Die HPV-Impfung aus pharmakologischer Sicht

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Welche HPV-Viren lösen Krebs aus?

Table 1. HPV types belonging to species and according to the level of evidence of carcinogenicity for cervical cancer

Species	Types							
α5	26	51	69	82				
α6	30	53	56	66				
α7	18	39	45	59	68	70	85	97
α9	16	31	33	35	52	58	67	
α11	34	73						

Adapted from IARC [1].

Group 1 carcinogens.

Group 2A carcinogens.

Group 2B carcinogens.

Phylogenetic analogy with carcinogenic types.

The Journal of Pathology
Volume 234, Issue 4, (Nov. 2014)

Zulassungsstudien: Surrogatparameter, exotische Länder

- Safety and immunogenicity of a vaccine targeting human papillomavirus types 6, 11, 16 and 18: a randomized, placebo-controlled trial in 176 Korean subjects.
  - Quadrivalent HPV vaccine induced seroconversion for each vaccine-related HPV type.
  - At month 7, vaccine-induced type-specific antibody titer was high. In
  - conclusion, administration of quadrivalent HPV VLP vaccine to Korean women aged 9-23 years was generally well tolerated and highly immunogenic.

- Aussage: Der Impfstoff induziert die Bildung von Antikörpern
- Keine Aussage, ob der Impfstoff das Krebsrisiko senkt

Int J Gynecol Cancer. 2008 Sep-Oct;18(5):1013-9.

Wo wurden die Studien durchgeführt?

- Geht Sie das ´was an?

Gender	Female
Ages	16 Years to 23 Years
Accepts Healthy Volunteers	Yes
Listed Location Countries	Not Provided
Removed Location Countries	

Dose-Ranging Study of Quadrivalent Human Papillomavirus (HPV) (Types 6,11,16,18) L1 Virus-Like Particle (VLP) Vaccine (V501-007) clinicaltrials.gov

A Study of Gardasil in Preadolescents and Adolescents (V501-018)

- **Safety, immunogenicity, and efficacy of quadrivalent human papillomavirus (types 6, 11, 16, 18) L1 virus-like-particle vaccine in Latin American women.**
  - The prevalence of HPV infection in Latin America is among the highest in the world.
  - A total of 6,004 female subjects aged 9-24 were recruited from **Brazil, Mexico, Colombia, Costa Rica, Guatemala and Peru**.
  - Subjects were randomized to immunization with intramuscular (deltoid) injections of HPV vaccine or placebo at enrollment (day 1), month 2 and month 6. Among vaccinated subjects in the per-protocol population from Latin America, quadrivalent HPV vaccine was 92.8 and 100% effective in preventing cervical intraepithelial neoplasia and external genital lesions related to vaccine HPV types, respectively.
- These data support vaccination of **adolescents and young adults in the region**, which is expected to greatly reduce the burden of **cervical and genital cancers**, precancers and genital warts.

Reine Mutmaßung!

Int J Cancer. 2008 Mar 15;122(6):1311-8.

A Study of Gardasil in Preadolescents and Adolescents

- Die Studie wurde in Brasilien, Mexico, Kolumbien, Costa Rica, Guatemala und Peru durchgeführt
- Dort reduzierte der Impfstoff durch HPV 6,11,16,18 hervorgerufene Läsionen
- Keine Aussagen über Läsionen durch andere kanzerogene HPV-Viren!

- **Diese Studie führte zur Impfempfehlung für Österreichische Volksschulkinder**

Zulassungsstudien (007/013/015)

Study limitations

Limitations of the current analyses include the fact that the generally HPV naive population was tested only for the presence of the four vaccine HPV types and 10 other HPV types prevalent in cervical cancer. However, other HPV types may contribute to condylomas, and there are several uncommon HPV types that we did not test for (such as HPV 68 and 73) that are classified as oncogenic. Failure to identify infections with these types at baseline would have resulted in an underestimation of the protective effect against any disease in the generally naive population. As these types are not common, this conservative bias is not likely to be substantial. Another limitation concerns the fact that rate estimates of disease are dependent on the intensity of assessment. There were some differences in assessment between studies, notably the fact that protocol 015 required cervical smear screening every 12 months, whereas protocol 013 required smear testing every six months. Although the studies eligibility criteria included a limit on the lifetime number of sexual partners, the generalisability of the results is probably high as the population studied was enrolled globally.

