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Hospital contacts and diagnoses five years prior to HPV vaccination among females referred for suspected adverse vaccine effects: A Danish nationwide case-control study

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ABSTRACT

Background: High health care utilization before Human Papilloma Virus (HPV) vaccination might be associated with increased risk of suspected adverse effects (AE's) after vaccination. We investigated the association between hospital contacts and diagnoses before HPV vaccination and risk of later referral to a specialized hospital setting (HPV center) for suspected AE's.

Methods: The study was a Danish register-based matched case-control study. Cases were females referred to an HPV center. Five controls per case were randomly selected in the source population of HPV vaccinated females. Information on hospital contacts and diagnoses was obtained from the Danish National Patient Registry. Conditional logistic regression analyses were used to investigate the association between having one or more diagnoses in each specific International Classification of Diseases 10th version (ICD-10) chapter five years before the HPV vaccination and subsequent referral to an HPV center.

Results: We identified 1496 cases and 7480 controls. In total, 80% of the cases versus 65% of the controls had at least one hospital contact prior to HPV vaccination (Prevalence Proportion Ratio - PPR: 1.24 (95% Confidence Interval - CI: 1.21–1.27)), with 24% vs 12% (PPR: 1.97 (95% CI: 1.76–2.19)) having six or more contacts. Cases were more likely to have had a diagnosis in 15 out of 19 ICD-10 chapters before the vaccination, with ORs larger than 1.8 for infectious diseases, psychiatric diseases, diseases of the nervous, circulatory, digestive and musculoskeletal system, unspecific symptoms and unspecific contacts.

Conclusion: Pre-vaccination morbidity and health care utilization seem to play a role in the path leading to suspected AE's after HPV vaccination. Since many of the diagnoses that were particularly increased before vaccination in referred females are overlapping with the most frequent symptoms reported, we cannot exclude that for some of the females, the suspected AE's might have been existing already before the vaccination.

1. Background

The three Human Papilloma Virus (HPV) vaccines (4 and 9-valent Gardasil®, 2-valent Cervarix®) are all found to be safe and effective in both pre- and post-licensure studies [1–12]. The World Health Organization (WHO) recommends the HPV vaccine to be included in national immunization programs [13–16]. In Denmark, the 4-valent HPV vaccine Gardasil® was implemented in the Danish childhood vaccination program in 2009 and was replaced with the 2-valent Cervarix in the period 2016/2017, whereas from November 2017 onwards the 9-valent Gardasil has been offered [17]. However, since 2013, a large number of Danish females have reported suspected adverse effects. In line of this a massive media attention and following public debate resulted in a sharply decline in the HPV vaccination coverage [18]. The most frequently reported suspected adverse effects were headache, stomach pain, fatigue, long-lasting dizziness and syncope [19]. Some of the suspected adverse effects were classified as postural tachycardia syndrome

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(POTS) and chronic fatigue syndrome [19,20]. In 2015 the Danish government established, five specialized hospital-based HPV centers, where females who had experienced adverse effects could be diagnosed and treated from a bio-psycho-social perspective. By the end of 2015, approximately 1500 females had been referred by the general practitioner to one of the five HPV centers. The criteria for referral are unspecific or unexplained symptoms occurring in temporal relation to the HPV vaccination.

Based on extensive international vaccine safety data, it is unlikely that the HPV-vaccination in itself can be a sufficient cause for the experienced symptoms of girls referred to the HPV centers. Other factors must play a part in the causal path leading to the experienced symptoms [1–12]. A previously published register-based case-control study found that females reporting severe adverse effects to the Danish Medicines Agency were more likely to have had previous contacts to both the primary and secondary health care system in the two years prior to receiving the HPV vaccination compared to a matched population with no reports of adverse effects [21]. These results are in concordance with a study by Lützen et al. reporting that young females referred to an HPV center had more contacts with their general practitioner and were more likely to have used psychiatric medication prior to the vaccination compared to the source population of those who had received the HPV vaccination [22]. These studies thus indicate that health status prior to HPV vaccination plays a role in the symptoms reported after the vaccination. However, there is a lack of evidence of secondary health care utilization before HPV vaccination for females referred to an HPV center. Hence, the aim of this study was to investigate the association between pre-vaccination hospital contacts (including number and type of contacts) and associated diagnoses and later referral to an HPV center, using the national registers in Denmark, which include complete data on healthcare services for all Danish citizens.

