La vaccination HPV après la prévention tertiaire : en post-thérapeutique

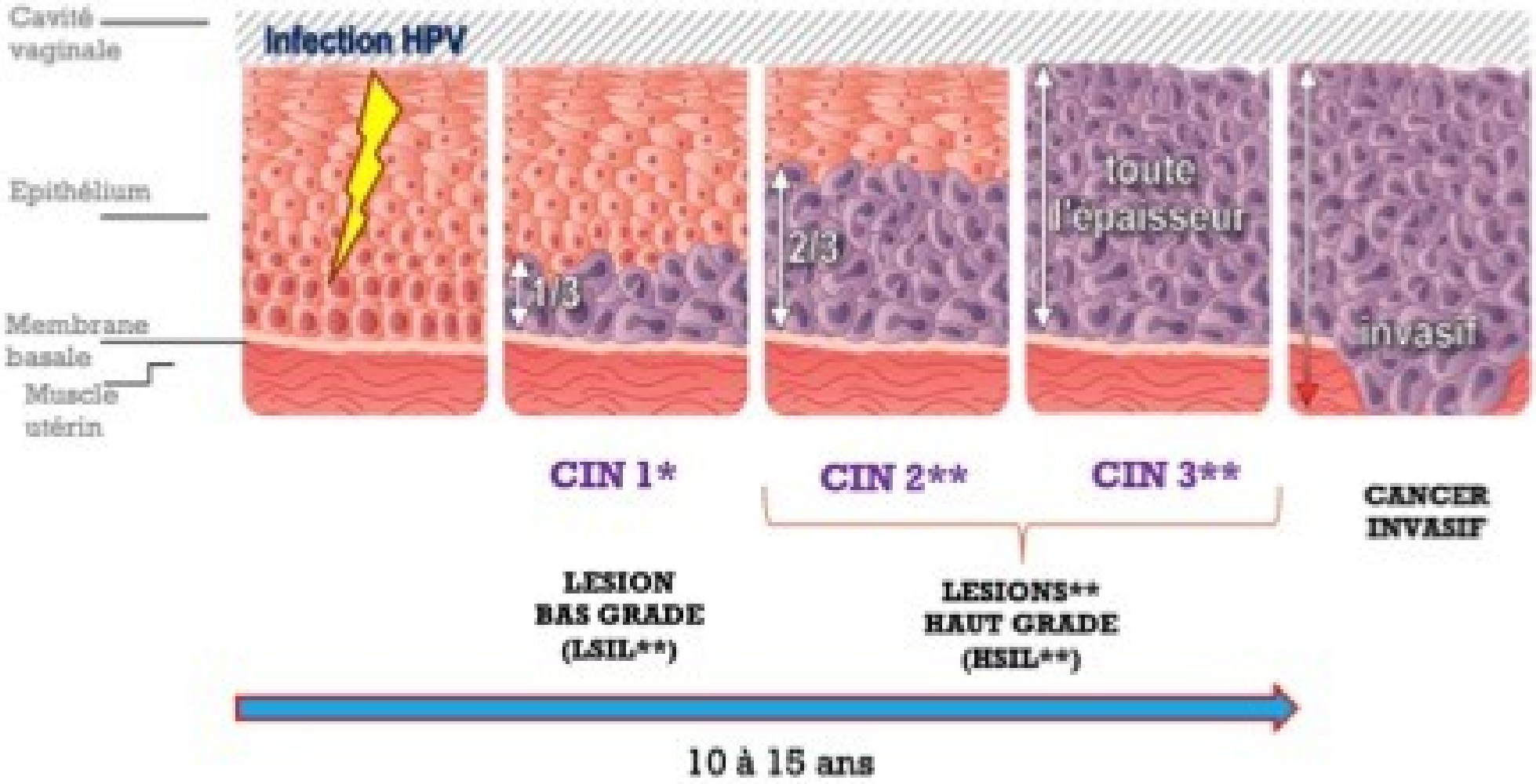
Didier Riethmuller

CHU GRENOBLE ALPES VOIRON

CNRP Centre National de Référence Papillomavirus

CARCINOGENÈSE ASSOCIÉE AUX HPV - EA3181

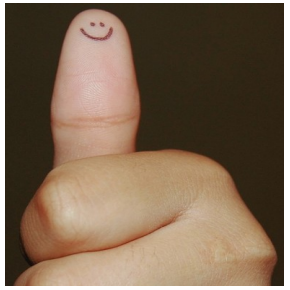
Progression lésionnelle



Nobbenhuis MA. Lancet 1999;354:20-5. Woodman CB. Lancet 2001;357:1831-6

De quoi parle-t-on ?

- PRÉVENTION PRIMAIRE
  - La prophylaxie vraie = **vaccination**
  - Protection incomplète (± 90 %)



- PRÉVENTION SECONDAIRE
  - **Dépistage**
    - ≠ frottis cervico-utérin ! (15 % FN…)
    - Optimisation…

- PRÉVENTION TERTIAIRE = **conisation** des HGSIL (CIN2-3)

La vaccination

contre les papillomavirus

protège du cancer du col de l'utérus

Plaidoyer pour la prevention primaire !

ars
Agence Régionale de Santé
Bretagne

2019

Dépistage aujourd'hui = test HPV !

- **Femmes de 25 à 29 ans : maintien des modalités de dépistage et des stratégies de triage**
  - *Examen cytologique* **tous les 3 ans après 2 tests normaux à 1 an d'intervalle**

Nb : Les infections HPV transitoires étant très fréquentes à cet âge => pas test HPV en 1ère intention

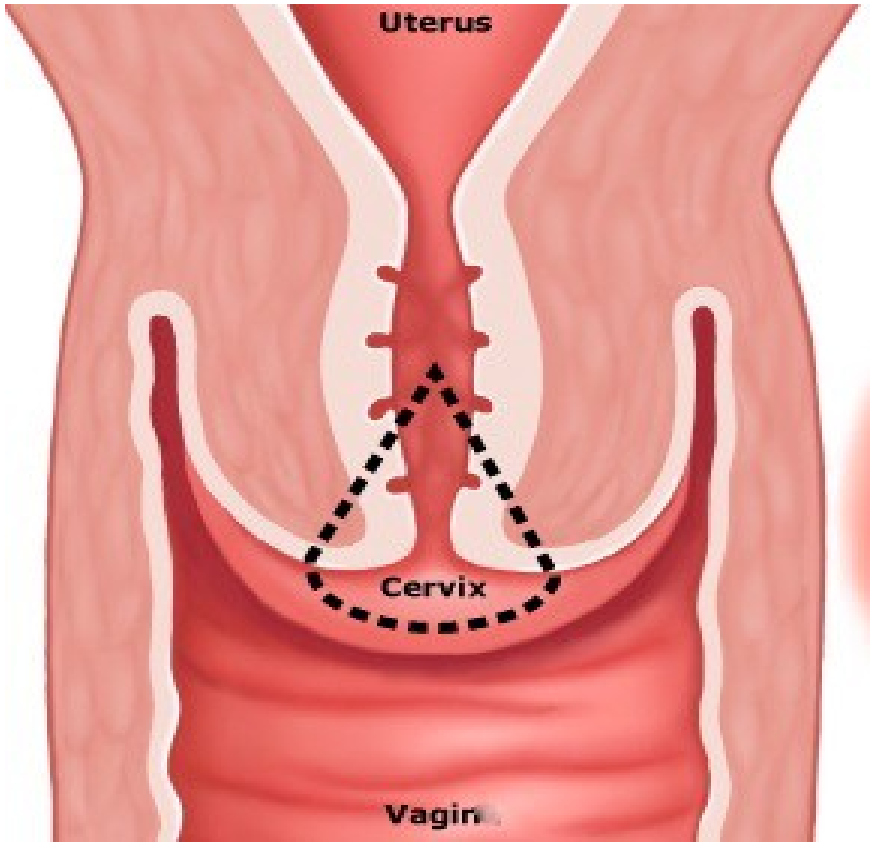
- **Femmes de 30 à 65 ans : évolution des modalités de dépistage et de triage**
  - **Test HPV remplace l'examen cytologique en dépistage primaire**
    - Test HPV : 3 ans après le dernier examen cytologique dont le résultat était normal
  - Si résultat du test HPV négatif : **intervalle de 5 ans** pour prochain test HPV
  - Si résultat positif : *triage par cytologie*

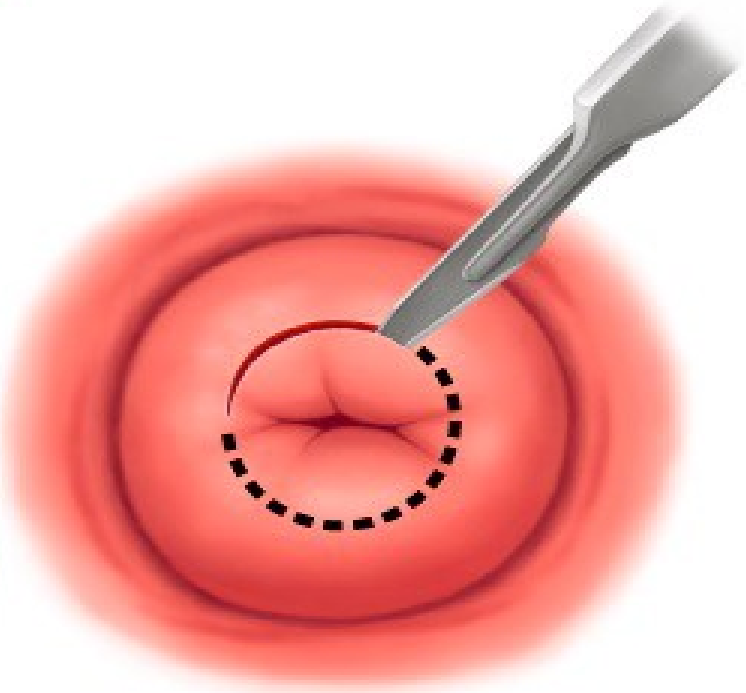
- **L'auto-prélèvement vaginal (APV) :** une alternative au prélèvement cervical par un professionnel de santé pour la réalisation d'un test HPV pour certaines femmes non ou insuffisamment dépistées

HAS - https://www.has-sante.fr/jcms/c_2806160/fr/evaluation-de-la-recherche-des-papillomavirus-humains-hpv-en-depistage-primaire-des-lesions-precancereuses-et-cancereuses-du-col-de-l-uterus-et-de-la-place-du-double-immuno-marquage-p16/ki67
(accédé le 06/09/19)

Conisation : prévention tertiaire

Résection et analyse anapath des HGSIL





LÉSIONS PRÉ-CANCÉREUSES DU COL

EVOLUTION ENTRE 2005 ET 2014 EN FRANCE

Lésions pré-cancéreuses du col :

En augmentation depuis 2005[1] :

