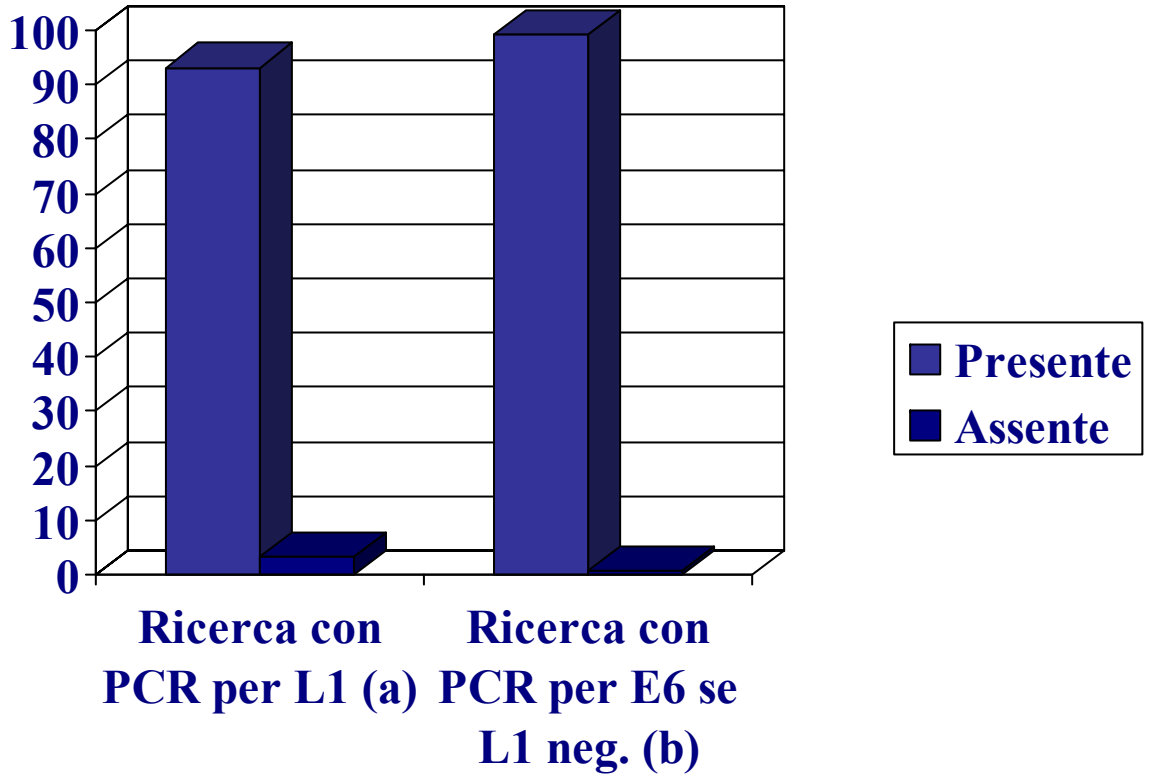
# Vaccini profilattici HPV

- Gardasil (Merck/Sanofi-Pasteur).
  Tipi 6,11,16,18.
- Registrato EMEA e AIFA  classe HRR.
  Fornito gratuitamente dal SSN su invito attivo alle adolescenti di 12 anni da inizio 2008. Altrimenti in vendita in farmacia fino a 26aa (“copagamento”?).
- Cervarix (Glaxo)
  Tipi 16 e 18.  In registrazione

