

BIOCEV



# Why not delay the HPV vaccination of children

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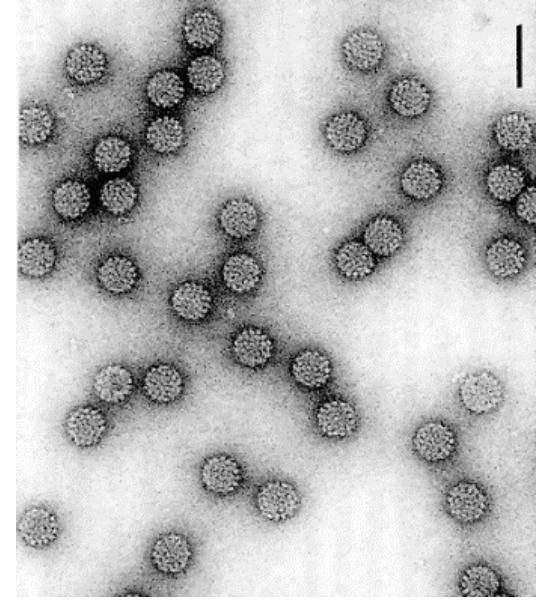
Faculty of Science, Department of Genetics and Microbiology, Charles University, Prague



RĪGA STRADIŅŠ  
UNIVERSITY

# 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



	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	
		101,18,42	Gut 17%
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	

# Clinical symptoms - skin

- **BENIGN**
- verruca plana
- verruca vulgaris
- verruca plantaris
- generalized verrucose

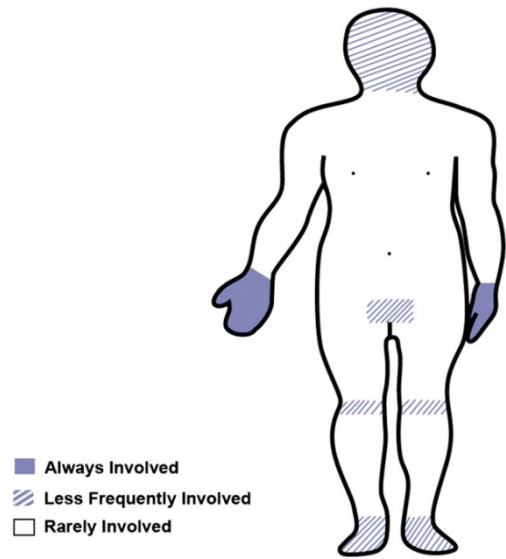


- **MALIGNANT**
- epidermodysplasia verruciformis
- (mutations in genes e.g. EVER1/EVER2 (17q25))
- nonmelanoma skin cancer





# Generalized verrucose



cyclic neutropenia,  
IgA deficiency, and  
autoimmune hemolytic  
anemia

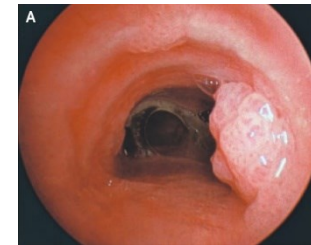
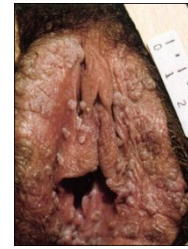
EV  
(epidermodysplasia verruciformis)

WHIM syndrome  
(warts, hypogammaglobulinemia,  
infection, myelokathesis)

# Clinical symptoms - mucosal

- **BENIGN**

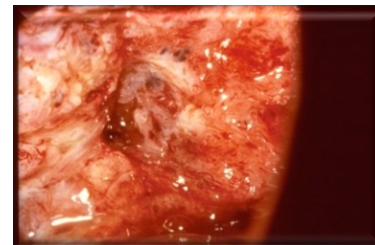
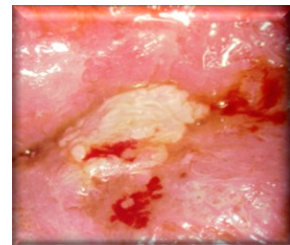
- condyloma acuminata (anogenital warts)
- recurrent respiratory papillomatosis
- HPV 6, 11, 42, 74, ...
- focal epithelial hyperplasia
- HPV 13, 32



HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68

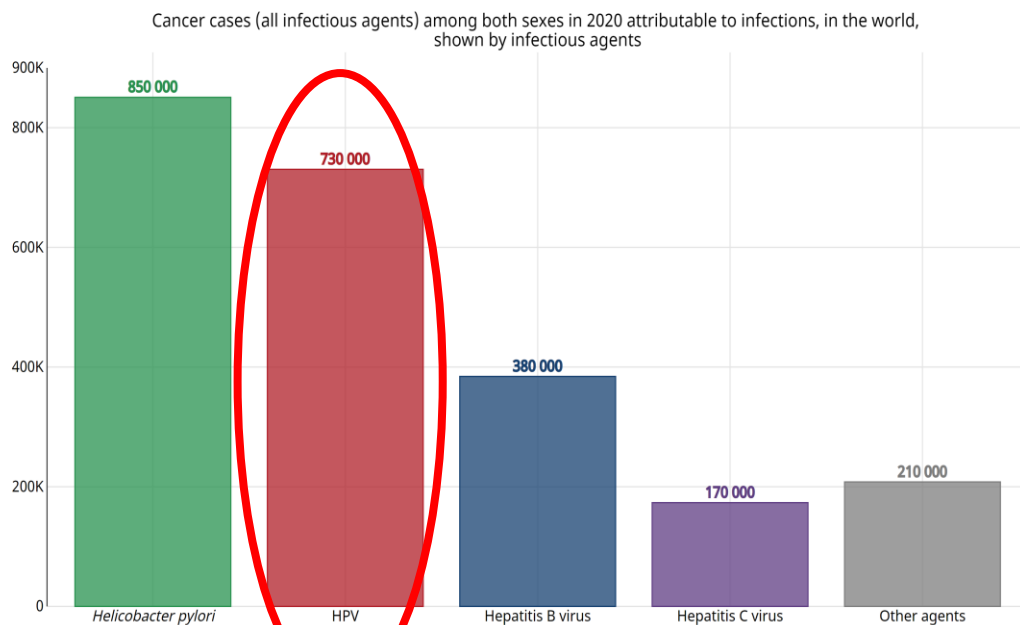
- **MALIGNANT**

- intraepithelial lesions
- invasive carcinomas



# Malignant diseases associated with HPV

- HPV 30 % of 2.2 milions
- HPV one of 5 human carcinogens associated with tumours in more than 5 anatomical locations



Data source: Methodology described in "Global burden of cancer attributable to infections in 2018: a worldwide incidence analysis; de Martel C, Georges D, Bray F, Ferlay J, Clifford GM; Lancet Glob Health, 2020" applied to 2020 cancer incidence estimates.  
 Graph production: Global Cancer Observatory (<http://gco.iarc.fr/>)  
 © International Agency for Research on Cancer 2023



	Number of new cases	Number of new cases attributable to infectious agents	Attributable fraction
<b>Carcinoma</b>			
Non-cardia gastric	820 000	730 000	89.0%
Cardia gastric	130 000	23 000	17.8%
Liver	780 000	570 000	73.4%
Cervix uteri	530 000	530 000	100.0%
Vulva	34 000	8 500	24.9%
Anus	40 000	35 000	88.0%
Penis	26 000	13 000	51.0%
Vagina	15 000	12 000	78.0%
Oropharynx	96 000	29 000	30.8%
Oral cavity	200 000	8 700	4.3%
Larynx	160 000	7 200	4.6%
Nasopharynx	87 000	83 000	95.5%
Bladder	430 000	7 000	1.6%

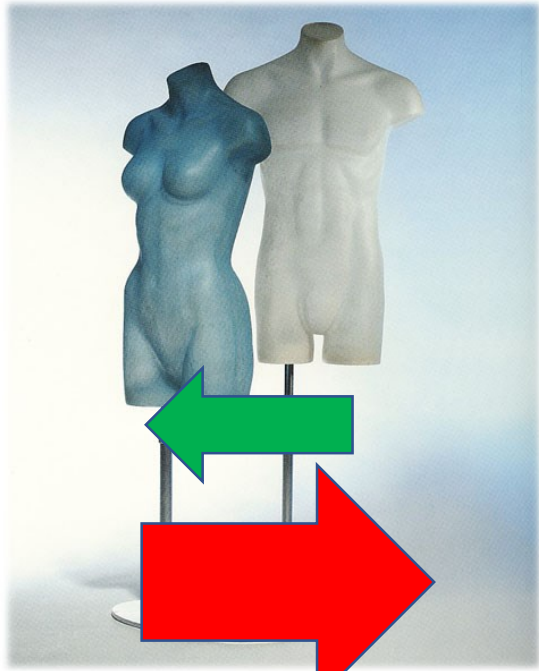
Plummer et al., Lancet Glob. Health, 2016; de Martel et al., Lancet Glob. Health, 2020  
[canceratlas.cancer.org](http://canceratlas.cancer.org)



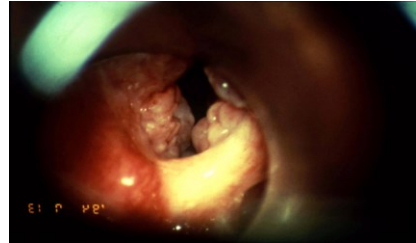
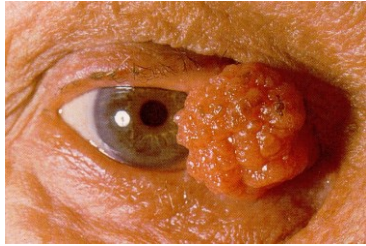
# Transmission

