

Il vaccino anti-hpv nonavalente: risultati e prospettive

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Vaccino anti HPV

Lo scopo della vaccinazione profilattica è quello di ridurre l'incidenza di tutta la patologia genitale HPV-correlata, compresi i cancri e le lesioni precancerose di cervice, pene, vulva, vagina e ano.

Inoltre ci si attende una riduzione dell'incidenza dei condilomi genitali, oltre ad una riduzione della papillomatosi laringea nella loro prole.

American Cancer Society Guideline for Human Papillomavirus (HPV) Vaccine Use to Prevent Cervical Cancer and Its Precursors. *CA Cancer J Clin* 2007;57:7-28.

HPVs

Produzione di anticorpi è tardiva
e comunque scarsa (no viremia!)

HPV evade il sistema immunitario

Infezioni pregresse non sempre inducono
immunità verso infezioni successive
(possibili reinfezioni e nuove infezioni)

Vaccino anti HPV

Picco di risposta anticorpale

100-200 volte più alto

del titolo anticorpale indotto

dall'infezione naturale

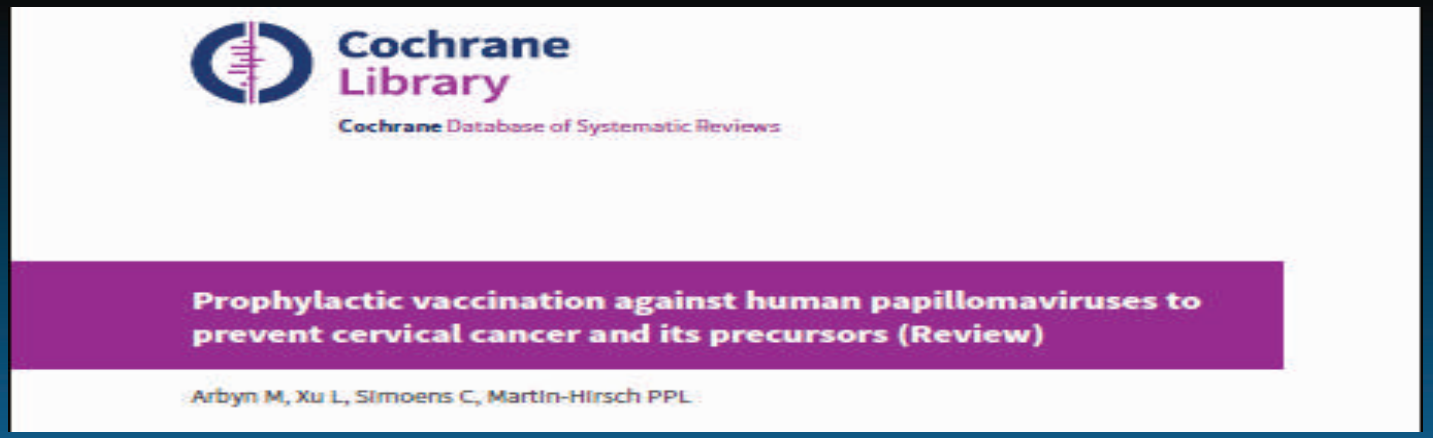
Vaccino anti HPV

Cervarix : 16/18

Gardasil4 : 6/11/16/18

Gardasil9 : 6/11/16/18/31/33/45/52/58





- 26 Trials (73.428 donne 15 – 26 anni, 3 trials fino a 45 anni)

- Follow-up : 7 - 8 anni

-Studi randomizzati : vaccino bivalente o quadrivalente vs placebo (vaccino adiuvante o vaccino controllo)

- Efficacia vaccino : CIN2+, CIN3+, AIS (HPV 16/18 e altri) in donne HPV negative, HPV 16/18 negative, indipendentemente da HPV

- Sicurezza vaccino

- Il vaccino HPV riduce il rischio di lesioni precancerose nelle donne tra i 15 e i 26 anni: *elevato livello di evidenza.*

- L'effetto è maggiore per le lesioni HPV 16/18 correlate e nelle donne HPV 16/18 negative all'arruolamento.