2. Methods

2.1. Study population

The study was designed as a nationwide register-based matched case-control study. The study population has been described in detail previously [22]. Shortly, every citizen in Denmark is registered with a unique 10-digit civil personal registration (CPR) number [23]. The CPR number was used to identify the source population consisting of all Danish HPV vaccinated females born in the period from 1974 to 2003 and to link information at the individual level between registers. The study population were defined as HPV vaccinated if having either received at least one HPV vaccination at the general practitioner or redeemed a prescription for the HPV vaccine (Gardasil® [Merck & Co., Whitehouse Station, NJ, USA] or Cervarix® [GSK Biologicals, Rixensart, Belgium]) between 01.01.2006 and 31.12.2015. This information was obtained from the Danish National Health Insurance Service Register [24] (service codes 8328, 8329, 8330 or 8334, 8335 and 8336) and from the Danish Register of Medical Product Statistics [25,26] (Anatomic Therapeutic Chemical (ATC) code J07BM01, J07MB02 or J07BM03). The source population included 534,580 HPV vaccinated females.

Cases were defined as HPV vaccinated females who were referred to one of the five regional HPV centers in the period from 01.06.2015 until 31.12.2015 (n = 1502). For each case, five controls were randomly selected from the source population and matched on age at vaccination (birth year), region and time of first HPV vaccine registration (±2 months). Six cases could not be matched with a full set of five controls and were excluded from the study. Thus, the final study population consisted of 1496 cases and 7480 controls.

2.2. Exposures

The exposures of interest were number and type (inpatient admission, outpatient visit, emergency visit) of hospital contacts as well as type of diagnosis five years prior to the HPV vaccination. Information on hospital contacts and diagnoses was obtained from the Danish National Patient Registry (DNPR) [27,28]. The DNPR contains nationwide information on primary and secondary diagnoses associated with each inpatient, outpatient and emergency visit according to the International Classification of Diseases 10th version (IDC-10) classification. Only the primary diagnoses (the main reason for hospital contact) were used in this study. We grouped the diagnoses according to overall chapters in the ICD-10 classification and females were defined as either exposed or non-exposed according to whether they had at least one diagnosis within each of these ICD-10 chapters five years prior to their first HPV vaccination. All contacts related to pregnancy, childbirth or the perinatal period only (ICD-10 chapters O, P and Z3) were excluded. We identified the top five diagnoses at a three-digit level within each ICD-10 chapter for the whole study population.

2.3. Covariates

Potential confounders were identified a priori of the association between hospital contacts and diagnoses five years prior to HPV vaccination and referral to an HPV center. Information on covariates was obtained from Statistics Denmark for the year before the time of first HPV vaccination. A study by Weye et al. [29] reported factors related to social inequality in the patterns of referral to the HPV centers. Thus, girls of mothers outside the workforce, girls with unemployed mothers and girls with low educated parents were more often referred. In addition to the matching variables, maternal educational level and occupational status of the girls referred were considered as potential confounders. Also, ethnicity was considered a potential confounder, as ethnicity has been associated with health care utilization in both the primary and secondary health care sector as well as HPV vaccination initiation [30–32].

2.4. Statistical analysis

For cases and controls, exposures, including type of hospital contact (inpatient, outpatient and emergency) and number of hospital contacts, matching variables, and other covariates are presented using numbers and percentages. Prevalence of each type and number of hospital contact for cases compared to the controls was calculated and presented as crude prevalence proportion ratios (PPR) with 95% confidence intervals (CI). The number of different ICD-10 diagnoses according to number of hospital contacts among cases and controls was visualized by a stacked bar graph.