# Presenza di HPV (qualsiasi tipo) in 932 tumori invasivi della cervice

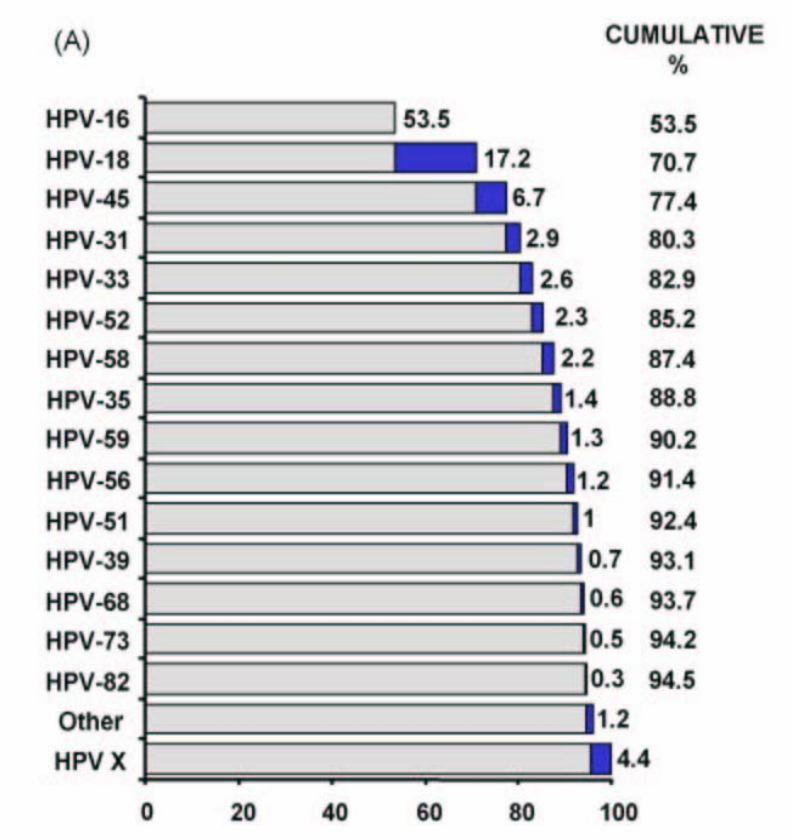



(a) Bosch et al - J.Natl Cancer Inst. 1995, 87:796-802

(b) Walboomers et al. - J. Pathol. 1999; 189:12-9

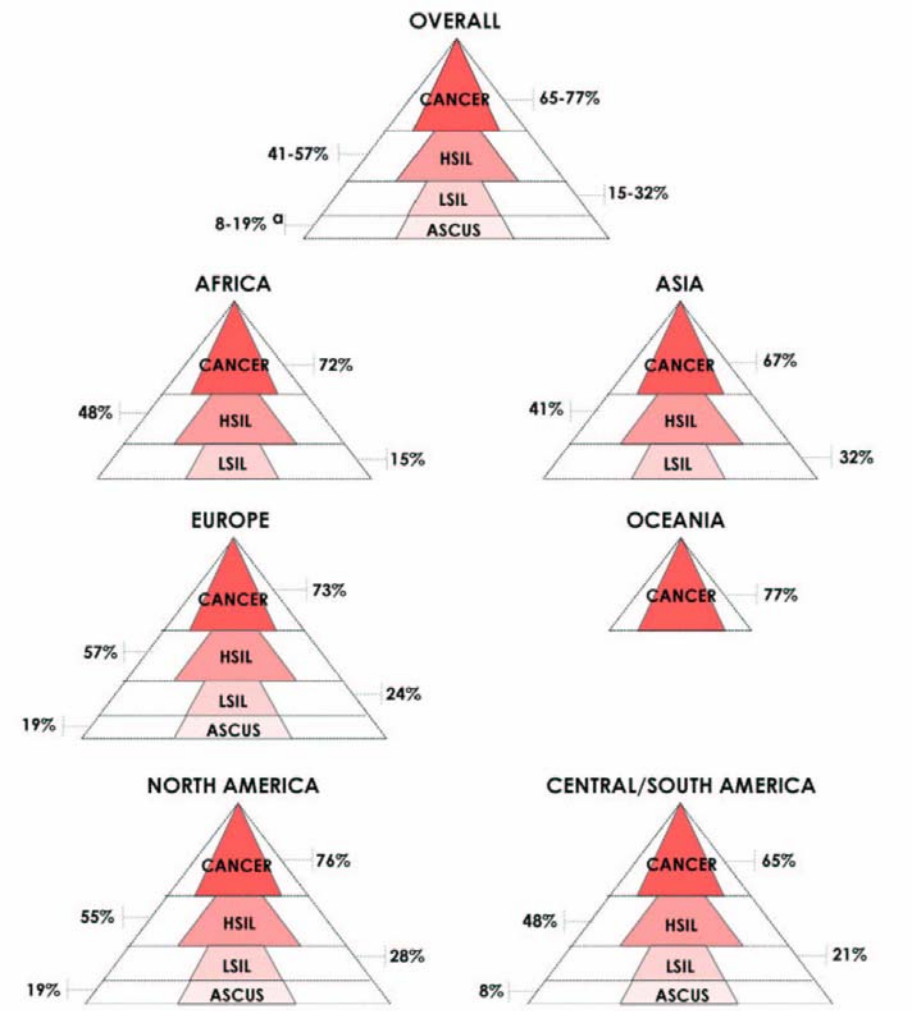
*G. Ronco - CPO Piemonte*

# % cervical cancer attributed to the most frequent HPV types worldwide




**Munoz et al. Int J Cancer 2004;111:258-85.**

# Estimated HPV16/18 positive among cervical abnormalities




**Clifford et al. Vaccine 2006;24 Suppl3:S26-S34.**

# Gardasil - Vaccine efficacy against CIN2/3/ACIS - Average 3-yr FU

| End Point | Vaccine Group (N=6087) | | | Placebo Group (N=6080) | | | Vaccine Efficacy |
|---|---|---|---|---|---|---|---|
| | Total Subjects | No. of Cases | Rate | Total Subjects | No. of Cases | Rate | %(95%CI) |
| **Lesions associated with any HPV -16 or HPV-18** | | | | | | | |
| **Subjects in per-protocol susceptible population** | 5305 | 1 | <0.1 | 5260 | 42 | 0.3 | 98(86-100) |
| Lesion type | | | | | | | |
| Cervical intraepithelial neoplasia grade 2 | 5305 | 0 | 0 | 5260 | 28 | 0.2 | 100(86-100) |
| Cervical intraepithelial neoplasia grade 3 | 5305 | 1 | <0.1 | 5260 | 29 | 0.2 | 97(79-100) |
| Adenocarcinoma in situ | 5305 | 0 | 0 | 5260 | 1 | <0.1 | 100(<0-100) |
| **Subjects in intention-to-treat population** | 6087 | 83 | 0.5 | 6080 | 148 | 0.8 | 44(26-58) |
| Lesion type | | | | | | | |
| Cervical intraepithelial neoplasia grade 2 | 6087 | 41 | 0.2 | 6080 | 96 | 0.5 | 57(38-71) |
| Cervical intraepithelial neoplasia grade 3 | 6087 | 57 | 0.3 | 6080 | 104 | 0.6 | 45(23-61) |
| Adenocarcinoma in situ | 6087 | 5 | <0.1 | 6080 | 7 | <0.1 | 28(<0-82) |

