IRE ISTITUTO NAZIONALE TUMORI REGINA ELENA
ISG ISTITUTO DERMATOLOGICO SAN GALLICANO
ISTITUTI DI RICOVERO E CURA A CARATTERE SCIENTIFICO

VACCINO HPV: STATO DELL'ARTE

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Istituto Nazionale Tumori Regina Elena, Roma

IHSG (Italian HPV Study Group)

VACCINO HPV

CONFLITTO DI INTERESSI

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

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

HPV VACCINE

1991-92 Frazer I, Kirnbauer R →L1 capsid protein self-assembled into a virus-like particle (VLP)

1998 L.Koutsky → landmark trial on efficacy of monovalent HPV-16 vaccine *(proof of principle that HPV oncogenic infections and related cancer/precursors may be preventable)*

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→National organized programs of HPV vaccines

2014 phase-2/3 trial with 9vHPV vaccine (VLPs 6,11,16,18,31,33,45,52,58)

→ licensed by FDA in 2014

overall balance

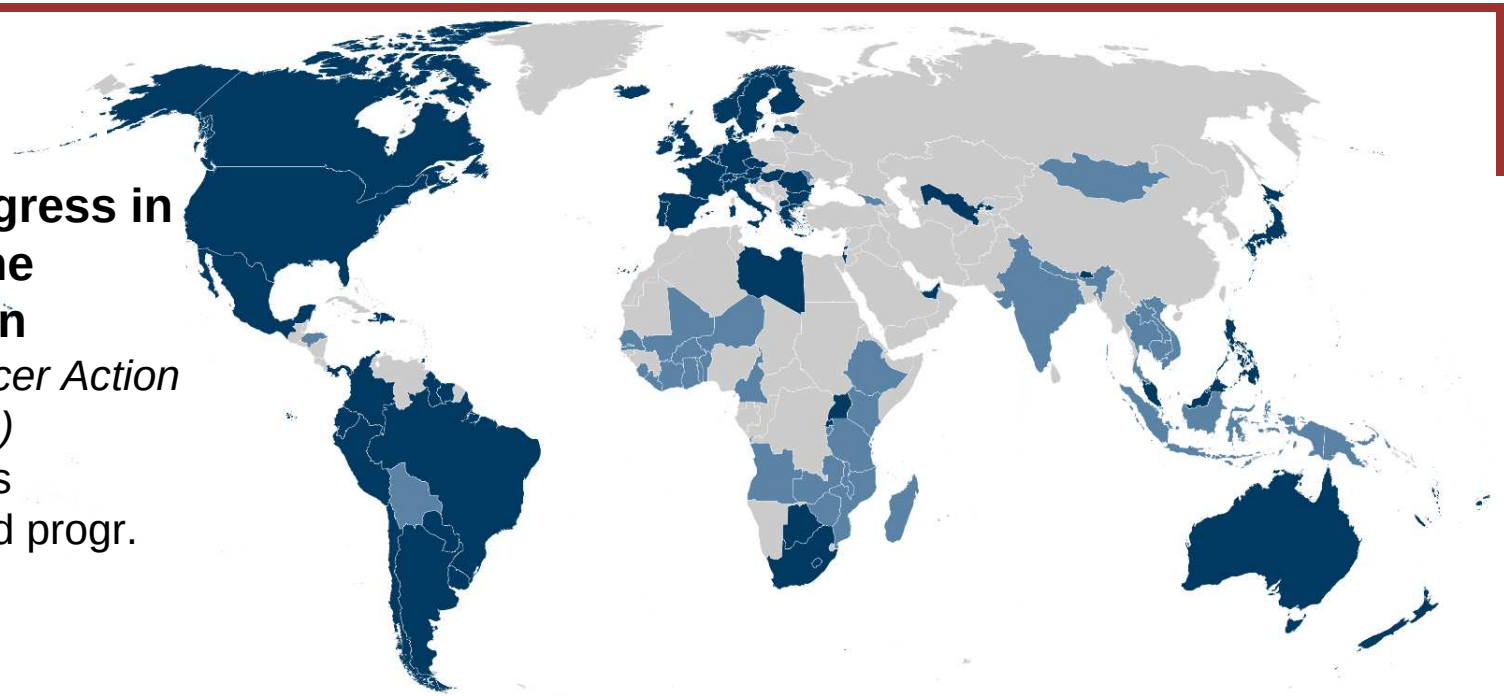
HPV

Global Progress in HPV vaccine introduction

Cervical Cancer Action (August 2015)

129 Countries

64 Organized progr.



National programs

American Samoa
Andorra
Argentina
Aruba
Australia
Austria
Bahamas
Barbados
Belgium
Belize
Bermuda
Bhutan
Botswana
Brazil
Brunei
Bulgaria
Canada
Cayman Islands
Chile
Colombia
Cook Islands
Curacao
Czech Republic
Denmark
Dominican Republic
Ecuador
Fiji
Finland
France
French Polynesia
Germany
Greece
Guam
Guyana
Hungary
Iceland
Ireland
Israel
Italy
Japan
Kiribati
Latvia
Lesotho
Libya
Luxembourg
Macedonia
Malaysia
Malta
Marshall Islands
Mexico
Micronesia
Monaco
Netherlands
New Caledonia
New Zealand
Niue
Northern Marianas
Norway
Palau
Panama
Paraguay
Peru
Philippines
Portugal
Romania
Rwanda
San Marino
Seychelles
Singapore
Slovenia
South Africa
Spain
St. Eustatius
Suriname
Sweden
Switzerland
Trinidad and Tobago
Uganda
United Arab Emirates
United Kingdom
United States
Uruguay
Uzbekistan
Vanuatu

Pilot programs

Angola
Benin
Bolivia
Burkina Faso
Burundi
Cambodia
Cameroon
Cote d'Ivoire
Ethiopia
Gambia
Georgia
Ghana
Haiti
Honduras
India
Indonesia
Kenya
Lao PDR
Liberia
Madagascar
Malawi
Mali
Moldova
Mongolia
Mozambique
Nepal
Niger
Papua New Guinea
Sao Tome
Senegal
Sierra Leone
Solomon Islands
Tanzania
Thailand
Togo
Vietnam
Zambia
Zimbabwe

I VACCINI HPV SONO MEGLIO DI QUANTO SPERASSIMO

WHO 2006

(*preparing for the introduction of HPV vaccines)*

Obiettivo: prevenzione cancro della portio

Target: popolaz. femminile 12anni

WHO 2014

Obiettivo: prevenzione cancro della portio **e/o patologie HPV-correlate** (*public health priority*)

Target: **popolaz. entrambi i sessi 12anni**

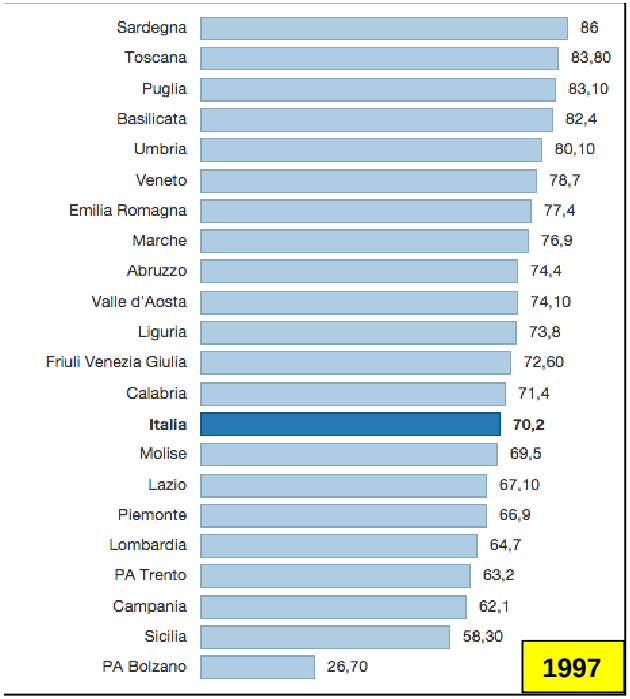
VACCINO HPV

"La sanità pubblica oggi si pone come obiettivo l'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"

(Piano Nazionale Prevenzione Vaccini 2016-18)

