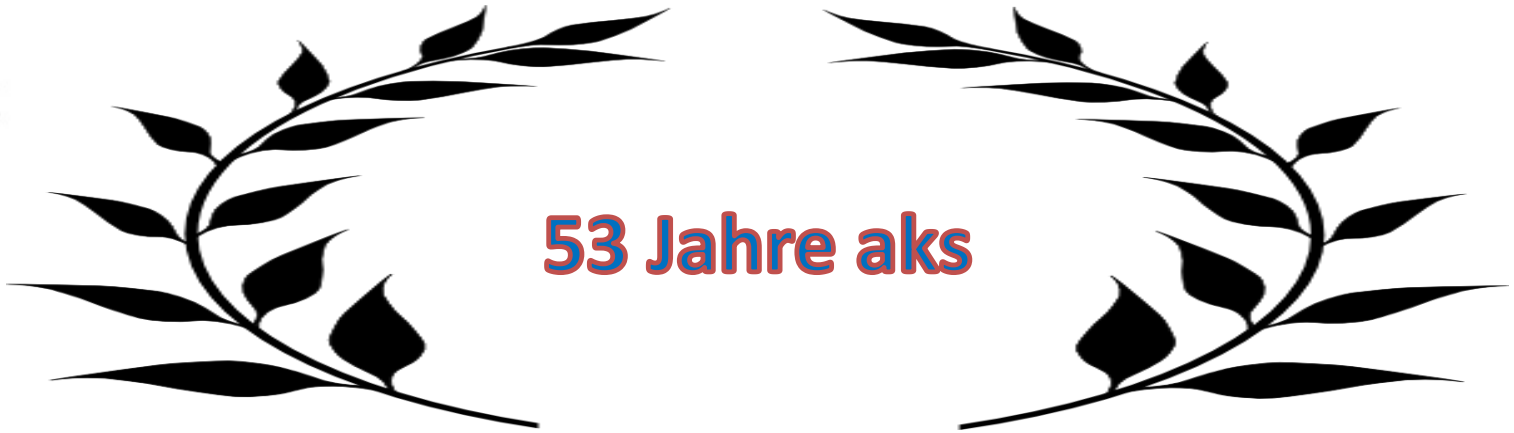
10 Jahre HPV Impfung-
in der breiten Anwendung besser als in den Studien

Hans Concin
aks Bregenz



Interessenskonflikte

- Keine

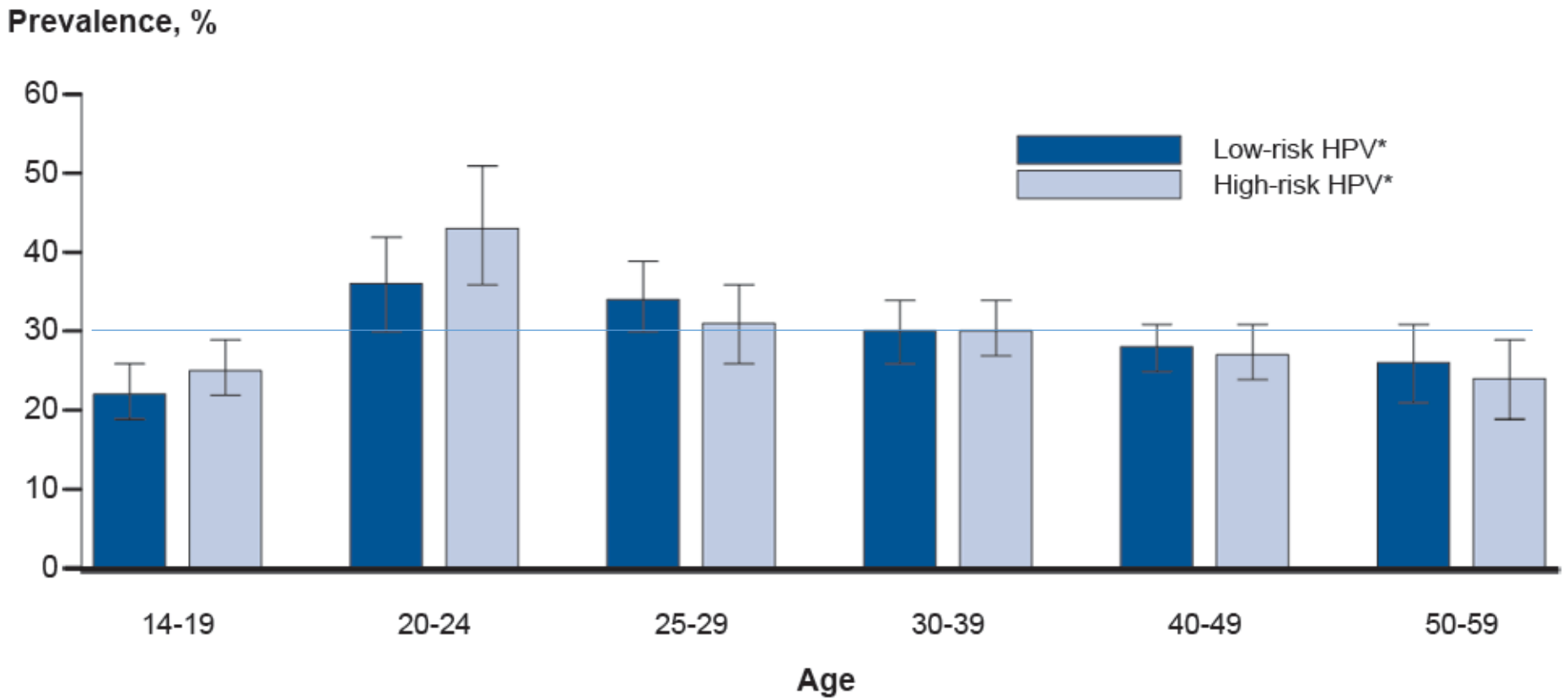
- Keinerlei Entgelte oder sonstige Zuwendungen von Pharmafirmen die Impfstoffe herstellen

10 Jahre HPV Impfung-
in der breiten Anwendung besser als in den Studien

Hans Concin
aks Bregenz

- Allgemeines
- Kondylome
- Präkanzerosen
- Zervixkarzinom
- Sicherheit
- 9-fach Impfung
- Österreich

Figure 52. Human Papillomavirus—Prevalence of High-risk and Low-risk Types Among Females Aged 14-59 Years, National Health and Nutrition Examination Survey, 2003-2006



* HPV = human papillomavirus

NOTE: Error bars indicate 95% confidence interval. Both high-risk and low-risk HPV types were detected in some females.

SOURCE: Hariri S, Unger ER, Sternberg M, Dunne EF, Swan D, Patel S, et al. Prevalence of genital HPV among females in the United States, the National Health and Nutrition Examination Survey, 2003–2006. J Infect Dis. 2011;204(4):566–73

Research

Published online January 19, 2017

JAMA Oncology | Original Investigation

Prevalence of Genital Human Papillomavirus Infection and Human Papillomavirus Vaccination Rates Among US Adult Men

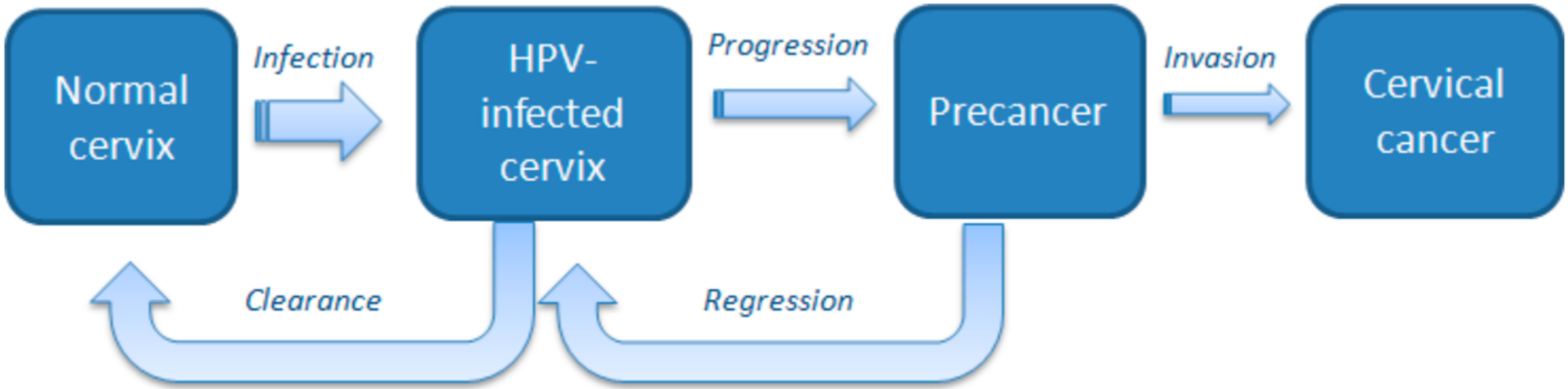
National Health and Nutrition Examination Survey (NHANES) 2013-2014

RESULTS During the NHANES 2013-2014, a total of 1868 men aged 18 to 59 years were examined. The overall genital HPV infection prevalence was 45.2% (95% CI, 41.3%-49.3%). The infection prevalence with at least 1 high-risk HPV subtype defined by DNA testing was 25.1% (95% CI, 23.0%-27.3%). In vaccine-eligible men, the prevalence of infection with at least 1 HPV strain targeted by the HPV 4-valent vaccine and HPV 9-valent vaccine was 7.1% (95% CI, 5.1%-9.5%) and 15.4% (95% CI, 11.7%-19.6%), respectively. Among vaccine-eligible men, the HPV vaccination coverage was 10.7% (95% CI, 7.8%-14.6%).

CONCLUSIONS AND RELEVANCE Among men aged 18 to 59 years in the United States, the overall prevalence of genital HPV infection was 45.2% (95% CI, 41.3%-49.3%). The overall genital HPV infection prevalence appears to be widespread among all age groups of men, and the HPV vaccination coverage is low.

Author Affiliations: Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, Womack Army Medical Center, Fort Bragg, North Carolina (Han); Department of Clinical Investigation, Womack Army Medical Center, Fort Bragg, North Carolina (Beltran, Klaric); Department of Medicine, Womack Army Medical Center, Fort

The natural history of HPV and cervical cancer



Credit: COHEAHR project. http://www.coheahr.eu/background/cervical-cancer

Übertragung und Verbreitung von HPV

Grundsätzlich werden die Krankheitserreger durch **Kontaktinfektion** beziehungsweise **Schmierinfektion** übertragen.

Es ist theoretisch möglich, dass **HP-Viren bei fast allen Haut-zu-Haut-Kontakten** übertragen werden können. **Kondome bieten keinen völligen Schutz**.

Global gesehen steigt die Anzahl an Neuinfektionen mit Feigwarzen kontinuierlich an. Es existieren verschiedene **Hypothesen** z.B., dass die bei **Intimrasuren** entstehenden kleinen Verletzungen das Risiko für Feigwarzen begünstigen.

Die Haupt-Risikofaktoren bleiben dennoch:

- **ungeschützter Geschlechtsverkehr, besonders Promiskuität in jungen Jahren**
- **Faktoren, die die Immunabwehr des Körpers schwächen**

Etwa 1 % bis 2 % der sexuell aktiven Bevölkerung haben sichtbare Feigwarzen.

Abstract

Background: No reports exist on genotype-specific human papillomavirus (HPV) acquisition in girls after first sex in sub-Saharan Africa, despite high HPV prevalence and cervical cancer incidence.

Methods: We followed 503 HP-unvaccinated girls aged 15-16 years in Mwanza, Tanzania, 3-monthly for 18 months with interviews and self-administered vaginal swabs. Swabs were tested for 13 higHRisk and 24 low-risk HPV genotypes. Incidence, clearance and duration of overall HPV and genotype-specific infections were calculated and associated factors evaluated.

Results: A total of 106 participants reported first sex prior to enrolment ($N = 29$) or during follow-up ($N = 77$). One was HIV-positive at the final visit. The remaining 105 girls contributed 323 adequate specimens. Incidence of any new HPV genotype was 225/100 person-years (pys), and incidence of vaccine types HPV-6, -11, -16 and -18 were 12, 2, 2 and 7/100 pys, respectively. Reporting sex in the past 3 months and knowing the most recent sexual partner for a longer period before sex were associated with HPV acquisition. Median time from reported sexual debut to first HPVinfection was 5 months, and infection duration was 6 months.

Conclusion: This is the first description of HPV acquisition after first sex in sub-Saharan Africa where the incidence of cervical cancer is amongst the highest in the world. HPV incidence was very high after first sex, including some vaccine genotypes, and infection duration was short. This very high HPV incidence may help explain high cervical cancer rates, and supports recommendations that the HPV vaccine should be given to girls before first sex.

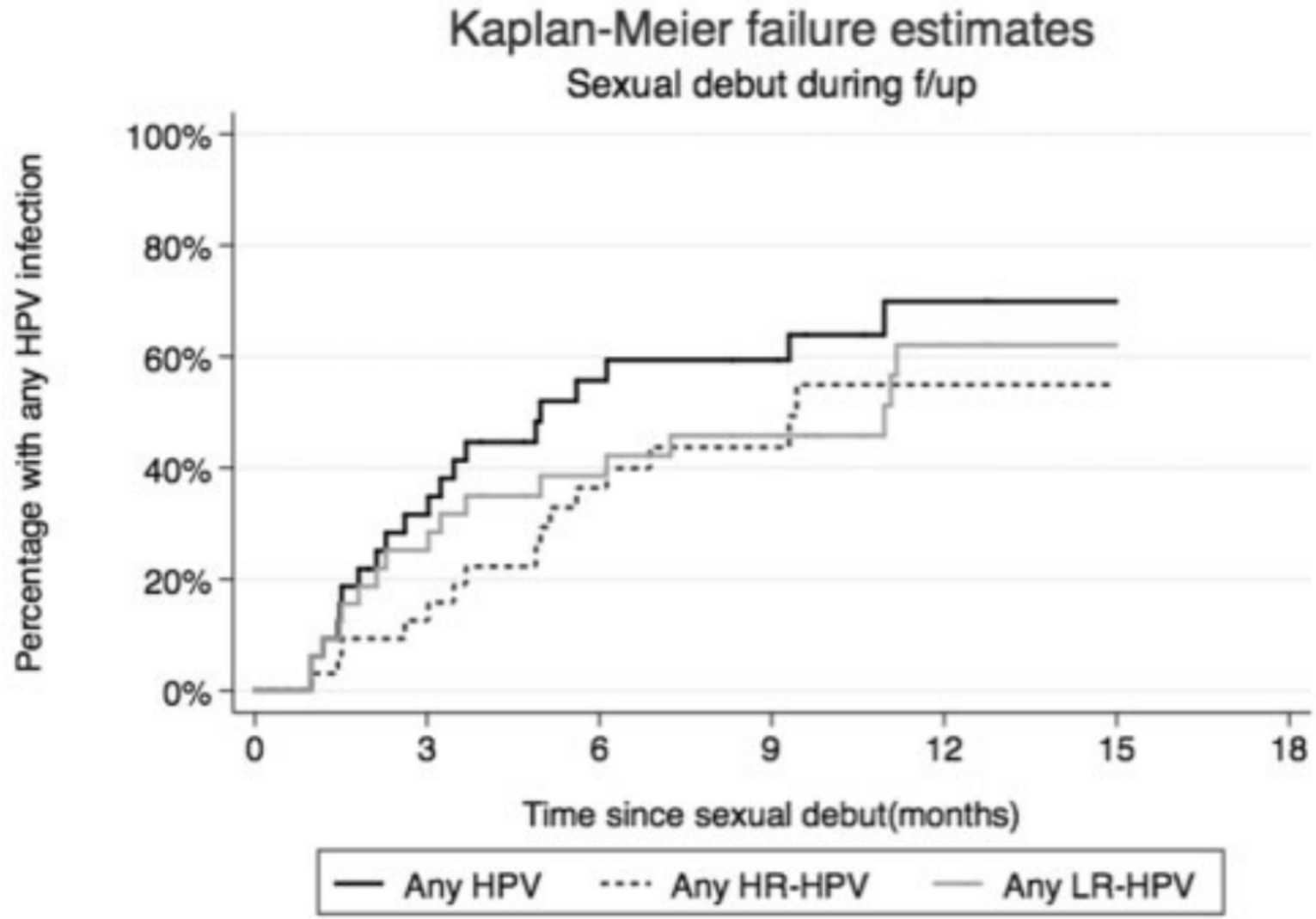
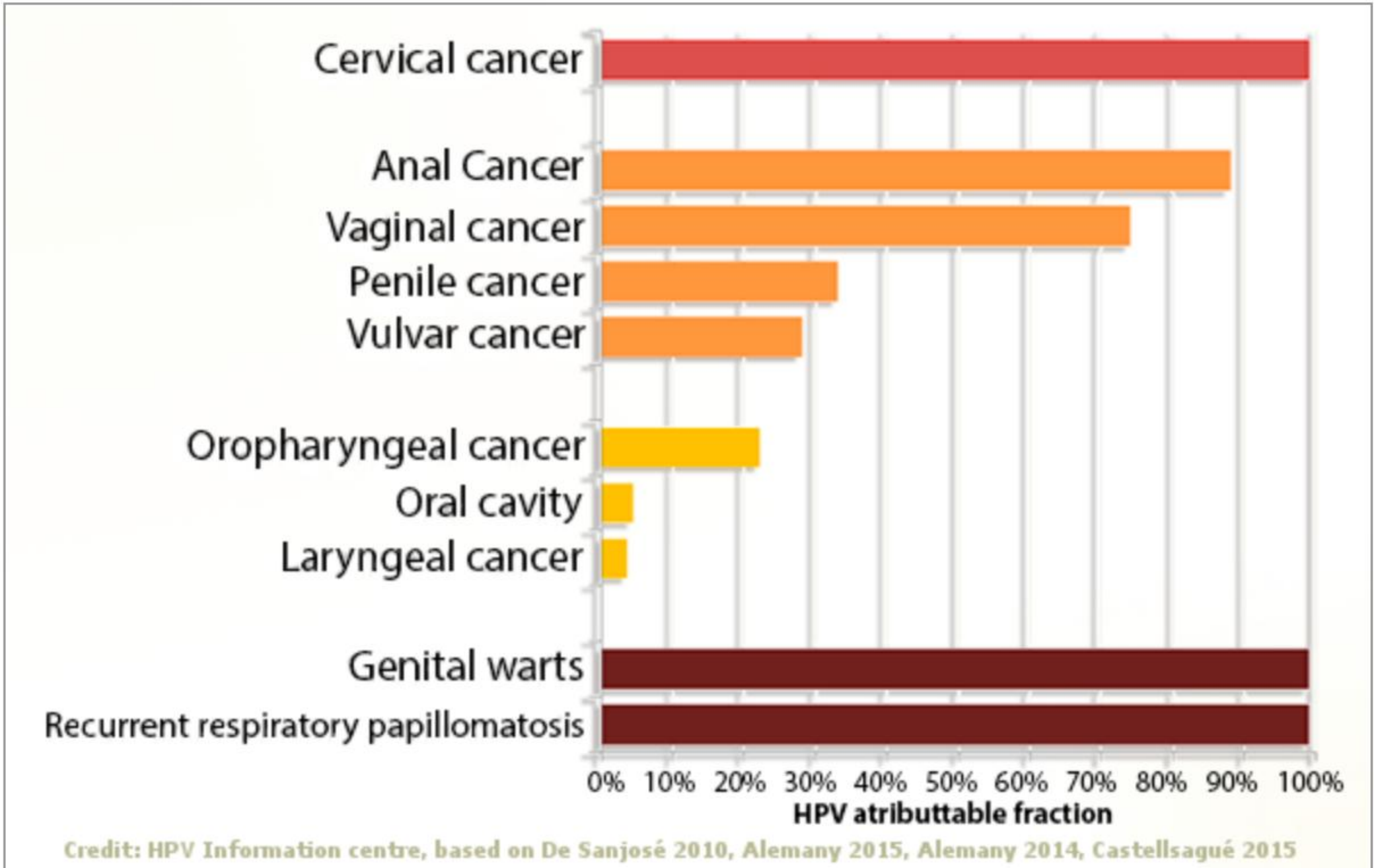


Figure 2. Time from sexual debut to first infection with any HPV, any HR HPV or any LR HPV, among 41 girls who reported sexual debut during follow-up and were HPV-naïve at time of reported sexual debut.

HPV prevalence



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

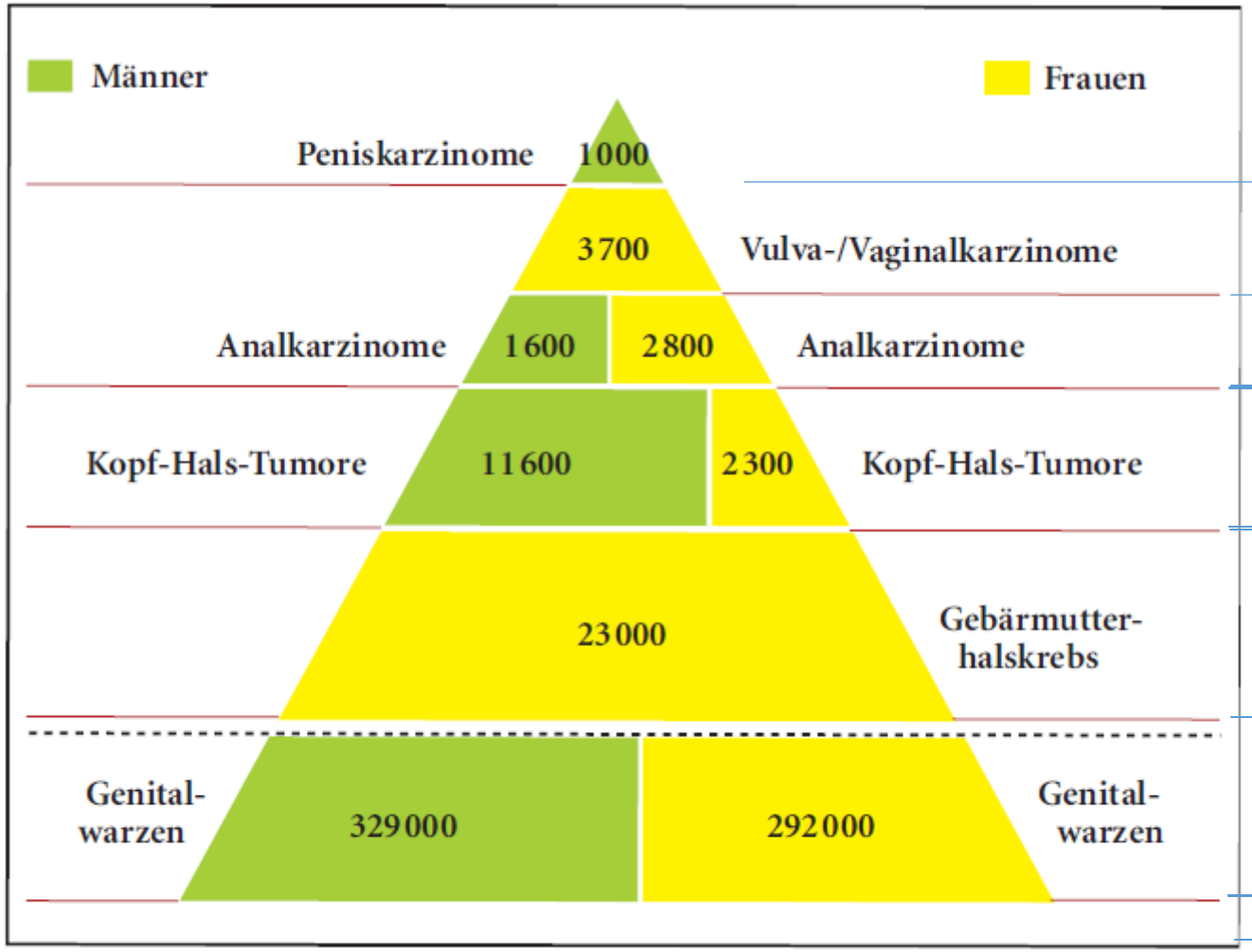
Extraction of Cellular DNA. Biopsy materials were examined histologically and stored at −20°C or −70°C until further processing. Extraction of cellular DNA was done as described (6).

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

Jährliche Neuerkrankungen durch HPV in EU/ A



HPV 6, 11, 16 oder 18 assoziierte Genitalwarzen und Malignome: Jährliche Neuerkrankungen in Europa.

