3+.

# Open vragen

- ❖ Zal het vaccin niet alleen precancereuze letsels, maar ook kanker zelf voorkomen ??
- ❖ Hoe lang blijft de “bescherming” duren ??
- ❖ Bescherming tegen andere HPV-types: 🙄
- ❖ Verschuivingen tussen HPV-types ?! 🙄
- ❖ Invloed van vaccinatie na HPV-besmetting ? CA < ! 🙄

# Negatieve effecten

Méér baarmoederhalskanker door

- ★ vaccinatie van besmette vrouwen
- ★ verwaarlozen van uitstrijkjes
- ★ nieuwe serotypes
- ★ daling van de natuurlijke immuniteit

Daling van de leeftijd bij diagnose

# Veiligheid

- ❖ Vals gevoel van veiligheid vs preventie (SOA's)
- ❖ Adjuvantia
- ❖ Geen lange termijn studies
- ❖ Geen placebo-gecontroleerde studies
- ❖ Geen studies bij jonge meisjes



# Veiligheid

## Aanwezig:

- 7 van de 9 opgegeven HPV-antigenen
- stam 20 (545 reads): hoort er niet thuis
- chemische contaminatie (productie, crosscontaminatie): 338 signals, 22% bekend
- 10 chemische toxines
- bacterieel DNA: 54% van totaal DNA => allergie, ontsteking, auto-immuniteit
- menselijk DNA
- muis DNA
- **HPV-DNA** (L1-fragment): gebonden aan alum, in macrofagen, mogelijkheid tot integratie in menselijk DNA, ontstekingen, auto-immuniteit, cancerogeen
- fagen: mogelijke integratie in het bacterieel DNA van de flora
- molluscum contagiosum virus
- retrovirussen: integratie in DNA; CA; mutaties;
  - muizen leukemie virus (DNA + RNA, dus actief)
  - menselijk endogeen retrovirus K

# Veiligheid

## Aanwezig:

- synthetisch RNA: recombinaatie met menselijk DNA?
- gist RNA (allergie); L-BC virus en narvavirus
- infectieus paardenanemie virus
- 338 signalen waarvan **78% niet identificeerbaar!**
- APDB (in lot R009338) = amfetamine! (Klacht afgewezen...)

# Nevenwerkingen

- ❖ **VEGETATIEF:** POTS (posturaal orthostatisch tachycardie syndroom): cfr. Thiamine (Vit B1) tekort ?!
- ❖ **REUMATOLOGISCH:** artritis (RA, juveniele artritis), lupus; macrofagen fasciitis; EN;
- ❖ **NEUROLOGISCH:** Epilepsie; encephalitis; hersenoedeem; verlammingen (Guillain-Barré), paresthesieën (tintelingen); demyelinisatie (M.S., opticusneuritis): **auto-immuun reacties !!!**
- ❖ **OFTALMOLOGISCH:** uveïtis
- ❖ **CARDIO-VASCULAIR:** bloedklonters, hartaanval; (intracerebrale) vasculitis; Raynaud; myocarditis oiv TNF van geactiveerde macrofagen.

# Nevenwerkingen

- ❖ **GYNECOLOGISCH:** miskraam (vaccinatie < 30d na conceptie); steriliteit (polysorbaat 80 - Gardasil)
- ❖ **ALLERGIE:** anaphylactische reacties (polysorbaat 80)
- ❖ **PSYCHIATRIE:** anorexie, agressief gedrag, psychose
- ❖ **GENETISCHE CONTAMINATIE** via macrofagen met virale of bacteriële DNA-fragmenten
- ❖ **ENDOCRINOLOGISCH:** thyreoiditis, hypo- en hyperthyreoidie, DM,
- ❖ **GASTRO-INTESTINAAL:** coeliakie, prikkelarm
- ❖ **NEFROLOGISCH:** nefritis
- ❖ **HUID:** Stevens-Johnson, psoriasis, scleroderma, pigmentstoornis;
- ❖ **Overlijden:** 159 (VAERS, 2014), tot 6m PV.

# Adjuvantia

## GARDASIL

- ❖ Aluminiumhydroxyfosfaat sulfaat (225  $\mu\text{g}$  Al);
- ❖ polysorbaat 80
- ❖ NaCl
- ❖ na-boraat;
- ❖ L-histidine

## CERVARIX

- ★ ASO4 =
  - aluminiumOH 0,5mg +
  - 3-O-desacyl-4'-monophosphoryl lipide A 50 $\mu\text{g}$
- ★ NaCl
- ★  $\text{NaH}_2\text{PO}_4 \cdot 2 \text{H}_2\text{O}$

# Adjuvantia

- ❖ Aluminium (Gardasil, Cervarix)
  - ❖ opstapeling in hersenen; gedrags- en geheugenstoornissen; schade BHB; Alzheimer; M.S., ALS, Parkinson; macrofagenmyofasciitis.
  - ❖ 225  $\mu\text{g}$  in Gardasil 4, 500  $\mu\text{g}$  in Gardasil 9
- ❖ Polysorbaat 80 (Gardasil)
  - ❖ steriliteit, afwijkingen ovaria, vagina en bm-slijmvlies,
  - ❖ anafylactische reacties (shock)
  - ❖ afwijkingen witte bloedcellen (thymocyten)
- ❖ Natriumboraat (Gardasil)
  - ❖ giftig voor zenuwstelsel, nieren, lever
  - ❖ onvruchtbaarheid; foetale schade
- ❖ MPL (3-deactylated monophosphoryl lipid A, GSK)

## **Safety evaluation of monophosphoryl lipid A (MPL): an immunostimulatory adjuvant.**

Baldrick P<sup>1</sup>, Richardson D, Elliott G, Wheeler AW.

