Well-being of women referred due to suspected side effects after human papilloma virus vaccination

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ABSTRACT

INTRODUCTION: Due to increased reporting of presumed side effects following human papilloma virus (HPV) vaccination, the Danish Health Authority established five HPV clinics aiming to improve the diagnostics and treatment of affected women. Here, we aimed to describe characteristics of affected women 1-2 years after they attended an HPV clinic and to explore whether women who believed their symptoms were caused by the HPV vaccine were less likely to report symptom improvement than those who did not.

METHODS: A hospital-based, cross-sectional study was conducted at the HPV clinic in Silkeborg, 2017-2018. Information on symptoms, HPV vaccination, basic characteristics, etc. was retrieved using a validated questionnaire. Data were analysed descriptively and by logistic regression.

RESULTS: A total of 120 women were included. The median age at the first vaccine dose and the first visit to the clinic was 15 years (interquartile range (IQR): 13-23) and 23 years (IQR: 20-27), respectively. The median time from the first visit to the time the questionnaire was completed was 1.3 years (IQR: 1-1.6). At the time of the questionnaire, most women reported a wide range of symptoms, with physical symptoms being more common than psychological symptoms, and 70% of the reported symptoms had not improved over time. Of note, 90% believed that their symptoms were caused by the HPV vaccine. No difference in symptom improvement was found between women who believed that their symptoms occurred because of the HPV vaccine and those who did not.

CONCLUSIONS: Most women did not experience any improvement in their symptoms over time, and no association was found between lack of symptom improvement and believing that the HPV vaccine was causing the symptoms.

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Human papilloma virus (HPV), the most common sexually transmitted infection, may cause cancer of the vulva, vagina, cervix, penis and of the head and neck [1]. To reduce the burden of HPV infections and HPV-related disease, particularly cervical precancer and cancer, the HPV vaccine was implemented in the Danish childhood vaccination programme in 2009. HPV vaccination is recommended for girls aged 12-18 years and, starting September 2019, for boys at the age of 12 [2]. As the vaccine was licensed in Denmark in 2006, some women may have received the vaccine prior to 2009.

Although several studies have proven that HPV vaccination is beneficial because it significantly reduces the risk of HPV infection, anogenital warts and cervical precancer among vaccinated people [3, 4], serious concerns have been raised about the safety of the HPV vaccine. Some studies have suggested that HPV vaccination may be associated with severe side effects. However, so far, there is no evidence of an association between HPV vaccination and severe conditions such as postural orthostatic tachycardia syndrome (POTS) and complex regional pain syndrome (CRPS) [5-8], neurological disease [9], chronic fatigue syndrome [10, 11], autoimmune disease or thrombo-embolic disease [9, 12].

As the reporting of presumed side effects to the Danish Medicines Agency increased and negative media attention arose, HPV vaccination coverage declined dramatically in Denmark. In 2014-2015, coverage dropped from 90% (one dose), 86% (two doses) and 82% (three doses) in birth cohorts 1998-2000, respectively, to 71% (one dose), 48% (two doses) and 18% (three doses) in the 2002 birth cohorts [13]. Recently, the coverage reached almost the same level as before 2015 [2]. As a result of the decline in coverage and concerns about vaccine safety, the Danish Health Authority established five regional outpatient clinics in 2015 (i.e. HPV clinics), aiming to improve the diagnostics and treatment of women reporting presumed adverse events following HPV vaccination. In the Central Denmark Region, comprising approximately one fifth of the Danish population, women aged 17 years and older were referred to the HPV clinic at Silkeborg Regional Hospital.

Whereas a previous study has described the characteristics and symptomatology of women suffering from presumed side effects at the time of the visit to the HPV clinic [14], no studies have explored how these women are doing 1-2 years after termination from the HPV clinic. It is important to explore the short-term and long-term health status of these people since the previous study reported that 90% of the women were terminated without a somatic diagnosis [14]. Furthermore, some of

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these women report feeling stigmatised and dismissed by the health authorities [15]. Here, we aim to describe the characteristics and symptomatology of the women previously terminated from the HPV clinic in Silkeborg and to explore whether a lack of symptom improvement may be associated with a belief in the vaccine as a causal agent of symptoms.

METHODS

Study population and design

This hospital-based, cross-sectional study was conducted at the HPV clinic in Silkeborg, Central Denmark Region, Denmark, from April 2017 to April 2018. Women were eligible for enrolment if they were aged 17 years or older, had received a minimum of one HPV vaccine dose (Gardasil/Silgaard or Cervarix), were referred due to suspected side effects following HPV vaccination and provided their signed informed consent.

