Surveillance of Effects of Human pappillomavirus Immunisation in Belgium (SEHIB): final analysis on cytology and virology

Weyers S (1), Vanden Broeck D (2), Guieu A (2), Depuydt C (3), Bogers JP (3), Temmerman M (2), Arbyn M (4).

(1) Department of Gynaecology and Obstetrics, Ghent University Hospital, Gent, Belgium.
(2) International Centre of Reproductive Health, Ghent University, Gent, Belgium
(3) Laboratory for Clinical Pathology (AML), Antwerp, Belgium
(4) Unit of Cancer Epidemiology, Scientific Institute of Public Health, Brussels, Belgium.

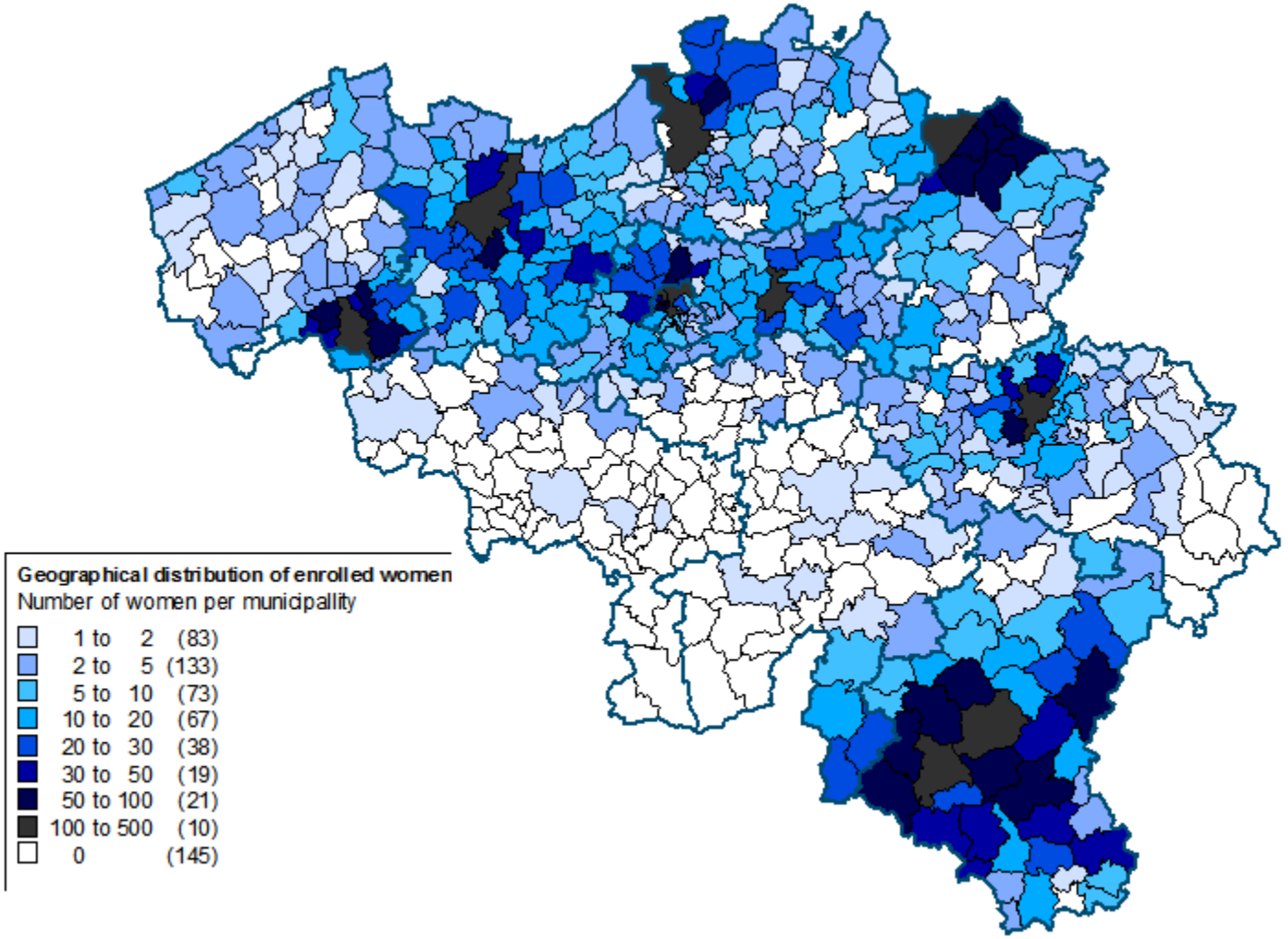
Objectives

- 1st: Generate **baseline data** at introduction of prophylactic HPV vaccination:
  - Opportunistic, partially reimbursed vaccination (12-18y)
    - started in 2006
    - best vaccinated cohort C1992:69%
  - Organized free vaccination (school-based):
    - started in Flanders in **September 2010** (12-13y; quadrivalent): Coverage >85%
    - Started in Wallonia (13-14y) in **September 2011** (13-14y; bivalent)

- 2nd: Provide a **surveillance framework** for measuring the impact of HPV vaccination in Belgium.

