vHPV post H-SIL : est-ce utile ?

Jean LEVÊQUE

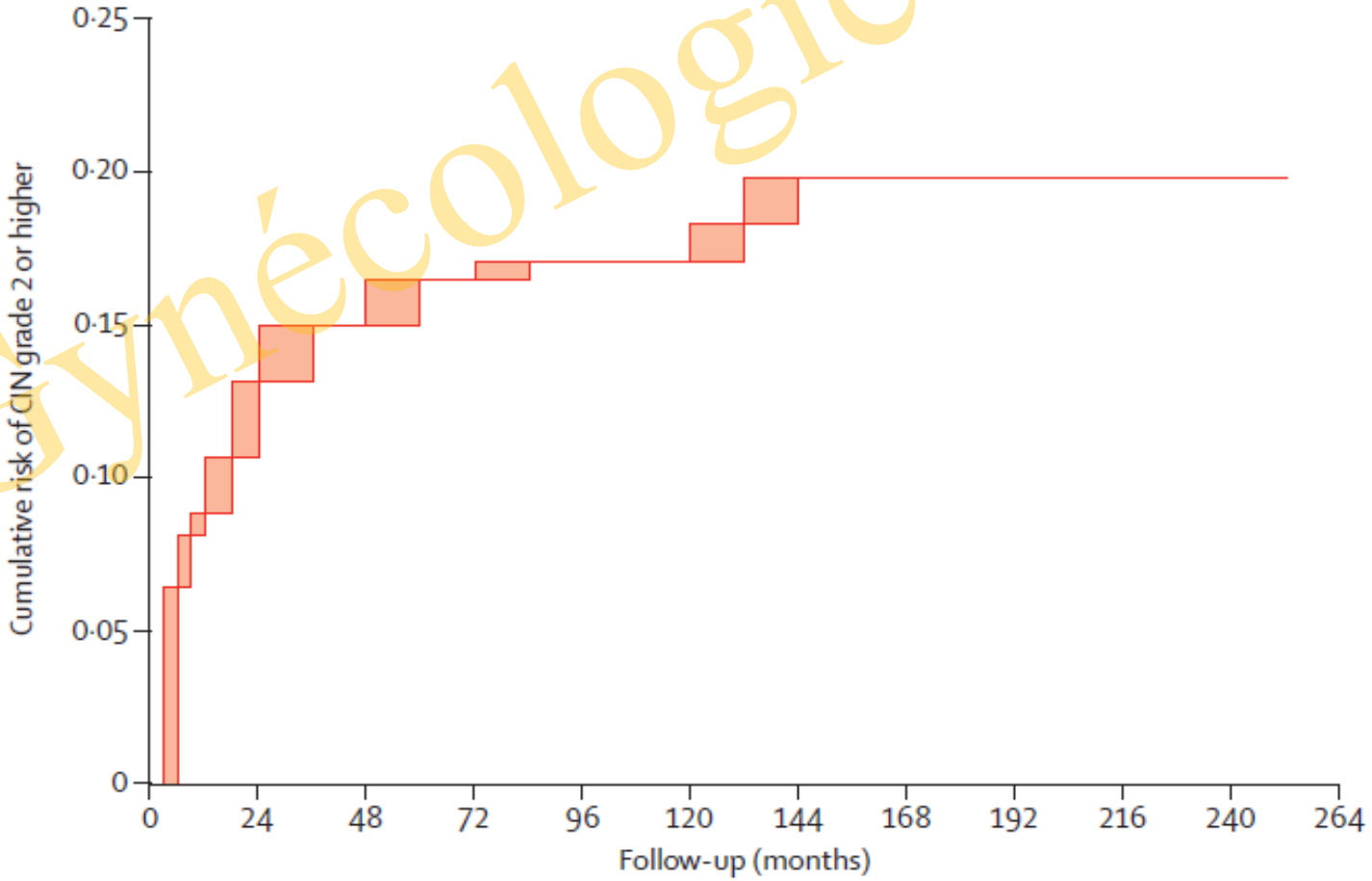
RENNES

Pas de conflits d'intérêts déclarés – Tours, 7 Décembre 2024

Rationnel de la vHPV post thérapeutique

Risque de récidive après conisation : # 10%

- 435 F. traitées de CIN2-3 par conisation
- F up : 5 ans
- Résultats :
  - **17% : CIN2+ post TRT**
  - **9% : CIN3 + post TRT**



Kocken M. Lancet Oncol 2011

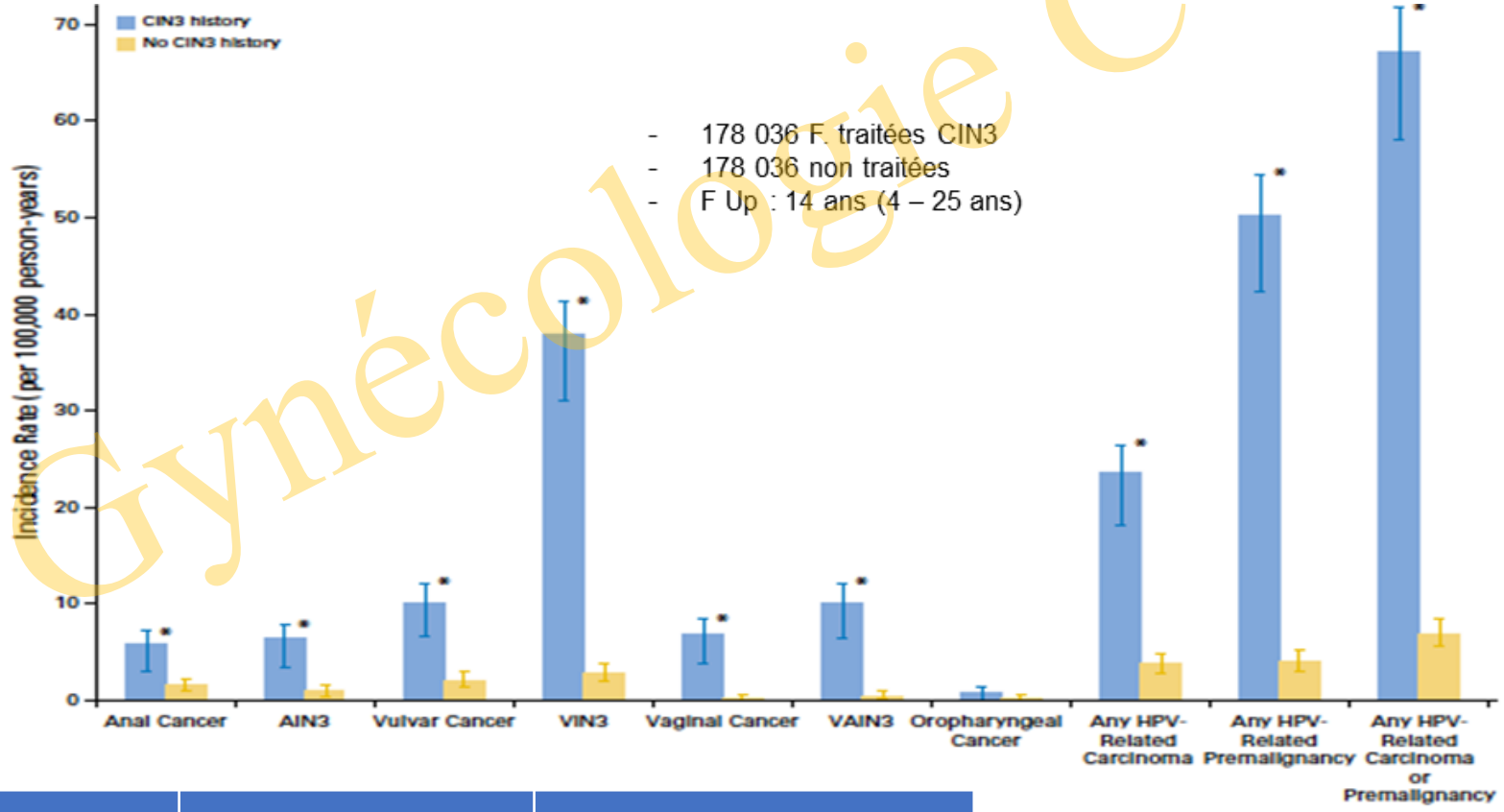
Après CIN3 traité : risque élevé d'autres lésions HPV induites

VOLUME 35 · NUMBER 22 · AUGUST 1, 2017

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL

Long-Lasting Increased Risk of Human Papillomavirus–Related Carcinomas and Premalignancies After Cervical Intraepithelial Neoplasia Grade 3: A Population-Based Cohort Study