For each specific ICD-10 chapter, we used a conditional logistic regression model to investigate the association between having at least one diagnosis and referral to an HPV center. The adjusted Odds Ratios (ORs) and 95% CI were estimated and are presented in a forest plot. In addition, we identified the most prevalent five diagnoses within each ICD-10 chapter in the study population and investigated the association between each specific diagnosis and referral to an HPV center using conditional logistic regression. All analyses were adjusted for maternal educational level (PhD, higher education, medium-length education, basic education, high school or vocational and primary school), maternal occupation (owner of business, chief executive or employee with high income, employee with middle income, employee with low income, employee with unspecified income, unemployed and pensioner) and ethnicity (Danish [Danish born girl and parents], descendent

of immigrants [Danish born girl, parents not born in Denmark] and immigrant [girl not born in Denmark]).

Since the HPV centers did not open until June 2015, we could only include prevalent cases of females experience adverse effects in our analyses. Time from HPV vaccination to referral differs among cases. Hence, type, severity and persistency of symptoms may be related to the waiting time to referral. Furthermore, a massive media attention in Denmark since 2013 regarding potential adverse effects of the HPV vaccination resulted in a substantial decrease in HPV vaccination coverage and thereby a change in the vaccinated population. In order to investigate if waiting time to referral to the HPV centers and the media attention had influenced our results, we performed a sub-analysis in which the primary analysis was stratified in two periods: 2006–2012 and 2013–2015.

3. Results

Characteristics of cases and controls are presented in Table 1. The majority of females were aged either 10–14 or 19–25 years at the time of HPV vaccination, corresponding to the ages when the Danish childhood HPV immunization program is offered as well as the HPV catch-up programs. Most females were vaccinated in 2008–2009 and in 2012–2013. In both of these periods, there were also catch-up programs for females born in 1993–1996 and 1985–1992. Compared to controls, more cases were ethnic Danes, and maternal levels of education and occupation were similar or slightly lower among cases compared with controls (Table 1).

A total of 80% of the cases and 65% of the controls had at least one hospital contact in the five-year-period prior to the HPV vaccination. Thus, cases had a 24% higher probability of having had any hospital contact five years before the HPV vaccination (PPR 1.24; 1.21–1.27) (Table 2). Cases were more likely to have had an inpatient admission (PPR 1.57; 1.44–1.72), an outpatient contact (PPR 1.38; 1.31–1.46) and emergency contact (PPR 1.30; 1.24–1.30) compared to controls (Table 2). In addition, cases were more likely to have had multiple hospital contacts; hence, the probability of having had more than six hospital contacts was almost twice as high for cases compared with controls (1.97; 1.76–2.19).

In addition, cases had a greater variety of diagnoses, and thus diagnoses in more different ICD-10 chapters for the same number of hospital contacts compared with controls (Fig. 1).

In each ICD-10 chapter, cases had elevated pre-vaccination adjusted ORs in 18 out of 19 ICD-10 chapters. However, estimates of congenital malformations, external causes of accidental injury, hematologic and immunologic diseases had wide confidence intervals. In eight out of 19 chapters, ORs larger than 1.8 were observed – infectious diseases (1.95; 1.17–3.25), psychiatric diseases (1.80; 1.32–2.45), diseases of the nervous system (1.97; 1.44–2.68), circulatory system (2.44; 1.58–3.77), digestive system (1.83; 1.48–2.25), musculoskeletal system (1.82; 1.51–2.20), unspecific symptoms (no diagnosis classified) (1.95; 1.66–2.28) and unspecific contacts (1.86; 1.65–2.11). In contrast, no notably altered risk was observed for diseases of the eye, ear and mastoid process (0.88; 0.61–1.26) (Fig. 2).