Methods

- 10 cytopathology labs (5 University, 5 Peripheral)
- Collect **10x600** residual liquid cervical cell **screening samples** in women aged 18-64 (Phase I)
- collect **5x240** (80 ASC-US, 80 LSIL, 80 HSIL) additional (Phase 2) **abnormal samples** from the 5 U labs (continues in second phase of study).
- Samples tested
  - presence of **DNA from individual HPV genotypes**
  - using a sensitive rtPCR targeting E6/E7 genes (AML).
- **HPV vaccination status is only recorded in U-centers**
  - Validated by contacting the vaccinating doctors (first phase).
  - For women declaring being non-vaccinated, status was not verified.


Geographical distribution of enrolled women
Number of women per municipallity
1 to 2 (83)
2 to 5 (133)
5 to 10 (73)
10 to 20 (67)
20 to 30 (38)
30 to 50 (19)
50 to 100 (21)
100 to 500 (10)
0 (145)

Results Phase 1 (1)

- First center started in **November 2010,** last patient in **July 2014 (45 months)**.
- Final analysis:
  - **6630 samples**,
  - 5980 phase 1(=target), 650 phase II (50% of target)

- These samples were collected by **8 centers** (4 U, 4 P), 2 centers did not start.
- **Vaccination status** was recorded for **1857** women (only U), 126 of which declared to be vaccinated (6.7%).

Crude prevalence of cervical epithelial abnormalities: age groups

30 years or older

Laboratory	N	NILM	ASC-US	ASC-H	LSIL	HSIL	Cancer	Total	ASC-US / SIL+
A	324	92.6	2.8	2.8	1.9	0.0	0.0	100.0	0.60
B	302	95.0	2.0	0.7	1.3	1.0	0.0	100.0	0.67
C	600	92.5	2.7	0.0	4.5	0.3	0.0	100.0	0.55
D	330	92.1	3.6	0.0	3.3	0.9	0.0	100.0	0.86
E	425	87.5	7.8	1.4	1.7	1.7	0.0	100.0	1.65
F	269	99.6	0.4	0.0	0.0	0.0	0.0	100.0	-
G	423	95.5	3.3	0.0	0.7	0.5	0.0	100.0	2.81
H	307	95.8	2.0	0.3	1.6	0.3	0.0	100.0	0.85
Total	**2,980**	**93.4**	**3.3**	**0.6**	**2.1**	**0.6**	**0.0**	**100.0**	**0.98**

Pearson chi2(28) = 124.5947 Pr = 0.000

<30 years

Laboratory	N	NILM	ASC-US	ASC-H	LSIL	HSIL	Cancer	Total	ASC-US / SIL+
A	274	86.5	9.1	0.7	2.2	1.5	0.0	100.0	2.08
B	297	93.3	2.4	0.0	4.0	0.3	0.0	100.0	0.54
C	601	87.4	3.5	0.2	8.0	1.0	0.0	100.0	0.38
D	268	85.1	4.1	0.0	9.7	1.1	0.0	100.0	0.38
E	408	80.2	10.3	3.4	3.4	2.7	0.0	100.0	1.08
F	149	96.0	2.7	0.0	1.3	0.0	0.0	100.0	2.00
G	291	88.7	7.6	0.0	3.1	0.7	0.0	100.0	2.00
H	386	88.9	4.2	0.0	6.5	0.3	0.3	100.0	0.59
Total	**2,674**	**87.4**	**5.5**	**0.6**	**5.3**	**1.1**	**0.0**	**100.0**	**0.79**

