



BIOCEV



HPV infection doesn't affect only girls and women

Ruth Tachezy

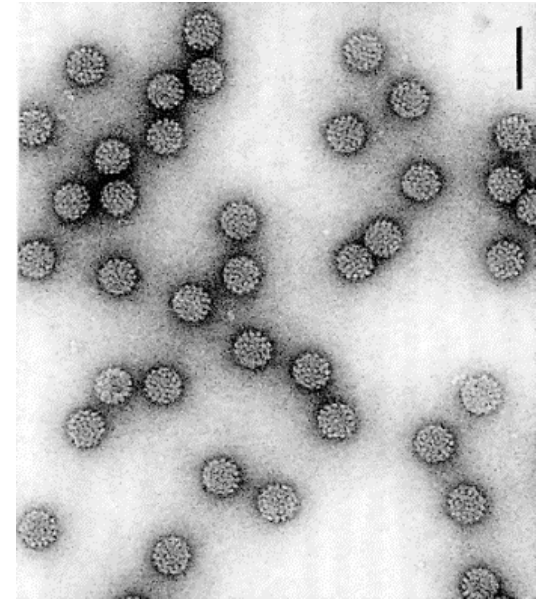
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Faculty of Science, Department of Genetics and Microbiology, Charles University, Prague



Papillomaviruses

- Small DNA viruses 55 nm, non-enveloped, stable, 8 000 pb
- Ubiquitous
- Evolutionary old viruses, evolved with their host
- **Species specificity and tissue tropism** – they infect stratified mucous and skin epithelia of the high vertebra
- 198 genotypes, 5 genuses (α , β , γ , μ , ν),

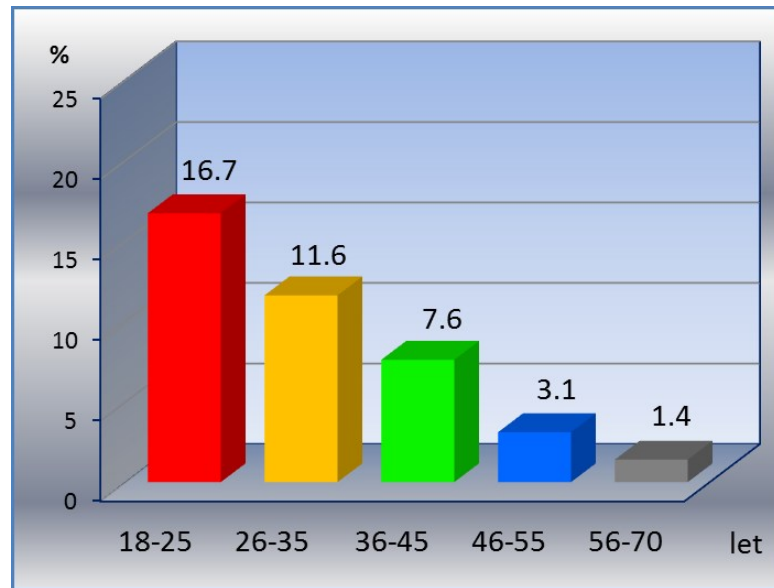


	Mouth 30%	Skin 61%	
1,	107,12,147	10,104,109,110,111,112	NGS 68%
138	148,155,17	115,116,119,120,122	
26	19,20,24,36	124,127,129,130,132	
32	4,49,5,50,58	133,136,137,139,14,141	
145	8,80,9,98	143,149,15,151,156,2	
		22,23,37,48,60,65,75,76	
		92,93,95,96	
		28,47	Gut 17%
		101,18,42	
135	144,126	103,106,16,39,43	Vagina 41%
62	146,153	51,52,53,56,59,6,61	
66	21,38,N	67,72,73,74,83,89	
		118,121,128,131,134	
		142,150,34,45,88	
		90,91	

Changes in sexual behavior of the population

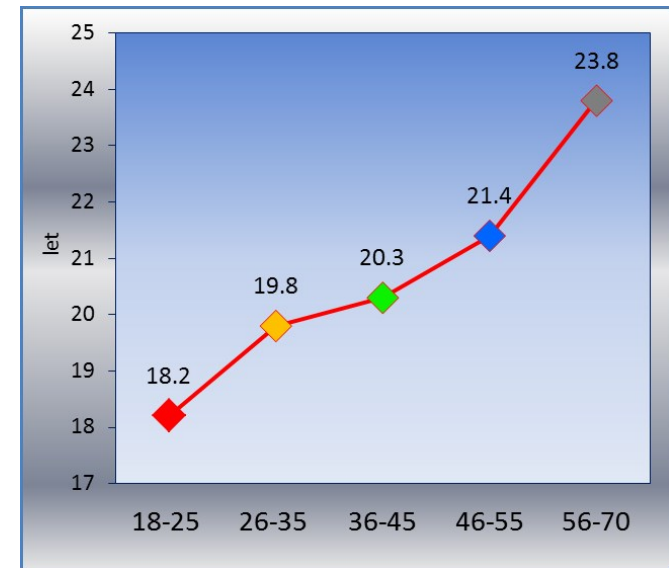
- The most frequent viral STD
- Earlier sexual debut
- Reduction of the monogamous relationship
- Better quality of life, sexual activity extended to older age

Y-percentage of women with the first sexual experience before 17 years of age
X-current age



12x more

Y-average age of the first sexual experience
X-current age

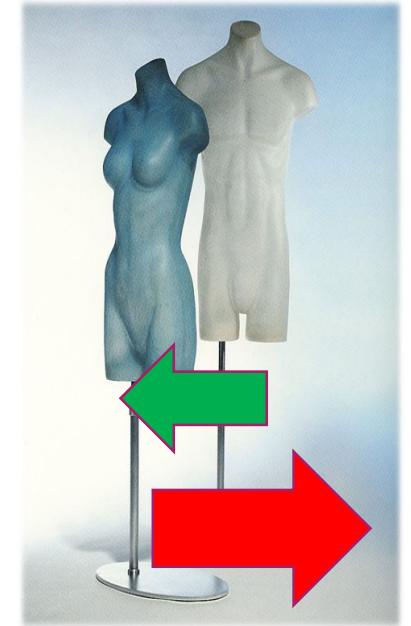


5.6x more

Minichiello et al., 2011
Lyons et al., 2011
Lindau et al., 2007

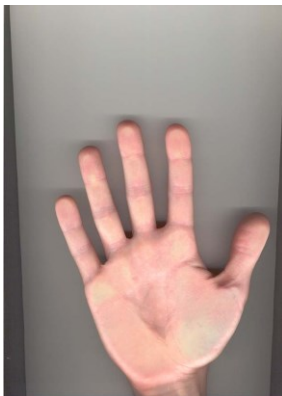
Transmission

- Sexual - hetero and homo; penetrative and non-penetrative
 - Prevalence of HPV DNA in virgins 2%
 - Cumulative incidence in 2 years non-penetrative sex **YES** 10% vs. **NO** 1% (Winer et al., 2003)
 - HPV-specific antibodies in virgins HPV 6/11/16/18 – 25/15/4/2% (Hamšíková et al. 2013)
 - Virgins after sexual debut HPV infected in 25%, within 2 years 41% (Hamšíková et al., 2013)
 - More efficient transmission from females to males (4x more frequent) (Hernandez et al., 2008)
 - HPV type specific concordance in couples (partial 66%, complete 41%) (Abalos et al., 2012, Rob et al., 2016)
 - Sexual behavior is a risk factor for HPV prevalence in oral cavity (0.9% vs. 7.5%) (Gillison et al., 2012)

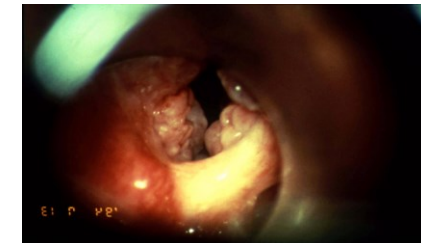
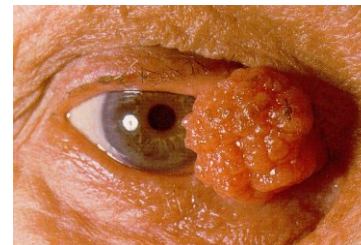


Transmission

Autoinoculation and heteroinoculation



From mother to child during the delivery, transplacental



Condom

- 2000 – FDA, CDC, NIH, I.S. Agency for International Development „Condom reduces the risk of pregnancy, HIV transmission, and among men, gonorrhea“.
- 2006 – Strong evidence that condom use reduces the risk of transmission of HIV, gonorrhea and chlamydia, and herpes simplex virus in both women and men“.
- 2006 Winer a spol., NEJM, 354, 25, 2645-54 „evidence that condom reduces also the risk of HPV infection in women“
- **Safer vs. safe sex**

HPV DNA prevalence in males

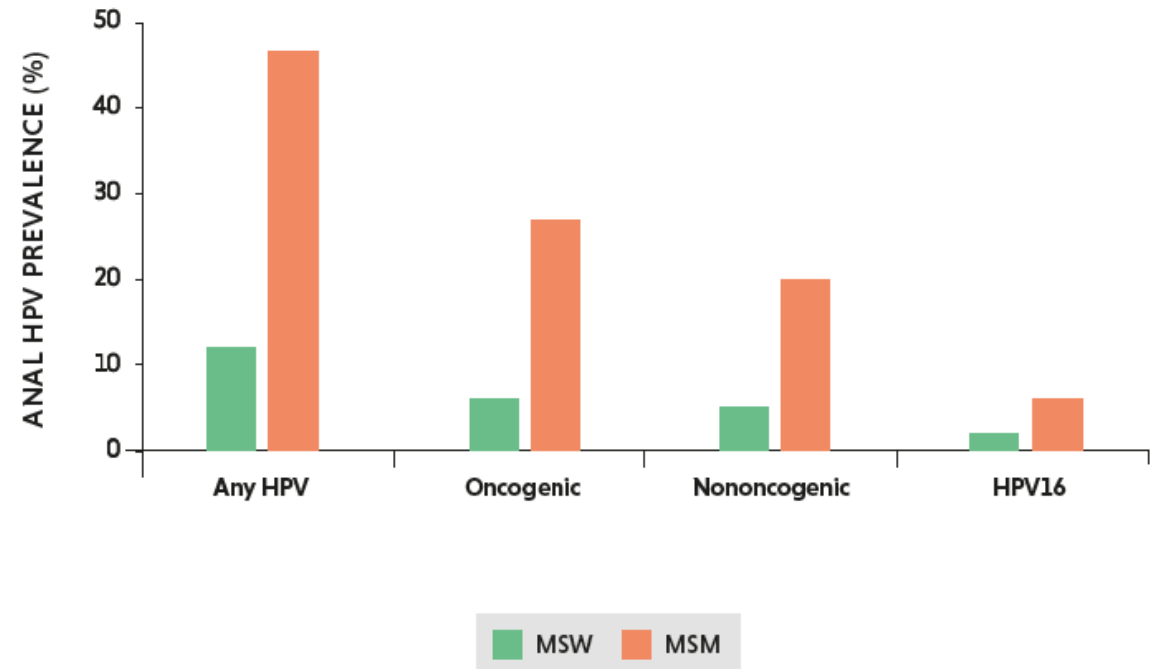
ANY HPV TYPE

	Prevalence	Incidence rate per 1,000 person-months	Median time to clearance (months)
Genital HPV	50.4%	38.4	7.5
Anal HPV*	12.0%	8.1	--
Oral HPV	4.0%	5.6	6.9

* Heterosexual men.

