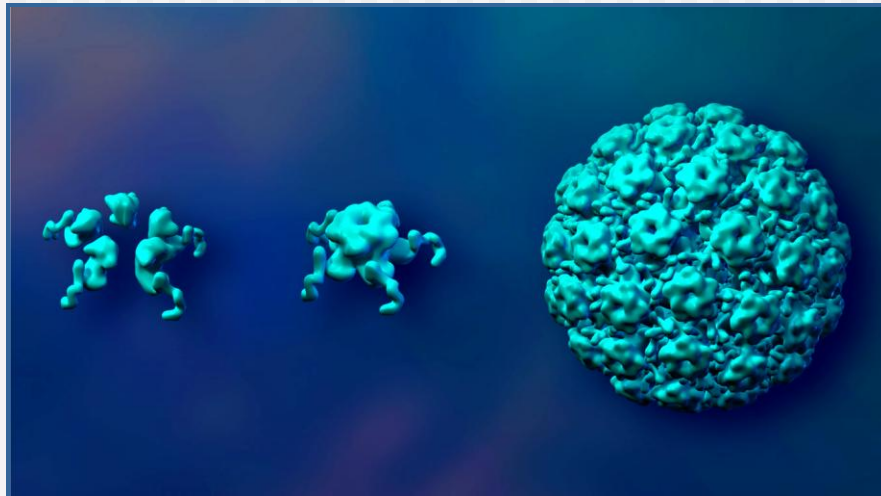


HPV- Impfung: Aktuelle Daten zu Wirksamkeit - Sicherheit



Elmar A. Joura

Universitätsklinik für Frauenheilkunde Wien

Obergurgl, 2. 2. 2009

41. Fortbildungstagung für Frauenärzte

Disclosure

- Investigator FUTURE I (Merck)
 - Publikationskomitee
 - Global Advisory Board
- Heracles HPV Studie GSK
- Vorträge für Merck, GSK, Sanofi Pasteur MSD

Nobelpreis für Medizin und Biologie 2008

Harald zur Hausen



Proc. Natl. Acad. Sci. USA
Vol. 80, pp. 560-563, January 1983
Medical Sciences

Human papillomavirus types 6 and 11 DNA sequences in genital and laryngeal papillomas and in some cervical cancers

(molecular cloning/blot hybridization/perinatal infection/genital cancer)

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Communicated by Gertrude Henle, October 13, 1982

ABSTRACT Human genital tumors as well as recurrent laryngeal papillomas were analyzed for the presence of human papillomavirus (HPV) 6 and HPV 11 sequences. HPV 11 DNA was found in 7 of 14 laryngeal papillomas; in the 7 other tumors no HPV DNA was demonstrated. HPV 11 DNA was also found in all five atypical condylomata of the cervix included in this study. Condylomata acuminata mainly contained HPV 6 DNA. From 63 biopsy specimens, 41 clearly harbored HPV 6 DNA and 13 harbored HPV 11 DNA. In three tumors accurate typing was impossible, and in six additional ones neither HPV 6 nor HPV 11 DNA could be demonstrated. The data support a genital origin of laryngeal papillomavirus infections. In 4 of 24 malignant tumors, HPV 11 DNA or related sequences were demonstrated; 2 of the 4 were biopsy specimens from invasive cancer, and the other 2 originated from carcinomata *in situ*. A possible role of this or related papillomavirus types in the induction of malignant genital tumors remains to be elucidated.

MATERIALS AND METHODS

Extraction of Cellular DNA. Biopsy materials were examined histologically and stored at -20°C or -70°C until further processing. Extraction of cellular DNA was done as described (6).

Labeling of HPV DNA. HPV 6 DNA has been cloned into pBR322 in two fragments representing approximately one-third and two-thirds of the total genome, respectively (5). HPV 11 DNA, which has been identified from a genomic library of laryngeal papilloma constructed in λ L47 (7), was subcloned in pBR322 at the single *Bam*HI site.

Both DNAs were prepared as described (10) and labeled with deoxynucleotide [α - ^{32}P]triphosphate by the nick-translation procedure to a specific activity of $>10^8$ cpm/ μg (6).

Blot Hybridization. About 10 μg of papilloma DNA was cleaved with restriction enzyme; the products were separated on agarose gels, transferred onto nitrocellulose, and hybridized

Outline

- Effektivität
 - Gebärmutterhals - CIN
 - Vulva - VIN, Condylome
- Frauen bis 45
- Männer
- Kreuzprotektivität
- Wirkungsdauer
 - Immungedächtnis
- Sicherheit

Impfstoffe

■ Gardasil[®]

- HPV 6, 11, 16, 18 + AAHS
- Frauen 9-26, Knaben 9-15
 - Klinische Daten für Frauen 16-45
- September 2006



■ Cervarix[®]

- HPV 16, 18 + AS04
- Frauen 10-25
 - Immunogenität 10-55
- Oktober 2007
 - Australien (bis 45)



GARDASIL® Human Papillomavirus [Types 6, 11, 16, 18] Recombinant, adsorbed vaccine

HPV virus like particles VLPs	HPV types 6, 11, 16, 18 L1 proteins (not truncated)
Adjuvant	AAHS - Amorphous Aluminium Hydroxyphosphate Sulphate
Production System	Saccharomyces cerevisiae CANADE 3C-5
Schedule	0, 2, 6 months - Flexibility up to 12 months
Indication	Females 9 - 26 years Males 9 – 15 years

HPV 16/18-Related Cervical Cancer

Per-Protocol Efficacy Population – Protocols 007, 013, 015
3 years follow-up post-dose 1

HPV 16/18-Related Cancer	HPV 16/18-Related Surrogate	GARDASIL®	Placebo	% Efficacy	95% CI
High Grade Cervical Dysplasia	CIN 2/3 or AIS	1	85	99	93, 100
Squamous Cell Cervical Cancer	CIN 3	1	51	98	89, 100
Cervical Adenocarcinoma	AIS	0	7	100	31, 100

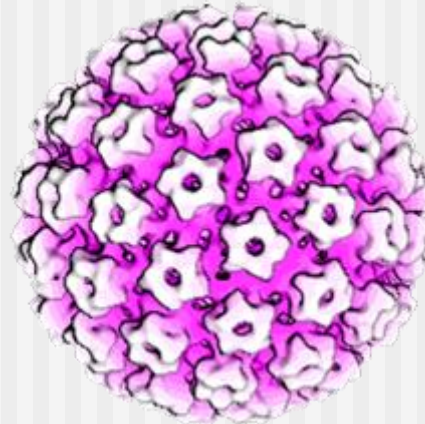
Ault KA, FUTURE II Study Group. Effect of prophylactic human papillomavirus L1 virus-like particle vaccine on risk of cervical intraepithelial neoplasia grade 2, grade 3, and adenocarcinoma in situ: A combined analysis of four clinical trials. *Lancet* 2007;369:1861–1968.

