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Seroepidemiology as basis for design of a human papillomavirus vaccination program

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ABSTRACT

We have performed a serological survey of HPV type 16-antibody prevalence by age and sex in Sweden and used it as a basis for modelling the optimal vaccination strategies in this population. Samples of 3317 subjects were tested for HPV16-specific antibodies. The observed age-specific seroprevalences along with sexual behaviour data were used to infer parameter values for a mathematical model representing Sweden and the preventive effect of possible strategies estimated. By the year 2055, vaccination of females starting at age 12 in 2008 was most efficient, estimated to prevent 5.8 million cumulative HPV16 infections. Catch-up programs had a strong additional preventive effect. Vaccination also targeting males increased protective effect by about 4%, but had lower preventive effect per vaccination given. Addition of an HPV serosurvey to existing models and data has enabled us to estimate effect of different vaccination strategies, optimized to the HPV epidemiology in our population.

1. Introduction

Cervical cancer is the second most common cancer in women worldwide, with approximately 450,000 newly diagnosed cases each year and a 50% mortality rate [1,2]. Rates of invasive cervical cancer incidence and mortality have decreased over the last decades owing to comprehensive screening programmes [3–6].

Human papillomavirus (HPV) is a common sexually transmitted infection that is the main cause of cervical cancer [7–10]. Human papillomavirus genotypes are divided into several risk groups based on the spectrum of lesions they induce. The low risk genotypes such as HPV6 and -11 cause benign genital warts (condylomas) and low-grade squamous intraepithelial lesions. High risk or oncogenic HPVs cause cervical intraepithelial neoplasias that may progress to cervical cancer, with the most important cancer-causing types being HPV16, −18, −31 and −45 [11]. HPV16 is by far the most important oncogenic HPV, causing more than 50% of HPV-associated cancers [11].

Recently, prophylactic HPV vaccines for prevention of cervical cancer have been developed [12,13]. These vaccines contain virus-like particles (VLPs) comprised of the L1 major capsid protein of individual HPV types [12–15]. Administration of either a monovalent HPV16 L1 VLP vaccine or quadrivalent HPV (types 6, 11, 16, 18) L1 VLP vaccine have been shown to be close to 100% effective in preventing the development of high-grade cervical pre-cancers caused by vaccine HPV types [12,13]. A bivalent HPV (types 16, 18) L1 VLP vaccine was also highly effective in prevention of precancerous lesions [15].

The quadrivalent vaccine was licensed for use in large parts of the world in 2006 [16]. The availability of effective HPV vaccines necessitates investigations of the vaccination strategies that would have the greatest effectiveness. Basic questions that need to be addressed are: at what age should subjects be vaccinated? What is the benefit of a catch-up program and what age groups should it target? Should both males and females be targeted? To address these questions the effects of vaccination in populations, in addition to individuals, has to be estimated. This is possible through the use of models of the transmission dynamics of the infection and disease.

To explore the impact of age and sex of vaccination a model of HPV transmission has been developed and analysed [17,18]. However, the age-specific incidence of HPV infection may vary between different populations and the model needs to be parameterized with country-specific data on HPV infection for each country that wants to use modelling as a basis for design of preventive strategies.

Genital samples for DNA testing in large-scale populations may be difficult to obtain, especially from children and young adolescents. The detection of serum IgG antibody to HPV provides a

Abbreviations: HPV, human papillomavirus; ELISA, enzyme-linked immunosorbent assay; PLL, parallel line method; VLPs, virus-like particles.

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straightforward method for assessing cumulative HPV exposure, as many countries routinely perform serosurveys and/or have comprehensive serum repositories that can be exploited [19,20]. We performed an age-specific HPV16 seroprevalence survey in Sweden and used it as a basis for modelling optimal vaccination strategies for Sweden. We illustrate a strategy by which any county with access to suitable serum biobanks can devise a scientifically based vaccination policy.

2. Materials and methods

2.1. Study population

A nationwide serological survey was performed by the Swedish Institute for Infectious Disease Control in 1997. Subjects (>19 years old) were selected using a random two-step stratified sampling procedure based on the comprehensive Swedish population registry. A random sample of 79 parishes was selected, with the probability of each parish being selected proportional to their population size. Eight females and eight males in these parishes were then randomly selected from each age group using the population registry. Thus, all subjects in Sweden in a given age stratum had the same probability to be selected. For subjects younger than 19 years old, 2 of the 25 counties in Sweden were not included, as suitable sample collection infrastructures were missing [21,22]. Selected subjects and the parents of selected children were informed by letter about the study. The average participation rate was 90.9% [23]. For this study of HPV16 seroprevalence, we used the 1163 samples that had been collected from subjects in the age group 9–26 years of age. Because this national survey represents the situation a decade ago, we sought to identify potential changes through a more recent, although more local survey. The Southern Sweden Microbiological biobank stores all samples submitted for microbiological diagnosis in Southern Sweden and currently contains over a million serum samples from 524,000 subjects, a sizeable part (45%) of the total population in the catchment area (1,157,000 subjects). For the present study, we selected an age-stratified sample in the age group 11–25 from subjects attending primary care, starting with recently submitted samples and extending back to 2004. Overall, samples from 2154 subjects were selected. For a random subsample of 1000 subjects among these, the medical diagnoses prompting the sampling were studied.

