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Examining determinants for reporting suspected adverse events following HPV vaccination in Denmark

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ABSTRACT

HPV vaccination has been offered to 12-year-old girls as part of the Danish Childhood Vaccination Programme since 2009. From 2013, an increasing number of suspected severe adverse events (AE) without a documented causal link to the vaccine was observed, resulting in public concerns about vaccine safety and a decline in uptake. This study aimed at describing the group of females reporting AE and comparing them to vaccinated peers not reporting AE. A questionnaire focusing on demographics, lifestyle, and health-related issues was distributed to 251 female cases who had reported severe AE and 1,003 female controls randomly selected from the population-based Danish Vaccination Registry. All had been HPV-vaccinated. There were no significant differences on measures of self-reported psychiatric or somatic conditions before vaccination. More cases reported being physically very active prior to first HPV vaccination (OR 4.2) whereas fewer cases than controls sometimes (OR 0.31) or often/always (OR 0.36) felt sad. This is unexpected because two recent Danish registry-based case-control studies concluded that females reporting severe AE were more likely to consult a psychologist/psychiatrist and to have pre-existing psychiatric conditions before first HPV vaccination. One of these studies also showed that cases had increased health-care seeking regarding a number of somatic conditions prior to first vaccination. Our study adds value when seeking to understand the lifeworld of the affected females and their interpretations of their everyday lives pre- and post-HPV vaccination.

1. Introduction

Human papillomavirus (HPV) vaccination has been offered to 12-year-old girls as part of the Danish Childhood Vaccination Program since 2009 to prevent cervical cancer. From 2013, the Danish Medicines Agency received an increasingly high number of reported suspected severe adverse events (AE) from the vaccine. Almost half of these were reported by vaccinated females or their relatives themselves rather than health care professionals [1]. The suspected severe AE were often non-specific symptoms like dizziness, fatigue, and headache – a majority of which remain medically unexplained [2]. The symptoms were for the most part classified as severe by the Danish Medicines Agency if they, according to the report, caused long-standing disability or incapacity; for example, instigating challenges going to work or attending school. It has been suggested that these symptoms can be characterised as Chronic Fatigue Syndrome (CFS) [3], Postural Orthostatic Tachycardia Syndrome (POTS) [2,4–5], or Complex Regional Pain Syndrome (CRPS) [6], and an autoimmune aetiology has been speculated. However, studies have found no association between the HPV vaccines and a number of autoimmune diseases [7–8] and CFS [9–10]. In November 2015, the European Medicines Agency reviewed the evidence surrounding the reports of young women developing CRPS and POTS after HPV vaccination and concluded that it does not support a causal link between the vaccines and these two syndromes [11]. Nevertheless, the increased number of reported suspected severe AE raised public concerns towards HPV vaccination in Denmark and resulted in extensive media coverage and an intense debate on social media focusing on vaccine safety issues. Although the clinical symptoms are undoubtedly real for these young women, the evidence indicates that the interpretation of them as AE might have been stimulated to a great extent by (social) media attention. During the same period and following the public debate, the uptake of HPV vaccine declined from around 90% in birth cohorts 1996–2002 to 51% in girls born in 2004 [12] (Fig. 1).

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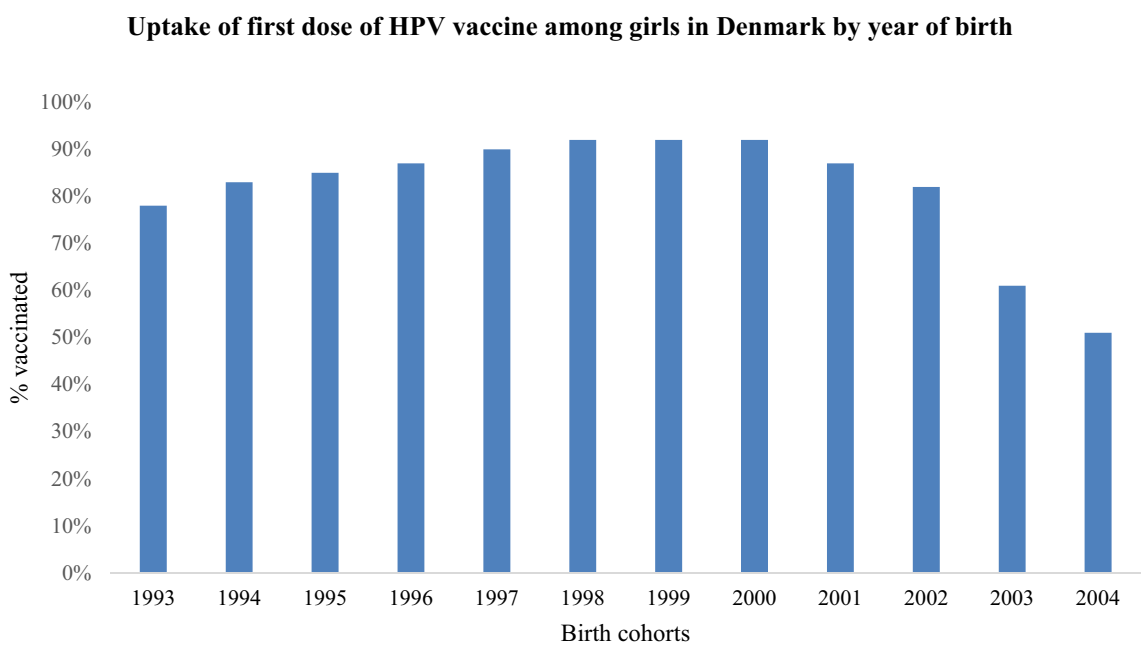