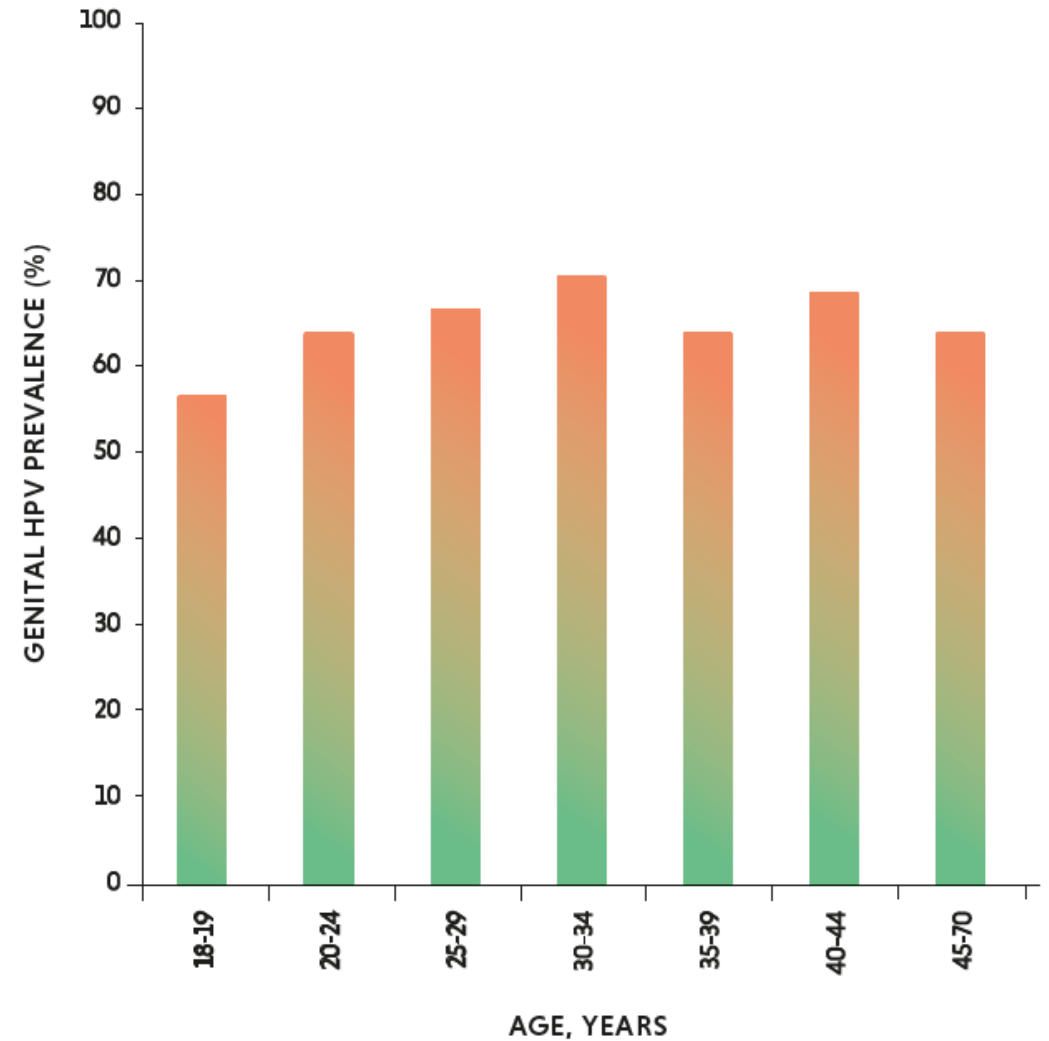
Incidence per 100 person-years

	penile/ scrotal	perineal/ perianal	anal
MSW	6.8	1.9	ND
MSM	3.2	9.0	16.8



HPV DNA prevalence in males

- In contrast to females is not age dependent
- Incidence 38 /1000 person-month
- Clearance of infection 7.5 months
- **Risk factors:**
- Race - Asiatic 👍
- Condom 👍
- Circumcision 👍
- Smoking 👎
- STD 👎



HPV in healthy tissues of males

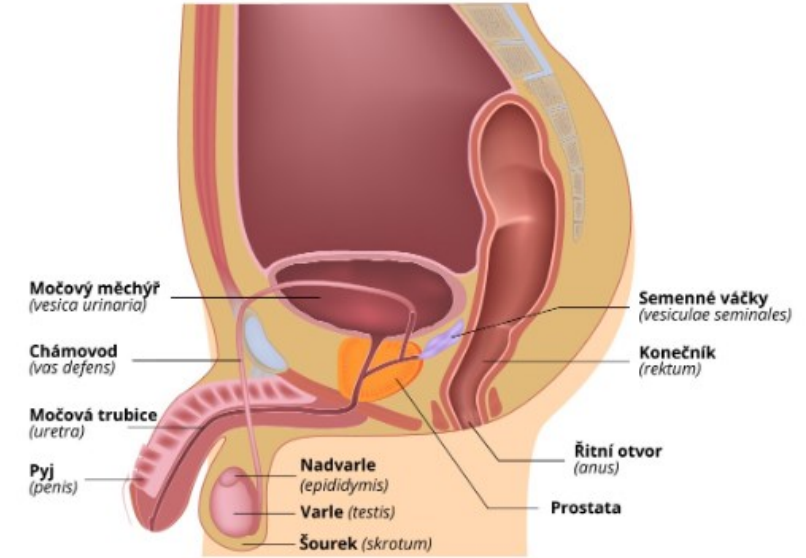


TABLE III. Prevalence of HPV in Healthy Tissue of Male Urogenital Tract

	No. of patients	No. of samples	No. of HPV positive samples (%)
Foreskin	27	27	4 (14.8) ^a
Prostate	51	80	2 (2.5) ^b
Urinary bladder	15	29	0
Seminal vesicles	54	77	2 (2.6) ^c
Ductus deferens	27	40	2 (5.0) ^d
Ureter	3	3	0
Total	74	256	10 (3.9)

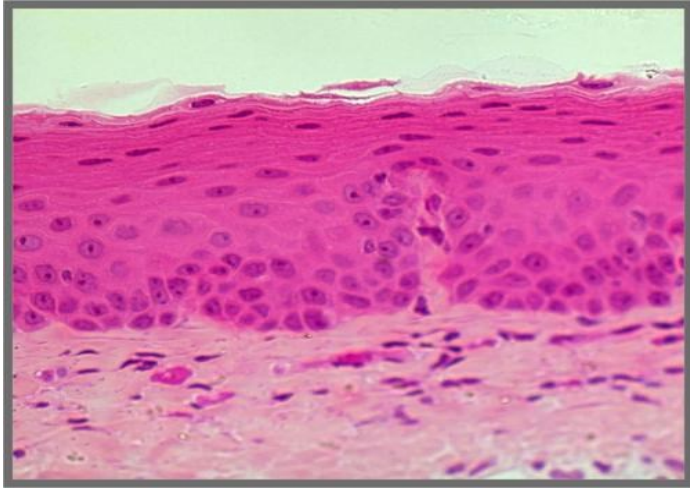
^aHPV 16 in three samples, one sample positive for unknown type.

^bTwo samples positive for unknown type.

^cHPV 52, one sample positive for unknown type.

^dHPV 16, one sample positive for unknown type.

Type of epithelium and immune response



Squamous non-keratinizing epithelium
(cornea, oral cavity, oesophagus, vagina, anus, cervix)

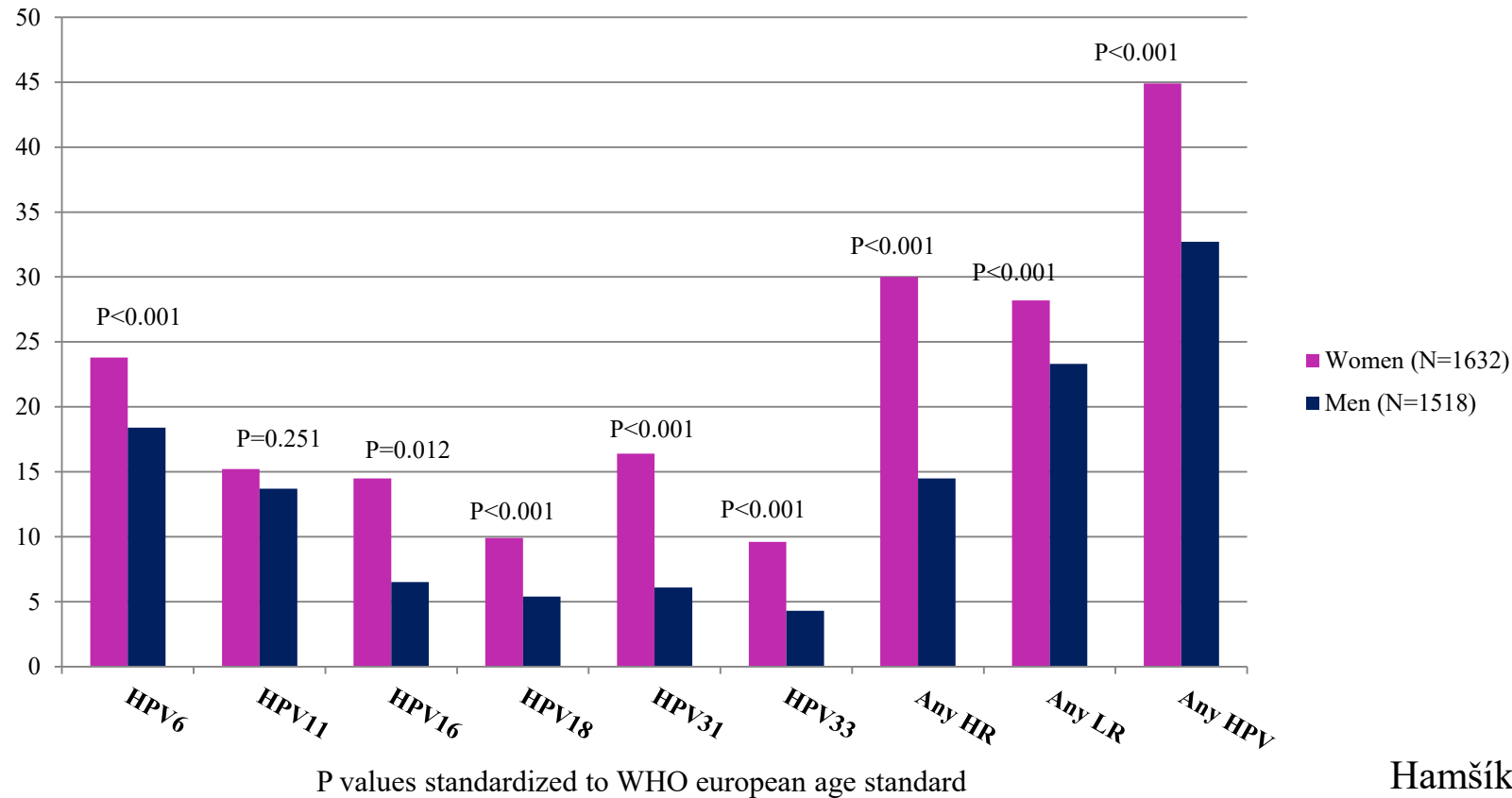


Squamous keratinizing epithelium
(perianal area, penis)

- Squamous non-keratinizing epithelium (mucosal) – easier access to lymphatic system, faster and stronger immune response

Prevalence of HPV-specific antibodies in males vs. females

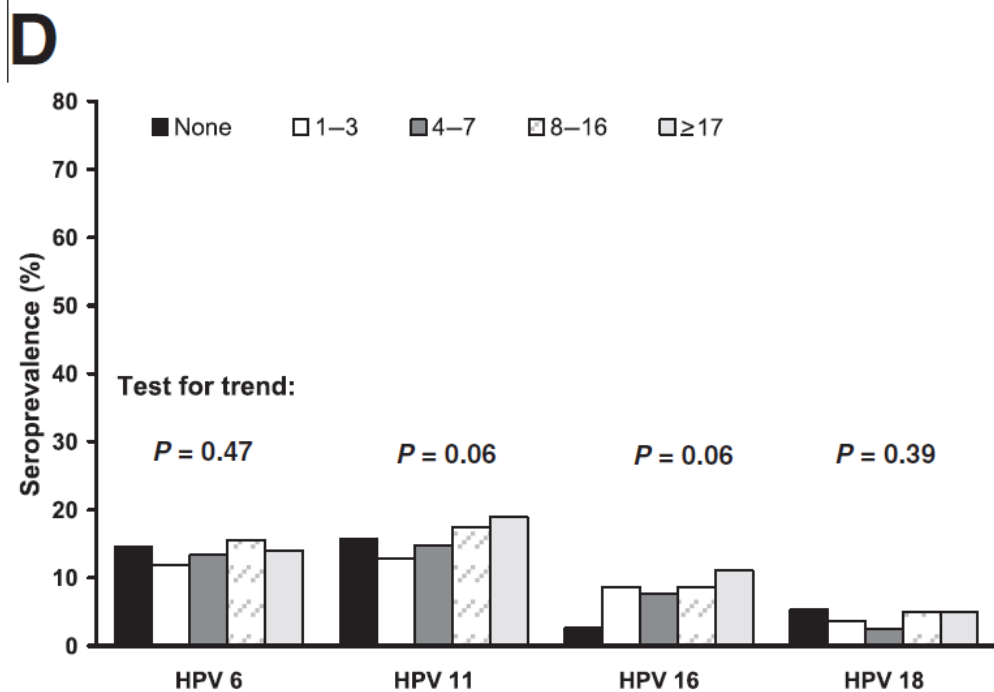
- The level of HPV-specific antibodies is lower in males vs. females (Lu et al., 2011; Newall et al., 2008; Markowitz et al., 2009; Michael et al., 2008)
- Czechia - females 45%, males 33% (any HPV), 37% females, 29% males (any vaccine HPV type) (Hamšíková et al., 2012)
- Non-existing protection for reinfection (Pamnani et al., 2016)