Pearson chi2(28) = 124.5947 Pr = 0.000

Crude prevalence of cervical glandular abnormalities: age groups

30 years or older

Laboratory	N	No abnormal glandular cells	AGC	Total
A	324	*100.0*	*0.00*	*100.0*
B	303	*99.3*	*0.66*	*100.0*
C	600	*100.0*	*0.00*	*100.0*
D	331	*99.7*	*0.30*	*100.0*
E	427	*99.5*	*0.47*	*100.0*
F	269	*99.6*	*0.37*	*100.0*
G	434	*99.8*	*0.23*	*100.0*
H	308	*100.0*	*0.00*	*100.0*
Total	**2,996**	***99.8***	***0.23***	***100.0***

Pearson chi2(7) = 6.5451 Pr = 0.478

<30 years

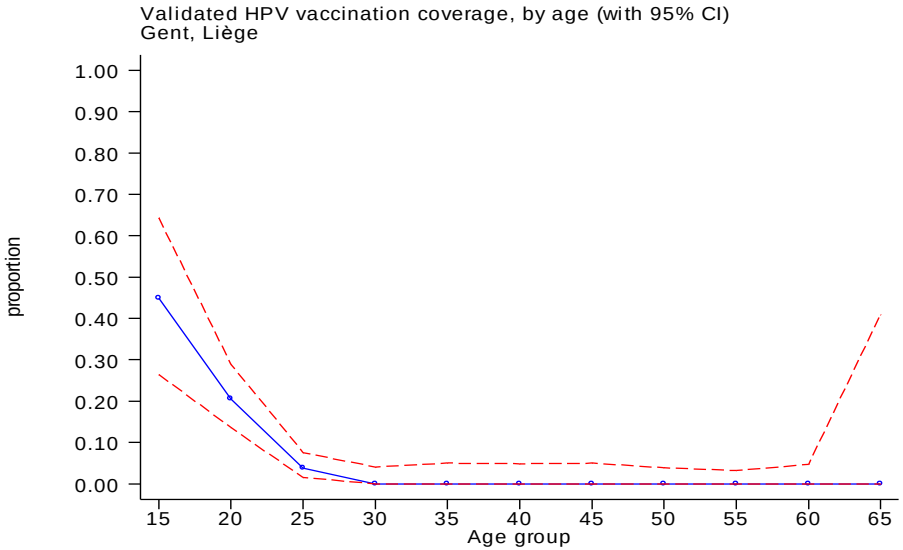
Laboratory	N	No abnormal glandular cells	AGC	Total
A	276	*99.6*	*0.36*	*100.0*
B	297	*100.0*	*0.00*	*100.0*
C	601	*100.0*	*0.00*	*100.0*
D	269	*99.6*	*0.37*	*100.0*
E	410	*99.5*	*0.49*	*100.0*
F	149	*100.0*	*0.00*	*100.0*
G	293	*100.0*	*0.00*	*100.0*
H	390	*100.0*	*0.00*	*100.0*
Total	**2,685**	**99.85**	**0.15**	**100**

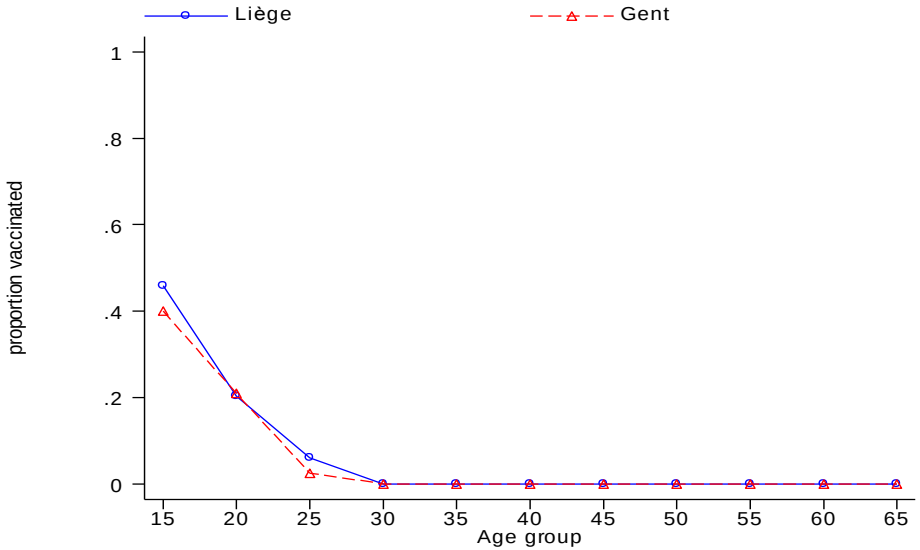
Pearson chi2(7) = 7.4874 Pr = 0.380

Results Phase 1 (2)

