

Il vaccino anti-HPV 10 anni dopo

Luciano Mariani
HPV-UNIT
Ginecologia Oncologica
Istituto Nazionale Tumori Regina Elena
Roma

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CONFLITTO DI INTERESSI

Ho partecipato a eventi congressuali e studi clinici come consulente scientifico per SPMSD, Merck, GSK, Roche.

In merito alla presentazione non ho alcun conflitto d’interessi, e le opinioni da me espresse sono totalmente personali.

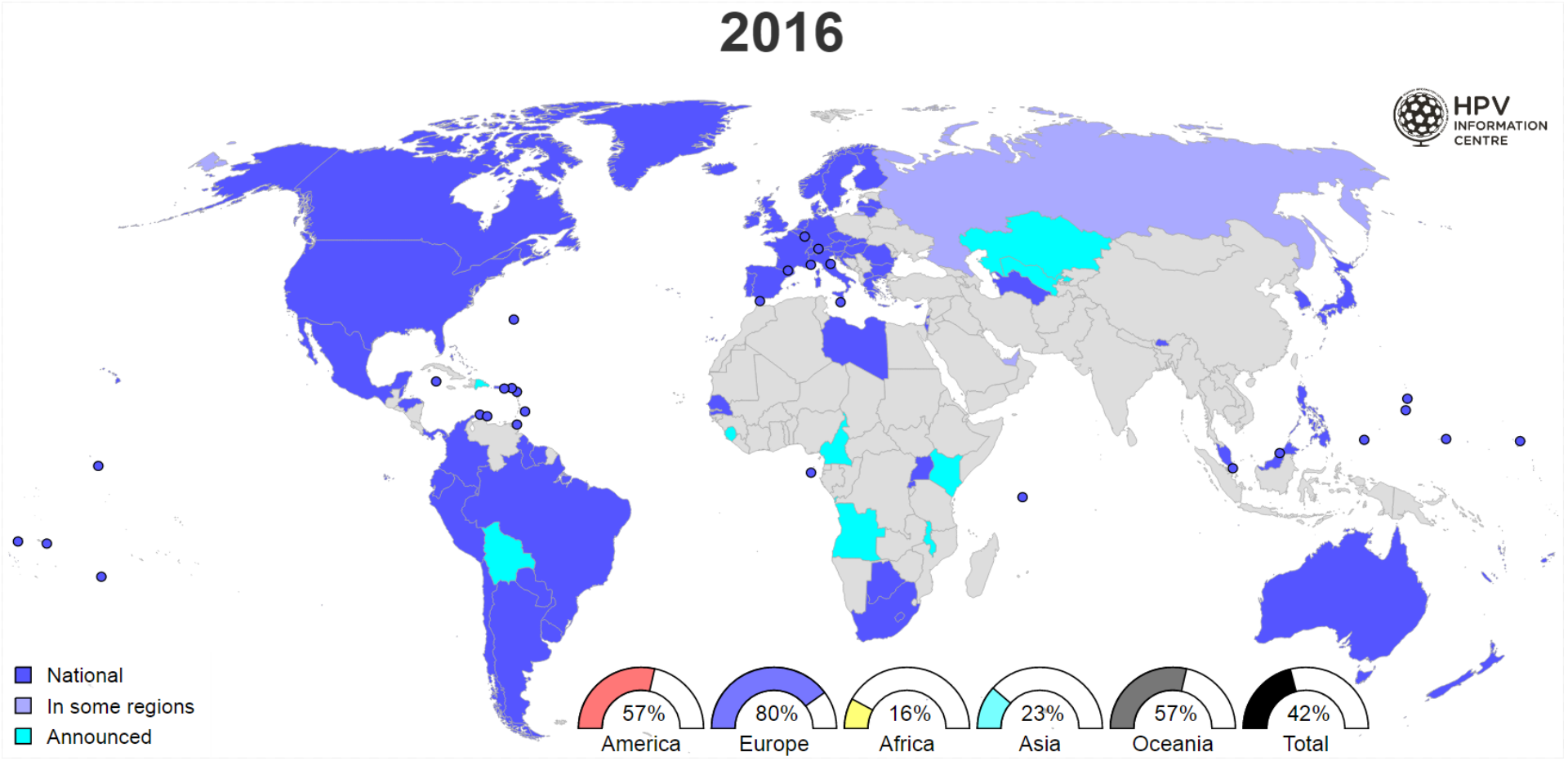
HPV VACCINE

1991-92	L1 capsid protein self-assembled into a virus-like particle, VLP. *(I.Frazer, R.Kirnbauer)*
2002	monovalent HPV-16 vaccine efficacy trial *(proof of principle that HPV oncogenic infections and related cancer/precursors may be preventable) (L.Koutsky)*
2002	phase-3 trial with 4vHPV vaccine (VLPs of HPV 6, 11, 16, 18)→ licensed by FDA in 2006
2004	phase-3 trial with 2vHPV vaccine (VLPs of 16, 18) →licensed in 2007
2007	**Worldwide national organized programs**
2014	phase-2/3 trial with 9vHPV vaccine (VLPs 6, 11, 16, 18, 31, 33, 45, 52, 58) → licensed by FDA 2014

Vaccination is a promise of prevention

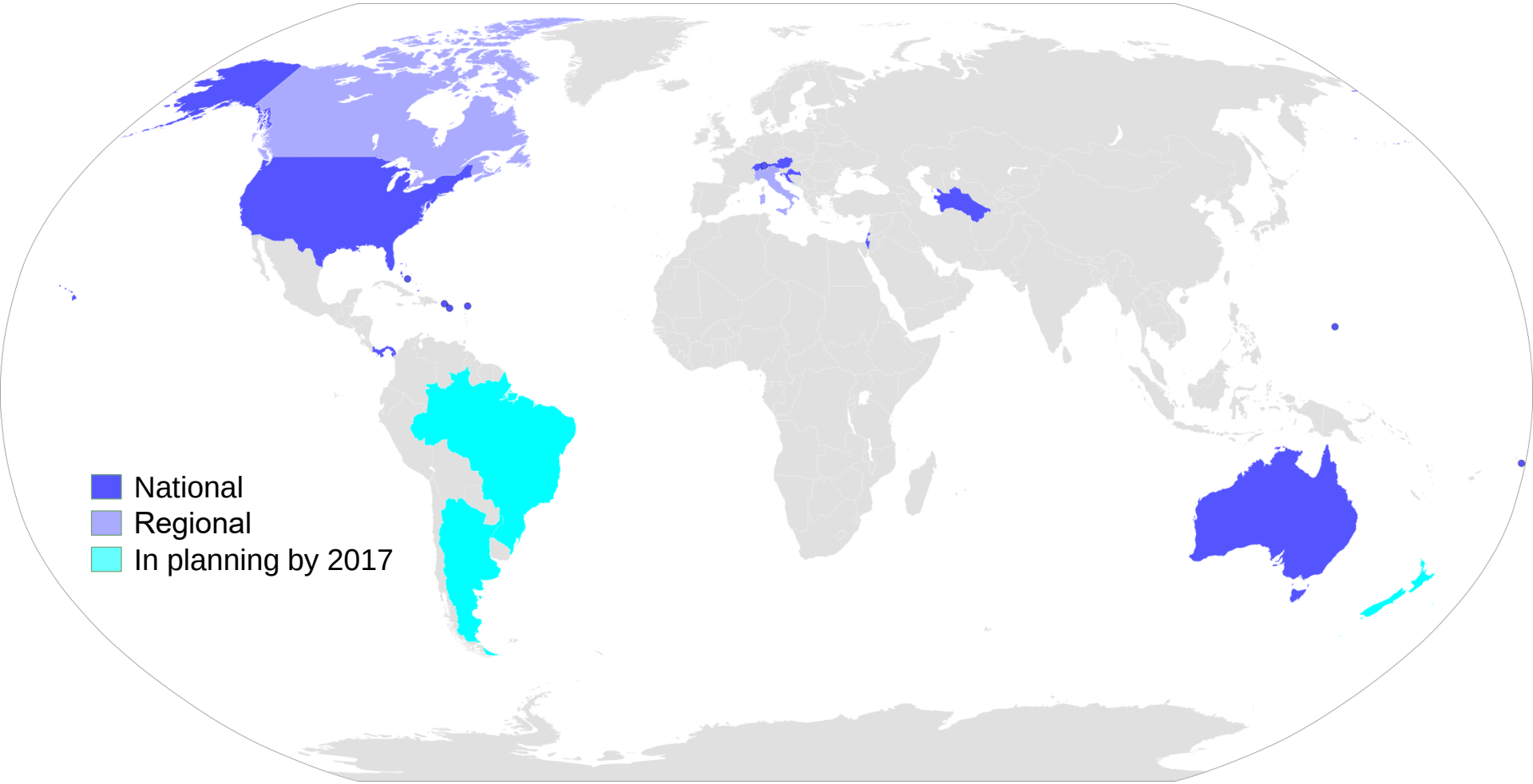
Pre-registration trials give us a measure of the expected benefit, but it has to be confirmed after the organized vaccination programs *(real-life results)*

Female HPV vaccination included in population programs



82 of the countries (42%) include HPV vaccination in 2016

Female HPV vaccination included in population programs 2016



13 Countries (7%)

BACKGROUND

	Screening (pap)	Screening (HPV)
Target disease	Cervical cancer/pre-cancer	
Impact	participant (target population)	
Number of intervention (lifetimes)	>10 test (every 3 yrs)	5+ test (every 5 yrs)
Side effects	mild	overdiagnosis communication
Impact on other cancers	none	

BACKGROUND

	Screening (pap)	Screening (HPV)	HPV vaccination
Target disease	Cervical cancer/pre-cancer		Cervical cancer /pre-cancer **HPV infection**
Impact	participant (target population)		participant + **herd effect**
Number of intervention (lifetimes)	>10 test (every 3 yrs)	5+ test (every 5 yrs)	**3 or 2 doses** (no booster to date)
Side effects	mild	overdiagnosis communication	local (short-term)
Impact on other cancers	none		**HPV-related cancers**

Evoluzione della strategia di vaccinazione organizzata HPV

	WHO 2006
Obiettivo	prevenzione cancro della portio
Genotipi target	16, 18
Popolazione target	popolaz. femminile 12anni
Schedula vaccinale	3 dosi
Offerta vaccinale	attiva e gratuita

Evoluzione della strategia di vaccinazione organizzata HPV

	WHO 2006	WHO 2014
Obiettivo	prevenzione cancro della portio	prevenzione cancro della portio e/o patologie HPV-correlate (*public health priority*)
Genotipi target	16, 18	maggior numero di genotipi
Popolazione target	popolaz. femminile 12anni	entrambi i sessi 12anni *(country-level decision)*
Schedula vaccinale	3 dosi	2 dosi
Offerta vaccinale	attiva e gratuita	attiva e gratuita

strategia di vaccinazione individuale HPV in età adulta

Obiettivo	prevenzione delle patologie HPV-correlate
Genotipi target	maggior numero di genotipi
Popolazione target	entrambi i sessi sino età massima in scheda tecnica *(dall'età di 9 anni)*
Schedula vaccinale	3 dosi
Offerta vaccinale	on-demand *(a carico del singolo)*

Piano Naz Prevenzione Vaccini 2017-19

- **Cambia l'obiettivo di sanità pubblica**: immunizzazione di adolescenti di **entrambi i sessi** verso il **più alto numero di ceppi HPV** per la **prevenzione di tutte le patologie HPV-correlate** direttamente prevenibili con la vaccinazione.
- È raccomandata la vaccinazione con offerta attiva e gratuita delle **donne di 25 anni di età**, anche utilizzando l'occasione della chiamata al primo screening.
- Consigliata la vaccinazione per
  - immunodepressi
  - uomini che fanno sesso con uomini



protezione individuale → **protezione collettiva**

Real-life results

I VACCINI HPV SONO MEGLIO DI QUANTO SPERASSIMO

BENEFICI ACQUISITI DOPO I PROGRAMMI ORGANIZZZATI

RIDUZIONE DI:

