

Vaccins HPV et cancers

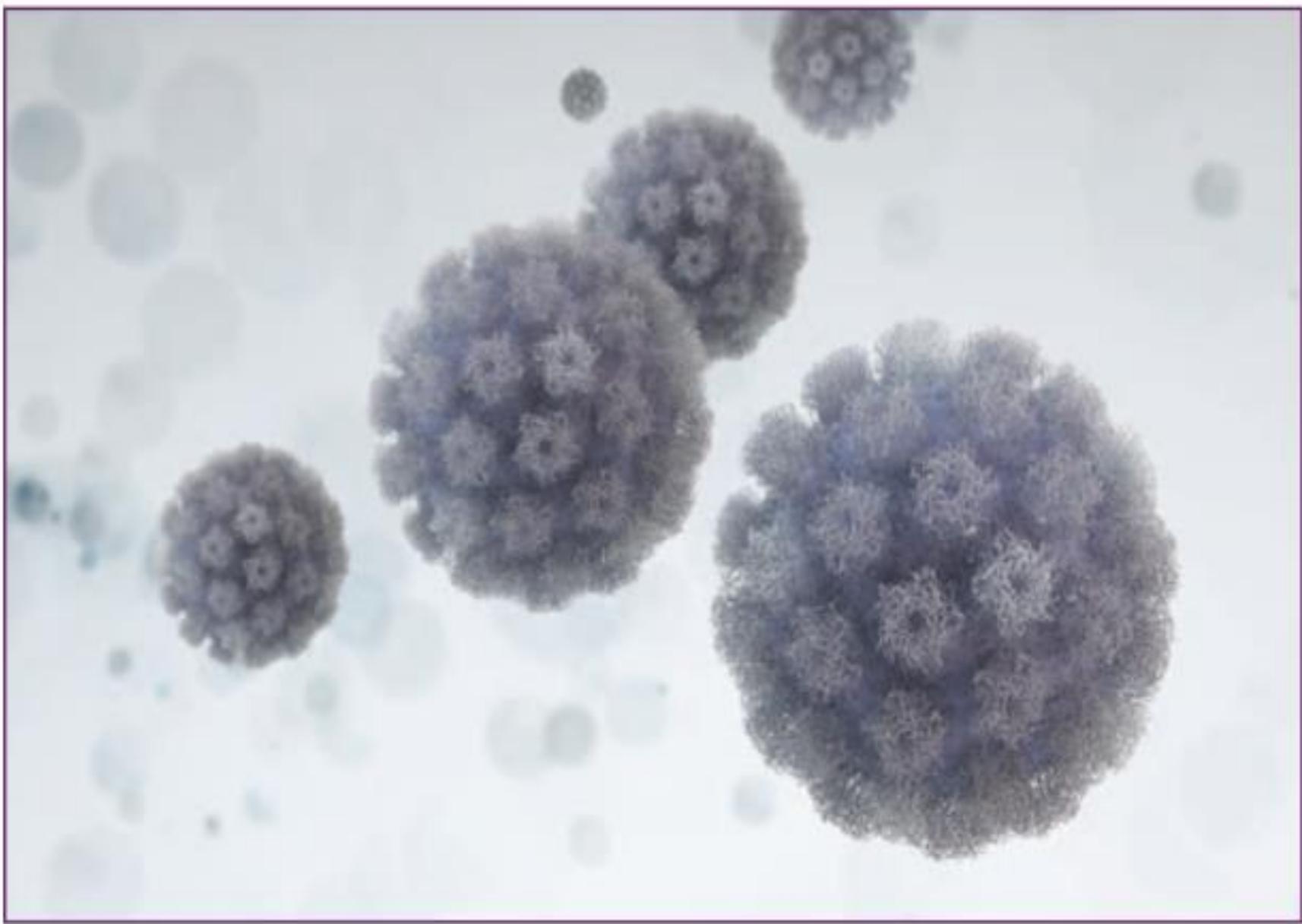
Groupe Prévention Vaccination de la SPILF
06 04 2016

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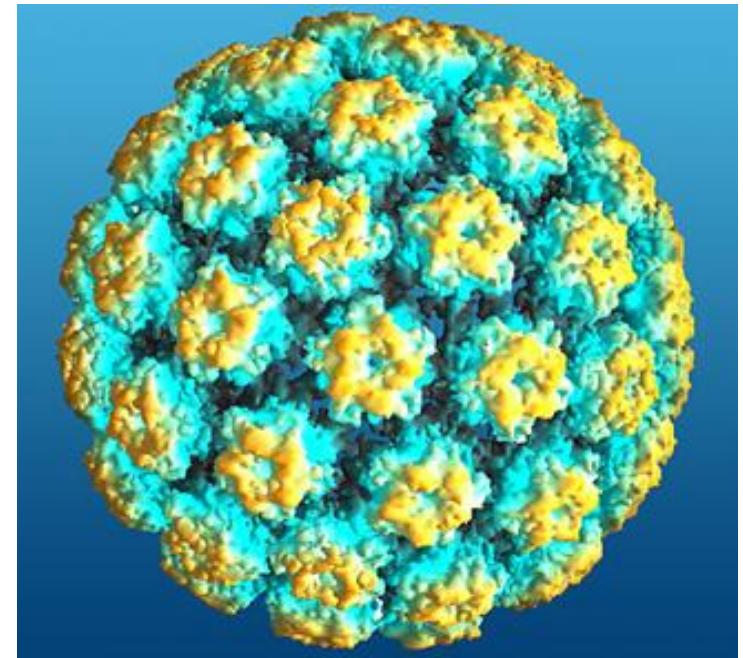
Groupe hospitalier Pitié-Salpêtrière, Paris, France

No competing interests



Human papillomavirus HPV

- HPV are 8000-base pair, double-stranded, circular DNA viruses
- The great majority of sexually active women and men have been infected with HPV at least once in their lifetime
- Most of infection are transient



High-risk types of HPV

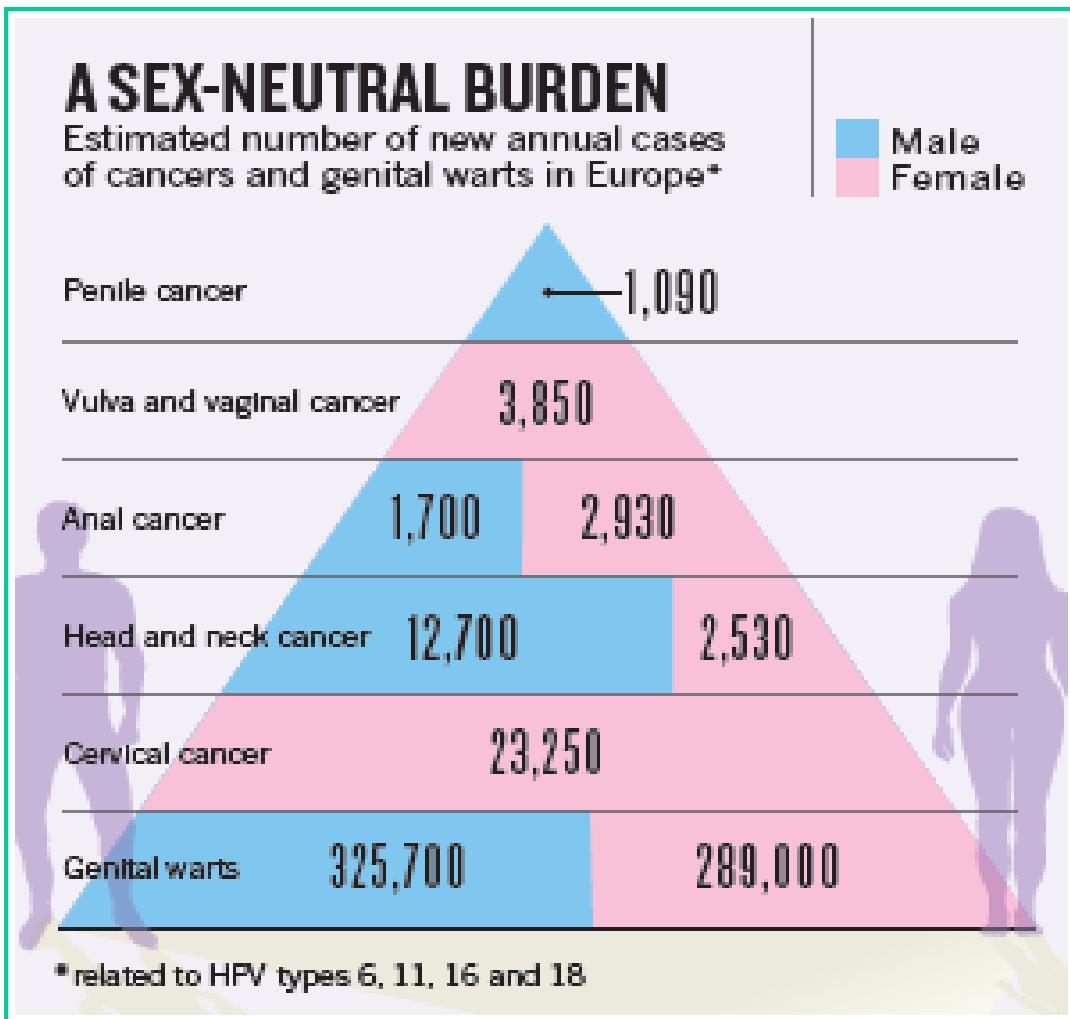
- Low risk genotypes
 - HPV **6, 11, 42-44, 55, 56...**
 - Genital warts, low grade lesions
- High-risk genotypes
 - HPV **16, 18, 31, 33, 35, 40, 45, 51-53, 56-59, 66-70...**
 - Precancerous lesions & cancers

High-risk types of HPV

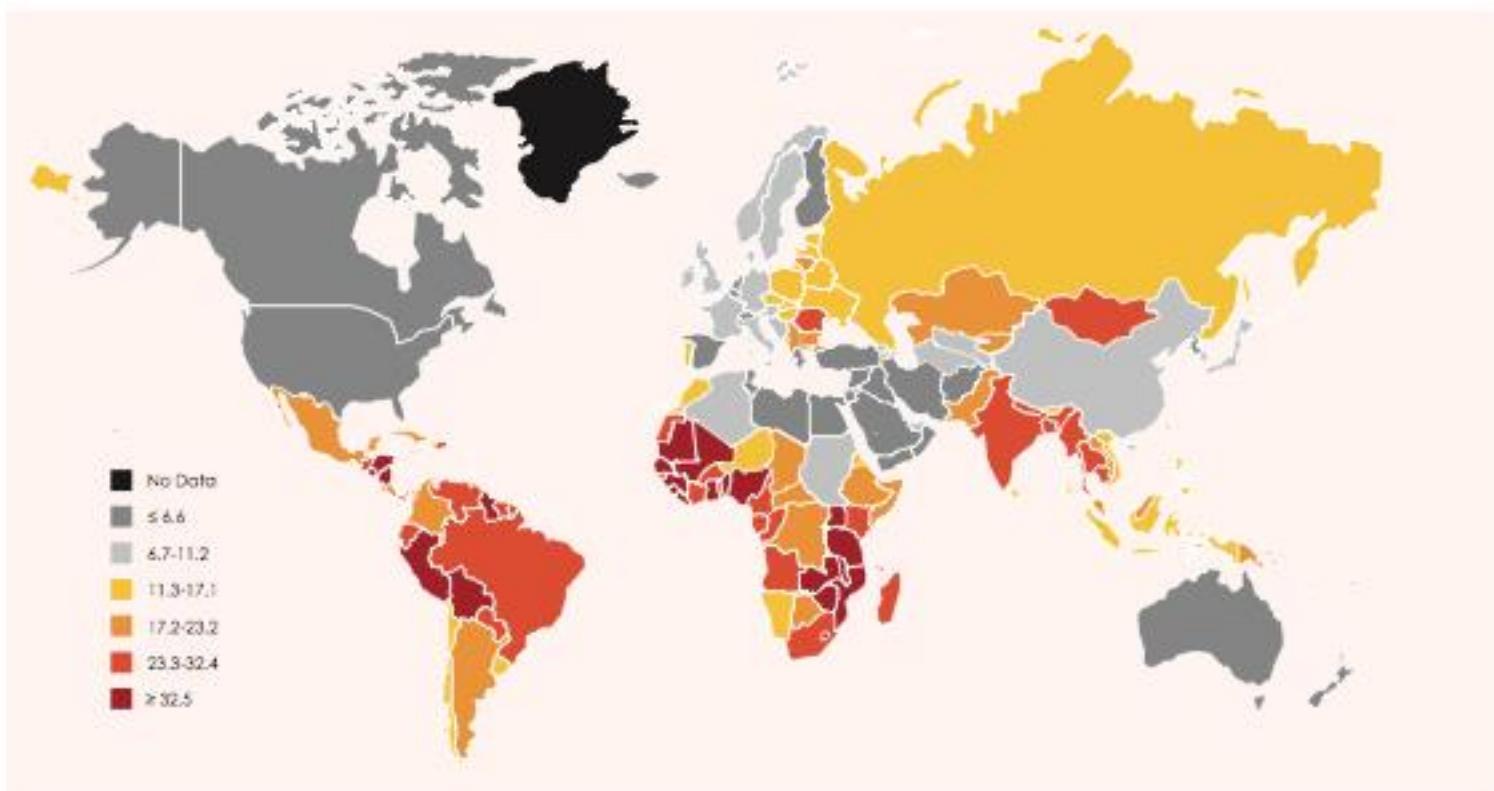
Group	HPV types	Comments
Alpha HPV types		
1	16	Most potent HPV type, known to cause cancer at several sites
1	18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59	Sufficient evidence for cervical cancer
2A	68	Limited evidence in humans and strong mechanistic evidence for cervical cancer
2B	26, 53, 66, 67, 70, 73, 82	Limited evidence in humans for cervical cancer
2B	30, 34, 69, 85, 97	Classified by phylogenetic analogy to HPV types with sufficient or limited evidence in humans
3	6, 11	..
Beta HPV types		
2B	5 and 8	Limited evidence for skin cancer in patients with epidermodysplasia verruciformis
3	Other beta and gamma types	..