Cervarix[®] : HPV L1 virus like particles+ adjuvant - AS04

Recombinant L1 protein



Self-assemble into virus-like particles



Resemble intact viruses



Non-infectious



Composition:

20 µg L1 HPV-16 & 20 µg L1 HPV-18

500 µg Al(OH)₃

50 µg MPL

AS04 adjuvant system

Phase III efficacy study HPV008: Efficacy against HPV-16/18 CIN2+ (TVC-E)

Pre-specified Case Definition based on PCR detection in lesion only

Endpoint	Group	N	n	Cervarix [®] Efficacy (97.9% CI)			
				%	LL	UL	P-value
CIN2+ HPV-16/18	Cervarix [®]	7788	2	90.4	53.4	99.3	<0.0001
	Control	7838	21				
CIN2+ HPV-16	Cervarix [®]	6701	1	93.3	47.0	99.9	0.0005
	Control	6717	15				
CIN2+ HPV-18	Cervarix [®]	7221	1	83.3	-78.8	99.9	0.1249
	Control	7258	6				

Prophylactic Efficacy Against HPV 6, 11, 16,18- related Vulvar condyloma

Vulvar condyloma	GARDASIL® (N = 9075)			Placebo (N = 9075)			Efficacy	95% CI
	n	Cases	Rate*	n	Cases	Rate*		
HPV 6-related	7,374	1	<0.1	6,867	71	0.7	99	(93, 100)
HPV 11-related	7,374	0	0.0	6,867	16	0.2	100	(77, 100)
HPV 16-related	7,071	0	0.0	6,474	14	0.1	100	(73, 100)
HPV 18-related	7,879	0	0.0	7,355	6	0.1	100	(23, 100)

Per-Protocol Population

Prophylactic Efficacy Against HPV 16 or 18-Related VIN 2/3 or VaIN 2/3

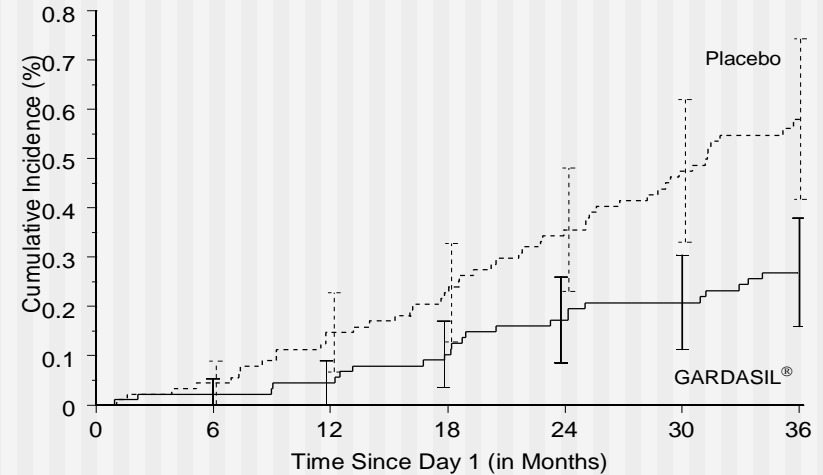
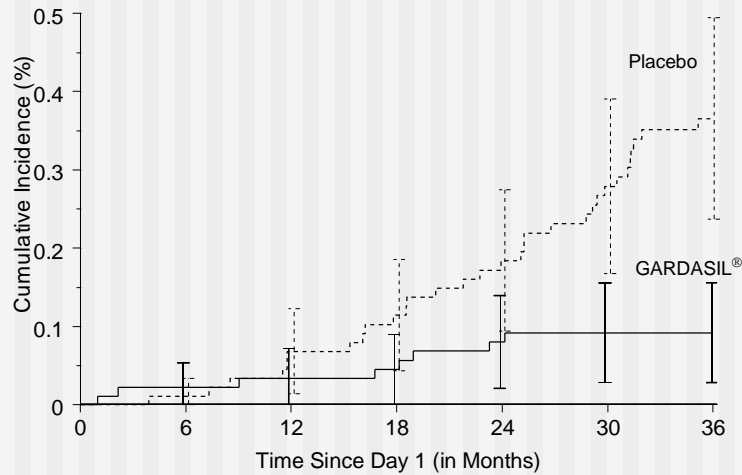
Type Specific Per-Protocol Population(s)

	GARDASIL® (N = 9075)		Placebo (N = 9,075)		%Efficacy	95% CI
	n	Cases	n	Cases		
HPV 16 or 18- related VIN 2/3	7,771	0	7,742	8	100	(42, 100)
HPV 16 or 18- related VaIN 2/3	7,771	0	7,742	7	100	(31, 100)

An additional 4 cases of HPV 6 or 11-related VIN 2/3 or VaIN 2/3 (not also associated with 16 or 18) were observed in the placebo group (none such cases in the vaccine group).

"All countries need...to achieve the maximum possible gain in survival and quality of life for cancer patients. If costs are the predominant consideration, health systems are failing."

The Lancet 2007;369:1693-1702



Vaccine	0	6	12	18	24	30	36	Total
GARDASIL®	9,087	8,830	8,715	8,620	8,488	8,310	4,342	8
At-risk								
Total	0	2	3	4	7	8		
Cases								
Placebo	9,087	8,850	8,722	8,640	8,509	8,320	4,387	31
At-risk								
Total	0	1	6	10	16	24		
Cases								

Vaccine	0	6	12	18	24	30	36	Total
Placebo	9,087	8,830	8,714	8,615	8,480	8,300	4,332	23
At-risk								
Total	0	2	4	9	15	18		
Cases								
GARDASIL®	9,087	8,847	8,715	8,630	8,494	8,303	4,374	49
At-risk								
Total	0	4	13	20	31	41		
Cases								

Figure 2.

EFFICACY AGAINST RECURRENT CIN (SEROPOSITIVE, DNA NEGATIVE)

	Vaccine			Placebo				
CIN1 OR WORSE	n	Cases	Rate	n	Cases	Rate	Efficacy (%)	95% CI
HPV 6/11/16/18	1,243	0	0.0	1,283	7	0.2	100.0	(28.7, 100.0)
by Severity*								
CIN 1	1,243	0	0.0	1,283	6	0.1	100.0	(12.7, 100.0)
CIN 2 or Worse	1,243	0	0.0	1,283	4	0.1	100.0	(<0, 100.0)
CIN 2	1,243	0	0.0	1,283	1	0.0	100.0	(<0, 100.0)
CIN 3 or Worse	1,243	0	0.0	1,283	4	0.1	100.0	(<0, 100.0)
CIN 3	1,243	0	0.0	1,283	3	0.1	100.0	(<0, 100.0)
AIS	1,243	0	0.0	1,283	1	0.0	100.0	(<0, 100.0)
by HPV type*								
HPV 6	538	0	0.0	568	0	0.0	N/A	N/A
HPV 11	140	0	0.0	146	0	0.0	N/A	N/A
HPV 16	574	0	0.0	625	6	0.3	100.0	(8.5, 100.0)
HPV 18	236	0	0.0	233	1	0.1	100.0	(<0, 100.0)

EFFICACY AGAINST RECURRENT EXTERNAL GENITAL LESIONS (SEROPOSITIVE, DNA NEGATIVE SUBJECTS)