VACCINAZIONE MASCHIO

1. principio di equità
2. prevenzione delle patologie HPV-correlate nel maschio *(pene, ano, orofaringe)*
3. riduzione della trasmissione *(reservoire)*
4. scarsa efficacia delle vacc.monogenere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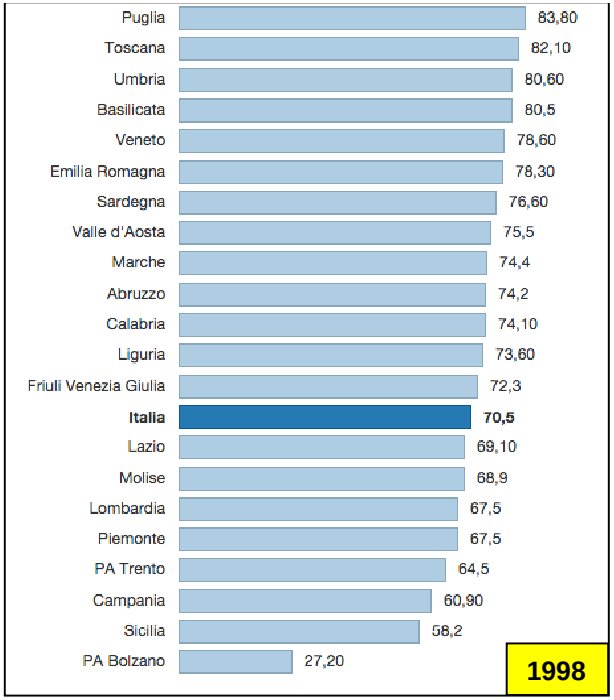
Toscana 83,80
Puglia 83,10
Basilicata 82,4
Umbria 80,10
Veneto 78,7
Emilia Romagna 77,4
Marche 76,9
Abruzzo 74,4
Valle d'Aosta 74,10
Liguria 73,8
Friuli Venezia Giulia 72,60
Calabria 71,4
Italia 70,2
Molise 69,5
Lazio 67,10
Piemonte 66,9
Lombardia 64,7
PA Trento 63,2
Campania 62,1
Sicilia 58,30
PA Bolzano 26,70
1997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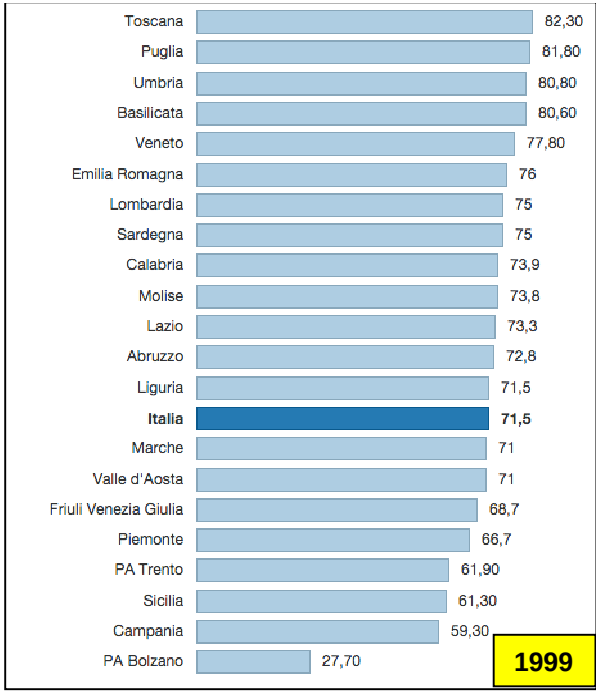
Sardegna 76,60
Valle d'Aosta 75,5
Marche 74,4
Abruzzo 74,2
Calabria 74,10
Liguria 73,60
Friuli Venezia Giulia 72,3
Italia 70,5
Lazio 69,10
Molise 68,9
Lombardia 67,5
Piemonte 67,5
PA Trento 64,5
Campania 60,90
Sicilia 58,2
PA Bolzano 27,20
1998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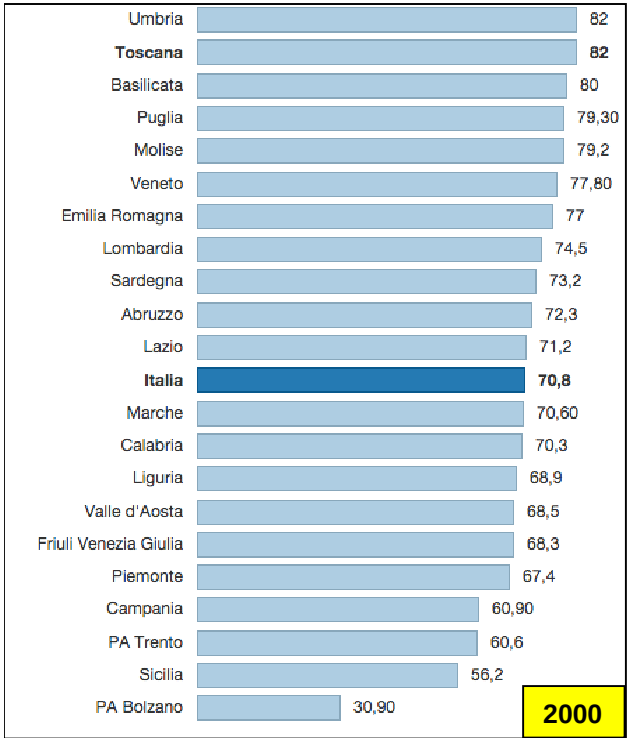
Umbria 80,80
Basilicata 80,60
Veneto 77,80
Emilia Romagna 76
Lombardia 75
Sardegna 75
Calabria 73,9
Molise 73,8
Lazio 73,3
Abruzzo 72,8
Liguria 71,5
Italia 71,5
Marche 71
Valle d'Aosta 71
Friuli Venezia Giulia 68,7
Piemonte 66,7
PA Trento 61,90
Sicilia 61,30
Campania 59,30
PA Bolzano 27,70
1999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Toscana 82
Basilicata 80
Puglia 79,30
Molise 79,2
Veneto 77,80
Emilia Romagna 77
Lombardia 74,5
Sardegna 73,2
Abruzzo 72,3
Lazio 71,2
Italia 70,8
Marche 70,60
Calabria 70,3
Liguria 68,9
Valle d'Aosta 68,5
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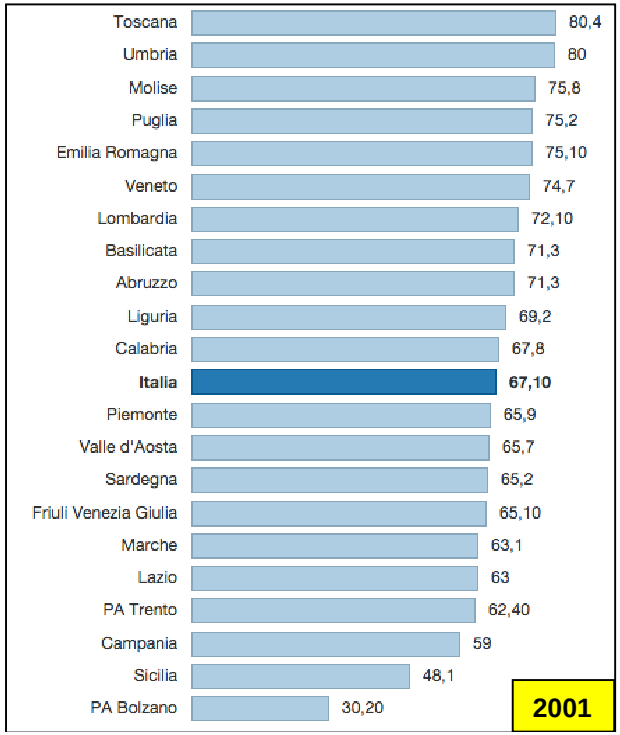
Piemonte 67,4
Campania 60,90
PA Trento 60,6
Sicilia 56,2
PA Bolzano 30,90
2000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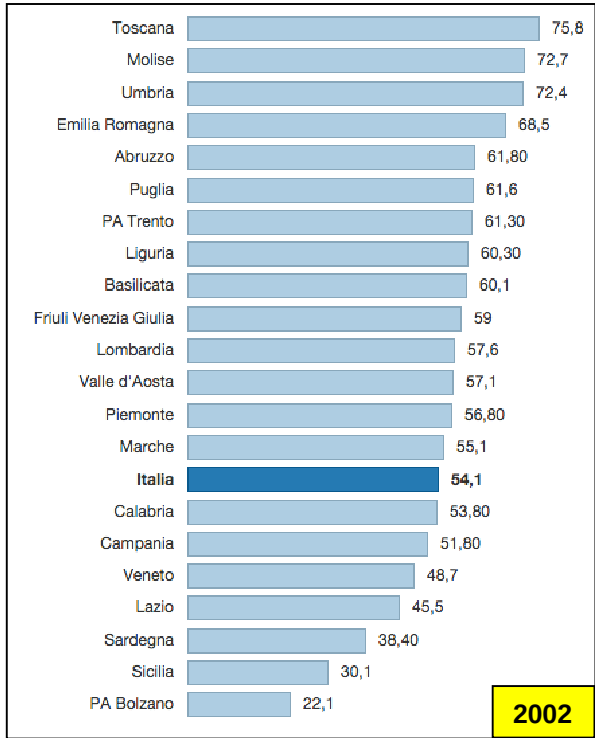
Puglia 75,2
Emilia Romagna 75,10
Veneto 74,7
Lombardia 72,10
Basilicata 71,3
Abruzzo 71,3
Liguria 69,2
Calabria 67,8
Italia 67,10
Piemonte 65,9
Valle d'Aosta 65,7
Sardegna 65,2
Friuli Venezia Giulia 65,10
Marche 63,1
Lazio 63
PA Trento 62,40
Campania 59
Sicilia 48,1
PA Bolzano 30,20
2001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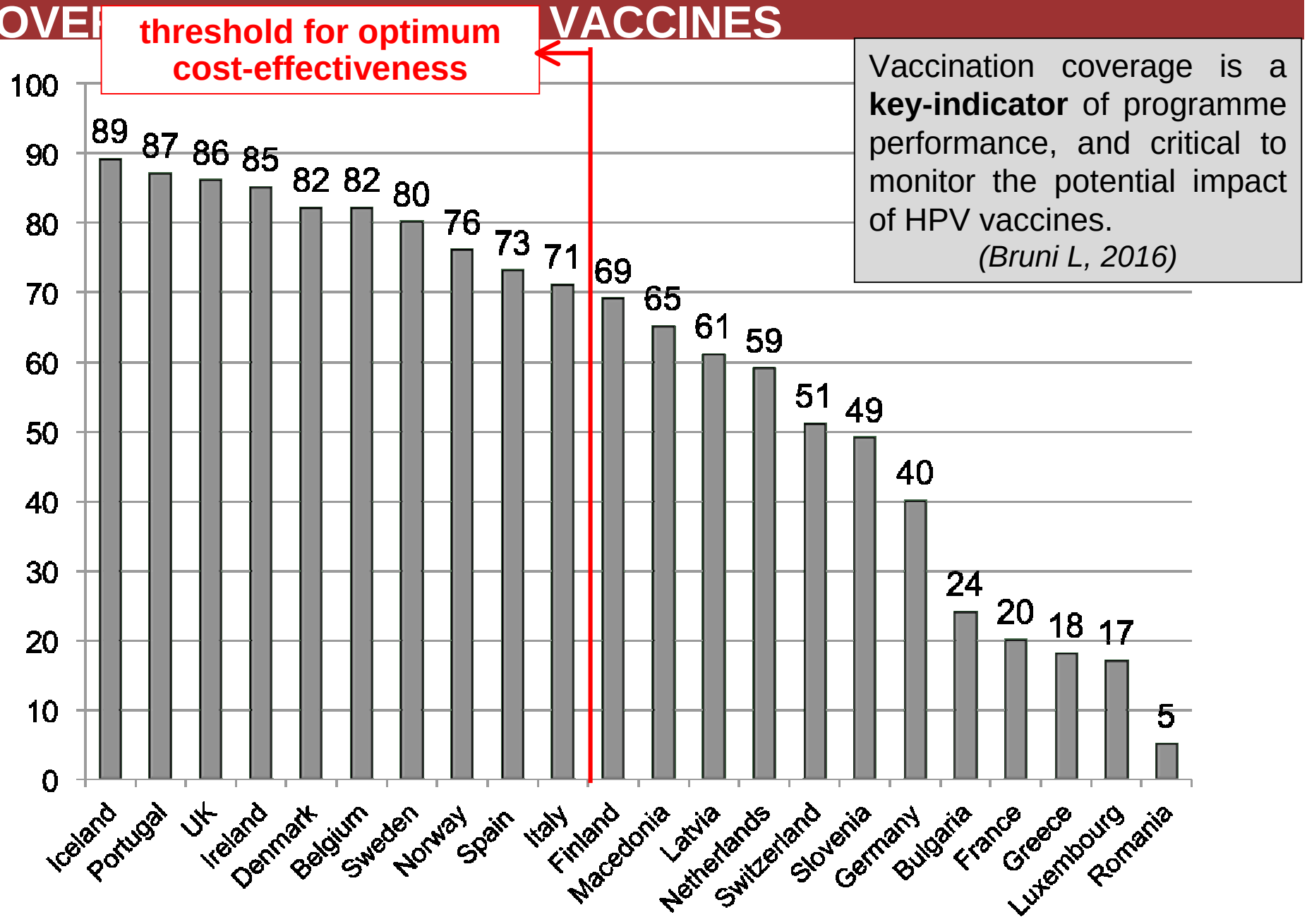
PA Trento 61,30
Liguria 60,30
Basilicata 60,1
Friuli Venezia Giulia 59
Lombardia 57,6
Valle d'Aosta 57,1
Piemonte 56,80
Marche 55,1
Italia 54,1
Calabria 53,80
Campania 51,80
Veneto 48,7
Lazio 45,5
Sardegna 38,40
Sicilia 30,1
PA Bolzano 22,1
2002

COVER VACCINES

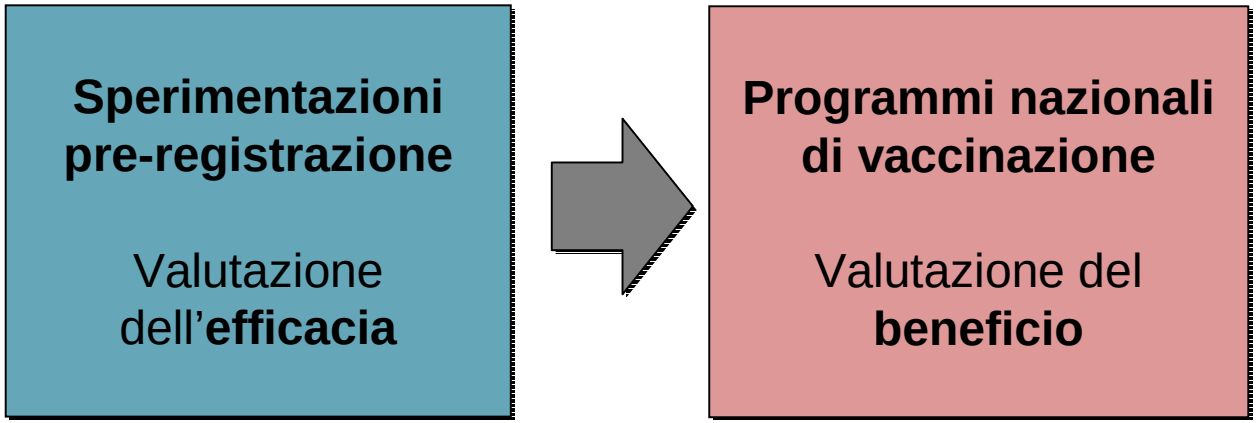


Vaccination coverage is a **key-indicator** of programme performance, and critical to monitor the potential impact of HPV vaccines.