ÖSTERREICH 2009:

58 Männer

128 Frauen/26 Frauen

49 Männer/80 Frauen

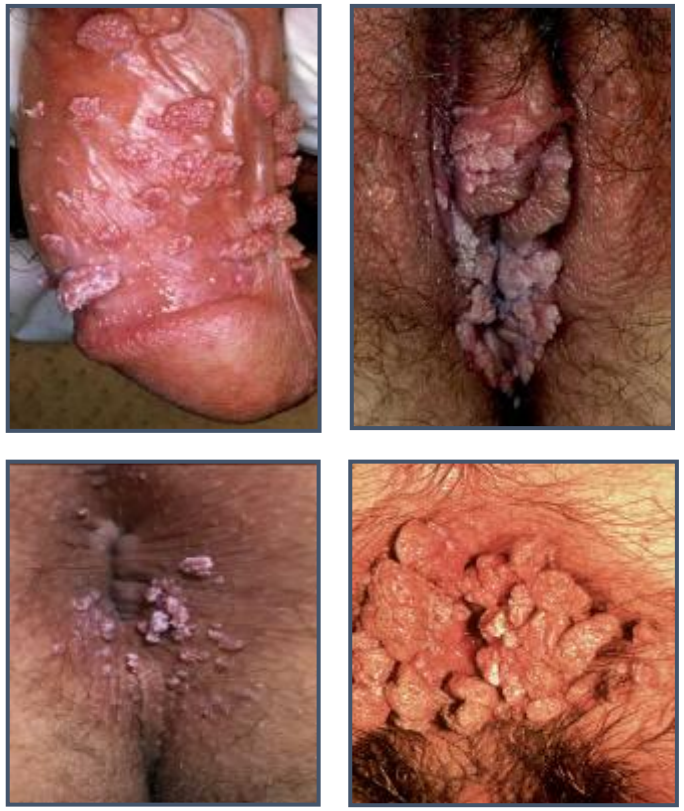
366 Männer
297 Frauen

394 Frauen

4918 Männer

6533 Frauen

HPV 6+11: Condylome



- Lebenszeitrisiko 10%
- Prävalenz 1-2%
- Inkubation 3 Monate
- Rezidivrate >30%

Significant Decrease in the Incidence of Genital Warts in Young Danish Women After Implementation of a National Human Papillomavirus Vaccination Program

Louise Baandrup, MD, Maria Blomberg, MD,* Christian Dehlendorff, MSc, PhD,†*
Carsten Sand, MD, DMSc,‡ Klaus K. Andersen, MSc, PhD,† and Susanne K. Kjaer, MD, DMSc§*

Background: Approximately 90% of genital warts (GWs) are caused by human papillomavirus (HPV) types 6 and 11. Denmark has provided the quadrivalent HPV vaccine to all 12-year-old girls since 2009 and catch-up vaccination to girls up to 15 years since 2008, with up to 80% to 85% vaccine
since 1996,
(October 20
Methods:
hospitalizati
1995 and Ju
annual perce
Results: T
cantly until
confidence i
by 6.2% per
significant d
aged 16 to
annual percentage change, −45.3%; 95% CI, −55.8 to −33.3). The incidences of genital *Chlamydia*, syphilis, and gonorrhea were stable or increased during the study period.
Conclusions: The incidence of GWs decreased substantially among women with high HPV vaccine coverage, pointing to the effect of the national HPV vaccination program.

Conclusions:
The incidence of GWs decreased substantially among women with high HPV vaccine coverage, pointing to the effect of the national HPV vaccination program.

the self-reported cumulative incidence of clinically diagnosed GWs was 7.9%.[2] Studies based on large populations with a wide age span have shown a somewhat lower but still high self-reported cumulative incidence of GWs. In the United Kingdom, 4.1% of women and 3.6% of men reported a history of GWs.[3] In the United
% and
in both
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against
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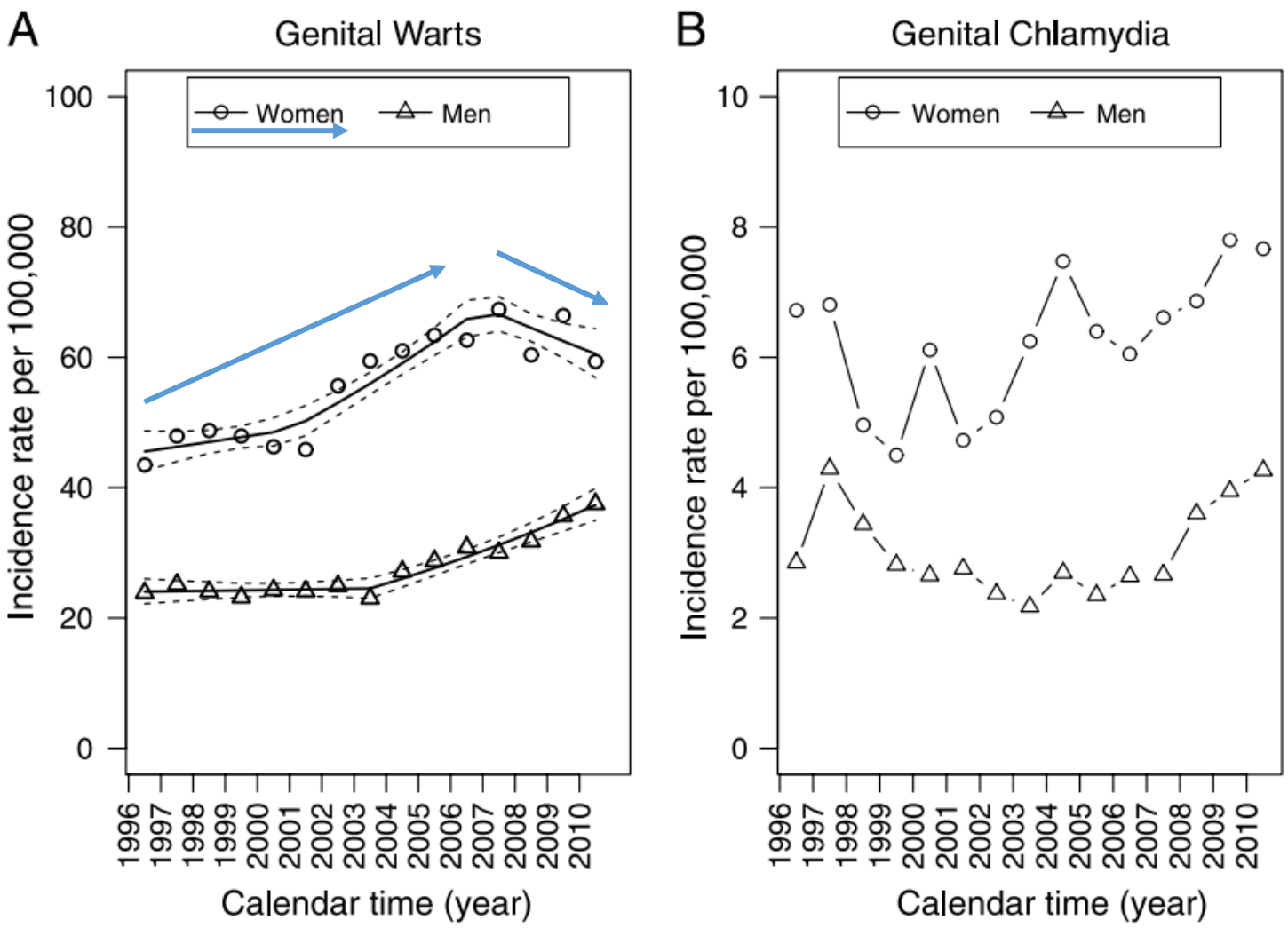
Genital
onths[8]
infec-
of the
opula-
period
before HPV vaccination show an increasing trend.[9–10] Australia began offering HPV vaccination free of charge to women aged 12 to 26 years in 2007 and is therefore one of the first countries to measure the effect of such a program.[11] Surveillance data from various areas of Australia, published recently, showed a marked reduction in the incidence of GWs among women in the

Sexually Transmitted Diseases 2012

Genital Warts
15 years of registration in Jutland and Funen



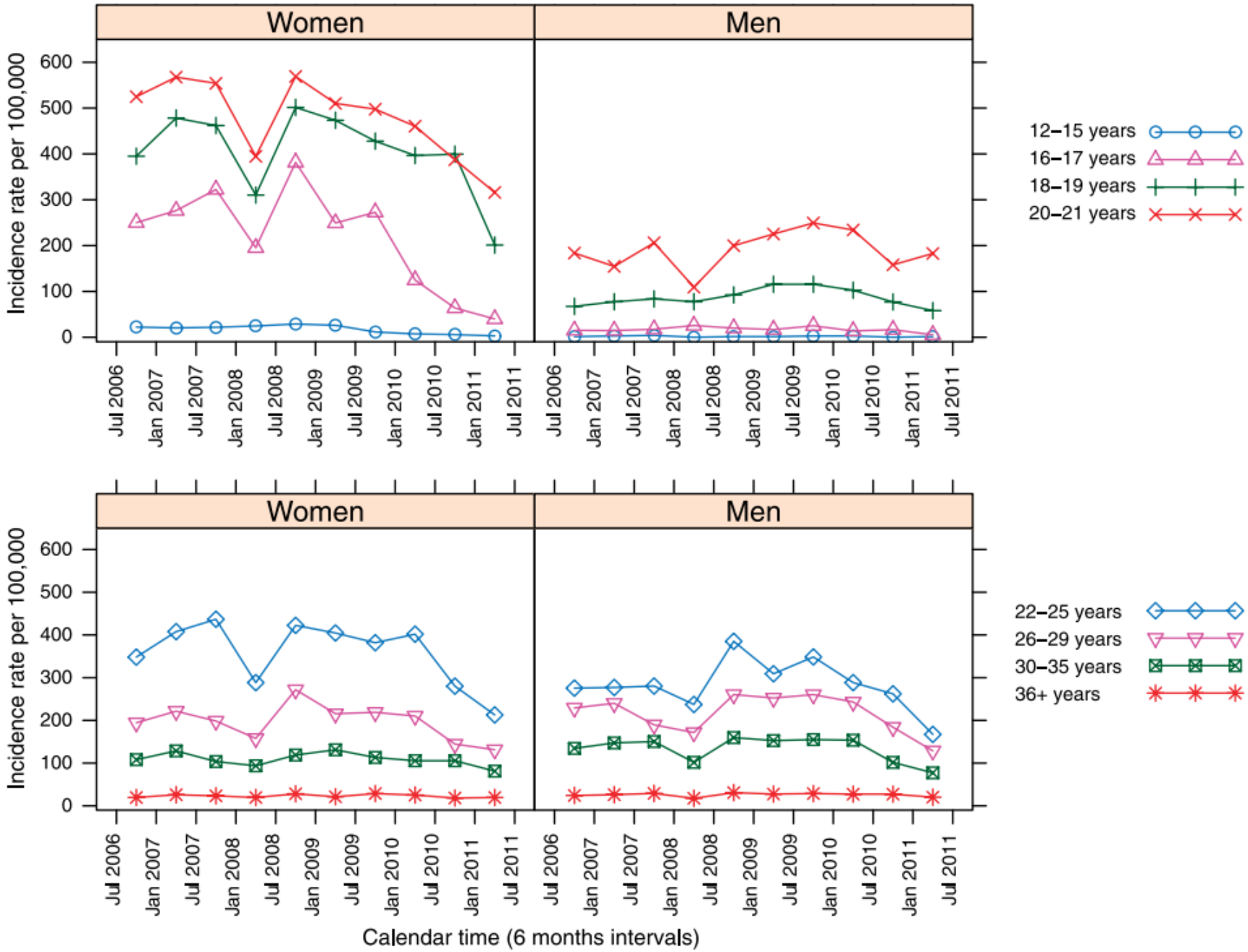
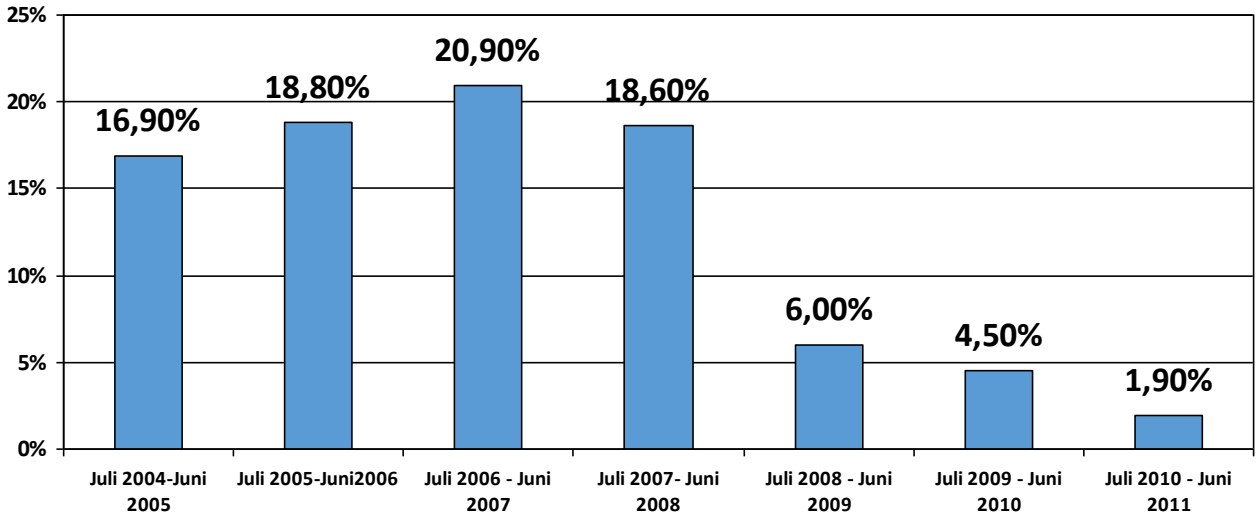


Figure 3. Nationwide incidence rates of GWs per 100,000 person-years, July 2006 to July 2011, stratified by sex and age.

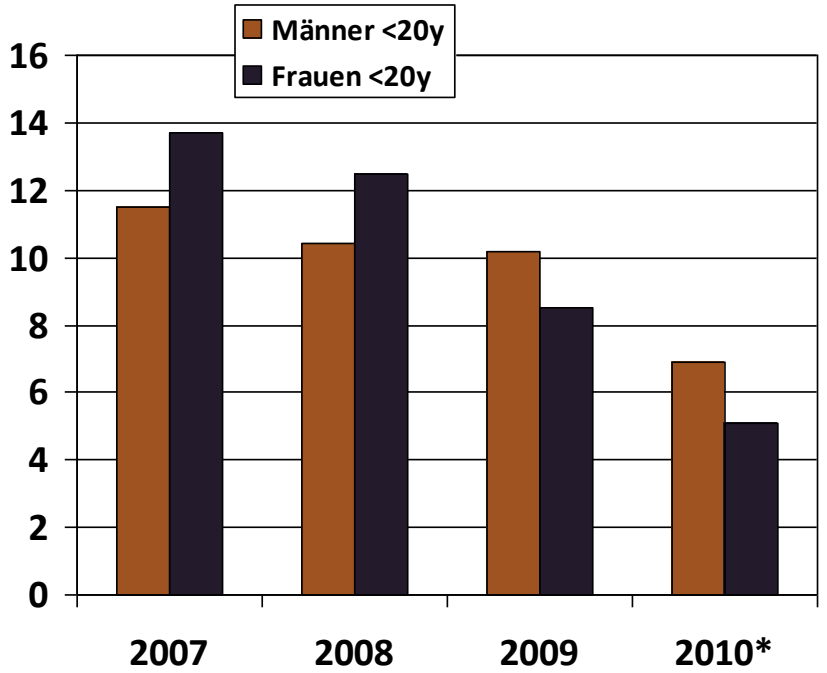
Rückgang der Neuerkrankungen GW in Australien



90% Reduktion von GW-Neuerkrankungen seit dem Start des Impfprogramms (2007) bei jungen Mädchen < 21 Jahre

Adpated from Read et al. Sex Transm Infect 2011

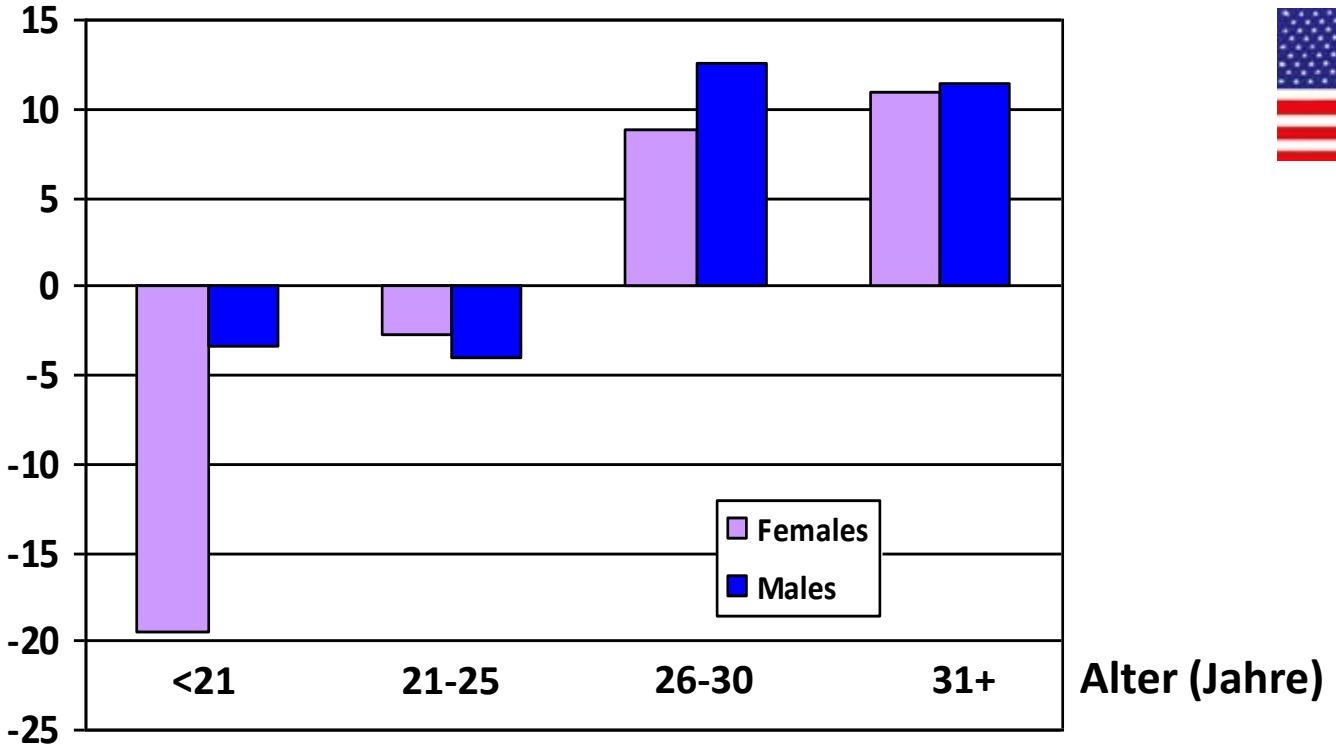
Rückgang der Neuerkrankungen GW in Neuseeland



63% Reduktion von GW-Neuerkrankungen seit dem Start des Impfprogramms (2007) bei jungen Mädchen < 20 Jahre

Oliphant J et al. NZMJ 2011

Rückgang der Neuerkrankungen GW in den USA



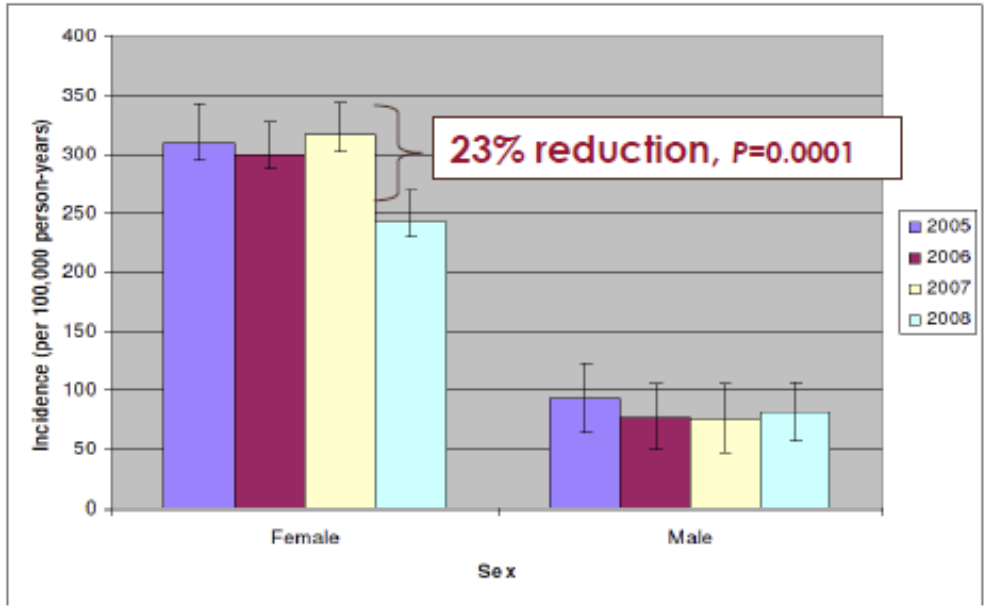
Bauer H et al. Presented at ISSTDR 2011

Doi: 10.1136/sextrans-2011-050109.10

Rückgang Genitalwarzen Deutschland

The Incidence of Anogenital Warts in Germany After Introduction of HPV Vaccination Schulze-Rath R.

Incidence rates of GW: 15 to 19 years by gender 2005 to 2008



From 2nd quarter of 2007 incidence decreased from 316 per 100,000 in 2007 to 242 per 100,000 in 2008

Rückgang der Genitalwarzen Belgien Daten Eurogin 2012

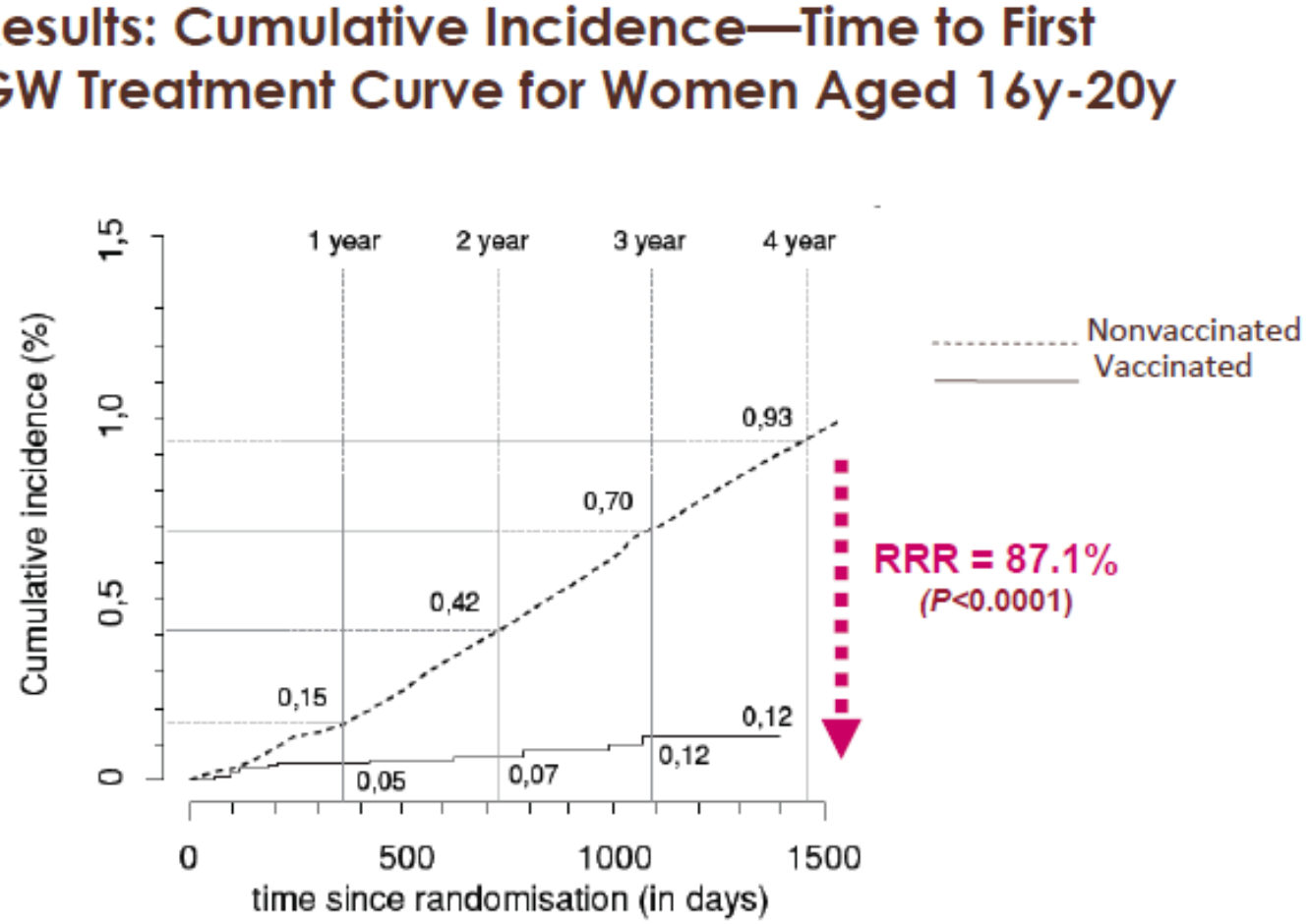
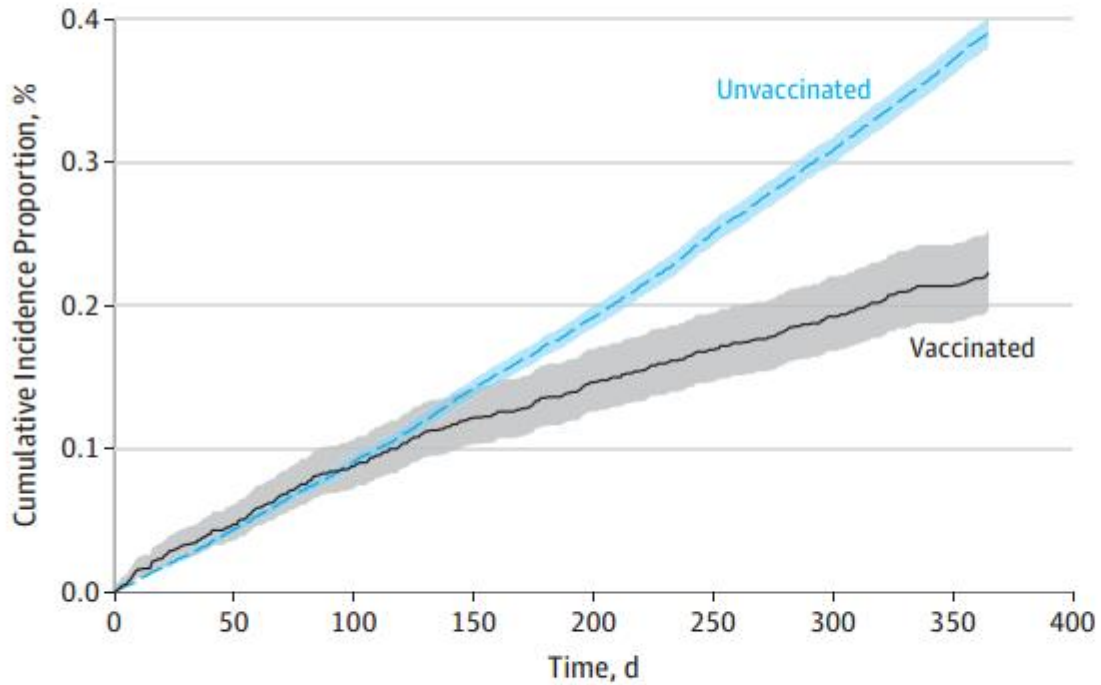


Figure 2. Cumulative Incidence Proportion of Condyloma in Vaccinated and Unvaccinated Individuals



No. at risk								
Unvaccinated	257 900	258 493	257 309	257 997	253 589	256 815	257 592	256 643
Vaccinated	119 046	117 515	114 723	111 659	107 991	103 305	98 327	93 283

Total time used to calculate curves was 1 year (365 days). Cumulative incidence proportion of condyloma in those vaccinated is shown as a function of time since vaccination with 1 dose in days. Cumulative incidence proportion of condyloma in those unvaccinated was calculated based on the age structure of those vaccinated. Shaded areas indicate 95% confidence intervals.

