

Surveillance of effects of HPV vaccination in Belgium



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ABSTRACT

Background: Early effects of HPV (human papillomavirus) vaccination are reflected by changes observable in young women attending cervical cancer screening.

Subject and methods: The SEHIB study included HPV geno-typing of ~6000 continuous and 650 pathological cervical cell specimen as well as biopsies, collected from women in Belgium in 2010–2014. Data were linked to vaccination status.

Results: HPV vaccination offered protection among women aged <30 years against infection with HPV16 (vaccine effectiveness [VE] = 67%, 95% CI: 48–79%), HPV18 (VE = 93%, 95% CI: 52–99%), and high-risk HPV (VE = 16%, 95% CI: 2–29%). Vaccination protected also against cytological lesions. Vaccination protected against histologically confirmed lesions: significantly lower absolute risks of CIN1+ (risk difference [RD] = −1.6%, 95% CI: −2.6% to −0.7%) and CIN3+ associated with HPV16/18 (RD = −0.3%, 95% CI −0.6% to −0.1%). Vaccine effectiveness decreased with age. Protection against HPV16 and 18 infection was significant in all age groups, however no protection was observed against cytological lesions associated with these types in age-group 25–29.

Conclusion: The SEHIB study demonstrates the effectiveness of HPV vaccination in Belgian young women in particular in age group 18–19. Declining effectiveness with increasing age may be explained by higher tendency of women already exposed to infection to get the vaccine.

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1. Introduction

In Belgium, a country in Western Europe of 11 million inhabitants, 623 new cases of cervical cancer were noted in 2011, and an estimated 275 women died from it [1,2]. Up to

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recently, cervical cancer screening was mainly opportunistic, characterised by a moderate coverage, too frequent screening and a poorly documented quality [3,4]. Sixty percent of women aged 25–64 years have had a Pap smear taken in the last three years [5]. Eighty two percent of all interpreted Pap smears are taken from women belonging to the target age group (25–64 years), whereas 10% and 8% of smears are taken from women younger than 25 years or older than 64 years, respectively [5]. In 2013, a new call-recall programme has been set up in the Flemish Region, where all women, without recent cervix cytology record in the cancer registry, are invited in agreement with European guidelines. In the other two regions (Wallonia, Brussels), no organised programme is in place.

In Belgium, HPV vaccines are reimbursed partially, via the National Health Insurance Institute (NHII), for girls in the range 12–18 years. There is still a personal contribution for the parents of 12€ (or 8€ for socially vulnerable categories)/dose, whereas the rest of the vaccine cost (~110€/dose) is paid by the NHII. An estimate was made of the coverage generated through this opportunistic HPV vaccination from individual reimbursement claims between November 2007 and May 2012. The 3-dose HPV coverage reached over this period showed a decreasing trend by birth cohort (C): 50% in C1992, 46% for C1993, 37% for C1994 [6].

Free school-based vaccination of girls in the first year of secondary education was introduced by the Flemish Community in 2010, using a three-doses schedule of the quadrivalent vaccine. The 3-dose coverage was 81% and 79% for the school years 2010–11 and 2011–12, respectively [7]. In 2011, also the French community introduced free vaccination with the bivalent vaccine targeting girls in the second year of secondary education. The 3-dose coverage in the French Community for the 2012–13 programme was estimated at 29% [8]. In 2014, health authorities of the Flemish and French Communities decided to switch to a two-doses vaccination schedule with the bivalent vaccine.

The SEHIB (Surveillance of Effects of HPV Immunisation in Belgium) study addressed three objectives: 1) to assess the prevalence of HPV infection and of cervical cytological lesions at the onset of HPV vaccination; 2) to assess the HPV vaccination coverage; and 3) to measure the early impact of HPV vaccination on the burden of HPV infection and HPV-related cervical disease using archived cervical cell and tissue material from women attending cervical cancer screening in Belgium between end 2010 and early 2014.

