Avances en la prevención de la patología cancerosa genital por VPH

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MURCIA, 14 de mayo de 2010

Salón de Actos de la
Caja de Ahorros del Mediterráneo

Contenidos

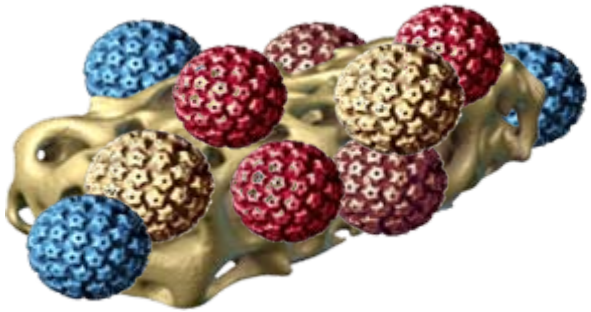
- Resumir y actualizar el estado actual de las vacunas VPH para la prevención de las lesiones cancerosas
- Consideraciones epidemiológicas de la introducción de la vacuna VPH en España
- Discutir el nuevo escenario de la prevención del cáncer de cuello de útero

Vacunas VPH

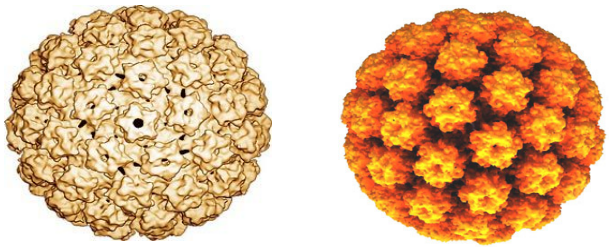
Antígeno + Adyuvante

L1 - VPH 16/18/6/11
GARDASIL

+

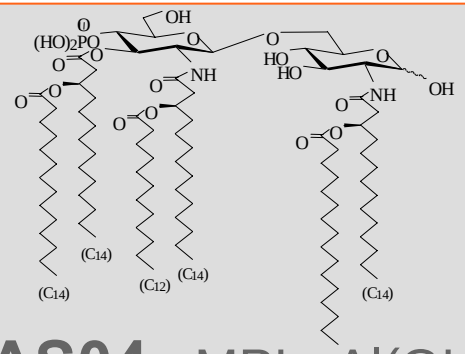


Hidroxifosfato sulfato de aluminio amorfo, 225 µg de aluminio



L1 - VPH 16/18
CERVARIX

+



AS04= MPL+$Al(OH)_3$

Antígenos muy purificados
VLPs

Potenciación
respuesta inmune

Inmunógenos

Sistema adyuvante

POTENCIACIÓN DE LA RESPUESTA INMUNE

* El MPL o monofosforil lípido A es una forma purificada y detoxificada de un lipopolisacárido derivado de *S. minnesota*

VACUNAS PROFILÁCTICAS CONTRA EL VPH

Merck / SPMSD
Gardasil®

VPH 6,11,16 & 18

- **VLPs de L1 de VPHs 6, 11, 16 y 18**
- **Producidas con levaduras**
- **Adyuvante: Aluminio**
- **Pauta: 0, 2 y 6 meses (0,5 ml, IM)**
- **Gardasil®**
- **Aprobada por FDA EE.UU., EMEA**
- **Comercializada en prácticamente todo el mundo**

GSK
Cervarix®

VPH 16 / 18

- **VLPs de L1 de VPHs 16 y 18**
- **Producidas con baculovirus**
- **Adyuvante: AS04**
  - Sales de Aluminio y lípido monophosphoryl A
  - Acentuar la respuestas de anticuerpos y causar respuesta celular inmunitaria
- **Pauta: 0, 1 y 6 meses (0,5 ml, IM)**
- **Cervarix®**
- **Aprobada por FDA Australia, EMEA**
- **Comercializada en prácticamente todo el mundo**

Programa Clínico Cervarix (GSK)

2004–en curso

n > 35.000

HPV 013
(Seguridad 10–14 años)
n = 2.067

HPV 014
(Inmuno 15-25 vs 26-45 vs 46-55 años)
n = 660

HPV 012
(Inmuno 15-25 vs 10 -14 años)
n = 767

HPV016
(Consistencia de lotes 18–25 años)
n = 800

Fase III

ICO

HPV 008
(Eficacia– 15–25 años)
n = 18.668

HPV 009
(Eficacia- 18-25 años NCI Costa Rica)
n = 7.467

HPV 015
(Eficacia – 25–55 años)
n = 5.400

n = 1.113

HPV001
(Eficacia-- 15-25 años)
n = 1.113
(seguimiento 27 meses)

HPV007
(Eficacia a largo plazo- 15-25 años)
n = 776
(seguimiento HPV001:
36 meses adicionales)

Fase IIb

n = 380

MI-CP-044
(HPV16/HPV18 *vs* vacunas monovalentes)
n = 4

MI-CP-058
(Seguridad en DNA+)
n = 61

MI-CP-055
(Selección del adyuvante)
n = 60

MI-CP-057
(Rango de dosis)
n = 210

Fase I/IIa

Programa clínico Gardasil (Merck & Co.)

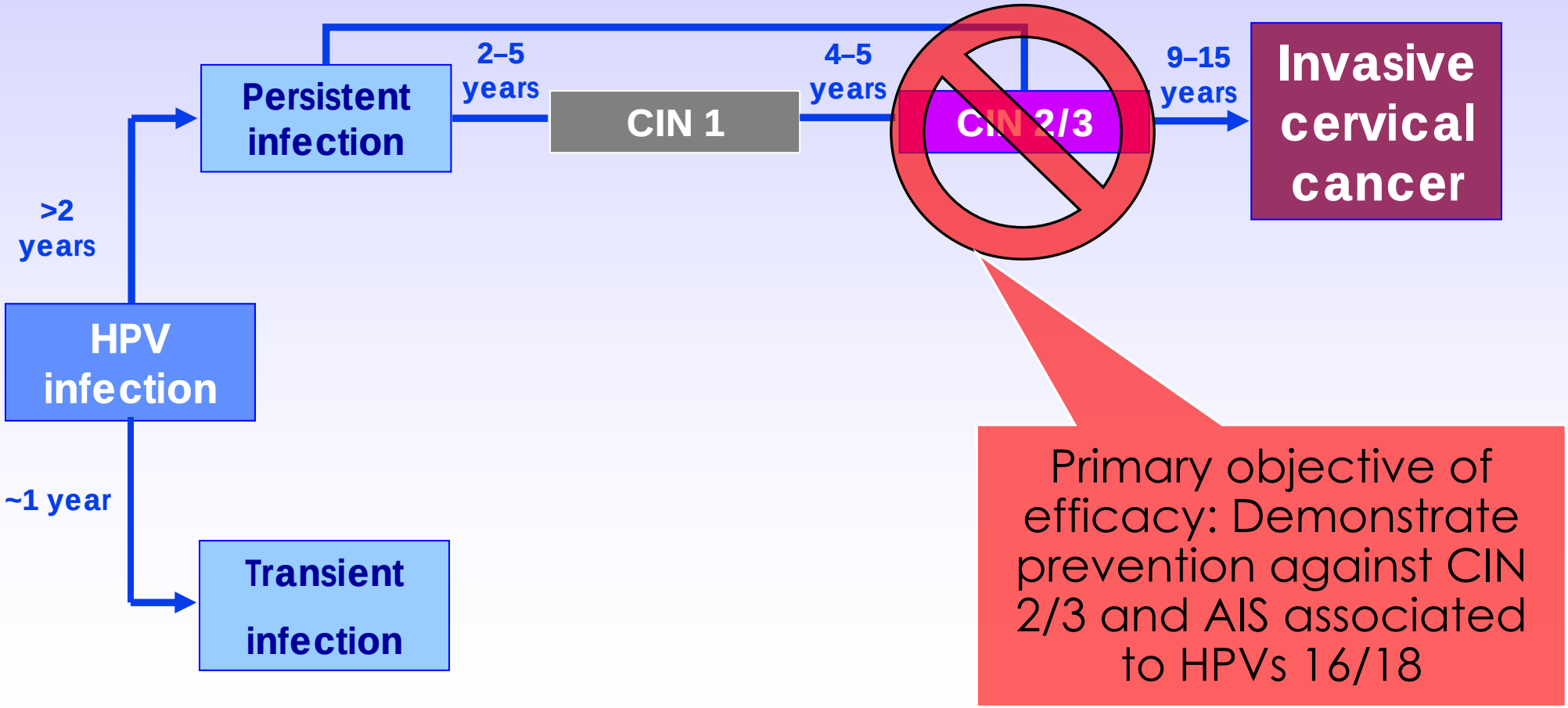
- **Fase I** : **300** sujetos: vacunas monovalentes
  - Inmunogenicidad y tolerabilidad de diversas dosis de vacunas monovalentes

- **Fase II** : **3.500** sujetos (incluye, 506 niñas y 508 niños). ICO
  - Demostración preliminar de la eficacia con la vacuna monovalente contra VPH 16
  - Estudio de dosis de la vacuna tetravalente (con seguimiento de la eficacia)

- **Fase III** : **>25.000** sujetos ICO
  - Eficacia de la vacuna tetravalente frente a incidencia genotipo específica de
    - CIN 2/3+
    - CIN 1
    - Verrugas genitales

WHO/FDA CLINICAL CRITERIA TO ASSESS CLINICAL EFFICACY

The natural history of HPV and cervical cancer conducted the design of the clinical program of HPV vaccines



CIN = cervical intraepithelial neoplasia. Adapted from Pagliusi SR and Aguado MT. Efficacy and other milestones for HPV vaccine introduction. *Vaccine* 2004;23:569–578.