Table 2. Selected Examples of Percentage of Reduction in the Prevalence of Genital Warts in the Vaccine Era Compared to the Prevaccine Era or in Vaccinated Females Compared With Contemporaneous Unvaccinated Females

Country	Supplementary Reference	Setting	% Reduction in Genital Warts
Australia (high vaccine uptake)	Chow 2015 [A27]	Melbourne Sexual Health Centre, Victoria, within 7 y after start of vaccine era	45% annually among females <21 y
	Smith 2016 [A43]	Hospital admissions for genital warts from national database, within 4 y after start of vaccine era	85%–87%, 10–19 y 62%–67%, 20–29 y
	Donovan 2011 [A28]	National surveillance, within 2 y after start of vaccine era	59%, 12–26 y
Denmark	Bollerup 2016 [A42]	National prescription inpatient/outpatient registries, within 5 y after start of vaccine era	43% annually, 12–15 y 55% annually, 16–17 y 39% annually, 18–19 y 21% annually, 20–21 y 12% annually, 22–25 y 6% annually, 26–29 y
Sweden	Herjweijer 2016 [A18]	National hospital admissions that included genital warts diagnosis code, within 4 y after start of vaccine era	82%, 10–16 y (3 vs 0 dose) 71%, 10–16 y (2 vs 0 dose) 69%, 10–16 y (1 vs 0 dose)
United States	Flagg 2013 [A30]	Claims data (inpatient/outpatient visits or pharmacy dispensing) from large claims database (Truven Health Analytics), within 3 y after start of vaccine era	No change, 10–14 y 38%, 15–19 y 13%, 20–24 y

More details regarding the impact and effectiveness of quadrivalent human papillomavirus vaccination on anogenital warts are provided in Supplementary Tables 4 and 5, respectively, in Supplementary Appendix II.

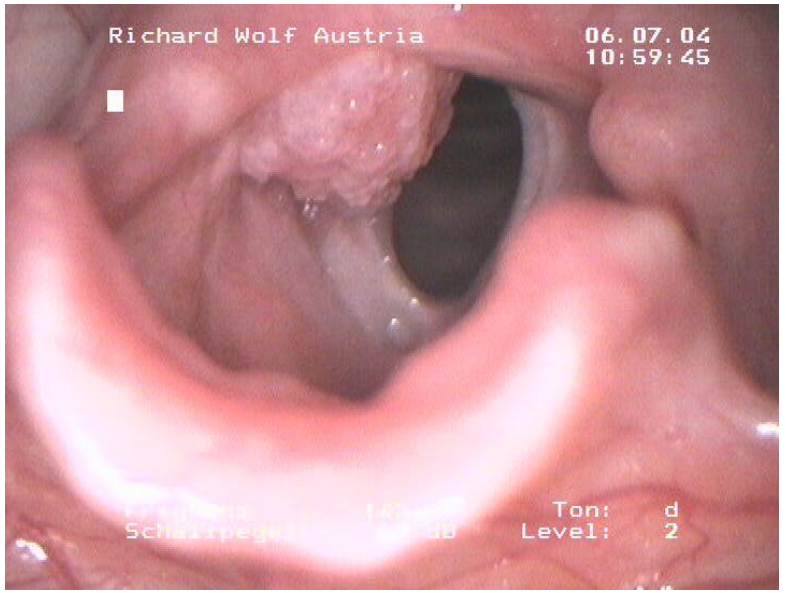
Reductions in genital warts occurred as early as 1 year after program implementation in Australia [A29] and Germany [A35].

Abbreviation: y, years.

Juvenile Larynxpapillome

HPV 6+11

- 20 jährige Patientin
- 43 Operationen!
- Keine Stimme



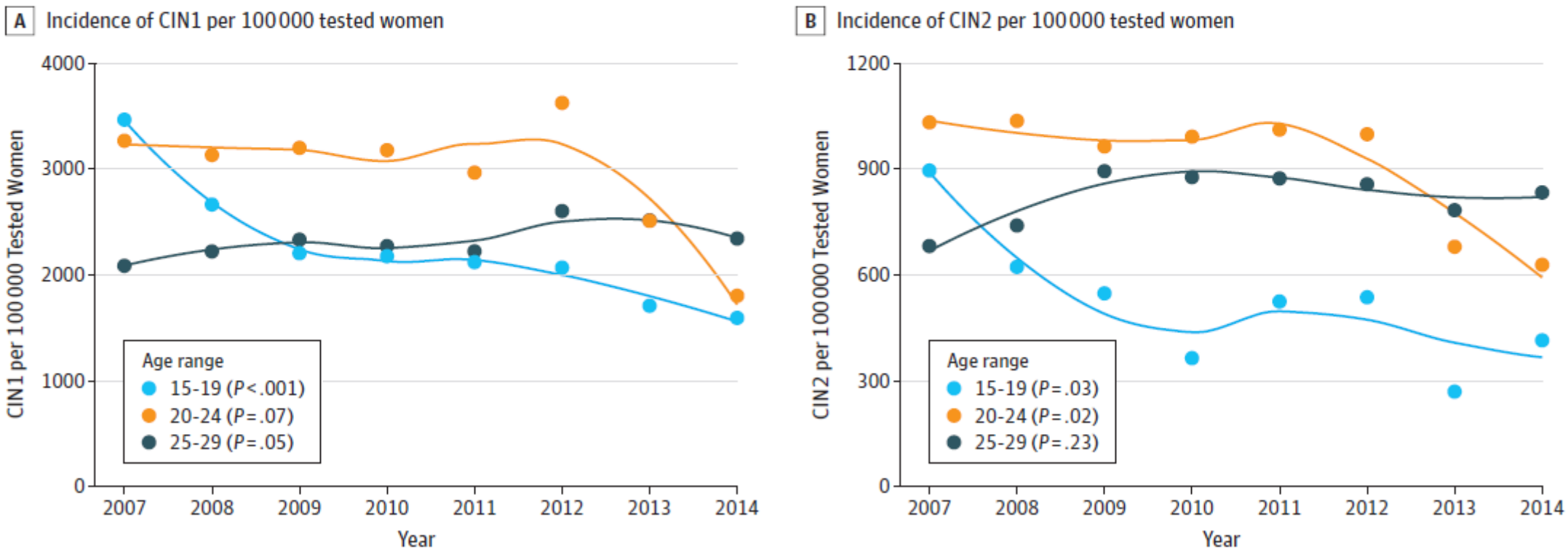
Prof. Biegenzahn HNO AKH Wien

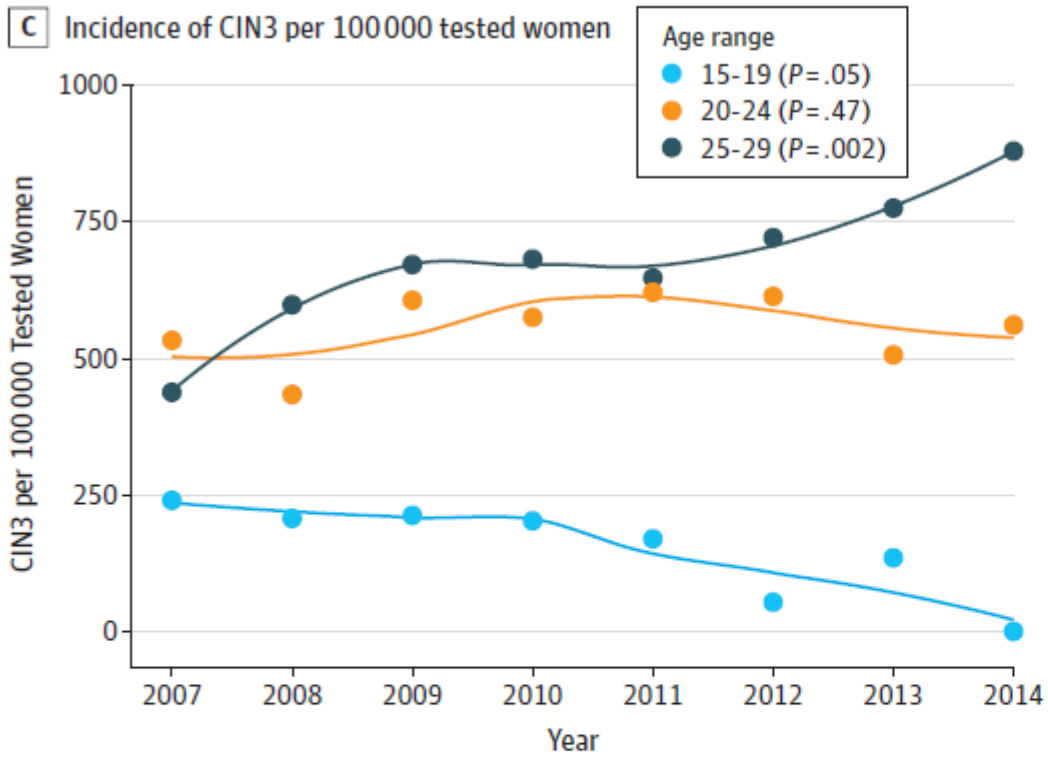
JAMA Oncology | Brief Report

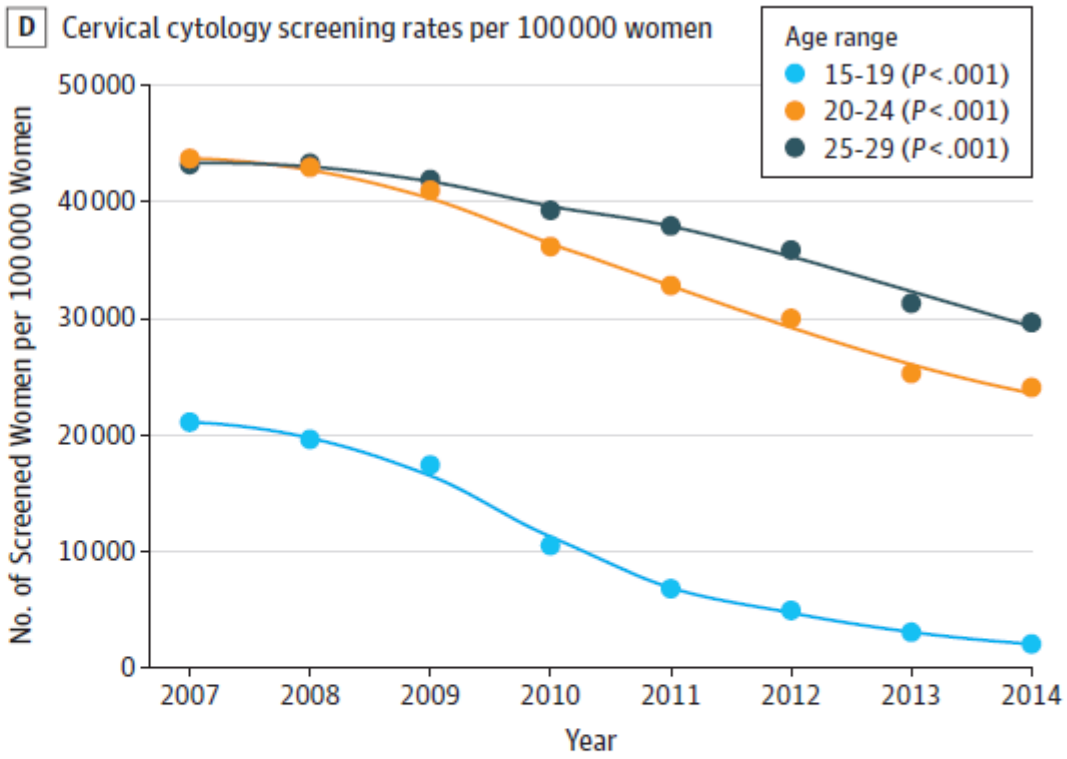
Population-Based Incidence Rates of Cervical Intraepithelial Neoplasia in the Human Papillomavirus Vaccine Era

CIN I
CIN II
CIN III
CIS

Figure. Annual Incidence of Cervical Intraepithelial Neoplasia (CIN) and Cervical Screening Rates by 5-Year Age Groups, 2007 to 2014







For the CIN1, CIN2, and CIN3 incidence rates, the numerator is the number of
women d
age categ
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year for an age category, and the denominator is the total number of women in
nsus;
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Based on vaccination coverage, reductions were greater than anticipated, supporting vaccine cross-protection, efficacy of less than 3 vaccine doses, and herd immunity contributions.

Reduktion von CIN2/3 bei Mädchen <18 Jahre in Australien

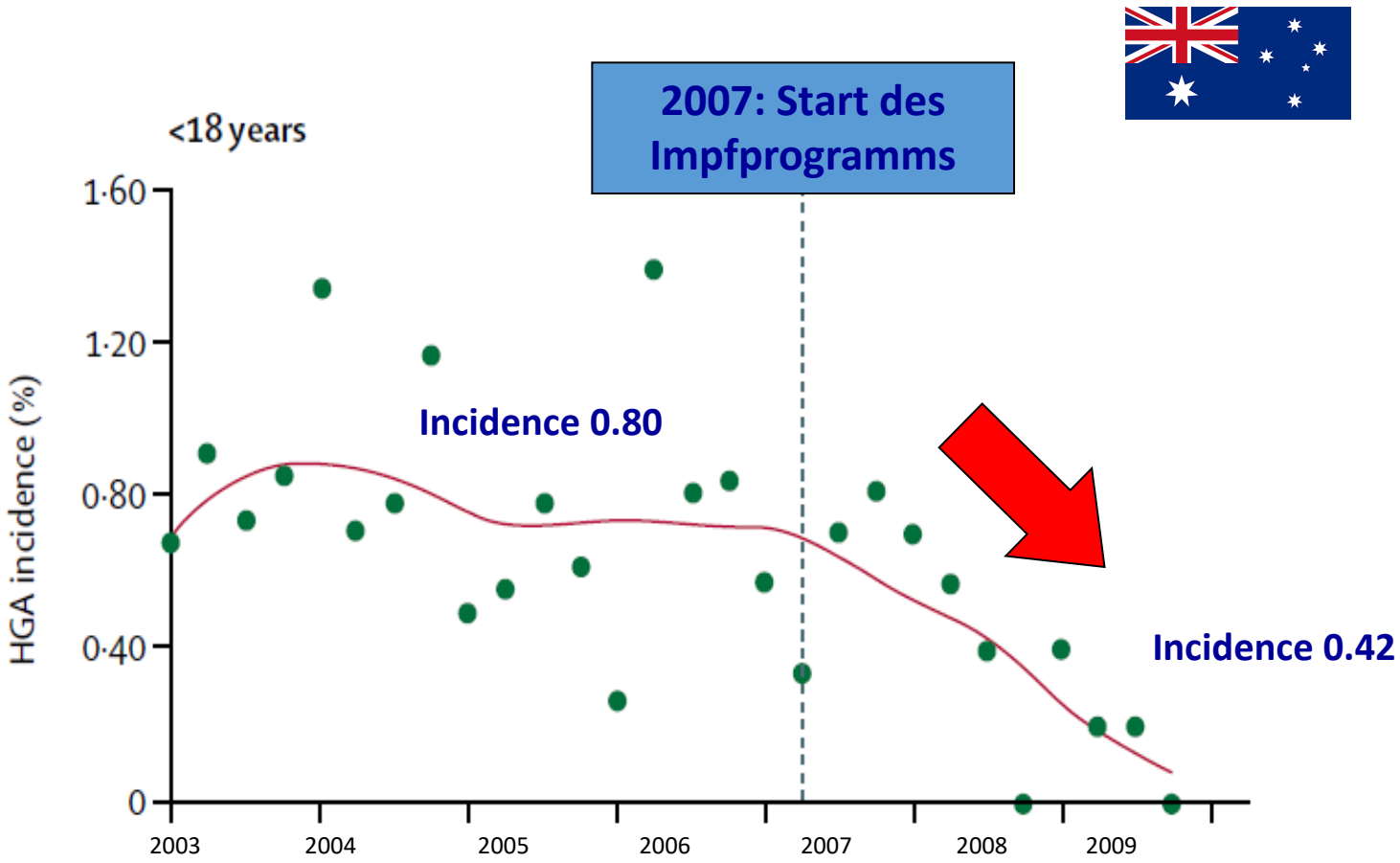


***Figure 2*: Incidence of high-grade cervical abnormalities, by age group**

Incidence of high-grade cervical abnormalities (HGA; green dots) is the number of new diagnoses within a 3-month period per 100 women tested. Lowess smoothing trends are shown with red lines. The vertical lines, at the start of the second quarter in 2007, signify the introduction of human papillomavirus vaccination.

(1) Brotherton et al. Lancet 2011

Zervixkarzinom

Primäre Prävention

- HPV Expositionsprophylaxe
- HPV Impfung

Sekundäre Prävention

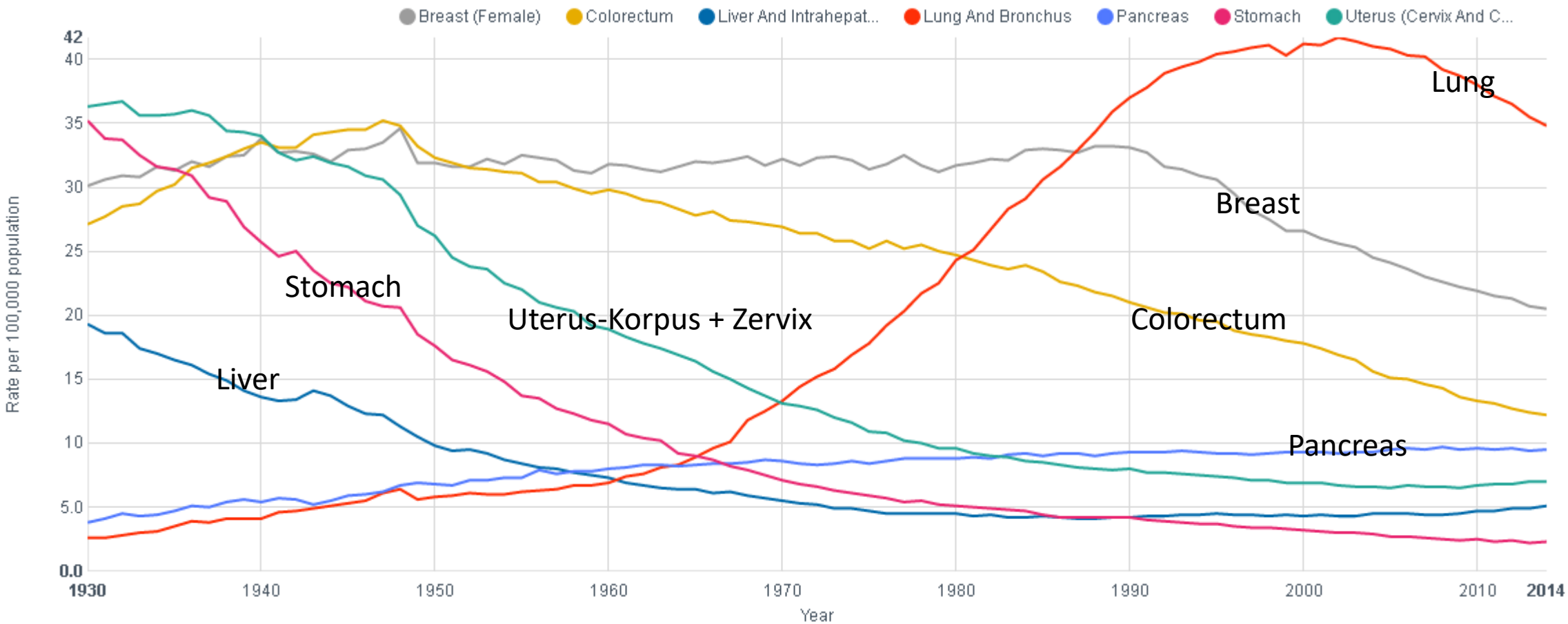
- PAP und HPV Co-Testung
- Konisation

Therapie / Rehabilitation

- Radikaloperation nach Wertheim
- Radio-Chemotherapie

Trends in death rates, 1930-2014

Females

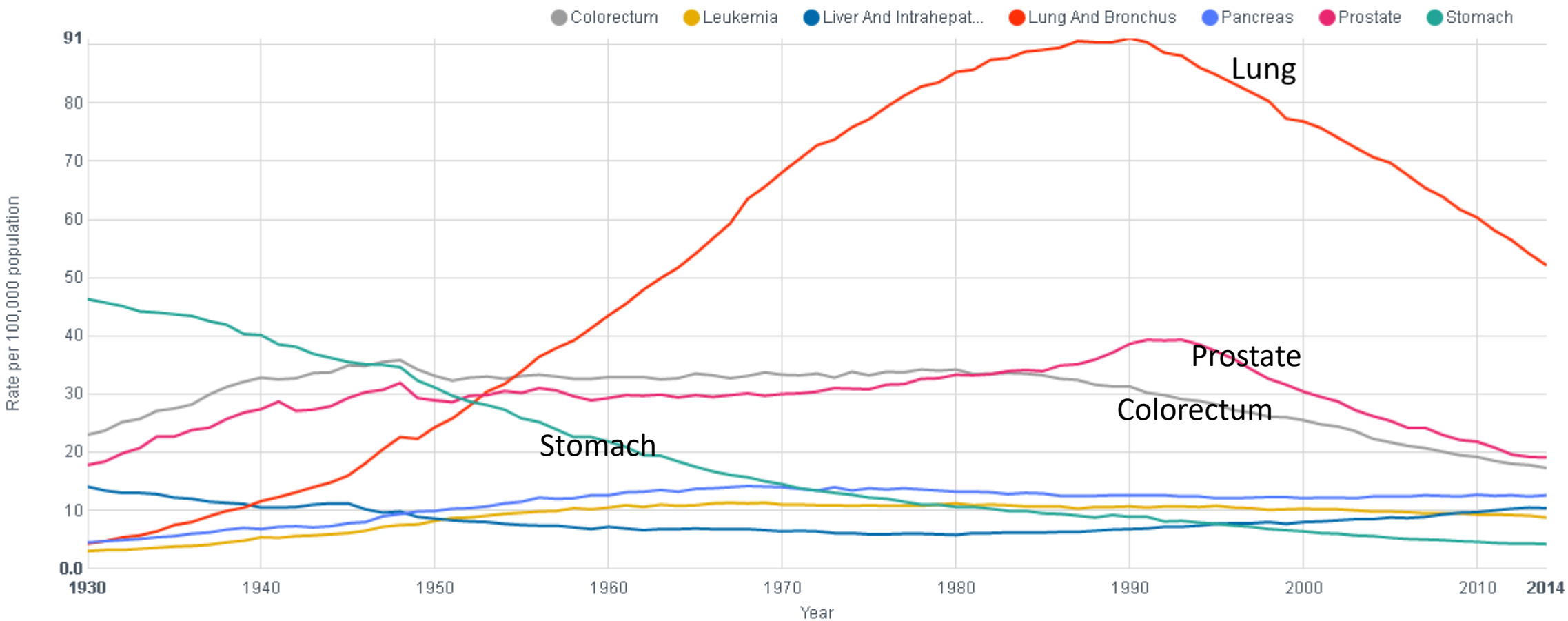


Per 100,000, age adjusted to the 2000 US standard population.