JRRP

-87% (Brotherton J. IPV CapeTown, 2017)

PREVALENZA HPV

-90% Canada (Kahn 2016)
-86% Australia (Tabrizi 2014)
-77% England (Mesher 2016)
-64% USA (Markowitz 2016)

CONDILOMI GENITALI

-90% Australia (Ali H 2013)
-72% Belgium (Dominiak-F 2015)
-62% N.Zealand (Oliphant J 2011)
-55% Denmark (Bollerup S 2016)

CIN 2-3

-80% Denmark (Baldur-F 2014)
-75% Sweden (Herweijer E '16)
-60% Scotland (Pollock K 2015)
-54% Australia (Brotherton '15)
-47% USA (Hariri S, 2015)

HERD IMMUNITY ♀

-32% USA (Kahn J 2016)

HERD IMMUNITY ♂

-82% Australia (Ali H 2013)
-50% Denmark (Bollerup S 2016)

I VACCINI HPV SONO MEGLIO DI QUANTO SPERASSIMO

BENEFICI ACQUISITI DOPO I PROGRAMMI ORGANIZZZATI

RIDUZIONE DI:

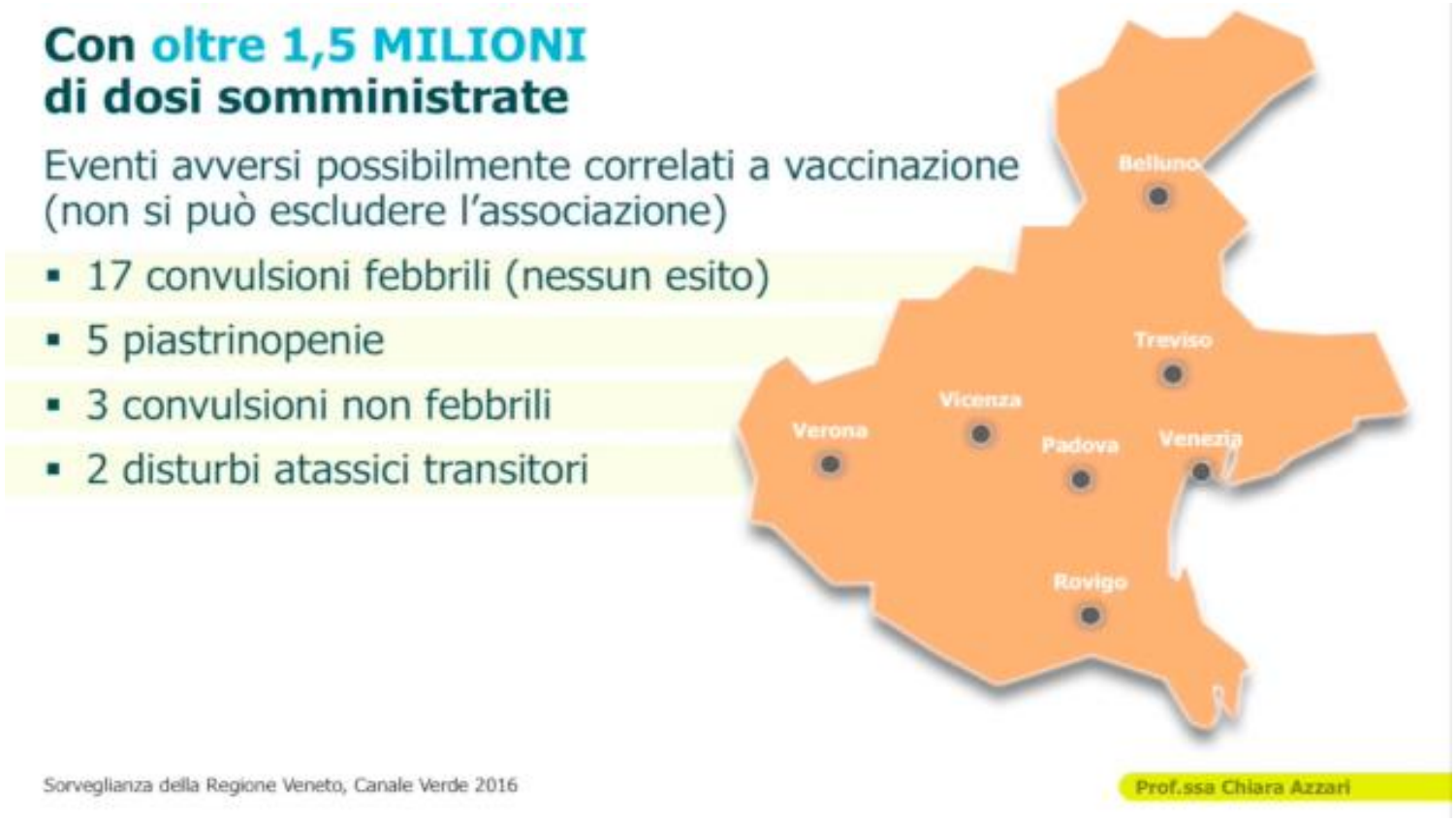
Vaccine effectiveness of bivavent vaccine in Scotland was greater in those women from the **most deprived backgrounds** against CIN 2 and 3 lesions.
The relative risk of **CIN 3** was most profound in the most-deprived women
(Cameron R, 2017)

CIN 2-3

-80% Denmark (Baldur-F 2014)
-75% Sweden (Herweijer E ‘16)
-60% Scotland (Pollock K 2015)
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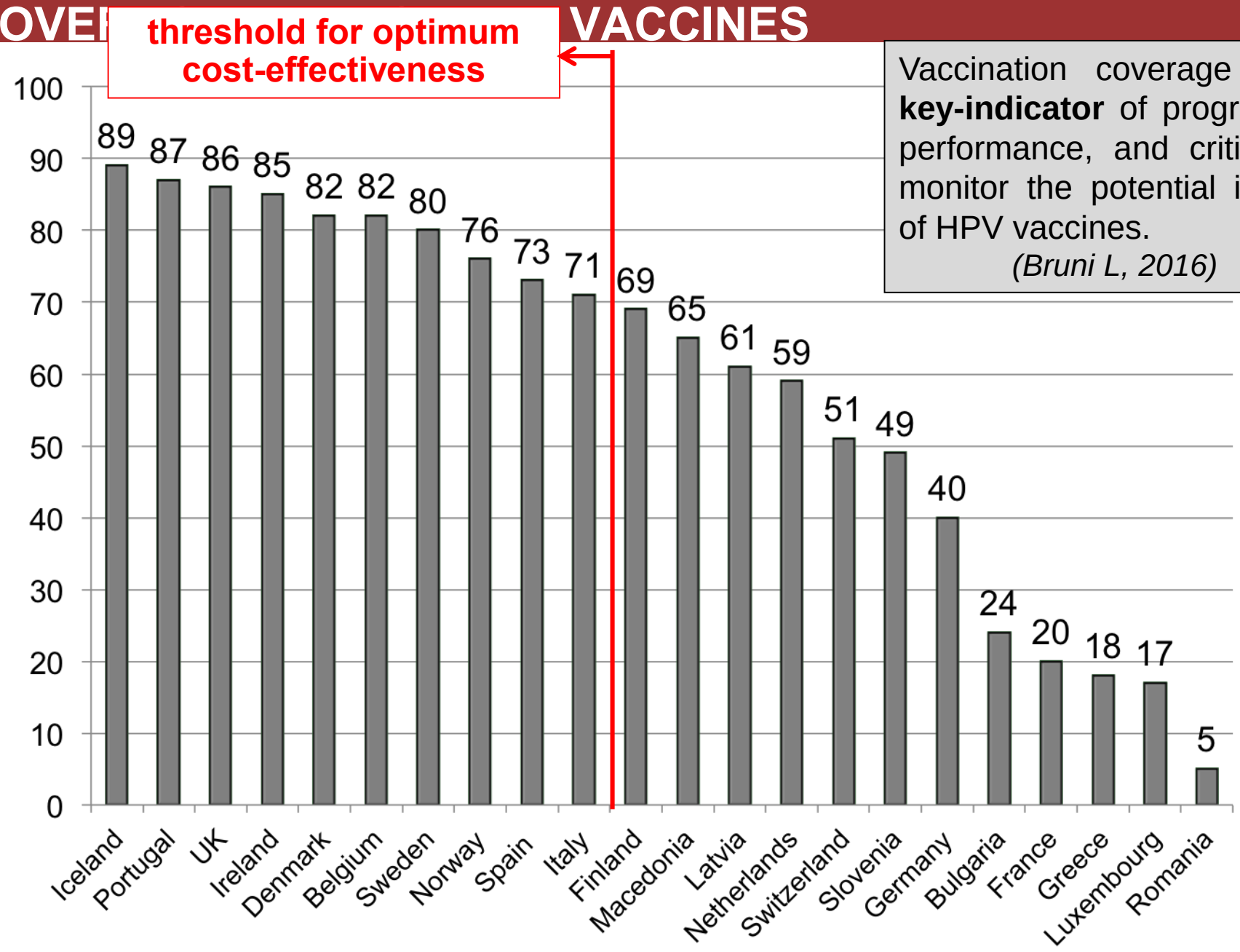
-over 250 million doses

-no safety concern: GAVCVS (WHO) last assessment reviewed in december 2015-16: autoimmune, neurologic, thromboembolic diseases *(Scheller 2015; Grimaldi-Bensauda 2014; Arnheim-Dalstrom 2013)* even if inadvertently administered in pregnancy *(Moro 2015; Gross 2014)*