Fig. 1. Uptake of first dose of HPV vaccine among girls in Denmark (October 2017).

Two recent Danish studies investigating pre-vaccination characteristics of females suspecting AE after HPV vaccination concluded that, prior to vaccination, these females had a more frequent contact with the health care system than vaccinated controls [13], including hospital contacts due to a psychiatric disorder [14]. These findings suggest that females reporting AE might be different on some parameters prior to the first vaccination when compared to vaccinated females who did not report AE. It has been proposed that these patients share several common features such as high levels of physical activity [2], high ambitions in school or at work, and psychosocial challenges. However, it is unknown how common these features are in the general population. The aim of this study was to describe the group of females reporting AE and compare them with vaccinated peers not reporting AE to inform initiatives aimed at clinically managing this group of patients and to improve the understanding of the females' own interpretation of the situation which may inform public health actions.

2. Methods

We conducted a matched case-control study investigating the distribution of a number of selected features among females who reported suspected severe AE after HPV vaccination and compared them to females who had been vaccinated but did not report severe AE.

Cases were defined as females who received at least one dose of HPV vaccine and subsequently reported one or more suspected severe AE to the Danish Medicines Agency between 1 January 2013 and 1 November 2015. Controls were defined as females who received at least one dose of HPV vaccine and did not report suspected severe AE in the same period of time. They were randomly selected from the population-based Danish Vaccination Registry and were individually matched to cases on date of birth (+/− one year), time of first vaccination (+/− one year), and municipality of residence at the time of vaccination. Based on power calculations and on experience that controls are less likely to participate in studies, it was decided to include approximately four controls for each case into the study, resulting in 251 cases and 1,003 controls being enrolled.

In January 2016, we distributed an identical questionnaire (appendix C) by mail to cases and controls asking about symptoms before and after HPV vaccination, on various lifestyle factors such as smoking, diet, alcohol consumption, level of physical activity, mental and physical health status, use of medication, as well as menstruation and first sexual intercourse. Informed consent was recorded in the first paragraph of the questionnaire. It was possible for participants to complete the questionnaire online or on paper and return it in a pre-paid envelope. Completed paper questionnaires were typed into the online version of the questionnaire upon which the assembled data were extracted from the online tool.

Partly completed questionnaires were followed up by phone. Non-responders were contacted by phone (if number was available) and if not reached sent a reminder letter followed by another phone call. If the number was not publicly available, they were only sent a reminder.

Data were analysed in STATA 14 [15] and carried out separately for pre-vaccination features and post-vaccination symptoms.

Using chi-square, we described the distribution of the variables on which all cases and controls were matched. Second, post-vaccination symptoms were analysed in a univariable conditional logistic regression analysis, using the matched sets of one case and up to four controls as the grouping variable. Finally, pre-vaccination features were analysed by conditional logistic regression analysis. Variables with a p-value above 0.1 in the univariable analysis were not considered for the final model and variables not significant at a 5% level were excluded in the backward stepwise selection for the final multivariable model.

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.vaccine.2018.08.061.

The study was carried out under the Danish Data Protection Agency record number 2008-54-0474.

3. Results

In total, 130 of 251 cases (52%) and 506 of 1,003 controls (50%) answered the questionnaire. Table 1 describes cases and controls in regard to the matching variables. Most respondents were in

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