Indicazioni, controindicazioni e limiti della vaccinazione HPV in età fertile

Carlo A. Liverani

Oncologia Ginecologica Preventiva

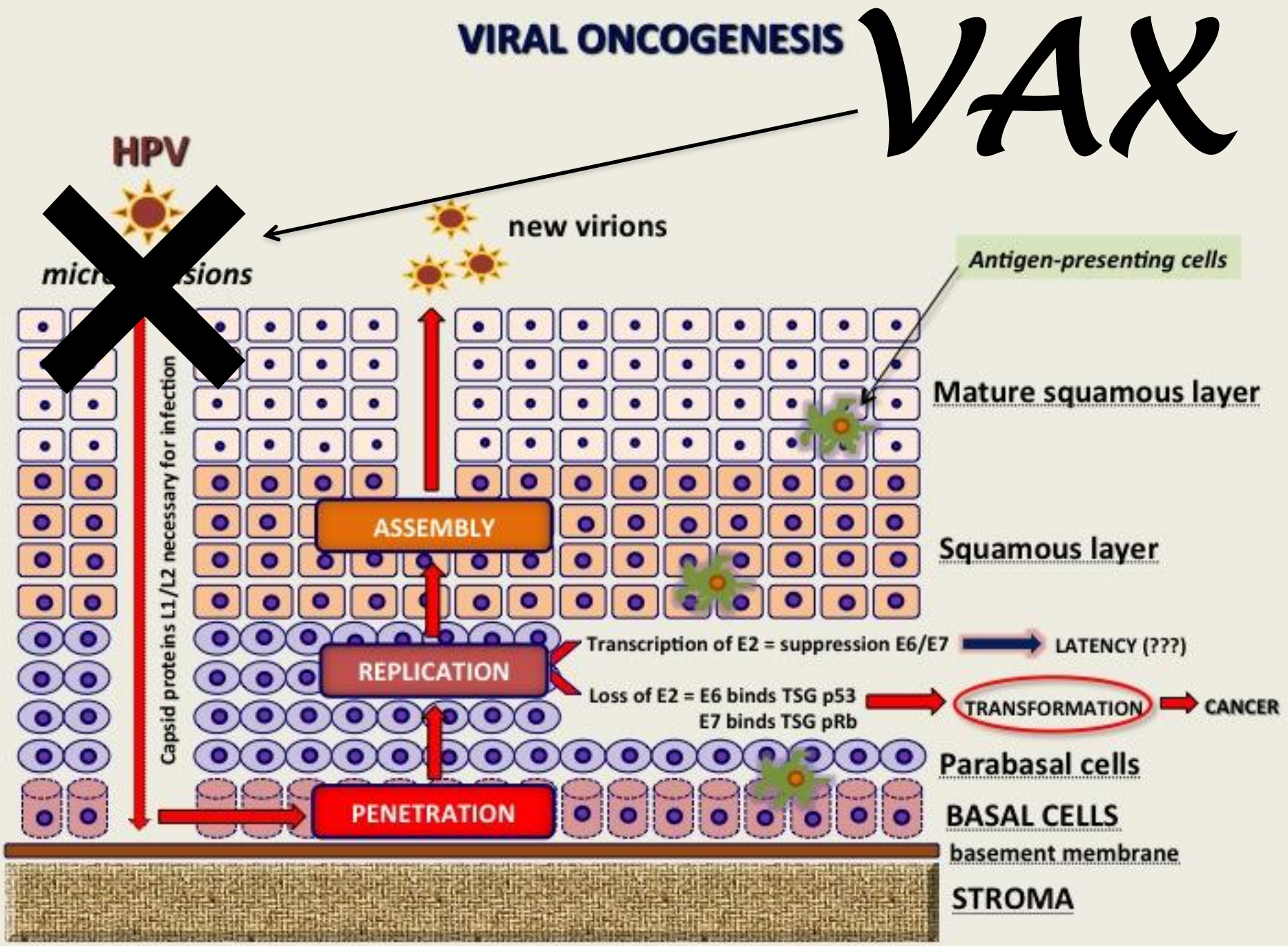
HUMANITAS
SAN PIO X

Il sottoscritto CARLO ANTONIO LIVERANI

ai sensi dell'art. 3.3 sul Conflitto di Interessi, pag. 17 del Reg. Applicativo dell'Accordo Stato-Regione del 5 novembre 2009,

dichiara

che NON ha mai avuto rapporti diretti di finanziamento con soggetti portatori di interessi commerciali in campo sanitario