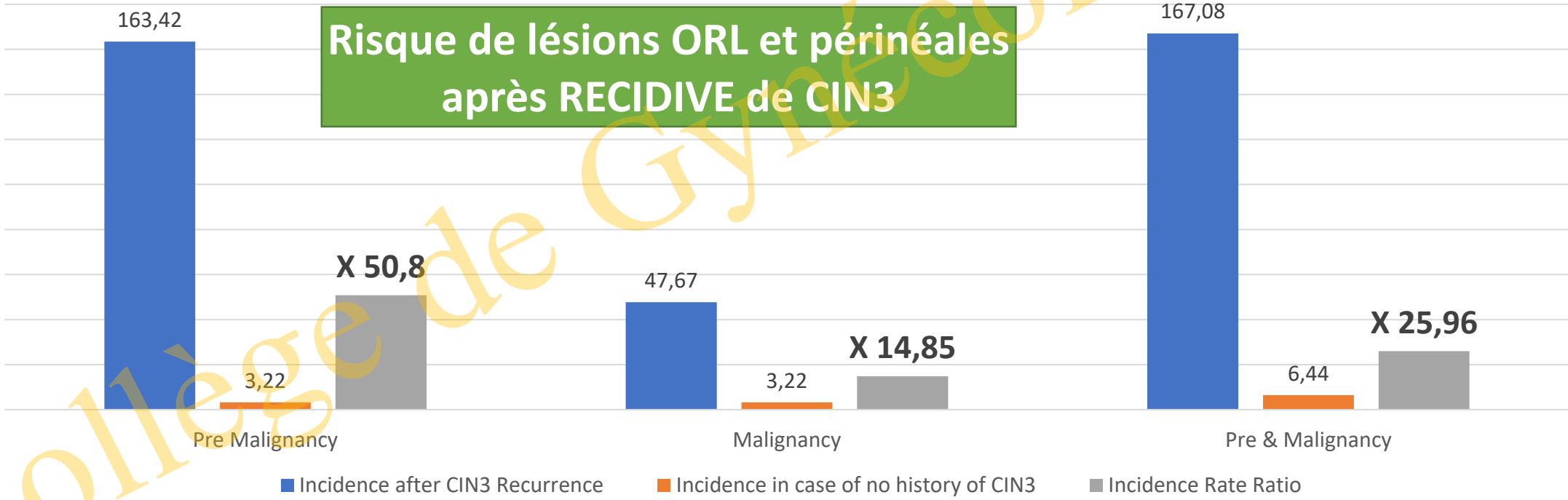
Renée M.F. Ebisch, Dominiek W.E. Rutten, Joanna IntHout, Willem J.G. Melchers, Leon F.A.G. Massuger, Johan Bulten, Ruud L.M. Bekkers, and Albert G. Siebers



Lésions (toutes localisations)	Invasives	Non Invasives	Invasives + Non Invasives
Incidence Rate Ratio	**X 6.24**	**X 12.75**	**X 9.68**

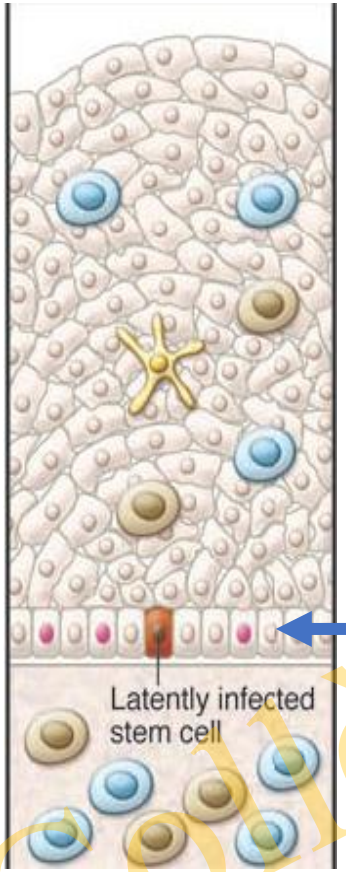
The relative risk of noncervical high-risk human papillomavirus-related (pre)malignancies after recurrent cervical intraepithelial neoplasia grade 3: A population-based study

Diede L. Loopik[1], Renée M. Ebisch[2], Joanna IntHout[3], Willem J. Melchers[4], Leon F. Massuger[5], Ruud L. Bekkers[2] and Albert G. Siebers[6,7]



Loopik DL. Int J Cancer 2020

Ré-infections avec un autre hr-HPV *VERSUS* **Ré-activation** d'une infection latente

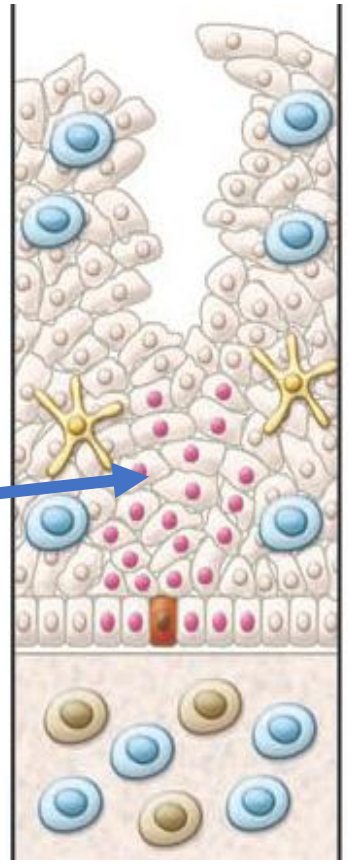


- Cohorte de 700 F. (*HIP Study*) :
  - Age moyen : 47 ans (35 à 65 ans)
  - 19% HPV + Base Line
  - Suivi : HPV / 6 mois

- ➔Infections INCIDENTES :

  - par **ré-infection : 13%** (F. avec nouveau partenaire)

  - par **ré-activation** : **71.9%** (= F. avec ≥ 5 partenaires)
    16% (= F. avec ancien partenaire)