Data collection

A questionnaire was sent by e-Boks (official Danish e-mail system) to all women who had previously been referred to the HPV clinic. Two reminders were sent by e-Boks and mail. The questionnaire included items about physical and psychological symptoms, HPV vaccination, comorbidity such as anxiety and depression, perceived health, physical and psychological level of function, belief in complete resolution of symptoms, and whether they believed that their symptoms were caused by the HPV vaccine. The questionnaire was developed for the purpose of this study and was subsequently validated qualitatively by interview and quantitatively in a pilot study prior to study start.

After having obtained informed consent, we collected additional information on HPV vaccination (i.e. date of vaccination, vaccine type, number of doses) and age from medical records.

Descriptive and statistical analysis

Results on whether symptoms had improved were dichotomised into Yes (better) and No (worse, unchanged, or "symptoms fluctuate, so I cannot tell the difference"). Descriptive results were presented as percentages and median values (interquartile range (IQR)). We calculated unadjusted and adjusted odds ratios with 95% confidence intervals using logistic regression and multiple regression models, respectively. Due to a low sample size, we were only able to adjust for one confounder at a time. All statistical analyses were conducted using Stata 15.

Ethical considerations

This study was approved by the Danish Data Protection Agency (1-16-02-466-16) and was deemed to be exempt from ethical approval.

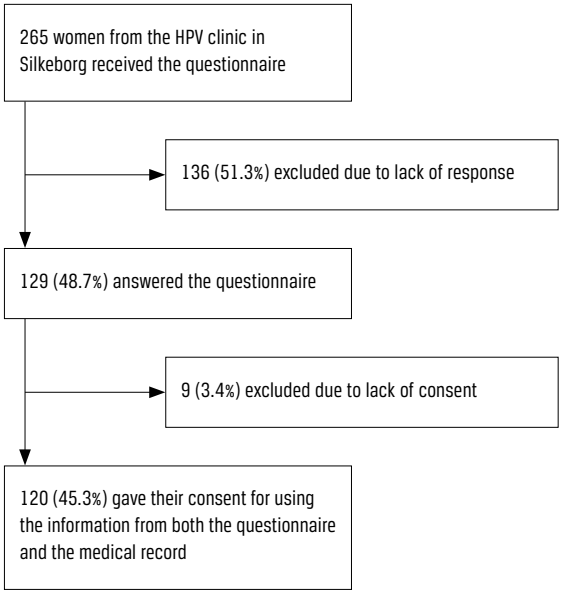
Trial registration: not relevant.

RESULTS

During the study period, a total of 265 women received the questionnaire, 120 (45.3%) of whom agreed to participate (**Figure 1**). **Table 1** summarises the characteristics of the study cohort. The median age of enrolled women at the first visit was 23 years (IQR: 20-27), and most women were fully vaccinated (i.e. at least two vaccine doses) (90.8%). The median age at the first vaccination dose was 15 years (IQR: 13-23), and half of the women reported onset of symptoms after the third dose. The median time from the first visit at the HPV clinic to the time of the questionnaire was 1.3 years (IQR: 1-1.6). Of note, one third reported having a current or previous history of depression and/or anxiety (Table 1).

At the time of the questionnaire, 70% of the women reported no improvement in their symptoms over time, and one third reported they had been either fully or partially absent from work or school due to their symptoms (**Table 2**). Women reported being affected by a variety of physical symptoms. Of all women, the majority were still affected by symptoms from the heart and/or lungs (e.g. palpitations, respiratory difficulties, chest pain, chest discomfort), gastrointestinal symptoms (e.g. stomach ache, diarrhoea, nausea, acid reflux), muscular and joint symptoms, general physical symptoms (e.g. fatigue, headache, concentration difficulty, vertigo) and other physical symptoms (e.g., skin problems, fever, visual disorder, hypersensitivity to light,

FIGURE 1 / Flow chart of the study population illustrating the inclusion and exclusion criteria of participants.



HPV = human papilloma virus.

TABLE 1 / Basic characteristics of the study cohort (N = 120).

Age at time of 1st appointment at the HPV clinic, yrs, median (IQR)	23 (20-27)
Age at 1st HPV vaccine dose, yrs, median (IQR)	15 (13-23)
Time from 1st visit to time of questionnaire, yrs, median (IQR)[a]	1.3 (1-1.6)
Year of HPV vaccination, n (%)	
2007[b]	4 (3.3)
2008[b]	29 (24.2)
2009	23 (19.2)
2010	9 (7.5)
2011	7 (5.3)
2012	34 (28.3)
2013	12 (10.0)
Missing	2 (1.7)
Fully vaccinated, n (%)	
Yes	109 (90.8)
No	8 (6.7)
Unknown	3 (2.5)
Symptom onset, n (%)	
After 1st dose	21 (17.5)
After 2nd dose	31 (25.8)
After 3rd dose	55 (45.8)
Unknown	13 (10.8)
Time interval from vaccination to symptom onset, n (%)	
1 wk	24 (20.0)
1 mo.	28 (23.3)
2-6 mo.s	25 (20.8)
〉6 mo.s	18 (15.0)
Unknown	25 (20.8)
Time since 1st appointment at the HPV clinic to time of questionnaire, n (%)	
≤ 1 yr	24 (20.0)
]1-1,5] yrs	60 (50.0)
]1,5-2] yrs	33 (27.5)
〉2 yrs	2 (1.7)
Missing	1 (0.8)
Current or previous history of depression, n (%)	
Yes	38 (31.7)
No	80 (66.7)
Unknown	2 (1.7)
Current or previous history of anxiety, n (%)	
Yes	35 (29.2)
No	84 (70.0)
Unknown	1 (0.8)