EGL	Vaccine			Placebo			Efficacy (%)	95% CI
	n	Cases	Rate	n	Cases	Rate		
HPV 6/11/16/18	1,268	0	0.0	1,301	8	0.2	100%	(39.5, 100.0)
by Severity*								
Condyloma	1,268	0	0.0	1,301	7	0.2	100.0	(28.3, 100.0)
VIN 1 or VaIN 1	1,268	0	0.0	1,301	1	0.0	100.0	(<0, 100.0)
VIN 2/3 or VaIN 2/3	1,268	0	0.0	1,301	2	0.0	100.0	(<0, 100.0)
by HPV type*								
HPV 6	546	0	0.0	579	5	0.3	100.0	(<0, 100.0)
HPV 11	142	0	0.0	149	0	0.0	N/A	N/A
HPV 16	587	0	0.0	632	2	0.0	100.0	(<0, 100.0)
HPV 18	241	0	0.0	234	1	0.1	100.0	(<0, 100.0)

Primary efficacy Midadult Women

Persistent Infection or clinical endpoint related to HPV 6/11/16/18
Per-protocol analysis

Age	Gardasil		Placebo		% Reduction	95% CI	P-value
	Cases	pyr	Cases	pyr			
All Subjects	4	2,721	41	2,654	91%	74 – 98	<0.001
24 to 34 Year-Olds	2	1,329	24	1,301	92%	67 - 99	<0.001
35 to 45 Year-Olds	2	1,393	17	1,353	89%	52 - 99	<0.001

Luna & FUTURE Investigators
IPV 2007 Beijing

Kreuzprotektion:

Wirksamkeit gegen CIN 2/3 oder AIS

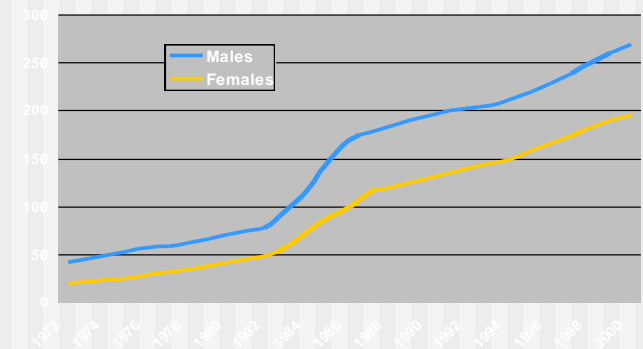
“HPV-naive” Population

Kombinierte Analyse Protokoll 013 und 015

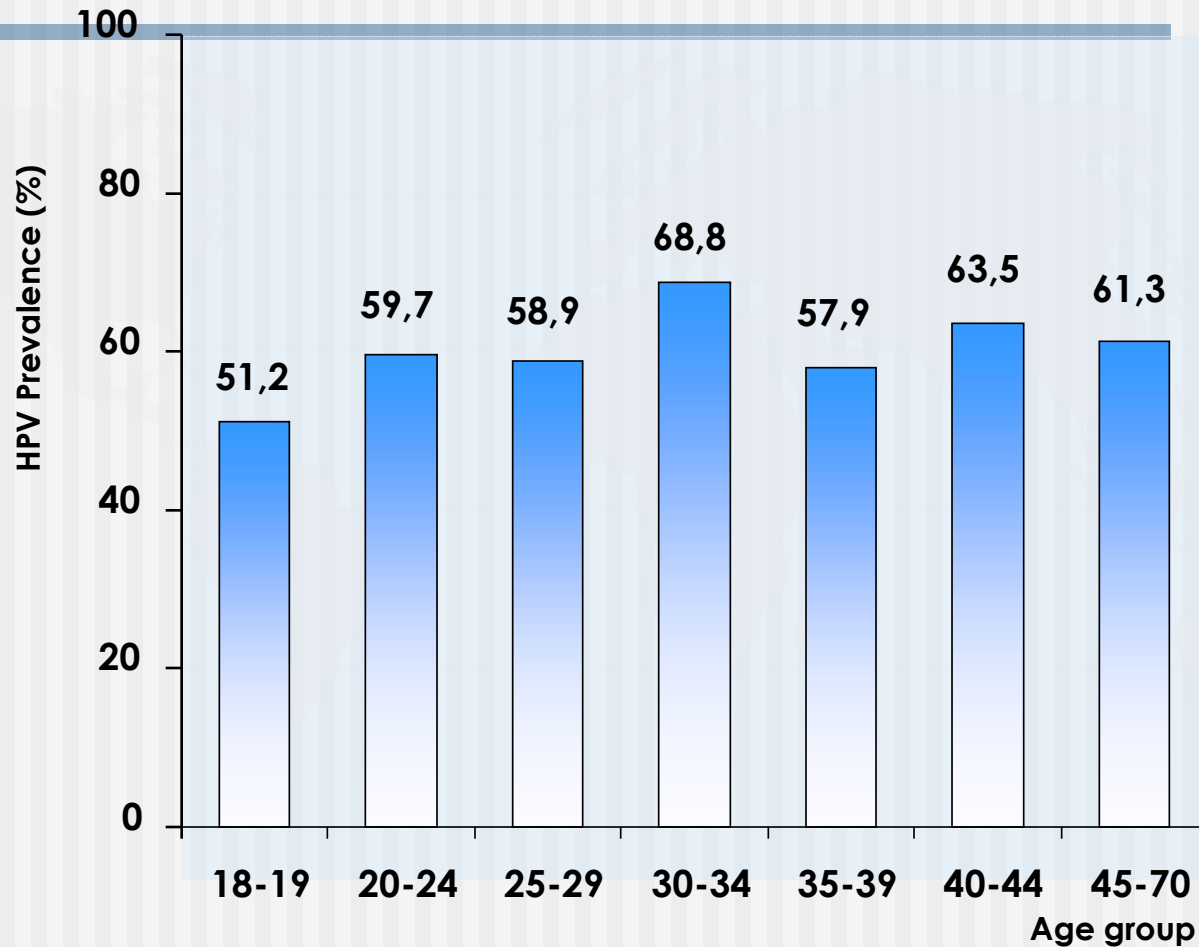
CIN2/3 or AIS	GARDASIL®	Placebo	Efficacy	95% CI
10 non-vaccine oncogenic HPV types 31, 33, 35, 39, 45, 51, 52, 56, 58, 59	38	62	38%	(6, 60)

HPV- Impfung für Männer

- Condylome
 - ♂ > ♀
 - Risikofaktor für die Partnerin (RR 10!)
 - Herdenimmunität



HPV PREVALENCE (ANY TYPE) AMONG MEN BRAZIL, MEXICO, US - HIM STUDY



Source: Adapted from Giuliano A, et al. CEBP 2008

Annual HPV-Related Disease Burden U.S.

