# Possible adverse effects of the quadrivalent human papillomavirus vaccine in the Region of Southern Denmark: a retrospective, descriptive cohort study

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## ABSTRACT

**INTRODUCTION:** Since the introduction of the quadrivalent human papillomavirus vaccine, young girls and women have reported a broad range of symptoms. These have been described as possible adverse effects of the vaccine. In this study, we describe demographic characteristics, symptomatology, clinical and laboratory test results in patients referred with suspected adverse effects in the Region of Southern Denmark.

**METHODS:** We conducted a retrospective, descriptive study. The patients filled out a questionnaire, were interviewed by a doctor and received a standard physical examination and laboratory tests.

**RESULTS:** The study comprised 200 patients. The median age at referral was 22 (interquartile range (IQR): 19.5-26) years, and age at first vaccination was 14 (IQR: 12-21) years. The most common symptoms were headache (93%), fatigue/tiredness (93%) and dizziness when standing up (90%). The median number of symptoms in each patient was 15. Five patients (2.5%) were diagnosed with postural orthostatic tachycardia syndrome (POTS). Of all patients, 183 (91.5%) were terminated without a somatic diagnosis, one patient (0.5%) was terminated with a functional disorder and 11 patients (5.5%) were still in diagnostic workup when the present study concluded.

**CONCLUSIONS:** The patients reported a wide range of symptoms. We found an overall low prevalence of POTS. It should be further investigated whether these patients might suffer from a functional disorder rather than from adverse effects associated with the vaccine.


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The quadrivalent vaccine against human papillomavirus (qHPV) protects against infections caused by HPV of types 6, 11, 16 and 18. Since 2009, the vaccine has been offered to girls aged 12 years as part of the Danish childhood vaccination programme [1]. For the time being, more than 500,000 Danish girls and women have been vaccinated against HPV [2].

HPV infections are prevalent in the Danish population, causing condyloma and cervical, oropharyngeal, anal, penile and vulvovaginal cancer [1]. In Denmark, approximately 375 women are diagnosed with cervical cancer, and 100 women die from this disease annually [2]. Studies have demonstrated a significantly lower risk of developing cervical dysplasia in women who were inoculated against HPV compared with unvaccinated women [3, 4]. Furthermore, the incidence of condyloma has been significantly reduced since the implementation of qHPV in Denmark [5].

Since the release of the vaccine, young girls and women have turned up with a variety of symptoms suspected to be adverse effects of qHPV. These possible adverse effects have received substantial publicity in the media. In 2015 and 2016, the number of Danish girls who were vaccinated against HPV was reduced markedly from > 90% to 23% [6].

The HPV vaccine has a number of well-documented side effects. Still, large cohort studies have found no increased frequency of severe diseases (e.g. autoimmune, neurological and thromboembolic diseases) or less severe diseases like postural orthostatic tachycardia syndrome (POTS) or complex regional pain syndrome [7, 8].

Until June 30 2016, 0.4% of the total number of vaccinated women (2,241) had reported possible adverse effects of the vaccine to the authorities [9]. In 2009-2012, the number of reported possible adverse effects compared with the number of sold vaccine doses was stable. In 2015, this ratio increased by factor 24 [10].

In order to standardize the examination and treatment of patients, five centres throughout Denmark were established in March 2015. These centres are responsible for referral regarding possible adverse effects of the HPV vaccine. In the Region of Southern Denmark, the Department of Infectious Diseases (DID) and the Department of Paediatrics (DP) at Odense University Hospital are responsible for these patients.

The aim of this study is to describe demographic characteristics, symptomatology and clinical and labora-

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tory test results among patients referred with possible adverse effects from qHPV vaccine in the Region of Southern Denmark.

## METHODS

### Study design and population

We conducted a retrospective, descriptive study of patients referred from general practitioners to the DID and the DP with possible adverse effects of qHPV vaccine during the period from March 2015 to October 2016. All patients had received at least one vaccine dose. The patients went through an interview with a doctor and underwent a standard physical examination and laboratory tests. Additionally, they filled-in a questionnaire before or after the examination. If data from the questionnaire were missing, the questionnaires were still included. Patients were excluded from this study if they failed to show up for examination, or if the questionnaire was not returned.

### Data collection

Questionnaire: The questionnaire contained information about demographic characteristics, symptomatology after any dose of the vaccine, medical treatment, dietary supplements, alternative treatment and previous medical history. The questionnaire was constructed when the centre was established based on the knowledge obtained from former studies.

Laboratory tests: We used baseline laboratory tests and vital parameters from local guidelines.