2. Methods

2.1. Participating centres, enrolment of women

The departments of gynaecology and cytopathology of four Belgian universities (Brussels, Ghent, Leuven, Liège) as well as four large regional cytopathology laboratories (Charleroi, Herentals, Kortrijk and Overpelt) participated in SEHIB. The centres were chosen based on yearly work load of Pap smears and geographical location. All centres were requested to enrol at least consecutive 600 women attending cervical cancer screening with the purpose to reach together a sample size of 6000 specimen. Enrolment was restricted to women aged 18–64 years, with at least 300 women younger than 30 per centre.

The gynaecological departments of the university centres recruited only women whose cervical samples were interpreted in the cytopathology laboratory of the same centres and who had given informed consent. The HPV vaccination status was queried during the gynaecological consultation. The coordinates of the physician having administered the vaccine were recorded during the first year in two university departments. Subsequently the physician was contacted by the SEHIB coordinating centre to

validate the reported vaccination status. Vaccination status was defined as positive when anamnesis indicated that the woman had received at least one dose of HPV vaccine. The recruitment of continuous screening samples took place in phase-1. During phase-2, the university centres enrolled additional pathologic cytology samples. The inclusion of specimen for the SEHIB took place between November 2010 and July 2014.

2.2. Cytology collection, sample processing and HPV testing

Cervical cell samples were collected by the woman's gynaecologist or GP and prepared according to current European guidelines [9]. Cytological results were reported following the Bethesda System [10]. Subsequently, residual LBC material of selected specimen was stored in the original vials at 4 °C, before shipping to the AML laboratory (Antwerp, Belgium) for HPV testing with a validated real-time qPCR assay targeting type-specific sequences of the E6 or E7 genes of 17 HPV types (HPV6 E6, HPV11 E6, HPV16 E7, HPV18 E7, HPV31 E6, HPV33 E6, HPV35 E6, HPV39 E7, HPV45 E7, HPV51 E7, HPV52 E7, HPV53 E6, HPV56 E7, HPV58 E7, HPV59 E7, HPV66 E6 and HPV68 E7) and the L1 gene of HPV67, as described previously [11,12].

Biopsies taken at the four universities from SEHIB women referred to colposcopy were also shipped to the AML laboratory for HPV genotyping after reviewing of the original histological diagnosis by an expert pathologist.

2.3. Data management

A pseudonymous SEHIB code was used to link cytology, histology and virology files with the demographic and clinical data (municipality, birth year, reason of testing, HPV vaccination status). Data compilation and statistical analyses were performed at the Scientific Institute of Public Health, Brussels. Approval of SEHIB was received from the Ethical Review Board of the University Hospital of Ghent (EC approval Nr. B67020109075), which was subsequently endorsed by the other centres.

2.4. Statistical analysis

Considerations regarding the computation of the study sample size and statistical power can be found in the supplementary material. Study records were weighted according to the phase and the reason for Pap smear taking by imposing the distribution of cytological findings observed in the screening population in phase-1 to phase-2. The purpose was to generate a virtual mother population that was substantially larger than the actual study size and to maximize power of the study without necessity to perform HPV testing in all subjects of the mother population. The computation of the reweighted population is shown in Supplementary Table 2.

Because of the oversampling of young women, and to account for differences in the age composition between study centres, directly age-standardised prevalences were computed, using the truncated Belgian female 2012 population aged 18–65 years as reference. The HPV vaccination coverage was estimated from the anamnestic data combined with information obtained from the vaccinating physician. The impact of vaccination status on occurrence of cytological and histological abnormalities associated with HPV vaccine types and irrespective of HPV types was assessed by computing VE (vaccine effectiveness) and RD (risk differences), where $VE = 1 - RR$ (risk ratio), $RR = P_{\text{vacc}} / P_{\text{n.vacc}}$, P_{vacc} being the prevalence of infection or lesion in vaccinated and $P_{\text{n.vacc}}$ being the prevalence in non-vaccinated women; $RD = P_{\text{vacc}} - P_{\text{n.vacc}}$. Perfect vaccine protection corresponds with $VE = 100\%$, absence of protection with 0% . Effectiveness is considered as statistically

significant when $VE > 0\%$ and the 95% confidence interval excludes zero, with $p < 0.05$. Statistical significance was defined at $p < 0.05$. Statistical analyses were performed with Stata, version 13 (StataCorp LP, College Station, TX, USA).