- Nelle donne di età > 26 anni la riduzione del rischio è inferiore.

- Non evidenza di aumentato rischio di SAE.

- Non aumentato rischio di aborto. Non dati sufficienti riguardo malformazioni o natimortalità.

- > 80 milioni di donne vaccinate nel mondo con i 3 vaccini

- Nessuna evidenza supporta nesso causale tra vaccino e CRPS (complex regional pain syndrome) o POTS (postural orthostatic tachycardia syndrome)

- I benefici superano i rischi potenziali del vaccino

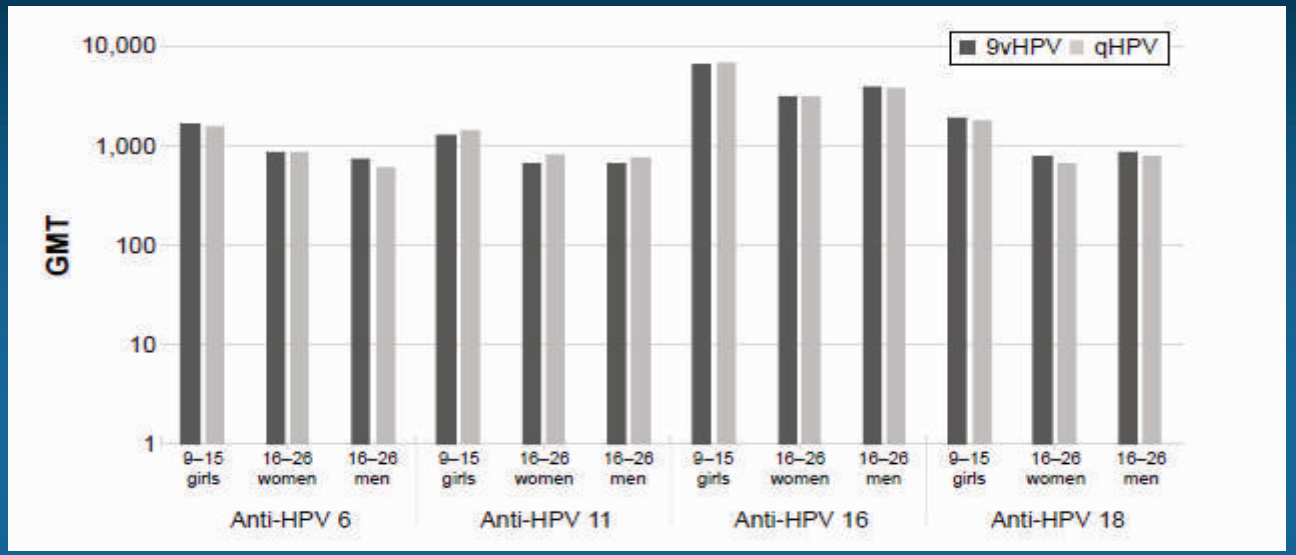
HPV vaccine : EMA 2016

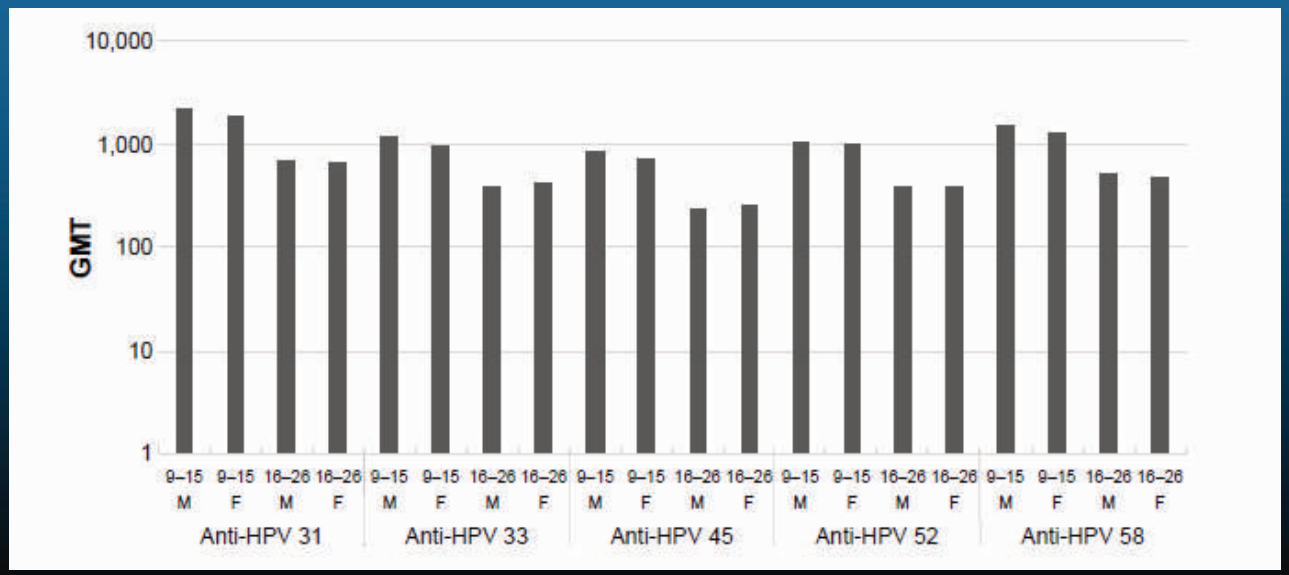
Gardasil-9

Study code	Objectives	Strategic objective	Population	References
001	Noninferior immunogenicity against HPV types 6, 11, 16, and 18 and efficacy against HPV types 31, 33, 45, 52, and 58 of 9vHPV compared to qHPV in women 16 through 26 years of age	Steps 1 and 2	N=14,204: 7,099 receiving 9vHPV and 7,105 receiving qHPV vaccine	Joura et al[14]
002	Immunogenicity of 9vHPV in girls and boys 9 through 15 years of age and women 16 through 26 years of age	Step 3	N=3,066: 1,932 girls; 666 boys; and 468 women receiving 9vHPV	Van Damme et al[18]
003	Immunogenicity of 9vHPV in men 16 through 26 years of age and women 16 through 26 years of age	Step 3	N=2,515: 1,103 HM; 313 MSM; and 1,099 women receiving 9vHPV	Castellsagué et al[19]