Conclusion of diagnostic workup: We categorized the patients' cases according to whether they were terminated with a diagnosis (other than the International Classification of Diseases, tenth version (ICD-10) diagnosis DT881: other complication to vaccination or immunization, which was given if no somatic explanation was found) and if they were referred to other medical departments.

The data were manually entered twice using Microsoft Excel.

### Outcome definitions

Categorical data were dichotomous with the values of Yes or No. Some categories were classified into subgroups for a more accurate differentiation. Continuous data were collected with numerical values.

### Statistical analysis

Continuous variables are described by median and interquartile range (IQR), and categorical variables are presented as percentage frequencies and compared using the chi-squared test. All statistical tests were two-tailed and the significance level was set to $p < 0.05$.

Stata version 14 (StataCorp LP, College Station, Texas, USA) was used for data analysis.

### Ethical considerations

The Danish Data Protection Agency (16/30720) and the Danish Health Authority (3-3013-1850/1/) granted permission to conduct the study.

*Trial registration:* not relevant.

## RESULTS

In total, 289 patients were referred to the DID and the DP in the study period. Of those, 200 girls and women – 170 from the DID and 30 from the DP – fulfilled the inclusion criteria.

**TABLE 1**

Demographic characteristics of the 200 girls who were referred with possible adverse effects to the quadrivalent human papillomavirus vaccine in the Region of Southern Denmark from March 2015 to October 2016.

| | Age, yrs, median (IQR) | n/respondents (%) |
|---|---|---|
| Referral | 22 (19.5-26) | – |
| 1st vaccination | 14 (12-21) | – |
| *Vaccine doses* | | |
| 1 | – | 200/200 (100) |
| 2 | – | 197/200 (99) |
| 3 | – | 184/200 (92) |
| Reported to be completely healthy before vaccination | – | 155/196 (79) |
| Seen by doctor elsewhere | – | 189/194 (97) |
| Hospitalization before or after vaccination | – | 142/195 (73) |
| *Living situation* | | |
| With parents | – | 84/193 (44) |
| Alone | – | 36/193 (19) |
| With room mate | – | 73/193 (38) |
| Patients able to go to school or work fulltime | – | 101/193 (52) |
| Smokers | – | 43/197 (22) |
| Drink > 7 U of alcohol per week | – | 0/197 |
| Ever abused drugs | – | 13/196 (7) |
| Adverse effects reported to authorities | – | 72/196 (37) |
| Followed the Danish childhood vaccination programme | – | 195/196 (99) |
| Measles vaccinated | – | 183/188 (97) |
| Any other vaccinations | – | 66/195 (34) |
| *Dispositions* | | |
| Epilepsy | – | 17/195 (9) |
| Heart diseases | – | 61/195 (31) |
| Coronary diseases | – | 41/194 (21) |
| Lung diseases | – | 54/195 (28) |
| Metabolic disorders | – | 33/194 (17) |
| Cancer | – | 113/194 (58) |
| Rheumatic diseases | – | 96/195 (49) |
| *Allergies* | | |
| Medicine | – | 27/195 (14) |
| Food | – | 36/195 (18) |
| Pollen | – | 41/196 (21) |
| Animals | – | 24/195 (12) |

IQR = interquartile range.

The demographic characteristics are shown in **Table 1**. The median age at referral was 22 years (IQR: 19.5-26.0), and the median age at time of first vaccination was 14 years (IQR: 12-21). All patients had at least received the first dose of the vaccine.

The symptoms and different treatment options are presented in **Table 2**. The five most common symptoms were headache (93%), fatigue/tiredness (93%), dizziness when standing up (90%), difficulties concentrating or loss of memory (83%) and nausea (79%).

The median number of reported symptoms from each patient was 15 (range: 3-26). Furthermore, 103 (52%) patients reported additional symptoms. Of these patients, 98 (95%) were from the DID and five (5%) from the DP.

Time elapsed between any dose of vaccination and symptom onset was typically less than one month (49%). Of all patients, 28% reported symptom onset 2-6 months after vaccination, and 23% of the patients reported that the symptoms presented more than six months after any dose of vaccination. When we stratified the population by time of vaccination (before or after six months), we found no difference between onset of headache (p = 0.39), fatigue/tiredness (p = 0.40), dizziness when standing up (p = 0.10), difficulties concentrating or loss of memory (p = 0.82) and nausea (p = 0.71).

Of all patients, 67% were using dietary supplements, and 56% had tried one or more alternative treatment methods. We found a significant difference between physical activity level before and after any dose of vaccination (p = 0.01) (Table 2).