Sexual hetero  
and homosexual

Autoinoculation  
and  
heteroinoculation

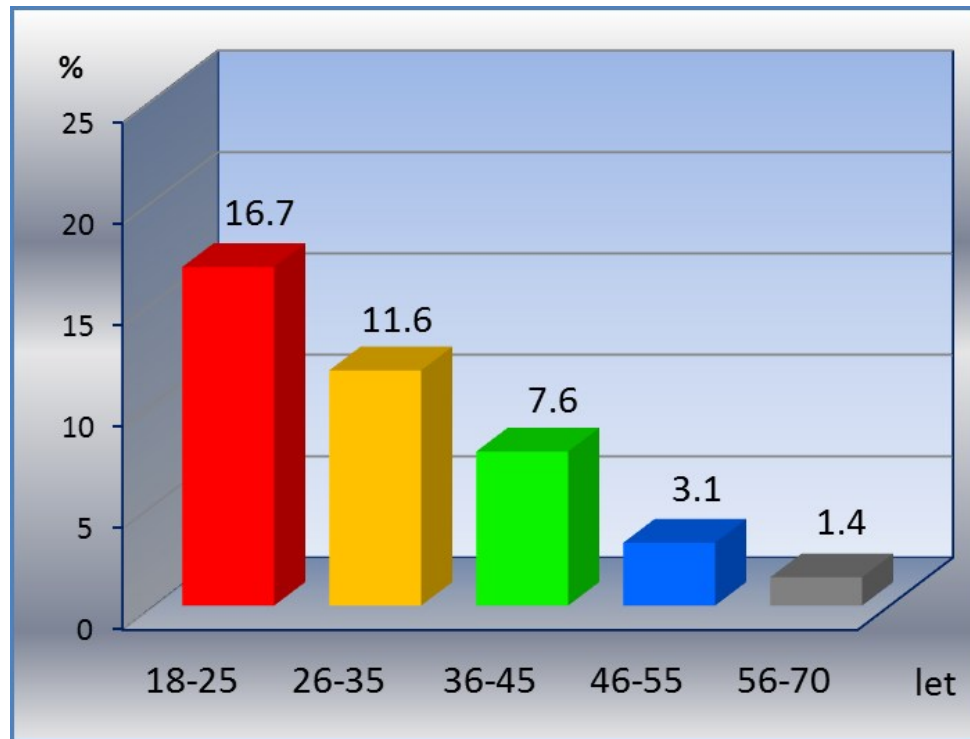


From mother to child  
during the delivery,  
transplacental



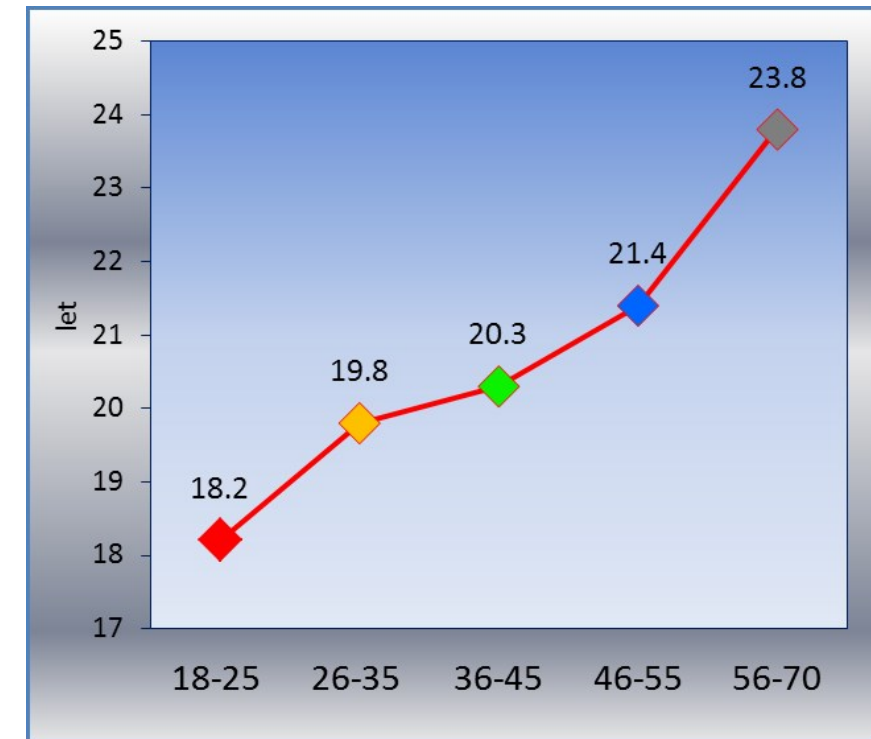
# Changes in sexual behaviour of the population

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



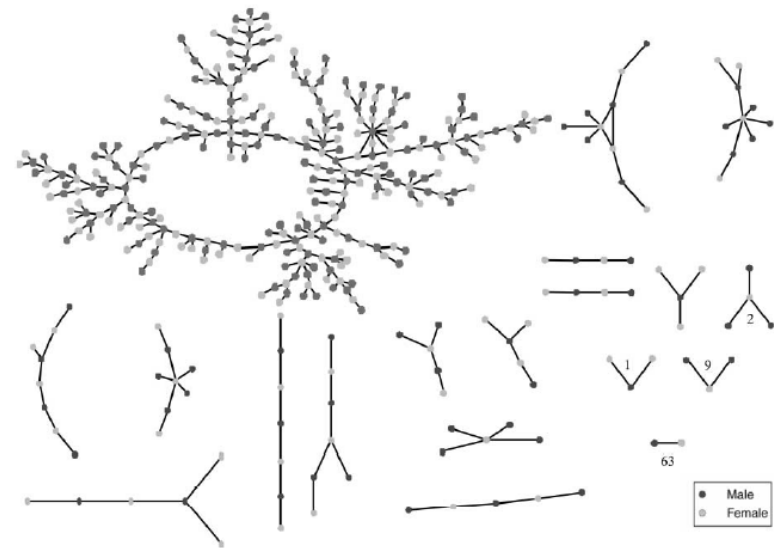
5.6x more

Minichiello et al., 2011  
Lyons et al., 2011

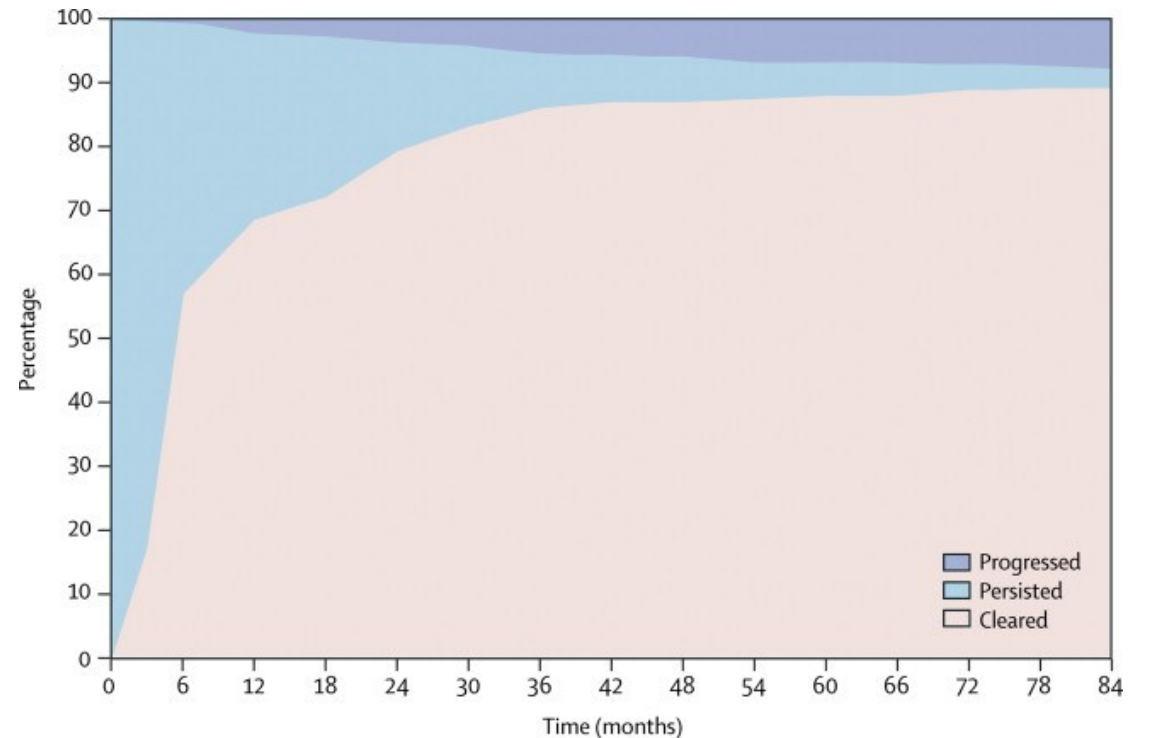


# Epidemiology

- at the age of 45 years – 80% infected at least once
- asymptomatic infections
- maximum prevalence - females at the age of 25 years
- in males the prevalence is high regardless of age
- most infections clear within 2 years

