

Alessandro Ghelardi

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research, treatment and innovation
Azienda ASL Nordovest Tuscany , Italy



**VACCINATION OF
YOUNG ADULTS IN ITALY
(FOCUS ON HPV)**

ADULT WOMEN HPV VACCINATION

WHY we should offer HPV vaccination to previously exposed women ?

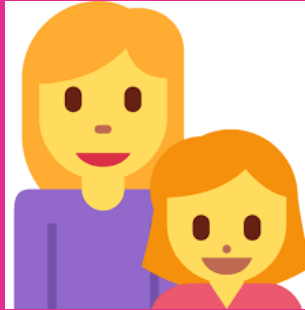


15 YEARS OF RESEARCH IN 15 MINUTES..



1

FIRST STEP



NOT ONLY FOR YOUNG WOMEN

Introduction ..to make a long story short

In 2006 HPV vaccination was licensed for primary prevention of HPV related disease in young females. [1].



Subsequently, only 3 years late.. [2].

2009: «Background: We tested the safety, immunogenicity, and efficacy of the quadrivalent HPV (types 6, 11, 16, 18) L1 virus-like-particle vaccine in women aged 24-45 years.»

The quadrivalent HPV vaccine demonstrated efficacy against HPV infection and disease in women up to 45 years **not infected with the prelevant HPV types at enrolment.**



THE LANCET

[1] Human papilloma virus vaccines: WHO position paper. Weekly epidemiological record, No. 15, 2009,84, 117-132. [2] N. Munoz, R. Jr Manalastas, P. Pitisuttithum et al., 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, Lancet 2009; 373:1949- 57.

..not only for child..

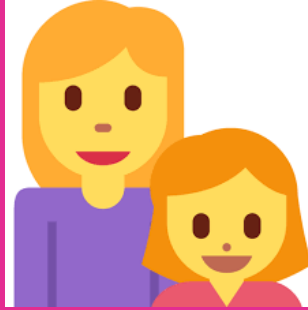


« Conclusions: Vaccination with qHPV vaccine provides generally safe and effective protection from HPV 6-, 11-, 16-, and 18- related genital warts and cervical dysplasia **through 6 years** following administration to 24–45 year-old women.» [3]

ADULT AGE: WE CAN TAKE CARE OF OUR PATIENTS

1

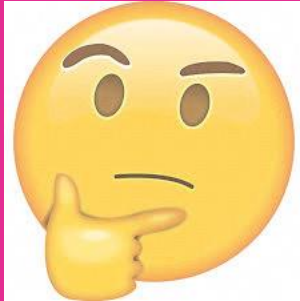
FIRST STEP



NOT ONLY FOR YOUNG WOMEN

2

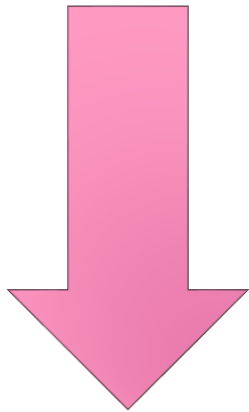
SECOND STEP



UNDERSTANDING ADULT
WOMEN IMMUNIZATION

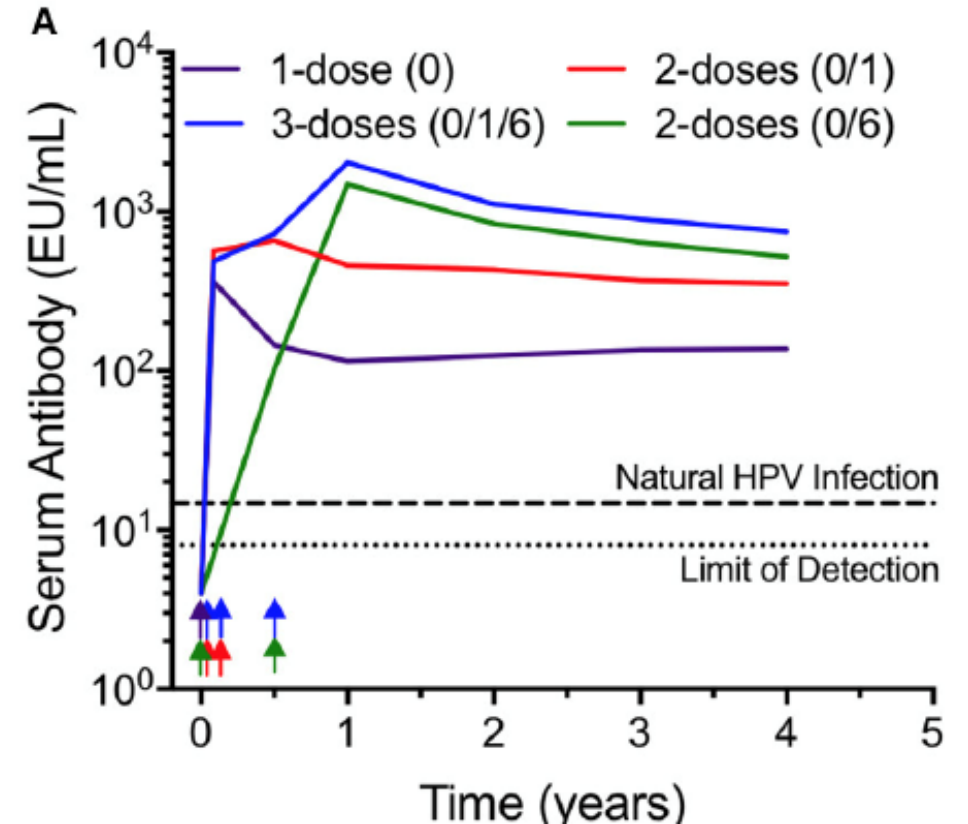
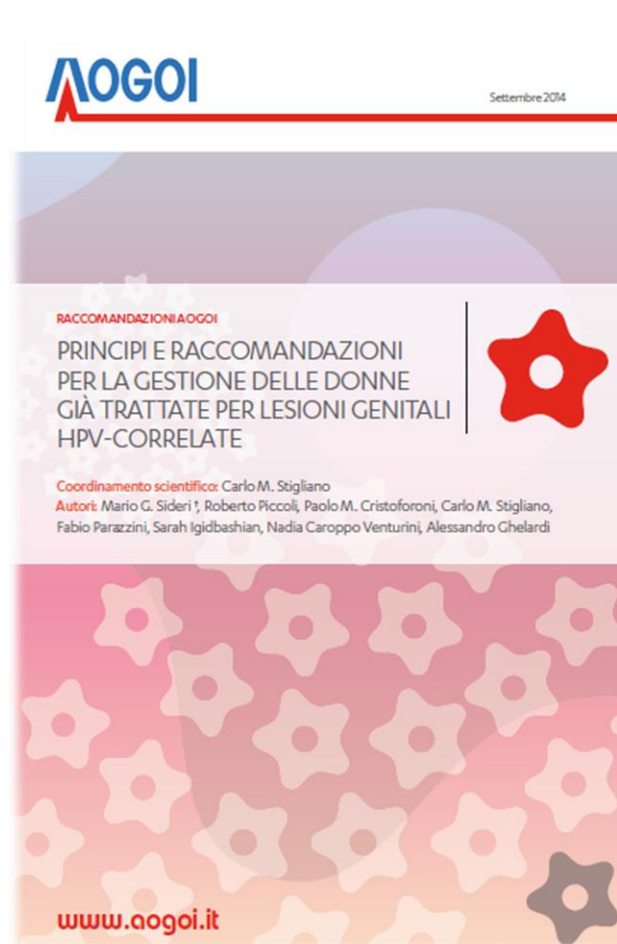
a matter of immunology..