### **⊖ Author information**

1 Covance Laboratories Ltd. Otley Road, Harrogate, North Yorkshire, HG3 1PY, England, United Kingdom.

### **Abstract**

Animal models have shown the potential use of monophosphoryl lipid A (MPL), a detoxified bacterial lipopolysaccharide, as a vaccine adjuvant. Immunostimulatory activity with diverse effects on the cellular elements of the immune system has been demonstrated and a range of vaccines incorporating MPL, including allergy vaccines, are currently under clinical evaluation. A series of preclinical safety investigations was performed to support clinical use of MPL as used in allergy vaccines and comprised cardiovascular/respiratory assessment in dog (up to 100 microg/kg/day); repeat-dose toxicity in rat, rabbit, and dog (up to 2500 and 1200 microg/kg/day in the rat and dog, respectively); reproduction toxicity in rat and rabbit (up to 100 microg/kg/day); and genotoxicity studies. Overall, repeat-dose toxicity studies in the rat and dog showed expected immunostimulatory effects and/or signs of toxicity associated with overstimulation of the immune system (notably increased spleen weight and white blood cell values). Studies in the rabbit with weekly doses of MPL produced no effects. MPL was shown to have no adverse effects on cardiovascular/respiratory function, reproduction, and genotoxicity.

## **Long-term toxicity/carcinogenicity study of L-histidine monohydrochloride in F344 rats.**

Ikezaki S<sup>1</sup>, Nishikawa A, Furukawa F, Enami T, Mitsui M, Tanakamaru Z, Kim HC, Lee IS, Imazawa T, Takahashi M.

### **⊖ Author information**

1 Division of Pathology, National Institute of Health Science, Tokyo, Japan.

### **Abstract**

The long-term toxicity and carcinogenicity of histidine, an essential amino acid for most animal species, were examined in Fischer 344 (F344) rats. Groups of 50 males and 50 females were given L-histidine monohydrochloride (HMHC) in their diet at concentrations of 0 (control), 1.25 and 2.5% for 104 wk; these dose levels were selected on the basis of the results of a subchronic toxicity study, in which body weights were depressed and formation of sperm granulomas in the epididymis was histologically evident in males fed 5.0% HMHC. All surviving rats were killed at wk 107. Increases in red blood cell count, haemoglobin value and haematocrit level were observed in male rats given 2.5% HMHC. A variety of tumours developed in all groups, including the control group, but all the neoplastic lesions were histologically similar to those known to occur spontaneously in this strain of rats, and no statistically significant increase in the incidence of any tumor was found in the treated groups of either sex. Thus, it was concluded that, under the present experimental conditions, HMHC is not carcinogenic in F344 rats.



# DELAYED EFFECTS OF NEONATAL EXPOSURE TO TWEEN 80 ON FEMALE REPRODUCTIVE ORGANS IN RATS

M. GAJDOVÁ\*, J. JAKUBOVSKY† and J. VÁLKY‡

\*Institute of Preventive and Clinical Medicine, Limbová 14, 833 01 Bratislava, †Institute of Pathologic Anatomy, Medical Faculty, Comenius University, and ‡Clinic of Gynaecology and Obstetrics, Teaching Hospital, Bratislava, Czechoslovakia

*(Accepted 23 October 1992)*

**Abstract**—Neonatal female rats were injected ip (0.1 ml/rat) with Tween 80 in 1, 5 or 10% aqueous solution on days 4–7 after birth. Treatment with Tween 80 accelerated maturation, prolonged the oestrus cycle, and induced persistent vaginal oestrus. The relative weight of the uterus and ovaries was decreased relative to the untreated controls. Squamous cell metaplasia of the epithelial lining of the uterus and cytological changes in the uterus were indicative of chronic oestrogenic stimulation. Ovaries were without corpora lutea, and had degenerative follicles.

Gajdova, M.; Jakubovsky, J.; Valky, J.; **Delayed effects of neonatal exposure to Tween 80 on female reproductive organs in rats.** Food Chem Toxicol. 1993 Mar;31(3):183-90

# Negatief effect

- ❖ Stelselmatige afname van Cervixkanker voor invoering van het vaccin: 1989 - 2000: 2,5% / jaar; 2000 - 2007: 1% / jaar
- ❖ Sedert 2007 (invoering van het vaccin) stelselmatige toename in landen waar vaccinatie algemeen werd toegepast.
  - ★ Australië: einde daling sinds invoering in 2007 (V)/2013 (M)
  - ★ toename in leeftijdsgroep van gevaccineerde vrouwen:

# Negatief effect

## Australië

Leeftijd	% gevaccineerd	2007	2014	RR
20 - 24	80	0,7	1,5	+114%
25 - 29	<	5,9	8,0	+35%
30 - 35	<	9,9	13,2	+33%
55 - 59	0			-17%

# Australie: évolution de l'incidence selon l'âge lors du début de la campagne de vaccination



source Australian Institute of Health and Welfare 2017

**Les femmes vaccinées alors qu'elles avaient entre 13 et 17 ans ont vu leur risque de cancer doubler en sept ans**

# Negatief effect

UK (2008)

Leeftijd	% gevaccineerd	2007	2014	RR
20 - 24	> 85	3,1	4,3	+38%
25 - 34	<			+17,6%
65 - 79	0			-13%
< 80	0			-10%