Eficacia con Gardasil

GARDASIL: PROPHYLACTIC EFFICACY AGAINST CIN 2/3 & AIS (mujeres 15 a 26 años)

HPV information centre

Type Specific Per-Protocol Population(s). 3 years mean follow-up

GARDASIL	GARDASIL® (N = 10,268)		Placebo (N = 10,273)			
	n	Cases	n	Cases	Efficacy	95% CI
HPV16/18 CIN 2/3 or AIS	8,492	1*	8,462	85	**99%**	**(93-100)**
HPV 16	7,401	1	7,203	73	**99%**	**(92-100)**
HPV 18	7,381	0	7,314	18	**100%**	**(78-100)**

*** Co-infected with HPV 52 since first visit and only HPV16 +ve in bx in month 32 which became negative thereafter**

N = number of subjects who received ≥ 1 vaccination

n = number of subjects in the per-protocol analysis population

GARDASIL: PROPHYLACTIC EFFICACY AGAINST CIN2, CIN3 & AIS

Type Specific Per-Protocol Population(s). 3 years mean follow-up

	GARDASIL® (N = 10,268)		Placebo (N = 10,273)			
	n	Cases	n	Cases	Efficacy	95% CI
CIN2	8,492	0	8,462	56	**100%**	**(93-100)**
CIN3	8,492	1*	8,462	51	**98%**	**(89-100)**
AIS	8,492	0	8,462	7	**100%**	**(31-100)**

*** Co-infected with HPV 52 since first visit and only HPV16 +ve in bx in month 32 which became negative thereafter**

N = women who received at least 1 dose

n = women included in the per-protocol analysis population

GARDASIL: PROPHYLACTIC EFFICACY AGAINST VIN OR VAIN 2/3

Type Specific Per-Protocol Population

	GARDASIL® (N = 9,075)		Placebo (N = 9,075)			
	n	Cases	n	Cases	Efficacy	95% CI
VIN2/3	7,771	0	7,742	8	**100%**	**(42-100)**
VaIN2/3	7,771	0	7,742	7	**100%**	**(31-100)**

N = number of subjects who received ≥ 1 vaccination n = number of subjects in the per-protocol analysis population
Joura et al., Lancet 2007

GARDASIL: PROPHYLACTIC EFFICACY AGAINST GENITAL WARTS

COMBINED RESULTS OF 4 TRIALS

	Gardasil (n=7,897)	Placebo (n=7,899)	Efficacy	95% CI
Genital warts*	1	91	99%	(94-100)

*ATP: 3 doses & HPV16/18 seronegative at day 1, & DNA negative Day1 through Mont 7
Endpoint counts began at Month 7

http://www.fda.gov/CBER/label/hpvmer060806LB.pdf

Gardasil

Eficacia en mujeres de 24 a 45 años

Safety, immunogenicity, and efficacy of quadrivalent human papillomavirus (types 6, 11, 16, 18) recombinant vaccine in women aged 24–45 years: a randomised, double-blind trial

Nubia Muñoz, Ricardo Manalastas Jr, Punee Pitisuttithum, Damrong Tresukosol, Joseph Monsonego, Kevin Ault, Christine Clavel, Joaquin Luna, Evan Myers, Sara Hood, Oliver Bautista, Janine Bryan, Frank J Taddeo, Mark T Esser, Scott Vuocolo, Richard M Haupt, Eliav Barr, Alfred Saah

Muñoz N, et al, Lancet, 2009

PROTOCOL 019 (FUTURE III) : STUDY DESCRIPTION
Efficacy in 24-45 year-old women

- Multi-center, international study
- Randomization (1:1 ratio) to GARDASIL or placebo (1:1 stratification to 24 to 34 or 35 to 45 year-olds)
- In **3,817 24-45 year-old women**
  - No history of LEEP or hysterectomy
  - No history of biopsy-diagnosed cervical HPV disease in past 5 years
  - No history of genital warts
  - Lifetime sexual partner number not an inclusion criterion
- Pap testing and cervicovaginal sampling at ~6 month intervals for a total of 48 months
  - Colposcopy for ≥ASC-US

Muñoz N, et al, Lancet, 2009

PROTOCOL 019: EFFICACY ENDPOINTS
Efficacy in 24-45 year-old women

- Primary analysis: per-protocol efficacy population
- Co-Primary endpoints
  - First co-primary: Combined incidence of persistent infection (≥6-month, CIN, or external genital lesions (EGLs) caused by HPV 6, 11, 16, or 18
  - Second co-primary: Combined incidence of persistent infection, CIN or EGLs caused by HPV 16 or 18
- Secondary endpoint
  - Combined incidence of persistent infection, CIN, or EGLs caused by HPV 6 or 11

Muñoz N, et al, Lancet, 2009

GARDASIL PROTOCOL 019 (FUTURE III)
24 TO 45 YEAR-OLD WOMEN

HPV information centre

Primary efficacy results (CONT)

Combined incidence of disease related to HPV 6/11/16/18

Population	Vaccine		Placebo		% Reduction	95% CI	P-value
	Cases	PYR	Cases	PYR			
All Subjects	4	2,721	41	2,654	91%	74, 98	<0.001
By age: 24- to 34-Year-Olds	2	1,329	24	1,301	92%	67, 99	<0.001
By age: 35- to 45-Year-Olds	2	1,393	17	1,353	89%	52, 99	<0.001

PYR= person years at risk

Muñoz N, et al, Lancet, 2009

GARDASIL PROTOCOL 019 (FUTURE III)
24 to 45 year-old women

Combined incidence of disease (primary and secondary endpoints)

Endpoint	Vaccine		Placebo		% Reduction	95% CI	P-value
	Cases	PYR	Cases	PYR			
HPV6/11/16/18	4	2,721	41	2,654	91%	74, 98	<0.001
HPV16/18	4	2,700	23	2,621	83%	51,96	<0.001
HPV6/11	0	2,243	19	2,204	100%	79,100	<0.001

By type

PYR= person years at risk

Muñoz N, et al, Lancet, 2009

GARDASIL EN HOMBRES

Eficacia frente a variables de eficacia combinadas asociadas a la infección por VPHs 6/11/16/18 (16-26 años)

Data presented by Palefsky et al., at the
25th International Papillomavirus Conference and Clinical Workshop

Malmö, Sweden
May 8-14, 2009

GARDASIL IN MEN

EFFICACY AGAINST HPV 6/11/16/18-RELATED PERSISTENT INFECTION AND DNA DETECTION

Palefsky et al., 25th IPC, Malmo, Sweden (May 8-14, 2009)

- Randomized, double-blind, placebo-controlled trial
- 4,065 young men aged 16-26 years
- Received Gardasil or placebo at 0, 2, and 6 months
- Subjects underwent detailed genital exams, sampling from the penis, scrotum, and perineal/perianal region at enrollment, month 7 and at 6-month intervals afterwards.
- After enrollment, all new lesions were biopsied for pathological diagnosis and PCR testing
- Per-protocol population analysis
- Among men who were seronegative at day 1 and HPV DNA-negative from day 1 through month 7 to the relevant vaccine HPV type.
- Median follow-up was 2.3 years (starting from month 7)

GARDASIL IN MEN

EFFICACY AGAINST HPV 6/11/16/18-RELATED PERSISTENT INFECTION AND DNA DETECTION

Palefsky et al., 25th IPC, Malmo, Sweden (May 8-14, 2009)

Endpoint	GARDASIL (n = 1,390)		PLACEBO (n = 1,400)		% Efficacy	95% CI	p-value
	Cases	Inc. per 100 PY	Cases	Inc. per 100 PY			
Persistent infection	15	0.6	101	4.1	**85.6**	75.1, 92.2	<0.001
HPV DNA detection	136	5.5	241	10.0	**44.7**	31.5, 55.6	<0.001

PERSISTENT INFECTION: HPV DNA detection in anogenital specimens from ≥2 consecutive visits ≥6 months apart or HPV 6/11/16/18-related disease with positivity to the same type at adjacent visit

DNA DETECTION: in anogenital specimens from ≥1 visit

n = number of subjects randomized who received at least one injection and have follow-up after month 7; PY = person years; CI = confidence interval.

GARDASIL IN MEN
EFFICACY AGAINST EXTERNAL GENITAL LESIONS (EGLS)

Palefsky et al., 25th IPC, Malmo, Sweden (May 8-14, 2009)

Per-protocol population

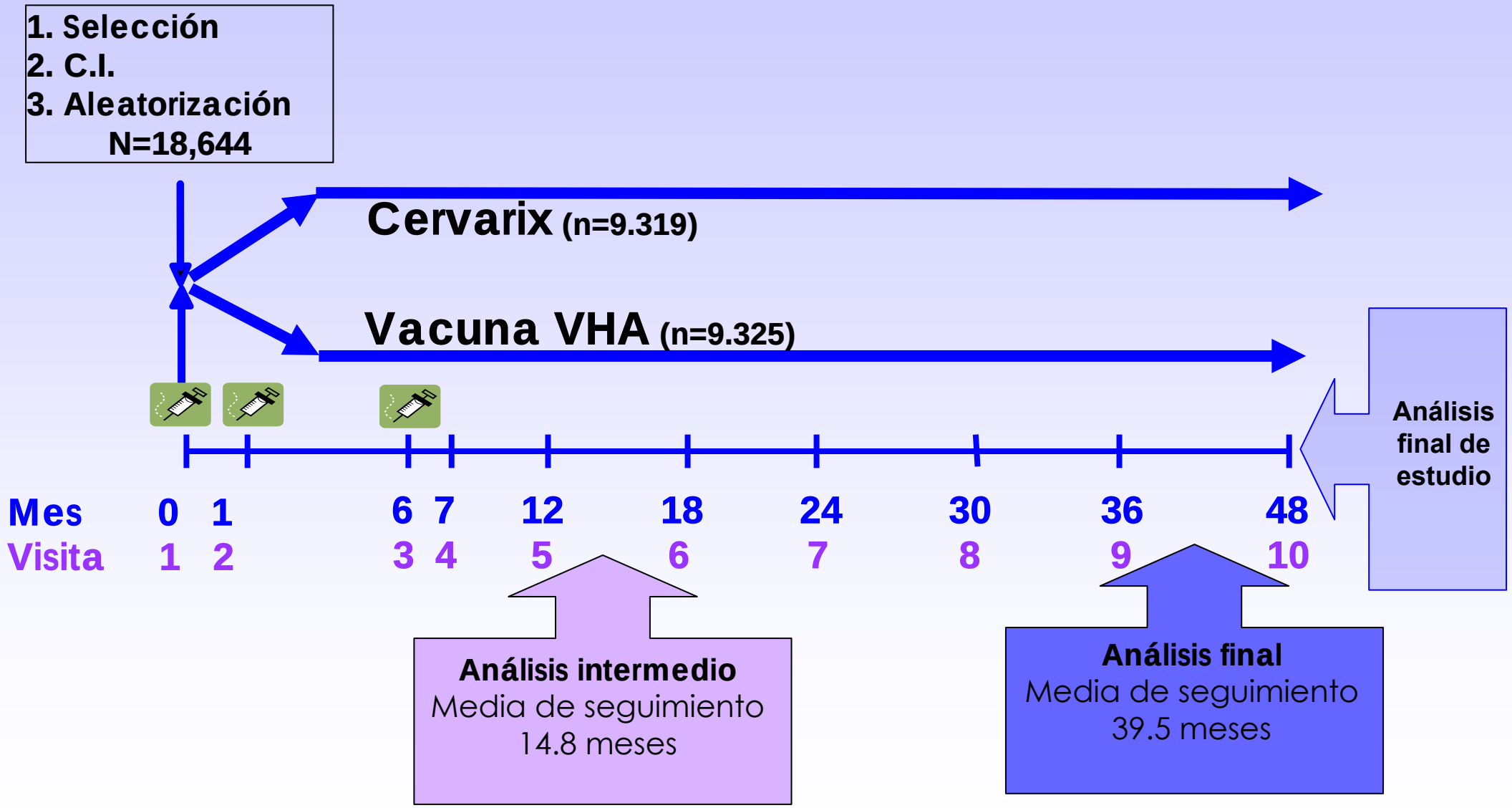
EGLs	GARDASIL (n = 1,397)		PLACEBO (n = 1,408)		% Efficacy	95% CI	p-value
	Cases	Inc. per 100 PY	Cases	Inc. per 100 PY			
All subjects	3	0.1	31*	1.1	90.4	69.2, 98.1	<0.001

Included 28 condylomas, 2 PIN1, 1 PIN2/3
n = number of subjects randomized who received at least one injection and have follow-up after month 7;
PY = person years; CI = confidence interval.