~ +5,5%/an en moyenne

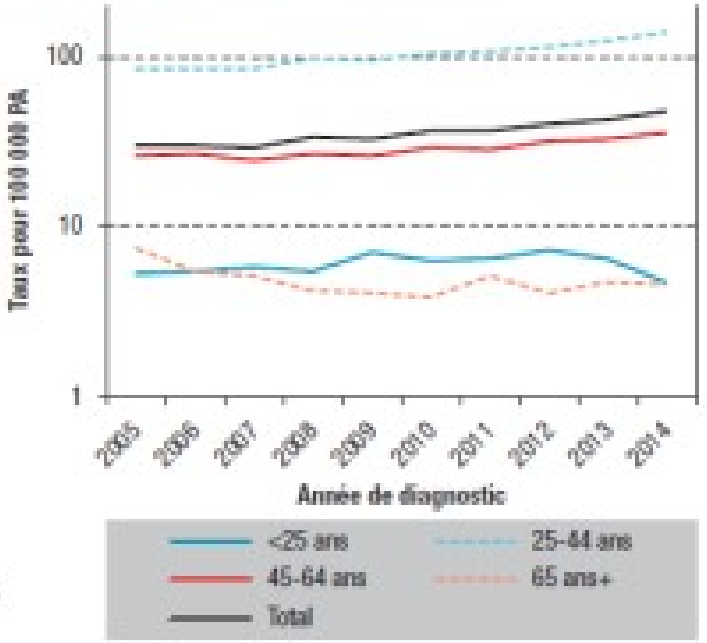
Taux d'incidence les plus élevés observés chez les 25-44 ans

Poids épidémiologique actuel:

~30 000 nouveaux cas de lésions pré-cancéreuses en France/an[2]

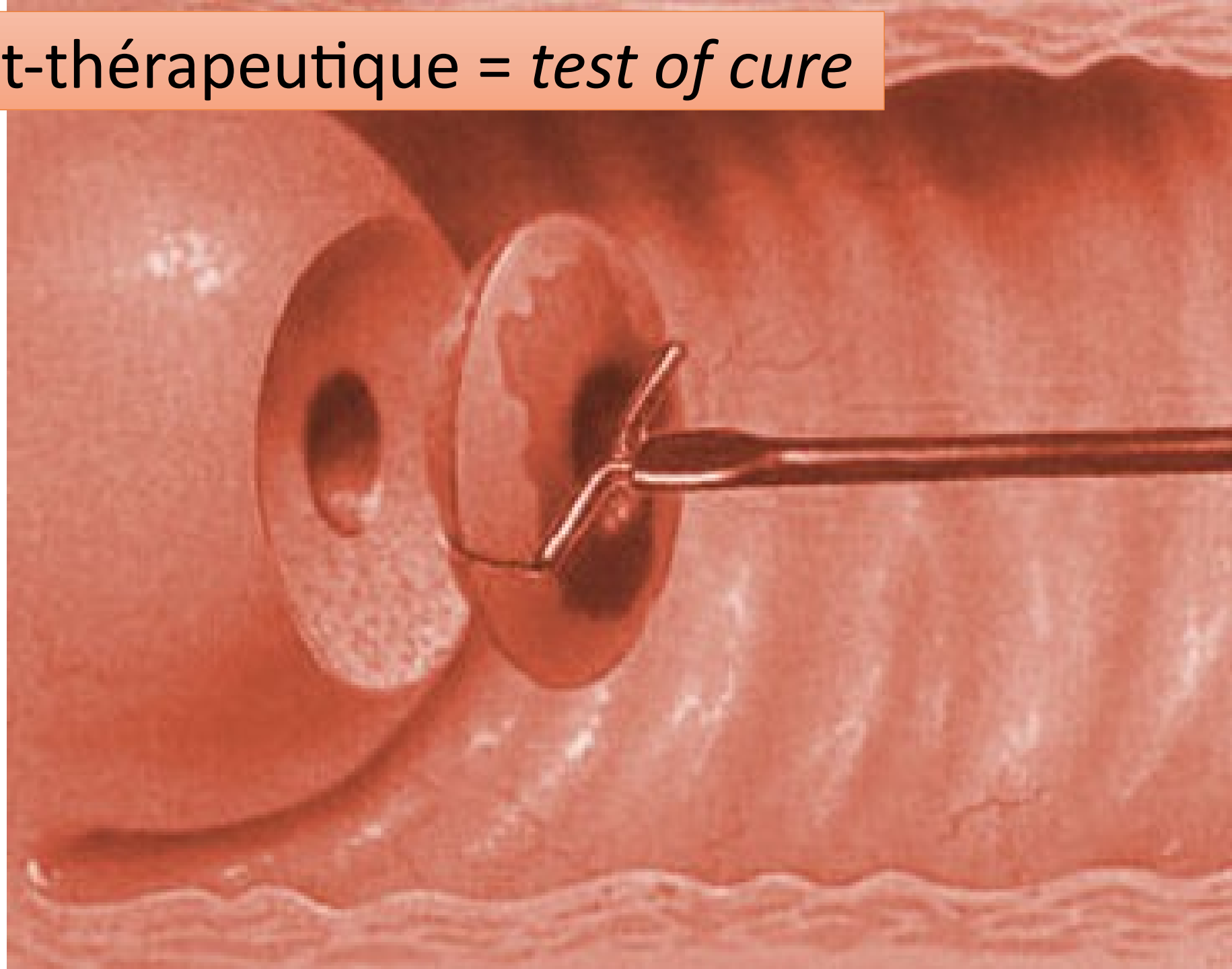
~ 36 000 conisations/an [3]

Taux d'incidence des lésions précancéreuses du col de l'utérus pour 100 000 personnes-années (PA) par groupe d'âge, zone registre, 2005-2014



- 1- Hamers et al. CCU en France : tendances de l'incidence et de la mortalité jusqu'en 2018. BEH 2019
- 2- INCA . IE-cancer. Vaccination anti-HPV et cancer du col de l'utérus. Avril 2017
- 3- De Rycke. Cervical cancer screening coverage, management of squamous intraepithelial lesions and related costs in France. Plos One 2020