Data sources: National Center for Health Statistics (NCHS), Centers for Disease Control and Prevention, 2016

Trends in death rates, 1930-2014

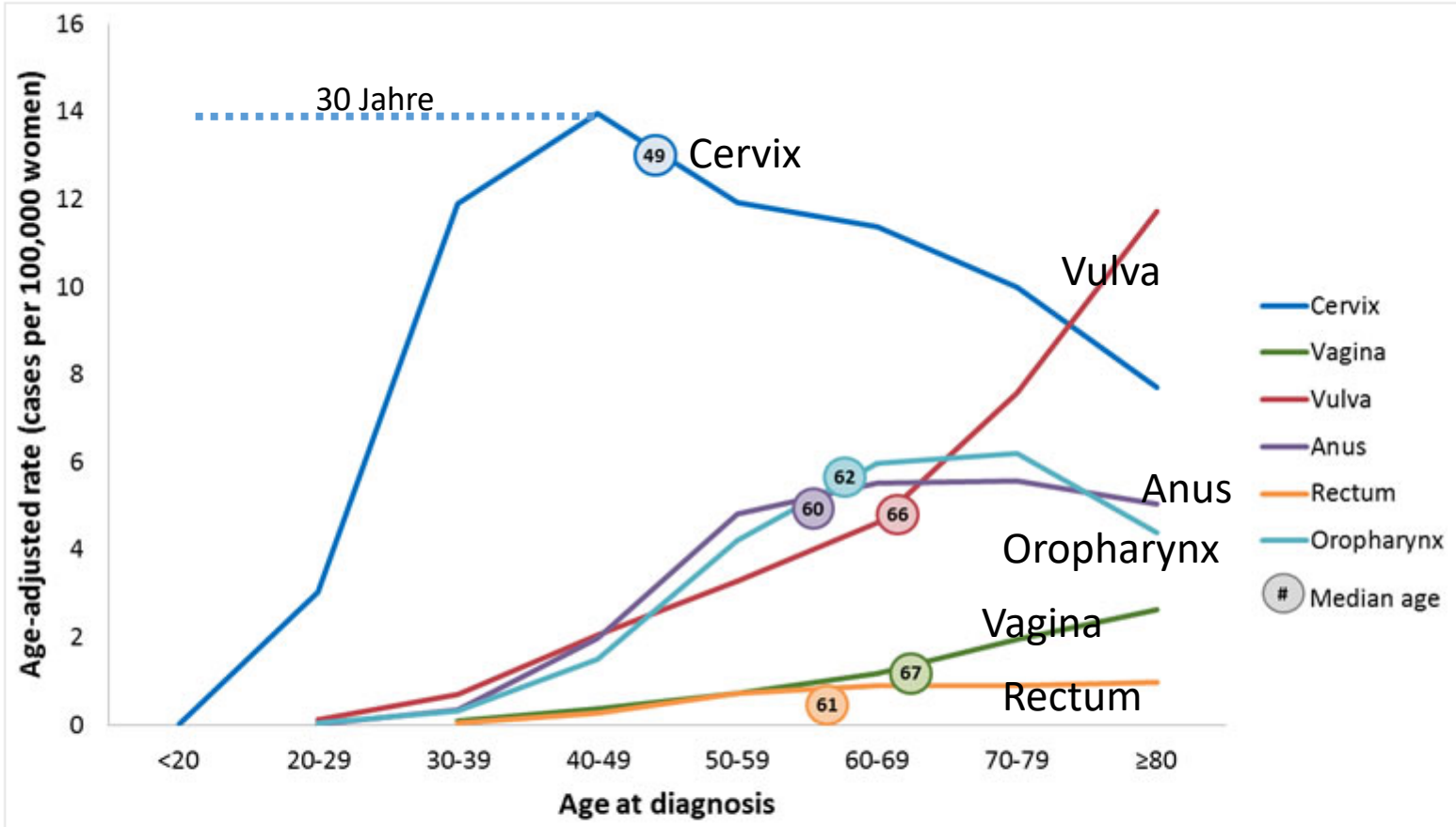
Males



Per 100,000, age adjusted to the 2000 US standard population.

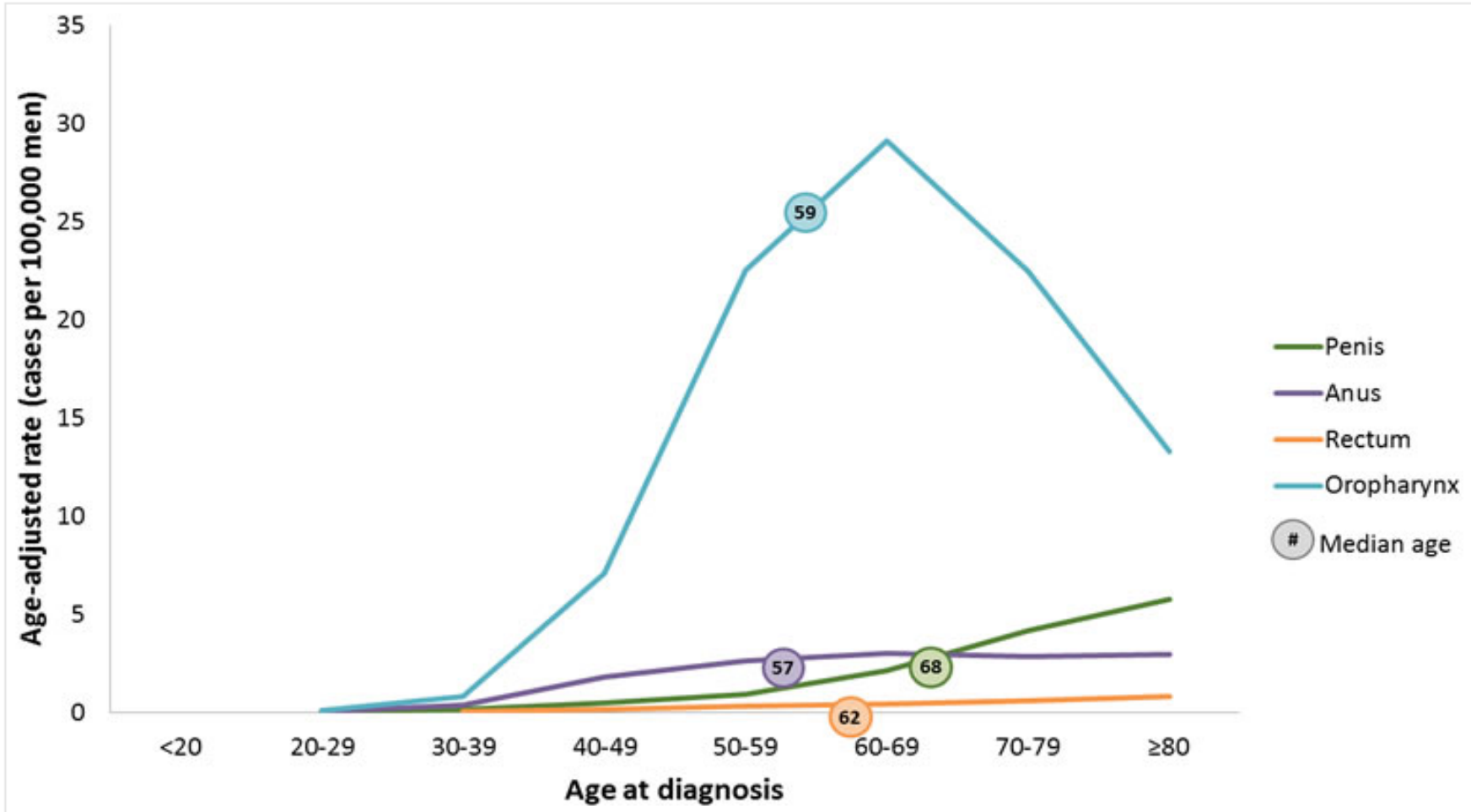
Data sources: National Center for Health Statistics (NCHS), Centers for Disease Control and Prevention, 2016

Rates of HPV-Associated Cancers and Median Age at Diagnosis Among Women in the United States, 2008–2012



The chart above shows rates by age group for HPV-associated cancers in the United States during 2008–2012. The rates shown are the number of women in each age group who were diagnosed with HPV-associated cancer for every 100,000 women. Rates were not shown for some cancer sites and age groups because there were fewer than 16 cases. The chart also shows that the median age at diagnosis (the age at which half were older and half were younger), is 49 years for HPV-associated cervical cancer, 67 for HPV-associated vaginal cancer, 66 for HPV-associated vulvar cancer, 60 among women for HPV-associated anal cancer, 61 among women for HPV-associated rectal cancer, and 62 among women for HPV-associated oropharyngeal

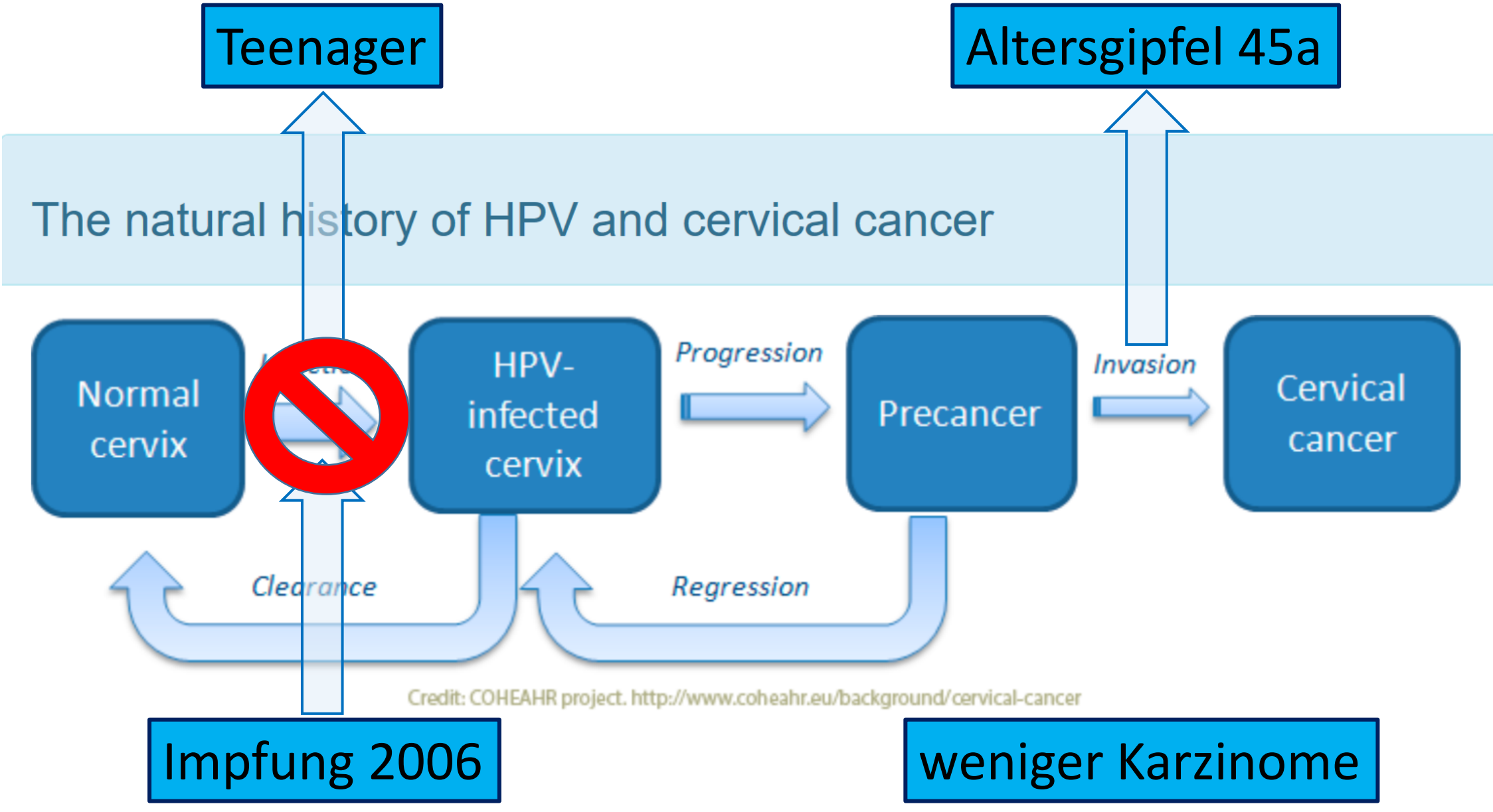
Rates of HPV-Associated Cancers and Median Age at Diagnosis Among Men in the United States, 2008–2012



The chart above shows rates by age group for HPV-associated cancers in the United States during 2008–2012. The rates shown are the number of men who were diagnosed with HPV-associated cancer for every 100,000 men. Rates are not shown for some cancer sites and age groups because there were fewer than 16 cases. The chart also shows that the median age at diagnosis (the age at which half were older and half were younger), is 68 for HPV-associated penile cancer, 57 among men for HPV-associated anal cancer, 62 among men for HPV-associated rectal cancer, and 59 among men for HPV-associated oropharyngeal cancers.

Teenager

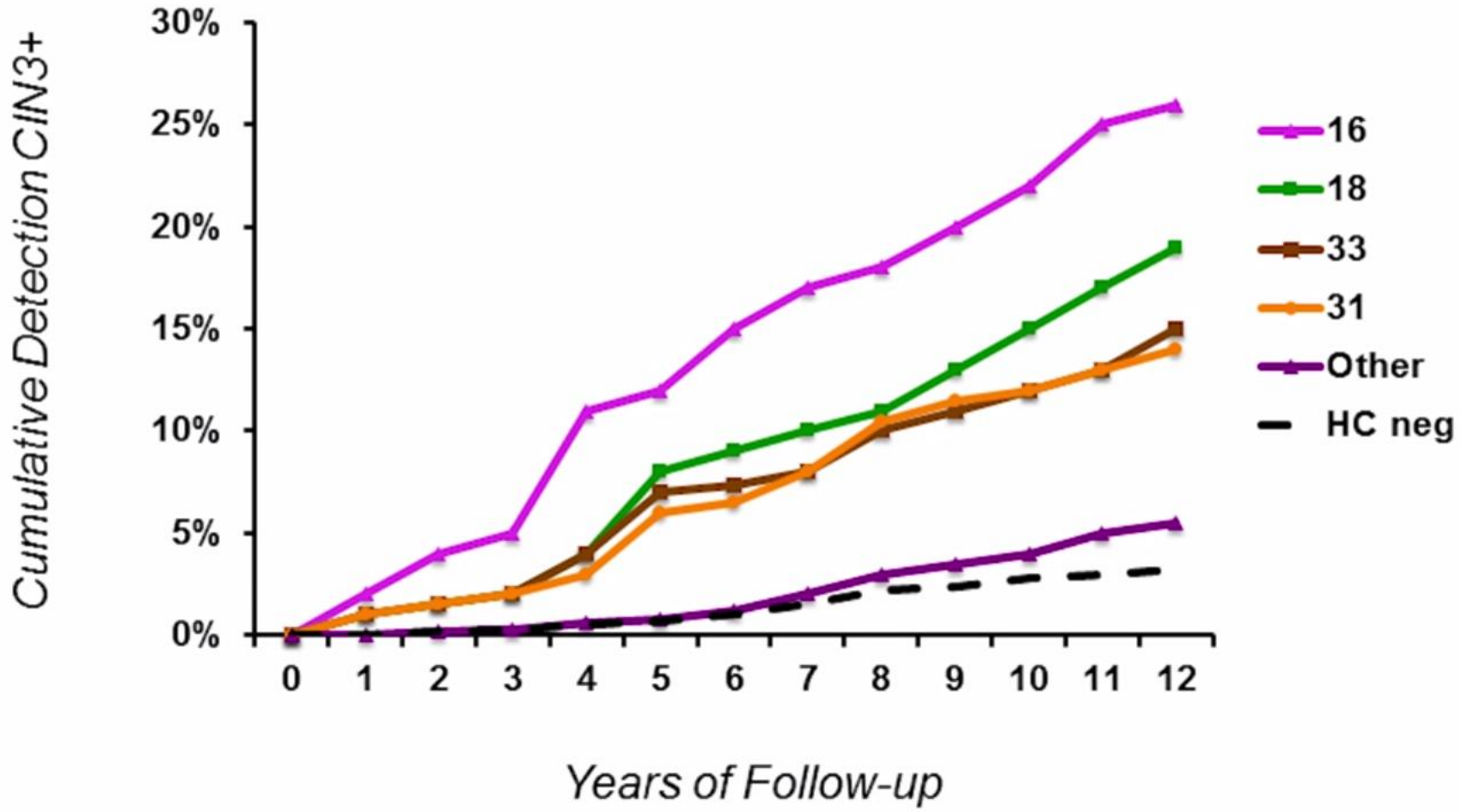
Altersgipfel 45a



Impfung 2006

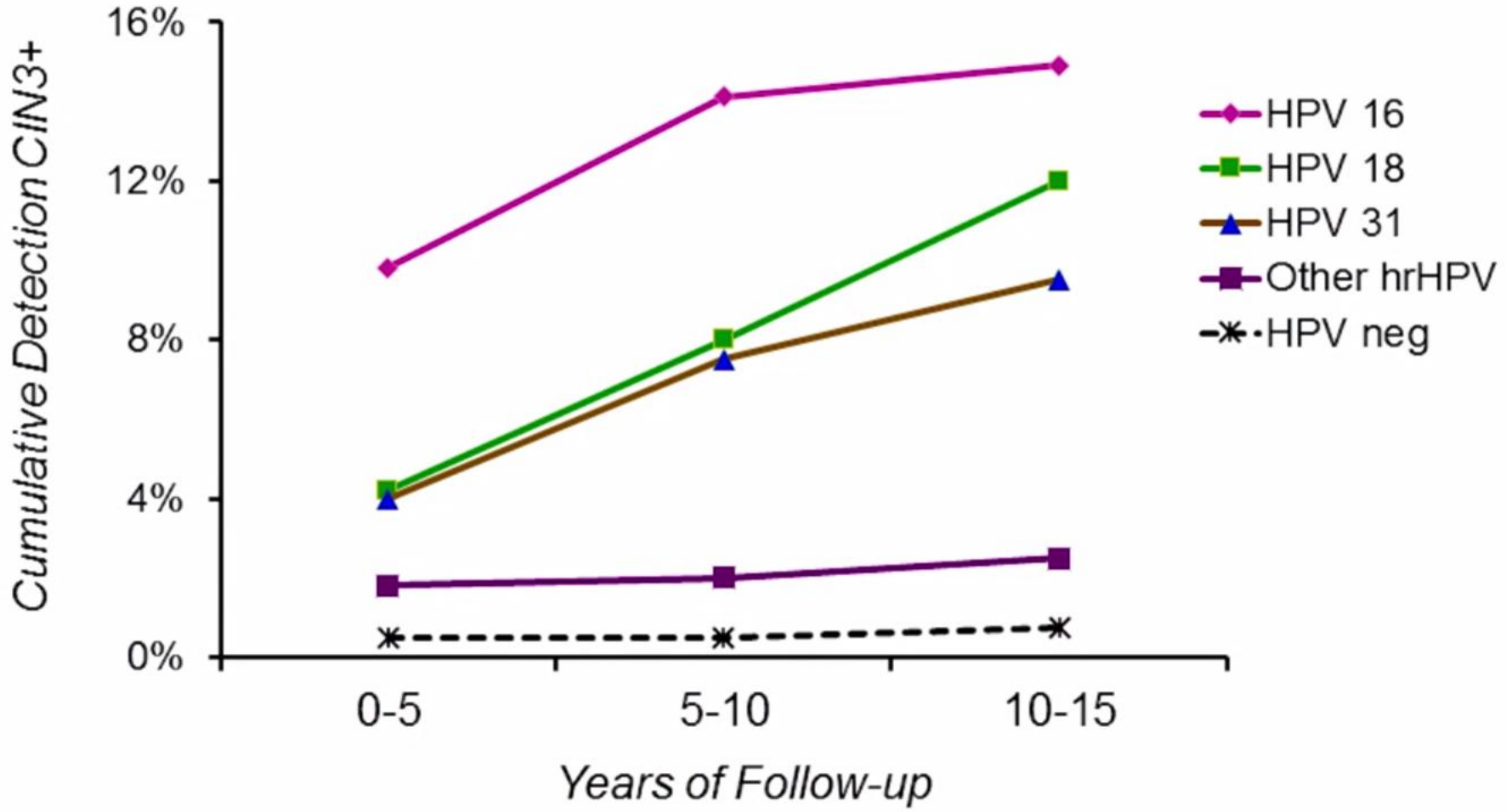
weniger Karzinome

12 Year Risk of CIN 3+ in Danish Cohort



Kjaer et al. JNCI, 2010

15 Year Risk of CIN 3+ in Kaiser Cohort



Schiffman et al. JNCI, 2011

Harvard Health Publications
HARVARD MEDICAL SCHOOL
Trusted advice for a healthier life

Cervical cancer screening update: Not your mother's Pap smear

POSTED DECEMBER 08, 2016, 9:30 AM

Andrea Chisholm, MD, Contributor

Confused about when to get your next Pap test? Anxious because your doctor said you don't need another Pap for five years? Well, you are not alone.

For several decades, getting a yearly Pap test has been the standard for cervical cancer screening. Cervical cancer, which still kills about 4,000 women annually in the United States, is really a preventable disease. The goal of cervical cancer screening is to detect areas of significant precancerous

Comparison of Cervical Cancer Screening Results Among 256,648 Women in Multiple Clinical Practices

Amy J. Blatt, PhD[1]; Ronald Kennedy, MD[1]; Ronald D. Luff, MD, MPH[2]; R. Marshall Austin, MD, PhD[3]; and Douglas S. Rabin, MD[1]

tive, and 29 (5.5%) were cotest negative. **CONCLUSIONS:** Compared with HPV-only testing, cotesting was more sensitive for the detection of ≥CIN3 in women ages 30 to 65 years. The current data suggest that approximately 19% of women with cervical cancer may be misdiagnosed by an HPV-only cervical screen. It is important to consider these data as the guidelines for cervical cancer screening undergo revision. ***Cancer (Cancer Cytopathol)* 2015;123:282-8.**

KEY WORDS: cervical cancer; cervical intraepithelial neoplasia 3; cotest; guideline; human papillomavirus; Papanicolaou.

WHY PAP+HPV TOGETHER IS THE PREFERRED SCREENING METHOD FOR WOMEN AGES 30 TO 65[3-5]

Screening with Pap+HPV Together (co-testing) **identified more than 70%** of the cervical cancers missed by HPV-Alone.* In addition, Pap+HPV Together **identified more precancer** than either HPV-Alone* or Pap-alone screening.

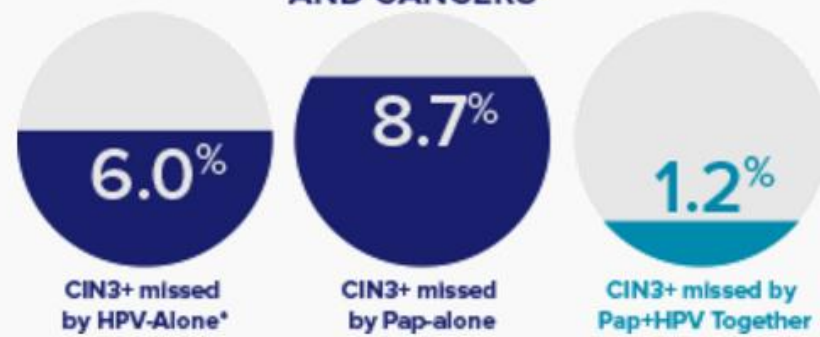
*A positive screening result may lead to further evaluation with cytology and/or colposcopy.