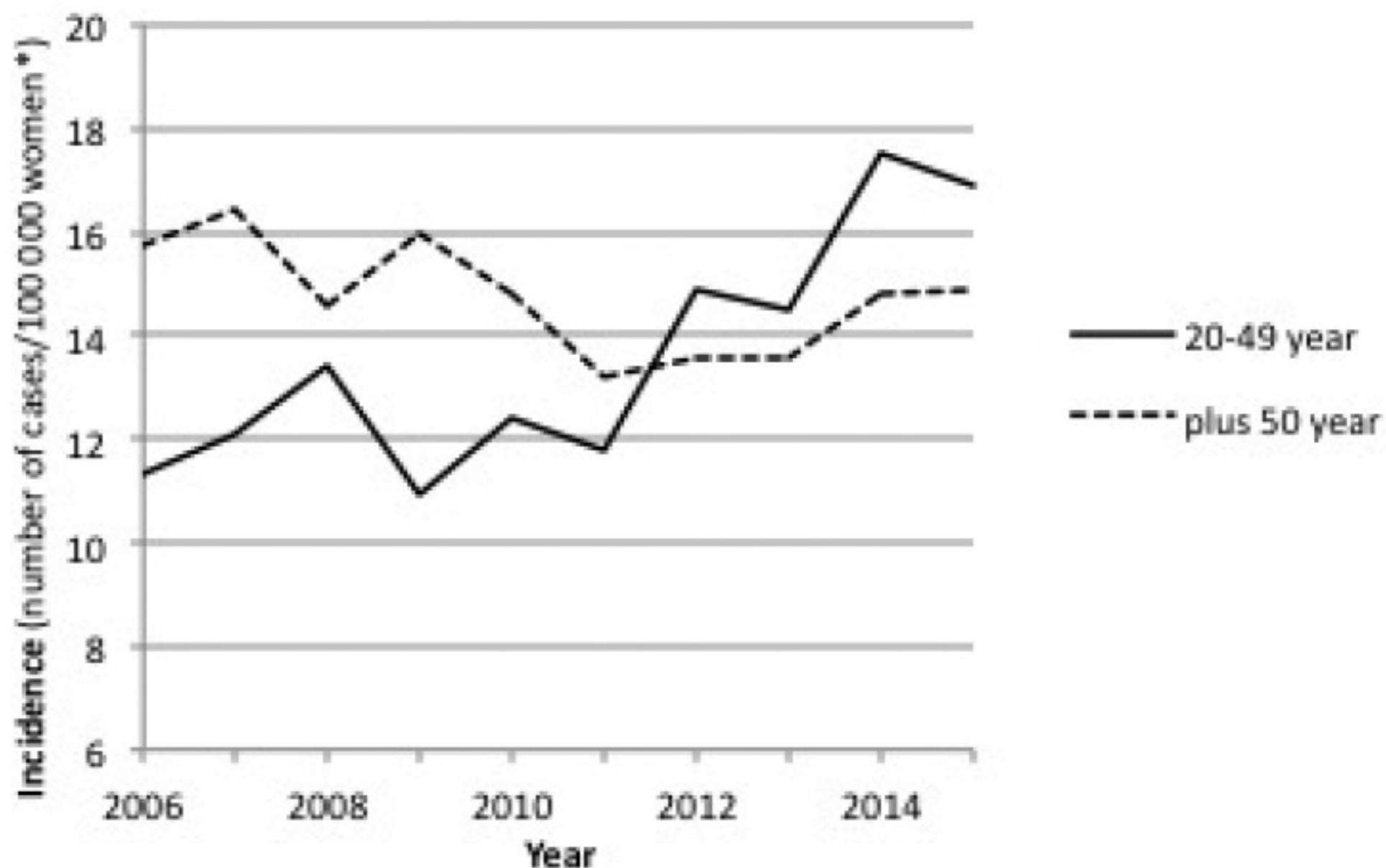
# Negatief effect

## Zweden (2006)

Leeftijd	% gevaccineerd	2006	2015	RR
20 - 29	85			+66%
25 - 49	< 85	11	17	+54%
> 50	0			+0%

Jaar	2006	2009	2012	2015
frequentie /100.000	9,6	9,7	10,3	11,49

## Invasive cervical cancer incidence in Sweden in age groups 20-49 and plus 50 years



\* Age adjusted according to the standard Swedish population in 2000.

Fig. 1: Increase in incidence of cervical cancer among younger women (<50 years) as compared with women  $\geq 50$  years. The data shows the number of cases/100,000 women from 2006 to 2015.