In most patients, vital parameters and laboratory test results were within the normal range (**Table 3**). Of 76 patients who were tested at the DID for POTS, eight (11%) had a positive stand test and were referred to the Department of Cardiology for further examination. Five (2.5%) obtained a confirmed POTS diagnosis (ICD-10-DI471J) by the cardiologists (**Table 4**).

Table 4 is a summary of the results of the diagnostic workup and the specialized departments used to obtain a definite diagnosis. At the DID and the DP, 183 (91.5%) patients were terminated with the diagnosis DT881.

**TABLE 2**

Frequency of the most common symptoms[a] and management in 200 girls referred with possible adverse effects to the quadrivalent human papillomavirus vaccine in the Region of Southern Denmark from March 2015 to October 2016. The values are n/respondents (%).

| | |
|---|---|
| *Most commonly presenting complaints* | |
| Headache | 186/200 (93) |
| Fatigue/tiredness | 185/200 (93) |
| Dizziness when standing in upright position | 180/200 (90) |
| Difficulty thinking or remembering | 166/200 (83) |
| Nausea | 158/200 (79) |
| *≥ 1 other symptoms added in the free text section* | |
| All patients | 103/200 (52) |
| Department of Infectious Diseases | 98/170 (58) |
| Department of Paediatrics | 5/30 (17) |
| *Time elapsed between any dose of HPV vaccination and symptom onset, mo.s* | |
| ≤ 1 | 87/179 (49) |
| 2-6 | 50/179 (28) |
| > 6 | 42/179 (23) |
| *Power of symptoms at time of referral compared to debut of symptoms* | |
| Decreased | 88/195 (46) |
| Unchanged | 81/195 (42) |
| Increased | 24/195 (12) |
| *Most commonly presenting medication at any time* | |
| Painkillers | 38/191 (20) |
| Prevention | 32/191 (17) |
| Anti-depressants | 20/191 (10) |
| Asthma medication | 16/191 (8) |
| Sleeping pills | 11/191 (6) |
| Effect of medical treatment | 45/166 (27) |
| Dietary supplements | 127/189 (67) |
| Changes in diet | 61/190 (32) |
| Alternative treatment | 108/192 (56) |
| *Activity level before vaccination* | |
| Low | 18/197 (9) |
| Moderate | 66/197 (34) |
| High | 113/197 (57) |
| *Activity level after vaccination* | |
| Low | 121/193 (63) |
| Moderate | 41/193 (21) |
| High | 31/193 (16) |

HPV = human papillomavirus.
a) Median (range) number of symptoms reported from the 27 symptoms listed in the questionnaire: 15 (3-26).

## DISCUSSION

In our study, the most commonly reported symptoms differed from those reported in other international studies. A cohort study from Slovenia describing adverse events following immunization with qHPV vaccine reported that the most common symptoms were malaise, headache and fever [11]. An American study reported that the most frequent symptoms were syncope, local-site reactions, dizziness, nausea, headache, hypersensitivity reactions and urticariae according to the Vaccine Adverse Event Reporting System [12], while musculoskeletal pain, fatigue and headache were reported as the most prominent symptoms in a questionnaire-based American study of HPV vaccination symptomatology [13].

Because the subject of this study remains highly unexplored, it was quite difficult to find comparable studies to include in the discussion.

The frequency of the most commonly reported symptoms differed as well. In our study, headache was the most frequently reported symptom. In contrast to this, 57% of the patients in the American study reported

## TABLE 3

The presenting clinical features and baseline laboratory tests in 200 girls referred with possible adverse effects to the quadrivalent human papillomavirus vaccine in the Region of Southern Denmark from March 2015 to October 2016.

