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Seroprevalence of seven high-risk HPV types in The Netherlands

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ABSTRACT

Background: To obtain insight into the age-specific seroprevalence for seven high-risk human papillomavirus (hr-HPV) serotypes (HPV16, 18, 31, 33, 45, 52, and 58) among the general population in the pre-vaccination era in The Netherlands.
Methods: From a cross-sectional population-based study (ISRCTN 20164309) performed in 2006/2007 6384 sera of men, women and children were tested for seven hr-HPV specific antibodies using a fluorescent bead-based multiplex immunoassay with virus-like particles of the seven HPV serotypes.
Results: An increase in seroprevalence was observed in adolescents, especially for the most prevalent HPV type 16 (up to 11.3%). The increase was most pronounced in women, but was less clear for the other six HPV serotypes. Relatively stable seroprevalences were found in the middle aged cohorts and a slight decrease in the elderly. For the age cohorts >14 years, the seroprevalence among women (25.2%) was higher compared with men (20.3%) ($p = 0.0002$). We found that 10.1% of the population was seropositive for multiple HPV serotypes.
Conclusions: The HPV vaccination program is targeted at preadolescents as is justified by the results in this study in which a step-up in HPV seroprevalence is observed at ages of sexual debut. Although direct interpretation of seroprevalence data are hampered by cross-reactivity and seroconversion rate, these data are useful as baseline to evaluate long-term population effects of the HPV16/18 vaccination program.

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1. Introduction

Human papilloma virus (HPV) is one of the most common sexually transmitted pathogens worldwide. From the general population it is established that 80% will be infected at some time during their live [1]. More than 100 different HPV genotypes have been identified, of which 40 infect the genital tract [2]. High-risk (hr) HPV, such as types 16 and 18, can cause cervical cancer and other genital cancers, and also oro-pharyngeal cancer. HPV16 and HPV18 are the most common HPV types detected in women worldwide and are responsible for 70% of all cervical cancer cases [1–3]. When infected with HPV, most genital transient HPV infections regress within two years [4]. Only a small proportion of infected individuals suffer from persistent infections and they are at risk for cervical cancer [5,6].

Assays developed for the detection of HPV specific IgG antibodies to virus-like-particles (VLPs), have been used for seroprevalence studies in several countries [7–9]. Not all HPV infected individuals seroconvert and 20–50% of the women who are carriers of HPV DNA do not have detectable HPV antibodies in their serum [1,3]. When HPV antibody responses develop after a natural HPV infection, they are relatively stable over time [10]. Therefore, the measurement of HPV specific antibodies will be useful to provide information about the HPV seroprevalence in population studies and can be used to estimate lifetime cumulative HPV exposure and past HPV infections.

In this study we describe the age-specific seroprevalence of seven hr-HPV types (16, 18, 31, 33, 45, 52 and 58) and the risk-factors associated with seroprevalence in a representative sample of the Dutch population before the implementation of the HPV vaccine in the national immunization program (NIP). In The Netherlands, HPV vaccination (Cervarix) was included in the NIP in 2010 for girls 12 years of age with vaccination coverage of 50% [11]. In addition, a catch-up vaccination campaign was performed

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for girls 13–16 years of age. Age-specific seroprevalence data from the pre-vaccination era in The Netherlands are scarce. Previous studies in The Netherlands were limited to the number of HPV types (only 6, 11, 16 and 18), age groups or focused only on a specific city (Amsterdam) in The Netherlands [12,13]. Our study provides insight in risk factors associated with seropositivity, in the distribution of high-risk HPV types and is valuable in the evaluation of long-term population effects of the HPV16/18 vaccination program.

2. Materials and methods

2.1. Study population

Serum samples from a cross-sectional population-based serosurveillance study performed from February 2006 to June 2007 were available ($n = 6384$) for analysis. Participants, women and men, were 0–79 years of age. The study design has been described previously [14]. Briefly, a total of 19,781 individuals were invited into the study of which 6386 (32%) participated. Two sera were not available for analysis (0.03%) because serum quality was not sufficient. The age strata 0 and 1–4 years and non-Western migrants were over-sampled. Each invited individual was requested to fill in a questionnaire and to provide a blood sample. The questionnaire included for instance demographic characteristics, vaccination history and information related to sexually transmittable infections (STIs). Information regarding sexual activity and STI was only available from participants older than 14 years of age. A signed informed consent was obtained from all participants and for those below 18 years of age also from the parents. The study proposal was approved by a medical ethics review committee (ISRCTN 20164309).