Copertura vaccinale

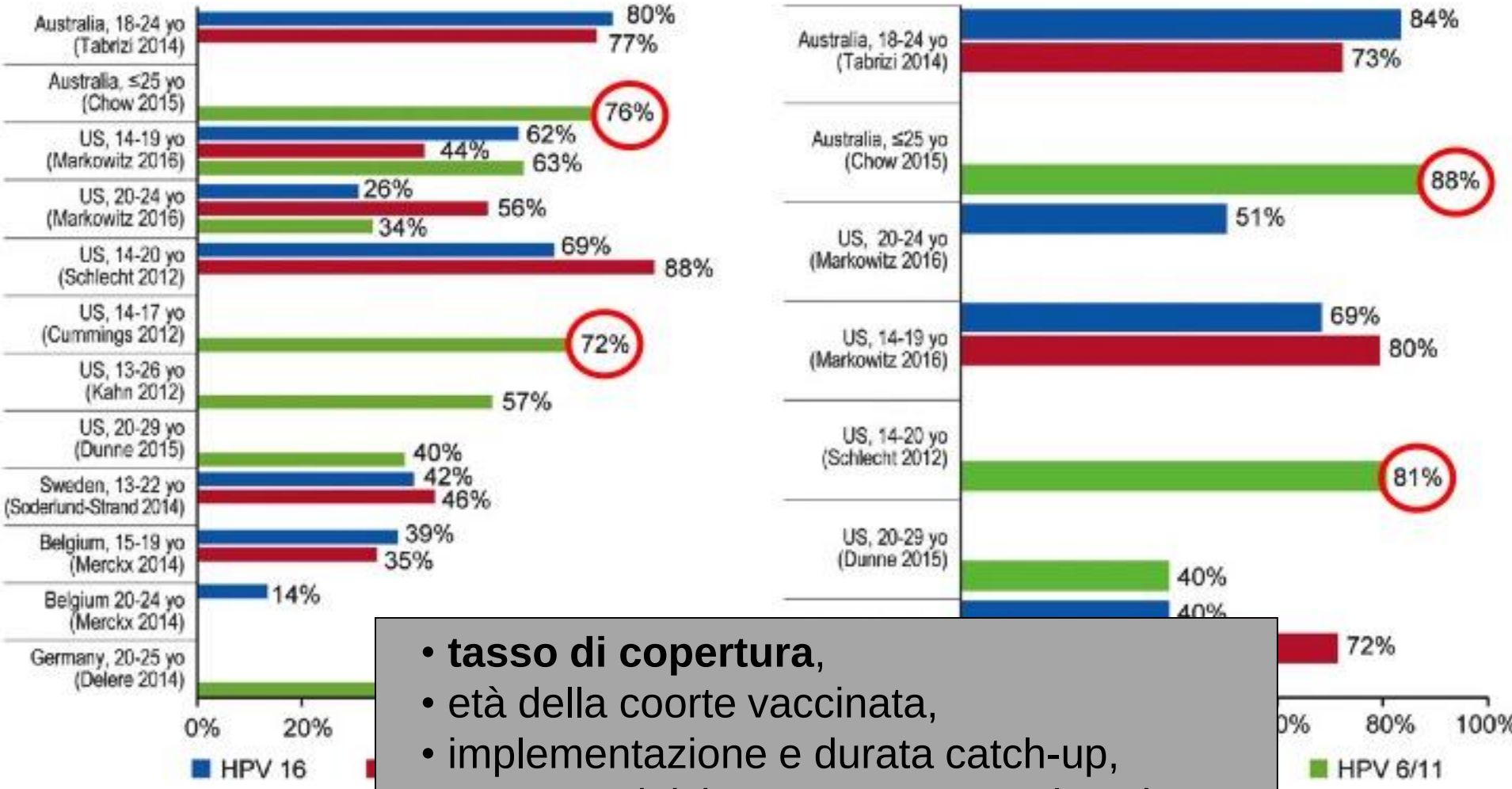
COVE VACCINES



Vaccination coverage is a **key-indicator** of programme performance, and critical to monitor the potential impact of HPV vaccines.

(Bruni L, 2016)

DECLINE OF HPV PREVALENCE: 4-HPV



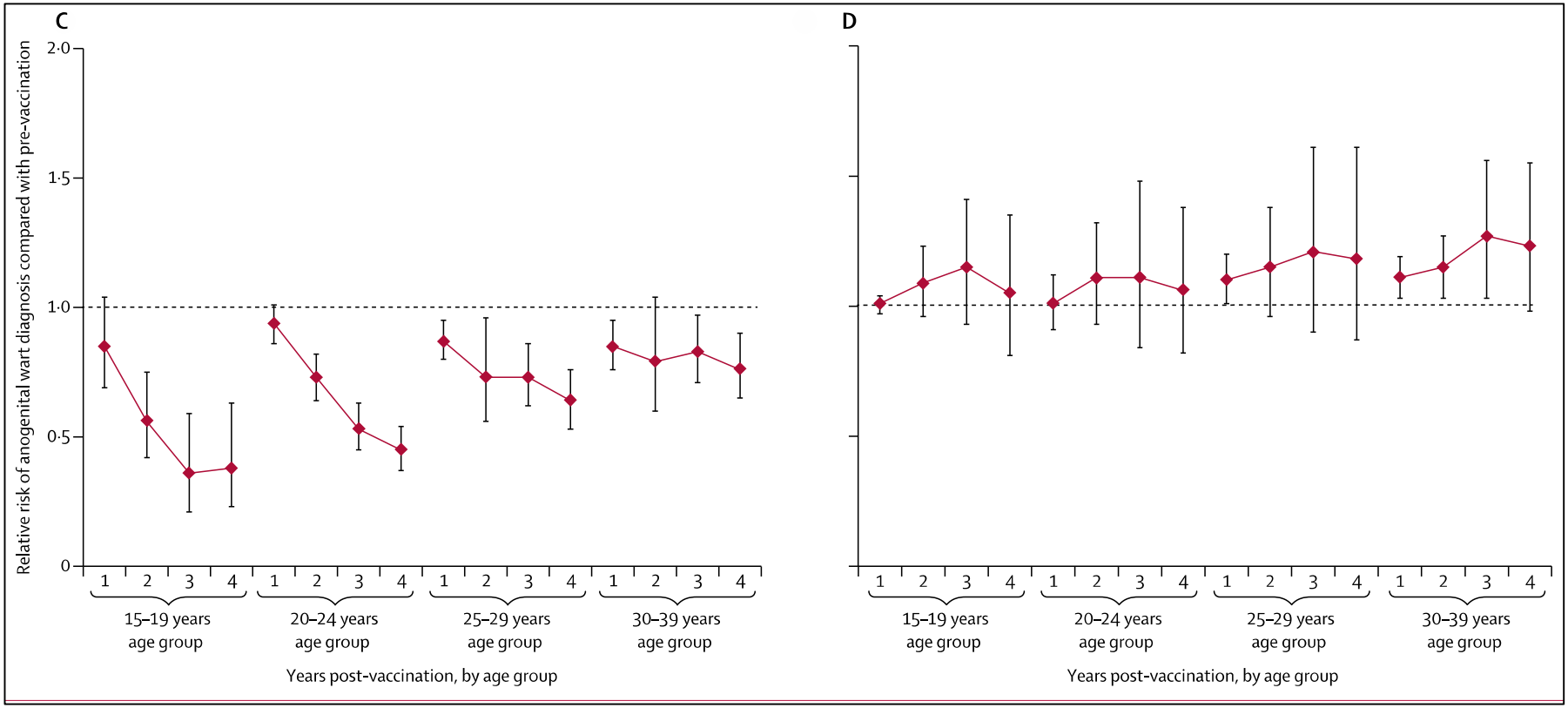
- **tasso di copertura**,
- età della coorte vaccinata,
- implementazione e durata catch-up,
- tempo tra inizio programma e valutazione dell'impatto
- durata del follow-up

DECLINE OF GENITAL WARTS: 4-HPV

HERD-IMMUNITY

Boys and men, with high female vaccination coverage **(>50%).**

Boys and men, with low female vaccination coverage **(<50%).**



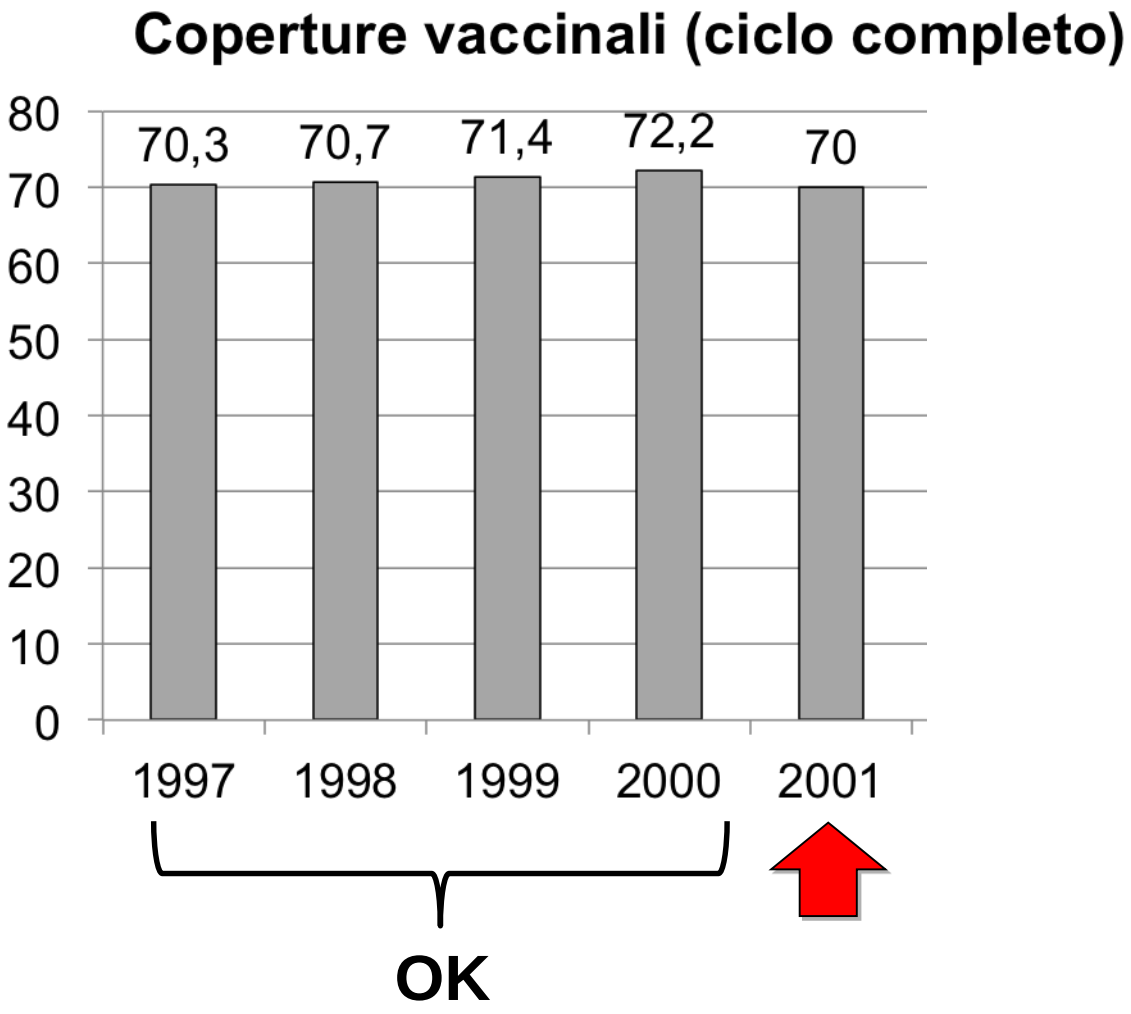
(Drolet M, 2015)

COPERTURA VACCINALE

2007
CSS
vacc.monogenere

coorte 2000 ≥ 70%, coorte 2001 ≥ 95%

Coperture vaccinali per HPV
(aggiornamento 13 febbraio 2017)