## Relative change (%) of invasive cervical cancer incidence in Sweden between 2006 and 2015 in different age groups

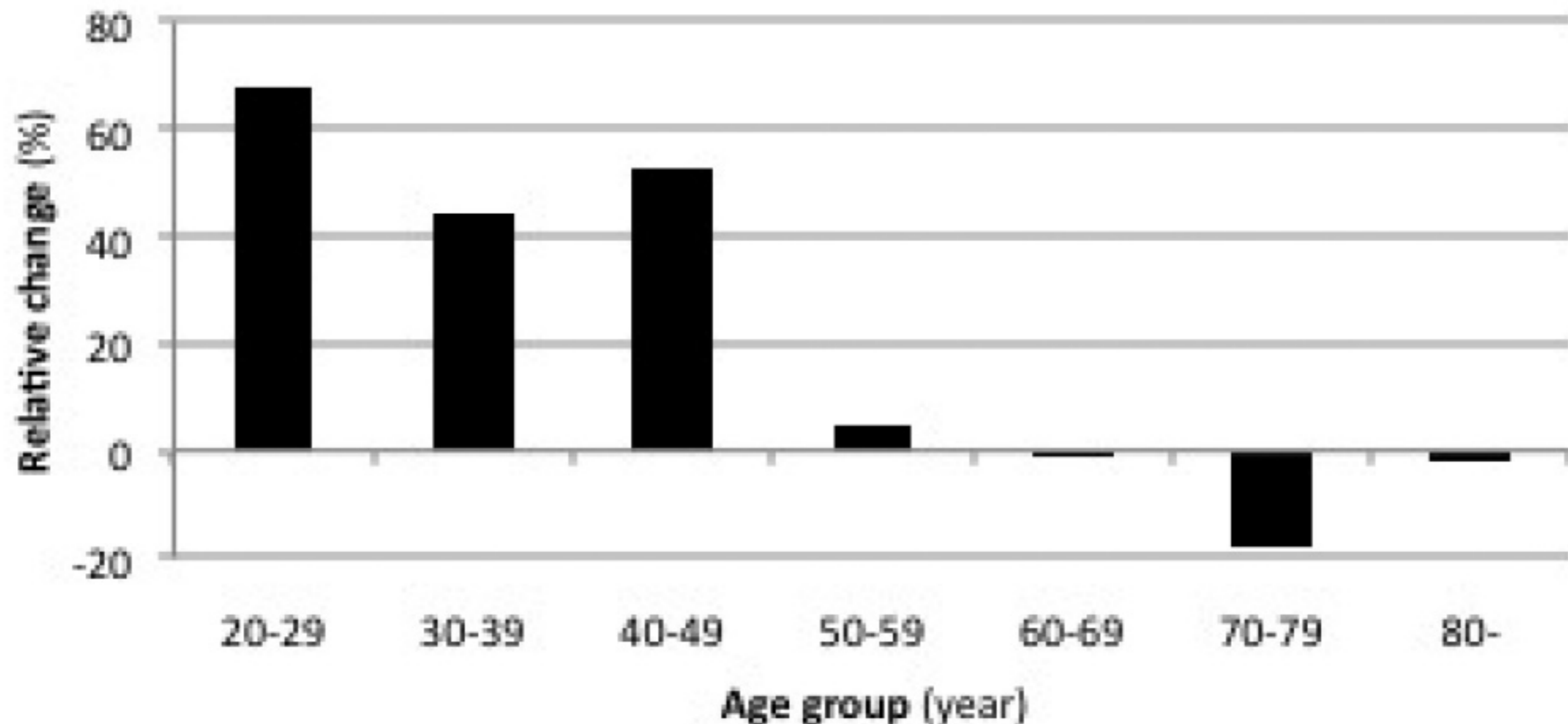


Fig. 2: The relative change in percentage of invasive cervical cancer incidence in Sweden between 2006 and 2015 in different age groups. The figure is based on data from the statistical database of the National Board of Health and Welfare in Sweden. The incidence of cancer is age-adjusted according to the standard Swedish population in 2000.

Andersson, 2018

For individuals exposed to Gardasil, evidence of a selective and significant reactivation of the oncogenic non-target HPV types 52 and 56 was reported in the genital tract for all women ([13](#)). This article studied women 13–22 and 23–40 years of age from 2008 to 2013. The target HPVs 16 and 18 decreased only in the younger age group but oncogenic non-target HPVs increased in both the groups, 20%–40% and 8%–30%, respectively. The increase in the total burden of non-target oncogenic HPVs for vaccinated individuals may be consistent with the findings in the FDA report where the efficacy of the HPV vaccine was less favourable for non-naïve women compared with those on placebo. A possible mechanism to explain the increased incidence of cervical cancer may therefore be virus reactivation as described above.

# Negatief effect

## Noorwegen

Jaar	2007	2009	2012	2015
frequentie /100.000	11	12,2	13,2	14,3

# Negatief effect

## USA (2007)

Leeftijd	%	1989	2007	2015	RR
		10,7	6,67		-38%
< 25	+++		5,24	5,47	+4%
> 50	0		10,37	9,87	-4,83%