2.2. Serological measurements

The serum samples collected were stored at −80 °C until analysis. HPV specific serum antibodies against L1 VLPs for serotypes 16, 18, 31, 33, 45, 52, and 58 were measured using a VLP-based multiplex immunoassay (MIA). GSK (GlaxoSmithKline Biologicals, Rixensart, Belgium) kindly supplied the HPV VLPs and transferred the developmental VLP-based MIA. VLPs were coupled to a set of seven distinct fluorescent microspheres (Luminex corporation, Austin, TX) through a carbodiimide coupling procedure that has been described elsewhere [15] with minor modifications. Sulpho-NHS (Pierce, Rockford, IL) and EDC (Pierce, Rockford, IL) were dissolved in 0.5 M NaH_2PO_4 (Sigma–Aldrich, St. Louis MO), pH 6.2. 25 μg VLPs/ml were diluted in PBS and coupled to 1×10^7 fluorescent microspheres. VLP-coupled microspheres were stored in a buffer containing 100 mM MES (Sigma–Aldrich, St. Louis MO), pH 6.0, 1% BSA (Sigma–Aldrich, St. Louis MO), and 0.2% Proclin300 (Sigma–Aldrich, St. Louis MO). The MIA was performed as described elsewhere [16] with modifications. Serumbuffer (PBS, 1% BSA, 0.2% Tween20 (Merck, Darmstadt, Germany) and 0.2% ProClin300) was used for prewetting the MultiscreenHTS assay plates (Millipore Corporation, Billerica, MA), for washing procedures and sample dilutions. Sera were 1/50 diluted and incubated with 4000 microspheres/HPV serotype/well. *R*-phycoerythrin (*R*-PE)-conjugated goat anti-human IgG (Jackson ImmunoResearch laboratories Inc., Westgrove, PA) diluted 1:200 was used as a conjugate. HPV specific IgG antibodies were analyzed by using a Bioplex system 200 with Bioplex software (Bio-Rad Laboratories, Hercules, CA). For each analyte, median fluorescent intensity (MFI) was converted to Luminex Units/ml (LU/ml) by interpolation from a 5-parameter logistic standard curve (log–log) using the linear part of that curve.

2.3. Reference and control sera

Four quality 'in house' control sera were used on each plate. These four sera were composed of a pool of HPV negative individuals, a pool of low-positive individuals, a pool of highly-positive vaccinated individuals, and a commercially available positive preparation: human intravenous immunoglobulin (IVIG, lot LE12G071AE, Baxter, Deerfield, IL). The 'in house' standard (IVIG, lot LE12H227AF, Baxter) was calibrated against reference serum of GSK for all the seven HPV types.

2.4. HPV-MIA characteristics and cut-off values

The intra- and inter- assay variation for HPV16 and the reproducibility of the assay for all seven HPV types were determined using a serum panel ($n = 55$) consisting of pre-vaccination samples and serum samples from women diagnosed with cervical cancer. Several monoclonal antibodies (mAbs) were used that recognize epitopes on HPV16 (Ritti (donated by M. Muller, Heidelberg), HPV16 L1 (GenWay Biotech, San Diego, CA), H16.V5 (donated by N.D. Christensen), Mab885 (Millipore, Billerica, MA)) and HPV18 (HPV18 L1 (GenWay Biotech, San Diego, CA)). MAbs were tested in a 1/100 dilution for HPV16 L1, 1/1000 dilution for Ritti, Mab885 and HPV18 L1, and in a 1/10,000 dilution for H16.V5. All mAbs recognized conformational epitopes except Mab885, which recognized a linear epitope. The cut-off values for the MIA were determined using the one-sided 99% prediction interval (PI) method as described by Frey et al. [17].

2.5. Statistical analysis

Data analyses were conducted using SAS version 9.2 and GraphPad Prism version 4.0.3. Seroprevalences were calculated for different age-cohorts and weighted. Weights were determined proportional to the reference population (Dutch population, 1st January 2007) taking into account sex, age, ethnic origin and urbanization degree. Associations between HPV seropositivity in individuals older than 14 years of age and sample characteristics including sex, ethnic origin, marital status, kind of partner, education level, socio-economic status, age of sexual debut, condom use and number of partners in the last six months and reported a history of STI were tested in a multivariate logistic regression analysis. Through a backward selection variables that were not statistically significant ($p < 0.05$, using the Wald statistic) were removed from the model. The model was also applied to analyze interactions with gender. Significance ($p < 0.05$) for combinations of HPV seropositivity was calculated using the Chi-square test and for comparisons between log-transformed antibody concentrations an unpaired *t*-test was used.

3. Results

3.1. Characteristics of the total study sample

Samples from the pre-HPV vaccination period were collected between February 2006 and June 2007, a median of 2.8 years before the introduction of HPV vaccination in The Netherlands in March 2010. Participants were 0–79 years of age. In this study 54% of the participants were female ($n = 3473$) and 46% were male ($n = 2911$).

3.2. HPV-MIA characteristics and cut-off values

The mean coefficient of variation (CV) for the intra-assay plate-to-plate variation and variation within a plate was 8% and 7%, respectively, while the inter-assay variation, performed on different days, had a mean CV of 12%. The reproducibility of the assay

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