**FUTUREII Study Group. N Engl J Med 2007;356:1915-27 modif.**

# Gardasil - Vaccine efficacy against CIN2/3/ACIS

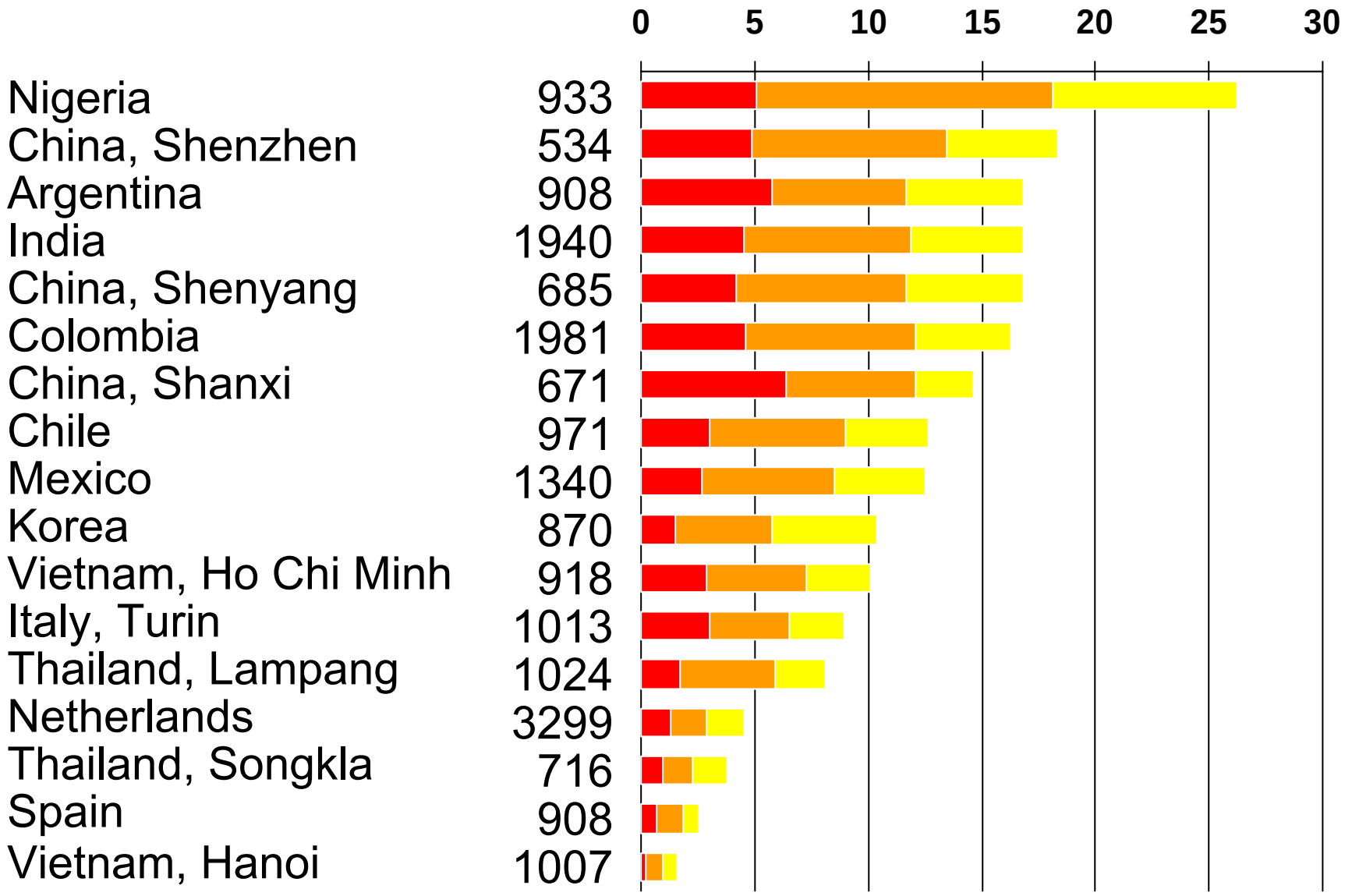
## Average 3-yr FU

| End Point | Vaccine Group (N=6087) | | | Placebo Group (N=6080) | | | Vaccine Efficacy |
|---|---|---|---|---|---|---|---|
| | Total Subjects | No. of Cases | Rate | Total Subjects | No. of Cases | Rate | %(95%CI) |
| **Lesions associated with any HPV type** | | | | | | | |
| **Subjects in intention-to-treat population** | 6087 | 219 | 1.3 | 6080 | 266 | 1.5 | 17 (1-31) |
| Lesion type | | | | | | | |
| Cervical intraepithelial neoplasia grade 2 | 6087 | 149 | 0.9 | 6080 | 192 | 1.1 | 22 (3-38) |
| Cervical intraepithelial neoplasia grade 3 | 6087 | 127 | 0.7 | 6080 | 161 | 0.9 | 21 (<0-38) |
| Adenocarcinoma in situ | 6087 | 5 | <0.1 | 6080 | 8 | <0.1 | 37 (<0-84) |

**FUTUREII Study Group. N Engl J Med 2007;356:1915-27 modif.**

# Prevalence of cervical HPV DNA in sexually active women

## IARC Multi-centre HPV Prevalence Survey, 1995-2002




Clifford et al. Lancet 2005;366:991-98 modif.