3. Results

3.1. Study characteristics

In total, cervical cell specimen from 6,630 women were included, among whom 5,980 in phase-1 and 650 in phase-2. The geographical origin of enrolled women is shown in Table S3 and Fig. S1. Forty seven percent of samples were from women younger than 30 and 53% were thirty or older (Figure S2). The four regional laboratories provided 45% of the samples (only phase 1), whereas the four university centres contributed 45% and 10%, in phase 1 and 2, respectively (Table S4). The large majority of Pap smears (91%) were taken for screening, the other 9% were collected for other reasons (Table S5). Three percent of cytological samples were judged inadequate. However, after recoding the samples with interpretation for squamous or glandular cells as satisfactory only 0.4% were considered as actually inadequate (Table S6). The age-standardized prevalence of cytological abnormalities in the Belgian screening population was derived from phase-1 (Tables S7 and S8): ASC-US (atypical squamous cells of undetermined significance, 3.7%), LSIL (low-grade squamous intraepithelial lesion, 2.7%), ASC-H (atypical squamous cells where HSIL cannot be excluded, 0.5%), HSIL (high-grade squamous intraepithelial lesion, 0.6%), AGC (atypical glandular cells, 0.1%) and cervical cancer (0.007%). The variation in the prevalence of cytological abnormalities by age is shown in Fig. 1.

3.2. HPV findings, cyto-virological correlation

The proportion of specimen not allowing PCR amplification of *b-globin* was 0.7% (Table S9). In the screening population, the prevalence of hr (high-risk) HPV infection reached a maximum of 20.4% in the age group 20–24 and decreased thereafter up to age group 45–49, interrupted by a peak in age group 50–54 which was followed by a further decrease in the older groups (Fig. 2). The prevalence of the separate HPV types showed similar age patterns with the exception of the high-risk types HPV45, HPV68 and low-risk type HPV11 that showed low rates (<1%) at all ages. Table 1 gives the age-standardized prevalence of infection with hrHPV, with 18 type-specific HPV infections by cytological categories. In

general, the prevalences increased by cytological severity of the lesion. The HSIL/NILM (negative for intraepithelial lesion or malignancy) ratio was highest for HPV18 (26.7), HPV58 (23.5) and HPV16 (18.6). HPV16 was the most frequent HPV type in all cytological categories.

3.3. Histological findings

Hundred seventy six biopsies were retrieved from women enrolled in SEHIB. However, 15 were considered as unsatisfactory at quality control review yielding 161 specimen for definite histological interpretation: 38 cases without dysplasia, 68 CIN1 (cervical intraepithelial neoplasia of grade 1), 34 CIN2, 19 CIN3 and 2 cases of squamous cervical cancer (Table S10). The proportion of cytological abnormalities with adequate biopsies varied from 4% for women with ASC-US to 67% for women with cytological suspicion of cancer (Table S11). Eighty three percent of the original histological interpretations (dichotomized as $\leq$ CIN1 and CIN2+) agreed with the definite diagnosis ($\kappa = 0.66$, Table S12). The hrHPV and HPV16 positivity rate in cytological specimen rose with the severity of the histological outcome. Ninety seven percent of the cases of CIN2 and all of CIN3 and cancer were hrHPV positive. HPV16 or HPV18 were present in 63%, 83% and 100% in CIN2, CIN3 and cancer, respectively (Table S13). The virological agreement between cytology and histology specimen was 84% ($\kappa = 0.66$) for HPV16, 95% ($\kappa = 0.57$) for HPV18, 76% ($\kappa = 0.46$) for hrHPV and 67% ($\kappa = 0.51$) for other non-HPV16/18 hrHPV types (Table S14).