Jaar	2007	2009	2012	2015
frequentie /100.000	11	12,2	13,2	14,3

# Negatief effect

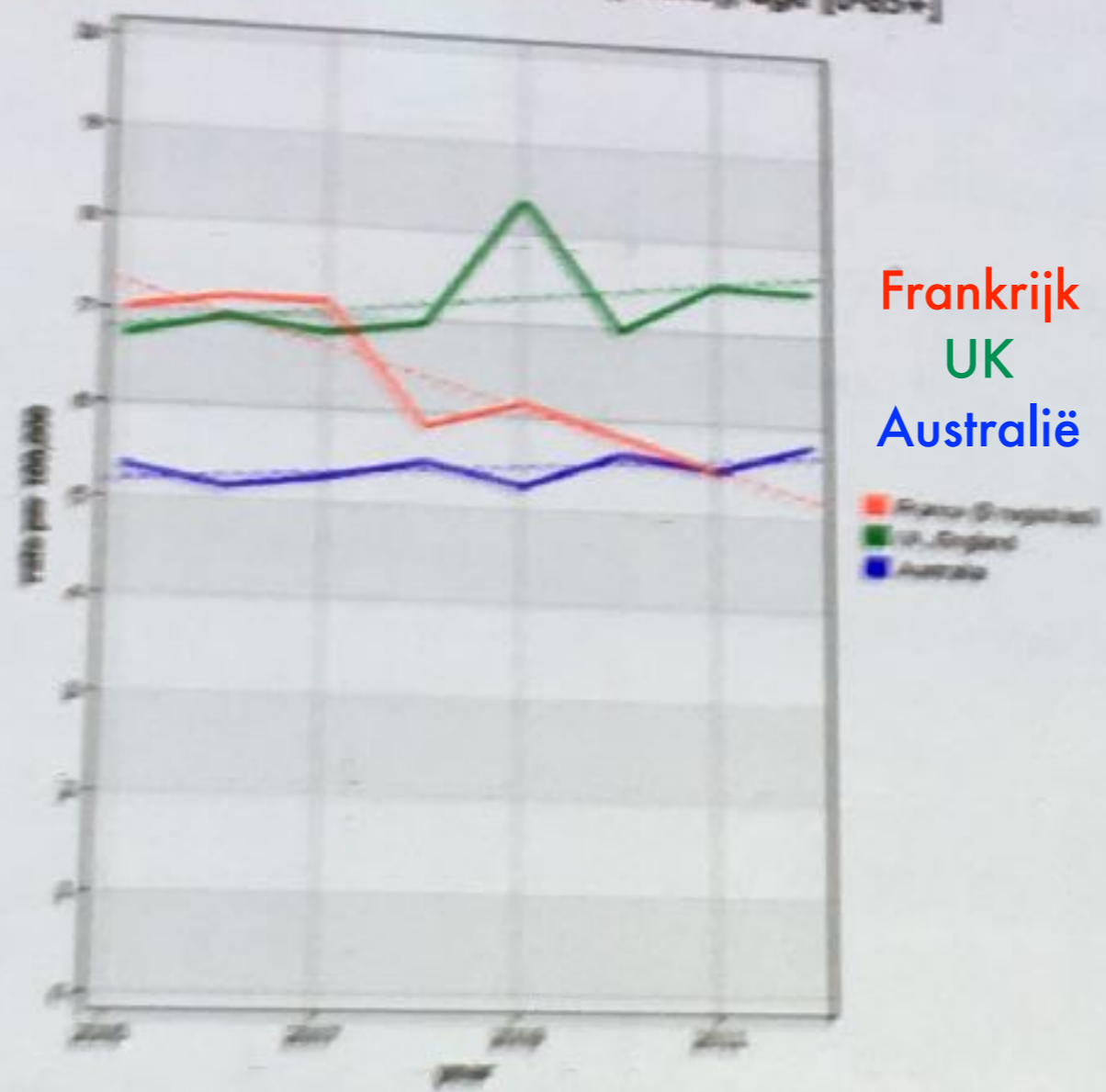
Frankrijk

(Vaccinatiegraad  $\pm$  15%)

Jaar	1980	1995	2007	2012	2017
frequentie /100.000		15	7,5	6,7	6,0
Sterfte	5			1,8	1,7

# Data from Drs. Delepine

Cervix uteri  
Age Standardised Incidence Rate (World), age [0-85+]