Competing interests: JD has received consultancy fees, lecture fees, and research grants from Merck & Company and Sanofi Pasteur MSD. SKK has received consultancy fees and has received funding through her institution to conduct HPV vaccine studies for Sanofi Pasteur MSD and Digene. SMG has received advisory board fees and grant support from Commonwealth Serum Laboratories and GlaxoSmithKline, lecture fees from Merck & Company, and funding through her institution to conduct HPV vaccine studies for GlaxoSmithKline. CMW has received funding through her institution to conduct HPV vaccine studies for GlaxoSmithKline, and has received reagents and equipment from Roche Molecular Systems for HPV genotyping studies. KS has received consultancy fees from Merck & Company. O-EI has received lecture fees from Merck & Company and GlaxoSmithKline. LLV has received lecture fees, advisory board fees, and consultancy fees from Merck & Company and Sanofi Pasteur MSD. KAA has received consultancy and advisory board fees. MH-A has received lecture fees and grant support from Merck & Company. GP has received lecture fees and consultancy fees from Merck & Company and Sanofi Pasteur MSD. DRB has received lecture fees, advisory board fees, and intellectual property fees. SLe has received lecture fees from Merck & Company and Sanofi Pasteur MSD. S-EO has received lecture fees from Merck & Company. DGF has received consultancy fees and funding through his institution to conduct HPV vaccine studies for GlaxoSmithKline, and lecture fees and consultancy fees from Merck & Company. JP has received consultancy fees, advisory board fees, and lecture fees from Merck & Company. MS has received lecture fees and grant support from Merck & Company. FXB has received lecture fees from Merck & Company and GlaxoSmithKline, and has received funding through his institution to conduct HPV vaccine studies for GlaxoSmithKline. EAJ has received lecture fees from Merck & Company, Sanofi Pasteur MSD, and GlaxoSmithKline. SM has received lecture fees, advisory board fees, and consultancy fees from Merck & Company and Sanofi Pasteur MSD. NM has received lecture fees, advisory board fees, and consultancy fees from Merck & Company and Sanofi Pasteur MSD. Additionally, S-EO, CMW, MH-A, LLV, O-EI, GWKT, FXB, JP, JD, EHT, SLe, EAJ, SKK, GP, DGF, KS, MS, LAK, and DRB have received funding through their institutions to conduct HPV vaccine studies for Merck & Company. FJT, CR, AT, JTB, RM, SV, TMH, RH, and EB are employees of Merck & Company and potentially own stock or stock options in the company.

BMJ 2010;341:c3493

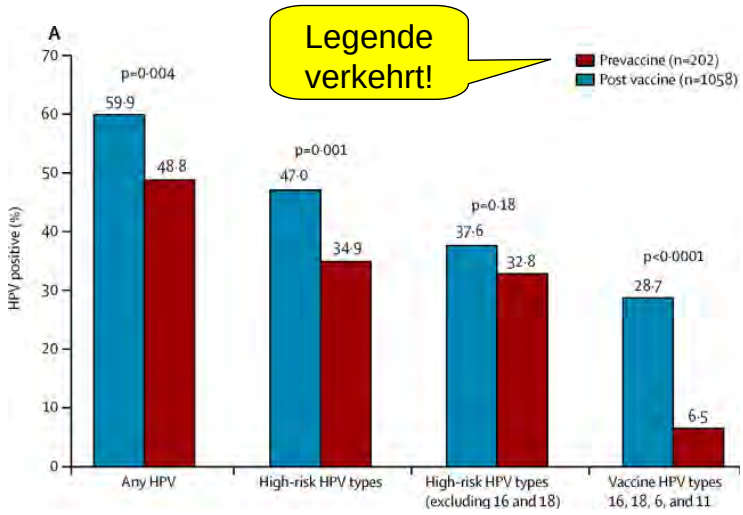
Kreuzimmunität

- The bivalent vaccine seems more efficacious against non-vaccine HPV types 31, 33, and 45 than the quadrivalent vaccine, but the differences were not all significant and might be attributable to differences in trial design. Efficacy against persistent infections with types 31 and 45 seemed to decrease in bivalent trials with increased follow-up, suggesting a waning of cross-protection; more data are needed to establish duration of cross-protection.
  (Cross-protective efficacy of two human papillomavirus vaccines:a systematic review and meta-analysis. Lancet Infect Dis, 12 (2012), pp. 781–789)

- Der Zweifachimpstoff führt (eventuell) zu Kreuzimmunnität gegenüber anderen HPV-Stämmen
  - 31, 33, 45
  - Teilweise nur kurzzeitiger Effekt
- Der Vierfachimpfstoff führt zu (nahezu) keiner Kreuzimmunität

Characteristics of HPV-Specific Antibody Responses Induced by Infection and Vaccination: Cross-Reactivity, Neutralizing Activity, Avidity and IgG Subclasses
PLoS One. 2013 Sep 18;8(9):e74797.