- The prevalence of **cytological abnormalities** (4788 samples) was:
  - ASC-US: 3.4%
  - AGC: 0.2%
  - LSIL: 3.1%
  - ASC-H: 0.7%
  - HSIL: 0.6%
- The prevalence of **abnormal cytology is nearly twice as high among women younger than 30** than among those of 30 and older (12.6% vs 6.6%).
- True for all cytological categories, **except for ASC-H**.
- The **prevalence of AGC is low**, on average 0.2%

Vaccination status: self reported vs confirmed (period 1)





Age group	Yes confirmed	Yes corrected to no	Yes not validated	Not vaccinated	No info	Total
15	44.8%	0.0%	20.7%	34.5%	0.0%	100.0%
20	20.4%	0.0%	3.5%	74.3%	1.8%	100.0%
25	2.7%	0.0%	1.1%	92.3%	3.8%	100.0%
30	0.0%	0.0%	0.0%	100.0%	0.0%	100.0%
35	0.0%	0.0%	1.4%	98.6%	0.0%	100.0%
40	0.0%	1.4%	0.0%	98.6%	0.0%	100.0%
45	0.0%	1.4%	0.0%	98.6%	0.0%	100.0%
50+	0.0%	1.4%	0.3%	98.3%	0.0%	100.0%
Total	4.5%	0.7%	1.5%	92.4%	1.0%	100.0%

Results Phase 1 (3)

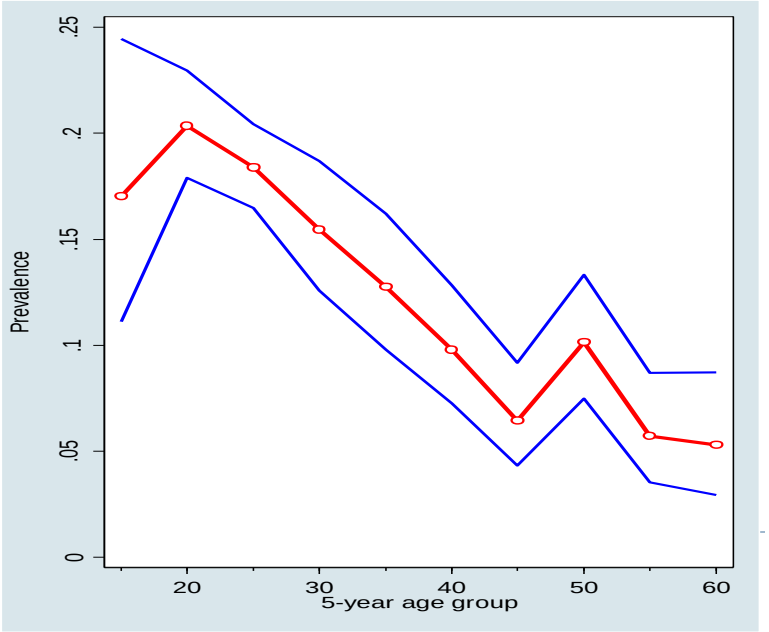
- **98%** of women with confirmed positive vaccination status received the **three doses** of vaccine while 2% received only 2 doses.
- Considering women whose *vaccination status could not be confirmed as vaccinated*, we can conclude that 63% (95% CI: 44-80%) of women younger than 20 years are fully vaccinated.
- Considering women with *missing/non-confirmed vaccination status as non vaccinated*, the estimated 3-dose vaccination coverage was:
  - 54% (95% CI: 33-74) for women < 20 years,
  - 20% (95% CI: 13-29) in age group 20-24,
  - 4% (95% CI: 2-8) in age group 25-29 and
  - zero in women of 30 and older.

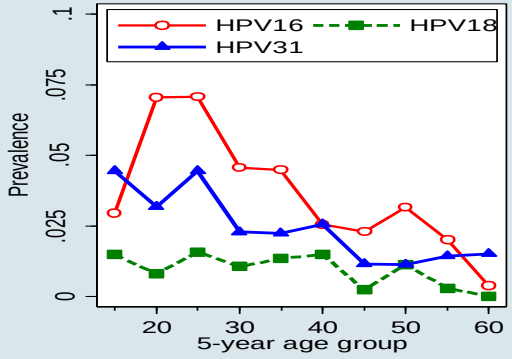
Prevalence of HPV-infection: screening population.

