Early effects of human papillomavirus vaccination in Belgium

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Human papillomavirus (HPV) vaccination has been reimbursed in Belgium since 2007 for girls (12–15 years), extended to girls up to 18 years in 2008. This study assesses the trend of HPV 16/18 infections in women less than 25 years of age participating in opportunistic cervical cancer screening. A significant reduction in the prevalence of HPV 16 [relative risk (RR) = 0.61, 95% confidence interval = 0.39–0.95] and a nonsignificant reduction in HPV 18 (RR = 0.65, 95% confidence interval = 0.29–1.48) was found in the youngest group (15–19 years). The prevalences in the older age group did not change significantly. These findings show the early effects of HPV vaccination and confirm the effectiveness of immunization in a real-life setting. ***European Journal of Cancer Prevention*** **00:000–000**

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Introduction

In the last decades, insights into the role of the human papillomavirus (HPV) as a causal agent in the development of cervical cancer became available (Snijders *et al.*, 2006). Over 150 HPV types are known, at least 14 of which have been associated with carcinogenous transformation of the cervical epithelium (Clifford *et al.*, 2003). Infection with HPV is a necessary but insufficient event in the carcinogenic process; persistent infection with a high-risk HPV type is essential to induce transformation of the cervical epithelial cells. HPV 16 is the most prevalent HPV genotype causing cervical cancer, followed by HPV 18. Combined, worldwide, more than 70% of all cervical cancer cases are associated with HPV 16 or HPV 18 infection (Seoud *et al.*, 2011).

Cervical cancer is in essence a preventable disease, its prevention strategies being historically based on secondary prevention with cytological detection of premalignant lesions or HPV infections. Since 2006, however, primary prevention measures, in the form of prophylactic HPV vaccines, became available. Currently, two vaccines are on the market: Gardasil providing protection against HPV 6, HPV 11, HPV 16, and HPV 18, and Cervarix, providing protection against HPV 16 and HPV 18. The effects of vaccination are suggested to include effects on HPV genotypes other than HPV 16 and HPV 18, including HPV 31 and HPV 45 (Malagon *et al.*, 2012).

Initially, in Belgium, an opportunistic approach was used. Reimbursement for girls between 12 and 15 years of age was obtained from the end of November 2007 with Gardasil (SPMSD) and from May 2008 for Cervarix (GSK) as well. By the end of 2008, this reimbursement was extended to girls between the age of 12 and 18 years. A school-based programmatic approach, based on the opt-out principle, was started from 2010 in the Flemish region and 1 year later in the French-speaking region. By this strategy, a vaccination coverage rate of 85% had been reached in the Flemish region in 2012 (Arbyn *et al.*, 2012).

Official guidelines in Belgium advocate 3-yearly Pap-smear testing for women aged 25–64 years (Arbyn and Van Oyen, 2000). However, up to 2012, cervical cancer screening was organized in an opportunistic manner and cervical smears were often performed for women younger than 25 years of age. Data from cytological screening in this young age group were used to assess the early effects of HPV vaccination by monitoring trends in the prevalence of HPV 16 and HPV 18.

Materials and methods

Study design and population

This retrospective descriptive study included 25 532 routine samples obtained from females younger than 25 years of age attending opportunistic cervical cancer screening. Samples collected between September 2009 and January 2012 from AML Laboratory, Antwerp (Belgium), were considered for routine analysis. Participants were divided into two groups according to age. The first group included females aged 15–19 years and the second group included females aged 20–25 years.

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The time scale was divided into 10 trimester periods (2009-3 through 2011-4).

Statistical analysis

Trend analysis was carried out using a Poisson regression model, where the logarithm of the number of individuals tested over a trimester was declared as the offset with coefficient constrained to unity and including age × period as an interaction term (Nelder, 1972). Coefficients were exponentiated to obtain a risk ratio corresponding with the average change over the observation period for each age group and HPV type.

Laboratory testing

All specimens were screened for HPV DNA by PCR amplification. DNA isolation from liquid-based cytology was performed as described previously (Micalessi *et al.*, 2012). All samples were tested for the presence of HPV 16 and HPV 18 using TaqMan-based qPCR, targeting type-specific sequences of the viral genes 16 E7 and 18 E7. Each patient was assigned an anonymous unique patient ID number.

Results

In total, 25 532 routine samples were analysed for presence of the two HPV types; 3395 samples were collected from girls younger than 19 years of age and 22 137 samples were collected from females between 19 and 25 years of age. In the third trimester of 2009, the prevalence of HPV 16 infection was 5.1% [95% confidence interval (CI) = 3.4–7.2%] and 7.5% (95% CI = 6.2–8.8%) in the age groups 15–19 and 20–24, respectively. The proportion of females testing positive for HPV 18 in the same period was 1.1% (95% CI = 0.4–2.4%) and 1.7% (95% CI = 1.1–2.4%) in the youngest and oldest age groups, respectively.