EGLs include external genital warts, penile/perianal/perineal intraepithelial neoplasia (PIN), penile, perianal, or perineal cancer;
case counting began after month 7.

Eficacia con Cervarix

PATRICIA. Diseño del ensayo



CERVARIX: VACCINE EFFICACY AGAINST CIN2+
(FINAL ANALYSIS, 39.5 MONTHS FOLLOW-UP)

ATP-E COHORT		Cervarix N = 7,344	Control N= 7,312	Vaccine efficacy % (96.1% CI)	P-value
HPV DNA in the lesion	HPV 16/18	4	56	**92.9** (79.9-98.3)	<0.0001
	HPV-16	2	46	**95.7** (82.9-99.6)	<0.0001
	HPV-18	2	15	**86.7** (39.7-98.7)	0.001
Type Assignment Analysis*	HPV 16/18	1	53	**98.1** (88.4-100)	<0.0001
	HPV-16	0	45	**100** (91.0-100)	<0.0001
	HPV-18	1	13	**92.3** (45.7-99.9)	0.0009

*Additional analysis for case assignment when multiple infections detected [33/60 (55%)] presence of HPV type in the lesion and in the 2 immediately preceding cytology samples (when multiple types present)

ATP-E: HPV DNA negative and seronegative at M0, DNA negative at M6 for the HPV type considered in the analysis, with or without ASCUS/LSIL (excludes subjects with HSIL)

Control, Hepatitis A vaccine

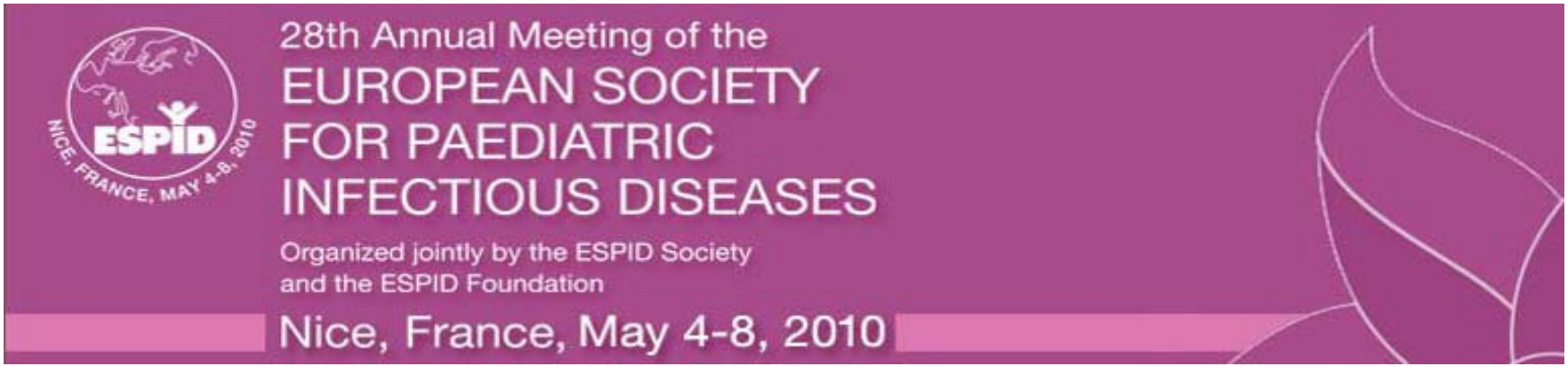
CERVARIX: VACCINE EFFICACY AGAINST CIN2+
(FINAL ANALYSIS, 39.5 MONTHS FOLLOW-UP)

TVC-naïve		Cervarix N = 5,449 n	Control N = 5,436 n	Vaccine efficacy % (96.1% CI)	P-value
HPV DNA in the lesion	HPV 16/18	1	63	**98.4** (90.4-100)	<0.0001
	HPV-16	1	56	**98.2** (89.1-100)	<0.0001
	HPV-18	0	12	**100** (61.3-100)	0.0002
Type Assignment Analysis*	HPV 16/18	1	61	**98.4** (90.1-100)	<0.0001
	HPV-16	1	54	**98.2** (88.7-100)	<0.0001
	HPV-18	0	12	**100** (61.3-100)	0.0002

TVC-naïve: Received ≥1 dose; Normal cytology at M1; HPV DNA negative for all oncogenic types at M0; Seronegative for HPV-16/18 at M0; Case counting: day after 1st dose

Vaccine, HPV-16/18 AS04-adjuvanted vaccine; **Contro**l, Hepatitis A vaccine
TAA, presence of HPV type in the lesion and in the 2 immediately preceding cytology samples

Últimos datos de Cervarix: seguimiento a 8,4 años



SUSTAINED IMMUNOGENICITY AND EFFICACY OF THE HPV-16/18 AS04-ADJUVANTED VACCINE: FOLLOW-UP TO 8.4 YEARS

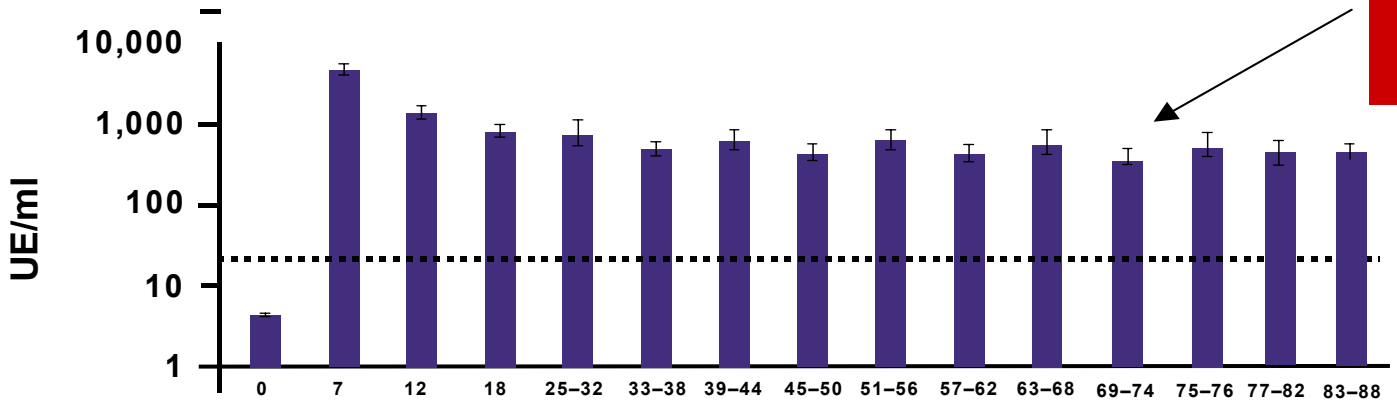
CM Roteli-Martins[1], P Naud[2], P Borba[3], J Teixeira[4], N De Carvalho[5], T Zahaf[6], N Sanchez[7], B Geeraerts8 and K Hardt6

Cervarix

Niveles de Anticuerpos a largo plazo

Seguimiento 7,3 años

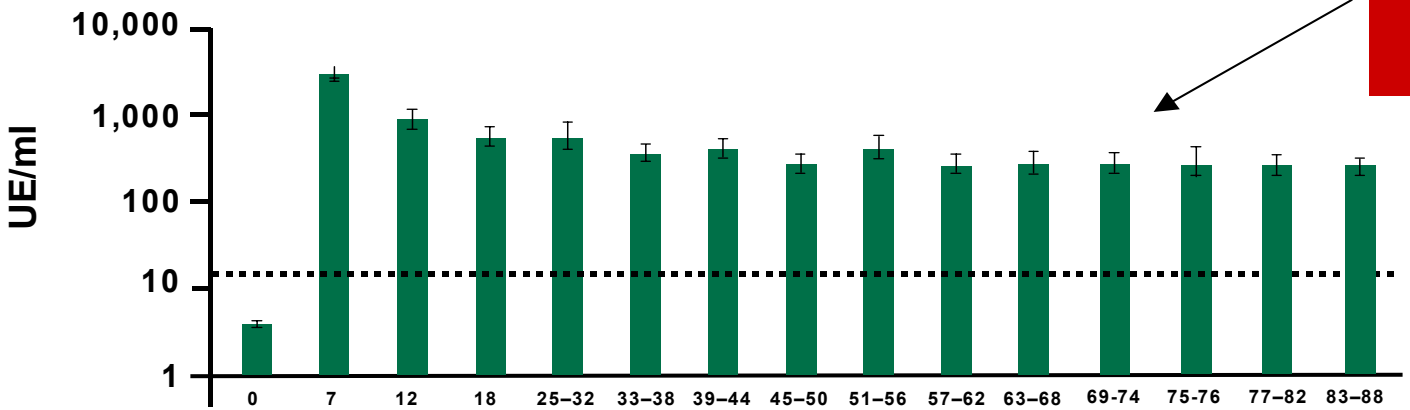
VPH 16



98,8%
seropositividad[1]

≥13 veces
superior

VPH 18



98,8%
seropositividad[1]

≥11 veces
superior

Meses

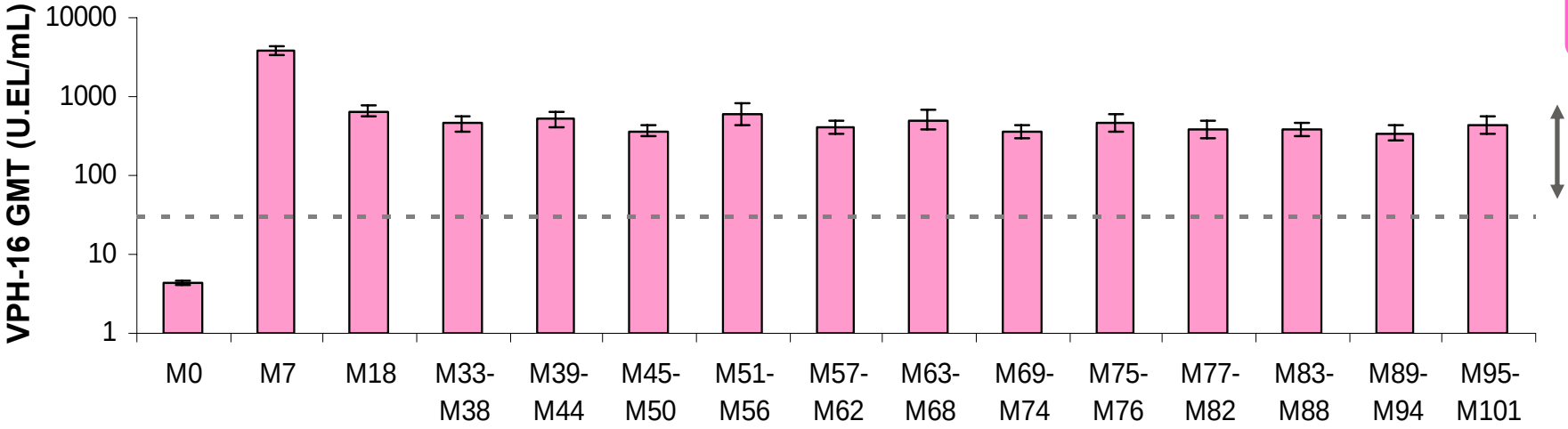
Elevada correlación entre ELISA y neutralización de pseudoviriones

De Carvalho, N *et al*. 25th International Papillomavirus Conference (Abstract P-29.15), 2009.