VIRAL ONCOGENESIS
VAX
HPV
new virions
Antigen-presenting cells
Capsid proteins L1/L2 necessary for infection
Mature squamous layer
ASSEMBLY
Squamous layer
Transcription of E2 = suppression E6/E7
LATENCY (???)
REPLICATION
Loss of E2 = E6 binds TSG p53
E7 binds TSG pRb
TRANSFORMATION
CANCER
Parabasal cells
PENETRATION
BASAL CELLS
basement membrane
STROMA

Circa il 100% dei cancri cervicali sono causati dall'HPV

In EU: circa il 90% dei cancri anali, il 15% di quelli vulvari, il 70% di quelli vaginali, dal 30 al 40% di quelli penieni

Gardasil9
(HPV 6-11-16-18-31-33-45-52-58)

- femmine e maschi: 9-14 anni (due dosi)
- femmine e maschi: 15 anni e oltre (tre dosi)

- Almeno un mese fra 1a e 2a dose
- Almeno tre mesi fra 2a e 3a dose
- Ciclo vaccinale completato entro un anno

I benefici sono maggiori rispetto ai rischi

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

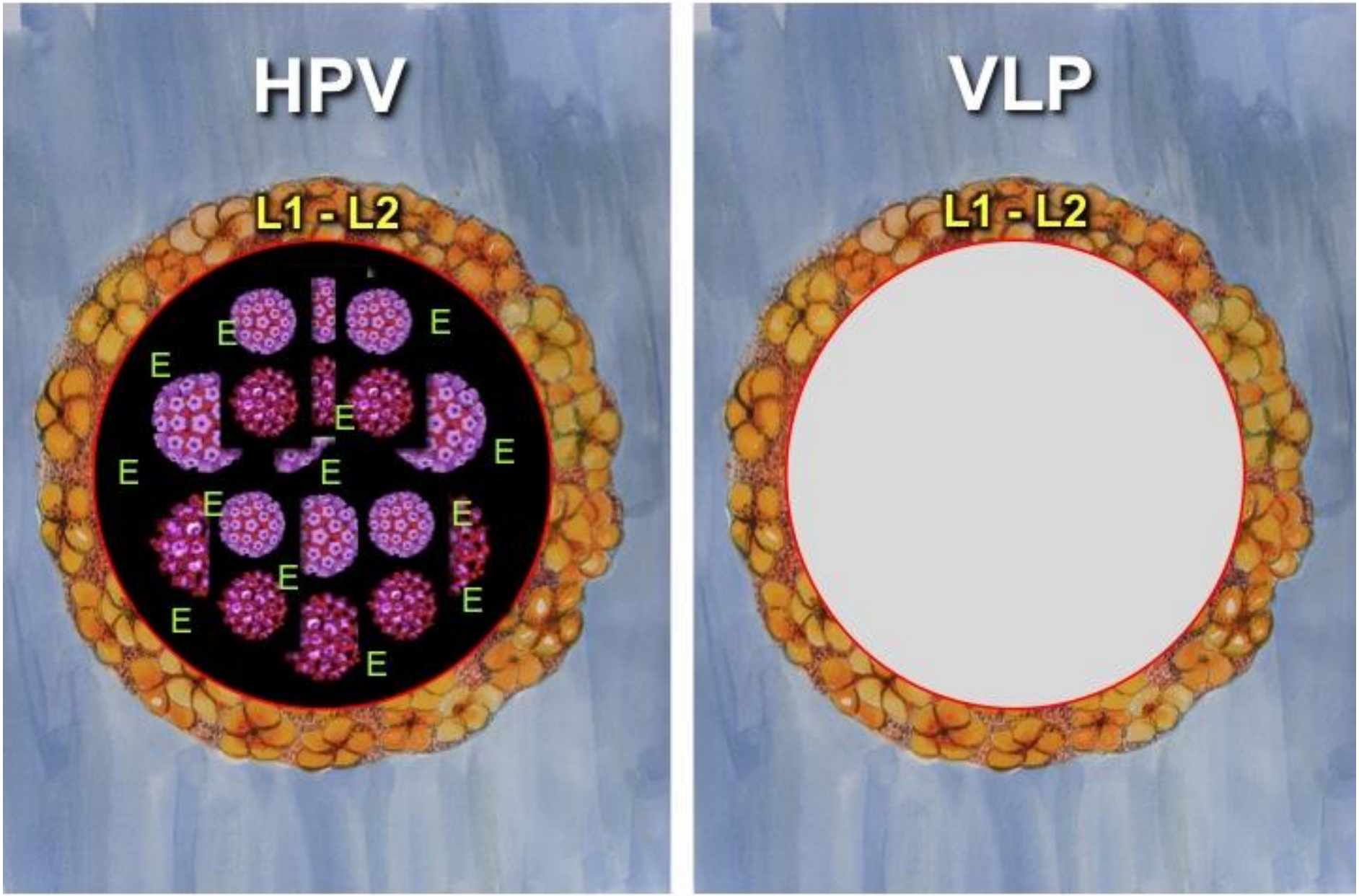
Picco di risposta anticorpale

100-200 volte più alto

del titolo anticorpale indotto

dall'infezione naturale

Margaret Stanley, University of Cambridge


HPV
L1 - L2
E
E
E
E
E
E
E
E
E
E
E
E
E
VLP
L1 - L2

Metanalysis

60 million individuals, up to 8 years post-vaccination follow-up

1702 potentially eligible articles

65 articles from 14 high-income countries:

- 23 for HPV infection
- 29 for anogenital warts
- 13 for CIN 2+

Drolet M, Bénard É, Pérez N, Brisson M; HPV Vaccination Impact Study Group. Population-level impact and herd effects following the introduction of human papillomavirus vaccination programmes: updated systematic review and meta-analysis. *Lancet* 2019; 394(10197):497-509.

HPV infection

After 5-8 years of vaccination, prevalence of HPV 16 and 18 decreased significantly by 83% among girls aged 13 to 19 and 66% among women aged 20 to 24.

Although not as significant as HPV 16/18, prevalence of HPV 31, 33, 45 decreased by 54% among girls aged 13 to 19. Among women aged 20 to 24, decrease was not significant.