HPV UNIT - TREATMENT



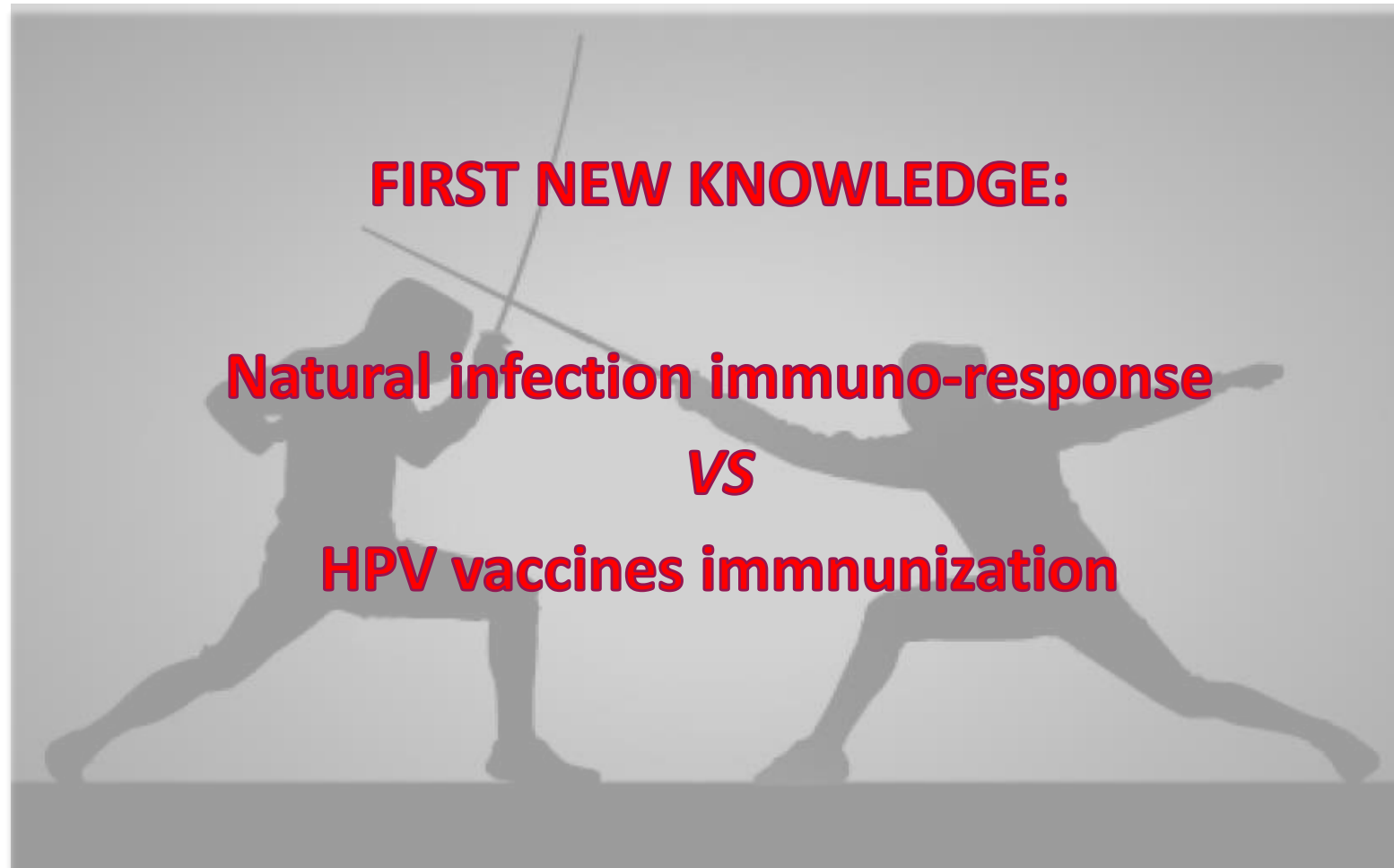
HPV VACCINATION CLINIC

(SPERANZA project 2012)



Slifka MK, Amanna IJ. Role of Multivalency and Antigenic Threshold in Generating Protective Antibody Responses. *Front Immunol.* 2019 May 1;10:956. doi: 10.3389/fimmu.2019.00956. PMID: 31118935; PMCID: PMC6504826.

UNDERSTANDING DIFFERENCES BETWEEN NATURAL INFECTION AND HPV_v IMMUNIZATION



Adult immunization

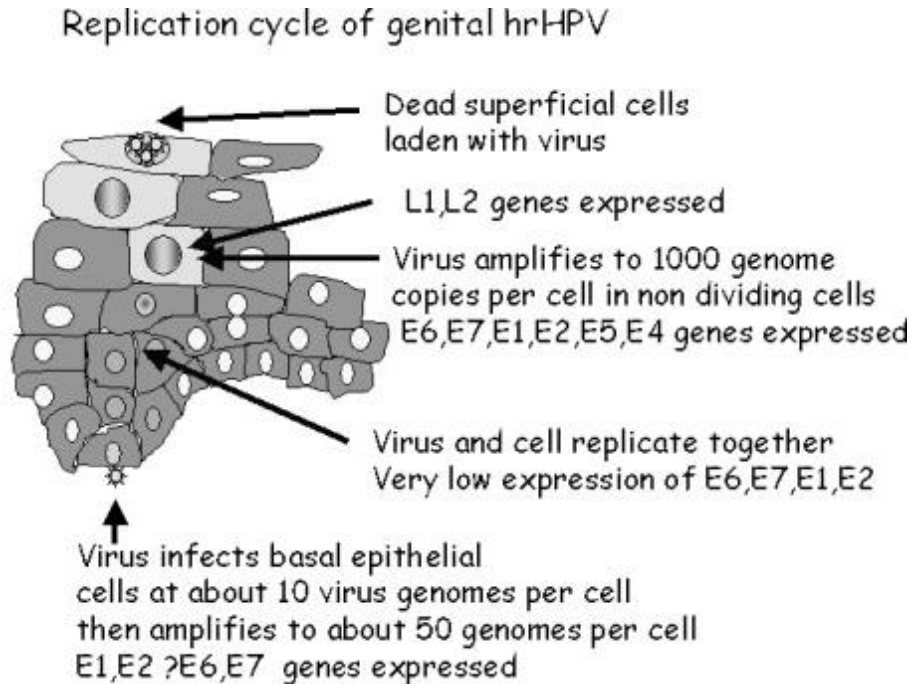


key



clinical immunology

NATURAL INFECTION



- there is no detectable viraemia
- permissive viral growth is exclusively intra-epithelial (no need of cellular-lysis)
- systemic responses to HPV antigens are low
- serum neutralising antibody levels in HPV infections are low

IMMUNO ESCAPE

NATURAL INFECTION - natural Ab

IMMUNO ESCAPE

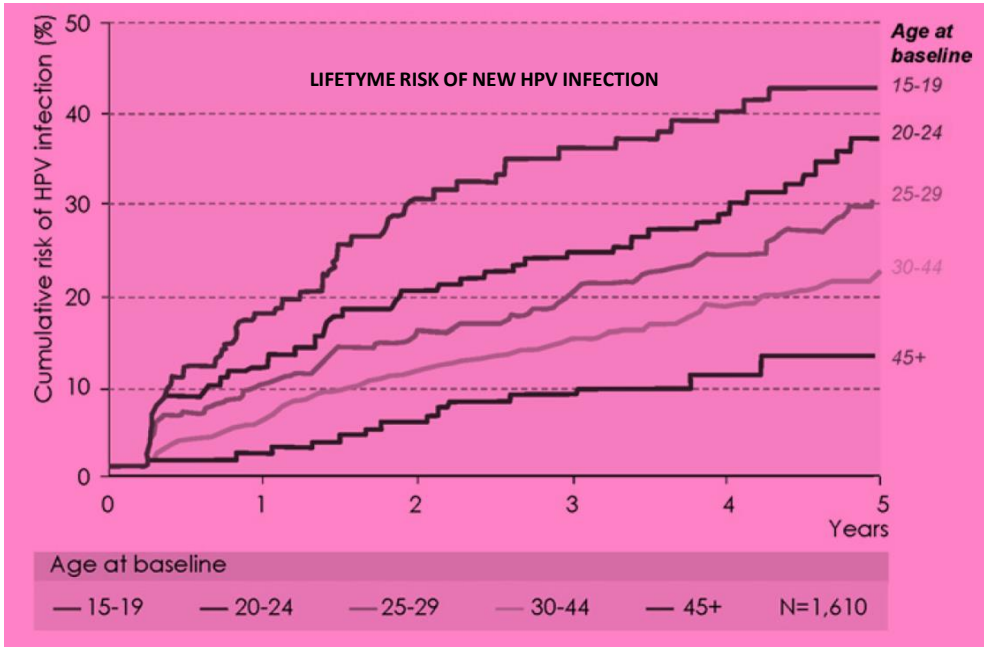
Seroconversion 6-18 months, Ab are present in 60-70% of the infected subjects, (a)