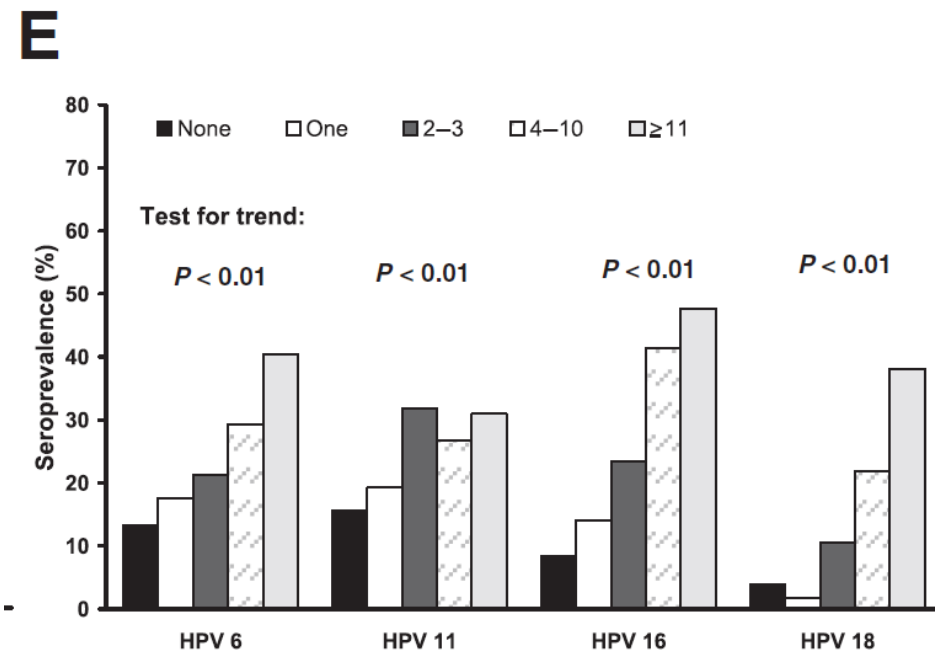
Prevalence of HPV-specific antibodies in males

- Prevalence of HPV-specific antibodies in males is driven by the number of sexual partners and by a mode of sexual intercourse

Number of female sex partners in MSW

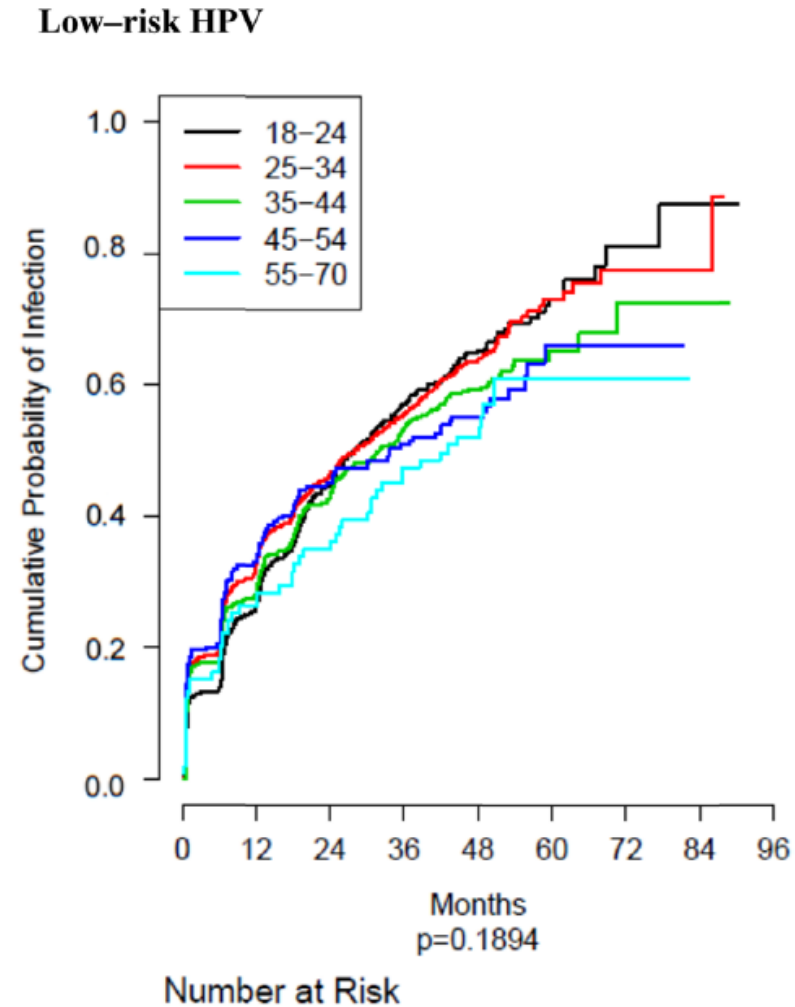
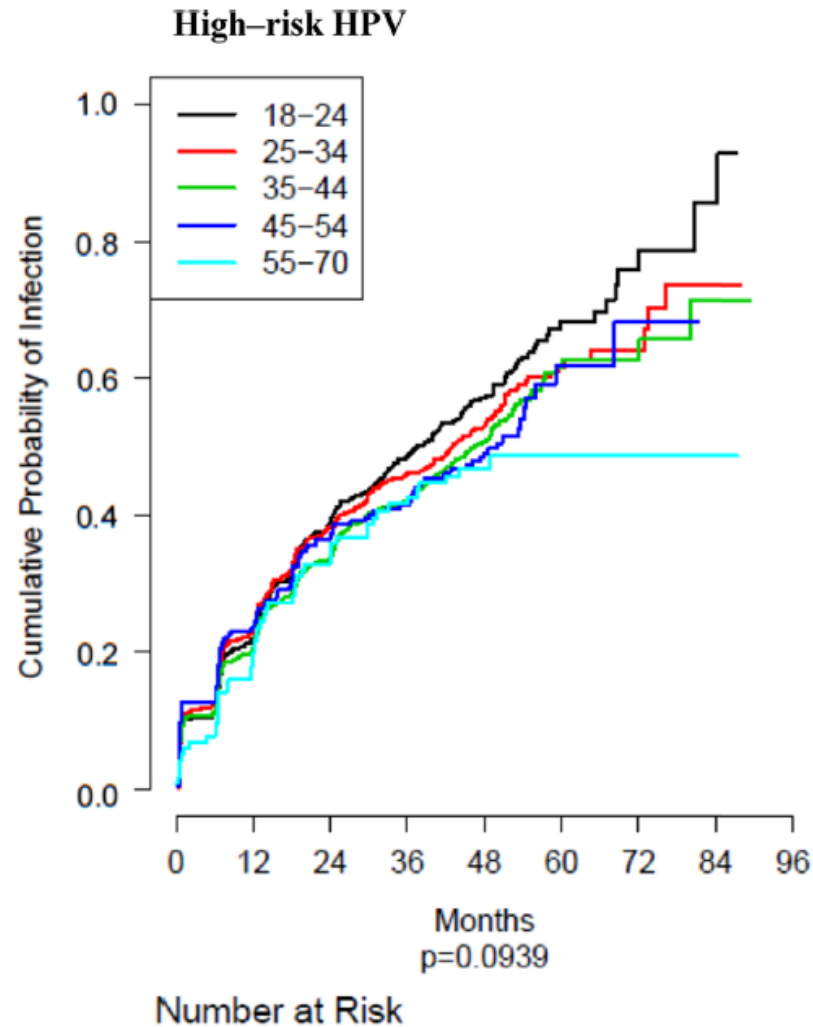


Number of male anal sex partners (MSM, MSMW)



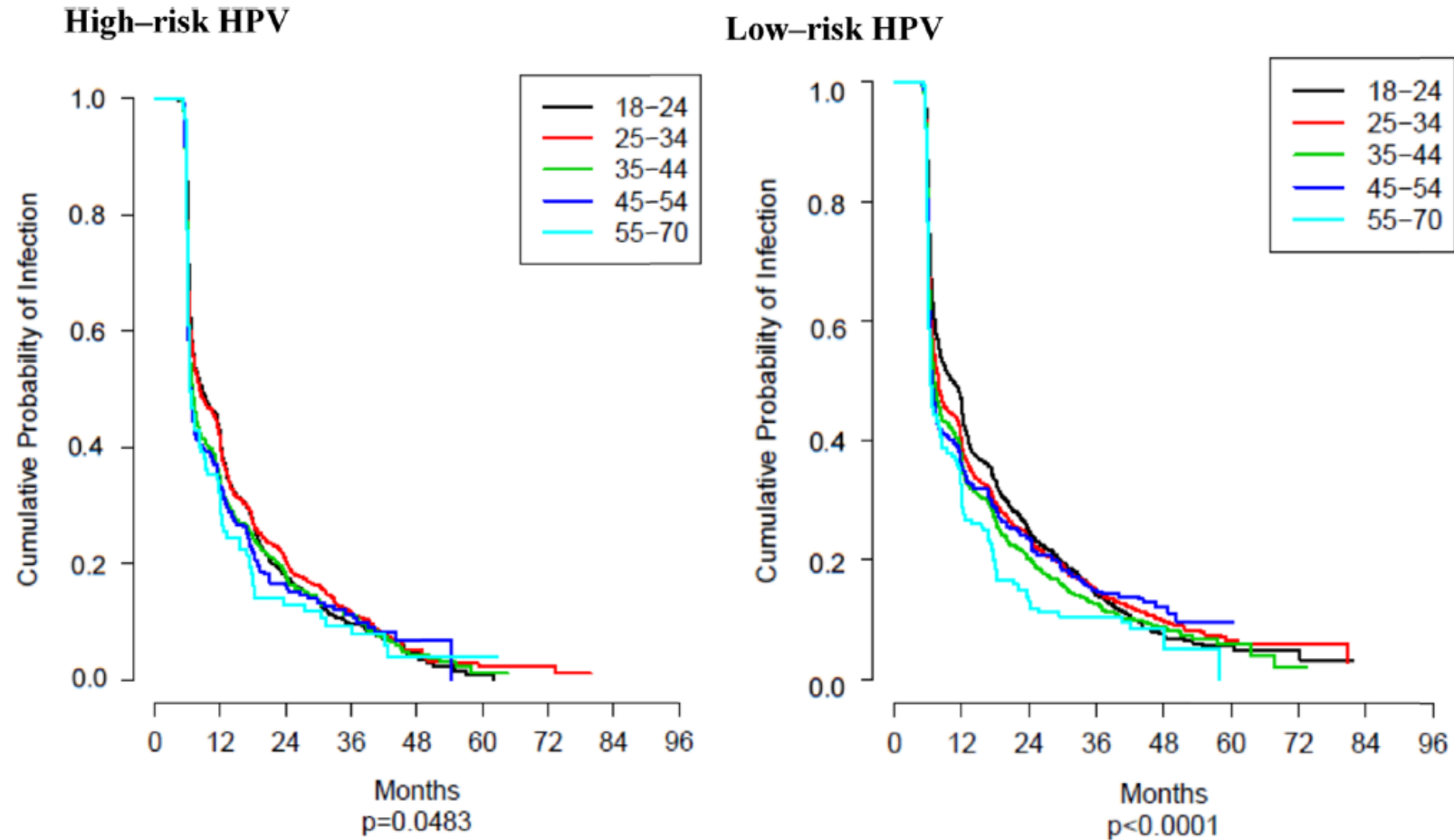
Age-specific incidence of HPV infection in males