Test HPV en post-thérapeutique = *test of cure*



Suivi post-traitement lésion de haut grade

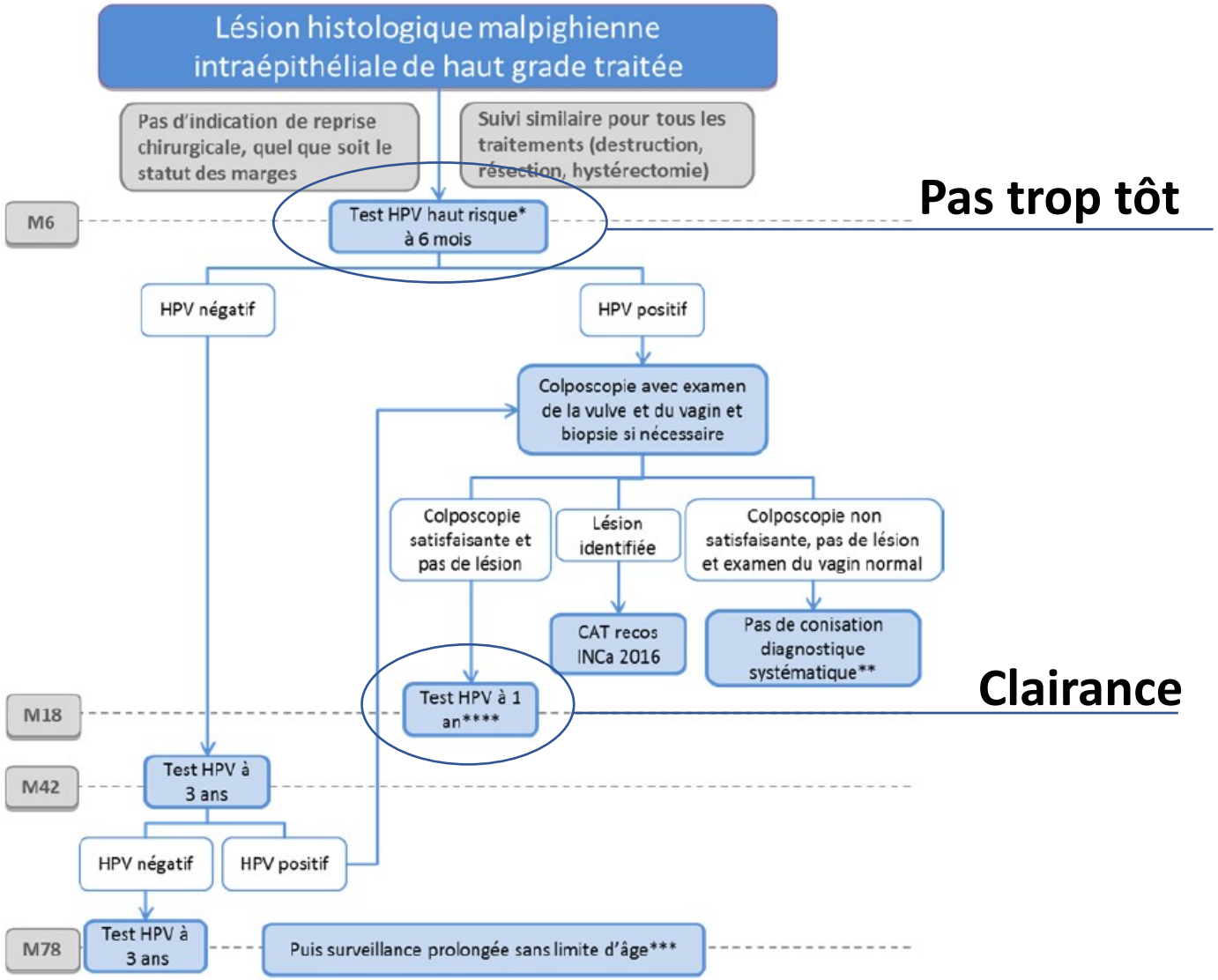
RECOMMANDATIONS ET RÉFÉRENTIELS

/Synthèse

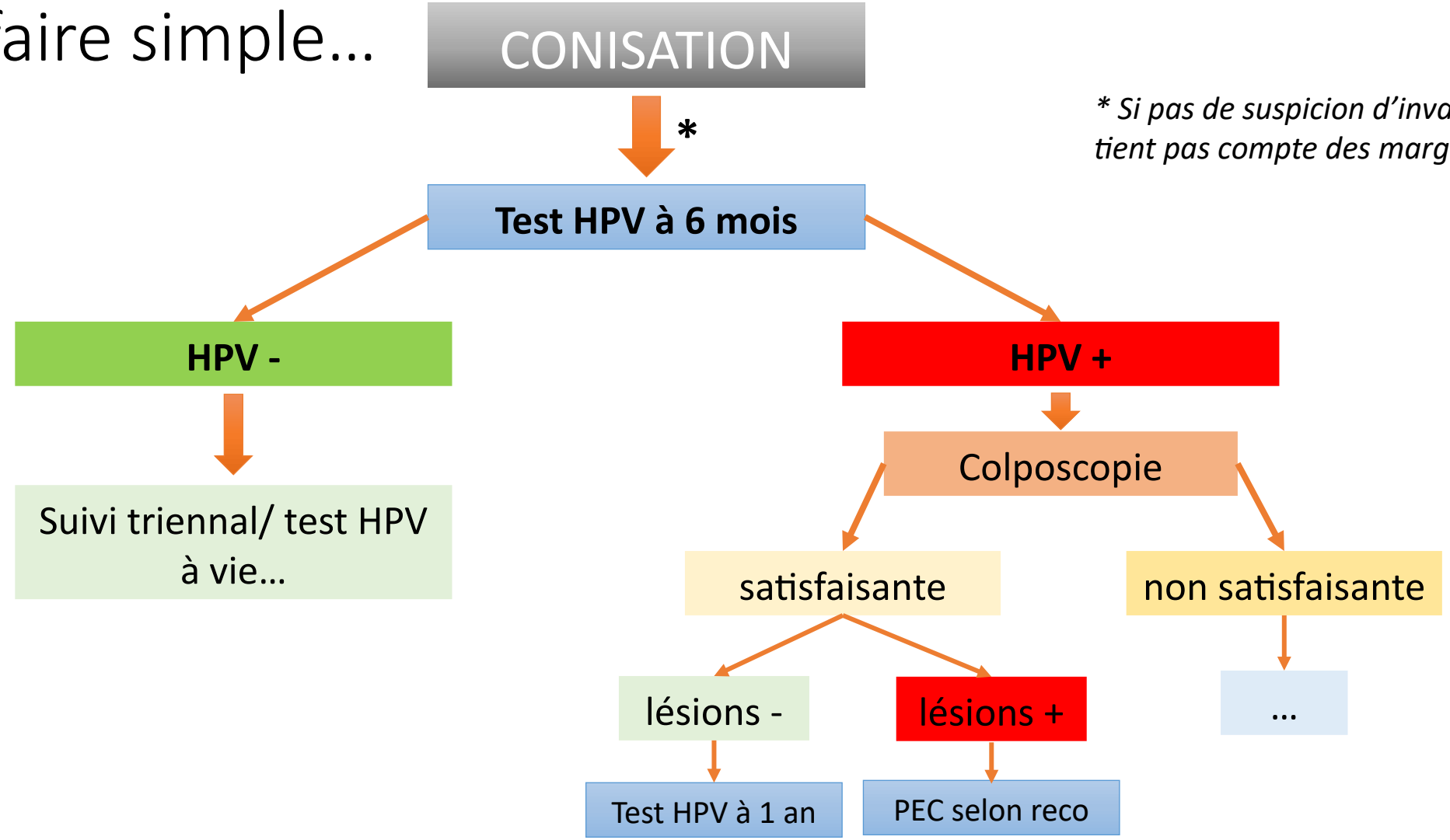
SURVEILLANCE POST-THÉRAPEUTIQUE DES LÉSIONS PRÉCANCÉREUSES DU COL DE L'UTÉRUS

INSTITUT NATIONAL DU CANCER

2019



Pour faire simple…



** Si pas de suspicion d'invasion, on ne tient pas compte des marges*

PLACE DE LA VACCINATION POST CONISATION ?

INTÉRÊT DE LA PRÉVENTION DES LÉSIONS PRÉCANCÉREUSES

Dans une étude portant sur plus de 178 000 femmes, les femmes ayant développé des lésions précancéreuses cervicales (CIN3) *avaient un risque durablement plus élevé* de développer *d'autres lésions / cancers HPV-induits*

Risque de développer un K col = 5 fois le risque de la population générale !

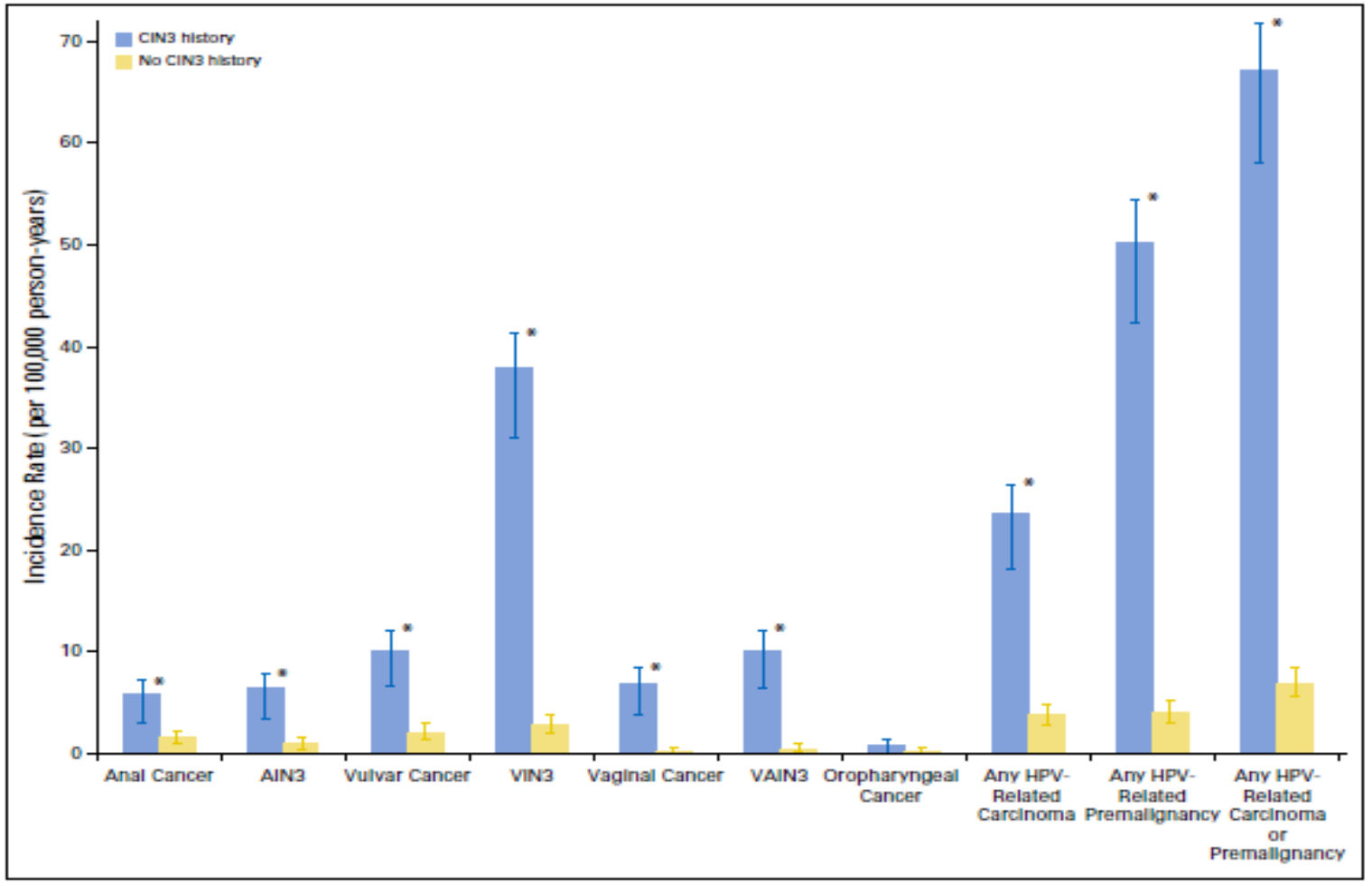


Fig 1. Estimated incidence rates of human papillomavirus (HPV)–related carcinomas and premalignancies, comparing women with and without a history of cervical intraepithelial neoplasia grade 3 (CIN3). The first year after diagnosis of CIN3 or benign dermal nevus was included in the incidence rate visualized in this figure. Error bars indicate 95% CIs of estimated incidence rates. The asterisks indicate a significant difference in incidence rates of the group with a history of CIN3 compared with the group without a history of CIN3. Data are in Table 2. AIN3, anal intraepithelial neoplasia grade 3; VAIN3, vaginal intraepithelial neoplasia grade 3; VIN3, vulvar intraepithelial neoplasia grade 3.

➢ 1 – Ebish et al. J Clinical Oncology. 2017

Prévention du cancer du col au-delà de 2024 ?

Place de la vaccination post-thérapeutique

Vaccination “thérapeutique” : décevante à ce jour…

Microbial Pathogenesis 165 (2022) 105462

Contents lists available at ScienceDirect

Microbial Pathogenesis

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

Check for updates

Immunoinformatics-based characterization of immunogenic CD8 T-cell epitopes for a broad-spectrum cell-mediated immunity against high-risk human papillomavirus infection

Alexandre Santos Matos [a], Fernanda Oliveira Prado [a], Paloma Aparecida Santos Rocha [a], Marcus Vinicius Aragão Batista [a,*]

[a] *Laboratory of Molecular Genetics and Biotechnology (GMBio), Department of Biology, Center for Biological and Health Sciences, Federal University of Sergipe, São Cristóvão, Brazil*

Effect of the human papillomavirus (HPV) quadrivalent vaccine in a subgroup of women with cervical and vulvar disease: retrospective pooled analysis of trial data

HPV4

BMJ

What is already known on this subject

Prophylactic vaccination with quadrivalent HPV vaccine is highly efficacious in preventing cervical intraepithelial neoplasia, adenocarcinoma in situ, vulvar intraepithelial neoplasia, vaginal intraepithelial neoplasia, and genital warts

HPV vaccination does not reduce progression to cervical pre-cancers in women with ongoing infections at the time of vaccination, but the effect of vaccination in preventing subsequent disease after treatment is unknown

What this study adds

Vaccination with quadrivalent HPV vaccine was associated with a reduction of subsequent cervical, vulvar, and vaginal intraepithelial neoplasia and genital warts in women who were diagnosed and treated for cervical and vulvar or vaginal disease in two clinical trials of four year duration

Vaccination was associated with a reduction of subsequent disease irrespective of causal HPV type by 35–46%

A total of 587 vaccine and 763 placebo recipients underwent cervical surgery

2012 Joura E et al.

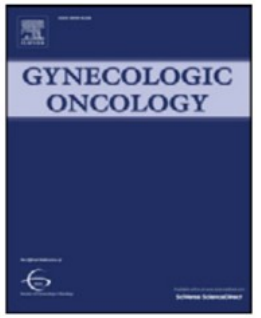
protocol 013 (FUTURE I) and protocol 015 (FUTURE II)