(Bruni L, 2016)

I VACCINI HPV SONO MEGLIO DI QUANTO SPERASSIMO

BENEFICI ACQUISITI DOPO I PROGRAMMI ORGANIZZATI



I VACCINI HPV SONO MEGLIO DI QUANTO SPERASSIMO

CONFERMA DELLA SICUREZZA E TOLLERABILITA'

Among over 200 million doses GAVCVS (WHO) in december 2015:
•no safety concern regarding autoimmune, neurologic, thromboembolic diseases *(Scheller 2015; Grimaldi-Bensauda 2014; Arnheim-Dalstrom 2013)*
•even if inadvertently administered in pregnancy *(Moro 2015; Gross 2014)*

World Health Organization
Organisation mondiale de la Santé

Weekly epidemiological record
Relevé épidémiologique hebdomadaire

22 JANUARY 2016, 91th YEAR / 22 JANVIER 2016, 91e ANNÉE
No 3, 2016, 91, 21–32
http://www.who.int/wer

Reviews of pre- and post-licensure data provide **no evidence** that "*post-vaccination syndromes*" are associated with HPV vaccination. Policy decisions based on weak evidence, leading to lack of use of safe and effective vaccines, can result in real harm.

I VACCINI HPV SONO MEGLIO DI QUANTO SPERASSIMO

BENEFICI ACQUISITI DOPO I PROGRAMMI ORGANIZZATI

RIDUZIONE DI:

PREVALENZA HPV

-86% Australia (Tabrizi 2014)

-77% England (Mesher 2016)

-64% USA (Markowitz 2016)

HERD IMMUNITY ♀

-30% USA (Kahn J 2016)

CONDILOMI GENITALI

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

HERD IMMUNITY ♂

-82% Australia (Ali H 2013)
-50% 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)

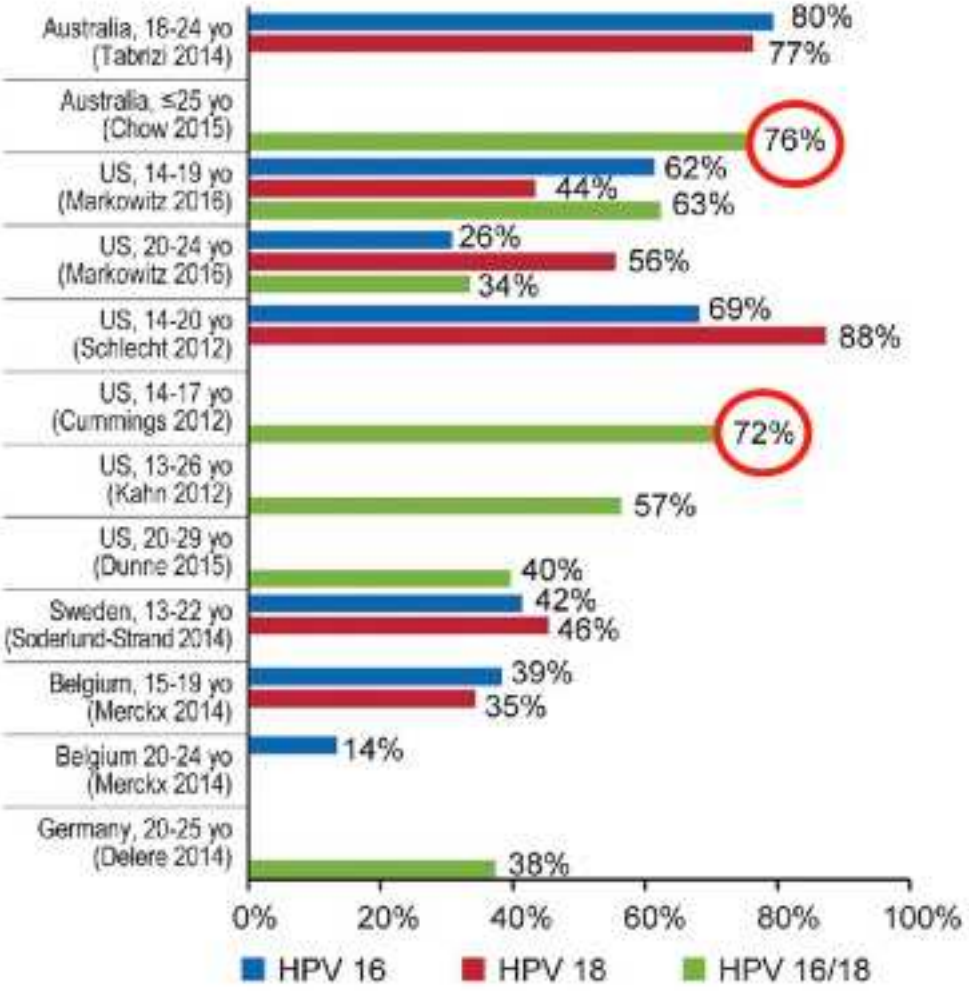
I VACCINI HPV SONO MEGLIO DI QUANTO SPERASSIMO

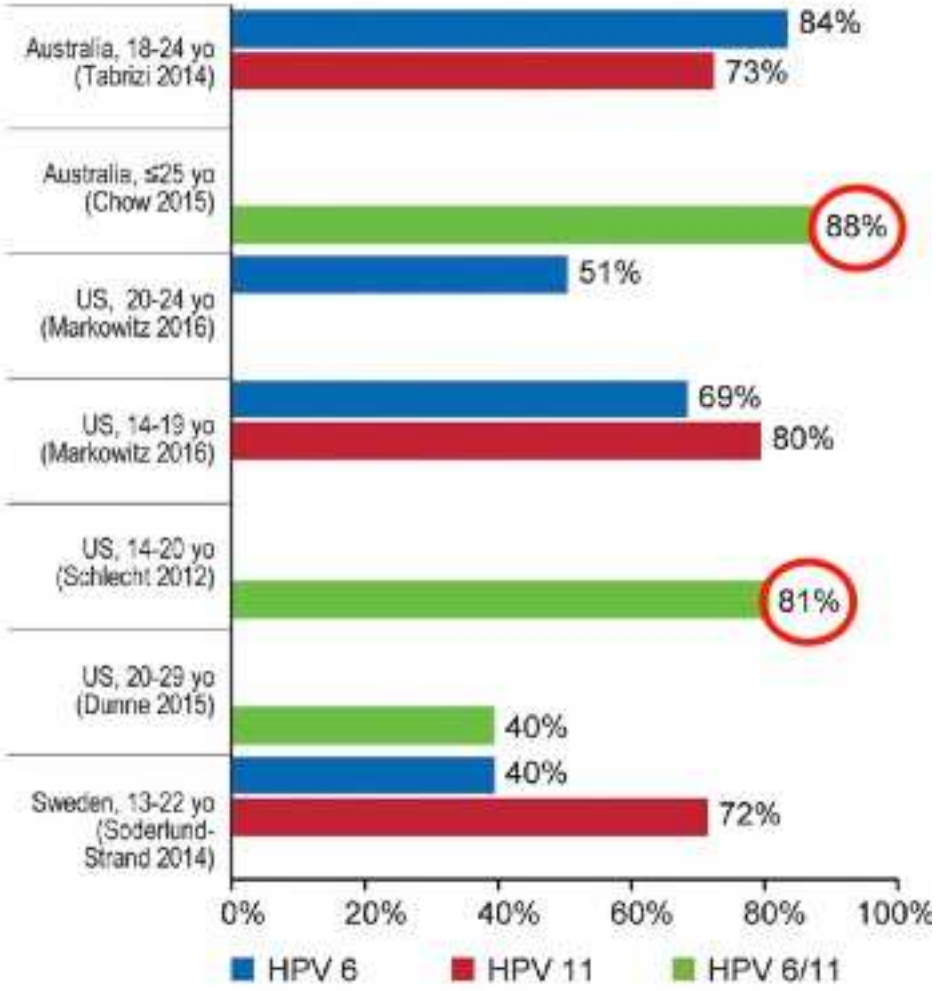
BENEFICI ACQUISITI DOPO I PROGRAMMI ORGANIZZATI

VARIABILITA' DELLA RIDUZIONE

- 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 HPV PREVALENCE: 4-HPV





Garland S, 2016

DECLINE OF HPV PREVALENCE: 2-HPV

ENGLAND

2-HPV vaccine from 2008; females 16-24 yrs; coverage 80%; period 2008 vs 2010-13

HPV type	Prevaccination prevalence (%) 2008 (95% CI) n=2354	Postvaccination prevalence (%) 2010–2011 (95% CI) n=3602	Postvaccination prevalence (%) 2012–2013 (95% CI) n=3719		p-value for trend
16–18 years					
(Estimated HPV16/18 vaccination coverage)	(0%)	(60.2%)	(73.4%)		
Any high-risk HPV	32.6 (29.7 to 35.4)	37.6 (34.5 to 40.7)	35.4 (32.5 to 38.3)		0.188
Any non-vaccine high-risk HPV	24.9 (22.3 to 27.6)	34.2 (31.1 to 37.2)	33.2 (30.4 to 36.0)		<0.001
Vaccine HPV types					
HPV16 and/or 18	17.6 (15.3 to 19.9)	8.5 (6.7 to 10.3)	4.0 (2.8 to 5.1)	**-77.1%**	<0.001
HPV16	11.9 (10.0 to 13.9)	6.8 (5.1 to 8.4)	3.0 (2.0 to 4.0)	**-74.3%**	<0.001
HPV18	7.8 (6.2 to 9.5)	2.8 (1.7 to 3.8)	1.1 (0.5 to 1.8)	**-85.8%**	<0.001
Nonavalent HPV types*					
HPV31/33/45/52/58	14.5 (12.4 to 16.7)	17.7 (15.2 to 20.1)	14.9 (12.7 to 17.0)		0.835
HPV31/33/45	8.4 (6.7 to 10.1)	6.9 (5.2 to 8.5)	5.8 (4.4 to 7.2)		0.021
HPV31	3.7 (2.6 to 4.9)	0.5 (0.1 to 1.0)	1.2 (0.6 to 1.9)		<0.001
HPV33	2.4 (1.5 to 3.3)	3.5 (2.3 to 4.7)	2.6 (1.7 to 3.6)		0.739
HPV45	2.9 (1.9 to 3.9)	2.9 (1.8 to 4.0)	2.2 (1.3 to 3.0)		0.314
HPV52	4.0 (2.8 to 5.2)	8.6 (6.8 to 10.4)	6.4 (4.9 to 7.9)		0.027
HPV58	3.7 (2.6 to 4.9)	4.0 (2.7 to 5.2)	3.9 (2.7 to 5.0)		0.875

Mesher D, et al. BMJ Open 2016

DECLINE OF HPV PREVALENCE: 2-HPV

ENGLAND

2-HPV vaccine from 2008; females 16-24 yrs; coverage 80%; period 2008 vs 2010-13

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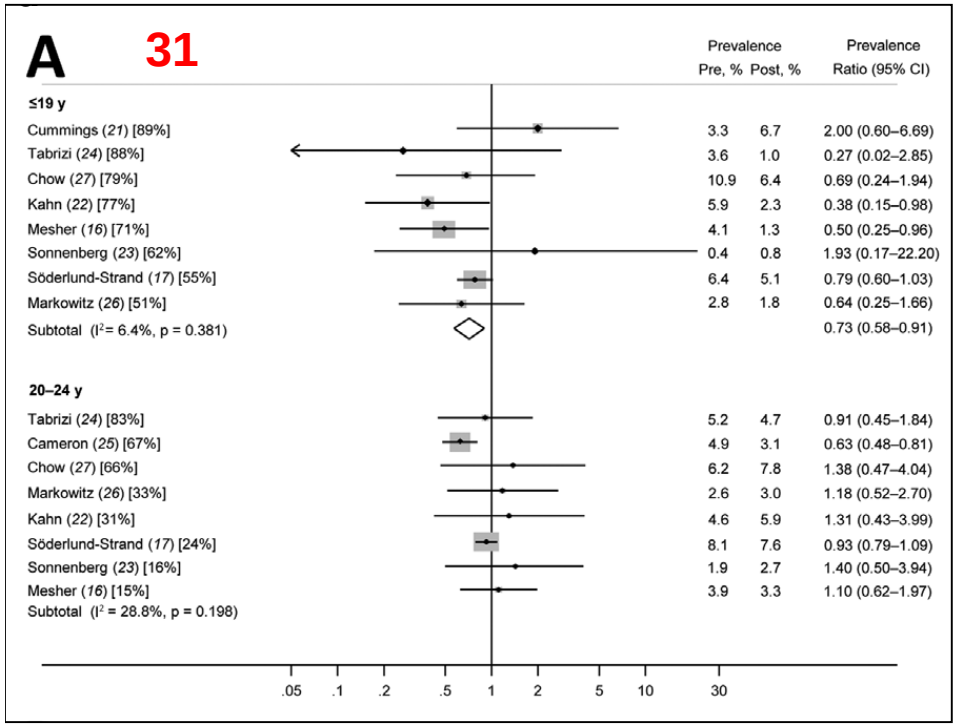
HPV58	3.7 (2.6 to 4.9)	4.0 (2.7 to 5.2)	3.9 (2.7 to 5.0)	0.875