HPV = human papilloma virus.; IQR = interquartile range.
a) Median value was calculated based on 117 observations due to missing values.
b) As the HPV vaccine was licensed in Denmark in 2006, some women may have received the HPV vaccine prior to 2009.

TABLE 2 / Characteristics of current health condition among women previously referred to the human papilloma virus (HPV) clinic. The values are n (%) (N = 120).

Symptoms	
Heart and lungs	115 (95.8)
Gastrointestinal	114 (95.0)
Muscles and joints	113 (94.2)
General symptoms[a]	117 (97.5)
Other symptoms, physical[b]	117 (97.5)
Other symptoms, psychological	107 (89.2)
Lower level of function	
Psychological causes:	
All the time	9 (7.5)
Most of the time	18 (15.0)
Some of the time	17 (14.2)
Rarely	28 (23.3)
Never	48 (40.0)
Physiological causes:	
All the time	24 (20.0)
Most of the time	29 (24.2)
Some of the time	23 (19.2)
Rarely	25 (20.8)
Never	19 (15.8)
Absence from work or school	
Fully	9 (7.5)
Partially	30 (25.0)
None	60 (50.0)
Unemployed/no school	20 (16.7)
Missing	1 (0.8)
Improvement in symptoms at the time of questionnaire	
Yes	34 (28.6)
No	85 (70.8)
Missing	1 (0.8)
Believing that the symptoms are caused by the HPV vaccine	
No	15 (13.0)
Yes, some belief	41 (35.7)
Yes, strong belief	59 (51.3)
Missing	5 (4.2)
Belief in complete resolution of symptoms	
No	48 (40.0)
Yes, some belief	46 (38.3)
Yes, strong belief	25 (20.8)
Missing	1 (0.8)

a) E.g. fatigue, headache, difficulty concentrating, vertigo.
b) E.g. skin problems, fever, visual disorder, hypersensitivity to light, frequent infections.

frequent infections). In terms of mental health, most women experienced other psychological symptoms (e.g. despondency, loneliness, angry outbursts, feeling unease). Overall, most women reported that physical symptoms had a greater negative impact on their ability to attend work, school, and other daily activities than their psychological symptoms did. Approximately one in five experienced a lower level of function all the time or most of the time due to their psychological symptoms, whereas nearly half experienced a lower level of

TABLE 3 / Association between believing that symptoms are caused by the human papilloma virus vaccine and improvement in health condition, crude and adjusted.

	No/a bit belief,	Some belief		Great belief	
	OR (95% CI)	OR (95% CI)	p-value	OR (95% CI)	p-value
Crude	1[a]	0.65 (0.18-2.34)	0.51	0.90 (0.27-3.02)	0.86
Adjusted for anxiety	1	0.58 (0.15-2.18)	0.42	0.78 (0.22-2.74)	0.70
Adjusted for depression	1	0.59 (0.16-2.21)	0.44	0.85 (0.25-2.89)	0.79
Adjusted for believing in complete resolution of symptoms	1	0.85 (0.21-3.48)	0.83	1.47 (0.38-5.64)	0.57

CI = confidence interval; OR = odds ratio.
a) Reference.

function all the time or most of the time due to their physical symptoms. Nearly 90% believed that their symptoms were caused by the HPV vaccine (strong belief 51.3% and some belief 35.7%), and 40% had no confidence in the complete resolution of their symptoms (Table 2).

In an ancillary analysis, we found that women were more likely to report symptom improvement if they strongly believed symptoms would resolve completely ($p < 0.01$). In contrast, women were less likely to report symptom improvement if they had a current or previous history of anxiety ($p = 0.03$). No association was found between depression and symptom improvement ($p = 0.4$). We found no association between believing that the vaccine was causing the symptoms and lack of symptom improvement (**Table 3**). Adjusting for depression, anxiety and believing that symptoms would eventually revolve did not change the results.