Disease	Organ	Females	Males	% HPV 16/18 - Related	% HPV 6/11 - Related
Cancer and Other Life-Threatening Diseases	Cervix	9700	--	70%	0%
	Genital Tract	6200	1530	35%	0%
	Anal Canal	2750	1900	70%	0%
	Oropharynx	3300	8500	45%	0%
	RRP	3000	3000	0%	100%
	Total		24,950	14,930	[18,060]
Pre-cancerous/ Dysplastic Lesions	CIN 2/3	225,000	--	60 to 70%	0%
	CIN 1	175,000	--	25 to 30%	10%
	Genital Warts	250,000	250,000	0%	90%
	Total		600,000	250,000	[195,000]

Program to Evaluate Efficacy of Quadrivalent HPV Vaccine in Young Men

- Placebo-controlled study of 4000 Men (600 MSM)
 - 16- to 26-year-olds with 0 to 5 lifetime partners
- Testing
 - genital sampling for HPV infection
 - genital inspection for genital warts
- Primary endpoint: HPV 6/11/16/18-related
 - Genital lesions (genital warts, penile dysplasia)
 - Persistent infection
- Substudy in MSM
 - Anal pap test/HPV testing at 6 month intervals
 - Referral to high-resolution anoscopy for abnormalities
 - Primary endpoint: HPV 6/11/16/18-related Anal Dysplasia
- Up to 4 years of follow-up

Prophylactic Efficacy Against HPV 6, 11, 16,18-related external genital lesions in men

Condyloma, PIN

EGL	GARDASIL®			Placebo			Efficacy	95% CI
	n	Cases	Rate*	n	Cases	Rate*		
HPV 6-related	1245	3	0.1	1244	19	0.7	84.3	(46, 97)
HPV 11-related	1245	1	0.0	1244	11	0.4	90.9	(38, 99)
HPV 16-related	1295	0	0.0	1271	2	0.1	100	(<0, 100)
HPV 18-related	1335	0	0.0	1354	1	0.0	100	(<0, 100)



A Giuliano, J Palewsky Eurogin 2008

Wirksamkeitsdauer

■ Phase II

- 9 Jahre Monovalent (HPV 16)
- 5 Jahre Quadrivalent (HPV 6/11/16/18)
 - Villa LL, Brit J Cancer 2006
- <6,5 Jahre Bivalent (HPV 16/18)

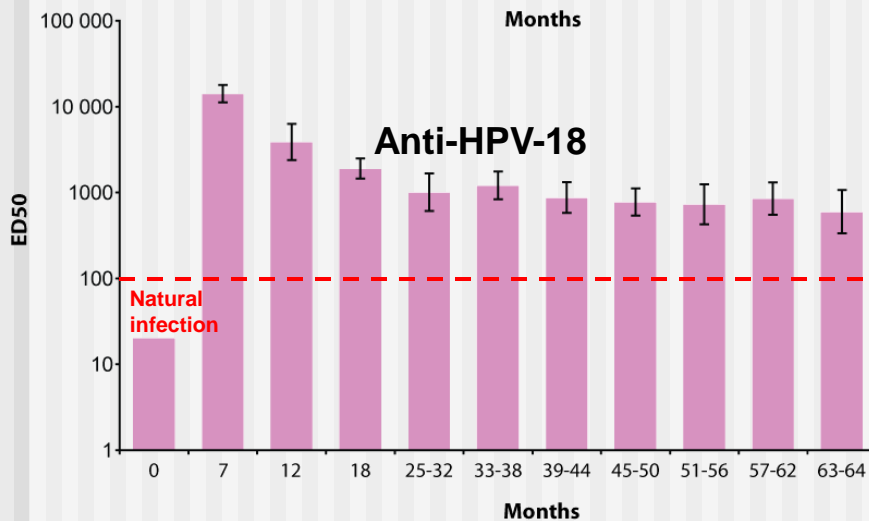
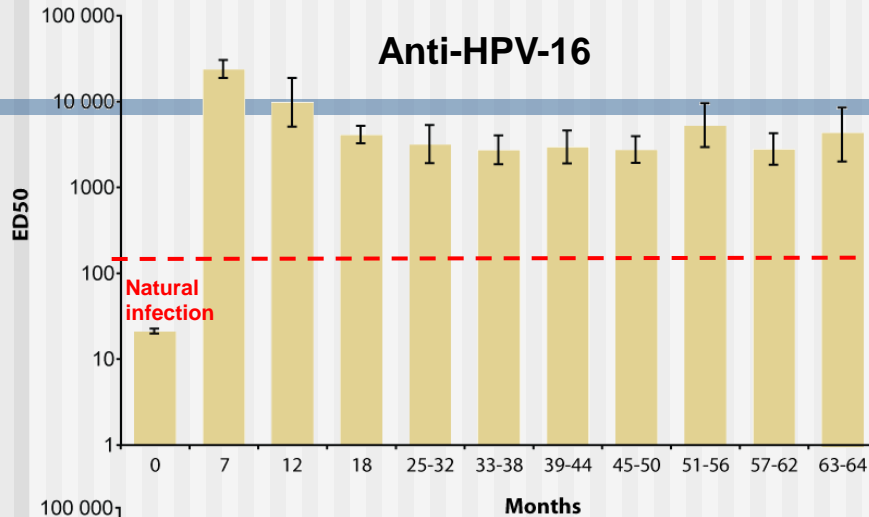
■ Phase III FUTURE I+II

- 4 Jahre Quadrivalent (end of study)
- 15 Monate Bivalent (interim)
 - Paavonen Lancet 2007

HPV-001/007:

Strong & Sustained Immune Response up to 5.5 years

Neutralizing Antibody Responses



**≥98% of women
remain seropositive
for both
HPV-16 and -18
up to 5.5 years**

Titers determined on HPV16/18 ELISA positive/ DNA negative subjects

6.4 Years: HPV-16/18 Incident, Persistent Infections & CIN

Combined analysis initial efficacy study and extended follow-up

HPV-16/18 Endpoints	<i>Cervarix</i> TM	Control	Vaccine Efficacy	
	n	n	%	95% CI
Incident Infection	4	70	95	87.4-98.7
6 Month Persistence	0	34	100	90.0 - 100
12 Month Persistence	0	20	100	81.8 - 100
CIN1+	0	15	100	73.4 - 100
CIN2+	0	9	100	51.3 - 100

HPV 16/18 CIN2+

	HPV 16/18 related CIN2+	<i>Cervarix</i> TM	Control	Vaccine Efficacy	
		n	n	%	95% CI
Initial efficacy study	27 months ¹	0	3	100	NA
Combined analysis initial efficacy study and extended follow-up	4.5 yrs ²	0	5	100	-7.7 - 100
		0	7	100	32.7 - 100
	5.5 yrs ³	0	9	100	51.3 - 100
	6.4 yrs				

n = 4900

1.
2.
3.

Cumulative efficacy through 5 years: Per-Protocol Population

HPV 6, 11, 16 or 18-related	GARDASIL™ (N = 276)		Placebo (N = 275)			
	n	Cases	n	Cases	Efficacy	95% CI
Persistent Infection	235	2	233	45	96%	(83, 100)
Disease	235	0	233	6	100%	(12, 100)
CIN 1, 2 or 3	235	0	233	3	100%	(<0, 100)
vulvar/vaginal lesions or genital warts	235	0	233	3	100%	(<0, 100)