Populationseffekte?



The crude prevalence of any HPV genotype differed between the two samples: 121 (60%) of 202 in the prevaccine-implementation group versus 516 (49%) of 1058 in the in the postvaccine-implementation group tested positive (p=0·004). For the vaccine-targeted HPV genotypes, the difference was even greater (58 [29%] *vs* 69 [7%]; p<0·0001).

Assessment of herd immunity and cross-protection after a human papillomavirus vaccination programme in Australia: a repeat cross-sectional study

The Lancet infectious diseases, Volume 14, Issue 10, October 2014, Pages 958–966

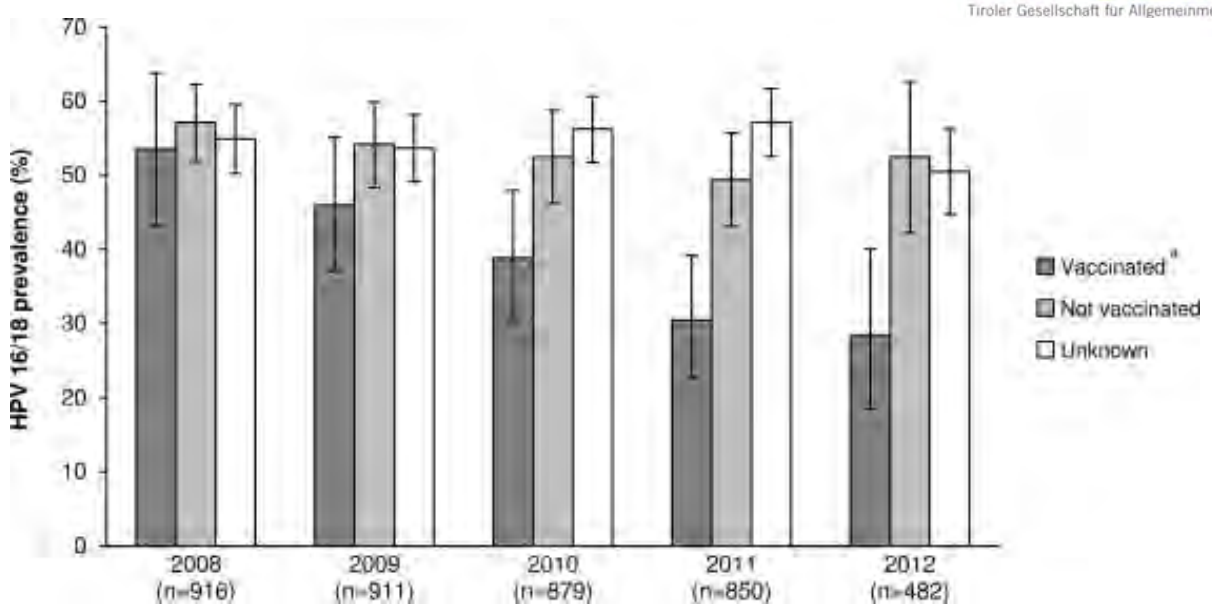
Anzahl der Geschlechtspartner in einem Jahr

- In den Zulassungsstudien galten mehr als 4 Geschlechtspartner stets als Ausschlusskriterium
- Manchmal hat man aber einfach nur vergessen, danach zu fragen….

Number of sexual partners in past 12 months	Prevaccine implementation (n=202)	Postvaccine implementation (n=1058)
0	..	19 (2%)
1	..	525 (50%)
2–4	..	398 (38%)
5–10	..	100 (9%)
≥11	..	13 (1%)
Not recorded	..	3 (<1%)

The Lancet infectious diseases,
Volume 14, Issue 10, October 2014, Pages 958–966

Populationseffekte?