The stratified analysis showed similar tendencies in the two periods (2006–2012 and 2013–2015). However, we found higher pre-vaccination ORs in the late period compared to the early period in the following ICD-10 chapters; circulatory system (3.75; 1.87–7.50 vs. 1.84; 1.02–3.31), digestive system (2.89; 1.94–4.29 vs. 1.52; 1.18–1.96) and unspecific contacts (2.65; 1.99–3.53 vs 1.72; 1.49 – 1.97) (Supplementary Fig. 1).

We found a similar pattern when studying the five most prevalent diagnoses within each ICD-10 chapter. Thus, those diagnosed with almost all specific diagnoses investigated had higher odds

Table 1
Characteristics of females referred to an HPV center (cases) and matched controls.*

Matched variables	Cases n (%) N 1496	Controls n (%) N 7480
Age at vaccination		
10–14 years	889 (59.4)	4445 (59.4)
15–18 years	178 (11.9)	890 (11.9)
19–25 years	242 (16.2)	1210 (16.2)
25+ years	187 (12.5)	935 (12.5)
Year of vaccination		
2006/2007	25 (1.7)	125 (1.7)
2008	223 (14.9)	1115 (14.9)
2009	274 (18.3)	1370 (18.3)
2010	143 (9.5)	718 (9.5)
2011	142 (9.5)	707 (9.5)
2012	360 (24.1)	1800 (24.1)
2013	231 (15.4)	1155 (15.4)
2014/2015	98 (6.6)	490 (6.6)
Region of residence		
North Jutland	179 (11.9)	895 (11.9)
Central Jutland	267 (17.9)	1335 (17.9)
South Denmark	301 (20.2)	1505 (20.2)
Capital	436 (29.1)	2180 (29.1)
Zealand	313 (20.9)	1565 (20.9)
Covariates (measured in the year before first HPV vaccination)		
Maternal level of education		
Higher education or Ph.D.	63 (4.3)	509 (7.0)
Middle education	333 (22.6)	1688 (23.1)
Basic education	74 (5.0)	387 (5.3)
High school or vocational	695 (47.1)	3142 (43.0)
Primary school	296 (20.0)	1440 (19.7)
Unknown	13 (1.0)	135 (1.9)
Missing	22	179
Maternal occupation		
Owner of business	51 (3.5)	323 (4.5)
Chief executive or employee with High income	238 (16.4)	1.419 (19.8)
Employee with middle income	247 (17.1)	1.156 (16.2)
Employee with low income	453 (31.3)	2.171 (30.4)
Employee unspecified income	128 (8.9)	702 (9.8)
Pensioners	129 (8.9)	462 (6.5)
Unemployed	201 (13.9)	916 (12.8)
Missing	49	331
Origin		
Danish	1423 (97.0)	6662 (90.6)
Immigrants	14 (1.0)	251 (3.4)
Descendents of immigrantsMissing	29 (2.0)30	442 (6.0)125

* Contols matched on region of residence, age at time of HPV vaccination, and calendar time of HPV vaccination.

Table 2
Type and number of hospital contacts* in the 5 years before HPV vaccination among females refereed to an HPV center (cases) and controls.

N	Cases n (%) 1496	Controls n (%) 7480	Crude PPR (95% CI)
Number of hospital contacts			
Any contact	1199 (80)	4822 (64)	1.24 (1.21–1.28)
1	267 (18)	1526 (20)	0.87 (0.78–0.98)
2	192 (13)	968 (13)	0.99 (0.86–1.15)
3	157 (10)	664 (9)	1.18 (1.00–1.39)
4	125 (8)	438 (6)	1.43 (1.18–1.73)
5	102 (7)	321(4)	1.59 (1.28–1.97)
6+	356 (24)	905(12)	1.97 (1.76–2.19)
Type of contact			
Inpatient	451 (30)	1435 (19)	1.57 (1.44–1.72)
Outpatient	839 (56)	3029 (41)	1.38 (1.31–1.46)
Emergency	937 (63)	3600 (48)	1.30 (1.24–1.36)

* Contacts measured as primary diagnosis. Contacts because of pregnancy, childbirth and perinatal period were excluded.