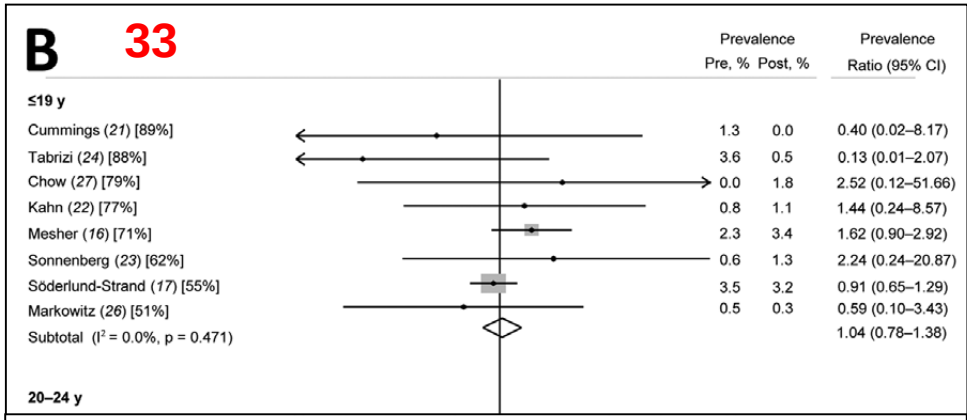
1. *no evidence of a reduction in the overall prevalence of HPV33 or of HPV45*
2. *increases in the other HR-HPV types: limitation of the study? replacement?*

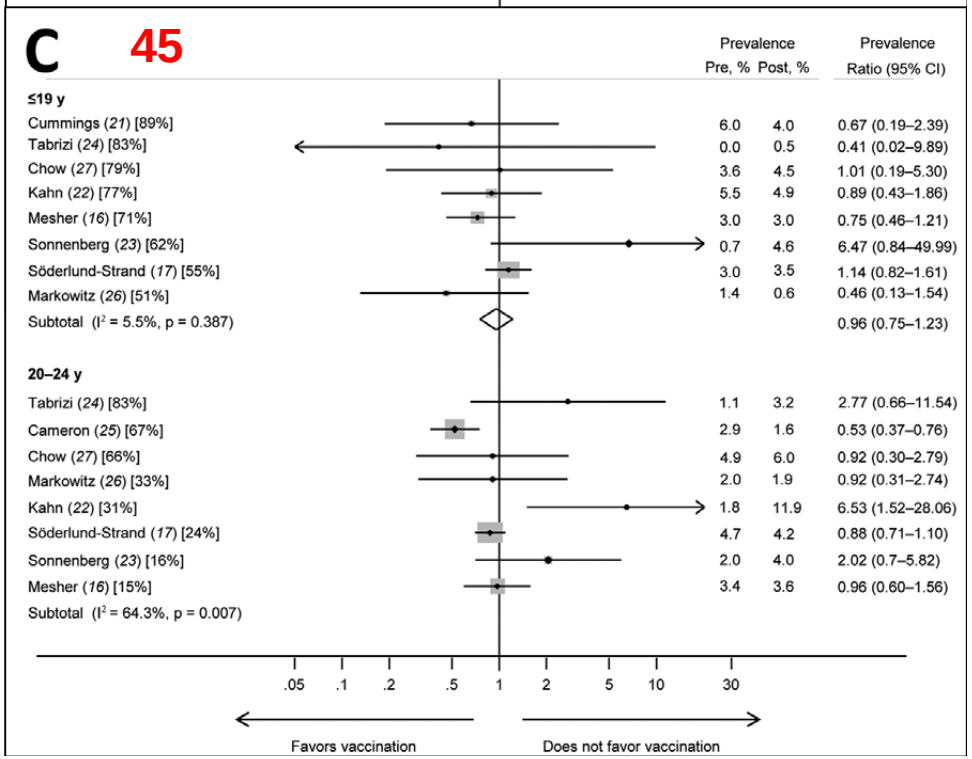
Mesher D, et al. BMJ Open 2016

CROSS-PROTECTION

META-ANALYSIS



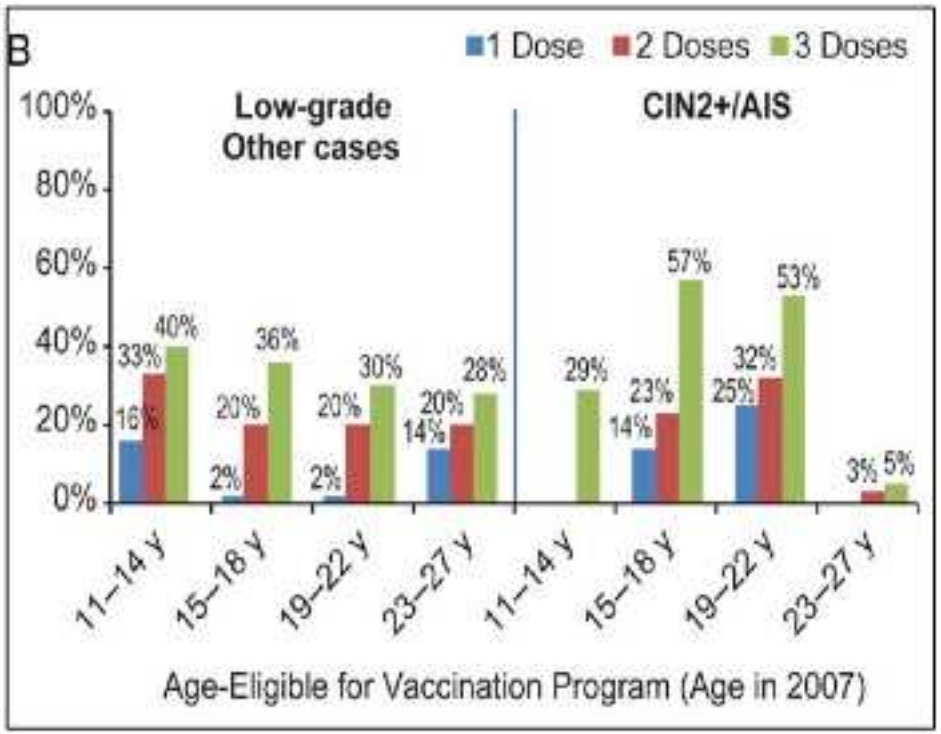


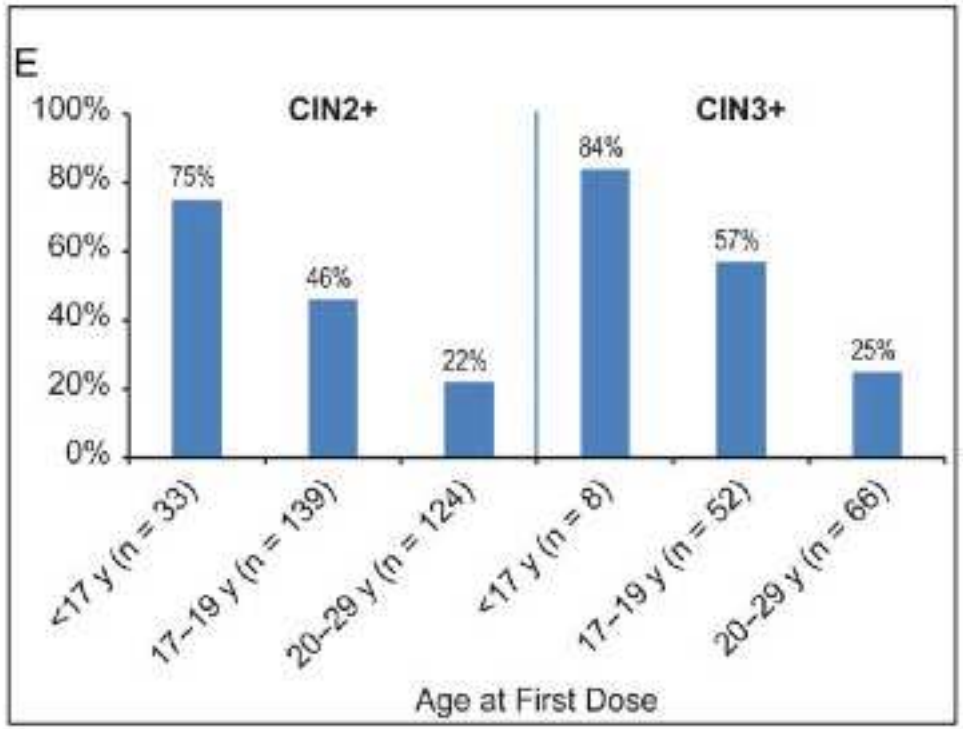


We found evidence of cross-protection for HPV31 among the younger age group after vaccine introduction but little evidence for reductions of HPV33 and HPV45.

(Mesher D, 2016)

DECLINE OF SIL: 4-HPV



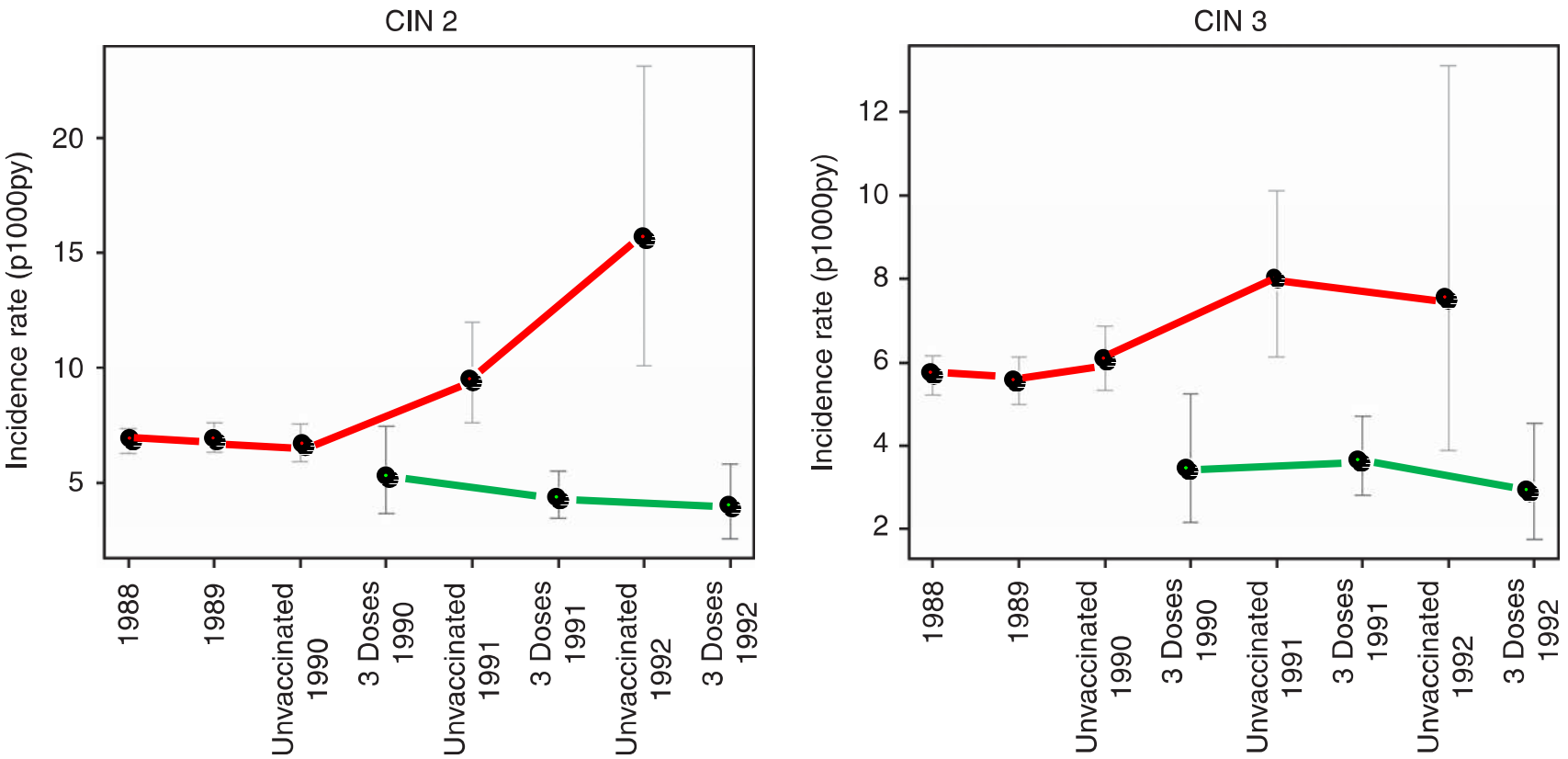


Crowe, 2014 (Australia)