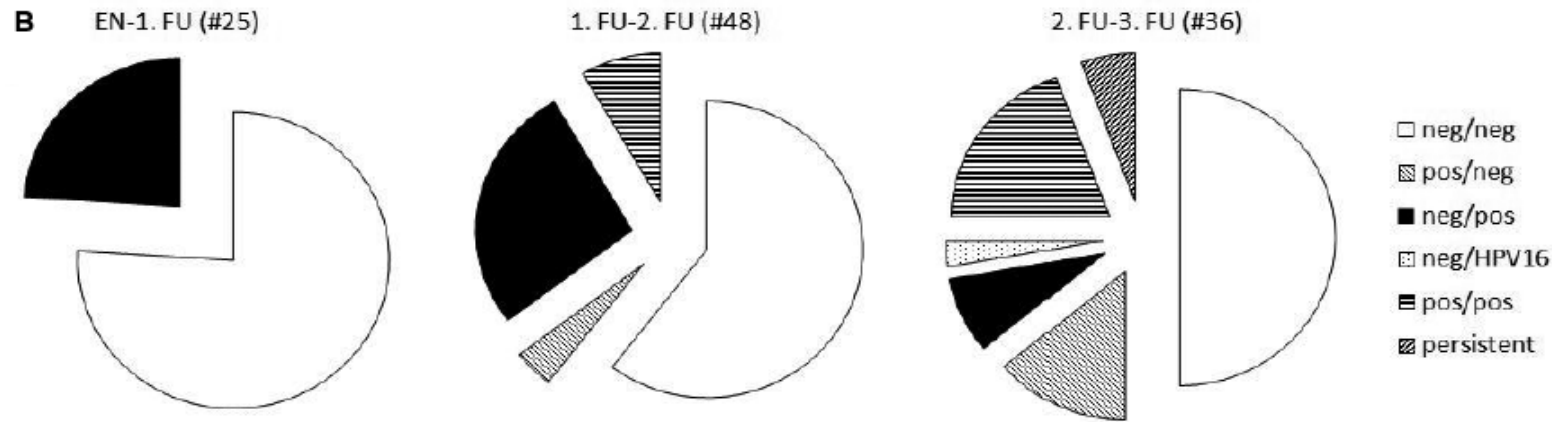


Bearman et al., AJS,110,44-91, 2004



Schiffman et al., 2007

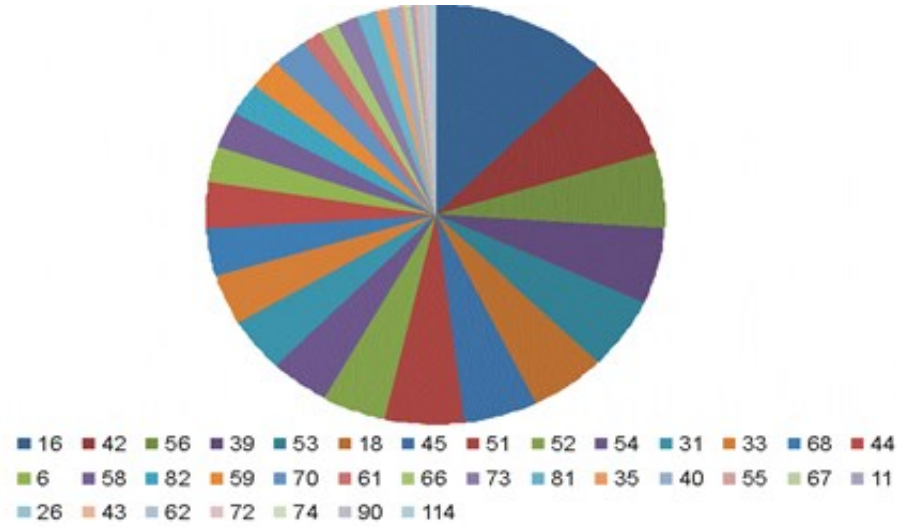
# Fast spread of HPV infection after sexual debut



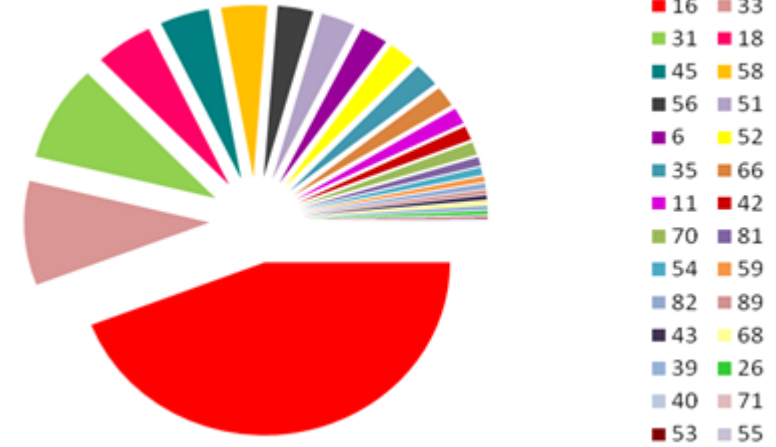
Group (age range [years])	1st Follow-up (mean 9–13 months) <sup>1</sup>			2nd Follow-up (mean 36–39 months) <sup>1</sup>			3rd Follow-up (mean 61–63 months) <sup>1</sup>		
	No	Any HPV DNA+ No (%)	HPV 16/18 DNA+ No (%)	No	Any HPV DNA+ No (%)	HPV 16/18 DNA+ No (%)	No	Any HPV DNA+ No (%)	HPV 16/18 DNA+ No (%)
Non-sexually active girls	24	7 (29.2)	0 (0.0)	48	17 (35.4)	0 (0.0)	32	11 (34.4)	1 (3.1)