COPERTURA VACCINALE

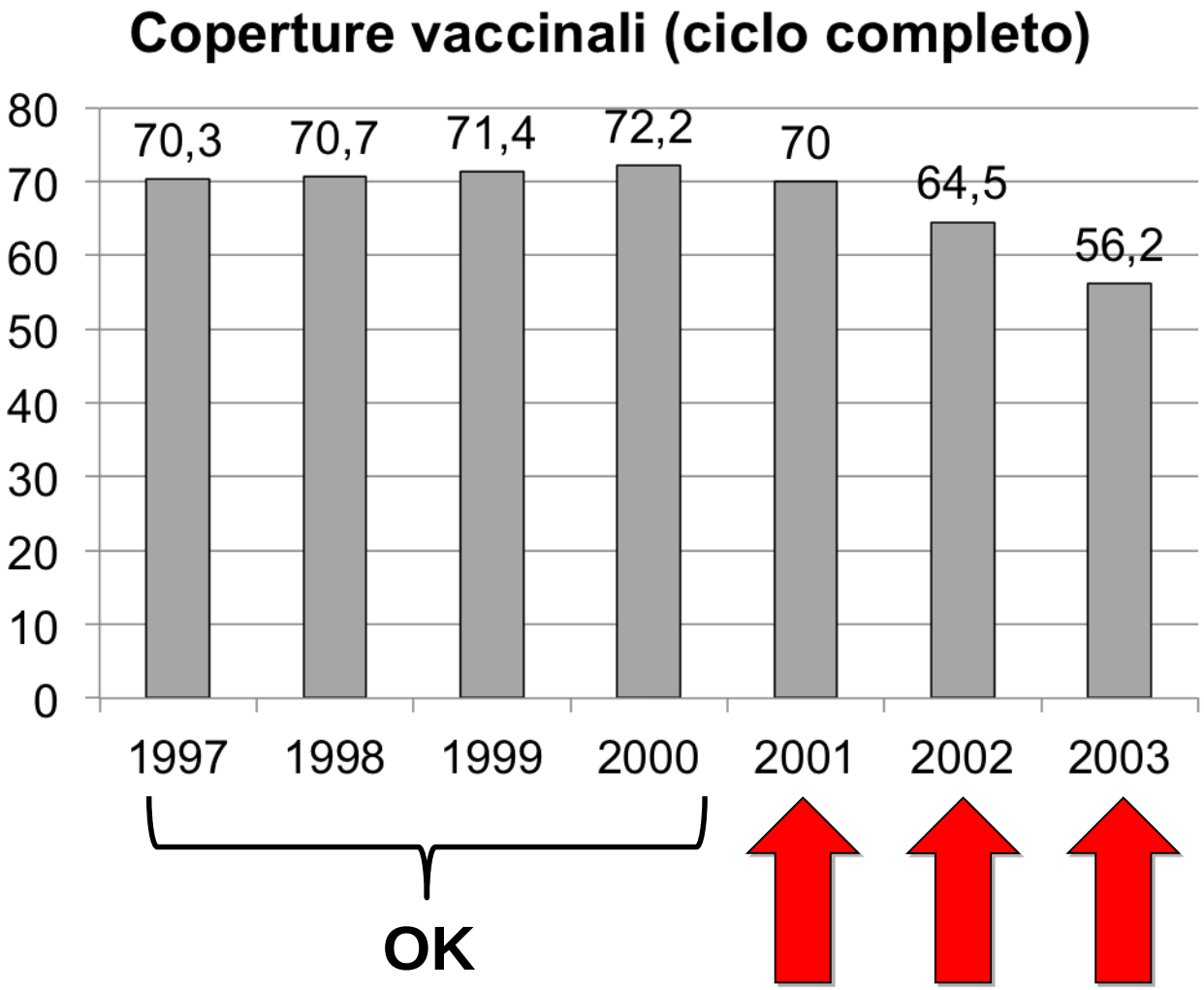
2007
CSS
vacc.monogenere

coorte 2000 ≥ 70%, coorte 2001 ≥ 95%

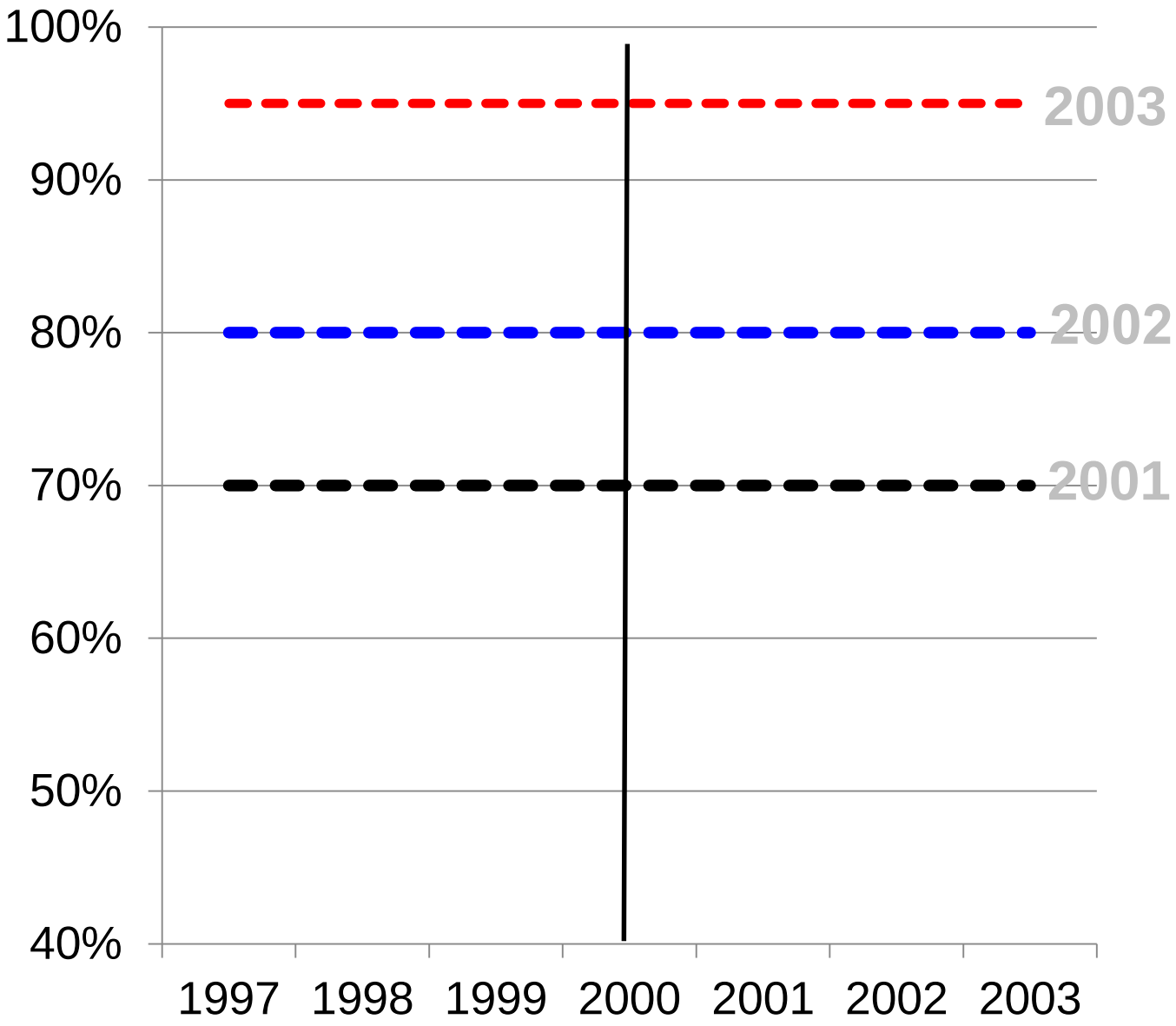
2012-14
PNPV
vacc.monogenere

coorte 2001 ≥ 70%, 2002 ≥ 80%, 2003 ≥ 95%

Coperture vaccinali per HPV
(aggiornamento 13 febbraio 2017)

