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Effectiveness of human papillomavirus vaccine against incident and persistent infections among young girls: Results from a longitudinal Dutch cohort study

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ABSTRACT

Introduction: Because of the long interval between infection with high-risk human papillomavirus (hrHPV) and development of cervical cancer surrogate markers for cancer incidence are necessary to monitor vaccine effectiveness (VE). The aim of this study was to calculate VE of HPV16/18 vaccination by annually assessing incident and persistent infections among (un)vaccinated girls from the general Dutch population up to 3 years after vaccination.
Methods: In 2009, 1668 girls (54% vaccinated) aged 14–16 years were enrolled in a prospective cohort study. Annually, questionnaire data were obtained, and a vaginal swab was tested for type-specific HPV DNA with SPF_{10}-LiPA. VE was estimated by a Poisson model comparing type-specific infection rates in (un)vaccinated girls.
Results: The adjusted VE (95% CI) was 73% (49–86%) against incident infections with HPV16/18 and 72% (52–84%) against HPV16/18/31/45. VE against persistent HPV16/18 was 100% and 76% (−17 to 95%) against HPV16/18/31/45. This number was lower (36%) when girls who were positive for HPV16 and 18 at baseline were included in the analysis. The overall VE for hrHPV types combined was small. Although 96% of girls were HPV-naïve at baseline, the cumulative 36-month incidence for any HPV was 20%, indicating high sexual activity.
Discussion: Vaccination is effective against incident and persistent infections with HPV16/18 and HPV16/18/31/45. Low VE against persistent HPV16/18 infection in girls positive at baseline indicates importance of vaccination before sexual debut.

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1. Introduction

Human papillomavirus (HPV) infection causes approximately 10% of all cancers in women, most notably cervical cancer [1,2]. Annually more than half a million women are diagnosed with cervical cancer worldwide, and a quarter of a million die of this disease [2].

Since 2006–2007, two prophylactic vaccines have been registered against oncogenic HPV genotypes 16 and 18, which are responsible for about 70% of cases of cervical cancer [3]. In clinical trials both vaccines have shown efficacy against persistent HPV16 and 18 infection of 6–12 months' duration and cervical intraepithelial neoplasia (CIN2+) lesions of more than 90% for at least 9 years after adminstration [4–6]. Both vaccines have also shown cross-protective potential. For the bivalent vaccine, the VE for HPV31 infection persisting for 6 months was 77%, and for HPV45 infection it was 79% after 4 years of follow-up [7], although the efficacy seemed to decrease with increased follow-up time [8].

Like other countries, The Netherlands includes HPV vaccination (bivalent HPV16/18 vaccine) for girls in the National Immunization Programme. The vaccine uptake amounted to 52% in the catch-up

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campaign in 2009 for cohorts born from 1993 to 1996 (13–16 years of age) and 59% in the standard programme targeting girls aged 12 years from 2010 onwards [9].

Alongside the introduction of HPV vaccination, the Health Council of the Dutch government advised monitoring its short- and long-term effectiveness in the general population [10]. One factor that complicates monitoring is the long duration (more than 20 years) between infection and development of cancer. With screening starting at the age of 30 years, vaccinated cohorts in the Netherlands are still too young to assess effectiveness against HPV-related cancers. Early and intermediate surrogate markers allow monitoring the more proximal impact, such as a decreasing trend in genital warts in countries where the quadrivalent vaccine is used [11,12]. Currently, one of the most informative outcomes to measure the potential vaccination impact on HPV-related cancers is the effect of the vaccine on intermediate precursors, such as incident and persistent infections in young girls.

This study presents 3-year follow-up results of the HPV Amongst Vaccinated and Non-vaccinated Adolescents (HAVANA) study [13] on effectiveness of early HPV vaccination against incident and persistent high-risk human papillomavirus (hrHPV) infections by comparing the findings in vaccinated and unvaccinated girls from the general Dutch population. In addition, we present data on the burden of DNA infections and sexual behaviour in this young age group pre- and post-sexual debut.

2. Materials and methods

2.1. Study population and data collection

In brief, 29,162 girls aged 14–16 years who were eligible for the national catch-up vaccination in 2009 and 2010 were invited to participate in a longitudinal study (HAVANA) to assess HPV VE in the general Dutch population [13]. At baseline (1 month prior to vaccination), 1800 (6%) girls were enrolled, and 1668 of those were included in the analysis (girls who did not receive the complete 3-dose regimen and girls who were vaccinated after baseline were excluded from the analysis). During follow up, we received data from 1420 girls at visit 1 (1 year after baseline), 1281 at visit 2 (2 years after baseline) and 1232 at visit 3 (3 years after baseline). All girls signed an informed consent form. In addition, the study was approved by the Medical Ethics Committee of the VU University in Amsterdam (2009/22).