Herweijer 2016 (Svezia)

DECLINE OF HSIL: 2-HPV

SCOTLAND



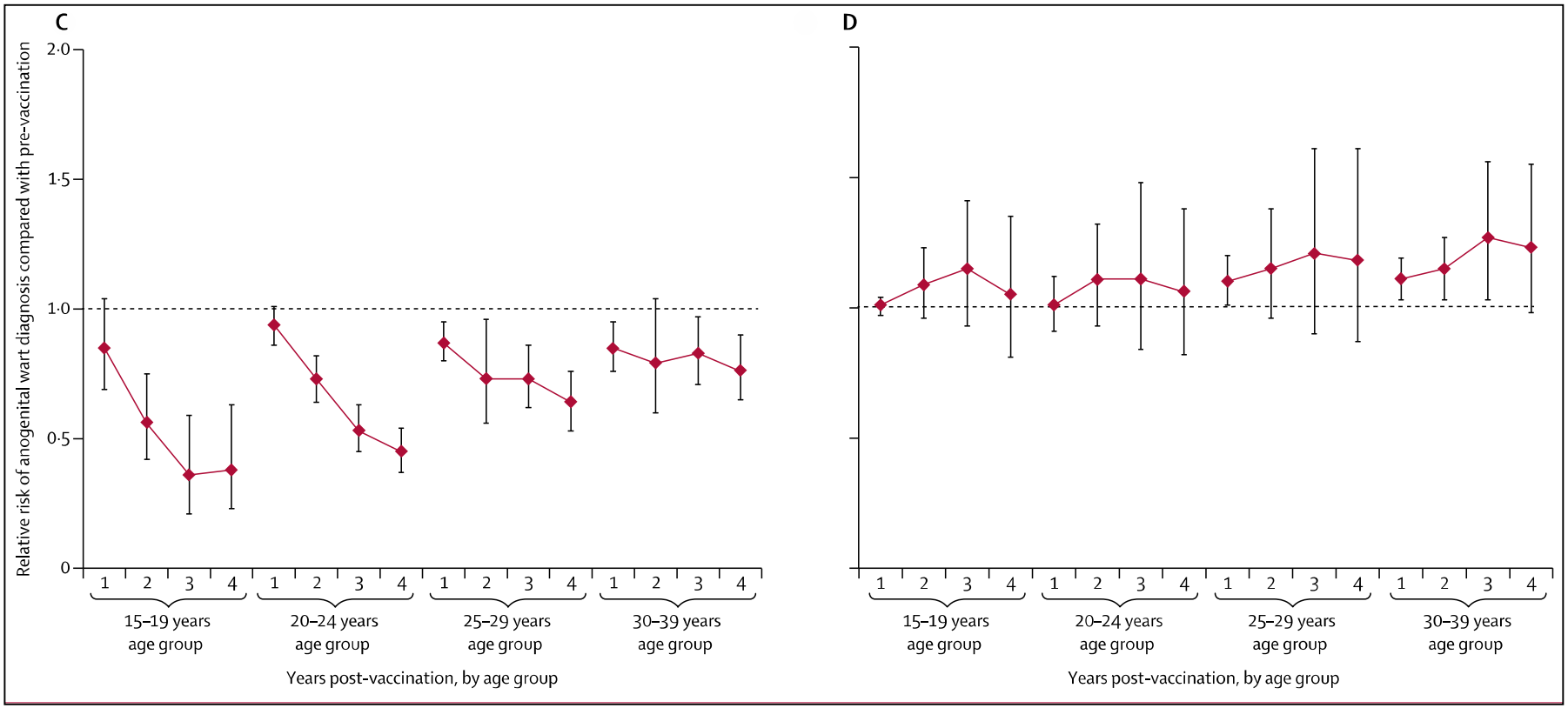
Significant decrease in incidence of CIN 1, 2 and 3 (**29**%, **50**% and **55**%, respectively) in women aged 20–21, associated with three doses of bivalent HPV vaccine (*KGJ Pollock 2014)*

DECLINE OF GENITAL WARTS: 4-HPV

HERD-IMMUNITY

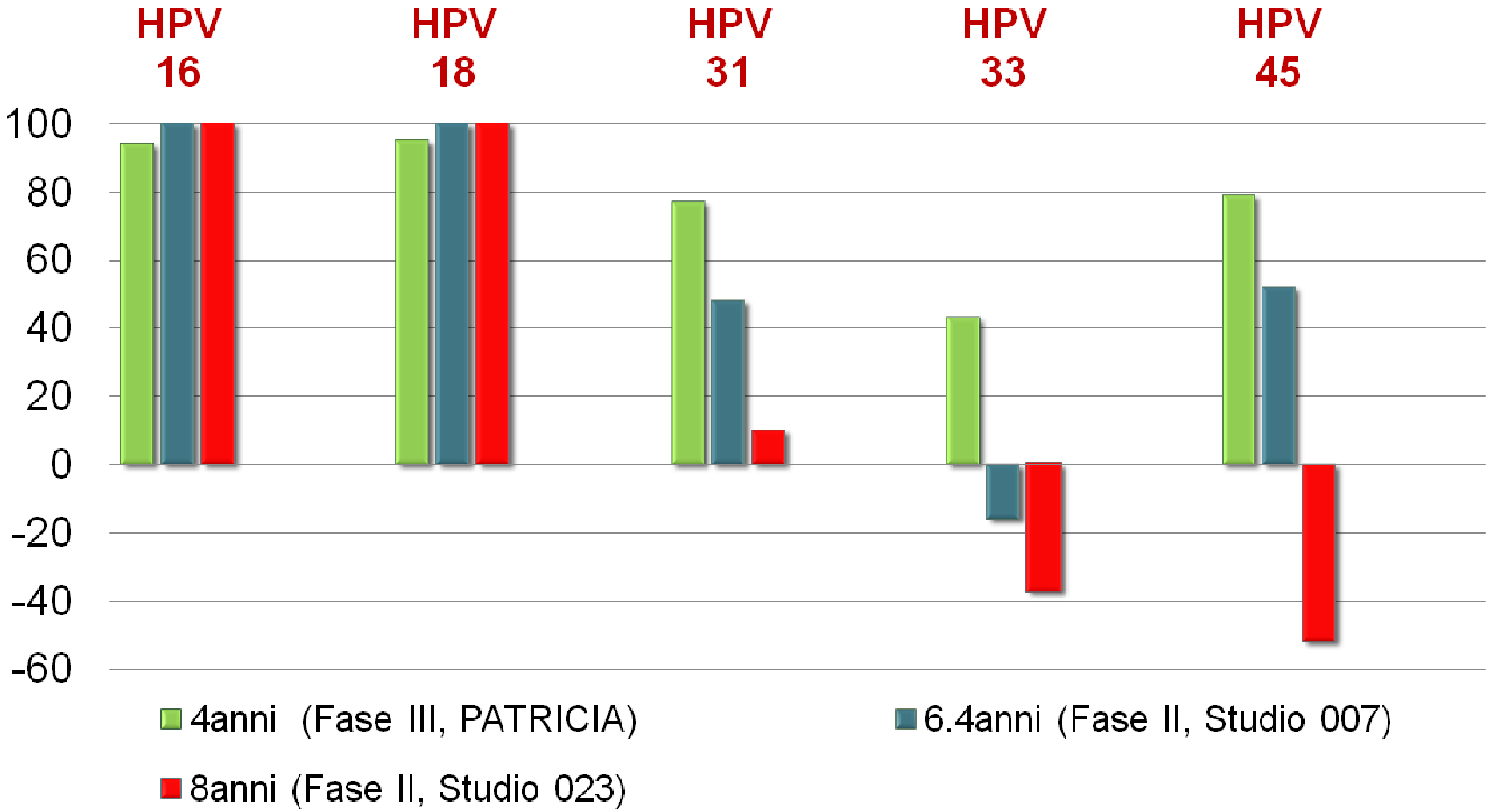
Boys and men, with high female vaccination coverage (>50%).

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



(Drolet M, 2015)

Vaccino bivalente: cross-reazione verso l'infezione persistente a 6 mesi



1. Malagón T et al. *Lancet Infect Dis.* 2012;12:781–789. 2. Paavonen J et al. *Lancet*. 2009;374:301–314. 3. GlaxoSmithKline Vaccine HPV-007 Study Group. *Lancet*. 2009;374:1975–1985. 4. De Carvalho N et al. *Vaccine*. 2010;28:6247–6255.

I VACCINI HPV SONO MEGLIO DI QUANTO SPERASSIMO

ESTENSIONI DELLE APPLICAZIONI
(in corso di valutazione)

PROFILASSI INDIV.

Soggetti adulti di entrambi i sessi sino a 45

GRUPPI HIGH-RISK

HIV-positivi
MSM
Trapiantati
Immunodepressi
Migranti
Sess. abusati

ADIUVANTE

Post-conizzazione
Post-terapia per condilomi
JORRP (?)
Durante la gravidanza (?)