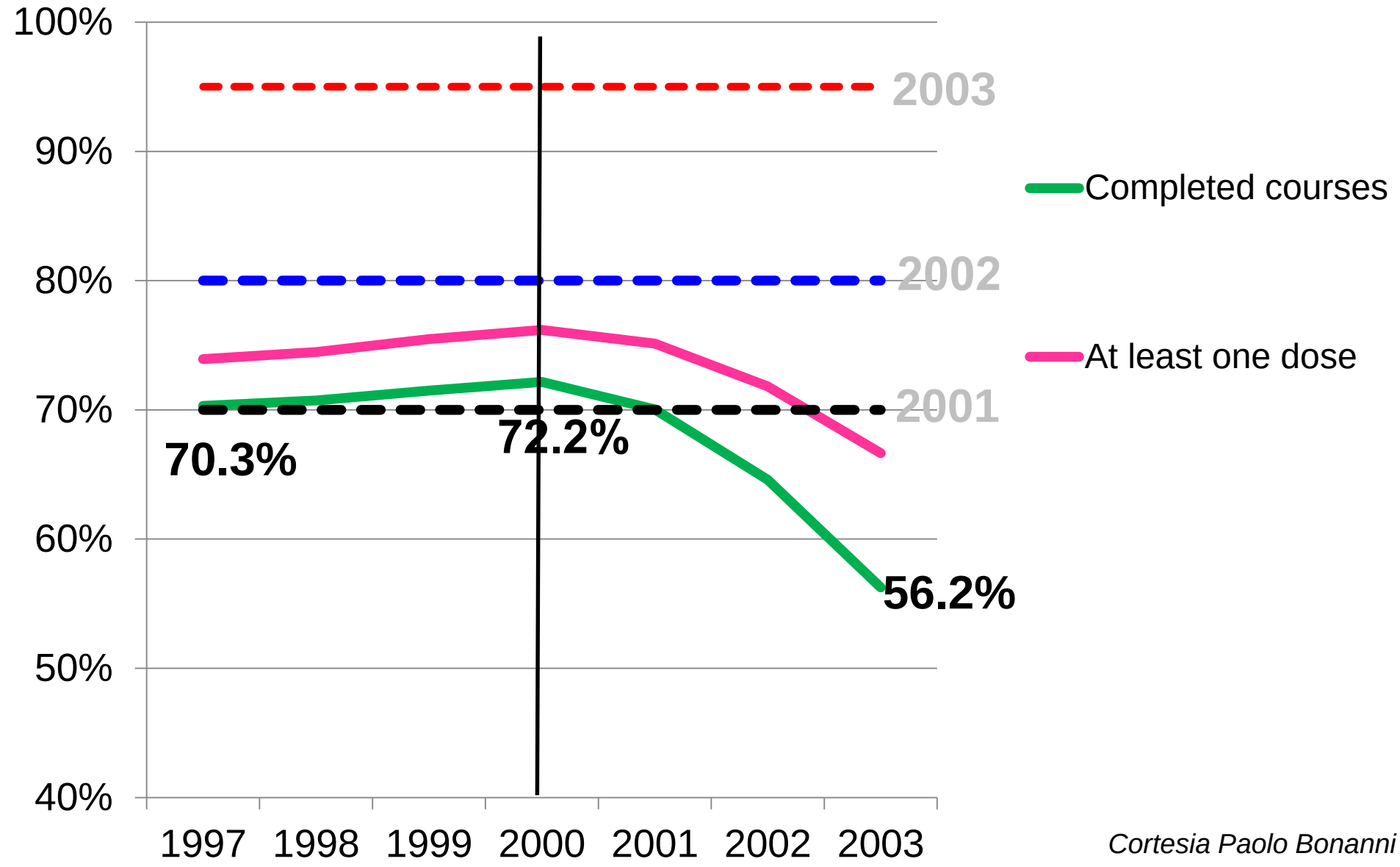


National HPV coverage, by birth cohort



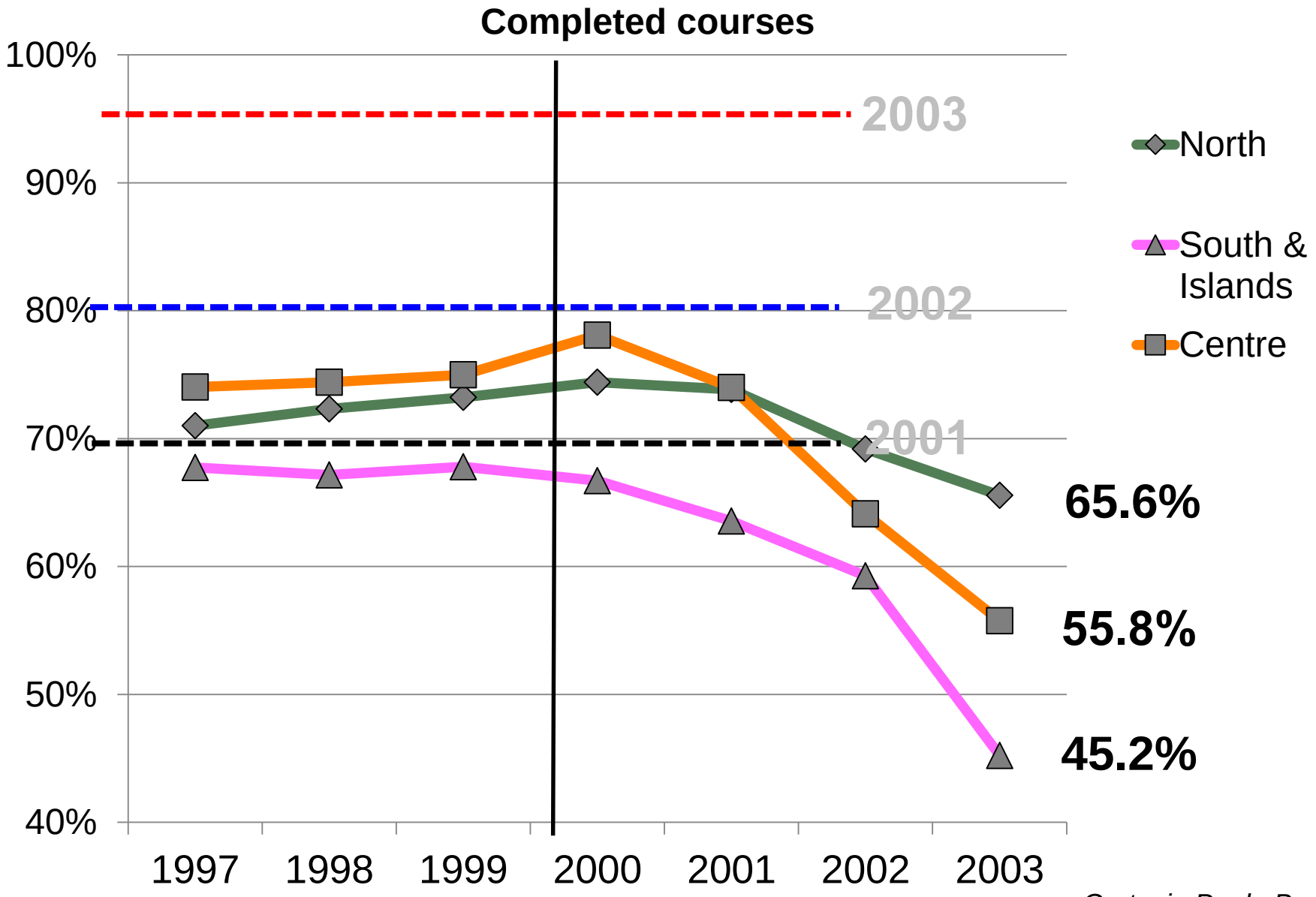
Cortesia Paolo Bonanni

National HPV coverage, by birth cohort



Cortesia Paolo Bonanni

National HPV coverage, by geographic area



Cortesia Paolo Bonanni

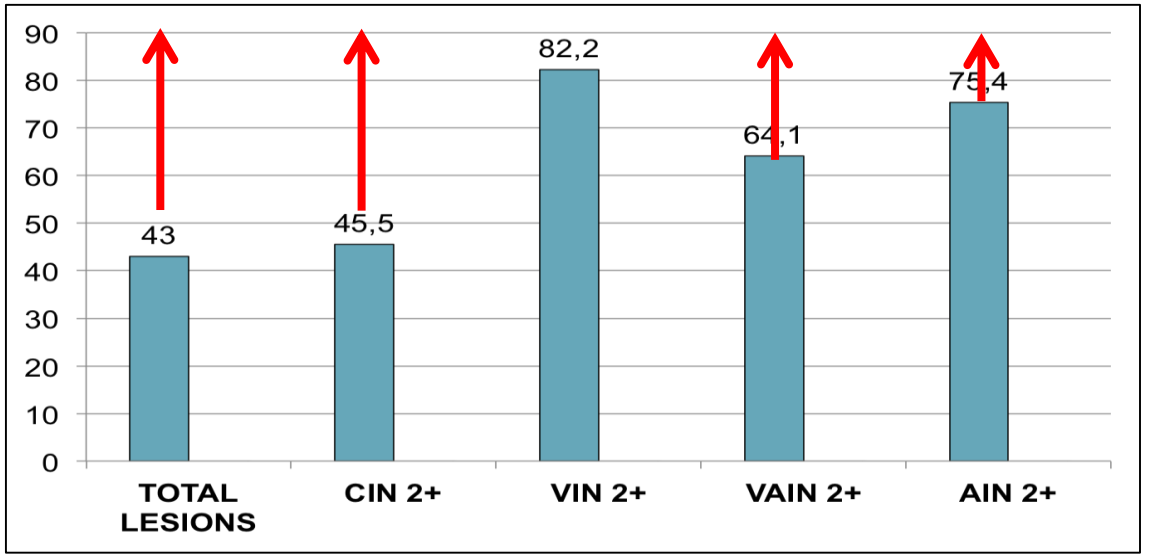
COPERTURA VACCINALE

2007 **CSS** *vacc.monogenere*	**coorte 2000 ≥ 70%, coorte 2001 ≥ 95%**
2012-14 **PNPV** *vacc.monogenere*	**coorte 2001 ≥ 70%, 2002 ≥ 80%, 2003 ≥ 95%**
2017-19 **PNPV** *vacc.universale*	**coorte 2006-7 ≥ 65%, 2008 ≥ 75%, 2009 ≥ 95%**

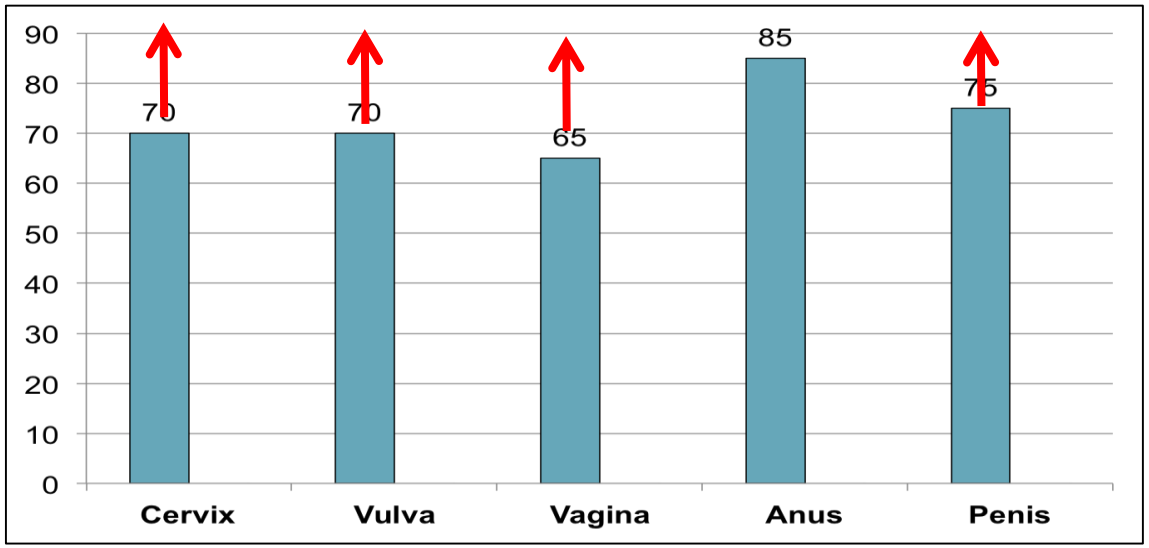
WHY TO EXTEND THE PROTECTION ?

Anti-HPV 16-18 vaccine: expected protection

Intraepithelial lesions



Invasive lesions



HOW TO EXTEND THE PROTECTION ?

CROSS-PROTECTION

vs

2nd GENERATION MULTIVALENT VACCINE

CROSS-PROTECTION

- The immuno-cross reactivity and cross-protection evoked by the two vaccines is in line with the phylogenetic similarity between the L1 capsid protein between species.

pre-registrative studies

4vHPV vaccine → HPV 31

2vHPV vaccine → HPV 31, 33, 45

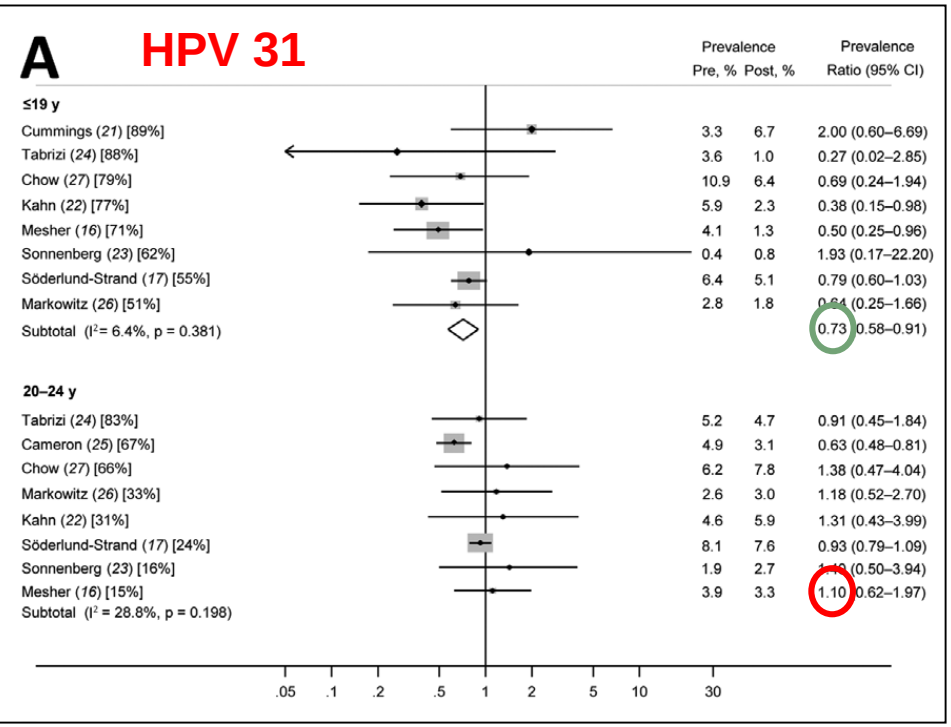
} *low magnitude of Abs titers*
waning over time

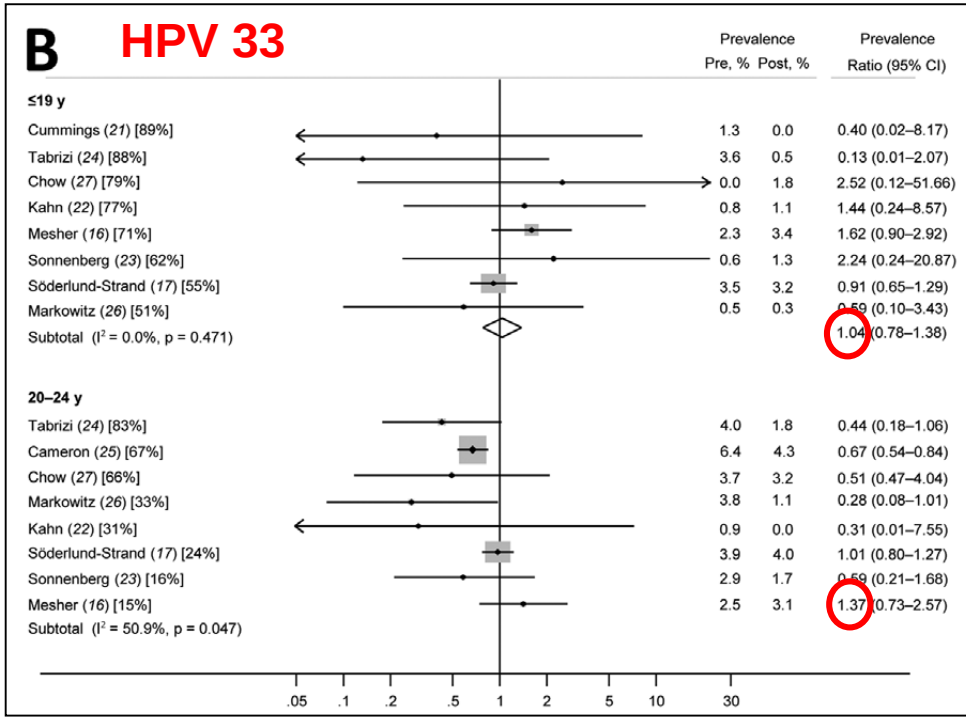
Real-life post-marketing study:

- ✓ no long-term cross-protection against HPV 31,33,45,52,58 in a systematic review *(T.Malacon, 2012)*
- ✓ no long-term cross-protection against HPV 33 and 45 in England *(D.Mesher, 2015)*
- ✓ no long-term cross-protection against HPV 6/11 in Netherland *(Woestenberg, 2017)*

CROSS-PROTECTION ?