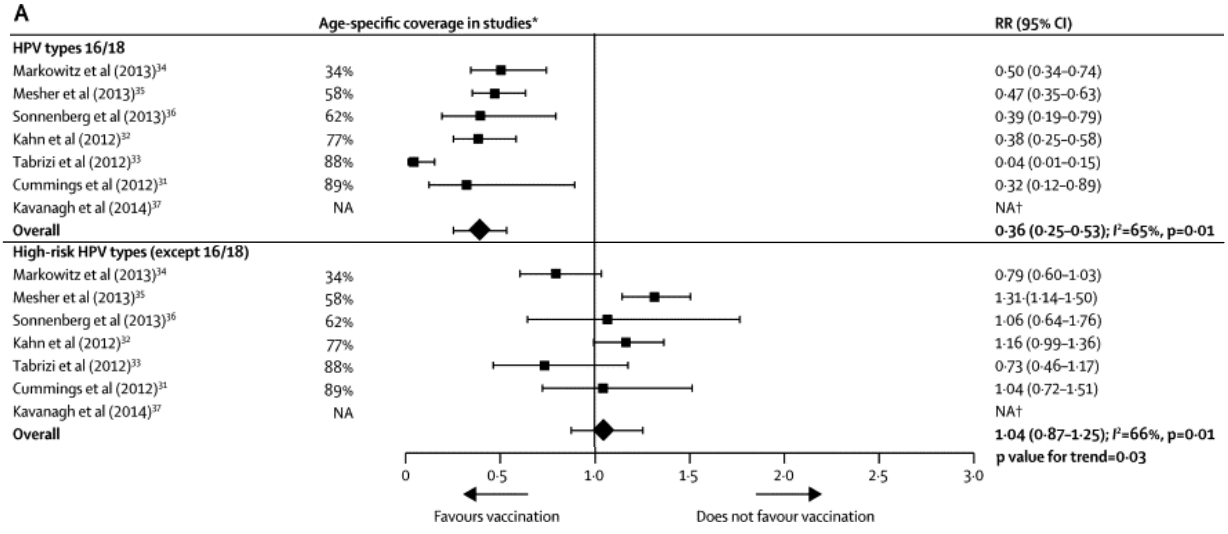


HPV 16/18 attribution to CIN2+ lesions among women age-eligible for vaccination, by year and vaccination status (USA)

Vaccine. 2015 Mar 24;33(13):1608-13.

Populationseffekte

Population-level impact and herd effects following human papillomavirus vaccination programmes: a systematic review and meta-analysis

