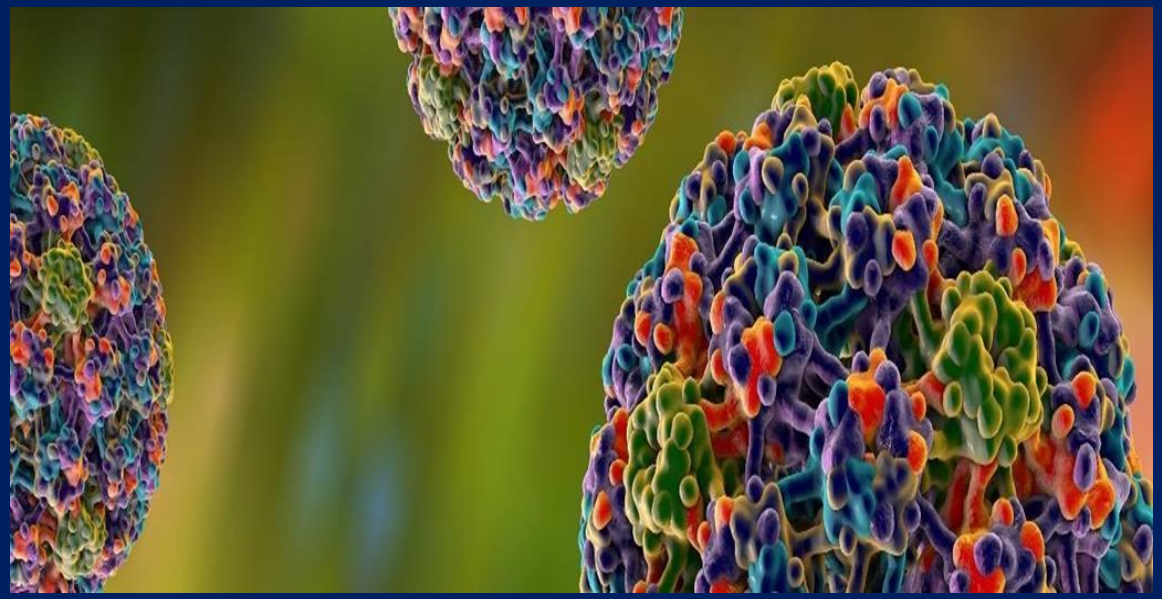
HPV
CERVICAL PRE CANCERS AND CANCERS
UPDATE AND NEW CHALLENGES

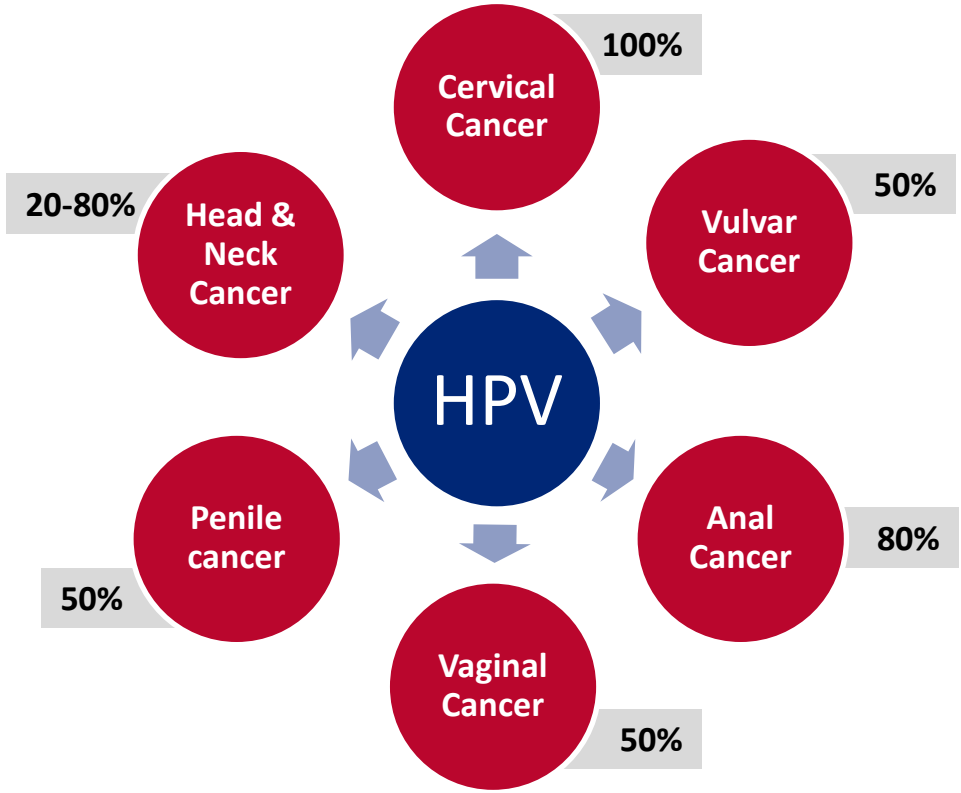


J Monsonego

Paris

Institut du Col
Institute of the Cervix

HPV Causes Multiple Cancers in Men and Women



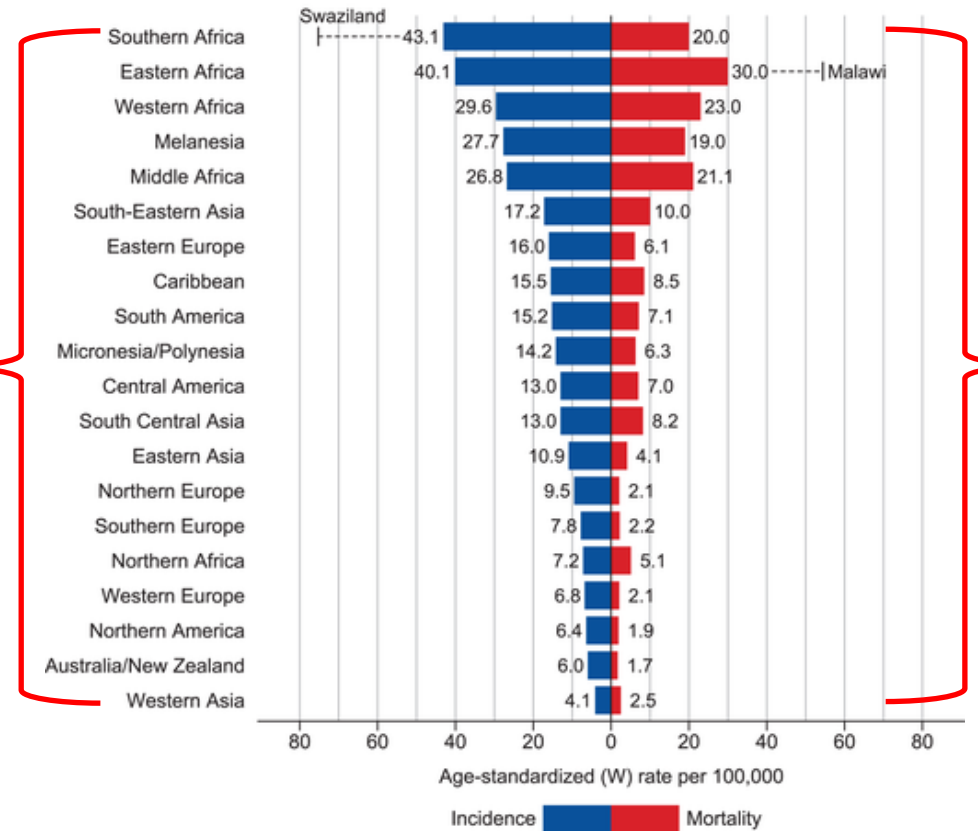
CANCERS ATTRIBUABLE TO HPV

Estimated numbers of infection-attributable cancer cases in 2018, worldwide

	Men		Women	
Cancer site	**New cases**	**Attributable to HPV**	**New cases**	**Attributable to HPV**
Cervical	-	-	570 000	**570 000**
Oropharyngeal	110 000	34 000	26 000	8 100
Oral cavity	190 000	3 900	91 000	2 000
Larynx	150 000	3 600	22 000	<1 000
Anus, squamous cell	9 900	9 900	19 000	19 000
Penis	34 000	18 000	-	-
Vagina	-	-	18 000	14 000
Vulva	-	-	44 000	11 000

de Martel C, Georges D, Bray F, Ferlay J, Clifford GM. Global burden of cancer attributable to infections in 2018: a worldwide incidence analysis. The Lancet Global Health. 2020 Feb 1;8(2):e180-90.

Global Variation in Cervical Cancer Incidence and Mortality, 2018

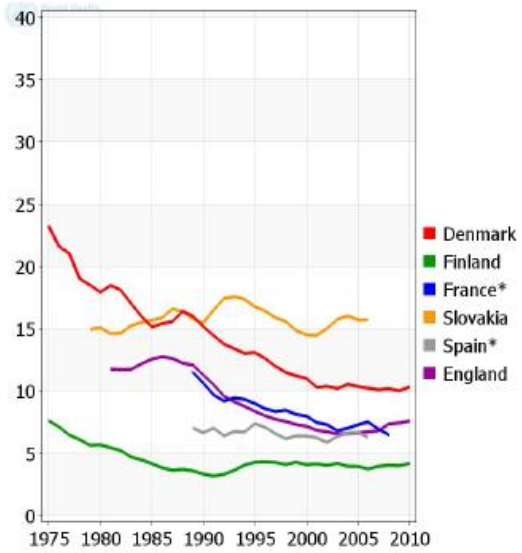


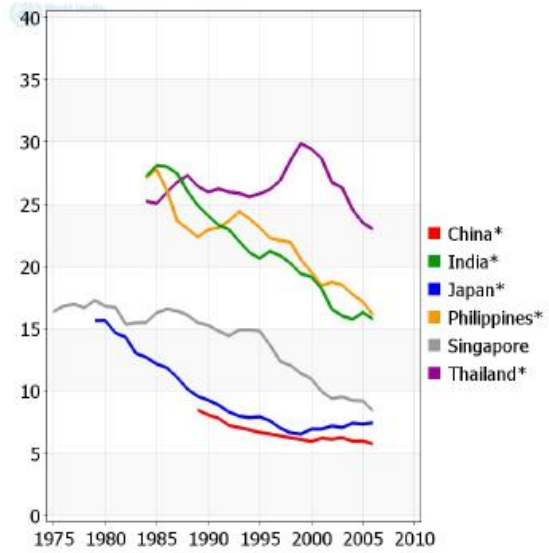
10-fold difference

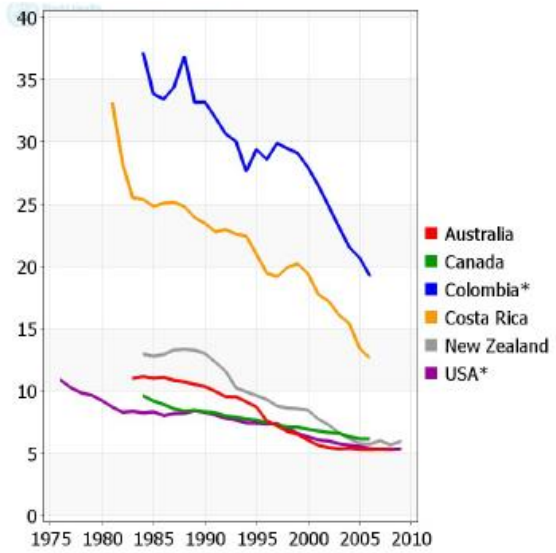
18-fold difference

Bray et al., CA 2018

Trends in Cervical Cancer in Select Countries before HPV vaccination





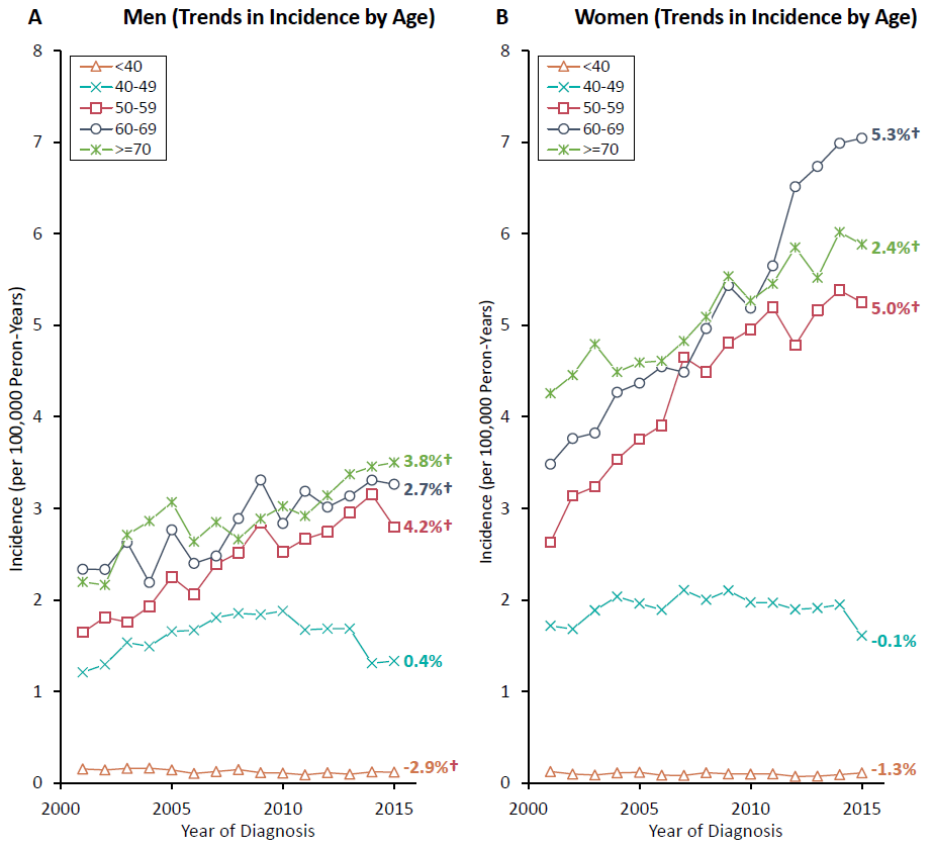


Overall, declines or plateaus in rates during recent years.

Data from IARC

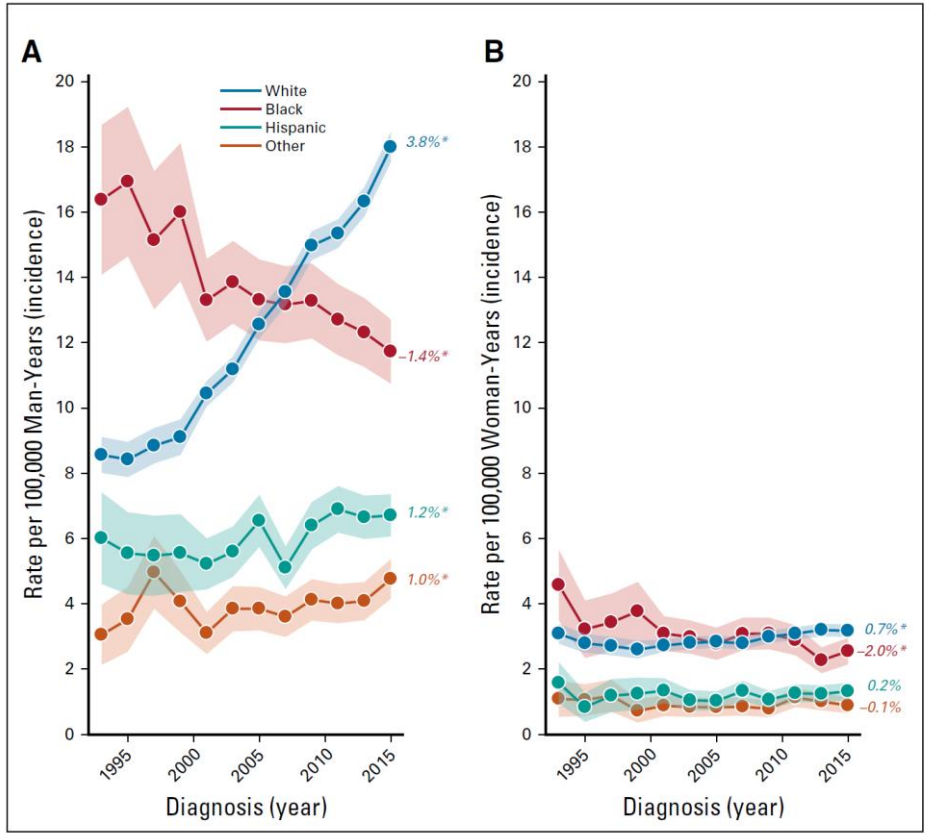
Rising Anal SCC Rates in the United States before HPV vaccination

- Increases anal cancer observed among men and women aged 50 and older
- Largest increases observed in 60-69 year-old women
- Anal cancer remains rare – age-standardized rate in 2011-15: 1.6 per 100,000

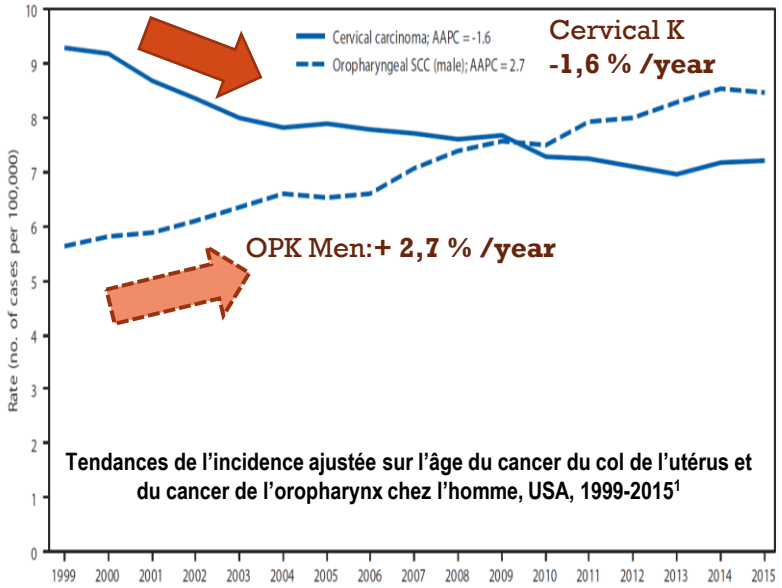


Deshmukh, JNCI 2019

Trends in Oropharynx Cancer in US, 1995-2015 before hpv vaccination



- Rates are far higher in men than women.
- Rates increased significantly among White men and women, Hispanic men and men of othe
- Rates declined significantly among Black men and women.



Prévalence of HPV infection (cervix) in over all population

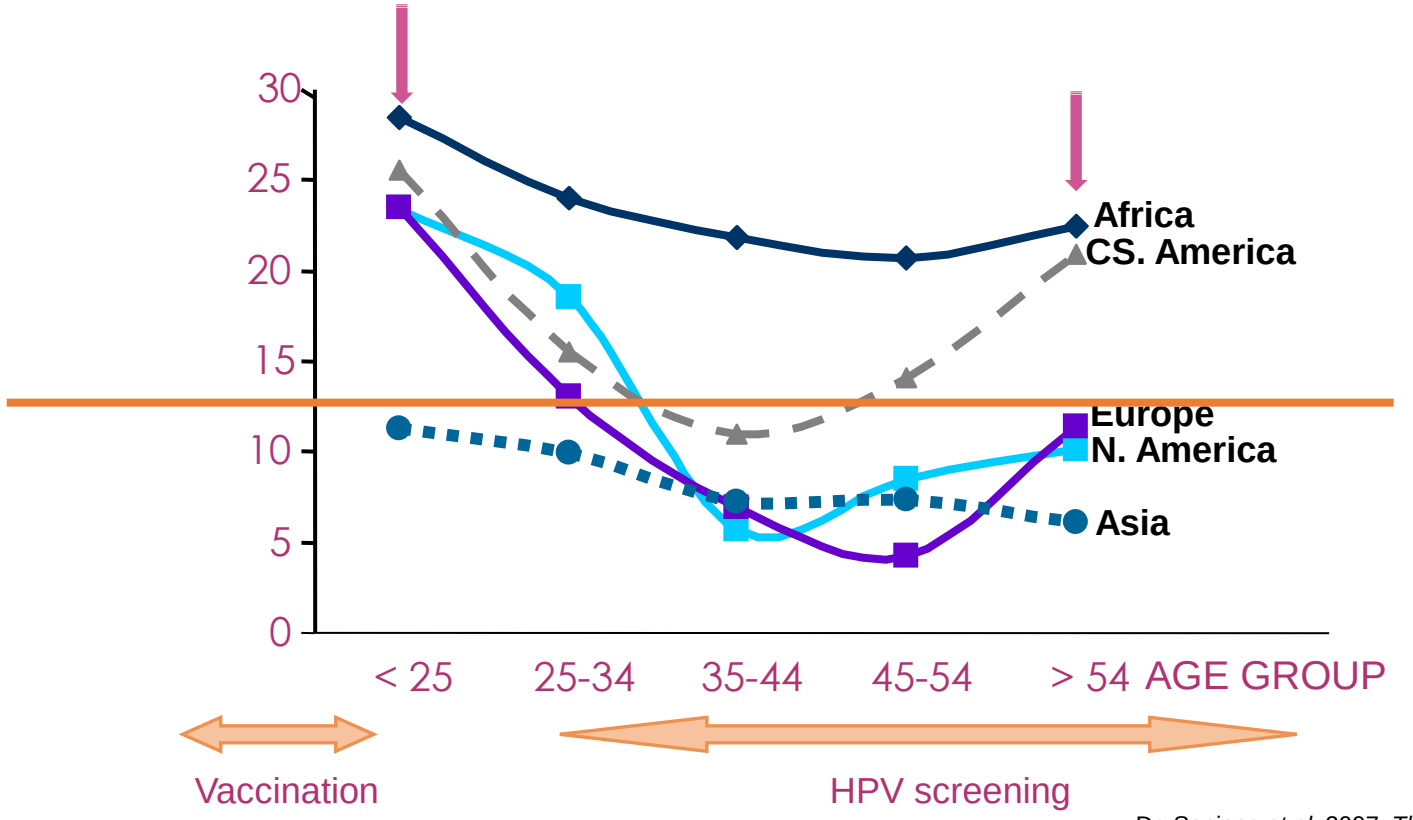
US (Athena)	N	HPV HR-LA(%)
25-29 ans	6647	17.8
Overall	40901	10.3