006	Administration of 9vHPV to girls and women 12 through 26 years of age previously vaccinated with qHPV vaccine	9vHPV revaccination after qHPV	N=921: 615 receiving 9vHPV and 306 receiving placebo	Garland et al[20]
005 and 007	Concomitant administration of 9vHPV with vaccines recommended routinely in girls and boys 11 through 15 years of age	9vHPV coadministration	N=2,295: 1,147 boys and girls in the concomitant group and 1,148 in the nonconcomitant group	Schilling et al;[21] Kosalaraksa et al[22]
009	Immunogenicity of 9vHPV in girls 9 through 15 years of age	Step 1	N=600: 300 receiving 9vHPV and 300 receiving qHPV vaccine	Vesikari et al[15]
010	Immunogenicity of two doses of 9vHPV in girls and boys 9 through 14 years of age and three doses of 9vHPV in girls 9 through 14 years of age and women 16 through 26 years of age	Two doses schedule evaluation	N=1,518: 753 girls; 451 boys; and 314 women	European Medicines Agency[17]
020	Evaluated immunogenicity of 9vHPV in men 16 through 26 years of age	Step 1	N=500: 249 receiving 9vHPV and 251 receiving qHPV vaccine	Van Damme et al[16]

Immunogenicità, efficacia e sicurezza ampiamente dimostrate

Gardasil-9


9vHPV
qHPV
GMT
10,000
1,000
100
10
1
9–15 girls
16–26 women
16–26 men
Anti-HPV 6
Anti-HPV 11
Anti-HPV 16
Anti-HPV 18