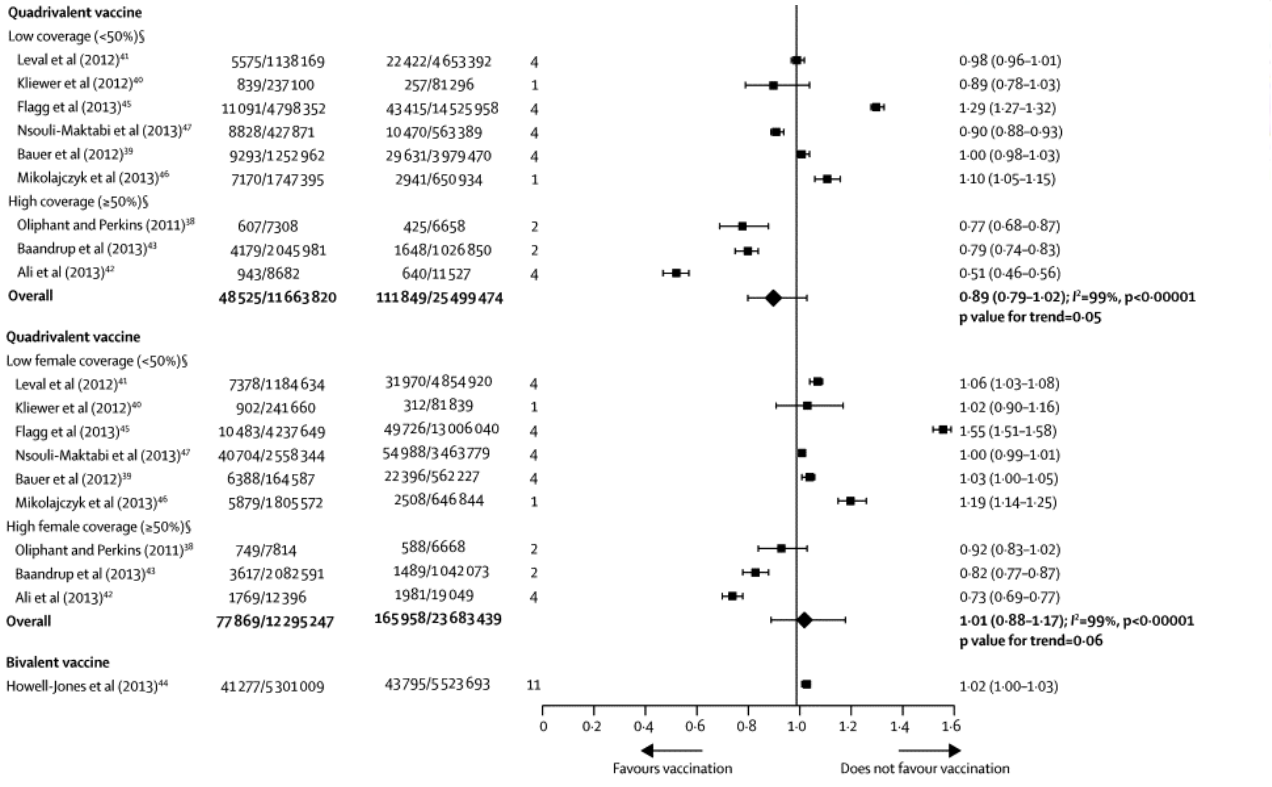


Changes in the prevalence of HPV infections between the prevaccination and postvaccination periods in (A) girls aged 13–19 years

THE LANCET Infectious Diseases

Populations / Herdeneffekte

- Der Zweifachimpfstoff führt zu einer leichten Abnahme von kanzerogenen HPV-Viren (Populationseffekt)
  - aber leider nur in Australien, nicht in den USA
- Keine Aussage, ob dadurch die Krebsrate gesenkt werden kann
- Die Impfstoffe führen zu einer Zunahme von anderen kanzerogenen HPV-Typen



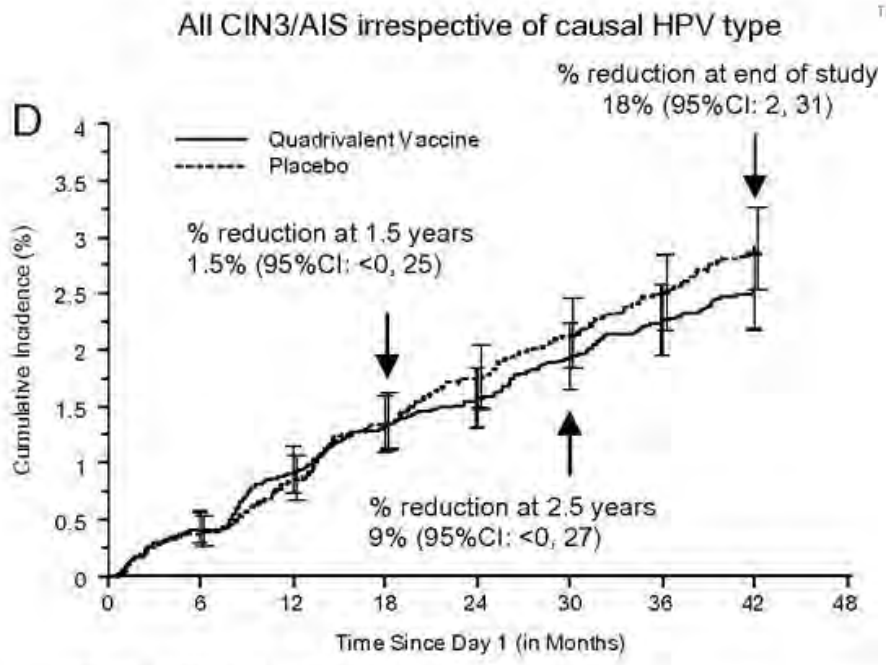
Changes in anogenital wart diagnosis between the pre-vaccination and post-vaccination periods in (A) girls aged 15–19 years, and (D) men aged 20–39 years