Últimos datos de Cervarix

Respuesta de anticuerpos totales

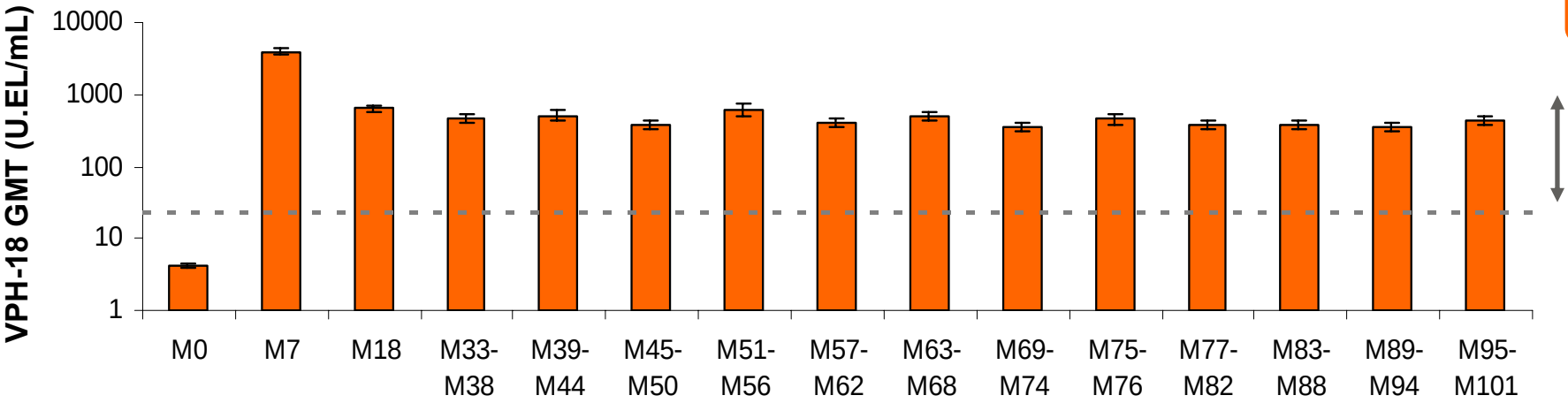
Seguimiento: 8,4 años



Seropositividad > 99%

> 11 veces superior a la infección natural

Meses después de la primera vacunación



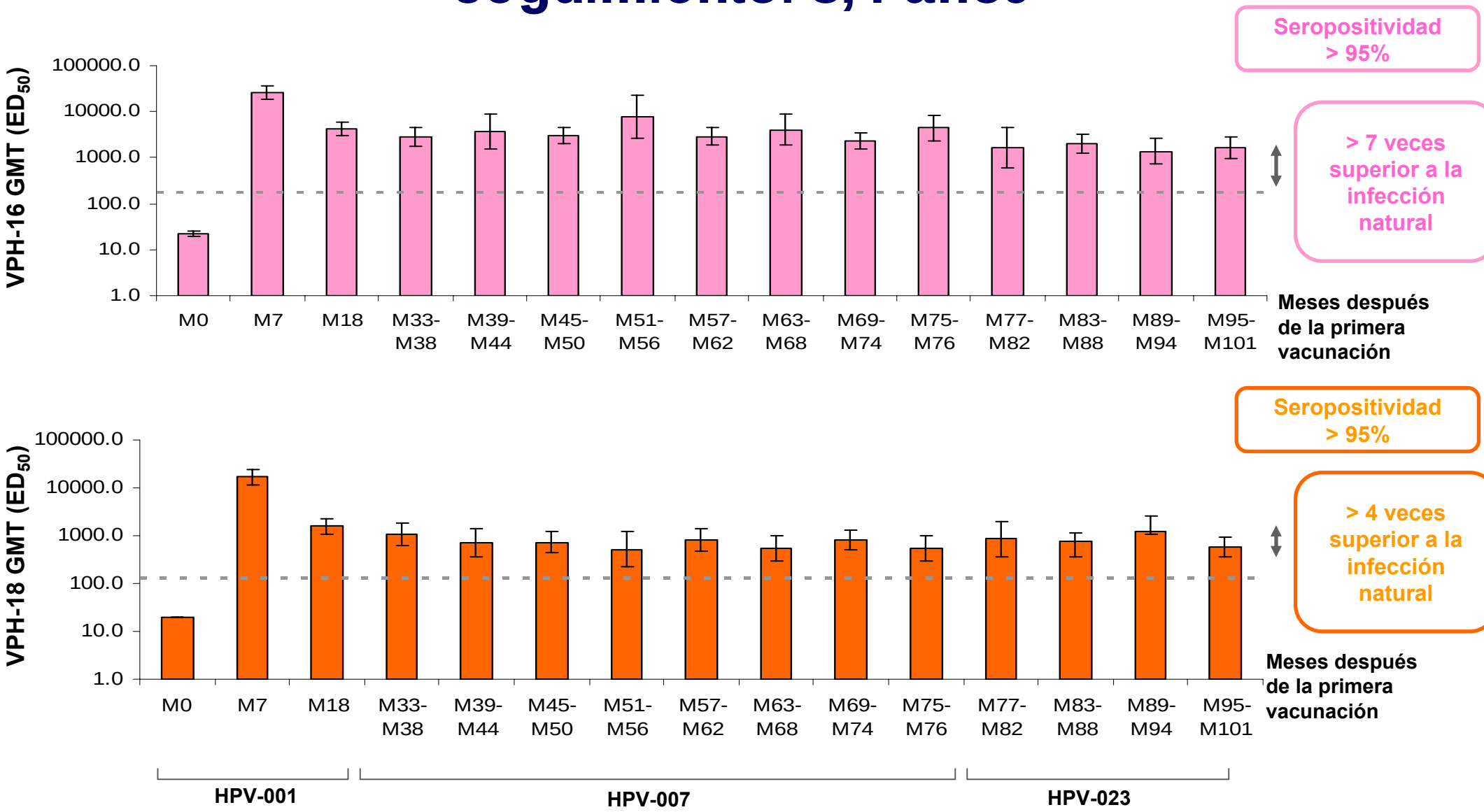
Seropositividad > 99%

> 10 veces superior a la infección natural

Meses después de la primera vacunación

HPV-001 HPV-007 HPV-023

Últimos datos de Cervarix
Respuesta de anticuerpos neutralizantes
Seguimiento: 8,4 años



Protección cruzada

(protección adicional contra tipos no vacunales)

GARDASIL: DISEASE CROSS-PROTECTION ANALYSIS
END OF STUDY EFFICACY AGAINST CIN2/3 OR AIS

HPV information centre

HPV naïve population*

CIN2/3 or AIS Related to	GARDASIL® (n=8,461)	Placebo (n=8,508)	Efficacy	95% CI
10 non-vaccine oncogenic HPVs 31, 33, 35, 39, 45, 51, 52, 56, 58, 59	62	93	**33%**	(6,52)
HPV 31	8	27	**70%**	(32,88)

***Study population**: women seronegative to 6/11/16 and 18 and PCR negative to 6/11/16/18 plus 10 other high-risk types at day 1. Had normal cytology at day 1. Generally HPV naïve adolescents. Protocols 013 & 015 combined

These 10 non-vaccine HPV types cause ~20% of cervical cancer

Brown et al, JID 2009

GARDASIL®: CROSS-PROTECTION AGAINST CIN 2/3 OR AIS

Combined results from Future I/II END OF STUDY–
~4 year follow up in women 16 – 26 years

HPV type	Vaccine (*n* = 4616) Cases	Vaccine (*n* = 4616) Rate[a]	Placebo (*n* = 4680) Cases	Placebo (*n* = 4680) Rate[a]	Efficacy (95% CI), %
HPV-31 or -45	11	0.1	27	0.2	58.7 (14.1 to 81.5)
HPV-31, -33, -45, -52, or -58	44	0.3	66	0.4	32.5 (−0.3 to 55.0)
HPV-31, -33, -35, -39, -45, -51, -52, -56, -58, or -59	62	0.4	93	0.6	32.5 (6.0 to 51.9)
Nonvaccine A9 species (HPV-31, -33, -35, -52, or -58)[b]	44	0.3	69	0.4	35.4 (4.4 to 56.8)
HPV-31	8	<0.1	27	0.2	**70%** to 88.2)
HPV-33	12	0.1	16	0.1	24.0 (−71.2 to 67.2)
HPV-35	4	<0.1	4	<0.1	−1.5 (−444.9 to 81.1)
HPV-52	17	0.1	23	0.1	25.2 (−46.4 to 62.5)
HPV-58	16	0.1	20	0.1	18.9 (−64.7 to 60.7)
Nonvaccine A7 species (HPV-39, -45, or -59)[b]	11	0.1	21	0.1	47.0 (−15.0 to 76.9)
HPV-39	4	<0.1	10	<0.1	59.6 (−40.2 to 90.7)
HPV-45	3	<0.1	2	<0.1	−51.9 (−1717.8 to 82.6)
HPV-59	5	<0.1	9	<0.1	43.8 (−86.9 to 85.2)
HPV-51[b]	16	0.1	15	0.1	−8.1 (−134.7 to 50.0)
HPV-56[b]	12	0.1	16	0.1	24.1 (−71.1 to 67.2)