# HPV type-specific variability in cervical samples

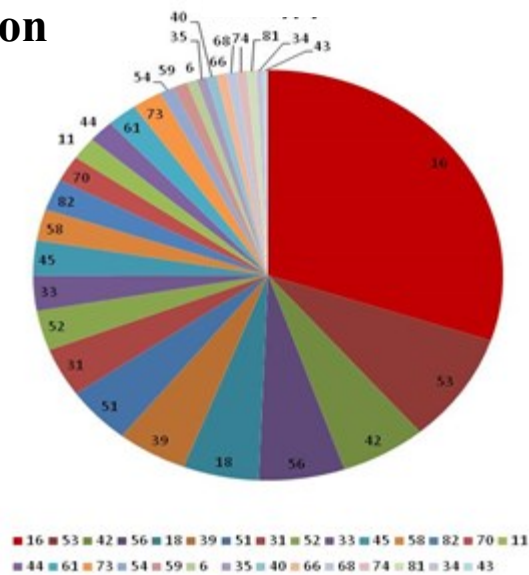
Screening population



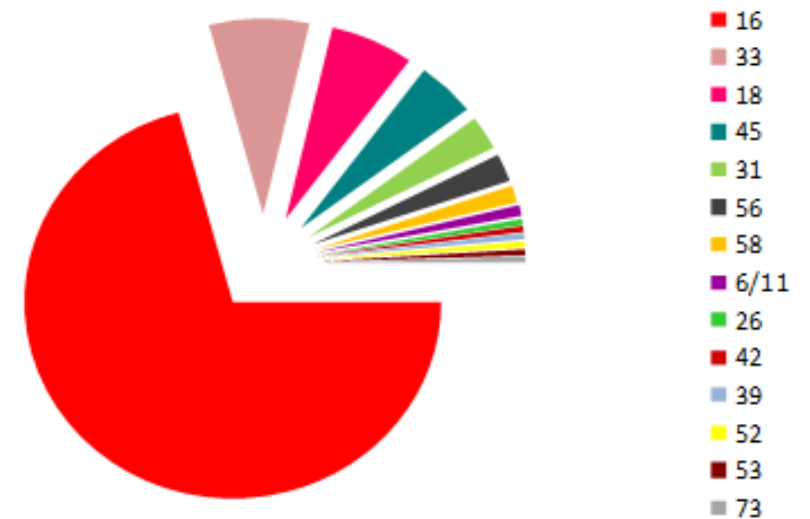
Intraepithelial lesions



Triage population

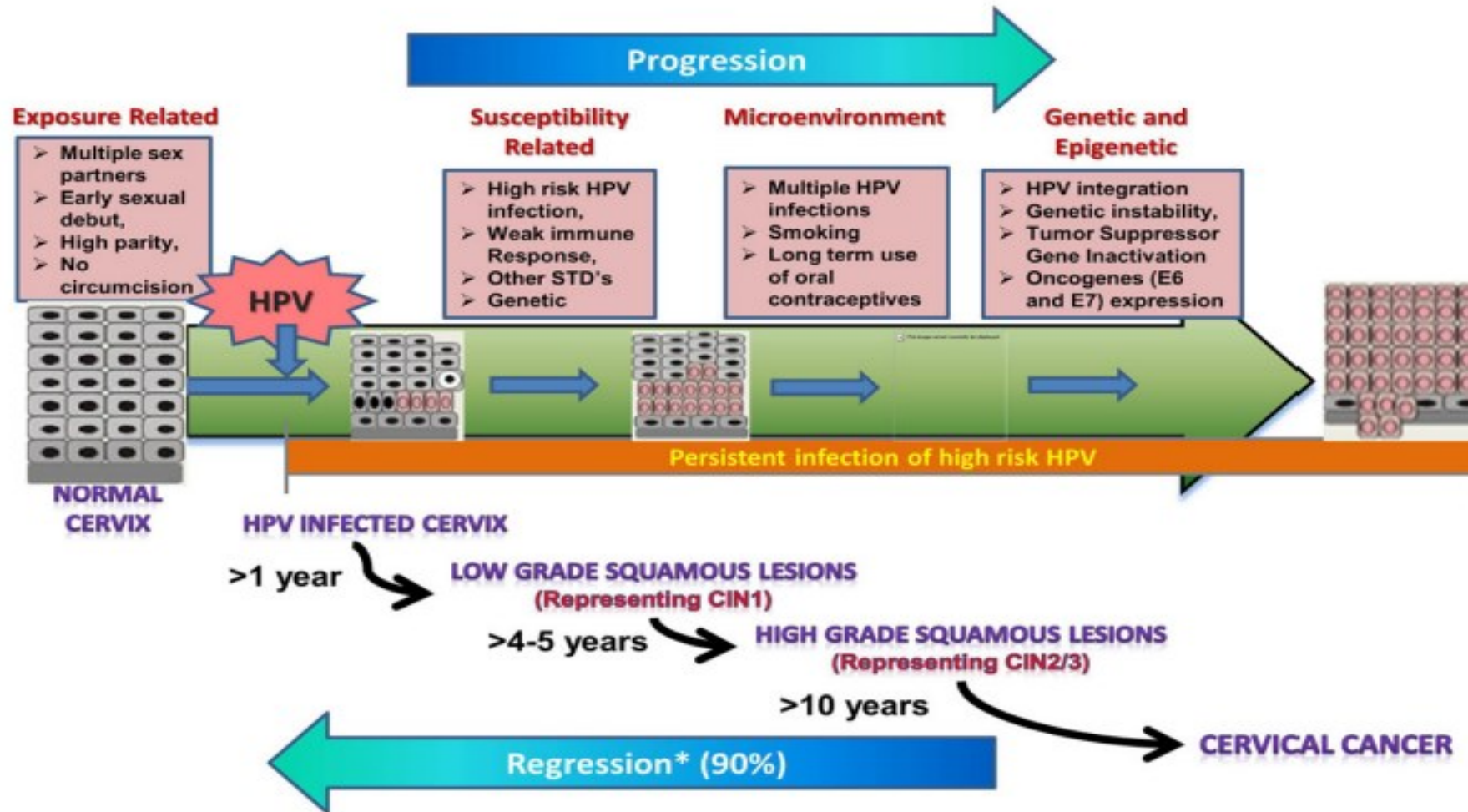


Cancer



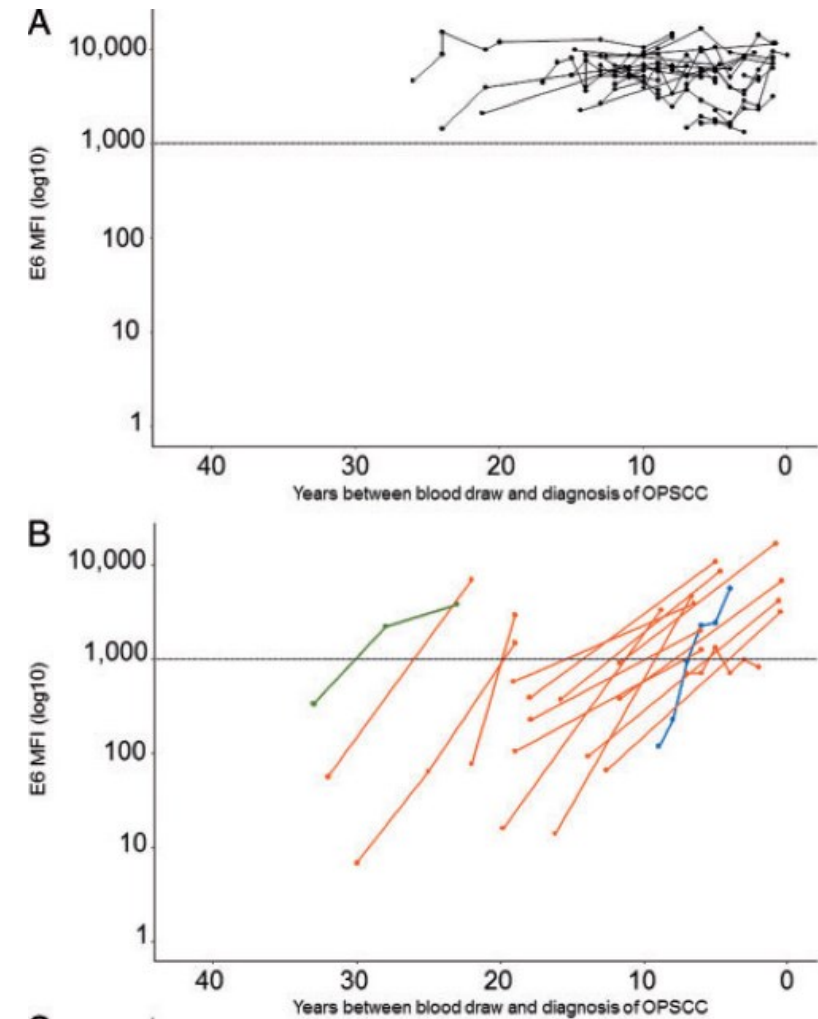


# Natural history of HPV infection at cervix uteri



# HPV infection many years before diagnosis of cancer

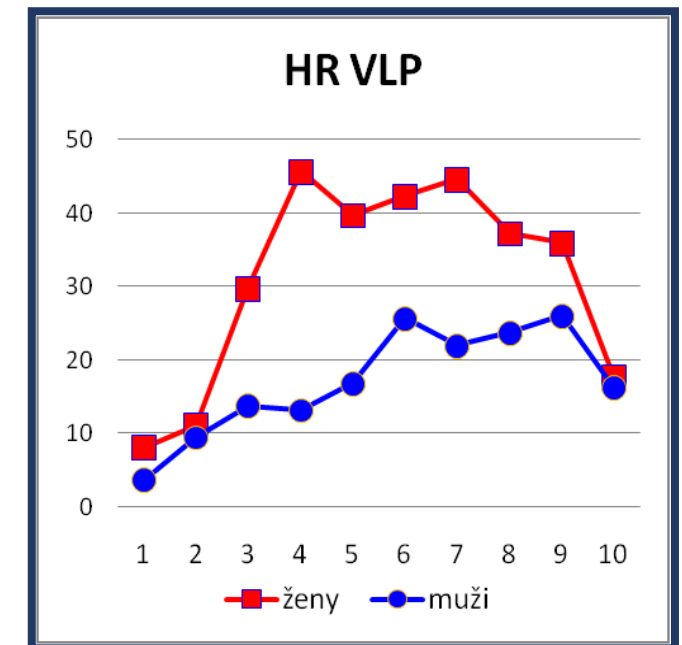
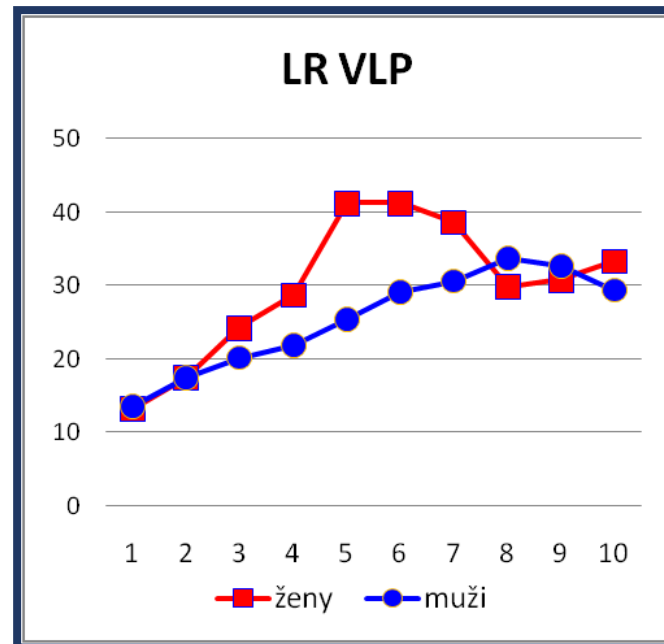
- HPV-specific antibodies to viral antigens (E6/7), oropharyngeal and anal cancer
- Detected up to 28 years before diagnosis
- These antibodies are very rarely detected in the healthy population



# 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%**

věková skupina (let)		# žen	# mužů
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





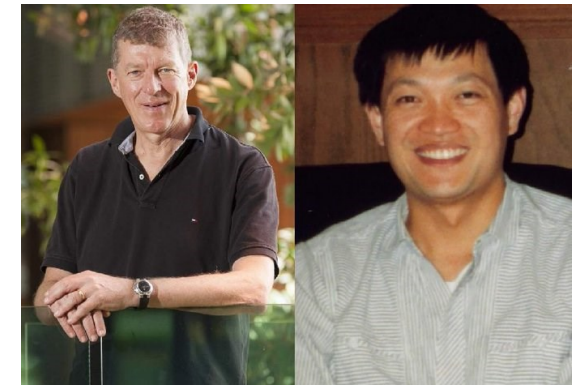
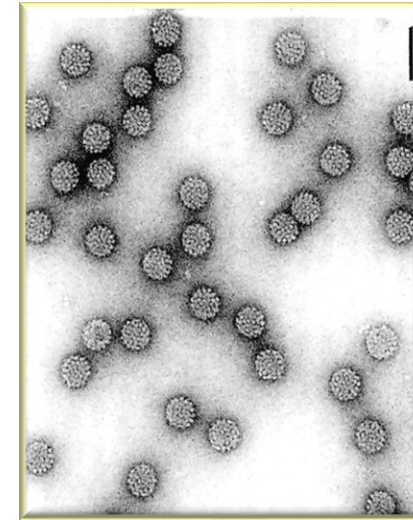
# Summary I.

- HPV's are widespread, the infection occurs mainly through sexual intercourse
- After the sexual debut most people get infected by multiple HPV types and repeatedly
- Most infections can be asymptomatic and/or transient
- However, HPV's cause many diseases, including malignancies, with high morbidity and mortality
- The true risk in terms of disease development and progression is persistent infections
- For some HPV-associated malignancies we don't know the precursors and therefore, the secondary prevention (screening of the healthy population, selection of individuals at higher risk) is not possible

**BUT!!!!!!!!!!!!!!!**

# 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

# Characteristics of HPV vaccines

	Bivalent (2V HPV)	Qvadrivalent (4V HPV)	Nonavalent (9V HPV)
Company	CERVARIX GlaxoSmithKline Biologicals SA	GARDASIL/SILGARD Merck & Co., Inc.	GARDASIL 9 Merck & Co., Inc.
HPV VLP	16, 18	6, 11, 16, 18	6, 11, 16, 18, 31, 33, 45, 52, 58
Antigen	20/20 µg	20/40/40/20 µg	30/40/60/40/20/20/20/20 µg
Rekombinant DNA technology	baculoviruses/Hi-5 Rix4446 Trichoplusia ni	Saccharomyces cerevisiae CANADE 3C-5	Saccharomyces cerevisiae CANADE 3C-5
Adjuvans	AS04 50 µg monophosphoryl lipid A 500 µg aluminium hydroxid	AAHS 225 µg aluminium hydroxyphosphate sulphate	AAHS 500 µg aluminium hydroxyphosphate sulphate
Registration	2007 EMA, 2009 FDA	2006 FDA, EMA	2014 FDA, 2015 EMA
Vaccination scheme	9–14 yrs d1, m5-13  ≥15 yrs d1, m1-2,5, m5-12	9–13 yrs d1, m6  ≥14 yrs d1, m1-2, m3-6	9-14 yrs d1, m5-13  ≥15 yrs d1, m2, m3-6
Indication	9 yrs – – premalignant anogenital lesions (cervical, vulvar, vaginal, anal) and cervical and anal cancers	9 yrs – – premalignant and malignant genital lesions (cervical, vulvar, vaginal, anal) – genital warts	girls 9–26 yrs boys 9–15 ys all 27-45 yrs – premalignant and malignant genital lesions (cervical, vulvar, vaginal, anal) – genital warts -head and neck cancer



# Prophylactic vaccines: characteristics

- **Immunogenic** (almost 100% of vaccinated persons develop antibodies; antibody titers of vaccinated persons 50-100 times higher than after natural infection)
- **Safe** (Global Advisory Committee on Vaccine Safety, WHO, EMA, EudraVigilance, FDA, CDC, post-marketing)
- **Efficient** (protects against infection with vaccine types, protects against HPV-associated diseases caused by vaccine types, partial protection against related HPV types)
- Not **therapeutic**, but may reduce the risk of recurrence
- **Effective** (post-marketing follow-up, routine vaccination)

# Immunogenicity of HPV vaccines and age

- In children:
- high titres of IgG HPV-specific antibodies (better primary response, slower decay of circulating antibodies)
- the number of memory HPV-specific B cells comparable
- higher numbers of immune cell precursors (naive B and CD4+ T lymphocytes)
- in the adolescent age occurrence of changes in the response of the immune system