DISCUSSION

This is the first study to describe the characteristics and symptomatology of women 1-2 years after attending an HPV clinic. At the time of the questionnaire, we found that 70% of all women reported no improvement in their symptoms, and more than 90% reported having a great variety of symptoms from multiple organ systems. Most women reported that physical symptoms affected daily life more than their psychological symptoms, with half of the women reporting a lower level of function all the time or most of the time due to physical symptoms. Of note, nearly 90% considered the vaccine to be causally related to their symptoms. We found no difference in symptom improvement between the women who believed that the vaccine was causing the symptoms and those who did not.

The fact that a large proportion of the included women remained heavily affected by symptoms and reported no symptom improvement is concerning, especially because the majority reported that the symptoms had a negative impact on their daily life and reduced their ability to work or attend school. Some of the most common physical symptoms reported in the present study were general and unspecific symptoms such as headache, fatigue and dizziness. These findings are in line with results reported in previous studies [14, 16, 17]. However, although the proportion of women with anxiety and/or depression was high (approx. 30%) in the present study, the women reported that physical symptoms affected their daily life more than psychological symptoms did. As we have no information on depression and anxiety prior to HPV vaccination, we are unable to assess whether the evolution of symptoms was associated with a psychological disorder. Previous studies have reported that women suffering from presumed side effects are more likely to have a preexisting psychological disorder and increased care seeking in the two years before the first HPV vaccine dose compared with women who report no side effects [18-20]. In the present study, we have no information on depression and anxiety prior to HPV vaccination. However, the high proportion of a current or previous history of anxiety and/or depression may suggest a vulnerable patient group in need of a specialised treatment plan.

We found no statistically significant association between believing that the vaccine was causing the symptoms and symptom improvement. We cannot rule out that this may be due to a low sample size or to the fact that nearly 90% believed that the HPV vaccine was a causal agent of their symptoms. Unsurprisingly, we did find that belief in complete resolution of symptoms was significantly associated with symptom improvement at the time of the questionnaire.

It is important to point out that the present study did not aim to investigate whether HPV vaccination may be causally related to the symptoms reported. Several studies have reported that HPV vaccination is not associated with an increased risk of serious conditions, such as POTS and CRPS, neurological disease, chronic fatigue syndrome, autoimmune disease or thromboembolic disease [9-12]. Our study results emphasise a need to explore the underlying reason for these symptoms, especially because most women did not receive a final diagnosis. Previous studies have suggested that the symptoms reported may possibly be a result of a functional disorder rather than an adverse reaction to

ABBREVIATIONS

CI = confidence interval
CRPS = complex regional pain syndrome
e-Boks = official Danish secure digital mail platform
HPV = human papilloma virus
IQR = interquartile range
POTS = postural orthostatic tachycardia syndrome

the HPV vaccine [14]. Whether this holds true or not remains unknown as most women in the present study and a previous study declined referral to the Department of Functional Disorders, resulting in women not receiving proper diagnostics and potentially beneficial treatment. This emphasises the importance of a constructive and informative dialogue between doctor and patient regarding the diagnostic workup and potential treatment options.

Strengths and limitations

First, we cannot rule out selection bias as only 45.3% of the eligible women participated in the study. As we have no information about the women who declined to participate, we were unable to determine the magnitude of this potential bias. Thus, it remains unclear whether non-responders decided not to participate because of symptom progression and lack of resources, or because of lack of relevance owing to symptom improvement. In addition, it is possible that some were reluctant to participate due to a general experience of being stigmatised as mentally ill and/or being hypochondriacs and not being taken seriously by healthcare professionals. The issue of stigmatisation and the accompanying distrust of the healthcare system has been reported to be a common phenomenon among women who are suffering from presumed side effects after HPV vaccination, and further investigation may be warranted to reverse this trend [19]. Second, given that we only included women at one of five HPV clinics we are unable to infer that our study results are generalisable to the other four clinics; and given that the establishment of specialised HPV clinics is rather unique for Denmark, we are unable to generalise to other countries. Third, as a result of a low sample size, our study results should be interpreted cautiously, demonstrating a need for further studies on this subject. Finally, because we had to rely on self-reported data obtained through a questionnaire, we cannot rule out recall bias. The strengths of the study include the use of a validated questionnaire and self-reported data, making it possible to collect information about symptom load and how symptoms affected daily life, which is not possible in register-based studies.

CONCLUSIONS

In conclusion, most women were still heavily affected by a wide range of physical and psychological symptoms, and > 50% experienced lower level of function due to physical symptoms. Nearly 90% of all women believed that the HPV vaccine was causing their symptoms. No association was found between lack of symptom improvement and believing that the HPV vaccine was causally related to the symptoms. However, due to risk of selection bias, these results should be interpreted with caution. More attention should be given toward optimising clinical counselling to ensure that patients receive a proper workup and sufficient treatment.

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