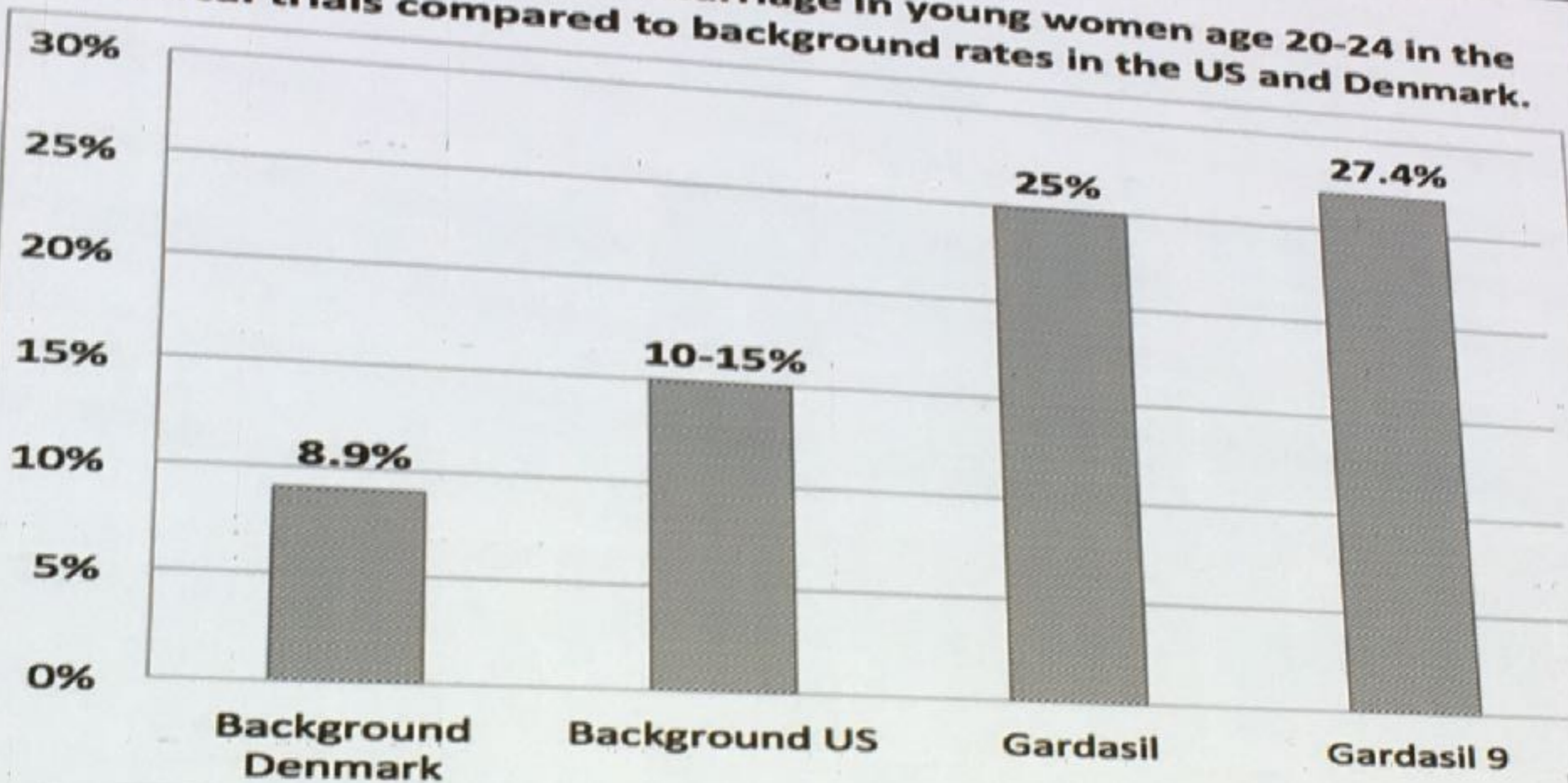


Frankrijk  
UK  
Australië

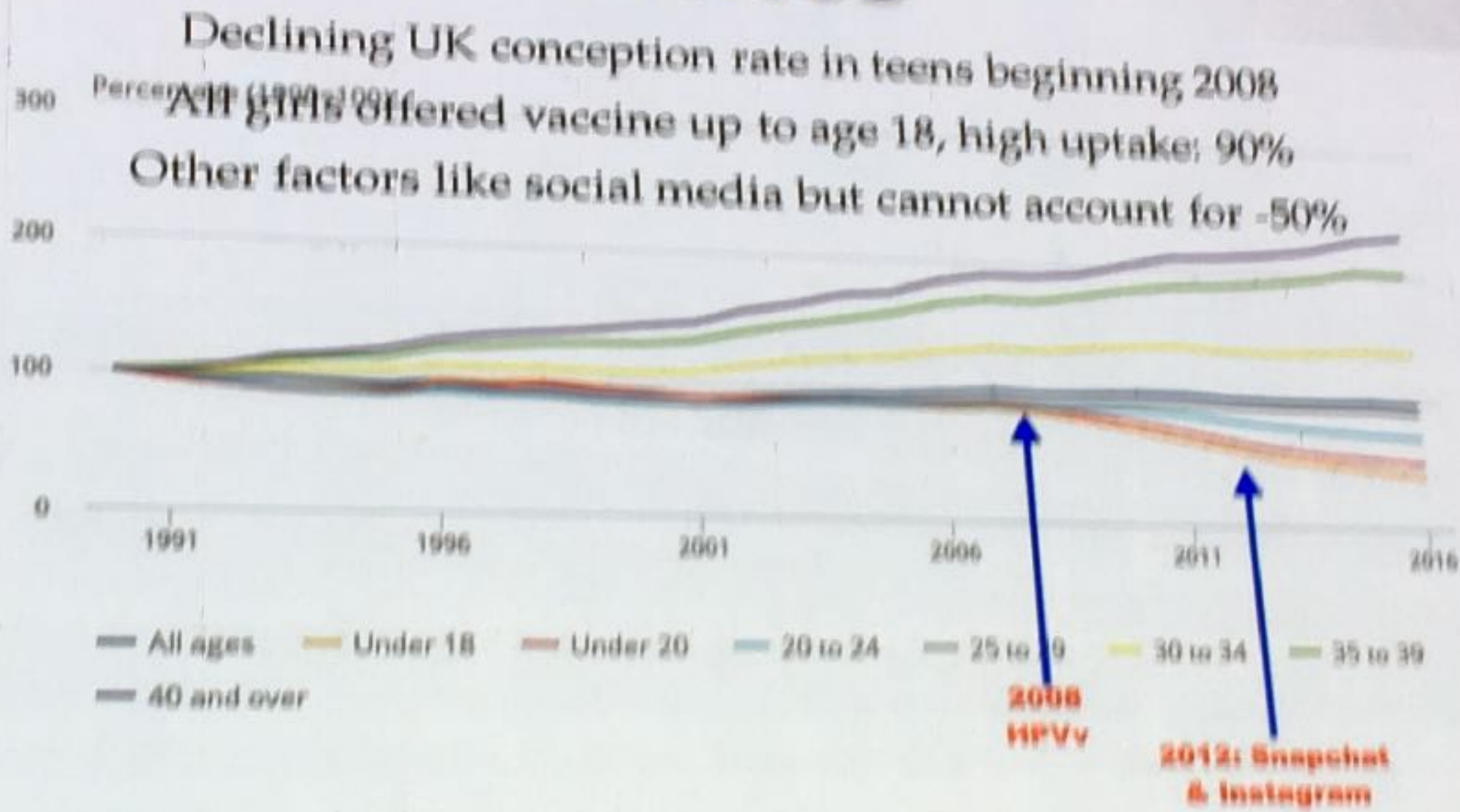
Figure 4: Comparison of the trends of incidence of invasive cervical cancer during the first years of vaccination (2007-2012). The incidence of cervix cancer improved in France and worsened in countries with large vaccination uptake.

# Miscarriages & Other Reproductive Effects

Rate of spontaneous miscarriage in young women age 20-24 in the clinical trials compared to background rates in the US and Denmark.



# Declining Pregnancy Rates



Source: Office for National Statistics



# Kosten - baten

- ❖ Pro (Kim & Goldie): wel bij 12-jarigen, niet bij ouderen.
- ❖ Maar (Haugh): enkel indien
  - ★ levenslange bescherming gegarandeerd, geen herhaling nodig; 🙅
  - ★ efficiëntie bij pre-adolescenten = adolescenten / volwassen vrouwen ???;
  - ★ geen nieuwe HPV-stammen; 🙅
  - ★ volhouden uitstrijkjes ???; 🙅
  - ★ geen invloed op natuurlijke immuniteit. 🙅

Haug, C.; NEJM, 2008; 359:861

to be tested in trials and follow-up studies. If the authors' baseline assumptions are not correct, vaccination becomes less favorable and even less effective than screening alone. For example, as shown in the article, if the protection of the vaccine wanes after 10 years, vaccination is much less cost-effective and screening is more effective than catch-up programs.