GMT
10,000
1,000
100
10
1
9–15 M
9–15 F
16–26 M
16–26 F
Anti-HPV 31
Anti-HPV 33
Anti-HPV 45
Anti-HPV 52
Anti-HPV 58

Gardasil-9

Table 3 Efficacy of 9vHPV on persistent HPV infection and on cervical, vulvar, and vaginal disease (HPV types 31, 33, 45, 52, or 58) in the per-protocol efficacy population[14]

Outcome	9vHPV (N=7,099)		qHPV (N=7,105)		Risk reduction
	Cases	Cases/1,000 person-years	Cases	Cases/1,000 person-years	95% CI
Persistent infection					
≥6 months	35	2.1	810	52.4	96.0 (94.4–97.2)
≥12 months	21	1.3	544	34.5	96.3 (94.4–97.7)
Cervical, vulvar, and vaginal					
CIN1, condyloma, VIN1, and VaIN1	2	0.1	82	4.3	97.6 (91.7–99.6)
CIN2/3, VIN2/3, VaIN2/3, or worse	1	0.1	30	1.6	96.7 (80.9–99.8)
Cervical disease					
CIN1	1	0.1	69	4.0	98.6 (92.4–99.9)
CIN2/3 or worse	1	0.1	27	1.5	96.3 (79.5–99.8)
Vulvar and vaginal disease					
Condyloma	0	0.0	3	0.2	100 (–71.6 to 100)
VIN1 or VaIN1	1	0.1	12	0.6	91.7 (51.3–99.6)
VIN2/3, VaIN2/3, or worse	0	0.0	3	0.2	100 (–71.5 to 100)

Note: Adapted with permission from Joura E, Giuliano AR, Iversen O-E, et al. A 9-valent HPV vaccine against infection and intraepithelial neoplasia in women. *N Engl J Med.* 2015;372(8):711–723.[14]

Impatto potenziale del vaccino 9vHPV:
protezione del 90% dei cancri cervicali nel mondo

VACCINO ANTI HPV
GARDASIL 9

QUALI
PROSPETTIVE ?

European Journal of Cancer (2015) 51, 1732–1741

Available at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Human papillomavirus genotype attribution for HPVs 6, 11, 16, 18, 31, 33, 45, 52 and 58 in female anogenital lesions

Beatriz Serrano [a], Silvia de Sanjosé [a,b,*], Sara Tous [a], Beatriz Quiros [a], Nubia Muñoz [c], Xavier Bosch [a], Laia Alemany [a,b]

[a] *Unit of Infections and Cancer (UNIC), Cancer Epidemiology Research Programme, Catalan Institute of Oncology (ICO) – IDIBELL, L'Hospitalet de Llobregat, Barcelona, Spain*
[b] *CIBER Epidemiología y Salud Pública (CIBERESP), Madrid, Spain*
[c] *National Institute of Cancer, Bogotá, Colombia*

Worldwide relative contribution of HPVs 16/18/31/33/45/52/58/6 and 11 in female anogenital lesions that tested positive for HPV DNA.

