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Effectiveness of varying number of doses and timing between doses of quadrivalent HPV vaccine against severe cervical lesions ☆

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ABSTRACT

Background: Based on immunogenicity studies, a 2 dose HPV vaccination-schedule was recently recommended for girls younger than 15 years. We aimed to investigate the effectiveness of quadrivalent HPV (qHPV) vaccination against CIN2 or worse (CIN2+), by age at vaccination, number of doses, and to test whether optimal timing of 2 doses of qHPV vaccine can confer the same level of protection as the originally recommended three dose-schedule.

Methods: A population-based cohort of all women aged 13–30 years, living in Denmark or Sweden during 2006–2013, was followed for qHPV vaccination status and first occurrence of CIN2+.

Results: The study cohort comprised 2,253,561 women, of which 33% were vaccinated during follow-up, and 1.7% were diagnosed with CIN2+. Vaccination at ages 13–16 and 17–19 was associated with a reduced risk of CIN2+ after 3 doses (IRR = 0.23, 95% CI 0.11–0.49, and IRR = 0.65, 95% CI 0.41–1.03, respectively), compared to being unvaccinated. After 1 and 2 doses there was a reduced risk, but not statistically significant. Women vaccinated ages 13–16 with 2 doses, where time between first and second dose was 5 months or longer showed no difference in risk compared to 3 doses.

Conclusions: Women vaccinated with 3 doses of qHPV showed a reduced risk of CIN2+ if they were vaccinated before age 20, with a further reduced risk if vaccinated before age 17. Vaccination with 2 doses, with the second dose 5 months or longer after the first dose, did not yield an increased risk of CIN2+, compared to 3 doses.

1. Introduction

Cervical cancer is a global health issue, particularly in developing countries with limited access to health care and insufficient cervical cancer prevention strategies [1–4]. In 2014, more than 57 countries worldwide had implemented human papillomavirus (HPV) vaccination as a preventative measure in national programs, and around 20 of these were low- or middle-income countries [5]. Resource requirements for cold-chain delivery of three doses is an important obstacle for wider global implementation.

Lately, a growing body of evidence shows the effectiveness of HPV vaccination against both condyloma and cervical abnormalities [6–11]. Based on few observational studies and immunogenicity data from clinical trials, the European Medicines Agency (EMA) and World Health Organization Strategic Advisory Group of Experts (SAGE) recommended, in 2014, a two-dose HPV vaccination schedule for girls younger than 15 years, with 0–6 months between first and second dose of the quadrivalent HPV vaccine (qHPV) [1].

The results of this new policy have not yet been evaluated and nationwide population-based studies play an important role, as they can give insight into the actual public health impact of vaccination on disease outcomes as well as continued monitoring of vaccine impact in settings with different vaccination uptake and cervical cancer screening coverage.

Denmark and Sweden implemented HPV vaccination soon after vaccines became available, although utilizing different strategies

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[6,7]. Both countries have an almost complete registration of HPV vaccinations and nationwide population-based cervical cancer screening programs. Both are prerequisites to efficiently evaluate effectiveness of HPV vaccination on the population level.

This is the first nationwide population-based study performed in two countries aiming to investigate effectiveness of qHPV vaccination against high-grade cervical intraepithelial neoplasia or worse (CIN2+) by age at vaccination, number of doses, and to test whether optimal timing of two doses of qHPV vaccine can confer the same level of protection as the originally recommended three dose-schedule.

2. Methods

2.1. Study population

All girls and women residing in Denmark or Sweden aged 13–30 years during 2006–2013 were included in an open cohort and followed up for HPV vaccination and first occurrence of CIN2+. The participants entered the cohort at October 1, 2006; on their 13th birthday; or on the date of immigration to Denmark or Sweden, whichever came last. They were followed to December 31, 2013; their 30th birthday; date of emigration or death; vaccination with the bivalent HPV vaccine; or to the first diagnosis of CIN2+, whichever occurred first. Participants with CIN2+ before study entry were excluded.

2.2. Exposure information

Data collection regarding HPV vaccination has previously been described in detail separately for Denmark and Sweden [6,7,12]. In brief, all Danish and Swedish citizens have a unique personal identification number with information on date of birth and sex, which is included in all health registries. Used as a key identifier, it ensures accurate linkage of information between registries.

