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# Identification of determinants associated with uptake of the first dose of the human papillomavirus vaccine in Denmark

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## ABSTRACT

**Background:** The human papillomavirus vaccine (HPV vaccine) was introduced into the Danish Childhood Vaccination Programme in 2009. Following a national debate questioning the safety of the vaccine, the coverage decreased from an uptake of >90% for the first dose of the HPV vaccine to an uptake of 52% in girls born in 2003. The aim of this study was to identify changes in determinants for HPV vaccine hesitancy in the period when the debate spiraled and to identify determinants for specific hesitancy towards the HPV vaccine among girls who received the second dose of the measles, mumps and rubella vaccine. **Methods:** We included girls born in the period 1999–2003 who were residing in Denmark between their 12th and 13th birthday (n = 161,528). Data from the Danish Vaccination Register were linked with demographic data from the Danish Civil Registration System. We used multiple logistic regression models to identify associations between determinants and the uptake of the first dose of the HPV vaccine (HPV1). **Results:** For girls born in 1999–2000, low uptake was seen in children of increasing birth order, young or old age of mother, non-Danish origin, low uptake of other childhood vaccines, and in girls living with one parent. For girls born in 2001–2003, most of these determinants of low uptake became less significant. Birth order and origin showed different tendencies when comparing birth cohorts 1999–2000 with birth cohorts 2001–2003.

**Conclusions:** We found demographic disparities in the uptake of HPV1 that were generally in line with existing literature. More importantly, the results indicate that determinants for hesitancy towards the HPV vaccines changed during a period of intense public debate regarding the safety of the HPV vaccine. This may indicate that the public concerns over safety disproportionately affect those who trusted vaccines prior to the debate.

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## 1. Introduction

Human papillomavirus (HPV) is one of the most common sexually transmitted infections [1]. Though most of the infections are asymptomatic and will resolve spontaneously, persisting infection with high-risk HPV types is a prerequisite to cervical cancer [2]. According to the Association of the Nordic Cancer Registries, the incidence rate of cervical cancer in Denmark is 10.2 per 100,000 women. When comparing with other developed countries, Denmark has one of the highest rates. Approximately 25% of the cases of cervical cancer in Denmark result in death [3].

Based on a Health Technology Assessment from the Danish health authorities, the human papillomavirus vaccine was introduced into the Danish Childhood Vaccination Programme in

January 2009. The four-valent vaccine Gardasil<sup>®</sup> was used until February 2016, where after it was replaced by the two-valent Cervarix<sup>®</sup> vaccine. As these vaccines are not produced by Statens Serum Institut (SSI), an authority under the Danish Ministry of Health, this replacement was the result of the statutory vaccine tender. This tender included criteria related to efficacy, adverse events, side-effects, and price [4]. It is recommended that girls receive the first dose of the HPV vaccine at the age of 12 [5]. The Danish health authorities have no recommendations on the national uptake of the HPV vaccine, but models from a Health Technology Assessment suggest that HPV 16 and 18 will be eradicated in respectively 33 and 50 years with a vaccination uptake of 70% [6]. According to records from SSI, the uptake of the HPV vaccine has decreased dramatically in the birth cohorts 2001–2003 compared with earlier birth cohorts [7]. Thus, figures from November 2017 show an uptake of the first HPV vaccine of >90% in girls born 1997–2000 but it was only 52% in girls born in 2003 [7].

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Determinants for not being HPV vaccinated have been studied in qualitative and quantitative studies. Some studies on safety concerns and attitudes towards vaccines have been summarized in a Health Technology Assessment and in reviews [6,8–11]. Register-based studies show that low uptake of other recommended vaccines is associated with low uptake of the HPV vaccine. Also, marital status of the mother, number of siblings, immigration status and maternal age has been shown to be associated with low uptake of the HPV vaccine [12–17]. In a Danish context, it is also found that girls living in the capital city, Copenhagen, and girls who had parents with low income or low educational level were less likely to receive the HPV vaccine [18,19]. Late in 2013 a public debate started questioning the safety of the HPV vaccine. The debate escalated into a TV-documentary in March 2015, interviewing girls who experienced what they suspected to be serious adverse events after HPV vaccination. This documentary led to a further massive public debate followed by a drastic decrease in the uptake of the HPV vaccine in Denmark [20]. To reach prior uptake and to reduce the risk of cervical cancer, it is of great importance to identify the determinants for not receiving the HPV vaccine. The aim of this study was to identify possible changes over time in determinants for not receiving the first dose of the HPV vaccine (HPV1). Furthermore, the purpose was to identify the determinants for not receiving the HPV1 among girls who did receive the second dose of the measles, mumps and rubella vaccine (MMR2), which was also recommended for 12-year old children.