3.4. Vaccination status

From November 2010 to October 2011, the vaccination status of women enrolled at the university centres 5 and 8 was verified for those who self-reported that they were vaccinated against HPV. For all women younger than 35 years, whose physician-vaccinator could be contacted, this information was confirmed, whereas for older women, the information was wrong at the exception of one woman aged 35 in phase-2. After October 2011, verification was stopped, accepting the self-reported vaccination status for all women <35 years of age as probable. Accepting this assumption, vaccination coverage could be estimated as: 68% (95% CI: 52–78%) for women younger than 20 years, 33% (95% CI: 29–38%) in age group 20–24 and 9% (95% CI: 7–11%) in age group 25–29, and 0.3% (95% CI: 0–1%) in age group 30–39, whereas zero among older women (Fig. 3). Women with unknown vaccination status were excluded from analysis.

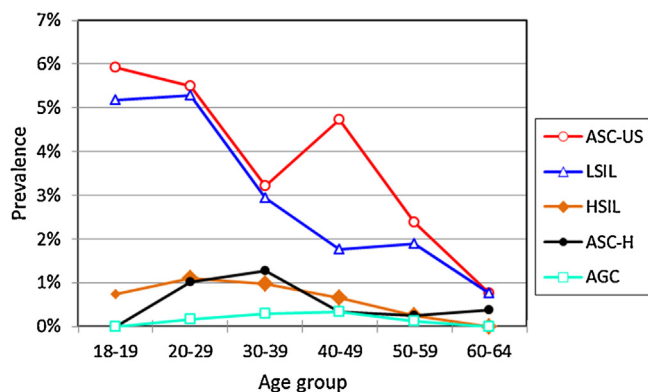


Fig. 1. Prevalence of cervical lesions by cytological category (restricted to the screening population of phase-1), by age group. Abbreviations: ASC-US: atypical squamous cells of undetermined significance, LSIL: low-grade squamous intraepithelial lesion, HSIL: high-grade squamous intraepithelial lesion, ASC-H: atypical squamous cells where HSIL cannot be excluded, AGC: atypical squamous cells.

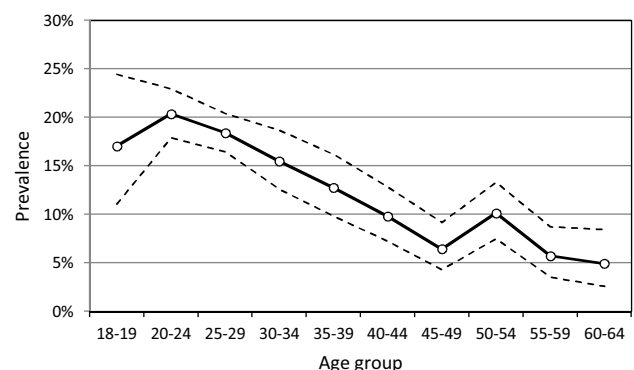


Fig. 2. Prevalence of hrHPV infection (and 95% confidence interval [interrupted lines]), by age group, in the screening population of the SEHIB study.

Table 1

Age-standardised prevalence of cytological findings and of HPV infections by cytological category in the screening population.