| | Reference value | Median (range) | n/respondents (%) |
|---|---|---|---|
| Systolic blood pressure, mmHg | – | 20.5 (94-177) | – |
| Diastolic blood pressure, mmHg | – | 76.5 (56-96) | – |
| Heart rate, bpm | – | 69 (40-107) | – |
| $O_2$ saturation, % | – | 99 (95-100) | – |
| Temperature, °C | – | 37.3 (35.5-37.7) | – |
| Weight, kg | – | 64.25 (46.3-150) | – |
| Height, cm | – | 167 (150-188) | – |
| BMI, kg/m$^2$ | – | 22.9 (16.9-51.3) | – |
| Positive stand test at the DID | – | | 8/76 (11) |
| *Normal urine* | | | |
| Glucose | – | – | 144/144 (100) |
| Ketone | – | – | 143/144 (99) |
| Blood | – | – | 116/145 (80) |
| Protein | – | – | 130/144 (90) |
| Nitrite | – | – | 140/144 (97) |
| Leucocytes | – | – | 96/144 (67) |
| pH | – | 6 (5-8.5) | – |
| *Normal blood test* | | | |
| Ferritin, µg/l | 15-200 | – | 135/156 (87) |
| Haemoglobin, mmol/l | 7.3-9.5 | – | 162/171 (95) |
| Leucocytes, × 10$^9$/l | 3.5-8.8 | – | 141/171 (82) |
| Reticulocytes, × 10$^9$/l | 31-97 | – | 144/154 (94) |
| SR, mm | 2-30 | – | 159/163 (98) |
| Thrombocytes, × 10$^9$/l | 165-400 | – | 165/171 (96) |
| Neutrofilocytes, × 10$^9$/l | 1.5-7.5 | – | 163/170 (96) |
| Lymphocytes, × 10$^9$/l | 1-4 | – | 167/169 (99) |
| Monocytes, × 10$^9$/l | 0.2-0.8 | – | 159/169 (94) |
| Basofilocytes, × 10$^9$/l | < 0.2 | – | 169/169 (100) |
| Eosinofilocytes, × 10$^9$/l | < 0.5 | – | 163/169 (96) |
| Albumin, g/l | 36-50 | – | 171/171 (100) |
| Potassium, mmol/l | 3.5-4.4 | – | 166/171 (97) |
| Carbamide, mmol/l | 2.6-6.4 | – | 153/167 (92) |
| Creatinine, µmol/l | 45-90 | – | 170/172 (99) |
| eGFR, ml/min | > 60 | – | 165/165 (100) |
| Sodium, mmol/l | 137-145 | – | 164/170 (96) |
| Coagulation factor II + V, arbitrary U/l | 0.7-1.3 | – | 143/167 (86) |
| ALT, U/l | 10-45 | – | 158/172 (92) |
| Alkaline phosphatase, U/L | 35-105 | – | 164/172 (95) |
| Bilirubin, µmol/l | 5-25 | – | 150/169 (89) |
| LDH, U/L | 105-205 | – | 130/167 (78) |
| $HBA_{1c,}$ mmol/mol | < 48 | – | 157/158 (99) |
| TSH, × 10$^{-3}$ IU/l | 0.5-4.3 | – | 161/168 (96) |
| CRP, mg/l | < 6 | – | 136/171 (80) |
| IgG, g/l | 6.1-15.7 | – | 160/165 (97) |
| IgM, g/l | 0.4-2.3 | – | 154/165 (93) |
| D-vitamin, nmol/l | 50-160 | – | 131/162 (81) |
| P glucose | – | 5.5 (4.3-13) | – |
| Normal ECG | – | | 140/160 (88) |

ALT = alanine transaminase; CRP = C-reactive protein; DID = Dept. of Infectious Diseases; ECG = electrocardiography; eGFR = estimated glomerular filtration rate; $HBA_{1c}$ = glycated haemoglobin; LDH = lactate dehydrogenase; SR = sedimentation rate; TSH = thyroid-stimulating hormone.

## TABLE 4

Overview of definite diagnosis and specialized departments used to obtain a definite diagnosis in the 200 girls referred with possible adverse effects to the quadrivalent human papillomavirus vaccine in the Region of Southern Denmark from March 2015 to October 2016.

| | n/respondents (%) |
|---|---|
| Terminated with DT881[a] | 183/200 (91.5) |
| Terminated with DI471J[b] | 5/200 (2.5) |
| Terminated with 662039[c] | 1/200 (0.5) |
| Still in diagnostic workup | 11/200 (5.5) |
| *Most common departments used for further diagnostic workup* | |
| Neurology | 63/159 (40) |
| Cardiology | 48/159 (30) |
| Rheumatology | 29/159 (18) |
| Gastrointestinal system | 27/159 (17) |
| Psychiatry | 21/159 (13) |
| Headache clinic | 19/159 (12) |

a) Other complication to vaccination or immunization.
b) Postural orthostatic tachycardia syndrome.
c) Functional disorder.

headache; and in the Slovenian study, headache comprised 11.4% of all adverse events. In a Danish study by Brinth et al, headache was reported by 82% of the patients [14]. This is consistent with the results in our study.

The number of reported symptoms was remarkably different from that reported in the Slovenian study, where each patient only reported an average of two adverse events compared with a median of 15 in our study. In general, our study and that of Brinth et al both reported various symptoms, all with a high frequency when compared to the above-mentioned international studies.