META-ANALYSIS





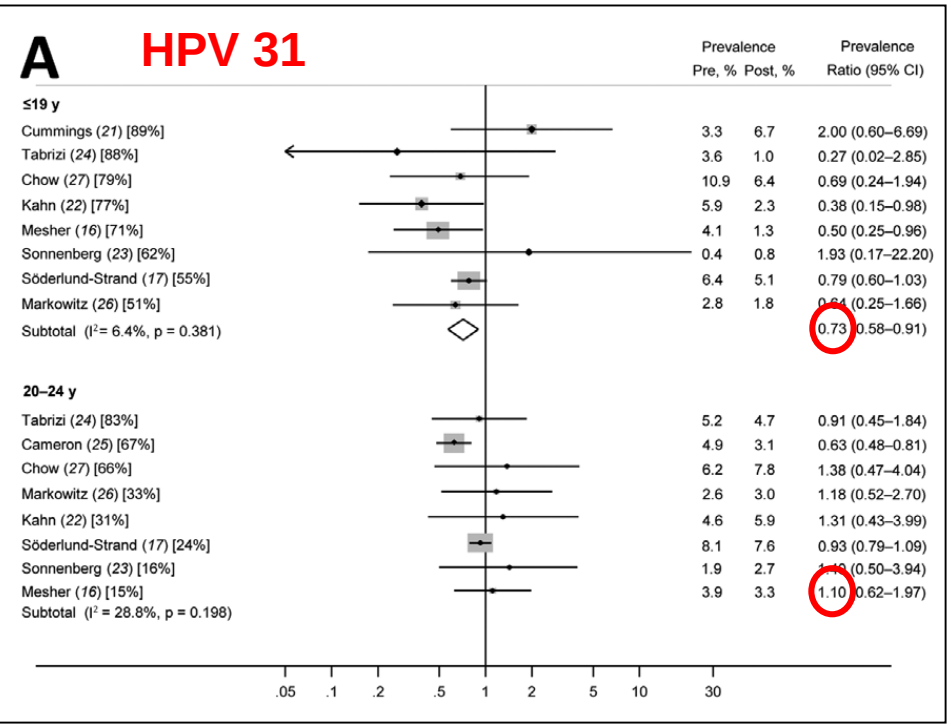
We found evidence of cross-protection for HPV31 among the younger age group after vaccine introduction but little evidence for reductions of HPV33 and HPV45.

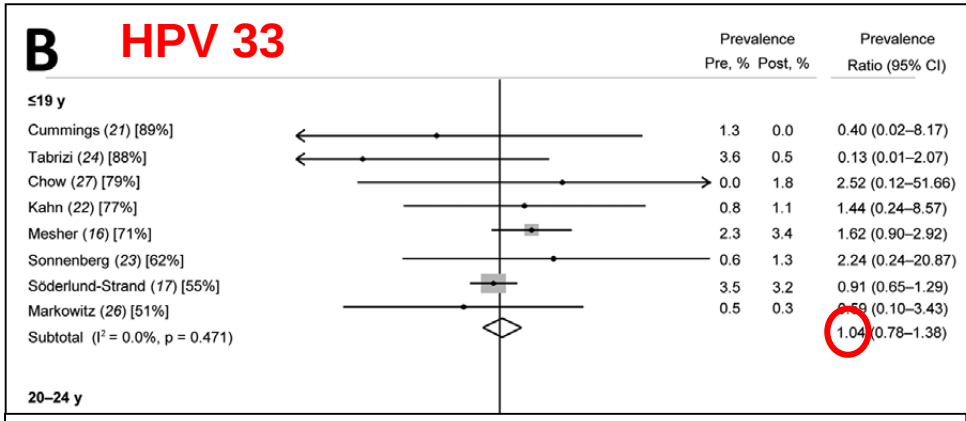
Mesher D, 2016

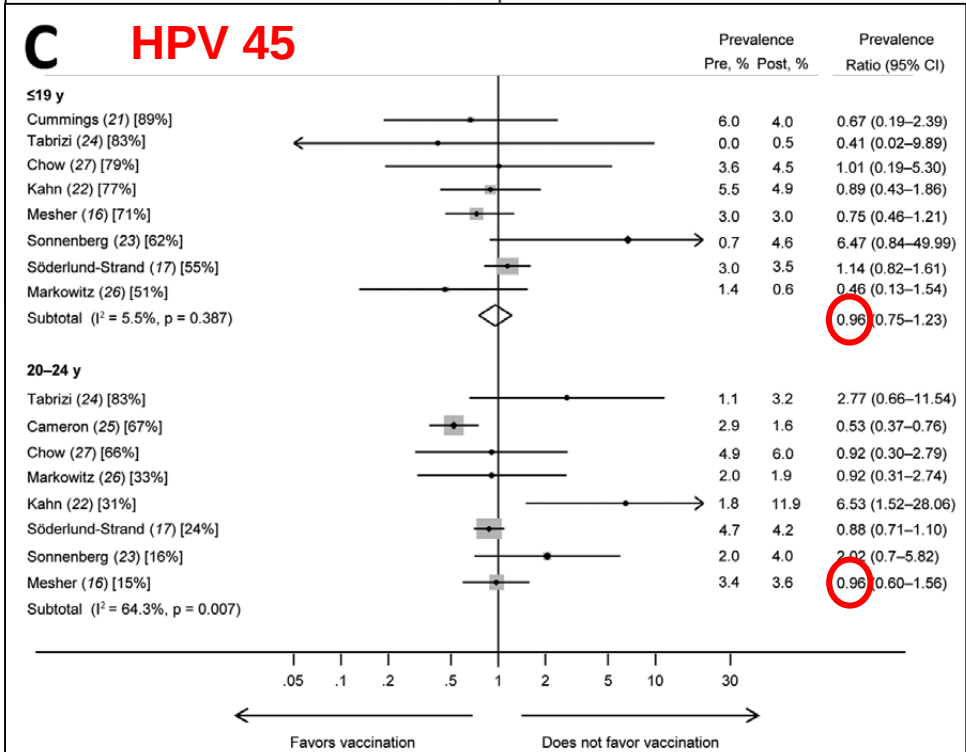
HIV & STI Department, Centre for Infectious Disease Surveillance and Control, Public Health England, London, UK

CROSS-PROTECTION ?

META-ANALYSIS







We found evidence of cross-protection for HPV31 among the younger age group after vaccine introduction but little evidence for reductions of HPV33 and HPV45.

Mesher D, 2016

HIV & STI Department, Centre for Infectious Disease Surveillance and Control, Public Health England, London, UK

CROSS-PROTECTION ?

UK general population survey

Prevalence of HPV among women aged 18–20 years

	Natsal-2 1999 2001		Natsal-3 2010 2012		52% with the 3 courses of bivalent vaccine	
	%	95%CI	%	95%CI	APR	95%CI
Denominator (unwt., wt)	*140, 150*		*331, 199*			
HPV-16/18	11.2%	[6.7–18.3]	5.8%	[3.9–8.6]	0.48	[0.24–0.93]
HPV-31/33/45/52/58	12.9%	[7.9–20.3]	14.8%	[11.1–19.6]	1.19	[0.69–2.05]
HPV-31/33/45	5.0%	[2.4–10.0]	7.2%	[4.5–11.4]	1.50	[0.66–3.44]
HPV-52/58	9.5%	[5.3–16.3]	8.7%	[6.1–12.3]	0.94	[0.48–1.80]
HPV-6/11	9.5%	[5.0–17.5]	8.9%	[6.1–12.7]	0.91	[0.44–1.89]

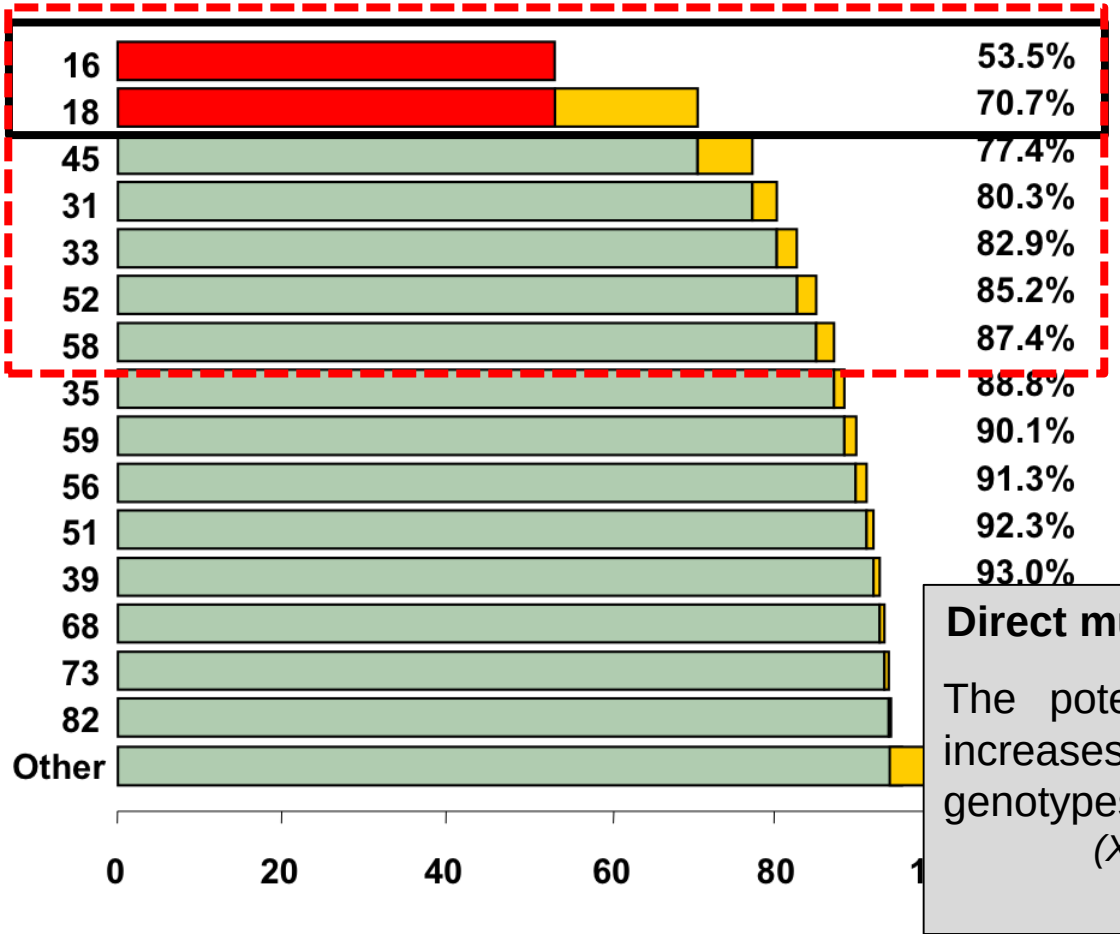
- prevalences of HPV-6/11,31/33/45 and 52/58 were unchanged
- in 16–20 year olds 20.7% had at least one 9-valent vaccine type.