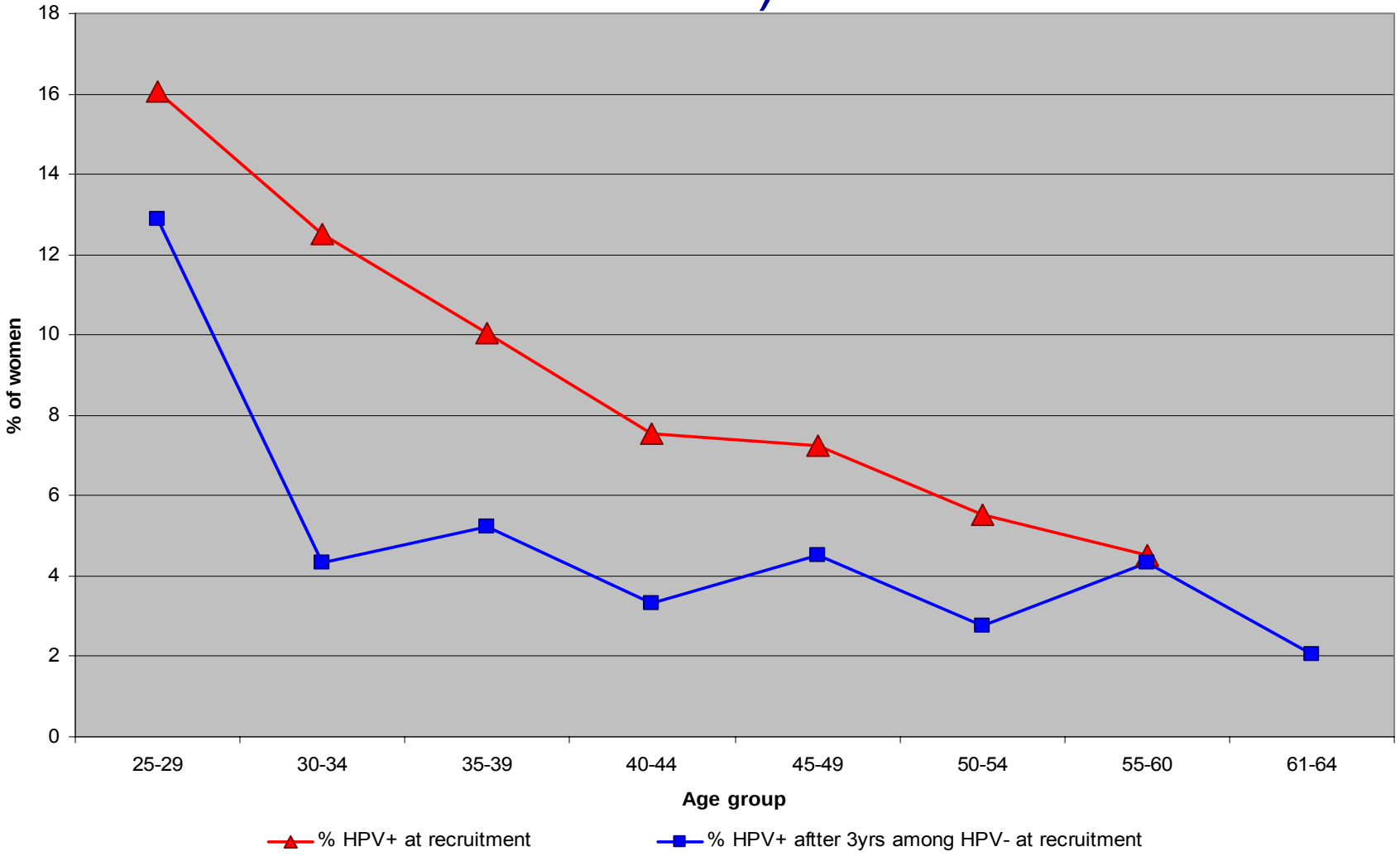
# NTCC STUDY - Phase I
## Women age 25-34
## HPV clearance at re-testing
## Women previously HPV+ cytology-

| Interval (days) | N women | N HPV negative | % clearance (95% ci.i) |
|---|---|---|---|
| 180-365 | 118 | 59 | 50.0% (40.7-59.3) |
| 366-547 | 196 | 78 | 60.2% (53.0-67.1) |
| >547 | 13 | 9 | 69.2% (38.6-90.9) |
| All | 327 | 186 | 56.9% (51.3-62.3) |

Ronco et al. Lancet Oncol 2006; 7:547-55 (modified)

# NTCC study phase 1

## HPV (HC2) prevalence at recruitment and acquisition at 3 year follow-up (preliminary data)



# STUDIO NTCC

- Trial randomizzato multicentrico
- convenzionale vs. sperimentale (due fasi)
  - sperimentale fase 1: HPV+ citologia in fase liquida (LBC)
  - sperimentale fase 2: solo HPV
- In entrambi i bracci (convenzionale e sperimentale) citologia convenzionale dopo 3 anni

# NTCC STUDY PHASE 1 YRS 35-60 YRS

## Detection rate, positive predictive value (PPV), relative sensitivity and relative PPV for histology-confirmed CIN2+ vs conventional cytology ≥ASCUS

| | Endpoint CIN2+ | | | |
|---|---|---|---|---|
| | Detection Rate per 1000 | Relative sensitivity (95% CI) | PPV % | Relative PPV (95% CI) |
| | | **Experimental arm** | | |
| Liquid-based cytology ≥ ASCUS or HPV ≥1pg/mL | 4.49 | **1.47** (1.03 to 2.09) | 4.5 | **0.40** (0.23 to 0.66) |
| Liquid-based cytology ≥ASCUS | 3.23 | 1.06 (0.72 to 1.55) | 6.5 | 0.57 (0.39 to 0.82) |
| Liquid-based cytology ≥LSIL | 2.39 | 0.78 (0.52 to 1.18) | 12.7 | 1.11 (0.75 to 1.64) |
| HPV ≥ 1pg/mL | 4.37 | **1.43** (1.00 to 2.04)† | 6.6 | **0.58** (0.33 to 0.98) |
| HPV ≥ 2pg/mL | 4.25 | **1.41** (0.98 to 2.01) | 8.5 | **0.75** (0.45 to 1.27) |
| Liquid-based cytology ≥ ASCUS and HPV ≥1pg/mL | 3.11 | 1.02 (0.69 to 1.50) | 18.8 | 1.66 (1.16 to 2.36) |
| | | **Conventional arm** | | |
| Conventional cytology ≥ ASCUS | 3.06 | 1.00 (referent) | 11.4 | 1.00 (referent) |
| Conventional cytology ≥ LSIL | 2.52 | 0.82 (0.69 to 0.95) | 21.4 | 1.88 (1.60 to 2.06) |

Ronco et al. J. Natl.Cancer. Inst. 2006; 98: 765-74 modified

# Relative sensitivity and relative PPV(95% CI) for CIN2+ of HPV testing (1 RLU) vs. conventional cytology ≥ASCUS

## women age 35-60

| | Phase 2 | Phase1 | Combined | P heterogeneity between phases |
|---|---|---|---|---|
| **Relative sensitivity** | | | | |
| Experimental arm HPV≥1pg/ml | **1.92** (1.28-2.87) | **1.43** (1.00-2.04) | **1.63** (1.25-2.12) | **0.28** |
| Experimental arm HPV≥2pg/ml | **1.81** (1.20-2.72) | **1.41** (0.98-2.01) | **1.57** (1.20-2.06) | **0.37** |
| **Relative Positive Predictive Value** | | | | |
| Experimental arm HPV≥1pg/ml | **0.80** (0.55-1.18) | **0.58** (0.33-0.98) | **0.67** (0.52-0.87) | **0.22** |
| Experimental arm HPV≥2pg/ml | **0.99** (0.67-1.46) | **0.75** (0.45-1.27) | **0.85** (0.66-1.09) | **0.28** |