J.Monsonego et al Gynecol Oncology 2015

France	N	HPV HR -HC (%)
-25	121	23.5
+25	634	14.1
Overall	755	15.1

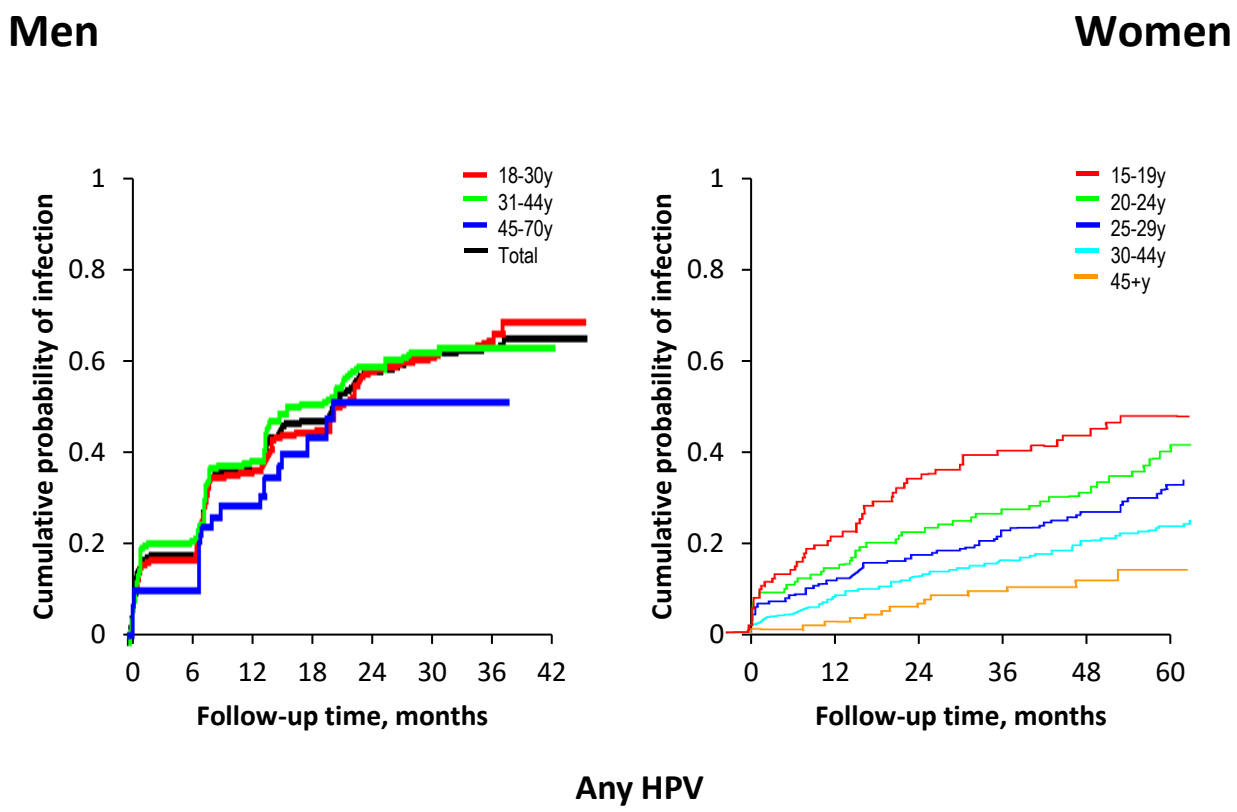
J.Monsonego et al Vaccine 2012

CERVIX:PREVALENCE OF HPV BY AGE



De Sanjose *et al.* 2007, *The Lancet*

Genital HPV Incidence Lowest in Older Women but Does NOT Vary with Age in Men

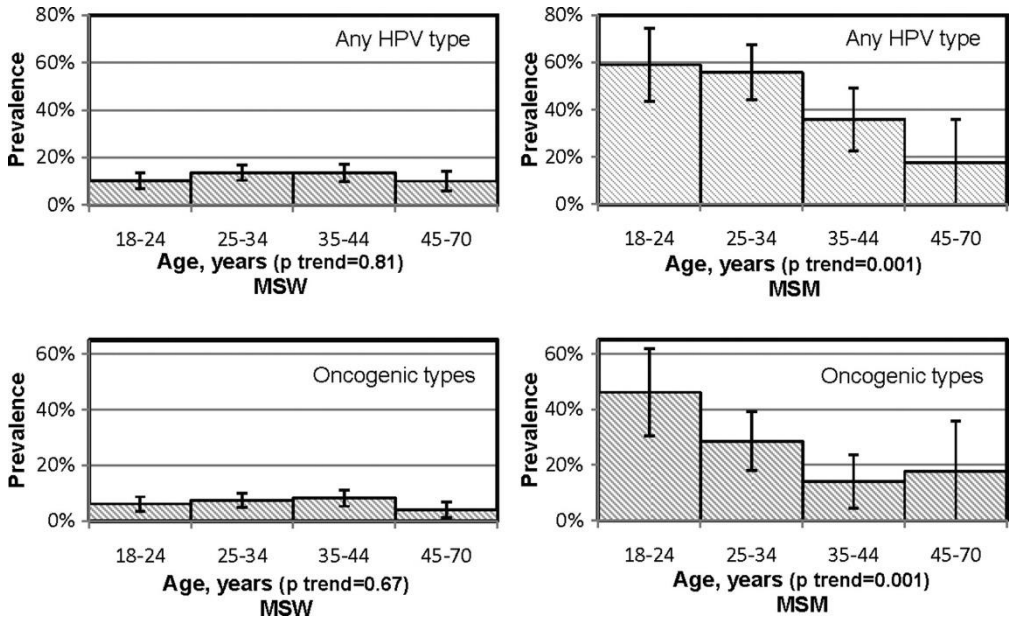


Any HPV

Giuliano AR et al., *Lancet* 2011; Muñoz N et al., *JID* 2004.

Anal prevalence HPV infection in men

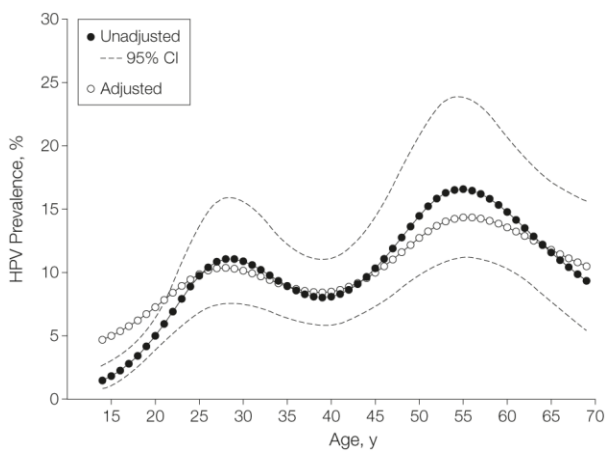
- High prevalence in MSM



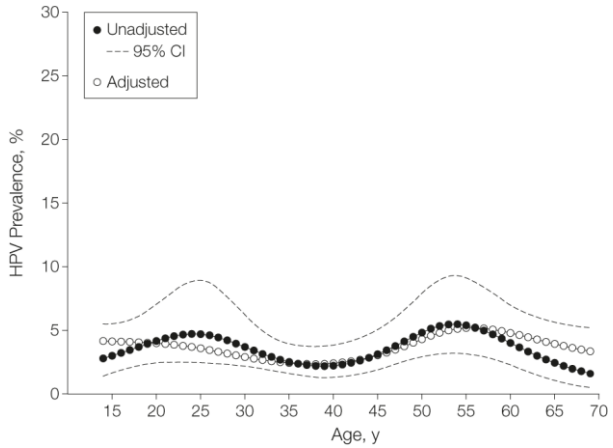
Nyitray et al. Age-specific prevalence of and risk factors for anal human papillomavirus (HPV) among men who have sex with women and men who have sex with men: the HPV in men (HIM) study. Journal of Infectious Diseases. 2011 Jan 1;203(1):49-57.

Oral HPV Prevalence is Significantly Higher in Men vs. Women

Men



Women



US NHANES 2009-2010

Gillison M et al., *JAMA* 2012.

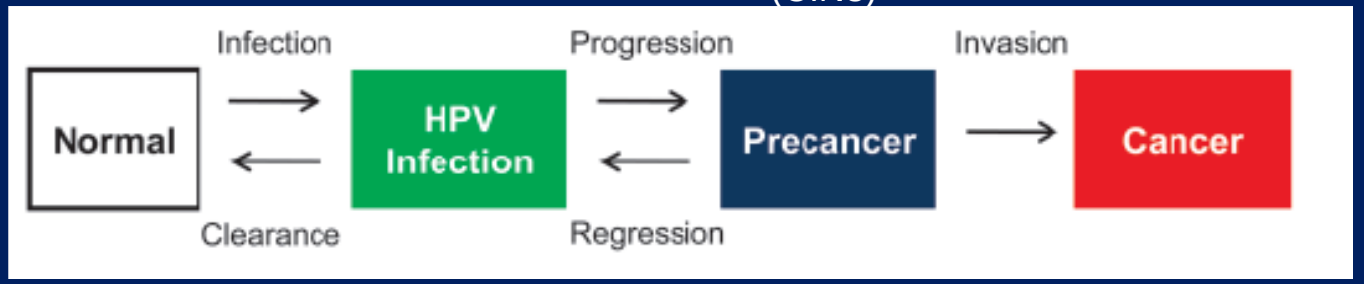
CARCINOGENESIS MODEL

NO PRECANCERS AND CANCER OF THE CERVIX WITHOUT HPV

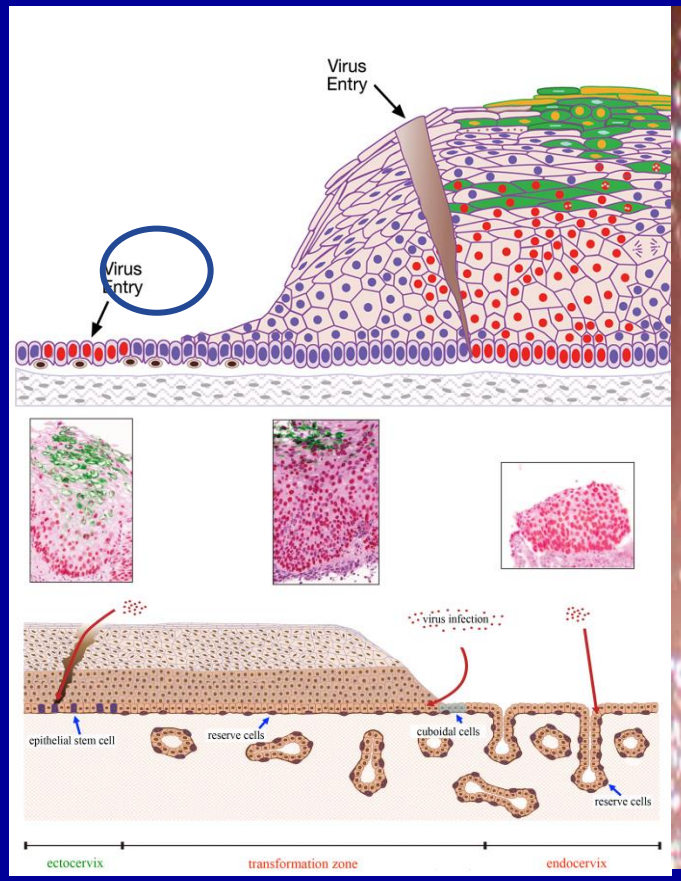
VACCINATION
2V/4V/9V

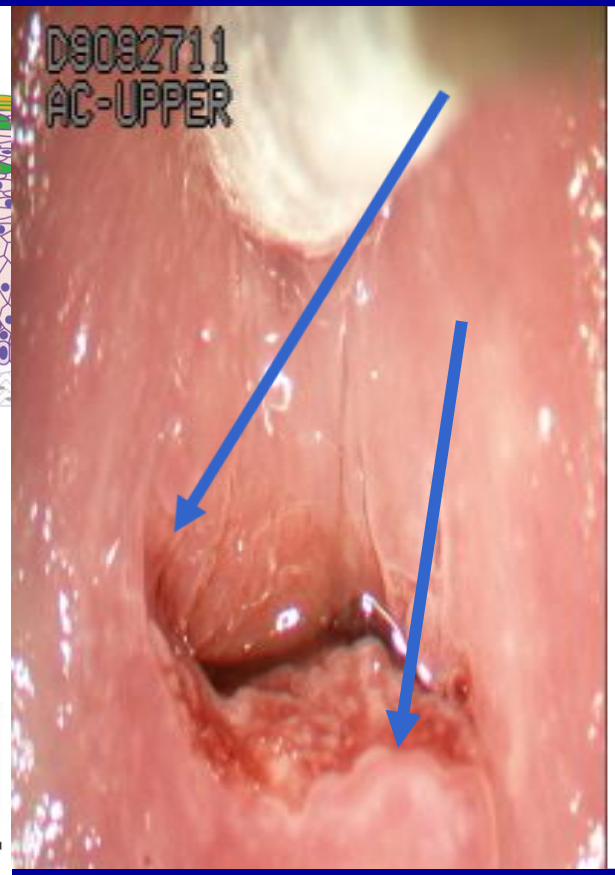
HPV SCREENING /CYTO?

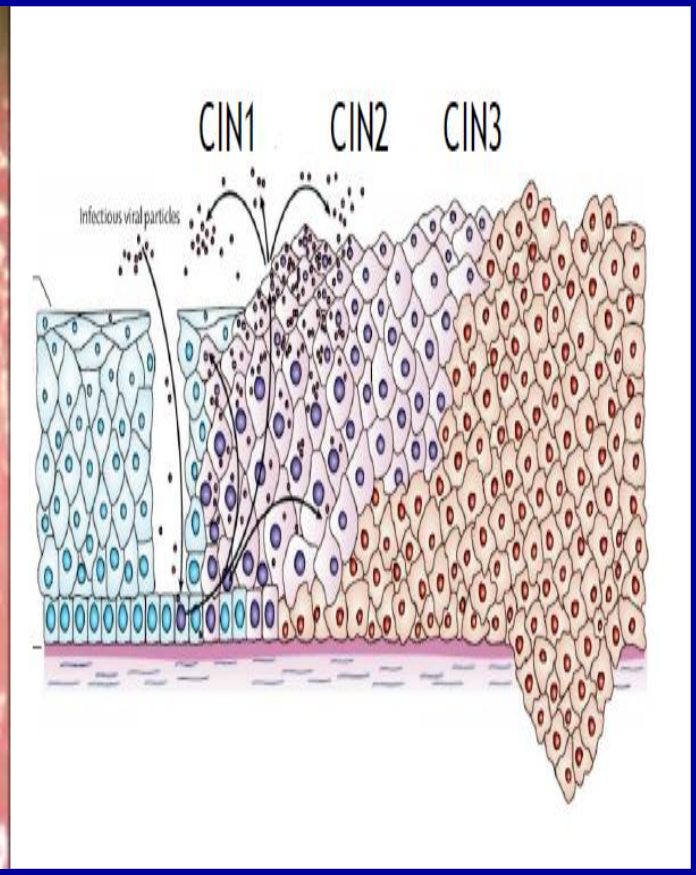
(CIN3)



ZT SUSCEPTIBILITY OF THE CERVIX
PENETRATION TRANSMISSION







New HPV detections are very common in young sexually-active women

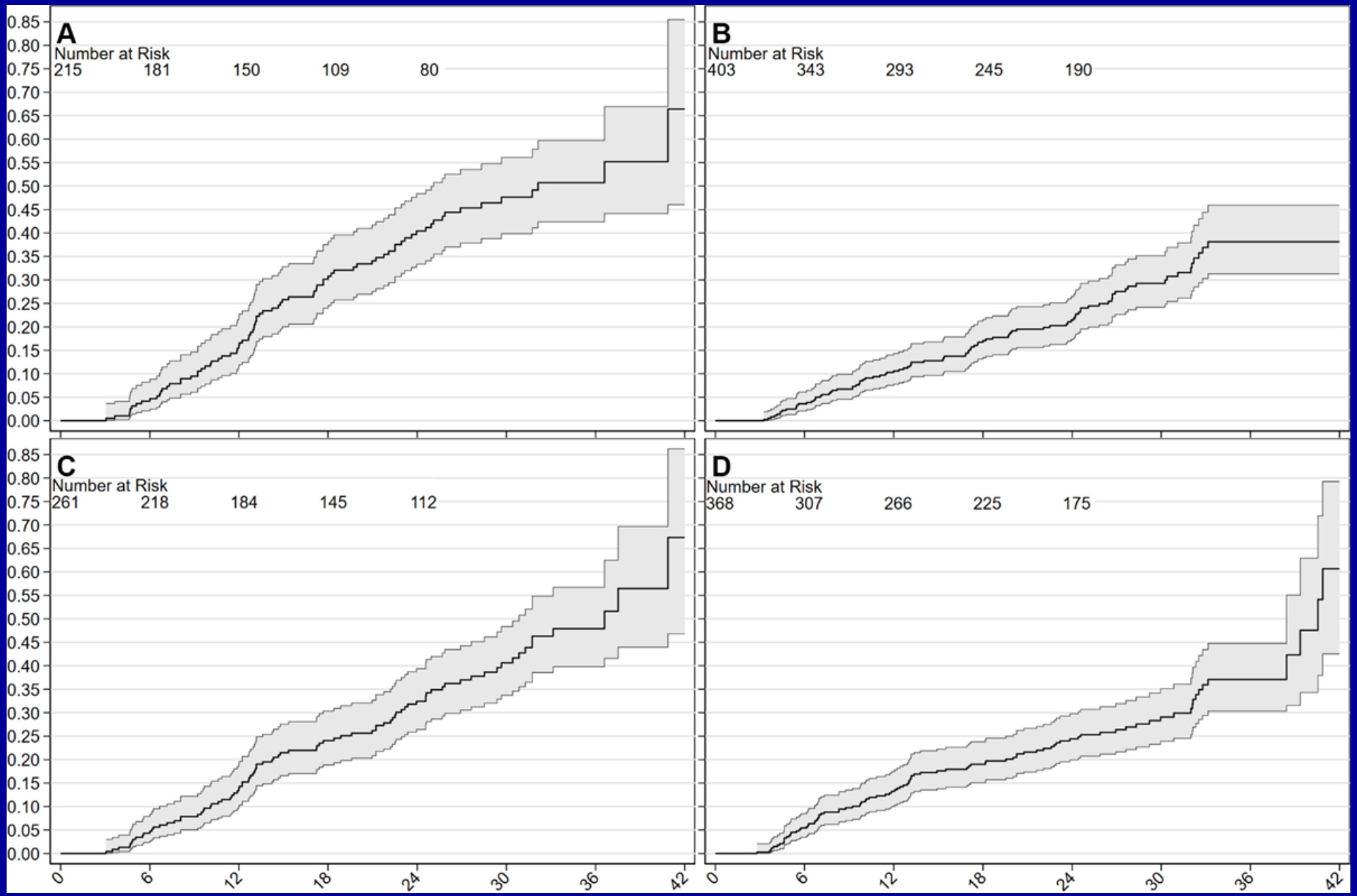
Data from the HITCH cohort study

A: Any Alpha HPVs

B: Alpha subgenus 1

C: Alpha subgenus 2

D: Alpha subgenus 3



Clearance of prevalent and incident HPV infections in young sexually-active women