Brown et al, JID 2009

CERVARIX: VACCINE EFFICACY AGAINST INDIVIDUAL ONCOGENIC NON-VACCINE TYPES

HPV information centre

TVC-naïve

HPV type	6-month persistent infection			CIN2+		
	Vaccine n	Control n	Vaccine efficacy % (96.1% CI)	Vaccine n	Control n	Vaccine efficacy % (96.1% CI)
HPV-31	32	140	**77.5** (66.1-85.5)	0	20	**100** (78.3-100)
HPV-33	53	93	**43.5** (18.6-61.2)	5	18	**72.3** (19.1-92.5)
HPV-45	12	64	**81.4** (64.3-91.2)	0	5	100 (-19.5-100)*
HPV-51	217	294	**27.2** (12.1-39.8)	2	17	**88.3** (47.9-98.9)
HPV-52	202	253	**21.0** (3.6-35.3)	7	11	36.5 (-88.4-80.3)

LL of the 96.1% CI >0

*in the TVC: 0 vs 6 cases VE=100% (7.0-100)

Skinner SR et al. 25th International Papillomavirus Conference (Abstract O-29.01), 2009

EFFICACY AGAINST CIN2+
IRRESPECTIVE OF HPV TYPE IN THE LESIONS

HPV information centre

TVC-naïve – two different studies

	Vaccine	Control	VE (%)	Confidence interval
CIN2+ (any HPV type)				
Gardasil*	NA	NA	**42.7**	23.7 - 57.3

*http://www.emea.europa.eu/humandocs/PDFs/EPAR/gardasil/H-703-PI-en.pdf - pag 9.
Includes 17,599 subjects enrolled in protocols 013 & 015
NA= not available
Among subjects who were naïve to 14 common HPV types and had a negative Pap test at Day

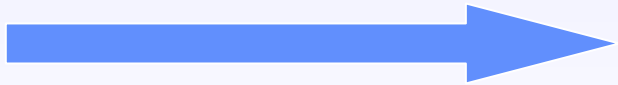
	Vaccine	Control	VE (%)	Confidence interval
CIN2+ (any HPV type)				
Cervarix*	33	110	**70.2**	54.7 - 80.9

*Paavonen J *et al.* 25th International Papillomavirus Conference (Abstract O-29.06), 2009.
Naïve to all oncogenic types and with normal cytology

Cervarix: potencial preventivo asumiendo protección cruzada

La eficacia de la protección cruzada de Cervarix® podría suponer una protección adicional frente al cáncer de cérvix de 11-16%

~70%
(VPH 16/18)



~ 81-86%
(Tipos No Vacunales)

Reducción de citologías y procedimientos derivados

Reducción de citologías procedimientos derivados

Jorma Paavonen for the PATRICIA HPV Study Group. Lancet 2009: 374: 301 – 14
Comunicación SS 4-1 a EUROGIN 2010. Monte Carlo.

	% Reducción
ASCUS	88.2
LSIL	92.6
HSIL	93.4
Colposcopias	26.3
Tratamientos	68.8

Coste anual del manejo del CIN en España: 147.284.811 €
Castellsagué X: Prog Obstet Ginecol 2008; 51: 520 - 30

Cortesía del Dr. Cortés. (Marzo 2010)

Reducción de citologías procedimientos derivados

Olsson S: Comunicación 0 – 01-08 a la 25IPV 2009, Malmö.
Iversen OE.: Comunicación SS 4-4 a EUROGIN 2010, Monte Carlo.

Seguimiento medio 3.6 años.	% Reducción
ASC.US	23%
ASC.H	35%
LSIL	16%
HSIL	43%
TRATAMIENTOS	42%

Aplicación en España de este potencial

17.627 resultados citológicos anómalos anuales menos para mujeres entre 15 y 24 años.

Cortés J: Prog Obstet Ginecol 2009; 52: 360 - 8.

Cortesía del Dr. Cortés. (Marzo 2010)

Impacto en las recidivas

IMPACTO DE LA VACUNACION EN MUJERES DESPUÉS DE TRATAMIENTO DEFINITIVO

Joura E.: Comunicación SS 4-3 a EUROGIN 2010, Monte Carlo.

Eficacia medida en términos de reducción observada en la reaparición de la lesión tratada o nueva lesión entre la cohorte vacunada (n: 587) y la cohorte placebo (n: 763)
Mujeres 16-26 años. 3,6 años de seguimiento

LESIÓN NUEVAS ASOCIADAS A LOS VPH 6/11/16/18	EFICACIA
CIN 1+	74%
Lesion Genital Externa	79%

LGE: VIN 1+, VaIN 1+, Verrugas Genitales

Gardasil® ofrece protección alta frente al riesgo de recidiva / 2ª lesión en pacientes tratadas por lesiones VPH del tracto genital inferior

Seguridad

- **Datos de los ensayos clínicos:**
  - Información de alta calidad: aleatorización, doble-ciego y controlado con placebo
  - No es útil para eventos adversos raros (<1 en 5.000)
- **Datos post-comercialización:**
  - Para identificar efectos adversos no vistos en los ECA
  - Proviene de sistemas de monitorización/notificación de eventos adversos
  - La atribución de causalidad requiere estudios epidemiológicos

TODAS las autoridades sanitarias CONFIRMAN una y otra vez la SEGURIDAD de las vacunas VPH

London, 24 January 2008
Doc. Ref. EMEA/37479/2008

PRESS RELEASE
EMEA statement on the safety of Gardasil

The European Medicines Agency (EMEA) has received reports of deaths in women who had previously received Gardasil, including two reports concerning the sudden and unexpected deaths of two young women in the European Union (EU). Gardasil is a vaccine approved in the EU for the prevention of cervical cancer and other diseases caused by human papillomavirus (HPV) types 6, 11, 16 and 18. It is estimated that about 1.5 million patients have been vaccinated with this HPV vaccine in Europe.

The two European cases were reported as part of the continuous monitoring of the safety of medicines. One of the cases occurred in Austria and the other in Germany. In both cases, the cause of death could not be identified. No causal relationship has been established between the deaths of the young women and the administration of Gardasil.

On the basis of the currently available evidence, the EMEA's Committee for Medicinal Products for Human Use (CHMP) is of the opinion that the benefits of Gardasil continue to outweigh its risks and that no changes to its product information are necessary.

The
new

¡¡60 millones de dosis!!

2009, 84, 37–40 No. 5

World Health Organization
Organisation mondiale de la Santé

Weekly epidemiological record
Relevé épidémiologique hebdomadaire

30 JANUARY 2009, 84th YEAR / 30 JANVIER 2009, 84e ANNÉE
No. 5, 2009, 84, 37–40
http://www.who.int/wer

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Le Comité consultatif mondial de la Sécurité

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Vaccine Safety

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Vaccine Safety Home > Vaccine Adverse Event Reporting System (VAERS)

Vaccine Safety Basics
- Information for Parents
- Why It's Important to Monitor Vaccine Safety
- How Vaccines Are Tested and Monitored
- Common Questions
- Vaccine Safety Concerns
- History of Vaccine Safety

Public Health Activities
- Vaccine Adverse Event Reporting System (VAERS)
  - Publications

Reports of Health Concerns Following HPV Vaccination

HPV Vaccine Safety

The safety of the HPV vaccine was studied in 5 clinical trials before it was licensed. There were over 21,000 girls and women ages 9 through 26 in these clinical trials.

Since it was licensed, CDC and FDA have been closely monitoring the safety of the HPV vaccine. There are 3 systems used to monitor the safety of vaccines after they are licensed and being used in the U.S. These systems can monitor side effects already known to be caused by vaccines as well as detect rare side effects that were not identified during a vaccine's clinical trials. The 3 systems are:

Quick Links
- HPV and HPV Disease Information
- HPV Vaccine Information
- Vaccine Safety Information
- HPV Questions and Answers
- FDA Center for Biologics Evaluation and Research
- To Report an Adverse Event in VAERS
- Related Information on Guillain-Barré Syndrome
- Information from FDA and CDC on Gardasil and its Safety

Press Release

Conclusions of the AEMPS Expert Panel on the safety of the human papilloma virus vaccine

23 April 2009

Regarding the administration of the human papilloma virus vaccine, and the two suspect cases of an adverse reaction in the Region of Valencia, the Expert Panel gathered by the Spanish Medicines and Health Products Agency (AEMPS) has issued its conclusions:

The Committee has examined the data of the cases communicated to the Spanish Pharmacovigilance System, and to the European database, where the term "convulsions" appears after administration of the human papilloma virus vaccine. Especially, the Committee examined in depth the cases of the adolescents from Valencia who were object of the alert, including the different

1. EMEA statement on the safety of GARDASIL®. EMEA/37479/2008. http://www.emea.eu/humandocs/PDFs/EPAR/gardasil/Gardasil_press_release.pdf - last accessed on 08.06.09. 2. Centers for Disease control website. Available at: http://www.cdc.gov/vaccinesafety/vaers/gardasil.htm- last accessed on 24.04.09. 3. RELEVE EPIDEMIOLOGIQUE HEBDOMADAIRE, No 5, 30 JANVIER 2009. 4. Press release Spain MINISTERIO DE SANIDAD Y POLÍTICA SOCIAL 23.04.2009

CERVARIX SAFETY UK

Drug Safety Update

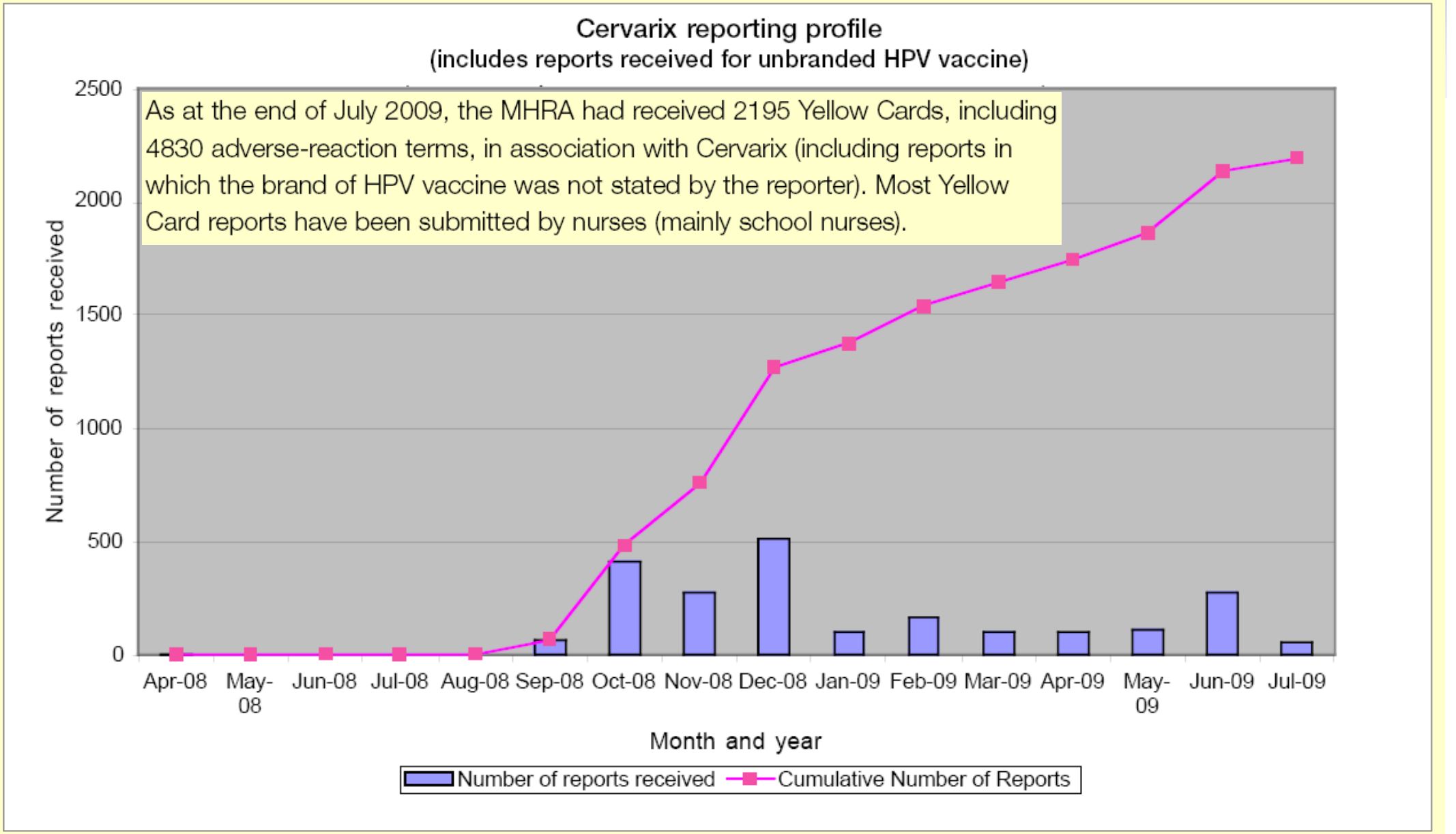
Volume 3, Issue 3 **October 2009** from MHRA and CHM