30-40% OF HPV 16 ARE CLINICALLY SILENT (b)



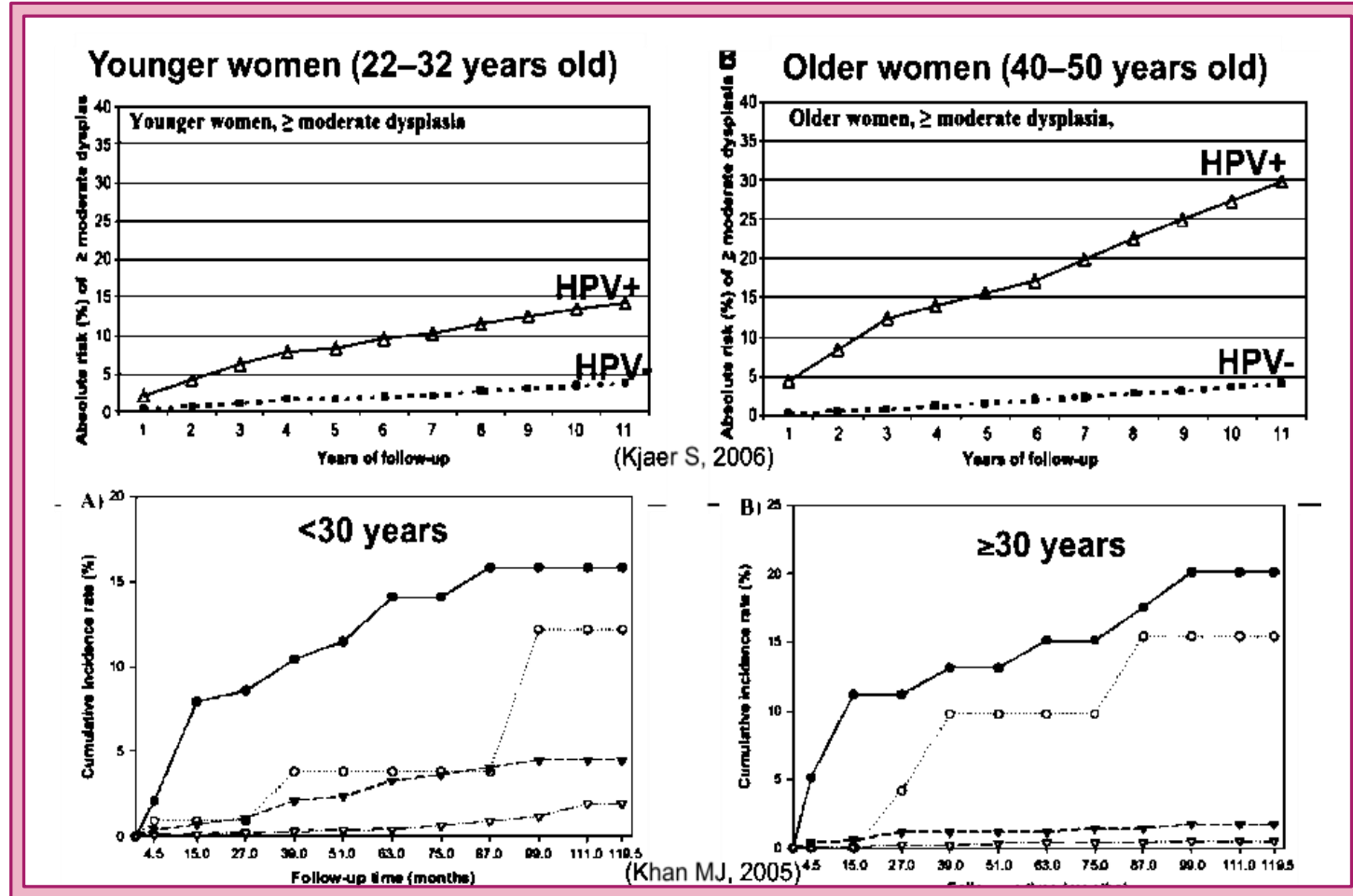
- a) Tong Y, Ermel A, Tu W, Shew M, Brown DR. Association of HPV types 6, 11, 16, and 18 DNA detection and serological response in unvaccinated adolescent women. *J Med Virol.* (2013) 85:1786–93. 10.1002/jmv.23664
- b) (b) Carter JJ, Koutsky LA, Hughes JP, Lee SK, Kuypers J, Kiviat N, Galloway DA, Bachmann MF, Rohrer UH, Kundig TM, Burki K, Hengartner H, Zinkernagel RM. Comparison of human papillomavirus types 16, 18, and 6 capsid antibody responses following incident infection. *J Infect Dis.* 2000 Jun;181(6):1911-9. Ho GY, Studentsov YY, Bierman R, Burk RD. Natural history of human papillomavirus type 16 virus-like particle antibodies in young women. *Cancer Epidemiol Biomarkers Prev.* 2004 Jan;13(1):110-6.\

NATURAL INFECTION – HPV natural history



all women remain at risk for acquisition of new HPV infections.

BOSCH FX, BURCHELL AN, SCHIFFMAN M, ET AL. VACCINE 2008;26(SUPPL. 10)



HPV NATURAL INFECTION IMMUNOLOGY

NATURAL HISTORY OF HPV INFECTION

- **Weak response**
- **LOSS OF PROTECTION DURING THE YS.**

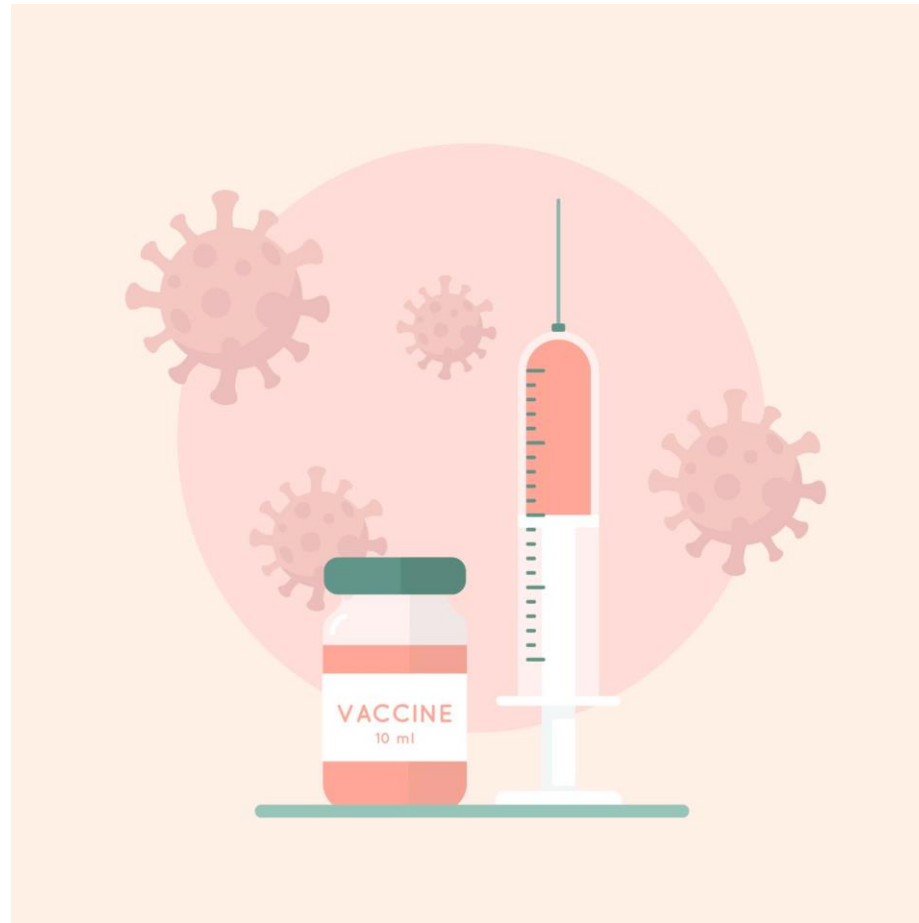


key

FREQUENTLY UNKNOWN «MASKED»



HPV vaccines IMMUNIZATION



HPV vaccines IMMUNIZATION

- **Seroconversion around 100% erasing immunological escape**
- **Abs Titers are significantly higher vs HPV natural infection**
- **Strong and long lasting immunological response**

Technical data:

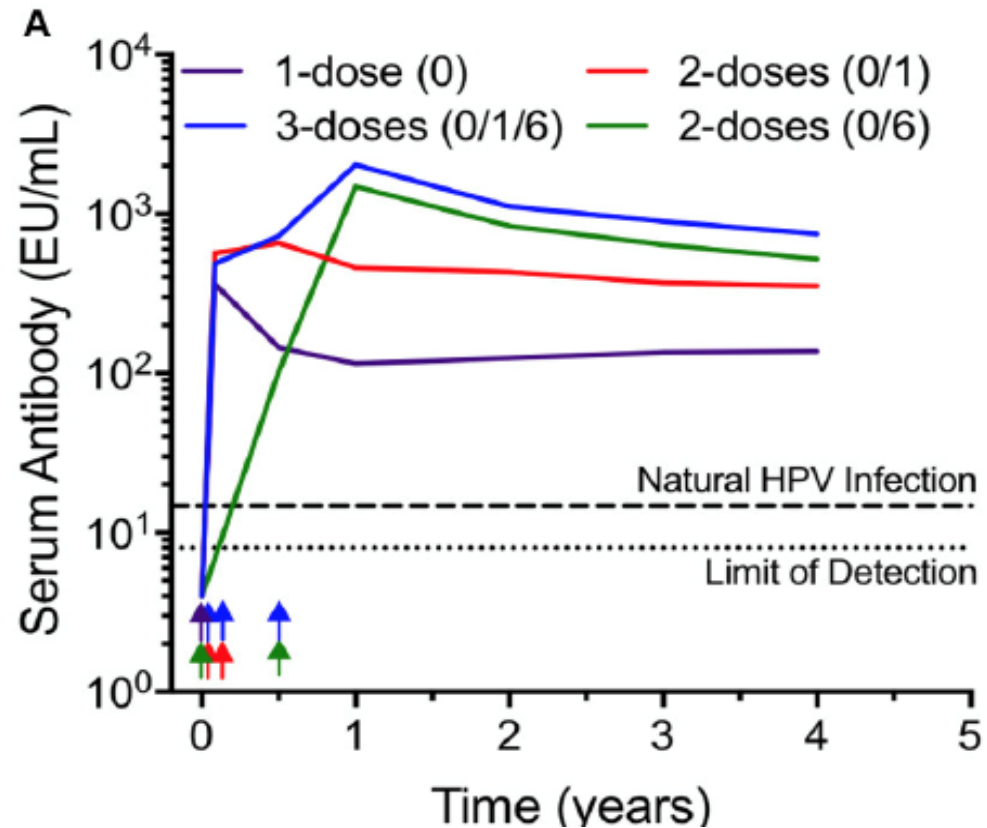
GMT, 1 month after vaccination (full cycle) 9341.5 (95% CI, 8760.4–9961.1) e 4769.6 (95% CI, 4491.2–5065.3)
EU/mL HPV-16 & HPV-18 respectively

..how can I
improve my IS ?



HPV vaccines IMMUNIZATION

Abs Titers – GMT



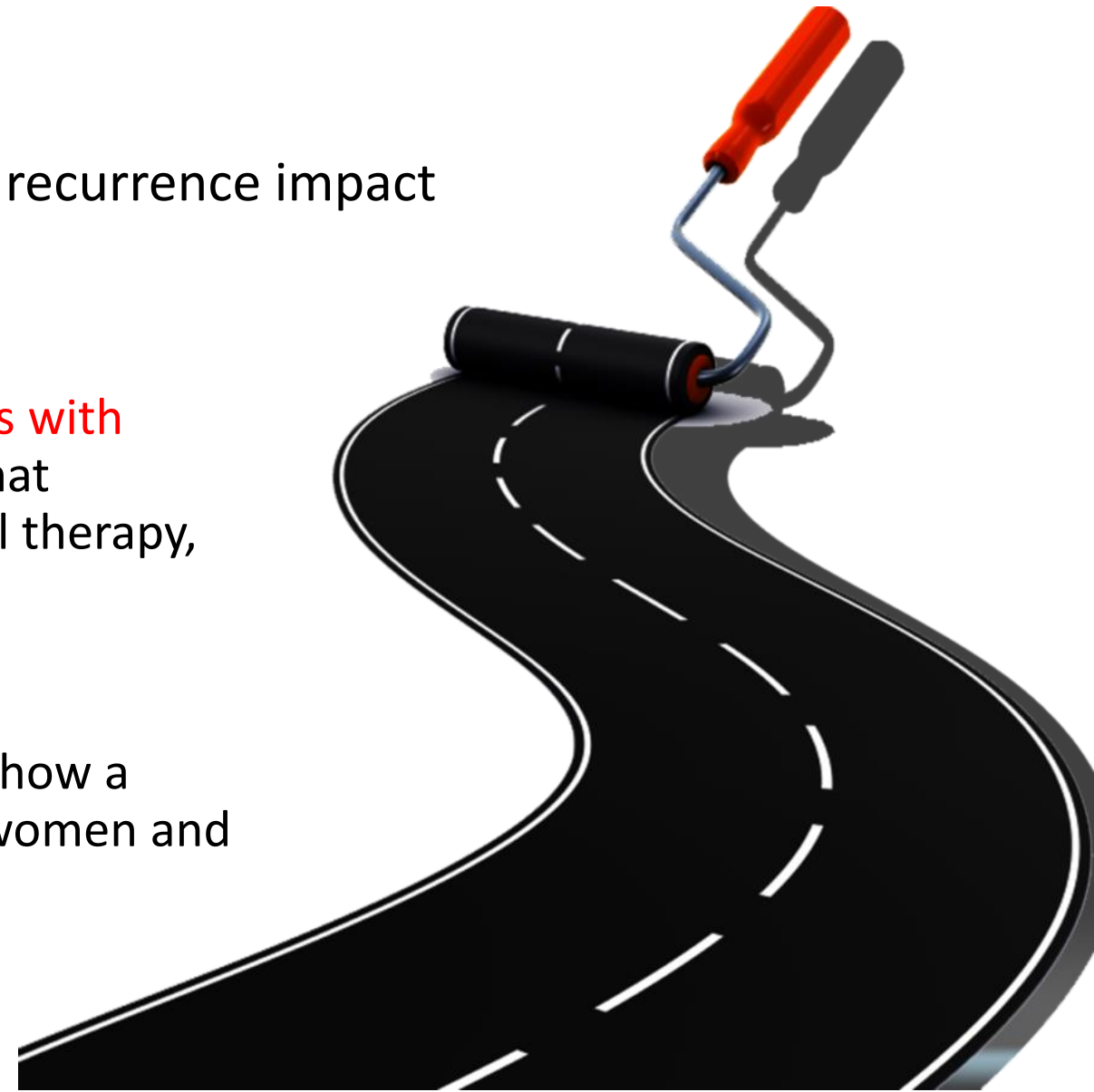
HPV vaccines will provide «strong benefits» to your IS



New streets to draw: vaccine and disease recurrence impact

Although vaccination is not effective in patients with prevalent HPV infection, recent data suggest that vaccination, in women who underwent surgical therapy, could impact on disease recurrence.

2012.. Some findings from retrospective data show a significant protective effect of HPV vaccine in women and men surgically treated for HPV disease [5-7].



OUR EXPERIENCE ..not only primary target..

AMBULATORIO VACCINALE HPV

COUNSELLING PER MALATTIE HPV CORRELATE
tutte le domande e tutte le risposte
alle malattie HPV



**Azienda
USL
Toscana
nord ovest**

VAX update
A. Ghelardi

SPER.AN.Z.A. project

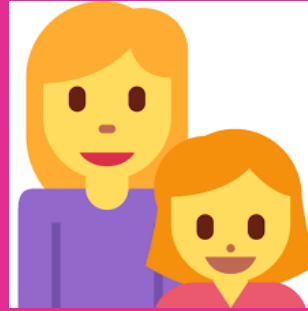
SPERANZA project HPV vaccination after surgical treatment for HPV related diseases: a prospective evaluation



VAX update
A. Ghelardi

1

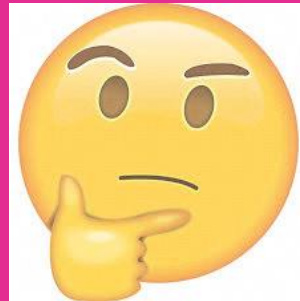
FIRST STEP



NOT ONLY FOR YOUNG WOMEN

2

SECOND STEP



UNDERSTANDING ADULT
WOMEN IMMUNIZATION

3

THIRD STEP



ADULT WOMEN IMM. &
HIGH RISK CATEGORIES

SPERANZA project: our studies

“SPERANZA PROJECT” MAIN TOPICS

SPERANZA STUDY N. 1
CIN 2+ RECURRENCE

SPERANZA STUDY N. 2
ANOGENITAL WARTS RECURRENCE

SPERANZA STUDY N. 3
POST-TREATMENT SURVEILLANCE

SPERANZA STUDY N. 4
POST TREATMENT SEX-HABITS

SPERANZA STUDY N. 5
PARTNER AS A RISK FACTOR

SPERANZA STUDY N. 6
IMPACT ON SEX-DYSFUNCTION

SPERANZA STUDY N. 7
COFACTORS OF RELAPSE: AIN?