Table 2: Human papillomavirus (HPV) types assessed by the IARC Monograph Working Group

HPV-associate new annual cases of cancer and GW in Europe



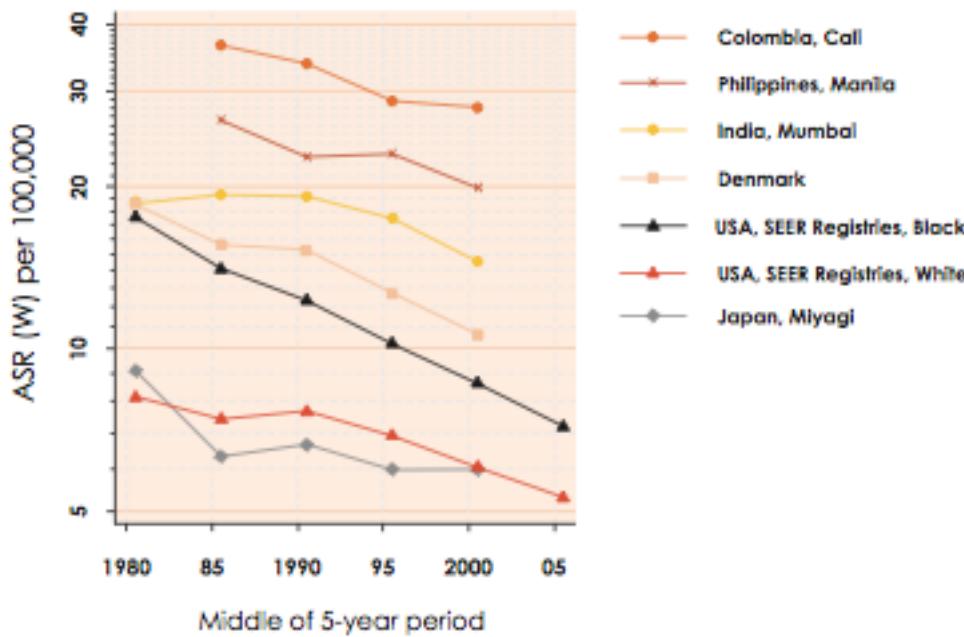
Cervical cancer map showing estimated age-standardized incidence rate per 100,000 in 2008



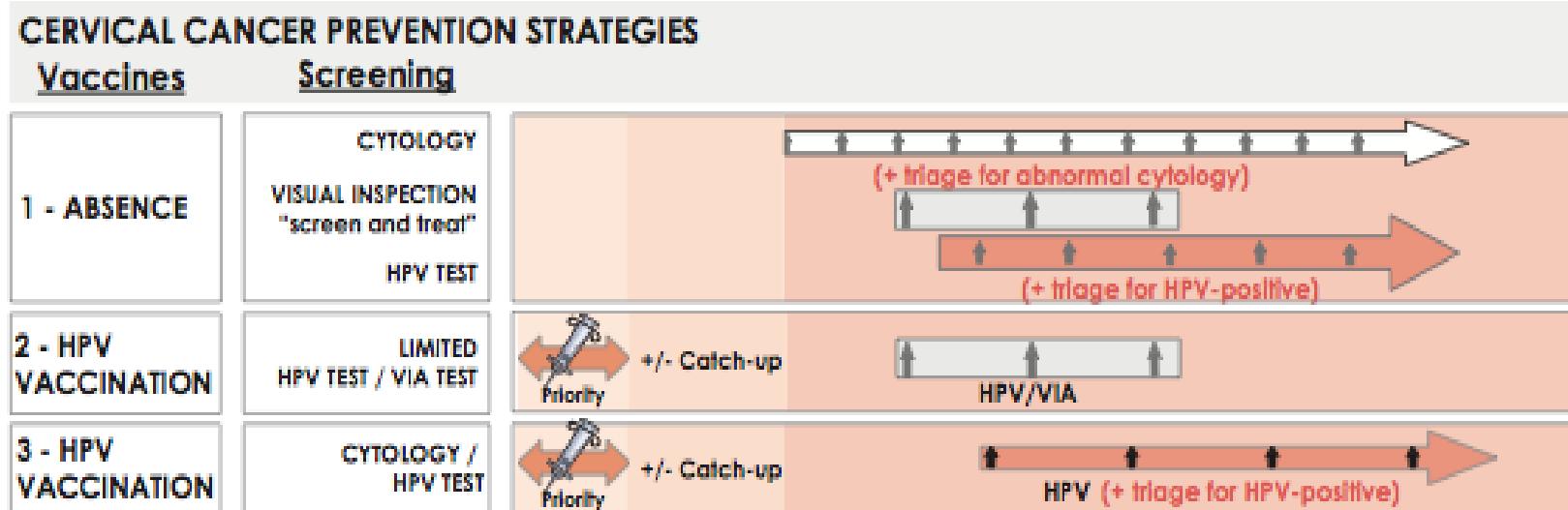
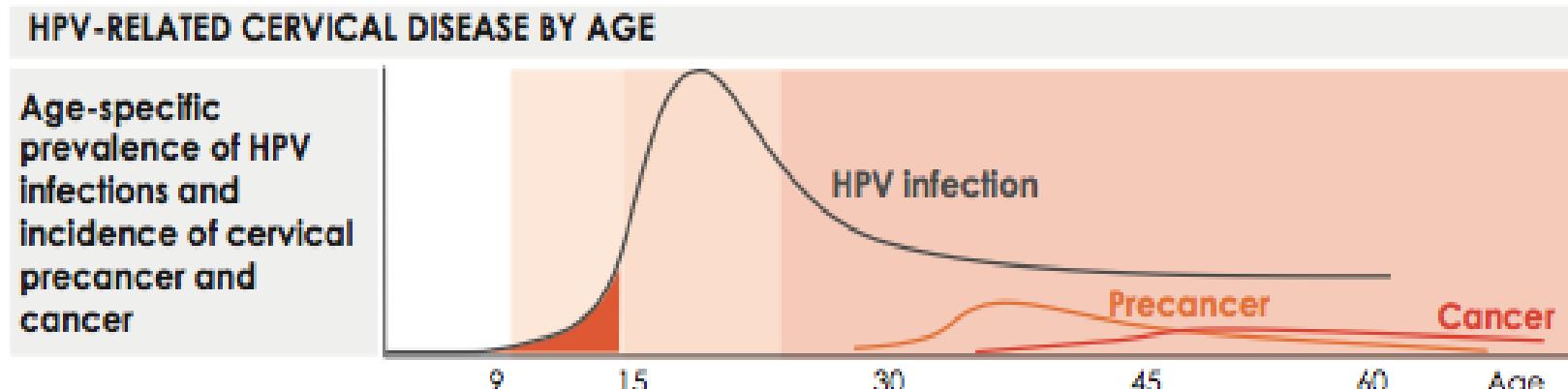
Cervical cancer, age-standardized incidence rates per 100,000

Incidence: 2% decrease per annum in high income countries
But due to population growth, a 2% increase is estimated

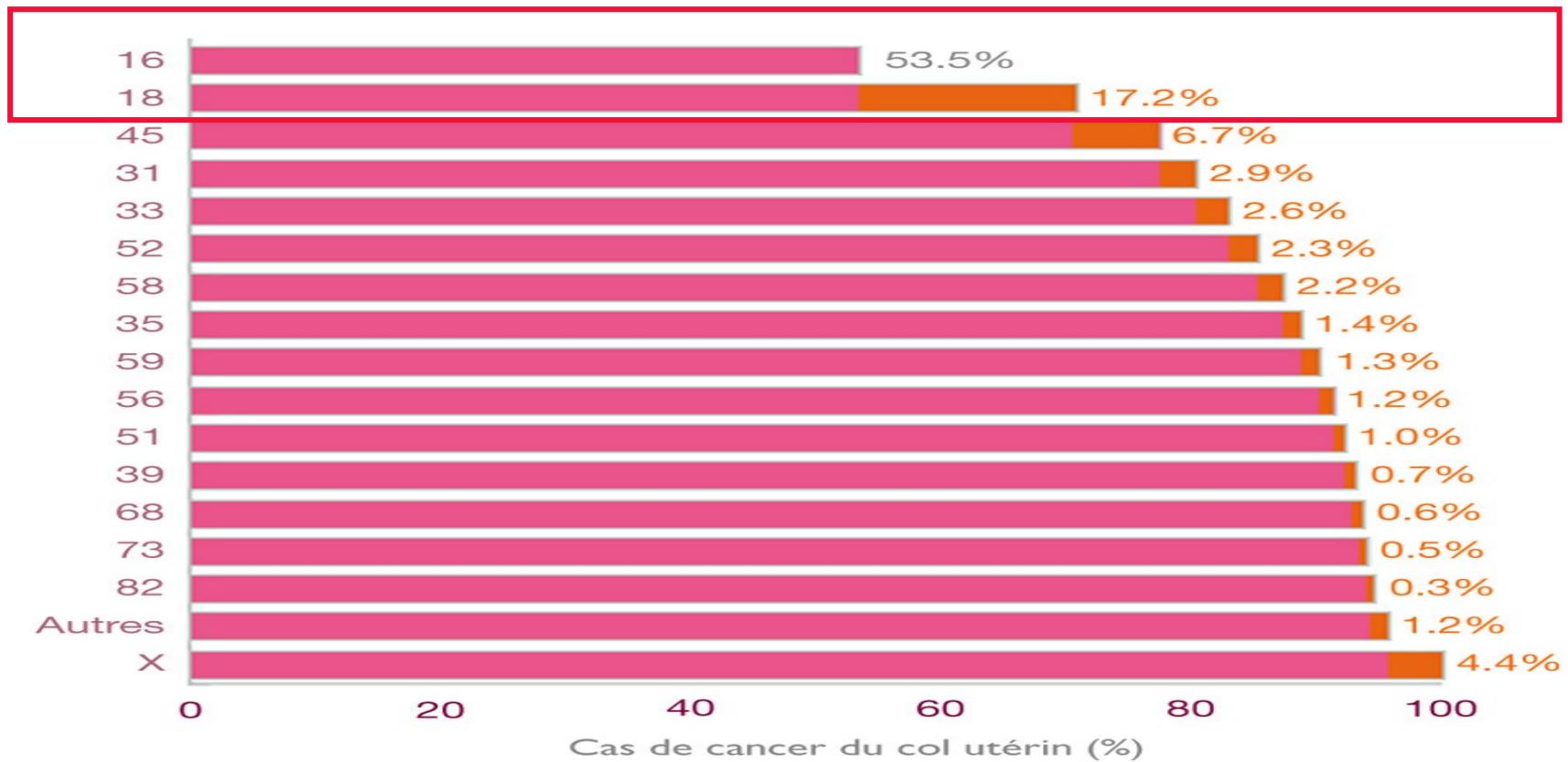
F.X. Bosch et al. / *Vaccine* 2013; 31: 103–109



Natural history and HPV-based prevention strategies according to age.