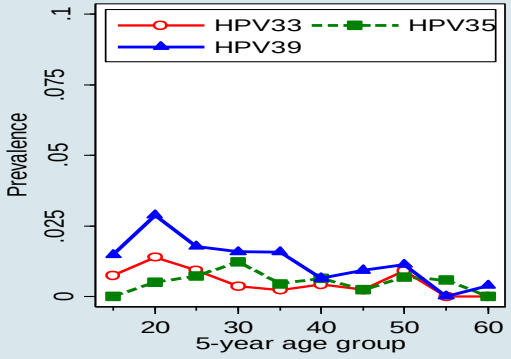
Types	NILM	ASC-US	ASC-H	LSIL	HSIL	Total	Ratio hrHPV in HSIL/NILM
N	5,096	242	34	205	47	5,624	
high-risk types							
hrHPV(13)	10.8	31.0	26.5	62.0	89.4	14.2	8.3
HPV 16	3.2	10.8	14.7	23.4	57.5	4.8	17.8
HPV 18	0.7	2.9	2.9	4.9	17.0	1.1	25.4
HPV 31	2.2	7.1	2.9	11.2	12.8	2.8	5.9
HPV 33	0.5	1.7	2.9	3.9	4.3	0.7	9.5
HPV 35	0.5	0.4	0.0	2.4	10.6	0.6	23.6
HPV 39	1.2	4.2	0.0	8.3	0.0	1.5	0.0
HPV 45	0.4	0.4	0.0	0.5	0.0	0.4	0.0
HPV 51	1.3	6.2	2.9	11.2	14.9	2.0	11.3
HPV 52	1.2	4.2	2.9	10.2	6.4	1.7	5.2
HPV 56	1.0	3.7	2.9	10.2	8.5	1.6	8.3
HPV 58	0.7	3.3	2.9	4.4	6.4	1.0	9.0
HPV 59	0.8	4.2	5.9	6.8	4.3	1.3	5.2
HPV 68	0.1	0.8	0.0	1.0	2.1	0.2	21.3
HPV1618	3.8	12.5	17.7	25.4	66.0	5.5	17.6
hrHPVnon1618	7.0	18.7	8.8	36.6	23.4	8.7	3.3
intermediate risk types							
HPV 53	1.1	5.0	5.9	13.2	2.1	1.7	2.0
HPV 66	1.0	2.1	2.9	10.7	6.4	1.4	6.6
HPV 67	1.4	4.6	5.9	7.8	2.1	1.8	1.6
low risk types causing genital warts							
HPV 06	0.5	0.4	2.9	4.9	2.1	0.7	4.2
HPV 11	0.1	0.4	0.0	1.5	0.0	0.2	0.0

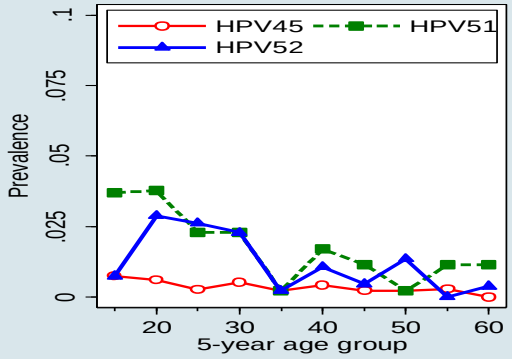
Prevalence of hr-HPV-infection: screening population, age groups

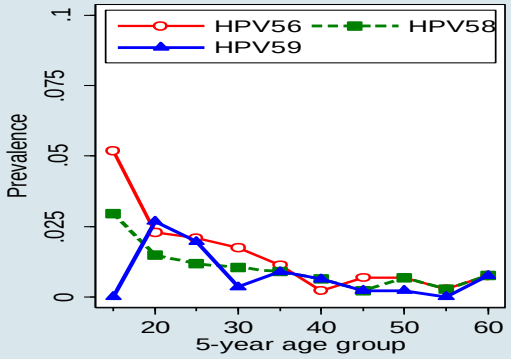
Age	Prevalence, in % (95% CI)
15 - 19	17.0 (11.6-24.3)
20 - 24	20.4 (18.0-23.0)
25 - 29	18.4 (16.5-20.4)
30 - 34	15.5 (12.7-18.7)
35 - 39	12.8 (10.0-16.2)
40 - 44	9.8 (7.4-12.8)
45 - 49	6.4 (4.5-9.2)
50 - 54	10.1 (7.7-13.3)
55 - 59	5.7 (3.7-8.7)
60 - 65	5.3 (3.2-8.8)