SPERANZA STUDY N. 8
COFACTORS OF RELAPSE: ORL?

SPERANZA STUDY N. 9
uVIN RECURRENCE

SPERANZA STUDY N.10
CIN2 REGRESSION

SPERANZA project
HPV CLINIC
FOR (NOT NAÏVE)
ADULT WOMEN
submitted to surgery
1832 pts. ENROLLED

POST SURGICAL
HPV-vaccination +
follow up

Standard follow up
schedule without
vaccination



SPERANZA project n.1

“SPERANZA PROJECT” MAIN TOPICS

SPERANZA STUDY N. 1 CIN 2+ RECURRENCE

SPERANZA STUDY N. 2
ANOGENITAL WARTS RECURRENCE

SPERANZA STUDY N. 3
POST-TREATMENT SURVEILLANCE

SPERANZA STUDY N. 4
POST TREATMENT SEX-HABITS

SPERANZA STUDY N. 5
PARTNER AS A RISK FACTOR

SPERANZA STUDY N. 6
IMPACT ON SEX-DYSFUNCTION

SPERANZA STUDY N. 7
COFACTORS OF RELAPSE: AIN?

SPERANZA STUDY N. 8
COFACTORS OF RELAPSE: ORL?

SPERANZA STUDY N. 9
uVIN RECURRENCE

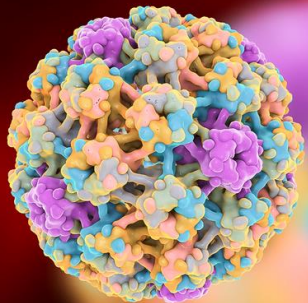
SPERANZA STUDY N.10
CIN2 REGRESSION

SPERANZA project
HPV CLINIC
FOR (NOT NAÏVE)
ADULT WOMEN
submitted to surgery
1832 pts. ENROLLED

POST SURGICAL
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SPERANZA project - st.1

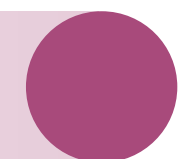
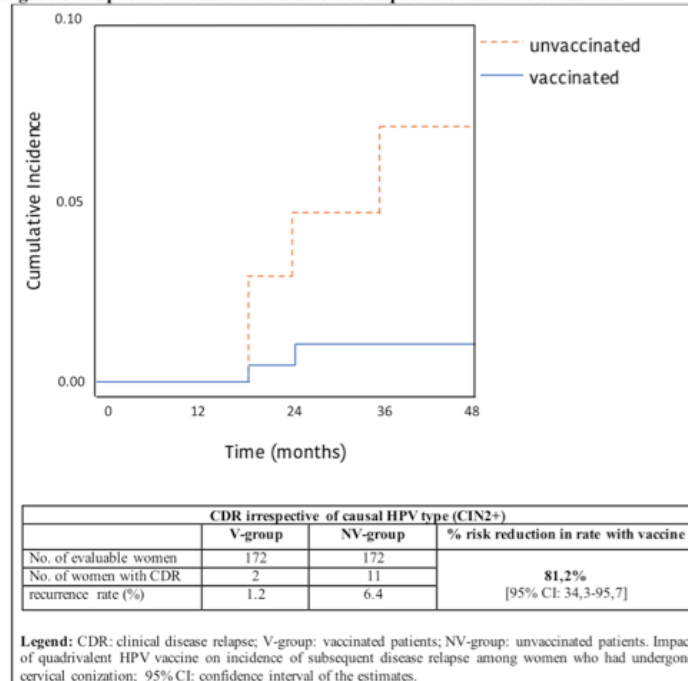


Figure 3. Impact of vaccination on disease relapse after cervical conization



SPERANZA PROJECT 1 : PUBLISHED – RESULTS

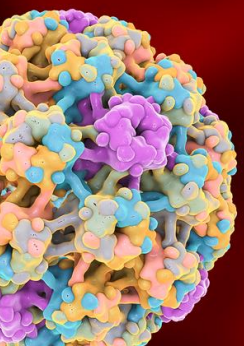


The rate of recurrence was significantly higher in the control group, 6.4% VS 1.2% with a $p=0.0112$ by Pearson's chi squared test.

Clinical effectiveness
at 4 years from surgical treatment
irrespective of HPV type **81.2%**
(95% CI: 34,3%-95,7%) against
CIN2+ recurrent disease.

*for details see the original article. Adapted from SPERANZA project: HPV vaccination after treatment for CIN2. Ghelardi A et al. Gynecol. Oncol. 2018 Nov;151(2):229-234. DOI: 10.1061/j.ygyno.2018.08.033

VAX update
A. Ghelardi



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Order Journal

Journal Metrics

> CiteScore: 7.4 [Ⓢ]

Impact Factor: 4.623 [Ⓢ]

5-Year Impact Factor: 4.701 [Ⓢ]

Source Normalized Impact per Paper (SNIP): 1.759 [Ⓢ]

SCImago Journal Rank (SJR): 2.105 [Ⓢ]

> View More on Journal Insights

Most Cited Gynecologic Oncology Articles

The most cited articles published since 2018, extracted from Scopus.

Validation of the 2018 FIGO cervical cancer staging system

Volume 152, Issue 1, January 2019, Pages 87-93

Koji Matsuo | Hiroko Machida | Rachel S. Mandelbaum | Ikuo Konishi | Mikio Mikami



Pembrolizumab in patients with programmed death ligand 1–positive advanced ovarian cancer: Analysis of KEYNOTE-028

Volume 152, Issue 2, February 2019, Pages 243-250

Andrea Varga | Sarina Piha-Paul | Patrick A. Ott | Janice M. Mehnert | Dominique Berton-Rigaud | Anne Morosky | Ping Yang | Jane Ruman | Daniela Matei



Comparison of survival outcomes between minimally invasive surgery and conventional open surgery for radical hysterectomy as primary treatment in patients with stage IB1–IIA2 cervical cancer

Volume 153, Issue 1, April 2019, Pages 3-12

Se Ik Kim | Jae Hyun Cho | Aeran Seol | Young Im Kim | Maria Lee | Hee Seung Kim | Hyun Hoon Chung | Jae Weon Kim | Noh Hyun Park | Yong Sang Song



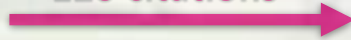
SPERANZA project: HPV vaccination after treatment for CIN2+

Volume 151, Issue 2, November 2018, Pages 229-234

Alessandro Ghelardi | Fabio Parazzini | Francesca Martella | Annalisa Pieralli | Paola Bay | Arianna Tonetti | Alessandro Svelato | Gloria Bertacca | Stefania Lombardi | Elmar A. Joura



120 citations



systematic review & meta-analysis

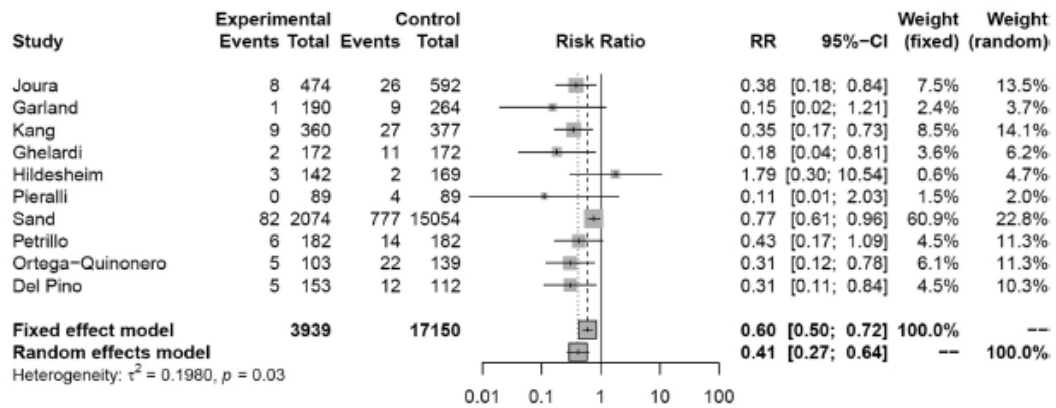


Fig. 3. Meta-analysis of all included studies, HPV independent.