# NTCC STUDY PHASE 1 - WOMEN 25-34 yrs

## Relative sensitivity and relative PPV vs. conventional cytology ≥ ASCUS.

| Criteria for referral (retrospectively applied) | Endpoint CIN2+ | | | |
|---|---|---|---|---|
| | Detection Rate per 1000 | Relative sensitivity (95%CI) | PPV % | Relative PPV (95%CI) |
| **EXPERIMENTAL ARM** | | | | |
| Experimental procedure | 9.16 | 1.61 (1.05-2.48) | 8.5 | 0.55 (0.37-0.82) |
| LBC ≥ASCUS | 7.50 | 1.32 (0.84-2.06) | 9.0 | 0.58 (0.38-0.89) |
| HPV **≥1pg/ml**; triage HPV+ by cytology; if cytology <ASCUS repeat both tests and refer if **either** is positive | 9.00 | 1.58 (1.03-2.44) | 12.1 | 0.78 (0.52-1.16) |
| HPV **≥2pg/ml**; if cytology <ASCUS repeat both tests and refer if **either** is positive | 9.00 | 1.58 (1.03-2.44) | 13.0 | 0.84 (0.56-1.25) |
| HPV **≥1pg/ml**; if cytology <ASCUS repeat both tests and refer if **both** are positive | 8.83 | 1.55 (1.01-2.40) | 15.0 | 0.97 (0.65-1.44) |
| HPV **≥2pg/ml**; if cytology <ASCUS repeat both tests and refer if **both** are positive | 8.83 | 1.55 (1.01-2.40) | 15.8 | 1.02 (0.69-1.52) |
| LBC ≥ASCUS and HPV ≥ 1pg/ml | 7.33 | 1.29 (0.82-2.02) | 14.7 | 0.94 (0.62-1.43) |
| **CONVENTIONAL ARM** | | | | |
| Conventional Cytology ?ASCUS | 5.68 | 1.00 | 15.5 | 1.00 |

Ronco et al. Lancet Oncol 2006; 7:547-55

# Relative sensitivity and relative PPV(95% CI) for CIN2+ of HPV testing (1 RLU) vs. conventional cytology ≥ASCUS

## women age 25-34

| | Phase 2 | Phase1 | | P heterogeneity between phases |
|---|---|---|---|---|
| **Relative senstivity** | | | | |
| Experimental arm HPV≥1pg/ml | **3.50** (2.11-5.82) | **1.58** (1.03-2.44) | | **0.019** |
| Experimental arm HPV≥2pg/ml | **3.45** (2.08-5.74) | **1.58** (1.03-2.44) | | **0.021** |
| **Relative Positive Predictive Value** | | | | |
| Experimental arm HPV≥1pg/ml | **0.89** (0.55-1.44) | **0.78** (0.52-1.16) | | **0.67** |
| Experimental arm HPV≥2pg/ml | **0.99** (0.62-1.62) | **0.84** (0.56-1.25) | | **0.58** |

# NTTC STUDY PHASE 1 – all ages

## Relative Sensitivity and relative PPV of experimental (LBC) vs. conventional arm (conventional cytology)

| Histological endpoint | | | |
|---|---|---|---|
| | CIN1+ | CIN2+ | CIN3+ |
| Positive if Cytology ≥ASCUS | | | |
| % Detection Rate (N cases) conventional arm | 0.82 (184) | 0.37 (84) | 0.24 (53) |
| % Detection Rate (N cases) experimental arm & | 1.38 (313) | 0.44 (99) | 0.20 (45) |
| Relative Sensitivity* (95%c.i.) | 1.68 (1.40-2.02) | 1.17 (0.87-1.56) | 0.84 (0.56-1.25) |
| % PPV conventional arm | 27.84 | 12.7 | 8.02 |
| %PPV experimental arm& | 23.41 | 7.4 | 3.37 |
| Relative VPP* (95%c.i.) | 0.84 (0.72-0.98) | 0.58 (0.44-0.77) | 0.42 (0.29-0.62) |

& only CIN cases detected by cytology considered * experimental/conventional

**Ronco et al. BMJ 2007 in press**

# Specificity (95% CI) of Hybrid Capture2 at different cutoff for CIN2+

## by cytology and age

## NTCC study -phase 1

| | 1 RLU | 2 RLU | 4 RLU | 10 RLU | 20 RLU | Total No CIN2+ |
|---|---|---|---|---|---|---|
| Cytology ASCUS | | | | | | |
| age 25-34 | 56.8% (50.1-63.3) | 60.3% (53.6-66.7) | 62.5% (55.8-68.7) | 66.8% (60.3-72.9) | 72.5% (66.2-78.2) | 229 |
| age 35-60 | 77.3% (73.4-80.9) | 82.5% (78.9-85.7) | 85.1% (81.6-88.1) | 87.7% (84.5-90.4) | 88.7% (85.5-91.3) | 502 |
| Cytology LSIL | | | | | | |
| age 25-34 | 31.5% (25.1-38.5) | 35.0% (28.4-42.1) | 37.1% (30.3-44.2) | 38.6% (31.8-45.8) | 41.6% (34.7-48.8) | 197 |
| age 35-60 | 61.3% (55.1-67.3) | 64.5% (58.3-70.3) | 67.2% (61.1-72.9) | 68.8% (62.7-74.4) | 70.7% (64.7-76.2) | 256 |

Ronco et al. *Europ J Cancer* 2007;43:476-80.