I VACCINI HPV SONO MEGLIO DI QUANTO SPERASSIMO

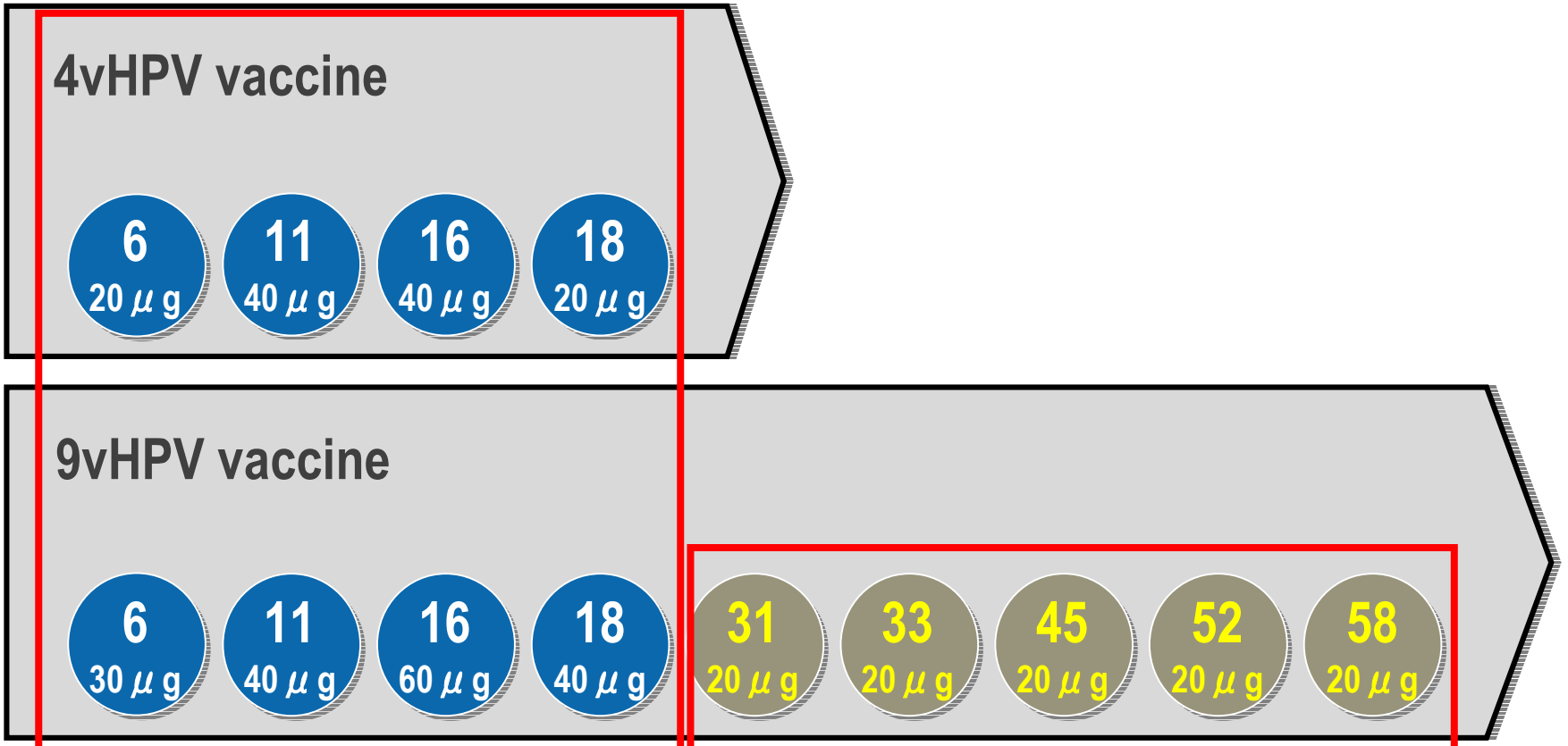
ESTENSIONE DELLA PREVENZIONE: VACCINO NONAVALENTE

Characteristic	Bivalent (2vHPV)*	Quadrivalent (4vHPV)†	9-valent (9vHPV)§
Brand name	Cervarix	Gardasil	Gardasil 9
VLPs	16, 18	6, 11, 16, 18	6, 11, 16, 18, 31, 33, 45, 52, 58
Manufacturer	GlaxoSmithKline	Merck and Co., Inc.	Merck and Co., Inc.
Manufacturing	*Trichoplusia ni* insect cell line infected with L1 encoding recombinant baculovirus	*Saccharomyces cerevisiae* (Baker's yeast), expressing L1	*Saccharomyces cerevisiae* (Baker's yeast), expressing L1
Adjuvant	500 μg aluminum hydroxide, 50 μg 3-O-desacyl-4′ monophosphoryl lipid A	225 μg amorphous aluminum hydroxyphosphate sulfate	500 μg amorphous aluminum hydroxyphosphate sulfate
Volume per dose	0.5 ml	0.5 ml	0.5 ml
Administration	Intramuscular	Intramuscular	Intramuscular

(E. Petrosky et al, MMWR / March 27, 2015)

9vHPV VACCINE: P001 (pivotal trial)

MAIN OBJECTIVES OF THE TRIAL



to provide a non-inferiority of 9vHPV **immune response** in respect to 4vHPV vaccine.

to prove **clinical efficacy** in infections or diseases caused by the added new genotypes.

9vHPV VACCINE: GMT and seroconversion

Geometric Mean Titer (GMT) and Seroconversion for HPV Types 6, 11, 16, and 18 in Noninferiority Analyses at Month 7 in the Per-Protocol Population

Anti-HPV Type	9vHPV Vaccine (N=6792)		qHPV Vaccine (N=6795)		GMT Ratio (95% CI)
	Participants	GMT	Participants	GMT	
	no.	*mMU/ml*	*no.*	*mMU/ml*	
Anti-HPV-6	3993	893.1	3975	875.2	1.02 (0.99 to 1.06)
Anti-HPV-11	3995	666.3	3982	830.0	0.80 (0.77 to 0.83)
Anti-HPV-16	4032	3131.1	4062	3156.6	0.99 (0.96 to 1.03)
Anti-HPV-18	4539	804.6	4541	678.7	1.19 (1.14 to 1.23)
Anti-HPV Response	**9vHPV Vaccine (N=6792)**		**qHPV Vaccine (N=6795)**		**Difference (95% CI)**
	Participants	Seroconversion	Participants	Seroconversion	
	no.	*no. (%)*	*no.*	*no. (%)*	*percentage points*
HPV-6 cLIA ≥30 mMU/ml	3993	3985 (99.8)	3975	3969 (99.8)	0 (–0.3 to 0.2)
HPV-11 cLIA ≥16 mMU/ml	3995	3994 (100)	3982	3980 (99.9)	0 (–0.1 to 0.2)
HPV-16 cLIA ≥20 mMU/ml	4032	4031 (100)	4062	4060 (100)	0 (–0.1 to 0.2)
HPV-18 cLIA ≥24 mMU/ml	4539	4532 (99.8)	4541	4528 (99.7)	0.1 (–0.1 to 0.4)

(E.A. Joura et al, NEJM 2015)

9vHPV VACCINE: vaccine efficacy

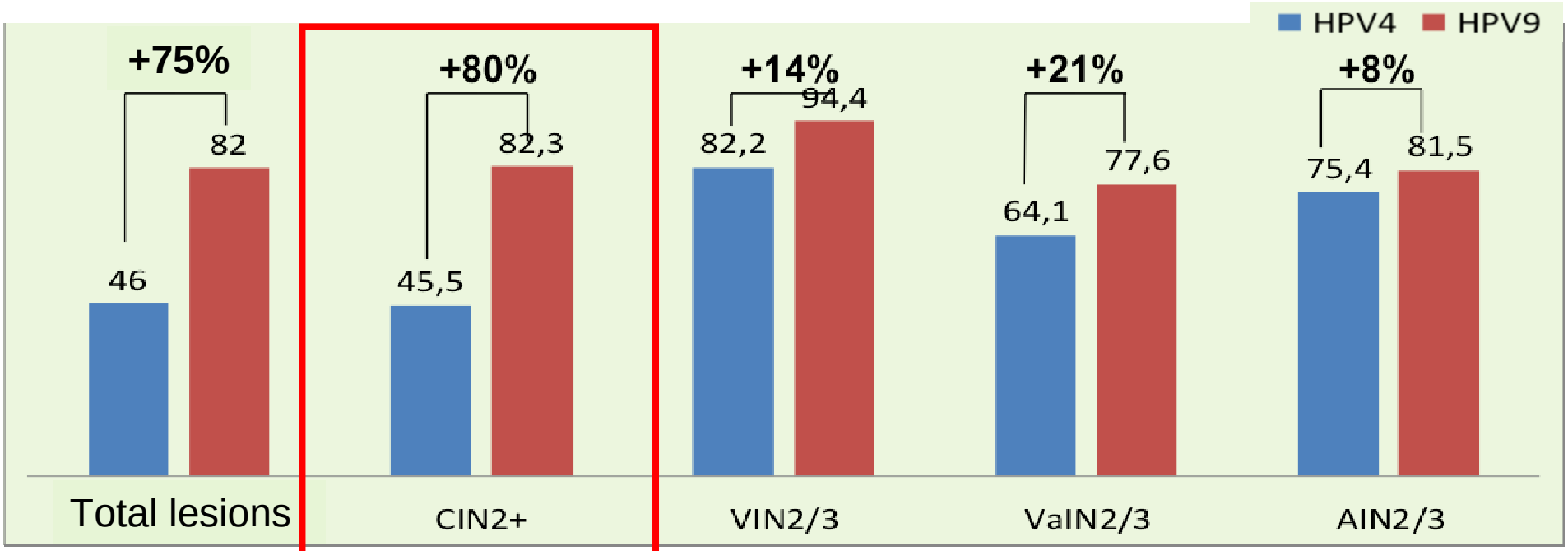
End Point	9vHPV Vaccine (N=7099)		qHPV Vaccine (N=7105)		Risk Reduction (95% CI)
	no./total no.	*cases/1000 person-yr*	*no./total no.*	*cases/1000 person-yr*	
Per-protocol efficacy population					
High-grade cervical, vulvar, and vaginal disease†					
Related to HPV-31, 33, 45, 52, or 58	**1/6016**	**0.1**	**30/6,017**	**1.6**	**96.7 (80.9 to 99.8)**
Related to HPV-6, 11, 16, or 18	1/5883	0.1	3/5898	0.2	66.6 (–203.0 to 98.7)
High-grade cervical epithelial neoplasia, adenocarcinoma in situ, and cervical cancer					
Related to HPV-31, 33, 45, 52, or 58	1/5948	0.1	27/5943	1.5	96.3 (79.5 to 99.8)
Related to HPV-6, 11, 16, or 18	**1/5823**	**0.1**	**1/5832**	**0.1**	**–0.4 (≤ –999 to 97.4)**
Persistent infection ≥6 months' duration¶					
Related to HPV-31, 33, 45, 52, or 58	**35/5939**	**2.1**	**810/5953**	**52.4**	**96.0 (94.4 to 97.2)**
Related to HPV-6, 11, 16, or 18	59/5812	3.6	80/5830	5.0	26.4 (–4.3 to 47.5)
Modified intention-to-treat population					
High-grade cervical, vulvar, and vaginal disease†					
All participants	340/7027	14.0	344/7027	14.0	0.7 (–15.7 to 14.8)
HPV-uninfected on day 1	26/3032	2.4	46/3077	4.2	42.5 (7.9 to 65.9)
Not related to 9 vaccine HPV types‡	26/3032	2.4	33/3077	3.0	19.7 (–34.5 to 52.5)
Related to 9 vaccine HPV types‡	0/3032	0.0	13/3076	1.2	100 (70.4 to 100)
HPV-infected on day 1	314/3995	23.1	298/3950	22.1	–4.8 (–23.3 to 10.8)
Not related to 9 vaccine HPV types‡	141/3995	10.0	137/3950	9.8	–2.0 (–30.0 to 19.9)
Related to 9 vaccine HPV types‡	173/3992	12.4	161/3946	11.6	–6.8 (–33.2 to 14.3)
Average risk reduction§	—	—	—	—	19.0 (–1.6 to 35.3)

(E.A. Joura et al. NEJM 2015)

VACCINO HPV

LESIONI PRENEOPLASTICHE ANO-GENITALI

Incremento atteso di protezione da 4vHPV to 9vHPH



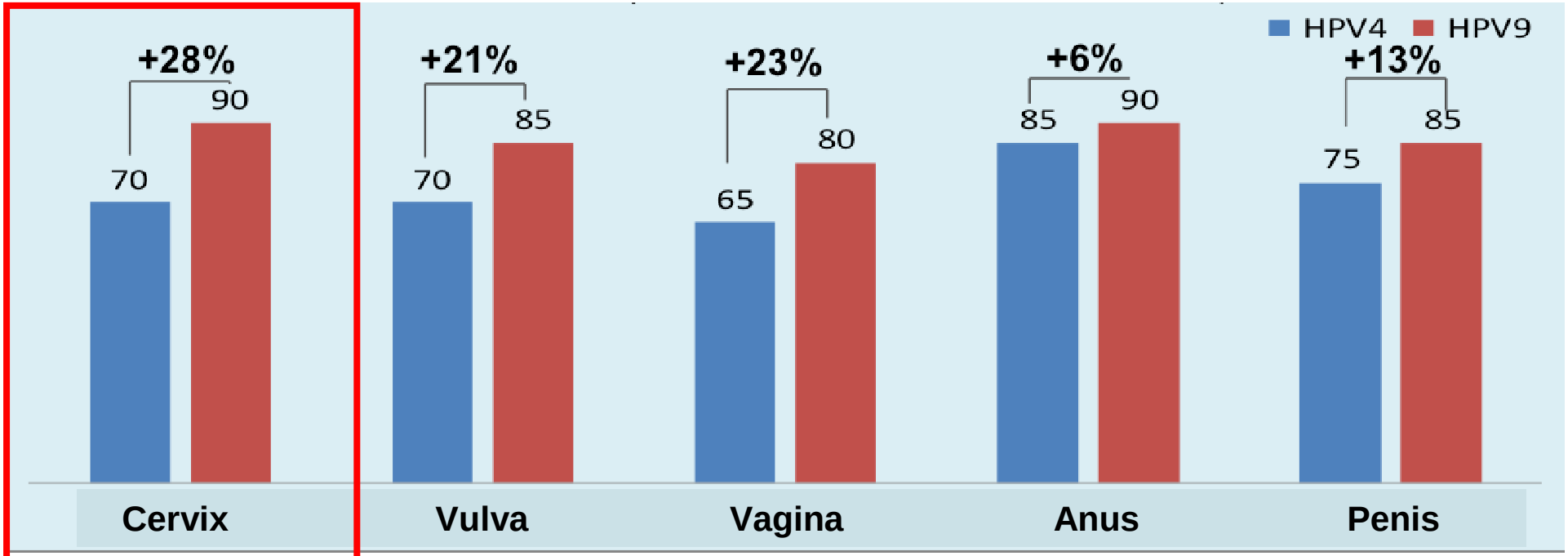
In base all'attribuzione dei singoli genotipi, la cervice uterina ha il **maggior potenziale beneficio con il vaccino 9vHPV**