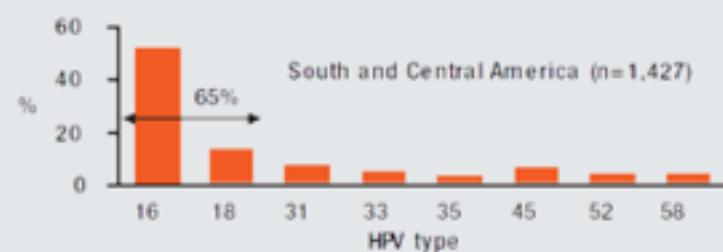
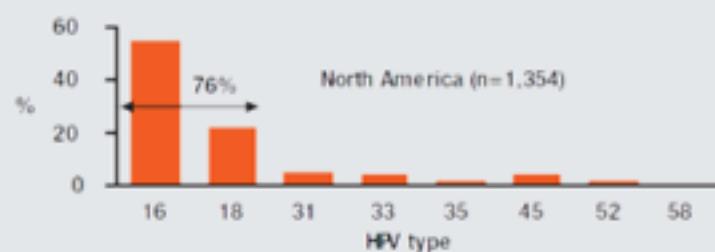
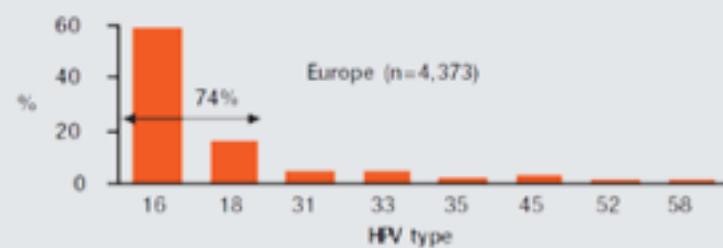
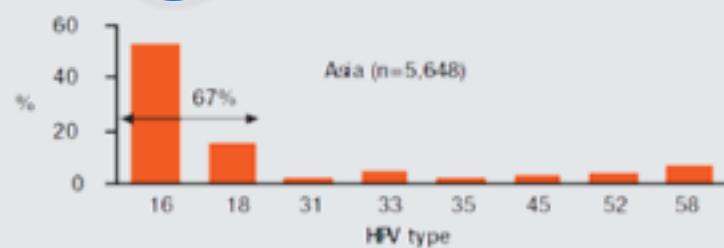
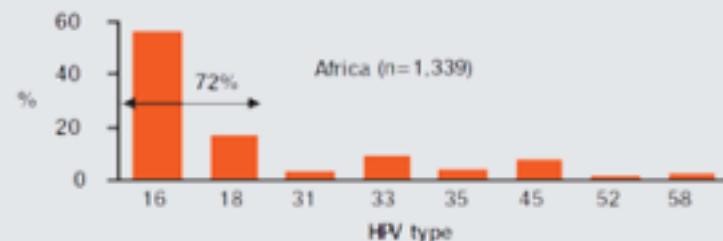
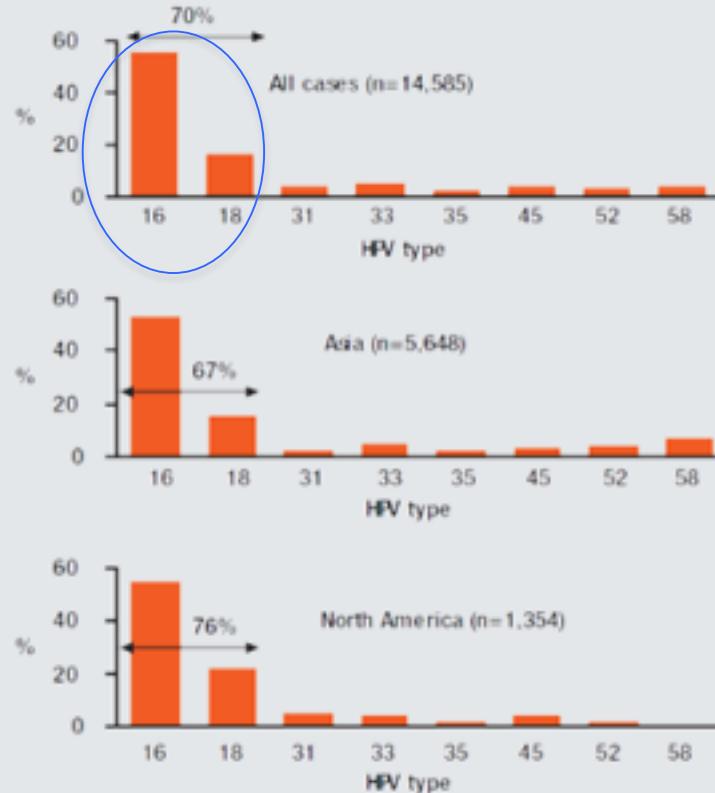


HPV in cervical cancers



HPV types in Cervical cancer

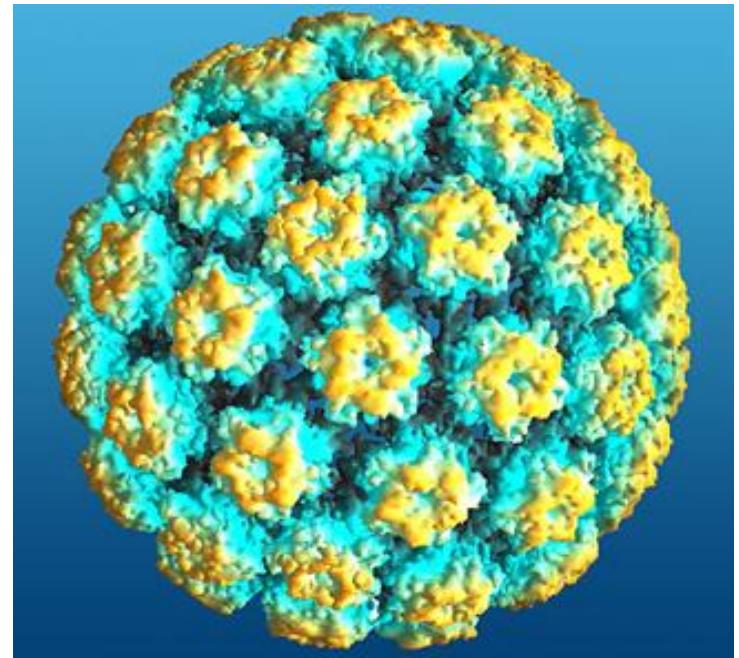
Percentages of Cervical Cancer Cases Attributed to the Most Prevalent High-Risk HPV Genotypes, by Region



HPV types 16 and 18 account for the majority of cervical cancer cases in all geographic areas surveyed, but the balance between 16/18 and other types differs by location. Image reproduced from WHO, 2008b.

HPV virus-like particle (VLP) vaccines

- Gardasil® and CervarixTM are both composed of HPV L1 proteins that spontaneously self assemble into VLPs.
- They have different valencies, adjuvants, and are produced in different types of cells
- VLP vaccines protect via antibody
- Systemic immunization with L1 VLPs generates antibody concentrations 1–4 logs higher than in a natural infection but the precise conformational and/or linear epitopes that are recognized are still not known



Characteristics of HPV VLP vaccines.

	Bivalent (Cervarix)	Quadrivalent (Gardasil)	Nonavalent (Gardasil 9)
Manufacturer	GlaxoSmithKline	Merck	Merck
L1 VLP types (dose)	16 (20 µg), 18 (20 µg)	6 (20 µg), 11 (40 µg), 16 (40 µg), 18 (20 µg)	6 (30 µg), 11 (40 µg), 16 (60 µg), 18 (40 µg), 31 (20 µg), 33 (20 µg), 45 (20 µg), 52 (20 µg), 58 (20 µg)
Producer cells	Baculovirus-infected <i>Trichoplusia ni</i> insect cell line	<i>Saccharomyces cerevisiae</i> (yeast)	<i>Saccharomyces cerevisiae</i> (yeast)
Adjuvant	500 µg AS04	225 µg AAHS	500 µg AAHS

AS04=aluminium hydroxide plus 50 µg 3-O-desacyl-4'-monophosphoryl lipid A. AAHS=amorphous aluminium hydroxyphosphate sulfate. L1= major capsid protein. VLP=virus-like particle.

Table 1: Licensed human papillomavirus vaccines

VLPs in the 2, 4 & 9valent vaccines

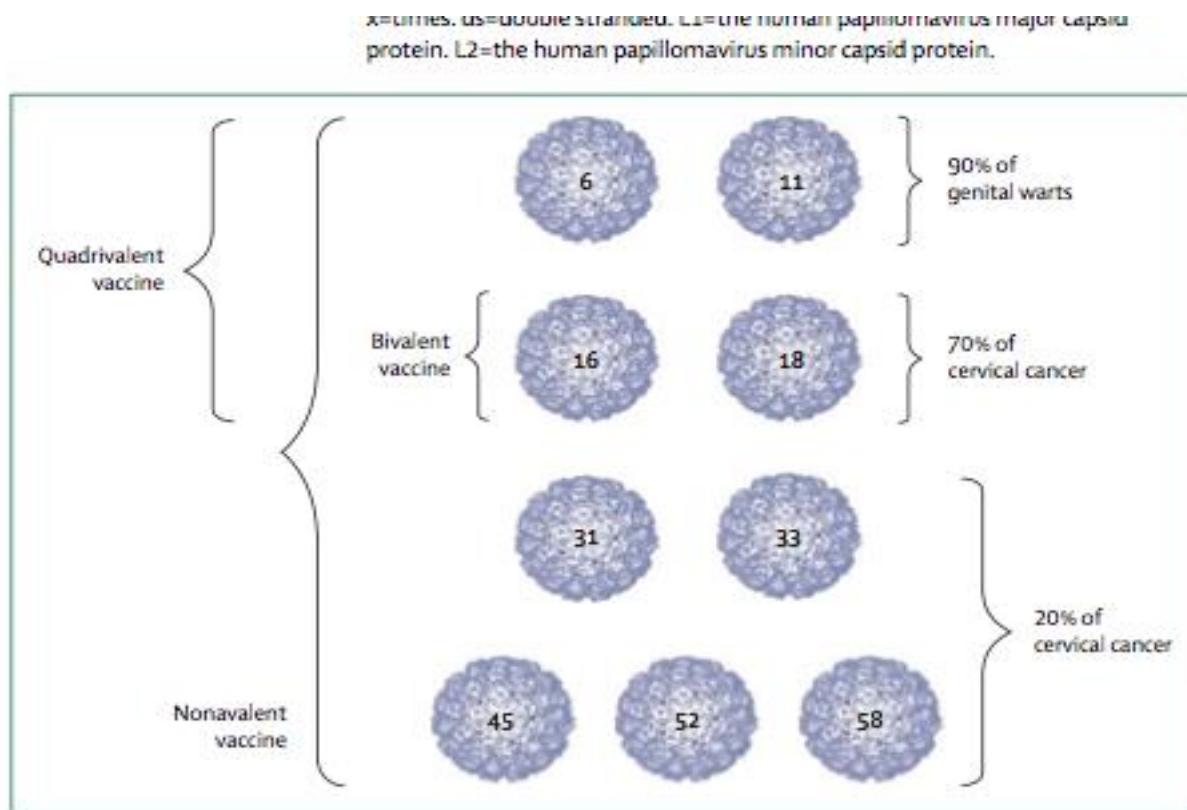


Figure 2: HPV VLP types in the nonavalent VLP vaccine

VLPs in the bivalent, quadrivalent, and the nonavalent vaccines are shown with the proportion of neoplastic disease attributed to each group. HPV=human papillomavirus. VLP=virus-like particle.

Prophylactic Efficacy

Table 4
Prophylactic efficacy of VLP vaccines against infection and lesions related to vaccine targeted HPV types

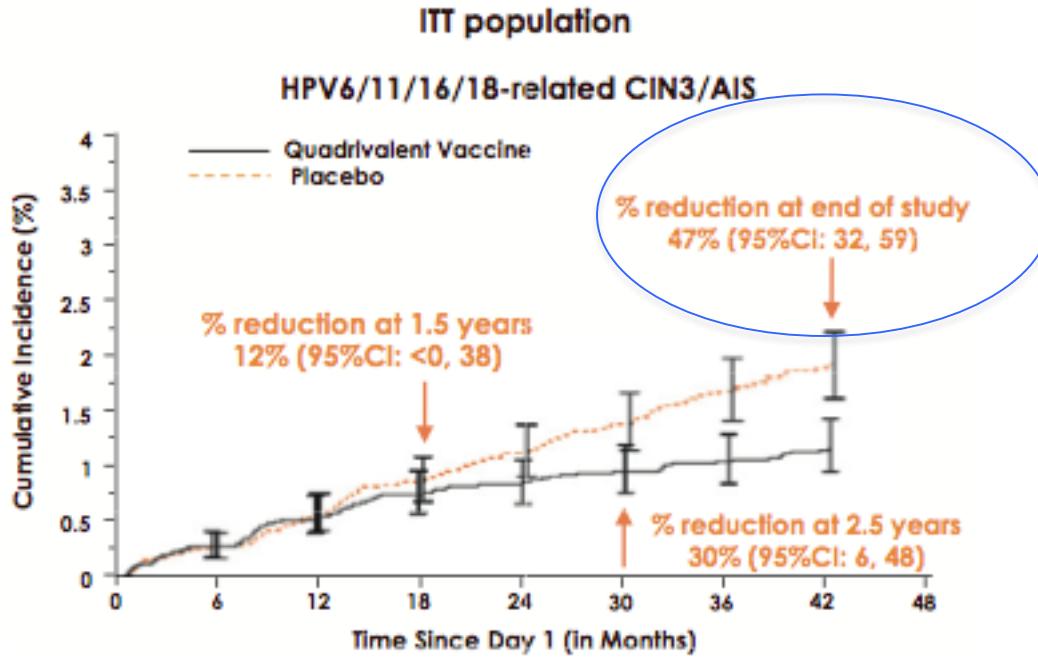
Vaccine	Study	Number of subjects		Endpoints	Vaccine efficacy (95% CI) ^a		
		Vaccine group	Placebo group		ATP	MITT	ITT
Gardasil®	Merck 007	235	233	HPV persistence (4 months)	96 (83–100)	94 (83–98)	NR
	Merck 007	235	233	External genital lesions	100 (<0–100)	100 (<0–100)	NR
	Merck 007	235	233	CIN1+, AIS	100 (<0–100)	100 (31–100)	NR
	FUTURE I	2,241	2,258	CIN1+, AIS	100 (94–100)	98 (92–100)	55 (40–66)
	FUTURE I	2,261	2,279	External genital lesions	100 (94–100)	95 (87–99)	73 (58–83)
	FUTURE II	6,087	6,080	CIN2+, AIS	98 (86–100)	95 (85–99)	44 (26–58)
Cervarix™	GSK 001/007	414	385	HPV persistence (6 months)	96 (75–100)	94 (78–99)	NR
	GSK 001/007	414	385	HPV persistence (12 months)	100 (52–100)	94 (61–100)	NR
	GSK 001/007	481	470	CIN1+	NR	100 (42–100)	NR
	GSK 001/007	481	470	CIN2+	NR	100 (–8–100)	NR
	PATRICIA	6,344	6,402	HPV persistence (6 months)	NR	80 (70–87)	NR
	PATRICIA	3,386	3,437	HPV persistence (12 months)	NR	76 (48–90)	NR
	PATRICIA	7,788	7,838	CIN1+	NR	89 (59–99)	NR
	PATRICIA	7,788	7,838	CIN2+	NR	90 (53–99) ^b	NR

^aATP: all treated patients in alive; ATP: according to protocol; CIN: condylomatous intraepithelial neoplasia; CIN1: CIN grade 1; CIN2: CIN grade 2; CIN3: CIN grade 3; NR: not reported.