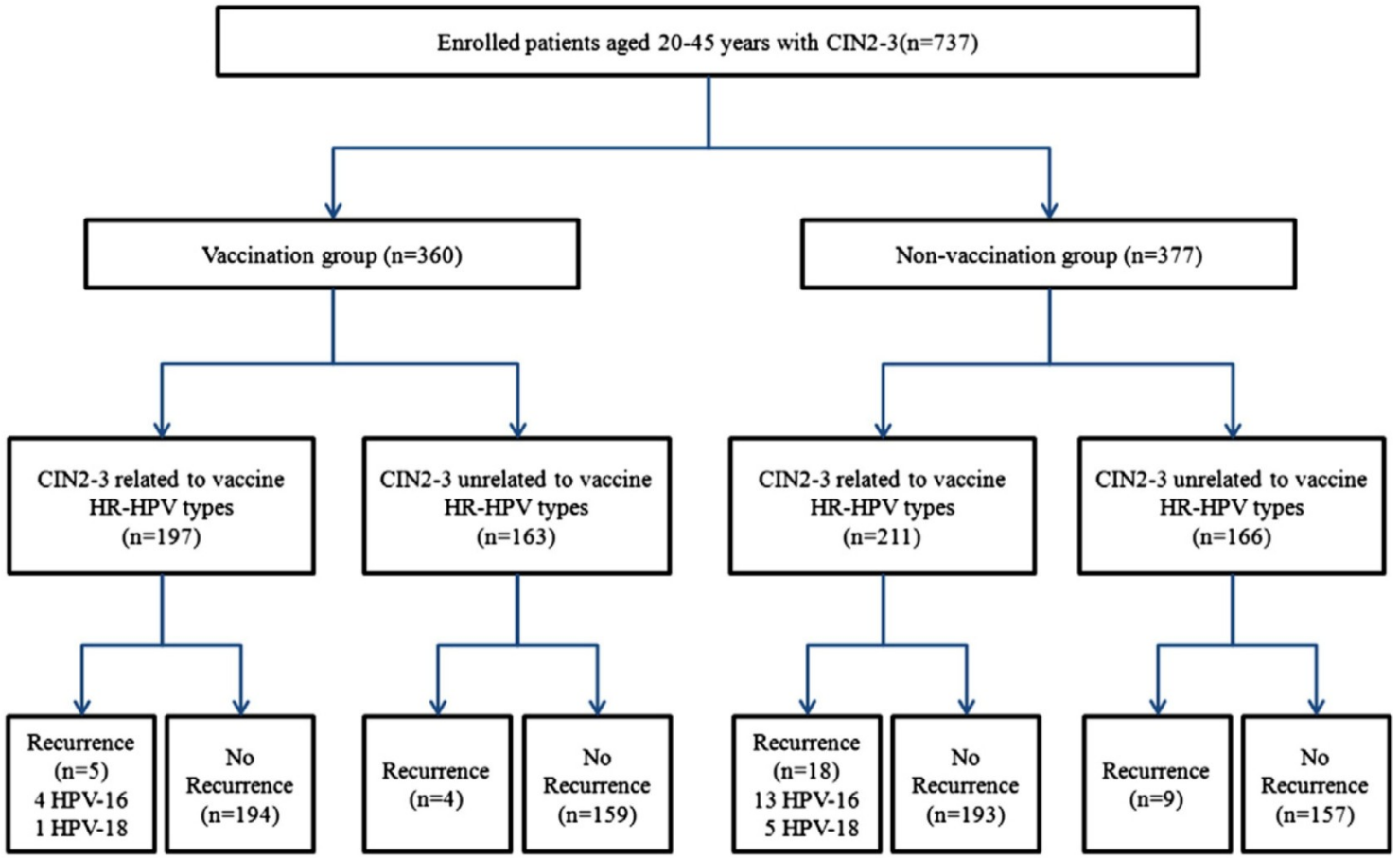
Is vaccination with quadrivalent HPV vaccine after loop electrosurgical excision procedure effective in preventing recurrence in patients with high-grade cervical intraepithelial neoplasia (CIN2–3)?☆

Woo Dae Kang, Ho Sun Choi, Seok Mo Kim *

HPV4

2013





*Vaccine HR-HPV types, HPV 16 or 18 types

Gynecologic Oncology 130 (2013) 264–268

Is vaccination with quadrivalent HPV vaccine after loop electrosurgical excision procedure effective in preventing recurrence in patients with high-grade cervical intraepithelial neoplasia (CIN2–3)?☆

HPV4

Woo Dae Kang, Ho Sun Choi, Seok Mo Kim *

2013

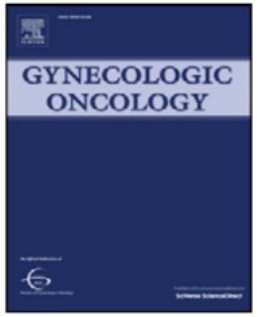


Table 5
Progression-free survival analysis by the Cox model.

	Hazards ratio (95% CI)	*P* value
Cone margin		
Positive versus negative	4.869 (2.365–10.221)	<0.01
Endocervical cytology		
Positive versus negative	3.102 (1.363–7.062)	<0.01
Vaccination		
Non-recipients versus recipients	2.840 (1.335–6.042)	<0.01

Gynecologic Oncology 130 (2013) 264–268

Prior human papillomavirus-16/18 AS04-adjuvanted vaccination prevents recurrent high grade cervical intraepithelial neoplasia after definitive surgical therapy: *Post-hoc* analysis from a randomized controlled trial

HPV2

2016

IJC
International Journal of Cancer

We evaluated the efficacy of the human papillomavirus (HPV)−16/18 AS04-adjuvanted vaccine in preventing HPV-related disease after surgery for cervical lesions in a *post-hoc* analysis of the PApilloma TRIal against Cancer In young Adults (PATRICIA; NCT00122681). Healthy women aged 15–25 years were randomized (1:1) to receive vaccine or control at months 0, 1 and 6 and followed for 4 years. Women were enrolled regardless of their baseline HPV DNA status, HPV-16/18 serostatus, or cytology, but excluded if they had previous or planned colposcopy. The primary and secondary endpoints of PATRICIA have been reported previously; the present *post-hoc* analysis evaluated efficacy in a subset of women who underwent an excisional procedure for cervical lesions after vaccination. The main outcome was the incidence of subsequent HPV-related cervical intraepithelial neoplasia grade 2 or greater (CIN2+) 60 days or more post-surgery. Other outcomes included the incidence of HPV-related CIN1+, and vulvar or vaginal intraepithelial neoplasia (VIN/VaIN) 60 days or more post-surgery. Of the total vaccinated cohort of 18,644 women (vaccine = 9,319; control = 9,325), 454 (vaccine = 190, control = 264) underwent an excisional procedure during the trial. Efficacy 60 days or more post-surgery for a first lesion, irrespective of HPV DNA results, was 88.2% (95% CI: 14.8, 99.7) against CIN2+ and 42.6% (−21.1, 74.1) against CIN1+. No VIN was reported and one woman in each group had VaIN2+ 60 days or more post-surgery. Women who undergo surgical therapy for cervical lesions after vaccination with the HPV-16/18 vaccine may continue to benefit from vaccination, with a reduced risk of developing subsequent CIN2+.

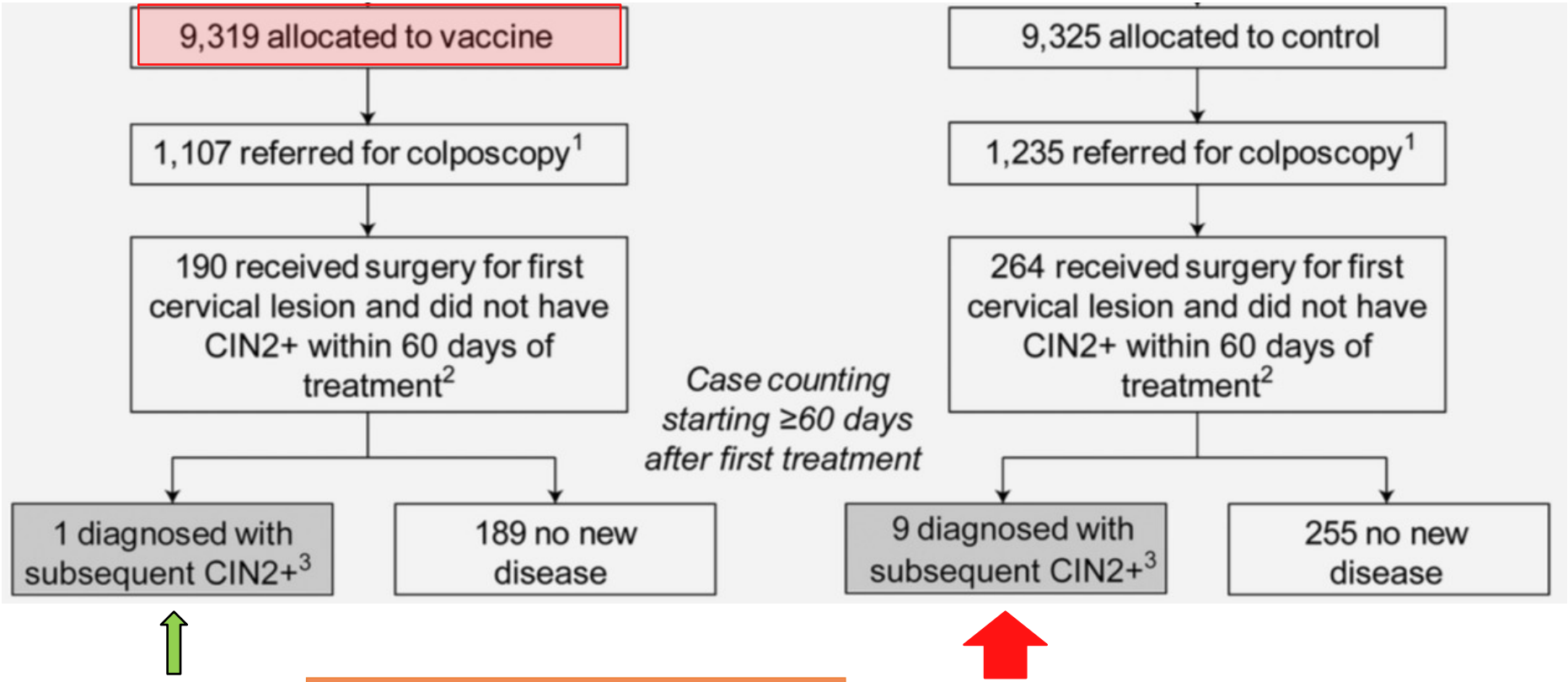
median follow-up 47.4 months after first vaccine dose

Garland SM et al.