HPV type	Female anogenital lesions													
	Cancer								High grade precancerous lesions					
	Cervix ($N = 8,977$)		Anus ($N = 296$)		Vagina ($N = 303$)		Vulva ($N = 488$)		Anus ($N = 29$)		Vagina ($N = 181$)		Vulva ($N = 509$)	
	RC%	(95%CI)	RC%	(95%CI)	RC%	(95%CI)	RC%	(95%CI)	RC%	(95%CI)	RC%	(95%CI)	RC%	(95%CI)
Combined nine HPV types*	89.5	(88.8–90.1)	95.9	(93.0–97.9)	85.3	(80.6–89.0)	87.1	(83.8–89.9)	86.2	(68.3–96.1)	78.7	(71.7–84.2)	94.1	(91.7–96.0)
HPVs 16/18	70.8	(69.9–71.7)	87.0	(82.4–90.5)	63.7	(58.0–69.1)	72.6	(68.4–76.5)	82.8	(64.2–94.2)	63.8	(56.1–70.5)	79.8	(76.0–83.2)
HPVs 31/33/45/52/58	18.5	(17.7–19.4)	7.9	(5.0–11.4)	20.3	(15.8–25.1)	13.0	(10.1–16.2)	3.4	(0.1–17.8)	13.5	(9.1–19.7)	13.0	(10.2–16.2)
HPV 16	60.6	(59.6–61.6)	83.4	(78.7–87.5)	58.7	(53.0–64.3)	68.0	(63.7–72.2)	82.8	(64.2–94.2)	58.2	(50.5–65.5)	77.2	(73.5–80.8)
HPV 18	10.2	(9.6–10.9)	3.6	(1.9–6.6)	5.0	(2.8–8.0)	4.6	(2.8–6.7)	0.0	(0.0–11.9)	5.5	(2.7–9.9)	2.5	(1.4–4.3)
HPV 31	3.7	(3.3–4.1)	1.8	(0.6–3.9)	5.3	(3.0–8.4)	1.3	(0.5–2.7)	3.4	(0.1–17.8)	0.8	(0.1–3.9)	1.2	(0.4–2.5)
HPV 33	3.8	(3.5–4.3)	3.1	(1.4–5.7)	4.8	(2.8–8.0)	5.9	(4.0–8.4)	0.0	(0.0–11.9)	4.4	(1.9–8.5)	10.6	(8.1–13.6)
HPV 45	5.9	(5.4–6.4)	0.7	(0.1–2.4)	3.6	(1.8–6.4)	2.9	(1.6–4.8)	0.0	(0.0–11.9)	1.7	(0.3–4.8)	0.4	(0.0–1.4)
HPV 52	2.8	(2.5–3.2)	0.3	(0.0–1.9)	2.9	(1.4–5.6)	1.8	(0.8–3.5)	0.0	(0.0–11.9)	5.5	(2.7–9.9)	0.6	(0.1–1.7)
HPV 58	2.3	(2.0–2.6)	2.0	(0.7–4.4)	3.6	(1.8–6.4)	1.1	(0.3–2.4)	0.0	(0.0–11.9)	1.1	(0.1–3.9)	0.2	(0.0–1.1)
HPV 6	0.1	(0.1–0.2)	0.7	(0.1–2.4)	1.0	(0.2–2.9)	1.1	(0.3–2.4)	0.0	(0.0–11.9)	1.4	(0.3–4.8)	0.9	(0.2–2.0)
HPV 11	0.0	(0.0–0.1)	0.3	(0.0–1.9)	0.3	(0.0–1.8)	0.5	(0.0–1.5)	0.0	(0.0–11.9)	0.0	(0.0–2.0)	0.5	(0.0–1.4)
Other HPV types	10.5	(9.9–11.2)	4.1	(2.1–7.0)	14.7	(11.0–19.4)	12.9	(10.1–16.2)	13.8	(3.9–31.7)	21.3	(15.8–28.3)	5.9	(4.0–8.3)

Burden of female anogenital cancer cases attributable to HPV infection by the nine types included in the 9-valent HPV vaccine.

Cancer site	HPV AF (%)	Nine HPV types AF (%)	Burden	Cases attributable to the nine HPV types
Cervix	100.0	89.5	528,000	472,560
Anus	100.0	95.9	13,000	12,467
Vagina	74.3	63.3	9000	5697
Vulva	28.6	24.9	12,000	2988

Contents lists available at ScienceDirect

Papillomavirus Research

journal homepage: www.elsevier.com/locate/pvr

Estimation of the epidemiological burden of HPV-related anogenital cancers, precancerous lesions, and genital warts in women and men in Europe: Potential additional benefit of a nine-valent second generation HPV vaccine compared to first generation HPV vaccines

Susanne Hartwig [a,*], Jean-Jacques Baldauf [b], Géraldine Dominiak-Felden [a], François Simondon [c], Laia Alemany [d], Silvia de Sanjosé [d], Xavier Castellsagué [d]