Human papillomavirus (HPV) immunisation programme—first year safety review

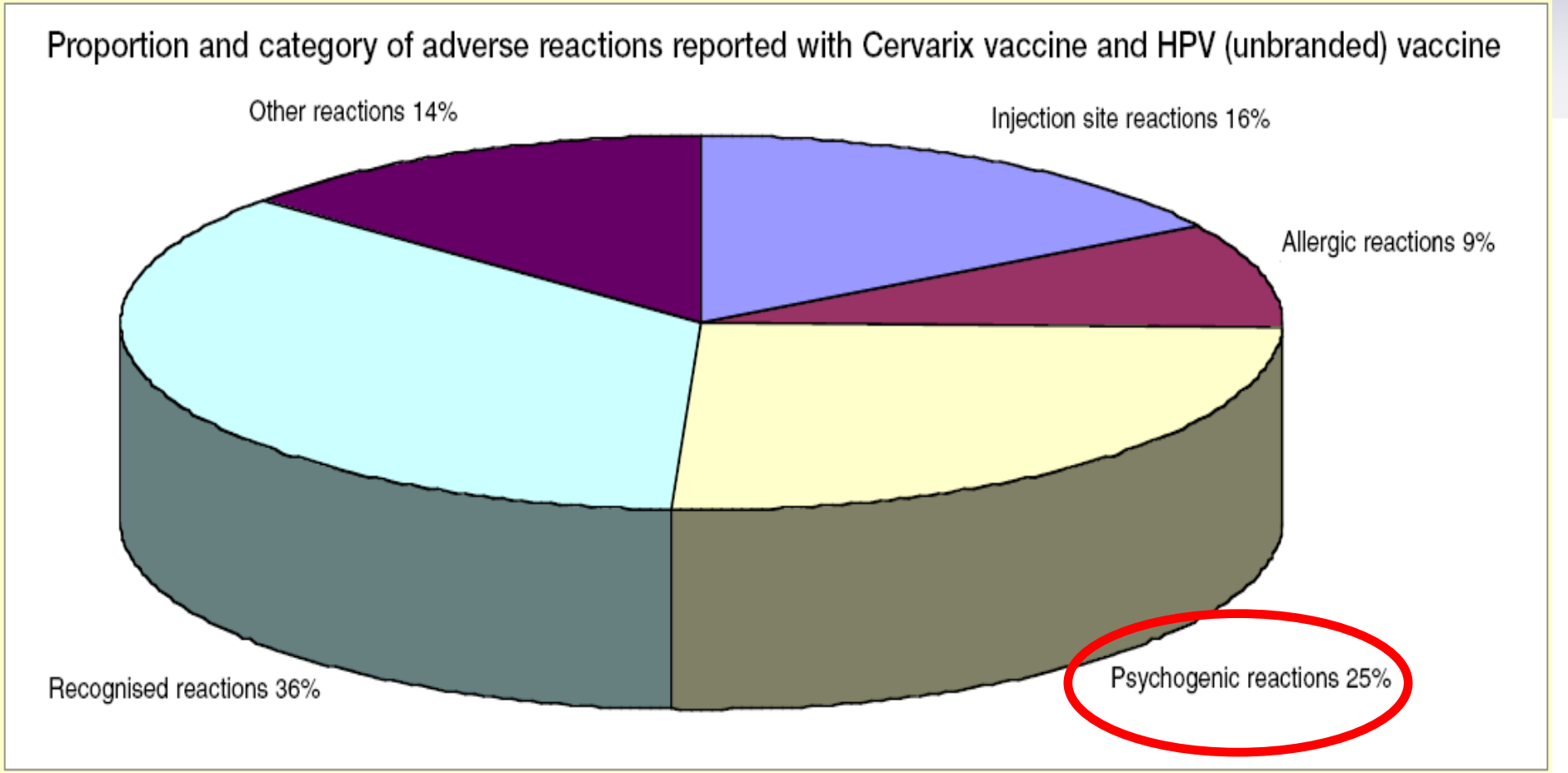
Yellow Card Scheme update

- The total number and nature of suspected side effects reported via the Yellow Card Scheme during the first year of the Cervarix vaccination programme has been very much as expected
- Most reports have related to the signs and symptoms of recognised side effects, which are generally not serious
- No new risks have been identified, and the balance of risks and benefits remains positive
- As with all vaccines, the MHRA and Commission on Human Medicines (CHM) will continue to monitor closely the safety of Cervarix during continued use in the UK

Number of reports received between April 2008 and July 2009:



Type of adverse reactions reported to the Yellow Card Scheme:



Psychogenic events include vasovagal syncope, faints, panic attacks, and associated symptoms. These can occur with any injection procedure, not only vaccination, and can be common in adolescents. Such events can be associated with a wide range of temporary signs and symptoms, including: loss of consciousness; vision disturbance; injury; limb jerking (often misinterpreted as a seizure or convulsion); limb numbness or tingling; and difficulty in breathing or hyperventilation. These are due to fear or anticipation of the needle injection and are not side effects of Cervarix vaccine as such. More information on the specific adverse reactions reported can be found at www.mhra.gov.uk/hpvvaccine.

Safeguarding public health

MHRA

Suspected Adverse Reaction Analysis

CERVARIX Human papillomavirus (HPV) vaccine

6 May 2010

SUMMARY OF UK SAFETY EXPERIENCE

Total number of reports received: 3,896
Total number of suspected reactions: 8,700
Estimated number of doses administered across the UK: at least 3.5 million doses[3]

Headline summary:

The vast majority of suspected adverse reactions reported to MHRA in association with Cervarix vaccine continue to be related to either the signs and symptoms of recognised side effects listed in the product information or to the injection process and not the vaccine itself (i.e. 'psychogenic' in nature such as faints).

For the isolated cases of other medical conditions reported, the available evidence does not suggest that the vaccine caused the condition and these may have been coincidental events.

Following administration of more than 3.5 million doses across the UK since last September, the balance of risks and benefits of Cervarix remains positive.

Primeras evidencias de impacto poblacional

Rapid decline in presentations of genital warts after the implementation of a national quadrivalent human papillomavirus vaccination programme for young women

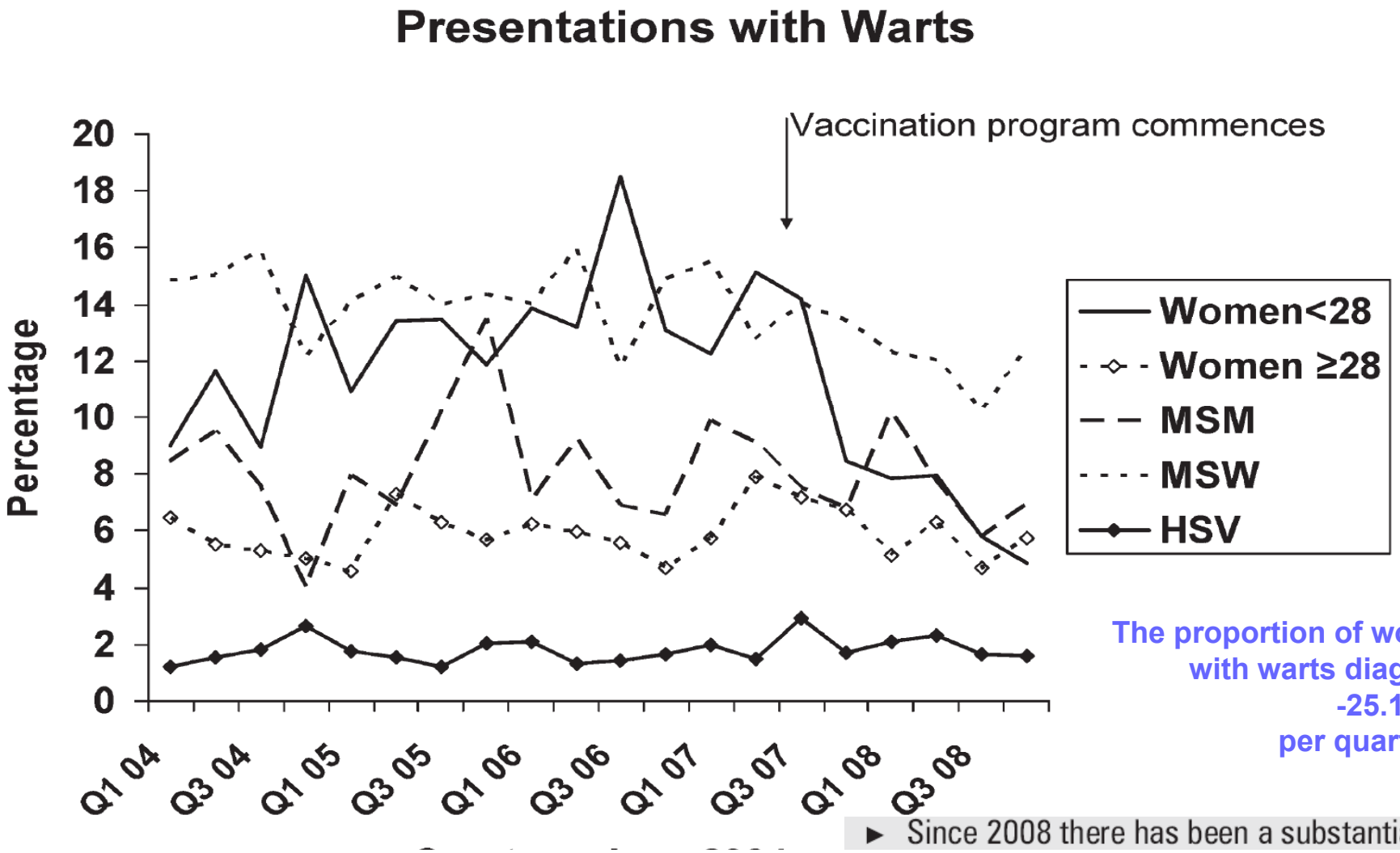
C K Fairley,[1] J S Hocking,[2] L C Gurrin,[3] M Y Chen,[1] B Donovan,[4] C S Bradshaw[5]

Sex Transm Inf published online 16 Oct 2009

- Australia began a free quadrivalent HPV vaccination programme in mid-2007 for schoolgirls and women under 28 years of age, with coverage of approximately 70%.