Prior human papillomavirus-16/18 AS04-adjuvanted vaccination prevents recurrent high grade cervical intraepithelial neoplasia after definitive surgical therapy: *Post-hoc* analysis from a randomized controlled trial

2016

IJC
International Journal of Cancer



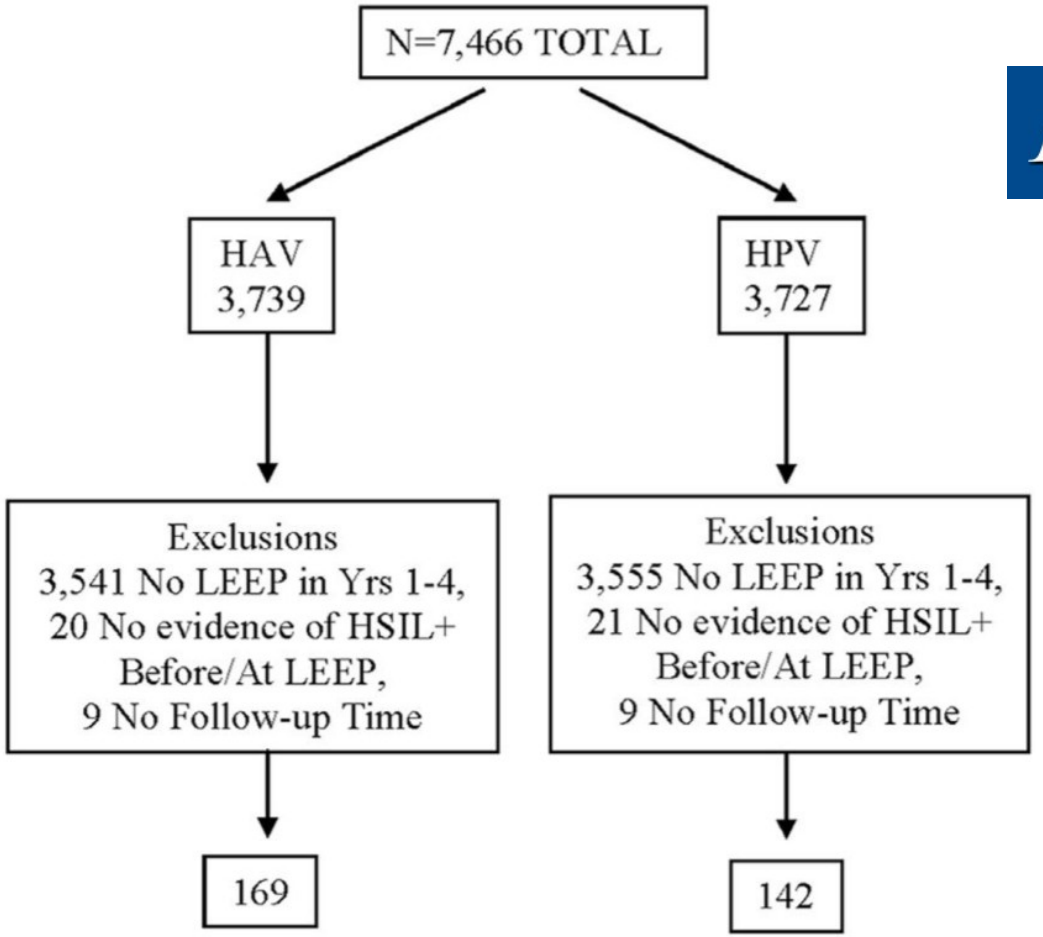
Réduction du risque > 88 %

Garland SM et al.

Impact of human papillomavirus (HPV) 16 and 18 vaccination on prevalent infections and rates of cervical lesions after excisional treatment

2016

HPV2



AJOG American Journal of Obstetrics & Gynecology

Hildesheim A et al. Am J Obstet Gynecol 2016; 215(2): 212.e1–212.e15

Impact of human papillomavirus (HPV) 16 and 18 vaccination on prevalent infections and rates of cervical lesions after excisional treatment

AJOG American Journal of Obstetrics & Gynecology

2016

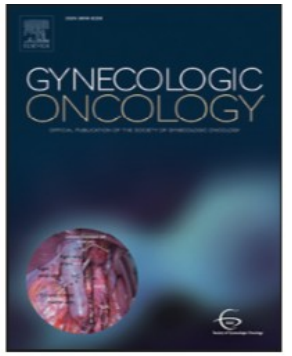
CONCLUSION—We find no evidence for a vaccine effect on the fate of detectable human papillomavirus infections. We show that vaccination does not protect against infections/lesions after treatment. Evaluation of vaccine protection against new infections and resultant lesions warrants further consideration in future studies.

- N'améliore pas clearance infection en cours
- Pas de diminution risque de nouvelles infections ou de nouvelles CIN mais…
- Mélange les infections et les lésions… et finalement…

- Efficacité vaccinale estimée après traitement des CIN2+ sur :
  - infections incidentes à HPV16/18 = 57,9% (IC 95% ; −44-88)
  - Infections HPV31/33/45 = 72,9% (IC95% ; 29-90)
  - infections à HPV oncogéniques après traitement des CIN2+ : 36,7% (IC95% : 1,5-59)

Hildesheim A et al. Am J Obstet Gynecol 2016; 215(2): 212.e1–212.e15

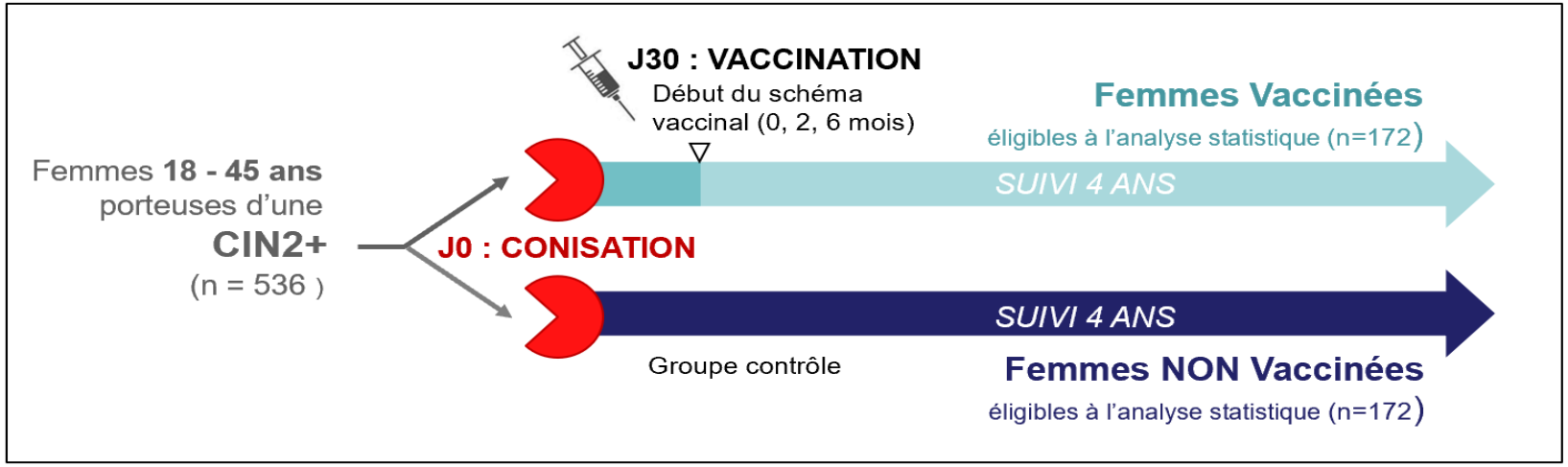
Bénéfice de la vaccination HPV quadrivalente en prévention des récidives de CIN2+ après conisation- **SPERANZA Project** : vaccin HPV après traitement CIN2



HPV4

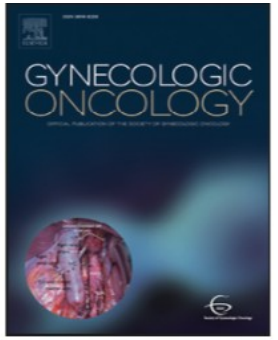
2018

- **Etude contrôlée <u>prospective</u>**
  - Etude non randomisée
    - Les femmes incluses décidaient, après une réunion d'information, d'être vaccinées ou pas
- **536 patientes de 18 à 45 ans porteuses d'une CIN2+ incluses**
  - 344 femmes retenues pour l'analyse
    - Exclusion des patientes perdues de vue, suivies pendant une durée <6 mois, ou présentant une lésion résiduelle
  - Le groupe *vaccinées* et le groupe *non vaccinées* étaient comparables
    - pour l'âge, le grade colposcopique et histologique de la lésion, l'état des marges de la conisation

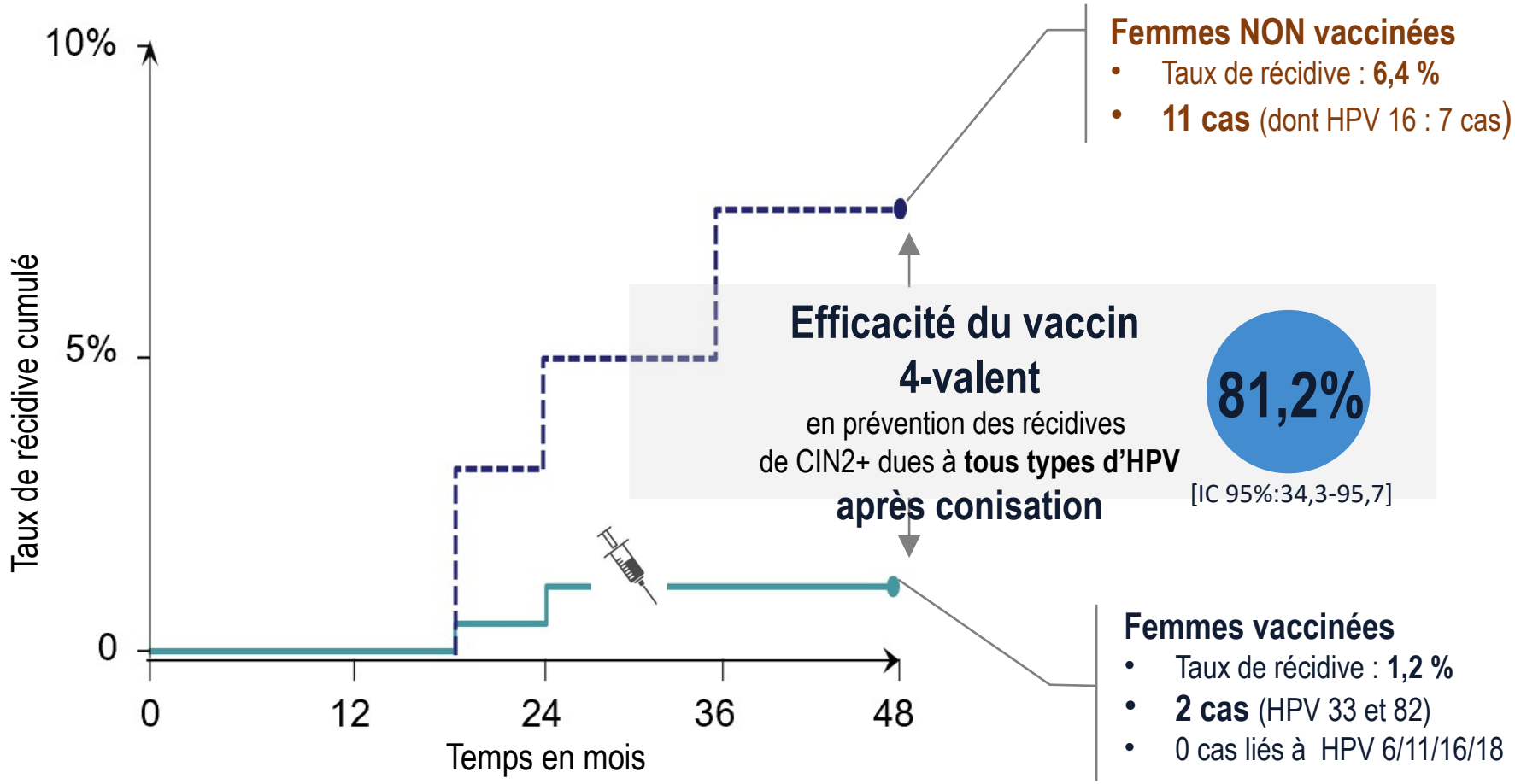


Ghelardi A et al. 2018

Bénéfice de la vaccination HPV quadrivalente en prévention des récidives de CIN2+ après conisation - **SPERANZA Project** : vaccin HPV après traitement CIN2