(mod. S.Hartwig 215)

VACCINO HPV

CANCRI HPV-CORRELATI ANO-GENITALI

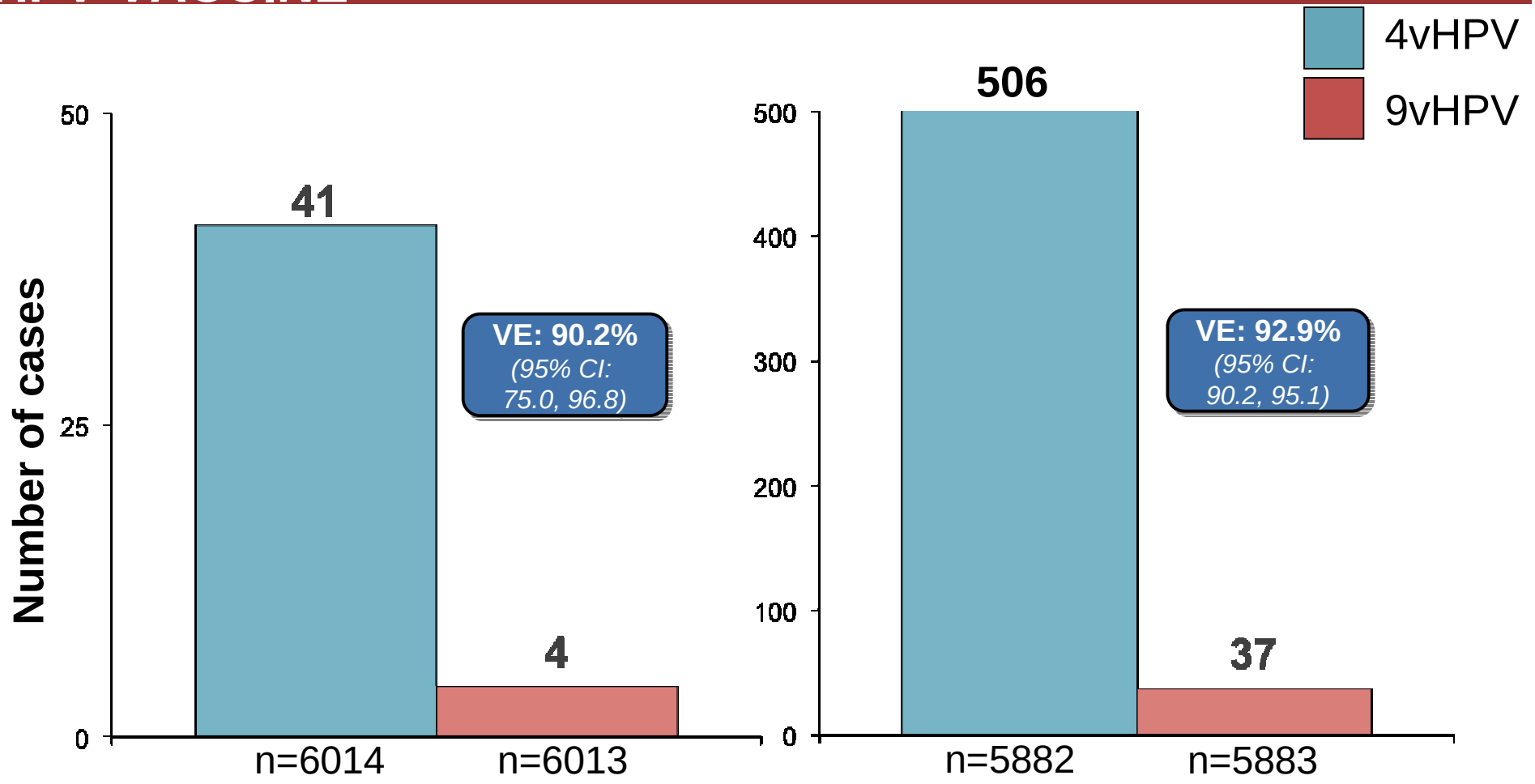
Incremento atteso di protezione da 4vHPV to 9vHPH



In base all'attribuzione dei singoli genotipi, la cervice uterina ha il **maggior potenziale beneficio con il vaccino 9vHPV**

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

HPV-VACCINE



Definitive therapy procedures
(LEEP, conization)

Pap-abnormalities
(≥ ASCUS HPV+)

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

VACCINO HPV

PREVENZIONE DELLE RECIDIVE DOPO ESCISSIONE

vaccino 4-HPV

•Riduzione significativa (**-64.9%)** di successive lesioni di alto-grado della cervice uterina e di altre patologie genitali HPV-correlate (Joura E 2012)

•Durante il follow-up di 3 anni il gruppo vaccinato mostrava recidive nel 2.5%, mentre era 7.2% nel gruppo controllo (**-65%**) (Kang W, 2013)

vaccino 2-HPV

•Nessuna evidenza di efficacia adiuvante; la vaccinazione **non protegge** dopo terapia (Hildesheim A, 2016)

•In donne già vaccinate, e sottoposte a conizzazione, la riduzione di recidiva era dell'**88.2**% verso CIN2+, irrispettivo dell'HPV-DNA test (Garland 2016)

COMPLETED 4vHPV-SCHEDULE	OVERALL	HPV-DNA pos at 6m	HPV-DNA pos at 12m	Relapse
45 out of 73	1 CIN1	0	0	0
	25 CIN2	2 (HPV39 &74) (HPV 31)	1 (HPV 31) -	0
	19 CIN3	0	0	0
Total	**45**	**2 (4.4%)**	**1 (2.2%)**	**0**

VACCINO HPV

EFFICACIA NELLE DONNE ADULTE (25→45 anni)

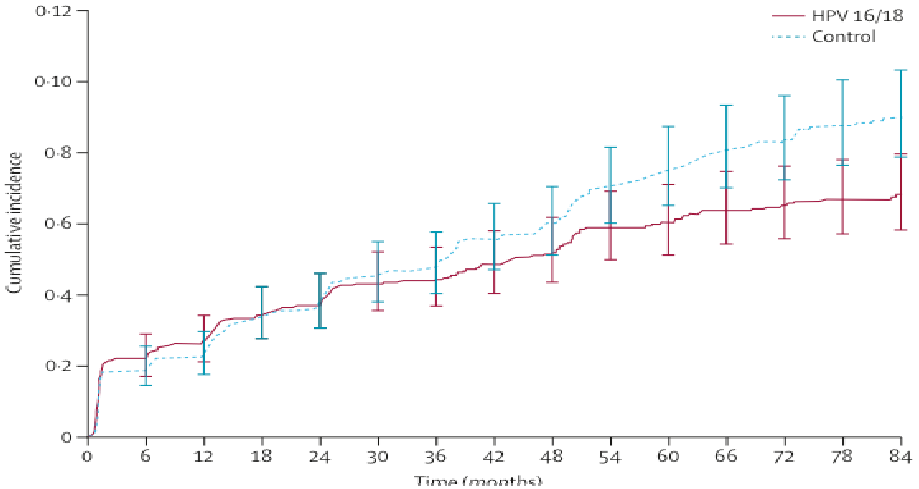
4HPV vaccino *(Munoz N 2010; Castellsaguè X 2011; Luna J 2013)*

Efficacia vaccinale
dopo 6 anni di follow-up

	PP	NRT	ITT
Overall persistent infection CIN, or EGL	84.7	78.3	41.6
24-34 yrs	86.0	78.7	39.4
35-45 yrs	81.8	78.0	43.9
CIN (any grade) efficacy	92.4	85.9	41.9

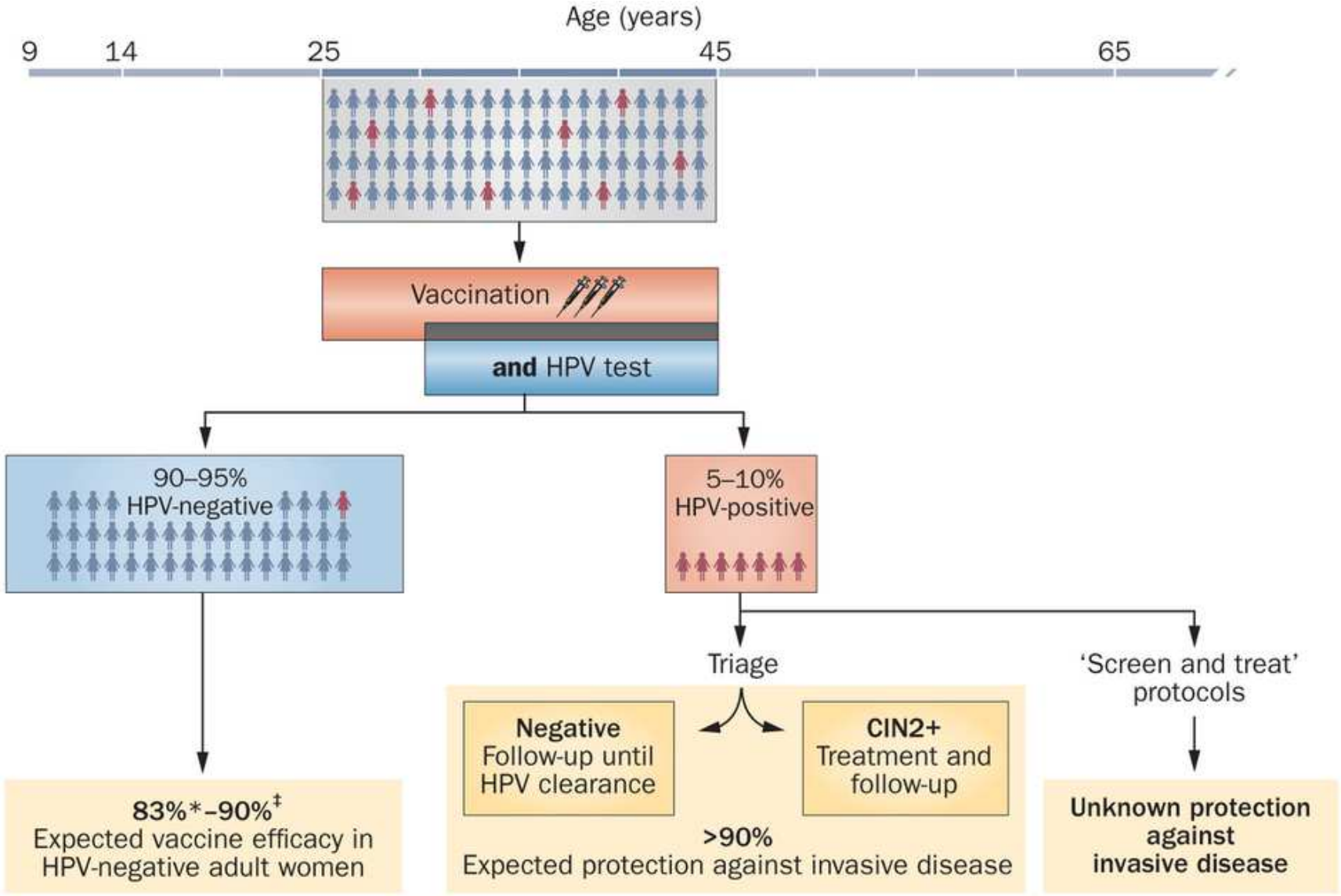
2HPV vaccino
(Skinner R 2014; Wheeler C 2016)

Incidenza di CIN1+ dopo 7 anni
di follow-up



In women older than 25 years, the HPV vaccines continue to protect against infections, cytological abnormalities and HPV associated lesions.

VACCINO HPV



(FASTER STUDY; Bosch FX, 2016)

VACCINO HPV

CHILDHOOD SEXUAL ABUSE

1. Global prevalence of childhood sexual abuse is estimated to be 8–31% for girls and 3–17% for boys (Barth J, 2013)
2. Sexual experiences with genital contact in adolescence increase the risk of cervical cancer (Jayasinghe Y 2015) →**the epithelial vulnerability of immature cervix could accelerate HPV acquisition and persistent carriage** (Garland S, 2015)
3. **Most childhood sexual abuse (70%) occurs at a mean age of 10–11 years, which is younger than the age at which HPV vaccinations are administered**.
4. Male and female victims of childhood sexual abuse should not only be screened for sexually transmitted infections (and offered appropriate treatment), but also be offered human papillomavirus vaccination.