Data from the HITCH cohort study

A: Any Alpha HPVs

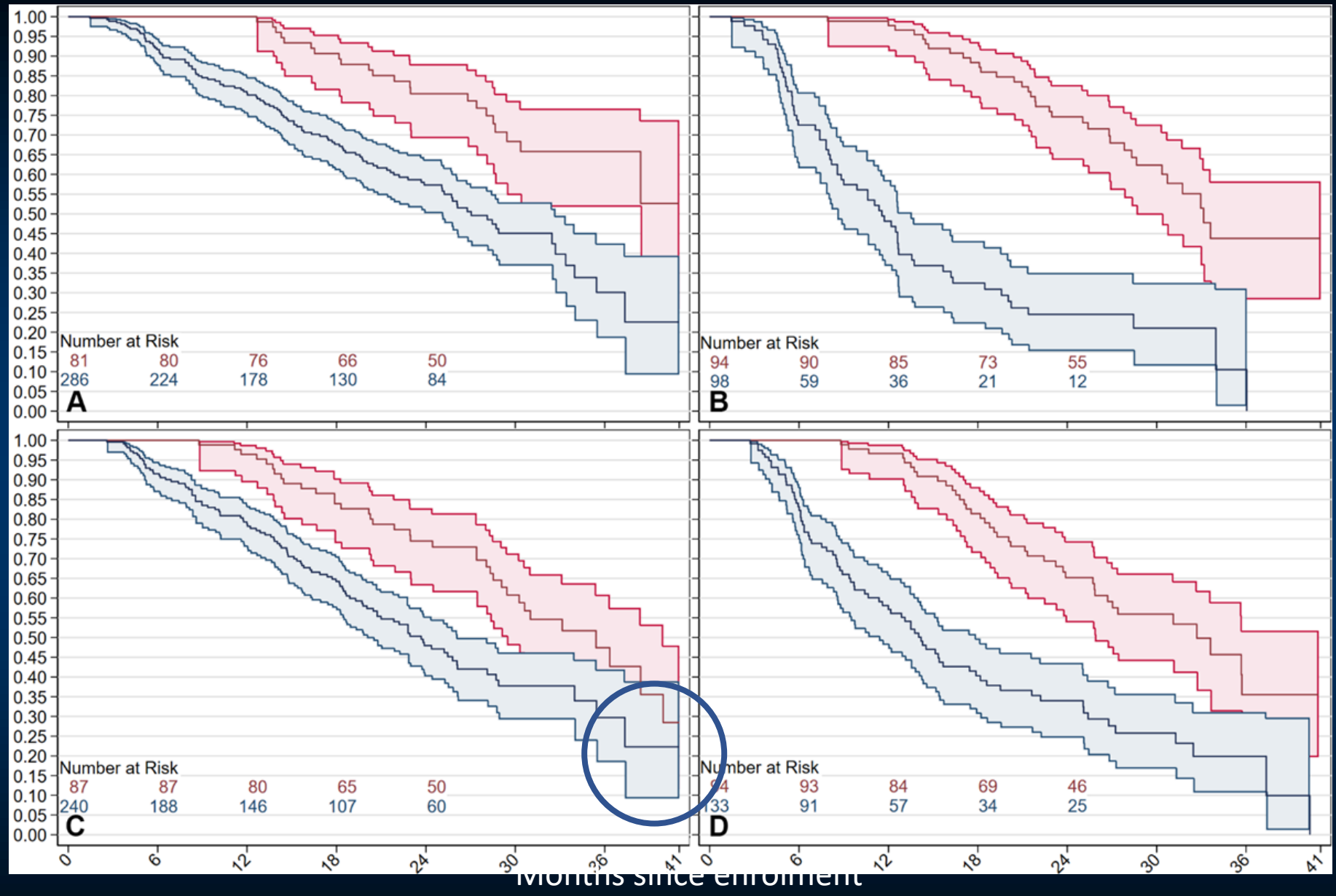
B: Alpha subgenus 1

C: Alpha subgenus 2

D: Alpha subgenus 3

Blue: prevalent

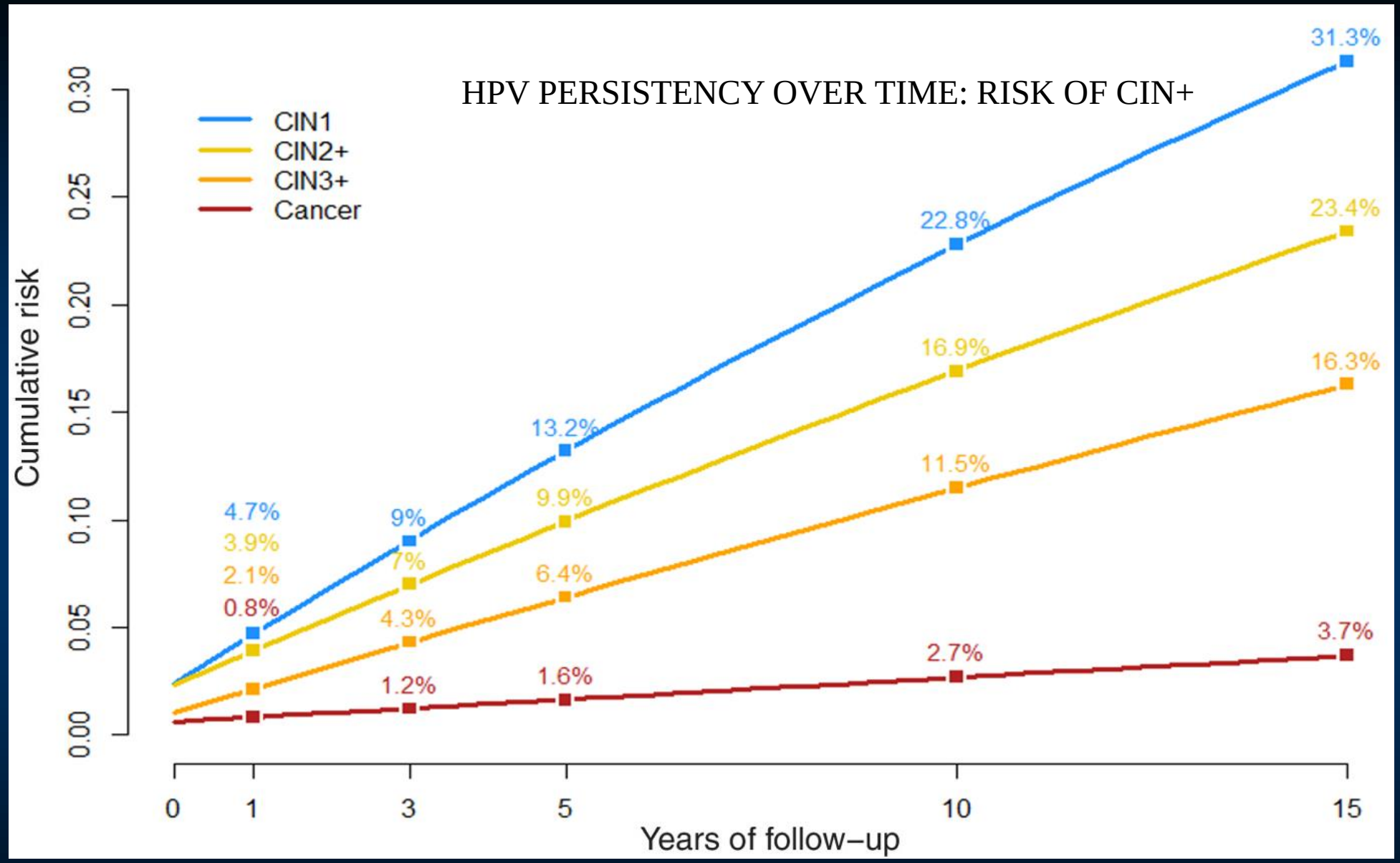
Red: incident



For illustration only; unpublished data from HITCH study. Andrew Arthur et al., to be submitted

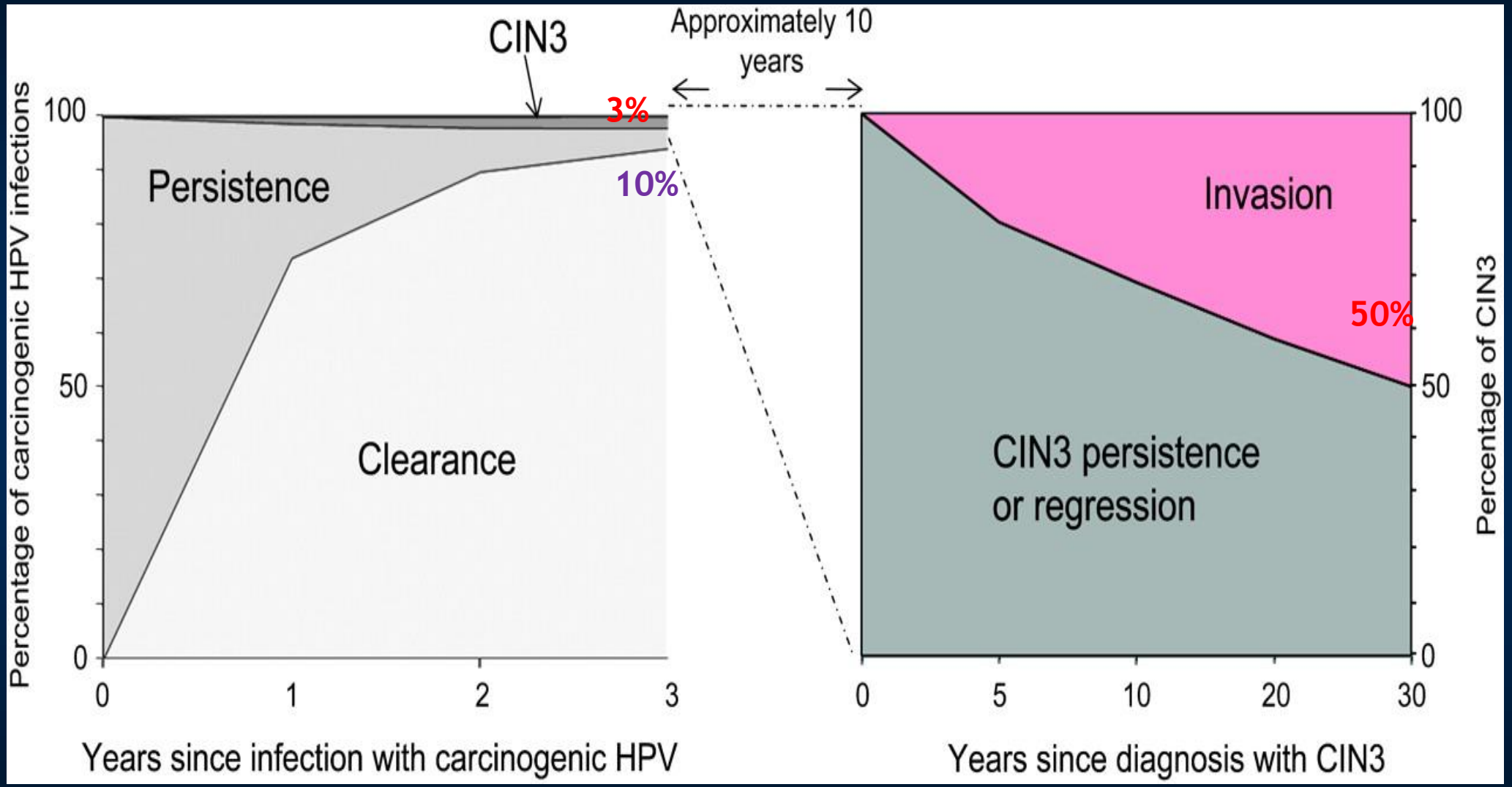
Predicted average cumulative risk of CIN and cancer in women who are HR-HPV positive but cytology/histology normal at baseline

Systematic review of 162 eligible papers from 87 different populations (after screening 4035 published papers). Estimates by multi-level random-effects meta-regression models



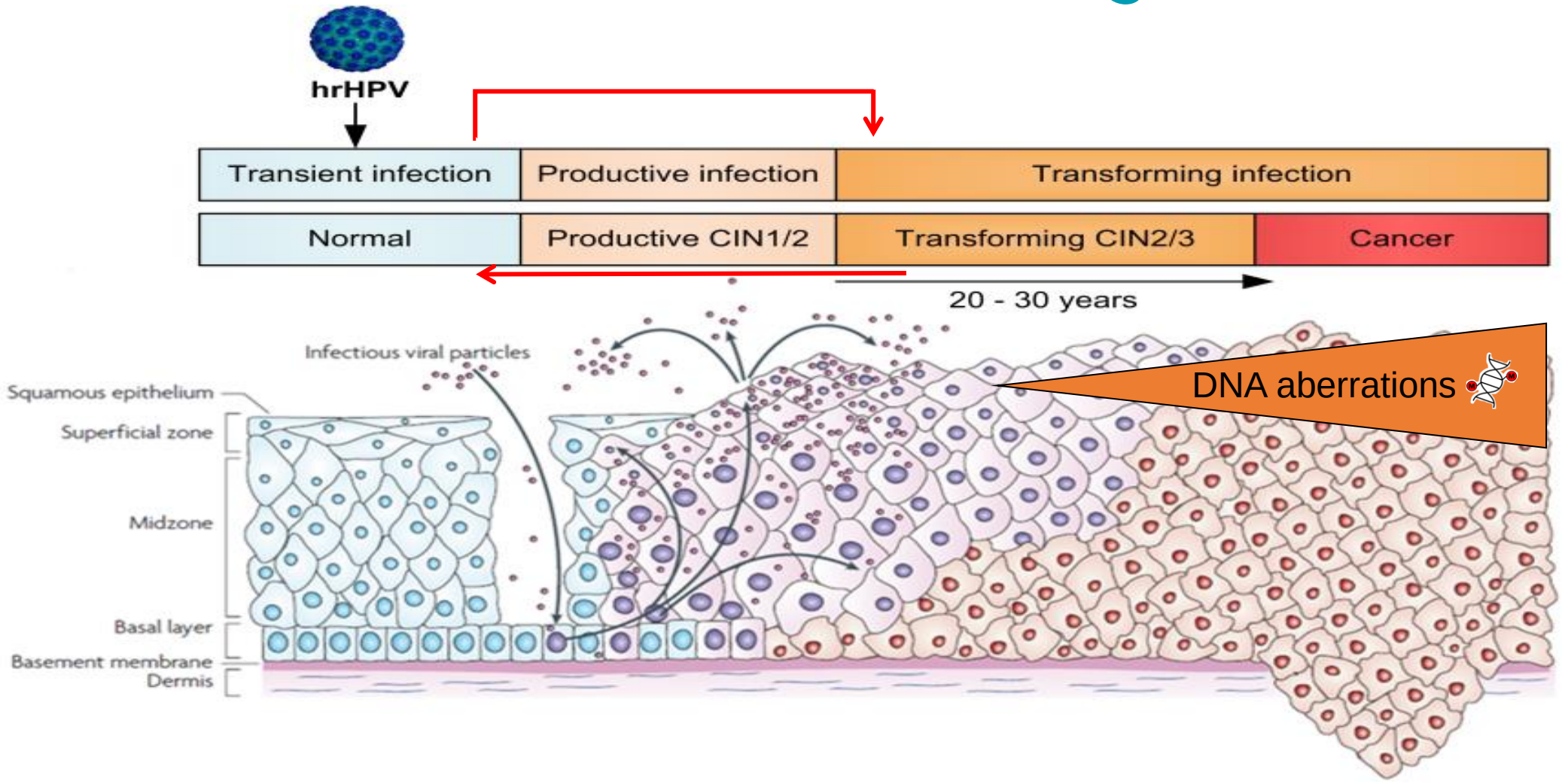
Malagón T, Volesky KD, Bouten S, Laprise C, El-Zein M, Franco EL. Cumulative risk of cervical intraepithelial neoplasia for women with normal cytology but positive for human papillomavirus: Systematic review and meta-analysis. *Int J Cancer.* 2020;147(10):2695-2707.

Progression from HPV infection to precancer and then cancer



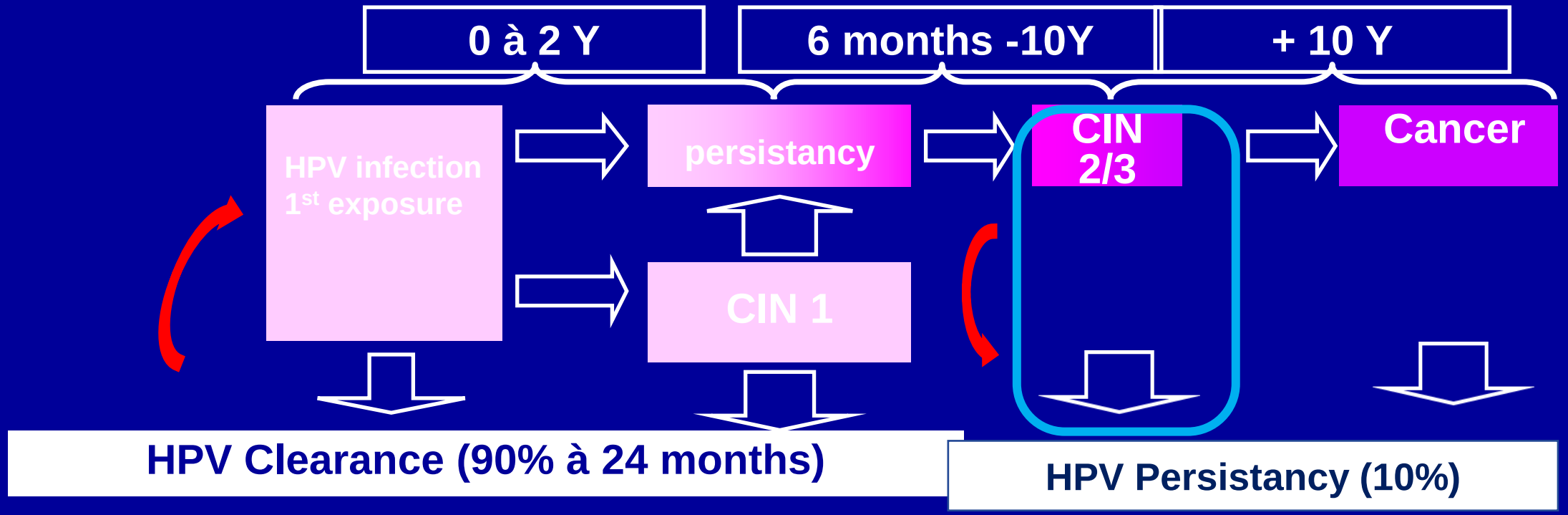
Schiffman et al. J Natl Cancer Inst 2011;103:368-383

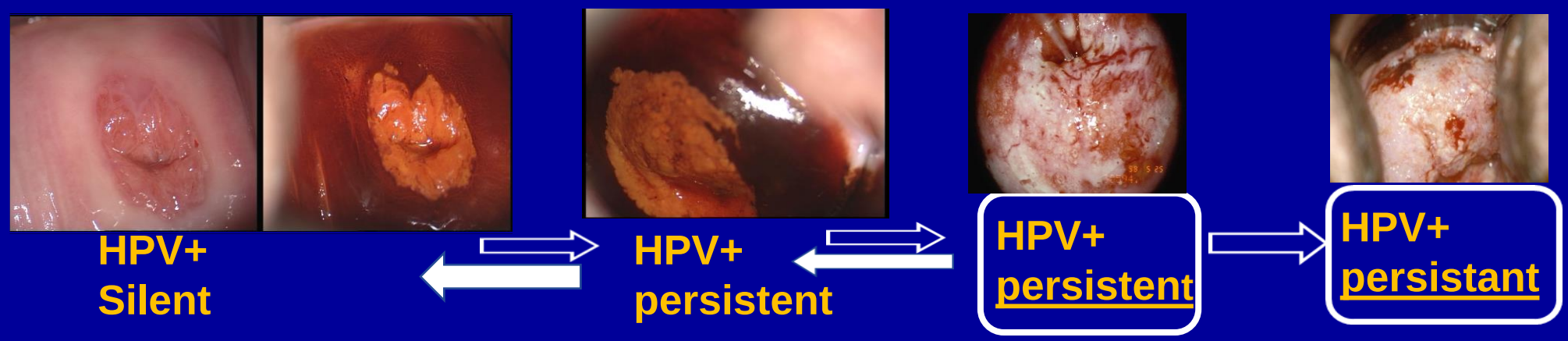
HPV-induced carcinogenesis

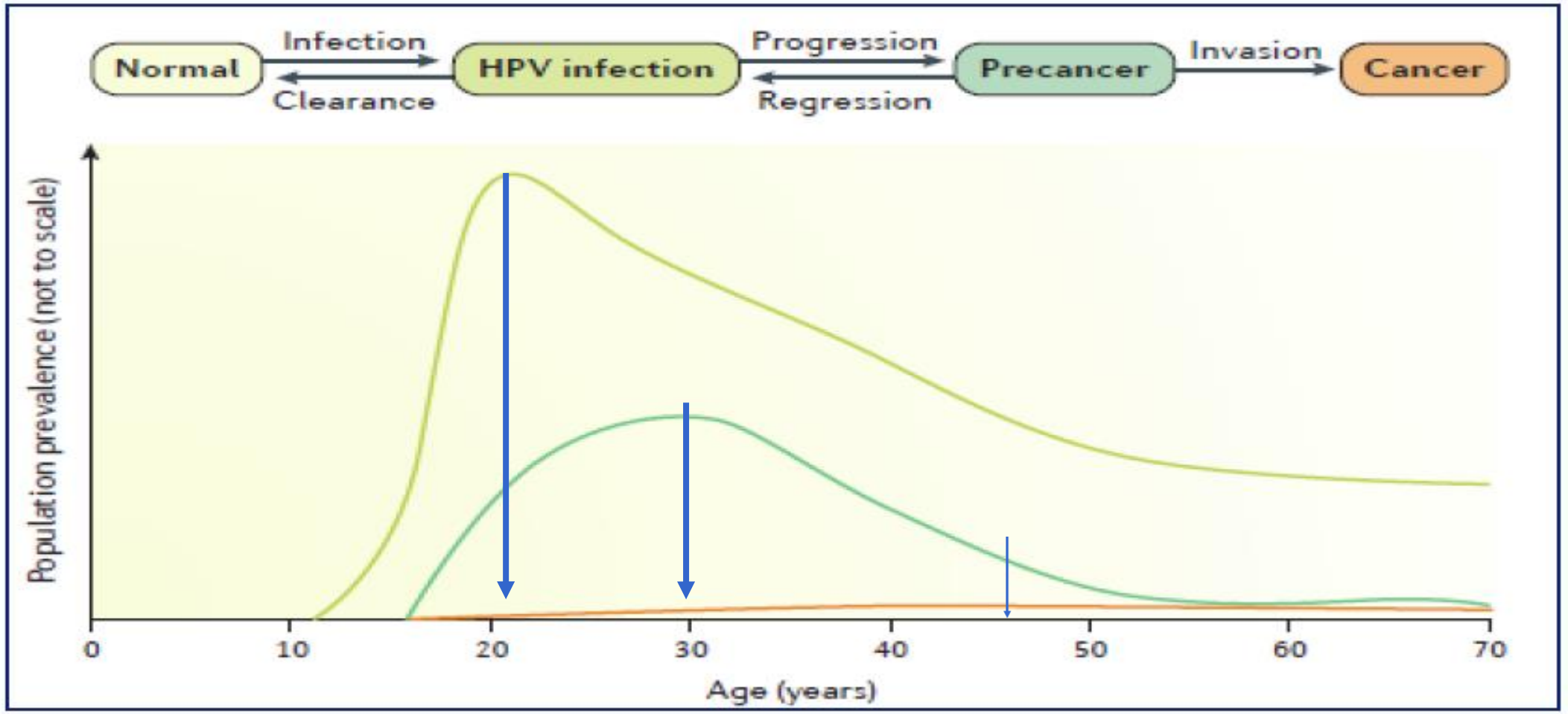


Adapted from Woodman *et al.*, Nature Reviews Cancer 2007; Steenbergen *et al.* Nature Reviews Cancer 2014

HPV doesn't allow to recognize the stage (low specificity)
HPV is not missing HG CIN(high sensitivity)

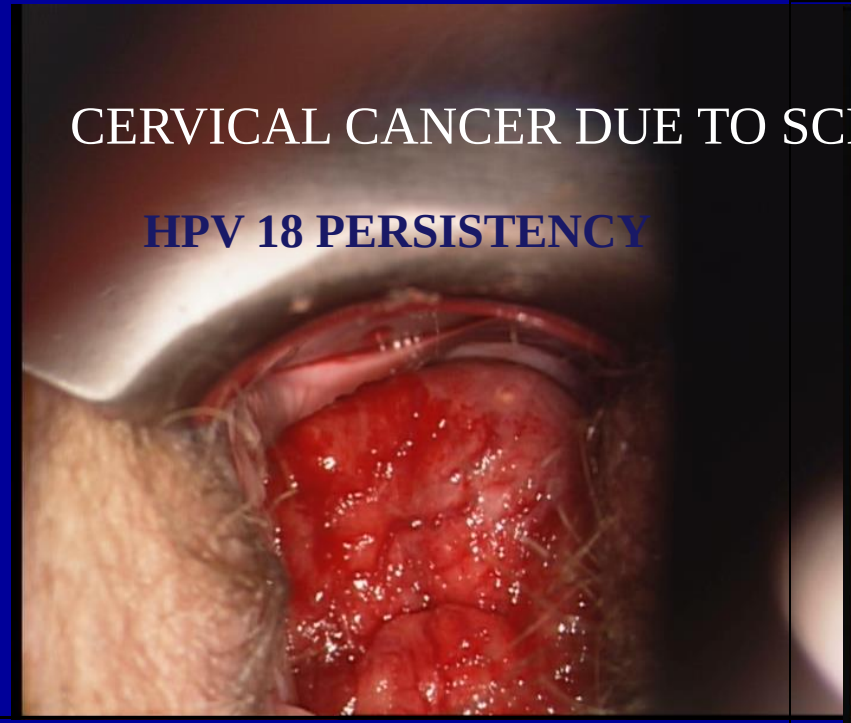




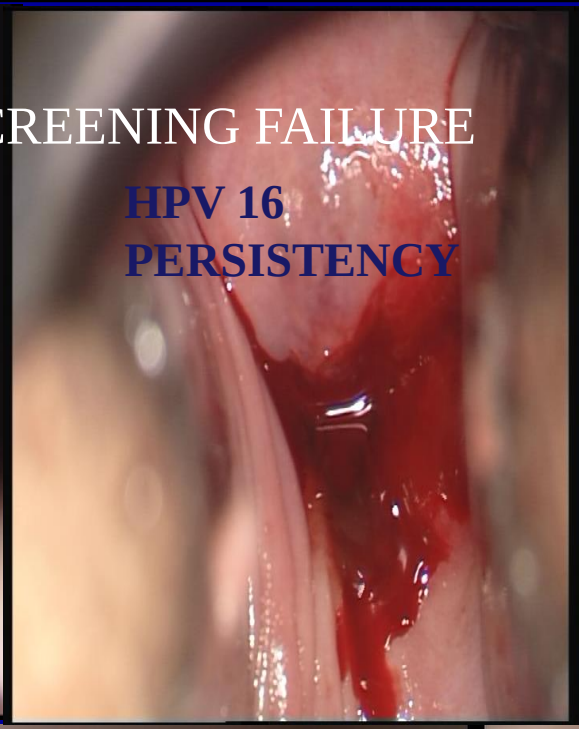


© Schiffman M, *et al.* Nat Rev Dis Primers 2016.