About the Quest Study

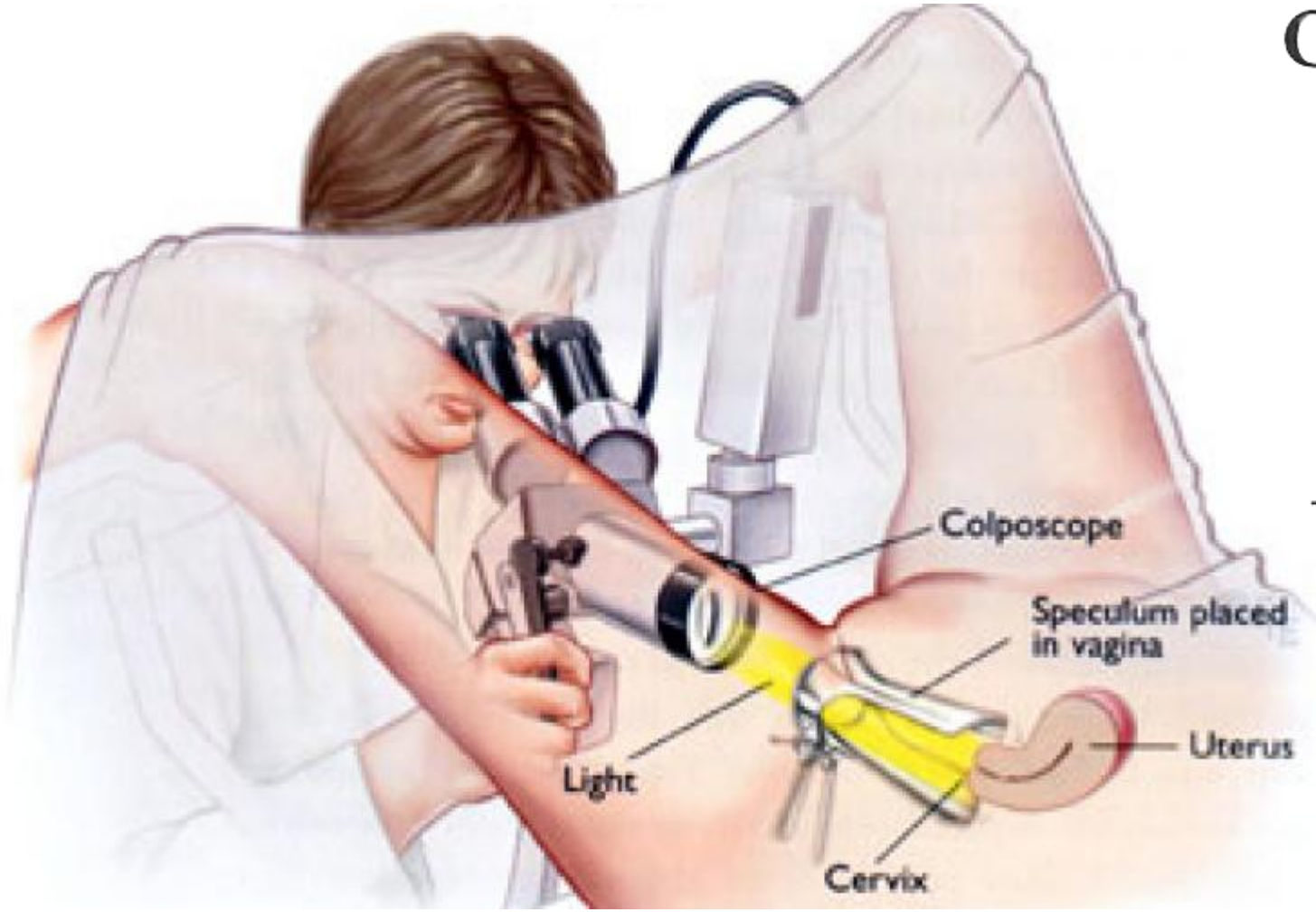
The study contained **65 times more cancer cases** than the clinical trial that led to the FDA approval of the additional indication for HPV-Alone* screening for an existing HPV test.

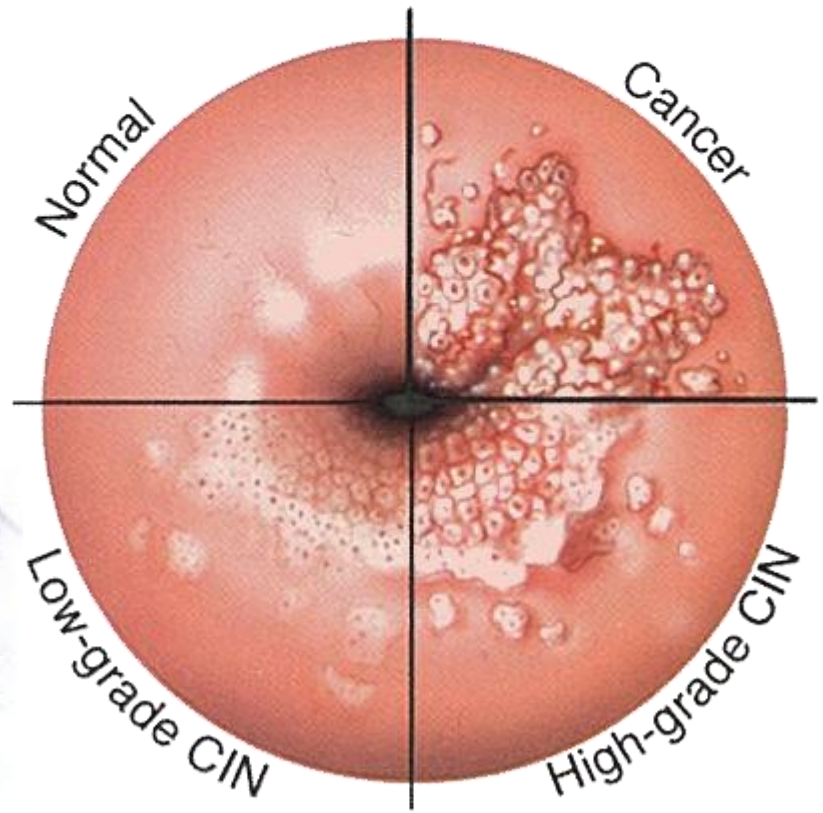
Data from approximately 8.6 million women ages 30 to 65 were analyzed, with over a quarter of a million of these women having received a cervical cancer biopsy based on their screening results.[1,2]

PAP+HPV TOGETHER MISSED THE FEWEST CASES OF CERVICAL PRE-CANCERS AND CANCERS[1*]

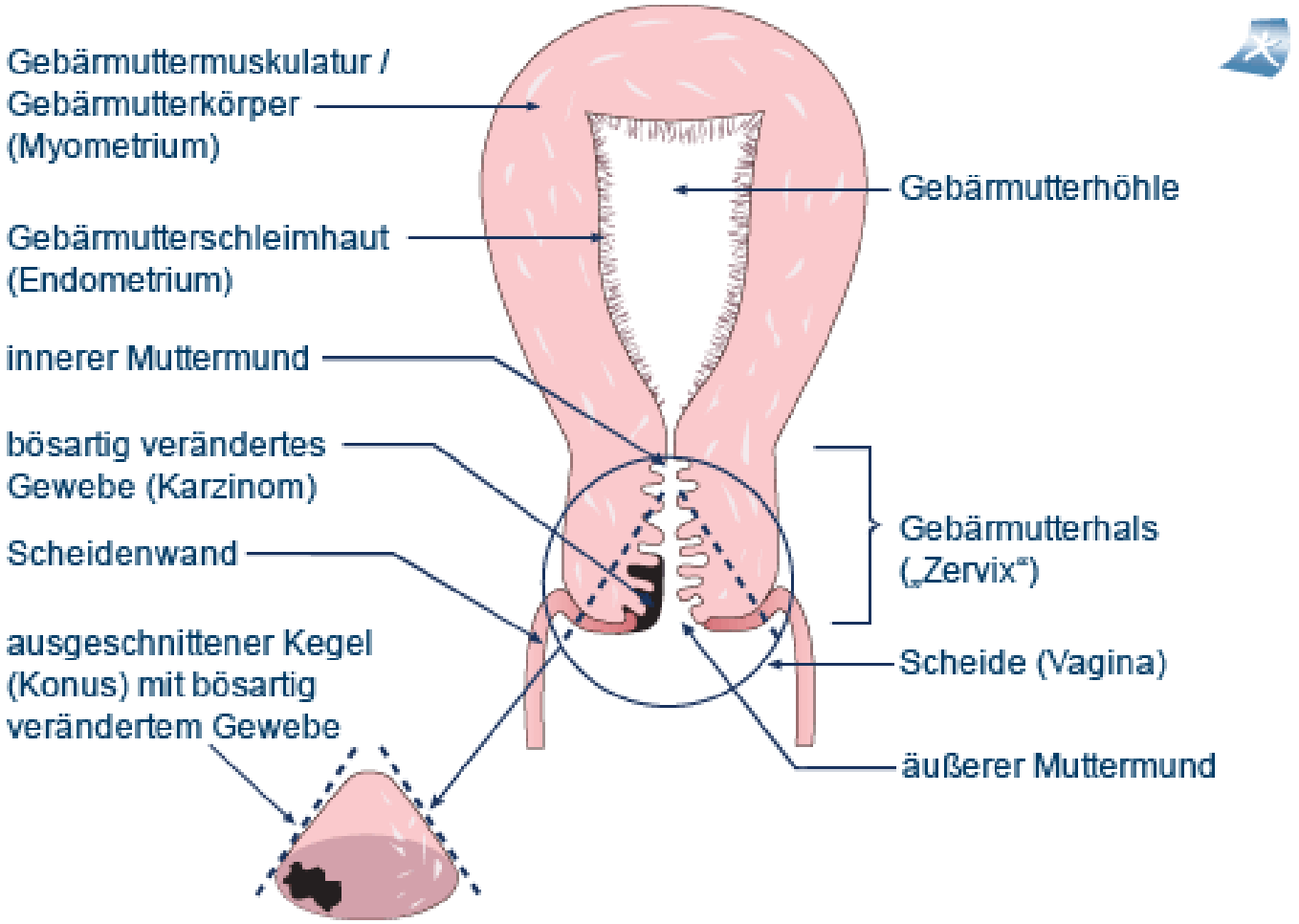


Cervix examination:

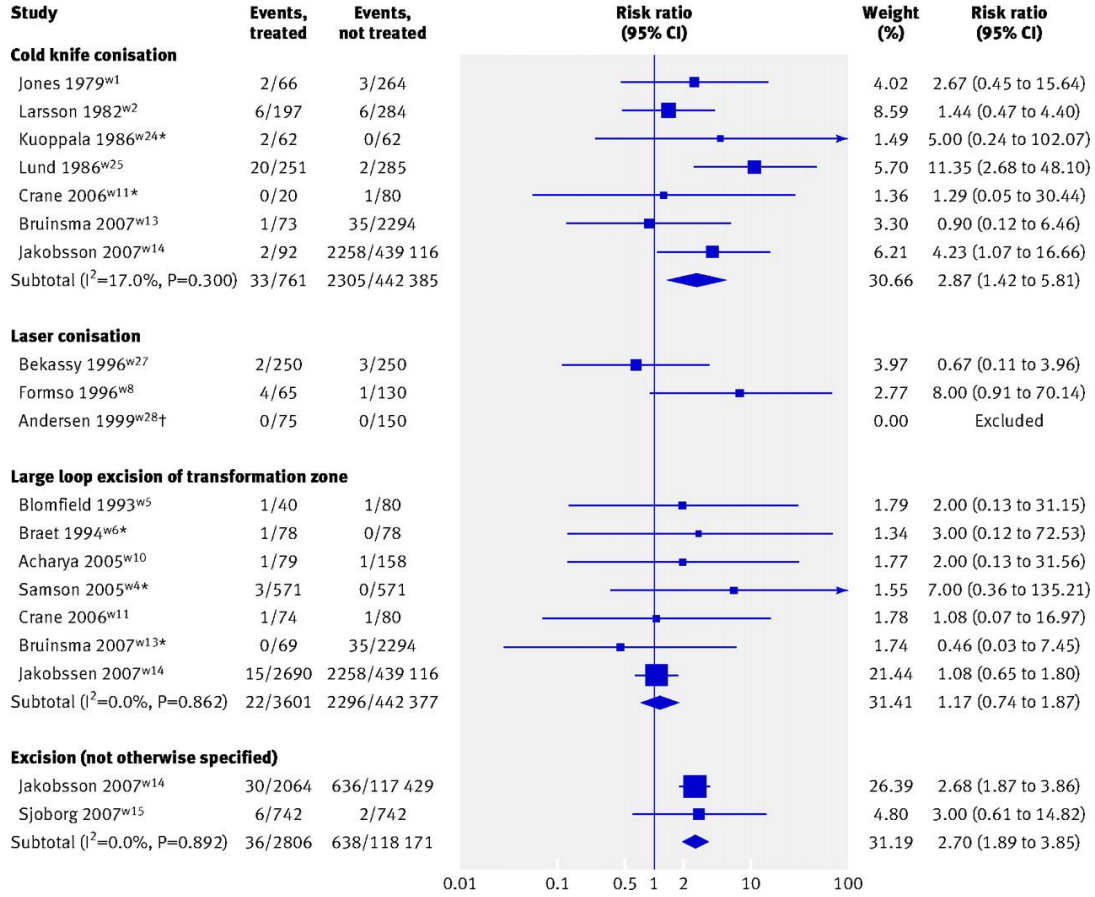




Konisation


Gebärmuttermuskulatur / Gebärmutterkörper (Myometrium)
Gebärmutterschleimhaut (Endometrium)
innerer Muttermund
bösartig verändertes Gewebe (Karzinom)
Scheidenwand
ausgeschnittener Kegel (Konus) mit bösartig verändertem Gewebe
Gebärmutterhöhle
Gebärmutterhals („Zervix")
Scheide (Vagina)
äußerer Muttermund

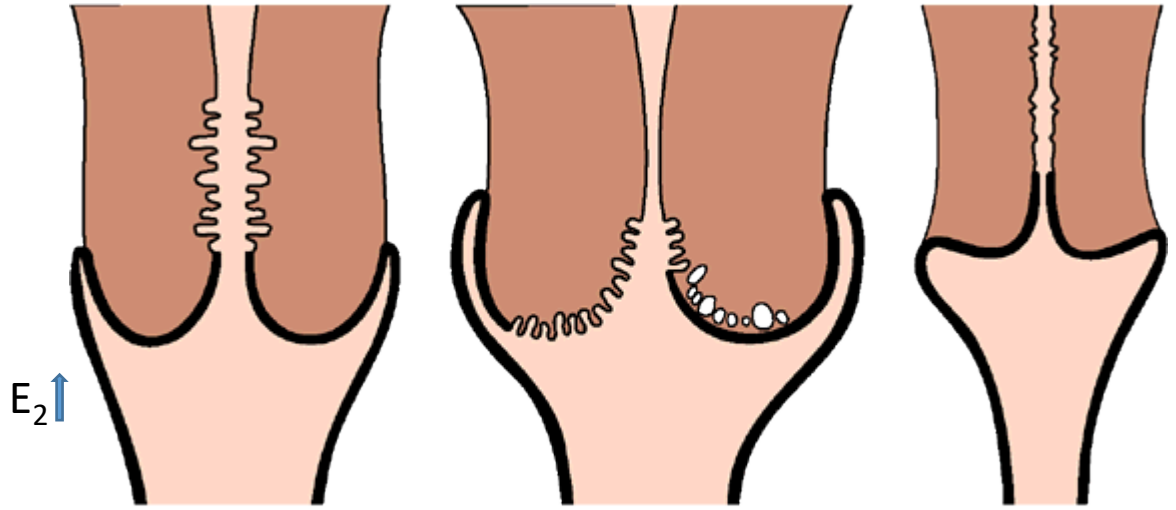
Meta-analysis of relative risk of perinatal mortality associated with excisional treatment for cervical intraepithelial neoplasia