# 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+

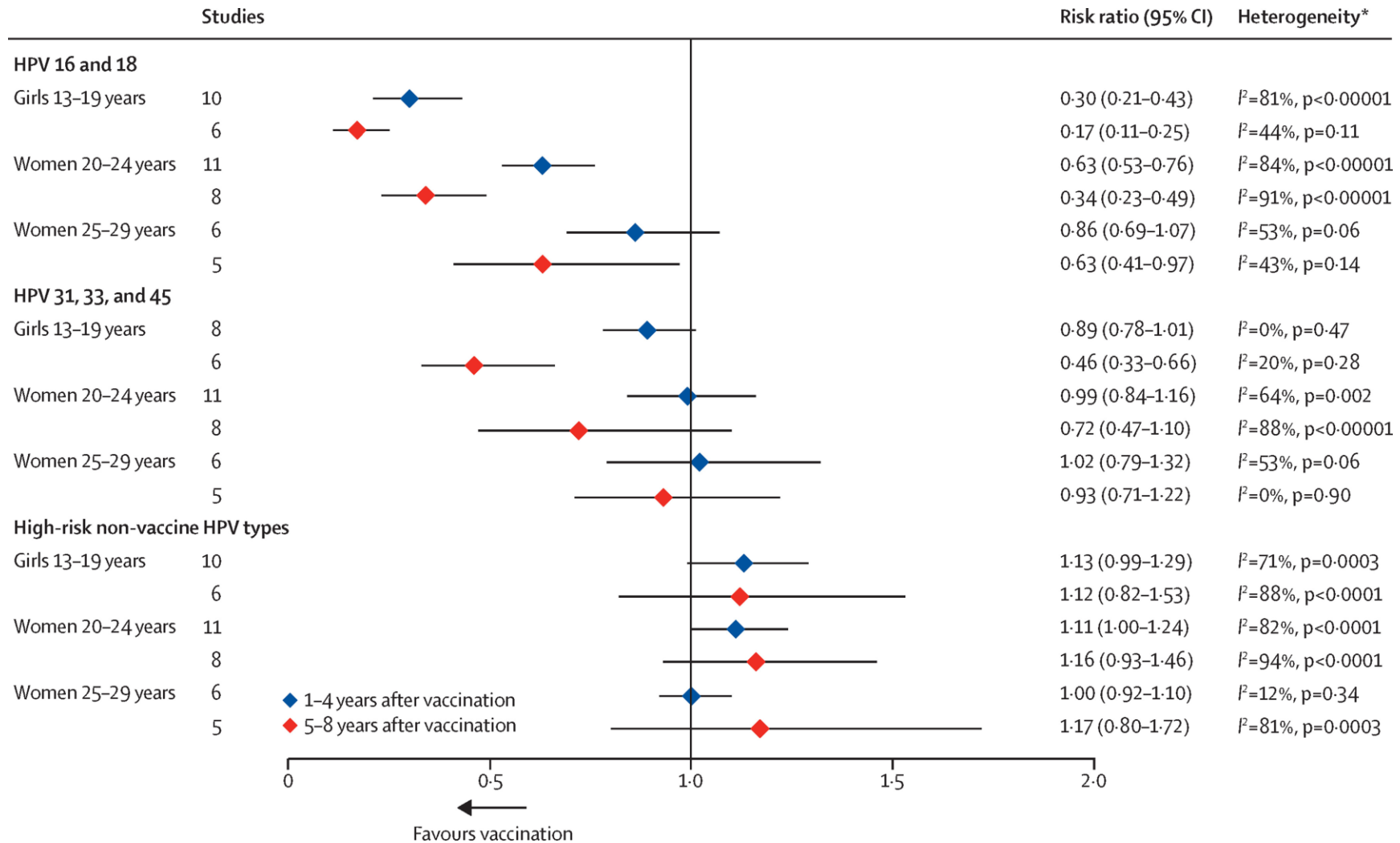
FU after vaccination

1-4 years 

5-8 years 

Drolet et al., Lancet, 2019

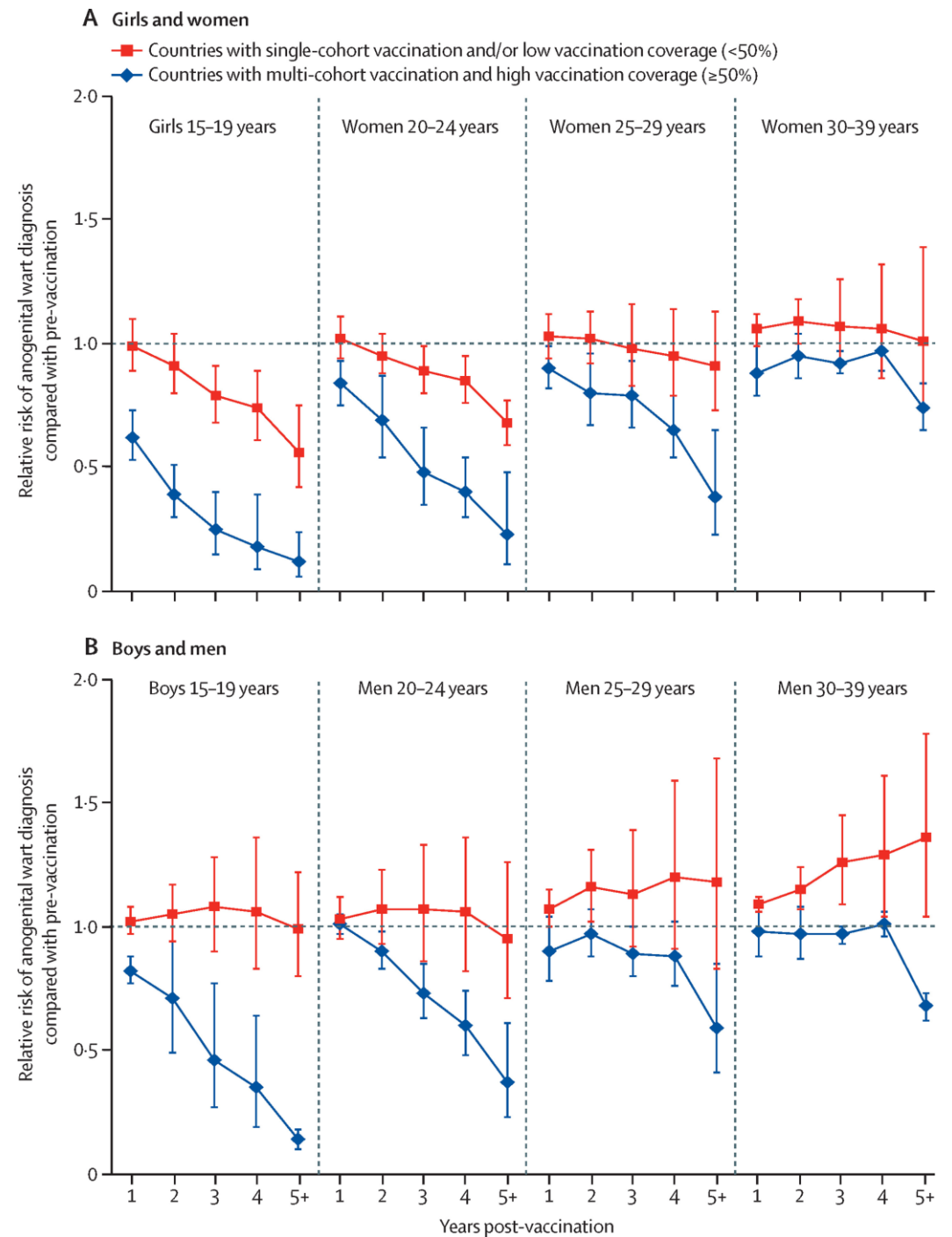
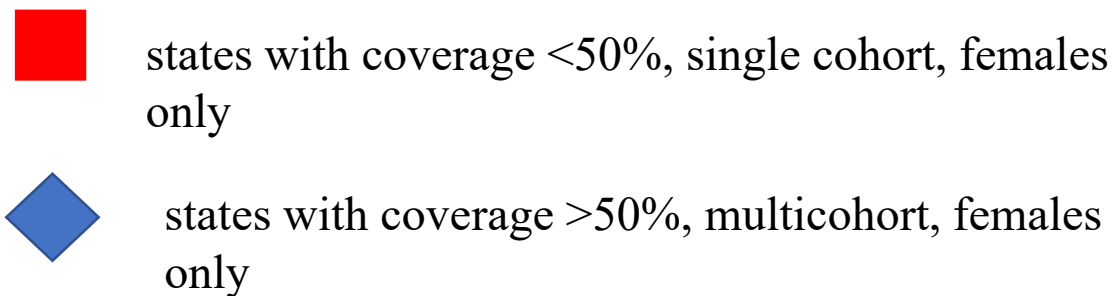
# Effect of routine vaccination on the prevalence of HPV types