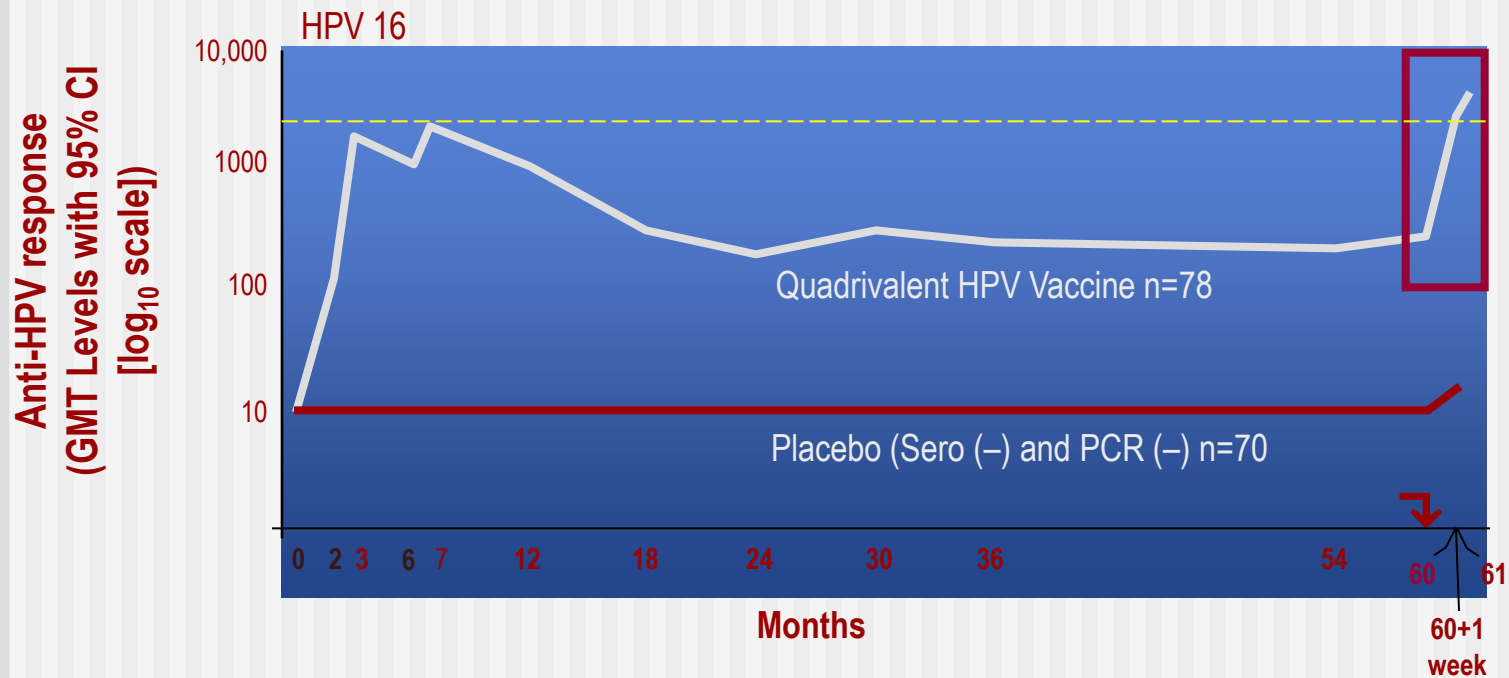
Cumulative efficacy through 5 years: Per-Protocol Population

	GARDASIL® (N = 276)		Placebo (N = 275)			
	n	Cases	n	Cases	Efficacy	95% CI
HPV 6, 11, 16 or 18- related infection or disease	235	2	233	46	96%	(84, 100)
HPV 6-related	214	0	209	17	100%	(76, 100)
HPV 11-related	214	0	209	3	100%	(<0, 100)
HPV 16-related	199	1	198	28	97%	(79, 100)
HPV 18-related	224	1	224	11	91%	(36, 100)

Cumulative efficacy through 5 years: Modified-Intention-to-treat population

HPV 6, 11, 16 or 18-related	GARDASIL™ (N = 276)		Placebo (N = 275)			
	n	Cases	n	Cases	Efficacy	95% CI
Persistent Infection	256	4	254	58	94%	(83, 98)
Disease	266	0	263	10	100%	(55, 100)
CIN 1, 2 or 3	258	0	256	7	100%	(31, 100)
vulvar/vaginal lesions or genital warts	265	0	261	4	100%	(<0, 100)

Immune Memory - Antigen Challenge at Month 60

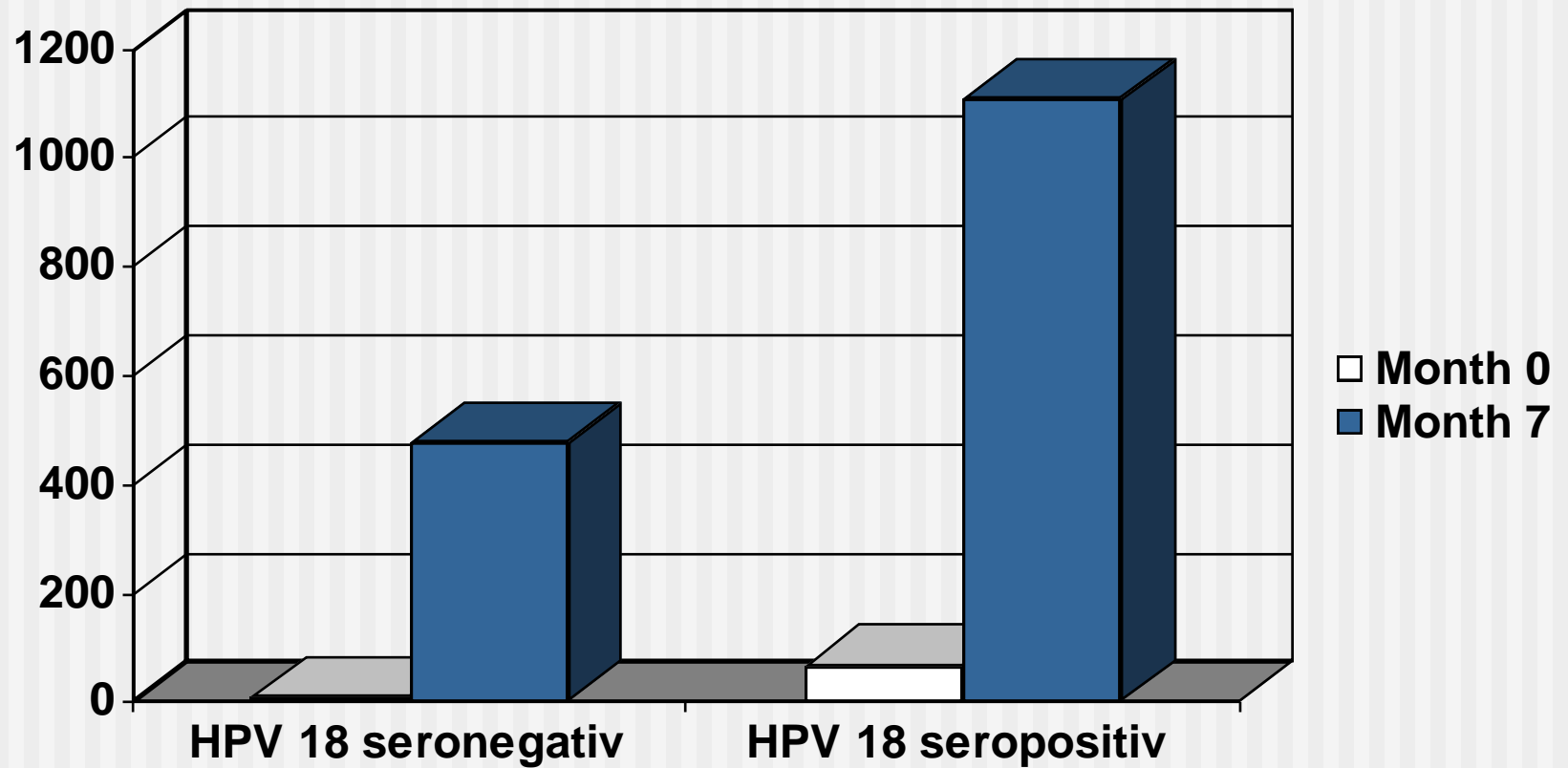


Vaccination on day 0, at 2 and 6 months
Immune challenge at 60 months

Similar results seen with HPV 16, 6, and 11

*In subjects naïve to the relevant HPV type from day 1 through month 60
Olsson Vaccine 2007