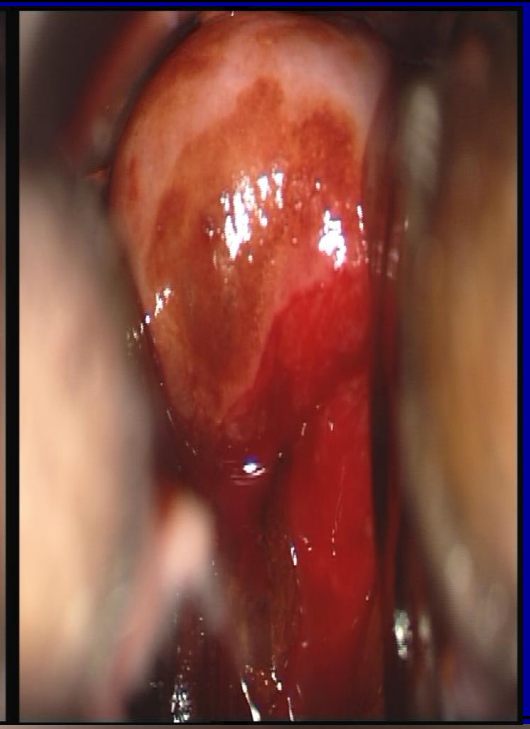
CERVICAL CANCER DUE TO SCREENING FAILURE

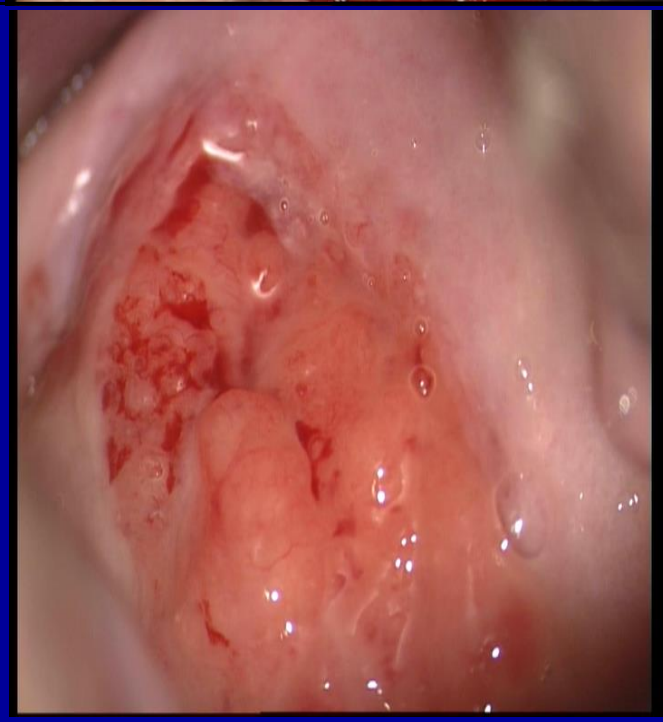


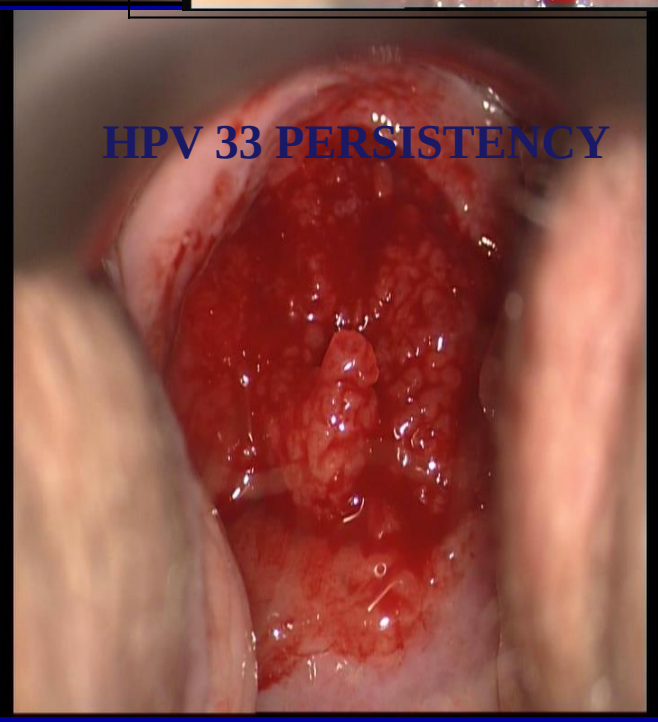
HPV 18 PERSISTENCY



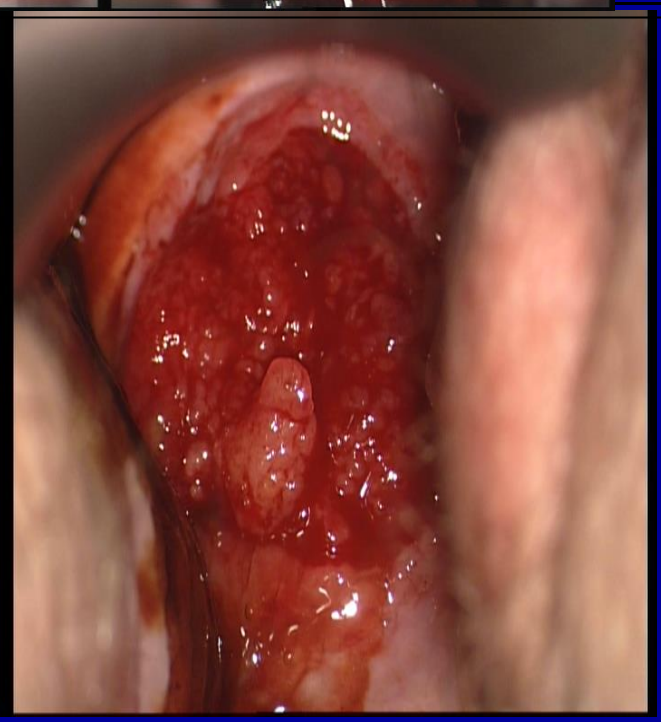
HPV 16 PERSISTENCY



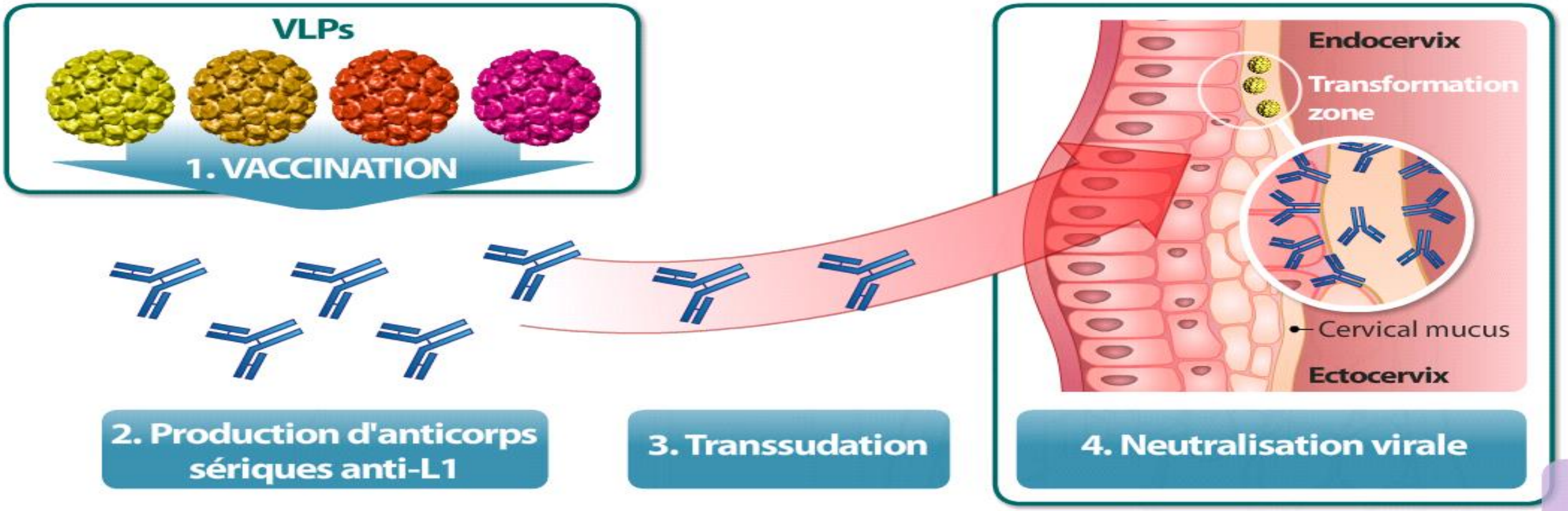




HPV 33 PERSISTENCY



HPV VACCINATION

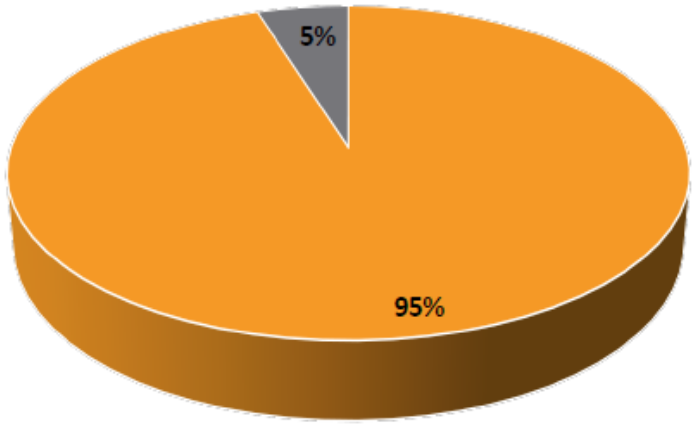


- La *vaccination* entraine une **production d'anticorps neutralisants sériques**
- Ces anticorps sériques **transsudent** à travers la muqueuse cervicale
- *Lors d'une contamination*, ces anticorps **se fixent sur la capside du virus** et **<u>l'empêchent de pénétrer dans les cellules</u>** de la muqueuse cervicale

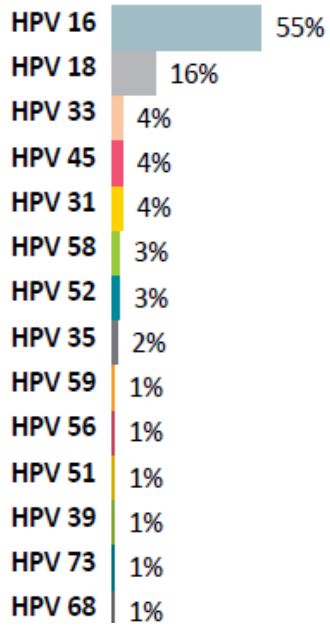
Modifié d'après Schiller JT Davis P Nature Reviews 2004

Almost all (≥ 95%) cases of cervical cancer are caused by an infection from human papillomavirus (HPV)

95% of all cervical cancer cases are caused by HPV[1]



A large proportion of cervical cancer cases is caused by HPV types 16 and 18[2]



HPV VACCINATION

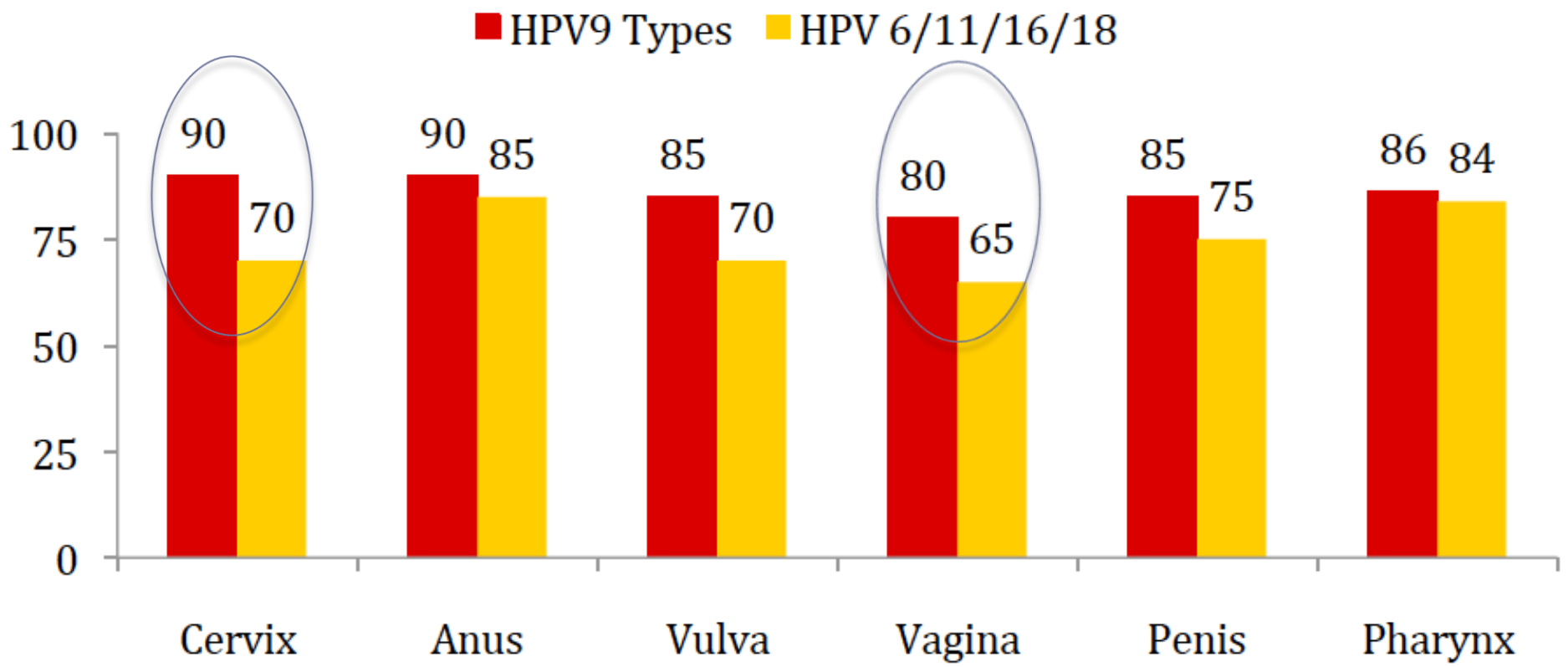
Rational for HPV ninevalent vaccine
16.18.6.11/31.33.45.52.58

Cancer du Col

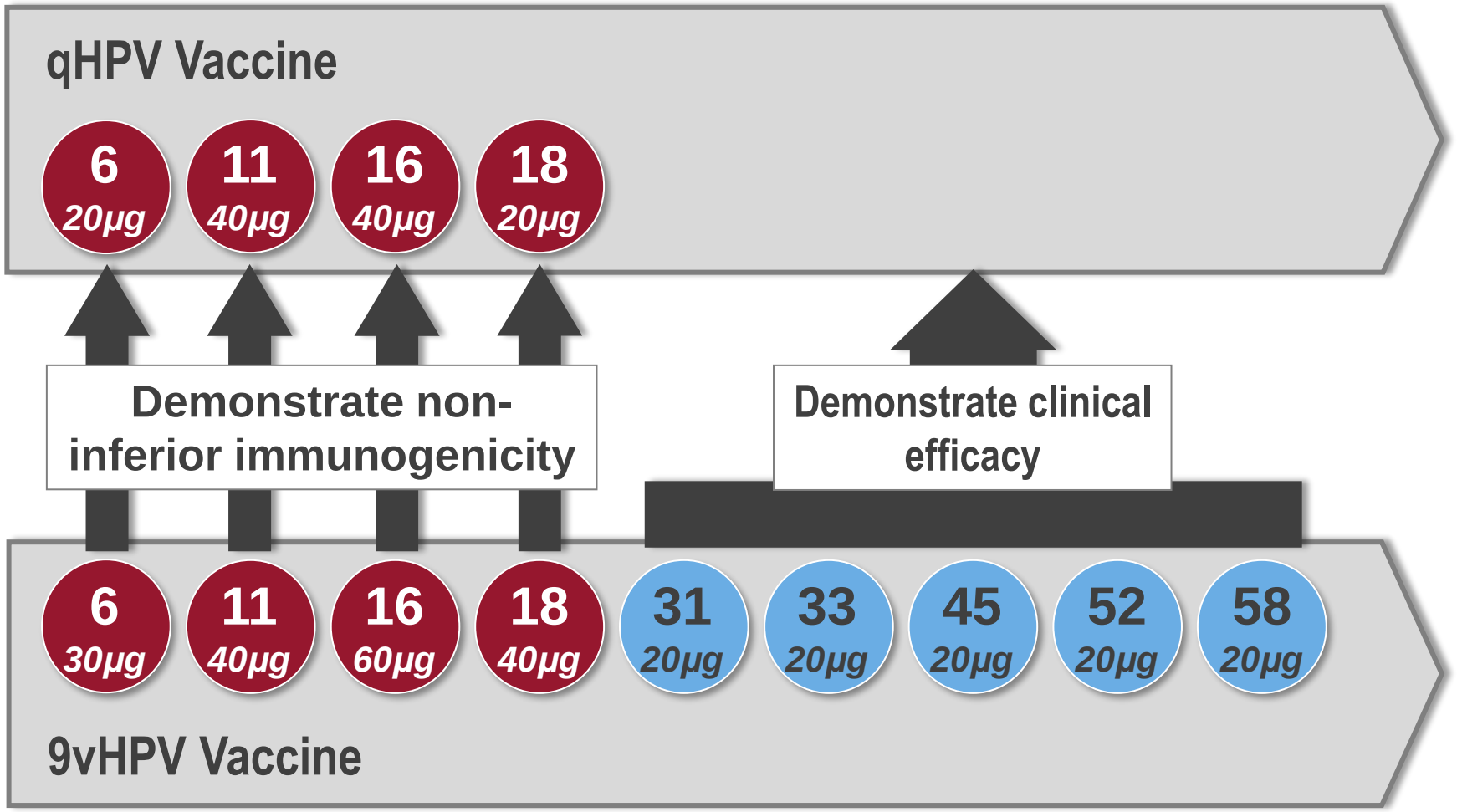
CIN 2/3, AIS

De Sanjose 2010, Hariri 2011, Serrano 2012, Joura 2014

Prevention of HPV related cancers



P001 efficacy study: Primary Objectives



HPV 6/11/16/18 Disease Endpoints
Protocol 001 and Gardasil Historical Cohorts

Supportive Analysis – Per Protocol Efficacy

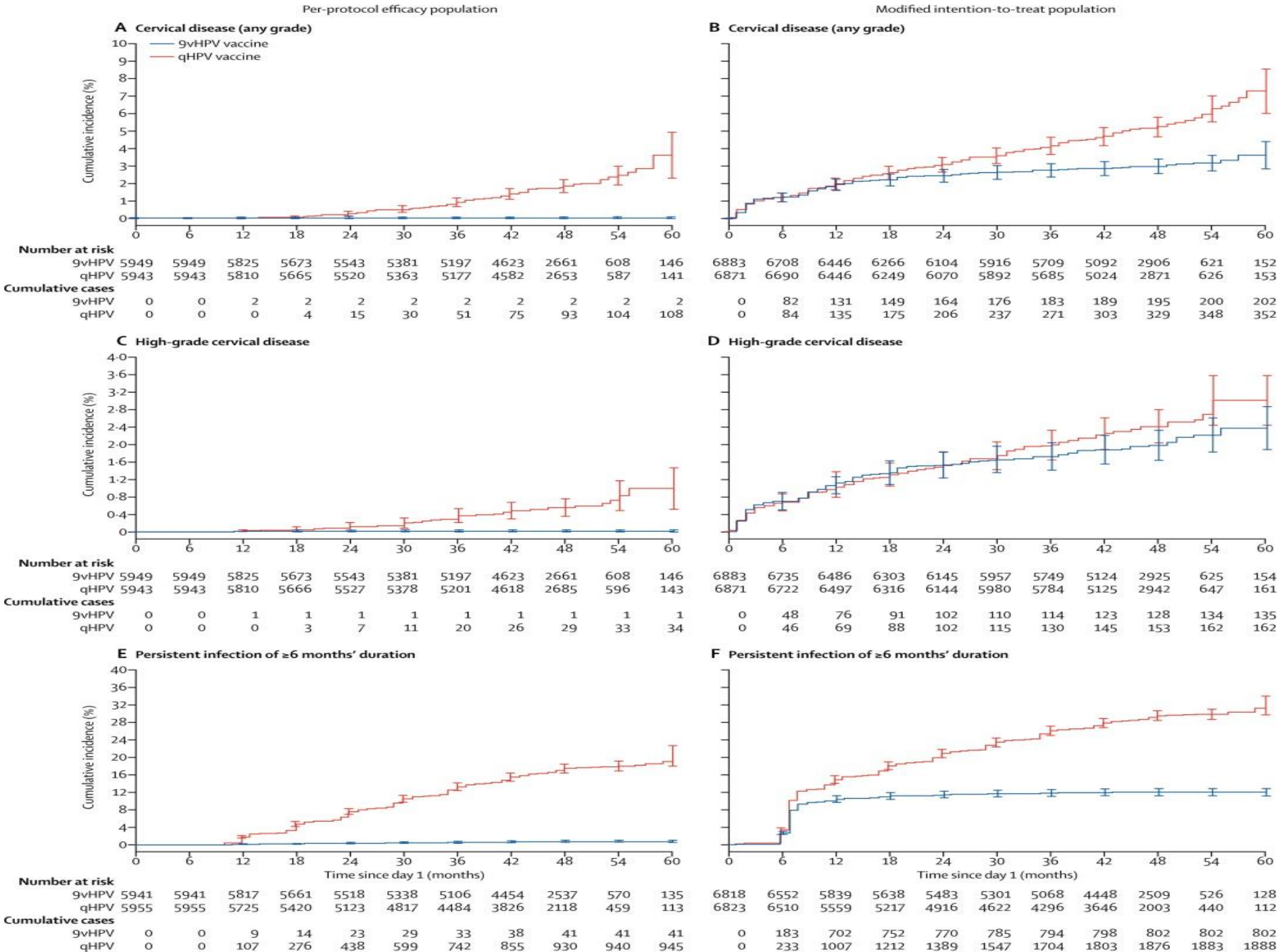
Endpoint	Protocol 001		Historic cohorts from Gardasil program*	
	9vHPV Cases/n	qHPV Cases/n	qHPV Cases/n	Placebo Cases/n
HPV 16/18-related				
CIN 2/3 or AIS	**1** / 5715	**0** / 5732	**2** / 8493	**112** / 8464
VIN 2/3	**0** / 5762	**0** / 5789	**0** / 7772	**10** / 7744
VaIN 2/3	**0** / 5762	**2** / 5789	**0** / 7772	**9** / 7744
HPV 6/11/16/18-related				
CIN (any grade)	**1** / 5823	**3** / 5832	**9** / 7864	**225** / 7865
Condyloma	**5** / 5876	**1** / 5893	**2** / 7900	**193** / 7902