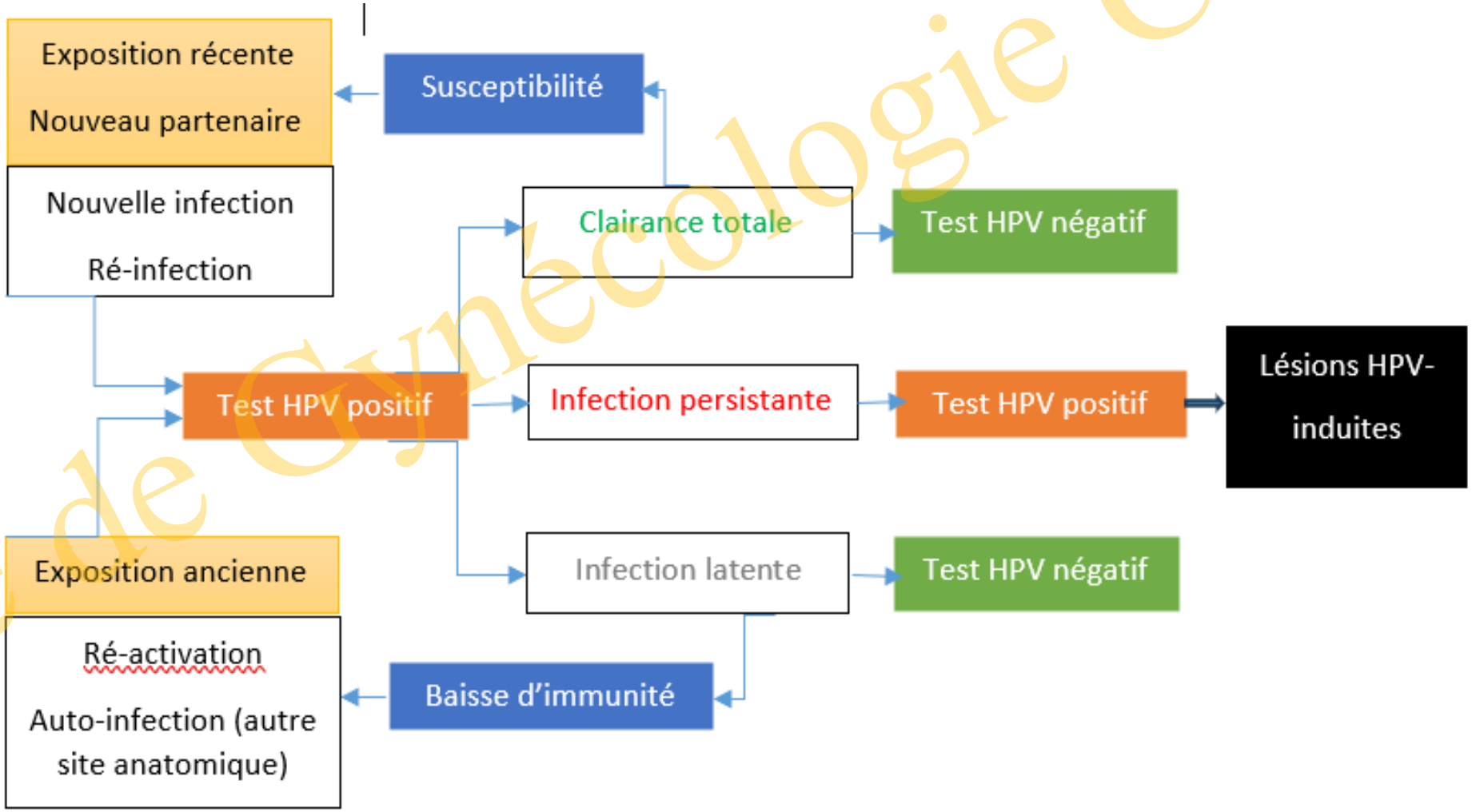


Gravitt PE. J Clin Invest 2011. Rositch AF. Cancer Res 2012

Donc v HPV post Trt : 2 cibles potentielles…

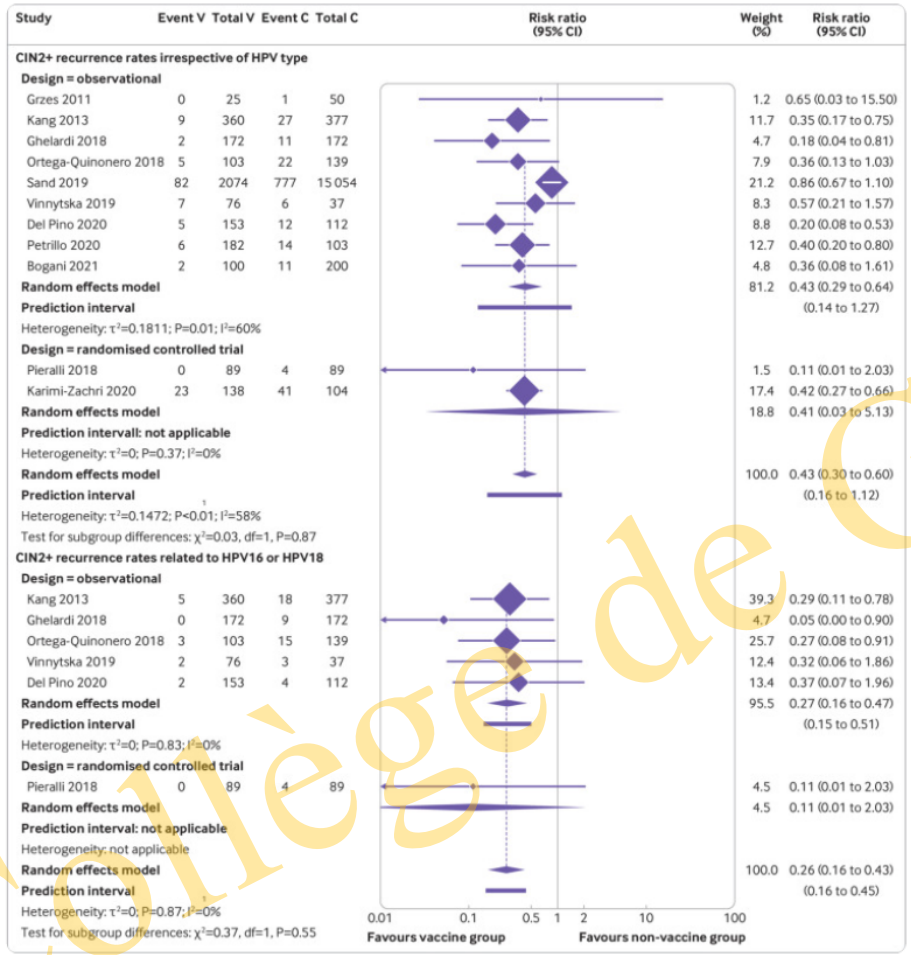
Hier :
test HPV nég = pas d'infection

Aujourd'hui :
Test HPV nég = charge virale non détectable



Gravitt PE. Viruses 2017

Les récidives cervicales chez les vaccinées



Comparaison des **antérieurement** vaccinées
versus non vaccinées

(Méta-Analyse : 18 séries – 19,909 Ptes)

Outcome	Vaccinées n CIN2+ / n total vaccinées	Non Vaccinées n CIN2+ / n total non vaccinées	Risk Ratio [95% IC]
CIN2+	141 / 3 472 4%	926 / 16 437 5,6%	**0.43** [0,30 – 0,60]

Kechagias KS. BMJ 2022

La littérature

Plutôt en faveur de la vaccination post thérapeutique… mais critiquable

Deux analyses *post hoc* de RCT (Future & Patricia)

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

1350 Patientes issues des « *Future Trials* »
- Traitées pour CIN 2/3 – AIS – CIN1 persistant
- N = 587 ayant été vaccinées (v4 HPV)
- N = 763 ayant reçu placebo

➔ Récidive post thérapeutique – F Up = 3.6 ans

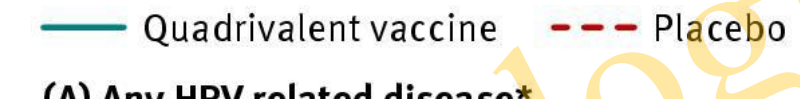
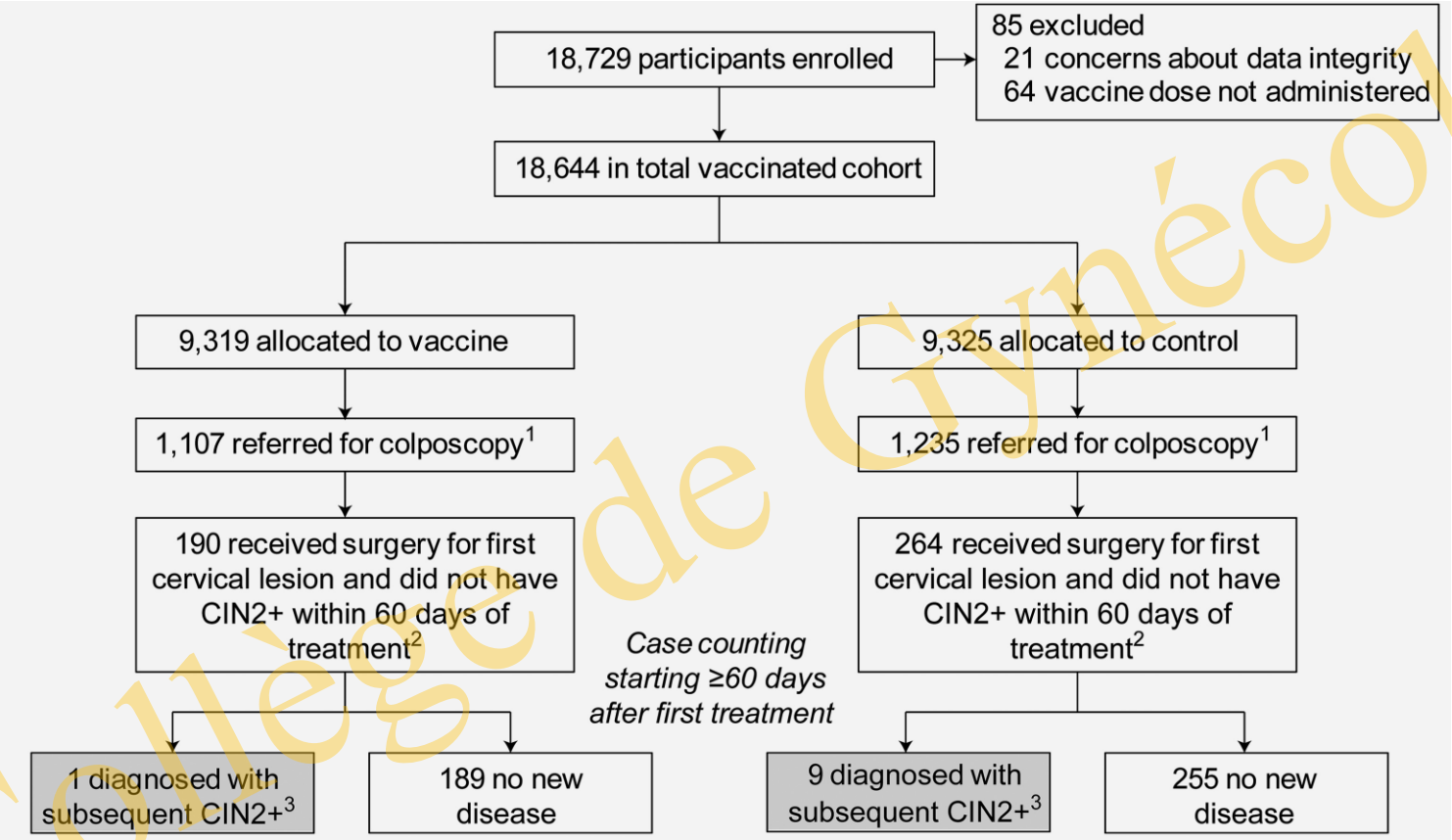


Table 2| **Impact of quadrivalent HPV vaccine on incidence of subsequent HPV related disease* among women who had undergone cervical surgery**

End point	Vaccine (n=587) No of women with a lesion†	Vaccine (n=587) Rate‡	Placebo (n=763) No of women with a lesion†	Placebo (n=763) Rate‡	% reduction (95% CI) in rate with vaccine
HPV related disease irrespective of causal HPV type					
Any disease:	45/475	6.6	94/593	12.2	46.2 (22.5 to 63.2)
Cervical intraepithelial neoplasia grade I or worse	30/474	4.3	65/592	8.2	48.3 (19.1 to 67.6)
Genital warts	7/474	1.0	22/589	2.6	63.0 (10.3 to 86.6)
Vulvar or vaginal intraepithelial neoplasia grade I or worse	12/474	1.7	19/589	2.3	26.5 (–59.5 to 67.5)
Cervical intraepithelial neoplasia grade II or worse	8/474	1.1	26/592	3.1	64.9 (20.1 to 86.3)
Cervical intraepithelial neoplasia grade III or worse	3/474	0.4	13/592	1.5	73.5 (3.4 to 95.2)
Vulvar or vaginal intraepithelial neoplasia grade II or worse	3/474	0.4	5/589	0.6	30.1 (–259.1 to 89.2)