Meta-analysis

Over all studies, the risk of recurrent CIN2+ after conization was 3.1% (121/3,939) with HPV vaccination and 5.3% (904/17,150) without. Random-effects meta-analysis showed a significant reduction of CIN2 + recurrence after vaccination with

a relative risk (RR) of 0.41 (95%-CI [0.27; 0.64]) (Fig. 3), independent from HPV type. The reduction of risk is therefore 59% after pre- or postoperative vaccination. Age-dependent analysis showed no differences between women under 25 years (RR 0.47 (95%-CI [0.28; 0.80])) and women of higher age (RR 0.52 (95%-CI



Jentschke M, Kampers J, Becker J, Sibbertsen P, Hillemanns P. Prophylactic HPV vaccination after conization:

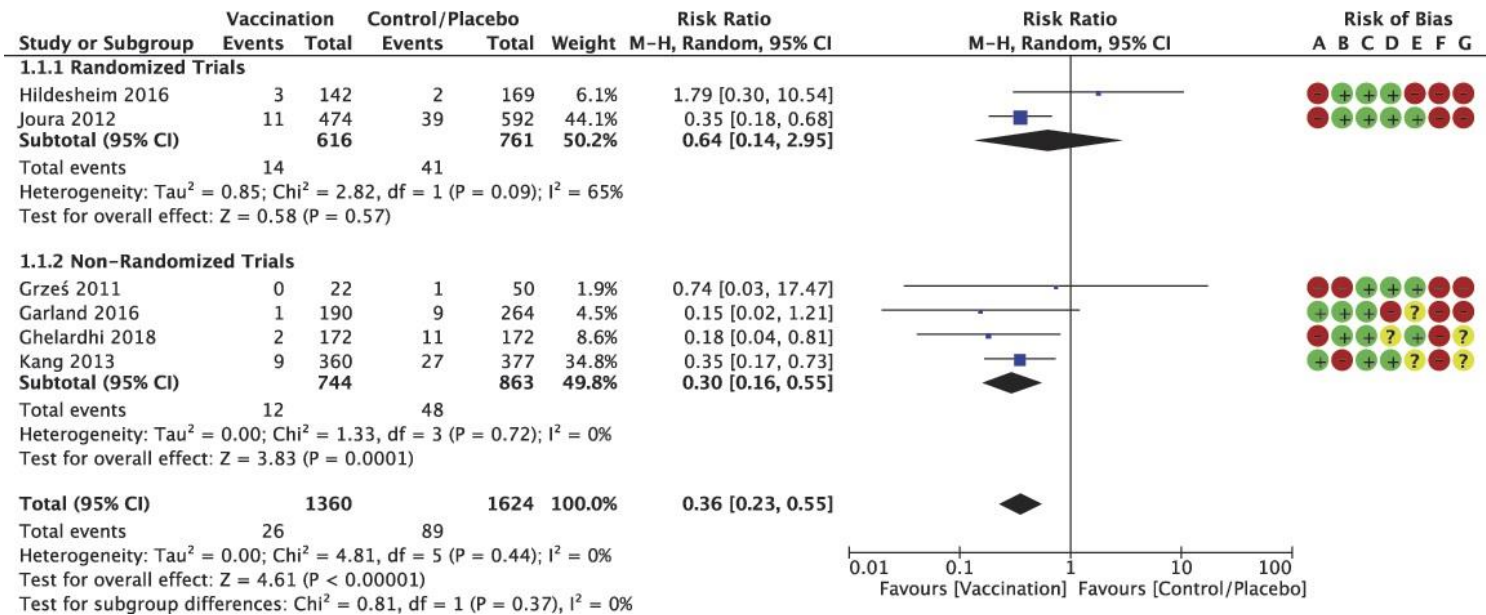
A systematic review and meta-analysis. *Vaccine*. 2020;38(41):6402-6409. doi:10.1016/j.vaccine.2020.07.055

VAX update
A. Ghelardi

systematic review & meta-analysis



ADJUVANT HUMAN PAPILLOMAVIRUS VACCINE TO REDUCE RECURRENT CERVICAL DYSPLASIA IN UNVACCINATED WOMEN: A SYSTEMATIC REVIEW AND META-ANALYSIS



Lichter K, Krause D, Xu J, Tsai SHL, Hage C, Weston E, Eke A, Levinson K. Adjuvant Human Papillomavirus Vaccine to Reduce Recurrent Cervical Dysplasia in Unvaccinated Women: A Systematic Review and Meta-analysis. *Obstet Gynecol.* 2020 May;135(5):1070-1083. doi: 10.1097/AOG.0000000000003833. PMID: 32282601.

VAX update
A. Ghelardi

How does it works..?

A lot of details are still unknown..



The more I learn the less I realize I know..



Immunological hypothesis **ADULT WOMEN EFFICACY**

«2 MAIN PATHWAYS»

The protective role of HPV vaccine in women with a prevalent HPV infection is still not fully understood:

- **Primary prevention:** for patients not previously exposed to HPV vaccine types, vaccination may provide protection against new HPV infection.

- **Reactivation/reinfection:** when the immune system is not effective to provide a long-lasting protection, HPV-vaccination may prevent loss of the immunological effectiveness, which in women without vaccination would lead to the development of HPV-related relapse. ?????

***for details see the original article.** Adapted from SPERANZA project: HPV vaccination after treatment for CIN2. Ghelardi A et al. Gynecol. Oncol. 2018 Nov;151(2):229-234. DOI: 10.1061/j.ygyno.2018.08.033

DRAWING A MODEL OF CLINICAL HPV DISEASE RELAPSE (CDR) .. «All together» project

COMPLETE SURGICAL ERADICATION

surgical eradication is a key
point
to avoid persistent disease,
configuring tree possible
pathways of CDR..



..VIRUS CLEARENCE AFTER
COMPLETE SURGERY :
>80%

IMMUNOLOGICAL
HYPOTHESIS

PROGETTO DI RICERCA CORRENTE 2018

N. identificativo progetto: IZS PLV 15/18 RC

Progetto presentato da:

ISTITUTO ZOOPROFILATTICO SPERIMENTALE
DEL PIEMONTE, LIGURIA E VALLE D'AOSTA

Area tematica: Sanità Animale

Sottoarea tematica: 2. Interfaccia ospite-patogeno

Linea di ricerca: SA 2.6. Sviluppo di modelli sperimentali
(in silico, in vitro e in vivo) per lo studio delle interazioni di
patogeni emergenti con l'ospite e l'ambiente, includendo
studi d'impatto a livello ambientale e sulla biodiversità.