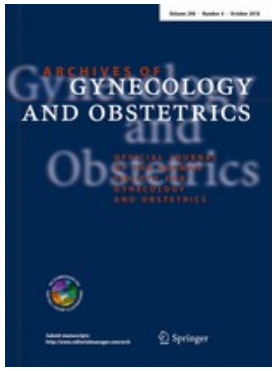


2018



Ghelardi A. &t al. Gynecol Oncol. 2018

Indication of prophylactic vaccines as a tool for secondary prevention in HPV-linked disease



HPV4

2018

RCT

178 patientes

À 3 mois

89 vaccinées

89 non vaccinées

Suivi tous les 6 mois pendant au moins 3 ans

Pieralli A et al. Arch Gynecol Obstet 2018

Indication of prophylactic vaccines as a tool for secondary prevention in HPV-linked disease

2018

Table 1 Statistical analysis using the Fisher's exact test showed that vaccination was a useful tool for reducing the incidence of post-treatment recurrence ($p = 0.0279$)

	Relapse	No relapse	Marginal row total
Vaccination	3	86	89
Non-vaccination	12	77	89
Marginal column total	15	163	178 (grand total)

The Fisher's exact test statistic value is 0.0279. The result is significant at $p < 0.05$

Pieralli A et al. Arch Gynecol Obstet 2018

Indication of prophylactic vaccines as a tool for secondary prevention in HPV-linked disease

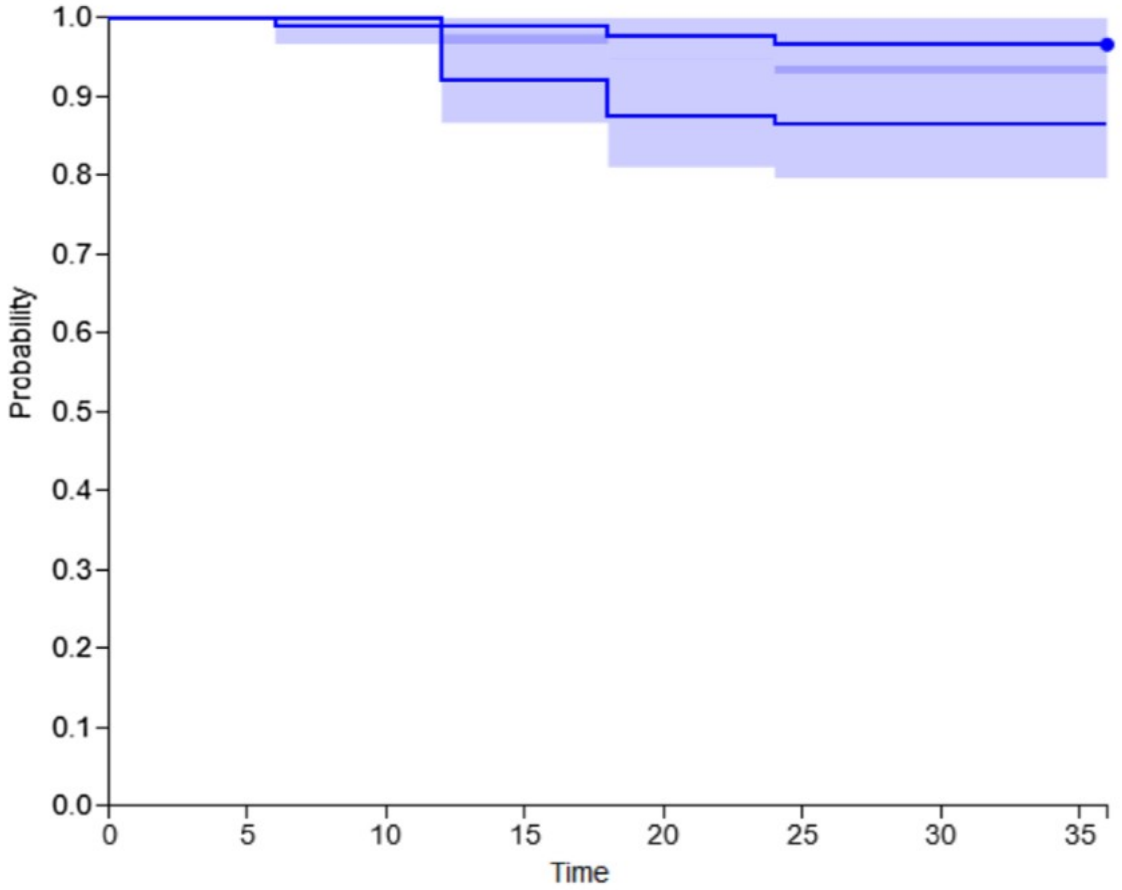
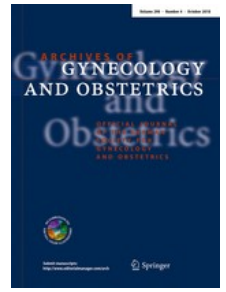


Fig. 1 Kaplan–Meier's curves show the difference during the follow-up period for the overall disease-free survival in two groups. The comparison between the two groups, done with the log rank test, was statistically significant ($z = 2.44$, $p = 0.0147$)



2018

Pieralli A et al. Arch Gynecol Obstet 2018

vaccines

MDPI

Article

HPV Vaccination as Adjuvant to Conization in Women with Cervical Intraepithelial Neoplasia: A Study under Real-Life Conditions

2020

Marta del Pino [1,2,*], Cristina Martí [1], Ines Torras [1], Carla Henere [1], Meritxell Munmany [1], Lorena Marimon [3], Adela Saco [3], Aureli Torné [1,2,†] and Jaume Ordi [3,4,†]

Table 4. Persistent/recurrent disease at the end of follow-up in vaccinated and non-vaccinated women related to the first post-conization control status. Values are absolute numbers and percentages.

	Clinical Outcome at the End of Follow-Up			
Status at the First Post-Conization Control (6 Months)	**No Disease**	**Persistent/Recurrent LSIL/HPV**	**Persistent/Recurrent HSIL**	***p* ***
No disease (n = 153)				0.032
Non-vaccinated	55 (83.3)	7 (10.7)	4 (6.1)	
Vaccinated	78 (89.7)	9 (10.3)	0 (0.0)	
Persistent LSIL/HPV (n = 101)				0.173
Non-vaccinated	28 (65.1)	9 (20.9)	6 (14.0)	
Vaccinated	33 (56.9)	21 (36.2)	4 (6.9)	
Persistent HSIL/CIN2-3 (n = 11)				0.131
Non-vaccinated	0 (0.0)	1 (33.3)	2 (66.7)	
Vaccinated	3 (37.5)	4 (50.0)	1 (12.5)	

Should we vaccinate women a the time of conization (Maria Kirgiou)

Conisation + vaccin HPV ?

EUROGIN
INTERNATIONAL MULTIDISCIPLINARY HPV CONGRESS
Accelerating detection and elimination of HPV and related cancers

2021

Women that have conisation for HSIL

- at high risk of HSIL recurrence – 8%
- at high risk of cervical cancer – 2-5xfold
- these women constitute a subgroup of infected women particularly sensitive to the infection & rapidly acquire re-infections
- need to risk-reducing adjuvant treatment for high-risk population
- repeat conisations multiply adverse reproductive outcomes

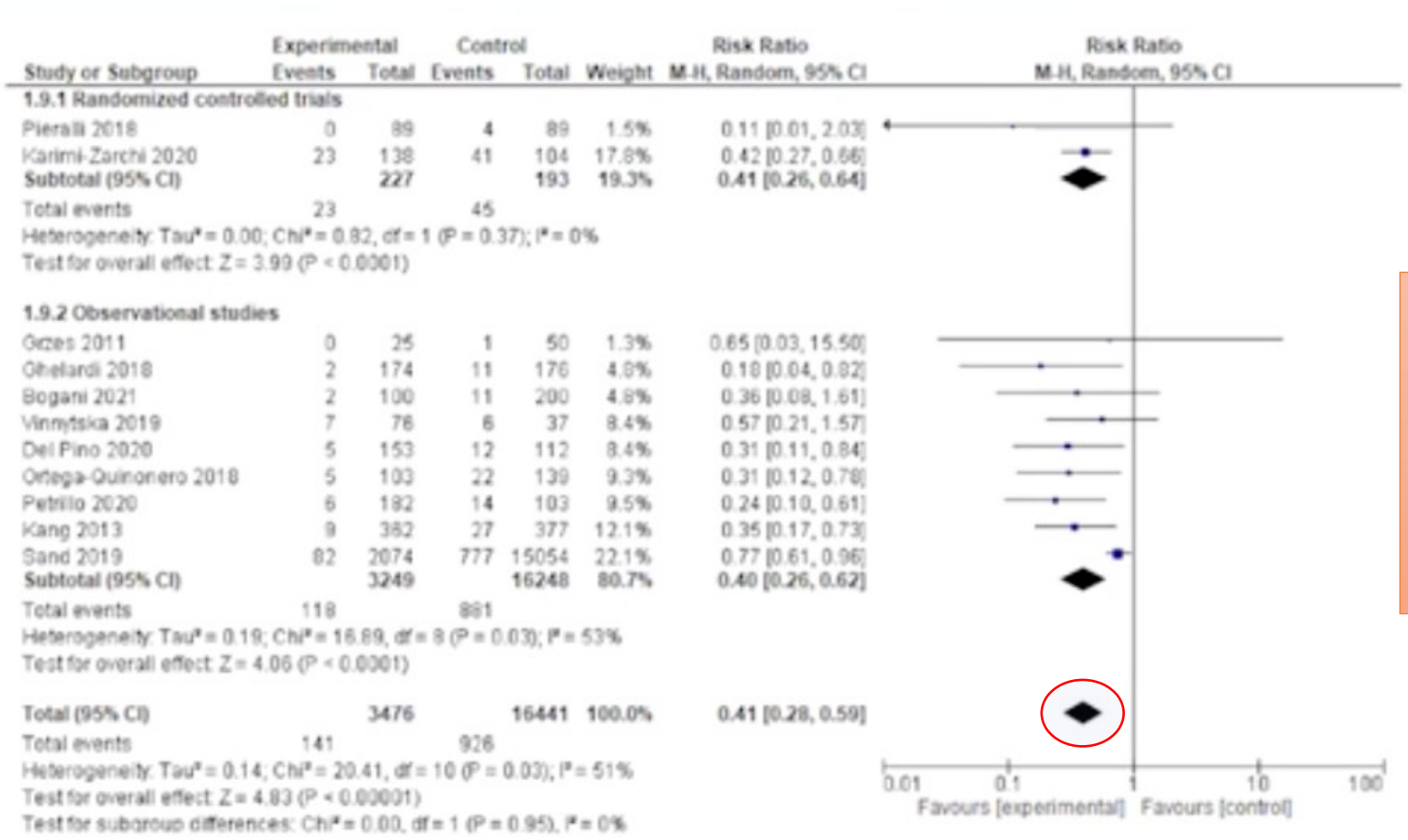
Rationnel

The vaccine

- Is expected to benefit against **new** infections (not present at Tx)
- Is expected to benefit **re-occurrence** of the same infection
- Remains an open question whether will **boost** the effect of treatment

NB : arrivée vaccin HPV9 !