Types	NILM	ASC-US	LSIL	ASC-H	HSIL+	Total	Ratio hrHPV in HSIL+/NILM
Prevalence of cytological findings							
N	5096	242	205	34	47	5,624	
%	92.4	3.7	2.7	0.5	0.6	92.4	
Prevalence of HPV infections (in %)							
High-risk types							
hrHPV(13)	9.2	20.0	46.5	12.2	81.9	9.2	8.9
HPV 16	2.5	5.8	15.3	7.3	47.1	3.5	18.6
HPV 18	0.6	1.7	3.3	1.0	16.0	0.9	26.7
HPV 31	1.9	3.2	4.3	1.5	18.4	2.2	9.8
HPV 33	0.4	0.5	1.5	1.5	0.9	0.5	2.4
HPV 35	0.5	0.1	0.7	0.0	7.0	0.5	15.4
HPV 39	1.0	2.7	5.3	0.0	0.0	1.2	0.0
HPV 45	0.3	0.1	0.2	0.0	0.0	0.3	0.0
HPV 51	1.3	4.1	7.3	1.0	9.2	1.7	7.3
HPV 52	0.9	2.0	6.0	1.0	5.0	1.2	5.7
HPV 56	0.8	2.8	8.2	1.0	4.3	1.2	5.1
HPV 58	0.6	2.9	2.8	1.0	14.3	0.9	23.5
HPV 59	0.5	2.3	7.7	2.4	4.3	0.8	8.4
HPV 68	0.1	0.9	0.3	0.0	0.5	0.1	4.9
HPV16/18	3.0	7.0	16.2	8.3	56.8	4.2	18.8
hrHPVnon16/18	12.2	26.9	62.7	20.5	138.8	15.7	11.3
Intermediate risk types							
HPV 53	0.8	2.5	11.2	3.1	0.5	1.2	0.6
HPV 66	0.7	1.1	8.5	1.7	2.6	1.0	3.4
HPV 67	1.0	2.3	4.1	2.5	0.5	1.2	0.5
Low-risk types causing genital warts							
HPV 06	0.4	0.1	4.0	1.0	0.5	0.5	1.1
HPV 11	0.05	0.1	2.7	0.0	0.0	0.1	0.0

HPV: human papillomavirus; hr: high-risk; NILM: negative for intraepithelial lesions or malignancy; ASC-US: atypical squamous cells of undetermined significance; ASC-H: atypical squamous cells where HSIL cannot be excluded; LSIL: low-grade squamous intraepithelial lesions; HSIL: high-grade squamous intraepithelial lesions.

3.5. HPV vaccination effects

For the computation of the impact of HPV vaccination, weighted data including all enrolled women from both phases were used. Data on protection against infection with HPV16, HPV18, HPV6 or HPV11 and against cytological and histological lesions associated with HPV16 or 18 in women younger than 30 are shown in Table 2. Significant protection was observed regarding infection with HPV16 (VE = 67%, 95% CI: 48% to 79%), HPV18 (93%, 95% CI: 52–99%), HPV16/18 (71%, 95% CI: 55–81%) and HPV 11, VE = 100%, CI not computable, but CI around RD excluding zero. The protection against HPV6 infection was not significant (VE = 33%, 95% CI: –55% to 71%). Overall hrHPV infection was lower in vaccinated versus non-vaccinated women (VE = 16%, 95% CI: 2–29%). However, vaccinated women had a non-significantly higher risk of infection with other hrHPV without HPV16/18 than non-vaccinated women VE = –15% (95% CI: –38% to 4%). HPV vaccination protected also against cytological lesions associated with HPV16/18 and even against cytological lesions irrespective of presence of hrHPV (significant for ASC-US+ and LSIL+ associated with HPV16/18 and for overall LSIL+ and HSIL+). Finally, vaccination protected against histologically confirmed lesions, which resulted in significantly lower absolute risks of CIN1+ (RD = –1.6%, 95% CI: –2.6% to –0.7%) and CIN3+ associated with HPV16/18 (–0.3%, 95% CI: –0.6% to –0.1%).

Protection against HPV16 or HPV18 infection and against cytological lesions associated with these infections, separated by finer age groups are shown in Table 3. Vaccine effectiveness decreased with age. Protection was significant against HPV16 and 18 infection in all age groups, against ASC-US in age group 18–19 and against LSIL in age groups 18–19 and 20–24. A non-

significant higher risk of HSIL associated with HPV16/18 was noted in vaccinated women aged 25–29 ($p = 0.3986$).