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[c] IRD UMR216, Mère et enfant face aux infections tropicales, Paris, 75006, France; COMUE Sorbonne Paris Cité, Université Paris Descartes, Faculté des Sciences Pharmaceutiques et Biologiques, Paris, 75270, France
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PREVALENCE IN EUROPE 2013

CERVICAL CANCER		
34.708 cases/year	**100% HPV related**	
HPV 16/18	72.8% = 25.267 cases	
HPV 16/18/31/33/45/52/58	89.0% = 30.890 cases	**+ 5.623**
VULVAR CANCER		
9.544 cases/year	**19.3% HPV related** = 1.842 cases	
HPV 16/18	73.6% = 1.356 cases	
HPV 16/18/31/33/45/52/58	84.0% = 1.547 cases	**+ 191**
VAGINAL CANCER		
2.171 cases/year	**71.1% HPV related** = 1.544 cases	
HPV 16/18	71.2% = 1.099 cases	
HPV 16/18/31/33/45/52/58	85.6% = 1.322 cases	**+ 223**
ANAL CANCER in women		
4.562 cases/year	**87.6% HPV related** = 3.996 cases	
HPV 16/18	87.1% = 3.481 cases	
HPV 16/18/31/33/45/52/58	89.8% = 3.589 cases	**+ 108**

Nine-valent vaccine: + 6.145 cases/year

PREVALENCE IN EUROPE 2013

CIN 2+

267.350-510.609 cases/year	**100% HPV related**	
HPV 6/11/16/18	45.5% = 121.644-232.327 cases	
HPV 6/11/16/18/31/33/45/52/58	82.3% = 220.029-420.231 cases	**+ 98.385-187.904**

VIN 2/3

13.886-27.592 cases/year	**86.9% HPV related** = 12.067-23.977 cases	
HPV 16/18	82.2% = 9.919-19.709 cases	
HPV 16/18/31/33/45/52/58	94.4% = 11.391-22.635 cases	**+ 1.472-2.925**

VaIN 2/3

2.549-4.719 cases/year	**95.8% HPV related** = 2.442-4.521 cases	
HPV 16/18	64.1% = 1.566-2.898 cases	
HPV 16/18/31/33/45/52/58	77.6% = 1.895-3.508 cases	**+ 329-610**

AIN 2/3 in women

1.545 cases/year	**95.3% HPV related** = 1.472 cases	
HPV 6/11/16/18	75.4% = 1.110 cases	
HPV 6/11/16/18/31/33/45/52/58	81.5% = 1.200 cases	**+ 90**

Nine-valent vaccine: + 100.276-191.529 cases/year

PREVALENCE IN EUROPE 2013

GENITAL WARTS in women

378.141-508.893 cases/year (**90% HPV 6/11 related**)

340.327-458.003 cases HPV 6/11

ANAL CANCER in men

2.729 cases/year	**87.6% HPV related** = 2.390 cases
HPV 16/18	87.1% = 2.082 cases
HPV 16/18/31/33/45/52/58	89.8% = 2.147 cases **+ 65**

AIN 2/3 in men

1.093 cases/year	**95.3% HPV related** = 1.042 cases
HPV 6/11/16/18	75.4% = 786 cases
HPV 6/11/16/18/31/33/45/52/58	81.5% = 849 cases **+ 63**

GENITAL WARTS in men

375.467-426.425 cases/year (**90% HPV 6/11 related**)

337.921-383.782 cases HPV 6/11

GENITAL WARTS in women and men in EU = 678.248-841.785 cases HPV 6/11

CANCERS

Contribution of **seven** HR types in EU = **89%**

44.480 cases cervix/vulva/vagina in women & anus in both sexes
33.285 cases related to 4-valent vaccine HPV types
39.494 cases related to 9-valent vaccine HPV types = **+ 6.210** cases/year/EU
(relative increase = **19%**)