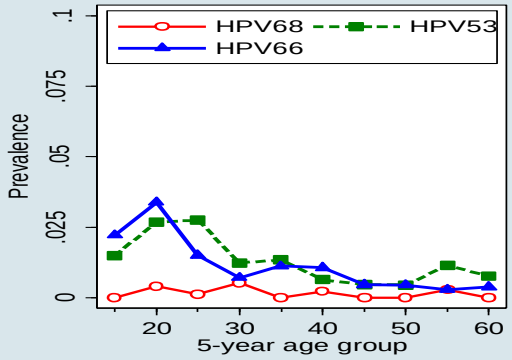












Results Phase 1 (4)

- Prevalence of **HPV-infection**:
  - hrHPV in 14.2% of samples
  - HPV 16, 31, 51, 52, 56 and 59 most prevalent
  - HPV 18 only 1.1%
  - HPV 6/11in less than 1% of samples
- The overall prevalence of **high-risk HPV varied by age**:
  - 19% among women younger than 29,
  - decreasing progressively with higher age (exc increase 50-54y)
  - reaching a prevalence of 5.3% among women aged 60-64 years
  - strongly correlated with cytological findings.

Results Phase 1 (5)

- In women with **normal cytology** HPV16 was the most common infection (3.2%), followed by HPV31 (2.2%) and HPV51 (1.3%).
- In **HSIL**, the 3 **most common types** were:
  - HPV16 (57.5%),
  - HPV18 (17%),
  - HPV51 (14,9%).
- The **prevalence of HPV16/18** was lower in vaccinated (3.4 %) than non-vaccinated women (7.4 %).
- **RR** of an HPV16/18 infection among vaccinated versus non-vaccinated women >30y was **0.35** (95% CI: 0.17-1.57).This corresponds with a VE=65% (32-82%)

Results (6)

Protection against	Age group	Vaccine efficacy	p	Risk difference	p
Infection with HPV16/18	18-19	49% (95% CI: -157% to 90%)	0.2702	-31.8% (95%CI:-87.0% to 23.4%)	n sign
	20-24	57% (95% CI: -8% to 83%)	0.0387	-19.2% (95%CI:-33.5% to -4.9%)	sign
	25-29	45% (95% CI: -292% to 92%)	0.5383	-2.8% (95%CI: -9.9% to 4.3%)	n sign
ASCUS+ associated with HPV16/18					
	18-19	100% (95% CI: .% to .%)	0.1867	-64.4% (95%CI:-78.4% to-50.5%)	sign
	20-24	53% (95% CI: -72% to 87%)	0.1981	-17.0% (95%CI:-37.5% to 3.4%)	n sign
	25-29	-28% (95% CI: -775% to 81%)	0.8041	1.7% (95%CI:-13.0% to 16.4%)	n sign
LSIL+ associated with HPV16/18					
	18-19	100% (not computable)	0.1867	-64.4% (95%CI:-78.4% to-50.5%)	sign
	20-24	100% (not computable)	0.0924	-32.3% (95%CI:-38.0% to-26.6%)	sign
	25-29	-141% (95% CI: -1444% to 62%)	0.3589	8.4% (95%CI:-17.7% to 34.4%)	n sign
HSIL+ associated with HPV16/18					
	18-19	-	-	-	-
	20-24	100% (not computable)	-	-31.7% (95%CI:-37.3% to-26.0%)	sign
	25-29	-325% (95% CI: -2329% to 26%)	0.1113	19.1% (95%CI:-23.4% to 61.6%)	n sign

Dark green	significant protection
Light green	non significant protection
Light yellow	non significant higher risk
Yellow	significant higher risk

- Sign protection against **infection (16/18)** in the age group 20-24. Sign protection against **lesions** in the youngest age group. The protection decreases by age.
- In women aged 25-29, there is even a non-significant negative protection

Conclusions Phase 1

- The SEHIB study provides crucial baseline information indicating that the **cyto-virological correlation** could be used in quality control of cervical cytology.
- Even though a high proportion of vaccinated women <30 years were most likely exposed to HPV before vaccination a **reduction of HPV 16/18 infections was observed** suggesting an early effect of HPV vaccination.
- Our data suggest that **vaccinated women older than 25 belong to a higher risk-group** who probably were vaccinated after being infected.
- More results are awaited to assess the impact of vaccination on the prevalence of cytological and histological cervical lesions, related to vaccine HPV types, related to non-vaccine high-risk types and irrespective of HPV types.

Thank you!