Titolo del progetto: Papillomavirus equino: modello di
studio in oncologia comparata

PROGETTO ISS - Dr.ssa Razzuoli Elisabetta



DRAWING AN
ANIMAL MODEL
OF CDR

ANIMAL MODEL
FOR DISEASE
RUCURRENCE



HUMAN MODEL
OF CLINICAL
DISEASE RELAPSE

HUMAN
MODEL



All Together

NUOVE PROSPETTIVE DI ONCOLOGIA COMPARATA ANIMALE - UOMO

L'ONCOLOGIA VETERINARIA IN OTTICA ONE HEALTH

24 NOVEMBRE 2023

AUDITORIUM "BIAGIO D'ALBA"
MINISTERO DELLA SALUTE

Via Ribotta - Roma

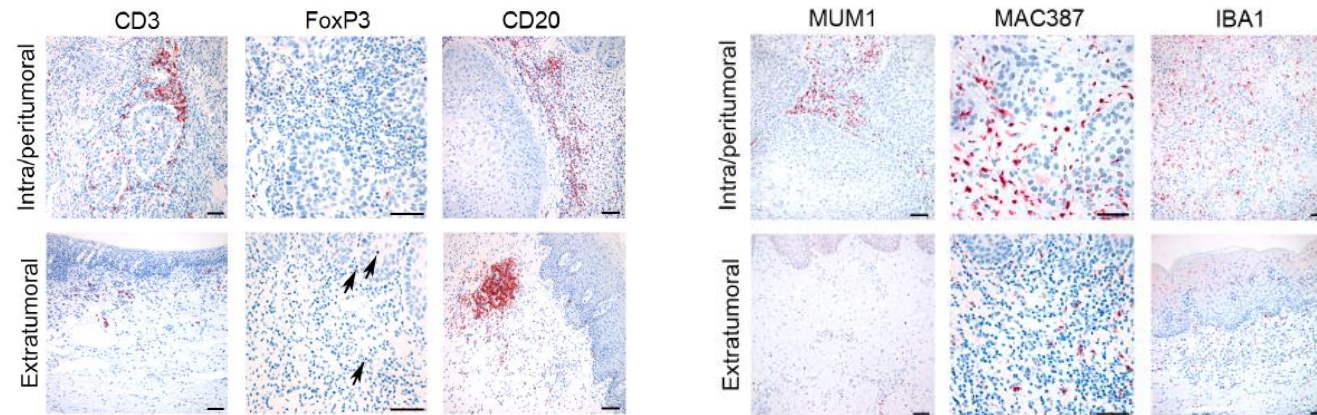
ATTIVITÀ DEL PROTOCOLLO D'INTESA

UN PROGETTO DI



«TARGETED» IMMUNOLOGICAL RESPONSE

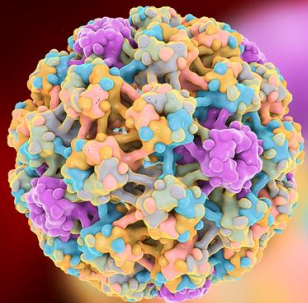
Tumor Immune
Microenvironment
(TIME) evaluation



Article

**Equine Penile Squamous Cell Carcinomas as a Model
for Human Disease: A Preliminary Investigation on
Tumor Immune Microenvironment**





ITALIAN recommendations 25 ys. & treated patients

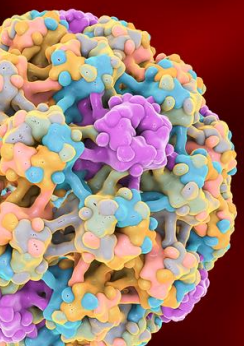


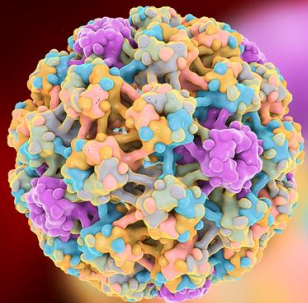
HPV Vaccination Is free
of charge for treated
women with high grade
cervical lesions (CIN2+)

Free catch-up vaccination
during the first screening
round (25 ys.)

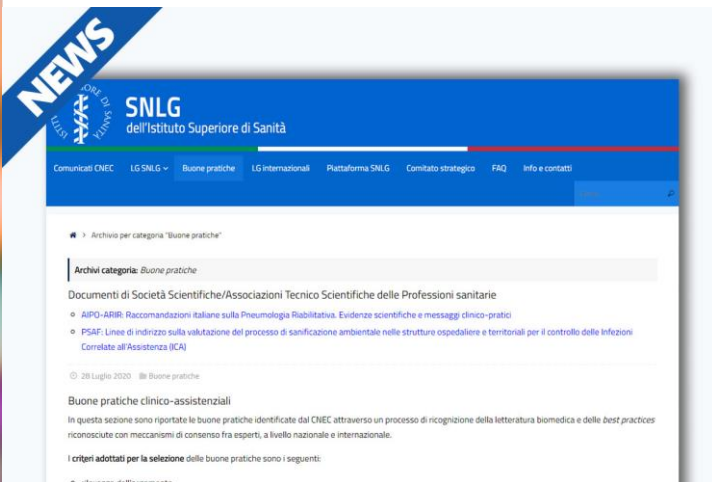
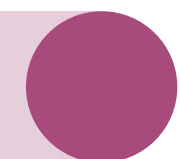
Source: www.haiprenotatovero.it

VAX update
A. Ghelardi





ITALIAN GUIDELINES NHS



SISTEMA NAZIONALE LINEE GUIDA DELL'ISTITUTO SUPERIORE DI SANITÀ

Linee guida condivise per la prevenzione del carcinoma della cervice uterina.
Follow-up post trattamento CIN2 e CIN3
Raccomandazione: vaccinazione anti-HPV post trattamento

Linea guida pubblicata nel Sistema Nazionale Linee Guida
Roma, 21 luglio 2020

CONCLUSIONI

Recommendation

Nelle donne con CIN 2 e CIN3 è raccomandata la vaccinazione anti-HPV perché migliora gli esiti al follow-up e riduce gli esiti avversi degli interventi chirurgici ripetuti.

Esito votazione:

- strong recommendation for the intervention: 13 (81%)
- conditional recommendation for the intervention: 3
- 1 assente

Justification

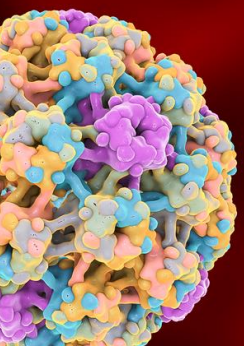
Overall justification

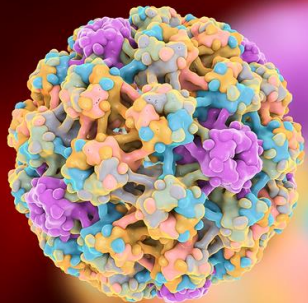
Il GDL ha espresso una raccomandazione forte in favore dell'utilizzo della vaccinazione anti-HPV nelle donne trattate per CIN2/3, considerando principalmente i rilevanti effetti desiderati attesi, a fronte di trascurabili eventi indesiderati.

Sebbene l'outcome inizialmente valutato come "incidenza di tumori invasivi" abbia una qualità delle prove "molto bassa", il panel all'unanimità in discussione plenaria ha valutato che gli outcomes "lesioni CIN2 e CIN3" fossero dei proxy validi del rischio di cancro invasivo, decisione coerente con le decisioni prese a livello internazionale nello sviluppo di raccomandazioni per la prevenzione del cancro della cervice uterina (ASCCP 2019, NHS 2020, SICPCV 2019). Inoltre, data l'efficacia preventiva del follow-up post trattamento, non è ragionevole aspettarsi tumori incidenti in popolazioni incluse in studi controllati sul vaccino nelle donne trattate per CIN2 e CIN3.

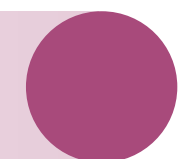


VAX update
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Something still unknown .. vaccination timing ?



HOPE 9

I risultati dello studio serviranno per la rivalutazione e stesura delle attuali linee guida.

in caso di esito positivo del trial, apertura verso una nuova indicazione del vaccino nonavalente.

SISTEMA NAZIONALE LINEE GUIDA DELL'ISTITUTO SUPERIORE DI SANITÀ

Linee guida condivise per la prevenzione del carcinoma della cervice uterina.
Follow-up post trattamento CIN2 e CIN3

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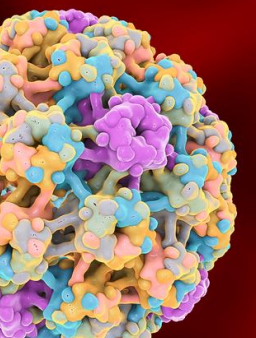


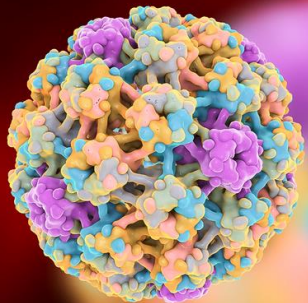
Research priorities

È necessario condurre studi per chiarire il timing ottimale della vaccinazione.