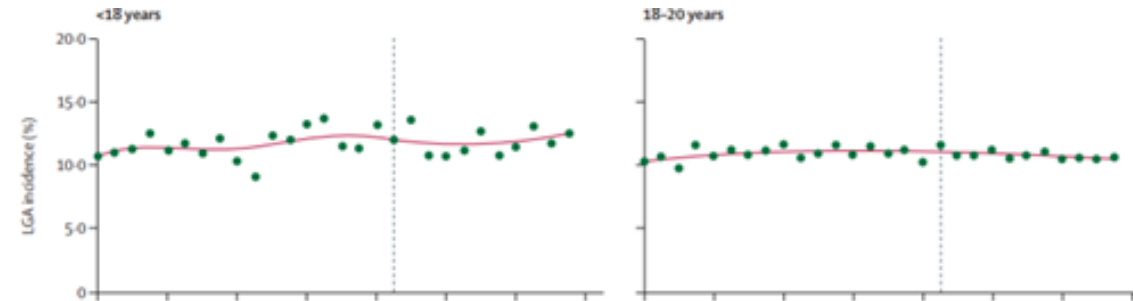
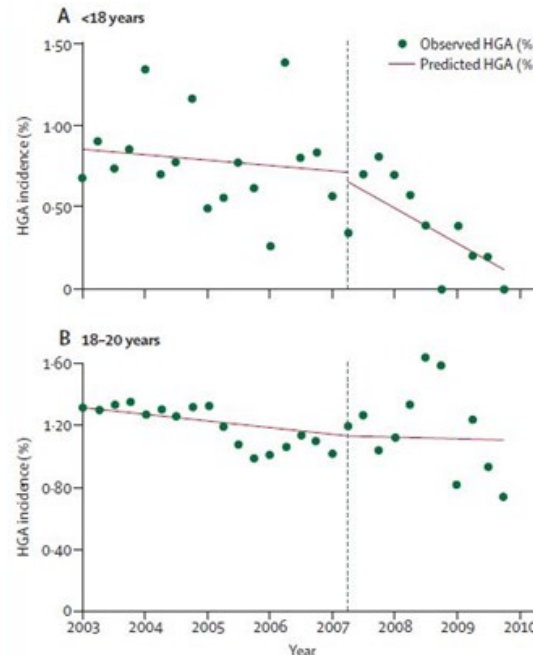
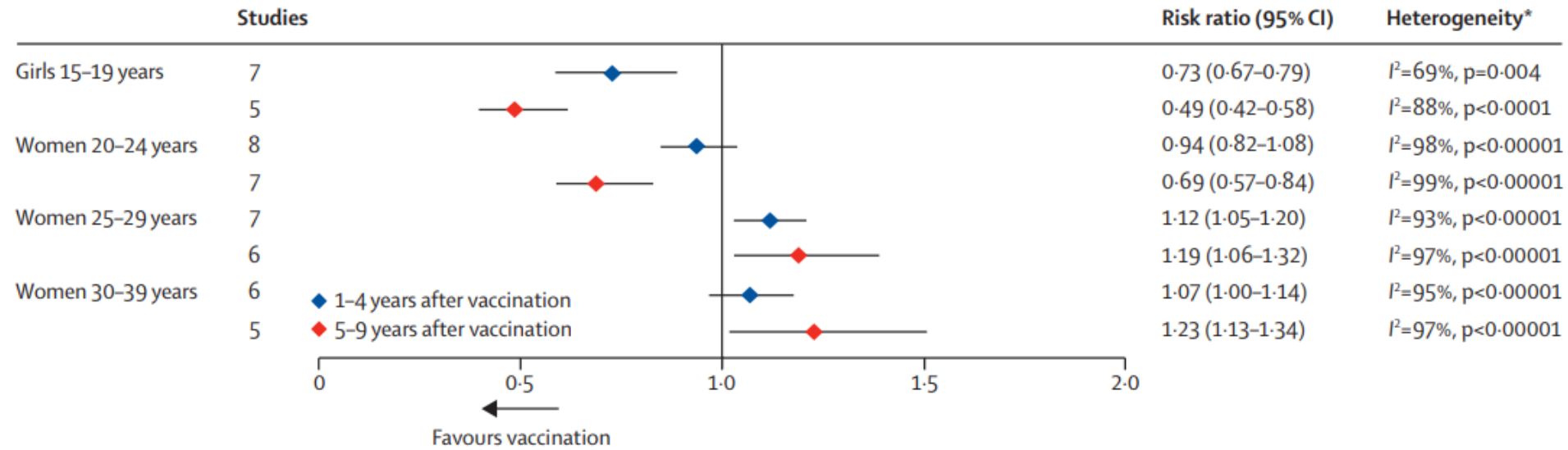


# The effect of the routine vaccination: genital warts, herd immunity

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



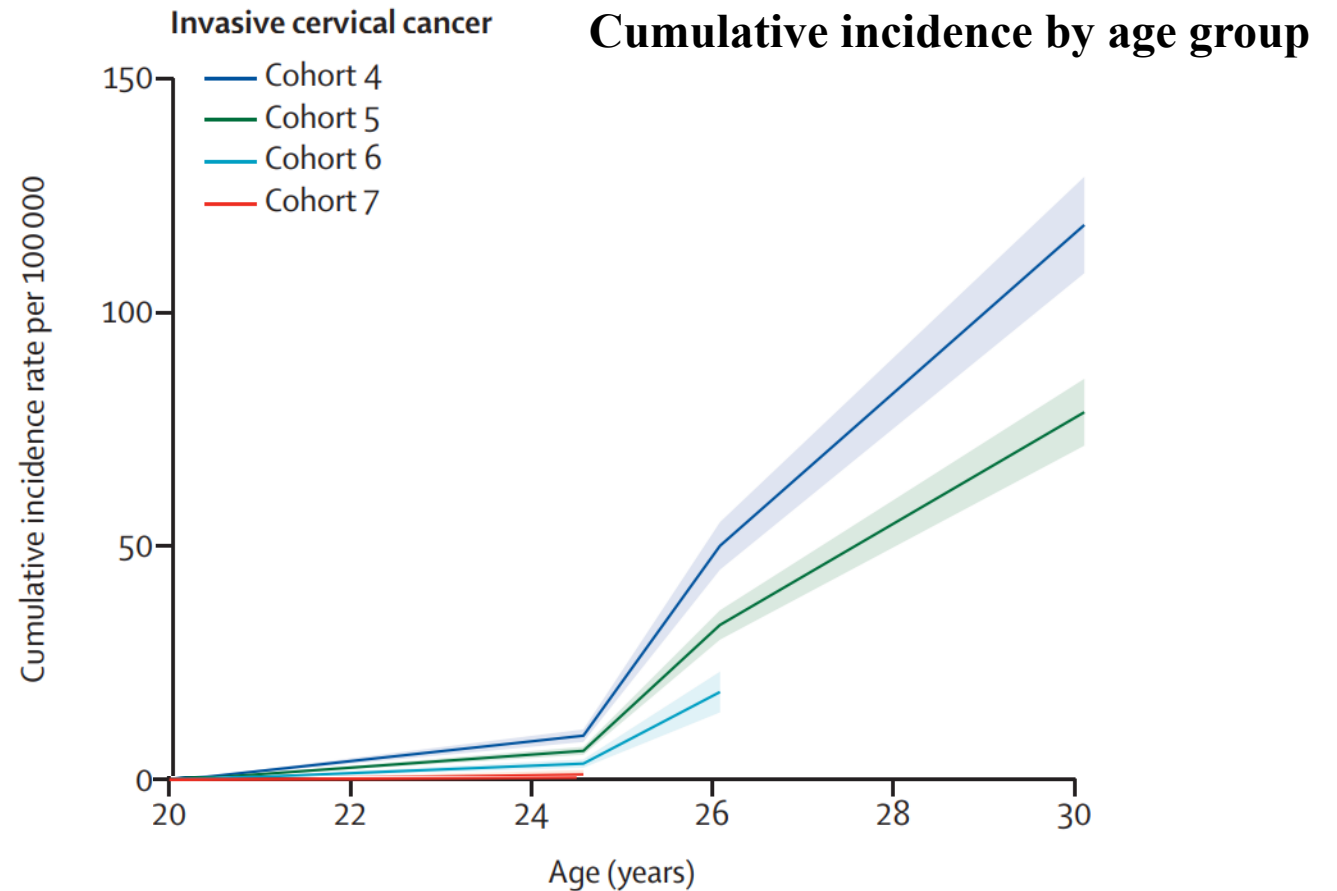
# Effect of routine vaccination - precancerous lesions cervix



Brotherton et al., Lancet, 2011

# The effect of routine vaccination: cervical cancer

- UK, routine vaccination in 2008, girls 12-13 years and 14-18 years of age; till 2010
- till 2010 bivalent, from 2012 tetravalent vaccine
- **Women born from 1995 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 <sup>1</sup>	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)



# Effectivity of 9V vaccine in prevention of HPV-associated malignancies in Czechia

HPV type in tumour	Cervical cancer	Vulvar cancer	Anal cancer	Anogenital cancers total	Oropharyngeal cancer
HPV16/18	75.6	24.5	81.8	60.5	61.5
HPV31/45	8.1	2.0	0	5.1	0
HPV33/52/58	8.1	8.2	0	7.0	2.7
Total	91.8	34.7	81.8	72.6	64.2

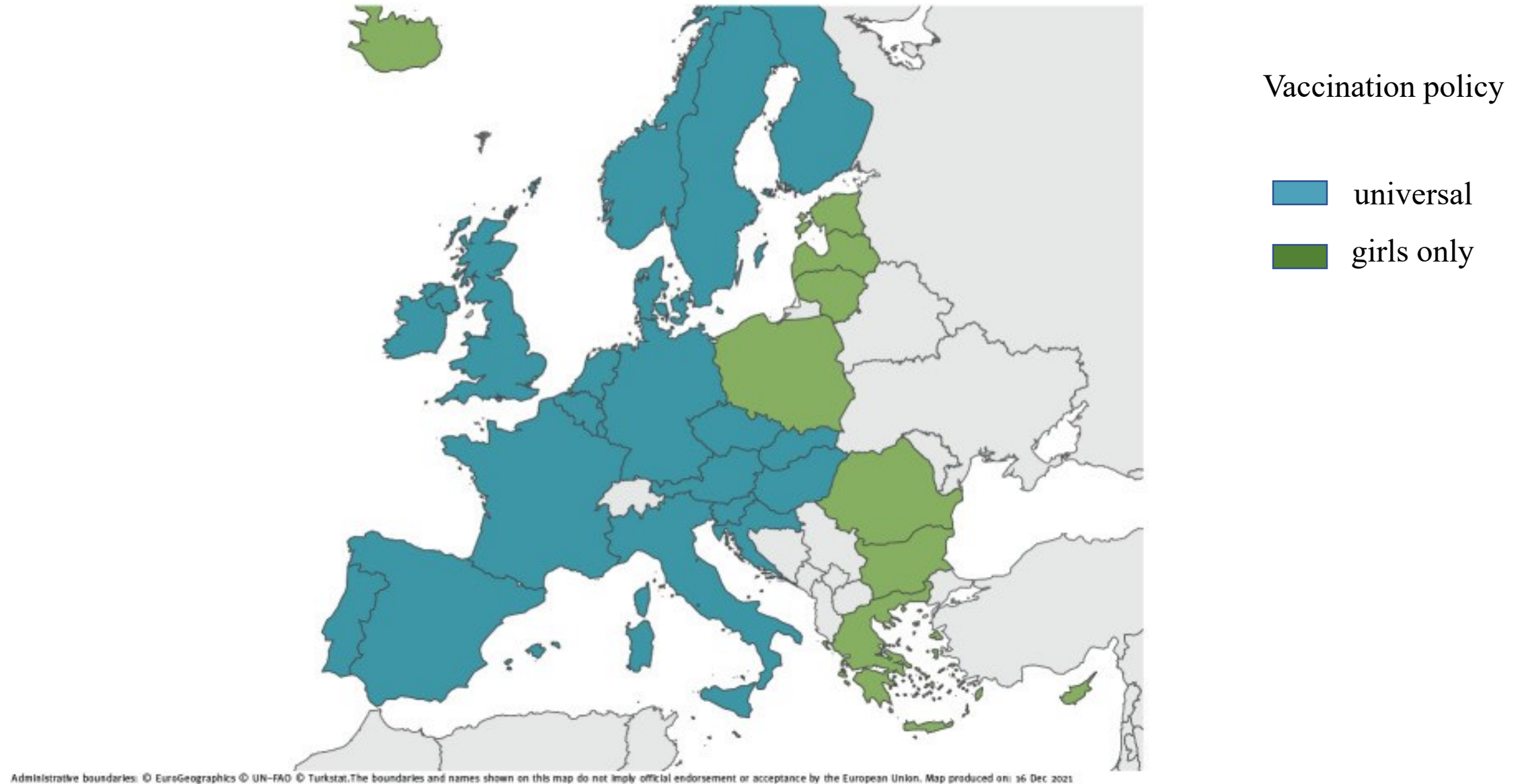
- **Decrease of incidence in absolute numbers:**
- **943 z 1300** cervical, vulvar, anal cancers
- **911 z 990** cervical cancers
- **300 z 467** oropharyngeal cancers
- **1252/1767 total 70 %**