# Studies

## ❖ Gardasil: FUTURE II

- ★ combinatie met HBV-vaccin
- ★ Al-OH in placebo !
- ★ 102 ernstige reacties, 37 doden.
- ★ Prescribing info package: 463 nieuwe aandoeningen (auto-immuun)/ 20.118 (2,3%)
- ★ FDA-rapport: reacties: 16.180 / 21.464 (75%)
- ★ selectieve deelnemers, HPV-vrij; intensieve follow-up;

# Resultaten studie

<b>New Medical Conditions Reported</b>	
Arthritis/Arthralgia/Arthropathy	218
Autoimmune Thyroiditis	5
Celiac Disease	16
Diabetes Mellitus Insulin Dependent	4
Erythema Nodosum (inflammatory skin disorder)	6
Hyperthyroidism (overactive)	48
Hypothyroidism (underactive)	73
Inflammatory Bowel Disease	17
Multiple Sclerosis	6
Nephritis (inflammation of kidneys)	7
Optic Neuritis (inflammation of optic nerves)	2
Pigmentation Disorder	7
Psoriasis	28
Raynaud's Phenomenon	7
Rheumatoid Arthritis	8
Sclerodoma/Morphea	3
Stevens-Johnson Syndrome	1
Systemic Lupus Erythematosus	4
Uveitis	4
<b>TOTAL</b>	<b>463</b>

# Meldingen

Zieken	1.073
Overlijden	159
Geen herstel	6.770
Abnormaal uitstrijkje	558
Celafwijkingen in de baarmoederhals	238
Kanker van de baarmoederhals	75
Bedreigende situaties	614
Bezoek aan dienst voor spoedgevallen	11.359
Hospitalisaties	3.504
Verlengde ziekenhuisopnames	247
Ernstige nevenwerkingen	4.633
Nevenwerkingen	33.903

VAERS, 2014

# HPV Clinical Trials in India

- Gross violations of clinical trial procedures; funded by Gates Fdn
- 30,000 tribal girls exploited; 120 had serious side effects; 7 died
- Scathing Parliamentary report on corrupt gov't and corporate action
- These "demonstration projects" ended all clinical trials in India pending new regulations

# Unethical Clinical Trials India, Nov. 19-21, 2019

- Conference on the "Controlled Human Infection Method" – CHIM
- Humans deliberately infected with diseases to test experimental vaccines
- "initially" limited to adults in academic institutions for malaria, flu, typhoid
- FDA, EMA and WHO will be there to legitimize this atrocity that directly violates the Nuremberg Code  
(Art. 3. must have knowledge of natural history and animal experiments)

# Pharma Paid \$35 Billion in Civil and Criminal Fines and Settlements

**Table 5. Pharmaceutical Company Penalties: Repeat Offenders (Federal Settlements Only), 1991-2015\***

Company**	Number of Settlements	Total Financial Penalties (\$ millions)	Percent of Total***
Pfizer	11	\$3,631	11.4%
Merck	9	\$1,725	5.4%
GlaxoSmithKline	8	\$7,393	23.1%



# Alternatief: échte preventie

## ❖ Primaire preventie

- ★ mijden van risicofactoren (cfr. supra)
- ★ condoom

## ❖ Secundaire preventie

- ★ Uitstrijkjes !!
  - vanaf 1 jaar na 1e seksueel contact, of vanaf 25J
  - om de 3 jaar, tot 65e
- ★ Tijdige behandeling van beginnende letsels