Fairley et al, Sexually Transmitted Infections 2009

Australia- reducción de verrugas genitales



The proportion of women under 28 years with warts diagnosed decreased by -25.1% (-30.5% to -19.3%) per quarter in 2008 (p<0.001).

Reducción en varones heterosexuales pero no en varones homosexuales

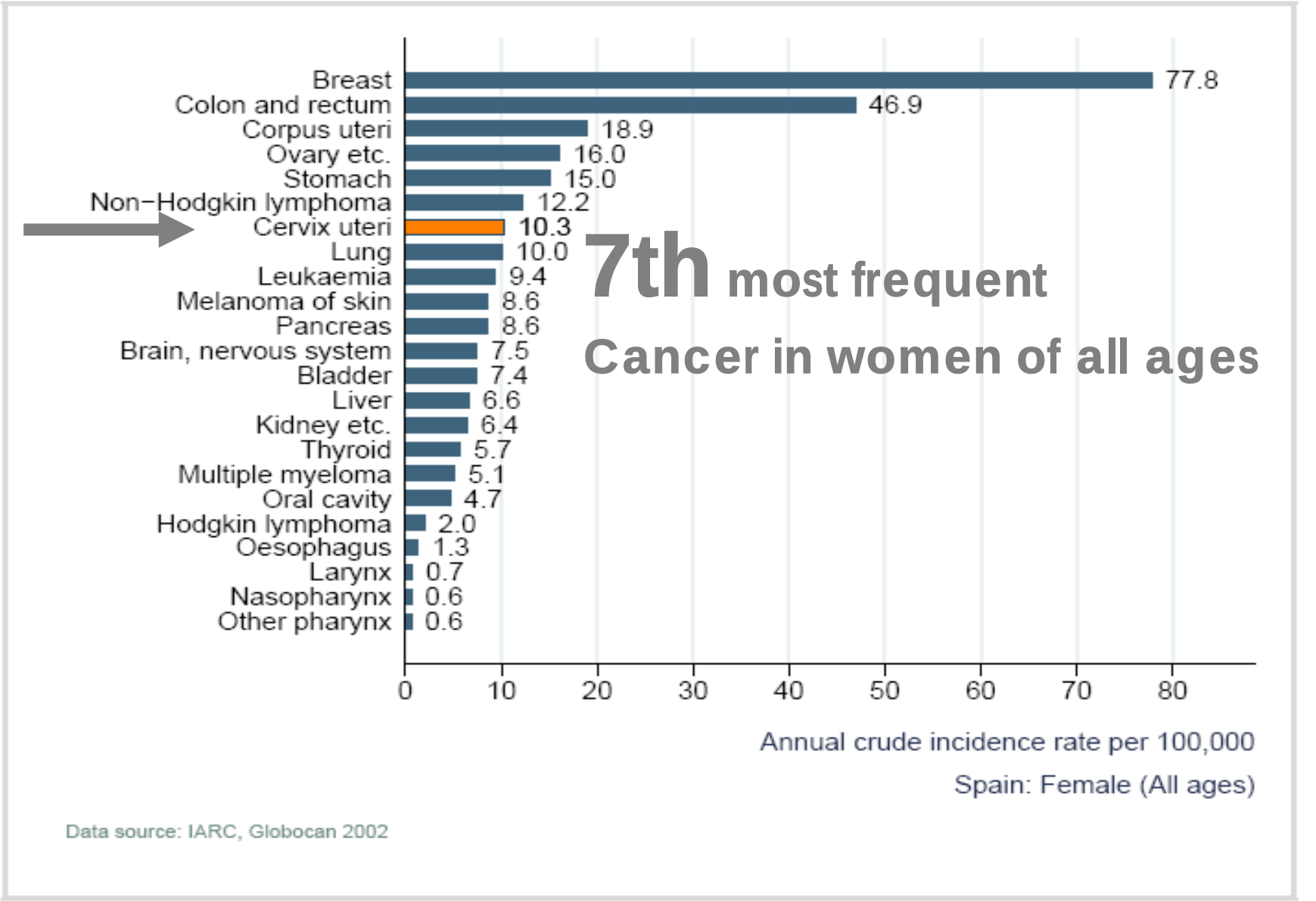
Primeros datos de beneficios "indirectos"

HS
MS
MSW, men who have had sex with women but not men in the past year.

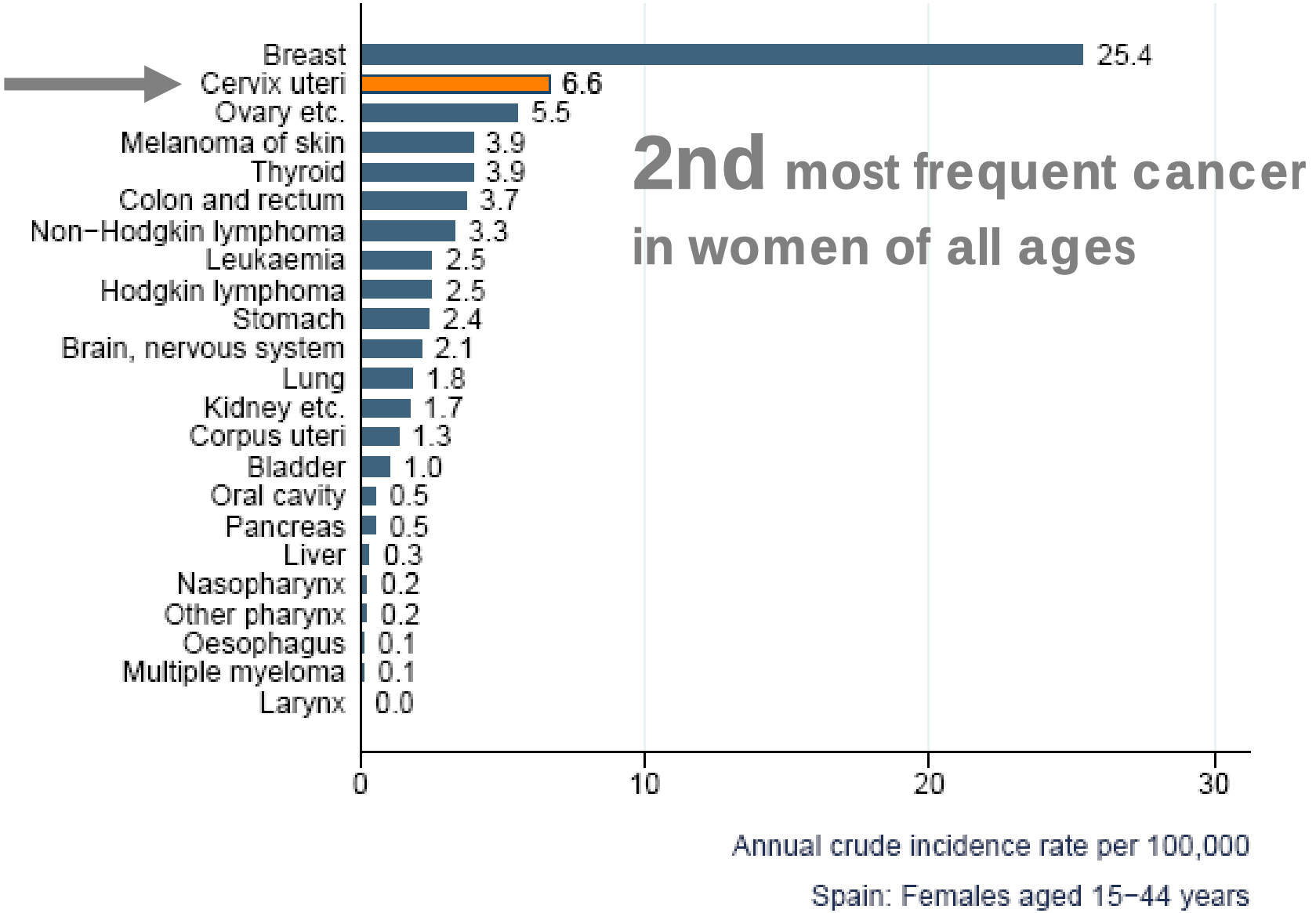
► Since 2008 there has been a substantial and significant decline
ger, but
lth clinic.
enital
warts in heterosexual but not homosexual men.