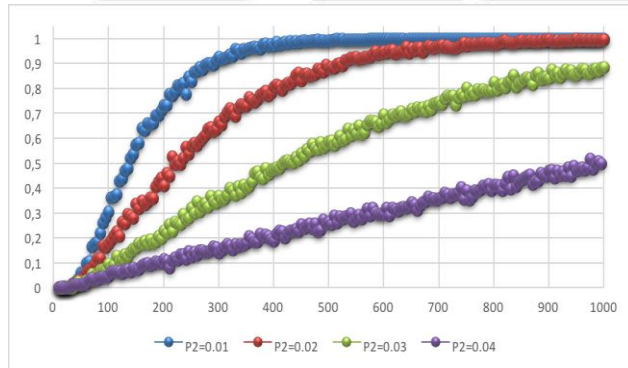
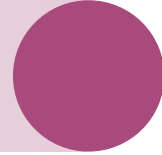
Perché i risultati siano più solidi e correttamente interpretabili in un modello di storia naturale della malattia, è importante che gli studi futuri, o re-analisi degli studi già pubblicati, siano in grado di distinguere recidive per trattamento inadeguato o persistenza dell'infezione originaria con lesioni dovute a nuove infezioni; Il GDL ritiene che sarà necessario rivalutare la raccomandazione alla luce di nuove evidenze prodotte dai trial in corso o pianificati, in particolare il trial pianificato in Italia ("HOPE9 STUDY" -HPV vaccine Opportunity Post-surgical Excision- ClinicalTrials.gov: NCT03848039) e il NOVEL trial -(ClinicalTrials.gov: NCT03979014) (1000 donne, Svezia e United Kingdom, descritto in Joura et al Eur J Cancer, 2018, allegato).

VAX update
A. Ghelardi





HOPE 9



Multicenter, randomised, double-blind clinical trial to evaluate the impact on disease relapse of presurgical 9-valent HPV vaccination in women treated with LEEP (loop electrosurgical excision procedure) for CIN2+ (high grade cervical intraepithelial neoplasia) and initially invasive cervical cancer.
(NTC03848039)
in order to investigate:

MECHANISM OF DISEASE RELAPSE

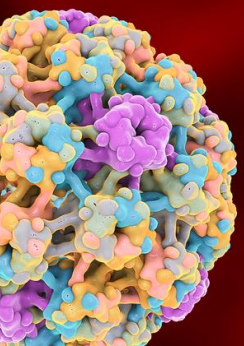
IMPACT ON DISEASE RELAPSE – NEW INDICATIONS

POST SURGICAL SURVEILLANCE – NEW GUIDELINES

NIH U.S. National Library of Medicine

ClinicalTrials.gov

VAX update
A. Ghelardi



CLINICAL IMMUNOLOGICAL EVALUATION OF EACH PATIENT..

TIME

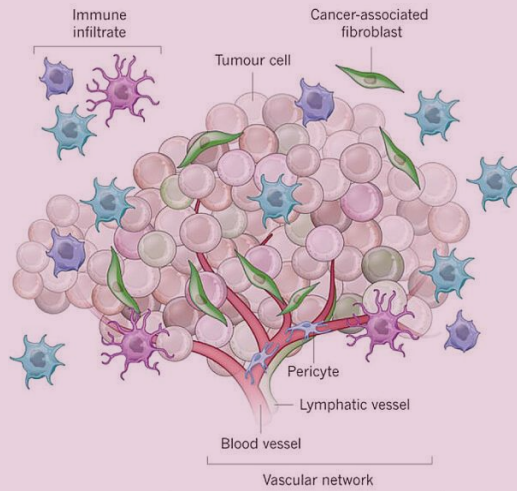
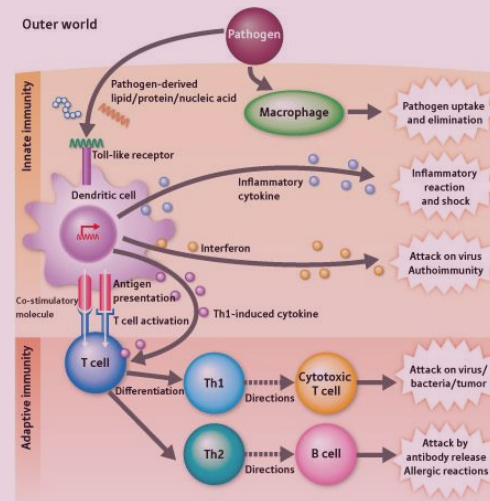


Figure 2: Cancer cells surrounded by microenvironment cells such as CAFs, immune cells, and pericytes. Image from Juntilla and de Sauvage, 2013 with permission.

CIRCULATING T&B CELLS



VAX update
A. Ghelardi

clinical findings

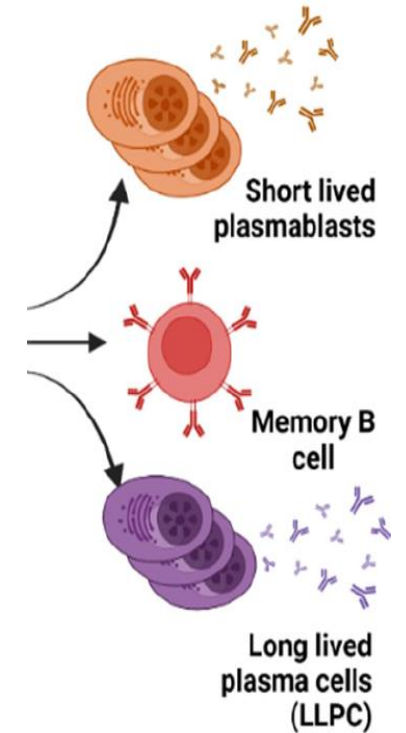
**NATURALLY ELICITED BMEM CELLS WERE GENERALLY NON-NEUTRALIZING,
VACCINATION WERE BOTH NEUTRALIZING AND OF HIGHER TITER.**

several studies have demonstrated the effectiveness of
the memory responses upon HPV vaccination..

HOPE 9



**B & T response to HPV vaccination in terms of:
cell number Ab production kinetics and durability**

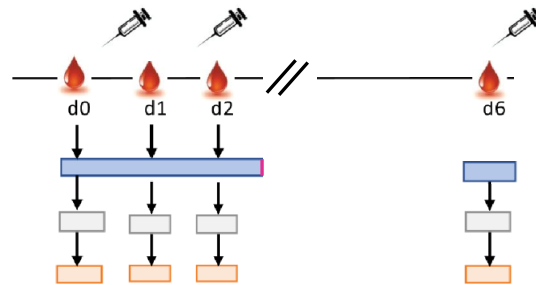


Einstein, M.H.; Baron, M.; Levin, M.J.; Chatterjee, A.; Edwards, R.P.; Zepp, F.; Carletti, I.; Dessy, F.J.; Trofa, A.F.; Schuind, A.; et al. Comparison of the immunogenicity and safety of Cervarix and Gardasil human papillomavirus (HPV) cervical cancer vaccines in healthy women aged 18–45 years. *Hum. Vaccines* 2009, 5, 705–719.

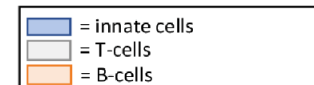
Einstein, M.H.; Levin, M.J.; Chatterjee, A.; Chakhtoura, N.; Takacs, P.; Catteau, G.; Dessy, F.J.; Moris, P.; Lin, L.; Struyf, F.; et al. Comparative humoral and cellular immunogenicity and safety of human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine and HPV-6/11/16/18 vaccine in healthy women aged 18–45 years: Follow-up through Month 48 in a Phase III randomized study. *Hum. Vaccines Immunother.* 2014, 10, 3455–3465.

Moscicki, A.B.; Wheeler, C.M.; Romanowski, B.; Hedrick, J.; Gall, S.; Ferris, D.; Poncelet, S.; Zahaf, T.; Moris, P.; Geeraerts, B.; et al. Immune responses elicited by a fourth dose of the HPV-16/18 AS04-adjuvanted vaccine in previously vaccinated adult women. *Vaccine* 2012, 31, 234–241.

IMMUNOLOGICAL EVALUATION



IMMUNOSYSTEM RESPONSE TO 9HPV VACCINE



- d0 ENROLLMENT PHASE - randomization 1:1 vaccine or placebo
- d1 7 days immunological evaluation
- d2 2 months after vaccination, surgical phase
- d6 test of cure 6 months after surgery

➔ VAGINAL MICROBIOMA EVALUATION during every phase of the study