4. Discussion

The SEHIB study provides a solid basis of information on the current burden of HPV infection and related cervical precancer in Belgium and provides an estimate of the early impact of the first years of HPV vaccination among young women attending screening. Significant protection was observed regarding infection with the HPV types included in the vaccines as well as cytological and histological precancerous lesions associated with HPV16 and HPV18.

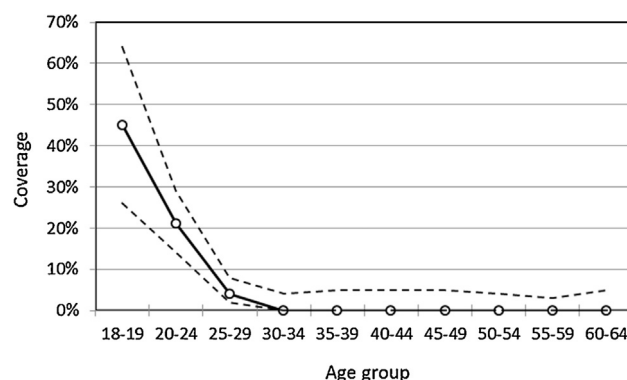


Fig. 3. HPV vaccination coverage (and 95% confidence interval [interrupted lines]), by age group, estimated in the screening population of the SEHIB study.

Table 2

Protection against infection with HPV16, HPV18, HPV6 or HPV11 and against cytological and histological lesions associated with HPV16 or 18, expressed as vaccine effectiveness and risk difference in women aged 18–29 years.

Protection against	Vaccine effectiveness	Risk difference
HPV16 infection	67% (95% CI: 48% to 79%)	-5.7% (95%CI: -7.2% to -4.1%)
HPV18 infection	93% (95% CI: 52% to 99%)	-1.9% (95%CI: -2.5% to -1.3%)
HPV16/18 infection	71% (95% CI: 55% to 81%)	-7.0% (95%CI: -8.5% to -5.4%)
HPV6 infection	33% (95% CI: -55% to 71%)	-0.4% (95%CI: -1.2% to 0.4%)
HPV11 infection	100% (CI non computable)	-0.4% (95%CI: -0.6% to -0.2%)
hrHPV infection	16% (95% CI: 2% to 29%)	-3.8% (95%CI: -7.0% to -0.6%)
hrHPV other than 16/18 infection	-15% (95% CI: -38% to 4%)	2.2% (95%CI: -0.9% to 5.3%)
ASC-US+ associated with HPV16/18	60% (95% CI: 26% to 78%)	-2.2% (95%CI: -3.3% to -1.1%)
LSIL+ associated with HPV16/18	74% (95% CI: 34% to 90%)	-1.8% (95%CI: -2.6% to -1.0%)
HSIL+ associated with HPV16/18	41% (95% CI: -78% to 81%)	-0.3% (95%CI: -0.9% to 0.2%)
ASC-US irrespective of HPV types	11% (95% CI: -10% to 28%)	-1.5% (95%CI: -4.1% to 1.1%)
LSIL irrespective of HPV types	32% (95% CI: 6% to 50%)	-2.6% (95%CI: -4.5% to -0.7%)
HSIL irrespective of HPV types	63% (95% CI: 3% to 86%)	-1.0% (95%CI: -1.7% to -0.3%)
CIN1+ associated with HPV16/18	75% (95% CI: -4% to 94%)	-0.8% (95%CI: -1.4% to -0.3%)
CIN2+ associated with HPV16/18	54% (95% CI: -98% to 89%)	-0.3% (95%CI: -0.8% to 0.1%)
CIN3+ associated with HPV16/18	100% (95% CI non computable)	-0.2% (95%CI: -0.4% to -0.1%)
CIN1+ irrespective of HPV types	69% (95% CI: 14% to 89%)	-1.6% (95%CI: -2.6% to -0.7%)
CIN2+ irrespective of HPV types	63% (95% CI: -57% to 91%)	-0.6% (95%CI: -1.3% to 0.0%)
CIN3+ irrespective of HPV types	100% (95% CI non computable)	-0.3% (95%CI: -0.6% to -0.1%)
Dark green	significant protection	
Light green	non-significant protection, VE>50%	
Very light green	non-significant protection, VE<50%	
Light yellow	non-significant higher risk	
Yellow	significant higher risk	

HPV: human papillomavirus; ASC-US+: atypical squamous cells of undetermined significance or worse, LSIL+: low-grade squamous intraepithelial lesion or worse, HSIL+: high-grade squamous intraepithelial lesion or worse; CIN1+: cervical intraepithelial neoplasia of grade 1 or worse.