# DETECTION RATE AT RE-SCREENING
# WOMEN NEGATIVE AT RECRUITMENT

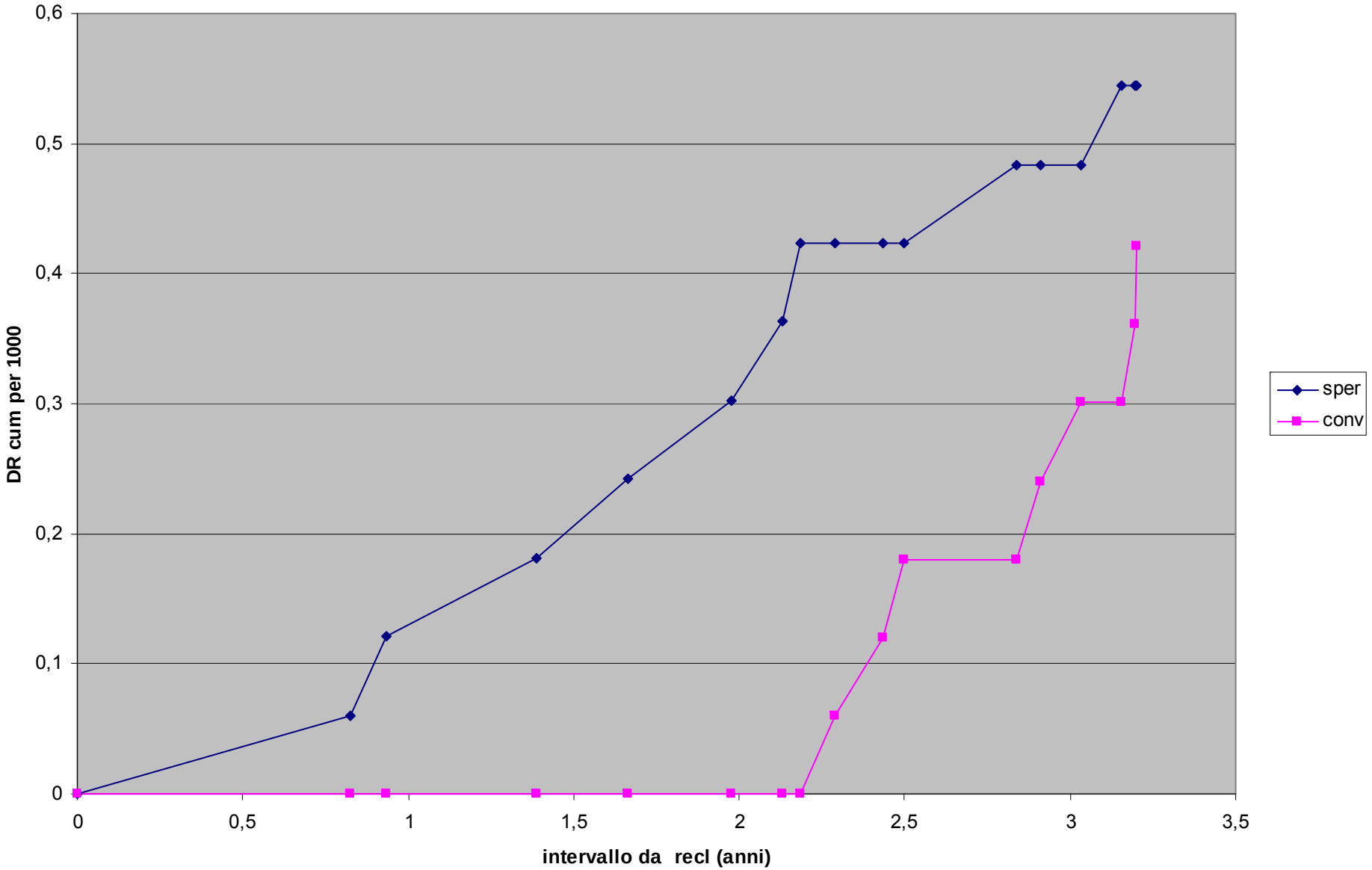
## All ages

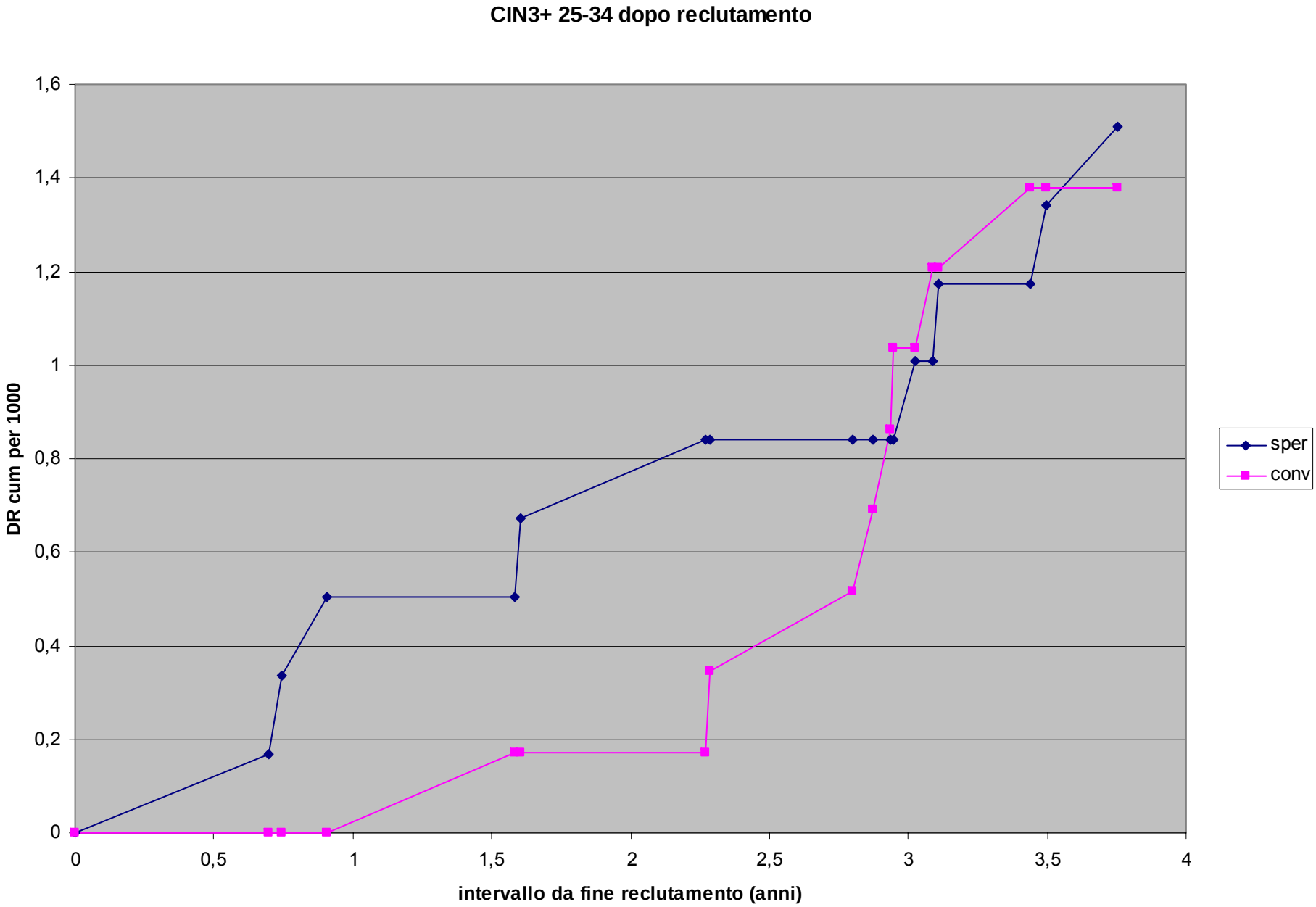
| | Total rescreened | CIN2+ | CIN3+ |
|---|---|---|---|
| **Experimental** | 15083 | 12<br>**0.08** | 3<br>**0.02** |
| **Conventional** | 15894 | 19<br>**0.12** | 12<br>**0.08** |
| **Total** | 30977 | 31 | 15 |
| **Relative DR (95%CI)** | | **0.67 (0.32-1.37)** | **0.26 (0.07- 0.93)** |