(C. Tanton 2017)

ROLE OF MULTIVALENT DIRECT VACCINES

Epidemiologic Classification of Human Papillomavirus Types Associated with Cervical Cancer

Nubia Muñoz, M.D., F. Xavier Bosch, M.D., Silvia de Sanjosé, M.D., Rolando Herrero, M.D., Xavier Castellsagué, M.D., Keerti V. Shah, Ph.D., Peter J.F. Snijders, Ph.D., and Chris J.L.M. Meijer, M.D., for the International Agency for Research on Cancer Multicenter Cervical Cancer Study Group*



Direct multivalent approach

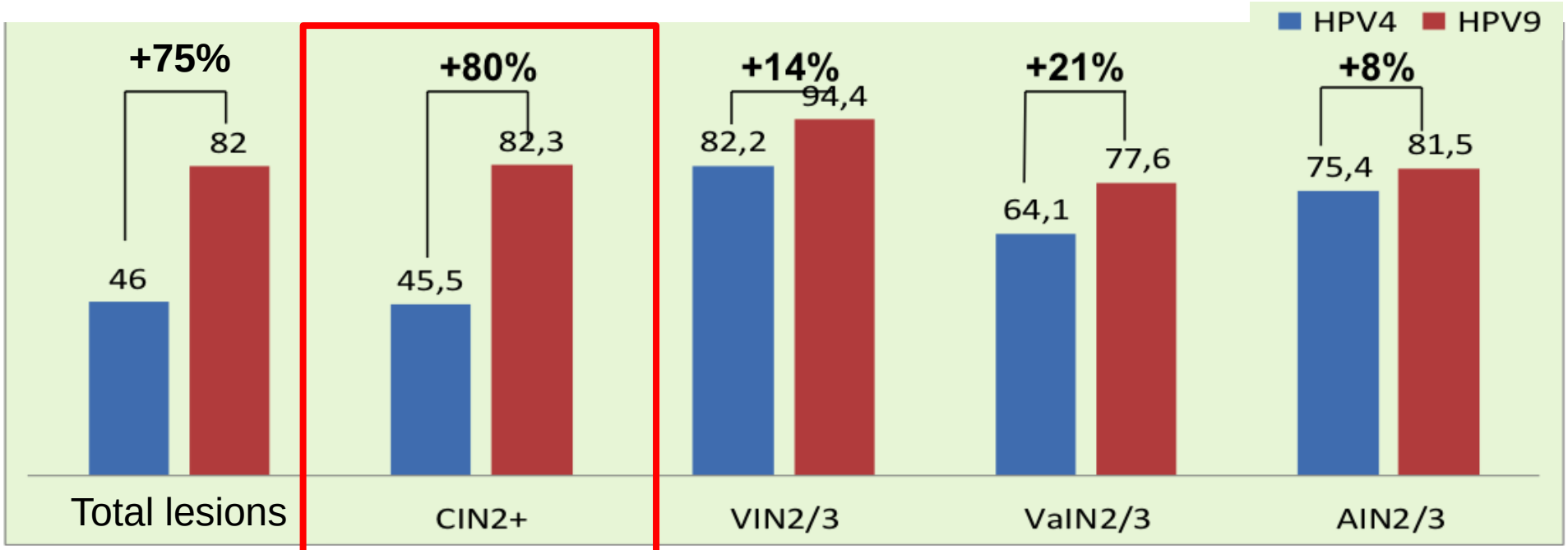
The potential of prevention increases with the number of genotypes.

(X.Bosch, 2015)

9-HPV VACCINE

Attribution to HPV of pre-neoplastic ano-genital lesions

Expected increase of protection from 4vHPV to 9vHPH vaccine



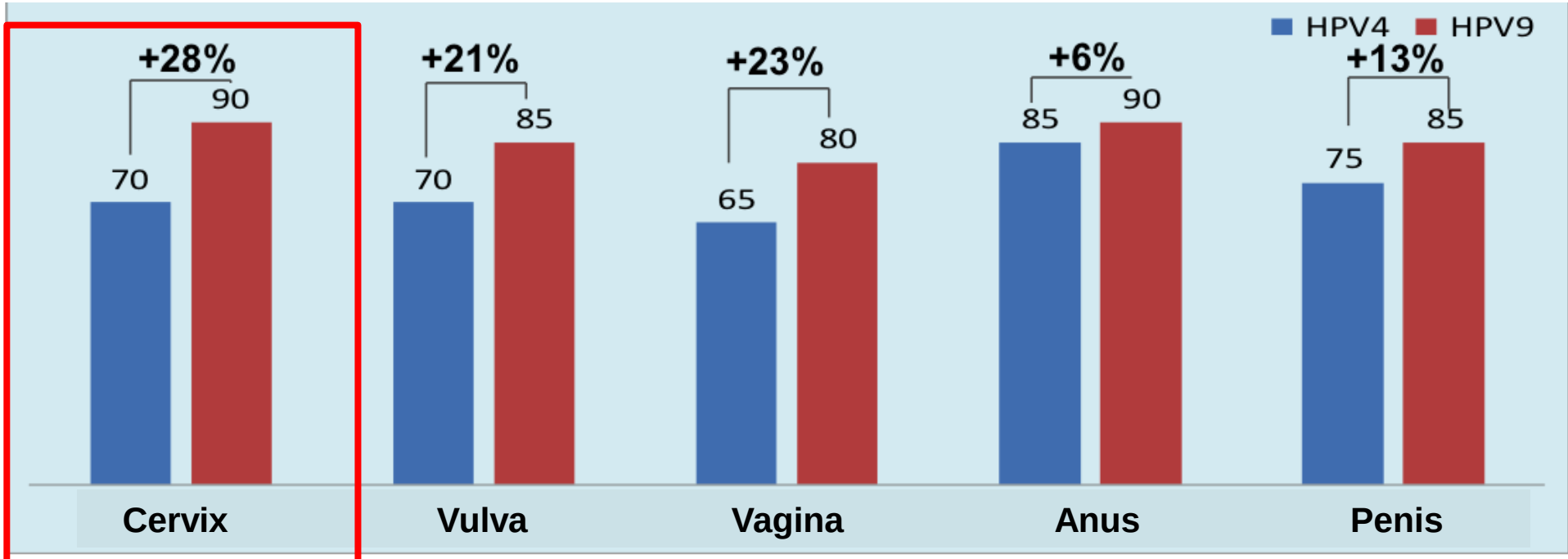
Due to the attribution of the single genotype, **uterine cervix has the highest potential to benefit** from 9v HPV.

(mod. S.Hartwig 215)

9-HPV VACCINE

Attribution to HPV of invasive ano-genital cancers

Expected increase of protection from 4vHPV to 9vHPH vaccine



Due to the attribution of the single genotype, uterine cervix has the **highest potential to benefit** from 9v HPV

(Hartwig S 2015; Saraiya M 2015; Serrano B 2012)

Classifica	Cervice	Vulva	Vagina	Pene	Ano	Orofaringe
1	HPV 16	HPV 16	HPV 16	HPV 16	HPV 16	HPV 16
2	HPV 18	HPV 18	HPV 40	HPV 18	HPV 18	HPV 33
3	HPV 33	HPV 33	HPV 6/11	HPV 6/11	HPV 33	HPV 35
4	HPV 45	HPV 6/11	HPV 31	HPV 22	HPV 31	HPV 18
5	HPV 31	HPV 45	HPV 33	HPV 74	HPV 6/11	HPV 26
6	HPV 58	HPV 52	HPV 18	HPV 31	HPV 45	HPV 45
7	HPV 52	HPV 51	HPV 58	HPV 45		HPV 52

de Sanjosé S, et al. Vaccine. 2012;30(Suppl 4):D1-83

Classifica	Cervice	Vulva	Vagina	Pene	Ano	Orofaringe
1	HPV 16	HPV 16	HPV 16	HPV 16	HPV 16	HPV 16
2	HPV 18	HPV 18	HPV 40	HPV 18	HPV 18	HPV 33
3	HPV 33	HPV 33	HPV 6/11	HPV 6/11	HPV 33	HPV 35
4	HPV 45	HPV 6/11	HPV 31	HPV 22	HPV 31	HPV 18
5	HPV 31	HPV 45	HPV 33	HPV 74	HPV 6/11	HPV 26
6	HPV 58	HPV 52	HPV 18	HPV 31	HPV 45	HPV 45
7	HPV 52	HPV 51	HPV 58	HPV 45		HPV 52

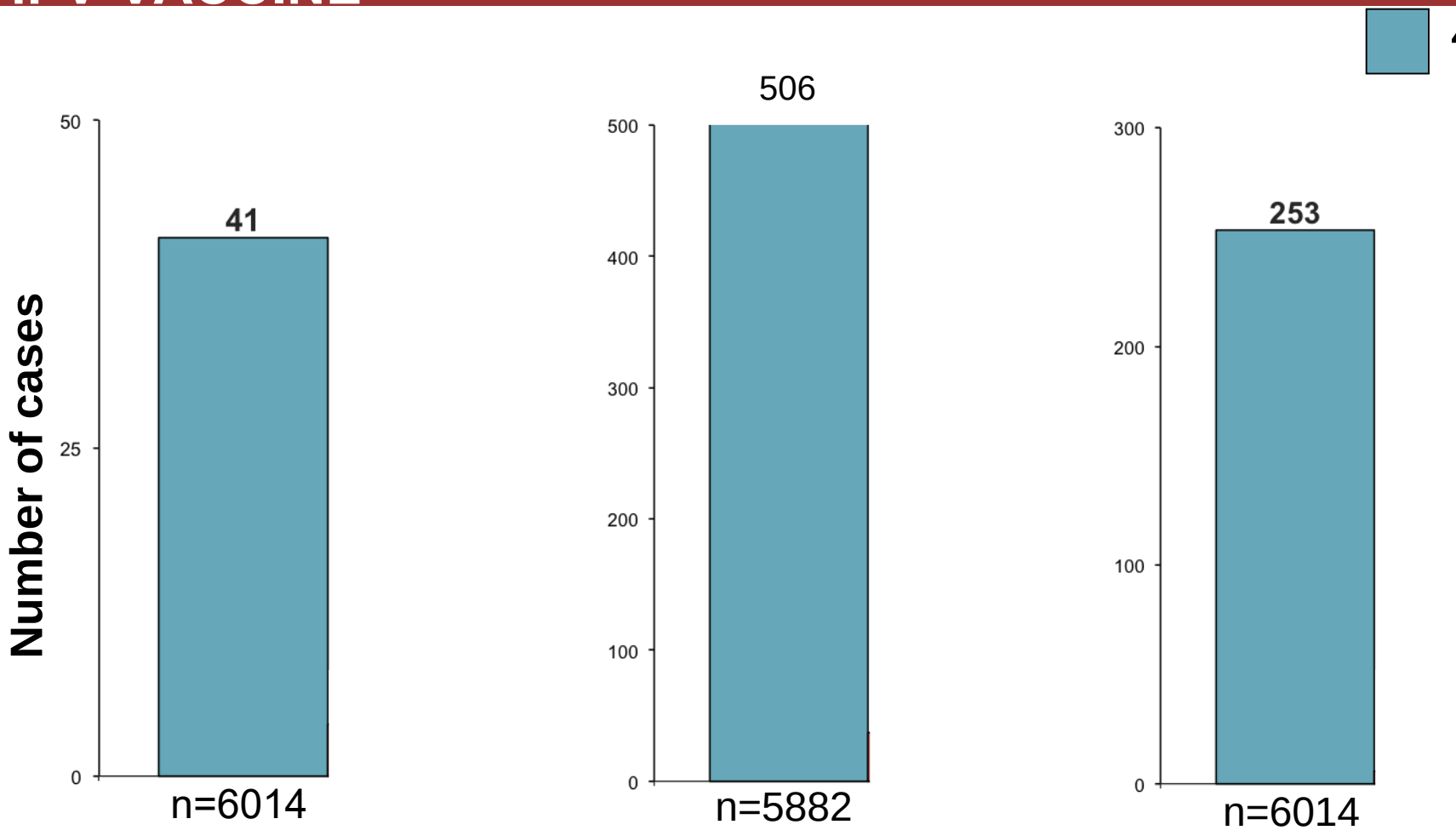
de Sanjosé S, et al. Vaccine. 2012;30(Suppl 4):D1-83