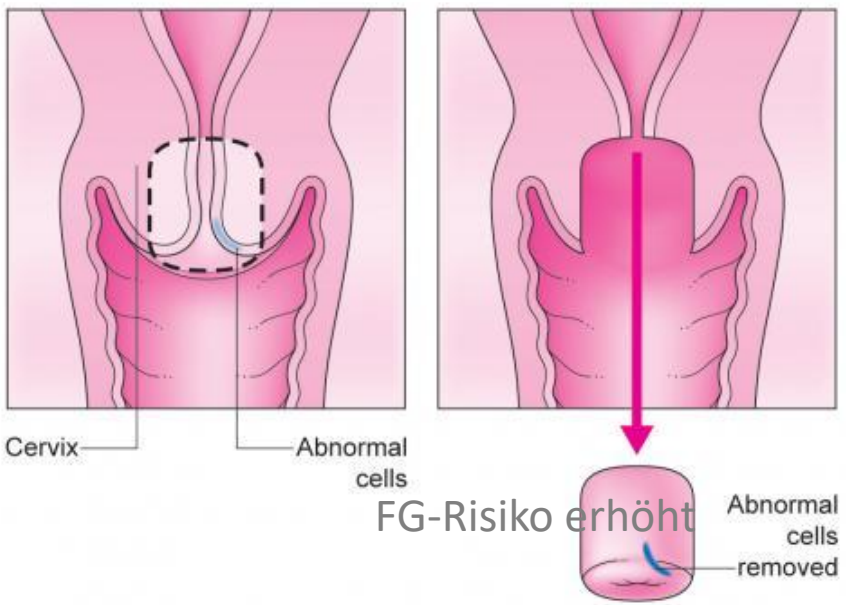


Arbyn M et al. BMJ 2008;337:bmj.a1284

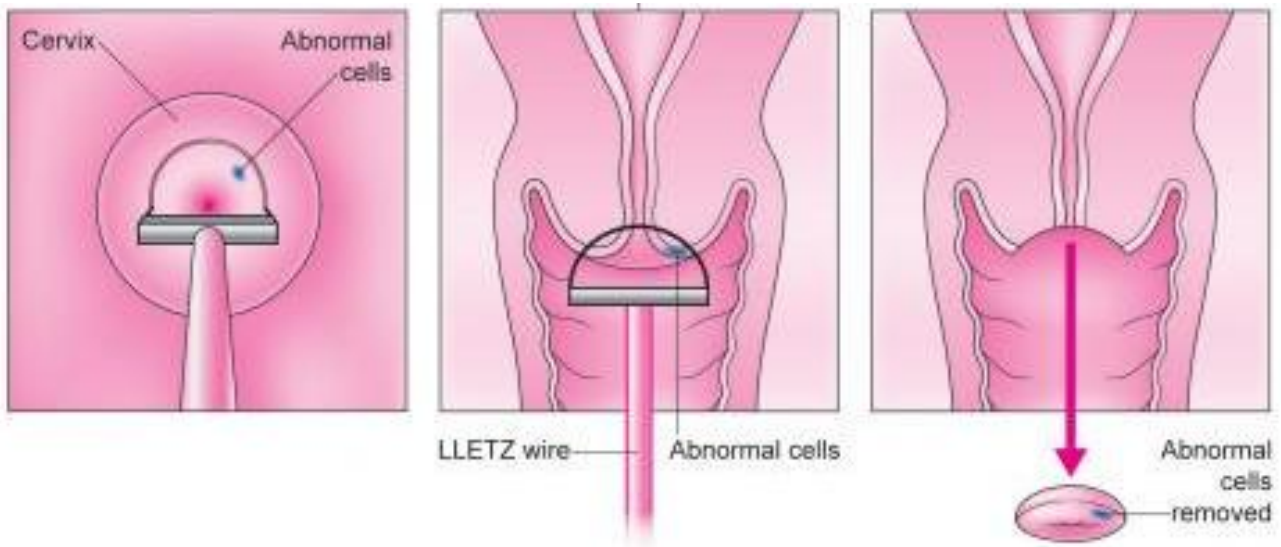
BMJ

Übergang vom mehrschichtigen Plattenepithel zum einschichtigen Zylinderepithel

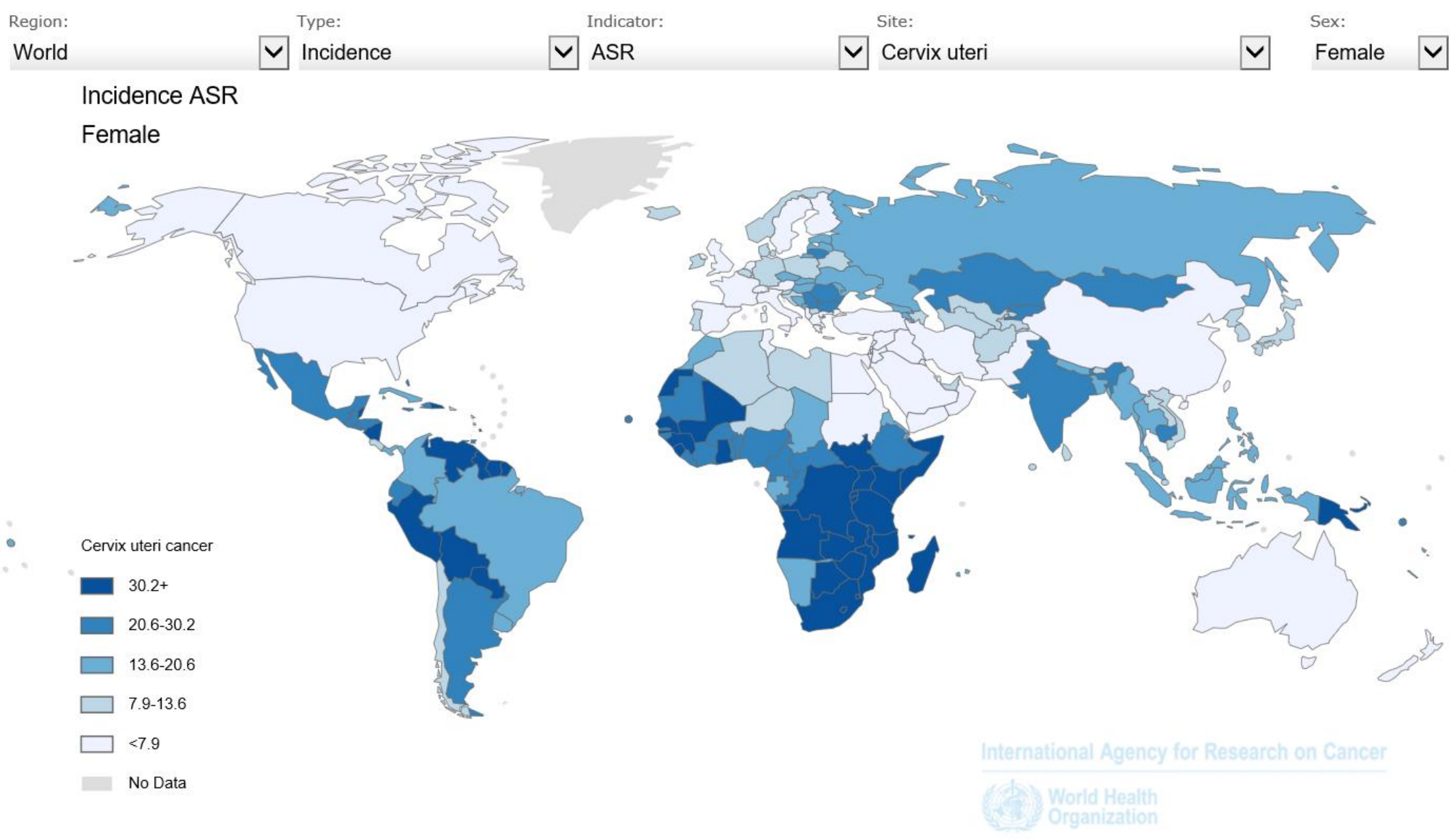




FG-Risiko erhöht



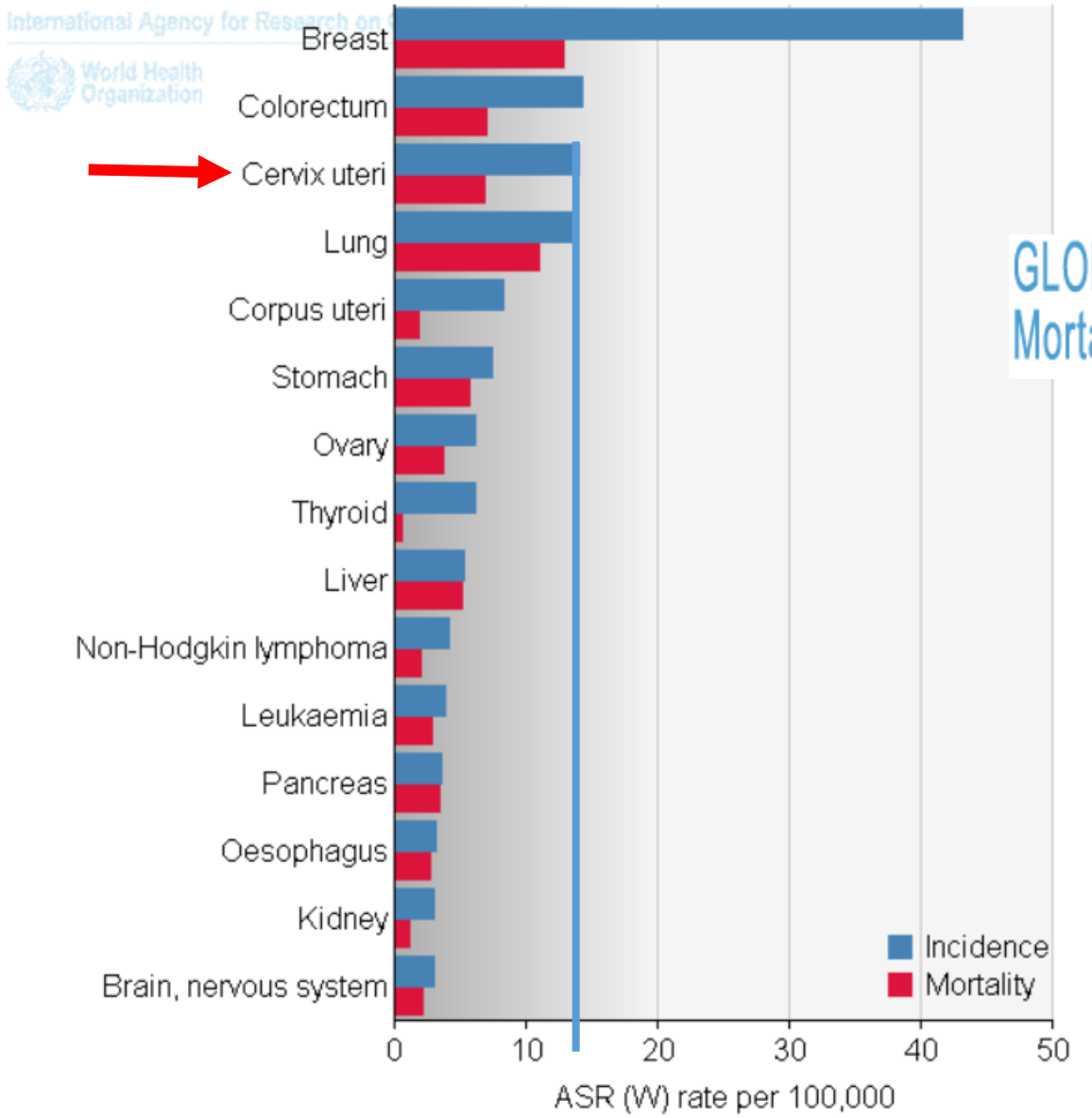
Zervixkarzinom-Inzidenz



Men
Women
Both sexes
Summary statistics

WORLD

Estimated age-standardised incidence and mortality rates: women



International Agency for Research on Cancer
World Health Organization

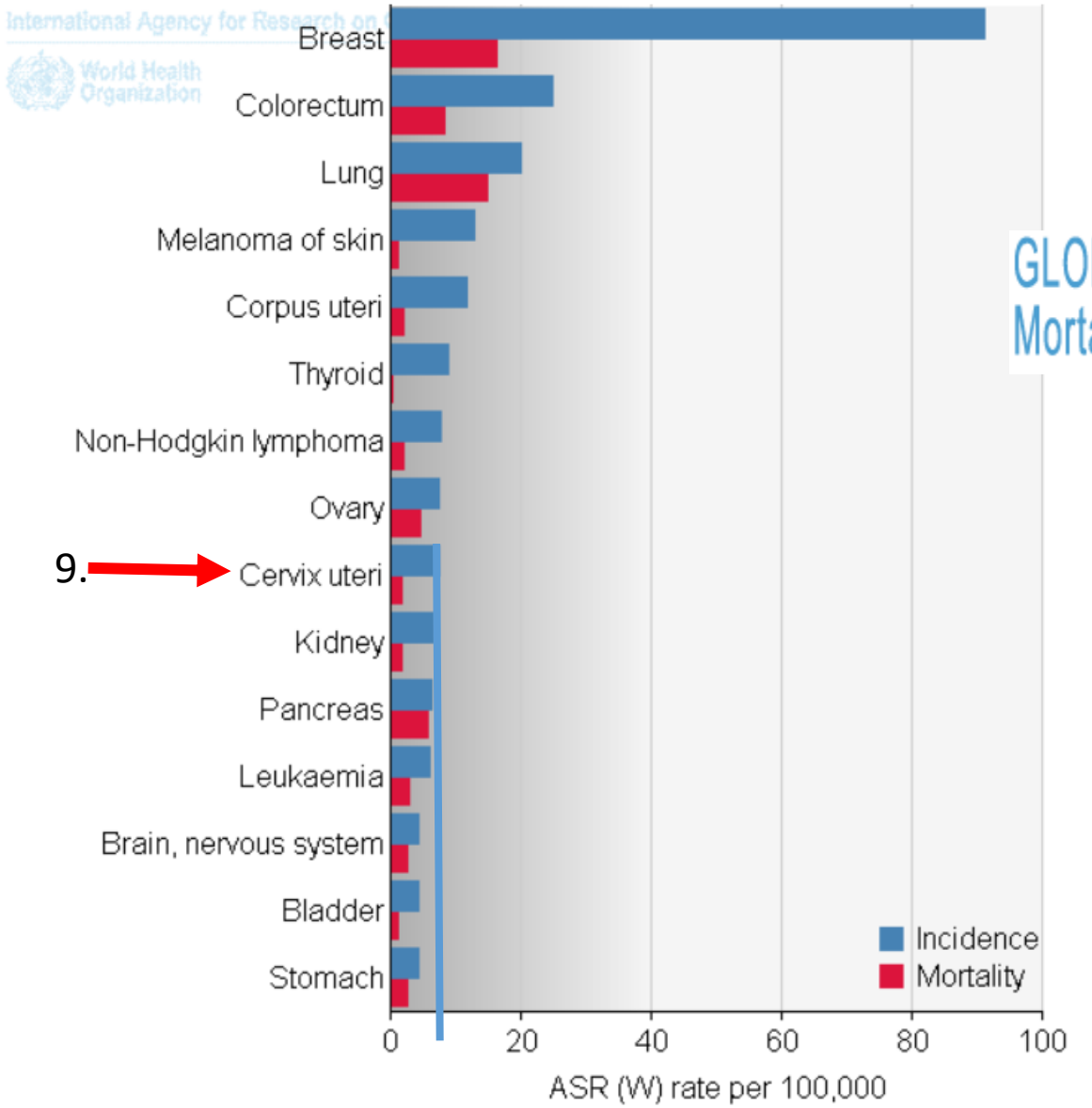
GLOBOCAN 2012: Estimated Cancer Incidence, Mortality and Prevalence Worldwide in 2012

14,0

Men
Women
Both sexes
Summary statistics

WESTERN EUROPE

Estimated age-standardised incidence and mortality rates: women



International Agency for Research on Cancer
World Health Organization

GLOBOCAN 2012: Estimated Cancer Incidence, Mortality and Prevalence Worldwide in 2012

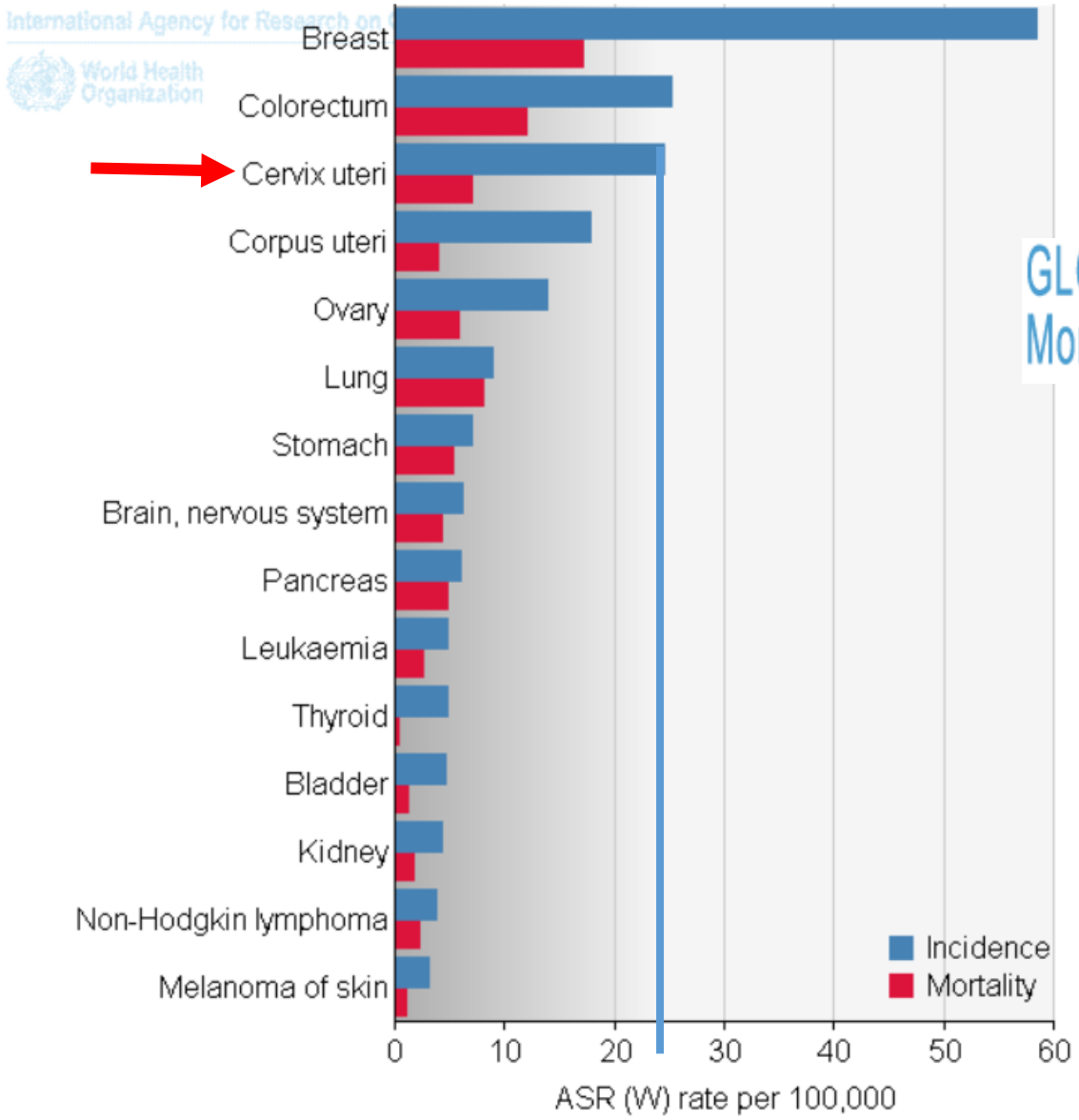
9.

7,3

Men
Women
Both sexes
Summary statistics

BULGARIA

Estimated age-standardised incidence and mortality rates: women



International Agency for Research on Cancer

World Health Organization

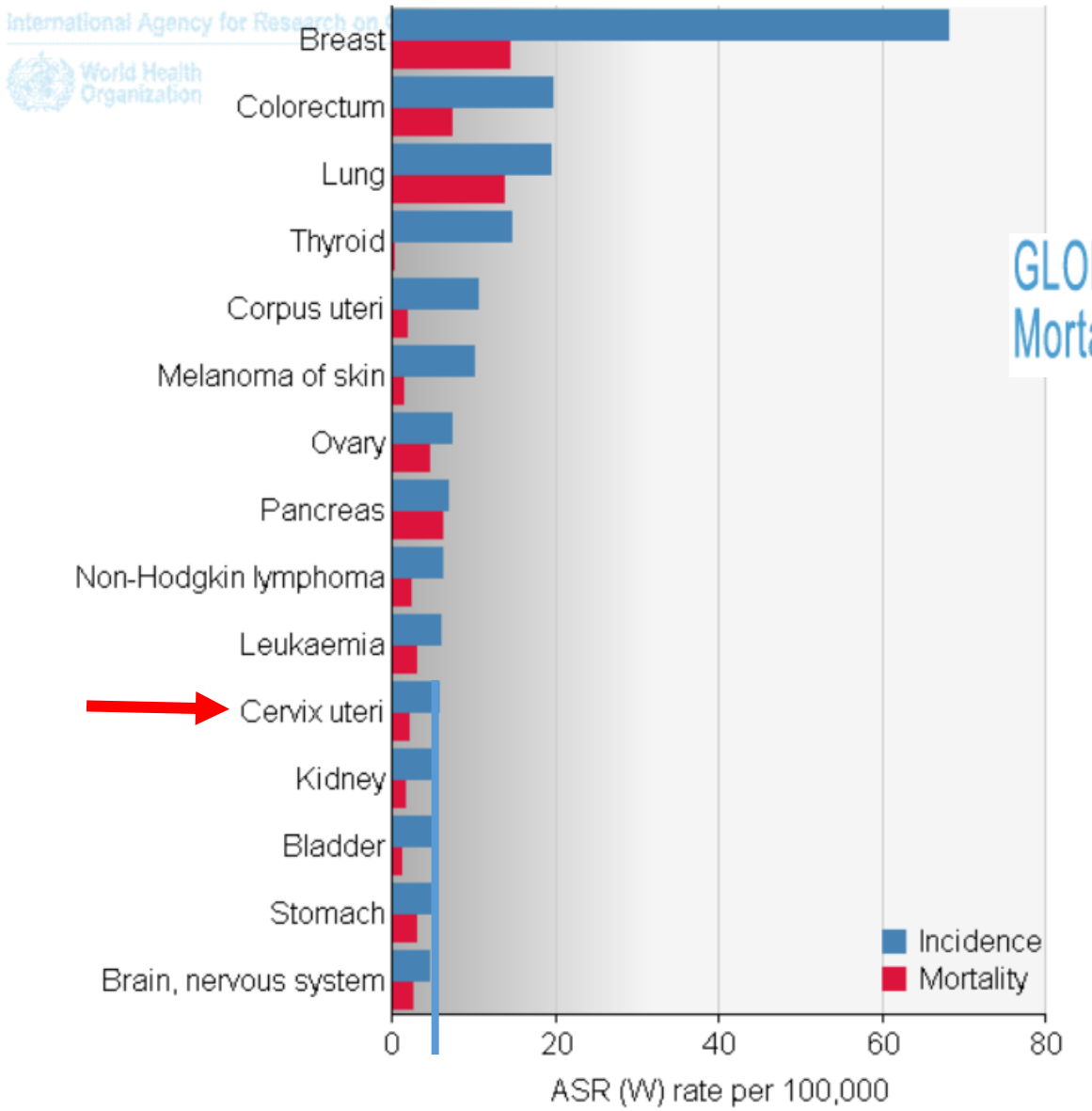
GLOBOCAN 2012: Estimated Cancer Incidence, Mortality and Prevalence Worldwide in 2012

24,5

Men
Women
Both sexes
Summary statistics

AUSTRIA

Estimated age-standardised incidence and mortality rates: women



International Agency for Research on Cancer
World Health Organization

GLOBOCAN 2012: Estimated Cancer Incidence, Mortality and Prevalence Worldwide in 2012

5,8

Unter 45 Jahre ist in Österreich die CxCa Inzidenz an 3. Stelle

5.8 Cervix uteri Hans Concin

Collo dell'utero
Gebärmutterhals
Maternični vrat

5.8.1 Summary and Call for Action

Summary and Call for Action

The predominant differences in incidence and mortality in cervical cancer are surprising and difficult to explain. Incidence and mortality are much higher in the northeast than in the southwest. This could be due to problems in coding. Studies have shown that quality-assured Pap screening can abolish

Cervix uteri /
Collo dell'utero /
Gebärmutterhals

Fig. 25: **Incidence/Incidenza/Inzidenz**

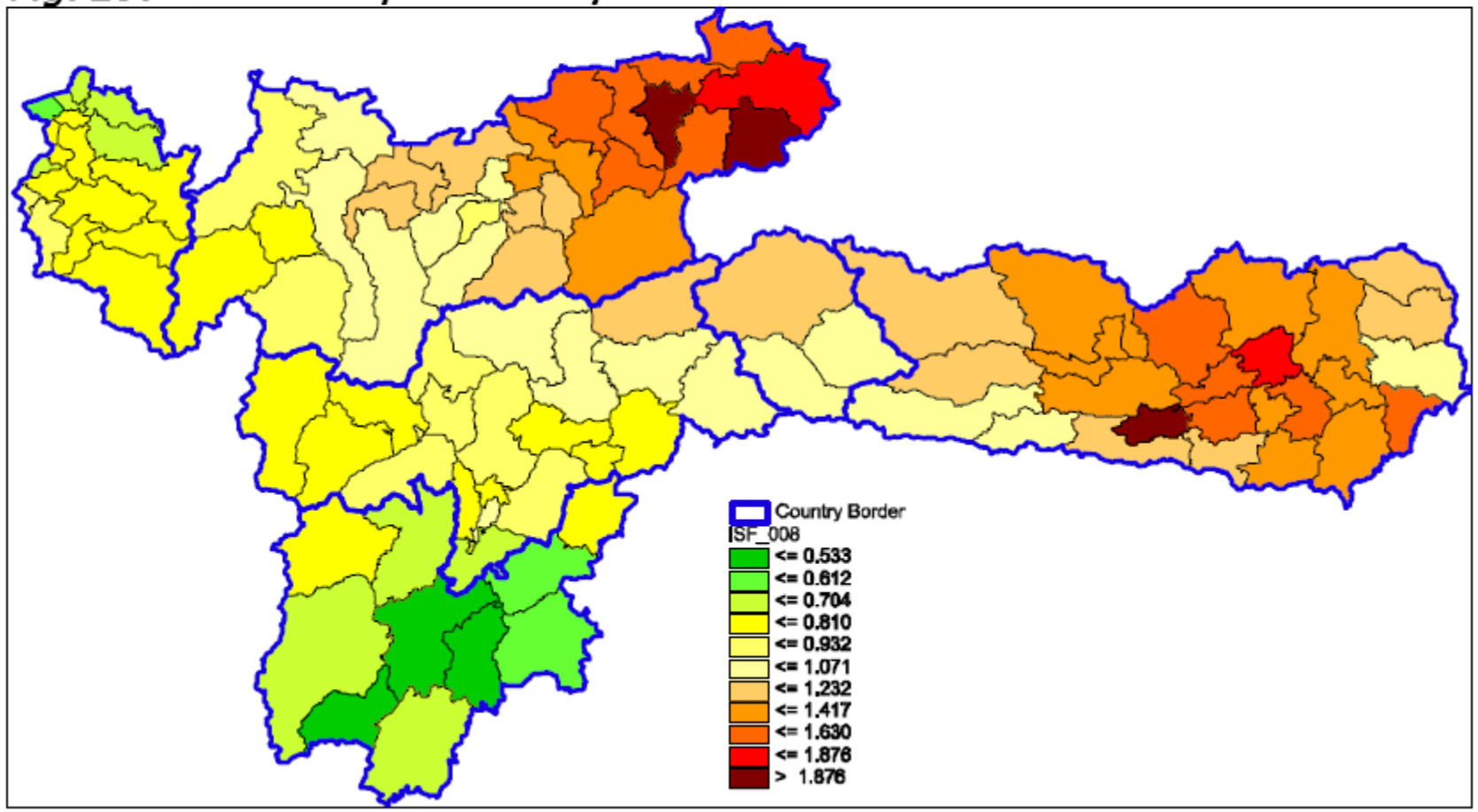
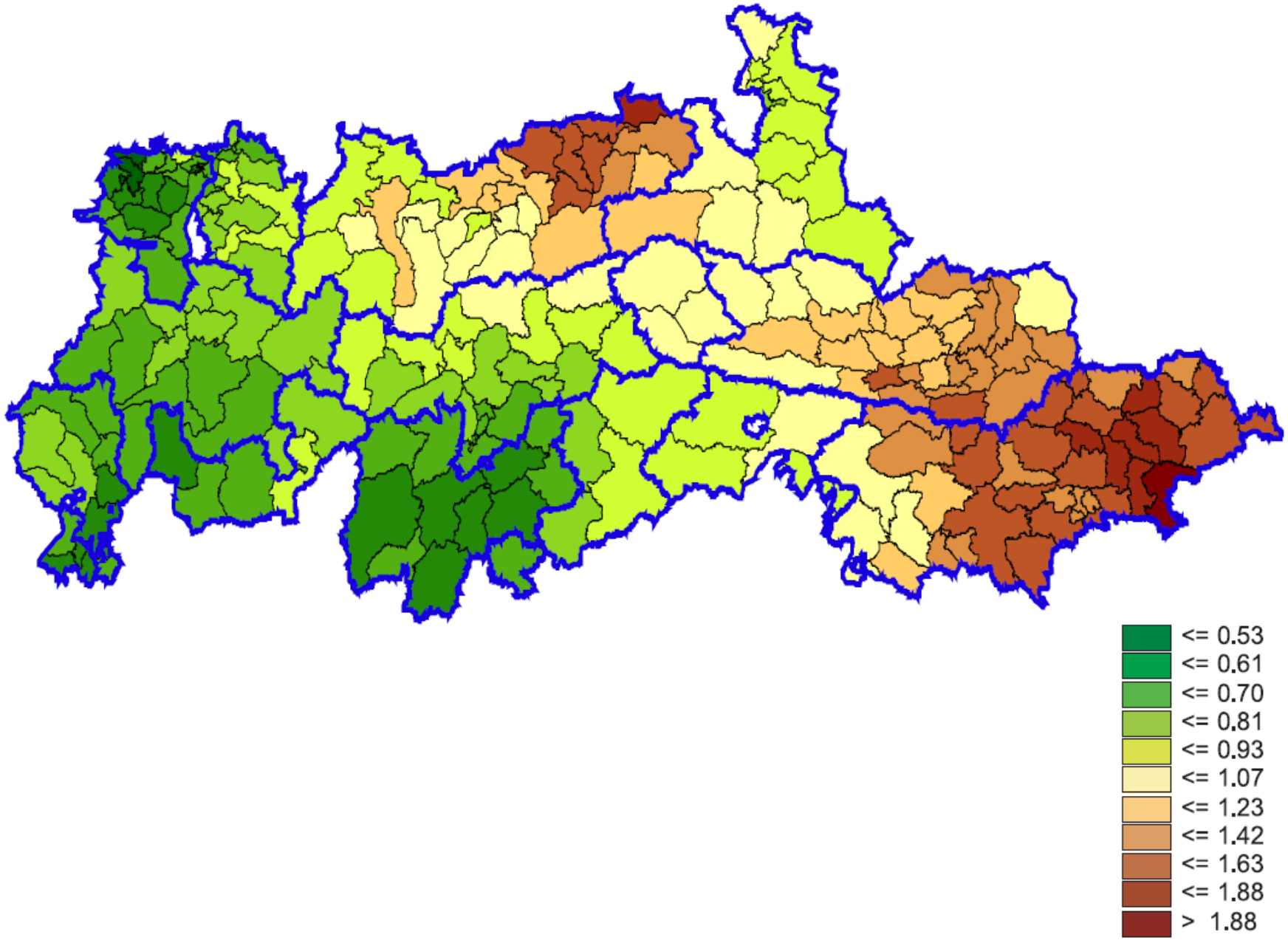


Fig. 29: Cervix uteri – Incidence – Smoothed Map



Clinical Infectious Diseases CID 2016:63 (15 August)

REVIEW ARTICLE

Impact and Effectiveness of the Quadrivalent Human Papillomavirus Vaccine: A Systematic Review of 10 Years of Real-world Experience

Suzanne M. G… … Kuter,[6] Gonzalo Perez…

[1]Royal Women's H… …gshospitalet, University of Cope… …bolis; [6]Merck & Co, Inc, Kenilw…

Prophylacti… …. We assessed the g… …ase were systematica… …l studies reporting th… …ancerous lesions. Ov… …specially among girl… …ximately

Maximal reductions of approximately

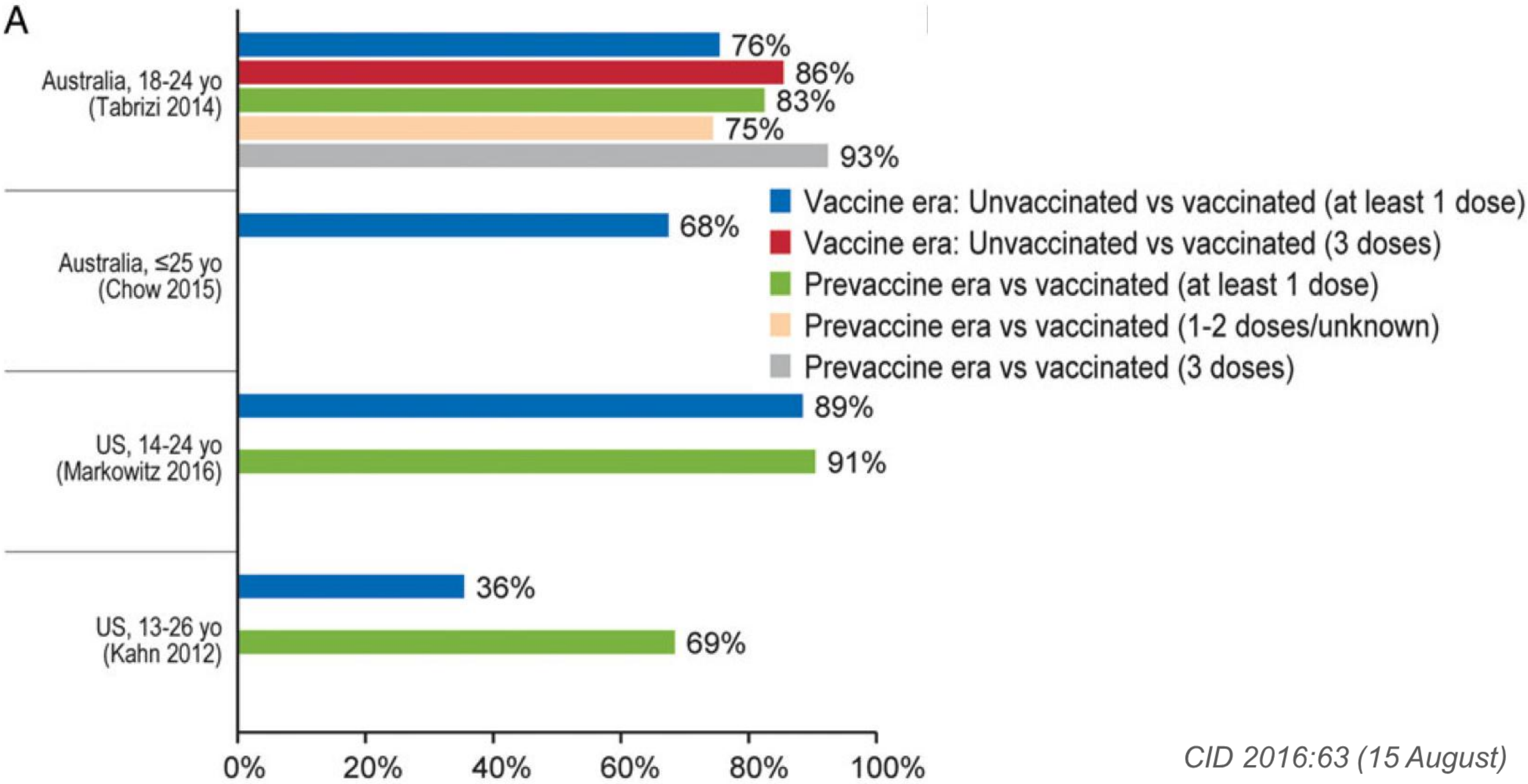
90% for HPV 6/11/16/18 infection,
90% for genital warts,
45% for low-grade cytological cervical abnormalities, and
85% for high-grade histologically proven cervical abnormalities

have been reported.