# DETECTION RATE AT RE-SCREENING
# WOMEN NEGATIVE AT RECRUITMENT

## Age 35-60

| | Total rescreened | CIN2+ | CIN3+ |
|---|---|---|---|
| **Experimental** | 11689 | 4<br>**0.03** | 1<br>**0.01** |
| **Conventional** | 12312 | 9<br>**0.07** | 7<br>**0.06** |
| **Total** | 24001 | 13 | 8 |
| **Relative DR (95%CI)** | | **0.46 (0.14- 1.52)** | **0.15 (0.02-1.22)** |


CIN3+ 35-60 dopo reclutamento
DR cum per 1000
0,6
0,5
0,4
0,3
0,2
0,1
0
0
0,5
1
1,5
2
2,5
3
3,5
intervallo da recl (anni)
sper
conv


CIN3+ 25-34 dopo reclutamento
DR cum per 1000
1,6
1,4
1,2
1
0,8
0,6
0,4
0,2
0
0
0,5
1
1,5
2
2,5
3
3,5
4
intervallo da fine reclutamento (anni)
sper
conv

# Vaccino HPV16 e 18 (Glaxo)

(Harper et al. Lancet 2004;364:1757-65)

- Trial randomizzato doppio cieco placebo
- 1113 donne età 15-25aa
- follow-up 27 mesi

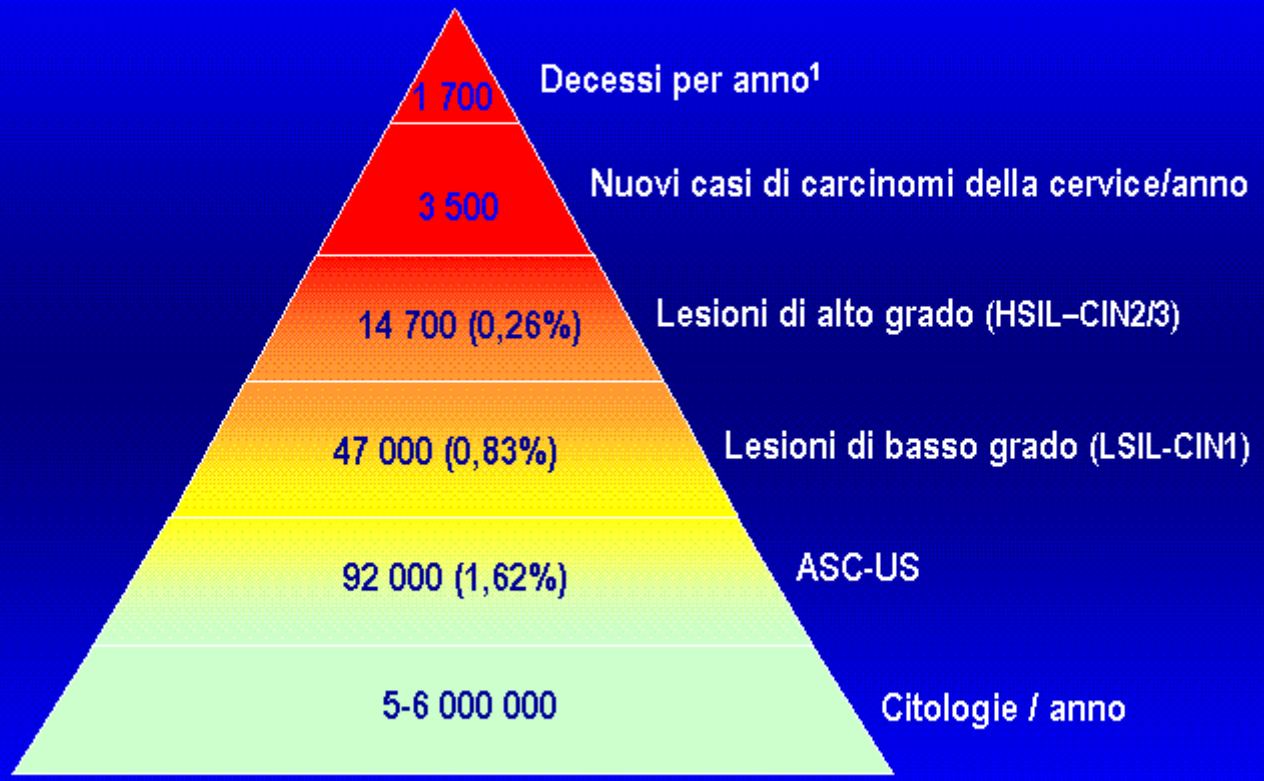
- Infezioni persistenti da HPV16/18 (per protocol) protezione 100% (95% ci 47.0-100)