Joura EA. BMJ 2012

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



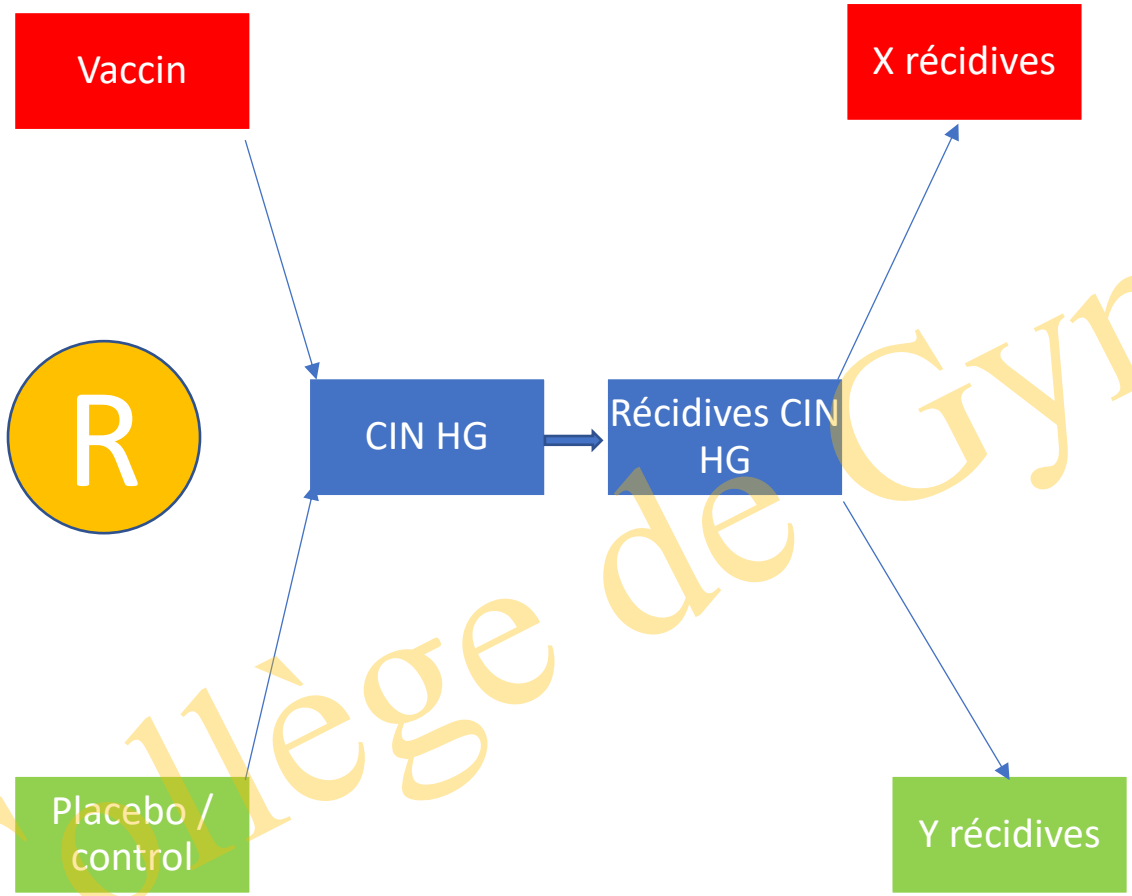
Efficacité de v2 HPV sur CIN2+

=

88.2% [14.8 – 99.7]

Garland SM. Int J Cancer 2016

Analyses *post hoc* issues des essais de phase 3
➔ la Randomisation a eu lieu **AVANT** la récidive



- Patientes JEUNES : # 20 ans
- Recul : 4 ans
- Peu de patientes
- Peu de cas

	Future (4vHPV)		Patricia (2vHPV)	
	4v HPV	*Plb.*	*2v HPV*	*Contr.*
CIN HG	587	763	190	264
Rec. CIN HG	3	13	1	9

Garland SM. Int J Cancer 2016. Joura EA. BMJ 2012

Quelques études observationnelles

Efficacy of Human Papillomavirus Vaccination 4 Years After Conization for High-Grade Cervical Neoplasia

Etude observationnelle après LEEP pour CIN2/3.

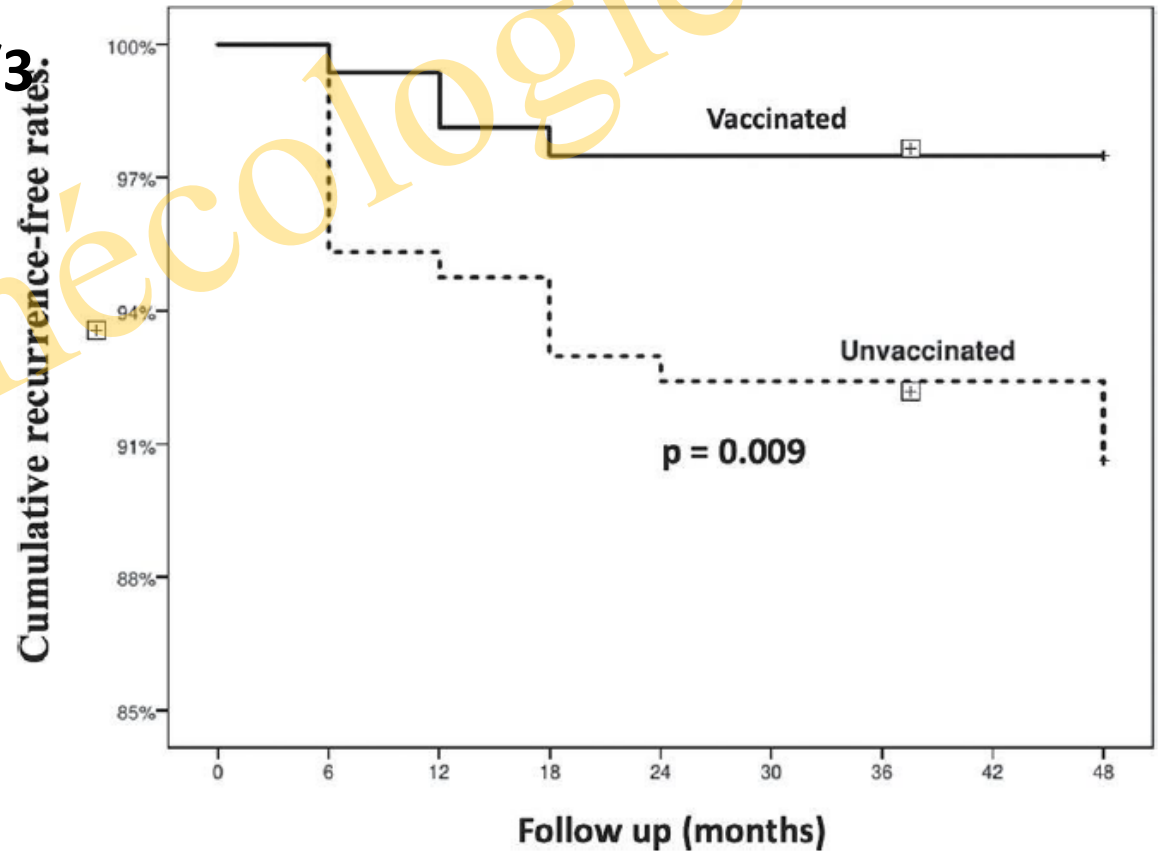
- v4 HPV = 160 Ptes
- Non v HPV = 171 Ptes

Résultats

- F Up = 4 ans
- v4 HPV Groupe : 4 récidives
- Non v4 HPV Groupe : 12 récidives

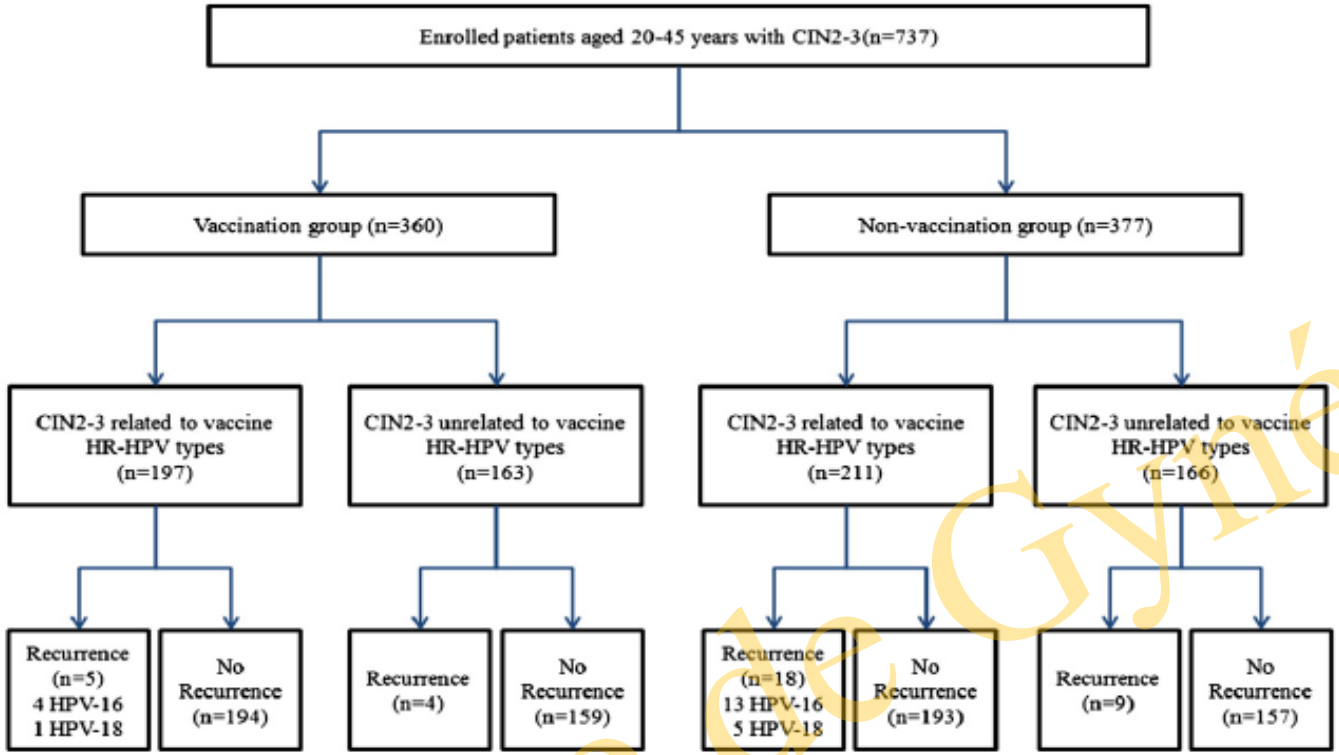
- Efficacité v4 HPV = **73.4%** [95% IC : 21.8 – 90.9]