Efficacy is **greater than 95%** against all reported vaccine-type specific end-points in the ATP analyses

Efficacy against cervical precancerous lesions with the QV

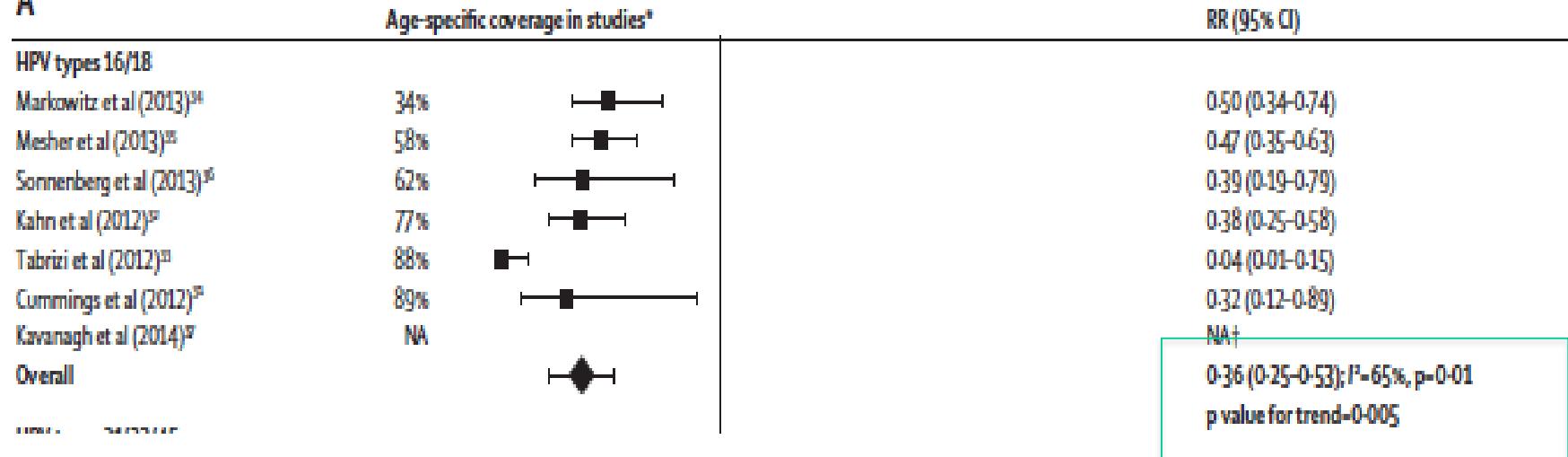
J.T. Schiller et al. / Vaccine 3



- Time- to-event curves for acquisition of HPV6/11/16/18-related CIN3/AIS in the QV and placebo recipients in the ITT cohort.
- Rate reduction for precancerous lesion at 47% after 3.5 years

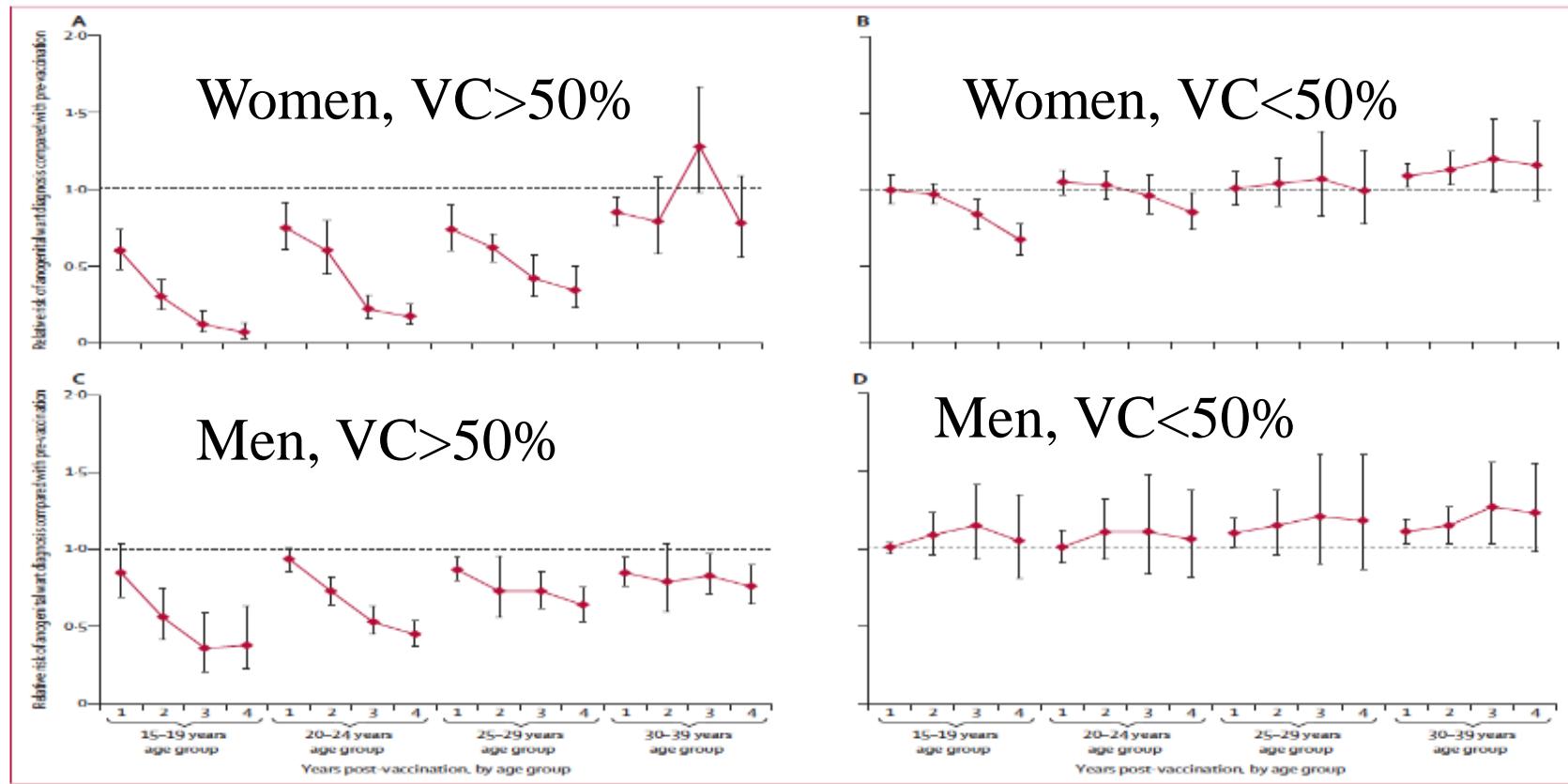
Changes in the prevalence of HPV infections between the prevaccination and postvaccination periods

A



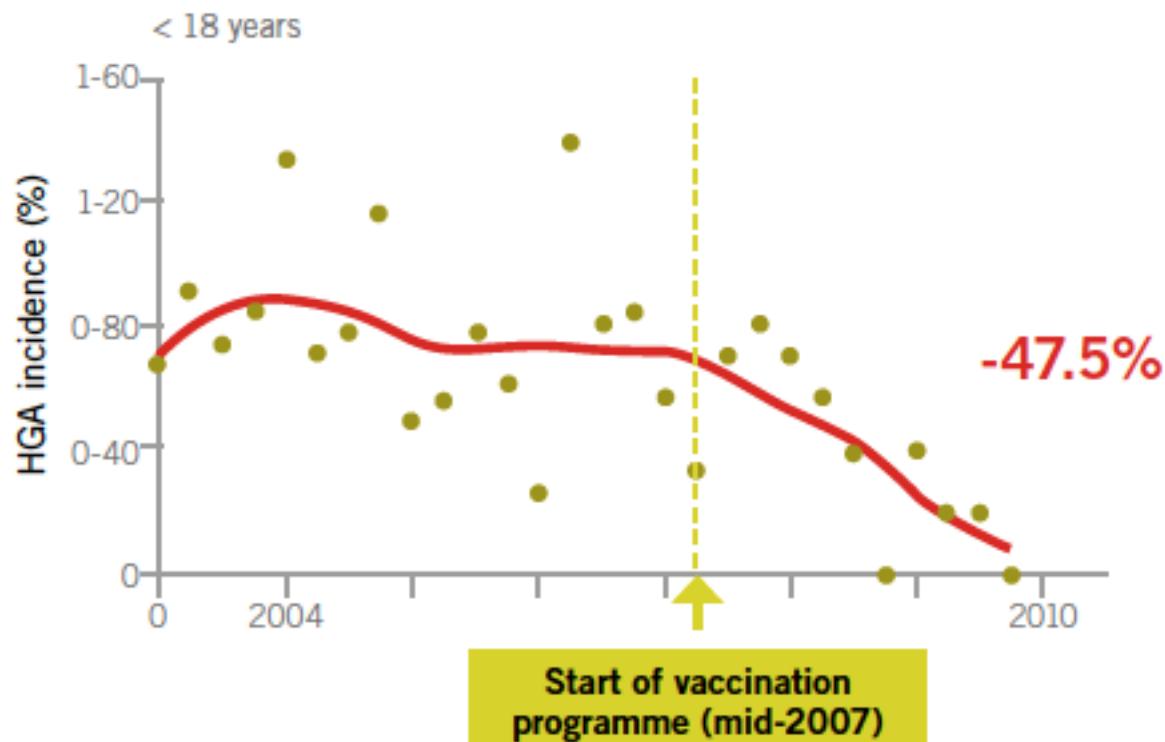
In girls 13–19 years of age, the overall prevalence of HPV types 16 and 18 decreased significantly by 64% in the post-vaccination period compared with the pre-vaccination period

Changes in anogenital wart diagnosis during the first 4 year



Incidence of high-grade cervical abnormalities

IMPACT OF HPV VACCINATION IN AUSTRALIA:
RAPID REDUCTION OF CERVICAL HIGH-GRADE ABNORMALITIES



Brotherton J et al. Lancet 2011

GARDASIL : local adverse effects

TABLE 7. Injection-site reactions within 5 days after receipt of quadrivalent human papillomavirus vaccine in females and males aged 9–26 years

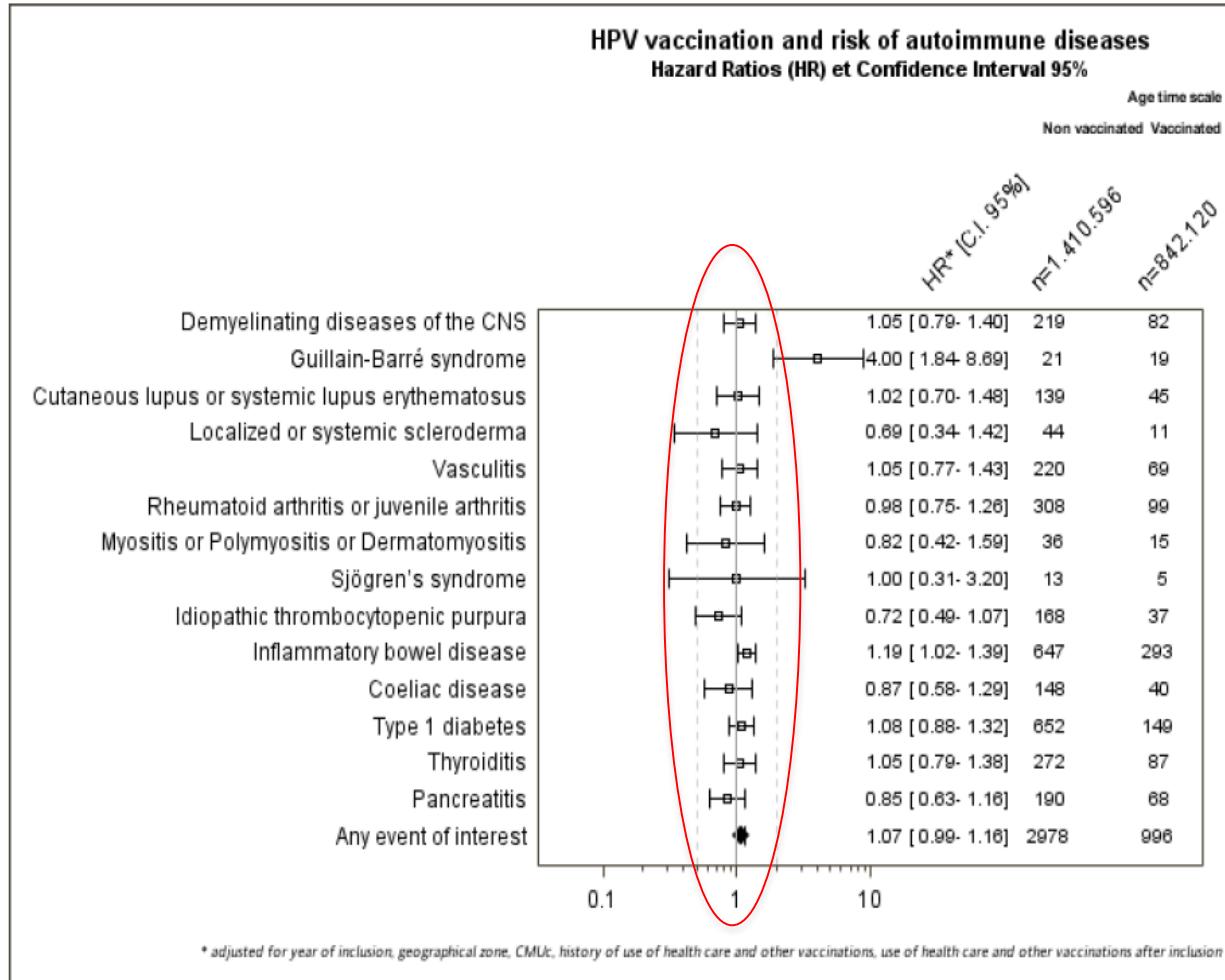
Adverse event	Quadrivalent vaccine %	AAHS control %	Saline control %
Females	N = 5,088	N = 3,470	N = 320
Pain	83.9	75.4	48.6
Swelling	25.4	15.8	7.3
Erythema	24.7	18.4	12.1
Males	N = 3,093	N = 2,029	N = 274
Pain	61.4	50.8	41.6
Swelling	13.9	9.6	8.2
Erythema	16.7	14.1	14.5