# Eradication of HPV

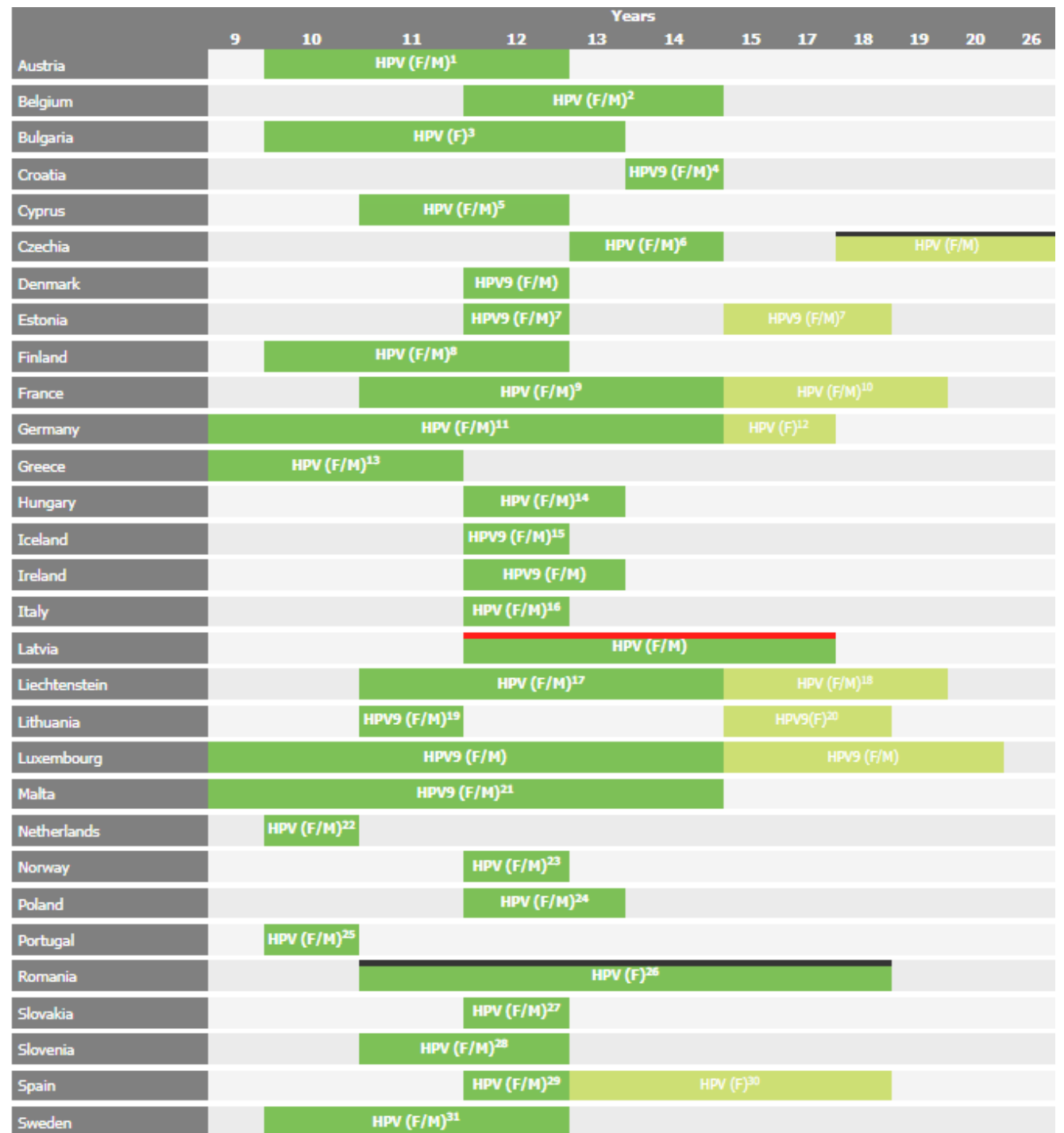
**Table 3. Model-Based Reproduction Numbers, Immunity Thresholds for Eradication of Vaccine-Covered Oncogenic Human Papillomaviruses (HPVs), and Corresponding Critical Coverage of Vaccination by Vaccine Efficacy for Gender-Neutral (Girls and Boys) and Girls-Only (Girls) Vaccination Strategies**

HPV Type	Reproduction Number <sup>a</sup>		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 <sup>b</sup>	NE <sup>b</sup>	NE <sup>b</sup>
HPV18	2.2	4.5	55%	78%	58%	82%	69%	98%	NE <sup>b</sup>	NE <sup>b</sup>
HPV31/33	1.7	2.9	40%	65%	42%	68%	50%	81%	80%	NE <sup>b</sup>
HPV45	1.7	2.9	40%	65%	42%	68%	50%	81%	80%	NE <sup>b</sup>
HPV35	1.3	1.5	20%	35%	21%	37%	25%	44%	40%	70%

# Vaccination in Europe: gender and reimbursement



# Recommended vaccination HPV



<https://vaccine-schedule.ecdc.europa.eu/Scheduler/ByDisease?SelectedDiseaseId=38&SelectedCountryIdByDisease=-122/3/2024>



# Arguments for very early vaccination against HPVs

- the best efficiency and effectivity is when vaccinated in childhood, before the sexual debut
- safe (continuous follow-up)
- immunogenic (primary and long-term immune response better when vaccinated in childhood)
- long time protection (9-14 years of follow-up)
- no increase in sexual activity in vaccinated cohort were observed
- only two doses (the complete compliance is more likely-2 doses as recommended in SPC)
- vaccination completed before the age of 13 years (better compliance)
- earlier age of vaccination resulted in superior effectivity in the real population in protection against HPV-associated diseases
- logistics (regular examinations at the age of 11, 13, 15 years)

# WHO strategy for elimination of cervical cancer

- Incidence of cervical carcinoma 4/100 000 females/years
- 90 % of females vaccinated till 15 years of age
- 70 % of females screening at the age of 35 and 45 with a high quality test
- 90 % of females identified with the disease treated
- Deadline in 2030



Health Topics ▾

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Data ▾

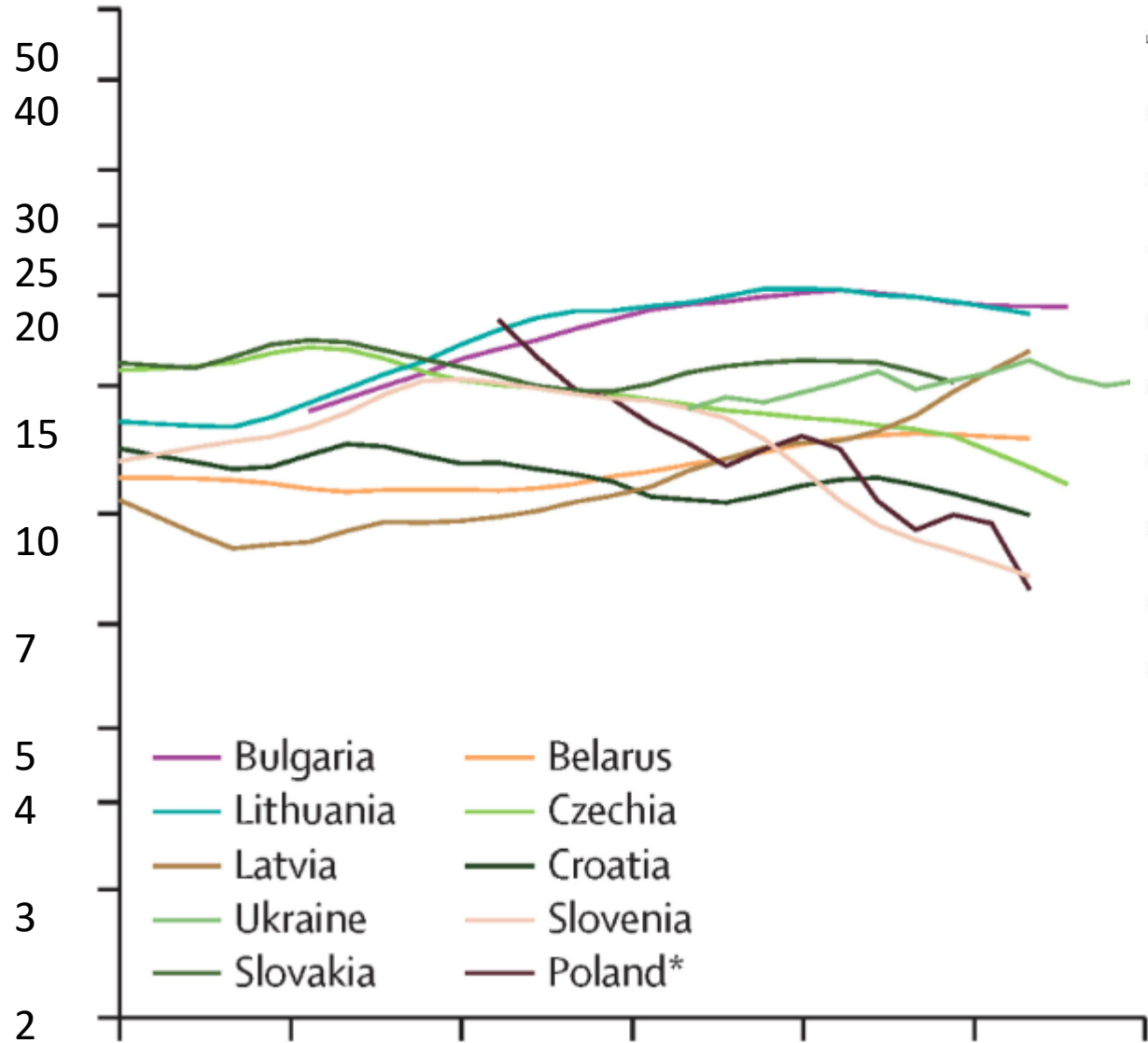
About WHO ▾

[Home](#) / [Initiatives](#) / [Cervical Cancer Elimination Initiative](#)