- Lower in younger age but not statistically different



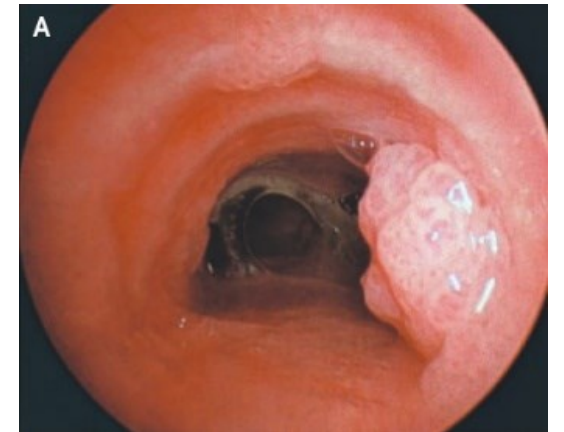
Age-specific clearance of HPV infection in males

- No difference by age group



Diseases caused by LR HPVs in males

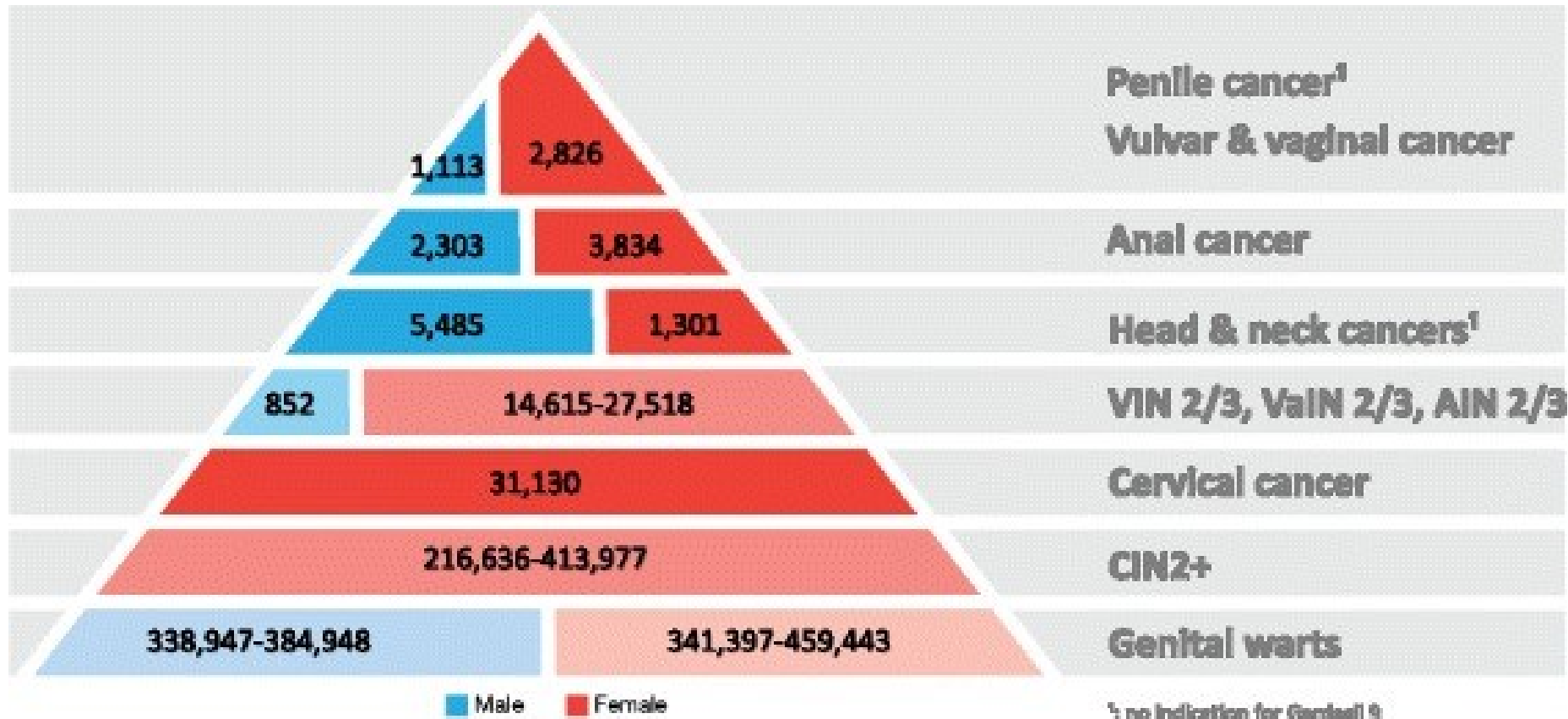
- **Genital warts**
 - Czechia 17-55 years of age, questionnaire, 32,974 individuals, **prevalence 5.8%** (Petráš et al., 2015)
 - Incubation time 5-12 months
 - Progression in 6-22% HPV infected (Sudenga et al., 2016)
 - Spontaneous clearance 10-20%
 - 65% of sexual partners develop GW
 - Risk factor
 - External genital lesions of partner (65% of sexual partners develop GW)
 - Number of sexual partners
- **Recurrent respiratory papillomatosis**
 - Juvenile and adult form
 - Prevalence of 4.3 and 1.8 cases per 100,000 persons
 - Men are affected more than women



Diseases caused by HR HPVs in males

- **Anal precancerous lesions and carcinoma**
- 91.5% in AIN1 and 93.9% in AIN2/3 (De Vuyst H et al. Int J Cancer 2009)
- 88% squamose HPV-associated
- Czechia 82% HPV-associated (Tachezy et al. 2011)
- Risk factor:
 - Sexual behaviour
 - MSW 12%, MSM 64%, HIV+ MSM 93%
- **Penile precancerous lesions and carcinoma**
- 51% HPV-associated
- **Oropharyngeal carcinoma**
- 31% HPV-associated, more in developed countries
- Czechia 62% HPV-associated (Tachezy et al., 2009)

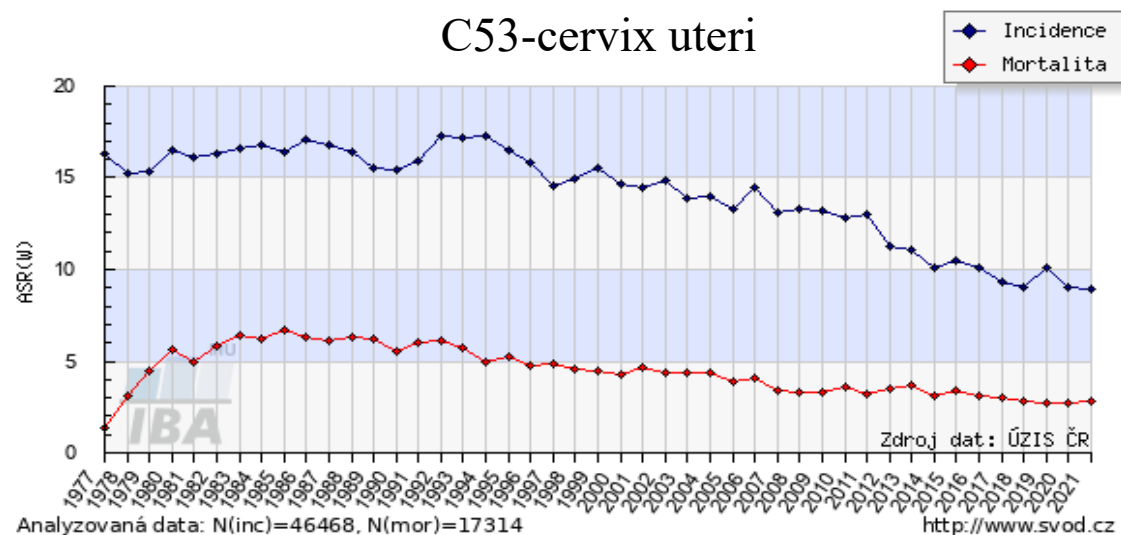
HPV-associated diseases annually in Europe



- Worldwide 1/3 carcinomas of infectious aetiology, HPV ~ 690,000/ year
- 9,500 / year in Europe males; 900 in Czechia
- 43,000 / year in Europe females; 1600 in Czechia