CERVARIX : local adverse effects

TABLE 10. Rates of solicited local adverse reactions and general adverse events in females aged 9–25 years, within 7 days of vaccination with bivalent human papillomavirus vaccine*

Adverse event	Bivalent HPV vaccine (9–25 yrs) %	HAV 720 (15–25 yrs) %	HAV 360 (10–14 yrs) %	Al(OH) ₃ control (15–25 yrs) %
Local	N = 6,669	N = 3,079	N = 1,027	N = 549
Pain	91.9	78.0	64.2	87.2
Redness	48.4	27.6	25.2	24.4
Swelling	44.3	19.8	17.3	21.3
General	N = 6,670	N = 3,079	N = 1,027	N = 549
Fatigue	54.6	53.7	42.3	53.6
Headache	53.4	51.3	45.2	61.4
GI†	27.9	27.3	24.6	32.8
Fever (\geq 99.5°F)	12.9	10.9	16.0	13.5
Rash	9.5	8.4	6.7	10.0
Myalgia§	48.8	44.9	33.1	—
Arthralgia§	20.7	17.9	19.9	—
Urticaria§	7.2	7.9	5.4	—

HPV vaccines and risk of autoimmune disease: pharmaco-epidemiological study



La vaccination HPV en France : Recommandations

Quadrivalent (0-2-6 mois)

JF 14 ans

Rattrapage 15-23 ans
avant ou dans l' année

suivant le début de
l' activité sexuelle

Quadrivalent préférentiel

Schéma 0-6 mois

JF 11-14 ans
Rattrapage 15-19 ans

Quadrivalent (0-2-6 mois)
ou bivalent (0-1-6 mois)

Mars 2007

Décembre
2007

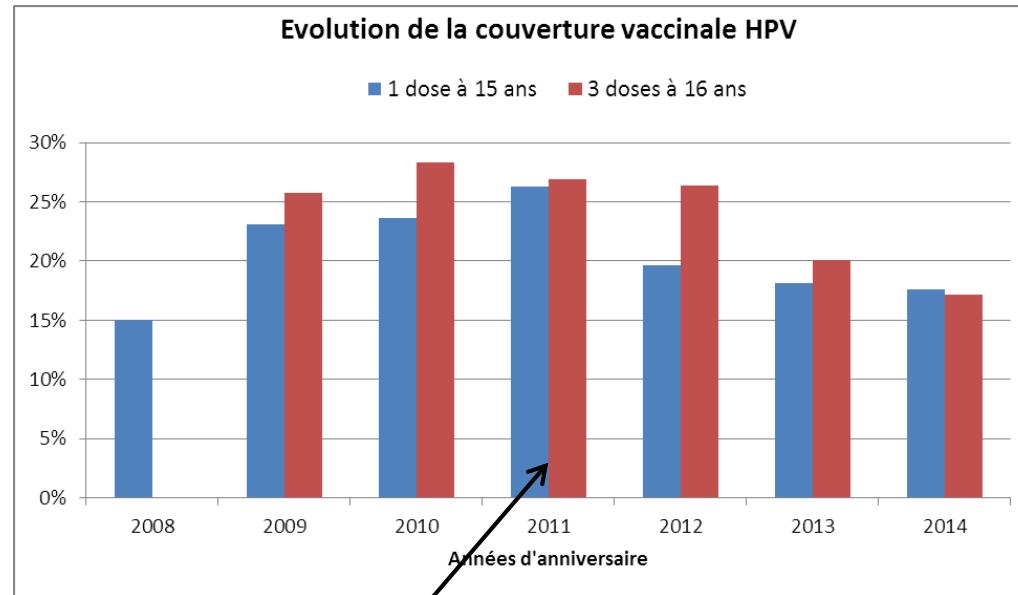
Décembre
2010

Septembre
2012

Mars 2014

Couverture vaccinale en France (source: InVS, EGB, mise à jour au 31/12/2013)

Année d'anniversaire	2008	2009	2010	2011	2012	2013	2014
CV à 15 ans (1 dose)	15,0 %	23,1 %	23,6 %	26,3 %	19,6 %	18,1 %	17,6 %
CV à 16 ans (3 doses)		25,8 %	28,3 %	26,9 %	26,4 %	20,1 %	17,2 %



Eté 2011
Plusieurs médias remettent en cause la sécurité du vaccin
Pétition de professionnels de santé

Automne 2011 :
Le HCSP réaffirme la balance bénéfices/risques en faveur de la vaccination

Move from a three-dose to a two-dose schedule? (2valent)

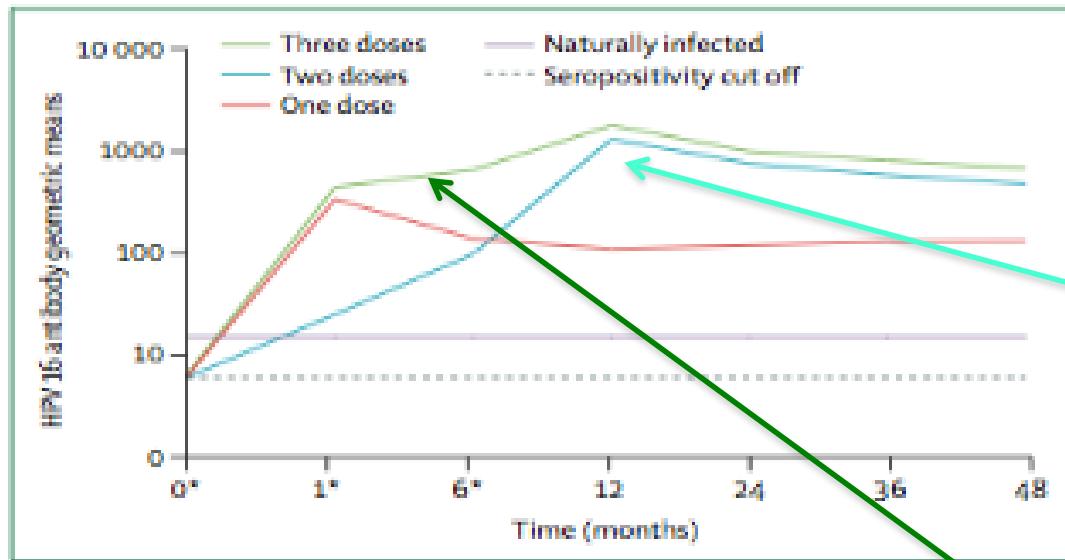
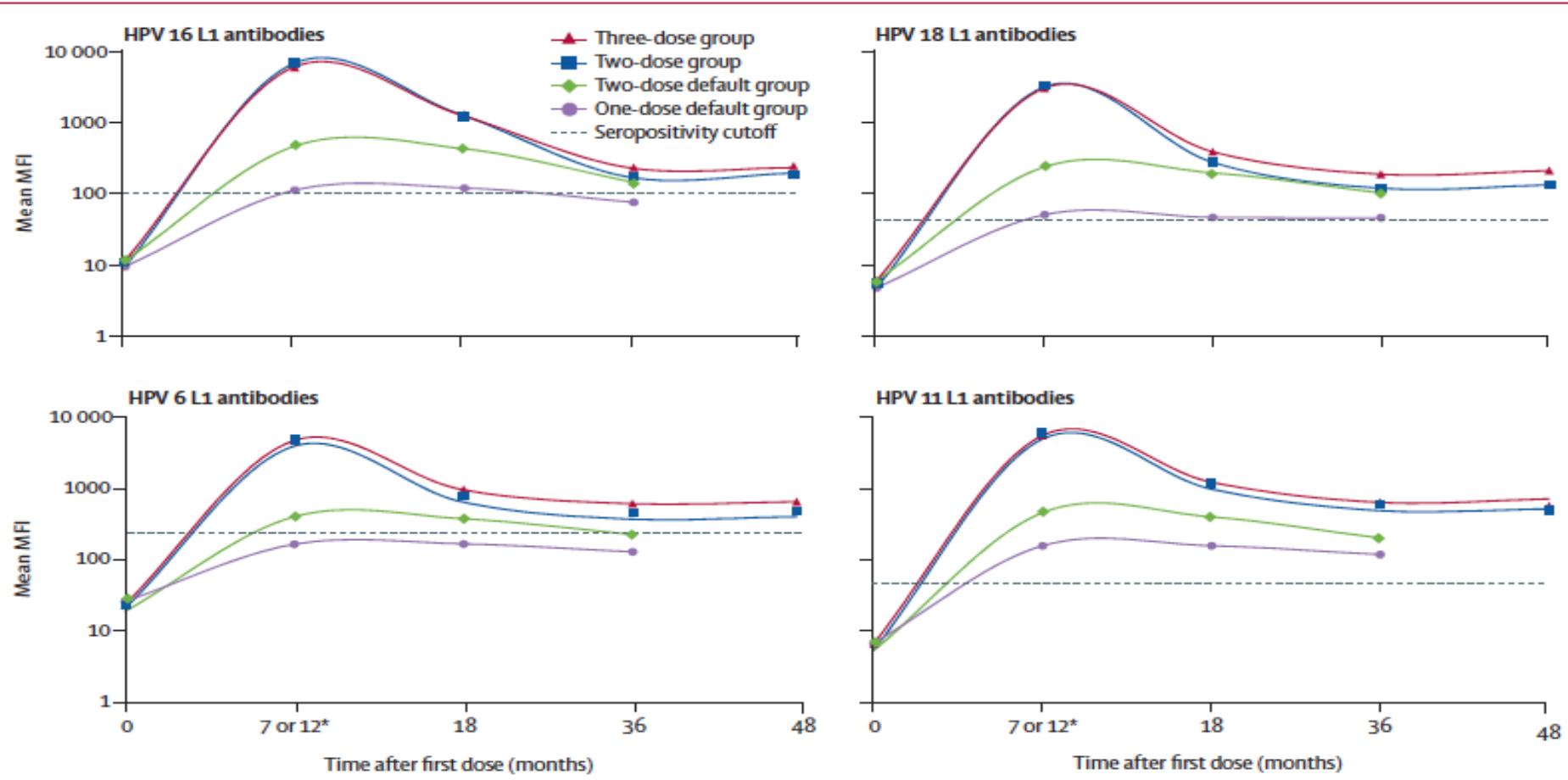


Figure 3: HPV 16 virus-like particle antibody geometric means during a 48 month trial of the bivalent vaccine in women in Costa Rica¹². Women included were aged 18–25 years. Three doses of the bivalent vaccine were given at months 0, 1, and 6; two doses were given at months 0 and 6; and one dose was given at month 0. HPV=human papillomavirus. *Indicates the months the vaccine was given.

- Clinical immunogenicity:
- non-inferior titres of virion neutralising antibodies **in adolescents**
 - after injection of **two** doses given 6 months apart,
 - compared with an injection of **three** doses within 6 months in **young adults**.