- NNT prévenir CIN2+ = **14.6 Ptes** [95% IC : 8.4 – 53.6]



Guacimara Gomez de la Rosa A. J Low Genit Tract Dis 2021

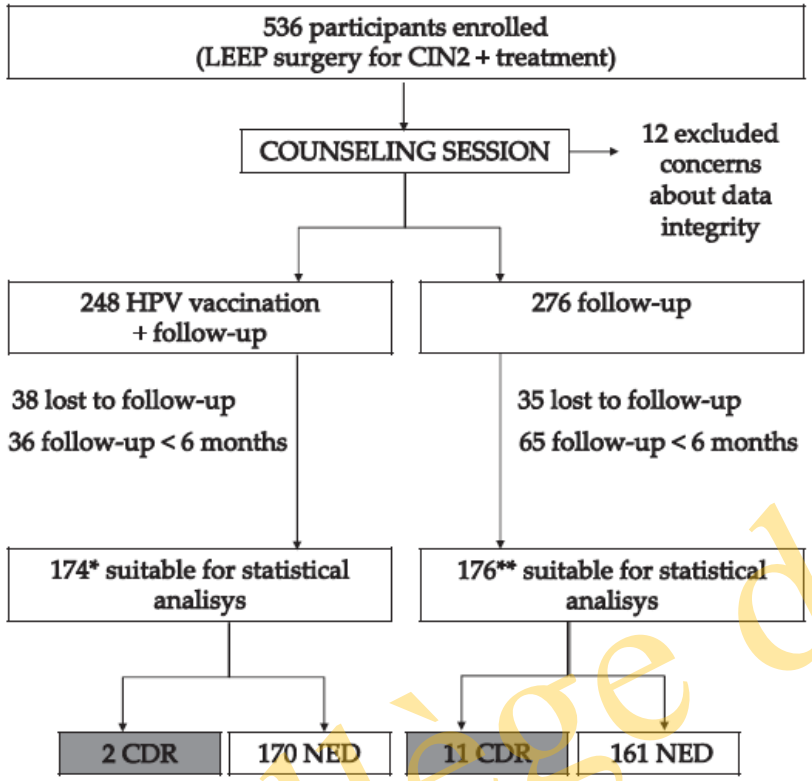
Is vaccination with quadrivalent HPV vaccine after loop electrosurgical excision procedure effective in preventing recurrence in patients with high-grade cervical intraepithelial neoplasia (CIN2–3)?☆

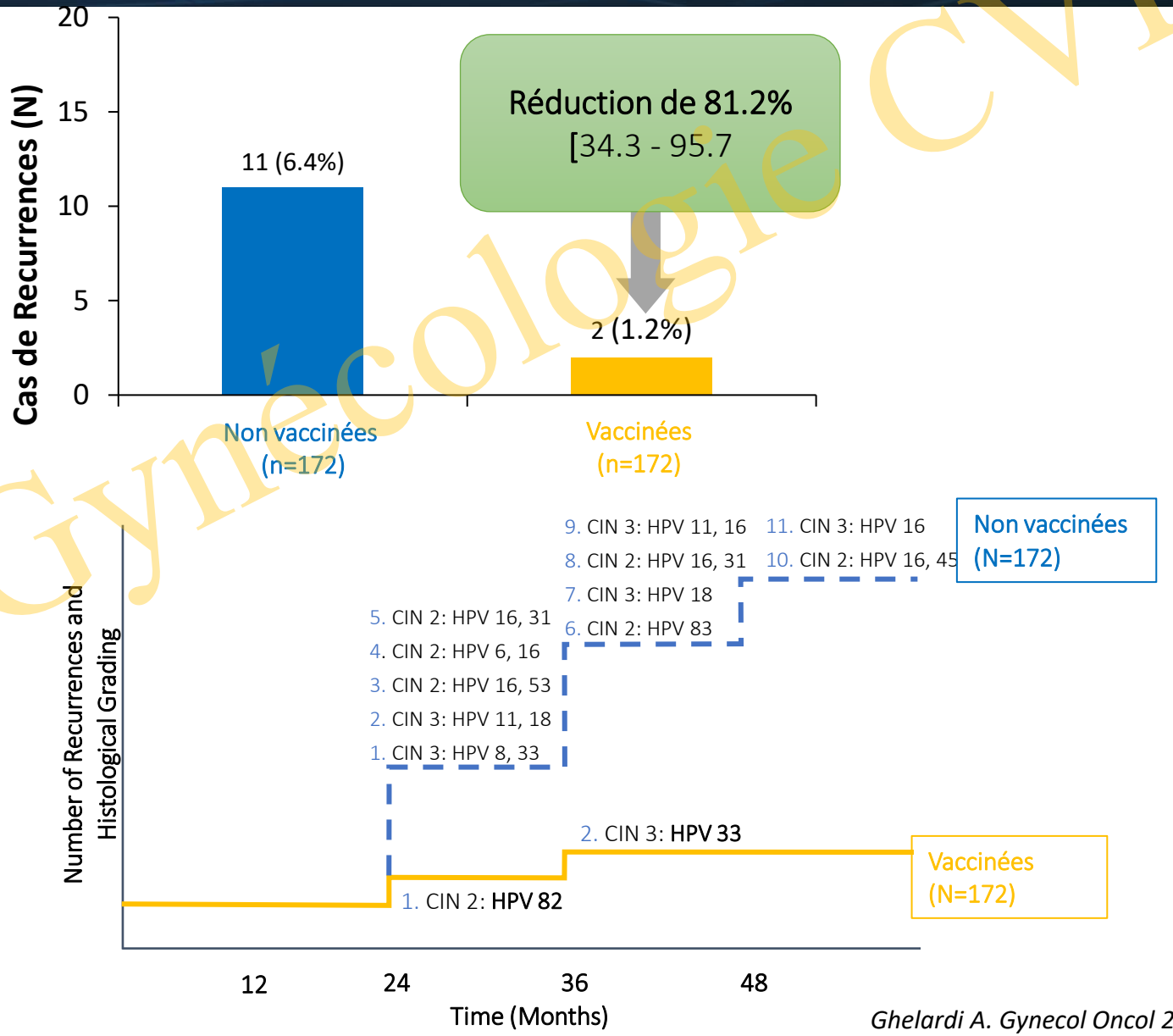


	CIN HG post LEEP		CIN HG HPV 16 / 18 post LEEP
v4 HPV n = 360	2.5% (n = 9 / 360)	**HR = 2.84** **[95% CI = 1.33 – 6.04]**	2.5% (n = 5 / 197)
No v4 HPV n = 377	7.2% (n = 27 / 377)		8.5% (n = 18 / 211)