Answers to a self-administered, web-based questionnaire and a vaginal swab were collected annually. At home, participants self-sampled the vagina by inserting a swab (Viba brush) 5 cm and rotating it for 5 s according to the manufacturer's instructions. Samples were stored in 1 ml of phosphate buffered saline for DNA analysis.

Individual vaccination status was extracted from the national vaccination registration system 'Praeventis' [14].

2.2. HPV DNA detection and genotyping

Vaginal samples were stored at −20 °C. DNA extraction was conducted using a MagNA Pure LC Total Nucleic Acid Isolation Kit (Roche, Mannheim, Germany). DNA was eluted in 100-μl elution buffer. Broad-spectrum HPV DNA amplification with the highly sensitive SPF_{10}-PCR [15] was conducted on 10 μl of DNA extract. Amplified HPV DNA was detected with a DNA enzyme-linked immunoassay (HPV-DEIA, Labo Biomedical Products, Rijswijk, The Netherlands). HPV-DEIA-positive amplicons were subsequently analyzed in a reverse line blot assay (HPV-$LiPA_{25}$, Labo Biomedical Products, Rijswijk, the Netherlands). The reverse line blot assay is able to detect the following hrHPV genotypes: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59; it can also detect 12 other genotypes (low-risk HPV) with limited evidence for a causal link with cancer: 6, 11, 34, 40, 42, 43, 44, 53, 54, 66, 70 and 74 (classification based on the most recent report of the International Agency for Research on Cancer) [1]. In addition, HPV types 68, 73, and 97 could be detected on the membrane, although no distinction between them could be made, and they were classified as HPV68. Samples that were HPV-positive in the DEIA analysis but did not reveal any of the 25 HPV genotypes in the line probe assay were considered clinically nonrelevant and classified as negative.

2.3. Statistical analyses

Differences in baseline characteristics between vaccinated and unvaccinated girls were determined with a chi-square test. Differences in possible risk factors for HPV among vaccinated and unvaccinated girls during follow-up were analyzed in a generalized estimating equation model (GEE) with a logit link. The dependent variable was the risk factor, and the independent variables were vaccination status, visit, and their interaction. A significant interaction term ($p < 0.05$) was interpreted as a different trend over time of that particular risk factor between vaccinated and unvaccinated girls.

Type-specific incidence and persistence rates were calculated. An incident infection was present if a girl was negative at one visit and positive at the next visit. A persistent infection was present if a girl was positive on at least two consecutive visits. Incidence and persistence rates were calculated as the number of infections divided by the person-years at risk (Poisson approach) Person-years were estimated as the sum of the number of visits in which girls were at risk for developing an incident or persistent infection. Persistence rates were first calculated for all girls for the particular HPV type. Secondly, we estimated persistence rates for girls who were negative at baseline for the particular HPV type to be able to look at new (not present before vaccination) persistent infections. VE (95% CI) was estimated by a Poisson model, comparing type-specific infection rates in vaccinated and unvaccinated girls. The Poisson model for the adjusted VE included possible risk factors for HPV infection (age, ethnicity, urbanization, education, past and current smoking, oral contraceptive use, and sexual activity) measured at baseline.

To assess the burden of infection in this young population, the prevalence (percentage of girls who tested positive) per visit was calculated among all girls with data available for that visit (1668 at baseline, 1420 at visit 1, 1281 at visit 2 and 1232 at visit 3). Next, cumulative incidence and persistence of HPV infections were calculated among girls HPV-negative at baseline ($n = 1064$) who participated in all four rounds and were defined as any incident or persistent infection during the total follow-up period.

To identify risk factors for incident and persistent infections, a time-dependent GEE with a Poisson distribution and a log-link was used. If more than 5% of the values per variable was missing an extra category for missing values was introduced to avoid loss of observations. All statistical tests were two-sided. Significance was determined at the 5% level (p-value ≤ 0.05).

All statistical analyses were performed using SAS software package version 9.3 (SAS Institute Inc., Cary, NC, USA).

3. Results

3.1. Population characteristics

The baseline characteristics of the study population stratified by vaccination status are shown in Table 1. The characteristics that differed significantly at baseline between vaccinated and

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