# Vaccino HPV16/18 ulteriore follow-up

Harper et al. Lancet 2006;367:1247-55

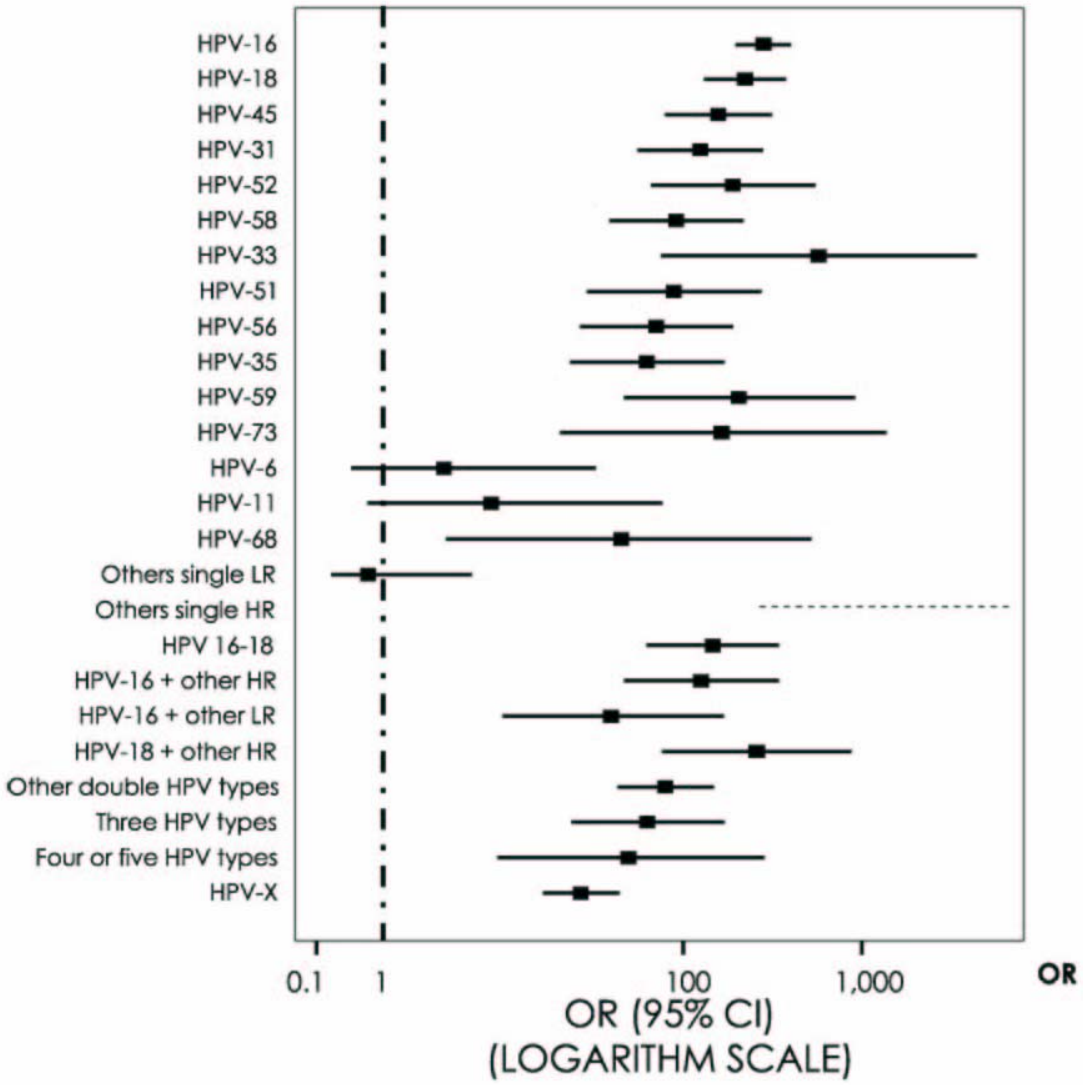
- Follow-up fino a massimo di 53 mesi
- Persiste protezione totale contro infezioni di durata almeno 12 mesi
- CIN2+ con HPV16 o 18
  placebo 5/470 vaccino 0/481
- Riduzione alterazioni citoistologiche anche da tipi 31(-54%) e 45 (-94%)

## 3% degli esami citologici presentano anomalie che necessitano ulteriori esami/trattamento. Italia, anni 2004 (Franceschi&Ronco)




IARC-ICE 2005

# Type specific ORs for cervical cancer




**Munoz et al. N.Engl.J.Med 2003;348:518-27 modif.**

# Centri Partecipanti

## Programmi Organizzati di screening:

- ***Piemonte***: Torino
- ***Trentino***: Trento
- ***Veneto***:
  - Verona e Padova
- ***Emilia Romagna***:
  - Imola, Ravenna, Bologna
- ***Toscana***: Firenze
- ***Lazio***: Viterbo

# Protocollo se HPV+

- **FASE 1**
- Se età > = 35 ⇒ colposcopia
- se età <35 ⇒ ripete entrambi dopo1 aa se citologia negativa (<ASCUS)
  - se HPV persiste o citologia + ⇒ colposcopia
  - se HPV regredisce ⇒ intervallo standard

- **FASE 2**
- Colposcopia indipendentemente dall'età

- Se HPV+ e **non lesioni** alla colposcopia

follow up (LBC e HPV annuali)

- se LBC+ → colposcopia
- quando entrambi negativi due volte ritorna a intervallo standard