Drolet M, Bénard É, Pérez N, Brisson M; HPV Vaccination Impact Study Group. Population-level impact and herd effects following the introduction of human papillomavirus vaccination programmes: updated systematic review and meta-analysis. *Lancet* 2019; 394(10197):497-509.

Anogenital warts

Anogenital warts significantly decreased among girls and women aged 15-19, 20-24, and 25-29 in the first 4 years following implementation.

Diagnoses 5 to 8 years after implementation also decreased by 67% among girls aged 15-19, by 54% among women aged 20-24, and by 31% among women aged 25-29.

Drolet M, Bénard É, Pérez N, Brisson M; HPV Vaccination Impact Study Group. Population-level impact and herd effects following the introduction of human papillomavirus vaccination programmes: updated systematic review and meta-analysis. *Lancet* 2019; 394(10197):497-509.

CIN 2+

At 5 to 9 years after implementation of vaccination, rates of CIN2+ decreased significantly by 51% among girls aged 15-19 and by 31% among women aged 20-24.

Among mostly unvaccinated women, CIN2+ significantly increased in women between ages 25-29 and 30-39, respectively 19% and 23%.

Drolet M, Bénard É, Pérez N, Brisson M; HPV Vaccination Impact Study Group. Population-level impact and herd effects following the introduction of human papillomavirus vaccination programmes: updated systematic review and meta-analysis. *Lancet* 2019; 394(10197):497-509.

HPV vaccination **does not** reduce progression to cervical precancers in women with prevalent infection at the time of vaccination

Non è un vaccino terapeutico

At month 2 (postdose 1), among women with vaccine-type antibodies at baseline, vaccine-induced anti-HPV responses were approximately 12- to 26-fold higher than those observed in baseline-naïve women, suggesting an *anamnestic response* in women 15-26 yrs seropositive before vaccination.