Kang WD. Gynecol Oncol 2013

SPERANZA project: HPV vaccination after treatment for CIN2+





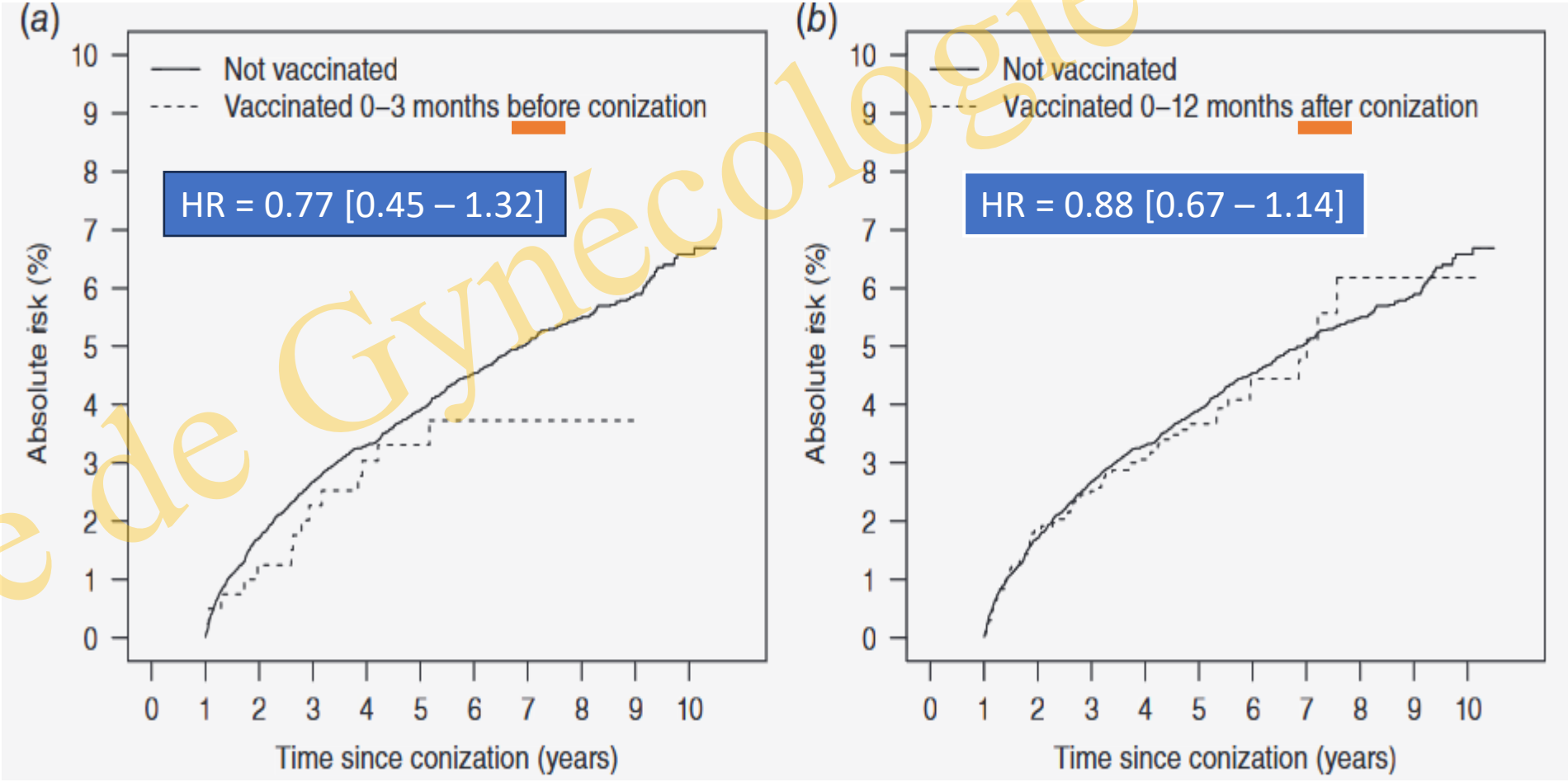
Ghelardi A. Gynecol Oncol 2018

Denmark : étude en **population** (La "Vraie Vie")

- 17,128 F. CIN3 conisées
- 2,074 v HPV vs

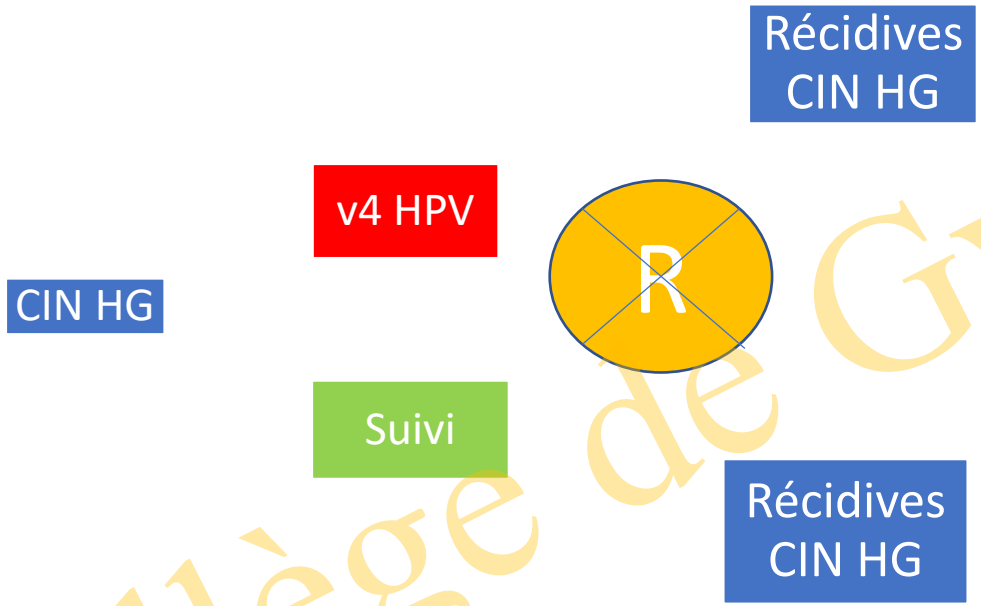
15,054 0 v HPV

- F Up 1 an
- **HR pop totale = 0.86**
  [0.67 – 1.09]



Sand FJ. Int J Cancer 2020

Etudes Observationnelles : ➔ PAS de Randomisation



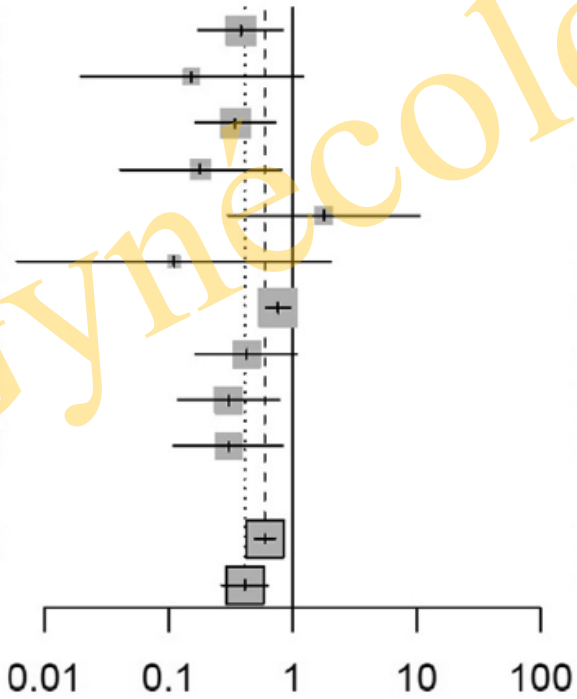
- Patientes "choisies"
- Suivi court (< 4 ans)
- Peu de patientes
- Peu de cas

Méta-analyses

Prophylactic HPV vaccination after conization: A systematic review and *meta*-analysis

M. Jentschke [a,1,*], J. Kampers [a,1], J. Becker [b], P. Sibbertsen [b], P. Hillemanns [a]

Vaccine 38 (2020) 6402–6409



Study	Experimental Events	Experimental Total	Control Events	Control Total	RR	95%−CI	Weight (fixed)	Weight (random)
Joura	8	474	26	592	0.38	[0.18; 0.84]	7.5%	13.5%
Garland	1	190	9	264	0.15	[0.02; 1.21]	2.4%	3.7%
Kang	9	360	27	377	0.35	[0.17; 0.73]	8.5%	14.1%
Ghelardi	2	172	11	172	0.18	[0.04; 0.81]	3.6%	6.2%
Hildesheim	3	142	2	169	1.79	[0.30; 10.54]	0.6%	4.7%
Pieralli	0	89	4	89	0.11	[0.01; 2.03]	1.5%	2.0%
Sand	82	2074	777	15054	0.77	[0.61; 0.96]	60.9%	22.8%
Petrillo	6	182	14	182	0.43	[0.17; 1.09]	4.5%	11.3%
Ortega−Quinonero	5	103	22	139	0.31	[0.12; 0.78]	6.1%	11.3%
Del Pino	5	153	12	112	0.31	[0.11; 0.84]	4.5%	10.3%
Fixed effect model	**3939**		**17150**		**0.60**	**[0.50; 0.72]**	**100.0%**	**--**
Random effects model					**0.41**	**[0.27; 0.64]**	**--**	**100.0%**

Heterogeneity: $\tau^2 = 0.1980$, $p = 0.03$

Number Needed to Vaccine to prevent 1 case of recurrent CIN2+ = 45.5

Overview of studies regarding the impact of vaccination on the recurrence rate after treatment.

References	Vaccine	No. of recurrent CIN2+ cases (event/ total)		Pe (%)	*Pc* (%)	RD (M−H, Random,95 %CI)	NNT
		Vaccinated	Control				
Vaccination before surgery							
Joura et al.2012 [21]	quadrivalent	8/474	26/592	1.69	4.39	−0.03(-0.05 , -0.01)	33
Garland et al.2016 [22]	bivalent	1/190	9/264	0.53	3.40	−0.03(-0.05 , 0.00)	33
Hildesheim et al. 2016 [7]	bivalent	3/142	2/169	2.11	1.18	0.01(-0.02 , 0.04)	–
Subtotal		12/806	37/1025	1.49	3.61	−0.02(-0.04 , 0.00)	50
Overall effect: Z = 1.53(P = 0.13)							
Vaccination after surgery							
Kang et al. 2013 [28]	quadrivalent	9/360	27/377	2.50	7.16	−0.05(-0.08 , -0.02)	21
Ghelardi et al.2018 [5]	quadrivalent	2/172	11/172	1.16	6.40	−0.05(-0.09 , -0.01)	19
Petrillo et al.2020 [25]	bivalent、quadrivalent	6/182	14/103	3.30	13.59	−0.01(-0.17 , -0.03)	10
Bogani et al. 2020 [11]	bivalent、quadrivalent	0/100	9/200	0.00	4.50	−0.04(-0.08 , -0.01)	22
Gómez et al. 2021 [26]	bivalent、quadrivalent	4/160	16/171	2.50	9.36	−0.07(-0.12 , -0.02)	15
Subtotal		**21/974**	**77/1023**	**2.16**	**7.53**	**−0.05(-0.07 , -0.04)**	**20**
Overall effect: **Z = 5.96 (P < 0.01)**							
Vaccination before or after surgery							
Del Pino et al. 2020 [23]	bivalent、quadrivalent、nine-valent	5/153	12/112	3.27	10.71	−0.07(-0.14 , -0.01)	13
Sand et al. 2020 [24]	bivalent、quadrivalent、nine-valent	82/2074	777/15054	3.95	5.16	−0.01(-0.02 , 0.00)	83
Casajuana-Pérez et al.2022 [27]	bivalent、quadrivalent	12/277	28/286	4.33	9.79	−0.05(-0.10 , -0.01)	18
Subtotal		99/2504	817/15452	3.95	5.29	−0.04(-0.08 , 0.00)	**25**
Overall effect: Z = 1.89 (P = 0.06)							
Total		132/4284	931/17500	3.08	5.32	−0.04(-0.05 , -0.02)	**25**
Overall effect: Z = 4.60 (P < 0.01)							