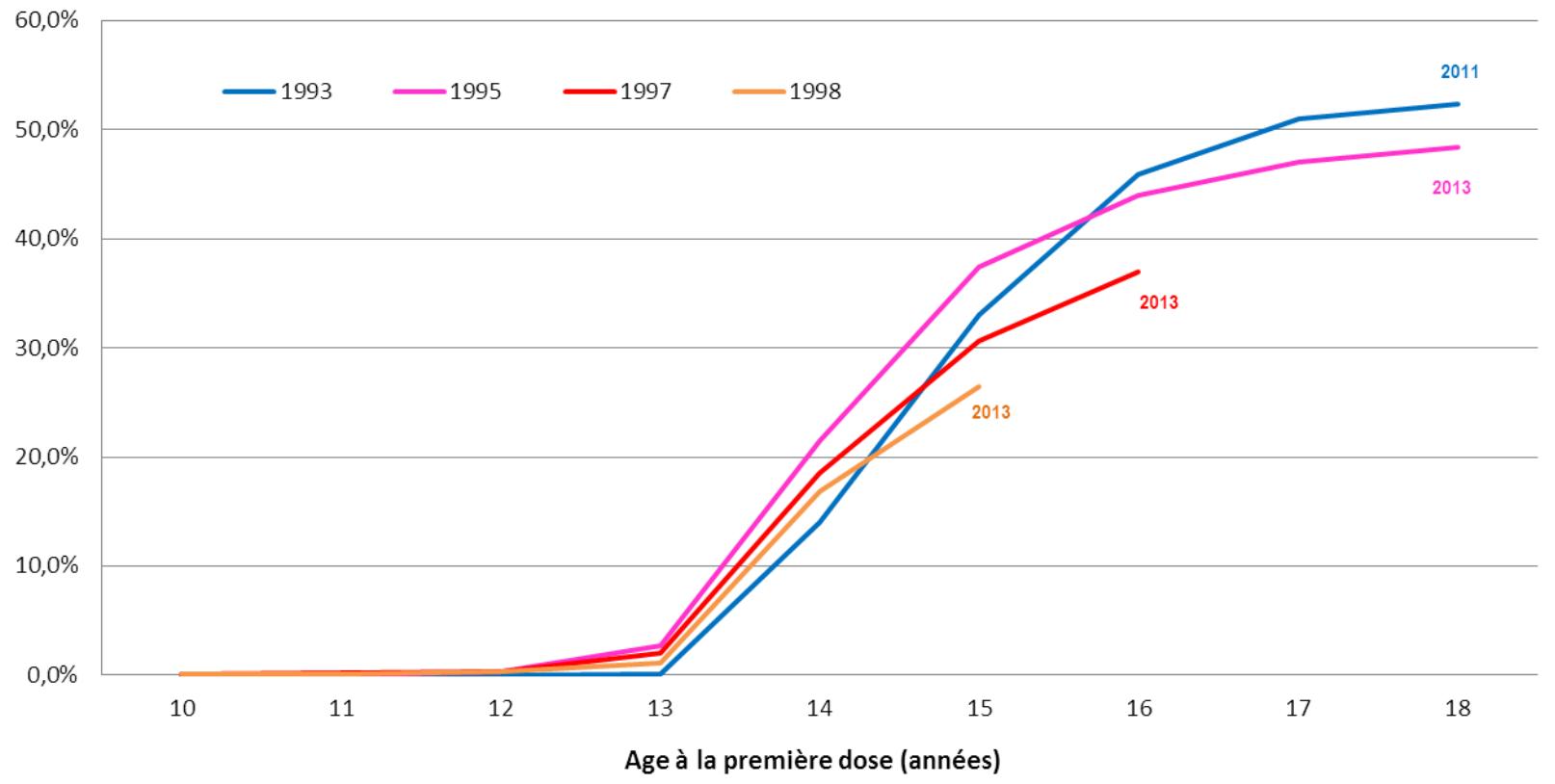
Immunogenicity and HPV infection after one, two, and three doses of quadrivalent HPV vaccine in girls in India: a multicentre prospective cohort study (4valent)



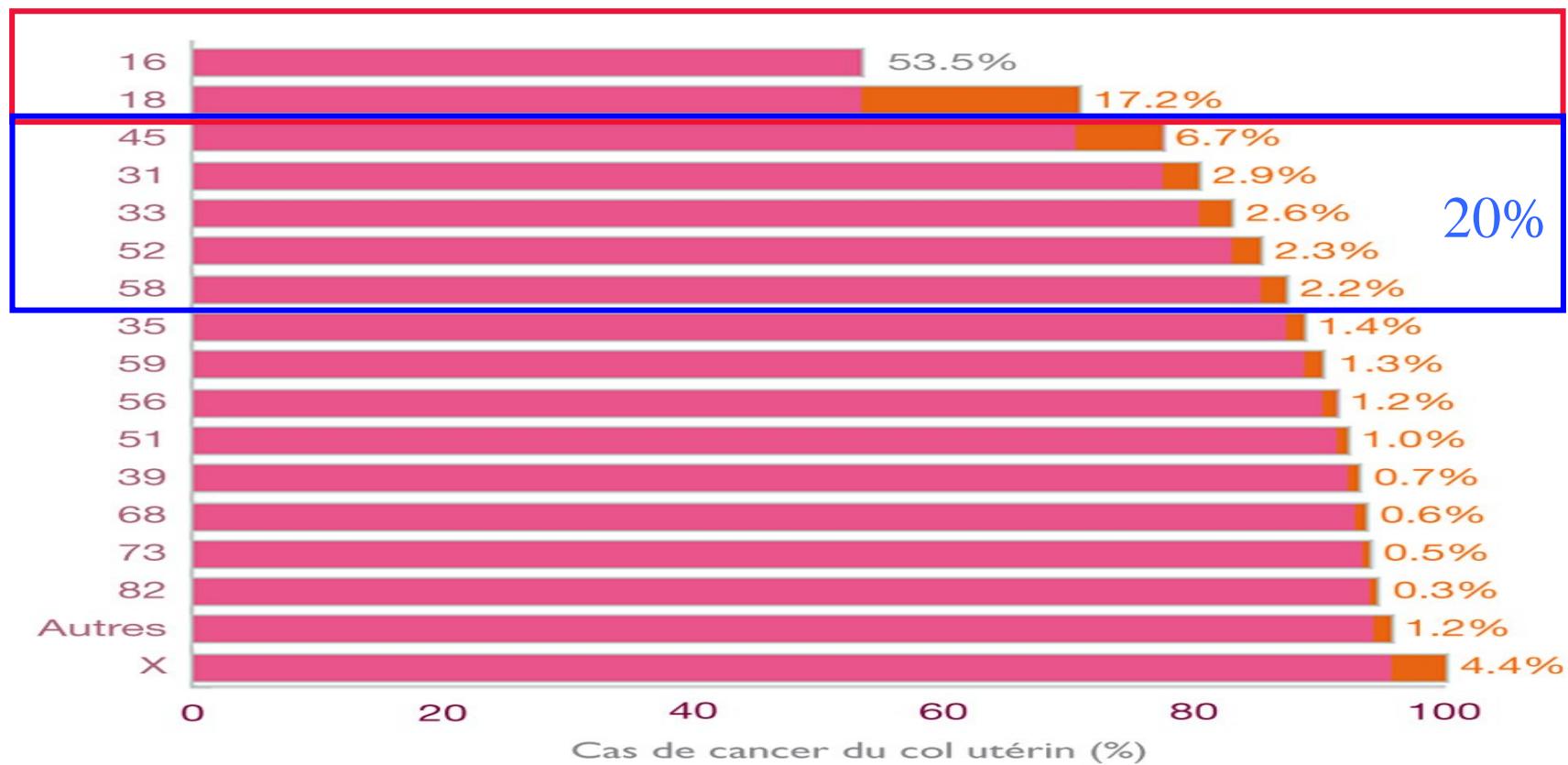
Estimation des couvertures vaccinales des vaccins HPV en fonction des cohortes de naissance

Source: EGB-InVS données provisoires

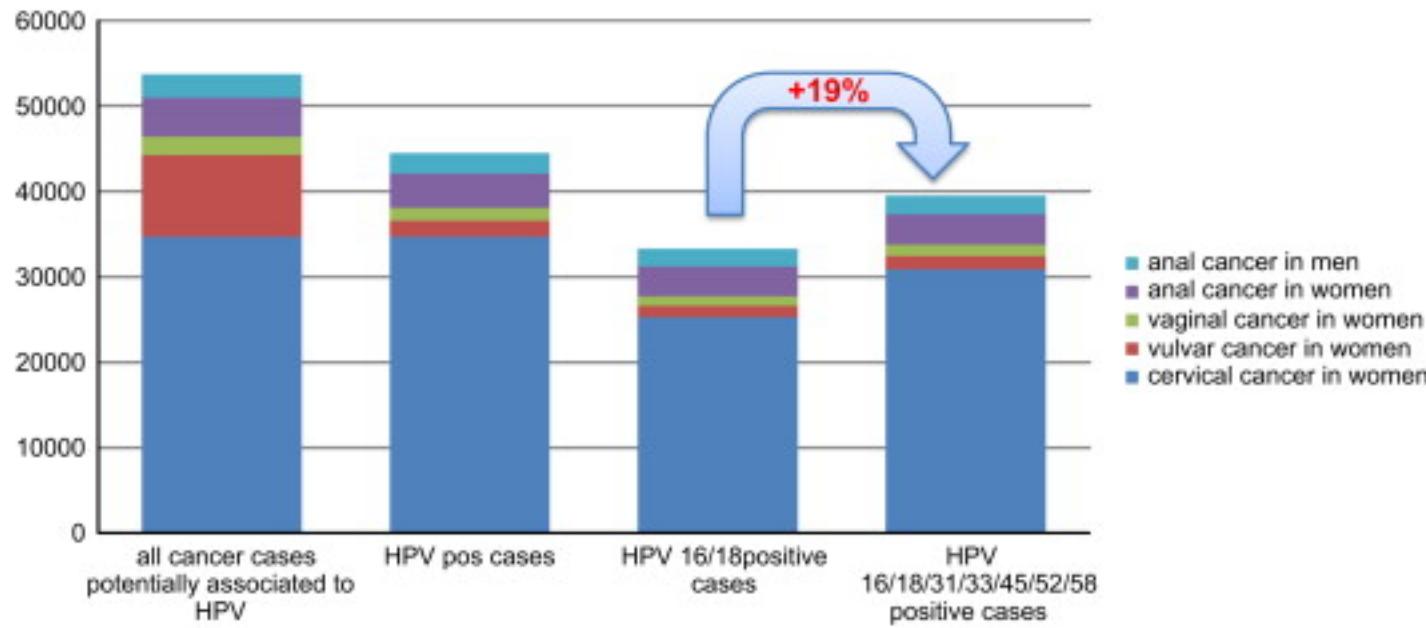
CV HPV (1 dose) cumulée en fonction de l'âge et des cohortes de naissance