Should we vaccinate women a the time of conization (Maria Kirgiou)



Données très encourageantes mais possibilités de biais dans ces études

Kachagias 2021 (unpublished)

Méta-analyse de 18 études dont 12 observationnelles, 2 études randomisées contrôlées et 4 analyses post-hoc d'études randomisées

La vaccination HPV était associée avec une réduction significative du risque de récurrence de CIN2+ :

RR = 0,41; IC95% : 0,28-0,59; I^2 = 51%

Should we vaccinate women a the time of conization (Maria Kirgiou 2021)

NOVEL Trial
Nonavalent prophylactic HPV vaccine (GARDASIL9) after local conservative treatment for cervical intra-epithelial neoplasia

- **Women that have conisation for HSIL:** High-risk population particularly sensitive to the infection & rapidly acquire re-infections and need to risk-reducing adjuvant treatment for high-risk population

- **Randomised controlled trial** – 51 months

  Vaccine: Gardasil 9™ vaccine (N=500)

  Control: no vaccine (N=500)

- **Inclusion:** Female (18-55y), attending for local treatment for presumed or biopsy-confirmed CIN2 - CIN3 - cGIN/AIS

- **Objective:** to demonstrate that the vaccine when initiated at the time of conisation will reduce subsequent persistent HPV infection in women with high-grade CIN

Essai randomisé multicentrique (UK, Finland, Sweden)

- > 30 mois de suivi
- > 7 visites

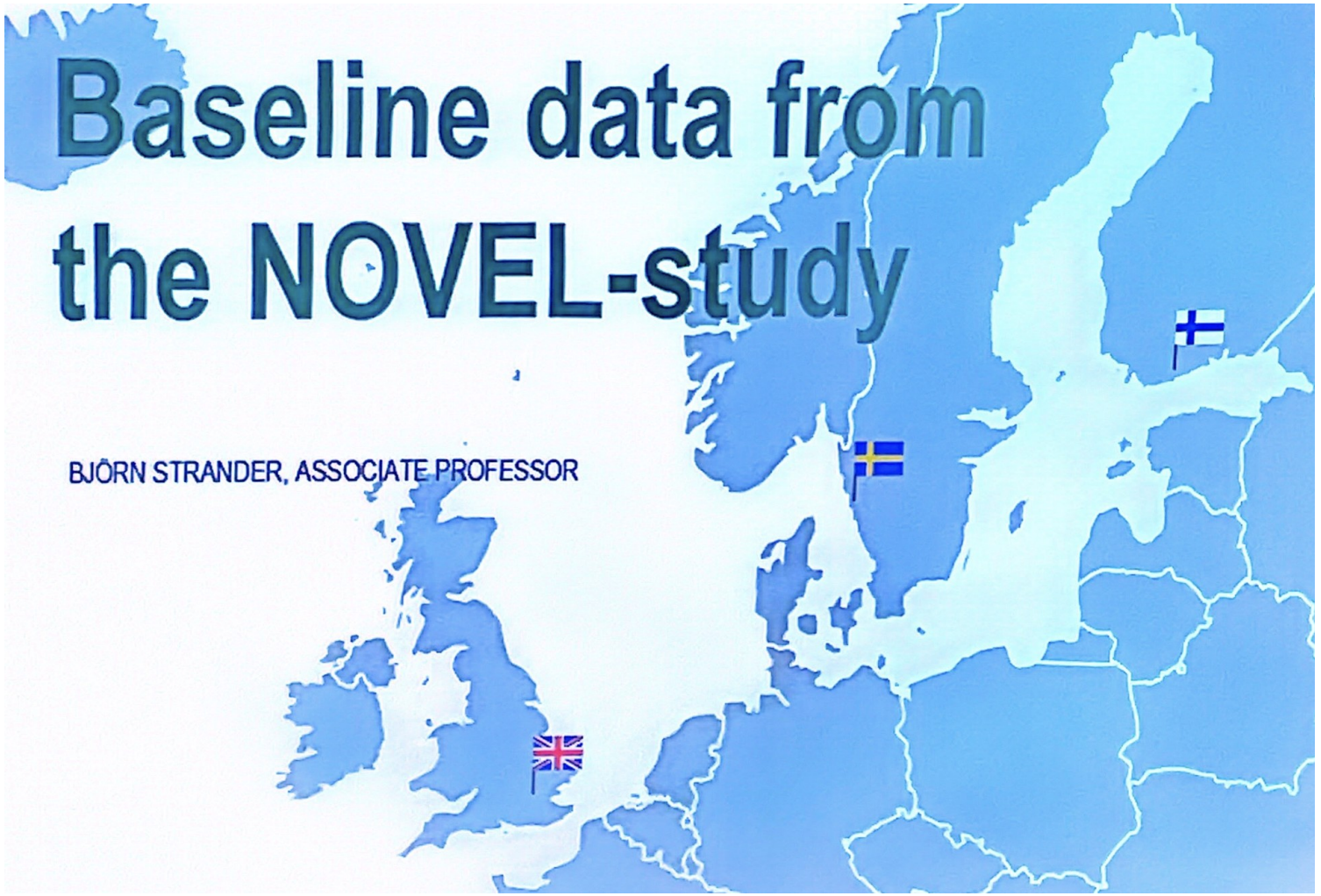
« il est temps de faire cet essai avant que les cohorte de vaccination n'arrivent à l'âge du dépistage »

NHS National Institute for Health Research

Karolinska Institutet

EUROGIN
INTERNATIONAL MULTIDISCIPLINARY HPV CONGRESS
Accelerating detection and elimination of HPV and related cancers

International HPV Reference Center



3 pays : UK, Suède et Finlande
1100 patientes incluses
Données exploitables

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SYSTEMATIC REVIEW

Human papillomavirus vaccination in women undergoing excisional treatment for cervical intraepithelial neoplasia and subsequent risk of recurrence: A systematic review and meta-analysis

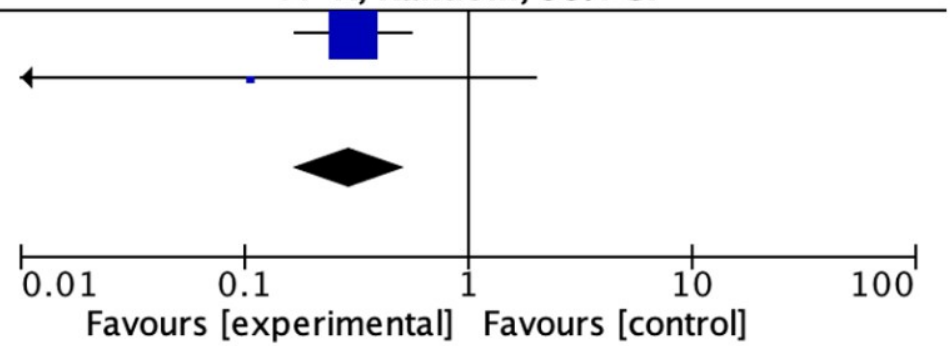
Dina Overgaard Eriksen[1,2,3] | Pernille Tine Jensen[1,2] | Jeppe Bennekou Schroll[4,5] | Anne Hammer[1,2,3]

9 études analysées dont 2 RCT

Study or Subgroup	HPV vaccine Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Karim-Zarchi 2020 (1)	23	138	41	104	96.0%	0.31 [0.17, 0.56]
Pieralli 2018 (2)	0	89	4	89	4.0%	0.11 [0.01, 2.00]
Total (95% CI)		**227**		**193**	**100.0%**	**0.29 [0.16, 0.53]**
Total events	23		45			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.49$, df = 1 (P = 0.48); $I^2 = 0\%$

Test for overall effect: Z = 4.10 (P < 0.0001)



Conclusions: HPV vaccination post-treatment was associated with a significantly reduced risk of CIN2+ recurrence when using unadjusted estimates from observational studies and RCTs. We found no significant effect of HPV vaccination on risk of CIN2+ recurrence when using the outcome measure from observational studies with the least risk of bias. Large, well-designed randomized placebo-controlled trials are needed to determine whether post-treatment HPV vaccination should be recommended to all women undergoing excisional treatment for CIN.

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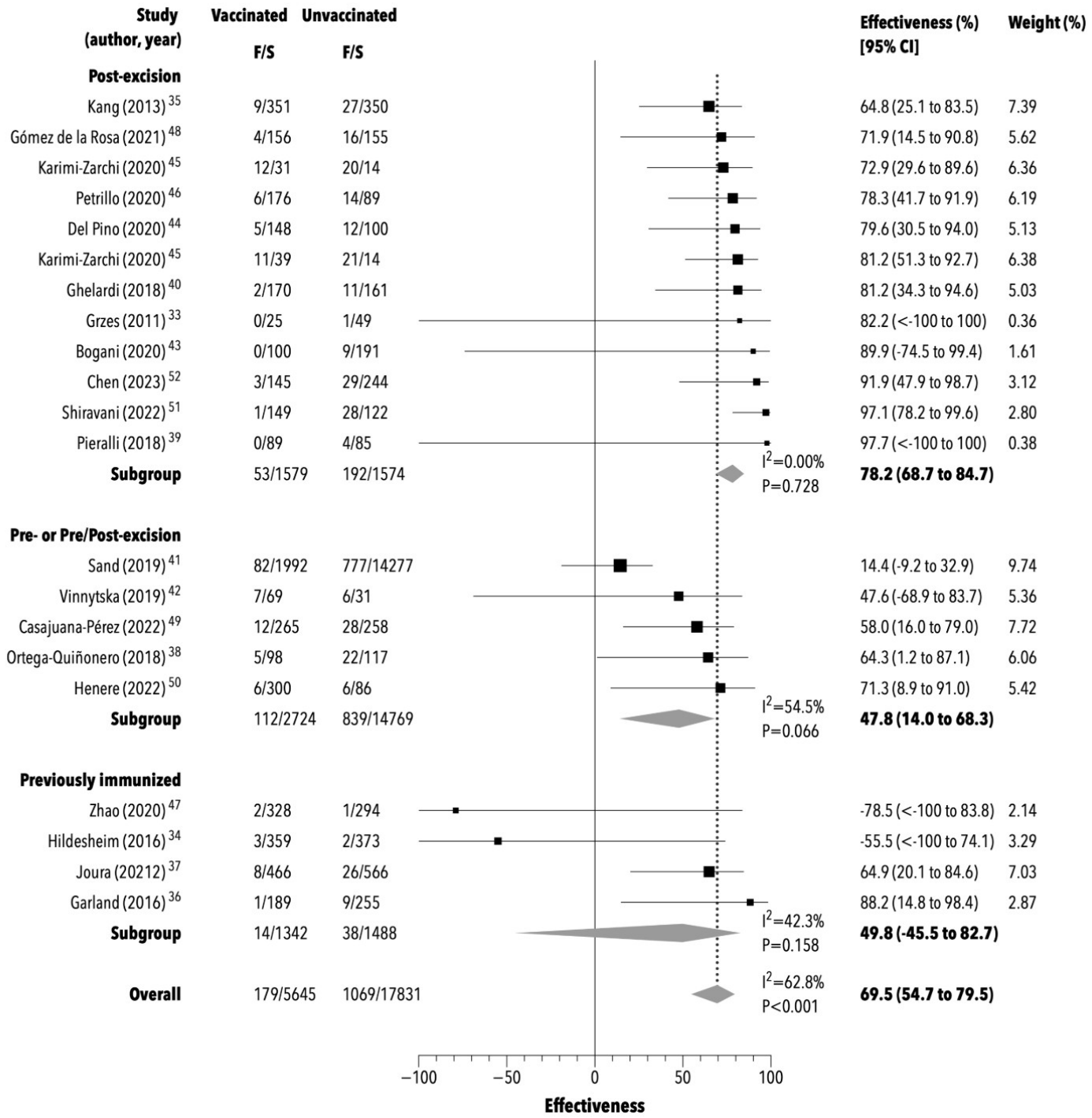
Systematic review