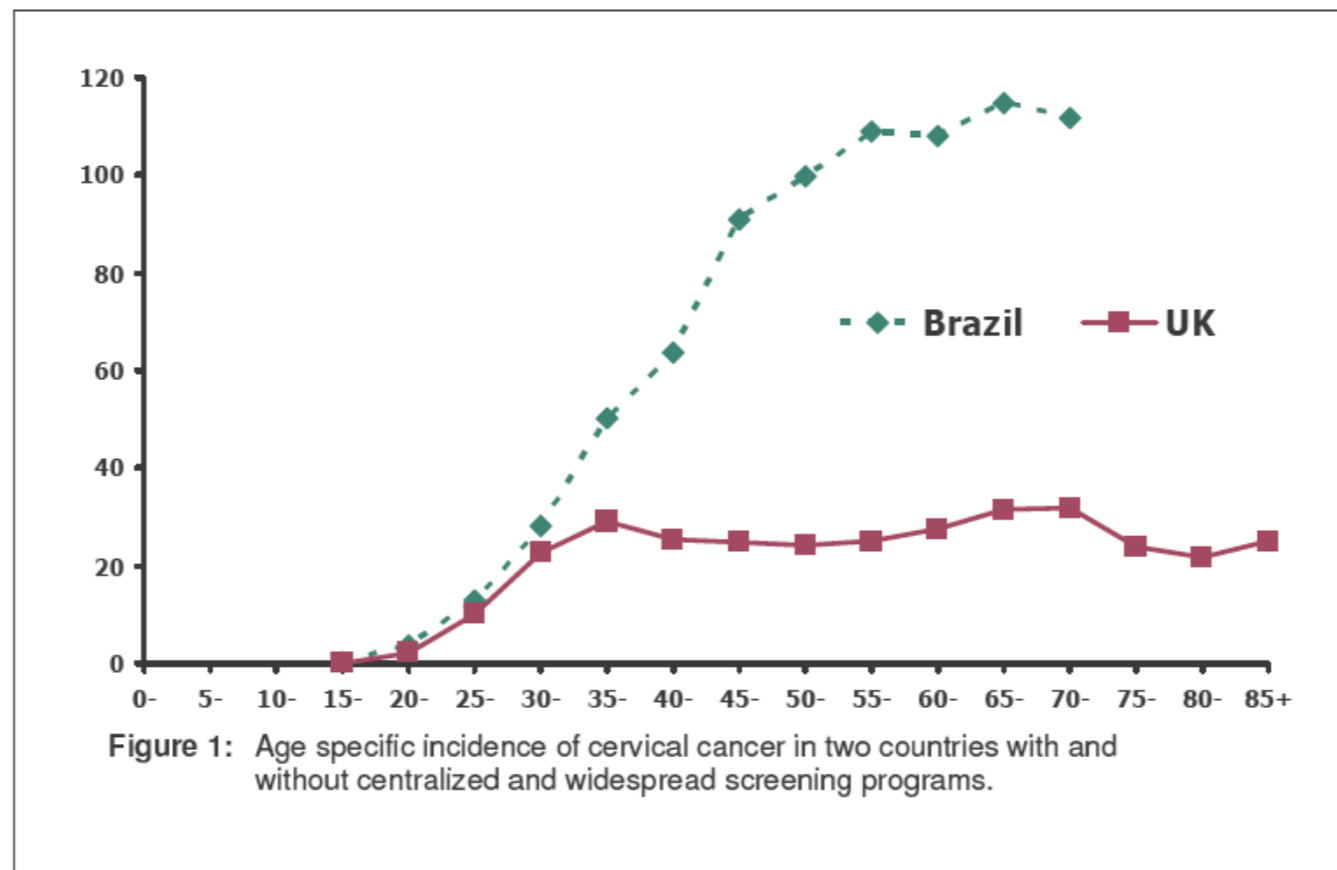
# Screening

- ★ 2 à 3 x meer kankers zonder screening;
- ★ 41% van de Belgische vrouwen wordt niet gescreend
- ★ Cytlogie + HPV-typering

# Screening



## Effect van screening



# The future is bright !

✿ jongens

✿ iedereen

★ anale CA

★ keelCA

★ huidCA

★ ...

# En jongens?

- ❖ Oorzakelijk verband tss anale CA en HPV?
- ❖ Verschillende motivaties:
  - ★ preventie verspreiding
  - ★ preventie van anale kanker
- ❖ Welk risico?
  - ★ Zeer beperkt probleem bij normale bevolking
  - ★ hoofdzakelijk bij immuunsuppressie en risicogroepen

# Enkele cijfers

- ❖ Fake news: “verdriedubbeling op 30 jaar” (Le Monde)
- ❖ Wereldwijd x 1,8
- ❖ géén toename in Spanje, Israël, India, Azië...
- ❖ Anale kankers in Frankrijk: 280 /jaar, 60 overlijdens

# Enkele cijfers

Aandoening	N	†	Jaar
Anale kanker	280	60	2015
Prostaatkanker	48.427	8.207	2013
Longkanker	28.211	21.326	2012
Dikdarmkanker	23.226	9.275	2012

# Risicofactoren voor anale kanker

- ❖ Immuunsuppressie (na behandeling x 5; AIDS)
- ❖ homoseksuele mannen x 1,5 à 3
- ❖ passieve anale seks bij homoseksuelen: x 60 à 90
- ❖ SOA's
- ❖ promiscuïteit
- ❖ hoge leeftijd



# Preventie van anale kanker

- ✿ condoom !
- ✿ correct seksueel gedrag
- ✿ behandeling van SOA's

# Teens in Some States Give “Informed Consent”

PARENTING

## States are finding ways for teens to get HPV shots without parental consent

**Sonja Haller** USA TODAY

Published 8:30 a.m. ET Aug. 21, 2019 | Updated 12:45 p.m. ET Aug. 22, 2019

The New York Department of Health has been allowing [teens to get the HPV shot since 2017](#).

[California; Delaware; New York; and Washington, D.C.](#), allow regulations permitting teens under 18 to be vaccinated against sexually transmitted diseases, including HPV.

The [National Center for Youth Law](#) says regulations and statutes could be interpreted in other states that would allow this right to minors. They are Alabama, Arkansas, Idaho, Iowa, Kansas, Louisiana, Maine, Maryland, Massachusetts, Michigan, Minnesota, Missouri, Montana, Nebraska, Nevada, New Hampshire, New Jersey, New Mexico, North Carolina, North Dakota, Oklahoma, Oregon, Pennsylvania, Rhode Island, South Dakota and South Carolina.

# HPV Vaccine

- If A0933 passes, all children must receive 2 doses of the HPV vaccine potentially starting as young as 9 years old
- **No religious or other opt-outs**
- Doctors afraid to write medical exemptions
- NYS would be the first to mandate no opt-out

# Financieel aspect

- ❖ winsten voor de farma-industrie: 100 miljard (2018, Delépine)

## Unprecedented global demand for Gardasil 9

Last month Merck & Co. presented its second quarter earnings for the year, reporting \$886m in global sales for its 9-valent human papillomavirus (HPV) vaccine Gardasil 9.

Revenue exceeded prior year earnings in Q2 of US \$608m by 46 per cent, positioning the vaccine to surpass total sales for 2018 of \$3.15bn.

Already a blockbuster product, Gardasil 9 has benefited from recently expanded recommendations from the Centers for Disease Control and Prevention (CDC) and strong uptake in emerging markets like China.

The widening commercial frontier for Gardasil 9 is a reflection of evolving vaccination objectives across the globe and presents an opportunity to decrease or potentially eliminate HPV-related cancers worldwide – given that Merck is able to keep up with demand.

# Actie ?!

Cfr. Japan: programma minimum 1 jaar uitgesteld !!

- ★ Pers en wetenschappers de uitdaging aanmeten
- ★ Patiënten mobiliseren
- ★ Overheid onder druk zetten
- ★ Publiek debat

Cfr. Frankrijk: debat !

Cfr Australië: opschorting

Dank voor uw aandacht



HPV-vaccin ? Nee dank u !