HPV in cervical cancers



Potential benefit of the 9valent vaccine in Europe

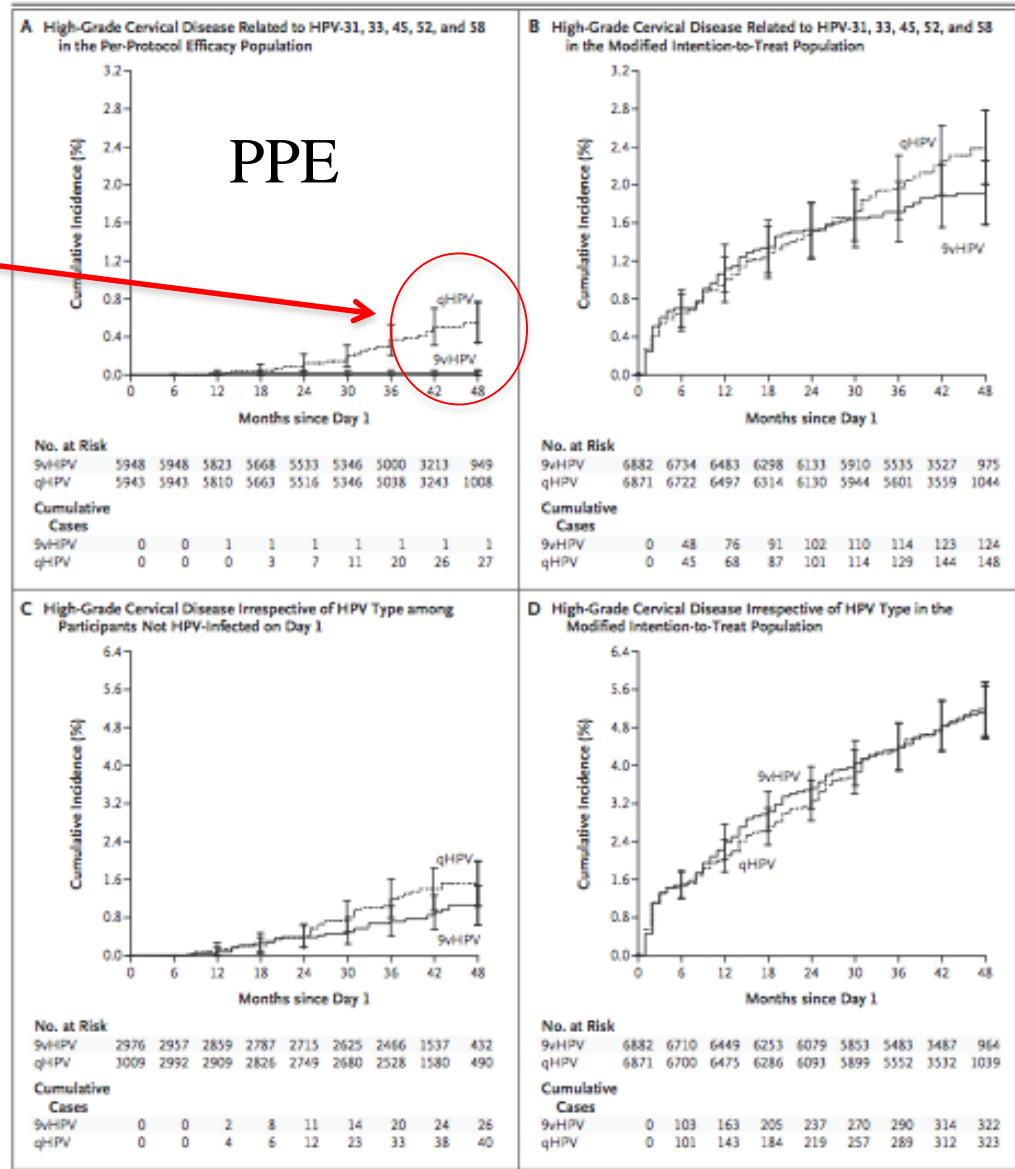


4 versus 9-valent vaccine, Efficacy

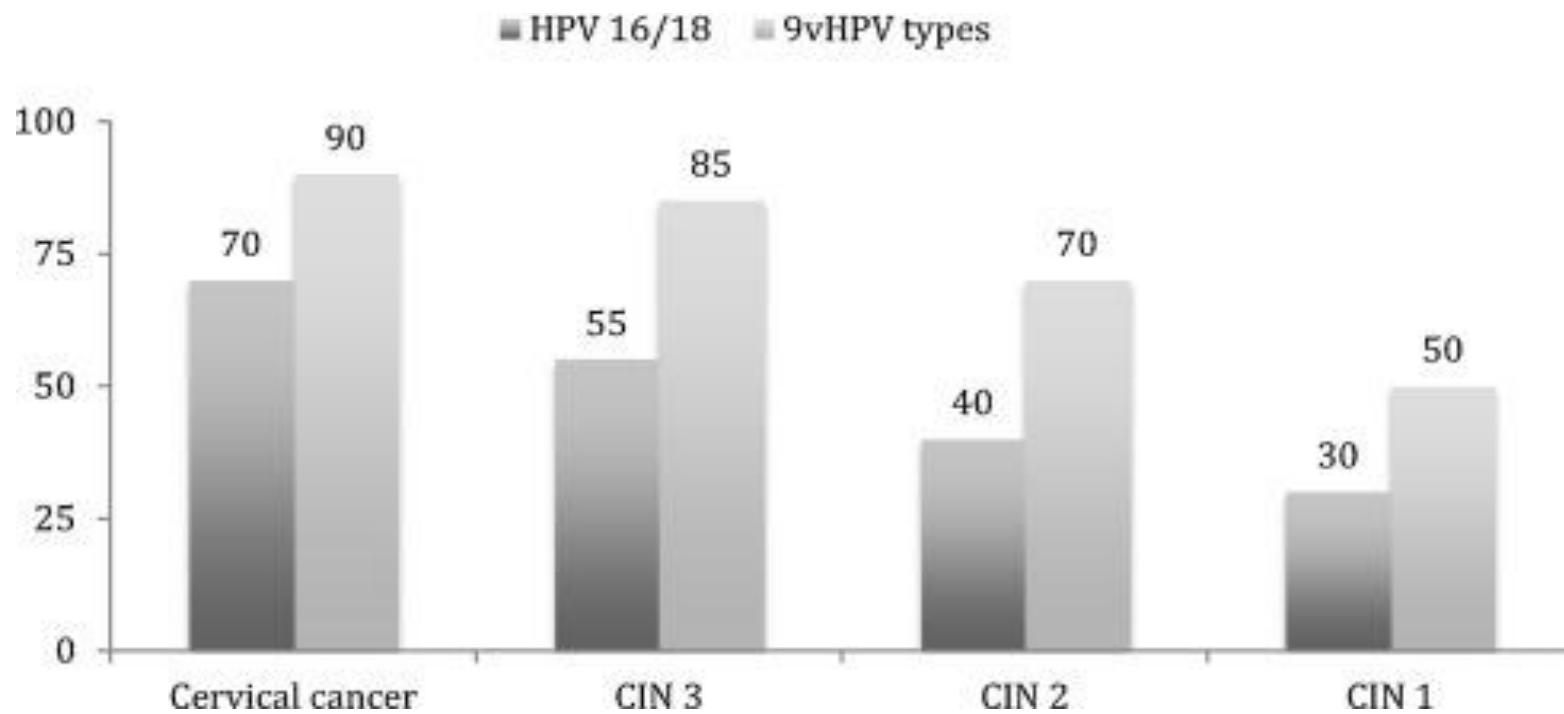
HG lesions
HPV31,33,45,52&58

Efficacy: 96.3%

95% CI, 79.5 to 99.8



Contribution of HRHPV types covered by the bi- and quadrivalent vaccines and the nonavalent vaccine to cervical cancer and precancerous cervical lesions.



Immunogenicity and safety of the 9-valent HPV vaccine in men

- Objective: evaluation of 9-valent HPV vaccine immunogenicity and tolerability in men and women 16–26 years old.
- GMTs for vaccine HPV types for HM were ***non-inferior to those of women at month 7.***
- Administration of 9vHPV vaccine to both 16–26 year old men and women was generally well tolerated.
- These results ***support bridging the efficacy*** findings with 9vHPV vaccine in young women 16–26 years of age to men 16–26 years of age.

Recommendations for Use of HPV Vaccines USA

- Routine HPV vaccination **at age 11 or 12 years**. The vaccination series can be started beginning at age 9 years.
- Vaccination is also recommended for females aged 13 through 26 years and for males aged 13 through 21 years who have not been vaccinated previously or who have not completed the 3-dose series.
- Males aged 22 through 26 years may be vaccinated.
- Vaccination of females: 2vHPV, 4vHPV, or 9vHPV.
- Vaccination of males: 4vHPV or 9vHPV.

Anal cancer incidence in France

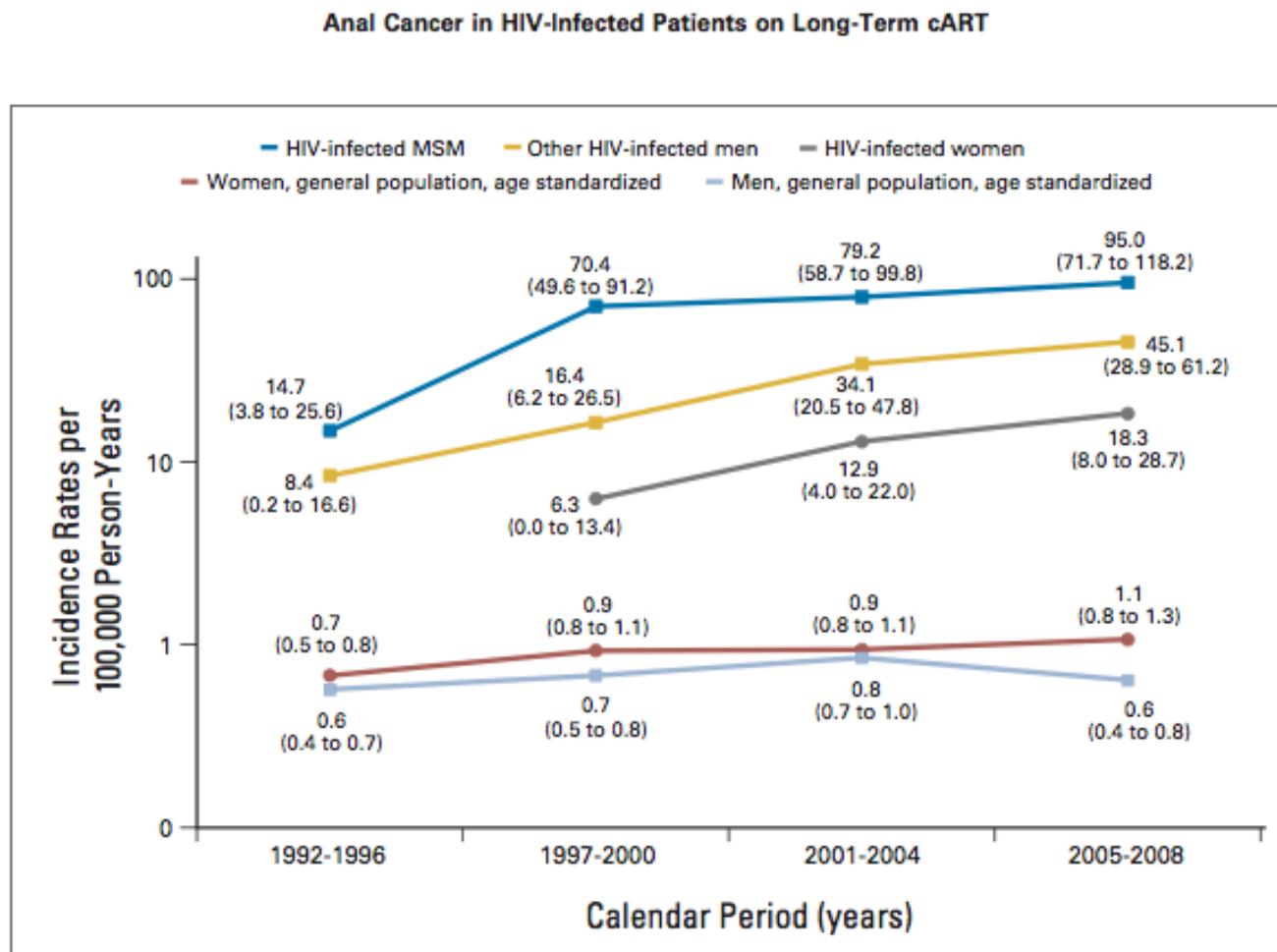
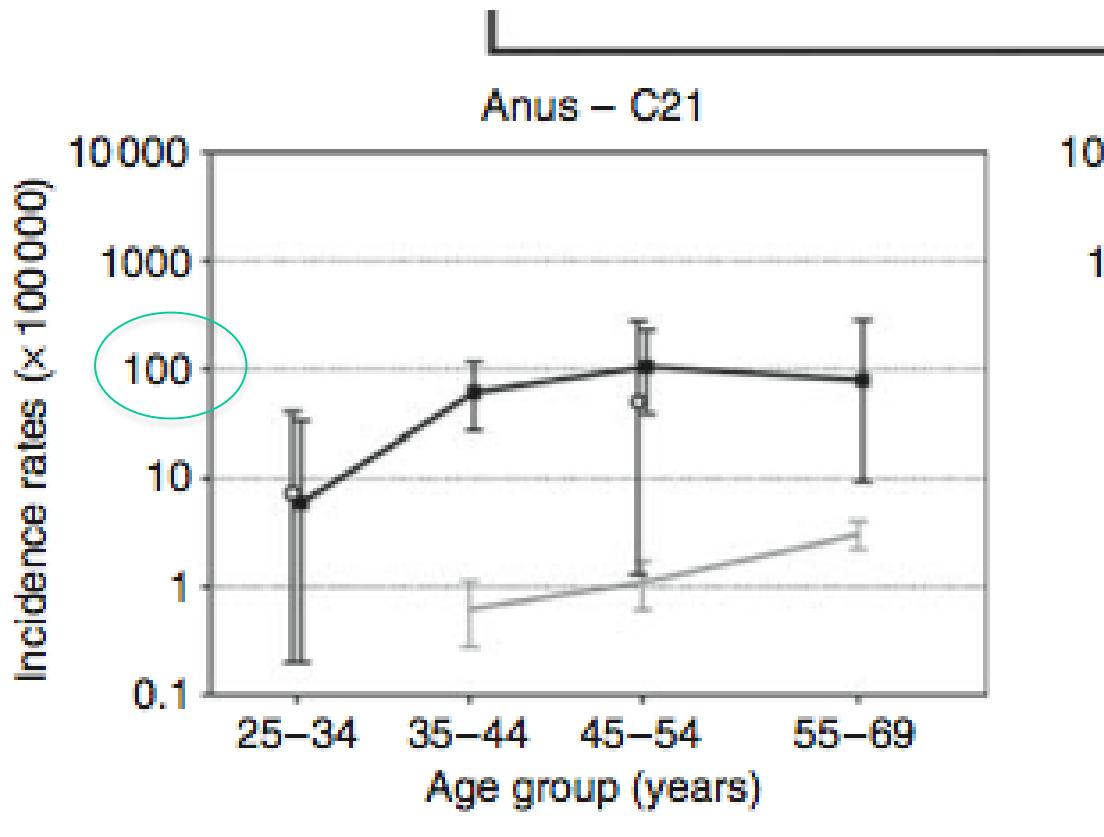


Fig 2. Incidence of anal cancer according to sex, HIV transmission group, and calendar period. For the general population, incidence rates were standardized by 5-year age groups on the basis of the age and sex distribution of the HIV-infected population in the French Hospital Database on HIV in the combined antiretroviral treatment period (1997-2008). Incidence rates are expressed per 100,000 person-years with 95% CIs in brackets. MSM, men who have sex with men.