PRECANCEROUS LESIONS

Contribution of **nine** HPV types in EU = **82%**

284.373-541.621 cases CIN 2+/VIN 2-3/VaIN 2-3 in women & AIN 2-3 in both sexes
135.025-256.830 cases 4-valent vaccine HPV types
235.364-448.423 cases 9-valent vaccine HPV types = **+ 100.339-191.592** cases/year/EU
(relative increase = **75%**)

CIN 1

23%-25% = related to 4-valent vaccine HPV types
46%-51% = related to 9-valent vaccine HPV types

Head & Neck cancers

17.676 cases in **women**/year/EU — 1.915 cases related to 4-valent vaccine HPV types
2.089 cases related to 9-valent vaccine HPV types

80.062 cases in **men**/year/EU — 7.144 cases related to 4-valent vaccine HPV types
7.911 cases related to 9-valent vaccine HPV types

GENITAL WARTS in both sexes in EU

753.608-935.318 cases/year (**90% HPV 6/11 related**) = **678.248-841.785** cases

López et al. Infectious Agents and Cancer (2018) 13:15
https://doi.org/10.1186/s13027-018-0187-4

Infectious Agents and Cancer

RESEARCH ARTICLE Open Access

Epidemiologic and economic burden of HPV diseases in Spain: implication of additional 5 types from the 9-valent vaccine

Noelia López[1], Aureli Torné[2*], Agustín Franco[3], María San-Martin[1], Elisabet Viayna[4], Carmen Barrull[4] and Nuria Perulero[4]

- 3.381 cancri/anno — 530 5vHPV (15,7%)
- 29.405 lesioni precancerose — 12.597 5vHPV (42,8%)
- 49.251 condilomi

Stima costi/anno

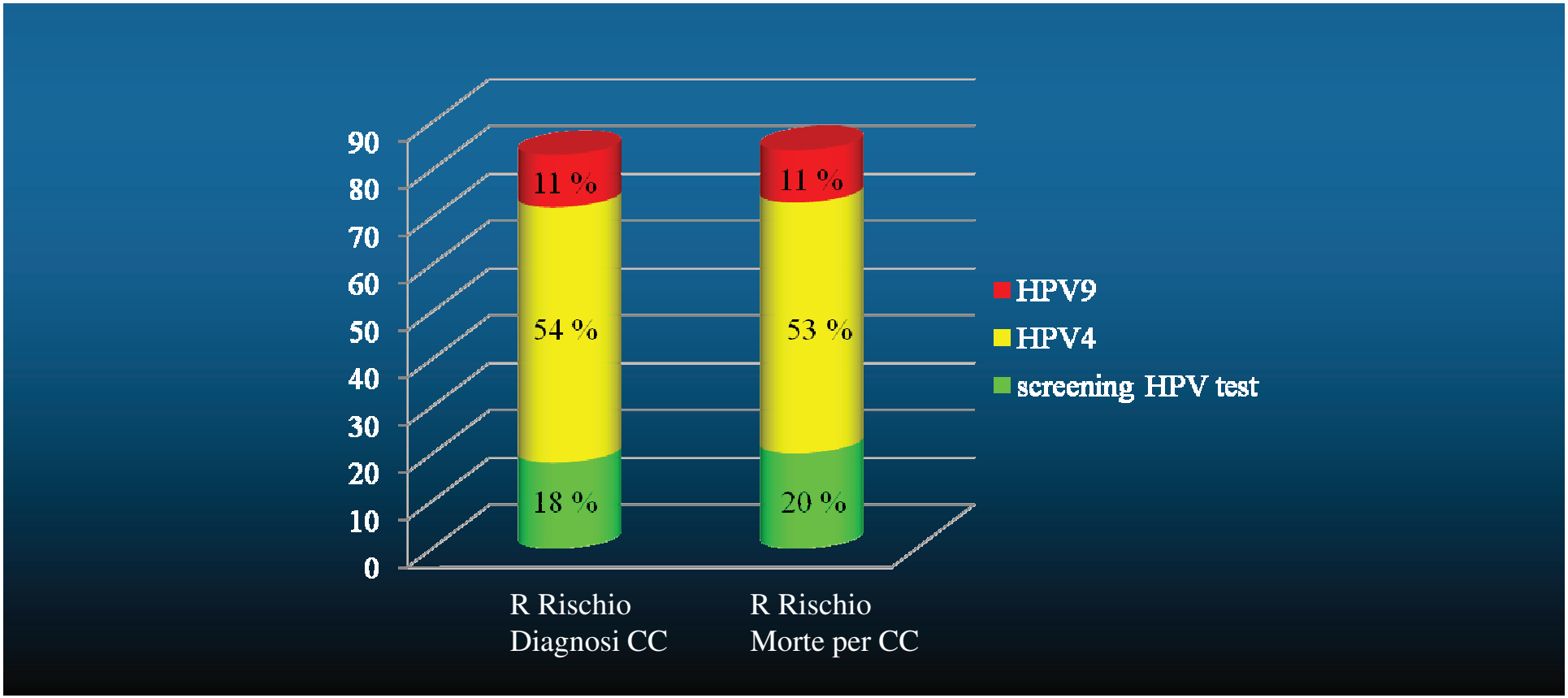
4vHPV 116 milioni di Euro
9vHPV 150 milioni di Euro