VACCINO HPV

VACCINATION DURING PREGNANCY??

(formally contra-indicated)

1. WHO (and ACOG, 2015) recommend avoiding during pregnancy, but:
   - *testing is not mandatory and no intervention is recommended in case of accidental administration*.
   - *If administered inadvertently during pregnancy, it is not necessary to consider termination of pregnancy; the remaining doses should be delayed until completion of the pregnancy.*
   - *DNA recombinant vaccine*
2. No concerns related to miscarriage, preterm birth, congenital malformations and other foetal outcomes *(Walcholder C 2010; Panagiotou O 2015; Garland S 2009; Dana A 2009; Angelo M 2014)*
3. Stat. significant increased risk of cesarean section.

I VACCINI HPV SONO MEGLIO DI QUANTO SPERASSIMO

DIREZIONE FUTURA ?

↓

ULTERIORE RIDUZIONE DELLA DOSE

una sola dose *(one-shot)* ??

INFEZIONE HPV

La somministrazione di **una dose** di vaccino bivalente *(A.Kremer, 2015)* o quadrivalente *(R. Sankaranarayanan 2016)* mostra, dopo 4 anni di follow-up, una protezione contro infezione da HPV 16/18 simile alle tre dosi

→ Al momento non ci sono dati di efficacia clinica (contro **CIN 2+**) di una sola dose.

→ La **durata** di protezione originata da una schedula vaccinale senza il boosting è altamente **incerta** *(M.Jit, 2015)*

GRAZIE…

DOPO LA VACCINAZIONE…

SCENARI APERTI

STRATEGIA DI SCREENING NELLE DONNE VACCINATE

2016-2017

screening delle vaccinate a 15-16 anni di età (in base alla strategia regionale) in Basilicata e Valle d'Aosta che hanno adottato una strategia vaccinale multi-coorte: coorti di nascita 1991 e 1992 *(target secondario)*

2018

screening delle coorti 1993 vaccinate in altre Regioni: Friuli Venezia Giulia, Piemonte, Toscana e Puglia *(target secondario)*

2021

screening di tutte le vaccinate a 12 anni di età (coorte 1997) secondo la strategia di offerta a livello nazionale *(target primario)*

Consensus Conference

per la definizione del percorso di screening del cervicocarcinoma nelle donne vaccinate contro l'HPV

1. E' opportuno modificare i protocolli dei programmi di screening
2. Per le vaccinate nai¨ve (a 12 anni) viene proposta una strategia combinata sequenziale:
   - strategia *tailored* → disponibilita` di un link tra registri vaccinali e screening
   - strategia *one size one fit* → quando i dati di copertura arrivano alla soglia stabilita dal Ministero per la copertura vaccinale (attualmente 95% per la coorte del 2003).
3. Si propone l'innalzamento dell'eta` di inizio dello screening a 30 anni per le vaccinate nai¨ve.
   - il cambiamento dell'eta` di screening avverra` nel 2021 (cioe` l'invito avverra` nel 2026, anziche´ nel 2021). Questo innalzamento potrebbe comportare un rischio di uso spontaneo di HPV test o Pap test nelle fasce giovanili → counseling e movimento di opinione.
4. Nelle vaccinate a 12 anni (inizio a 30 anni) → HPV-test come test di screening
5. Nelle vaccinate a 15 anni od oltre (inizio screening a 25 anni)→ Pap test
6. C'è orientamento ad allungare l'intervallo di screening→ definire il livello accettabile di malattia residua (CIN3+) per effettuare un nuovo round di screening (→analizzare I dati relativi alle 15enni).

(GISCI 2015)

SCENARI APERTI

PERFORMANCE DEI TEST DI SCREENING

LE DONNE VACCINATE AVRANNO UN
MINORE RISCHIO DI LESIONI INVASIVE E PRE-INVASIVE

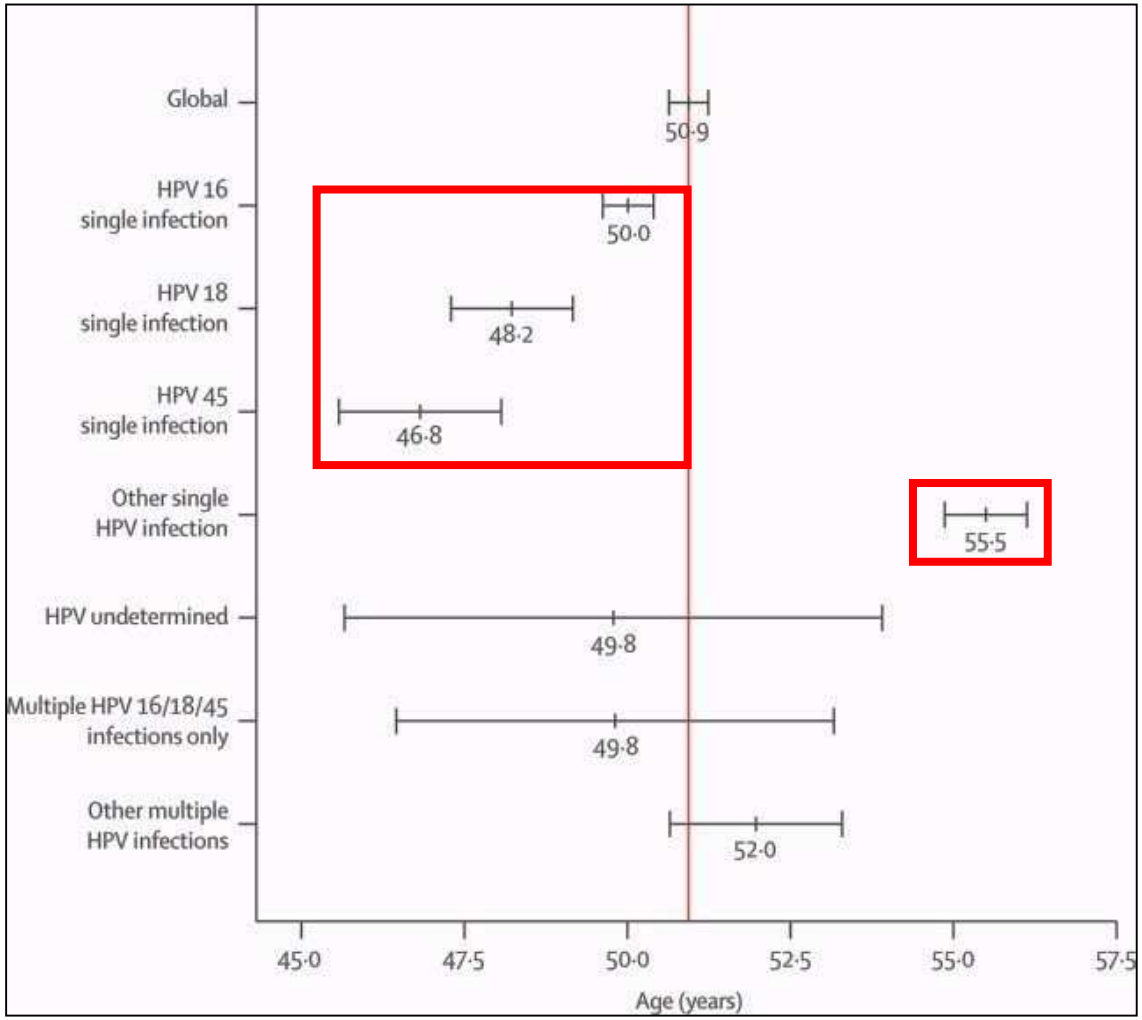
1.Riduzione della patologia HPV-correlata, per minore prevalenza di HPV 16 e 18:

- *-25% basso-grado (CIN1)*
- *-50-60% alto-grado (CIN2-3)*
- *-70% cancri*

2.Modifica dei genotipi prevalenti a favore degli **genotipi non-16/18**

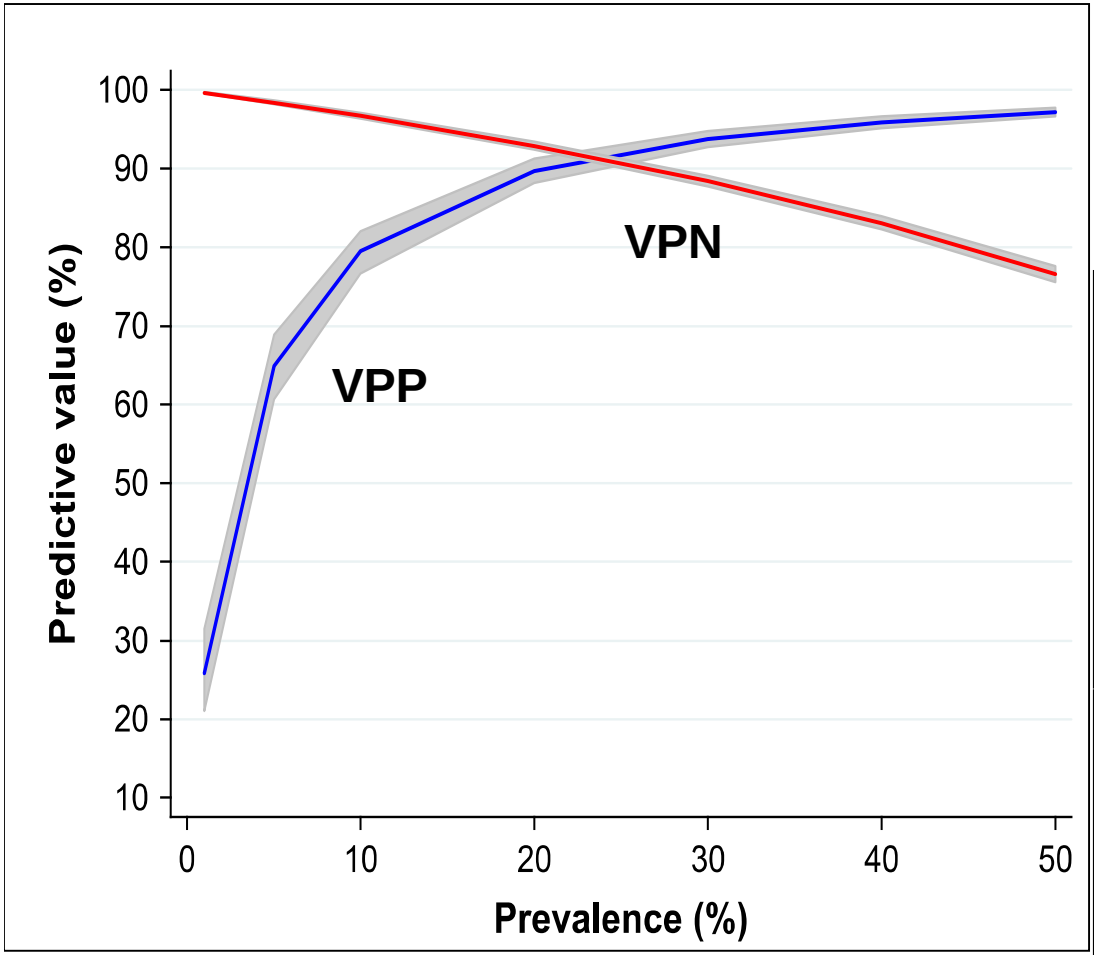
- minore probabilità di progredire verso il cancro
- tempo di trasformazione più lungo

DISTRIBUZIONE DEI GENOTIPI



(S. de Sanjosè, 2010)

SCENARI APERTI



(E.Franco, 2009)

Ricadute sui test di screening

- **Riduzione VPP** *(aumento falsi-positiviti)*
- **HPV-test: sensibilità invariata**
- **Citologia: sensibilità ridotta**
  centralizzazione dei test
  citologia di triage informata

- **Colposcopia:** "as a result of vaccination and HPV-testing, **PPV** for colposcopy is likely to **decline**. Specificity will become a priority → increased risk of overtreatment"

(European Federation for Colposcopy, Leeson S 2013)

GRAZIE