Consideraciones epidemiológicas de la introducción de las vacunas VPH en España

Most frequent cancers in women in Spain (all ages)



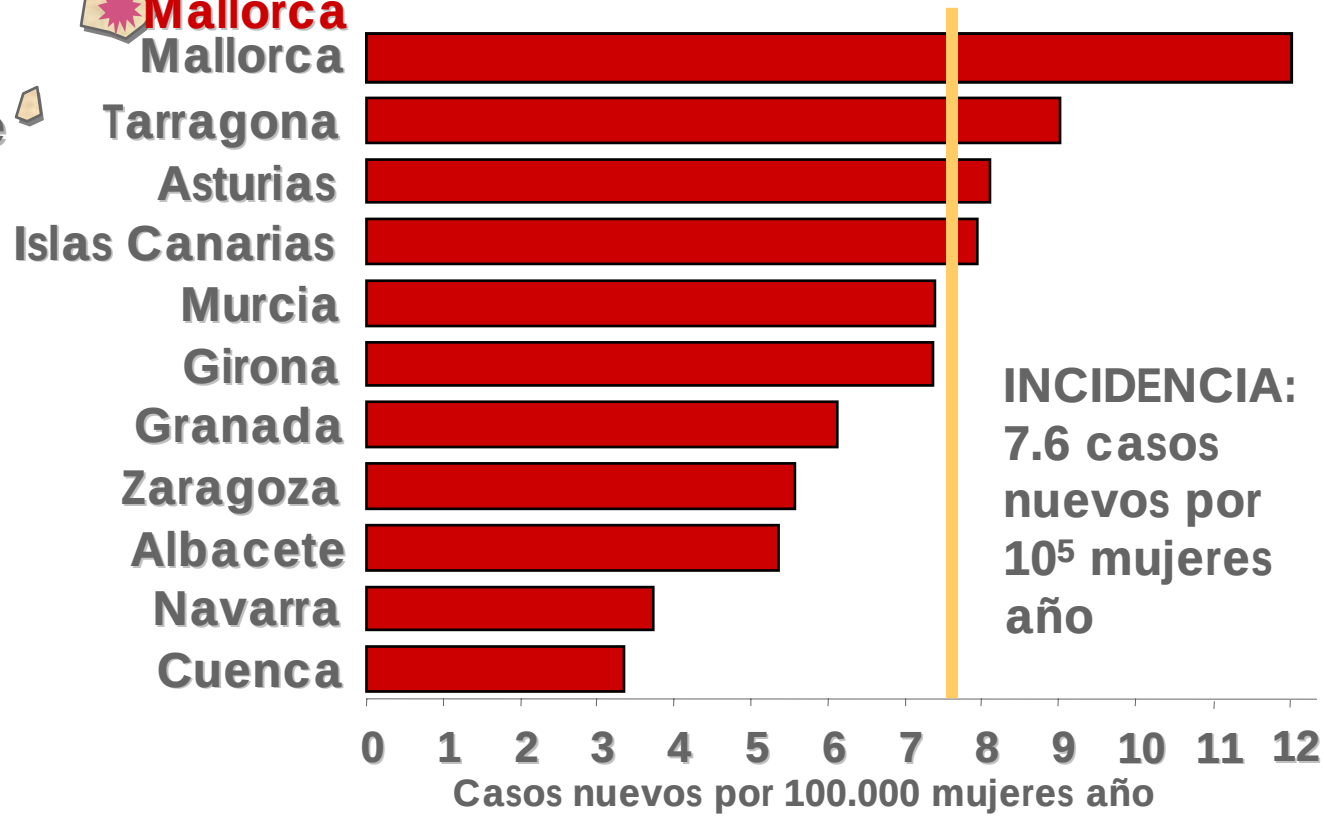
Most frequent cancers in women in Spain (15-44 years old)



Data source: IARC, Globocan 2002

INCIDENCIA DEL CÁNCER DE CÉRVIX EN ESPAÑA

2.103 casos nuevos por año (739 muertes)

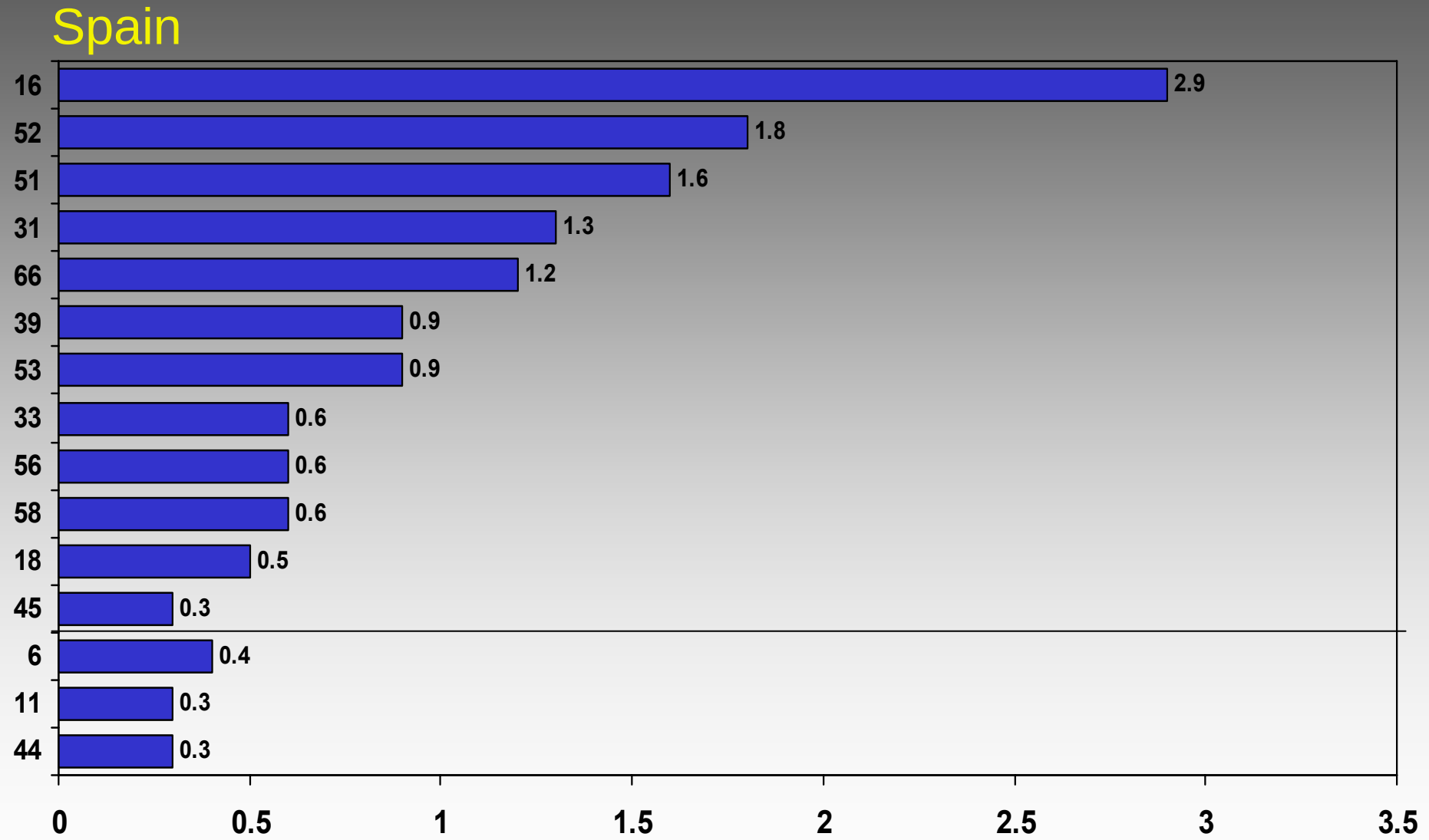


INCIDENCIA: 7.6 casos nuevos por 10^5 mujeres año

Fuente: CI5C VIII, IARC Globocan 2002

Type-specific HPV distribution by INNO-LiPA

(age-standardized to the Spanish female population)



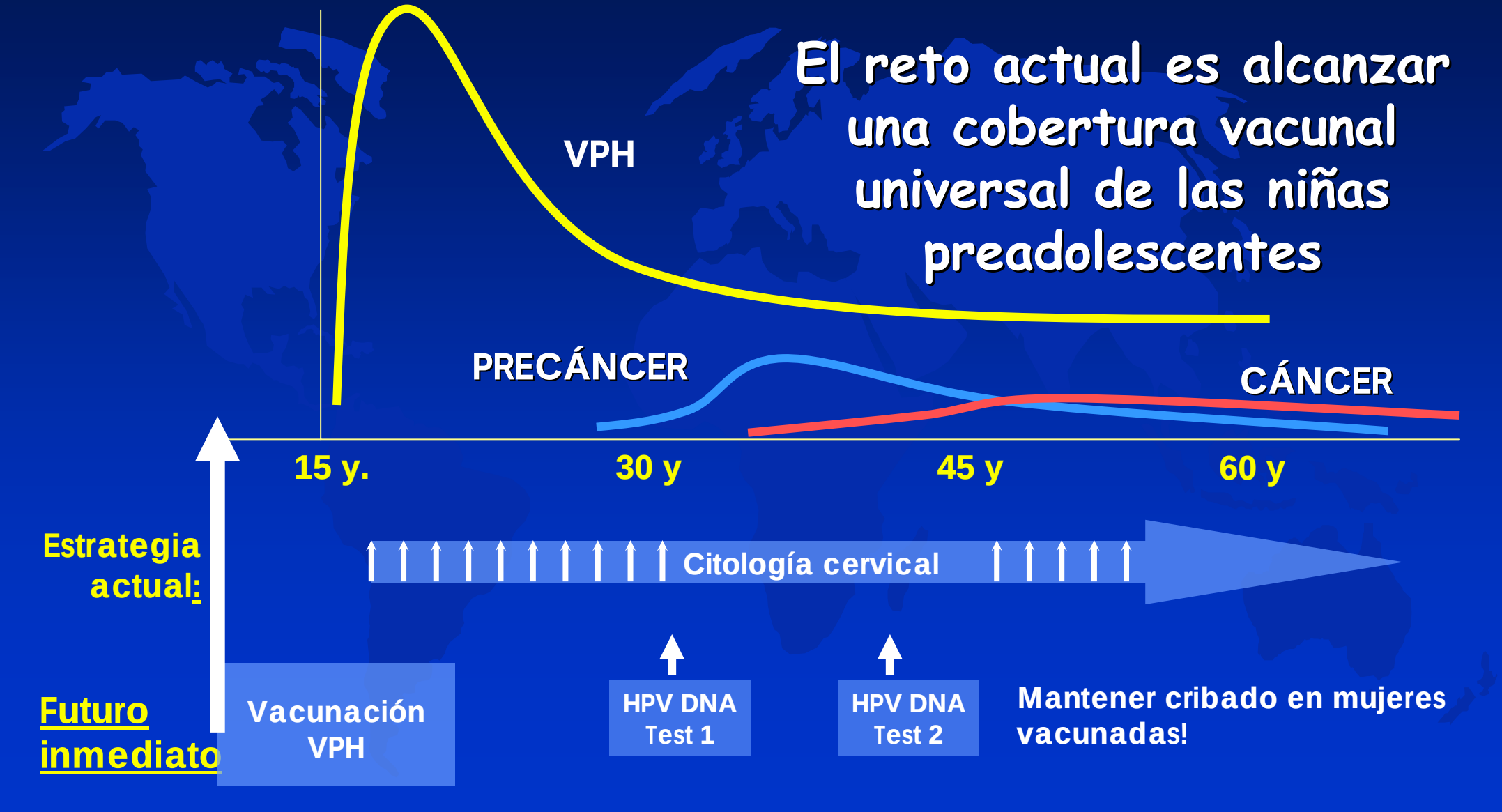
Nota: Distribución entre el total de mujeres. Numerador: infecciones; denominador: mujeres.

Prevención del cáncer de cuello de útero

¿Un nuevo escenario?

Vamos hacia una prevención basada en el VPH

El nuevo escenario de la prevención del cáncer de cuello de útero



Gracias por su atención