- Condilomi : 51 milioni Euro
- CIN2/3 4vHPV : 35 milioni Euro
- CIN2/3 9vHPV : 64 milioni Euro
- Cancro cervice 4vHPV : 15 milioni Euro
- Cancro cervice 9vHPV : 18 milioni Euro

Lancet Public Health 2016

Cost-effectiveness of the next generation nonavalent human papillomavirus vaccine in the context of primary human papillomavirus screening in Australia: a comparative modelling analysis

Kate T Simms, Jean-François Laprise, Megan A Smith, Jie-Bin Lew, Michael Caruana, Marc Brisson, Karen Canfell



Cost-effectiveness of the next generation nonavalent human papillomavirus vaccine in the context of primary human papillomavirus screening in Australia: a comparative modelling analysis

Kate T Simms, Jean-François Laprise, Megan A Smith, Jie-Bin Lew, Michael Caruana, Marc Brisson, Karen Canfell

HPV9 will remain a cost-effective alternative to HPV4 if the additional cost per dose remains less than AUS $23-36, under assumptions of lifelong vaccine protection, full efficacy at two dose, additional costs of HPV9 would be incurred in girls only and might be dependent on the screening programme.

Gardasil-9

Vaccino : costo – efficacia

- donne > 26 anni : NO
- uomini eterosessuali : SI – 2 dosi
- *MSM : < 40 anni/HIV*

Should human papillomavirus vaccination target women over age 26, heterosexual men and men who have sex with men? A targeted literature review of cost-effectiveness. Soe NN et al. Hum Vaccin Immunother. 2018 Jul 19

Gardasil-9
Raccomandazioni

- femmine e maschi *dai 9 ai 26 anni*
- femmine e maschi *9 – 14 anni* 2 dosi

EMA - FDA

Gardasil-9

- nelle femmine e nei maschi
- a tutte le età
- dopo trattamento per lesioni preneoplastiche o condilomi

Ambulatorio vaccinale

GARDASIL 4 (2011-2017)	
FEMMINE ***Età media 30 aa***	***859 :*** ***51 LEEP*** ***89 DTC condilomi***
MASCHI **Età media 24,4 aa**	**9 :** **• 6 DTC condilomi**

GARDASIL 9 (da 10/2017)	
FEMMINE ***Età media 30,6 aa***	***190 :*** ***• 33 LEEP*** ***• 29 DTC condilomi***
MASCHI **Età media 22,5**	**4 :** **• 1 DTC condilomi**

Cosa cambierà

La vaccinazione è destinata a rimpiazzare lo screening per il cancro cervicale come mezzo primario di prevenzione del cancro

Frazer IH. *The Journal of Immunology* 2014;192:4007-4011.


Grazie