** Based on the Gardasil US label*

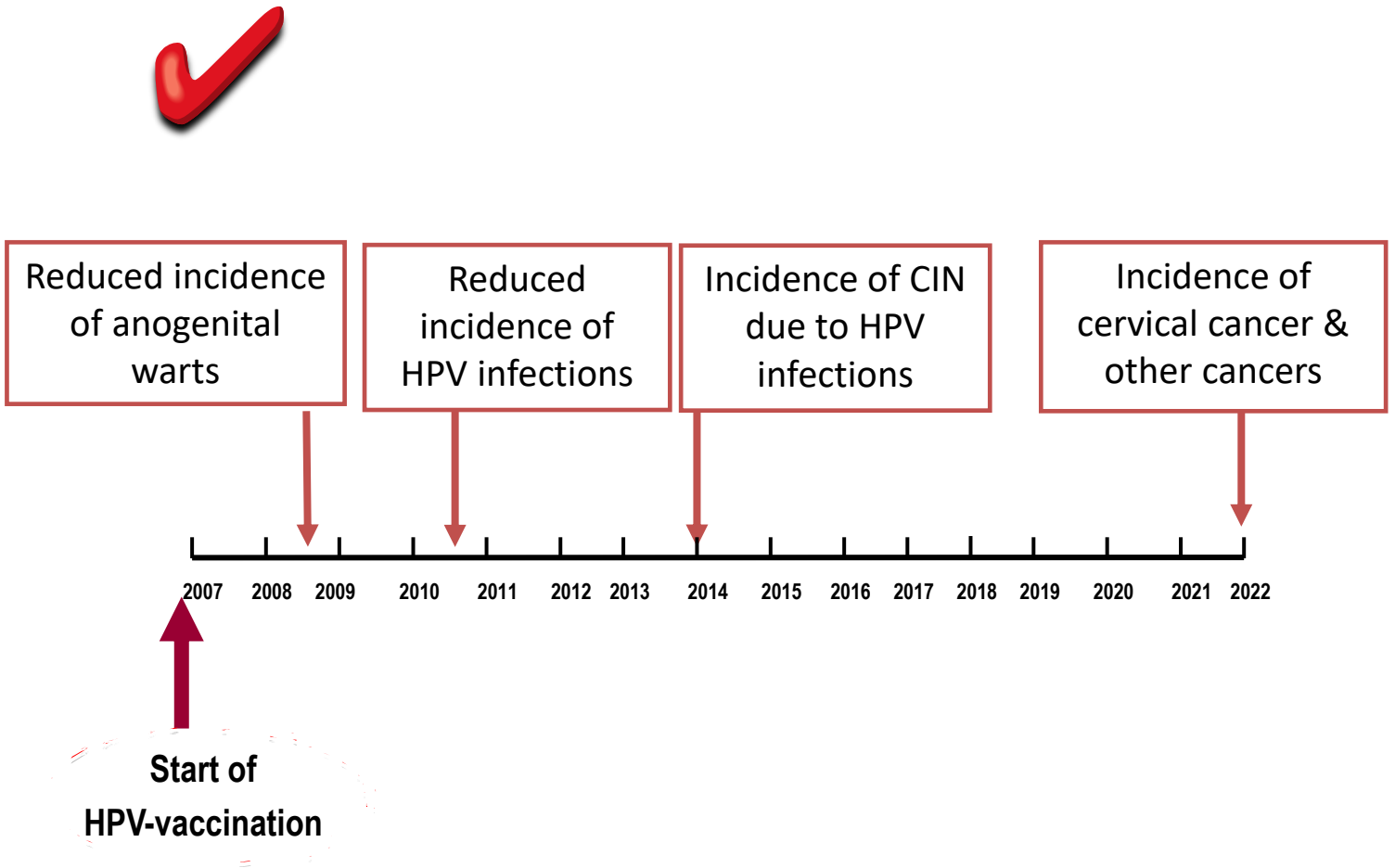
HPV 31/33/45/52/58 Vaccine Efficacy

Per-Protocol Efficacy Population- end of study

Endpoint	9vHPV n	qHPV n	Vaccine Efficacy
All CIN	2 / 5949	110 / 5943	**98.2%** (93.7, 99.7)
> CIN2	1 / 5949	35 / 5943	**97.1%** (83.5, 99.9)
> CIN3	0 / 5949	7 / 5,943	**100%** (39.4, 100)
All VIN, VaIN	1 / 6009	18 / 6012	**94.4%** (67.7, 99.7)
> VIN2/3, VaIN2/3	0 / 6009	3 / 6012	**100.0%** (-71.5, 100)


Per-protocol efficacy population
Modified intention-to-treat population
A Cervical disease (any grade)
B Cervical disease (any grade)
9vHPV vaccine
qHPV vaccine
Cumulative incidence (%)
Number at risk
9vHPV 5949 5949 5825 5673 5543 5381 5197 4623 2661 608 146
qHPV 5943 5943 5810 5665 5520 5363 5177 4582 2653 587 141
6883 6708 6446 6266 6104 5916 5709 5092 2906 621 152
6871 6690 6446 6249 6070 5892 5685 5024 2871 626 153
Cumulative cases
9vHPV 0 0 2 2 2 2 2 2 2 2 2
qHPV 0 0 0 4 15 30 51 75 93 104 108
0 82 131 149 164 176 183 189 195 200 202
0 84 135 175 206 237 271 303 329 348 352
C High-grade cervical disease
D High-grade cervical disease
Number at risk
9vHPV 5949 5949 5825 5673 5543 5381 5197 4623 2661 608 146
qHPV 5943 5943 5810 5666 5527 5378 5201 4618 2685 596 143
6883 6735 6486 6303 6145 5957 5749 5124 2925 625 154
6871 6722 6497 6316 6144 5980 5784 5125 2942 647 161
Cumulative cases
9vHPV 0 0 1 1 1 1 1 1 1 1 1
qHPV 0 0 0 3 7 11 20 26 29 33 34
0 48 76 91 102 110 114 123 128 134 135
0 46 69 88 102 115 130 145 153 162 162
E Persistent infection of ≥6 months' duration
F Persistent infection of ≥6 months' duration
Time since day 1 (months)
Number at risk
9vHPV 5941 5941 5817 5661 5518 5338 5106 4454 2537 570 135
qHPV 5955 5955 5725 5420 5123 4817 4484 3826 2118 459 113
6818 6552 5839 5638 5483 5301 5068 4448 2509 526 128
6823 6510 5559 5217 4916 4622 4296 3646 2003 440 112
Cumulative cases
9vHPV 0 0 9 14 23 29 33 38 41 41 41
qHPV 0 0 107 276 438 599 742 855 930 940 945
0 183 702 752 770 785 794 798 802 802 802
0 233 1007 1212 1389 1547 1704 1803 1876 1883 1888

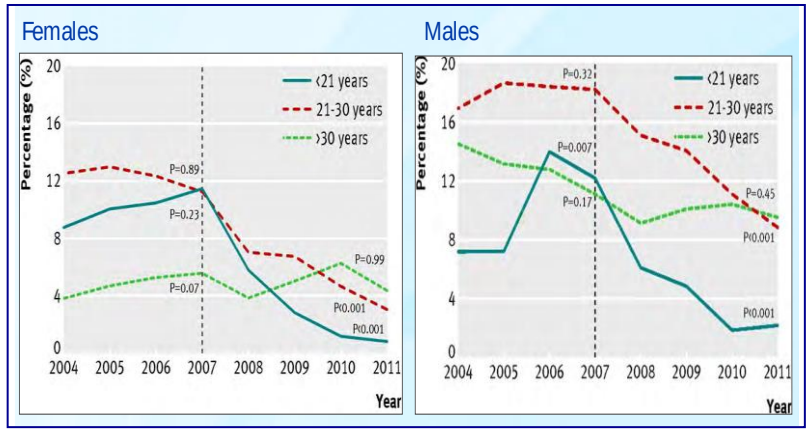
Real-life populations

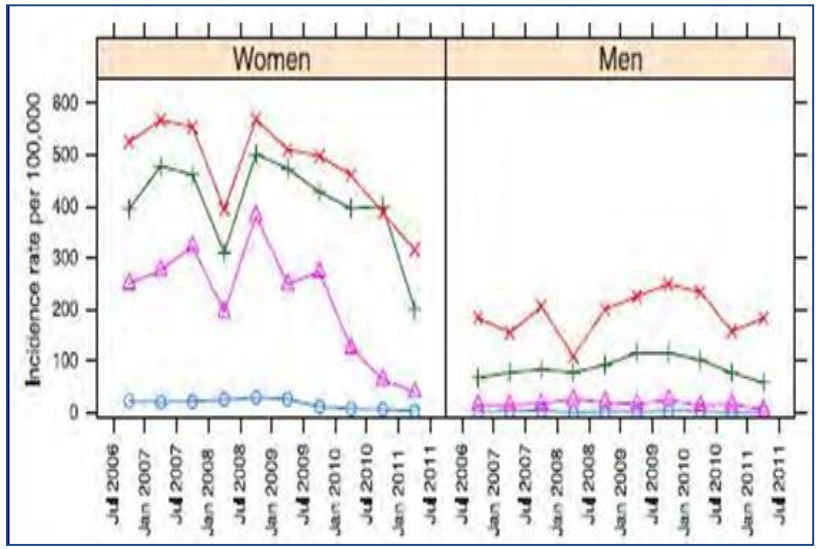


Gross MS J Pediatr Adolesc Gynecol 2010; Brotherton J Abstract 408. IPC 2010; Fairley CK Sex Trans Dis 2009; Donovan B et al. Lancet Infect Dis 2010; Crowe BMJ 2014

Anogenital warts

% of Australian born women & heterosexual men with first diagnosis of genital warts 2004-2011





Australia

Reduction 93% in <21y & 73% in 21-30y

Reduction 82% in <21y & 51% in 21-30y

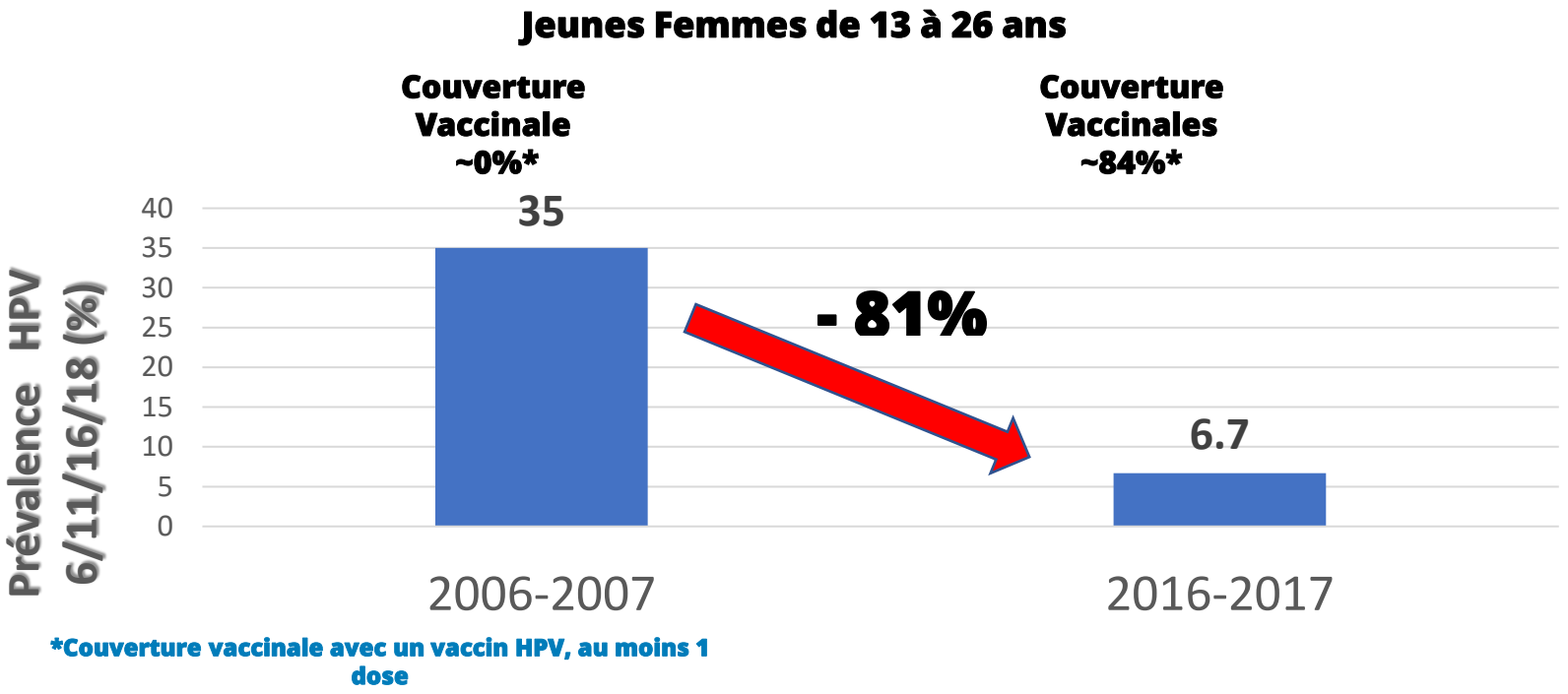
Ali BMJ 2013

Denmark

Reduction 90% in 16-17y (2008-2011)

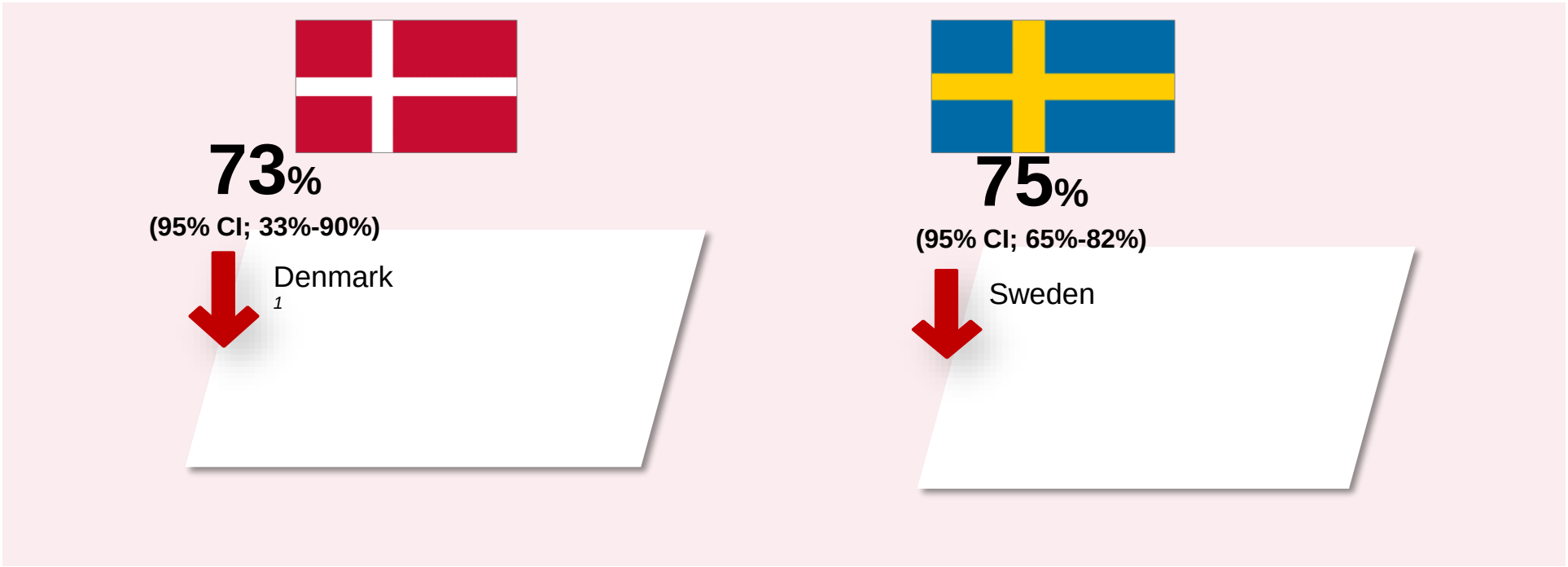
Baandrup STD 2013

Actual trends
USA-10 years follow up , major reduction of **vaccine HPV related types**



Spinner et al. Pediatrics 2019

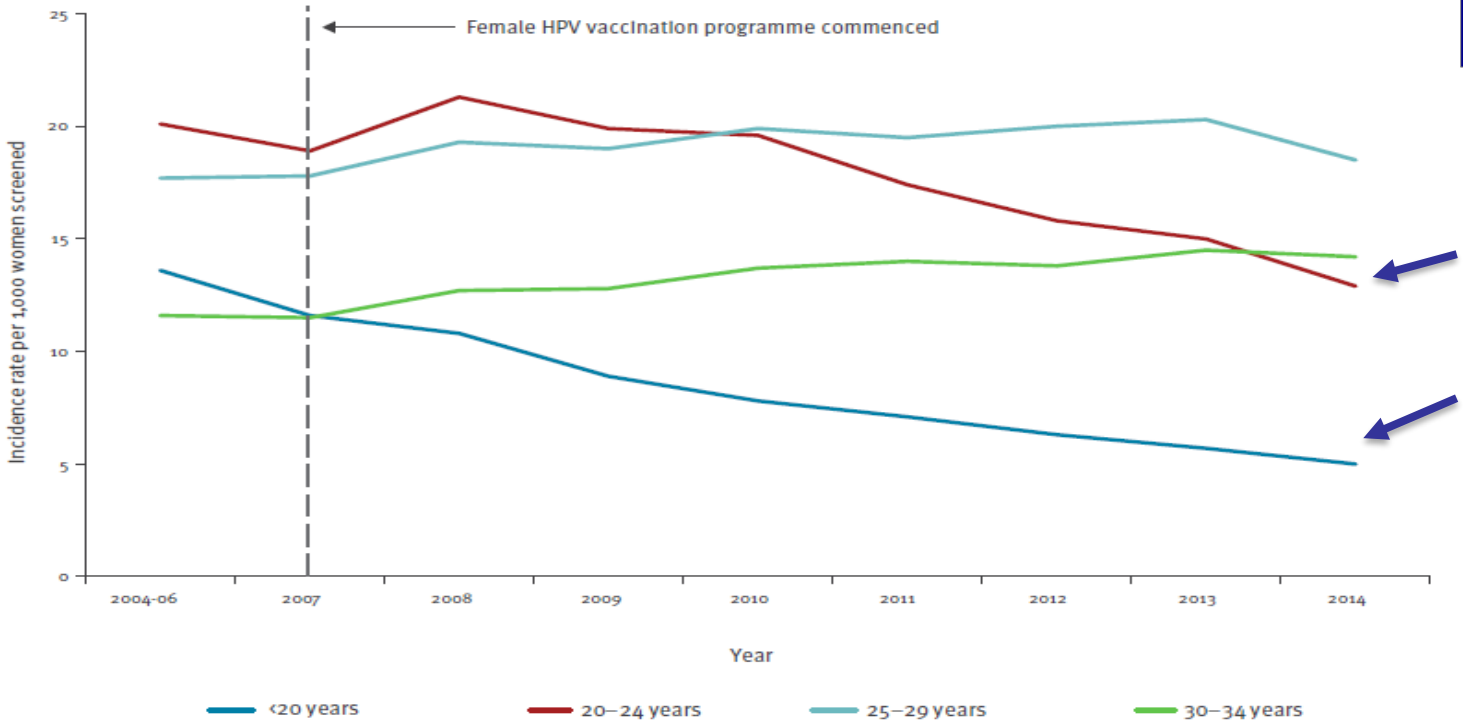
Significant reduction of HG CIN in young women



*Réduction de risque de CIN2/3, cohorte de jeunes filles nées entre 1993 et 1994
**Réduction du risque CIN2+, initiation de la vaccination avant 17 ans

1. Baldur-Felskov B et al. *J Natl Cancer Inst*. 2014;106:djt460. **2.** Herweijer E et al. *Int J Cancer.* 2016;138:2867–2874.