Incidence des cancers de l'anus/VIH, MSM



--○-- PWHA, 1985–1996 —■— PWHA, 1997–2006 ——— General population, 1998–2002

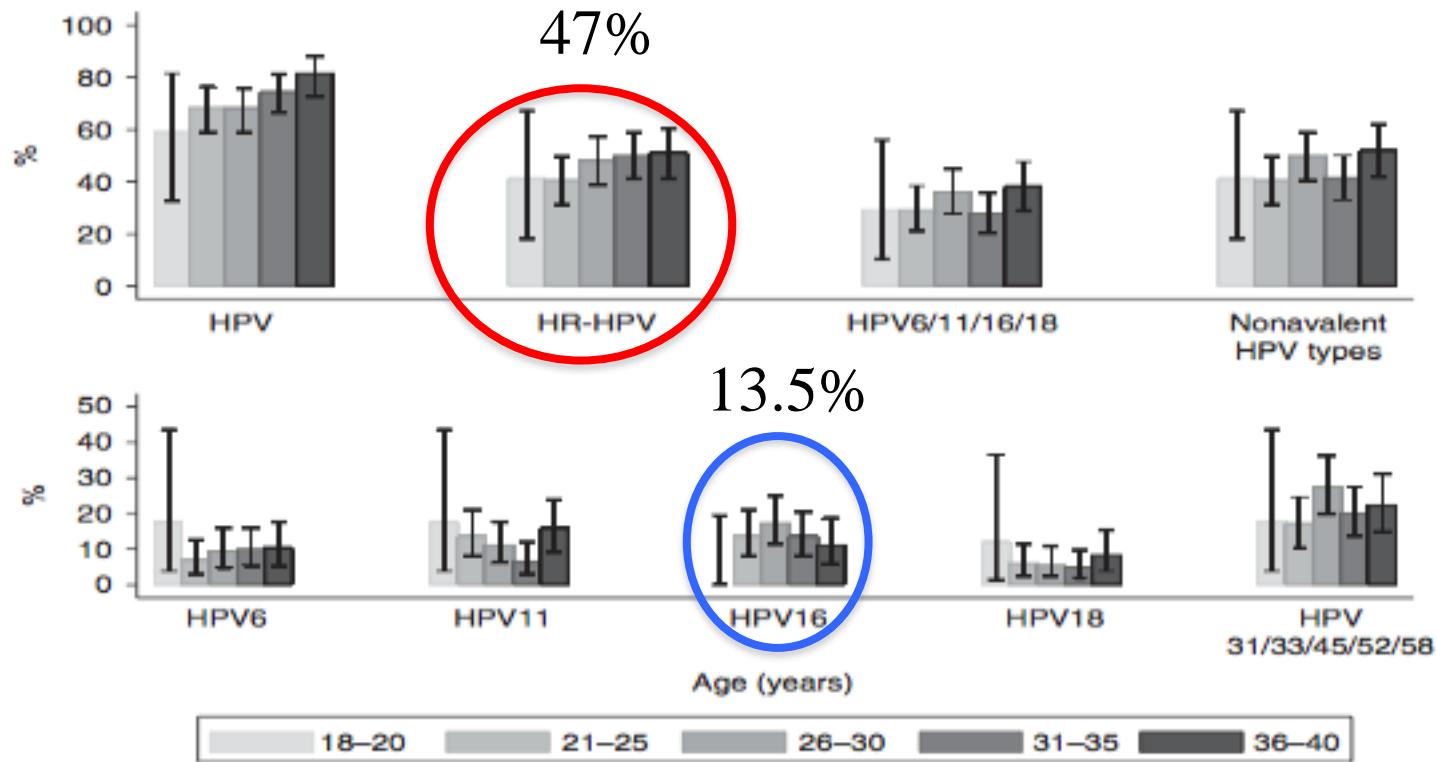
HPV 4valent in anal lesions in MSM

HPV vaccine in men: What the studies show

Outcomes evaluated	Type of study	Population	Outcomes	Data analysis, by protocol type	Results (reduction compared to placebo)	Comments
AIN and persistent HPV infection associated with HPV types 6, 11, 16, and 18	Placebo-controlled double-blind RCT ¹	602 MSM, ages 16-25 yr	AIN grades 1, 2, and 3	ITT	50.3% (95% CI, 25.7%-67.2%)	PP group (n=194) included only men who tested negative for HPV before vaccination (serum, anal cytology, anal biopsies), who were proven to have received all vaccine doses, and who had 5 or fewer lifetime sexual partners
				PP	77.5% (95% CI, 39.6%-93.3%)	
			AIN grades 2 and 3	ITT	54.2% (95% CI, 18%-75.3%)	
				PP	74.9% (95% CI, 8.8%-95.4%)	
			Persistent anal HPV infection	ITT	59.4% (95% CI, 43%-71.4%)	
				PP	94.9% (95% CI, 80.4%-99.4%)	

Palefsky et al., 2011

HPV DNA in 522 men who have sex with men: type-specific prevalence



Median age: 30 years

HPV types in 200 MSM (16-20)

	Definite infection			Possible infection			Definite or possible infection		
	Incident definite infections	Person-years at risk	Incidence (95% CI)	Incident possible infections	Person-years at risk	Incidence (95% CI)	Incident infections	Person-years at risk†	Incidence (95% CI)
High-risk HPV types									
Any high risk HPV type	21	83	25.3 (16.4-36.0)	75	166	45.2 (34.5-53.1)	96	125	76.8 (68.4-83.9)
HPV 16	4	79	5.1 (1.4-12.5)	8	157	5.1 (2.2-9.8)	12	118	10.2 (5.4-17.1)
HPV 18	7	81	8.6 (3.5-17.0)	8	162	4.9 (2.1-9.5)	15	122	12.3 (7.0-19.5)

Median age: 17 years

HPV Incidence rate 3 to 4 times higher than in women entering sexual activity;

Probability of transmission per partner 50%, vs 20% in heterosexuals

HPV vaccination early and coverage >>70% to obtain similar reduction

Zou et al., 2016



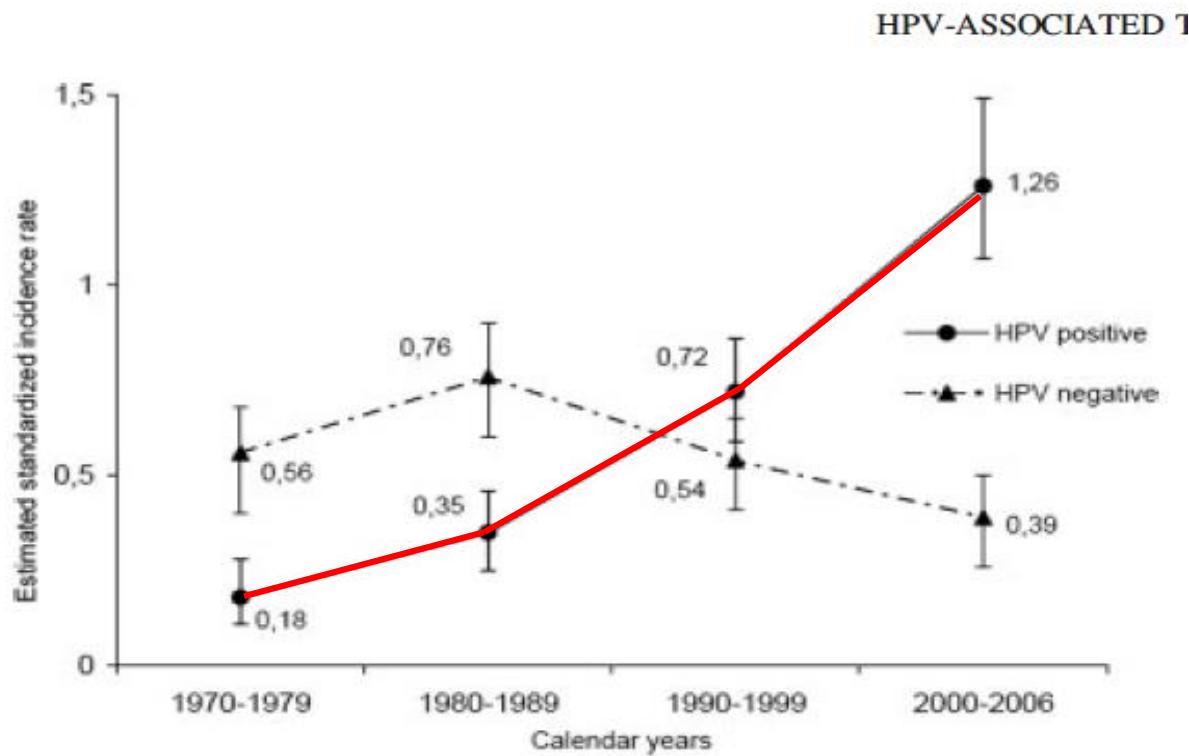
Haut
Conseil de la
Santé
Publique



Vaccination des garçons contre les infections à papillomavirus



Incidence du cancer de l'amygdale en Suède



Näslund et al, 2009

Multisite HPV16/18 Vaccine Efficacy Against Cervical, Anal, and Oral HPV Infection

Table 2. HPV16/18 vaccine efficacy against prevalent cervical, anal, and oral HPV16/18 DNA four years after vaccination in the "Naïve" cohort*,†

Study population	Arm	Women or sites	No. events	HPV16/18 prevalence, %	Efficacy (95% CI), %
Cervical, anal, or oral HPV16/18	HPV vaccine	970	15	1.5	83.5 (72.1 to 90.8)
Multisite woman level‡	Control	949	89	9.4	
Cervical HPV16/18	HPV vaccine	970	8	0.8	89.4 (79.0 to 95.2)
	Control	949	74	7.8	
Anal HPV16/18	HPV vaccine	970	7	0.7	85.1 (68.4 to 93.8)
	Control	949	46	4.8	
Cervical, anal, oral HPV16/18	HPV vaccine	2910	15	0.5	88.2 (79.6 to 93.1)
Multisite infection level§	Control	2847	124	4.4	
HPV16/18 at two or three sites	HPV vaccine	970	0	0.0	100.0 (91.0 to 100.0)
	Control	949	34	3.6	

This randomized trial demonstrated multisite vaccine efficacy

- against cervical, anal, and oral HPV16/18
- at the 4-year follow-up visit
- among women with no evidence of HPV16 or HPV18 exposure

Cost-effectiveness of female human papillomavirus vaccination in 179 countries: a PRIME modelling study

Mark Jit, Marc Brisson*, Allison Portnoy*, Raymond Hutubessy

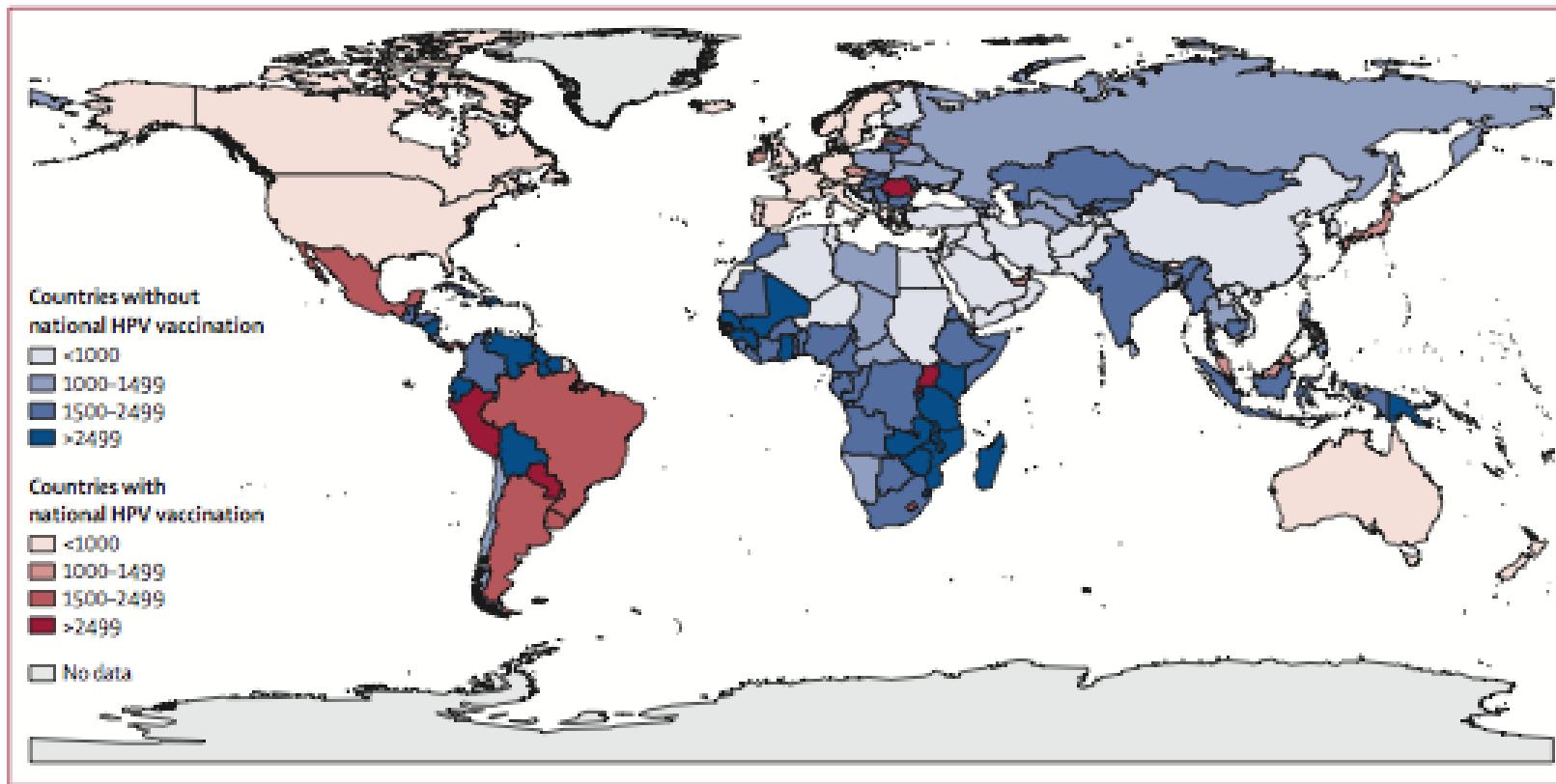


Figure 2: Estimated number of cervical cancers prevented per 100 000 girls vaccinated against human papillomavirus (HPV) in 186 countries

Vaccination programme in 4 of 33 countries with likely a major impact and in 24 of 55 countries with the least effect.

En conclusion,

- Infection HPV très fréquente,
- Cause de cancers anogénitaux et des VADS
- Diagnostic repose sur la détection de l'ADN (pas de culture, pas de sérologie)
- Les vaccins sont efficaces en prévention
- Risque de cancer chez les immunodéprimés dans le contexte de l'augmentation de la durée de vie ?