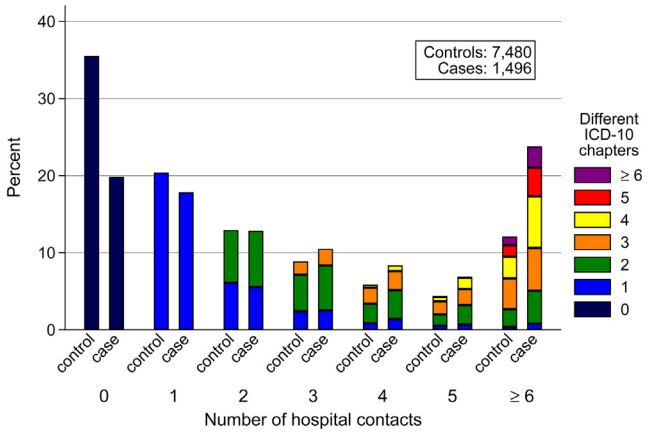

Fig. 1. Percentages of cases and controls by number of hospital contacts and number of different ICD-10 chapters in the five years before HPV vaccination. Contacts because of pregnancy, childbirth and perinatal period were excluded.

of being referred (Supplementary Table 1). The following associations had statistically significantly increased point estimates larger than 2: unspecific viral infections, anxiety disorders, migraine, headache, tachycardia, other cardiac arrhythmias, non-specific lymphadenitis, asthma, atopic dermatitis, acute tonsillitis, functional intestinal disorders, dorsalgia, unspecific muscle disorders, pain associated with female genital organs/menstrual cycle and abnormalities of breathing. It is important to note that the number of individuals in each category was low for some specific diagnoses.

4. Discussion

Our study adds to the knowledge about morbidity and health care utilization before HPV vaccination in females experiencing suspected adverse effects after HPV vaccination. We found that females referred to an HPV center had an overall substantial higher number of hospital contacts and more different diagnoses five years prior to the first HPV vaccination when comparing with all vaccinated females. This was also observed when taking number of hospital contacts into account. Furthermore, there was a general pattern of the referred females having higher odds for a previous diagnosis in most ICD-10 chapters compared to their matched controls. The strongest associations were observed for psychiatric diseases, diseases of the nervous system, circulatory system, digestive system, musculoskeletal system and abnormal symptoms or unspecific contacts.

4.1. Strengths and limitations

An important strength of this study is its register-based nature in a universal coverage healthcare system with almost complete registration. Information on both exposures and covariates was register-based and collected prospectively and independently of our research question. Hence, there is no difference in the quality of the information among cases and controls. The information on primary hospital diagnosis in terms of ICD-10 codes from the DNPR is highly valid [28]. Any problems in relation to different coding practices between doctors and hospitals and over time are most likely non-differential, as cases were matched with controls on year of HPV vaccination (calendar-time) and geographical region of residence. Furthermore, we primarily compared the risk of