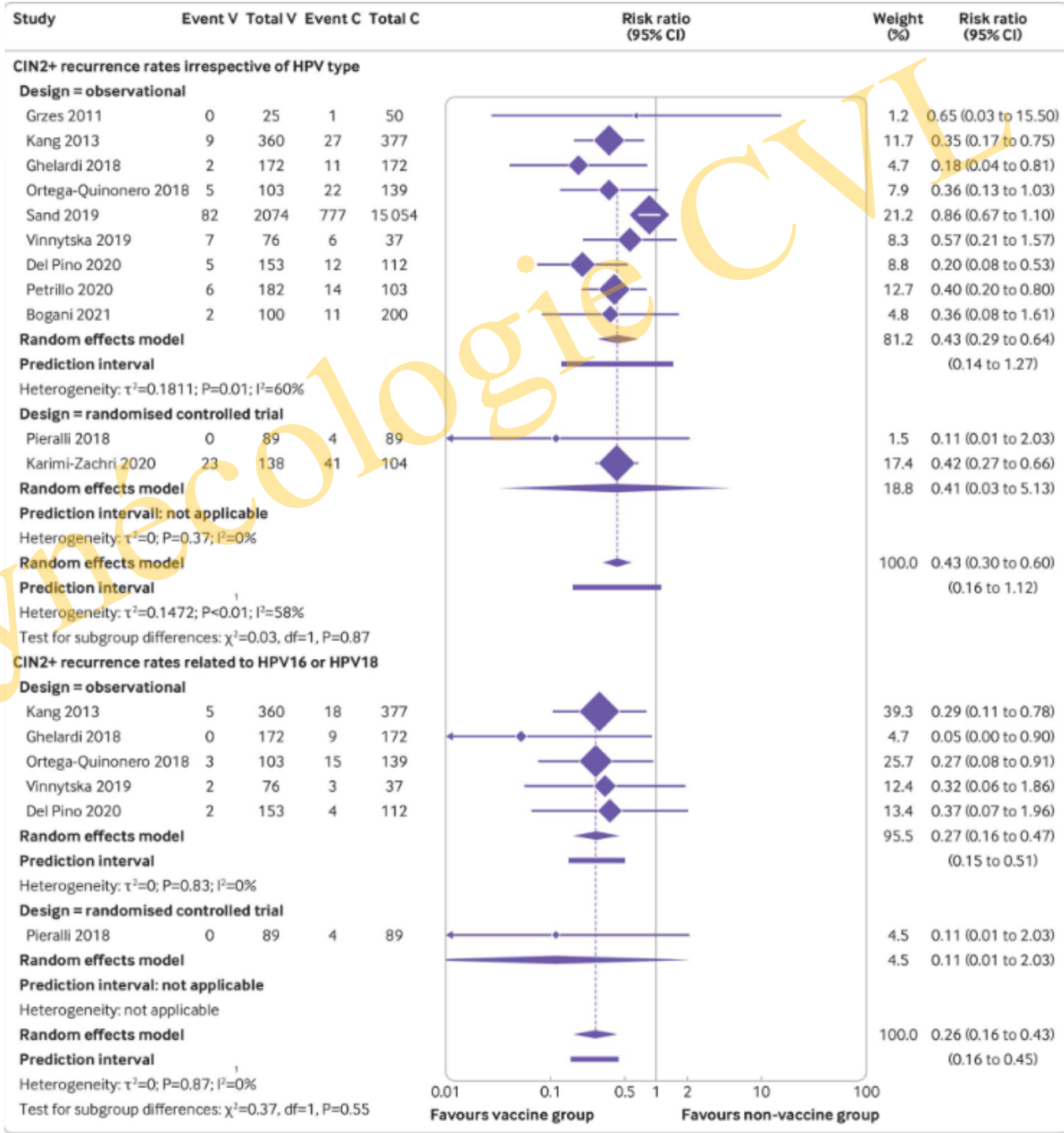
Abbreviation: Recurrence = CIN 2 + relapse regardless of HPV types; Pe, the recurrent rate of vaccinated cohort; Pc, the recurrent rate of control cohort; RD, risk difference; NNT: number needed to treat.

Chen M. Eur J Obstet Gynecol Reprod Biol 2023

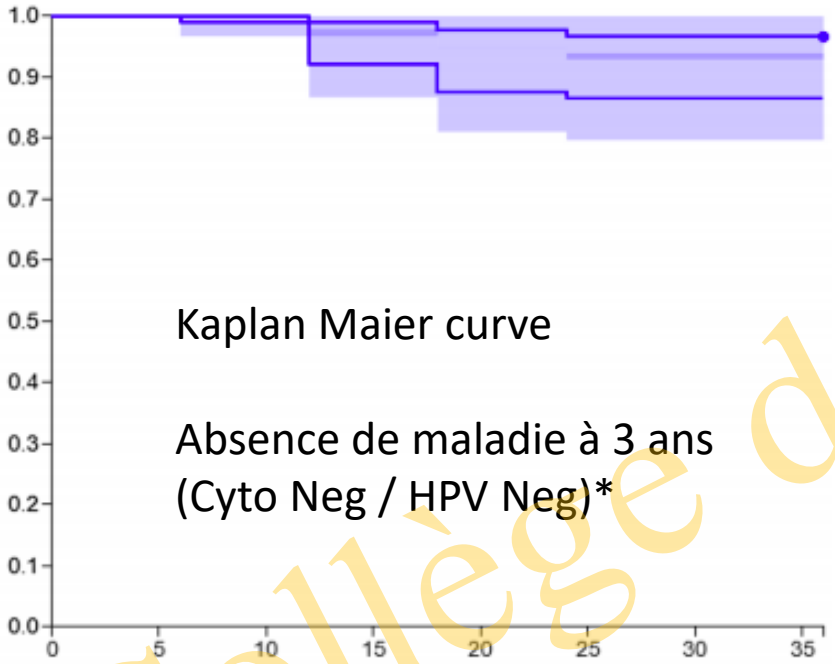
Role of human papillomavirus (HPV) vaccination on HPV infection and recurrence of HPV related disease after local surgical treatment: systematic review and meta-analysis

Méta-Analyses : ↗ le nombre des sujets

- On empile les BONS résultats
- On empile les ERREURS



Une étude **randomisée** italienne



Kaplan Maier curve

Absence de maladie à 3 ans
(Cyto Neg / HPV Neg)*

178 Patientes :

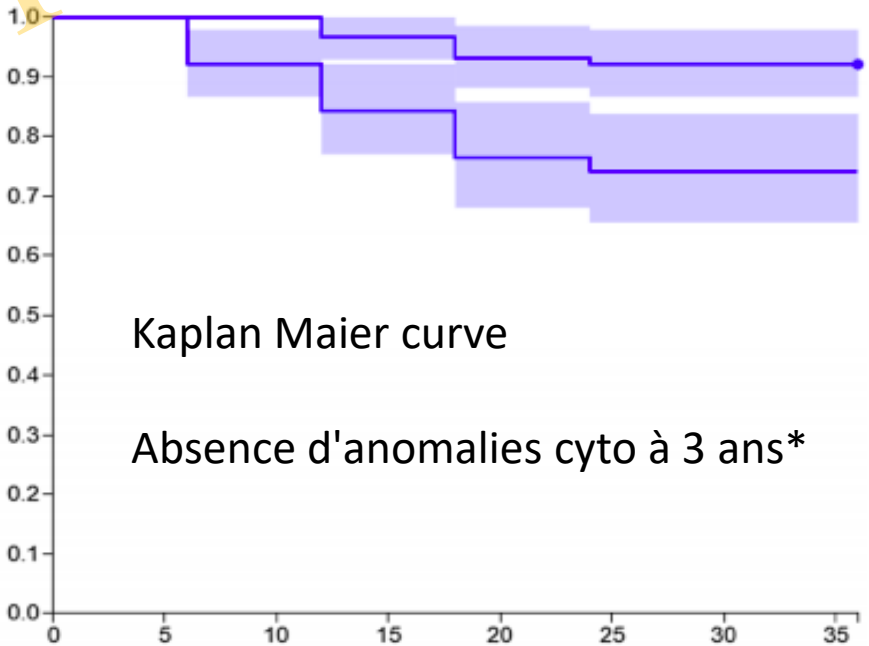
- 30 avec CIN1 et 148 CIN 2-3

RANDOMISATION

- ***89 v4 HPV à 3 mois ➔ 3 récidives***
- ***89 non v HPV ➔ 12 récidives***

F Up : 3 ans

Groupe	N =	Récidive
v4 HPV	89	3 (3.4%)
0 v HPV	89	12 (13.5%)



Kaplan Maier curve

Absence d'anomalies cyto à 3 ans*

Pieralli A. Arch Obstet Gynecol 2018

Des questions "à part"

Quand vacciner : avant, pendant, après la conisation ?