Significant reduction of HG CIN in young women



Incidence des lésions pré-cancéreuses du col de l'utérus avant et après introduction du programme de vaccination anti-HPV

Réductions importantes à l'échelle de la population dans les classes d'âge les plus jeunes, concernées par le programme de vaccination HPV

1. Patel et al. The impact of 10 years of human papillomavirus (HPV) vaccination in Australia: what additional disease burden will a nonavalent vaccine prevent?. . Euro Surveill. 2018;23(41):pii=1700737. https://doi.org/10.2807/1560-7917.ES.2018.23.41.1700737

HPV vaccines are efficient and safe

Cochrane Library

Cochrane Database of Systematic Reviews

26 essais RCT, > **73 000 women**

Reduction of pre K cervical lesions related to HPV vaccine types :

164 / 10 000 vs 2 / 10 000

⇒Similar side events in vaccinated vs non vaccinated women

*CIN2+

Arbyn et al. Cochrane Database of Systematic Reviews 2018

IMPACT OF HPV VACCINE ON CERVICAL CANCER GARDASIL4

Méthode

- Etude d'efficacité en vie réelle (*effectiveness*), sur la base des registres suédois
- Comparaison de *l'incidence des cancers du col invasifs* (CCU) entre des jeunes filles/femmes *vaccinée*s et *non-vaccinées pour le HPV*
- Etude réalisée sur l'ensemble de la population des jeunes filles/jeunes femmes suédoises, âgées entre 10 et 30 ans, entre 2006 et 2017

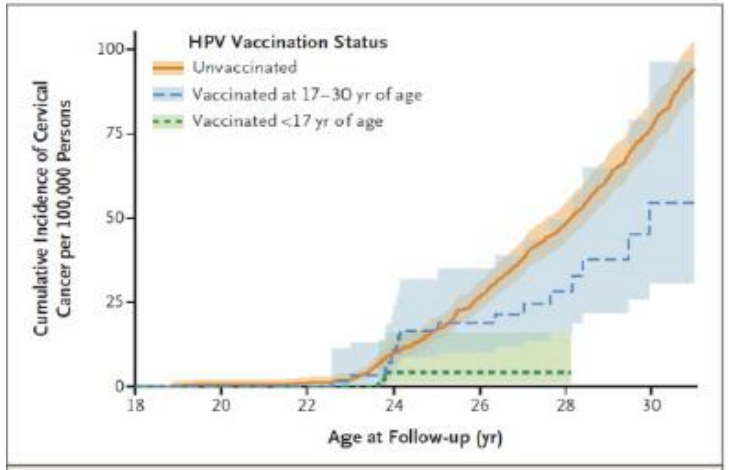


Figure 2. **Cumulative Incidence of Invasive Cervical Cancer According to HPV Vaccination Status.**
Age at follow-up is truncated in the graph because no cases of cervical cancer were observed in girls younger than 18 years of age.

Résultats : Sur la base de **> 1,6 M de jeunes filles/femmes**

Réduction significative du risque de CCU après vaccination HPV:

✓ **88%** [95% CI : 66-100%] *vs non-vaccinées*, lorsque la vaccination était initiée **avant l'âge de 17 ans**

✓ **53%** [95% CI: 25-73%] *vs non-vaccinées*, lorsque la vaccination était initiée **entre 17 et 30 ans**

La vaccination HPV était associée à un risque significativement plus bas de CCU.
La réduction observée était ***d'autant plus importante*** que la vaccination HPV ***était initiée jeune.***

Lei et al. NEJM. 2020

CERVARIX

Findings We used data from a total of 13·7 million-years of follow-up of women aged 20 years to younger than 30 years. The estimated relative reduction in cervical cancer rates by age at vaccine offer were 34% (95% CI 25–41) for age 16–18 years (school year 12–13), 62% (52–71) for age 14–16 years (school year 10–11), and 87% (72–94) for age 12–13 years (school year 8), compared with the reference unvaccinated cohort. The corresponding risk reductions for CIN3 were 39% (95% CI 36–41) for those offered at age 16–18 years, 75% (72–77) for age 14–16 years, and 97% (96–98) for age 12–13 years. These results remained similar across models. We estimated that by June 30, 2019 there had been 448 (339–556) fewer than expected cervical cancers and 17 235 (15 919–18 552) fewer than expected cases of CIN3 in vaccinated cohorts in England.

	Cervical cancer			CIN3		
	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3
Unvaccinated cohorts						
Cohort 1: invited from age 20·0 years and no vaccine	0·99 (0·89–1·10)	1·00 (0·90–1·11)	0·99 (0·89–1·10)	0·97 (0·93–1·00)	0·98 (0·94–1·01)	0·97 (0·94–1·01)
Cohort 2: invited from age 20·0 years or 25 years and no vaccine	1·08 (0·95–1·22)	1·09 (0·97–1·23)	1·08 (0·96–1·22)	1·02 (0·98–1·06)	1·03 (0·99–1·07)	1·03 (0·99–1·06)
Cohort 3: invited from age 25·0 years and no vaccine	1·03 (0·93–1·15)	1·04 (0·94–1·16)	1·04 (0·93–1·15)	1·01 (0·97–1·04)	1·02 (0·98–1·05)	1·01 (0·98–1·05)
Cohort 4: invited from age 24·5 years and no vaccine (reference category)	1·00	1·00	1·00	1·00	1·00	1·00
Vaccinated cohorts						
Cohort 5: invited from age 24·5 years and offered vaccine in school years 12–13	0·67 (0·59–0·75)	0·66 (0·58–0·74)	0·66 (0·59–0·75)	0·61 (0·59–0·64)	0·61 (0·58–0·64)	0·61 (0·59–0·64)
Cohort 6: invited from age 24·5 years and offered vaccine in school years 10–11	0·39 (0·31–0·50)	0·37 (0·29–0·47)	0·38 (0·29–0·48)	0·26 (0·24–0·29)	0·24 (0·22–0·27)	0·25 (0·23–0·28)
Cohort 7: not invited before age 24·5 years and offered vaccine in school year 8	0·13 (0·06–0·27)	0·12 (0·06–0·26)	0·13 (0·06–0·28)	0·03 (0·02–0·04)	0·03 (0·02–0·04)	0·03 (0·02–0·04)

Data are IRR (95% CI). Model 1 adjusts for all main effects for age and cohort, age-by-cohort interactions, linear trend (drift), and dummy variables for the Jade Goody and seasonal effects. Model 2 contains all effects in model 1 plus adjustment for under-registration. Model 3 includes all effects in model 1 plus adjustment for the screening awareness campaign. The estimates are adjusted for the covariates included in the models, details in the methods. IRRs=incidence rate ratios. CIN=cervical intraepithelial neoplasia.

Table 3: Estimated IRRs and 95% CIs of either cervical cancer or CIN3 among the vaccinated and unvaccinated birth cohorts.

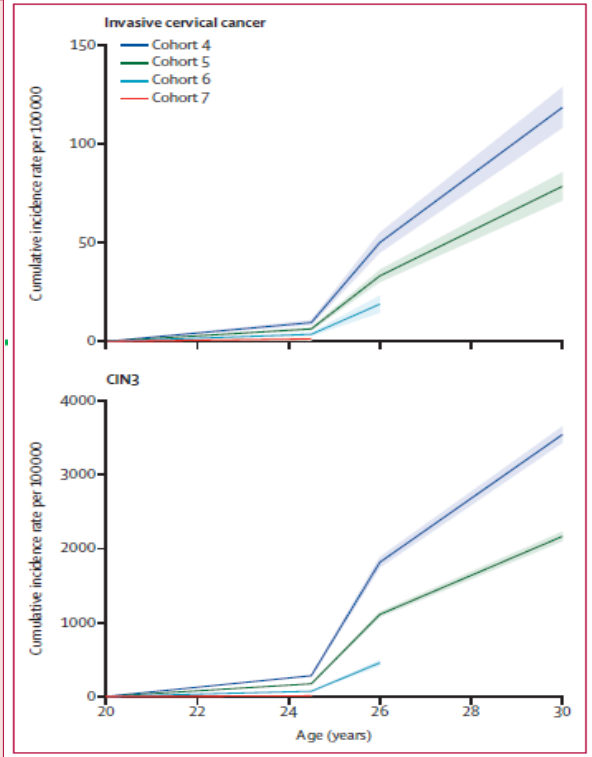


Figure 2: Cumulative incidence rates of cervical cancer and CIN3 by birth cohort

www.thelancet.com **Published online November 3, 2021 https://doi.org/10.1016/S0140-6736(21)02178-4**

Drug Saf
https://doi.org/10.1007/s40264-017-0625-z

REVIEW ARTICLE

Safety of Human Papillomavirus Vaccines: An Updated Review

Anastasia Phillips[1] · Cyra Patel[2] · Alexis Pillsbury[2] · Julia Brotherton[3,4] · Kristine Macartney[1,2]

- **109 études, dont 15 en population entre 2012 et 2016**
- **> 2,5 Millions de vaccinés**

«HPV vaccines are safe

Phillips et al. Drug Safety. 2017 .

HPV vaccination in Post-conisation

Rationale

Women that have conisation for HSIL

- at high risk of HSIL recurrence – 8%
- at high risk of cervical cancer – 2-5xfold
- these women constitute a subgroup of infected women particularly sensitive to the infection & rapidly acquire re-infections
- need to risk-reducing adjuvant treatment for high-risk population
- repeat conisations multiply adverse reproductive outcomes

The vaccine

- Is expected to benefit against **new** infections (not present at Tx)
- Is expected to benefit **re-occurrence** of the same infection
- Remains an open question whether will **boost** the effect of treatment

Indirect Evidence

Joura BMJ 2008 - FUTURE trial – GARDASIL

65% reduction in future CIN2+ in women receiving treatment & previously vaccinated

Garland IJV 2016 – PATRICIA trial – CERVARIX

Vaccinated women who undergo conisation reduced risk of subsequent CIN2+ (efficacy: all HPV 88.2% (14.8, 99.7), HPV-16/18 100% (63.1, 100) NS)

Hidelsheim AJOG 2016

Vaccinated cohorts that went on to have conisation against new incident infections from 16/18 and 31/33/45 types with vaccine efficacy of 58% and 37%, respectively

Retrospective Evidence

Kang Gyn Oncol 2013 - non-randomised study

vaccine 1 week post-conisation - 65% reduction in the risk of recurrent CIN2+

Swedish Clin Infect Dis 2012

non-RCT in men that has sex with men: 56% reduction in recurrent HG AIN

Ghelardi Gyn Oncol 2018

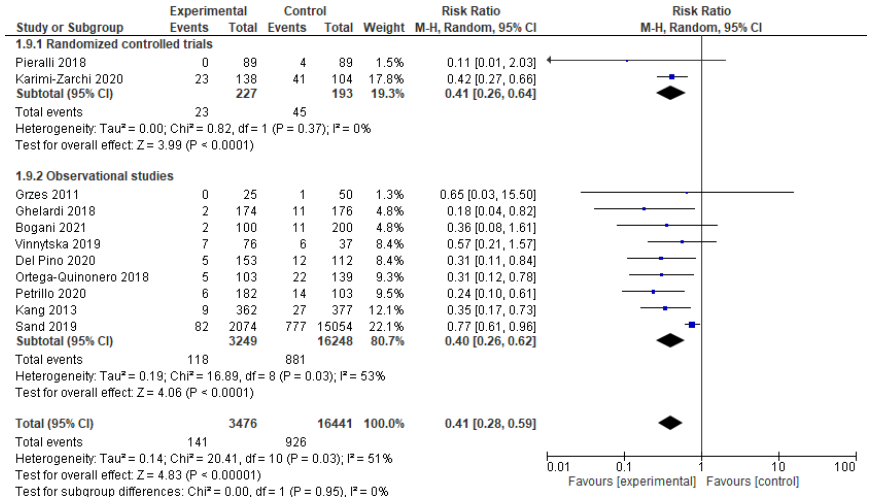
80% clinical effectiveness in disease relapse prevention up to 4y - No therapeutic effect - Beneficial as adjuvant to surgical treatment - Limitations: non-RCT, choice, small

HPV vaccine after Local Treatment for CIN: a meta-analysis Kechagias et al 2021

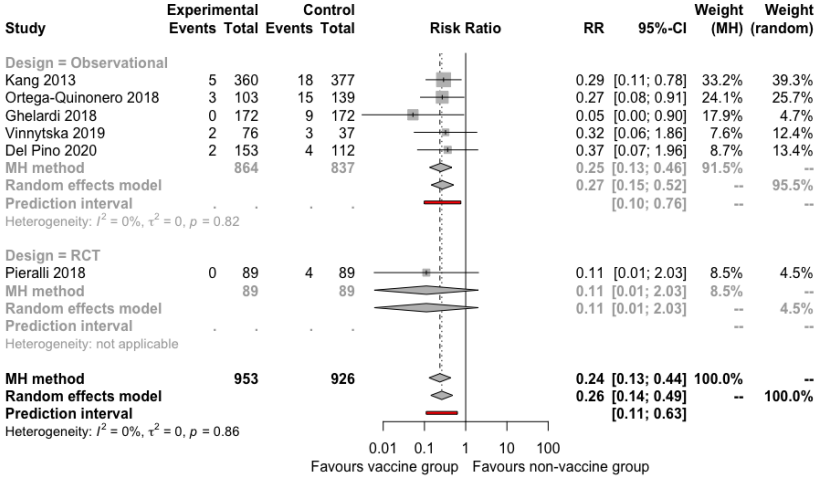
- 18 studies: 12 observational, 2 RCTs and 4 post-hoc analyses of RCTs
- All HPV-related disease
- HPV vaccination was associated with reduced risk of recurrence for CIN2+ lesions (RR 0.41, 95% CI 0.28-0.59, I^2=51%)

CIN2+ recurrence rates HPV vaccine vs non-vaccine

a. irrespective of HPV type



b. HPV16/18-related disease

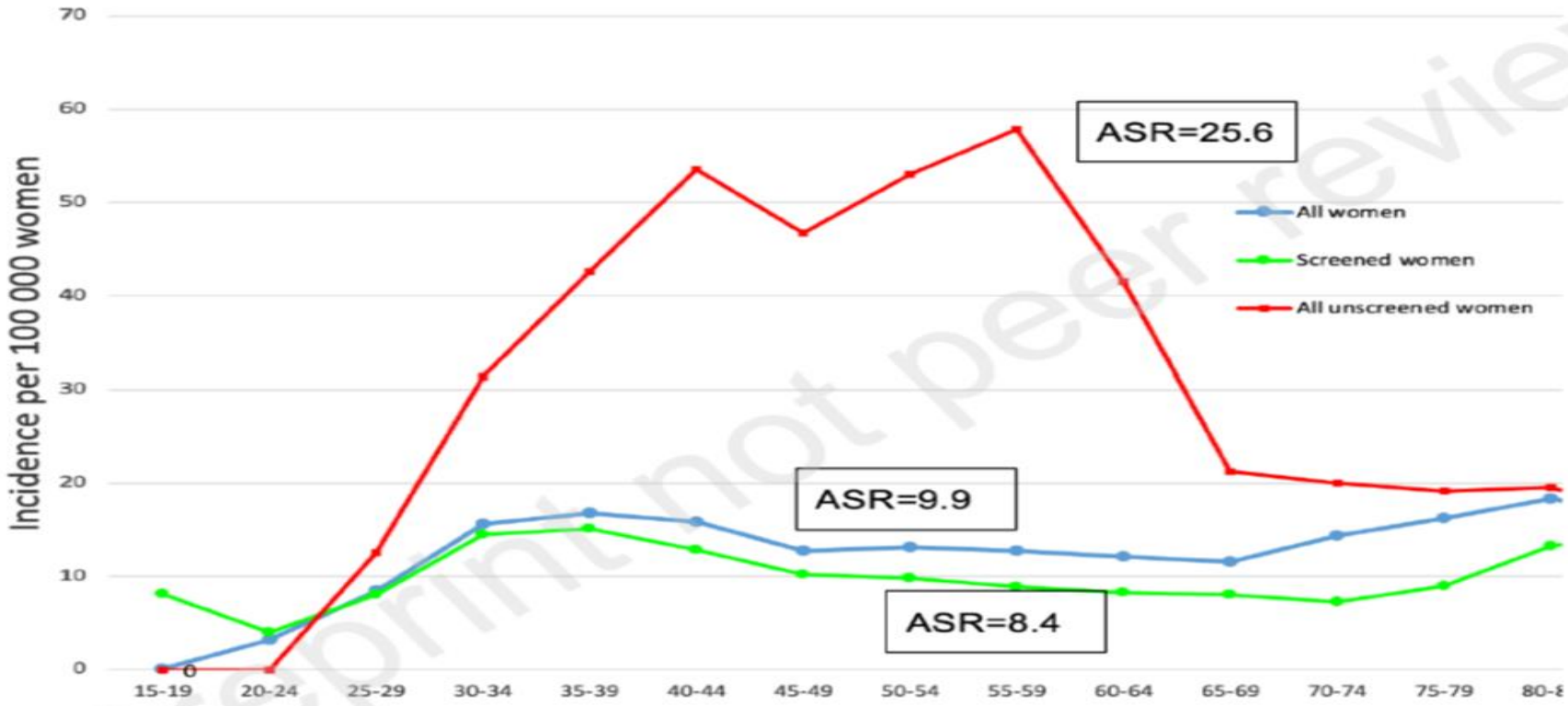


Should women be vaccinated after local excision?

- At present it remains an individual choice
- There is no harm…but not funded
- Promising data but at risk of bias
- Well designed RCT is required to assess effectiveness… and cost-effectiveness
- Before this can be introduced in national vaccination programmes
- Extended to multi-focal disease, immunosuppressed individuals etc

HPV SCREENING

Figure 2: Age-specific incidence rate of invasive cervical cancer in Sweden 2004-2011 by screening status within 10 years prior to each calendar year



Dillner et al 2022

HPV in primary screening
20-25% improvement sensitivity for HG CIN

	Outcome	#Studies	Sensitivity (%)	Specificity (%)
Cytology(ASC-US+)	CIN2+	**25**	70.0 (62.5-77.6)	91.9 (90.3-93.6)
HPV	CIN2+	**31**	**90.4** (88.0-92.8)	88.5 (87.0-90.0)
Cytology(ASC-US+)or hc2 positive	CIN2+	**13**	94.2 (90.8-97.6)	87.7 (85.0-90.3)

1: Updated from Arbyn Vaccine 2012 and Arbyn KCE report 2015=
http://kce.fgov.be/sites/default/files/page_documents/KCE__238_HPV_DNA_Testing_Report2_.pdf

HPV TEST NEGATIVE: OPTIMAL PROTECTION FOR 5 YEARS PERIOD

the bmj | BMJ 2016;355:i4924 | doi: 10.1136/bmj.i4924

Safety of extending screening intervals beyond five years in cervical screening programmes with testing for high risk human papillomavirus: 14 year follow-up of population based randomised cohort in the Netherlands

Maaike G Dijkstra,[1-2] Marjolein van Zummeren,[1] Lawrence Rozendaal,[1] Folkert J van Kemenade,[3] Theo J M Helmerhorst,[4] Peter J F Snijders,[1] Chris J L M Meijer,[1] Johannes Berkhof[5]