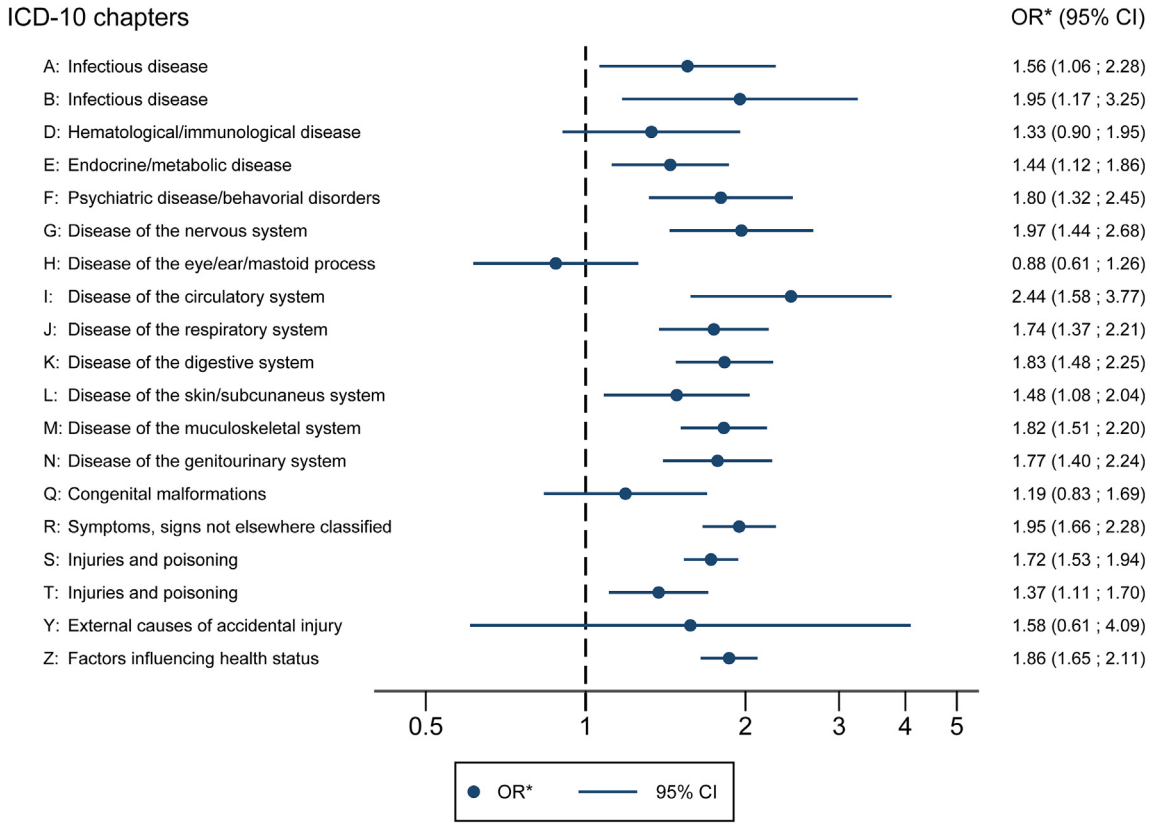

Fig. 2. *Odds Ratios (OR) and 95% confidence intervals (CI) for referral to an HPV center by having a diagnosis in each ICD-10 chapter five years before first HPV vaccination, adjusted for maternal education, maternal occupation and ethnicity of the female. Diagnosis in relation to pregnancy, childbirth and perinatal period were excluded. Estimates with less than five females diagnosed are not shown (Chapter C- cancers).

having a diagnosis within each of the ICD-10 chapters, and minor differences in coding practice at three-digit disease level has not influenced our main results. We were able to adjust for a number of different confounders in addition to the matching variables. The confounder adjustment only changed the estimates slightly. Inherent in our study design, there is a possibility of confounding by unmeasured factors and residual confounding from imperfectly measured covariates. Another strength of the study is that we investigate health care utilization in terms of hospital contacts and hospital diagnosis. In Denmark, the general practitioners act as gatekeepers and referral from a general practitioner is required to initiate any non-emergency in- and outpatient hospital treatment. Thus, hospital contacts may reflect more severe symptoms and are probably less sensitive to health care seeking behavior and therefore may be a better measure of morbidity than general practitioner contacts.