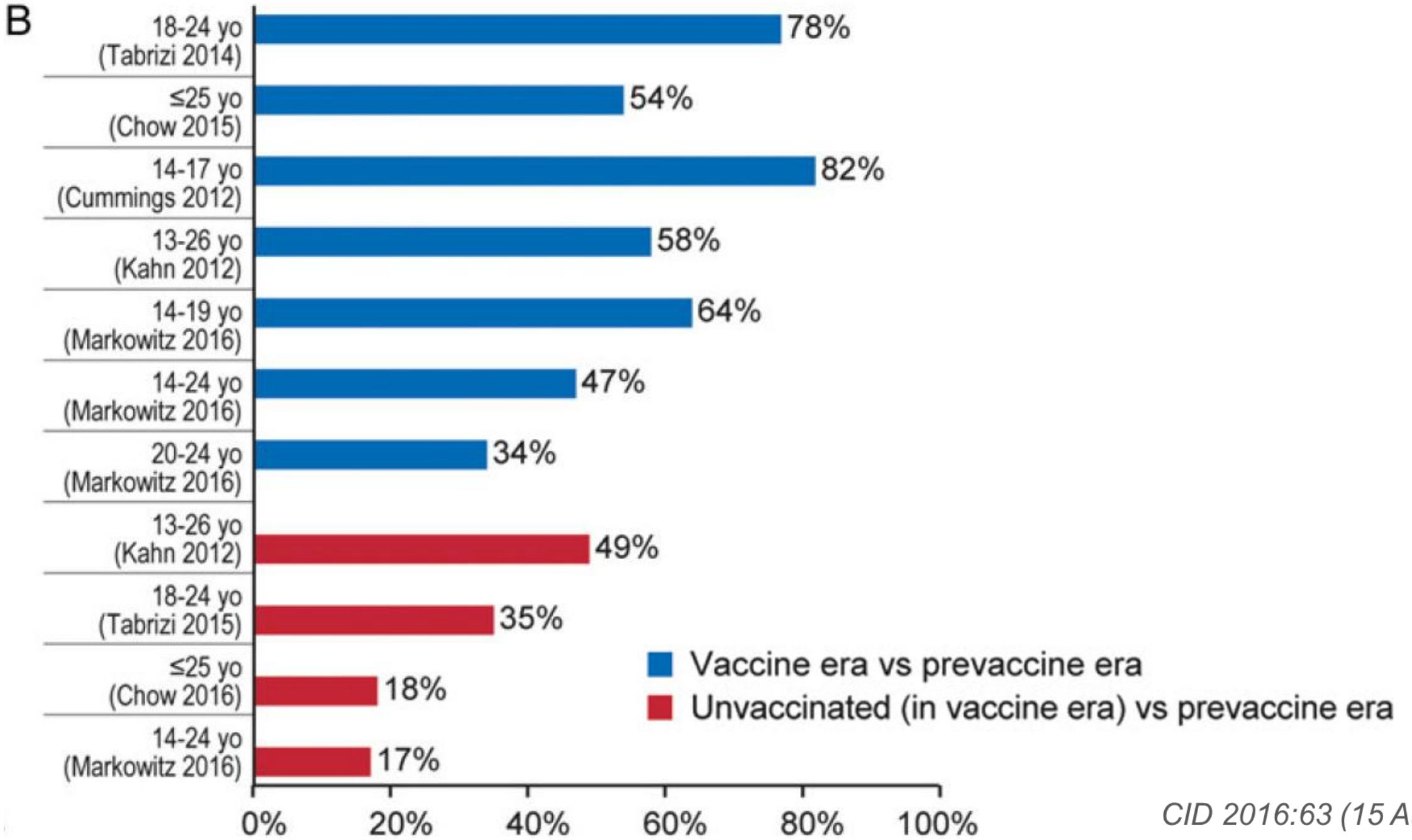
Table 1. Summary of Publications Reporting the Impact and Effectiveness of Quadrivalent Human Papillomavirus Vaccination Programs in 9 Countries

Country (No. of Included Publications) and HPV Vaccination Program	Publications (No.) per Endpoint[a]			
	Genital Warts	HPV Infection	Cervical Cytological Abnormalities	Cervical Histological Abnormalities
Australia (18 publications)	**10**	**3**	**5**	**5**
• Since April 2007: ongoing publicly funded school-based national program, girls aged 12–13 y • Up to December 2009: school-based catch-up for females aged 12–17 y and community-based catch-up for women aged 18–26 y • Since February 2013: ongoing school-based national program for boys aged 12–13 y, with catch-up 14–15 y in 2013–2014[b]	Fairley 2009 [A29] Donovan 2011 [A28] Read 2011 [A37] Ali 2013 [A23, A24] Liu 2014 [A34] Harrison 2014 [A31] Chow 2015 [A27] Smith 2015 [A39], 2016 [A43]	Tabrizi 2012 [A4], 2014 [A5] Chow 2015 [A8]	Brotherton 2011 [A53] Gertig 2013 [A46] Crowe 2014 [A45] Brotherton 2015 [A44, A54]	Brotherton 2011 [A53] Gertig 2013 [A46] Crowe 2014 [A45] Brotherton 2015 [A44, A54]
Belgium (2 publications)	**1**	**1**	. . .	. . .
• November 2007: females 12–15 y reimbursed • End of 2008: reimbursement extended to age 18 y • Since 2010/2011: school-based, girls aged 12–13 y	Dominiak-Felden 2015 [A17]	Merckx 2014 [A14]		
Canada (3 publications)	**1**	. . .	**2**	**1**
• Since 2007–2009: school-based, targeting girls grades 4–8 in all provinces/territories	Smith 2015 [A20]		Mahmud 2014 [A47] Smith 2015 [A20]	Ogilvie 2015 [A58]
Denmark (8 publications)	**5**	. . .	**2**	**3**
• 2006: licensed • October 2008: 1st catch-up, females aged 13–15 y, free • Since 2009: females aged 12 y, free • August 2012: 2nd catch-up, females aged ≤27 y old	Baandrup 2013 [A25] Blomberg 2013 [A21] Sando 2014 [A38] Blomberg 2015 [A16] Bollerup 2016 [A42]		Baldur-Felskov 2014 [A48, A51]	Baldur-Felskov 2014 [A48, A51], 2015 [A52]

Percentage reduction of prevalent HPV 6/11/16/18 infection



CID 2016:63 (15 August)



CID 2016:63 (15 August)

BMJ

What is already known on this topic

Vaccines against human papillomavirus (HPV) have been available since 2006

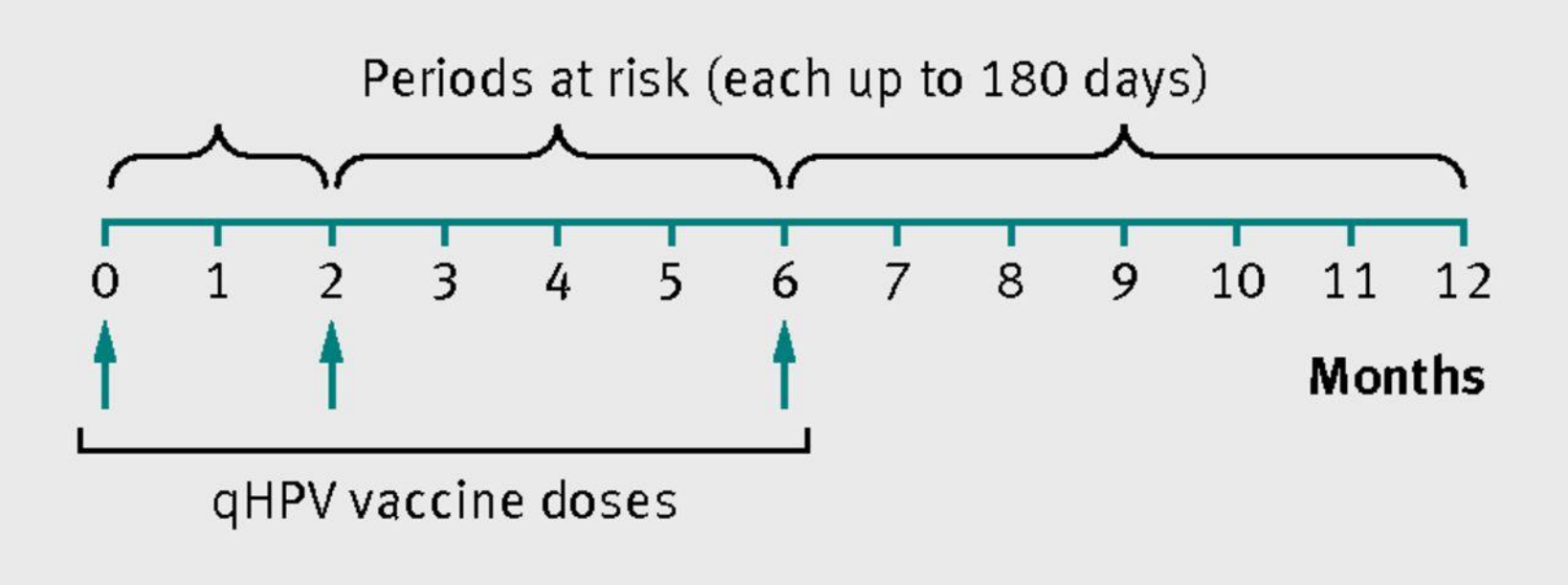
Clinical trials and post-licensure studies from the United States have not identified any increase in the risk of serious adverse events after vaccination

What this study adds

This European cohort study found no evidence supporting associations between exposure to qHPV vaccine and autoimmune, neurological, and venous thromboembolic adverse events in almost one million adolescent girls

Autoimmune, neurological, and venous thromboembolic adverse events after immunisation of adolescent girls with quadrivalent human papillomavirus vaccine in Denmark and Sweden: cohort study

Fig 1 Periods at risk for autoimmune and neurological events in adolescent girls after exposure to quadrivalent human papillomavirus (qHPV) vaccine.



Lisen Arnheim-Dahlström et al. BMJ 2013;347:bmj.f5906

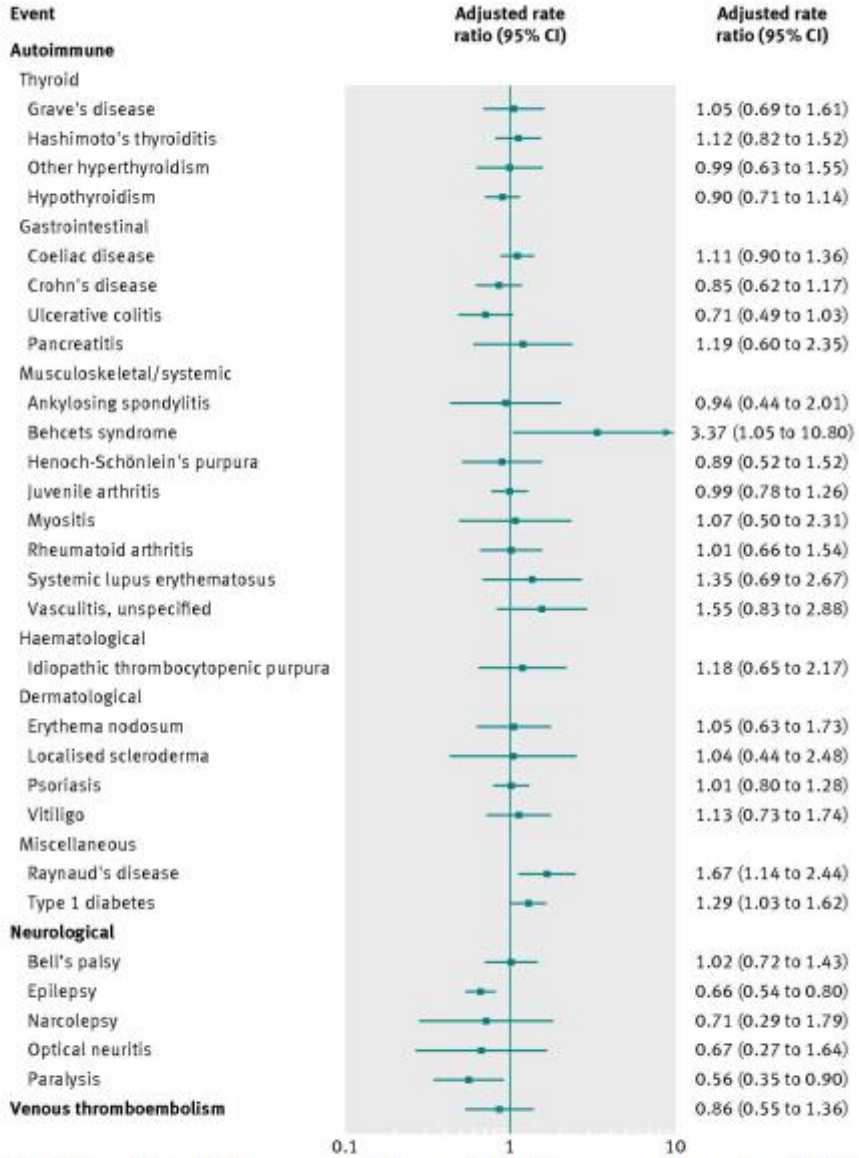


Fig 2 Association between exposure to quadrivalent human papillomavirus (qHPV) vaccine and adverse events in adolescent girls in Denmark and Sweden, October 2006-December 2010. Rate ratios are adjusted for country, age in two year intervals, calendar year, and parental country of birth, parental education, and paternal socioeconomic status

Participants
997 585 girls aged 10-17,
among whom 296 826 received a total of 696 420 qHPV vaccine doses.

Conclusions
This large cohort study found no evidence supporting associations between exposure to qHPV vaccine and
autoimmune,
neurological, and
venous thromboembolic
adverse events.

Autoimmune events

The rate ratios for 20 of the 23 analysed autoimmune outcomes were not significantly increased.
Exposure to qHPV vaccine was significantly associated with
Behcet's syndrome (RR 3.37, 95% CI 1.05 to10.80),
Raynaud's disease (1.67, 1.14 to 2.44), and
type 1 diabetes (1.29, 1.03 to 1.62).

Neurological events

The rate ratios were not significantly increased for any of the five analysed neurological outcomes.
For two of these outcomes, **epilepsy and paralysis, the rate ratios were significantly decreased**.

Venous thromboembolism

The rate ratio for the association between exposure to qHPV vaccine and venous thromboembolism was **0.86 (0.55 to 1.36).**

HPV Vaccine Found Safe in Large Study

2012 Oct. 1 online edition of the
Archives of Pediatrics & Adolescent Medicine.

The quadrivalent (HPV4) vaccine **is given to girls aged 9 and up**.

Among nearly **190,000 girls or young women vaccinated**, **only fainting on the day of vaccination and skin infections within the next two weeks were deemed likely to be associated with the vaccine.**

Fainting on the same day as vaccination has been associated with other injections as well as Gardasil -- particularly among adolescents -- and skin infection is a concern with any injection.

U.S. Department of Health and Human Services
Centers for Disease Control and Prevention

What Parents Should Know About HPV Vaccine Safety and Effectiveness

Last updated JUNE 2014

HPV vaccines prevent cancer

About 14 million people, including teens, become infected with human papillomavirus (HPV) each year. When HPV infections persist, people are at risk for cancer. Every year, approximately 17,600 women and 9,300 men are affected by cancers caused by HPV. HPV vaccination could prevent many of these cancers.

HPV vaccines are safe

There are two vaccines licensed by the Food and Drug Administration (FDA) and recommended by CDC to protect against HPV-related illness. All vaccines used in the United States are required to go through extensive safety testing before they are licensed by FDA. Once in use, they are continually monitored for safety and effectiveness.

Numerous research studies have been conducted to make sure HPV vaccines were safe both before and after the vaccines were licensed. No serious safety concerns have been confirmed in the large safety studies that have been done since HPV vaccine

HPV vaccine is recommended and safe for boys

One HPV vaccine (Gardasil) is recommended for boys. This vaccine can help prevent boys from getting infected with the HPV-types that can cause cancers of the mouth/throat, penis and anus as well as genital warts.

Like any vaccine or medicine, HPV vaccines might cause side effects

HPV vaccines occasionally cause adverse reactions. The most commonly reported symptoms among females and males are similar, including injection-site reactions (such as pain, redness, or swelling in the area of the upper arm where the vaccine is given), dizziness, fainting, nausea, and headache.

Brief fainting spells and related symptoms can happen after many medical procedures, including vaccination. Fainting after getting a shot is more common among adolescents. Sitting or lying down for about 15 minutes after a vaccination can help prevent fainting and injuries that can be caused by falls.

HUMAN VACCINES & IMMUNOTHERAPEUTICS
2016, VOL. 12, NO. 8, 1960–1964
http://dx.doi.org/10.1080/21645515.2016.1160178

Taylor & Francis
Taylor & Francis Group

REVIEW

Is HPV vaccination in pregnancy safe?

Ulla Bonde[a,b], Jan Stener Joergensen[a,b], Ronald F. Lamont[a,b,c], and Ole Mogensen[a,b]

[a]Department of Gynecology and Obstetrics, Odense University Hospital, Odense, Denmark; [b]Institute of Clinical Research, University of Southern Denmark, Odense, Denmark; [c]Division of Surgery, University College London, Northwick Park Institute for Medical Research Campus, London, UK

ABSTRACT

Millions of doses of HPV vaccine have been administered globally. Inadvertent administration of HPV vaccine during pregnancy occurs given that the main recipients of the vaccine are fertile young women, who might be unaware of their pregnancy at the time of their vaccination. To investigate the subject of HPV vaccine and pregnancy , the databases of PubMed and Embase were searched to find the relevant literature published in English within the last 10 y. Most of the evidence pertaining to fetal adverse events following HPV vaccination relates to spontaneous miscarriage. None of the relevant studies found any significantly increased rate of spontaneous abortion in the overall analyses. There was no indication of other HPV vaccine-associated adverse events in pregnancy or immediately post-conception.

ARTICLE HISTORY
Received 20 November 2015
Revised 7 February 2016
Accepted 25 February 2016

KEYWORDS
adverse events; HPV; pregnancy; spontaneous abortion; vaccine

Introduction

response higher than a natural infection.[3] A 9-valent HPV

HUMAN VACCINES & IMMUNOTHERAPEUTICS
2016, VOL. 12, NO. 8, 1960–1964
http://dx.doi.org/10.1080/21645515.2016.1160178

Taylor & Francis
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REVIEW

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[a]Department of Gynecology and Obstetrics, Odense University Hospital, Odense, Denmark; [b]Institute of Clinical Research, University of Southern Denmark, Odense, Denmark; [c]Division of Surgery, University College London, Northwick Park Institute for Medical Research Campus, London, UK

For women who conceive around the time of a HPV vaccination based on the current evidence, there is no reason for concern with respect to the potential Aes for the pregnancy.

Therapeutic termination should not be considered leaving the pregnancy to be continued with a standard level of observation and health care.

However, it should be emphasized that the true safety of vaccination in pregnancy has not yet been formally established by a randomized controlled trial.

The NEW ENGLAND JOURNAL of MEDICINE

n engl j med 376;13 nejm.org March 30, 2017 1233

ORIGINAL ARTICLE

Quadrivalent HPV Vaccination and the Risk of Adverse Pregnancy Outcomes

Nikolai M. Scheller, M.D., Björn Pasternak, M.D., Ph.D., Ditte Mølgaard-Nielsen, M.Sc., Henrik Svanström, Ph.D., and Anders Hviid, Dr.Med.Sci.

In conclusion, in this large nationwide study we found that the risks of spontaneous abortion, major birth defect, stillbirth, preterm birth, small size for gestational age, and low birth weight **were not significantly higher with quadrivalent HPV vaccination** during pregnancy than without vaccination.

BACK
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hagen S, Denmark, or at nims@ssi.dk.