HPV-18 Antikörper vor und nach Impfung

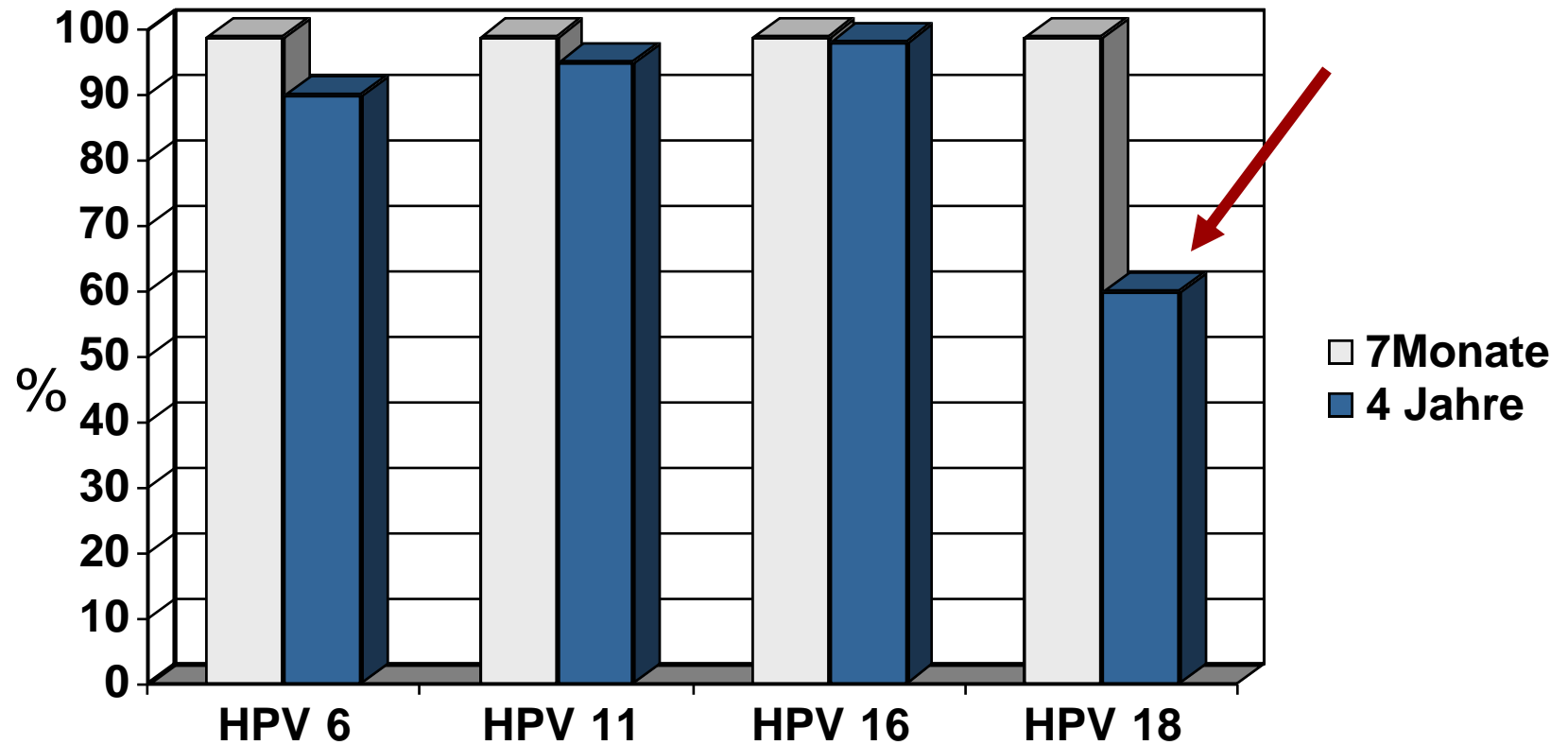


Immungedächtnis

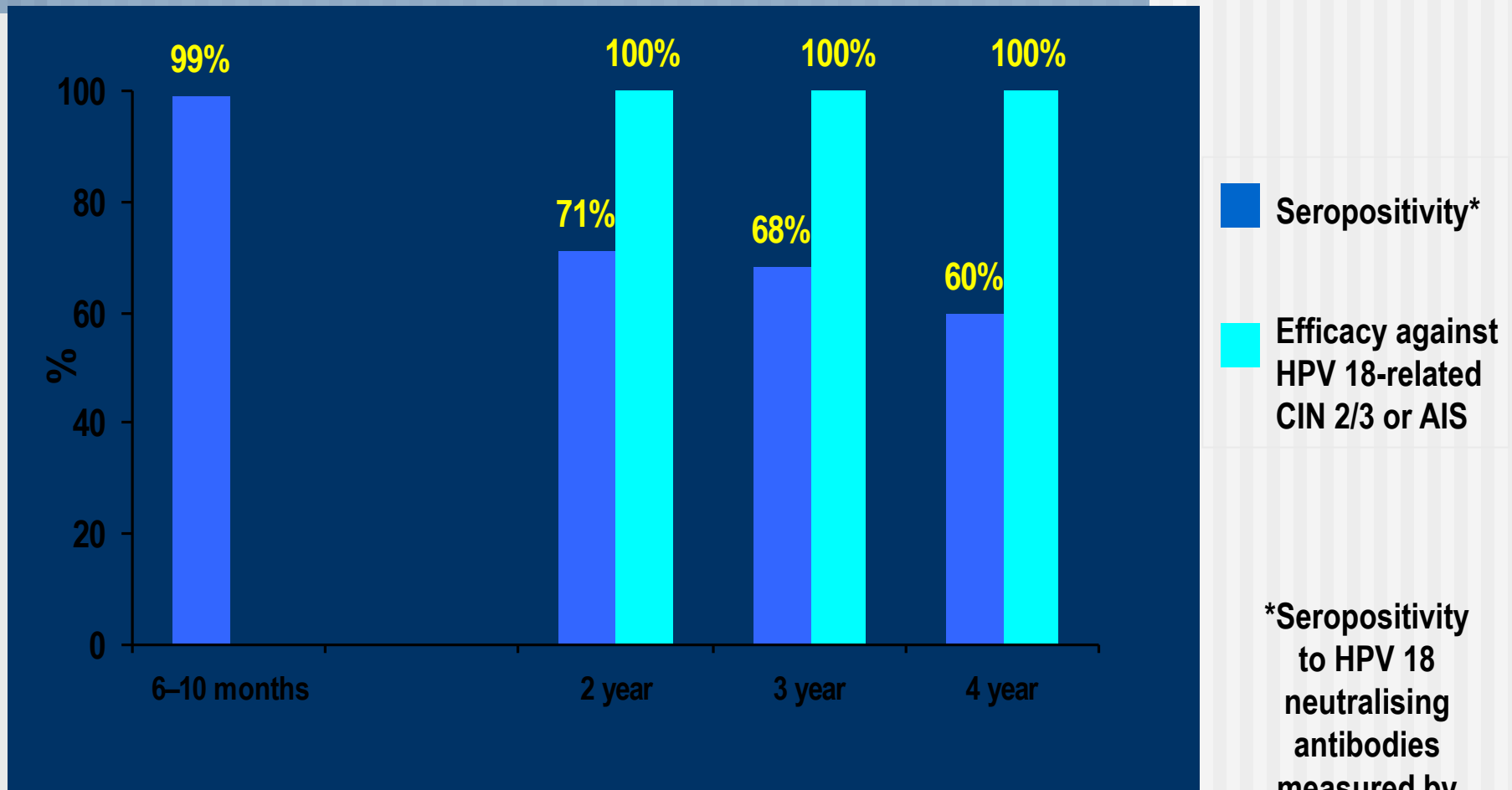
- B- Lymphozyten (B-memory cells)
- Hepatitis B
 - Nach Impfung keine Erkrankung
 - Auch wenn keine AK nachweisbar