2.2. Serological analysis

HPV16 antibodies were detected using an HPV16 L1 virus-like particle-based enzyme-linked immunosorbent assay (ELISA). ELISA plates were coated overnight at 4 °C with HPV16 VLPs in cold PBS pH 7.2. As negative control, disrupted VLPs generated by incubation at room temperature for 4 h in carbonate buffer (pH 9.6) were used. After washing of the plates four times with PBS-0.5% Tween 20 (PBS-T), they were blocked with PBS with 10% horse serum (10% HS-PBS) at room temperature for 1 h. The human sera were added and incubated for 2 h at room temperature. After washing a mouse monoclonal anti-human IgG (gamma-chain-specific) antibody (Eurodiagnostica, diluted 1:800 in 10% HS-PBS) was added and allowed to react for 90 min at room temperature. Sheep anti-mouse-IgG horseradish peroxidase conjugate (Southern Biotech) 50 μl (diluted 1:2000 in 10% HS-PBS) was added to the ELISA plates after washing four times with PBS-T. The plates were incubated for 1 h at room temperature and washed four times with PBS-T. The peroxidase substrate ABTS was added and incubated for 30 min and the absorbances were measured at 415 nm.

The H16.V5 monoclonal antibody or the D9 monoclonal antibody (kindly provided by Dr. Neil Christensen, Departments of Pathology, Microbiology and Immunology, Pennsylvania State University College of Medicine, Hershey, USA) were used as positive- and negative-controls for VLP-integrity (conjugate used was sheep anti-mouse-IgG horseradish peroxidase conjugate (Southern Biotech). For quality control and evaluation we used known positive and negative human serum samples. The background absorbance of each serum was subtracted from the VLP reactivity and then the optical density values were transformed into ELISA units using the PLL (parallel line) method [24]. The interassay coefficients of variation (CV) were: 14% and the intraassay CV for one test during 1 day: was 6%. The HPV16 reference serum was a WHO international reference reagent obtainable from the National Institute of Biological Standards and Controls (http://www.nibsc.ac.uk) [25]. The cut off level was preassigned before the start of the study and had been previously assigned as giving optimal distinction of cases (HPV16 DNA-positive cervical cancer patients) and controls in a previous study [26] and was in this study further validated using a panel of 49 HPV16 DNA-positive women and as negative control 20 women without sexual experience [27]. As there were good agreement between previous validation studies and our validation results, the previous cut off (0.165 units) was maintained. Age-specific seroprevalences were fitted to a fourth order polynomial seroprevalence curve. This type of curve was chosen because there existed previous data that HPV seroprevalence curves have a sigmoid shape, being essentially flat in pre-adolescence and middle age and increasing linearly during adolescence [16,19,20].

2.3. Modelling vaccination scenarios in Sweden

To model the transmission of HPV and the introduction of a vaccine, a previously described [17,18] compartmental dynamic transmission model of HPV16 infection and progression to cervical cancer with detailed age structure was used. The model population was stratified by age, sex and sexual activity class. Sexual behaviour data from the Swedish National Institute of Public Health [28] was used to define four sexual activity classes in Sweden in terms of rates of sexual partner change. Data from the Swedish National Institute of Public Health on the proportion of the population sexually active at different ages was used to define the rate of onset of sexual activity in the model [28].

The model was parameterized for Sweden by comparison with HPV16 seroprevalences in different ages, assuming a 50% sensitivity for the ELISA [29–31] (Table 1) and cervical cancer incidence data from the Swedish Cancer Registry for different ages and over time, adjusted to represent the proportion of cancer associated with HPV16 (55%) [11,32]. To gain a reasonable fit of this complex model to multiple observed outcomes the parameters were varied manually until a reasonable fit was obtained through subjective judgment (Fig. 1). We assumed the vaccine has no effect on those already infected and that the vaccine was 100% effective for a lifetime. As the extent and duration of immunity after natural infection is unclear [29,30], we tried three different models that either assumed no natural immunity, lifelong immunity or waning immunity with an average duration of 5 years. The model using waning immunity provided a better fit to the data than assuming lifelong or no natural immunity and was used throughout. The impact of vaccination on HPV16 infections was investigated for 90% coverage vaccine delivery at ages 12, 15, 18 and 21. The high coverage assumed reflects the experience of previous vaccination programs in Sweden. Several catch-up vaccination strategies, including up to 12 additional ages vaccinated, were investigated.

To assess the effectiveness and efficacy of the proposed programs, results are presented as the proportion of HPV16 infections