Incidence and mortality of HPV-associated diseases in Czechia

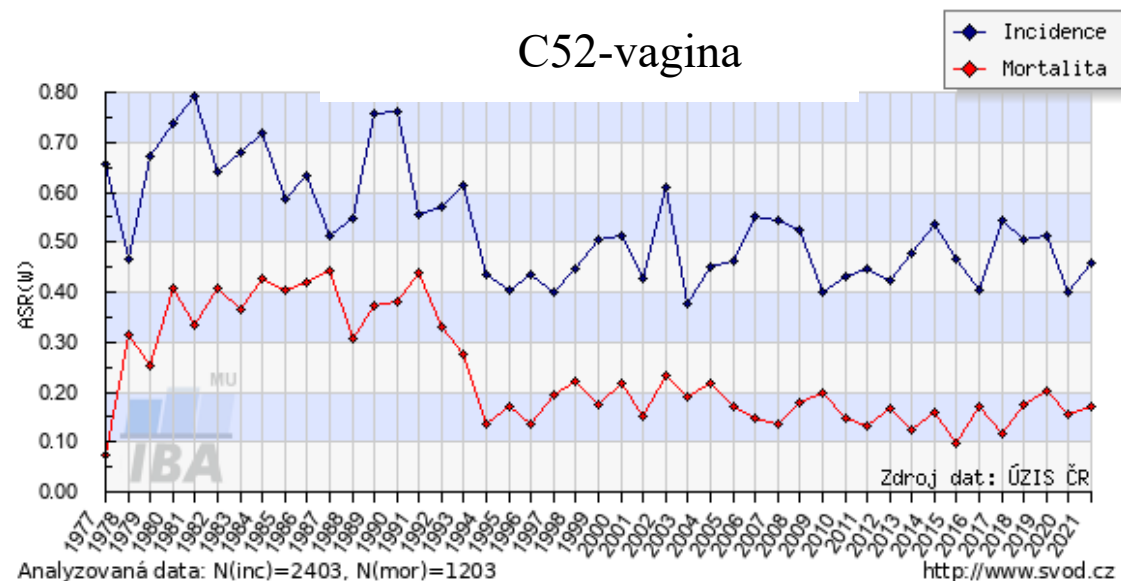
C53-cervix uteri



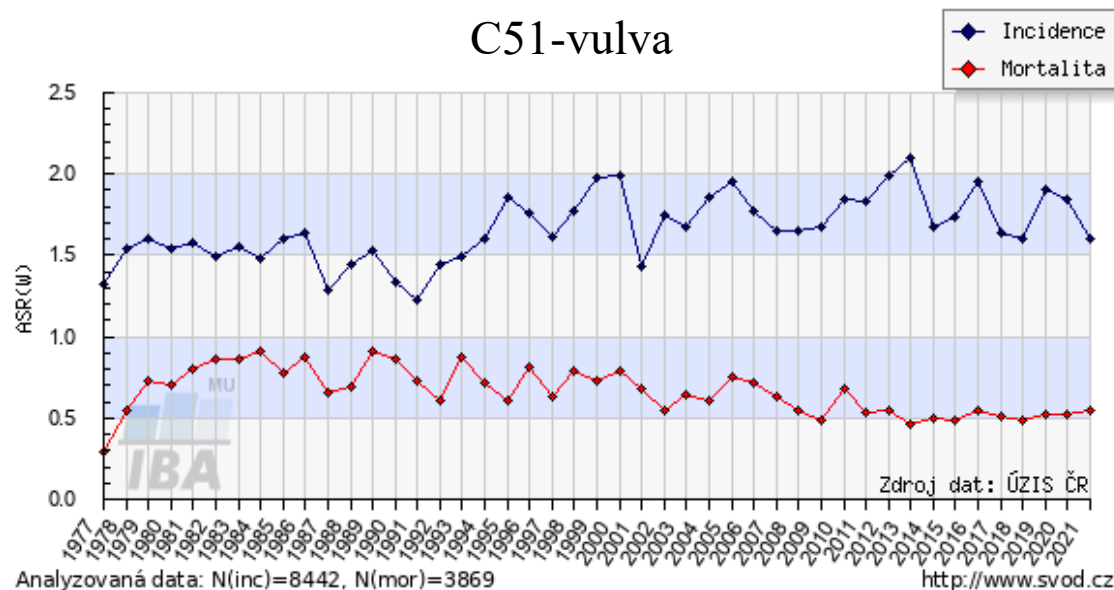
**Tendency of an increase
2006-16**

Cervix -20,5%
 Vulva +12,5%
 Vagina +5.1%

C52-vagina

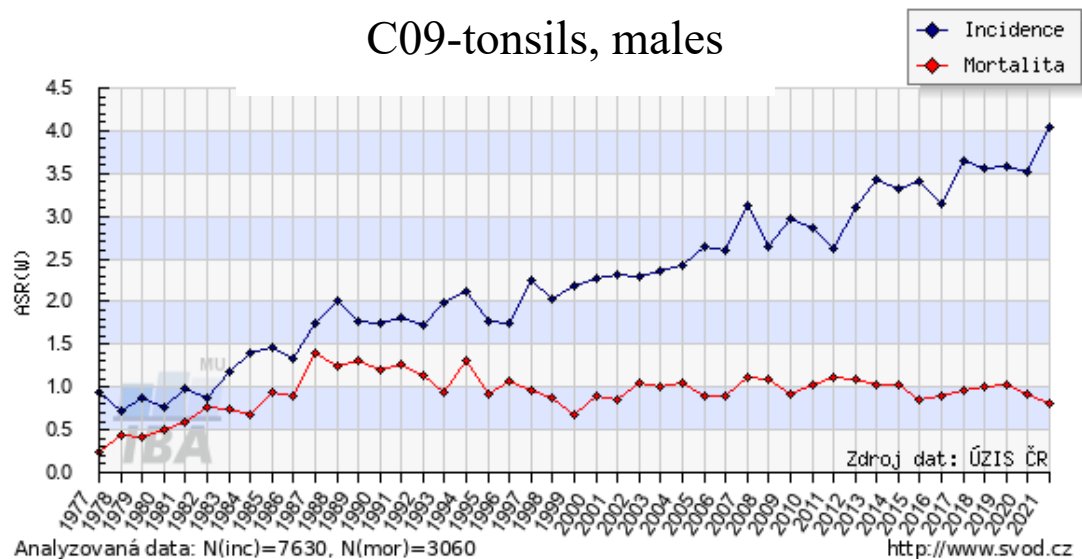


C51-vulva

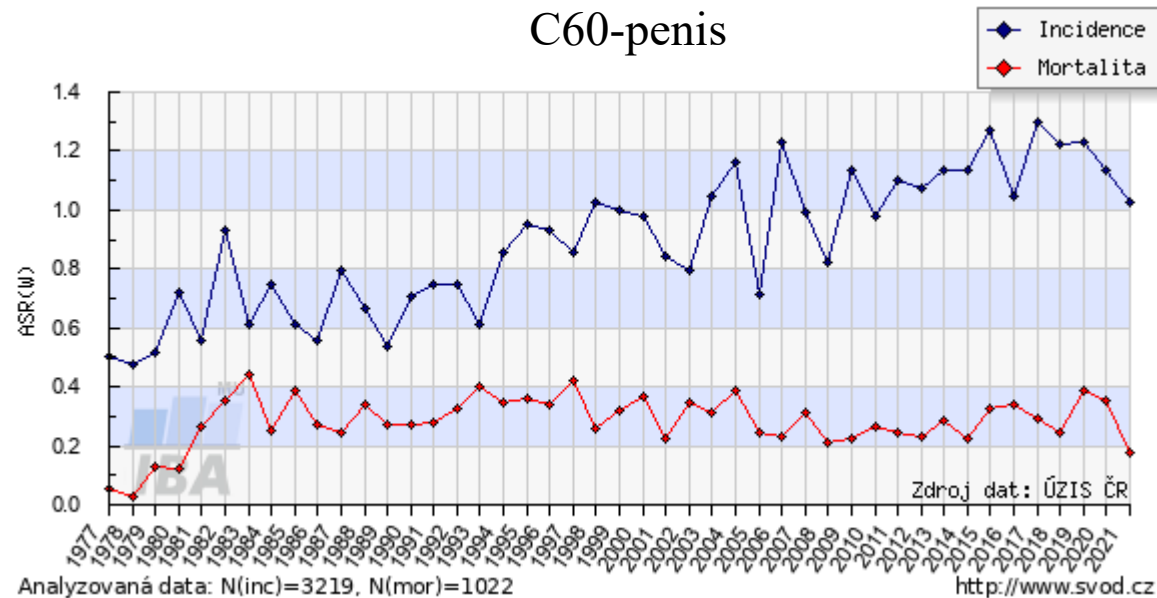


Incidence and mortality of HPV-associated diseases in Czechia

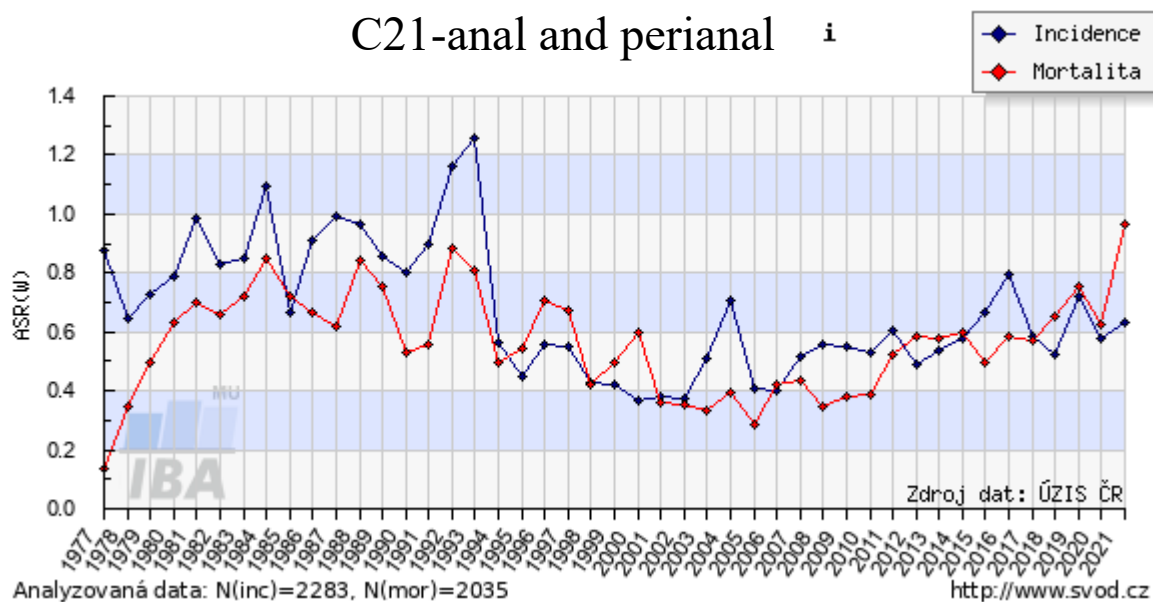
C09-tonsils, males



C60-penis



C21-anal and perianal

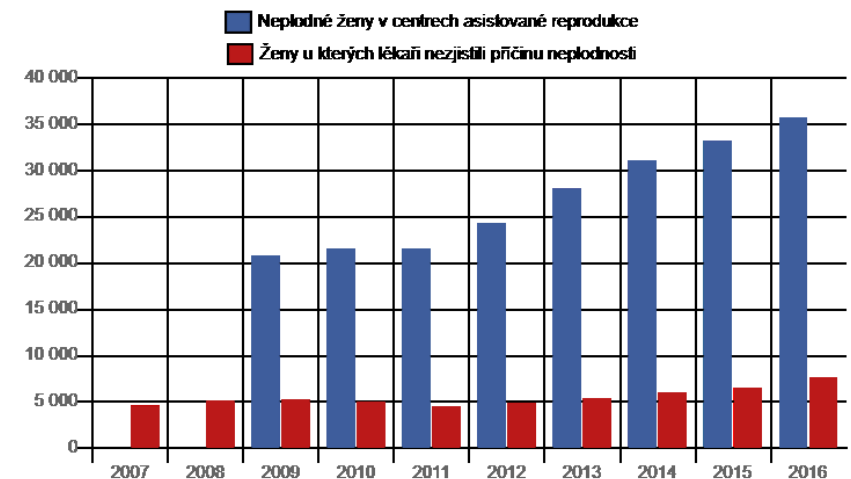


HPV and assisted reproduction

- In Czechia 20% of couples need AR
- men are infected lifelong at a high percentage, usually asymptomatic, and HPV is also present in the male reproductive tract
- HPV prevalence in semen and sperm is higher in infertile compared to healthy men
- HPV-infected sperm show poorer motility and morphology
- HPV binds to sperm via syndecan 1 in the equatorial part of the head and enters the cell
- infected sperm can transfer HPV to the oocyte, where the viral genes are transcribed
- HPV infection affects the development and implantation of the embryo
- HPV vaccination in men with HPV in their semen speeds up the clearance of the virus and increases the likelihood of successful ART

HPV and assisted reproduction

- Evidence suggests that HPV infection affects sperm characteristics and thus male fertility
- Also likely to negatively affect the success of assisted reproduction
- Data suggest a possible benefit of including HPV detection in sperm donors and couples undergoing AR
- HPV vaccination could increase the success rate of AR in HPV-positive couples

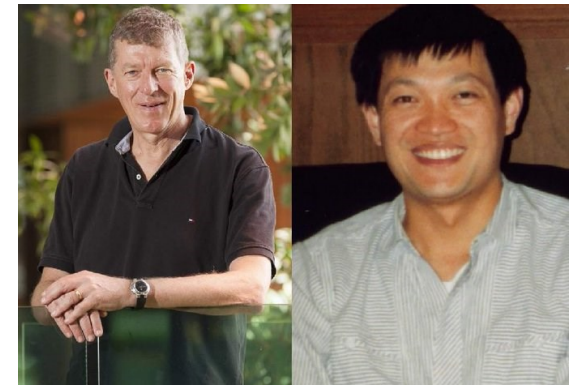
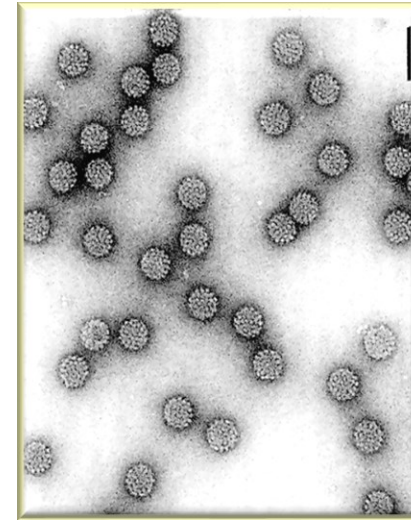


HPV genotypes by the disease

Location	HPV type (prevalence)	HPV type (prevalence)	HPV type
Cervical carcinoma	HPV16 (50%)	HPV18 (12%)	HPV31, HPV45, HPV33
Cervical carcinoma-Asie	HPV16 (50%)	HPV18 (12%)	HPV58, HPV33, HPV52
Other cancers	HPV16		
Genital warts	HPV6/11 (90%)		
Laryngeal papillomatosis	HPV6/11 (100%)		

Primary prevention

- Prophylactic vaccines, block viral entry into the cell
- HPV 6/11 – 90% of GW
- HPV 16/18 – 70% of cervical cancers
- Vaccination of children before coitarche
- Gender neutral vaccination
- Coverage
- No therapeutic effect ???