HPV Vaccine Safety Monitoring

NO link to Ovarian failure
NO link to Guillian Barre Syndrome

HPV Vaccine Safety Monitoring

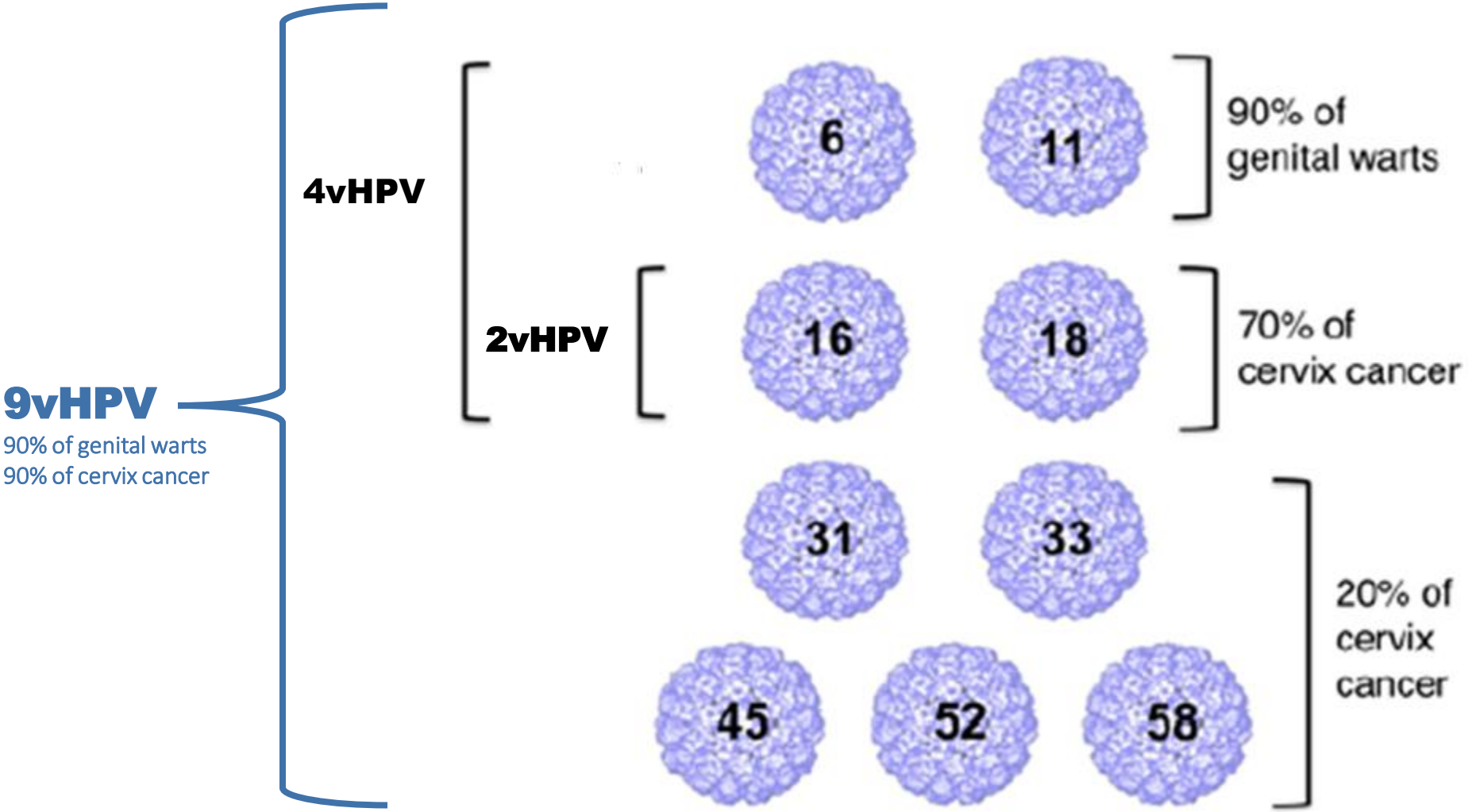
NO link to POTS (Postural Orthostatic Tachycardia Syndrome)

NO link to CRPS (Complex Regional Pain Syndrome)

http://www.cdc.gov/vaccinesafety/vaccines/hpv/hpv-safety-faqs.html

9-Valent HPV (9vHPV) Vaccine

HPV VLP L1 Vaccine development



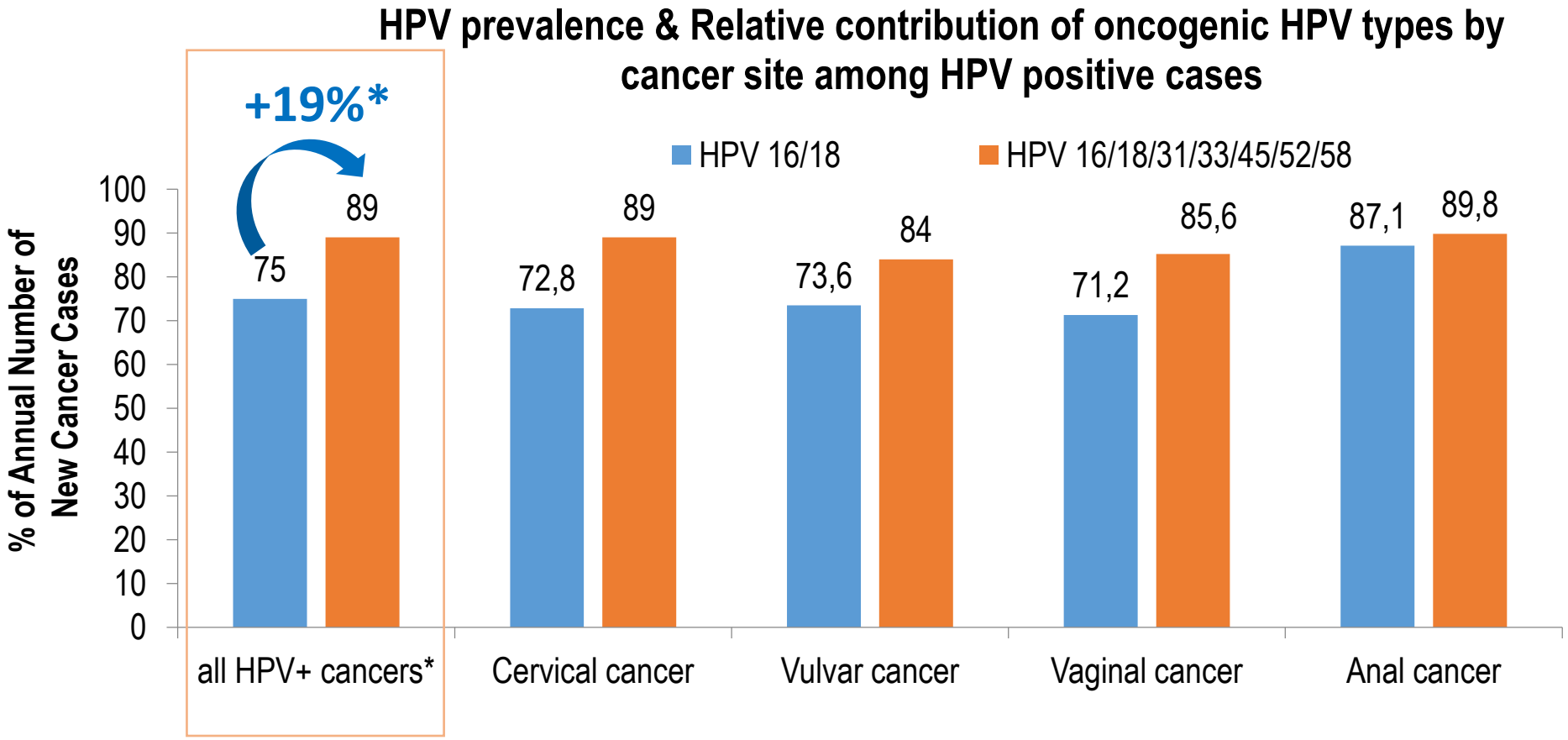
9vHPV Vaccine Clinical Studies

Study	Population	N	Objective
Pivotal efficacy study			
001[1]	16-26 yo women	14 215	Efficacy and immunogenicity study
Pivotal immunobridging studies			
002[2]	9-15 yo boys & girls and 16-26 yo women	3 066	Women-to-adolescent immunobridging
009[3]	9-15 yo girls	600	4vHPV-to-9vHPV immunobridging
003[4]	16-26 yo men and women	2 520	Women-to-men immunobridging
Supportive studies			
005[5]	11-15 yo boys & girls	1 241	Coadministration with Menactra*/Adacel** *Not registered in the EU*
007[6]	11-15 yo boys & girls	1 054	Coadministration with Repevax***
006[7]	12-26 yo girls and women	924	Study in prior 4vHPV vaccine recipients

**A/C/Y/W135 meningococcal vaccine; **Tdap vaccine; ***Tdap-IPV vaccine*

EU data

89% of HPV+ cancers are estimated to be related to the 7 HPV types 16/18 / 31/33/45/52/58

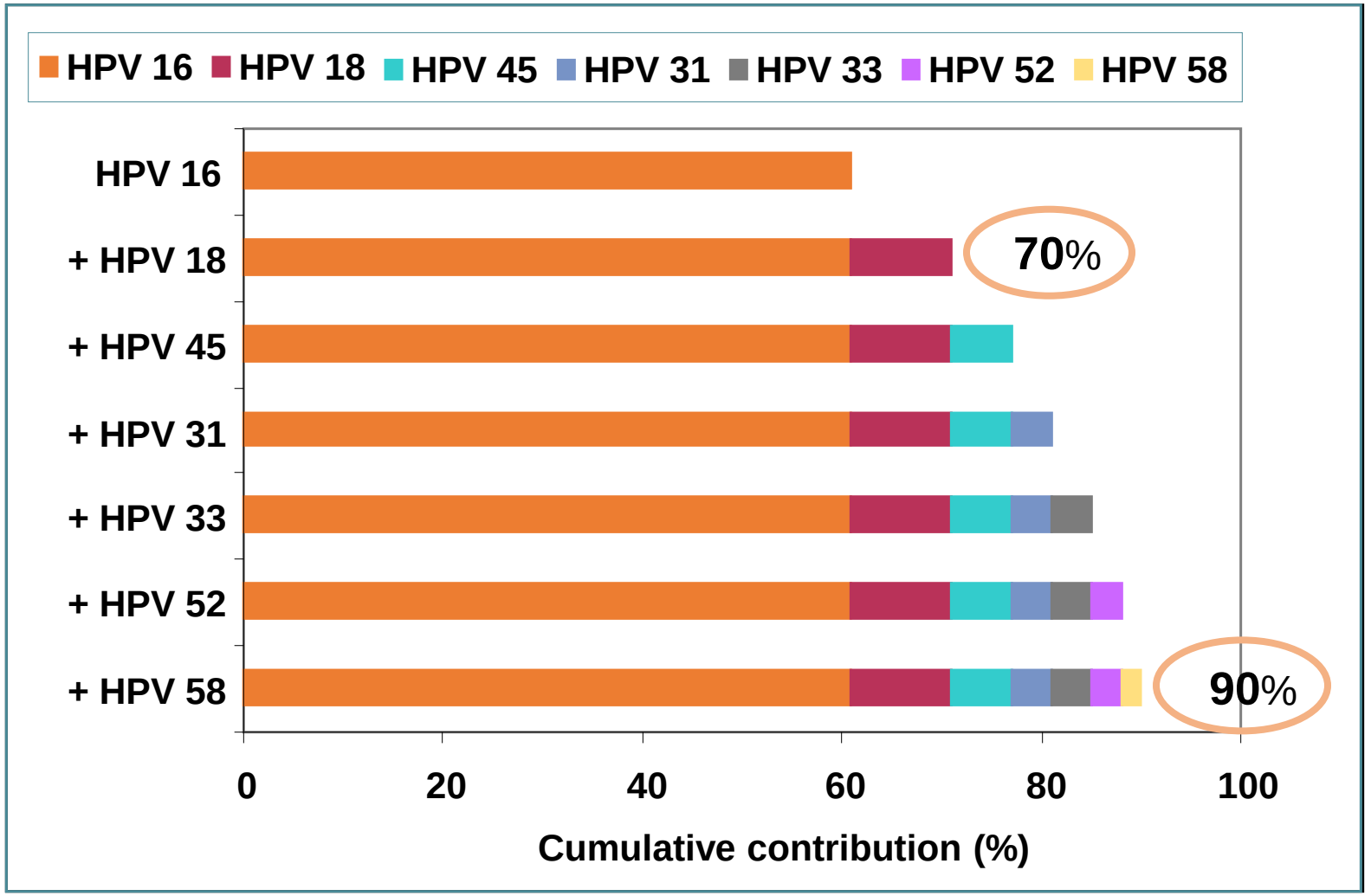


Hartwig et al , Papillomavirus research, 2015;1: 90–100

Rationale of 5 additional types in 9vHPV vaccine

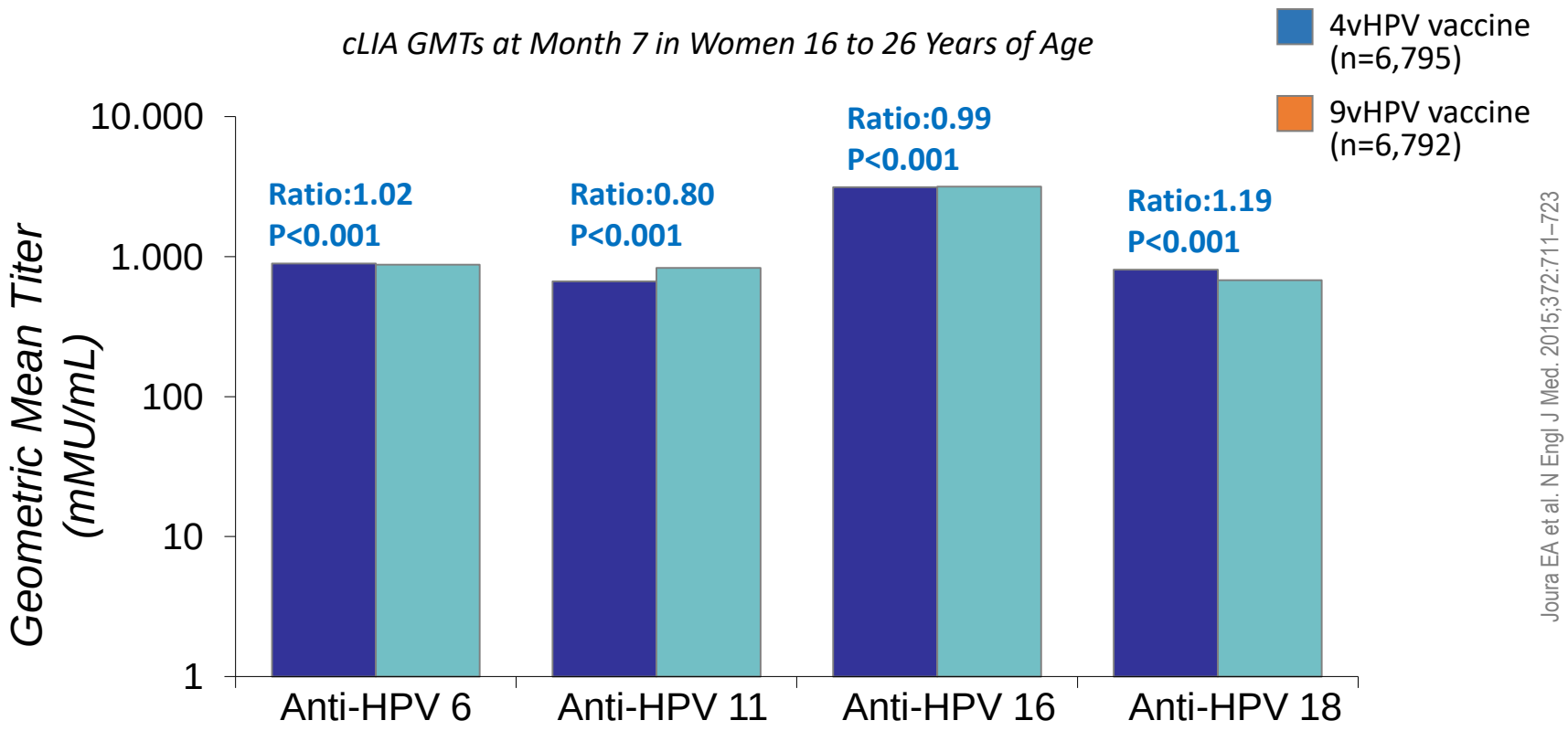
Relative Contribution of HPV Types in 9vHPV Vaccine to Cervical Cancers Worldwide[1]

WW data



Non inferior[a] immunogenicity demonstrated against HPV types 6/11/16/18 in 9vHPV vs 4vHPV vaccinees

Immunogenicity Results in women 16-26 years of age (PPI)[1]



Endpunkt	9vHPV	qHPV	Vakzinwirksamkeit
Alle CIN	2/5.949	110/5.943	98,2% (93,7; 99,7)
> CIN2	1/5.949	35/5.943	97,1% (83,5; 99,9)
> CIN3	0/5.949	7/5.943	100% (39,4; 100)
Alle VIN, VaIN	1/6.009	18/6.012	94,4% (67,7; 99,7)
> VIN2/3, VaIN2/3	0/6.009	3/6.012	100% (-71,5; 100)

9vHPV: Gardasil 9
qHPV: Gardasil
CIN: zervikale intraepitheliale Neoplasien
VIN: vulväre intraepitheliale Neoplasien
VaIN: vaginale intraepitheliale Neoplasien

Joura EA et al:
N Engl J Med
2015; 372: 711-723

Tab. 1: Wirksamkeit von Gardasil 9 bei intraepithelialen Neoplasien durch Zusatz von 5 Stämmen in der Per-Protokoll-Population am Studienende[9]

9vHPV Vaccine Injection-site AEs (Incidence ≥2%)

Combined analysis P001, 002, 003, 005, 006, 007, 009)

Days 1 to 5 Following Any Vaccination with 9vHPV Vaccine

Injection-site AE	Subjects Who Received 9vHPV Vaccine (N=15,776) n (%)
Pain	13,118 (83.2)
Swelling	5,698 (36.1)
Erythema	4,859 (30.8)
Pruritus	636 (4.0)

Most injection-site AEs were mild to moderate in intensity

9vHPV Vaccine Systemic Vaccine-Related*AEs

Combined analysis

P001, 002, 003, 005, 006, 007, 009

Days 1 to 15 Following Any Vaccination with 9vHPV Vaccine

Systemic Vaccine-related AEs[b] (≥1%)	Subjects Who Received 9vHPV Vaccine (N=N=15,776) n (%)
Headache	2,090 (13.2)
Pyrexia	955 (6.1)
Nausea	503 (3.2)
Dizziness	355 (2.3)
Fatigue	294 (1.9)

**Determined by the investigator to be related to the vaccine.*

Klassifikation	Virus	Tumor	Vorkommen/besonders häufig betroffene Regionen
DNA-Viren	Humane Papillomviren (HPV)	Zervixkarzinom	weltweit
	Epstein-Barr-Virus (EBV)	Burkitt-Lymphom	Äquatorialafrika, Teile von Papua-Neuguinea
		B-Zell-Lymphome bei immunsupprimierten Patienten	weltweit
		Hodgkin-Lymphom (?)	weltweit
		Nasopharynxkarzinom	Südchina, Grönland (Inuit), afrikanischer Mittelmeerraum
		bestimmte Formen von Magenkrebs	weltweit
		seltene T-Zell-Lymphome	Japan, Taiwan, Korea
		Sarkome der glatten Muskulatur bei Kindern mit Aids	weltweit
	Humanes Herpesvirus 8 (HHV-8)	Kaposi-Sarkom (KS)	Klassisches KS: Mittelmeerraum und Osteuropa
			Endemisches KS: Äquatorial-, Ost- und Südafrika
			Iatrogenes KS: weltweit
			Aids-assoziiertes KS: weltweit
	Hepatitis-B-Virus (HBV)	Hepatozelluläres Karzinom	Südostasien, Afrika südlich der Sahara
RNA-Viren	Hepatitis-C-Virus (HCV)	Hepatozelluläres Karzinom	Südostasien, Afrika südlich der Sahara
	Humanes T-Zell-Leukämievirus Typ I (HTLV-I)	Adulte T-Zell-Leukämie	Japan, karibische Inseln, Südamerika, Teile von Zentralafrika

Seit 2014 gibt es in Österreich ein voll finanziertes Impfprogramm

Dabei handelt es sich um das erste in Europa, das geschlechtsneutral ist.

Die Impfung ist für Kinder in der 4. Klasse Volksschule vorgesehen und bis zum 12. Lebensjahr kostenlos.

Danach kann sie bis zum 15. Lebensjahr zu einem Preis von ca. 50 Euro/Dosis in öffentlichen Gesundheitsstellen bezogen werden.

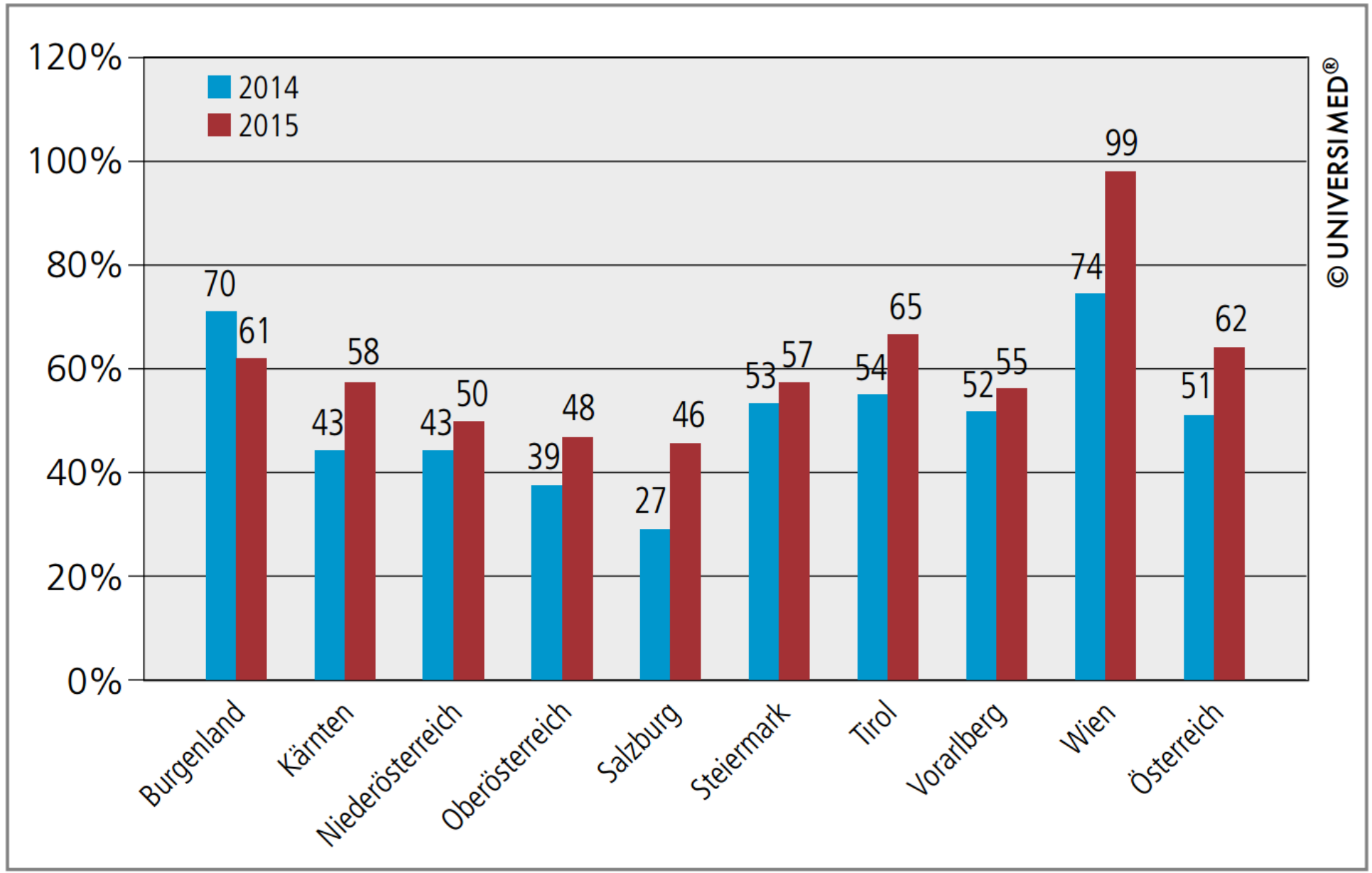
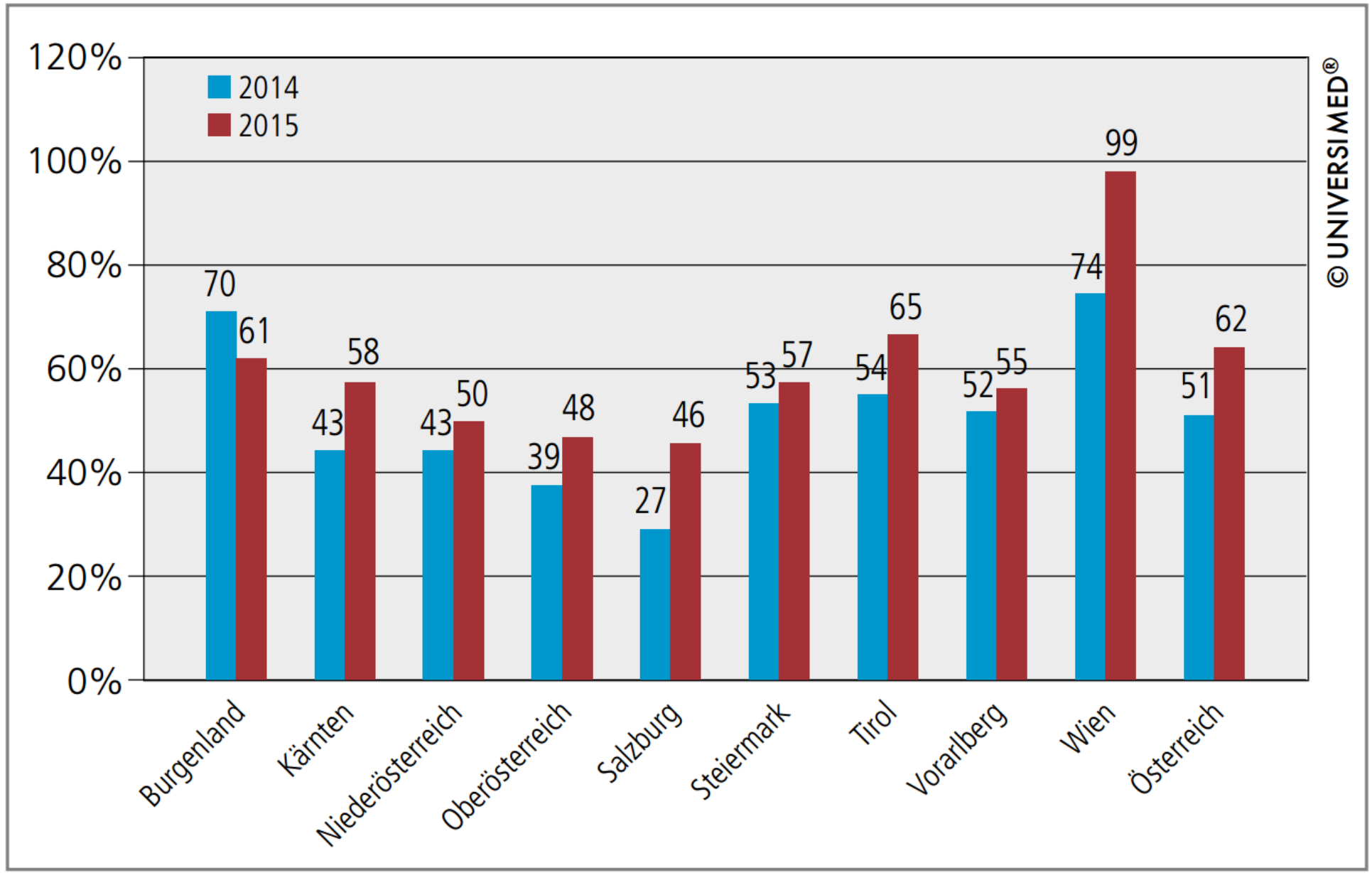


Abb. 1: Durchimpfungsrate 2014 und 2015 gemäß dem Bundesministerium für Gesundheit (http://www.bmg.gv.at/)



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