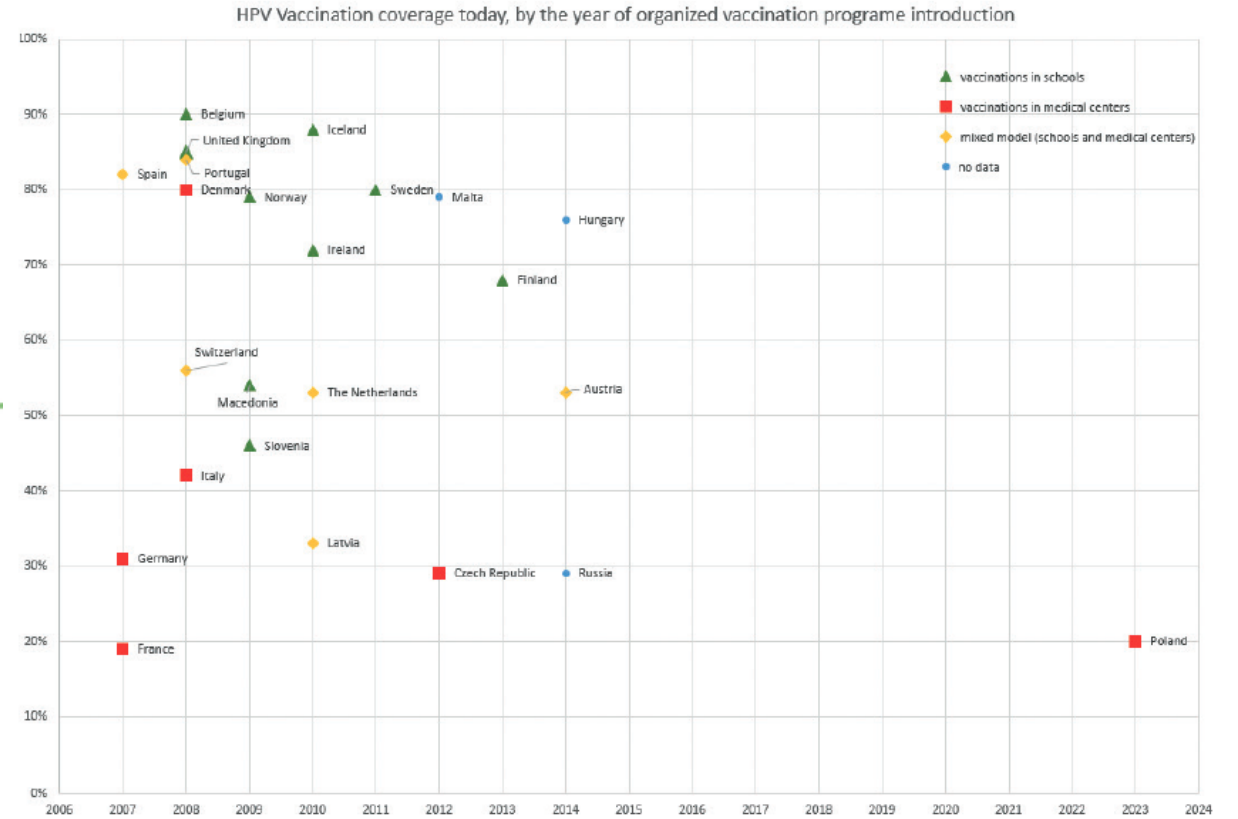
# Age-standardized incidence of cervical cancer

## C Central and eastern Europe

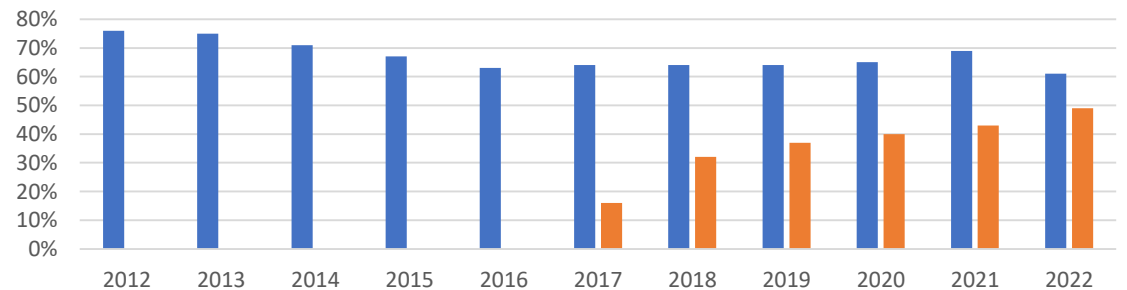


Singh et al., Lancet, 2023

# HPV vaccination coverage



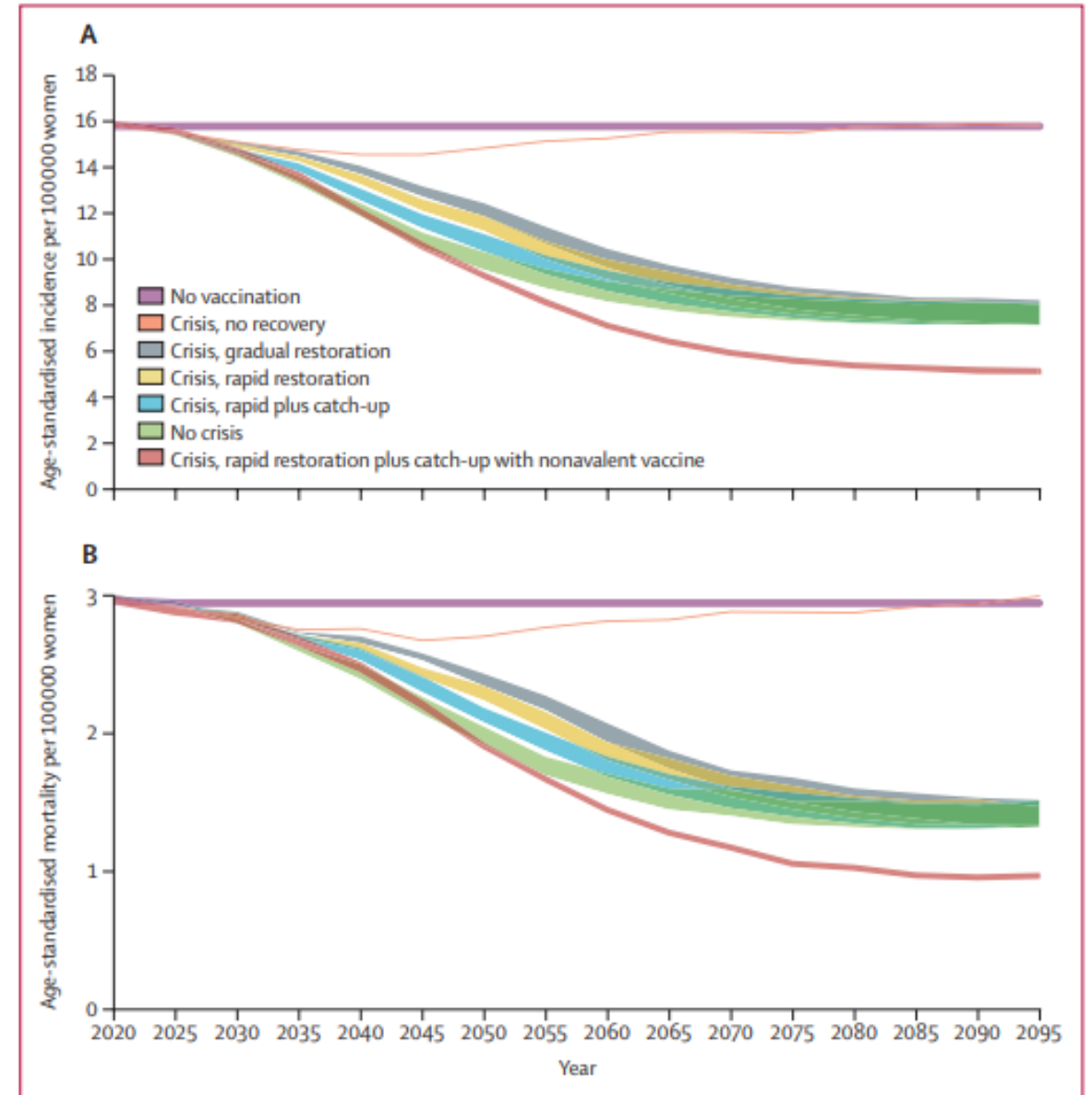
Borowska et al., Nowotwory Journal of Oncology, 2024



# Failure of the vaccine campaign

- **Japan**
- Vaccine program from 2010
- Girls 12-16 yrs
- Side effects reported in media, 2013 MH ended the program
- from 70% to 0% coverage
- 2013-2020 3 mil. girls no vaccine

- **Romania**
- CC incidence is the highest in Europe
- 2008 vaccine program
- Girls 10-11 years
- 2,5 % coverage
- Craciun a kol., 2012





# Summary II

- Tool for primary prevention available
- Vaccines safe, immunogenic
- The earlier vaccination the higher efficiency and effectivity (immunity, compliance, number of doses)
- Long protection 9-14 years
- Vaccination coverage
- Gender-neutral vaccination
- Combination with cervical screening
- It is also important to explain the limitation of protection with primary and secondary prevention
- Even the slightest questioning of vaccines can lead to dramatic changes in a population's willingness to be vaccinated

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



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