A main limitation of our study is that the HPV centers did not open until June 2015. Firstly, the severity of the symptoms leading to the referral might differ between females vaccinated in the early period compared to those vaccinated in close proximity to the opening of the centers. Secondly, a massive media attention and public debate about HPV vaccine safety from 2013 and onwards led to a dramatic decrease in vaccination coverage and the characteristics of the HPV vaccinated girls may thus differ between the periods. The stratified analysis showed no overall differences between the two periods; however, a tendency towards higher pre-vaccination ORs for diseases in the circulatory system, digestive system and unspecific contacts was observed in the late period compared to the early period. The reason for this is unknown but might be explained by several potential factors. *First of all*, females vaccinated in the early calendar period have had longer time for further medical examination, treatment and spontaneous recovery in relation to symptoms occurring both before and after the HPV vaccination compared to females vaccinated in the late period. Hence, a possible explanation for the difference between the two periods could be that females with previous diagnoses within these chapters either spontaneously recovered or were treated for their post-vaccination symptoms and therefore did not need a referral to an HPV center in 2015. *Secondly*, since the diagnoses showing a stronger association in the late versus early period (e.g., circulatory symptoms, disease of the digestive system) are overlapping with the most frequent symptoms experienced by those referred to HPV centers [19], another explanation could be that these diagnoses were already present prior to the vaccination, and that the opening of the centers provided a possibility to be treated for these symptoms.

4.2. Comparison with other studies

Our findings are in line with findings by Lützen et al. [22], showing that referred females had an increased frequency of contacts to general practitioners five years before the HPV vaccination. Furthermore, they reported an association between having had psychiatric disorders and usage of psychiatric medications five years before the HPV vaccination and referral to an HPV center. Correspondingly, a study by Molbak et al. [21] found that females reporting adverse effects to the Danish Medicines Agency had a higher health care utilization two years before the first HPV vaccination compared with a matched control population. Also, a higher risk of having had a diagnosis two years before HPV vaccination was found for diseases in the digestive system, musculoskeletal system, abnormal symptoms and injuries. The findings in our study corroborate these results, as the strongest associations were detected for infectious diseases, psychiatric diseases, diseases of the nervous system, circulatory system, digestive system, musculoskeletal system, symptoms (no diagnosis classified) and unspecific contacts.

A substantial part of the most frequently reported adverse symptoms after HPV vaccination are included in the specific ICD-10 chapters in which we found the highest ORs compared to the source population [13,14]. Thus, some of the reported symptoms leading to referral might have been present before the HPV vaccination. However, a general pattern of cases having higher odds for almost all ICD-10 chapters diagnoses was found. This indicates that the referred females had more pre-vaccination morbidities and symptoms in general and/or had a different health care seeking pattern than the source population.

In the study by Molbak et al., it was discussed if the increased risk for injuries and musculoskeletal symptoms could be explained by higher levels of physical activity among cases before onset of the suspected adverse effects [21]. Brinth et al. [19] suggested that females with adverse effects often had a high level of physical activity prior to vaccination. In accordance with our study, HPV center cases were 72% more likely to have had injuries before the HPV vaccination, compared to the source population of vaccinated females, possibly explained by higher levels of physical activity among cases. Looking into the specific top five diagnoses in this chapter, cases had an increased risk of superficial injuries as well as dislocations, sprains and strains. In contrast, there was no notably increased risk of more severe injuries, such as fracture of the forearm, which would also be expected if the increased risk of injury was solely linked to a higher level of physical activity. Thus, the increased risk of recorded injuries could potentially be explained by a different health care seeking pattern among cases.

5. Conclusion

In conclusion, pre-vaccination morbidity and health care utilization seem to play a role in the path leading to suspected adverse effects after HPV vaccination. Females referred to an HPV center had a substantially higher number of hospital contacts and more different diagnoses before receiving the first HPV vaccination compared with the source population of HPV vaccinated females. Since many of the diagnoses that were particularly increased before vaccination in females referred to HPV centers are overlapping with the most frequent symptoms reported [19], we cannot exclude that for some of the females, the suspected adverse symptoms might have been existing already before the HPV vaccination.

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Conflicts of interest

None declared.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2019.02.029.

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