## 2. Materials and methods

### 2.1. Study design and population

This register-based cohort study included all girls born between 1999 and 2003 who lived in Denmark in February 2017 and who were residing in Denmark between their 12th and 13th birthday.

### 2.2. Data sources

Demographic data were extracted from the Danish Civil Registration System [21], and data on vaccinations were extracted from the Danish Vaccination Register [22]. Data from the two registers were merged using a unique personal identification number.

### 2.3. Outcome and exposure

This study focused on the uptake of HPV1 as the primary outcome. To secure equal opportunities for vaccination among included girls, the outcome was defined as whether the girls received HPV1 before reaching the age of 13. The following potential determinants for not receiving HPV1 were identified a priori through the existing literature; Birth order (1st, 2nd, 3rd, 4th, and  $\geq$ 5th born). Age of the mother when giving birth to the daughter (12–19, 20–24, 25–29, 30–34, 35–39, and 40–60 years). Origin of the girl (Danish; Girls with at least one Danish born parent. Descendant; Danish born girls with two non-Danish born parents or missing information on both parents. Immigrant; Non-Danish born girls with two non-Danish born parents or missing information on both parents) [23]. Mother's marital status (married, divorced/widowed, unmarried, or dead). Household type (girl lived with both parents, only the mother, only the father, or none of the parents). Place of residence (Copenhagen City, Copenhagen surroundings, North Zealand, Bornholm, East Zealand, West & South Zealand, Funen, South Jutland, East Jutland, West Jutland, North Jutland) [24]. Having received all three doses of the vaccine used against diphtheria, tetanus, pertussis, polio, haemophilus influenzae type b (DTap/IPV/Hib), given at 3, 5, and 12 months of age in

the Danish Childhood Vaccination Programme (Yes or no). Having received the first dose of the measles, mumps, and rubella vaccine (MMR1) (Yes or no).

### 2.4. Statistical analysis

Initially, Kaplan-Meier estimates were used to assess the cumulative uptake of HPV1. Subsequently, we used both simple and multiple logistic regression models to investigate the association between different determinants and receiving HPV1. All estimates are presented as odds ratios (OR) with 95% confidence intervals (95%CI). Stratified analyses were conducted to examine if the determinants for not receiving HPV1 changed over time. This was done by separating the five birth cohorts into two groups, 1999–2000 and 2001–2003. Furthermore, to examine the determinants for specific hesitancy towards the HPV1 vaccine, a sub-analysis was restricted to girls who did receive the MMR2 vaccine. Cluster analysis was included in all models to meet the assumption of independency between observations, which in this study applied to sisters. Multiple logistic regression models were mutually adjusted for all covariates. However, the association between origin of the girl and not receiving HPV1 was based on analyses not including the variables DTap/IPV/Hib and MMR1. These vaccines are offered at the ages 3, 5, 12 and 15 months, which meant that immigrants were at risk of not living in Denmark at the recommended age and having received the vaccines in their country of origin. All analyses were carried out in Stata 14 IC (StataCorp, College Station, Texas).

### 2.5. Ethical approval

According to Danish law, ethical approval is not required in register-based studies. This study was approved by the Danish Data Protection Agency (2008-54-0474).

## 3. Results

Characteristics of the 161,528 included girls are shown in Table 1. There were no major differences between the two groups of birth cohorts. Fig. 1 illustrates the association between the age of the girl and the cumulative uptake of HPV1 for each birth cohort. A delay and a decrease in the uptake of the HPV1 vaccine was seen for girls born in 2001 but it was particularly pronounced for girls born in 2003. When the girls reached the age of 13, 88% of the 32,544 girls born in 1999, 90% of the 33,004 girls born in 2000, 83% of the 32,249 girls born in 2001, 76% of the 31,551 girls born in 2002 and only 41% of the 32,180 girls born in 2003 received the HPV1 vaccine by February 2017. Table 2 shows the proportion of non-vaccinated girls and the unadjusted and adjusted odds ratios for not having received the HPV1 vaccine before reaching the age of 13 for girls born in 1999–2000 and 2001–2003, respectively. For girls born in 1999–2000, we found low uptake in children of increasing birth order, in children born by mothers <25 years and a similar tendency for low uptake for older mothers, children of non-Danish origin (immigrants and descendants), children with low uptake of other childhood vaccines, and in girls living with one parent measured as household type or mother's marital status. Furthermore, the area of residence was associated with vaccine uptake. For the girls born in 2001–2003, similar tendencies were seen for most of the variables, but the odds ratios were smaller. This change can be attributed to a disproportional drop in vaccination uptake among the groups that previously had highest vaccination uptake. For example, non-vaccination in girls of Danish origin increased by 23.4 percentage points (from 10.1% to 33.5%) whereas the change in descendants of immigrants was

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