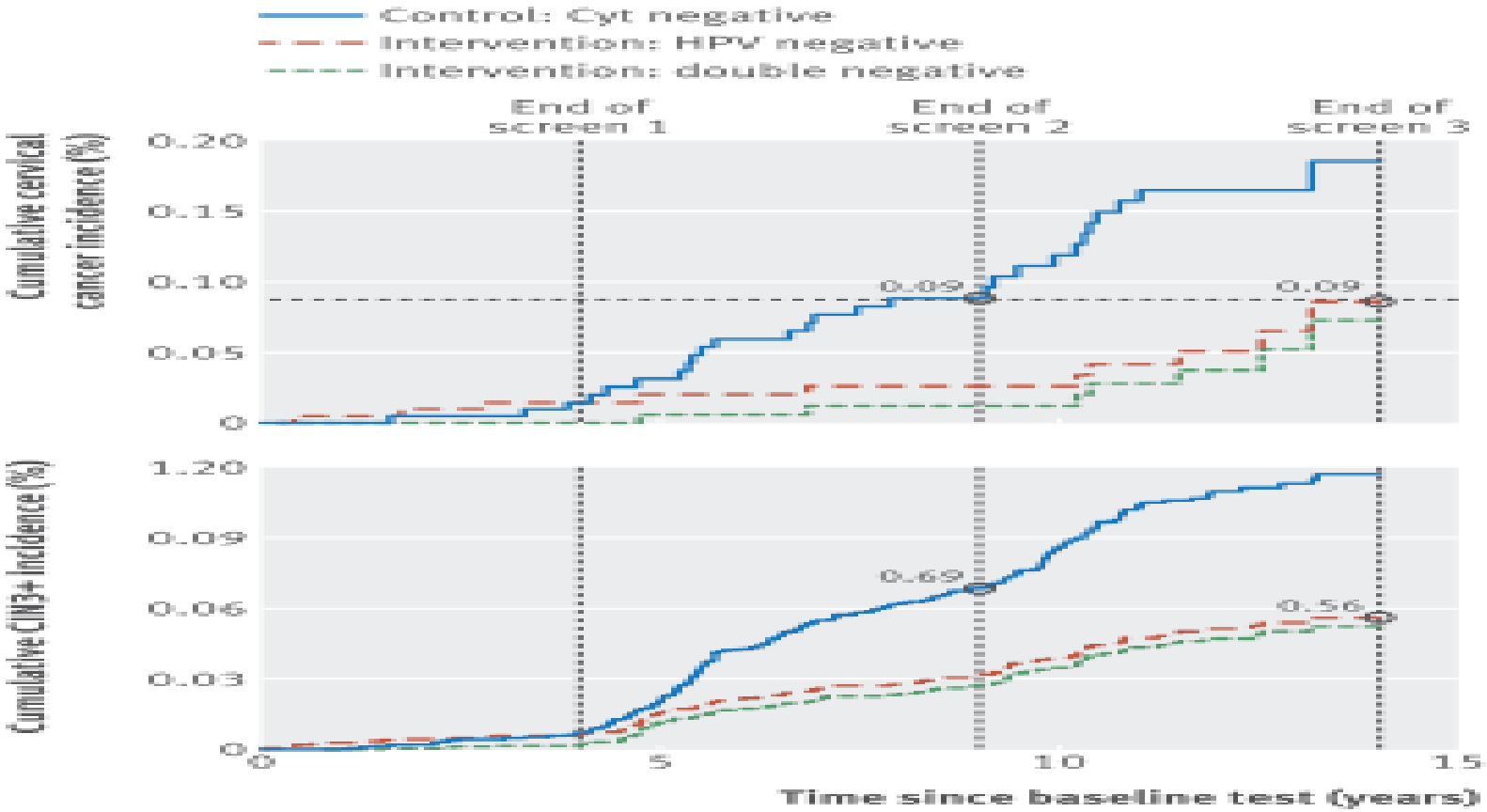
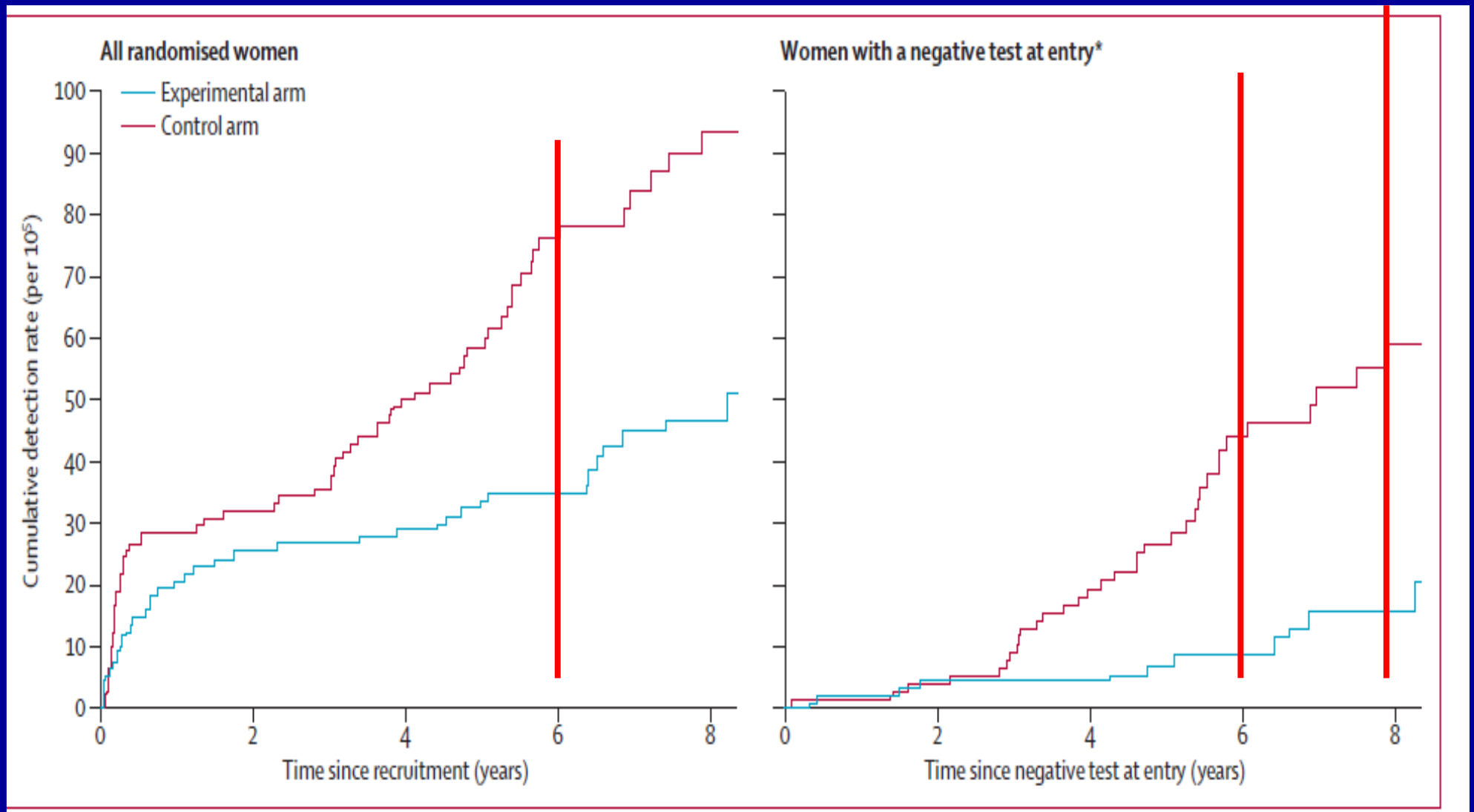


Fig 2 | Cumulative incidence of cervical cancer and CIN3+ per trial group and baseline screening result, after up to three screening rounds. Double negative=women who had negative results for both HPV and cytology testing; Cyt=cytology; HPV=human papillomavirus

CERVICAL K:1 HPV TEST IS MORE PROTECTIVE THAN CYTOLOGY



R Sankarayanan N Engl J Med 2009; 360:1385-1394

Figure 2: Cumulative detection of invasive cervical carcinoma

*Observations are censored 2·5 years after CIN2 or CIN3 detection, if any.

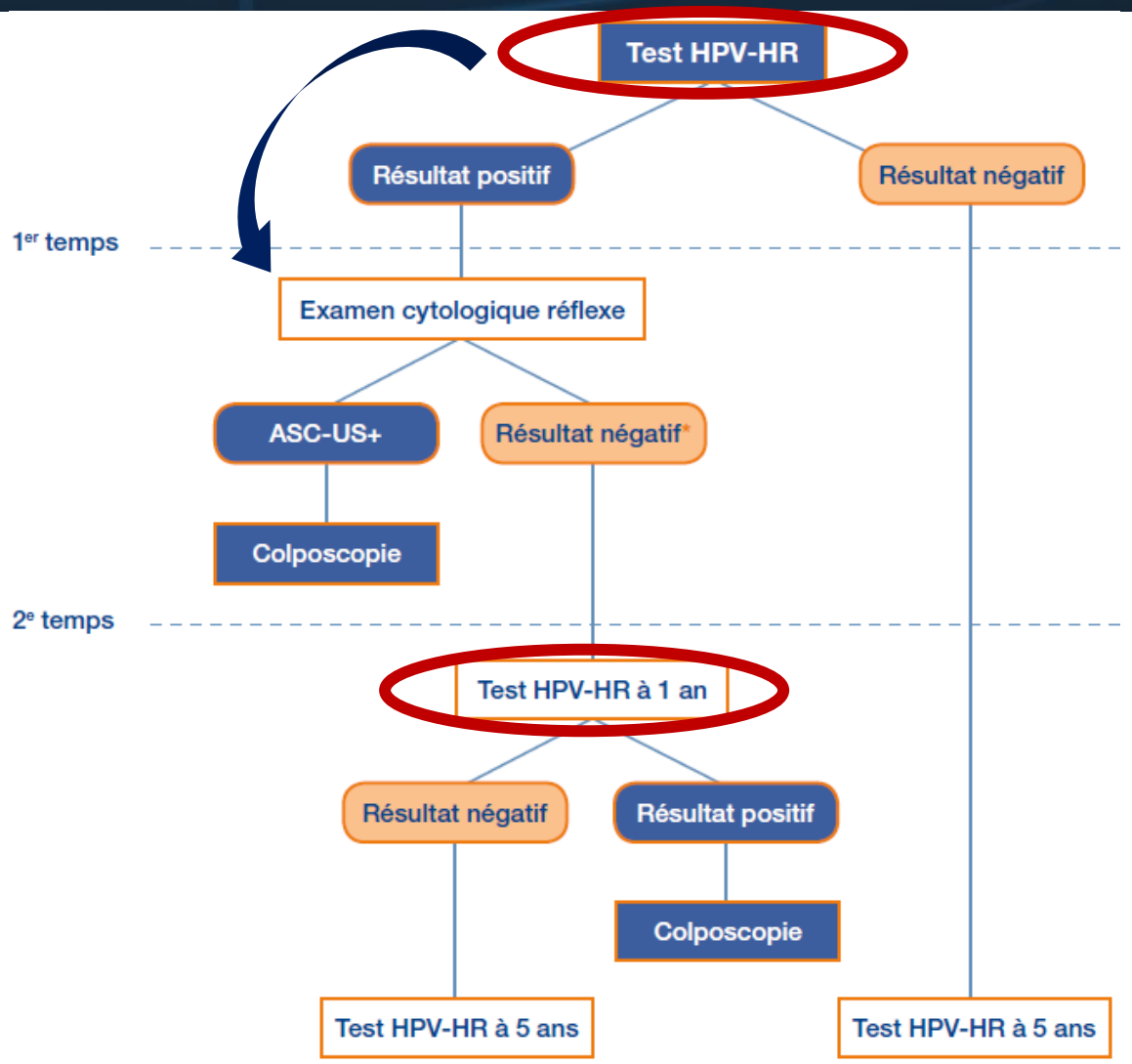
HPV in primary screening has inconveniences benefits exceed the limitations

---

HPV + (+30 ans prevalence 10 -12%) needs **triage** or **risk stratification** in order to reduce:

- Unnecessary colpo(+30-100%!)
- Over-assessment of cyto histology
- Over-diagnosis and over-treatment
- Over-expenses
-Harm for patients

HPV primary screening 30 - 65 years



HAS, juillet 2019

Cervical Cancer ,HPV neg are at bad prognosis

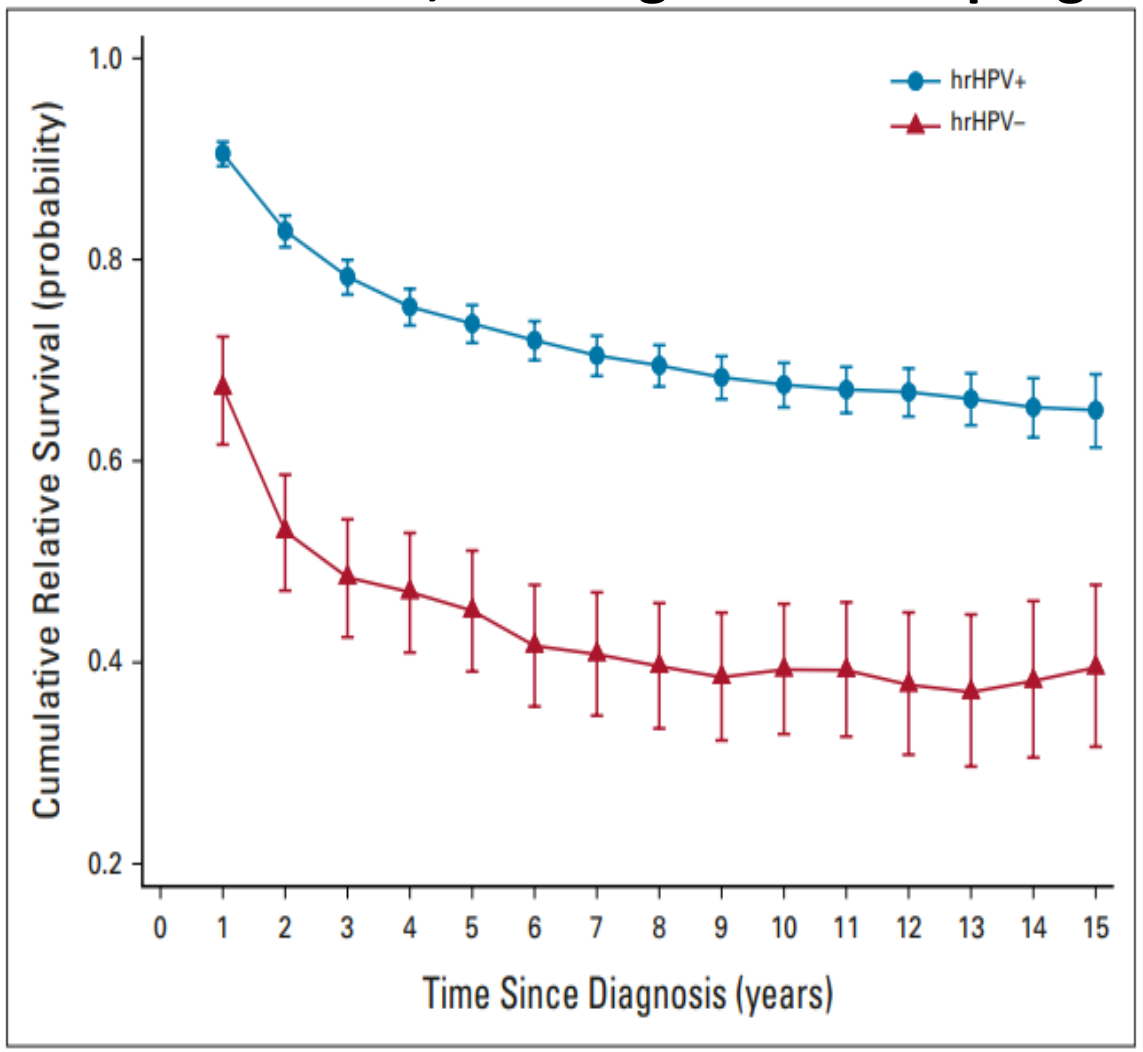


FIG 1. Cumulative relative survival of invasive cervical cancer by tumor hrHPV status. Cumulative relative survival corresponds to the relative survival ratio in relation to the general female population with comparable age and during the same calendar period over the indicated years since diagnosis. hrHPV, high-risk human papillomavirus.

Ji Lei ICO 2021

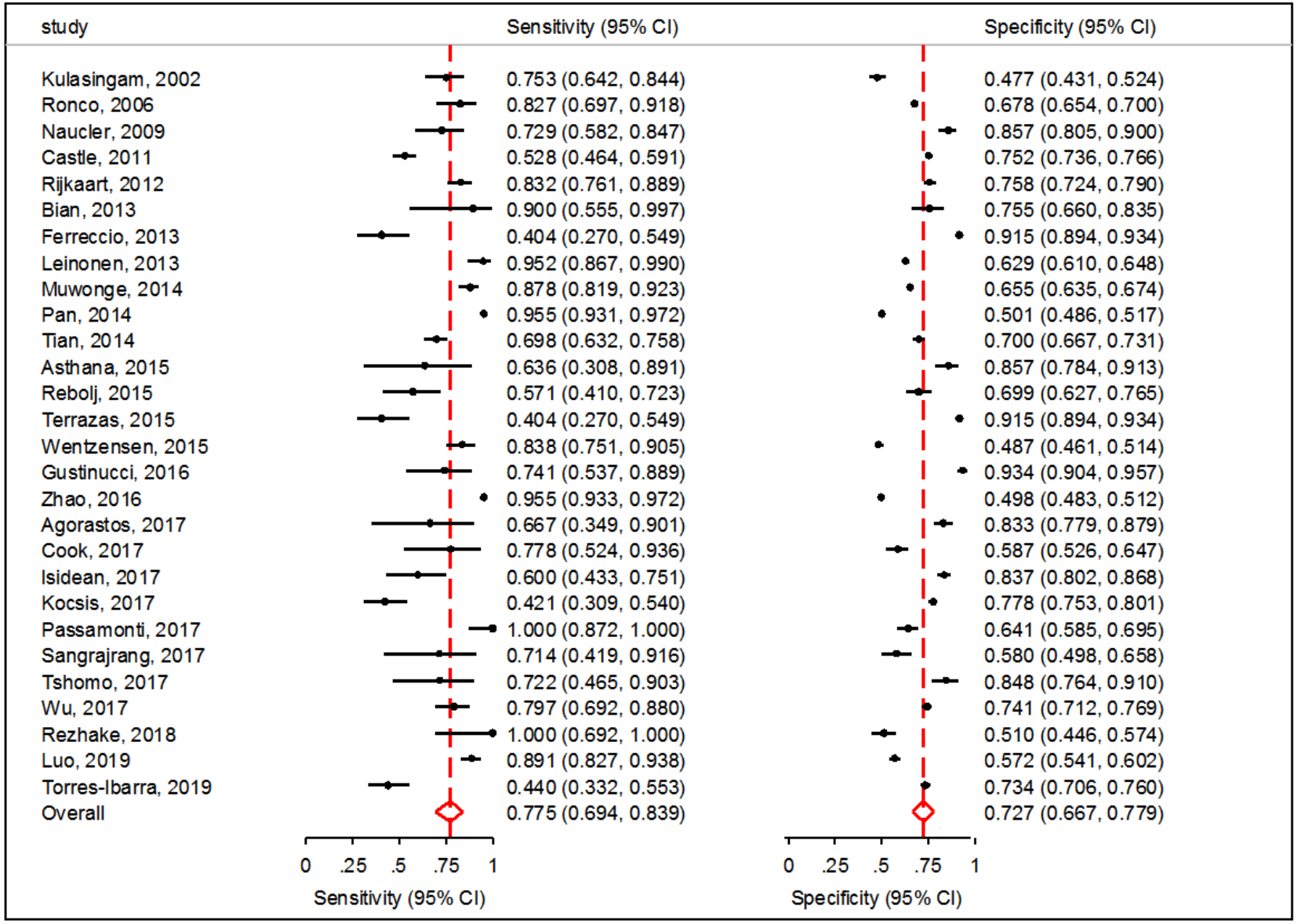
HPV NEGATIVE CIN3

NPV 98%

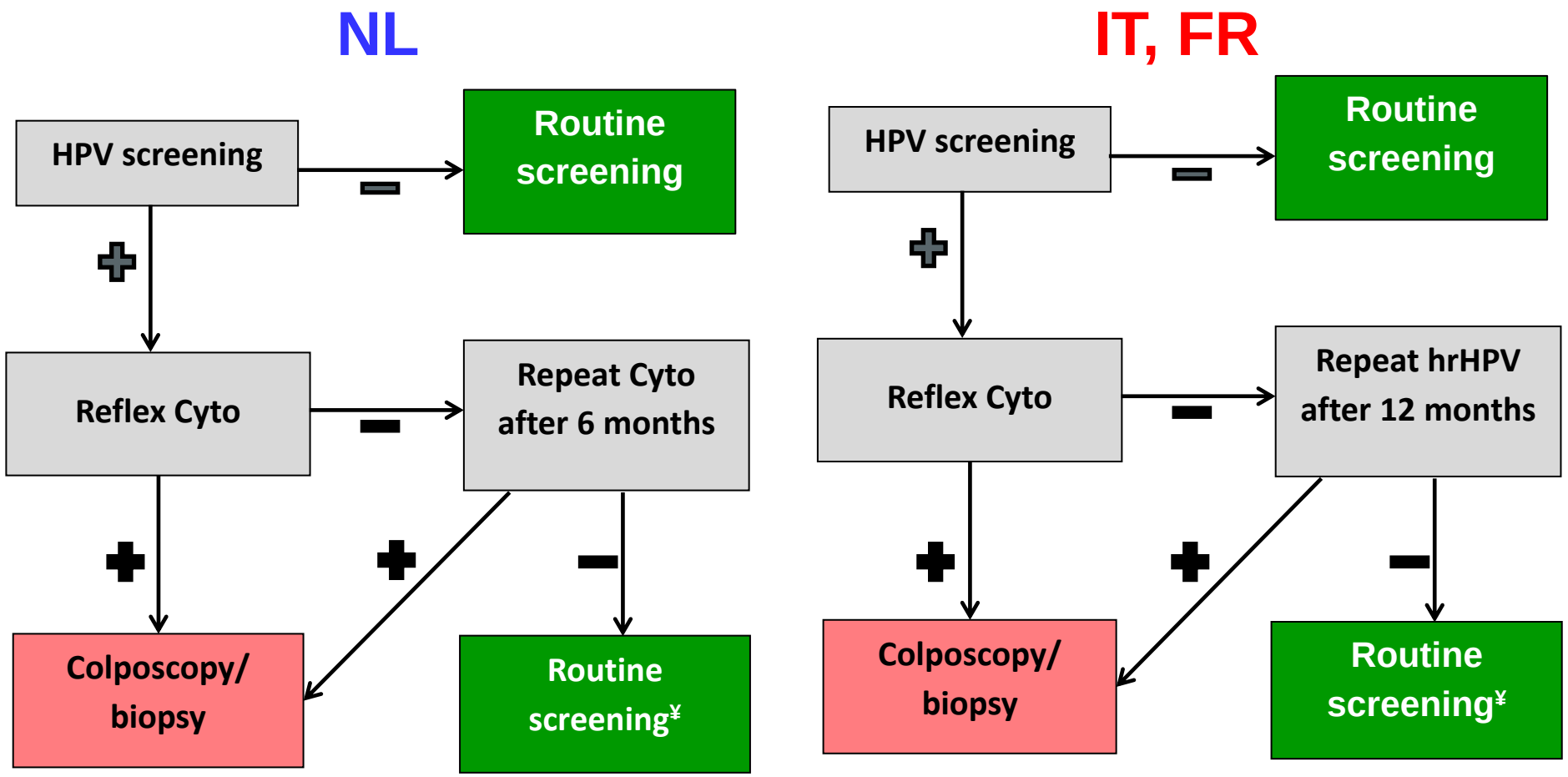
FALSE NEGATIVE OF THE HPV TEST 1 - 3%

J Monsonego et al Int. J. Cancer: 129, 691–701 (2011)