4.1. Observed vaccination effects

The protection against infection with the vaccine types 16 and 18 observed in SEHIB (68 to 77% in the age groups 18–30, see Table 3) is comparable with the VE against HPV16/18 infection reported from randomised trials in the group of all included women regardless of HPV DNA status at enrolment (age group 15–26 years) [13]. Protection against incident HPV16/18 infection in this group is reported only for the bivalent vaccine: 76% (95% CI: 67–83%) [14]. The vaccine efficacy against 6-month persistent HPV16/18 infection was 56% (95% CI: 49–62%) [13], with two included trials assessing the bivalent vaccine where VE was 52% [15] and 59% [16], respectively. Although the SEHIB study could not distinguish between incident or persistent infection, we can conclude that the observed effectiveness against prevalent HPV16/18 is of the same order of magnitude as the protection against incident and persistent infection reported from the trials.

In the vaccine trials, the pooled VE against CIN2+ due to HPV16/18 in the total vaccinated group was 54% (95% CI: 43% to 63%) [13]. This pooled VE was estimated from three trials where VE was 48% [17] and 64% [18] for the quadrivalent and 60% [16] for the bivalent vaccine, respectively. The SEHIB VE estimate (54%) is within this range. The VE against CIN2+ irrespective of HPV types pooled from RCTs was 26% (95% CI: 13% to 37%) [13]. This pooled estimate was

derived from three trials where VE was 19% [17], 33% [16] and 36% [18], respectively. The corresponding SEHIB VE estimate was again non-inferior (63%, but with large confidence intervals). In SEHIB, vaccine effectiveness was in general best in the 18–19 year age group and dropped with increasing age. In the 25–29 age group, HPV vaccination did not protect against cytological lesions due to HPV16/18. This finding is compatible with the higher probability that young adult women (who are beyond the target age for reimbursement) were vaccinated after exposure to HPV infection and that women with high-risk sexual behaviour may be more motivated to buy the vaccine than those with a lower risk profile [19]. It was already known that current prophylactic HPV vaccines do not clear existing infection with one of the vaccine types [20]. There was a slight non-significant increase in other non16/18-hrHPV infection among vaccinated women versus non vaccinated women (VE = -15%, 95% CI -38 to 4%). Although this phenomenon may be explained by chance ($p=0.14$), type replacement, not detectable because of insufficient power, cannot be excluded. Nevertheless, no repercussion on protection against cytological or histological lesions irrespective of HPV types was noted in SEHIB. This latter finding may support the statement that type replacement – if it would occur – may not result in higher rates of cervical (pre) cancer because of the lower malignant potential of the other high-risk types. It is expected that the lower vaccine protection

Table 3

Protection against HPV16 or HPV18 infection and against cytological lesions associated with these infections, expressed as vaccine effectiveness and risk difference in age groups 18–19 years, 20–24 years, 25–29 years.