9-HPV VACCINE *(per-protocol population 16-26 yrs; 6 yrs LTFU)*

	9vHPV vaccine (N=7099)*		qHPV vaccine (N=7105)*		Risk reduction (%; 95% CI)
	n/total n†	Cases per 10 000 person-years	n/total n†	Cases per 10 000 person-years	
Condyloma					
Related to HPV 6, 11, 16, or 18	5/5876	2·6	2/5893	1·0	−150·9 (−∞ to 48·0)
Related to HPV 31, 33, 45, 52, or 58	0/6009	0	4/6012	2·0	100 (−11·5 to 100)
Vulvar intraepithelial neoplasia 2/3 and vulvar cancer					
Related to HPV 6, 11, 16, or 18	0/5876	0	0/5893	0	NA
Related to HPV 31, 33, 45, 52, or 58	0/6009	0	0/6012	0	NA
Vaginal intraepithelial neoplasia 2/3 and vaginal cancer					
Related to HPV 6, 11, 16, or 18	0/5876	0	2/5893	1·0	100 (−248·3 to 100)
Related to HPV 31, 33, 45, 52, or 58	0/6009	0	3/6012	1·5	100 (−71·5 to 100)
Cervical intraepithelial neoplasia 1					
Related to HPV 6, 11, 16, or 18	0/5824	0	2/5832	1·1	100 (−248·1 to 100)
Related to HPV 31, 33, 45, 52, or 58	1/5949	0·5	87/5943	45·2	98·9 (94·1 to 99·9)
Cervical intraepithelial neoplasia 2					
Related to HPV 6, 11, 16, or 18	1/5824	0·5	0/5832	0	NA
Related to HPV 31, 33, 45, 52, or 58	1/5949	0·5	32/5943	16·6	96·9 (81·5 to 99·8)
Cervical intraepithelial neoplasia 3, adenocarcinoma in situ, and cervical cancer					
Related to HPV 6, 11, 16, or 18	0/5824	0	1/5832	0·5	100 (−∞ to 100)
Related to HPV 31, 33, 45, 52, or 58	0/5949	0	7/5943	3·6	100 (39·4 to 100)

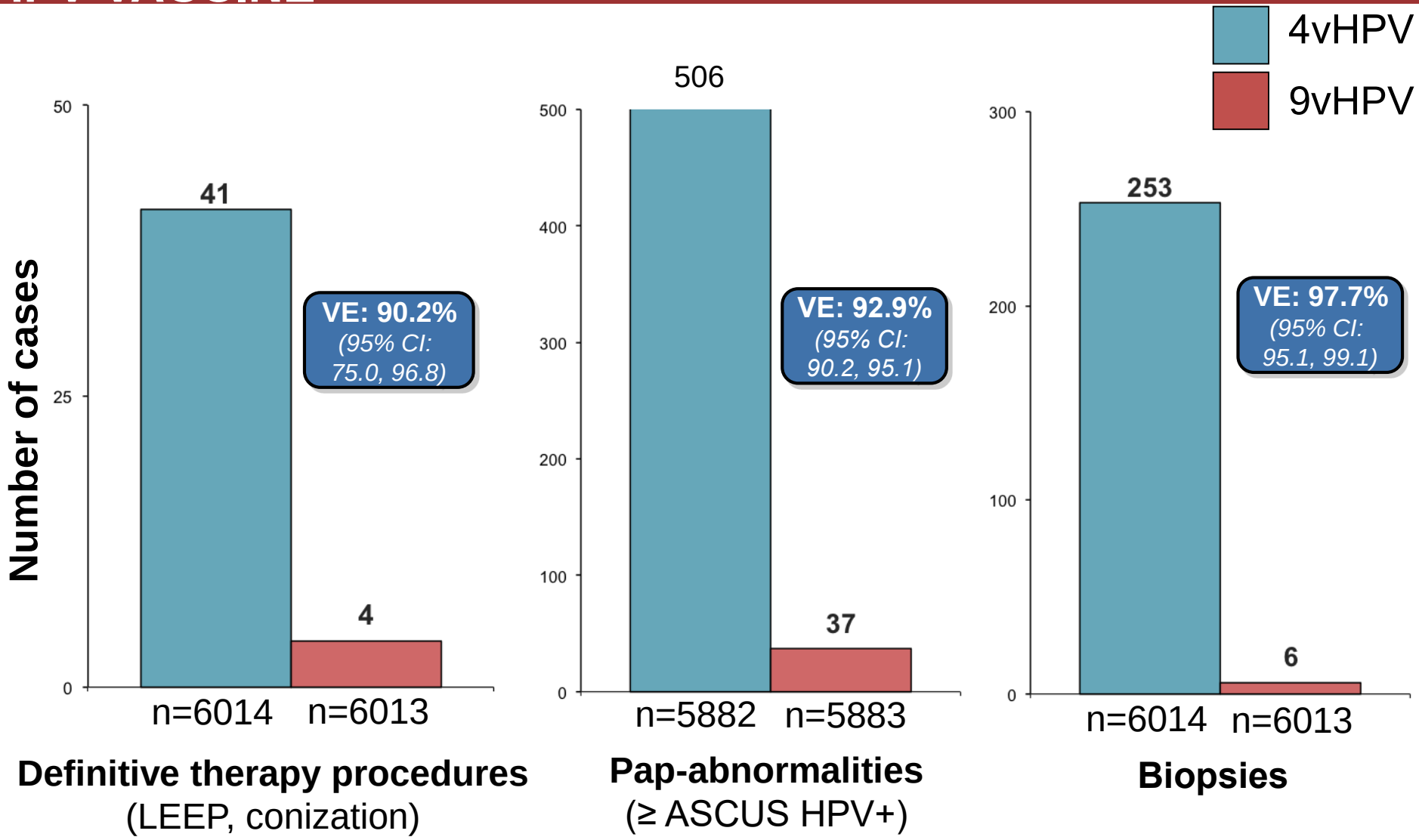
W.Huh, 2017

HPV-VACCINE



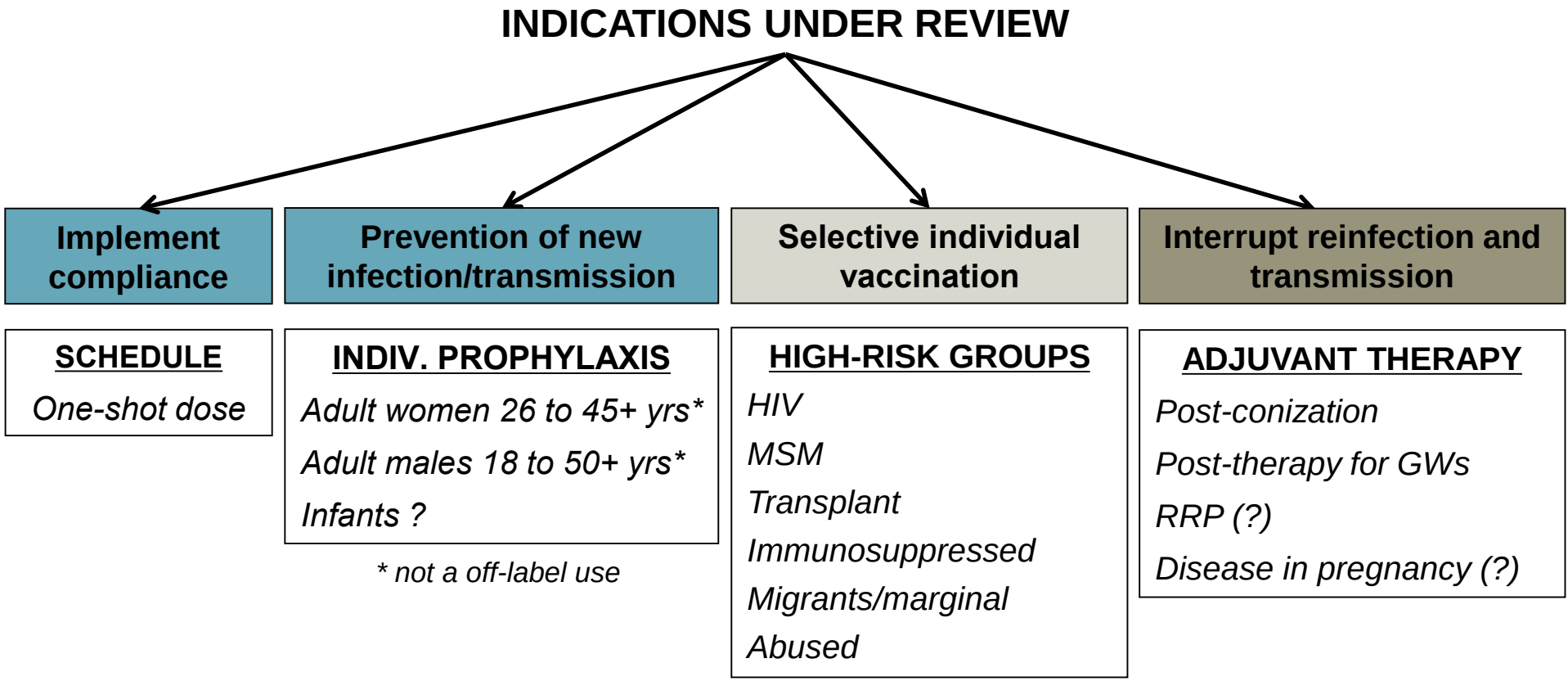
http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_Product_Information/human/003852/WC500189111.pdf

HPV-VACCINE



http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_Product_Information/human/003852/WC500189111.pdf

THE HPV VACCINES ARE EVEN BETTER THAN WE HOPED



THE HPV VACCINES ARE EVEN BETTER THAN WE HOPED

INDICATIONS UNDER REVIEW

Implement compliance

SCHEDULE

One-shot dose

Bivalent vaccine

- *Safaeian M et al; Cancer Prev Res 2013*
- *Kreimer AR et al; Lancet Oncol 2015*

Quadrivalent vaccine

- *Herweijer E et al; JAMA 2014*
- *Sankaranarayanan R et al; Lancet Oncol 2016*
- *Zheng Quan Toh et al; Clinical Infectious Diseases 2017*

Protective effcacy depends upon the quantity but also the quality (affinity) of vaccine-induced antibodies. **Memory B cells elicited by the first vaccine dose require at least 4–6 months to mature and differentiate into high-affnity B cells.**

(WHO, Position Paper 2017)