Ian Frazer, Jian Zhou

Effect of routine vaccination

- Meta-analyses
- 60 mil subjects
- Up to 8 years follow-up
- 23 studies on HPV infection
- 29 studies on genital warts
- 13 studies on CIN2+

FU after vaccination

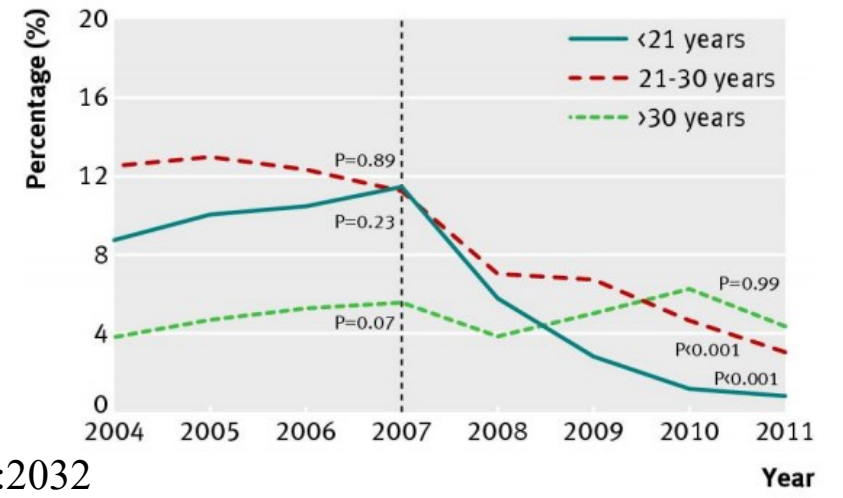
1-4 years 

5-8 years 

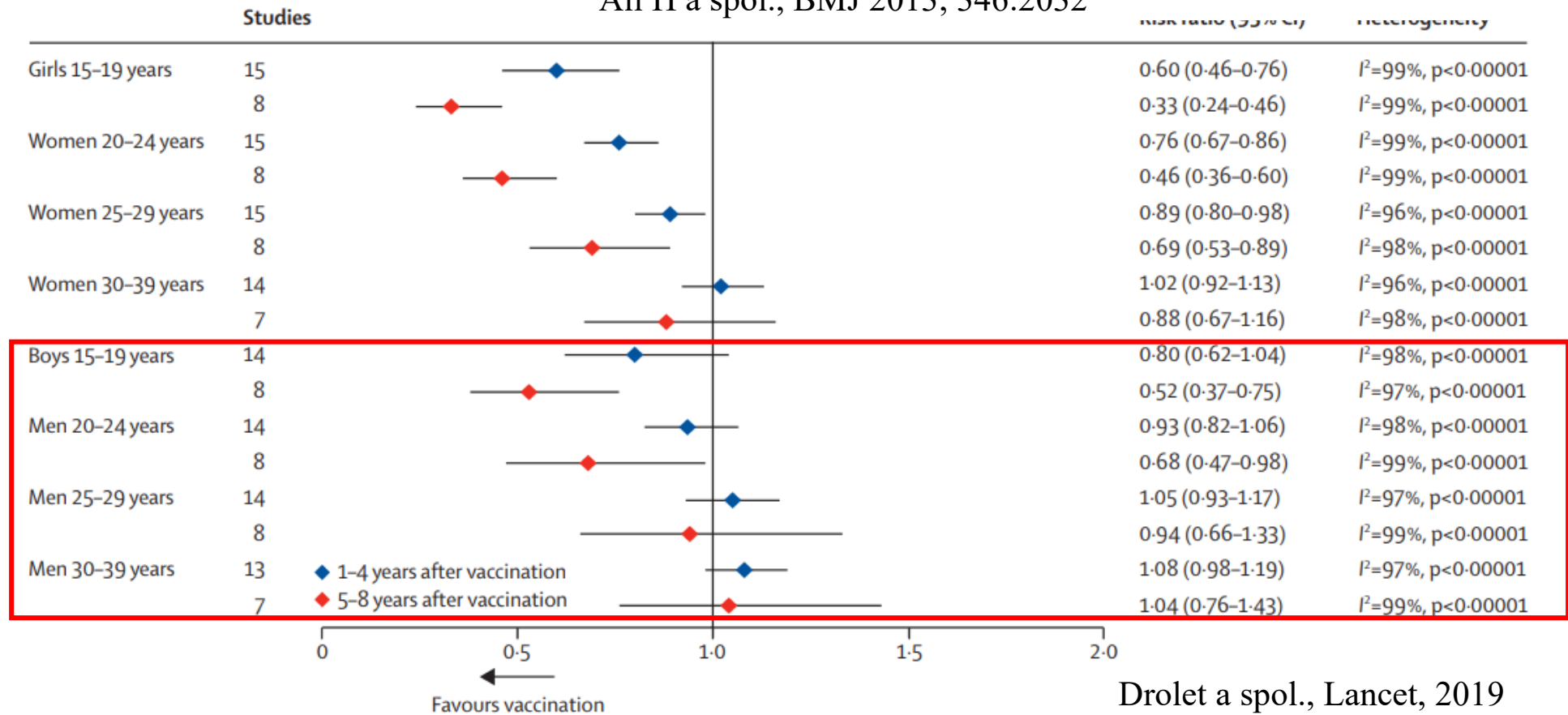
Drolet et al., Lancet, 2019

Effect of routine vaccination -GW

- Lower number of invasive treatment procedures
 - females <21 years of age by 92.6%
 - 21-30 years by 72.6%
 - **MSW <21 years by 81.8%**
 - 21-30 years by 51.5%



Ali H a spol., BMJ 2013; 346:2032

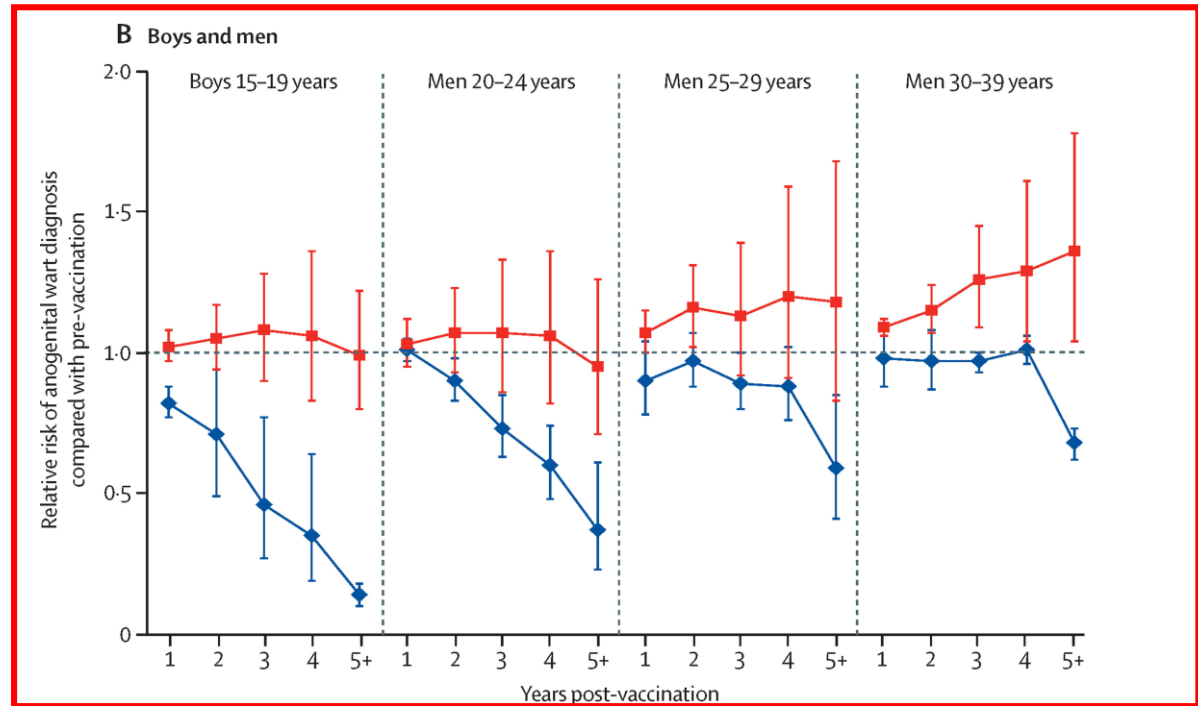
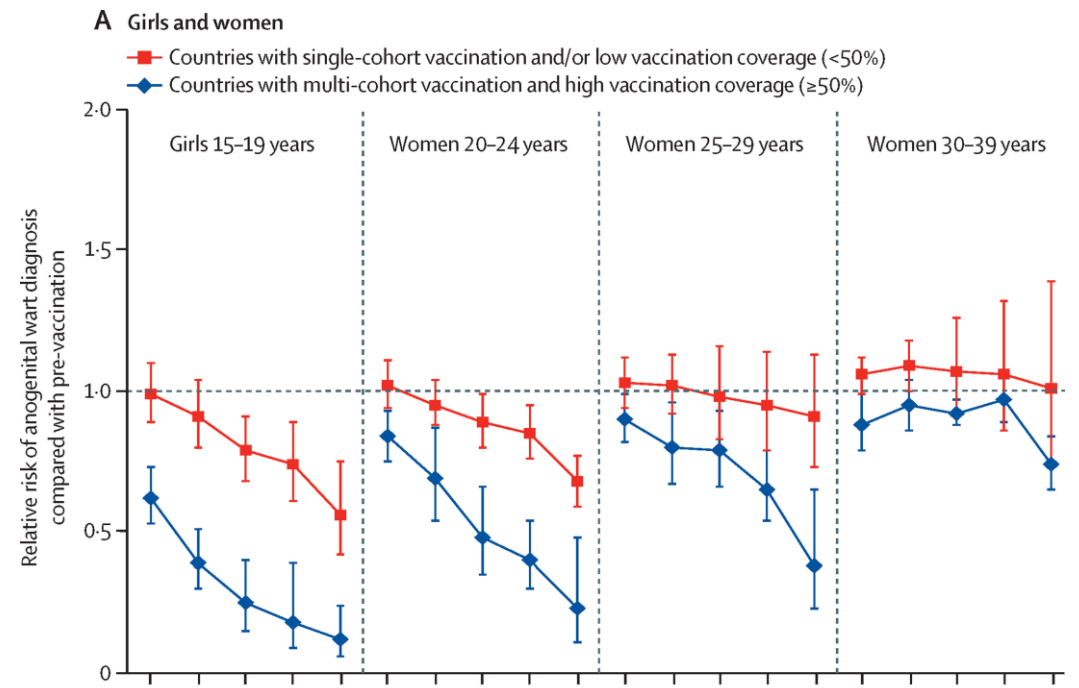


Drolet a spol., Lancet, 2019

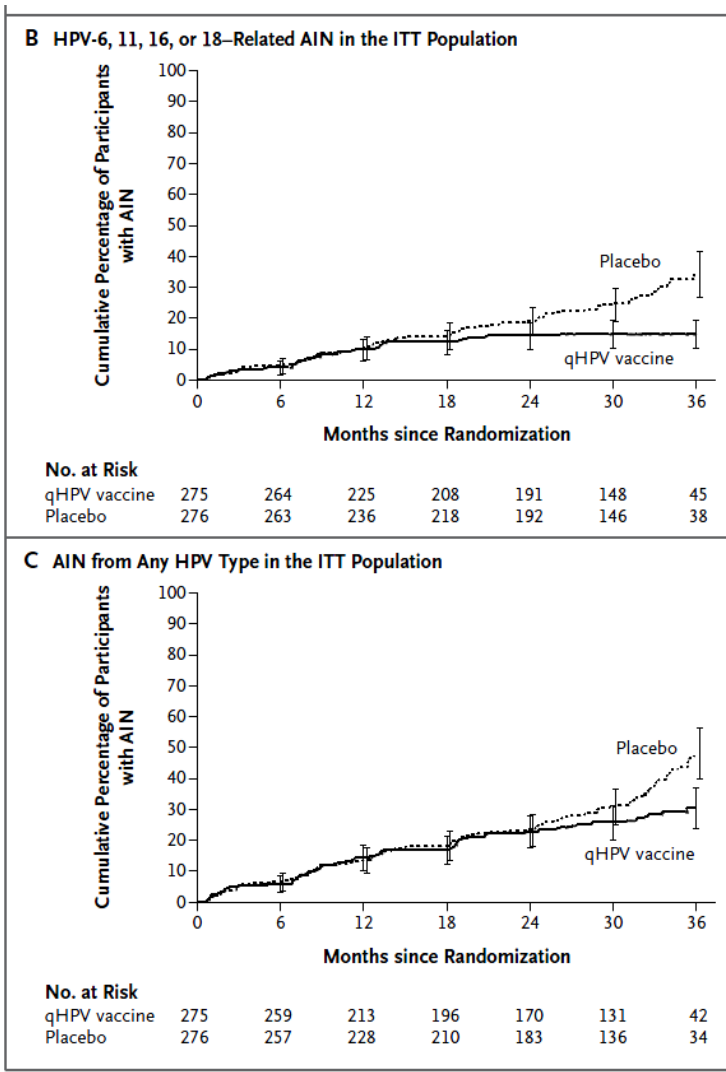
The effect of the routine vaccination: genital warts, herd immunity

- In populations with $>50\%$ coverage of girls – **herd effect**
- The efficiency of vaccination in females on GW prevalence depends on the age group ~ **coverage**