Quadrivalente HPV- Impfung

Serokonversion



Seropositivity and efficacy of GARDASIL[®] against HPV 18-related disease (CIN 2/3 or AIS)



Prophylactic Efficacy Against HPV 18-Related CIN 2/3 or AIS

FUTURE I/FUTURE II End-of-Study Database

Population	Endpoint	Vaccine	Placebo	Efficacy	95% CI
PPE	CIN 2/3 or AIS	0	29	100%	87, 100
MITT-2	CIN 2/3 or AIS	0	38	100%	90, 100

PPE = Per-Protocol Efficacy

Naïve at Day 1 to the relevant HPV type, free of HPV infection through Month 7, received 3 doses of vaccine/placebo, case counting starting after Month 7

MITT-2 = Broad HPV-Naïve Population

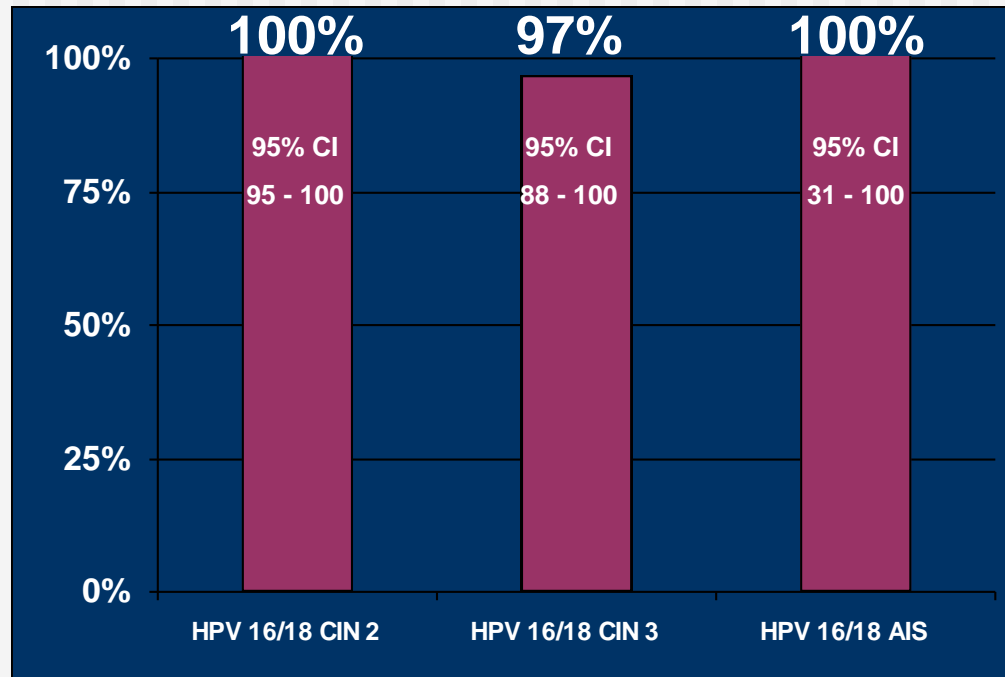
Naïve at Day 1 to the relevant HPV type, received ≥ 1 dose of vaccine/placebo (most subjects received 3 doses), case counting starting at Day 31

Immungedächtnis Conclusio

- Klinische Endpunkte (Histologie) entscheidend
 - WHO, FDA, EMEA empfohlen
- AK- Spiegel sind Surrogatparameter
 - Abhängig von der Nachweismethodik
- Nachweis des Immungedächtnis
 - sehr lange Wirkung des Impfstoffes

4- Jahresergebnisse Gardasil CIN2/3 und AIS, Frauen 16 – 26

Combined results from 4 phase II/III trials
~4 year follow up - Per Protocol Population (END OF STUDY)



n (GARDASIL®) = 8493; n (placebo) = 8464

Summary of Safety- Gardasil

1. Garland SM et al. *New Engl J Med.* 2007. 2. The FUTURE II Study Group. *New Engl J Med.* 2007.

	FUTURE I ¹		FUTURE II ²	
	Vaccine (n=2,673)	Placebo (n=2,672)	Vaccine (n=6,019)	Placebo (n=6,031)
Injection site AE	86.8	77.4	84.4	77.9
• Pain	85.3	75.4	83.0	75.8
Systemic AE	65.3	63.7	61.4	60.0
Serious AE	1.8	1.7	0.7	0.9
Serious vaccine-related AE	<0.1	0.0	<0.1	<0.1
Discontinuation due to serious AE	0.1	0.1	0.1	0.1
Discontinuation due to serious vaccine-related AE	0.0	0.0	0.0	<0.1
Discontinuation due to death*	0.1	0.1	0.1	0.1

*None of the deaths were judged by the research investigator to be vaccine- or placebo-related.
Data are presented as percentages, AE = Adverse Event

Hintergrundinzidenz

Disease	Cases per 100,000 adolescents per year	Cases per 100,000 adults per year
Multiple Sclerosis (MS)	7.5 – 8.4 ¹	4.3 ¹
Guillain-Barré-Syndrome (GBS)	1.3 – 2.7 ²	1.3 ²
Rheumatoid Polyarthritits (female to male ratio is 2-3:1)	0.02 ¹ - 3.2 ⁸ (France) - 22.6 ⁸ (Norway)	20 ⁸
Systemic Erythematous Lupus (female to male ratio is 9:1⁴)	10 – 20 ³	3.5 – 9.2 ¹
Dermatomyositis (female > male)	0.2 ¹ – 0.6 ¹	1.8 ⁷
Spontaneous hypothyroidism	No data	350 – 410 in women ⁶ 60 in men ⁶
Spontaneous hyperthyroidism	No data	80 in women ⁶ in men negligible ⁶
Diabetes	7.2 - 16.8 ⁷	8 - 17 ⁴
Unknown and unspecified causes of Deaths	1.3 - 4.2 ⁵	146 - 160 ⁵
Suicide	5.1 – 7.8 ⁵	115 – 128 ⁵
Deaths of undetermined intent	1.2 - 2.4 ⁵	19 – 27 ⁵