Following an initial, similar sized decline, anti-HPV responses plateaued and remained stable through end-of-study (3 yrs).

Villa LL, Ault K, Giuliano AR, Costa RLR, Petta CA, Andrade RP, et al. Immunologic responses following administration of a vaccine targeting human papillomavirus types 6, 11, 16 and 18. *Vaccine* 2006; 24:5571-5583.

Women HPV seropositive, DNA negative at enrollment

(natural infection, subsequently cleared):

NO EVIDENCE OF DISEASE after 4-valent vaccination

(40 mos follow-up)

Quadrivalent HPV vaccine prevents reinfection or reactivation of disease that is related to vaccine HPV types.

Olsson SE et al. Evaluation of quadrivalent HPV 6/11/16/18 vaccine efficacy against cervical and anogenital disease in subjects with serological evidence of prior vaccine type HPV infection. *Human Vaccines* 2009; 5(10):696-704.

Recurrent disease related to vaccine HPV types after LEEP

In patients infected with HPV 16 and/or 18 type:

- **8.5%** in the non-vaccination group and
- **2.5%** in the vaccination group

Vaccination with the 4-HPV vaccine after treatment may be considered in preventing recurrence of CIN 2-3.

Kang WD et al. Is vaccination with quadrivalent HPV vaccine after loop electrosurgical excision procedure effective in preventing recurrence in patients with high-grade cervical intraepithelial neoplasia (CIN 2-3)? *Gynecol Oncol* 2013; 130:264-268.

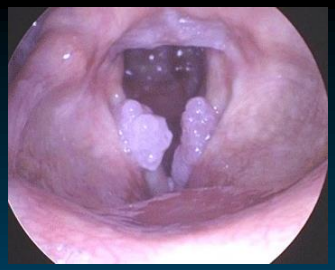
Cross-protection for certain but not all HPV strains

A 77 year-old white man with a long-term history of immunosuppression (no HIV) presented with a 6-month history of pruritic and eruptive white papules on the trunk and extremities (several treatments).

70 verrucas (no HPV typing) 2-20 mm: *9-valent HPV vaccine*

The warts did not fully clear, but the number of warts decreased over time without a change in his immunosuppressive medications, down to a low of 3 warts 15 months after the initial vaccine dose.

Ferguson SB et al. Nonavalent human papillomavirus vaccination as a treatment for warts in an immunosuppressed adult.
JAAD Case Rep 2017; 3(4): 367-369.



When HPV vaccination was used as an adjuvant treatment for active clinical disease, 9 of 12 studies reported decreased disease recurrence, decreased disease burden, or increased intersurgical interval.

In contrast, none of the 7 studies of vaccination in individuals with HPV DNA positivity and/or seropositivity without clinical disease reported improved outcomes.

Dion GR et al. Adjuvant Human Papillomavirus Vaccination for Secondary Prevention: A Systematic Review.
JAMA Otolaryngol Head Neck Surg 2017; 143(6):614-622.

A woman in her 90s with multiple, inoperable cutaneous basaloid SCCs treated with a combination of systemic and intratumoral delivery of the 9-valent HPV vaccine from March 2016, through February 2017, and then followed through May 2018.

All tumors resolved 11 months after the first intratumoral injection of the vaccine.

The patient remained free of tumors at the end of follow-up.

Nichols AJ et al. Combined Systemic and Intratumoral Administration of Human Papillomavirus Vaccine to Treat Multiple Cutaneous Basaloid Squamous Cell Carcinomas. *JAMA Dermatol* 2018; 154(8):927-930.

30 patients with multiple warts

Regarding therapeutic response 4-HPV vaccine:

- 14 patients (46.67%) «complete response»
- 5 patients (16.67%) «partial response»
- 11 patients (36.67%) «No response»

No severe adverse events after 4-valent vaccine

Yang MY et al. Quadrivalent human papilloma virus vaccine for the treatment of multiple warts: a retrospective analysis of 30 patients.
J Dermatolog Treat 2019; 30(4):405-409.

11 studies comprising 133 patients
(63 patients eligible for metanalysis)

The number of surgical procedures per month was significantly reduced after HPV vaccination compared with before vaccination (estimated mean, 0.06 vs 0.35)

The mean intersurgical interval increased from 7 mos (range, 0.30-45 mos) before to 34.45 mos (range 2.71-82 mos) after HPV vaccination.