Reflex cytology (ASCUS+), outcome CIN3+

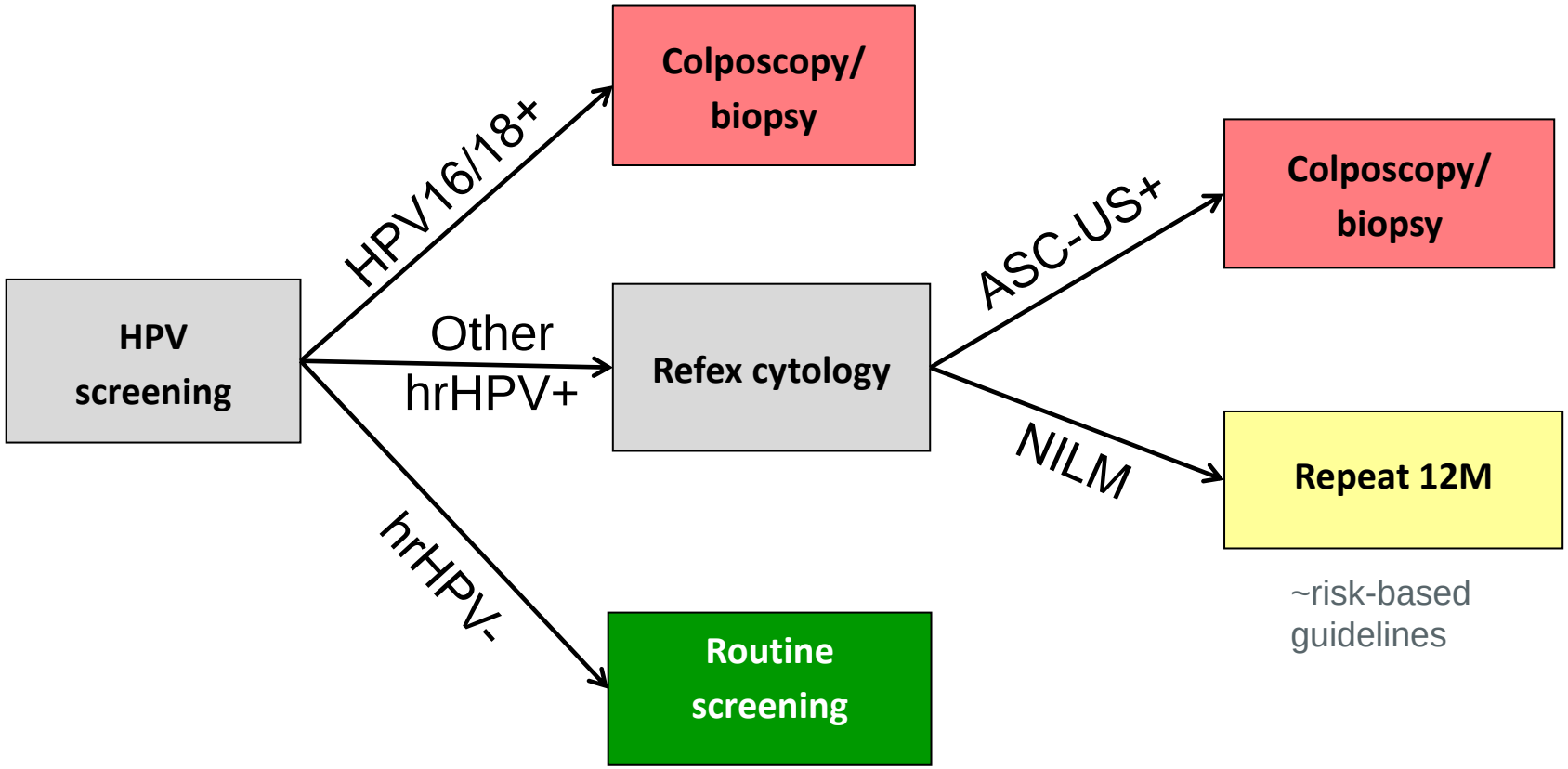


Triage algorithms for hrHPV+



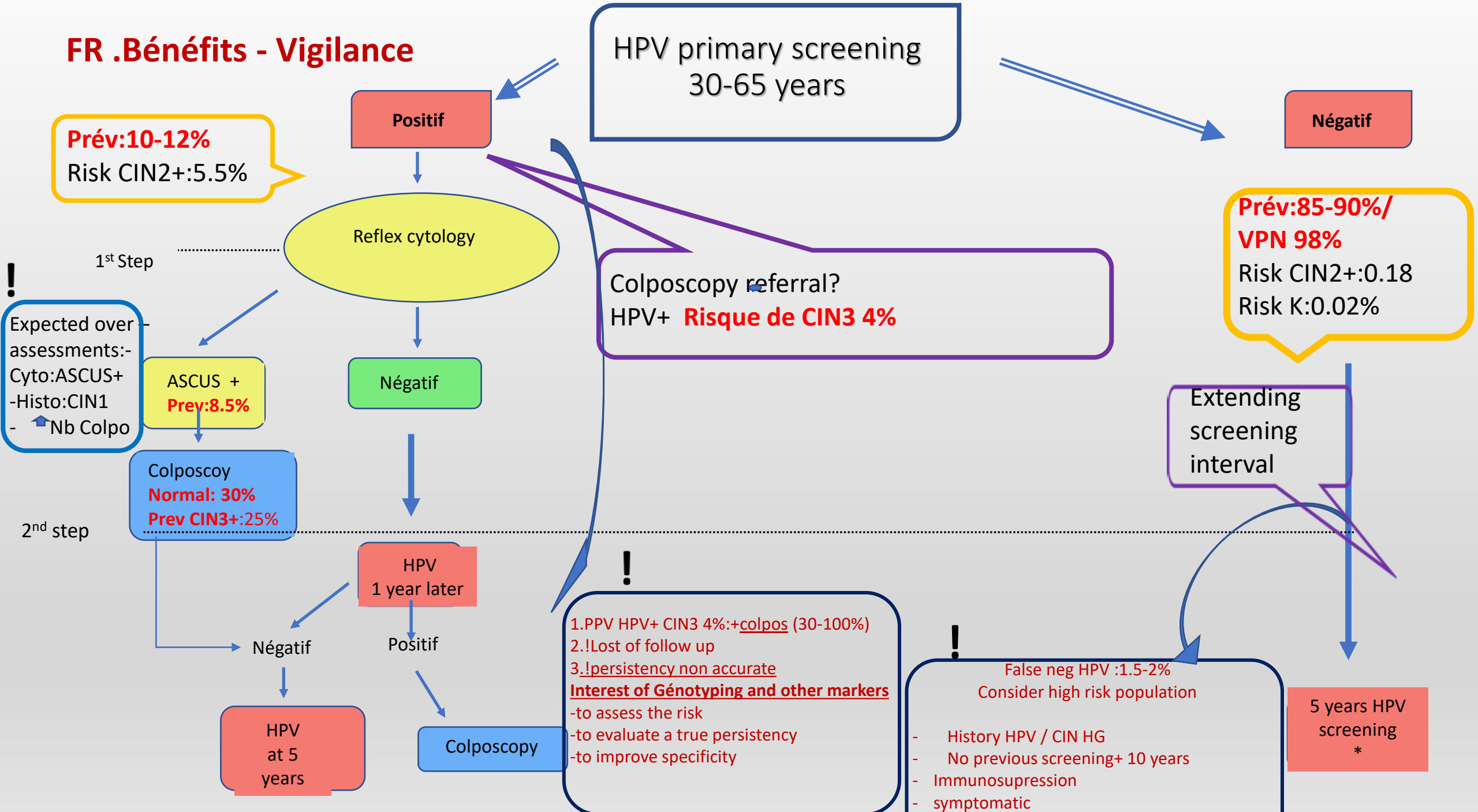
Many more other triage tests & combinations: not shown

USA Triage algorithms for hrHPV+



~risk-based guidelines

FR .Bénéfits - Vigilance



Génotyping

Risk of CIN3+ associated to the most frequents 8 HR HPV types (HPV 16, 18, 31, 33, 35, 45, 52 and 58) FRANCE

J Monsonego et al Vaccine 2012

High-risk HPV type		Adjusted OR*		95% C I	p-value
Other HR types	Other HR vs No HR types	1.768		(0.29,10.65)	0.534
Type specific	HR (specified) vs Other HR types	10.871		(2.53,46.80)	0.001
Type16	16 vs Not 16	10.414	1	(4.74,22.87)	<.001
Type18	18 vs Not 18	1.614	7	(0.21,12.44)	0.646
Type31	31 vs Not 31	2.498	3	(0.84, 7.43)	0.100
Type33	33 vs Not 33	6.656	2	(1.42,31.18)	0.016
Type35	35** vs Not 35	2.370	4	(0.00,14.91)	1.000
Type45	45 vs Not 45	2.093	6	(0.27,16.29)	0.481
Type52	52 vs Not 52	1.416		(0.18,11.02)	0.740
Type58	58 vs Not 58	2.175	5	(0.28,16.98)	0.459

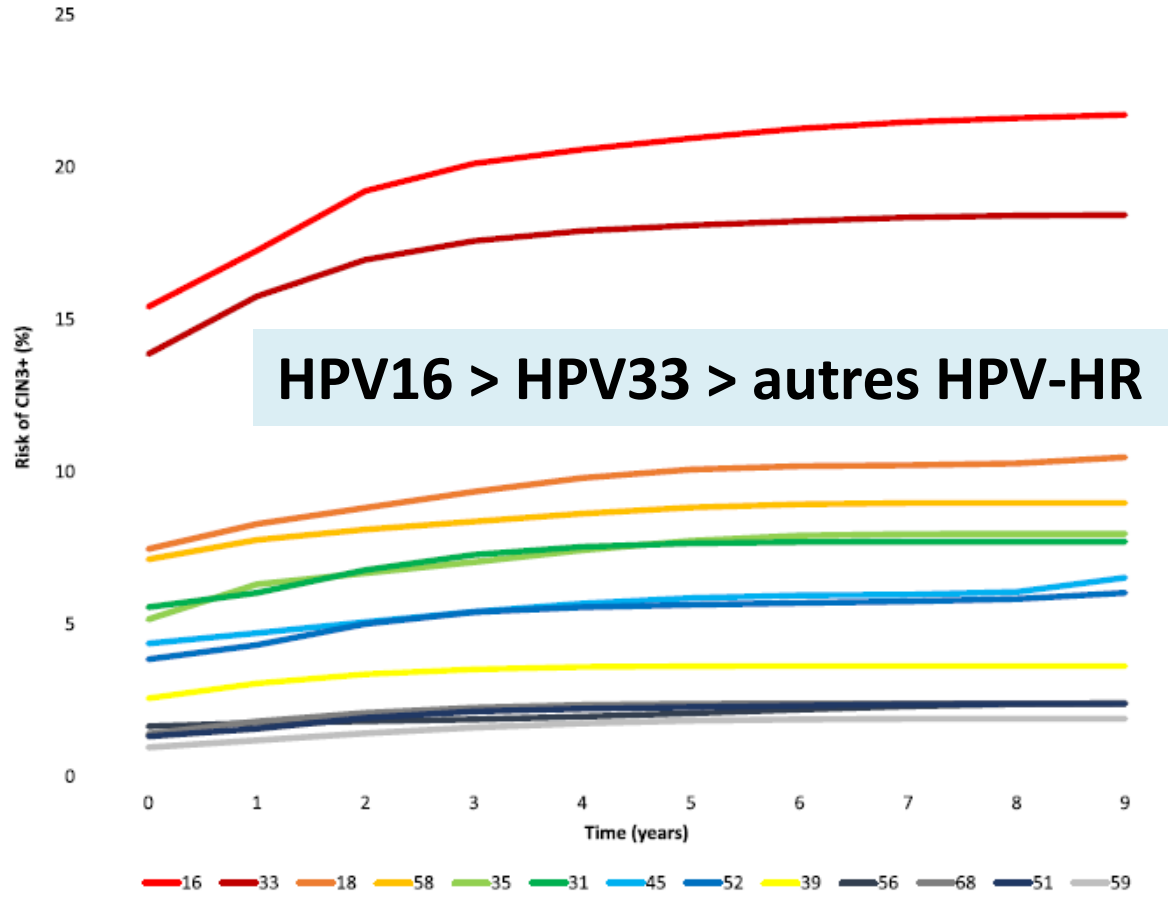
Risk of CIN 3+ by HPVGenotype
ATHENA – women ≥30 years(US)

Genotype	***Absolut Risk CIN 3+***
HPV 16	**15.1 (12.3 - 18.4)**
HPV 18	**9.0 (5.9 - 13.4)**
HPV 31	**7.9 (5.3 - 11.7)**
HPV 33	5.4 (2.3 - 12.0)
HPV 52	4.4 (2.6 - 7.3)
HPV 45	4.3 (2.1 - 8.7)
HPV 58	1.7 (0.6 – 4.8)

Monsonego, J et al. Gyn Oncol (2015) (All women >30 yrs – single infections)

HR HPV Genotypes: risk over time

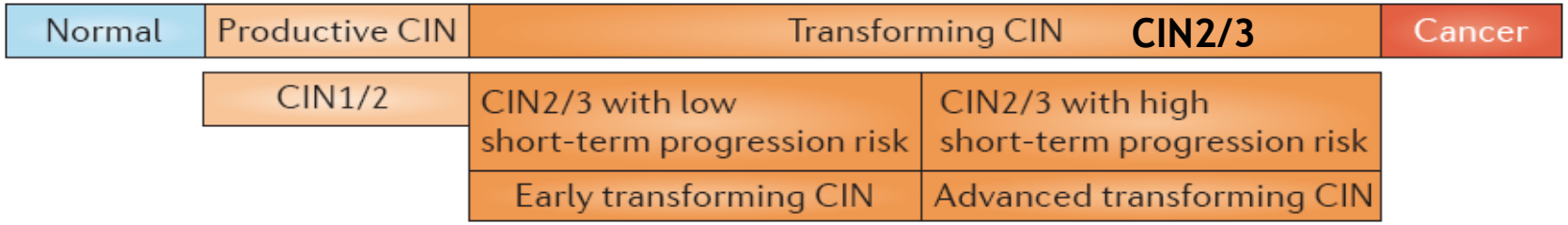
Risque par type (n = 14 158)



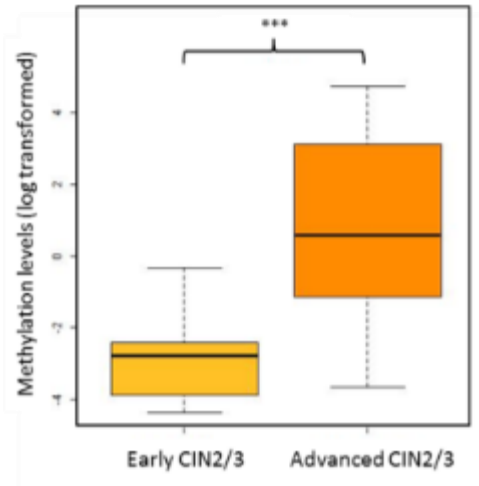
HPV16 > HPV33 > autres HPV-HR

Demarco M, *EClinicalMedicine*, 2020

CIN2/3 : how does methylation relate to clinical behaviour?



Methylation negative CIN2/3 show more regression (QIAsure)

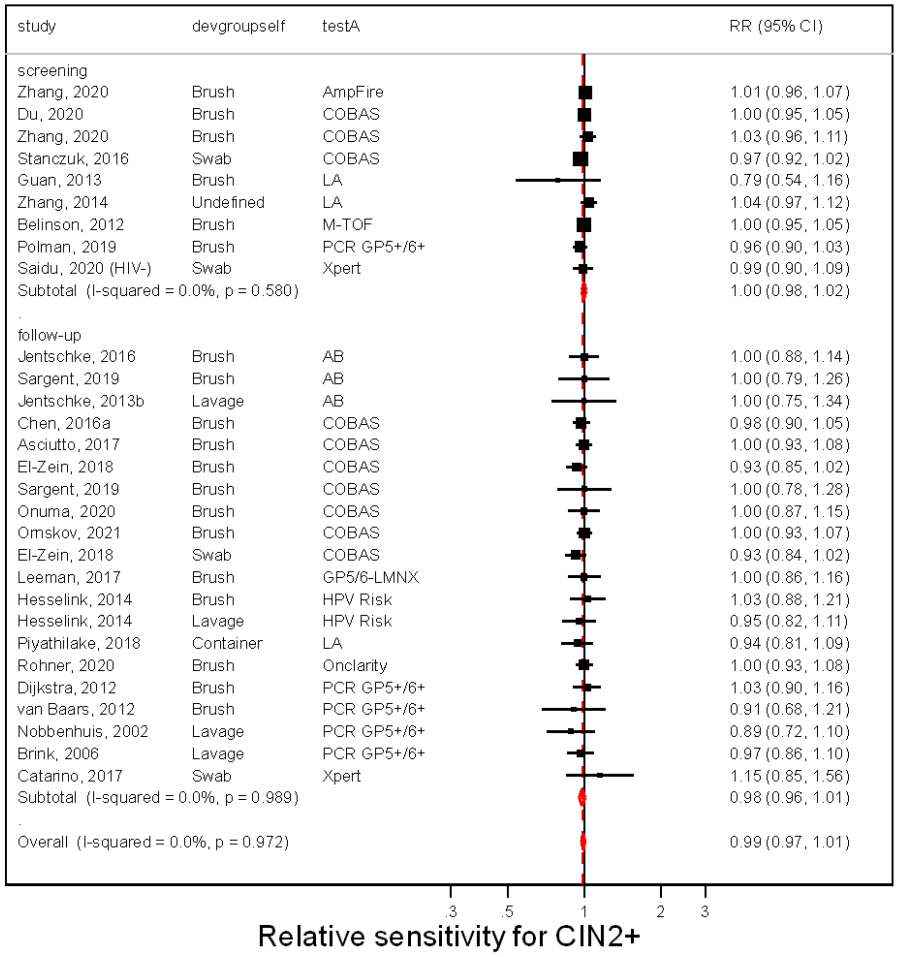


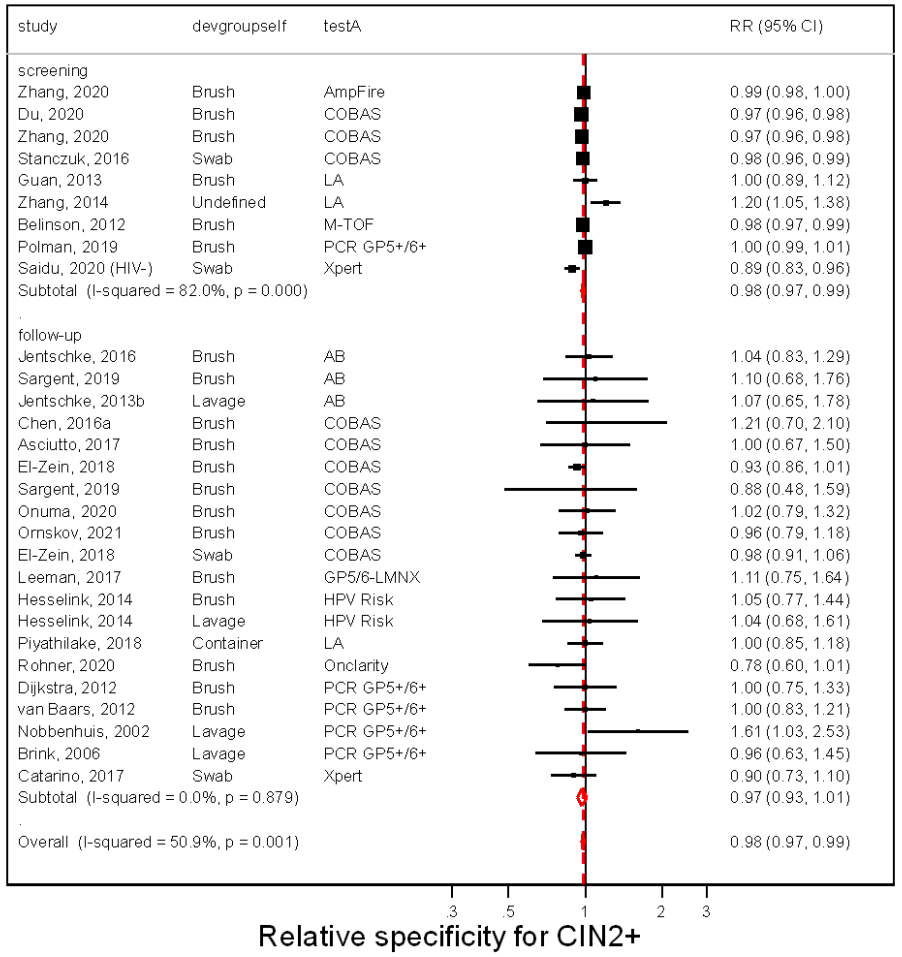
Advanced CIN2/3 display high methylation levels (cancer-like)

Dick *et al*. J. Clin Oncology, in press
Louvanto *et al*., Clin Inf Dis 2019

De Strooper *et al*. Cancer Prev Res 2014;
Verlaat *et al*., Clin Cancer Res 2017

Relative accuracy for CIN2+ (self- vs clinician samples
Clinically validated PCRs





Rel sensitivity:
0.99 (95% CI 0.97-1.01)

Rel specificity:
0.99 (95% CI 0.97-0.99)

Arbyn, BMJ 2018 (Update 2021)

Impact of screening and vaccination on natural history of C.Cancer

Screening ♀	Screening every 2 years 16 – 69 Y	HPV screening every 5 years 25-69 Y
Nombre tests-vie /	15	9
	Cumulative Risk	
Not vaccinated		
-Conisation	12 %	14% (44 %)
-Cervical.K.	0,52 %	0,44% (- 33 %)
-Mortality	0,16 %	0,12 % (- 38 %)
	Residual cumulative Risk	
Vaccinated (12-13Y) (4 val– cov. 80 %)		
• Conisation	7 %	6 % (- 13 %)
• Cervical.K	0,18 %	0,14 % (- 33 %)
• Mortality	0,06 %	0,04 % (- 28 %)

-30%

K. Canfel et all Int. J. Cancer, 2017

Elimination of UCC

WHO STRATEGY FOR 2030

VACCINATION

90%

Before 15 years

SCREENING

70%

2 hpv test during life

TRAITEMENT

90%

Hpv+ screened women

World Health Organization

Dr Tedros Adhanom Ghebreyesus, WHO Director-General