Gardasil Anwendungen bis 10/2008

- 36 Millionen Dosen weltweit
 - USA 20 Mio
 - Europa 8 Mio
 - Deutschland 2 Mio
- Australien: 80% 11- 26a
- USA: 25% 11-19a
- Deutschland
 - 39% 12-14a
 - 59% 15-17a

CDC update 21.10.2008

- All serious VAERS reports (6%) for Gardasil have been carefully analyzed by medical experts
- Experts have not found a common medical pattern to the reports of serious adverse events reported for Gardasil that would suggest that they were caused by the vaccine

The screenshot shows the CDC website's 'Vaccine Safety' page. At the top, the CDC logo and 'Department of Health and Human Services, Centers for Disease Control and Prevention' are visible. A search bar and 'CDC en Español' link are on the right. The main heading is 'Vaccine Safety'. Below it, there are three columns of content:

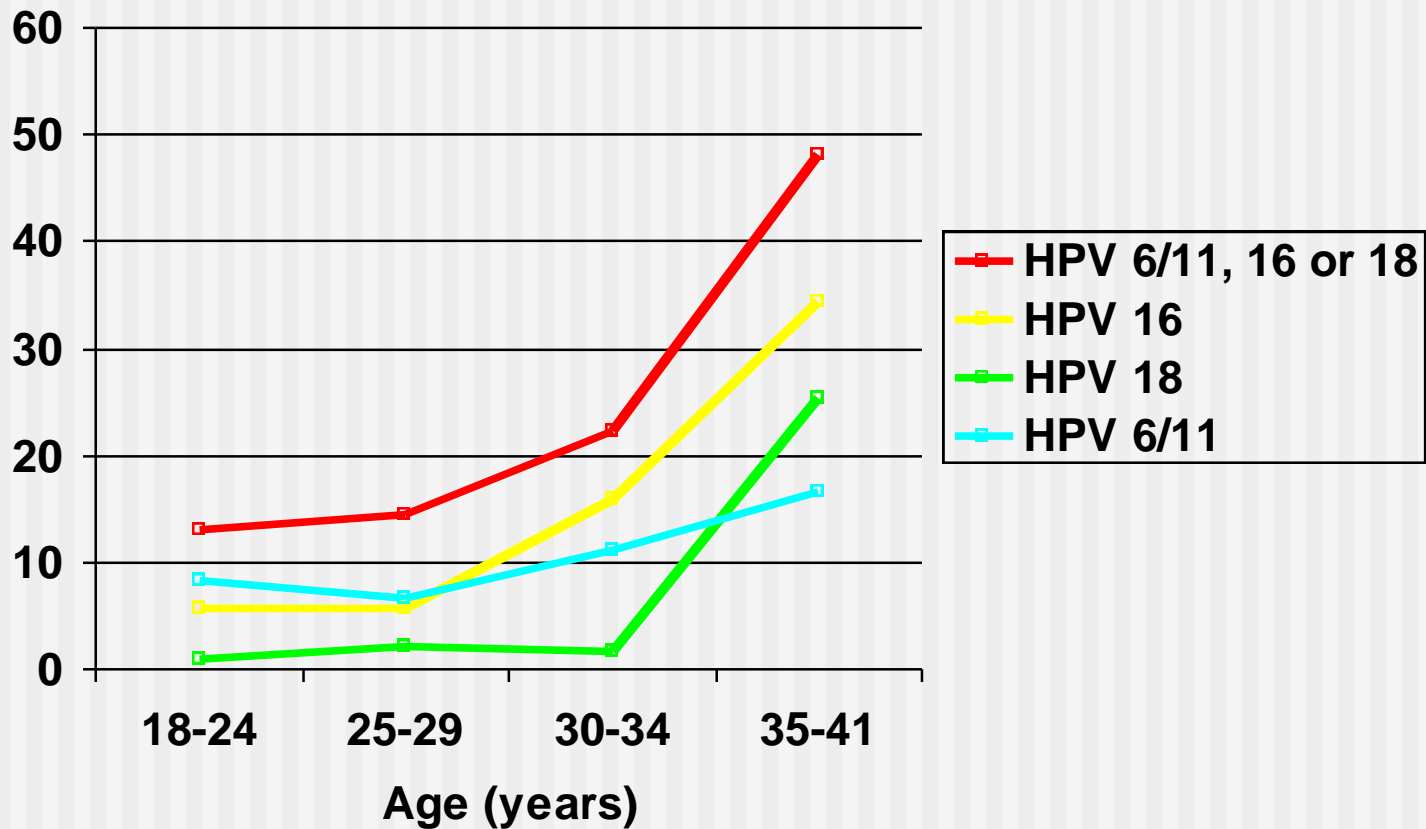
- Vaccine Safety Basics**: Includes links for 'Information for Parents', 'Why It's Important to Monitor Vaccine Safety', 'How Vaccines Are Tested and Monitored', 'Common Questions', 'Vaccine Safety Concerns', and 'History of Vaccine Safety'.
- Public Health Activities**: Includes links for 'Vaccine Adverse Event Reporting System (VAERS)', 'Publications', 'Gardasil Vaccine Reports', and 'Intussusception after RotaTeq Vaccination'.
- Reports of Health Concerns Following HPV Vaccination**: This section is titled 'HPV Vaccine Safety' and contains text about the safety of the HPV vaccine, mentioning 7 clinical trials and over 21,000 girls and women. It also states that CDC and FDA have been monitoring the safety of the HPV vaccine since it was licensed. A bullet point lists 'The Vaccine Adverse Event Reporting System (VAERS)–a useful early warning public health system that helps CDC and FDA detect possible side effects or adverse events following vaccination.'
- Quick Links**: Includes links for 'HPV and HPV Disease Information', 'HPV Vaccine Information', 'Vaccine Safety Information', 'HPV Questions and Answers', 'FDA Center for Biologics Evaluation and Research', 'To Report an Adverse Event in VAERS', 'Related Information on Guillain-Barré Syndrome', and 'Information from FDA and CDC on Gardasil and Its Safety'.

Conclusio

- Hohe Effektivität
 - Gebärmutterhals - CIN
 - Vulva - VIN, Condylome
 - Scheide - VaIN
 - Frauen 9-45
 - Männer 16-26 - Condylome
 - Kreuzprotektivität
- Lange Wirkungsdauer
 - Immungedächtnis
- Hohe Sicherheit

Backup

Male exposure to HPV 6, 11, 16,18 increases with age



Per-Protocol Quadrivalent Vaccine Efficacy Against Cervical Lesions (HPV 6/11)

Protocols 007, 013, and 015 Combined
(3-year follow-up)

HPV 6/11-related lesion	Cases / Evaluable Subjects		Efficacy	95% CI
	Vaccine (n = 9075)	Placebo (n = 9075)		
All CIN (grades 1,2,3)	0 / 6901	36 / 6826	100%	89, 100
CIN 1	0 / 6901	30 / 6826	100%	87, 100

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