OPEN ACCESS

Timing of HPV vaccination as adjuvant treatment of CIN2+ recurrence in women undergoing surgical excision: a meta-analysis and meta-regression

Marek Petráš ,[1] Vladimír Dvořák,[2] Danuše Lomozová,[1] Roman Máčalík,[1] Sylva Neradová,[1] Pavel Dlouhý,[3] Jana Malinová,[4] Jozef Rosina,[5,6] Ivana Králová Lesná[7,8]



Cela semble bien fonctionner en post-conisation

Probablement pas d'intérêt à refaire vaccin si déjà fait

HUMAN VACCINES & IMMUNOTHERAPEUTICS
2024, VOL. 20, NO. 1, 2343552
https://doi.org/10.1080/21645515.2024.2343552

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2024

RESEARCH ARTICLE

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Reduced risk of CIN2+ recurrence in women immunized with a 9-valent HPV vaccine post-excision: Retrospective cohort study

HPV9

Vladimír Dvořák[a,b], Marek Petráš[c], Vladimír Dvořák[a], Danuše Lomozová[c], Pavel Dlouhý[d], Ivana Králová Lesná[e,f], and Radovan Pilka[b]

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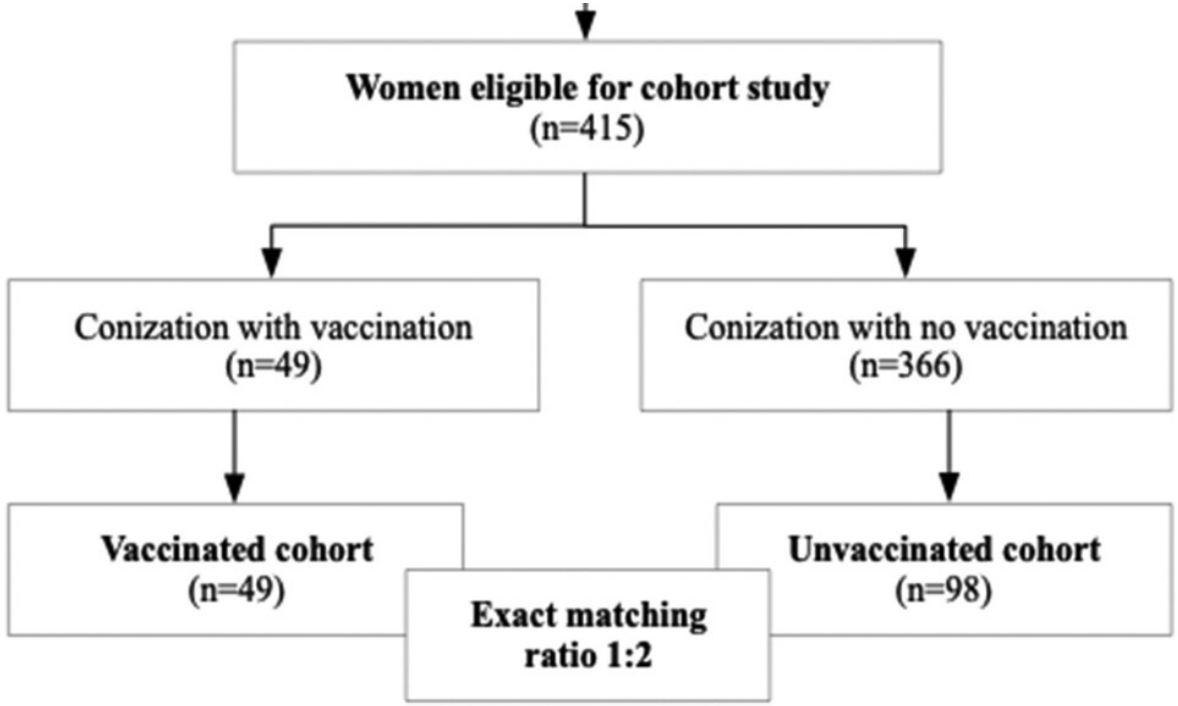
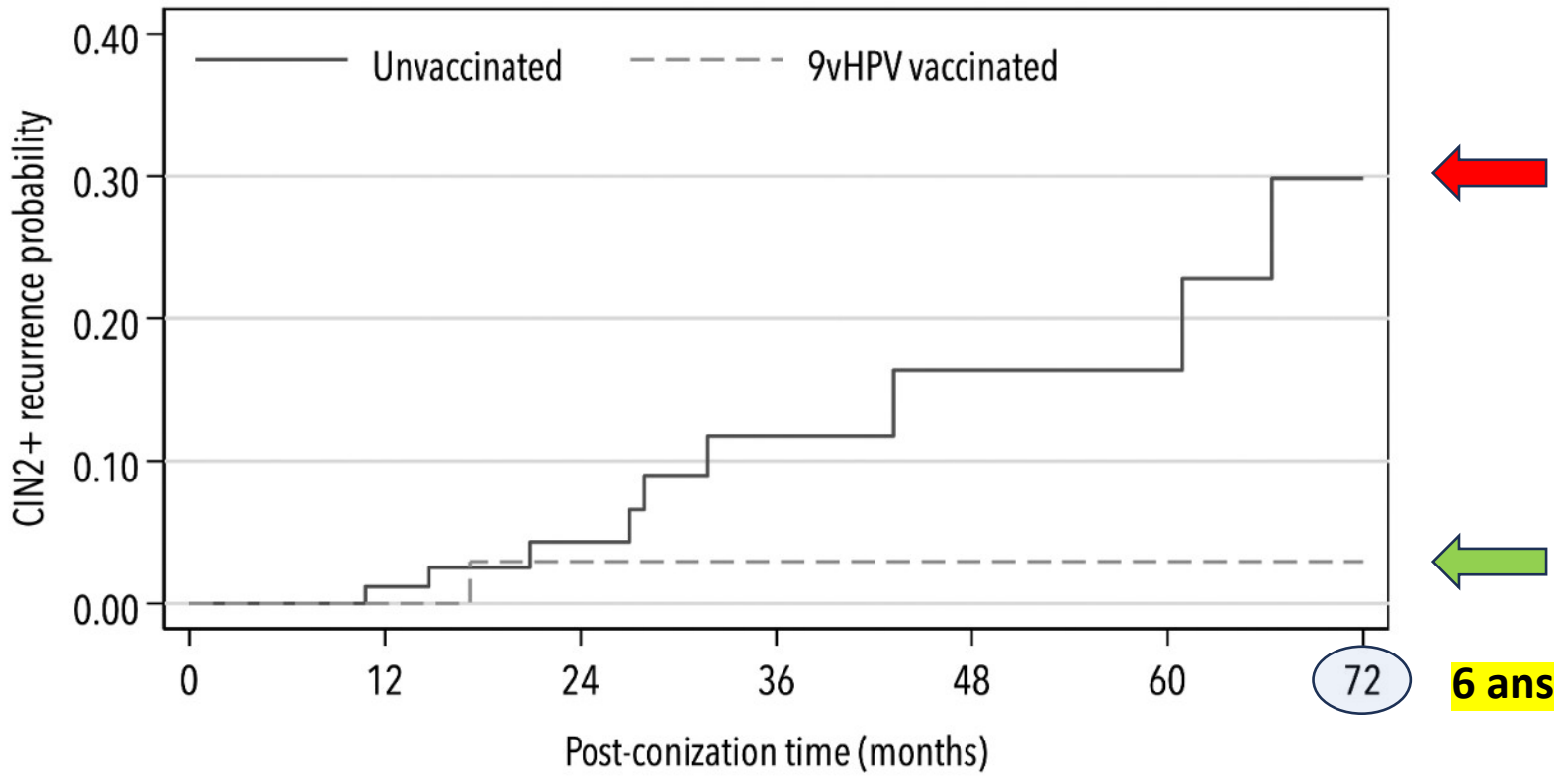
Petits effectifs
Non randomisé



HPV9



Number at risk							
Unvaccinated	98	82	50	28	16	14	8
9vHPV vaccinated	49	41	25	14	8	7	4

Figure 2. Probability of CIN2+ recurrence in 9vHPV-vaccinated and unvaccinated women relative to time since conization. 9vHPV – 9-valent vaccine against human papillomavirus infection.

pathogens

2024

Article

Post-Conization HPV Vaccination and Its Impact on Viral Status: A Retrospective Cohort Study in Troms and Finnmark, 2022

Marie Rykkelid [1,†], Helga Marie Wennberg [1,†], Elin Richardsen [2,3] and Sveinung Wergeland Sørbye [3,*]

Table 2. Frequency table that compares the HPV vaccination status (no/yes) with the result of the HPV test taken at the six-month follow-up (HPV−/HPV+).

Vaccinated (after Conization)	HPV− (n = 166)	HPV+ (%) (n = 77, 31.7%)	Total (n = 243)	p-Value
No	107	59 (35.5)	166	0.039
Yes	59	18 (23.4)	77	

Effectifs faibles

Rétrospectif

Attente résultats NOVEL Study !

Conclusion

- Cancer du col = prototype du cancer évitable !

- 3 niveaux de prévention :
  - Vaccin prophylactique : pour TOUS les pré-ado et jeunes adultes !
  - Biologie moléculaire pour le dépistage puis colposcopie de qualité au besoin
  - Conisation des HGSIL mais à rationaliser et très probablement à vacciner !

- Mieux vaut prévenir que guérir !