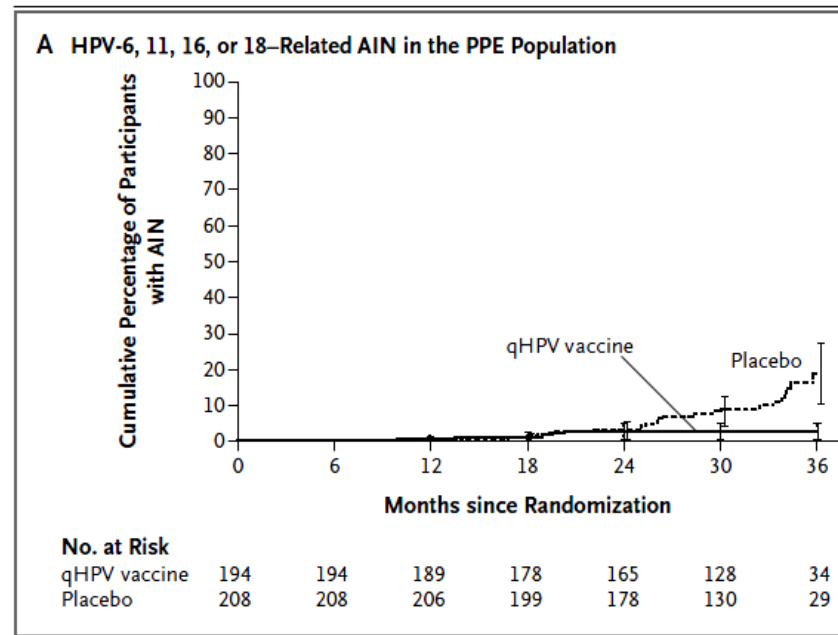
- states with coverage $<50\%$, single cohort, females only
- ◆ states with coverage $>50\%$, multicohort, females only



The effect of HPV vaccination against AIN in MSM



- Effectivity of HPV vaccination against AIN in ITT males
 - Associated with HPV vaccine types 50%
 - Associated with any HPV type 26%
- Effectivity of HPV vaccination against AIN in PPT males
 - Associated with HPV vaccine types 78%
 - Associated with any HPV type 55%

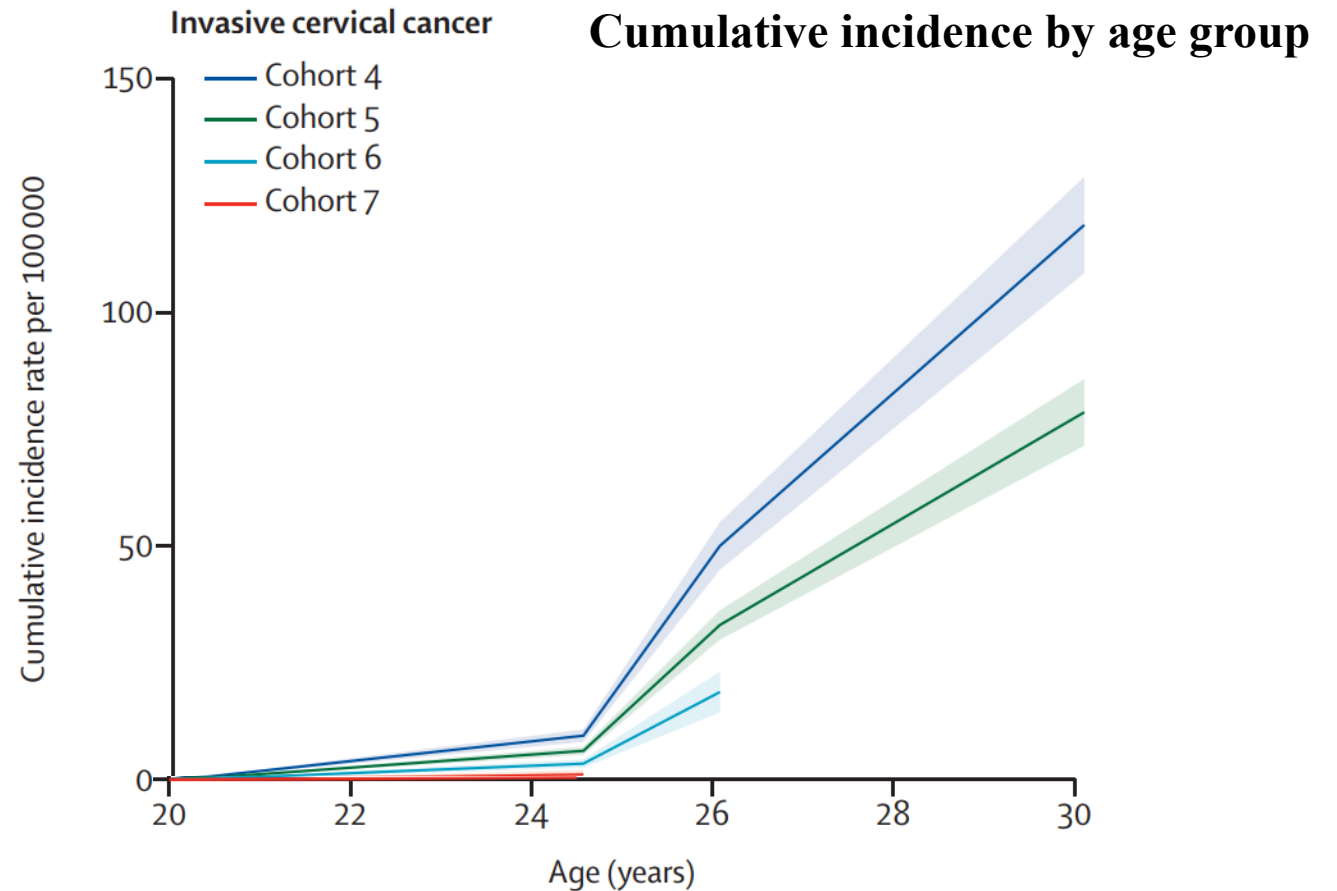


AIN1 91-93%; AIN2/3 90; anal cancer 92% efficacy of vaccines

Palevsky a spol., NEJM, 2011
Rosado et al., Vaccines, 2023

The effect of routine vaccination: cervical cancer

- UK, routine vaccination in 2008, girls 12-13 years and 14-18 years of age; till 2010 bivalent, from 2012 tetravalent vaccine
- **Women born from 1995** (26 years in 2021) on **ELIMINATION of CC**



Falcaro et al., 2021

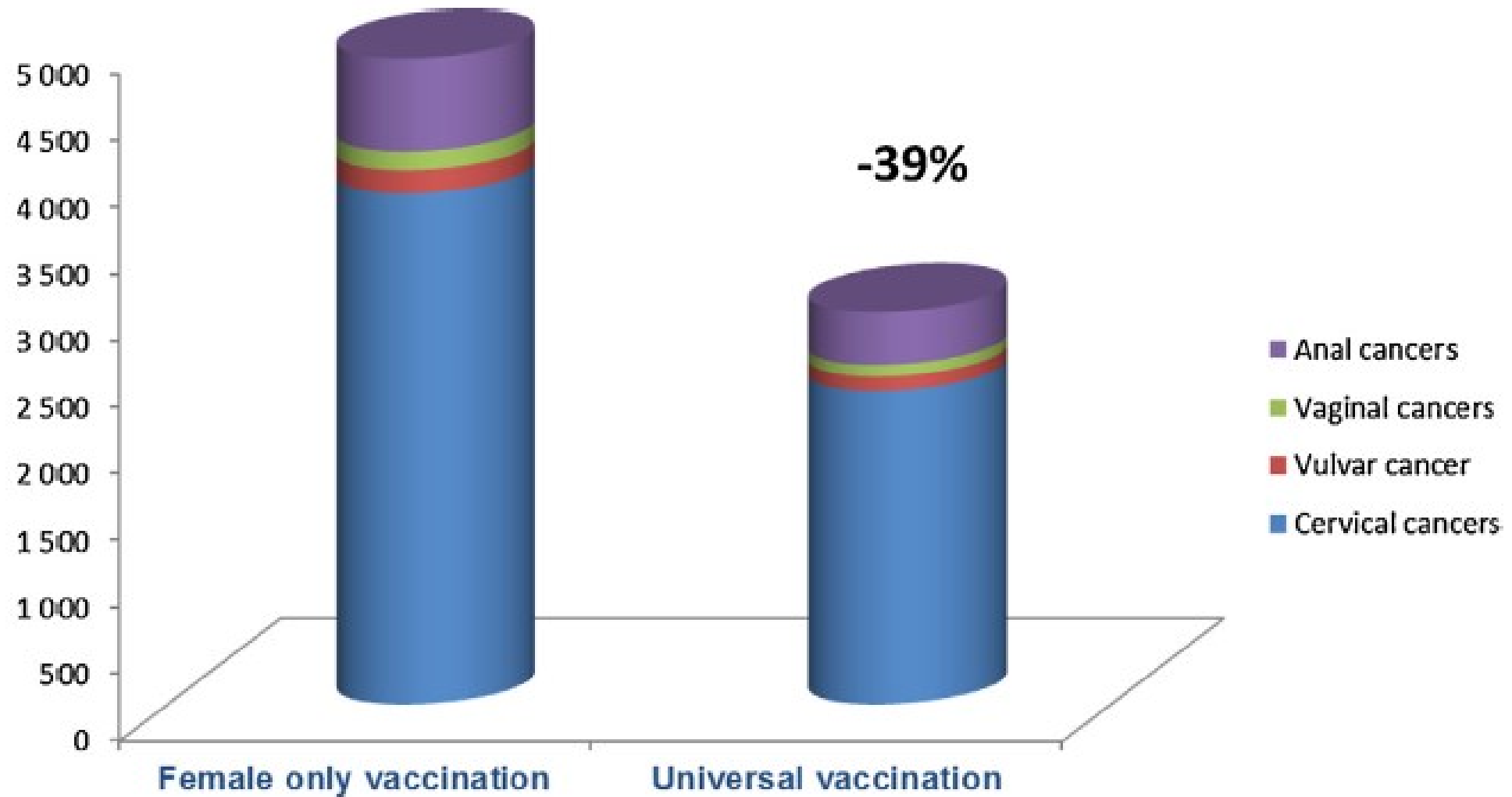
Group	Age of vaccination	Coverage	Reduction incidence
C4	non-vaccinated	0	0
C5	16-18 yrs	44.8%	34%
C6	14-16 yrs	73.2%	62%
C7	12-13 yrs	84.9%	87%

The effect of the routine vaccination: HPV-associated and non-associated carcinomas

- Finland
- The decrease in the incidence of HPV-associated cancers
- The effect for all HPV-associated cancers was statistically significant

Malignancy	HPV vaccinated women			Non-HPV vaccinated women		
	Person years	<i>n</i>	Rate (95% CI)	Person years	<i>n</i>	Rate (95% CI)
Cervix cancer	65,656	0	–	124,245	8	6.4 (3.2, 13)
Vulva cancer	65,656	0	–	124,245	1	0.8 (0.1, 5.7)
Oropharyngeal cancer	65,656	0	–	124,245	1	0.8 (0.1, 5.7)
Other HPV cancers ¹	65,656	0	–	124,245	0	–
All HPV associated invasive cancers	65,656	0	–	124,245	10	8.0 (4.3, 15)
Breast cancer	65,656	2	3.0 (0.8, 12)	124,245	10	8.0 (4.3, 15)
Thyroid cancer	65,656	1	1.5 (0.2, 11)	124,245	9	7.2 (3.8, 14)
Melanoma	65,656	3	4.6 (1.5, 14)	124,245	13	10.5 (6.1, 18)
Non-melanoma skin cancer	65,656	2	3.0 (0.8, 12)	124,245	3	2.4 (0.8, 7.5)