In the present study, five patients (2.5%) had a confirmed POTS diagnosis. Brinth et al [14] reported that 21 of 35 (60%) patients fulfilled the criteria for POTS. The variation in these results must be considered in relation to the different settings of the studies. Brinth et al conducted a study of selected patients referred to a specialized syncope unit, and these patients were already suspected of having POTS. The prevalence of persons suffering from POTS in Denmark is uncertain, but is estimated to be 0.2% of the total population [14, 15]. POTS most commonly presents between 15 and 25 years of age, which is the same age at which the girls in this study are presenting symptoms [16]. Still, the prevalence in this particular age group is unknown, but it may explain the higher incidence in this study compared with the general population. The European Medicines Agency (EMA) has concluded that the number of vaccinated girls who are diagnosed with POTS is comparable to the expected incidence of POTS in this age group. Finally, the

EMA has investigated the suspected association between POTS and qHPV vaccine and found none [8].

For the time being, there is no statistical evidence of a correlation between vaccination and onset of adverse effects. Specifically, we found no significant difference between onset of the five most frequent symptoms and time of vaccination.

Despite the experienced severity and intensity of the patients' symptoms, 91.5% of the patients were terminated from the DID and the DP without a diagnosis. However, one patient from the DP was terminated with a functional disorder. A functional disorder is characterized by symptoms from one or more organ systems without a somatic explanation. Many people experience these symptoms every day without having a disease. If the symptoms become so severe and persistent that they affect the patients' quality of life or ability to attend school/work, a diagnosis of a functional disorder is established [17]. In the present study, we did find a decrease in the level of physical activity before and after vaccination, respectively. However, it is not possible for us to determine whether this change in physical activity was due to a physical or functional problem.

The study population was medically examined to clarify if there was any somatic explanation of their symptoms. The DP does have the expertise to diagnose functional disorders, and one patient was discharged with this diagnosis. The DID does not have the expertise to diagnose functional disorders. Instead, patients with no somatic diagnosis were referred to the Centre for Functional Disorders – unfortunately almost all patients declined. Yet, the symptomatology of this patient cohort is compatible with the symptomatology seen in functional disorders. Patients with severe symptoms but no somatic diagnosis might try to explain their disease as adverse effects to qHPV vaccine.

The girls in this study frequently used dietary supplements and alternative treatment methods. This underlines that the symptoms are experienced to be very problematic by the patients; and in despair due to the absence of any medical treatment, they try other methods.

A survey showed that the attendance to HPV vaccination in the childhood vaccination programme in Sweden is continuously high (80%). In Denmark, the attendance has decreased remarkably from 90% to 27% since the precipitous rise of media attention following the documentary "The vaccinated girls" that was broadcast on national Danish television in 2015 [18]. This is consistent with a study from the Netherlands, which suggested that the media attention given to possible side effects to qHPV vaccine may explain the increased awareness hereof [19].

In our study, the young girls from the DP reported fewer symptoms than the older girls from the DID. This age-trend was also seen in a study from the Netherlands [19]. The reason for this age-trend is unknown, but it indicates that, regardless of their origin, the symptoms increase over time. A Japanese study showed that the symptomatology of adolescent females suffering from possible adverse effects of qHPV was significantly improved by intervention [20]. Therefore, it might be important to investigate these patients at an early point in time to prevent the development of a more severe symptomatology. Despite that, the underlying cause remains unknown; the patient cohort described in the present study is presenting symptoms which must be solemnly viewed. There are no doubt that we are facing a group of girls and women who are desperately seeking an explanation of their symptoms.

Our study has limitations. The main weakness is the descriptive nature of the study in a highly selected group of girls without any control group. Furthermore, the study is based on a questionnaire; hence most of the data are self-reported. The study is retrospective, which might lead to recall bias. It is reasonable to believe that the patients experiencing the most severe symptomatology are more likely to complete the questionnaire. It is also unknown whether the younger girls received help from their parents to fill out the questionnaire. The strength of this study is the possibility for the patients to add other symptoms than the ones provided in the questionnaire and to describe how the symptoms affect their lives. The study comprised a considerable amount of information about symptomatology, demographic characteristics and an extended physical examination, which makes it possible to describe a large patient cohort.

## CONCLUSIONS

The patients in our study reported a wide range of symptoms. The prevalence of POTS in this study was probably slightly higher than the anticipated prevalence in the background population. The symptomatology of the patients is compatible with the symptomatology seen in functional disorders. It may be important to investigate these patients at an early point to prevent the development of a more severe symptomatology. It should be further investigated whether these patients may suffer from a functional disorder rather than from adverse effects to the HPV vaccine.

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