Rosenberg T et al. Therapeutic Use of the Human Papillomavirus Vaccine on Recurrent Respiratory Papillomatosis: A Systematic Review and Meta-Analysis. *J Infect Dis* 2019; 219(7):1016-1025.

Recurrences vulvar and anal HSIL = 30% after initial treatment

Target: 345 adults aged 27 to 69 years in the prevention of secondary anal and vulvar HSIL (2017-2022) followed 36 mos in the clinic and 42 mos by telephone.

… possible use of the 9vHPV vaccine as an adjuvant therapy to reduce the risk of HSIL recurrence by 50%.

… the duration of protection against recurrent HSIL.

Stankiewicz KHC et al. Effect of Human Papillomavirus Vaccine to Interrupt Recurrence of Vulvar and Anal Neoplasia (VIVA). A Trial Protocol. *JAMA Network Open* 2019; 2(4):e190819.

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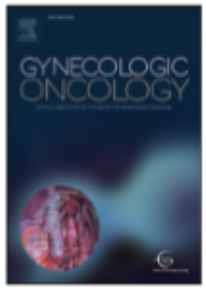


SPERANZA project: HPV vaccination after treatment for CIN2+

Alessandro Ghelardi [a,*], Fabio Parazzini [b], Francesca Martella [c], Annalisa Pieralli [d], Paola Bay [a], Arianna Tonetti [a], Alessandro Svelato [a], Gloria Bertacca [e], Stefania Lombardi [e], Elmar A. Joura [f]

[a] *Azienda Usl Toscana Nord-Ovest, UOC Ostetricia e Ginecologia, Ospedale Apuane, Massa, Italy*
[b] *Policlinico Mangiagalli, Dipartimento di Scienze Cliniche e di Comunità, IRCCS, Milano, Italy*
[c] *Azienda Usl Toscana Centro, SOC Oncologia, Firenze, Italy*
[d] *Azienda Ospedaliero Universitaria Careggi, Ginecologia Chirurgica Oncologica, Firenze, Italy*
[e] *Azienda USL Toscana Nord Ovest, SSD Analisi ChimicoCliniche ed ImmunoAllergologia, Ospedale Apuane, Massa, Italy*
[f] *Medical University of Vienna, AKH Department of Obstetrics and Gynecology, Comprehensive Cancer Center Vienna, Italy*

SPERANZA project – study 1

536 patients enrolled (4 years follow-up CIN 2+):
- Clinical recurrence = 1,16% (surgery + QHPV vaccine)
- Clinical recurrence = 6,39% (surgery alone)

81.2% reduction of cervical HSIL recurrences

Time factor: the vaccine effectiveness becomes statistically significative after 24 months of follow-up

Ghelardi A et al. SPERANZA project: HPV vaccination after treatment for CIN 2+. *Gynecol Oncol* 2018; 151(2):229-234.

SPERANZA project – study 2

446 patients enrolled (2 years follow-up anogenital warts):
- Clinical recurrence = 24,3% (surgery + QHPV vaccine)
- Clinical recurrence = 37,7% (surgery alone)

64.4% reduction of anogenital warts recurrences

Time factor: the vaccine effectiveness becomes statistically significative after 12 months of follow-up

Ghelardi A et al. SPERANZA project: HPV vaccination after treatment for CIN 2+. *Gynecol Oncol* 2018; 151(2):229-234.

- After LEEP, HPV vaccination shows 80% clinical effectiveness in disease relapse prevention
- Clinical benefits of vaccination are demonstrated up to 4 years
- HPV vaccine has no therapeutic effect on prevalent HPV infection or disease
- HPV vaccination is beneficial as an adjuvant additional to surgical treatment

Ghelardi A et al. SPERANZA project: HPV vaccination after treatment for CIN 2+. *Gynecol Oncol* 2018; 151(2):229-234.