Reduction of HPV-associated disease by vaccination

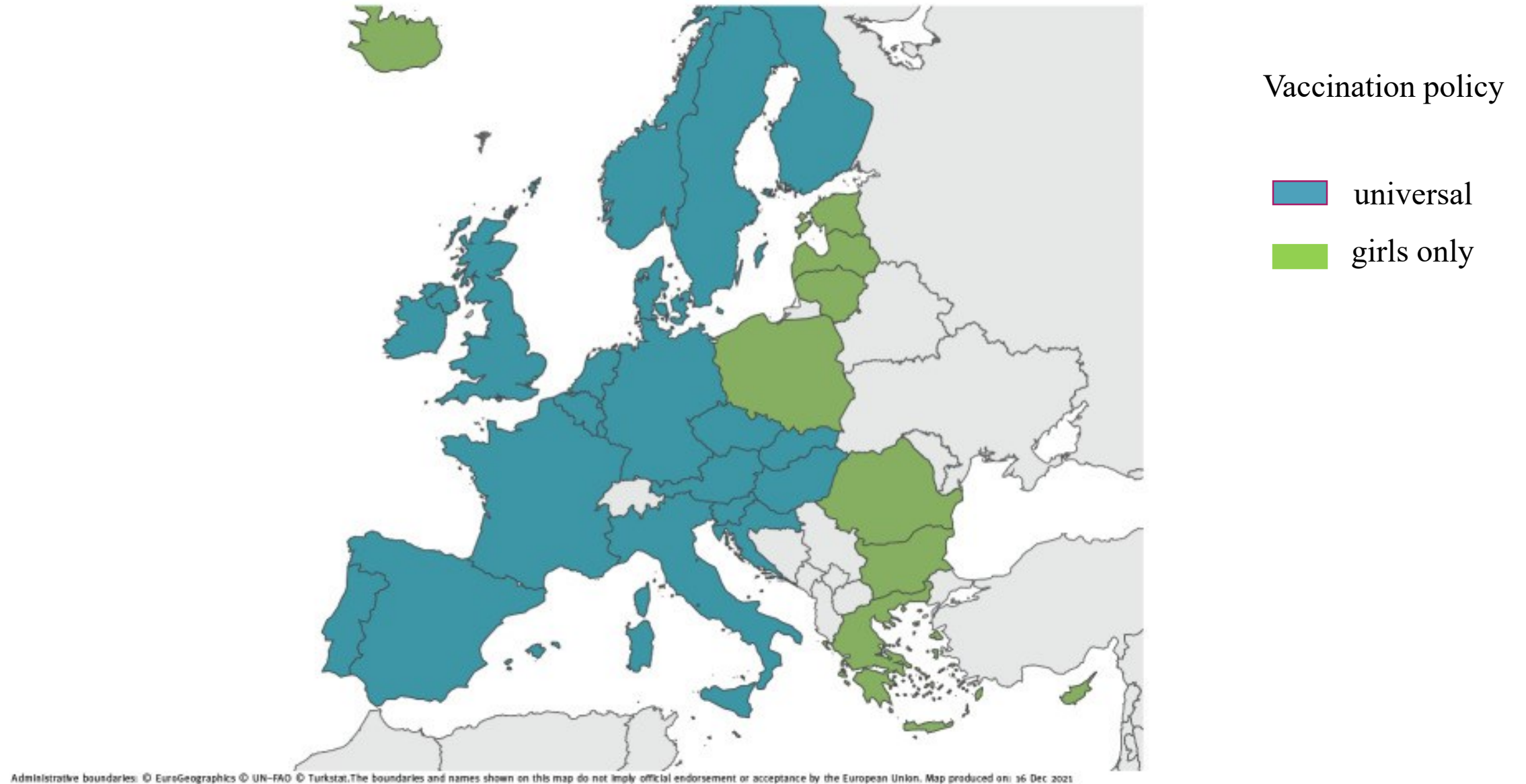


Eradication of HPV

Table 3. Model-Based Reproduction Numbers, Immunity Thresholds for Eradication of Vaccine-Covered Oncogenic Human Papillomaviruses (HPVs), and Corresponding Critical Coverage of Vaccination by Vaccine Efficacy for Gender-Neutral (Girls and Boys) and Girls-Only (Girls) Vaccination Strategies

HPV Type	Reproduction Number ^a		Immunity Threshold		Critical Coverage of Vaccination					
	Girls and Boys	Girls	Girls and Boys	Girls	VE 95%		VE 80%		VE 50%	
					Girls and Boys	Girls	Girls and Boys	Girls	Girls and Boys	Girls
HPV16	3.3	10	70%	90%	74%	95%	88%	NE ^b	NE ^b	NE ^b
HPV18	2.2	4.5	55%	78%	58%	82%	69%	98%	NE ^b	NE ^b
HPV31/33	1.7	2.9	40%	65%	42%	68%	50%	81%	80%	NE ^b
HPV45	1.7	2.9	40%	65%	42%	68%	50%	81%	80%	NE ^b
HPV35	1.3	1.5	20%	35%	21%	37%	25%	44%	40%	70%

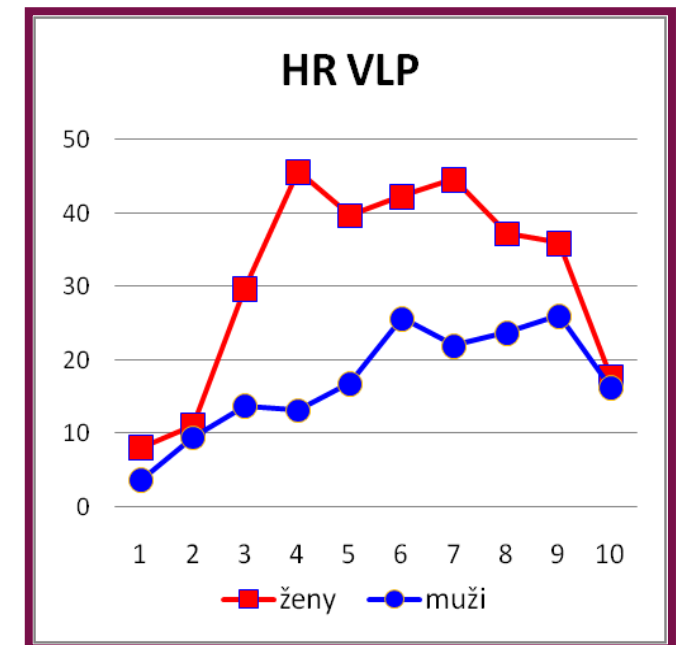
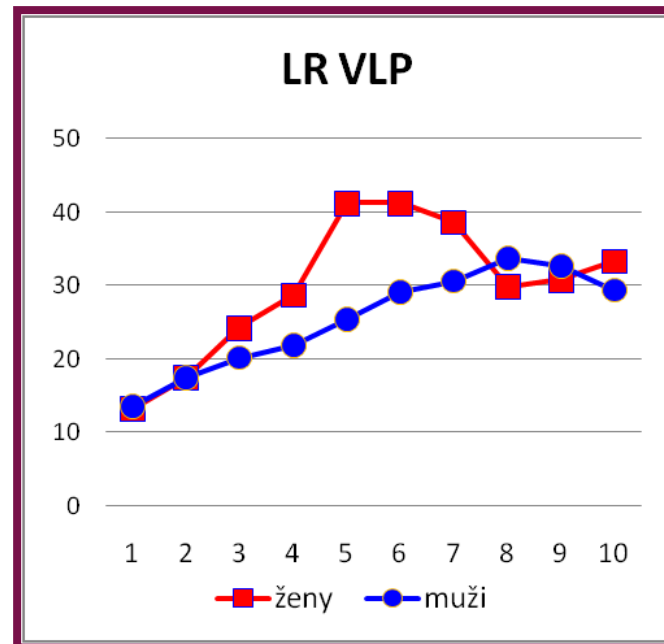
Vaccination in Europe: gender and reimbursement



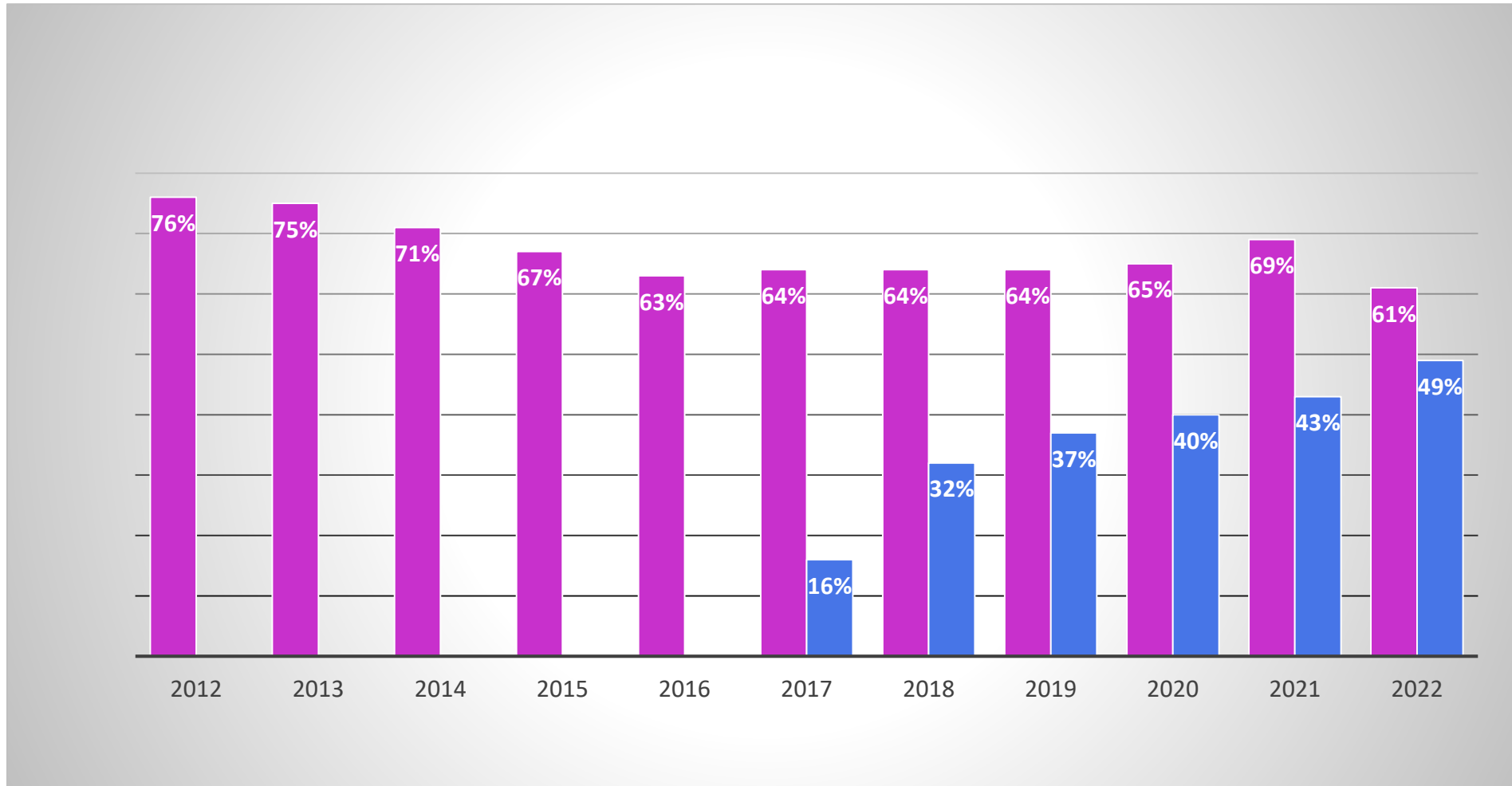
Prevalence of HPV-specific antibodies in the Czechia

- Serum of the healthy individuals (N=3 150)
- Age category **6-10 years LR HPV** antibodies prevalence 10 %
- Age category **11 -14 years HR HPV** antibodies prevalence 10 %
- Age category **15 -20 years HR HPV** antibodies prevalence 30 %
- Age category **6-9 years LR HPV6 11.3%; LR HPV11 10.6%**

Age group (years))		# female	# male
1	6-10	99	111
2	11-14	126	138
3	15-20	289	233
4	21-25	289	183
5	26-30	136	346
6	31-35	97	250
7	36-40	101	137
8	41-50	188	299
5	51-60	195	392
10	>60	51	68



Coverage of 13 years old girls and boys in Czechia



data ÚZIS ČR,

Summary

- The prevalence of HPVs in males is very high and age-independent
- The incidence of HPVs decreases with age but sustains high to higher age
- The clearance of HPVs is not influenced by age
- The incidences of HPV-associated cancers of males are increasing
- The HPV vaccines are registered from 9 years of age also for males
- Gender-neutral vaccination is important to cover all groups e.g. MSM
- Gender-neutral vaccination is necessary to lower the incidence of HPV-associated carcinomas in males
- Elimination/eradication of certain HPV types will not be possible without gender-neutral vaccination

**Thank you for
your attention
!!!!!!!!!!!!!!!!!!!!**



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