THE LANCET Infectious Diseases
Available online 3 March 2015

Bevölkerungseffekte

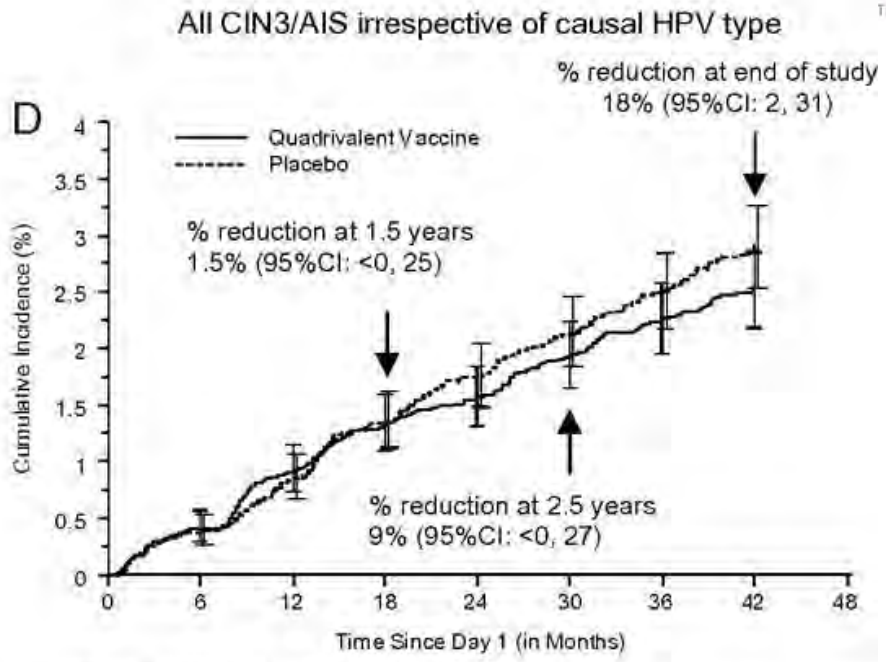
- Der Vierfachimpfstoff führt zu einer Abnahme der Diagnosen an anogenitalen Warzen bei Mädchen (15-19)
- Der Vierfachimpfstoff führt zu einer Zunahme der Diagnosen an anogenitalen Warzen bei Männern (20-39)
  - Erhöhte Warnehmung von HPV in der Bevölkerung
- Keine Aussage, ob die Impfung eine Wirkung gegen Gebärmutterhalskrebs besitzt

Wirkung auf Neoplasien



J Natl Cancer Inst. 2010 Mar 3;102(5):325-39. Impact of human papillomavirus (HPV)-6/11/16/18 vaccine on all HPV-associated genital diseases in young women.

Wirkung auf Neoplasien



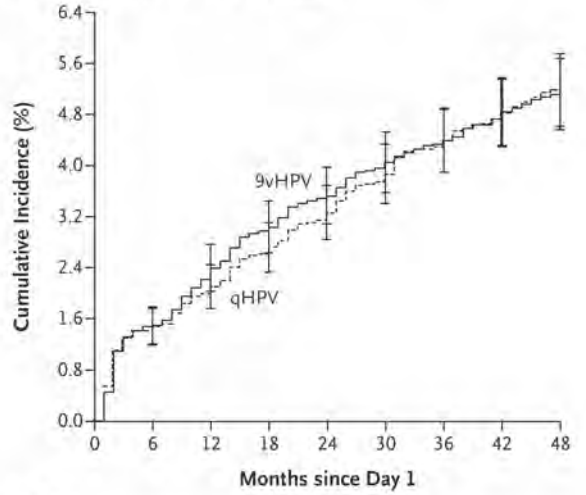
J Natl Cancer Inst. 2010 Mar 3;102(5):325-39. Impact of human papillomavirus (HPV)-6/11/16/18 vaccine on all HPV-associated genital diseases in young women.

Wirkung auf Neoplasien

- Der Vierfachimpfstoff senkt die Anzahl an Neoplasien, die durch HPV 6,11,16 und 18 hervorgerufen werden
- Der Vierfachimpfstoff führt aber zu keiner Reduktion an Neoplasien (CIN3+, AIS)
- Keine Aussage bezüglich Zervixkarzinom

Vergleich 9-fach-Impfstoff vs. 4-fach-Impfstoff

D High-Grade Cervical Disease Irrespective of HPV Type in the Modified Intention-to-Treat Population



No. at Risk									
9vHPV	6882	6710	6449	6253	6079	5853	5483	3487	964
qHPV	6871	6700	6475	6286	6093	5899	5552	3532	1039
Cumulative Cases									
9vHPV	0	103	163	205	237	270	290	314	322
qHPV	0	101	143	184	219	257	289	312	323

N ENGL J MED 372;8 NEJM.ORG FEBRUARY 19, 2015

Der 9-fach-Impfstoff reduziert höhergradige zervicale Neoplasien ebensowenig wie der 4-fach Impfstoff

Zusammenfassung

- Impfprogramme reduzieren die Rate an Infektionen („Durchseuchung) durch HPV 16 und 18
- Impfprogramme erhöhen die Infektionsrate durch andere kanzerogene HPV-Stämme
- Die Impfstoffe und Impfprogramme führen zu keiner Reduktion von höhergradigen Neoplasien

- Es gibt (2015) keinen Beleg, dass die „Krebsimpfung“ zu weniger Gebärmutterhalskrebs führt