Une population TRES à risque : F. VIH Pos

Meta-Analyse PAVIVE : efficacité et timing vHPV post conisation sur CIN2+ récidive

Effectiveness	Strata	No of estimates	Pooled VE (95% CI)
Overall		21	69.5% (54.7% to 79.5%)
Stratified by	Timing of immunisation		
	Post-excision	12	78.1% (68.7% to 84.7%)
	Pre-excision or pre/post-excision	5	47.8% (14.0% to 68.3%)
	Previously immunised	4	49.8% (–45.5% to 82.7%)
	HPV vaccine		
	HPV2	4	48.4% (–55.0% to 82.8%)
	HPV4+	14	75.9% (58.3% to 86.1%)
	Unspecific	3	59.8% (32.1% to 76.3%)
	Follow-up duration		
	≤2 years	5	72.3% (17.5% to 90.7%)
	3–4 years	10	68.4% (53.9% to 78.3%)
	≥5 years	6	70.1% (53.7% to 80.6%)

BENEFICES de la vHPV sur récidive CIN2+

Timing / conisation	Récidive CIN2+ [95% IC]
vHPV AVANT	49,8 [-45,5 – 82,7]
vHPV LORS	78,1 [68,7 – 84,7]
vHPV APRES	47,8 [14,0 – 68,3]
vHPV GLOBAL	69,5 [54,7 – 79,5]
Pas de variation : v2 ou v4 HPV – selon durée de suivi (≤ 2 ans ≥ 5 ans	

It is not quite clear why the timing of HPV vaccine administration could have a variable impact on VE.

Petras M. Sex Trans Inect 2023

Méta-analyse : timing toujours peu clair…

Overview of studies regarding the impact of vaccination on the recurrence rate after treatment.

References	Vaccine	No. of recurrent CIN2+ cases (event/ total)		Pe (%)	*Pc* (%)	RD (M–H, Random,95 %CI)	NNT
		Vaccinated	Control				
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Hildesheim et al. 2016 [7]	bivalent	3/142	2/169	2.11	1.18	0.01(-0.02 , 0.04)	–
Subtotal		12/806	37/1025	1.49	3.61	−0.02(-0.04 , 0.00)	50
Overall effect: Z = 1.53(P = 0.13)							
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Petrillo et al.2020 [25]	bivalent、quadrivalent	6/182	14/103	3.30	13.59	−0.01(-0.17 , -0.03)	10
Bogani et al. 2020 [11]	bivalent、quadrivalent	0/100	9/200	0.00	4.50	−0.04(-0.08 , -0.01)	22
Gómez et al. 2021 [26]	bivalent、quadrivalent	4/160	16/171	2.50	9.36	−0.07(-0.12 , -0.02)	15
Subtotal		**21/974**	**77/1023**	**2.16**	**7.53**	**−0.05(-0.07 , -0.04)**	**20**
Overall effect: **Z = 5.96 (P < 0.01)**							

Abbreviation: Recurrence = CIN 2 + relapse regardless of HPV types; Pe, the recurrent rate of vaccinated cohort; Pc, the recurrent rate of control cohort; RD, risk difference; NNT: number needed to treat.

Chen M. Eur J Obstet Gynecol Reprod Biol 2023

Human Papillomavirus Vaccination Prior to Loop Electroexcision Procedure Does Not Prevent Recurrent Cervical High-grade Squamous Intraepithelial Lesions in Women Living With Human Immunodeficiency Virus: A Randomized, Double-blind, Placebo-controlled Trial

Characteristic	4vHPV Arm (n = 90)	Placebo Arm (n = 90)	Total (N = 180)
Cervical cytology			
ASCUS	2 (2.2)	3 (3.3)	5 (2.8)
ASC-H	8 (8.9)	7 (7.8)	15 (8.3)
LSIL	1 (1.1)	4 (4.4)	5 (2.8)
HSIL	78 (86.7)	76 (84.4)	154 (85.6)
Unsatisfactory	1 (1.1)	0 (0)	1 (.6)
Cervical histology			
CIN2	40 (44)	46 (51)	86 (48)
CIN3	49 (54)	44 (49)	93 (52)
Inadequate	1 (1)	0	1 (1)
Race			
Black	90 (100)	86 (96)	176 (98)
Other	0	3 (3)	3 (2)
White	0	1 (1)	1 (1)
Current tobacco use			
Yes	3 (3)	5 (6)	8 (4)
No	87 (97)	85 (94)	172 (96)
Plasma HIV-1 RNA, copies/mL			
<200	77 (95)	76 (93)	153 (94)
200–1000	1 (1)	1 (1)	2 (1)
>1000	3 (4)	5 (6)	8 (5)
Missing[a]	9	8	17
Age, y, median (IQR)	40.1 (34.8–46.6)	39.1 (35.2–44.2)	39.2 (34.9–45.5)
CD4 count, cells/μL, median (IQR)[b]	511 (300–689)	483 (337–745)	489 (302–724)
Nadir CD4 count, cells/μL, median (IQR)[c]	125 (61–200)	108 (50–200)	116 (50–200)

Endpoint	4vHPV (n = 87)	Placebo (n = 87)
Cytologic or histologic HSIL (primary endpoint)	46 (52.9)	39 (44.8)
Histologic HSIL (CIN2 or CIN3)	28 (32)	27 (31)
CIN3	9 (10)	11 (13)

Firnhaber C. Clin Infect Dis 2020

Donc littérature : plutôt **présomption**

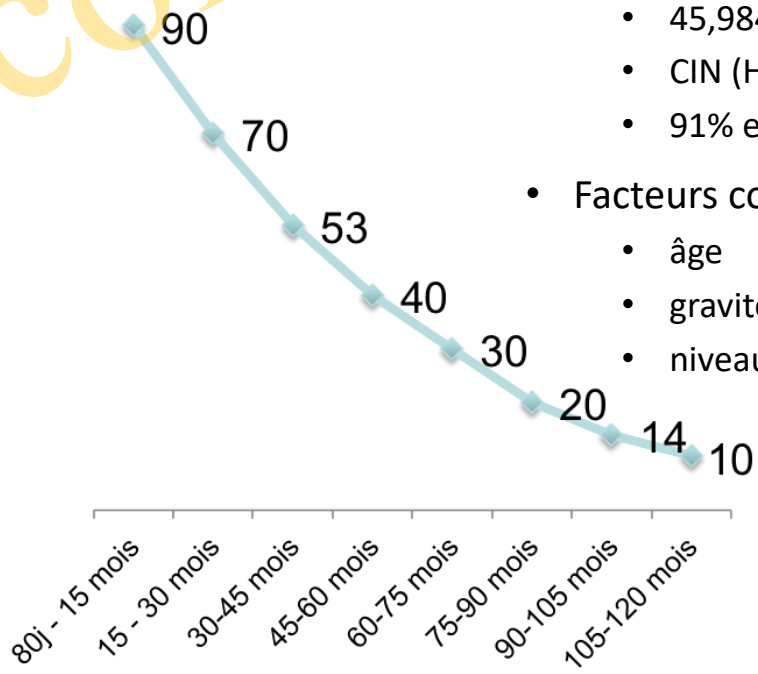
NIVEAU DE PREUVE SCIENTIFIQUE FOURNI PAR LA LITTERATURE	GRADE DES RECOMMANDATIONS
Niveau 1 - Essais comparatifs randomisés de forte puissance – Méta-analyse d'essais comparatifs randomisés - Analyse de décision basée sur des études bien menées	**A** Preuve scientifique établie
Niveau 2 - Essais comparatifs randomisés de faible puissance - Études comparatives non randomisées bien menées - Études de cohorte	**B** Présomption scientifique
Niveau 3 - Études cas-témoin **Niveau 4** - Études comparatives comportant des biais importants - Études rétrospectives - Séries de cas - Études épidémiologiques descriptives (transversale, longitudinale)	**C** Faible niveau de preuve scientifique

Attention au message délivré…

Me faire vacciner après ma conisation :

- Alors pourquoi vacciner à 11 -19 ans ?
- Je ne risque plus rien : plus de suivi

% Patientes compliantes au suivi



- Etude en population :
  - 45,984 Ptes
  - CIN (HG = 2/3)
  - 91% entre 20-49 ans
- Facteurs compliance :
  - âge
  - gravité du CIN
  - niveau socio-économique

Barken SS. Acta Obstet Gynecol Scand 2013

Les essais (RCT) : peut-être une réponse

Etude ID/ Pays	Critère principal	Design	Statut
NCT03979014 / (NOVEL Trial) UK (+ Finlande + Suède) https://clinicaltrials.gov/study/NCT03979014	Incidence infection HPV 2 ans après la 1ère dose	RCT vaccinées VS non vaccinées, staff de laboratoire en aveugle - femmes 18-55 ans CIN + - vaccination durant TTT (0, 2, 6 mois) - taille prévue: 1000 patientes	Fin de recrutement Date de complétion estimée: 31/08/2025
NL7938 / (VACCINE study) Pays Bas https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7285539/	efficacité sur CIN2+ à 24 mois	RCT double aveugle VS placebo - femmes ≥ 18 ans CIN2+, - vaccination durant TTT (0, 2, 6 mois) - taille prévue: 750 patientes	En cours Date de complétion estimée: inconnu
NCT03848039 / (HOPE9) Italie https://clinicaltrials.gov/study/NCT03848039	efficacité sur CIN2+ à 5 ans	RCT double aveugle VS placebo - femmes ≥ 18 ans CIN2+ - vaccination à 0-1 mois du TTT - taille prévue: 1220 patientes	En cours Date de complétion estimée: 05/2028