In Denmark, free-of charge qHPV vaccination was implemented for 12-year-old girls in January 2009, preceded by a catch-up program for 13–15-year-old girls from October 2008. The Danish program was further supplemented from August 2012 with a second catch-up program, targeting women up to 27 years of age. Since the autumn 2017, the nine-valent HPV vaccine has been included in the Danish children's vaccination program. Information on girls and women vaccinated within the Danish programs was obtained from the National Health Service Registry [13]. Data on girls and women vaccinated outside the program after licensure of qHPV vaccine in October 2006 and throughout the study period were obtained through information on prescriptions redemptions for qHPV and the bivalent HPV vaccines in the Danish National Prescription Registry [14], using the Anatomical Therapeutic Chemical (ATC) codes J07BM01 and J07BM02, respectively. Danish HPV vaccination coverage was high in the study period, with approximately 90% of girls receiving first dose and the majority (~80%) receiving three doses in both the general and the first catch-up vaccination programs [15][. In the second catch-up program, 75% received first dose and 56% received three doses by the end of 2013 [15].

As in Denmark, qHPV was licensed in Sweden in October 2006 and could be purchased using a prescription. Organized HPV vaccination started with an opportunistic, partially subsidized, program for 13–17-year-old girls in 2007–2011. The vast majority (>98%) was vaccinated with qHPV. In 2012, a school-based, free-of-charge vaccination program with qHPV was implemented for 10–12-year-old girls, supplemented with a free-of-charge catch-up program for 13–18-year-old girls. In Sweden, the nine-valent vaccine has been on the market since 2017, but has not yet been included in the Swedish HPV vaccination program. Information on HPV vaccination was obtained from the Swedish vaccination register [16]. This data was supplemented with information on prescription redemptions from the Prescribed Drug Register [17], using ATC codes as previously described. [16]. Swedish coverage for first dose of qHPV in the school based program is 82% and 59% for the catch-up program.

2.3. Identification of outcomes

Information on cervical lesions in Denmark was identified from the nationwide Danish Pathology Data Bank, which holds information on all cervical cytology and all cervical histology [18]. In Sweden the information was identified from the Swedish National Cervical Screening Registry, which contains information on Swedish cytological and histological samples [19], and from the Swedish Cancer Registry [20]. In this study, we assessed CIN2+, comprising histological diagnoses of CIN2, CIN3, carcinoma in situ, adenocarcinoma in situ and cervical cancer. The date of diagnosis of CIN2+ was backdated six months to compensate for some of the lag-time from infection with a high-risk HPV type to development of the lesion. Finally, we truncated the follow-up to June 30, 2013 to avoid immortal time bias in the last six month introduced by backdating outcomes.

2.4. Additional covariates

We considered socioeconomic status as a potential confounder, and used mothers' highest attained education at the beginning of follow-up as a proxy, classified as basic school or high school, vocational education, higher education, and unknown. Mothers of cohort members were identified through the Civil Registration System (Denmark) and the Multigeneration Register (Sweden) respectively. Information on education was linked from the population-based Statistics Denmark and the Swedish Education Register.

2.5. Statistical analysis

We estimated unadjusted incidence rates (IRs) of CIN2+ per 100,000 person-years and report corresponding Poisson-based 95% confidence intervals (CIs).

We accounted for age- and dose effects, and potential confounding by fitting separate Poisson regression models for all strata of age at vaccination ($\leq$16, 17–19, and 20+ years). Each model had the same structure, using the natural logarithm of person-time as offset and adjusting for attained age in five age groups (13–16, 17–19, 20–22, 23–25, and 26–30 years), as well as mothers' highest attained education. We included vaccine dosage as time-varying exposure with four categories (0/unvaccinated, 1, 2 and 3 doses), allowing the same woman to contribute person-time to multiple dose categories, depending on her individual follow-up. To estimate the effect of varying time intervals between first and second dose, we fitted the same models, but only for two dose levels (2 and 3 doses), and included timing as a categorical exposure variable with two levels (0–4 or more than 5 months). All reported incidence rate ratios (IRRs) were estimated as regression coefficients and their contrasts in the corresponding Poisson models. In a post-hoc sensitivity analysis, we further excluded all girls and women with any cervical dysplasia prior to study entry to assess the impact of prevalent HPV-infections.

P-values of less than 0.05 were considered statistically significant, and all statistical tests were two-sided. The statistical software program R version 3.4.2 was used [21], using the Epi-package [22]. The study was approved by the Danish Data Protection Agency and the Regional Ethical Review Board of Stockholm,

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