Table 1 Relative change over the period July 2009–January 2012

	Age group (years)	Relative risk[a]	Lower CI	Upper CI
HPV 16	15–19	0.61	0.39	0.95
	20–24	0.86	0.72	1.03
HPV 18	15–19	0.65	0.29	1.48
	20–24	1.23	0.89	1.69

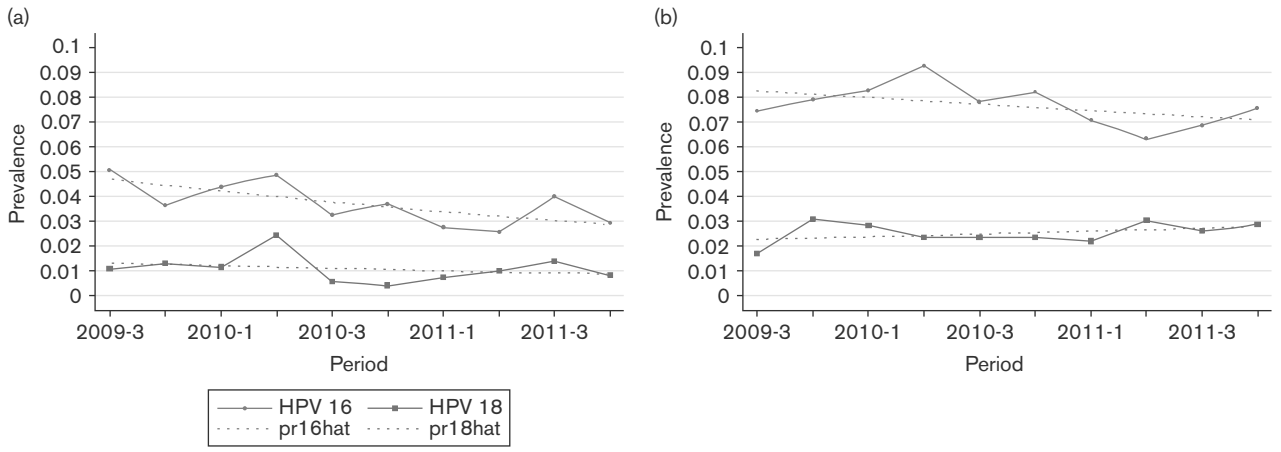
CI, confidence interval; HPV, human papillomavirus.
[a]Relative risk and 95% CI computed by Poisson regression.

The curvilinear trends showed a significant reduction for HPV 16 (RR = 0.61, 95% CI = 0.39–0.95) and a non-significant reduction for HPV 18 (RR = 0.65, 95% CI = 0.29–1.48) in the younger group (Fig. 1a; Table 1). The prevalences in the older age groups did not change significantly: HPV 16 (RR = 0.86, 95% CI = 0.72–1.03) and HPV 18 (RR = 1.23, 95% CI = 0.89–1.69) (Fig. 1b; Table 1).

Discussion

The effects of prophylactic HPV vaccination have been shown in clinical trials (FUTURE II Study Group, 2007a; FUTURE II Study Group, 2007b; Paavonen *et al.*, 2009; Wheeler *et al.*, 2012). After introduction of the vaccine in the general population, phase IV clinical trials have been initiated aiming to monitor the wider effects of the vaccine in the general population. In Belgium, the SEHIB (Surveillance of the Effects of HPV Immunisation in Belgium) study has been set up to observe shifts in HPV genotypes in the population and in abnormal samples (Weyers *et al.*, 2013). It is expected that the prevalence of HPV 16 and HPV 18 will reduce, also paralleled potentially by other HPV types (HPV 31, HPV 33, HPV 45) as shown from the clinical trials (Malagon *et al.*, 2012). It is still unclear whether other HPV types will appear and take over the development of cervical neoplastic lesions, and close surveillance is hence warranted.

Fig. 1



Trend in human papillomavirus (HPV) 16 and HPV 18 infection, Belgium July 2009–January 2012. (a) Age group 15–19 years. (b) Age group 20–24 years.

In the Belgian system, free organized vaccination for girls aged 12–13 years has been introduced through a school-based programme since 2010, with high coverage in the Flemish Region (Arbyn *et al.*, 2012). Furthermore, an opportunistic vaccination effort has been in place in Belgium, reaching girls between the age of 13 and 18 years of age (Simoens *et al.*, 2009; Arbyn *et al.*, 2010). According to current national screening recommendations, cervical cancer prevention, on the basis of cytology, targets women in the age range 25–64 years. However, despite recommendations, screening was and still is also offered at earlier ages. In certain cytopathology laboratories, not only cytological screening but also parallel HPV testing was performed as part of the routine.

Within the line of expectations, a decrease in both HPV 16 and HPV 18 could be detected in the youngest group (15–19 years of age), having the highest number of vaccinated girls. This decrease was significant for HPV 16. The trend for HPV 18 was similar in magnitude, but not significant, most likely because of the lower number of HPV 18 infections in the population. However, the stable trends in women 20 years of age and older, where HPV vaccination must be very low, suggest that the trend in the age group 15–19 years may be ascribed plausibly to vaccination.

The current trend analysis is correlational as it is not linked to vaccination registration data. Such a vaccination registry should be set up urgently to enable comparison of the effect of vaccination as a function of vaccination status. However, recent data from the SEHIB study lend further support to the thesis that the observed decreasing trends in the youngest groups may indeed be an effect of vaccination (Weyers *et al.*, 2013). Finally, vaccine safety monitoring is an additional important postmarketing obligation. It is essential to monitor side effects after administration of the vaccine and register them rigorously.

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Conflicts of interest

There are no conflicts of interest.

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