No treatment, BUT prevention of recurrences

Even if HPV vaccine is not able to alter a presurgical **prevalent HPV infection**, adjuvant quadrivalent HPV vaccine shows:

- ***clinical effectiveness***, *demonstrating a reduced risk of developing recurrent cervical disease by 80% and AGW recurrence by 65%*

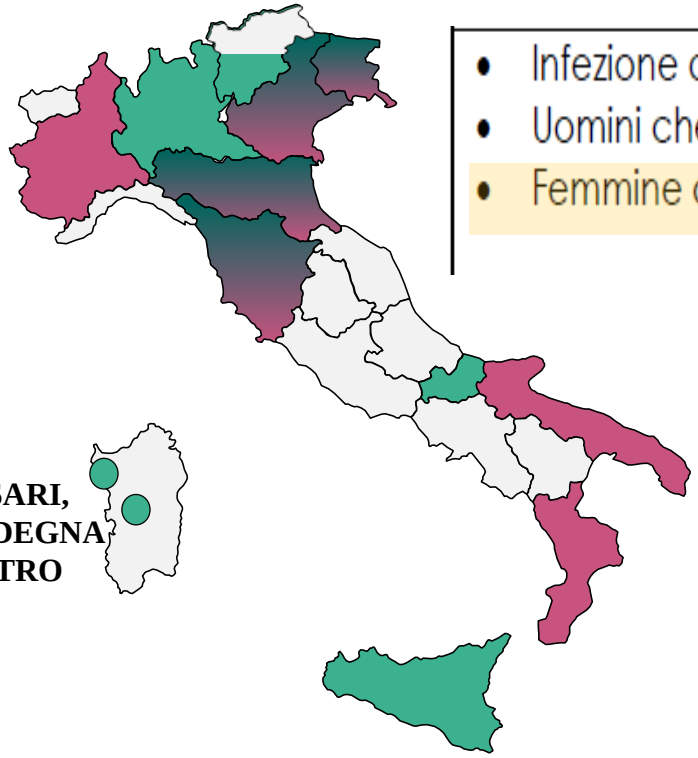
- ***overall free disease time*** *(from infections – diseases)*
- ***free interval from positive Pap smears***
- ***prevention of de novo infections***

CONTROL OF REACTIVATION (prevention of persistent infection)

Women treated for CIN2+, represent a high-risk group for HPV persistent infection, cervical disease recurrence and obstetrical complications due to repeated surgical treatments

Raccomandazioni regionali per 25enni e donne con lesioni da HPV

LOMBARDIA



- Infezione da HIV
- Uomini che fanno sesso con uomini (MSM)
- Femmine con diagnosi recente (entro 12 mesi) di lesioni CIN 2+

SASSARI, SARDEGNA CENTRO

TOSCANA

È inoltre opportuna la verifica dello stato vaccinale e il recupero con offerta della vaccinazione alle donne di 25 anni di età in occasione della chiamata al primo screening per la citologia cervicale (Pap-test), come indicato dal PNPV 2017-2019.

La vaccinazione è offerta gratuitamente: alle donne che hanno subito un intervento per lesioni cervicali dovute ad infezioni da HPV ed alle donne HIV positive.

Gratuità per donne con lesioni da HPV (9/21)

Gratuità per 25enni (7/21)

Sistema Socio Sanitario

Regione Lombardia

ATS Milano
Città Metropolitana

VAX BOOK

Atto di indirizzo del piano di offerta vaccinale

Attività 211 - Governo profilassi vaccinale

VACCINAZIONI PER SOGGETTI A RISCHIO

ANTI HPV

Per chi?	Per le categorie a rischio
Come?	Vaccino in uso **Età** — **Ciclo** Fino a 45 anni (maschi e femmine) — 3 dosi (0 – 2 – 6 mesi)
Condizioni di rischio	• Infezione da HIV • Uomini che fanno sesso con uomini (MSM) • Femmine con diagnosi recente (entro 12 mesi) di lesioni CIN 2+

Per offerta attiva si intende una modalità di proposta vaccinale caratterizzata dalla selezione della popolazione target, dall'invio di lettera invito personalizzata con appuntamento e da azioni di sollecito per i non rispondenti.

Gardasil9

- *nelle femmine e nei maschi*
- *a tutte le età*
- *dopo trattamento per lesioni preneoplastiche (CIN-VaIN-VIN-AIN) o condilomi floridi*

HUMANITAS
SAN PIO X

Grazie