Protection against	Age group	Vaccine effectiveness	Risk difference
Infection with HPV16/18	18–19	77% (95% CI: 19% to 94%)	-10.2% (95%CI: -19.6 % to -0.7%)
	20–24	74% (95% CI: 52% to 85%)	-7.7% (95%CI: -10.3% to -5.1%)
	25–29	68% (95% CI: 25% to 86%)	-5.9% (95%CI: -8.6% to -3.3%)
ASCUS+ associated with HPV16/18	18–19	100% (CI not computable)	-7.4% (95%CI: -14.3% to -0.5%)
	20–24	75% (95% CI: -13% to 94%)	-4.4% (95%CI: -8.0% to -0.8%)
	25–29	4% (95% CI: -127% to 59%)	-0.1% (95%CI: -2.6% to 2.3%)
LSIL+ associated with HPV16/18	18–19	100% (CI not computable)	-7.4% (95%CI: -14.3% to -0.5%)
	20–24	91% (34% to 99%)	-2.4% (95%CI: -3.5% to -1.2%)
	25–29	7% (95% CI: -175% to 68%)	-0.1% (95%CI: -2.1% to 1.8%)
HSIL+ associated with HPV16/18	18–19	100% (CI not computable)	-0.3% (95%CI: -1.0% to 0.4%)
	20–24	56% (95% CI: -287% to 95%)	-32.6% (95%CI: -20.7% to -27.9%)
	25–29	-76% (95% CI: -565% to 53%)	0.6% (95%CI: -1.1% to 2.2%)

Dark green	significant protection
Light green	non-significant protection, VE>50%
Very light green	non-significant protection, VE<50%
Light yellow	non-significant higher risk
Yellow	significant higher risk

HPV: human papillomavirus; ASC-US+: atypical squamous cells of undetermined significance or worse, LSIL+: low-grade squamous intraepithelial lesion or worse, HSIL+: high-grade squamous intraepithelial lesion or worse.

observed now in women older than 25 will disappear when more subjects vaccinated at school age will reach the screening group, since they belong to cohorts who received their vaccine doses before onset of sexual activity (exposure to HPV).

The SEHIB findings are in line with surveillance reports and trend analyses from other countries [21–25] and demonstrate the utility of HPV genotyping of archived cervical samples collected in the framework of routine cervical cancer screening to evaluate the impact of HPV vaccination [26].

4.2. Strengths and weaknesses of SEHIB

SEHIB confirms that the protective effects of HPV vaccines, demonstrated in randomised trials, also are reflected in protective effects observable in a real life screening setting. By using a weighting of records from continuous screening samples enriched with pathological samples, we were able to identify a number of cervical precancer lesions from a virtual screening population of ~20,000 women (increasing the statistical power) while genotyping only ~6000 samples (reducing testing costs to less than one third). The fact that the vaccination status was based on anamnestic data was one of the weaknesses of SEHIB. Nevertheless, validation by contacting the vaccinating physician in a first phase revealed a high level of concordance, allowing the interruption of this time consuming verification procedure. A recent survey among Australian young women also reported good agreement between the self-reported and administratively validated HPV vaccination status [27].

The suboptimal rate of biopsy retrieval has reduced the power for histological endpoints and even may have generated bias. Reasons for the low biopsy rate may be: biopsy in other gynaecological centres, lost-to-follow-up of patients and insufficient available tissue from small punch biopsies. In spite of the potential bias, we believe that its magnitude may be small given the consistency between cytological and histological outcomes.

4.3. Recommendations for further research and surveillance

Setting up comprehensive vaccination registries linked with screening and cancer registries and combinable with cervical cytology and histology biobanks would guaranty more reliable information [28]. Such comprehensive linked databases are crucial to verify the impact of HPV vaccination such as the evolution of the incidence of cervical and other HPV-associated cancers, effects of 2-dose vaccine schedules, the duration of protection as well as the occurrence of possible type-replacement and cross-protection [26,29]. Moreover, joined screening and vaccination registries may offer the framework to evaluate new experimental screening and vaccination combinations and will allow physicians to diversify future screening according to the vaccination history of the individual woman.

5. Conclusions

The SEHIB study constitutes a baseline of the current burden of HPV infection and associated cervical disease in Belgium and clearly demonstrates effectiveness of HPV vaccination in the community of women younger than 30 years. Reduction in HPV16 and HPV18 infection was strongest in the age group of 18–19 years and declined with increasing age.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.canep.2015.12.011>.

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